Compendium of Case Studies on the Impact of Gene Patents and Licensing Practices on Access to Genetic Testing

Prepared for SACGHS by the
Duke University Center for Genome Ethics, Law & Policy
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Impact of Gene Patents and Licensing Practices on Access to Genetic Testing Compendium of Case Studies Commissioned for SACGHS by the Duke University Center for Genome Ethics, Law & Policy

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Impact of Gene Patents and Licensing Practices on Access to Genetic Testing for Inherited Susceptibility to Cancer: Comparing Breast and Ovarian Cancers to Colon Cancers

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Executive Summary

A natural case study in the field of cancer genetics enables us to compare the development of testing for inherited susceptibility to colorectal cancers to inherited breast and ovarian cancers. Specific mutations in the *BRCA1* and *BRCA2* genes can dramatically increase patients' risks for breast and ovarian cancers; Myriad Genetics, Inc., holds broad patents on both of these genes and their mutations in the United States. Similarly, specific mutations in several other genes can give rise to two inherited conditions highly-associated with developing colorectal cancer, known as Lynch Syndrome (or Hereditary Non-Polyposis Colorectal Cancer, HNPCC) and Familial Adenomatous Polyposis (FAP), but the involved gene patents are predominantly held by non-profit institutions, and licensed non-exclusively. Myriad is the sole provider of full-sequence *BRCA* testing in the U.S. For FAP, Myriad and four non-profits offer full-sequence analysis of the FAP-associated *APC* gene (and from some testing services, another gene, MYH). For Lynch Syndrome, Myriad, Quest Diagnostics, Huntington Diagnostic Laboratories and four non-profits offer full-sequence analysis for three HNPCC-causing genes (*MLH1*, *MSH2*, and *MSH6*).

The clinical decision tree and the role of full-sequence genetic testing differs between BRCA and colon cancer predisposition (and details about exactly how best to do genetic testing for colorectal cancer are particularly unsettled). But for purposes of comparing the impact of patents and licensing practices, those uncertainties about clinical practice do not directly interfere with expected effects attributable to patents and licensing.

Basic and Clinical Research

- As of September 2008, Myriad has submitted over 18,000 entries (>80% of total entries) for over 2600 unique mutations to the Breast Cancer Information Core database and cites over 4,300 follow-up publications on *BRCA1* and *BRCA2* (as of Feb. 2005) and more than 100 individual research projects (including a 1999 Memorandum of Understanding with the NCI) as evidence that it supports research.[1]
- Some argue that Myriad's definition of infringing research is too broad. Specifically, Myriad asserted that even though Genetic Diagnostics Laboratory (GDL) limited testing to patients in NCI research

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[1] William Rusconi, Myriad Genetics. *Patenting and Licensing of the Breast Cancer Susceptibility Genes - BRCA1 and BRCA2.* PowerPoint. Given February 11, 2005, to National Acadmies of Science. Email from William Rusconi to Christopher Heaney, January 15, 2009.
A search of the Breast Cancer Information Core for mutations catalogued as deposited by Myriad Genetics revealed 8,826 mutations in BRCA1 and 9,891 mutations in BRCA2. (*Breast Cancer Information Core.* National Human Genome Research Institute. See http://research.nhgri.nih.gov/bic/ [accessed September 25, 2008].)

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protocols, because GDL was performing a third-party service for which it charged other laboratories, it infringed the patent. As Parthasarathy says, "So long as GDL disclosed results to the patient, [it provided] a commercial service and violat[ed] the patent."[2]

- NCI Director Richard Klausner signed a December 1999 Memorandum of Understanding (MOU) that included an explicit definition of genetic testing for research.[3] That MOU provided deeply discounted testing for any NCI-funded project with no reach-through rights to new discoveries. Under this definition, researchers could perform research testing within their institutions without a license from Myriad.
- A 2005 Lewin Group report concluded that, based on incentive effect theory, Myriad's exclusive patents on the *BRCA* genes stifled further basic research; however, few empirical data support or refute the Lewin Group's conclusion.[4]
- While Myriad maintains it has not enforced its patents against researchers, neither has it publicly stated that it would not do so in a written, actionable form except in the NCI MOU. This ambiguity may itself be a factor in stifling further research to the extent that this has occurred.
- Myriad responds that it collaborates with many academic groups, and they simply have to contact Myriad. This is only a partial remedy, however, as contacting Myriad would alert the patent-holder about actions it could regard as infringement.
- A recent controversy in Australia, precipitated when Myriad's licensee Genetic Technologies Ltd. announced it would reverse its 2003 announcement allowing testing laboratories to do BRCA testing without a license, led it to clarify that its license does not cover research testing, and so any enforcement for research use would be from Myriad or the University of Utah (neither of which has indicated any intention to enforce against research use in Australia).

Development

- A 2003 French study on the cost-effectiveness of full-sequence *BRCA* testing versus other methods stated:

  > The results of our cost-effectiveness analysis strongly suggest that negative [monopolistic] effects of this kind are occurring in the case of *BRCA1*…. [Such monopoly control] may prevent health care systems from identifying and adopting the most efficient genetic testing strategies.[5]

- The same study found that:

  > "…there exist alternative strategies for performing BRCA1 diagnosis: prescreening techniques such as FAMA [fluorescent assisted mismatch analysis] and, potentially, DHPLC [denaturing high performance liquid chromatography] or DGGE [denaturing gradient gel electrophoresis], based on the current estimates of their sensitivity, would minimize the cost of diagnosis while

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[2] Parthasarathy S. Architectures of genetic medicine: comparing genetic testing for breast cancer in the USA and UK. *Social Studies of Science* 2005 (February). 35(1):5-40, at 24.
[3] The crucial definition was Definition 2.4 "Research Testing Services" of a December 1999 Memorandum of Understanding between Myriad Genetics and the U.S. National Cancer Institute (signed on 10 December by Gregory Critchfield, President of Myriad Genetic Laboratories, Inc., and 14 December by Richard Klausner, NCI Director): "part of the grant supported research of an Investigator, and not in performance of a technical service for the grant supported research of another (as a core facility, for example). Research Testing Services are further defined as paid for solely by grant funds, and not by the patient or by insurance."
[4] The Lewin Group. *The Value of Diagnostics*: *Innovation, Adoption, and Diffusion into Health Care*. 2005, 62-3.
[5] Sevilla C et al. Impact of gene patents on the cost-effective delivery of health care: the case of *BRCA1* genetic testing. *International Journal of Technology Assessment in Health Care* 2003. 19:287-300.

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also ensuring a comparable level of effectiveness to that of applying DS [direct sequencing] to the entire gene."[6]

These uncertainties for BRCA testing parallel the uncertainty about which genetic testing protocols are optimal for colorectal cancer susceptibility, except that in the case of BRCA testing, Myriad is the only testing service in the US market and so its practices are a *de facto* standard, whereas practices for colon cancer vary among health care providers.

- Myriad notes that its sequencing technologies are a gold standard method, as alternatives are confirmed by sequence analysis.[7] Some health systems outside the US have chosen to use a diagnostic decision tree that uses full-sequence analysis later in the process and more selectively to reduce expenses. We know of no head-to-head comparison studies on health outcomes. The comparable comparative studies for colon cancer testing found no clear "winner" strategy among four examined, one of which was initial full-sequence testing of multiple genes.[8]
- Using multiplex ligation-dependent probe amplification (MLPA), a 2006 study published in the *Journal of the American Medical Association* (JAMA) noted that Myriad's testing strategy (short-range PCR followed by genomic sequencing) missed up to 12% of large genomic deletions or duplications.[9] This led to criticism of the Myriad test algorithm. In congressional testimony on October 30, 2007, Drs. Marc Grodman and Wendy Chung attributed this problem to Myriad's sole provider status and patent monopoly, concluding, "It was only after considerable pressure from the scientific community that the company added methods to detect these deletions, insertions, and re-arrangements in 2006, over 10 years after they first introduced clinical genetic testing, and barred anyone else from performing the tests. In a competitive marketplace, this delay never would have occurred."[10]
- Myriad disagrees with this characterization. Myriad notes it launched testing for the five most common rearrangements (accounting for about a third of all rearrangements) in 2002—and simultaneously began developing testing for all large rearrangements (BART®) that it launched in 2006 for the higher risk patients (similar to the JAMA paper's criteria) as part of its BRAC*Analysis*™. This technology was the subject of poster presentations in 2004.[11] Myriad notes

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[6] Ibid.

[7] William Rusconi, Myriad Genetics. *Patenting and Licensing of the Breast Cancer Susceptibility Genes - BRCA1 and BRCA2.* Op. cit.

[8] Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. Recommendations from the EGAPP Working Group: genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome relatives. *Genetics in Medicine* 2009. 11(1):35-41.
Palomaki GE, McClain MR, Melillo S, Hampel HL, Thibodeau SN. EGAPP supplementary evidence review: DNA testing strategies aimed at reducing morbidity and mortality from Lynch syndrome. *Genetics in Medicine* 2009. 11(1):42-65.

[9] Walsh T et al. Spectrum of mutations in BRCA1, BRCA2, CHEK2, and TP53 in families at high risk of breast cancer. *Journal of the American Medical Association* 2006 (March). 295(12):1379-1388.

[10] Dr. Marc Grodman, testimony before the House Judiciary Committee, Subcommittee on the Courts, the Internet and Intellectual Property; oversight hearing on "Stifling or Stimulating?—The role of gene patents in research and genetic testing," October 30, 2007, 2237 Rayburn House Office Building, Washington, DC. Oral testimony and written statement of Marc M. Grodman, CEO of BioReference Laboratories, Inc., at 5. Quote taken from Appendix A, October 25, 2007, supplementary written statement from Dr. Wendy Chung, Columbia University, at 3.

[11] After the Walsh et al. paper was published, Myriad issued Clinical Update, Vol. 4, No. 5, "Testing for Hereditary Breast and Ovarian Cancer Syndrome," in September 2006. It cited ongoing work and intention to have a test for large-scale rearrangements by later that year. An abstract submitted Feb. 2004 and a poster presented fall 2004 that report on Myriad efforts to detect large-scale rearrangements were cited in that update. Judkins T, Hendrickson BC, Gonzales D et al. Detection of large rearrangement mutations in *BRCA1* and *BRCA2* in 528 high risk families from North America by quantitative PCR based gene dose analysis. Abstract from 2004 American Society of Human Genetics annual meeting. [See http://www.ashg.org/genetics/abstracts/abs04/f518.htm [accessed 11 July 2008]]. Hartmann C, John AL, Klaes R et al. Large *BRCA1* gene deletions are found in 3% of German high-risk breast cancer families. *Human Mutation* 2004 (December). (Mutation in Brief #762.) 24(6): 534.) Presentations were: Hendrickson BC, Judkins T, Deffenbaugh AM, Pyne K, Ward BE,

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that rearrangement testing it was already conducting would have detected roughly 1/3 of the "missing" cases reported in the JAMA article, so the problem was overstated, and Myriad incorporated more extensive testing for rearrangements in 2006, the year the JAMA article appeared.

- The congressional testimony also alluded to limits on availability of BRCA tests in forms that Myriad itself does not perform. This includes testing of paraffin-embedded samples or pre-implantation genetic diagnosis. Some patients and families lack access to a relative's blood (but potentially with access to a deceased relative's preserved paraffin-embedded tumor sample). Myriad states it has not enforced patents for services it does not provide (such as paraffin-embedded tissues), and has sublicensed BRCA testing to three laboratories offering pre-implantation genetic diagnosis.[12]

Commercialization

- A centralized testing service offers some benefits, including Myriad's ability to provide free testing to first-degree relatives once a mutation has been identified to further characterize uncertain variants. Testing is CLIA-certified and reportedly has faster turn-around time than most other laboratories, and Myriad's reports are characterized as clear and detailed.
- Based on available data as described in the text (derived primarily from phone calls to testing laboratories and online pricing guidelines), calculating the price for each genetic test per DNA segment amplified by PCR (an "amplicon") yields a rough estimate of Myriad's patent premium:
    - For *BRCA*, Myriad charges $3,120 total, or $38.05 per amplicon (including separate testing for common rearrangements).
    - For FAP – where Myriad has four competitors – Myriad charges $1,795 or $40.80 per amplicon (including Southern Blot rearrangement and insertion-deletion testing plus two common mutations of the MYH gene).
        - Non-profit competitors' prices range from $1,200 to $1,675 ($28.57 to $ 39.88 per amplicon) though rearrangement testing is generally not included in this price.
    - For HNPCC – where Myriad has six competitors – Myriad charges $2,950 or $49.17 per amplicon (for three genes, which includes Southern Blot testing for insertions, deletion and rearrangements).
        - Non-profit competitors' prices range from $1,800 to $ 4,646.16 ($30.00 to $ 77.44 per amplicon) and generally does not include rearrangement testing.
    - These data show little consistent *price* effect of the BRCA patents, based on two-step logic: (1) comparing intra-laboratory cost per amplicon for Myriad' s testing of BRCA versus colon

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Scholl T. Recurrent intragenic rearrangement mutations in the tumor suppressor gene *BRCA1*: prevalence results from 12,272 patients at high risk for breast and/or ovarian cancers and methods of biochemical analysis. 40th Annual Meeting of the American Society of Clinical Oncology, New Orleans, LA, June 2004 (Poster); Judkins T, Hendrickson BC, Gonzales D, Eliason K, McCulloch J, Ward BE and Scholl T. Detection of large rearrangement mutations in *BRCA1* and *BRCA2* in 528 high risk families from North America by quantitative PCR based gene dose analysis. *54th Annual Meeting of the American Society of Human Genetics*, Toronto, Canada, Poster, Program Number 518, October 2004. The first year's experience at Myriad with large-scale rearrangment testing was summarized in a poster for the 2007 American Society for Human Genetics meeting: Spence WC, Ludkins T, Schoenberger J et al. Clinical testing experience for large genomic rearrangements in the BRCA1 and BRCA2 genes for hereditary breast and ovarian cancer.

[12] Harmon A. The DNA age: couples cull embryos to halt heritage of Cancer. *New York Times* 2006 (September 3). The article quotes William Hockett, MD, of Myriad Genetics and states that preimplantation BRCA testing had been licensed to three fertility clinics. A search of genetests.org shows several foreign BRCA prenatal testing services (not necessarily PGD, but Myriad does not offer any form of prenatal testing) and two US services, at the University of Calfornia, San Francisco and Boston University. Online research also found two services offering preimplantation BRCA mutation detection, at Reproductive Genetics Institute in Chicago and Genesis Genetics Institute in Detroit.

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cancer genes, and (2) comparing Myriad's price for full-sequence testing of colon cancer genes compared to other (competitor) services. [13]

- An analysis done in three French public hospitals showed the incremental costs of testing an additional family member with a previously identified *BRCA* mutation is only 17% of the price charged by Myriad.[14] An alternative technology of two-dimensional electrophoretic mutation scanning was claimed to be highly sensitive but possible as a screening test, estimated at $70/test and perhaps possible to reduce to $10/test direct costs.[15]
- Alternative low-cost testing methods may be used in some health systems, but not in the United States; these low-cost alternative methods have not been adopted widely for colon cancer testing either, and effects are therefore not specific to BRCA testing or patent status. Any failure to adopt alternative technologies cannot be directly attributed to the BRCA patents or sole-provider status. Patent impediments to adoption of inexpensive technologies cannot be excluded entirely, however, because colon cancer sequences and testing methods are also patented.
- A controversy about BRCA testing in Australia erupted in July 2008, when Genetic Technologies Ltd. (GTG), the BRCA licensee in Australia and New Zealand, announced it would enforce its patents against unlicensed laboratories in Australia. GTG sent "cease and desist" letters with an initial deadline of October 2008, then extended to November 2008. On 31 October, GTG announced it "suspended any enforcement activity pending the outcome of further dialogue with all relevant stakeholders."[16]
- Myriad mainly benefits from the *volume* it receives as a monopoly-provider of *BRCA* testing. Myriad can direct all US full-sequence *BRCA* tests to its laboratories, and we have learned of European reference laboratories that also use Myriad, either directly or through its licensed foreign laboratories, because of turnaround time and reliability. Any price effect attributable to patent status is equivocal; the volume effect is unequivocal.

Communication/Marketing

- Marketing can increase awareness of *BRCA* mutations in the general and at-risk patient populations.
- A survey of 300 women following Myriad's 2002 public advertising campaign noted 85% "would contact their physician regarding *BRCA* testing" and 62% would switch providers to find one who offered the test.[17]

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[13] The comparison of BRCA and FAP/HNPCC testing is confounded by several variables that are not controlled, so it is inexact. Different laboratories use somewhat different methods, and different numbers of amplicons, and different degrees of testing for insertions, deletions, and rearrangements. FAP and HNPCC genes do have patents on them, and prices may include licensing fees, so this is not a "patented versus nonpatented gene" pricing comparison. The rearrangement testing is included in total prices, but the details of those aspects of testing differ between BRCA and colon cancer predisposition mutations. The data cannot rule out a monopoly price effect, but only suggest that any such effect is buried in the counfounding variables. One other powerful constraint on pricing is reimbursement practices for genetic tests, which tend to start from per-amplicon unit prices and are negotiated for specific tests from that baseline.

[14] Sevilla C et al. Impact of gene patents on the cost-effective delivery of health care: the case of *BRCA1* genetic testing. Op. cit.

[15] van Orsouw NJ, Dhanda R, Elhaji Y, Narod S, Li F, Eng C, Vijg J. A highly accurate, low cost test for *BRCA1* mutations. *Journal of Medical Genetics* 1999. 36(10):747-753.

[16] Genetic Technologies Ltd. *Further clarifications on BRCA testing.* (Public announcement "for personal use only.") October 31, 2008. See http://www.gtg.com.au/index.asp?menuid=060.070.130&artid=10740&function=NewsArticle [accessed November 8, 2008].

[17] Parthasarathy S. *Building Genetic Medicine: Breast Cancer, Technology, and the Comparative Politics of Health Care.* Cambridge: MIT Press, 2007.

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Adoption by Clinical Providers and Testing Laboratories

- Provider, lab, and third-party payer metrics of testing services are only rough proxies for patient access.
- A 2003 survey of laboratory directors demonstrates nine instances of patent enforcement by Myriad on its *BRCA* patents. The same directors noted two FAP patent enforcements and zero Lynch Syndrome (HNPCC) patent enforcements.[18]
- BRCA accounted for 2 cases of gene patent litigation and colon cancer genes for none (out of 31 collected gene patent litigation cases, 5 of which were related to diagnostics).[19] Two gene patent lawsuits between OncorMed and Myriad (accounting for two cases in Holman's count, a suit and counter-suit) were consolidated into a single case, and then settled out-of-court, with Myriad gaining control of Oncormed's BRCA patent rights. The other Myriad-University of Pennsylvania lawsuit over BRCA testing was settled even earlier in the process.

Adoption by Third-Party Payers

- Based on available data and authors' calculations, if gene patents conferred a premium of $750, this would reduce the likelihood of third party coverage by 11 percentage points.[20]
- In one study, only 59% of women undergoing full sequence *BRCA* analysis filed a health insurance claim (99% of whom had insurance).[21] A second study found that 15% of women seeking *BRCA* analysis chose to self-pay for their services and that every woman did so in fear of insurance or employment discrimination.[22]
- The published data do not reflect two major trends. One is the May 2008 enactment of the Genetic Information Nondiscrimination Act, which may reduce fear of BRCA testing having consequences for health insurance and employment. The other is Myriad's current experience with third-party payers, with self-pay reported as having dropped to approximately 5 percent as more insurers and health plans cover testing in high-risk patients. Average reimbursement pays for over 90 percent of charges (so average co-pay is less than 10 percent).[23]
- Adoption by third-party payers is becoming more common. Individuals who are not covered either are uninsured (some of whom qualify for Myriad's financial assistance program), or are covered by state Medicaid plans for which reimbursement is evolving (and some Medicaid programs have been slow to adopt BRCA testing). A small percentage (5-10%) of private insurance plans fail to cover any kind of genetic testing (whether it is BRCA, HNPCC or even CF). This is often due to policy or blanket exclusions on the molecular diagnostic CPT codes[24] through which genetic tests are reimbursed.

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[18] Cho M et al. Effect of patents and licenses on the provision of clinical genetic testing services. *Journal of Molecular Diagnostics* 2003 (February). 5(1):3-8. NB: FAP and HNPCC "patent enforcements" are more unlikely given non-exclusive licensing and multiple rights-holders.
[19] Holman CM. The impact of human gene patents on innovation and access: a survey of human gene patent litigation. *UMKC Law Review* 2007. 76(2):295-361, at 347-348. For a draft, see http://papers.ssrn.com/sol3/papers.cfm?abstract_id=1090562 [accessed March 28, 2008].
[20] Schoonmaker M et al. Factors influencing health insurers' decisions to cover new genetic technologies. *International Journal of Technology Assessment in Health Care* 2000. 16: 78-189.
[21] Lee S et al. Utilization of BRCA1/2 genetic testing in the clinical setting. *Cancer* 2002 (March 25). 94(6):1876-85.
[22] Peterson E et al. Health insurance and discrimination concerns and BRCA1/2 testing in a clinic population. *Cancer Epidemiology Biomarkers & Prevention* 2002 (January). 11:79-87.
[23] Figures estimated by William Rusconi, Myriad Genetics. Personal communication to Robert Cook-Deegan, May 29, 2008.
[24] CPT codes are billing codes for reimbursement of health services. CPT® is formally a trademarked term that refers to a system of Current Procedural Terminology maintained by the American Medical Association.

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Consumer Utilization

- Consumers may pay a different price for a given genetic test depending on whether or not insurance covers it, which holds true for both Myriad Genetics and non-profit providers.
- While early publications estimated that as many as 19-74% of at-risk individuals who could benefit from *BRCA* testing were not being tested,[25] no systematic evaluation of this question has been conducted as coverage and reimbursement have become more common. The Genetic Information Nondiscrimination Act of 2008 will take effect in 2009 (health insurance provisions) and 2010 (employer provisions), and this may also affect use of genetic testing, including breast and ovarian cancer as well as family risk of colon cancer.
- Companies offering genetic testing have incentives to negotiate the complex coverage and reimbursement landscape on behalf of patients using their services.
- In one study, nearly 70% of patients eligible for free *BRCA* testing elected to get tested; however, cost certainly matters since only 22% of self-pay patients in the same sample chose to be tested.[26] These data are out-of-date as Myriad reports only approximately 5 percent self-pay in recent experience.
- Any price effect of the BRCA patents is buried in the noise once prices are normalized, first by comparing Myriad's prices for BRCA to its price for colon cancer gene testing and then by comparing Myriad's prices for colon cancer gene testing to other providers. Myriad's costs per unit are lower for BRCA full-sequence testing than for colon cancer gene tests. Its prices are higher than some nonprofit colon cancer testing services for FAP, though Myriad includes rearrangement testing and comparison services that other providers price differently. Myriad is mid-range among providers of Lynch Syndrome (HNPCC) testing (and low relative to the one for-profit HNPCC testing service). This makes it impossible to calculate a meaningful price premium for BRCA testing or to conclude that BRCA patents have led to prices far above comparable tests for other conditions provided by other laboratories.
- It is therefore difficult to attribute reduced access to BRCA testing to patents. We cannot exclude the possibility that patent holder's investments in education about hereditary breast and ovarian cancer (HBOC) and testing have actually had the opposite effect of increasing access to testing.

Introduction

One natural case study in the field of cancer genetics can address whether and to what degree intellectual property law affects patients' access to genetic testing. The parallel discovery of inherited mutations for two classes of cancer: breast, ovarian and some other cancers associated with BRCA 1&2 genes, compared to a cluster of genes in which mutations predispose to cancer of the colon and rectum. Specific mutations in genes known as *BRCA1* and *BRCA2* can dramatically increase patients' risks for breast cancer and ovarian cancer (and more rarely, some other cancers). Similarly, specific mutations in other genes can give rise to two inherited conditions highly associated with developing colon cancer, known as Familial Adenomatous Polyposis (FAP) and Lynch Syndrome (sometimes called Hereditary Non-Polyposis Colorectal Cancer, or HNPCC).

Mutations in all six cancer susceptibility genes were discovered in the 1990s, and genetic tests to detect them were patented over a four-year period. Myriad Genetics, Inc., a for-profit company, gained control over the U.S. patents on genetic tests for *BRCA1* and *BRCA2*. The patents for inherited colon cancer family syndromes remain more broadly distributed, with some key patents held by Johns Hopkins University, Oregon Health Sciences University, Dana Farber, and other non-profit entities. The licensing

[25] William Rusconi, Myriad Genetics. Personal communication to Robert Cook-Deegan, May 29, 2008.
[26] Ibid.

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patterns for these tests vary, again providing a natural case-study to compare for-profit patenting and licensing practices versus non-profit patenting and licensing practices. Finally, as of early 2006 there were 62 genetic tests for cancer available for clinical use but only five used for primary prevention, including the tests for BRCA, FAP, and Lynch Syndrome (HNPCC) discussed in this case study.[27]

Background: Breast Cancer, Ovarian Cancer and *BRCA1* / *BRCA2*

According to the American Cancer Society (ACS), over 178,000 American women were diagnosed with invasive breast cancer in 2007, and another 62,000 with *in situ*, or non-invasive breast cancer. This made breast cancer the most common cancer diagnosis after skin cancer for women. Finally, over 40,000 women were expected to die from breast cancer in 2007, second only to lung cancer.[28]

In 2007, the ACS also projected 22,430 women were diagnosed with ovarian cancer, accounting for 3% of all cancers among women. Furthermore, 15,280 women were projected to die from ovarian cancer in 2007, more than any other cancer of the female reproductive tract.[29]

Both breast and ovarian cancer are associated with age–ovarian cancer incidence peaks around age 70,[30] while 95% of new breast cancer cases and 97% of breast cancer deaths occur in women over the age of 40.[31] Obesity is also a risk factor for both breast and ovarian cancers, and both cancers correlate with family history.

Approximately 20% of women with breast cancer have either a first-degree or a second-degree relative with breast cancer.[32] Scientists have identified several genes associated with elevated risk of breast cancer. Two of these are powerful cancer susceptibility genes, meaning mutations can be traced through families in a classic Mendelian dominant inheritance pattern: *BRCA1* and *BRCA2*. Breast cancers arising from *BRCA1* and *BRCA2* mutations account for between 5 and 10 percent of all breast cancers,[33] or between 20,000 and 40,000 cases annually. Overall, the relative lifetime risk of breast cancer is 2.7 to 6.4 times greater for those with *BRCA* mutations compared to other women (Appendix 1). For ovarian cancer the relative risk for *BRCA* positive women rises 9.3 to 35.3 times (Appendix 1).

Though the Agency for Healthcare Research and Quality (AHRQ) notes that *BRCA1* and *BRCA2* mutations occur at a frequency of around 1 in 300-500 in the general population, the risk of inheriting one of these mutations is much higher in some ethnic groups. For example, specific mutations have been identified in the Ashkenazi Jewish population, and certain families in the Netherlands, Iceland, and Sweden have a high frequency of *BRCA1* or *BRCA2* mutations.[34]

Background: Colorectal Cancer and FAP / Lynch Syndrome (HNPCC)

According to the ACS, colorectal cancer is the third most common cancer among both men and women in the United States. Over 150,000 Americans will be diagnosed with colorectal cancer and over 52,000

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[27] AHRQ Technology Assessment Program. *Genetic Tests for Cancer*. January 9, 2006. See http://www.ahrq.gov/clinic/ta/gentests/gentests.pdf [accessed May 5, 2007].
[28] American Cancer Society. *Cancer Facts and Figures, 2007*. See http://www.cancer.org [accessed March 2007].
[29] Ibid.
[30] Ibid.
[31] American Cancer Society. *Breast Cancer Facts and Figures, 2005-2006*. See http://www.cancer.org [accessed March 2007].
[32] AHRQ. Genetic risk assessment and *BRCA* mutation testing for breast and ovarian cancer susceptibility. Evidence synthesis 37. September 2005.
[33] American Cancer Society. *Breast Cancer Facts and Figures, 2005-2006*. Op. cit.
[34] Ibid.

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Americans will die of colon cancer in 2007, accounting for 10 percent of all cancer deaths.[35] Risk factors for developing colorectal cancer include age, diet, obesity, smoking, physical inactivity, and family history.[36]

Almost one-third of colorectal cancer cases are thought to be related to family history, of which two major conditions have been correlated with specific genetic mutations. Combined, these two conditions are thought to account for between 3 to 5 percent of all US colorectal cancers.

Familial adenomatous polyposis (FAP)

FAP accounts for approximately 1% of all colorectal cancers. The disease is inherited in an autosomal dominant fashion. More than 90% of FAP cases are associated with mutations in the *adenomatous polyposis coli* gene, or *APC* gene. The *APC* gene encodes a tumor-suppressing protein, analogous to the tumor suppressing gene p53 which is found mutated in many kinds of cancer. The percent of individuals with FAP who develop colorectal cancer approaches 100% - or 16.7 times the risk of the general population (Appendix 1) – with most affected individuals developing cancer around age 40.[37] A milder and less common form of FAP is attributed to mutations in the MYH gene.

Lynch Syndrome (Hereditary nonpolyposis colorectal cancer, or HNPCC)

Lynch Syndrome accounts for 1-3% of colorectal cancer in the United States, and mutations are inherited in an autosomal dominant pattern. Lynch syndrome is rapidly becoming a disease category defined by DNA characterization, caused by mutations in genes that encode enzymes that repair DNA base-pair mismatches during DNA replication. This molecular definition replaces the traditional symptomatic and descriptive label hereditary nonpolyposis colorectal cancer, or HNPCC.

The most recent review of evidence about genetic testing in this condition defined Lynch Syndrome as a "predisposition to colorectal cancer and certain other malignancies as a result of a germline mismatch repair gene mutation—including those with an existing cancer and those who have not yet developed cancer." [38] Mutations in specified genes are thus becoming the basis for disease classification, replacing and refining previous clinical criteria. Lynch Syndrome is becoming the preferred term for those who have these mutations, although we also use HNPCC to refer to the clinical findings in this review.

Individuals must inherit a copy of one mutated gene from either their mother or their father to develop the HNPCC disease. The genes already known to give rise to Lynch Syndrome when mutated include: MLH1, PMS1, PMS2, MSH6, TFGBR2, and MLH3.[39] Of these, mutations in MSH2 account for approximately 60% of cases, and MLH1 another 30%.[40] "Mismatch repair proteins are responsible for correcting errors that occur during DNA replication, typically the addition or deletion of one or more nucleotides."[41] Patients with Lynch Syndrome have an approximately 80% lifetime risk of developing colorectal cancer–or over 13 times the risk of the general population (Appendix 1)–though the specific

[35] American Cancer Society. *Cancer Facts and Figures, 2007*. Op. cit.
[36] Ibid.
[37] Kaz A, Brentnall TA. Genetic testing for colon cancer. *Nature Clinical Practice: Gastroenterology & Hepatology* 2006 (December). 3(12):670-679.
[38] Palomaki GE et al. Op. cit. at 42.
[39] Online Mendelian Inheritance in Man. Entry 120435. See http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=120435 [accessed January 19, 2009].
[40] Ibid.
[41] Kaz A, Brentnall TA. Genetic testing for colon cancer. *Nature Clinical Practice: Gastroenterology & Hepatology* 2006 (December). 3(12):670-679.

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risk varies by mutation.[42] There is significantly higher risk of developing endometrial (uterine) cancer and ovarian cancer as well in women with these mutations. In fact, about half of women with Lynch Syndrome who develop cancer present with one of these gynecological cancers as their first malignancy.

Patents and Licensing

Breast Cancer

Myriad Genetics owns or has licensed the patents for both *BRCA* genes and their mutations. Some BRCA1 patents are co-assigned to the University of Utah and US Department of Health and Human Services, as the research was supported in part by NIH grants (governed by the Bayh-Dole Act) and intramural research at the National Institute of Environmental Health Sciences (governed by the Stevenson-Wydler Act). While NIH investigators were listed a co-inventors on some patents, NIH assigned administration of those patents to the University of Utah. The BRCA patents have been administered by the University of Utah, with exclusive licensing to Myriad, and Myriad in effect controls the patent rights. We therefore refer to them as "Myriad patents."

Myriad's first patent, U.S. 5753441, is on *BRCA1* testing and includes both method claims and a testing kit. Its second patent, U.S. 6051379, is on *BRCA2* and includes parts of the *BRCA2* gene in oligonucleotide sequences, method claims, and kits. According to Dr. Shobita Parthasarathy, Myriad purchased this patent along with testing services from OncorMed in 1998 for an "undisclosed sum."[43] Patent rights were included in $525,000 paid to OncorMed, reported in its Securities and Exchange Commission (SEC) quarterly report from June 30, 1998.[44] (For more information on patents, see Appendix 4.)

Having sold off its BRCA assets, OncorMed entered into a reorganization agreement in which the company Gene Logic, Inc., bought OncorMed for a sum "not to exceed approximately $38 million."[45] OncorMed registered its termination with the SEC on September 30, 1998.[46]
Myriad became the sole-provider for both *BRCA1* and *BRCA2* full-sequence tests in the United States, as shown in Appendix 1. "To perform *BRCA* 1/2 mutation analysis, Myriad Genetics and its licensees only use direct sequencing of the whole genomic DNA (DS [double-stranded]) of both genes (BRACAnalysis®)."[47] In 2003 the *Journal of Molecular Diagnostics* noted that of the twelve tests that laboratory directors across the United States were called on to stop performing by patent enforcers, Myriad's *BRCA* testing tied for first with nine labs reporting enforcement efforts.[48]

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[42] Ibid.
[43] Parthasarathy S. *Building Genetic Medicine: Breast Cancer, Technology, and the Comparative Politics of Health Care.* Op. cit. at 117.
[44] Oncormed, Inc. *SEC EDGAR Filing Information: Form 10-Q - Quarterly Report 1998-30-06*. Page 11. See http://www.sec.gov/Archives/edgar/data/922821/0000950133-98-003049.txt [accessed June 2007]. The document which contains the following statement: "On May 18, 1998, the Company [OncorMed] and Myriad Genetics, Inc. ("Myriad") settled all outstanding lawsuits… [T]he Company granted to Myriad exclusive rights to all current and pending Company patents in the field of *BRCA1* and *BRCA2*… [T]he Company recorded a $525,000 gain related to the sale of the breast cancer testing service, which includes certain customer lists, databases and other intangible assets."
[45] Oncormed, Inc. *SEC EDGAR Filing Information: Form 8-K - Current Report 1998-07-07*. Page 4. See http://www.sec.gov/Archives/edgar/data/922821/0000950133-98-002539.txt [accessed June 2007].
[46] Oncormed, Inc. *SEC EDGAR Filing Information: Form 15-12B - Securities registration termination 1998-30-09*. See http://www.sec.gov/Archives/edgar/data/922821/0000936392-98-001309.txt [accessed June 2007].
[47] Sevilla C et al. Impact of gene patents on the cost-effective delivery of health care: the case of *BRCA1* genetic testing. Op. cit. at 289.
[48] Cho M et al. Op. cit.

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Lynch Syndrome (HNPCC)

Multiple gene patents cover the major genes involved in Lynch Syndrome (HNPCC). The first patent, U.S. 5922855, covering the *MLH1* gene, was filed by Oregon Health Sciences University and Dana Farber in 1999. The second patent application, U.S. 5591826, was filed by Johns Hopkins in 1997. It covers the *MSH2* protein. Johns Hopkins also later patented a diagnostic method to find mutations in the *MSH2* gene (U.S. 5693470). There are multiple providers, both non-profit and for-profit, for full sequence tests on both genes (see Appendix 1). Neither patent was noted by laboratory directors as having been enforced.[49] Finally, some providers add a third gene to their test – *MSH6* – but the patent situation for *MSH6* is unclear.

FAP

One patent, U.S. 5352775, covers the *APC* gene and was filed by Johns Hopkins in 1994. Again, multiple non-profit entities and one for-profit provider offer full sequence testing for *FAP* as described in Appendix 1. Finally, Dr. Cho and her colleagues note Johns Hopkins enforced its patent on at least two of the laboratories surveyed in 2001.[50]

Genetic Tests

Breast Cancer

For patients suspected to have one of the *BRCA* mutations–based on strong family history and an early age of onset among cancer-developing family members–two types of genetic testing are available. First, if the patient comes from an ethnic group already known to have specified mutations, or a mutation known from another member of that family, several non-profit university laboratories and one commercial laboratory can perform a targeted genetic test. These tests range in cost from $325 to $2,975.[51] If the patient is not a member of a known risk-group, or if her physician believes full DNA sequencing analysis is necessary, Myriad Genetic Laboratories is the United States' sole provider of full DNA sequencing for the *BRCA* genes. [52]

AHRQ reports that Myriad's tests have "analytic sensitivity and specificity both >99%"[53] and Myriad's price for "full sequence analysis," which also includes rearrangement testing, is $3,120.[54] Myriad performs redundant testing of each amplicon in both the forward and reverse direction to reduce PCR

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[49] Ibid.
[50] Ibid.
[51] AHRQ. Genetic risk assessment and *BRCA* mutation testing for breast and ovarian cancer susceptibility. Evidence synthesis 37. Op. cit.
[52] The patent story outside the United States is more complicated, and described in a separate case study by E. Richard Gold and Julia Carbone. (Gold ER, Carbone J. *Myriad Genetics: In the Eye of the Policy Storm.* 2008. International Expert Group on Biotechnology, Innovation and Intellectual Property, Centre for Intellectual Property Policy, McGill University. See http://www.theinnovationpartnership.org/data/ieg/documents/cases/TIP_Myriad_Report.pdf [accessed January 15, 2008].) For example, patents have been obtained but the patents are being ignored by provincial health systems in Canada. In Australia and the UK, Myriad's licensee permitted use by health systems, but announced a change of plans in August 2008. Only a single mutation has been patented in Myriad's lone European-wide patent, although some patents remain under review of an opposition proceeding. In effect, the United States is the only jurisdiction where Myriad's strong patent position has conferred sole-provide status. (See also Parthasarathy S. *Building Genetic Medicine: Breast Cancer, Technology, and the Comparative Politics of Health Care*. Op. cit.)
[53] AHRQ. Genetic risk assessment and *BRCA* mutation testing for breast and ovarian cancer susceptibility. Evidence synthesis 37. Op. cit.
[54] Karen (refused last name). Receptionist, Myriad Genetics, via phone May 4, 2007.
Confirmed by "List of Services" (price list) effective April 15, 2008, Myriad Genetics.

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failure from DNA sequence variants in PCR primers. Myriad resequences any amplicon in which a mutation is detected twice and offers free sequencing of family members to characterize variants of uncertain clinical significance. Finally, when new information is found about a mutation (i.e., an uncertain variant reclassified as a mere polymorphism or as deleterious mutation), Myriad sends an amended report to the ordering physician of every patient in whom this variant has been found.[55] Myriad performs the same variant characterization services for Lynch Syndrome (HNPCC) and FAP testing.

One report in the *European Journal of Human Genetics* questions the cost-effectiveness of using full-sequence analysis testing as a screening method for at-risk women (defined as women with two first-degree relatives with breast cancer) noting that their "results on genetic testing for breast cancer show that [direct DNA sequencing] is not the most cost-effective method available" and that "The monopolist approach of the firm which owns the patents on the [*BRCA1* and *BRCA2*] genes may, therefore, limit the use of the most cost-effective strategies."[56]

Lynch Syndrome (HNPCC)

Several laboratories offer full-sequence analysis for Lynch Syndrome, including both non-profit centers and two commercial labs. With the exception of the price listed for Quest Diagnostics, prices are list prices for insurance companies. Prices were collected in 2008.

- Baylor: $1,150 per gene or $3,200 for the *MLH1*, *MSH2* and *MSH6* genes[57]
- Boston University: $2,995 for all three genes (*MLH1*, *MSH2* and *MSH6*)[58]
- City of Hope: $1,771.20 for *MLH1*, $1,474.56 for *MSH2*, $1,400.40 for *MSH6*[59]
- Harvard: $2,700 for all three genes (*MLH1*, *MSH2* and *MSH6*)[60]
- Huntington Laboratory: $1,200 for two genes (*MLH1* and *MSH2)* plus $600 for *MSH6* ($1,800 for all three genes)[61]
- Mayo Clinic: $2,000 for two genes (*MLH1* and *MSH2*) and $ 1,100 for *MSH6* ($3,100 for all three genes) [62]
- University of Pennsylvania: $1,360 for *MLH1*, $740 for *MSH2* and $740 for *MSH6* ($2,840 for all three genes)[63]
- Quest Diagnostics: $2,940.00 for full sequencing of both *MLH1* and *MSH2* and $1820.00 for *MSH6* ($4,760 for all three genes)[64]

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[55] William Rusconi, Myriad Genetics. *Patenting and Licensing of the Breast Cancer Susceptibility Genes - BRCA1 and BRCA2.* Op. cit.
[56] Sevilla C et al. Testing for *BRCA1* mutations: a cost-effectiveness analysis. *European Journal of Human Genetics* 2002. 10:599-606.
[57] Baylor College of Medicine Medical Genetics Laboratories. *Prices and CPT Codes.* See http://www.bcm.edu/geneticlabs/cptcodes.html [accessed June 6, 2008].
[58]Alison Nicoletti. Boston University Center for Human Genetics, via phone June 11, 2008. (617)-638-7083
[59] Email from Dr. Juan-Sebastian Saldivar, City of Hope Clinical Molecular Diagnostic Laboratory, to Christopher Heaney, July 8, 2008. Prices effective August 1, 2008.
[60] Harvard Medical School. *MLH1, MSH2, and MSH6 Sequencing and Deletion/Duplication Analysis for Hereditary Non-Polyposis Colorectal Cancer (HNPCC) and HNPCC-like Syndromes.* See http://www.hpcgg.org/LMM/comment/HNPCC_info.jsp [accessed June 20, 2008].
[61] Faye A Eggerding. Huntington Medical Research Institutes, via phone June 11, 2008.
[62] Marie (refused last name). Mayo Medical Laboratories via phone June 18, 2008.
[63] Susan Walther, University of Pennsylvania Medical Center, via phone June 23, 2008.
[64] Email from Sam Garetano, Quest Diagnostics, to Christopher Heaney, July 18, 2008.

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Among for-profit testing laboratories, Myriad charges $2,950 for its COLARIS® test which includes full-sequencing of the *MLH1*, *MSH2* and *MSH6* genes as well as testing for major rearrangements[65] Rearrangement testing complicates the picture further, as each laboratory has its own price:

- Baylor: Rearrangement testing for either *MLH1* and *MSH2* is $625, rearrangement testing for *MSH6* is not available[66]
- Boston University: Rearrangement testing is included in the cost of $2,995 for sequencing *MLH1*, *MSH2*, and *MSH6*[67]
- City of Hope: Rearrangement testing and dosage analysis for 7 exons in *MSH2* is $547.56, rearrangement testing and dosage analysis for all exons in *MSH 6* is $658.80[68]
- Harvard: Rearrangement testing for *MLH1* or *MSH2* is $600, rearrangement testing for both is $800[69]
- Huntington Laboratory: Rearrangement and gene dosage analysis for both *MLH1* and *MSH2* is $600[70]
- Mayo: Rearrangement testing is included in the above prices[71]
- Quest Diagnostics: Rearrangement testing for both MLH1 and MSH2 is $540.00; Rearrangement testing for MSH6 is not available[72]

A representative of the University of Pennsylvania Medical Center's lab stated that while rearrangement testing for all of the colon cancer genes discussed here, rearrangement testing is not available as a listed service but can be done on a research basis.[73] Finally, the reported sensitivity of these tests ranges from 50-70%.[74]

FAP

Four non-profit organizations offer direct DNA sequencing for FAP, as does Myriad Genetics:

- Baylor: $1,675 for full sequence analysis; rearrangement testing $625.[75]
- Harvard: $1,500 for full-sequence analysis; rearrangement testing $600.[76]
- Huntington Laboratory: $1,200 for full-sequence analysis; gene dosage and rearrangement testing $600[77]

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[65] Karen (refused last name), Receptionist, Myriad Genetics, via phone May 4, 2007; confirmed by "List of Services" (price list) effective April 15, 2008, Myriad Genetics.
[66] Patricia Ward. Medical Genetics Laboratories, Baylor College of Medicine, via phone June 23, 2008.
[67] Alison Nicoletti. Boston University Center for Human Genetics, via phone June 11, 2008.
[68] Email from Dr. Juan-Sebastian Saldivar, City of Hope Clinical Molecular Diagnostic Laboratory, to Christopher Heaney, July 8, 2008. Prices effective August 1, 2008.
[69] Harvard Medical School. *MLH1, MSH2, and MSH6 Sequencing and Deletion/Duplication Analysis for Hereditary Non-Polyposis Colorectal Cancer (HNPCC) and HNPCC-like Syndromes.* Op. cit.
[70] Faye A Eggerding. Huntington Medical Research Institutes, via phone June 11, 2008.
[71] Marie (refused last name). Mayo Medical Laboratories via phone June 18, 2008.
[72] Email from Sam Garetano, Quest Diagnostics, to Christopher Heaney, July 18, 2008.
[73] Susan Walther, University of Pennsylvania Medical Center, via phone June 23, 2008.
[74] Kaz A, Brentnall TA. Op. cit.
[75] Baylor College of Medicine Medical Genetics Laboratories. *Prices and CPT Codes.* See http://www.bcm.edu/geneticlabs/cptcodes.html [accessed June 18, 2008].
[76] Harvard Medical School. *APC Gene Sequencing and Deletion/Duplication Analysis for Familial Adenomatous Polyposis (FAP) and FAP-like Syndromes.* See http://www.hpcgg.org/LMM/comment/*APC*_info.jsp [accessed July 14, 2008].

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- University of Pennsylvania: $1,360 for full-sequence analysis[78]
- Boston University: full-sequencing analysis $1,675; rearrangement testing $495[79]
- Mayo Clinic: Full sequencing $1,300; includes rearrangement testing[80]

Among commercial laboratories, Myriad charges $1,795 for its COLARIS AP® test, providing a full-sequence analysis for the *APC* gene as well as major rearrangements and two mutations of MYH.[81] The reported sensitivity for these FAP tests ranges from 80-90%.[82]

MYH

In addition to Myriad, four other providers test the MYH gene for cancer-related mutations.

- Baylor: $1,150 full-sequence analysis, 2 mutation analysis $300, no rearrangement testing available[83]
- Huntington Laboratory: $600 full-sequence analysis, no rearrangement testing available; 2 mutation analysis available for $250[84]
- University of Pennsylvania: Full sequencing $500; targeted mutation for 2 mutations $600[85]
- Mayo: Testing for 2 mutations $306.60[86]

Summary of Costs

Table 1 notes the approximate sizes of each of the genes discussed above. Table 2 gives the number of "amplicons" used by Myriad Genetics for its BRCA and hereditary colon cancer tests.[87] We use these figures because Myriad, as sole provider of the BRCA test, is the only laboratory for which we can compare prices for BRCA and colon cancer testing. For other laboratories, we assume that they are using comparable methodology, although they do not use the same PCR primers, likely use a somewhat different number of amplicons, and may not use exactly the same protocols for testing. The comparisons are therefore only rough benchmarks, and the overall price is the main metric. Myriad Genetics is on the high side of pricing for colon cancer testing in overall price (and the only provider for breast cancer testing), but Myriad also includes rearrangement testing and (for FAP and Attenuated FAP) tests common mutations in a gene, MYH, that some other laboratories price as separate tests but do not necessarily

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[77] Faye A Eggerding. Huntington Medical Research Institutes, via phone June 11, 2008.
[78] Susan Walthers. University of Pennsylvia, via phone June 24, 2008.
[79] Alison Nicoletti. Boston University Center for Human Genetics, via phone June 11, 2008.
[80] Marie (refused last name). Mayo Medical Laboratories via phone June 18, 2008.
[81] Karen (refused to give last name), Receptionist, Myriad Genetics, via phone call May 4, 2007; confirmed by "List of Services" (price list) effective April 15, 2008, Myriad Genetics.
[82] Kaz A, Brentnall TA. Op. cit.
[83] Patricia Ward. Medical Genetics Laboratories, Baylor College of Medicine, via phone June 23, 2008.
[84] Faye A Eggerding. Huntington Medical Research Institutes, via phone June 11, 2008.
Email from Faye Eggerding to Christopher Heaney, July 20, 2008.
[85] Susan Walthers, University of Pennsylvia, via phone July 15, 2008.
[86] Mayo Medical Laboratories. *84304 Overview: MYH Gene Analysis for Multiple Adenoma, Y165C and G382D*. See http://www.mayomedicallaboratories.com/test-catalog/print.php?unit_code=84304 [accessed July 15, 2008].
[87] The full-sequencing tests are done by choosing PCR primers that flank exons or subsections of exons, amplifying the DNA that spans the relevant exonic sequences, and sequencing those stretches of DNA. The "amplicons" include the protein-coding regions of the genes, plus a small amount of flanking sequence for each unit. Amplicons may span an entire (short) exon, or may break a protein-coding region into segments that can be amplified by PCR (so long exons are represented by several amplicons). At Myriad Genetics, each amplicon is amplified from two sets of PCR primers, so that each amplicon is sequenced twice. We did not obtain details of laboratory procedure at other testing services, because we did not need to make intra-laboratory comparisons.

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analyze with the standard FAP full-sequence test. Table 2 uses these gene sizes to determine the approximate total number of base pairs sequenced per genetic test for both breast and ovarian cancer, as well as colorectal cancers tests, then estimates charge per kilobase (one thousand base-pairs) for each test as well.

Table 1: Approximate Sizes of Genes[88]

Gene	Amplicons*	Size (Base-pairs)
BRCA1[89]	35	81,155
BRCA2[90]	47	84,193
APC [91]	42	108,353
MLH1[92]	19	57,359
MSH2[93]	16	80,098
MSH6[94]	25	23,807

* Amplicons used by Myriad for its "full sequence" analysis

Table 2: Comparison of Cost-per-Base-Pair among Genetic Tests

Disease	Genetic Test	Total Amplicons	Test Provider	Provider's Charge*	*Charge per Amplicon*
Breast / Ovarian Cancer	*BRCA1* and *BRCA2* full sequencing	35 + 47 = **82**	Myriad*	$3,120	***$38.05***
FAP	*APC* full sequencing	**42**	Baylor	$ 1,675	***$ 39.88***
			Boston	$1,675	***$39.88***
			Harvard	$1,500	***$35.71***
			Huntington	$1,200	***$28.57***
			Univ. of PA	$ 1,360	***$ 32.38***
			Mayo Clinic	$1,300	***$30.95***
			Myriad[Ψ] (44 amplicons)	$1,795	***$40.80***

[88] The number of amplicons is based on Myriad Genetics' method of "full sequence" analysis, based on publicly available data from Myriad's technical specification sheets for its tests, and confirmed by phone conversations with Myriad staff. This allows rough comparison of BRCA versus colon cancer gene tests at Myriad. The amplicons and testing protocols are different from other laboratories, but for those laboratories the overall cost is the relevant metric. The objective of the table for hereditary colon cancer susceptibility testing is to compare *inter*-laboratory prices for hereditary colon cancer susceptibility, so overall price is the relevant measure, and per-amplicon cost is merely a rough indicator marginal price per unit among laboratories. Gene sizes are taken from the National Center for Biotechnology Information database, and cross-checked with the Genome Browser, University of California Santa Cruz. Full-length gene sizes do not reflect the number of bases sequenced in the actual gene tests, because actual genetic tests sequence neither the entire genomic sequence nor the cDNA sequence (with introns edited out) of the genes, but rather "amplicon" fragments of the gene that can be amplified by PCR.

[89] NCBI Sequence Viewer. *Homo Sapiens Breast Cancer 1*. See http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?val=NG_005905.1&from=10511&to=91665&dopt=gb [accessed June 2007].

[90] NCBI Sequence Viewer. *Homo Sapiens Chromosome 13, Reference Assembly*. See http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?val=NC_000013.9&from=31787617&to=31871809&dopt=gb [accessed June 2007].

[91] NCBI Sequence Viewer. *Homo Sapiens Chromosome 5, Reference Assembly*. See http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?val=NC_000005.8&from=112101483&to=112209835&dopt=gb [accessed June 2007].

[92] NCBI Sequence Viewer. *Homo Sapiens Chromosome 3, Reference Assembly*. See http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?val=NC_000003.10&from=37009983&to=37067341&dopt=gb [accessed June 2007].

[93] NCBI Sequence Viewer. *Homo Sapiens Chromosome 3, Reference Assembly*. See http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?val=NC_000002.10&from=47483767&to=47563864&dopt=gb [accessed June 2007].

[94] NCBI Sequence Viewer. *Homo Sapiens Chromosome 2, Reference Assembly*. See http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?val=NC_000002.10&from=47863790&to=47887596&dopt=gb [accessed June 2007].

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Lynch Syndrome (HNPCC)	*MLH1*, *MSH2*, and *MSH6* full sequencing	19 + 16 + 25 = **60**	Baylor	$ 3,200	***$ 53.33***
			Boston Univ.	$2,995	***$49.92***
			City of Hope	$ 4646.16	***$ 77.44***
			Harvard	$2,700	***$45.00***
			Huntington	$1,800	***$30.00***
			Mayo Clinic[ϑ]	$ 3,100	***$ 51.67***
			Myriad[ϑ]	$2,950	***$49.17***
			U. Pennsylvania	$ 2,840	***$ 47.33***
			Quest Diagnostics	$4,760	***$79.33***

Notes: Cost per base-pair represents authors' calculations based on costs reported by the testing facilities and the size of each gene as reported by NCBI.
* Includes major rearrangement testing (5 common insertions/deletions and analysis for any other rearrangements in high-risk individuals)
[Ψ] Includes Southern Blot analysis for rearrangements and 2 MYH mutations (an additional 2 PCR amplicons) with full sequence of MYH if one of the 2 common mutations is detected.
[ϑ] Includes rearrangement analysis

As Table 2 shows, Myriad's charge per amplicon varies over the three tests it offers, ranging from $38.05 for its *BRCA1&2* test, to $40.80 for its FAP test, to $49.17 for its Lynch Syndrome (HNPCC) test. Myriad's charge per amplicon is actually lower for its *BRCA1&2* tests, which are done under exclusive provider status associated with Myriad's dominant patent position, compared to the colon cancer tests, despite there being multiple providers and lack of dominant patent position for the various hereditary colon cancer susceptibility tests. This shows no clear *price* premium for the BRCA full-sequence tests.

Myriad's normalized price for colon cancer testing is at the high end for FAP (but that includes two mutations in another gene, MYH, as well as rearrangement testing), and is in the middle of the range for Lynch Syndrome (HNPCC) testing for the three DNA repair genes in that pathway, MLH1, MSH2, and MSH6. All laboratories offering colon cancer testing are presumably paying comparable licensing fees to the patent-holders, although the licensing arrangements are not public information so we do not know details.

The result is somewhat different if normalization is done on cost "per base pair," rather than per PCR amplicon. Calculated per base pair of the full length native gene, BRCA testing price is 15 to 48 percent higher than for colon cancer testing ($18.87 per kilobase of gene sequence for BRCA1 and 2, compared to $16.57 for APC, and $12.71 for the MLH1, MSH2 and MSH6 test). The "length of gene" basis for normalization is not as relevant for normalization, however, because the test is done by sequencing gene fragments as PCR amplicons, and the unit cost is more related to number of amplicons than total gene size. The price comparisons may be surprising to some, as normalized prices show little if any price premium. **This, in turn, suggests the main market impact of the BRCA patents is not on price but rather on volume, by directing BRCA full-sequence testing in the United States to Myriad, the sole provider.**

Current Genetic Testing Guidelines

Breast Cancer

Though in 2005 the United States Preventative Services Task Force (USPSTF) recommended against routine genetic testing for the *BRCA1 / BRCA2* mutations, the USPSTF does recommend testing for

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women with "certain specific family history patterns" suggesting *BRCA1* or *BRCA2* risk.[95] Specifically, the USPSTF recommends that women with family histories suggestive of *BRCA1/BRCA2* mutations be referred for appropriate genetic counseling, stating "the benefits of referring women with an increased-risk family history to suitably trained health care providers outweigh the harms."[96]

In terms of clinical algorithms, the National Comprehensive Cancer Network (NCCN) publishes and maintains guidelines on its website http://www.nccn.org/. The NCCN clinical algorithms for breast and ovarian cancer are attached as Appendix 2, and were updated in early 2007.

Colorectal Cancer

The Evaluation of Genomic Applications in Practice and Prevention Working Group (EGAPP) published recommendations for genetic testing among newly diagnosed individuals with colorectal cancer.[97] They examined four genetic testing strategies and found no decisive winner. All four protocols involve genetic testing, but the methods, cost, and selection criteria for which patients get which kind of test differ. The most expensive but also most sensitive method is full-sequence testing, the pathway most comparable to Myriad's BRCA testing. The EGAPP recommendations are based on a January 2009 supplementary evidence review.[98] That review, in turn, builds on a massive 2007 evidence review by the Tufts-New England Medical Center Evidence-Based Practice Center.[99] The NCCN has published its clinical guidelines on testing for FAP and HNPCC, reproduced in Appendix 3. And a joint committee of the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer and the American College of Radiology (ACS/MSTFCRC/ACR) produced a consensus statement on screening and surveillance for colorectal cancer and polyps in May 2008, with Table 3 recommending genetic testing in individuals from high-risk families included in Appendix 3.[100]

New EGAPP analysis, in addition to sifting through evidence and assessing four genetic testing strategies, also shifts the framework for genetic testing away from family history, and toward genetic testing of those newly diagnosed with colorectal cancer. This is a significant change, indicating the many individuals who do not know about cancer in relatives or when they are the first individuals in their families identified with the mutations that can now be identified as conferring risk. That is, clinical practice appears to be shifting from genetic testing only when family risk is evident to using genetic testing to identify new individuals and families at risk. This is mainly because many individuals carrying mutations will be missed if family history is a threshold criterion for testing. It is worth noting that if genetic testing becomes less expensive and more widely available, and as more mutations associated with cancer risk are identified, DNA analysis could move higher up the clinical decision tree, not just in Lynch Syndrome but in other cancers as well.

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[95] United States Preventative Services Task Force. Genetic risk assessment and *BRCA* mutation testing for breast and ovarian cancer susceptibility. *Ann Intern Med* 2005. 143: 355-61.
[96] Ibid.
[97] Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. Op. cit.
[98] Palomaki GE et al. Op. cit.
[99] Bonis PA, Trikalinos TA, Chung M, Chew P, Ip S, DeVine D, Lau J. Hereditary nonpolyposis colorectal cancer: diagnostic strategies and their implications. Evidence report/technology assessment No. 150 (Prepared by Tufts-New England Medical Center Evidence-based Practice Center under Contract No. 290-02-0022). AHRQ Publication No. 07-E008. Rockville, MD: Agency for Healthcare Research and Quality. May 2007. Available at http://www.ahrq.gov/downloads/pub/evidence/pdf/hnpcc/hnpcc.pdf (accessed 4 June 2008).
[100] Levin B et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer and the American College of Radiology. *CA: A Cancer Journal for Clinicians* 2008. 58:130-160.

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NCCN guidelines specify the following inclusion criteria to consider genetic testing for any of the various inherited colorectal cancers:

- Early-onset colorectal cancer (age < 50), or
- Clustering of same or related cancer in close relative, or
- Multiple colorectal carcinomas or >10 adenomas in the same individual, or
- Known family history of hereditary cancer syndrome with our without mutation.[101]

From here, the NCCN guidelines split between FAP and HNPCC

FAP

In patients with the FAP phenotype (more than 100 colorectal polyps), genetic testing is recommended to establish the diagnosis. From there, the NCCN recommends:

> Genetic testing in individuals with familial polyposis should be considered before or at the age of screening. The age for beginning screening should be based on the patient's symptoms, family phenotype and other individual considerations.[102]

In the event that a familial mutation is unknown, the NCCN further recommends:

> In some families, APC mutations cannot be found with available testing technology, recognizing that the sensitivity to identify APC mutations is currently only about 80%. In other families, affected individuals have died or are not immediately available. Under these circumstances, APC testing should be considered for at-risk family member. If the mutation responsible for FAP within a family is not found, it is important to remember the limitations of interpreting a gene test in a presymptomatic individual. Evaluating presymptomatic individuals at risk in these families presents a difficult problem, since the mutation responsible for FAP within the family is not known. Certainly, a positive test in a presymptomatic person is informative even when the familial mutation has not been previously identified. But interpreting a test in which "no mutation is found" in a presymptomatic person is not the same as a "negative test."[103]

The ACS/MSTFCRC/ACR guideline identifies those with a genetic diagnosis of FAP or suspected FAP without genetic testing as "high risk" and recommends considering genetic testing (if not already done). It recommends monitoring starting age 10 to 12, with an annual flexible sigmoidoscopy exam. If genetic testing is positive, "colectomy should be considered."[104]

HNPCC

The NCCN only recommends HNPCC genetic testing only for certain patients:

- Individuals in families meeting either the Amsterdam I or II criteria, and

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[101] National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology – Colorectal Cancer Screening.* V.1.2007. See http://www.nccn.org/professionals/physician_gls/PDF/colorectal_screening.pdf [accessed May 2007].
[102] Ibid.
[103] Ibid.
[104] Levin B et al. Op. cit. At Table 3, p. 154.

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- Affected individuals meeting Revised Bethesda guidelines.[105]

The 2008 ACS/MSTFCRC/ACR guideline recommends offering genetic testing for all first-degree relatives of a confirmed case. Monitoring for those with confirmed or at increased risk of HNPCC should begin at age 20 to 25, or a decade before the youngest case in a family (whichever is younger), with colonoscopy every 1-2 years.[106]

The 2007 Tufts Evidence-Based Practice Center report noted a major gap in knowledge about how best to do the genetic testing and differing views on test algorithms in the literature. The report also noted that sequencing was the "method of choice" for mutation detection, but with many different technologies for doing such sequencing and a need to supplement it with rearrangements/insertion/deletion testing. No clear, consistent "winner" was found among technologies.

Regarding test utility, the report concluded:

> Pre-test genetic counseling had good efficacy in improving knowledge about HNPCC and resulted in a high likelihood of proceeding with genetic testing, satisfaction in the decision to undergo genetic testing, and decreasing depression and distress levels among family members of HNPCC probands with cancer and among asymptomatic individuals from HNPCC families.
>
> Identification of HNPCC mutations was associated with an increase in the likelihood that family members of probands with CRC [colorectal cancer] would undergo cancer-screening procedures. HNPCC family members who underwent cancer-screening procedures had a lower risk of developing HNPCC-related cancers and lower mortality rates than those who did not take actions.[107]

These conclusions will now be updated by the January 2009 EGAPP recommendations, which do not choose among the four genetic testing strategies, but do recommend genetic testing in newly diagnosed colorectal cancer.[108] The trend appears to be moving towards genetic testing earlier in the diagnostic process, in order to guide treatment and to identify others in families who might be at risk but do not know it.

If a tumor sample is available, the NCCN recommends testing for both immunohistochemistry and microsatellite stability testing first rather than beginning with DNA sequencing. The results of either of these preliminary tests can direct a clinician to the appropriate gene to sequence for "germline analysis," thus avoiding the shotgun-like approach of a full-sequence analysis on all three genes.[109]

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[105] National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology – Colorectal Cancer Screening.* Op. cit.
[106] Ibid.
[107] Bonis PA, Trikalinos TA, Chung M, Chew P, Ip S, DeVine D, Lau J. Op. cit. at p. vi.
[108] Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. Op. cit.
[109] Ibid.

Non-genetic screening options

Breast Cancer

The USPSTF currently recommends mammography for all women once every 1-2 years after the age of 40.[110] AHRQ reports that the Cancer Genetic Studies Consortium recommended annual mammography for women beginning between the ages of 25 and 35, with annual clinical breast exams also beginning between ages 25 and 35 and monthly self breast exams beginning between ages 18 and 21.[111] AHRQ also notes that the USPSTF does not currently recommend screening women at any age for ovarian cancer.[112] The American Cancer Society issued guidelines in April 2007 calling for MRI screening, in addition to mammography, for women carrying BRCA mutations and first-degree relatives of those with BRCA mutations.[113]

Colorectal Cancer

Beginning at age 50, the American Cancer Society recommends:

- Fecal occult blood testing (FOBT) annually, or
- Flexible sigmoidoscopy every five years, or
- Annual FOBT plus flexible sigmoidoscopy every five years, or
- A double-contrast barium enema every five years, or
- A colonoscopy every 10 years.[114]

However, according to the USPSTF:

> The USPSTF found good evidence that periodic fecal occult blood testing (FOBT) reduces mortality from colorectal cancer and fair evidence that sigmoidoscopy alone or in combination with FOBT reduces mortality. The USPSTF did not find direct evidence that screening colonoscopy is effective in reducing colorectal cancer mortality; efficacy of colonoscopy is supported by its integral role in trials of FOBT, extrapolation from sigmoidoscopy studies, limited case-control evidence, and the ability of colonoscopy to inspect the proximal colon. Double-contrast barium enema offers an alternative means of whole-bowel examination, but it is less sensitive than colonoscopy, and there is no direct evidence that it is effective in reducing mortality rates.[115]

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[110] AHRQ. *U.S. Preventive Services Task Force: Screening for Breast Cancer Summary of Recommendations*. Published February 2002. See http://www.ahrq.gov/clinic/uspstf/usps*BRCA*.htm [accessed May 2007].
[111] AHRQ. Genetic risk assessment and *BRCA* mutation testing for breast and ovarian cancer susceptibility. Evidence synthesis 37. Op. cit.
[112] Ibid.
[113] Saslow D et al. American Cancer Society Guidelines for breast screening with MRI as an adjunct to mammography. *CA: A Cancer Journal for Clinicians* 2007. 57(2):75-89.
[114] American Cancer Society. *Cancer Facts and Figures, 2007*. Op. cit.
[115] AHRQ. *U.S. Preventive Services Task Force: Screening for Colorectal Cancer Summary of Recommendations*. July 2002. See http://www.ahrq.gov/clinic/uspstf/uspscolo.htm [accessed May 2007].

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Interpreting Test Results / Options for Prophylactic Treatment

Breast and Ovarian Cancer

The clinical utility of *BRCA1* and *BRCA2* screening may be summarized as follows:

- For those testing positive, there are cost-effective approaches to chemoprevention (prophylactic tamoxifen for breast cancer and oral contraceptives for ovarian cancer), screening, and surgery (prophylactic mastectomy, prophylactic salpingo-oophrectomy or tubal ligation), all of which result in gains in both life expectancy and quality-adjusted life years (QALYs) relative to watchful waiting.[116]
- For high-risk patients who test negative, there may be reduced anxiety about the future risks of breast or ovarian cancer. These gains must be balanced against the losses experienced by those who test positive, including elevated anxiety, depression and guilt.[117]
- Finally, though $50,000 per QALY is the conventional benchmark for cost-effectiveness analysis,[118] some authors do argue for a standard of $100,000 - $150,000 per QALY.[119,120]

According to AHRQ, interpretation of the test results for *BRCA1* and *BRCA2* genetic testing can be difficult. For example, if a patient with known positive family history for a specific mutation tests negative, she can be "reassured about her inherited risk." On the other hand, a negative test is "less useful if her relatives have cancer but no detected deleterious mutations." Finally, AHRQ noted that up to 13% of tests produce results of "uncertain clinical significance."[121] More recent (2008) data are that variants of uncertain clinical significance are found in fewer than 6% of cases (with the highest rate of "variants of unknown significance" among African Americans, at 11%).[122]

When women do test positive, the USPSTF first noted in 2002 that women at high risk for breast cancer should consider taking chemoprevention (e.g., tamoxifen)[123] but then noted in 2005 that there is "insufficient evidence to determine the benefits of chemoprevention or intensive screening in improving health outcomes."[124] The ACS recommends that women positive for *BRCA1/BRCA2* mutations consider

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[116] Goldman N et al. Screening and primary and secondary interventions for patients at high risk for ovarian cancer. *Women's Oncology Review* 2003 (December). 3(4):269-274.
[117] Higashi M et al. Managed care in the genomics era: assessing the cost effectiveness of genetic tests. *American Journal of Managed Care* 2003. 9(7):493-500
[118] Carroll A et al. Comprehensive cost-utility analysis of newborn screening strategies. *Pediatrics* 2006 (May). 117(5):S287-S295.
[119] Cutler D et al. *Intensive Medical Care and Cardiovascular Disease Disability Reductions*. National Bureau of Economics Research Working Paper No. 12184. November 16, 2006.
[120] Murphy K et al. The economic value of medical research. In: *Measuring the Gains from Medical Research: An Economic Approach.* Chicago: University of Chicago Press, 2003.
[121] AHRQ. Genetic risk assessment and *BRCA* mutation testing for breast and ovarian cancer susceptibility. Evidence synthesis 37. Op. cit.
[122] Saam J, Burbidge LA, Bowles K, Roa B, Pruss D, Schaller J, Reid J, Frye C, Wenstrup RJ. Decline in rate of *BRCA1/2* variants of uncertain significance: 2002-2008. Abstract for presentation at National Society of Genetic Counselors annual meeting. Fall 2008. The crucial data are: "Overall, the VUS [Variants of Unknown Significance] rate decreased from 12.8% in 2002 to 5.9% in 2006, a 54% reduction, including decreases of 50.1% (Western European), 58.3% (African), and 48.6% (Asian). From 2006 to 2008 the identification of variants of uncertain significance continued to decline to 5.1% of tests performed. This continued decrease was observed in all ethnic groups, with the largest decline in the African American population where the VUS rate declined from 38.6% in 2002 to 10.9% in 2008."
[123] AHRQ. *U.S. Preventive Services Task Force: Chemoprevention: Breast Cancer*. July 2002. See http://www.ahrq.gov/clinic/uspstf/uspsbrpv.htm [accessed May 2007].
[124] United States Preventative Services Task Force. Genetic risk assessment and *BRCA* mutation testing for breast and ovarian cancer susceptibility. *Ann Intern Med* 2005. 143: 355-61.

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tamoxifen therapy.[125] See Table 3 for a break-down of the results found in three different cost-effectiveness studies on chemoprevention in at-risk women.

Table 3: Cost Effectiveness Studies Comparing Chemoprevention to Surveillance Alone

Study	Context	Results (Cost per QALY)
Grann (2000)[126]	Positive *BRCA* test	30 year old women = $990 40 year old women = $1,800 50 year old women = $3,600
Hershman (2002)[127]	Two-or-more first-degree relatives diagnosed with breast cancer	30 year-old women = $45,000 50 year-old women = $89,000 60 year-old women = $140,000
Eckermann (2003)[128]	Hypothetical cohort of healthy women at high risk of breast cancer	5 yrs of tamoxifen / 5 yrs of benefit = $32,000 5 yrs of tamoxifen / 10 yrs of benefit = $16,000 5 yrs of tamoxifen / no reduced incidence at 10 yrs = $170,000

Notes: QALY = "Quality Adjusted Life Year"

Surgical options. Both the ACS and the USPSTF note that prophylactic surgery (e.g., bilateral mastectomy and bilateral oophorectomy) significantly decreases the chances of developing cancer in *BRCA* mutation-positive women and should be strongly considered.[129,130] Table 4 shows the results from two cost-effectiveness studies on prophylactic surgery.[131]

Table 4: Cost Effectiveness Studies Comparing Prophylactic Surgery to Surveillance Alone

Study	Context	Results (Cost per QALY)
Grann (1998)[132]	Positive *BRCA* test in 30-year-old women at high-risk	Prophylactic Oophorectomy and Mastectomy = Dominated Prophylactic Oophorectomy = $5,600
Tengs (2000)[133]	High-risk 30-year-old women assuming varying risks of mutation	*BRCA* testing then oophorectomy if positive by mutation probability: *High Risk* *BRCA1* (p=0.5) and *BRCA2* (p=0.0) = $3,900 *BRCA1* (p=0.25) and *BRCA2* (p=25) = $4,700 *BRCA1* (p=0.0) and *BRCA2* (p=0.5) = $5,400

[125] American Cancer Society. *Breast Cancer Facts and Figures, 2005-2006*. Op. cit.
[126] Grann V et al. Prevention with tamoxifen or other hormones versus prophylactic surgery in *BRCA1*/2-positive women: a decision analysis. *Cancer J Sci Am* 2000. 6:13-20.
[127] Hershman D et al. Outcomes of tamoxifen chemoprevention for breast cancer in very high-risk women: a cost-effectiveness analysis. *J Clin Oncol* 2002. 20(1):9-16.
[128] Eckermann S et al. The benefits and costs of tamoxifen for breast cancer prevention. *Aust N Z J Public Health* 2003. 27(1): 34-40.
[129] United States Preventative Services Task Force. Genetic risk assessment and *BRCA* mutation testing for breast and ovarian cancer susceptibility. Op. cit.
[130] American Cancer Society. *Breast Cancer Facts and Figures, 2005-2006.* Op. cit.
[131] For a complete cost-effectiveness analysis of all preventative strategies surrounding positive *BRCA* findings, please see: Anderson K et al. Cost-effectiveness of preventive strategies for women with a *BRCA1* or a *BRCA2* mutation. *Annals of Internal Medicine* 2006 (March 21). 144(6): 397-407.
[132] Grann VR et al. Decision analysis of prophylactic mastectomy and oophorectomy in *BRCA1*-positive or *BRCA2*-positive patients. *J Clin Oncol* 1998. 16:979-85.
[133] Tengs T et al. The cost effectiveness of testing for the *BRCA1* and *BRCA2* breast-ovarian cancer susceptibility genes. *Disease Management and Clinical Outcomes* 2000. 1:15-24.

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Moderate Risk
BRCA1 (p=0.1) and *BRCA2* (p=0.1) = $17,000

Slight Risk
BRCA1 (p=0.05) and *BRCA2* (p=0.05) = $42,000

Average Risk
BRCA1 (p=0.0006) and *BRCA2* (p=0.0002) = $1,600,000

Notes: "QALY" = Quality Adjusted Life Year. "Dominated" means that prophylactic mastectomy and oophorectomy in the Grann article actually saved money compared to surveillance alone.

Colon Cancer

According to the American Gastrological Association (AGA), patients with Lynch Syndrome should receive subtotal colectomy (removal of almost the entire colon, sparing the rectum) with ileorectal anastomosis. This surgical method can preserve some bowel-function by fusing the small intestine to the rectum and creating a "pouch" out of small intestine. Thus, patients should not require a permanent colostomy. The AGA recommends the same surgical approach for patients Lynch Syndrome, both those who already have colon cancer and those who are positive for a mutation but have yet to develop any detectable colon tumors or known symptoms. After surgery, patients should still be followed with regular rectal screening for additional rectal polyps.[134]

We were unable to find cost-effectiveness studies of prophylactic colectomy, but two decision analyses have been published on clinical effectiveness. The first paper was published in *Gastroenterology* in 1996 and demonstrated that compared to a colonoscopic surveillance program, prophylactic colectomy for a 40 year-old male with positive HNPCC mutation yields a life expectancy benefit of 8 months to 1.5 years. For a thirty-year old male with positive HNPCC mutation, this benefit increased to between 1 and 2 years.[135] However, the authors did not analyze quality of life and did not analyze the subtotal colectomy option.

The second clinical effectiveness paper was published in the *Annals of Internal Medicine* in 1998 and addressed both life-expectancy and quality of life. This paper demonstrated that immediate prophylactic surgery (e.g., either total proctocolectomy or subtotal colectomy) extended overall life-expectancy compared to surveillance alone (defined as "colonoscopy every 3 years if no surgical intervention had been performed and flexible sigmoidoscopy of the remaining rectal segment every 3 years after subtotal colectomy" plus segmental resection if cancer was found)[136] in a hypothetical cohort of twenty-five year-olds with HNPCC mutations. However, in terms of quality-adjusted life-years (QALYs) both methods of prophylactic surgery actually fared worse than surveillance:

> Surveillance leads to the greatest quality-adjusted life expectancy compared with all colectomy strategies. Surveillance led to a gain of 14.0 quality-adjusted life-years (QALYs) compared with no surveillance, 3.1 QALYs compared with immediate proctocolectomy, and 0.3 QALYs compared with immediate subtotal colectomy. Incorporation of quality adjustments resulted in greater quality-adjusted life expectancies for all subtotal colectomy strategies compared with

[134] American Gastroenterological Association. AGA technical review on hereditary colorectal cancer and genetic testing. *Gastroenterology* 2001 (July). 121(1):198-213.
[135] Vasen H et al. Cancer risk in families with hereditary nonpolyposis colorectal cancer diagnosed by mutation analysis. *Gastroenterology*1996 (April). 110(4): 1020-7.
[136] Syngal S et al. Benefits of colonoscopic surveillance and prophylactic colectomy in patients with hereditary nonpolyposis colorectal cancer mutations. *Annals of Internal Medicine* 1998 (November 15). 192(10):787-796.

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> proctocolectomy strategies, with benefit ranging from 0.3 QALYs if colectomy was performed when colorectal cancer was diagnosed to 2.8 QALYs if colectomy was performed at 25 years of age.[137]

For FAP, the American Gastrological Association (AGA) recommends that patients who are positive for FAP receive immediate total proctocolectomy (removal of the colon and rectum) to minimize the potential for malignancy except in certain "life-style" choices. For example, the AGA would accept delaying surgery in teenagers with minimally-concerning polyps (small and non-villous) to accommodate "work and school schedules."[138] Appropriate follow-up should include endoscopic monitoring any remaining colon (e.g., if a subtotal colectomy is performed) every 6 months as well as additional endoscopic monitoring of the upper gastrointestinal tract with biopsies (including the stomach and small intestine) every 6 months to 4 years.[139] In contrast, the guidelines state "use of chemoprevention as primary therapy for colorectal polyposis is not proven and is not recommended."[140]

Lessons Learned

This comparison was selected because it provides a natural case-study to compare for-profit testing and exclusive licensing practices for BRCA versus a mix of for-profit and non-profit patenting with nonexclusive licensing practices for colon cancer susceptibility genes. Using the conceptual framework developed for a parallel literature synthesis, we now consider what lessons might be learned from this case.

For both breast cancer and colon cancer, the genetic tests discussed above have two major implications. First, genetic tests can distinguish genetic (and thus inheritable) susceptibility from non-genetic cancers in the original patient. Thus, if the original patient tests positive other family members can then test themselves and know with relative certainty whether or not they have inherited the same mutation as their cancer-suffering relative. Second, BRCA and colon cancer genetic tests guide treatment decisions for the original patient as well alerting relatives that they may also be at risk (and can be tested for the same mutation at much lower cost and with greater specificity).

Basic Research

As of August 2008, Myriad has submitted over 18,000 entries (>80% of total entries) for over 2,600 unique mutations to the Breast Cancer Information Core http://research.nhgri.nih.gov/bic database. As of February 2005, over 4,300 follow-up publications on *BRCA1* and *BRCA2* resulted from more than 100 collaborations between Myriad and independent investigators.[141] Patent rights are much narrower in Europe, although details of the recent European patent re-issue have not yet been made public. Europe also differs because several countries have explicit research exemptions and diagnostic use exemptions from patent infringement liability that would cover clinical research testing in several European countries.

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[137] Ibid.
[138] Church J et al. Practice parameters for the treatment of patients with dominantly inherited colorectal cancer (familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer). *Diseases of the Colon and Rectum* 2003 (August). 46(8):1001-1012.
[139] Ibid.
[140] Ibid.
[141] William Rusconi, Myriad Genetics. *Patenting and Licensing of the Breast Cancer Susceptibility Genes - BRCA1 and BRCA2.* Op. cit.
Personal communication to Robert Cook-Deegan 29 May 2008.
A search of the Breast Cancer Information Core for mutations catalogued as deposited by Myriad Genetics revealed 8,826 mutations in BRCA1 and 9,891 mutations in BRCA2. (*Breast Cancer Information Core.* National Human Genome Research Institute. See http://research.nhgri.nih.gov/bic/ [accessed September 25, 2008].)

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Research, and in some countries also genetic testing, have therefore proceeded in Europe with less concern about patent infringement.

Some argue that even in the United States, Myriad's definition of infringing research is too broad. Specifically, in 1998 Myriad asserted that even though Genetic Diagnostics Laboratory (GDL) limited testing to patients in NCI research protocols, GDL was performing a patent-infringing third-party service in which it charged other laboratories and rendered clinical services. As Parthasarathy summarizes Myriad's reasoning, "So long as GDL disclosed results to the patient, [it provided] a commercial service and violat[ed] the patent."[142] The 1999 NCI/Myriad Memorandum of Understanding established ground rules permitting use of BRCA testing within a research institution, and discounted testing for research clinical testing contracted to Myriad.[143]

According to a 2005 Lewin Group Report published for AdvaMed:

> An unintended effect of patents is that they may slow further innovation by blocking R&D efforts along avenues patented by other companies. This was the case with genetic testing for the *BRCA1* and *BRCA2* genes [mutations], the presence of which are [is] associated with an elevated risk for developing breast or ovarian cancer. The US Patent and Trademark Office (USPTO) issued patent rights for *BRCA1* and *BRCA2* to a privately owned diagnostics firm. These rights included the gene sequences and any resulting applications developed from them, including laboratory tests and targeted drug therapies. The patents allow the firm to control breast cancer susceptibility testing and research.[144]

Though the Lewin Group concluded that Myriad's exclusive patents on the *BRCA* genes stifled further basic research based on this theory, we found few data either to support or to refute this conclusion. The Gold and Carbone case study did identify a decision not to report some BRCA mutation analysis by Canadian researchers.[145] The researchers were cautioned not to leave a public trace that they had done BRCA testing without a license, and this meant they did not contribute their research results that would have been of general interest.

Myriad maintains it has never enforced its patents against researchers, and does not enforce its patents against laboratories providing BRCA testing services in a form it does not do itself (such as pre-implantation genetic diagnosis and real-time PCR of DNA amplified from paraffin-embedded tissues). Myriad notes it permitted rearrangement testing, and even referred patients to Mary-Claire King and others until it began to offer such testing itself. Myriad says it has never even threatened to take action against basic researchers or those doing pre-implantation diagnostic testing.

A chilling effect, however, does not take hold only when each and every instance of potential infringement is the subject of patent enforcement. Moreover, Myriad never publicly stated its *de facto* research use exemption policy. Myriad either passed on an opportunity to demonstrate its intentions

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[142] Parthasarathy S. Architectures of genetic medicine: comparing genetic testing for breast cancer in the USA and UK. Op. cit. at 24.
[143] Memorandum of Understanding between Myriad Genetics and the U.S. National Cancer Institute (signed on 10 December 1999 by Gregory Critchfield, President of Myriad Genetic Laboratories, Inc., and 14 December by Richard Klausner, NCI Director).
[144] The Lewin Group. Op. cit. at 62-3.
[145] Gold ER, Carbone J. Op. cit. at 40. Specifically, at a November 2006 workshop in Edmonton, researchers from a Canadian university reported that they had refrained from reporting BRCA testing results to the public database because they had been advised by their university's general counsel that it could alert Myriad to infringing activity.

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publicly in written form, or avoided comment to keep legal options open. And keeping options open equates to a chilling effect in zones of uncertainty. Myriad therefore cannot fully elude responsibility for any chilling effect on research, because the company could fully anticipate that others would refrain from research for fear of being sued for infringement. Requesting "simple notification" to Myriad is not a full remedy, as it requires notifying the very party that might, at its option, take legal action once alerted. That is, for Myriad to make credible claims of being fully supportive of unfettered research, it would need to express that policy in a form that could be the basis for others' actions, and not passively rely on others to ask them for permission. Other laboratories would need to know what activities Myriad would and would not pursue as infringement, specified in a way that courts could interpret. Ambiguity may itself stifle basic or clinical research as researchers either avoid the work altogether or are wary of publicly reporting results.

We have not found similar evidence of a chilling effect in the basic science arena for either FAP or HNPCC. This may be due to three related features: (1) lack of enforcement actions, (2) patent holders are academic institutions, and (3) licenses are nonexclusive.

Development

The Lewin report concluded that Myriad's patents "also were found to affect development and provision of potentially more cost-effective testing strategies."[146] More specifically, a French study found that:

> …there exist alternative strategies for performing BRCA1 diagnosis: prescreening techniques such as FAMA [fluorescent assisted mismatch analysis] and, potentially, DHPLC [denaturing high performance liquid chromatography] or DGGE [denaturing gradient gel electrophoresis], based on the current estimates of their sensitivity, would minimize the cost of diagnosis while also ensuring a comparable level of effectiveness to that of applying DS [direct sequencing of the whole genomic DNA] to the entire gene.[147]

When compared to the most cost-effective mutation detection strategy analyzed (in common use in French testing labs), the average cost per mutation detected using the Myriad approach was 5 times as high.[148] That is, leaving aside the issue of pricing, the costs entailed—including consumable supplies, equipment and personnel—to carry out the Myriad approach was much higher than alternative approaches that had been developed and were in use in Europe. This criticism suggests that Myriad has eschewed cheaper testing methods because as a monopoly provider it has little incentive to support them. It is difficult to judge this assertion. The comparison to colon cancer genetic testing suggests, however, that (1) Myriad is well within range in its pricing of colon cancer tests compared to other providers, and (2) its cost per unit for BRCA testing is in the same range as colon cancer testing and, if anything, a bit less expensive. Moreover, the analysis of genetic testing strategies has low-cost and high-cost options analogous to BRCA testing, and it is not clear which strategy is optimal.[149]

The technologies for testing are not qualitatively different among these different genes, so if Myriad has failed to shift to cheaper testing technology, then so have other providers for comparable colon cancer tests. Both BRCA and colon cancer susceptibility genes are large and complex, and there are hundreds of

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[146] The Lewin Group. Op. cit. at 62-3.
[147] Sevilla C et al. Impact of gene patents on the cost-effective delivery of health care: the case of *BRCA1* genetic testing. Op. cit. at 296.
[148] Ibid.
[149] Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. Op. cit.
Palomaki GE et al. op. cit.

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documented mutations in them that cannot be predicted in advance except in subpopulations (such as Ashkenazim).

The pricing data do **not** address whether early resort to full-sequence testing in high-risk families is optimal for a health system. Myriad believes it is, and in the United States with Myriad as sole provider, that becomes policy *de facto*. In other countries, Myriad can still supply full-sequence testing, but health systems may adopt testing algorithms that resort to full-sequence testing later in the process, and use other tests as screens. **Myriad's patent position in effect allowed it to establish the standard of care in the United States, but in other countries it did not.**

Those in human genetics and cancer also tell of a patent race between Johns Hopkins University and Oregon Health Sciences University-Dana Farber Cancer Institute for the HNPCC gene *MLH1*. Both Oregon Health Sciences and Johns Hopkins hold patents claiming *MLH1*. The Oregon patent is shared with Dana Farber. It was filed December 9, 1994, and was issued as U.S. 6191268 on February 20, 2001 (Oregon Health Sciences and Johns Hopkins later filed two method patents as well). The Johns Hopkins patent, on the other hand, is shared with the for-profit firm Human Genome Sciences. The Hopkins/Human Genome Sciences patent application was filed on June 6, 1995 and issued as U.S. 6610477 on August 26, 2003. Though the details of this race do not appear in the literature, clearly patenting and ultimately test development played a role in the search for *MLH1* as Johns Hopkins ultimately partnered with a for-profit corporation to complete its work.

Dr. Merz notes the additional concern that Myriad's patents could allow it to collect license royalties as new mutations are sequentially patented, in effect extending the patent term. Dr. Merz writes:

> Think of it this way: new mutations are continually being found in the *BRCA1* and *BRCA2* genes. Assuming that patent applications are continually being filed on them, then the patent holders may have an effective monopoly on testing for the period extending from the grant of the first patent for the first discovered mutation until the end of the patent term on the last discovered mutation. If the patentee were to license the patents, royalties could only be collected for the term of each individual patent (the courts would invalidate attempts to extend the patent term by contract or to tie licenses of the patented and off-patent tests). Thus, by monopolizing the testing service, the patentee undermines the time limitation on the grant of monopoly.[150]

Another critique of patenting centers on reduced incentives of a monopoly provider to introduce newer, cheaper, or otherwise better alternative tests. For example, there is an alternative diagnostic technique to *BRCA* called multiplex ligation-dependent probe amplification, or MLPA, a molecular way to detect genetic variations, including *BRCA1* and *BRCA2* mutations, under development at University of Washington.[151] Using MLPA, a 2006 study published in the *Journal of the American Medical Association* found that Myriad's testing strategy missed up to 12% of large genomic deletions or duplications.[152] The authors noted that the missed mutations were not due to a technical error in Myriad's testing, but a flaw in the testing strategy. That is, the rearrangements were missed not because of sequencing errors in the amplicons, but because sequencing fragments of BRCA as amplicons did not detect large-scale chromosome rearrangements and deletions. The paper noted "many mutations are inherently not detectable by short-range polymerase chain reaction (PCR) followed by genomic sequencing."[153] Drs.

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[150] Merz J. Disease gene patents: overcoming unethical constraints on clinical laboratory medicine. *Clinical Chemistry* 1999. 45(3):324-330.
[151] Doheny K. Genetic tests for cancer not perfect. *HealthDay* 2006 (March 21). See http://www.healthfinder.gov/news/newsstory.asp?docID=531683 [accessed May 2007].
[152] Walsh T et al. Spectrum of mutations in BRCA1, BRCA2, CHEK2, and TP53 in families at high risk of breast cancer. Op. cit.
[153] Ibid., 1380.

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Grodman and Chung state in their testimony before the House Subcommittee on Intellectual Property that this testing deficit was only corrected after "considerable pressure from the scientific community,[154] but Myriad notes it began testing for the 5 most common rearrangements (accounting for about a third of all rearrangements) in 2002 and would have detected one-third of those the JAMA paper reported as "missing"—and simultaneously began developing a test for large rearrangements (BART®) that it launched in August 2006 for the higher risk patients (similar to the JAMA article's criteria) as part of BRACAnalysis®. Myriad's claim that it was already working on BART® before the JAMA paper appeared is corroborated by poster presentations on large-scale rearrangement testing in 2004, a chronology that does not fit with the characterization of Myriad responding "under considerable pressure" only after the JAMA paper. The JAMA publication no doubt accelerated Myriad's efforts to introduce the new BART® test, however, as indicated by Myriad's Clinical Update of September 2006. [155]

In her written statement to the House Judiciary Committee, Dr. Chung noted that she believed, "In a competitive marketplace, this delay would have never occurred."[156] Myriad does not agree, and asks: "Could a cost-effective, high throughput, scientifically valid assay be designed and used clinically? It must be noted that the MLPA kits are not FDA approved and are labeled for research use only."[157]

Rearrangements are also common in colon cancer susceptibility genes, and are included as part of such testing at Myriad and many other laboratories. However, we found no literature about a major controversy among test providers for colon cancer comparable to the very public brouhaha over breast/ovarian genetic testing.

Dr. Chung's written statement for the October 30 House Judiciary hearing states that Myriad's decision not to test paraffin-embedded tissue has hampered availability of that type of testing in instances where it might be clinically useful.[158] According to Myriad's technical specifications sheet available online, Myriad isolates only the white blood cells from each sample to extract and purify DNA for testing.[159] Without market pressure to innovate, Dr. Chung notes that Myriad has little incentive to develop techniques to analyze samples other than blood samples, thereby "leaving families at risk with no remedy."[160] Myriad responds that it refers such cases to known testing services with relevant technical capacity when it learns of instances where such testing is needed. And it notes that in most cases where paraffin-embedded testing is relevant, the living person (or persons) at risk could be directly tested using full-sequence analysis, followed by mutation-specific testing for others in the family. Myriad states it has

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[154] Grodman, Marc. Statement before House Judiciary Subcommittee on Courts, the Internet and Intellectual Property in Connection with its hearing on "Stifling or Stimulating – The Role of Gene Patents in Research and Genetic Testing." October 30, 2007.

[155] Myriad Genetics, 2006. Clinical Update, Vol. 4, No. 5. Testing for Hereditary Breast and Ovarian Cancer Syndrome. An abstract submitted Feb. 2004 and a poster presented fall 2004 report on Myriad's BART test for large-scale rearrangements. (Judkins T, Hendrickson BC, Gonzales D et al. Op. cit. Hartmann C, John AL, Klaes R et al. Op. cit.) For presentations, see those listed in note 10.

[156] Grodman, Marc. Statement before House Judiciary Subcommittee on Courts, the Internet and Intellectual Property in Connection with its hearing on "Stifling or Stimulating – The Role of Gene Patents in Research and Genetic Testing." Op. cit.

[157] MRC Holland. "SALSA MLPA Kit P002-B1 BRCA1" specification sheet. April 8, 2008.

[158] See written statement provided by Wendy Chung, MD, Columbia University, to accompany the written statement and oral testimony of Marc Grodman, CEO of Bio-Reference Laboratories, Inc., before the Judiciary Committee, U.S. House of Representatives, in a hearing "Stifling or Stimulating - The Role of Gene Patents in Research and Genetic Testing," 30 October 2007, 2237 Rayburn House Office Building, Washington, DC, 2 p.m. (at page 4 of her statement).

[159] Myriad Genetic Laboratories. *BRACAnalysis® Technical Specifications.* August 29, 2005. See http://www.myriadtests.com/provider/doc/tech_specs_brac.pdf [accessed December 19, 2007].

[160] See written statement provided by Wendy Chung, MD, Columbia University, to accompany the written statement and oral testimony of Marc Grodman, CEO of Bio-Reference Laboratories, Inc., before the Judiciary Committee, U.S. House of Representatives, in a hearing "Stifling or Stimulating - The Role of Gene Patents in Research and Genetic Testing," 30 October 2007, 2237 Rayburn House Office Building, Washington, DC, 2 p.m. (at page 4 of her statement).

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never enforced its patents against a provider offering testing in a form Myriad does not offer itself, such as pre-implantation diagnosis, prenatal diagnosis, or real-time PCR of paraffin-embedded tissue samples.[161] The implication is that Myriad would not enforce its patents in such circumstances, although again, as in research, there is no public written statement of that policy. Myriad has licensed three laboratories to perform preimplantation diagnosis, for example.[162] While this may be a policy, we did not find a public statement to this effect on Myriad's website (indeed it took some digging to find this information). Thus, individuals likely would not know about this policy unless they contacted Myriad, thereby alerting them of their intention to test, and alerting Myriad of the option of taking legal action to prevent patent infringement.

Finally, the U.S. Food and Drug Administration has also approved an investigational device exemption study for a breast cancer risk test developed by InterGenetics called OncoVue®. Billed as "the next-generation genetic breast cancer risk test," OncoVue® reports it is "the nation's first genetic-based breast cancer risk test to undergo the FDA approval process."[163] Opaldia plans to release OncoVue® in the U.K. and Ireland under an exclusive agreement.[164]

These are not isolated counter-examples: AHRQ estimated that for all three areas of cancer included in this case study there are more genetic tests for cancer in the pipeline than are currently available. While we cannot be certain of what this picture would have looked like absent patents, it appears that gene patents notwithstanding, the genetic testing for inherited risk of cancer is moving in the direction of an even more bountiful range of clinical genetic tests.

	Breast	**Colorectal**	**Ovarian**
Currently Available	**15**	**15**	**7**
Under Development	**22**	**19**	**14**
Primary prevention	1	1	0
Detection	0	8	7
Prognosis	2	0	0
Diagnosis	12	8	4
Management	7	2	3

Compiled by author based on raw data presented in AHRQ, Genetic Tests for Cancer, January 9, 2006.

The foregoing also is a reminder that patent protection never guarantees permanent protection from competition. It remains to be seen whether these developments culminate in Myriad's having to reduce its price or relax its licensing well before its patent expires, and to offer new testing modalities. And the same competitive effects may enter colon cancer genetic testing, for which there is no single provider with a dominant patent position.

[161] William Rusconi, Myriad Genetics. *Patenting and Licensing of the Breast Cancer Susceptibility Genes - BRCA1 and BRCA2*. Op. cit.
[162] Harmon A. Op. cit. quoting William Hockett, MD, of Myriad Genetics and stating that preimplantation BRCA testing had been licensed to three fertility clinics.
[163] Page D. FDA approves study for breast cancer risk test by InterGenetics. *The Oklahoma City Journal Record*. September 20, 2006.
[164] First genetic-based breast cancer risk test available in the U.K. and Ireland. *Genetic Engineering & Biotechnology News* 2007 (March 1). See http://www.genengnews.com/news/bnitem.aspx?name=13573820 [accessed May 2007].

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BRCA and colon cancer genes also differ in measures of patent enforcement activity. Dr. Cho's 2003 survey of laboratory directors demonstrates nine instances of patent enforcement by Myriad Genetics on its *BRCA* patents; by comparison, Johns Hopkins enforced its *APC* patent for FAP genetic testing twice, and no laboratory directors reported enforcement of the HNPCC patents.[165]

In a paper reviewing litigation over U.S. gene patents, Christopher Holman found 31 total cases of litigation (covering an estimated 1 percent of gene patents). Two of those cases centered on BRCA patents, compared to none for patents associated with colon cancer genes.[166] One case entailed a suit and counter-suit between OncorMed and Myriad, which was settled out-of-court. The other BRCA case was between Myriad and University of Pennsylvania, which was also settled out-of-court.

Commercialization

Myriad's centralized testing service does provide some benefits to patients, including Myriad's ability to provide free testing to first-degree relatives to elucidate variants of uncertain clinical significance.

This case study demonstrates several major implications of patents on access:

First, the main effect of the patent appears to be on volume rather than price.

1. Any price effect attributable to patents is buried in noise and confounding variables.

2. Myriad's patent position has made it in effect a sole provider of clinical BRCA testing in the United States, and indeed BRCA testing in clinical research except when such testing is conducted at the same research institution as the research.

Based on per-amplicon charges, price data—comparing mutation testing for colon and breast cancer at Myriad and comparing BRCA testing to colon cancer predisposition testing—suggest a small price effect, if any, and suggest the main impact of patenting is to drive volume to Myriad for BRCA testing. The price data constitute an imperfect comparison for many reasons. Colon and BRCA cancer testing does not compare patented to unpatented sequences, but rather a group of patents aggregated by Myriad genetics compared to colon cancer gene tests nonexclusively licensed by several academic institutions that are presumably collecting royalties. Moreover, one major constraint on pricing is the reimbursement system, which codes genetic tests and limits price flexibility. The price comparison does, however, at least provide a benchmark and shows any price effects of patents in these two kinds of genetic testing are not of the magnitude associated with therapeutic pharmaceuticals and some other technologies, for which patents command dramatic price premiums for a patented versus generic product.

The downstream costs of a positive test can be far greater than the test itself, including counseling and potential surgical action.[167] Thus, for any patient contemplating the combined costs of the test and surgery in the event of a positive test, the cost of genetic testing would be a relatively small share of the total.

Second, the coverage and reimbursement practices of insurers and other payers are crucial. Anecdotal reports from interviews with laboratory employees note that many non-profit centers charge patients up front for genetic testing. These anecdotal reports note that insurance companies are slow to respond to

[165] Cho M et al. Op. cit.
[166] Holman CM. Op. cit. at 347-348.
[167] Phillips K et al. Genetic testing and pharmacogenomics: issues for determining the impact of healthcare delivery and costs. *American Journal of Managed Care* 2004 (July). 10(7):425-432.

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claims for genetic tests, and that such tardy reimbursements induced non-profit centers to either charge differential rates for cash-paying and third-party tests or to drop the third-party payer option altogether (so that payment is paid out-of-pocket up front, and patients seek reimbursement for themselves from their insurer or health plan). For its part, Myriad provides a wide variety of payment options as noted on its "Reimbursement Assistance Program" website, both insurance-based and cash-based.[168] Myriad reports that initial inconsistency of coverage and reimbursement is less of an issue now. A much larger number of agreements and more consistent coverage and reimbursement have reduced the number of self-pay patients to single-digit percentages of its clientele. Myriad has established contracts or payment agreements with over 300 carriers and has received reimbursement from over 2500 health plans.[169]

Finally, as the monopoly provider for *BRCA* testing Myriad will benefit from receiving the entire volume of *BRCA* tests through its laboratories no matter what it charges, though that volume will certainly vary with the price-point. The price comparison we made is compatible with a scenario in which Myriad, as a monopolist, maximizes its profit through price discrimination in which it charges the highest price to those women who most value the test. According to standard economic analysis of monopolist behavior, such discrimination in pricing for different customers would be expected, and paradoxically can enable the monopolist to lower prices for those with lower willingness or ability to pay (in Myriad's case, through its patient access programs). This flexibility is, however, entirely at the discretion of the company. Thus, the patent premium depends on both the price-elasticity of demand for *BRCA* testing and on how Myriad has chosen to set its price point for different purchasers, including consumers with lower ability to pay.

Other firms may enter the breast cancer susceptibility testing market. Myriad is not alone in building a dedicated testing facility around its gene patents. InterGenetics, Inc., is developing OncoVue®, the "next-generation" genetic breast cancer risk test that will be available through a network of breast care centers.[170] How this facility will affect the *BRCA* market is yet to be seen. OncoVue-BRE® tests genes that, when combined, confer a moderately increased risk. The target population is the general population rather than those with family history. Effectively, this test seeks to determine risk for those not in the BRCA risk category. So, the tests are more complementary than competitive. In September 2008, Perlegen announced that it will release a breast cancer diagnostic panel intended to guide treatment choices as well as provide risk stratification, in which case it would compete with Myriad's testing.[171] Many of the "personal genomics" firms offering genome-wide scans, such as 23andMe, Navigenics, SeqWright, Knome, and deCODEme also include some analysis of cancer risk, including breast and colon cancers. None of these genome-wide cancer risk-assessment tests, however, offers comprehensive analysis of BRCA, FAP, or HNPCC genes, and so genome-wide scans are not comparable to those genetic testing services for high-risk families. The exception is the full-sequence Knome service. If a cancer susceptibility mutation were identified in the Knome full genomic sequence, it would require re-testing for the identified mutation in a CLIA-certified laboratory to ensure reliability of the result, which the patient could obtain by referral, or which Knome might bundle with its initial price as a subcontracted service.[172]

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[168] Myriad Genetics. *Myriad Reimbursement Assistance Program*. See http://myriadtests.com/mrap.htm [accessed July 12, 2008].
[169] William Rusconi, Myriad Genetics, comments on review draft of case study to SACGHS, September 2008.
[170] InterGenetics builds DNA analysis and genotyping laboratory; laboratory essential to commercialization of nation's first genetic-based breast cancer risk predictive test applicable to all women. *Business Wire* 2005 (September 7). See http://findarticles.com/p/articles/mi_m0EIN/is_2005_Sept_7/ai_n15346276 [accessed May 2007].
[171] Winnick E. Perlegen eyes first-half '09 launch of breast cancer Dx panel. *GenomeWeb News*. See http://www.genomeweb.com/issues/news/149640-1.html [accessed September 30, 2008].
[172] The price on Knome's website was originally $350,000 for full-genome, full-sequence analysis. The website now asks prospective customers to call for individualized pricing, but Steven Pinker reported it to be $99,000 in his January 2009 article in the New York Times Magazine. (Pinker S. My genome, my self. *New York Times Magazine* 2009 (January 7). See http://www.nytimes.com/2009/01/11/magazine/11Genome-t.html?_r=1&scp=1&sq=pinker&st=cse [accessed January 21, 2009].)

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What's Going on in Australia?

As this case study was being prepared, a controversy over BRCA testing erupted in Australia. This was precipitated when Genetic Technologies Ltd. (GTG), Myriad's licensee in Australia and New Zealand, sent "cease and desist" letters to laboratories testing for BRCA in its licensing territory.[173] GTG had announced in 2003, when it secured the license, that it would allow unlicensed testing as "gift" to the people of Australia. It changed this policy and decided to enforce its patent rights, and the policy change became public in July 2008 when it was widely covered in the Australian public media.[174] On October 31, as the November 6 deadline it had set in the cease and desist letters loomed, GTG announced it would refrain from enforcing its patent rights pending discussions with "all the relevant stakeholders."[175] It is now the subject of an Australian Senate inquiry.[176] The decisions about enforcement of licensing for BRCA testing may have stemmed from financial pressures GTG, a need to generate revenues, and some disarray in the company's governance.[177] While not directly relevant to US policy, the developments in Australia did spill over to coverage in the United States; GTG actions in Australia also indicate that companies under financial stress may turn to patent assets as revenue sources when their company's survival is being threatened.

Communication/Marketing

Myriad's position as sole US provider of BRCA testing increases its incentives for communication and marketing up to the point of market saturation. The incentive to advertise the service and broaden the market is stronger for a monopoly provider than in a shared market because a monopolist will gain the full benefit of market expansion. In a competitive market, advertising may increase market *share* of a given provider, or it can expand the size of the market, but the expansion effect spills over to benefit competitors as well, and so the incentive to advertise is weaker. Once a market is saturated, a monopolist no longer gains from advertising to expand market (but may advertise for other reasons).

For the same reason, communication and marketing incentives are also strong to educate health professionals who order the tests, because any increase in orders results in higher volume of testing for

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The idea of subcontracting to CLIA-approved laboratories was discussed by Duke research assistant professor Misha Angrist and Knome CEO and founder Jorge Conde in November 2008.

[173] O'Connor M. Genetic technologies and breast cancer. *Courier-Mail* (Queensland), 2008 (27 October).
Shanahan L. Call to act on breast cancer test. *The Age* (Australia), 2008 (28 October).
Macey J. Company seeks to monopolise breast cancer test. *The World Today*, ABC News Radio, 2008 (23 October).
GenomeWeb. Genetic technologies to enforce BRCA test rights in Australia, New Zealand. July 21, 2008. See http://www.genomeweb.com/issues/news/148308-1.html [accessed 8 November 2008].

[174] The public media reported on GTG's enforcement action in July. (See, for example, Cresswell A. A price on your genes. *The Australian* 2008 (30 July). The story was also covered in most of the major dailies in Melbourne, Sydney, Canberra, and elsewhere in Australia.) Controversy flared up again in late October as GTG's announced deadline neared. See, for example, Jennifer Macey's coverage on ABC radio Australia at http://www.abc.net.au/worldtoday/content/2008/s2399139.htm (accessed November 8, 2008).

[175] Genetic Technologies Ltd. *Further Clarifications on BRCA Testing*. Op. cit.

[176] *Community Affairs Committee. Examination of Budget Estimates 2008-2009. Additional Information Received.* Incomplete Consolidated Volume 5. Health and Ageing Portfolio. December 3, 2008. At 6-18.
Transcript of Senate Standing Committee on Community Affairs Estimates. Australian Senate. October 22, 2008. At CA14-CA17.

[177] According to NASDAQ pricing data, GTG's stock price drifted downward during the year from a high of $5.00 per share on 29 November 2007 to $0.66 on 4 November 2008. In addition to the July 2008 change of policy about BRCA testing, the company also announced its intention to remove five of seven directors at its 19 November 2008 Board meeting, leaving only two directors, which would cause it to fall out of compliance with its corporate bylaws. The proposed new Board member declined to serve, leading to a proposal for an interim board appointment. (Genetic Technologies Ltd. *Intention to Appoint a Director*. November 3, 2008. See http://www.gtg.com.au/index.asp?menuid=060.070.130&artid=10741&function=NewsArticle [accessed 8 November 2008].)

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Myriad. Again, this increase is not shared with other providers; Myriad gets the full benefit of any market expansion. The downside of this incentive is that Myriad's financial incentive is to expand testing, not just appropriate testing. Myriad makes money off of any test, regardless of whether the person is actually at risk. The incentive is not just for appropriate testing; the risk is overutilization.

There are some checks on overutilization. Medical societies establish guidelines for their membership which, in turn, form the basis for payer coverage criteria. Insurers and other payers work not to reimburse for tests when patients do not meet clinical appropriateness criteria. One further check is the bottleneck of determining eligibility for testing. The limited pre-test counseling resource is used to fulfill specific payer criteria for high-risk patients eligible for coverage and reimbursement. Low-risk candidates can clog the pre-test filters of counseling and coverage determination, occupying them with cases that would not ultimately lead to testing, or if tested, would not be reimbursed by third parties.

In the context of breast cancer testing, Myriad has a strong incentive to "get the word out" about genetic testing for inherited risk of breast cancer. That incentive is stronger for BRCA testing, for which Myriad is sole US provider, than for colon cancer testing, where there are alternative providers. This may be one reason Myriad's past direct-to-consumer advertising—both the 2002 pilot in Denver and Atlanta and the 2007-8 campaign in the northeastern states–focused on breast-ovarian cancer testing rather than Myriad's colon cancer testing services. The social benefit from this incentive is more public knowledge of test availability. The potential harms are overutilization of BRCA genetic testing, and public fear of genetic risk of breast cancer amplified by advertising.

Caulfield and Gold note in their 2000 article from *Clinical Genetics* that:

> Myriad Genetics, a commercial testing company that holds patent rights underlying the [*BRCA1* and *BRCA2*] test, does not exclude women without any family history of breast or ovarian cancer from taking its test. This contrasts sharply with the Working Group with Stanford's Program in Genomics, Ethics and Society, which recommends that 'for most people, testing for *BRCA1* and *BRCA2* mutations is not appropriate.' While all genetic testing policies are undoubtedly motivated by a degree of self-interest, it is hard to deny the strong, and possibly adverse, impact of the profit motive in this context.[178]

Myriad states it does not want to expand inappropriate testing, but rather to saturate testing among high-risk families. Myriad's "television, radio, and print advertising campaign" in September 2002, included ER, *Oprah* and *Better Homes and Gardens*.[179] A follow-up survey on 300 women who had seen the ads noted that "85 percent would contact their physician regarding *BRCA* testing and 62 percent would go so far as to switch health care professionals in order to find one who would help them gain access to the test."[180] This interest can include spurious demand for the tests, and consumes the time of health professionals in filtering out such spurious demand and explaining the complicated genetics of cancer susceptibility to many not actually at elevated risk.

A CDC survey done during the 2003 direct-to-consumer pilots in Denver and Atlanta compared experience in those DTC campaign cities to Raleigh-Durham and Seattle, which did not experience regionally targeted advertising. CDC found an increase in test requests and questions about testing

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[178] Caulfield T, Gold ER. Genetic testing, ethical concerns, and the role of patent law. *Clinical Genetics* 2000 (May). 57(5):370-375, at 371.
[179] Parthasarathy S. *Building Genetic Medicine: Breast Cancer, Technology, and the Comparative Politics of Health Care.* Op. cit. at 120-129.
[180] Ibid., 129.

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among women, an increase in test-ordering among physicians and providers, and no difference in levels of reported anxiety.[181] CDC concluded that:

> Advertisements might have motivated women interested in learning more about BRCA1/2 testing to talk to their physicians and request testing. Findings from the consumer survey suggest that women in the pilot cities were more aware of BRCA1/2 testing than those in the comparison cities. No evidence suggested an increased interest in the test among women most suited for BRCA1/2 testing (i.e., those having a first-degree relative).[182]

Judy Mouchawar and colleagues did the most systematic studies of consumer, provider, and health plan responses to the Denver DTC advertising campaign. They surveyed health professionals and consumers and assessed impact on health systems in the advertising market (Denver Kaiser Permanente) and in a comparison city (Detroit) and health system (Henry Ford) not exposed to the advertisements. The number of women at high risk who got referred went up by 2.38 times, from 100 to 238, suggesting that over 100 women at high risk got tested who otherwise might not have known about the test. The number of women contacting the systems about testing rose 3.46 times (from 144 to 499) with advertising, including a higher fraction of women not at high risk and therefore not warranting testing (the fraction at high risk dropped from 69 to 48 percent).[183] Thus the number of women at risk who might benefit from testing went up, but there was also a dilution of such high-risk women among an even greater increase of contacts about testing. There was no increase in actual testing among women with low risk *in the population studied*. This caveat is important, because Kaiser Permanente has practice guidelines for BRCA testing, and it cooperated with Myriad to prepare for a surge in demand during the DTC advertising period. Physician surveys showed a modest effect on physicians, with 3 percent reporting significant patient anxiety, 19 percent reporting significant increase in time spent explaining and another 23 percent a little extra time, and 7 percent reporting significant and 8 percent a little strain on the doctor-patient relationship.[184] Eighty-two percent reported the DTC campaign had no effect on their relationship with patients.

Consumers reporting "any anxiety" varied from 28 percent (low family risk) to 55 percent (high risk). Anxiety was most pronounced among Latina/Hispanic women (65 percent), and much more common in low-income (62 percent among those making less than $30,000) than high-income women (30 percent among those making over $80,000).[185] Among those exposed to the ad, 63 percent reported no anxiety at all, but 65 percent reported feeling somewhat or very concerned. It is hard to fully interpret the answers to various questions. Physicians were asked to assess the effect overall on their practice, and 6 percent were positive or very positive, 14 percent were negative or very negative, and 79 percent reported no effect.[186]

The overall impact of the DTC ad campaign on the Kaiser Permanente health system in Denver was a more than two-fold increase in number of women in the high risk category getting tested, a more than

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[181] Centers for Disease Control and Prevention. Genetic testing for breast and ovarian cancer susceptibility: evaluating direct-to-consumer marketing--Atlanta, Denver, Raleigh-Durham, and Seattle, 2003. *Morbidity and Mortality Weekly Report* 2004 (July 16, 2004). 53(27): 603-606.
[182] Ibid., 606.
[183] Mouchawar J, Hensley-Alford S, Laurion S, Ellis J, Kulchak-Rahm A, Finucane ML, Meenan R, Axell L, Pollack R, Ritzwoller D. Impact of direct-to-consumer advertising for hereditary breast cancer testing on genetic services at a managed care organization: a naturally occurring experiment. *Genetics in Medicine* 2006 (March). 7: 191-197, at Table 3.
[184] Mouchawar J, Laurion S, Ritzwoller DP, Ellis J, Kulchak-Rahm A, Hensley-Alford S. Assessing controversial direct-to-consumer advertising for hereditary breast cancer testing: reactions from women and their physicians in a managed care organization. *American Journal of Managed Care* 2005. 11(10):601-608, at Table 4.
[185] Ibid., Table 2.
[186] Ibid., Table 4.

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three-fold surge in contacts about testing, a moderate increase in anxiety among consumers and a mixed reaction among physicians, but with the vast majority reporting no effect. A comparison between the experience of physicians and women in Kaiser Permanente to other parts of the health system in Denver at the same time would have been immensely useful, as the Kaiser Permanente system is much more organized for genetic services than general medical care. The Mouchawar studies are illuminating as a "best case" of a health system prepared for a surge and with practice guidelines in place; it is very unlikely to represent the effects of the ad campaign elsewhere in Denver (or anywhere else) with a less organized and prepared genetic services program and with physicians less educated about how to triage testing.

Myriad Genetics' marketing campaign both to providers and patients is concisely summarized in Dr. Parthasarathy's book (pages 120-129).[187] Myriad aggressively marketed its *BRCA* genetic tests to providers through a "Professional Education Program," through continuing education accredited by the American Medical Association and at various professional meetings. Highlighting the importance of reaching providers with such educational campaigns, one study showed that high-risk women—those eligible for BRCA testing based on family history—were three times as likely to get tested following a physician recommendation as those who did not get such a recommendation.[188]

On September 10, 2007 Myriad announced it would begin a new "public awareness campaign" throughout the northeastern United States to spread the word about *BRCA* testing.[189] This campaign concluded in March 2008. Myriad's quarterly report through March 2008 reported a jump in molecular diagnostic revenue from $38 million to $59 million, and attributed the 55 percent jump to its northeast advertising campaign.[190] Given these financial results, it is not surprising Myriad is said to be contemplating similar DTC advertising initiatives in Texas and Florida or elsewhere.[191] This clearly illustrates the link between status as a single provider and incentives for direct-to-consumer advertising, with single provider status in this case associated with exclusive patent rights for BRCA testing.

We have not found similar marketing campaigns launched by Myriad or other groups on behalf of other tests. However, a future research project could compare *BRCA* testing uptake in the Denver and Atlanta markets in 2002 or in the northeast 2007-8, where Myriad's advertising was concentrated, to utilization in other regions. This could be done through a large health-insurer's database or using billing records of Medicare/Medicaid for relevant CPT codes matched to clinical indications. The link between DTC advertising and patenting is mediated by the monopoly incentive for advertising noted above. Dynamics in genetic testing markets have changed considerably since 2002. The growing number of physicians ordering genetic tests, the greater availability of third party coverage, the accumulating experience in using genetic tests to manage hereditary cancer risk, and the greater consumer awareness about genetic testing all suggest the 2003 surveys may not predict current or future behavior. Moreover, the increasing conspicuousness and commercial interest in personal genomics may also change perceptions and behaviors. DTC advertising is not directly related to access *per se* although it is highly relevant to projections of demand and perceptions of access.

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[187] Parthasarathy S. *Building Genetic Medicine: Breast Cancer, Technology, and the Comparative Politics of Health Care.* Op. cit. at 120-129.
[188] Schwartz M et al. Utilization of *BRCA1*/*BRCA2* mutation testing in newly diagnosed breast cancer patients. *Cancer Epidemiology Biomarkers and Prevention* 2005 (April). 14:1003-1007.
[189] Myriad Genetics. *Myriad Genetics Launches Awareness Advertising Campaign to Educate Women About Hereditary Risks of Breast and Ovarian Cancers.* See http://www.myriad.com/news/release/1049527 [accessed December 19, 2007].
[190] Myriad Genetics. Myriad Genetics reports results for third quarter of fiscal 2008. May 6, 2008.
[191] Suggestions of future DTC advertising plans were reported to us, but were neither confirmed nor denied by Myriad staff.

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Adoption by Third-Party Payers

Myriad has a strong incentive to develop the infrastructure to handle billing and payment for BRCA testing because it captures all the revenues from market expansion. This benefits the company, but it also benefits patients to the degree it relieves them of the hassle and paperwork of dealing with health plans and insurers, and it benefits providers by relieving them of those duties as well as legal liability for test inaccuracies. The countervailing force here is that Myriad as a sole-source provider requires providers to send samples, track paperwork, and bill for services providers might otherwise handle at their own institution through internal billing and administrative procedures. The comparison to colon cancer testing is suggestive here. Most colon cancer genetic testing is done by the handful of laboratories set up to offer this complex set of tests, and the test algorithms for BRCA and colon cancer susceptibility genes appear to have comparable costs and decision pathways. It thus appears there is some advantage to consolidating testing at a few laboratories that can attain sufficient volume to justify sunk costs in developing the test and resources to ensure quality and reduce legal liability for errors. In the case of colon cancer testing, this has resulted in an oligopoly, BRCA patents have made testing a Myriad monopoly in the United States.

The US monopoly on BRCA testing may not be absolute; there is no legal barrier to sending samples abroad, and US courts would be unlikely to interpret merely sending results from tests performed abroad (information) back to the United States an infringement. Myriad would have grounds for infringement liability only if the invention (making and using the patented sequences and methods) were performed abroad in a jurisdiction where those activities are claimed in patents, and Myriad would have to sue in those jurisdictions. Laboratories in countries with diagnostic use exemptions would not face infringement liability.

Regarding third-party payers, at least one study noted in the Lewin Group report showed that as of late 1995, "only 4% of insurance providers… had granted coverage of *BRCA* testing[, and] 55% of respondents cited concerns about the high cost of *BRCA* testing, averaging $2,400 per patient."[192] As noted above, these data no longer represent practices for BRCA testing, which Myriad reports now generally is covered for roughly 95% of those requesting tests, and reimbursed to cover 90% of their charges. The same study cited by the Lewin Group had two other findings of relevance to patented gene tests. First only 6 percent of the decision-makers for private health insurance plans would cover *BRCA* testing if were extended to all women in the general population, whereas 48% would offer it if it were restricted only to women with a positive family history who were enrolled in an approved research trial. Second, the proclivity to offer coverage was sharply dependent on cost: 25% were willing to cover it if the testing cost were $250, but only 14% would cover if the cost rose to $1,000 (it was $2400 at the time). Taken at face value, the figures imply that even if gene patents confer a premium of $750 this would only reduce the likelihood of third party coverage by 11 percentage points. However, the low response rate (22%) and early timing of this study limit the current usefulness of this study.[193]

In 1998, Myriad reported that over 300 different insurers covered *BRCA1* and *BRCA2* testing; they further stated that 94.3% of processed claims for *BRCA1* and *BRCA2* testing had resulted in at least partial payment from insurance companies (suggesting the test was covered to some extent).[194] As of 2002, 38% of testers said they had no problems in getting coverage for genetic services from their insurance plan. But a more telling statistic was that only 59% of women[195] undergoing full sequence *BRCA* analysis in

[192] The Lewin Group. Op. cit. at 153.
[193] Schoonmaker M et al. Op. cit.
[194] Shappell H et al. Writing effective insurance justification letters for cancer genetic testing: a streamlined approach. *Journal of Genetic Counseling* 2001 (August). 10(4):331-341.
[195] Of note, 99% of women in the study did actually have health insurance.

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one study filed health insurance claims.[196] Furthermore, 15% of women in a second study undergoing *BRCA* analysis chose to self-pay, and each of those women did so in fear of insurance or employment discrimination.[197] As noted above, Myriad states that only approximately 5 percent of patients now self pay, and more than 2500 payers and health plans have reimbursed testing with Myriad. Finally, the enactment of the Genetic Information Nondiscrimination Act of 2008, and its implementation in 2009 and 2010, may reduce fears of discrimination in employment and health insurance.

In the most recent study to address reimbursement for genetic testing, 56% of non-testers from a sample who had received genetic counseling services and declined testing said they could not afford all costs of the test or their share not covered by insurance, yet more than half also reported income of over $70,000 annually.[198] Of only 77 individuals for whom insurance status was reported, 42% had insurance that provided no coverage for testing, 25% had partial coverage and the remainder had full coverage. But this was not a random sample of the population, since no one was reported as uninsured. Nationally, 18.8% of women age 19-64 are uninsured,[199] so if we assume the same is true of women with *BRCA* mutations and that 42% of the remainder are insured but have no coverage for *BRCA* testing, this would imply that roughly half of the at-risk group had no insurance coverage for this test at that time.

One conclusion from multiple studies is that when payment is out-of-pocket, price has a strong and direct impact on testing utilization, and thus affects patient access. People do forego potentially beneficial genetic tests when they are expensive and not covered by health plans or insurance. Access is thus linked tightly to coverage and reimbursement policies, which are far more important than any direct patent effects. Patent status matters to the degree it affects price, where high prices require payers to assess a specific new test. Patent status may also affect likelihood to create a bargaining impasse with payers, if patent-holders and payers simply cannot agree on reimbursement. The BRCA experience suggests that over ten years, the vast majority of payers have decided to cover most of the cost of a test when its use is restricted to those at high risk. For those who are not covered by such payers, access is still a problem, in part because of price.

Problems in access may still occur with: 1) Medicaid programs, 2) insurance policies that exclude all genetic testing, and 3) practices and health plans (e.g., in southern California) where there is a strong financial incentive to minimize utilization. These access constraints, however, do not appear to be keyed to patent status, but rather blanket policies focused on cost containment and contractual transaction costs.

Coverage for Risk-Reducing Surgery

A national study on coverage for prospective mastectomy or oophorectomy showed that 10-11% of private insurers and 48 to 50% of public health plans had policies that specifically denied coverage for risk-reducing surgery for women with BRCA mutations; 52 to 64% of private insurers and 40% of public carriers had no identifiable policy regarding coverage of either form of surgery for such women.[200]

A retrospective analysis of 219 Memorial Sloan-Kettering Cancer Center patients with known BRCA1/2 mutations found that of 35 women undergoing 39 risk-reducing mastectomies or oophorectomies, 97%

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[196] Lee S et al. Op. cit.
[197] Peterson E et al. Op. cit.
[198] Kieran S et al. The role of financial factors in acceptance of clinical *BRCA* genetic testing. *Genetic Testing* 2007 (March). (11)1:101-110.
[199] Economic Research Initiative of the Uninsured. *Table 2 – CPS Adult Population (Age 19-64) Calendar Year 2005*. University of Michigan. See http://www.umich.edu/~eriu/fastfacts/cps2005_2.html [accessed May 2007].
[200] Kuerer H et al. Current national health insurance coverage policies for breast and ovarian cancer prophylactic surgery. *Annals of Surgical Oncology* 2000. 7(5):325-332.

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were covered in full (minus applicable deductibles and coinsurance). The single instance in which an indemnity plan refused to provide coverage occurred in 1997 when there were few data about the efficacy of prophylactic oophorectomy.[201] This study is now eight years old, however, and clinicians with whom we have spoken believe that prophylactic surgery in mutation-positive women is broadly covered, although we have no empirical data to corroborate that impression.

Adoption by third-party payers as well as providers and testing laboratories is only a rough proxy for patient access. If possible, future research should focus on getting at direct patient access data, or at least at utilization rather than highly indirect measures such as number of providers or price.

Consumer Utilization

In studies done several years ago, 19-74% of at-risk individuals who could benefit from BRCA testing were not being tested.[202] Cost was not the only consideration: nearly 70% of patients eligible for free BRCA testing elected to get tested; however, cost certainly mattered since only 22% of self-pay patients in the same sample chose to be tested.[203] The financial barriers to individual patients appear to have been reduced considerably for those who have health plans so the financial access questions reduce to how many have such coverage, which as shown above, is still a grey area in terms of hard numbers. In the RAND Health Insurance Experiment, the price elasticity of demand for outpatient health services for those with high cost-sharing was -0.31.[204] If the patent premium on BRCA were 50 percent, for example, this would predict 15.5% fewer high-risk patients without coverage would purchase the test. Any reduction in access due to cost, however, is difficult to attribute to BRCA patents because of the absence of a clear price effect of the patents. Our data do not allow us to tease out any price-utilization effects attributable to patents *per se*.

Finally, Appendix 1 notes the difference in number of providers for the three genetic tests, with Myriad as the sole *BRCA* full-sequence provider, nine providers for the Lynch Syndrome tests, and five for the FAP test. This sole-provider status of Myriad for BRCA testing in the United States is clearly attributable to patent status, although differences in patent status and patent enforcement outside the United States have resulted in Myriad not being sole provider in other jurisdictions.

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We wish to thank David Ridley, Tracy Lewis, and Wesley Cohen of the Fuqua School of Business for their helpful comments. The case study was also reviewed by William Rusconi, Faye Eggerding, and Michael Hopkins for the Secretary's Advisory Committee on Genetics, Health and Society.

Research for this case study funded under grant P50 HG03391 from the National Human Genome Research Institute (National Institutes of Health) and the US Department of Energy.

[201] Kauff N et al. Insurance reimbursement for risk-reducing mastectomy and oophorectomy in women with *BRCA1* or *BRCA2* mutations. *Genetics in Medicine* 2001 (November/December). 3(6):422-425.
[202] Kieran S et al. Op. cit.
[203] Ibid.
[204] Liu S et al. Mathematica Policy Research, Inc. *Price and Income Elasticity of the Demand for Health Insurance and Health Care Services: A Critical Review of the Literature.* March 26, 2006. See http://www.mathematica-mpr.com/publications/pdfs/priceincome.pdf [accessed June 2007].

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Appendix 1: Summary Table[205]

Measures	Breast / Ovarian Cancer *BRCA1* / *BRCA2*		Colorectal Cancer HNPCC / FAP	
Total annual number of new diagnoses (deaths)	*Breast*	178,480 (40,910)	*Colorectal*	153,760 (52,180)
	Ovarian	22,430 (15,280)		
Percent of cancers caused by mutation	*Breast and Ovarian*	5-10%	*Colorectal*	~5%
Lifetime percent risk if positive for mutation	*Breast*	35 – 85%	*HNPCC*	80%
	Ovarian	16 – 60%	*FAP*	~100%
Lifetime relative risk if positive for mutation	*Breast*	2.7 – 6.4	*HNPCC*	13.3
	Ovarian	9.4 – 35.3	*FAP*	16.7
Patent holder	Myriad Genetics, 1998 U.S. 5753441 (*BRCA1*) U.S. 6051379 (*BRCA2*)* *Purchased from OncorMed in 1998 (See Appendix 4 for more patent information.)		*HNPCC*	*MLH1* gene: Oregon Health Sciences Univ. and Dana-Farber, 1999[6] – U.S. 5922855 *MSH2* protein: Johns Hopkins, 1997 – U.S. 5591826
			FAP	*APC* gene: Johns Hopkins, 1994 U.S. 5352775
U.S. licensees	Myriad Genetics		*HNPCC*	*Non-profit* Baylor College of Medicine, Boston University School of Medicine, City of Hope National Medical Center, Harvard-Partner's Center for Genetics and Genomics, Huntington Medical Research Institutes, Mayo Clinic, University of Pennsylvania School of Medicine
				For profit Myriad Genetics, Quest Diagnostics

[205] Based on AHRQ. Genetic risk assessment and *BRCA* mutation testing for breast and ovarian cancer susceptibility. Evidence synthesis 37. September 2005. Op. cit.
National Cancer Institute. *Learning about Colon Cancer.* August 2006. See http://www.genome.gov/10000466 [accessed February 2007].
Kaz A, Brentnall TA. Op. cit.
Centers for Disease Control. Colorectal cancer test use among persons aged >50 years --- United States, 2001. *MMWR* 2003 (March 14). 52(10):193-196.
Myriad Genetics, via phone call March 2007.
Cho M et al. Op. cit.
Patents obtained via standard Delphion Patent Database search. According to GeneTests.org – limited search to "Analysis of the entire coding region: Sequence analysis."
Parthasarathy S. *Building Genetic Medicine: Breast Cancer, Technology, and the Comparative Politics of Health Care.* Op. cit. at 117.

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		FAP	*Non-profit* Baylor College of Medicine, Harvard-Partner's Center for Genetics and Genomics, Huntington Medical Research Institutes, University of Pennsylvania School of Medicine
			For profit Myriad Genetics
Cost of genetic test	**$3,120 for two genes**	***HNPCC***	**$600 - $1,800 for one gene** **$1,200 to $2,000 for two genes** **$2,050 to $2,995 for three genes**
		FAP	**$1,200 - $1,800 for one gene**

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Appendix 2: Clinical Algorithm for *BRCA1* / *BRCA2* Genetic Testing[206]

NCCN® Practice Guidelines in Oncology – v.1.2007 | Hereditary Breast and/or Ovarian Cancer

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MS, References

HBOC TESTING CRITERIA[a,b]

- Member of family with a known BRCA1/BRCA2 mutation
- Personal history of breast cancer[c] + one or more of the following:
  - Diagnosed age ≤ 40 y,[d] with or without family history
  - Diagnosed age ≤ 50 y or two breast primaries,[e] with ≥ 1 close blood relative with breast cancer ≤ 50 y and/or ≥ 1 close blood relative with epithelial ovarian cancer
  - Diagnosed at any age, with ≥ 2 close blood relatives with breast and/or epithelial ovarian cancer at any age
  - Close male blood relative with breast cancer
  - Personal history of epithelial ovarian cancer
  - For an individual of ethnicity associated with deleterious mutations (eg, founder populations of Ashkenazi Jewish, Icelandic, Swedish, Hungarian or other) no additional family history may be required[f]
- Personal history of epithelial ovarian cancer
  - For an individual of ethnicity associated with deleterious mutations (eg, founder populations of Ashkenazi Jewish, Icelandic, Swedish, Hungarian or other) no additional family history may be required[f]
- Personal history of male breast cancer particularly if one or more of the following is also present:
  - ≥ 1 close male blood relative with breast cancer
  - ≥ 1 close female blood relative with breast or ovarian cancer
  - For an individual of ethnicity associated with deleterious mutations (eg, founder populations of Ashkenazi Jewish, Icelandic, Swedish, Hungarian or other), no additional family history may be required[f]
- Family history only—Close family member meeting any of the above criteria

Criteria met → Follow-up (see HBOC-2)

Criteria not met → Refer to NCCN Breast Cancer Screening and Diagnosis Guidelines

[a]One or more of these criteria is suggestive of hereditary breast/ovarian cancer syndrome that warrants further professional evaluation. Individuals with limited family history may have an underestimated probability of familial mutation.
[b]When investigating family histories for HBOC, the maternal and paternal sides should be considered independently. Close relatives include first-, second-, and third-degree relatives. Other malignancies reported in some families with HBOC include prostate, pancreatic, and melanoma. The early onset of breast or epithelial ovarian cancers also increases suspicion of HBOC.
[c]For the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancers should be included.
[d]May consider age range between ≤ 40 and ≤ 50 y if clinical situation warrants.
[e]Two breast primaries including bilateral disease or cases where there are two or more clearly separate ipsilateral primary tumors.
[f]Testing for founder-specific mutation(s), if available, should be performed first. Full sequencing may be considered if other HBOC criteria met.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Back to Assessment (see BR/OV-1)

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HBOC-1

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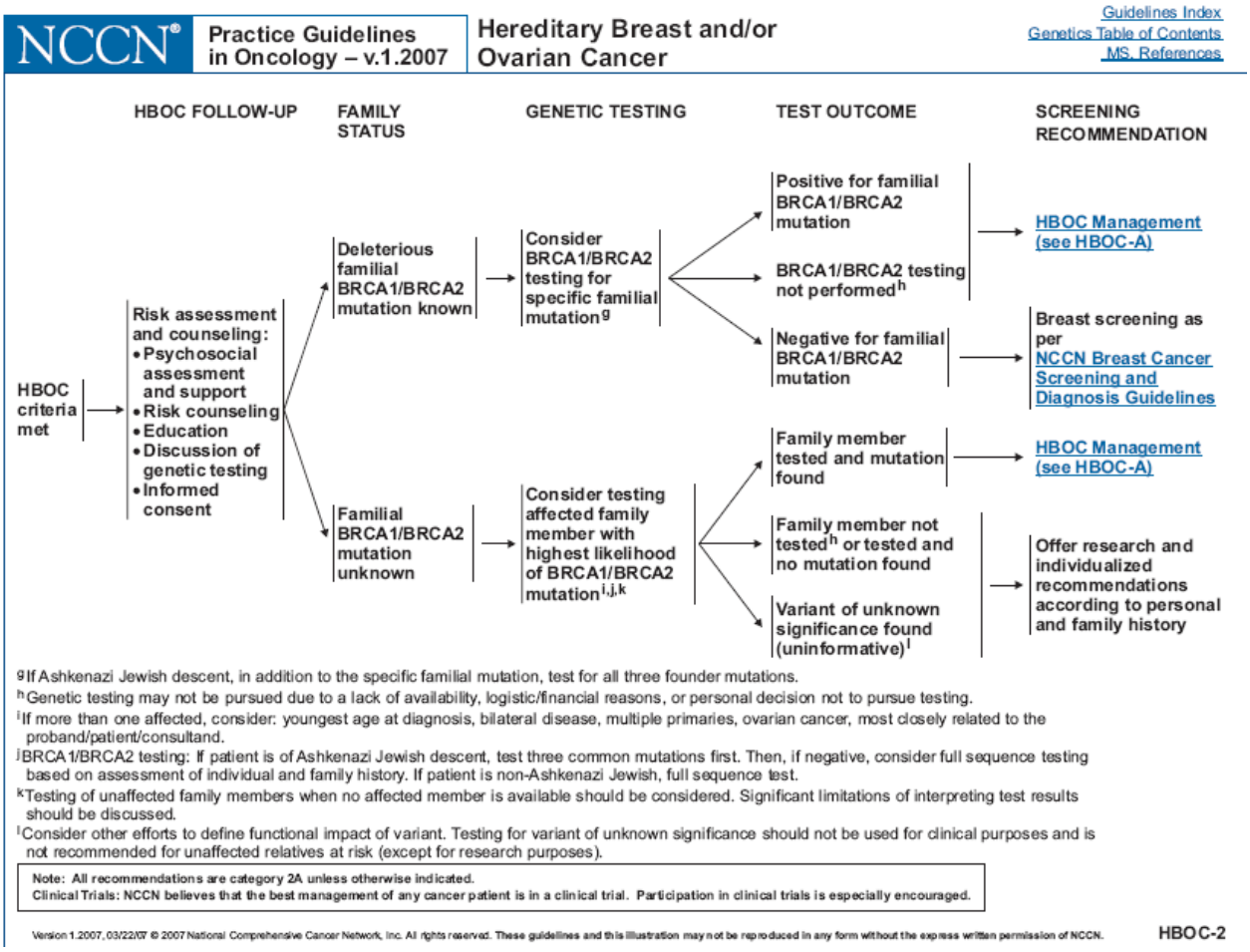
[206] Source: National Comprehensive Cancer Network. "NCCN Clinical Practice Guidelines in Oncology – Genetic/Familial High-Risk Assessment: Breast and Ovarian." V.1.2007. Accessed May 2007 at: http://www.nccn.org/professionals/physician_gls/PDF/genetics_screening.pdf

Appendix 2 (Cont.): Clinical Algorithm for *BRCA1* / *BRCA2* Genetic Testing



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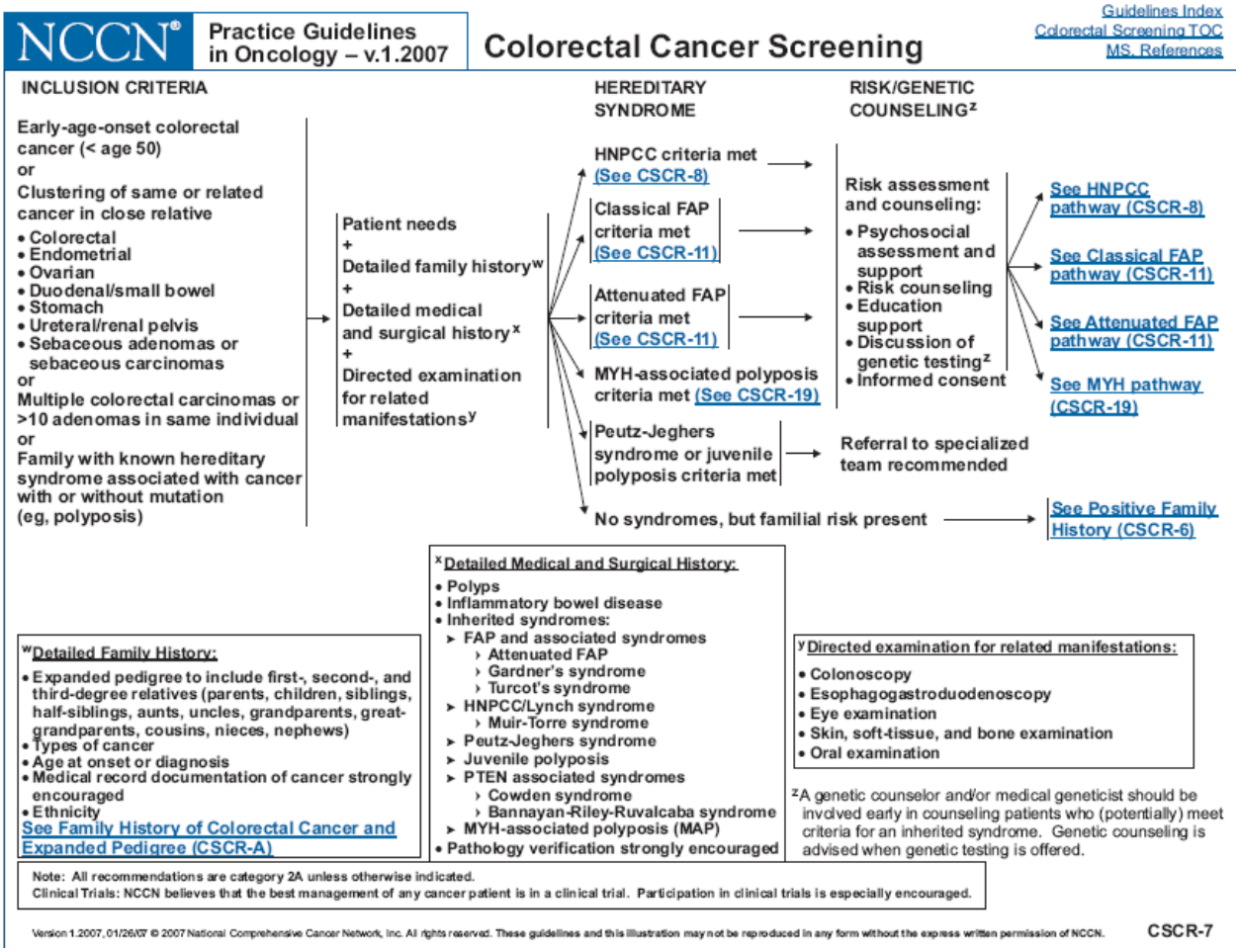
Appendix 3: Clinical Algorithm for FAP / HNPCC Genetic Testing[207]



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[207] National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology – Colorectal Cancer Screening.* V.1.2007. See http://www.nccn.org/professionals/physician_gls/PDF/colorectal_screening.pdf [accessed May 2007]

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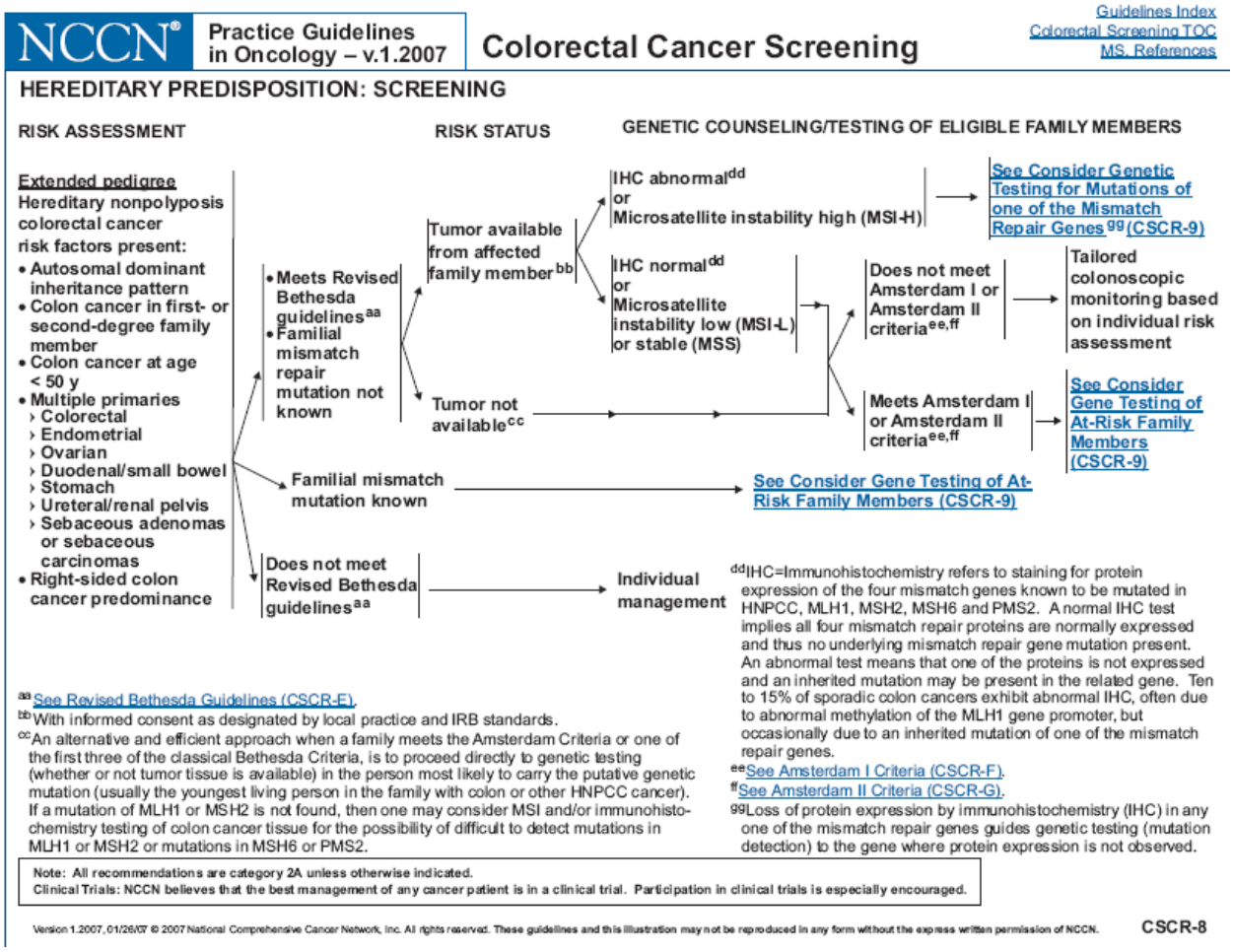
Appendix 3 (Cont.): Clinical Algorithm for FAP / HNPCC Genetic Testing



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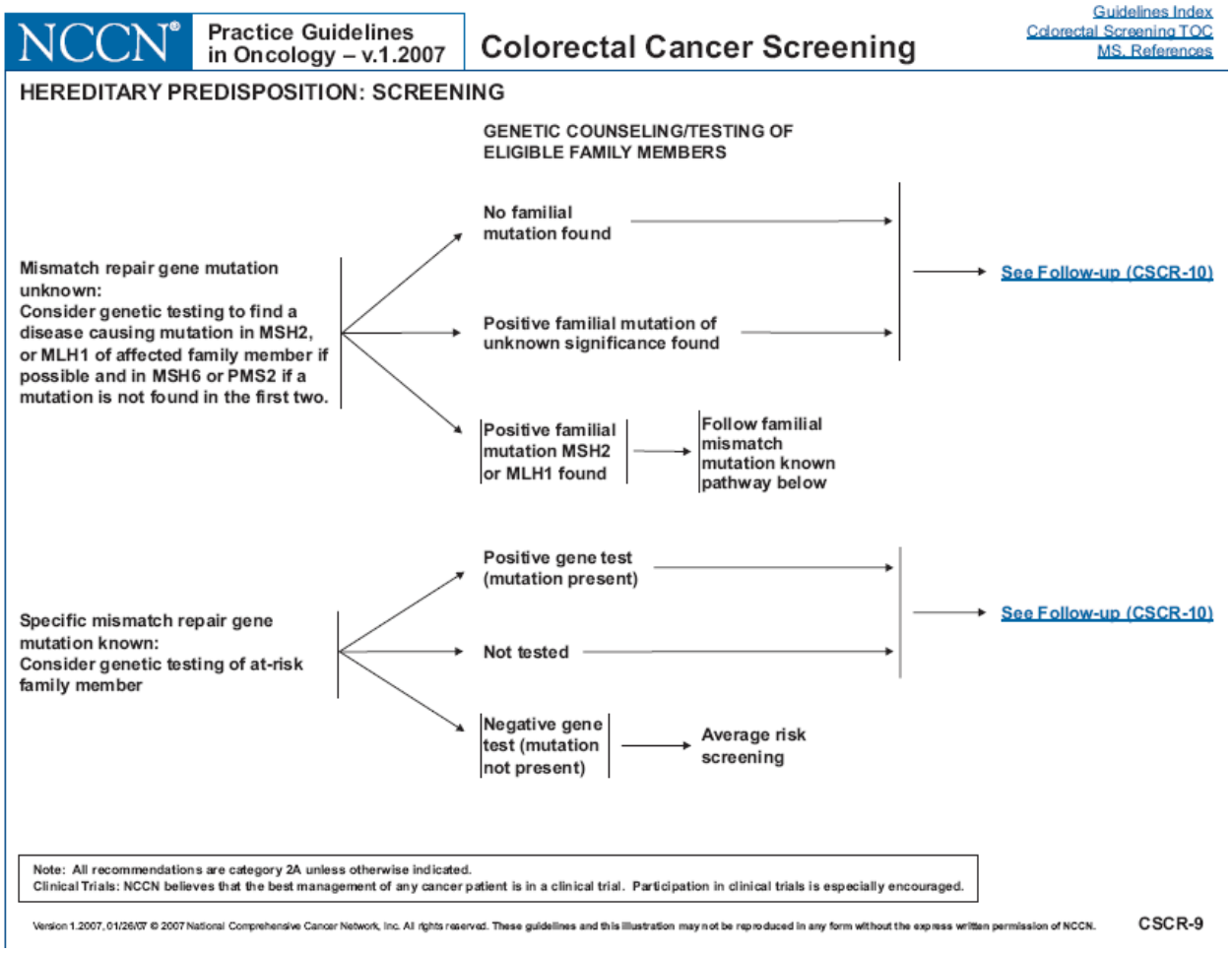
Appendix 3 (Cont.): Clinical Algorithm for FAP / HNPCC Genetic Testing



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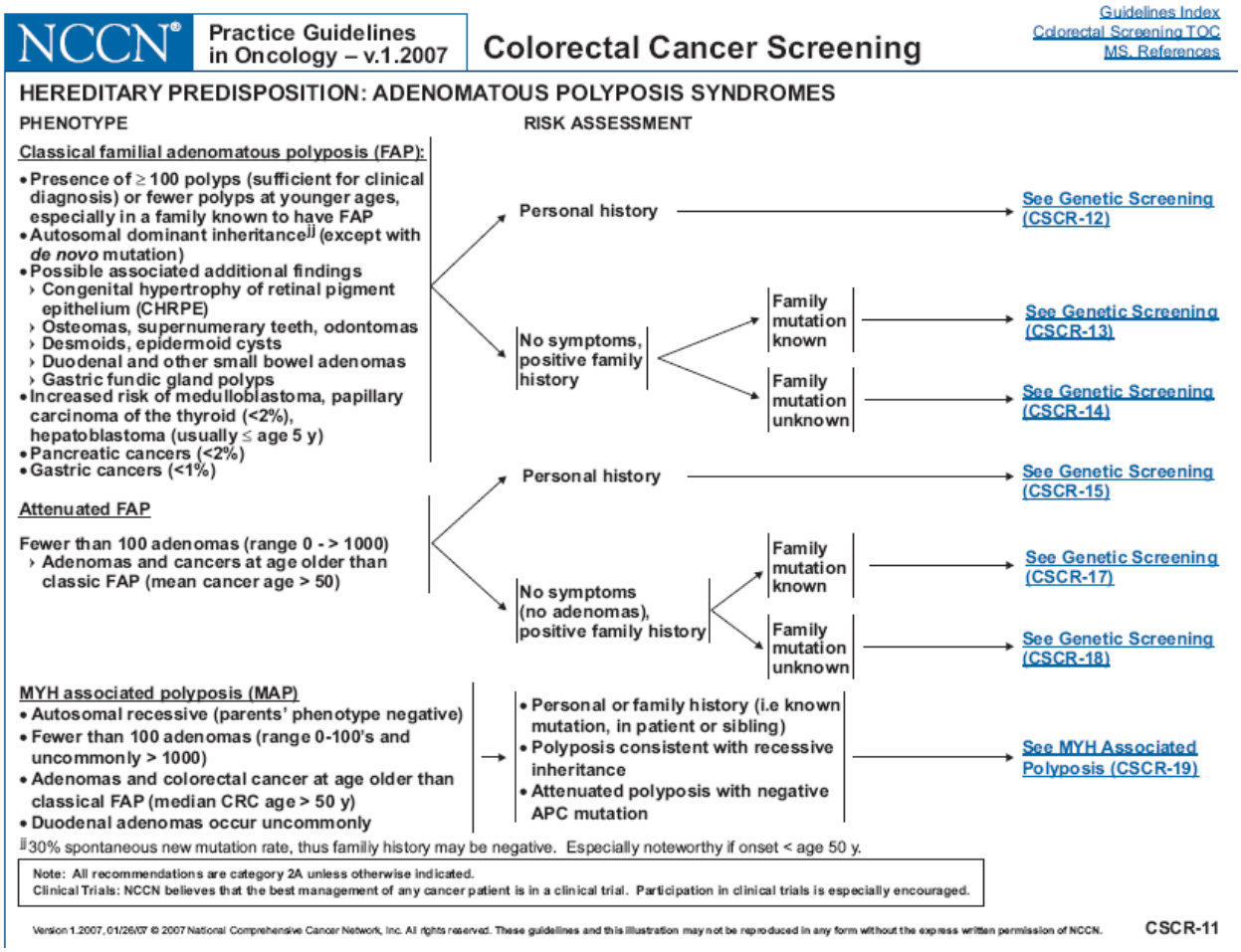
Appendix 3 (Cont.): Clinical Algorithm for FAP / HNPCC Genetic Testing



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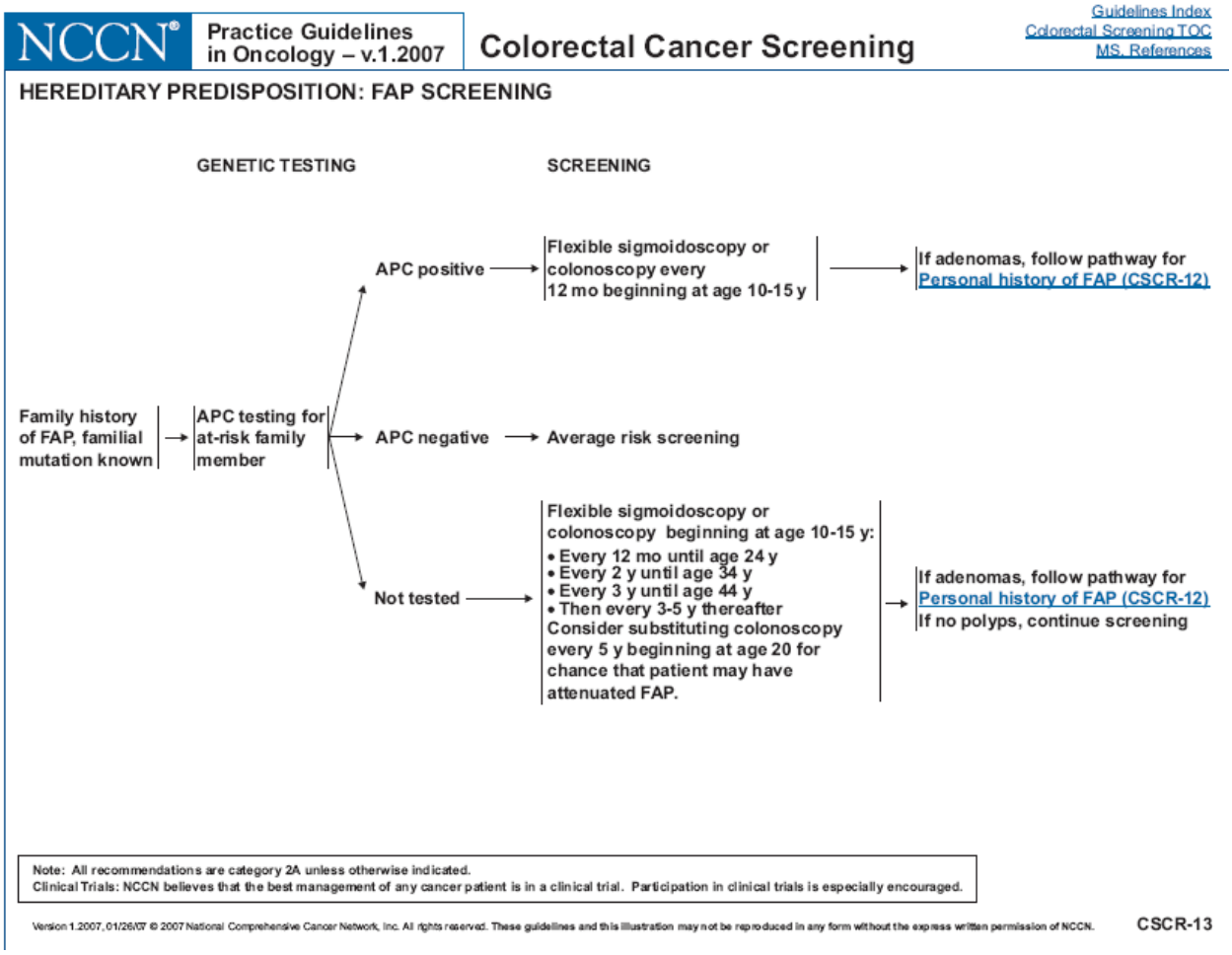
Appendix 3 (Cont.): Clinical Algorithm for FAP / HNPCC Genetic Testing



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These Guidelines are a work in progress that will be refined as often as new significant data becomes available.

The NCCN Guidelines are a statement of consensus of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN guideline is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

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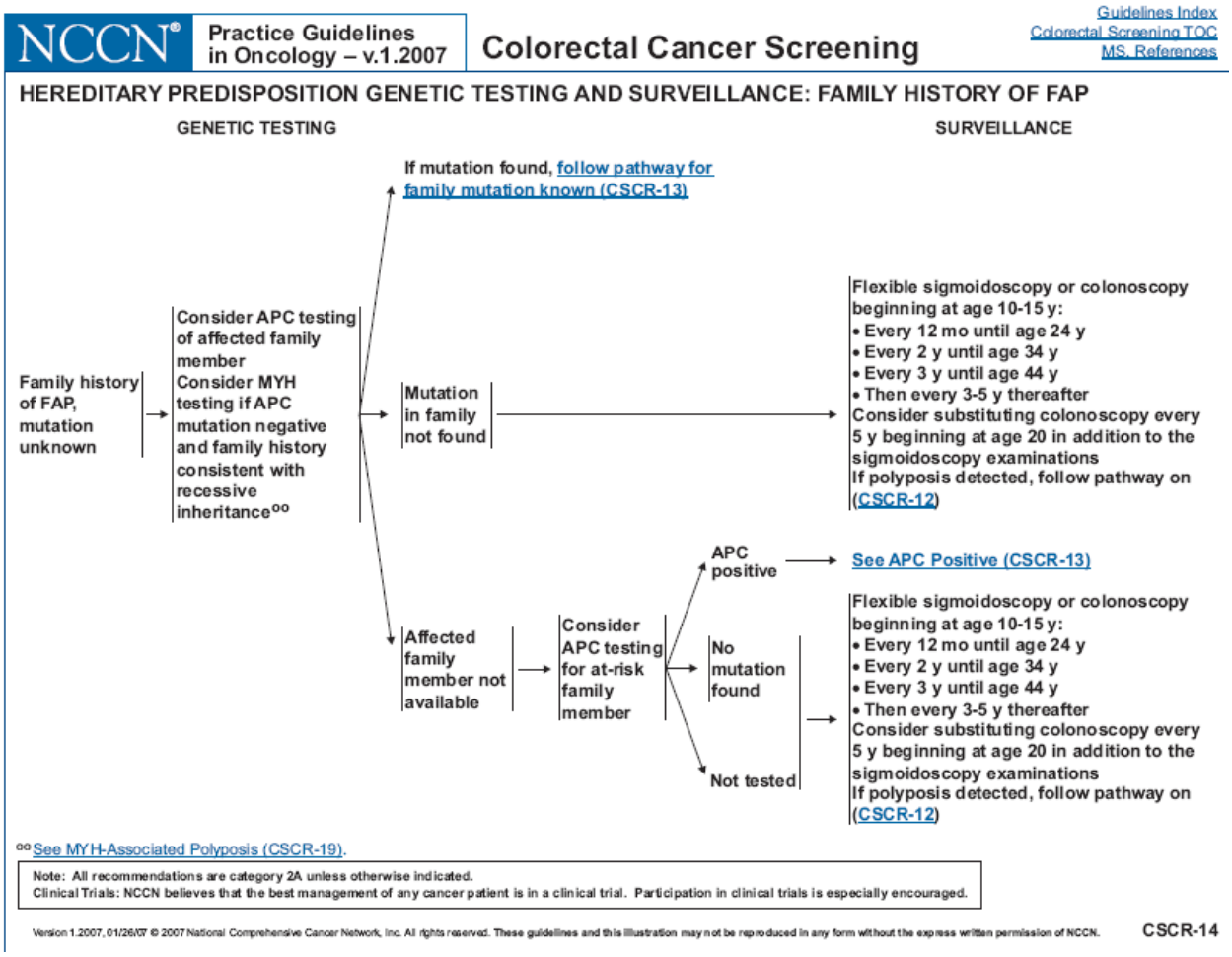
Appendix 3 (Cont.): Clinical Algorithm for FAP / HNPCC Genetic Testing



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Appendix 4: *BRCA1* and *BRCA2* Patents

US Patent	Nature of Claims	Assignee	US Licensee
5654155	Consensus cDNA sequence for BRCA1, method for detecting *BRCA1* mutations	OncorMed	Rights acquired by Myriad
5622829	Mutant allele probes and methods for BRCA1	University of California	OncorMed (acquired by Myriad)
5693473	*BRCA1* mutations	Myriad Genetics; Centre du Recherche du Chul; Tokyo Cancer Institute	Myriad Genetics
5709999	Method for detecting *BRCA1* mutations	Myriad Genetics; Centre du Recherche du Chul; Tokyo Cancer Institute	Myriad Genetics
5710001	Method for detecting BRCA1 mutations in tumors	Myriad Genetics, University of Utah Research Foundation, and the United States of America	Myriad Genetics
5747282	cDNA sequence for *BRCA1*, cloning vectors containing *BRCA1* cDNA, kit for detecting mutations in *BRCA1*, and method for screening for therapeutics for cells with *BRCA1* mutations	Myriad Genetics, University of Utah Research Foundation, and the United States of America	Myriad Genetics
5750400	cDNA sequence for *BRCA1 and* methods for detecting *BRCA1* mutations	OncorMed	Rights acquired by Myriad
5753441	Method and kit for detecting *BRCA1* germline mutations	Myriad Genetics, University of Utah Research Foundation, and the United States of America	Myriad Genetics
5837492	*BRCA2* sequence and methods	Myriad Genetics, Endo Recherche, HSC (Hospital for Sick Children) Research & Development Limited Partnership, and Trustees of the University of Pennsylvania	Myriad Genetics
6045997	*BRCA2* sequences and methods	Duke University and Cancer Research Campaign (UK)	Expired
6051379	Probes, methods, and kits for detecting *BRCA2* mutations and rearrangements	Myriad Genetics, University of Utah Research Foundation, and the United States of America	Myriad Genetics
6130322	cDNA sequence for segments of *BRCA1*	Gene Logic	*
6162897	Amino acid sequence translated from *BRCA1*	Myriad Genetics, University of Utah Research Foundation, and the United States of America	Myriad Genetics

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6686163	*BRCA1* mutations and cloning vectors containing mutations	Gene Logic	*
6720158	*BRCA1* sequence for splicing variations	Philadelphia Health & Education Corp. (now assigned to Drexel University) **	Unlicensed
6838256	*BRCA1* consensus coding sequences, mutations, vector comprising sequence, methods for detecting mutations	Gene Logic	*
6951721	Method for determining functional sequence variations in *BRCA1*	Gene Logic	*

*Duke University researchers requested licensing information from Gene Logic but to date have not received licensing information.

**Drexel University Office of Technology Commercialization, via phone October 20, 2008. (215) 895-0304.

Information compiled by authors.

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Impact of Gene Patents and Licensing Practices on Access to Genetic Testing for Alzheimer's Disease

Katie Skeehan, Christopher Heaney, and Robert Cook-Deegan, MD[1]

Introduction

As the most common form of dementia, Alzheimer's Disease (AD) currently afflicts over 5 million Americans, a number expected to increase to 16 million by 2050.[2] Total estimated costs of healthcare for AD were $33 billion in 1998; rising to $61 billion by 2002.[3] Because it strikes so many and costs so much, it is important to understand whether and how patenting and licensing practices might affect the millions of people who will be concerned about genetic risks associated with Alzheimer's disease.

Alzheimer's disease as currently classified has several forms. Two are relevant to genetic testing. A very small percentage of AD cases arise in family clusters with early onset. Familial early-onset AD (EOAD) is usually caused by an autosomal dominant mutation in one of three genes: PSEN1 (chromosome 14), PSEN2 (chromosome 1), or APP (chromosome 21). A person with one of these fully penetrant mutations will contract the disease if they live long enough, usually developing symptoms before age 60. These families are quite rare, but the 50% risk of each child of an affected member means these tests can be important for those at risk.

The vast majority of people who develop AD have the late-onset form (LOAD), which has only one clearly established and robust genetic risk factor known as APOE (the gene that encodes the protein apolipoprotein E). Those who inherit the ε4 allele from one parent have an elevated risk of developing AD, and those who inherit ε4 alleles from both parents have a markedly elevated risk (up to an odds ratio of 16 relative to the population average for Caucasian males, for example). Recent studies based on genome-wide association with markers suggest there may be other genetic risk factors, but the next most significant locus after APOE, on chromosome 12, is many, many orders of magnitude less predictive.[4] The high-risk ε4 genotype is not necessary to predict or diagnose AD. While the APOE genetic test is used in a relatively small fraction of LOAD cases, the much larger number of late-onset AD cases means it is more frequently used than the genetic tests for PSEN1, PSEN2, or APP in high-risk families.

Patents relevant to genetic testing for all four genes have been granted in the United States. The patenting landscape is complex. The APOE gene itself is not patented, nor are mutations or polymorphisms, but testing to predict Alzheimer's risk is the subject of three "methods" patents issued to Duke University and licensed exclusively to Athena Diagnostics. PSEN1 and PSEN2 gene sequences and their variants have been patented and exclusively licensed to Athena Diagnostics. APP is the subject of several patents for making animal models, but not of a sequence patent *per se*. Athena offers genetic testing for PSEN1, PSEN2, APP, and APOE. When this case study was first being prepared in summer 2007, testing for PSEN2 and APP was not listed on Athena's website, and clinicians did not know of a CLIA-certified laboratory offering such testing, but starting February 2008, these tests were offered by Athena.

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[1] Center for Genome Ethics, Law & Policy, Institute for Genome Sciences & Policy, and Sanford Institute of Public Policy, Duke University

[2] Alzheimer's Association. *Alzheimer's Disease Facts and Figures 2007*. 2007. See http://alz.org/national/documents/Report_2007FactsAndFigures.pdf [accessed November 14, 2008], at 5.

[3] Ibid., 14.

[4] Beecham GW et al. Genome-wide association study implicates a chromosome 12 risk locus for late-onset Alzheimer disease. *Am J Hum Gen* 2009 (January 9). 84:35-43.

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Direct-to-consumer APOE testing was available March-October 2008 through Smart Genetics.[5] Smart Genetics ceased offering APOE risk assessment for Alzheimer's disease to consumers in October 2008.[6] Direct-to-consumer APOE testing remains advertised through Graceful Earth's website, and APOE ε4 status is indirectly assessed by at least one of the "personal genomics" firms (see below).

Background

AD accounts for 50% to 70% of all cases of dementia. Even without genetic factors, the lifetime risk of AD in the general population is estimated at 15%, with prevalence of the disease doubling every five years after the age of 65 so that nearly 40% of the population aged 85 and older has AD.[7] The most common symptom is gradually worsening memory loss, especially short-term memory, learning, and new memory formation. As the disease advances, victims typically experience confusion and disorientation, impaired judgment, and difficulty speaking and writing. Eventually AD patients lose their ability to do simple everyday tasks like bathing, dressing, and eating. Ultimately those with AD reach a point where they no longer recognize family and friends, lose the ability to communicate, and become bed-bound.[8] AD is incurable and fatal, though the average patient can expect to live 8 to 10 years beyond the initial appearance of symptoms.[9] Some live far longer.

The neuropathology of AD consists of plaques of beta-amyloid protein deposited in the brain and neurofibrillary tangles of another protein called tau inside nerve cells.[10] Scientists and clinicians debate whether the plaques and tangles are the cause or the result of cell death. Most researchers now ascribe to the "amyloid cascade" hypothesis, which postulates that the accumulation of A-beta amyloid is toxic to nerve cells. Elucidating the pathogenic pathway and developing new leads for treatment are extremely active areas of research. Other abnormalities in the brain of a person with AD can include inflammation and oxidative stress.[11] While correct diagnosis of AD has improved greatly since its discovery (it is now at near or beyond 90% in academic centers[12]), the gold standard for AD is autopsy confirmation, when the brain can be examined for the telltale plaques and tangles, combined with a clinical history of dementia. [13]

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[5] Athena initially sublicensed the APOE patents to Smart Genetics, which began offering direct-to-consumer genetic risk assessment for AD in March 2008. The test was widely advertised, including a 28 March "survey" of consumers' willingness to undergo genetic testing through *Parade Magazine*, the most widely circulated publication in the nation. Allen Roses was asked to become a consultant of Smart Genetics, refused, and notified Duke University that it was his understanding the license for the patents on which he is first inventor permitted APOE testing only for those with a physician's certification of a diagnosis of dementia. Smart Genetics ceased operations in October 2008 (Smart Genetics shuts its doors. *Eye on DNA*. See http://www.eyeondna.com/2008/10/06/smart-genetics-shuts-its-doors/ [accessed November 14, 2008]. Genetic testers Smart Genetics closes. *Philadelphia Business Journal*. See http://www.bizjournals.com/philadelphia/stories/2008/09/29/daily42.html [accessed November 14, 2008]).

[6] Hayden EC. Alzheimer's Tests Under Fire. *Nature* 2008. 455: 1155.

[7] Post SG, Whitehouse PJ, Binstock RH, Bird TD, Eckert SK, Farrer LA, Fleck LM, Gaines AD, Juengst ET, Karlinsky H, Miles S, Murray TH, Quaid KA, Relkin NR, Roses AD, St George-Hyslop PH, Sachs GA, Steinbock B, Truschke EF, Zinn AB. The clinical introduction of genetic testing for Alzheimer disease. An ethical perspective. *JAMA* 1997. 277, (10): 832-6.

[8] See Alzheimer's Association. *Alzheimer's Disease Facts and Figures 2007*. Op. cit. at 3.

[9] Small GW, Rabins PV, Barry PP, Buckholtz NS, DeKosky ST, Ferris SH, Finkel SI, Gwyther LP, Khachaturian ZS, Lebowitz BD, McRae TD, Morris JC, Oakley F, Schneider LS, Streim JE, Sunderland T, Teri LA, Tune LE. Diagnosis and treatment of Alzheimer disease and related disorders. Consensus statement of the American Association for Geriatric Psychiatry, the Alzheimer's Association, and the American Geriatrics Society. *JAMA* 1997. 278, (16): 1363-71.

[10] Bird TD. Genetic Aspects of Alzheimer Disease. *Genetics in Medicine* 2008. 10, (4): 231-39.
Schutte DL, Holston EC. Chronic Dementing Conditions, Genomics, and New Opportunities for Nursing Interventions. *Journal of Nursing Scholarship* 2006. 38, (4): 328-34.

[11] Ibid.

[12] Bertram L, Tanzi RE. Alzheimer's disease: one disorder, too many genes? *Human Molecular Genetics* 2004. 13, (Review Issue 1): R135-R41.

[13] Bird TD. Genetic Aspects of Alzheimer Disease. *Genetics in Medicine* 2008. 10, (4): 231-39.231 – 232.

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Early-onset AD

EOAD accounts for fewer than 3% of all AD cases, which amounts to less than 50,000 people in the U.S.[14] Some inherited cases are missed. Early-onset cases lacking family history may truly lack inherited risk, or the family history may have missed past cases for one of many reasons. Current classifications have only been in place for the past three decades in a disease with onset late in life, and with few autopsies performed to give definitive diagnosis. Until recent decades, premature deaths (before usual AD onset) were common, so those dying might have developed dementia had they lived long enough. Or affected cases may have died with dementia but it was not reported as the cause of death, nor recorded in family records. Moreover, expectations of "senility" were common, so that those developing symptoms often were not understood to have disease-related dementia. Family history of past cases is thus even more uncertain than for most other conditions.

Familial EOAD (or EOFAD) is usually caused by autosomal dominant mutations in the APP, PSEN1 or PSEN2 genes, although there are additional families with autosomal dominant inheritance pattern in which no mutation has yet been identified.[15] In families with autosomal dominant EOAD, each child of an affected parent has a 50% chance of also having the mutant gene, and therefore developing EOAD if they live long enough. Upon genetic testing, sometimes a new EOAD family reveals a mutation in one of the three known genes; other times no mutation is found to explain the inheritance pattern and testing is inconclusive.[16] In one of the larger studies of EOAD families to date, mutations in the PSEN1 gene accounted for 66% of EOAD families, mutations in APP for another 16%, and 18% were unknown.[17] (Note these numbers are for familial cases, not sporadic ones. EOAD is not always inherited and genetic testing has a very low yield in nonfamilial cases.)

APP

The amyloid precursor protein (APP) was discovered in the 1980s.[18] A mutation in the gene encoding this protein was the first to be linked with AD, in 1991.[19] The APP gene resides on chromosome 21 and contains at least 36 mutations, of which 30 are believed pathogenic.[20] However, this is an extremely rare cause of AD, affecting only approximately 30 known families worldwide. Age of onset ranges from 39 to 67 years. APP-related disease can be influenced by the individual's APOE genotype, the gene that plays a

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[14] Ibid. 232.
Strobel G, *What Is Early-onset Familial Alzheimer Disease (eFAD)?*, 9 April 2007 2007, Alzheimer Research Forum. See: http://www.alzforum.org/eFAD/overview/essay2/default.asp, July 16 2007].
[15] Bird TD. Genetic Aspects of Alzheimer Disease. *Genetics in Medicine* 2008. 10, (4): 231-39. At 233.
[16] Ibid.
[17] Raux G, Guyant-Marechal L, Martin C, Bou J, Penet C, Brice A, Hannequin D, Frebourg T, Campion D. Molecular diagnosis of autosomal dominant early onset Alzheimer's disease: an update. *Journal of Medical Genetics* 2005. 42: 3.
[18] Glenner G, Wong C. Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein. *Biochemical and Biophysical Research Communications* 1984. 120, (3): 885-90.
Glenner G, Wong C. Alzheimer's disease and Down's syndrome: sharing of a unique cerebrovascular amyloid fibril protein. *Biochemical and Biophysical Research Communications* 1984. 122, (3): 1131-35.
[19] Goate A, Chartier-Harlin M-C, Mullan M, Brown J, Crawford F, Fidani L, Giuffra L, Haynes A, Irving N, James L, Mant R, Newton P, Rooke K, Roques P, Talbot C, Pericak-Vance M, Roses A, Williamson R, Rossor M, Owen M, Hardy J. Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. *Nature* 1991. 349, (6311): 704-06.
[20] *Alzheimer's Disease and Frontotemporal Dementia Mutation Database*. See http://www.molgen.ua.ac.be/ADMutations/default.cfm?MT=1&ML=1&Page=MutByGene [accessed October 18, 2008].

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role in late-onset AD.[21] Those with an APP mutation and the ε4 high-risk allele of APOE generally have an even earlier age of onset than relatives with APOE-ε2 or ε3.[22]

PSEN1

Presenilin-1 mutations are the most common among the three known EOAD-associated genes. PSEN1 mutations account for the majority of EOAD cases where onset is before age 50. Discovered in 1992, PSEN1 is located on chromosome 14 and harbors over 180 different mutations, of which 173 are believed pathogenic.[23] Victims of such mutations generally have more severe clinical syndromes, such as earlier onset of seizures and language disturbance, than those with mutations in APP or PSEN2 genes.[24] AD associated with PSEN1 has onset between ages 28 and 64, with an average age of onset of 45 years.[25]

PSEN2

The PSEN2 gene that encodes the presenilin-2 protein was discovered quickly after PSEN1 because of its similar DNA sequence. It is known as "the Volga German gene" since mutations in PSEN2 were isolated on chromosome 1 in a group of apparently related German families that settled in the Volga River region of Russia before coming to the U.S., where their mutation was subsequently discovered.[26] Mutations in PSEN2 are extremely rare, having only been identified in one familial group. The average age of onset is 52 years (with a wide range from 40 to 75 years) with APOE ε4 again associated with somewhat earlier onset.[27] Twenty-two mutations in PSEN2 have been reported, fourteen of which are deemed pathogenic.[28]

Late-onset AD

LOAD is associated with both genetic and other risk factors. While the primary risk factors are age and family history, other factors such as susceptibility genes, exposure to toxins, previous head injury, female gender, and low level of education may also play a part.[29]

APOE

Apolipoprotein E is a cholesterol transport protein (generally written APOE for the gene, and ApoE or apoE for the protein). ApoE protein is encoded by a gene on chromosome 19. There are three common alleles, ε2, ε3, and ε4. In the general population, APOE ε4/4 represents approximately 2%; 3/4 represents 21%; 3/3 represents 60%; 2/3 represents 11%; 2/4 represents 5%; and 2/2 represents less than 0.5%.[30]

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[21] Blacker D. New insights into genetic aspects of Alzheimer's disease. *Postgraduate Medicine* 2000. 108, (5): 119-29.
[22] Strobel, *What is Early-Onset Familial Alzheimer Disease (Efad)?* Op. cit.
[23] *Alzheimer's Disease and Frontotemporal Dementia Mutation Database*. Op. cit.
[24] Post SG, Whitehouse PJ, Binstock RH, Bird TD, Eckert SK, Farrer LA, Fleck LM, Gaines AD, Juengst ET, Karlinsky H, Miles S, Murray TH, Quaid KA, Relkin NR, Roses AD, St George-Hyslop PH, Sachs GA, Steinbock B, Truschke EF, Zinn AB. The clinical introduction of genetic testing for Alzheimer disease. An ethical perspective. *JAMA* 1997. 277, (10): 832-6.
[25] Blacker D. New insights into genetic aspects of Alzheimer's disease. Postgraduate Medicine 2000. 108, (5): 119-29. At 120.
[26] Pollen D, *Hanah's Heirs: The Quest for the Genetic Origins of Alzheimer's Disease* (New York: Oxford University Press, 1993).
[27] Ibid.
Bird TD. Genetic Aspects of Alzheimer Disease. *Genetics in Medicine* 2008. 10, (4): 231-39. At 234.
[28] *Alzheimer's Disease and Frontotemporal Dementia Mutation Database.* Op. cit.
[29] Small GW, Rabins PV, Barry PP, Buckholtz NS, DeKosky ST, Ferris SH, Finkel SI, Gwyther LP, Khachaturian ZS, Lebowitz BD, McRae TD, Morris JC, Oakley F, Schneider LS, Streim JE, Sunderland T, Teri LA, Tune LE. Diagnosis and treatment of Alzheimer disease and related disorders. Consensus statement of the American Association for Geriatric Psychiatry, the Alzheimer's Association, and the American Geriatrics Society. *JAMA* 1997. 278, (16): 1363-71.
[30] Roses AD. Apoliopoprotein E alleles as risk factors in Alzheimer's disease. *Annu. Rev. Med.* 1996. 47: 387-400.

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APOE ε4 is associated with an increased risk of AD, while APOE ε2 acts as a mildly protective factor. Persons with APOE ε4/ ε4 have increased risk—more than sixteen-fold higher among Caucasian males at peak relative risk—and they have earlier age of onset than individuals with only one ε4 (three-fold higher risk in Caucasian males). Individuals with only one ε4 have a higher risk and earlier onset, in turn, than those with no ε4 alleles. (There are some variants among the ε3 alleles themselves also, although risk curves for sub-subgroups have not been developed for clinical use in detail.) The median onset among those homozygous for ε4 (ε4 /ε4) is before age 70, while among those who develop AD with the ε2/ε3 genotype, the median age of onset is over 90.[31]

Ashford estimates that approximately 50% of the risk of AD is attributable to APOE genotype.[32] Yet APOE is *neither necessary nor sufficient* to predict or diagnose AD.[33] "Although Alzheimer's disease occurs in many patients who carry the [APOE ε4] allele, a significant number of carriers do not get the disease. In addition, only about half of patients with late-onset Alzheimer's disease have the [APOE ε4] allele."[34] By age 90, it is rare to identify ε4/ε4 individuals without onset of dementia. Relative odds of developing AD based on the three alleles differ according to sex and race.[35]

Other Possible Genetic Influences

Because AD affects so many people, research in the field is abundant, to the point that in 2004, Bertram and Tanzi reported "more than 10 genes are reported to show either positive or negative evidence for disease association *per month*."[36] In 90 studies reporting 127 association findings in 2003, only 3 associations between candidate genes and AD were confirmed by three or more independent studies. These loci occurred at chromosomal locations 6p21, 10q24, and 11q23.[37] The recent turn to genome-wide association methods has turned up some signals, but all are far weaker than the APOE genotype.[38] Nothing conclusive has been determined, however, so APOE remains the only established clinically significant susceptibility gene for late-onset AD.

The vast majority of contributions to the Human Genome Mutation Database and Alzheimer and FTD Mutation Database, which catalog AD mutation research, come from academic research centers, and not from Athena Diagnostics, in contrast to the heavy contribution of Myriad Genetics to the analogous mutation database for BRCA1/2 mutations. Athena Diagnostics presumably tracks utilization of its various genetic tests as part of its royalty agreements, but these data are not publicly reported. The system of studying AD thus relies primarily on clinicians and academic researchers rather than family studies conducted or carried out by Athena.

<u>Patents and Licensing</u>

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[31] Ibid.;
Bird TD. Genetic Aspects of Alzheimer Disease. *Genetics in Medicine* 2008. 10, (4): 231-39.234 – 235.
[32] Ashford JW. APOE Genotype Effects on Alzheimer's Disease Onset and Epidemiology. *Journal of Molecular Neuroscience* 2004. 23, (3): 157-65.
[33] Ibid. 235.
[34] Blacker D. New insights into genetic aspects of Alzheimer's disease. *Postgraduate Medicine* 2000. 108, (5): 119-29. At 120.
[35] Farrer L, et al. Effects of Age, Sex, and Ethnicity on the Association Between Apolipoprotein E Genotype and Alzheimer Disease: A Meta-analysis. *JAMA* 1997. 278, (16): 1349-56.
Bird TD. Genetic Aspects of Alzheimer Disease. *Genetics in Medicine* 2008. 10, (4): 231-39. At 234.
[36] Bertram L, Tanzi RE. Alzheimer's disease: one disorder, too many genes? *Human Molecular Genetics* 2004. 13, (Review Issue 1): R135-R41.
[37] Ibid.
[38] Beecham GW et al. Op. cit.

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Athena Diagnostics has exclusive licenses to three APOE patents, all of which were granted to Duke University: U.S. 5508167, U.S. 5716828, and U.S. 6027896. The first and third patents have methods claims and the second claims a testing kit. The methods claims are based on APOE genotype (both direct and indirect determinations) and "observation" of AD risk. These may be claims of the type that the October 2008 decision of the Court of Appeals for the Federal Circuit (CAFC) *In re Bilski* cast into doubt.[39] The CAFC states an invention is patent-eligible under section 101 of the patent statute if "(1) it is tied to a particular machine or apparatus, or (2) transforms a particular article into a different state or thing."[40] Duke's patents have not been challenged under this standard.

According to Dr. Allen Roses, first inventor on the patents, the patents were sought because of well known chicanery in publication and reviewing in academic AD research at the time. The gene hunts for PSEN1, PSEN2, and APP were characterized by competitive races and nasty controversies, including conflicting claims of scientific priority. [41] Dr. Roses' solution was to file a patent application for APOE screening to establish a documentary record. The Duke APOE patents were exclusively licensed to ensure that the genotyping was only done "for physicians who confirmed a finding of dementia… [and] we felt that we could monitor the activity better with one license."[42] Because APOE is neither necessary nor sufficient to diagnose AD, Dr. Roses indicated the intention was to use the patent license from Duke to ensure APOE testing would not be used as a presymptomatic screening test; it could only be used for patients already clinically diagnosed with dementia.

We have not been able to confirm these licensing terms, although we submitted questions to both Duke's Office of Licensing and Ventures and to Athena Diagnostics.[43] An October 2008 report in *Nature* corroborates the cessation of Smart Genetics risk-assessment testing, and attributes it to licensing terms between Duke and Athena, although the licensing terms between Duke and Athena are not public.[44] Athena Diagnostics has sent several cease-and-desist letters to laboratories offering APOE testing, including one to the University of Pennsylvania to stop APOE testing (Appendix 1).[45]

Athena also licensed two patents for the presenilin genes. U.S. 5840540 covers the PSEN2 gene and mutations and U.S. 6194153 includes methods claims for PSEN1. These are two patents in a series of

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[39] *In Re Bilski*, F.3d (Fed. Cir. 2008)(*en banc*).
[40] Ibid.
[41] Interview with Dr. Allen Roses, July 5, 2007. In races for other Alzheimer genes, there were allegations of papers in review being held up while reviewers geared up to claim contemporary discovery, disputes over agreements to share or not to share data and materials, use of family pedigrees and clinical materials without permission, withholding such permission arbitrarily for competitive purposes, and other shenanigans. These are recounted, in somewhat muted form, in two books: Pollen D, *Hanah's Heirs: The Quest for the Genetic Origins of Alzheimer's Disease* (New York: Oxford University Press, 1993). The race is also recounted in Tanzi RE, Parson AB, *Decoding Darkness: The Search for the Genetic Causes of Alzheimer's Disease* (Cambridge: Perseus, 2000). According to Roses, the first APP717 mutation reported in *Nature* in 1991 used two families, the larger of which was provided by the Roses Laboratory, but the patenting of the discovery and the submitted publication did not acknowledge this; similarly, the Roses Laboratory provided approximately one-fourth of the patients for discovery of the PSEN1 locus, but was excluded from authorship of the publication.
[42] Email from Dr. Roses, received July 24, 2007.
[43] In an email from Robert Cook-Deegan to Rose Ritts, director of Duke's Office of Licensing and Ventures, on 10 February 2008 (repeated 18 October 2008), ten questions were posed, with an invitation to share the questions with Athena Diagnostics, the Duke licensee. The text of the email is in Appendix 5. Dr. Michael Henry of Athena Diagnostics has had verbal opportunities to answer the same questions but has not done so as of November 1, 2008.
[44] Hayden EC. Alzheimer's Tests Under Fire. *Nature* 2008. 455: 1155. "The test was never intended to be used for wholesale screening of non-cognitively impaired individuals,' adds Alan Herosian, director of corporate alliances for Duke University. He says he has contacted Athena many times in recent months to press this point. Michael Henry, Athena's vice-president of business development, wouldn't comment on whether the company agreed with this interpretation of its licence. But Smart Genetics is no longer taking new orders for Alzheimer's Mirror."
[45] Leonard D. Presentation to Secretary's Advisory Committee on Genetics, Health, and Society (2006). See http://oba.od.nih.gov/oba/SACGHS/meetings/June2006/Leonard3.pdf [accessed January 14, 2009].

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five on PSEN1 and PSEN2, four of which were assigned to the Hospital for Sick Children (Toronto) and the University of Toronto. They include U.S. 5986054 (covering the proteins of PSEN1), U.S. 6194153 (which Athena licensed), U.S. 6117978 (covering the proteins of PSEN2), and U.S. 6485911 (covering the methods of PSEN2). The remaining patent is U.S. 5840540, which Athena also licensed. It was assigned only to the Hospital for Sick Children. What is noteworthy here is that Athena only licensed two of the patents and that the patents are two different types of patents. Athena exclusively licensed the gene (sequence) patent for PSEN2 and the methods patent for PSEN1. The Toronto group, under lead inventor-scientist Peter St. George-Hyslop, has another patent that appears to cover the PSEN1 sequence, called the Alzheimer's Related Membrane Protein in their patent (U.S. 6531586), but this does not appear on Athena's list of exclusively licensed patents.[46]

Another patent, U.S. 6248555, was assigned to the General Hospital Corporation (Massachusetts General Hospital's holding trust for patents) in Boston. This patent covers a mutant PSEN1 gene. Athena did not license it. Instead, another pharmaceutical licensing partner originally paid for its prosecution. When the licensing partner's interest terminated, Massachusetts General Hospital (MGH) abandoned the patent, allowing it to enter the public domain.[47] MGH did so because at that point, the patent had less than half its life left and thus had very limited licensing potential and no immediate licensee options. MGH chose to conserve their patent resources and concentrate efforts on newer technologies.

Finally, an April 2008 search of patents found 355 US patents with claims mentioning an Alzheimer's-specific term.[48] Many of these are clearly for research methods, transgenic animal models, and other purposes, and do not bear directly on genetic testing. A few, however, are of clear interest. Perlegen, for example, has a patent application for "Genetic Basis of Alzheimer's Disease and Diagnosis and Treatment Thereof" that claims a collection of polymorphic sites (US 2006/0228728 A1/WO06083854A2). Its initial claim is for an AD genotype profile, which includes APOE and APP along with many other loci associated with AD risk. Even though the patent application may not be granted, it indicates that multiplex testing for AD is being commercially pursued and is the subject of patent applications.

International Patent Landscape

For APOE, a patent application assigned to Duke University was filed with the World Intellectual Property Organization (WIPO), WO/1994/009155: Methods of Detecting Alzheimer's Disease. This application lists over 60 countries, but appears to have lapsed, been abandoned or rejected in most nations. There are patents in New Zealand, Canada, Germany, and UK. The US patents claim increased risk assessment in individuals, while the WIPO application claims "a method of diagnosing or prognosing Alzheimer's disease in a subject, wherein the presence of an apolipoprotein E type 4 (ApoE4) isoform indicates said subject is afflicted with Alzheimer's disease or at risk of developing Alzheimer's disease."[49] The Canadian Intellectual Property Office (CIPO) issued patent number CA 2142300 in August 2005, 12 years after the application was filed.[50]

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[46] *Test Catalog*. See http://www.athenadiagnostics.com/content/test-catalog/ [accessed November 14, 2008].
[47] Email from Dr. Colm Lawler, Senior Licensing Associate, MGH, received July 31, 2007.
[48] On April 13, 2008, Robert Cook-Deegan performed a search for patents granted with "presenilin or PSEN1 or PSEN2 or Alzheimer or 'amyloid precursor'" in the claims. That search returned 355 granted US patents. The same text terms returned 5,172 patents and applications when the search was broadened to all fields, all jurisdictions in the Delphion database, and to both patents and applications.
[49] WIPO Patent WO/1994/009155, claim 1. Gathered from WIPO online database.
[50] From CIPO online database. See http://patents.ic.gc.ca/cipo/cpd/en/introduction.html [accessed December 10, 2008].

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Three patent applications for the presenilin genes were filed with the World Intellectual Property Organization (WIPO): WO/1996/034099, WO/1997/027296, and WO/1998/001549. The first two were assigned to both the Hospital for Sick Children (HSC) and the University of Toronto, while the last patent was assigned only to the University. Four patents were granted in Canada. The first, CA 2200794, was assigned only to the University but the remaining three – CA 2219214, CA 2244412, CA 2259618 – were assigned to both HSC and the University of Toronto.

Genetic Tests

In the United States, AD testing is provided almost exclusively by Athena Diagnostics, which tests for LOAD using APOE, as well as EOAD using PSEN1, PSEN2 and APP genes. Athena has offered PSEN1 testing based on sequence analysis since 1997. The PSEN1 genotype test is priced at $1,675.[51] Prices for APP and PSEN2 are not public.[52]

Using targeted mutation analysis, Athena offers APOE testing for $475. The Duke license to Athena gives worldwide exclusive rights for the Alzheimer's ApoE patents.[53] Within the past year, the Saint Louis University Health Science Center has offered APOE testing for cardiovascular purposes for $365. As of June 2007, some parties expressed interest, but none pursued testing.[54] Because the indication is for cardiovascular risks and not AD, this use does not infringe Athena's patents (recall that Duke could not patent the DNA sequence, only the association with AD). Genotyping for cardiovascular risk thus does not infringe the Duke patents licensed to Athena Diagnostics. Several knowledgeable clinicians indicated in interviews and emails that APOE genotyping can be obtained through laboratories other than Athena, even when it is being used to assess AD risk.

In Canada, McGill University Health Center and Sunnybrook Molecular Genetics Laboratory both offer APOE testing for AD. McGill charges $100 (US dollars) and Sunnybrook $120 (Canadian dollars).[55] McGill has offered the test since 1993 by physician referral only, as the individual needs to exhibit realistic pre-test probability of having the disease. Sunnybrook also only offers testing for individuals with documented cases of AD.

Smart Genetics announced on February 7, 2008, that it entered an agreement with Athena Diagnostics to offer direct-to-consumer genetic testing for APOE.[56] Part of the service, called "Alzheimer's Mirror," included educational materials, a saliva sampling kit, a post-test phone session with a genetic counselor, and ongoing support for managing test results. Initially priced at $399 and later dropped to $249, the test incorporated data on ethnicity, gender, family history, and APOE genotype to assess an individual's AD risk. The testing was performed at a CLIA-certified laboratory.[57] While not claiming to predict with certainty whether or not one would develop AD, it was the only direct-to-consumer AD genetic test that included genetic counseling and further support for users. As of October 2008, the Alzheimer's Mirror

[51] Phone interview with Athena Diagnostics Customer Service Representative, June 19, 2007.
[52] In phone interviews in May 2008 with Duke research assistant Christopher Heaney, various Athena employees declined to provide test price information.
[53] Email from Rose Ritts, Director, Duke Office of Licensing and Ventures, February 1, 2008, to Robert Cook-Deegan.
[54] Phone interview with St. Louis University Health Science Center representative, June 19, 2007.
[55] Phone interview with McGill University Health Center, June 19, 2007.
Phone interview with Sunnybrook Molecular Genetics Laboratory, November 19, 2008.
[56] *Smart Genetics Announces Plans to Launch New Alzheimer's Risk Assessment Service*. See http://www.smartgenetics.com/index.php/News/Latest/alzm-press-release.html [accessed November 14, 2008].
[57] *Smart Genetics Launches New Alzheimer's Risk Assessment Service For Customers*. See http://www.smartgenetics.com/news/press/sg-alzmirror-launch.html [accessed November 14, 2008].

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website was still open, but the company apparently ceased operations early that month, and the website was unavailable by January 2009.[58]
For $280, Graceful Earth, Inc., an online health alternatives website, promises "a genetic test…to accurately evaluate your risk for Alzheimer's Disease and Atherosclerosis."[59] This is a direct-to-consumer test that does not require physician approval. Consumers send Graceful Earth a saliva sample. Genetic counseling is not listed as a service on the company's website. There is no indication of a license from Duke or a sublicense from Athena Diagnostics on the Graceful Earth website.

Insurance Coverage and Reimbursement

In general, private insurers deem genetic testing as medically necessary when the following conditions are met: (1) family history shows a high likelihood of inherited AD risk; (2) sensitivity of the test is known; (3) the results have direct impact on treatment for the patient; (4) the diagnosis would be unclear without testing; and (5) in some cases, if pre- and post-test counseling is provided.[60] In the case of AD, the largest roadblocks to insurance coverage occur with the issues of direct impact on treatment (since AD is incurable). For late-onset AD (LOAD), APOE genotyping has an unclear value for diagnosis. Insurance coverage would presumably increase if APOE genotyping became important in deciding among drug or other treatment choices. The cost of genotyping would then be offset by avoiding the use of drugs or treatments that would not benefit people with particular genotypes.[61]

While approximately a dozen insurers have policies on testing for genetic markers of familial AD, none of the policies formally and explicitly covers the test.[62] BlueCross/BlueShield considers genetic testing to

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[58] Smart Genetics, *Alzheimer's Mirror*. See http://www.alzmirror.com/order-your-test.php [accessed October 18, 2008]. As of October 18, 2008, the final webpage for ordering a test reported: "We're sorry, but due to high demand for Alzheimer's Mirror we are currently unable to process new orders. To be added to our waiting list and notified as we become able to process new orders, please fill out the form below." The 6 October "Eye on DNA" and the Philadelphia Business Journal both reported that Smart Genetics closed its doors (Smart genetics shuts its doors. *Eye on DNA*. See http://www.eyeondna.com/2008/10/06/smart-genetics-shuts-its-doors/ [accessed November 14, 2008]. Genetic testers Smart Genetics closes. *Philadelphia Business Journal*. See http://www.bizjournals.com/philadelphia/stories/2008/09/29/daily42.html [accessed November 14, 2008]. By 19 January 2009, the website was no longer operating.
[59] Graceful Earth APOE genotyping service available at http://www.gracefulearth.com/index.asp?PageAction=VIEWPROD&ProdID=3&HS=1 [accessed January 19, 2009].
[60] Schoonmaker M. Presentation to Secretary's Advisory Committee on Genetics, Health, and Society (2004). See http://oba.od.nih.gov/oba/sacghs/meetings/March2004/FullDay030104.pdf [accessed January 16, 2009], at 81.
[61] The possibility of using APOE as a pharmacogenomic test is suggested by some developments in AD drug development:
Risner M, Saunders A, Altman J, Ormandy G, Craft S, Foley I, Zvartau-Hind M, Hosford D, Roses AD, Rosiglitazone in Alzheimer's Disease Study Group. Efficacy of rosiglitazone in a genetically defined population with mild-to-moderate Alzheimer's disease. *Pharmacogenomics Journal* 2006. 6, (4): 9.
Roses AD, AM S, Y H, J S, KH W, RW M. Complex disease-associated pharmacogenetics: drug efficacy, drug safety, and confirmation of a pathogenetic hypothesis (Alzheimer's disease). *The Pharmacogenomics Journal* 2007. 7: 10-28.
Roses AD. Commentary on 'A roadmap for the prevention of dementia: The inaugural Leon Thal Symposium meeting report.' An impending prevention clinical trial for Alzheimer's disease: Roadmaps and realities. *Alzheimer's and Dementia* 2008. 4: 3.
Risner et al. reported in 2005 that rosiglitazone appeared effective in AD patients who lacked an ε4 allele in a 24 week monotherapy clinical trial involving 511 patients. These data were reviewed with the FDA at a Voluntary Genomic Data Submission in December 2005 and formed the basis for a 48 week Phase III program including a second monotherapy trial and two adjuvant therapy trials. Two of these clinical trials with thousands of patients conclude in 4q08. Notable in the Phase III clinical trial designs is the role of APOE testing to test and determine the dose for patients without an ε4 allele [2 mg] and with an ε4 allele [4-8 mg]. If these Phase III trials are positive and approved, than APOE testing may be necessary to determine proper dose of therapy, not as a diagnostic for AD, but as a prognostic for effective treatment. The 2 mg dose is almost homeopathic with a drug experience of 8 mg in more than 1 million people. As such, it is anticipated that the drug label would contain the relevant pharmacogenetic information, and APOE genotypying would be linked to therapy and therefore much more likely to become a standard of care for those considering use of this drug. This also has relevance for potential prevention study designs which would include normal individuals at genotype-specific ages of increased probability of becoming symptomatic and, portentially APOE would thus become part of an intervention to delay age of onset.
[62] Schoonmaker M. Op. cit. at 82.

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be investigational.[63] Aetna also does not distinguish between EOAD and LOAD genetic testing. It concludes that all genetic testing for AD is experimental and investigational because the tests have not been shown to improve clinical outcomes of AD.[64] In 2007 Kaiser Permanente stated that it would cover genetic testing if a doctor deemed it medically necessary. [65] As of November 2008, the company website says, "Most experts do not consider ApoE-4 testing a necessary or useful part of evaluating a person with suspected Alzheimer's disease."[66] CIGNA HealthCare currently does not cover APOE genotyping because it is considered experimental, investigational, or unproven.[67] Alzheimer's Mirror was not covered by insurance and, according to Smart Genetics, was priced for out-of-pocket payment.[68]

In summary, testing for the rare early onset familial forms is sufficiently rare that it appears to be usually handled case by case; testing for APOE has not apparently become a standard of care with regular coverage and reimbursement under health plans. If APOE genotyping predicted response to drugs or other treatments, then its use might substantially increase, it would become incorporated into clinical standards, and coverage and reimbursement would become routine.

Current Genetic Testing Guidelines

EOAD

A 1998 consensus statement, based on work from Stanford University, states, "Predictive or diagnostic genetic testing for highly penetrant mutations (such as APP, PS1 or PS2 mutations) may be appropriate for adults from families with a clear autosomal dominant pattern of inheritance, particularly those with a family history of early onset of symptoms. Testing is an option that should be discussed, and that could reasonably be accepted or declined."[69] Tests must be ordered by a physician.

LOAD

Testing is much more controversial for LOAD because of its inconclusive nature. Originally, Athena marketed the APOE testing as a predictor of AD but then backed away from it when several professional societies judged such testing as inappropriate. All scientific and governing bodies that have reviewed the matter advise against APOE genotyping as a predictive or screening test, especially for asymptomatic

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[63] *BlueCross BlueShield Plans Comprising the Regence Group.* (Approved December 18, 2007, effective January 1, 2008.) See http://www.regence.com/trgmedpol/lab/lab21.html [accessed November 14, 2008].
BlueCross BlueShield of Rhode Island. (Last updated September 2, 2008, effective June 15, 2008). See https://www.bcbsri.com/BCBSRIWeb/plansandservices/services/medical_policies/GeneticTesting.jsp [accessed November 5, 2008].
[64] *Clinical Policy Bulletin: Alzheimer's Disease: Diagnosis, Number: 0349.* (Last reviewed May 23, 2008, effective September 13, 1999.) See http://www.aetna.com/cpb/medical/data/300_399/0349.html [accessed November 14, 2008].
[65] Phone interview with Kaiser Permanente Customer Service representative, July 12, 2007.
[66] *Apolipoprotein E-4 Genetic (DNA) Test*. See https://members.kaiserpermanente.org/kpweb/healthency.do?hwid=hw135696&sectionId=hw135696-sec&contextId=hw136623 [accessed November 14, 2008].
[67] *CIGNA HealthCare Coverage Position, Coverage Position Number: 0392.* (Revised date August 15, 2008, effective date July 15, 2005). See http://www.cigna.com/customer_care/healthcare_professional/coverage_positions/medical/mm_0392_coveragepositioncriteria_genetic_testing_alzheimers.pdf [accessed November 14, 2008].
[68] *Frequently Asked Questions for Alzheimer's Mirror.* See http://www.alzmirror.com/alzheimers-common-questions.php#12 [accessed November 14, 2008].
[69] McConnell L, Koenig B, Greely H, Raffin T, Alzheimer Disease Working Group of the Stanford Program in Genomics, Ethics & Society,. Genetic testing and Alzheimer disease: Has the time come? *Nature Medicine* 1998. 4, (7): 757-59.

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individuals.[70] These groups include the American College of Medical Genetics/American Society of Human Genetics Working Group, the United Kingdom Alzheimer's Disease Genetics Consortium, the Medical and Scientific Advisory Committee of Alzheimer's Disease International, the National Institute on Aging and the Alzheimer's Disease and Related Disorders Association.[71] A 2008 literature review stated, "There is general agreement that *APOE* testing has limited value [when] used for predictive testing for AD in asymptomatic persons."[72]

Although APOE genotyping can provide an increase in diagnostic confidence, diagnostic accuracy with current methods can already exceed 90%. Therefore, APOE is used as an adjunct diagnostic test for patients already presenting with symptoms of dementia. One study of LOAD diagnosis pooled pathological confirmation data from more than 2,500 patients from 26 Alzheimer's research centers and concluded that "APOE genotyping does not provide sufficient sensitivity or specificity to be used alone as a diagnostic test, but when used in combination with clinical criteria it improves the specificity of diagnosis" to greater than 97%.[73] This study is a decade old is still one of the largest and most elaborate studies to date.

A series of studies of disclosing APOE genotype to relatives of those with AD has been conducted in a multi-center clinical research consortium based at Boston University (BU).[74] The Risk EValuation and Education for ALzheimer's disease (REVEAL) study began in 2000 at BU, Case Western Reserve University, and Cornell University as a randomized trial of disclosing genotype and risk versus standard counseling and risk evaluation *without* genotype disclosure. The major paper reporting results from REVEAL I has been accepted for publication at the *New England Journal of Medicine*, but is not yet available. REVEAL II expanded to include Howard University, and oversampled African Americans who also received counseling based on ethnicity-specific risk curves. The protocol for disclosure was abbreviated from REVEAL I. REVEAL III is ongoing, with the addition of University of Michigan (replacing Cornell/Weill Medical College) and a further streamlining of protocol and the inclusion of cardiovascular risk assessment. REVEAL did not study *diagnostic* use of APOE testing, but rather *disclosure of risk* information to relatives of those affected with AD. It did, however, extensively use APOE genotyping. Athena Diagnostics performed the tests for the REVEAL trials at a deep discount.

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[70] Post SG, Whitehouse PJ, Binstock RH, Bird TD, Eckert SK, Farrer LA, Fleck LM, Gaines AD, Juengst ET, Karlinsky H, Miles S, Murray TH, Quaid KA, Relkin NR, Roses AD, St George-Hyslop PH, Sachs GA, Steinbock B, Truschke EF, Zinn AB. The clinical introduction of genetic testing for Alzheimer disease. An ethical perspective. *JAMA* 1997. 277, (10): 832-6.

[71] American College of Medical Genetics/American Society of Human Genetics Working Group on ApoE and Alzheimer disease. Statement on Use of Apolipopritein E Testing for Alzheimer Disease Ibid.1995. 274, (20): 1627-29.
Lovestone S. The Genetics of Alzheimer's Disease—New Opportunities and New Challenges *International Journal of Geriatic Psychiatry* 1995. 10: 1-7.
Brodaty H, Conneally M, Gauthier S, Jennings C, Lennox A, Lovestone S. Consensus statement on predictive testing for Alzheimer disease. *Alzheimer disease and associated disorders* 1995. 9, (4): 182 - 87.
Relkin N, Kwon Y, Tsai J, Gandy S. The National Institute on Aging/Alzheimer's Association recommendations on the application of apolipoprotein E genotyping to Alzheimer's disease. *Annals of the New York Academy of Sciences* 1996. 802: 149-76.
Post SG, Whitehouse PJ, Binstock RH, Bird TD, Eckert SK, Farrer LA, Fleck LM, Gaines AD, Juengst ET, Karlinsky H, Miles S, Murray TH, Quaid KA, Relkin NR, Roses AD, St George-Hyslop PH, Sachs GA, Steinbock B, Truschke EF, Zinn AB. The clinical introduction of genetic testing for Alzheimer disease. An ethical perspective. *JAMA* 1997. 277, (10): 832-6.
McConnell L, Koenig B, Greely H, Raffin T, Alzheimer Disease Working Group of the Stanford Program in Genomics, Ethics & Society. Genetic testing and Alzheimer disease: Has the time come? *Nature Medicine* 1998. 4, (7): 757-59.

[72] Bird TD. Genetic Aspects of Alzheimer Disease. *Genetics in Medicine* 2008. 10, (4): 231-39. At 235.

[73] Mayeux R, Saunders A, Shea S, Mirra S, Evans D, Roses A, Hyman B, Crain B, Tang M-X, Phelps CH for the ADCenters Consortium on Apolipoprotein E and AD. Utility of the Apolipoprotein E Genotype in the Diagnoisis of Alzheimer's Disease. *New England Journal of Medicine* 1998. 338: 506-11.

[74] Several members of the original REVEAL team advised Smart Genetics. Robert Green, PI of the overall REVEAL study, is an unpaid consultant for several "personal genomics" firms and also for Smart Genetics.

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REVEAL is the largest clinical study of APOE genotyping, and as its results are reported, they will likely influence clinical use.

Non-genetic Screening and Diagnosis Options

Since AD can appear in many ways, it is important that individuals, friends, family members, and family physicians be watchful for changes in an individual's symptoms. A symptom checklist is provided in Appendix 1. Appendix 2 contains criteria for diagnosis of Alzheimer's type dementia. Appendix 3 contains an algorithm for dementia evaluation and diagnosis.

Clinical recognition of progressive memory decline is usually a first step in diagnosing dementia. A physical examination can help determine the specific cause of dementia, for example, those caused by vascular disease or Lewy body disease (although these often occur in combination with AD).[75] Physical examination should include evaluation of aphasia (speech), apraxia (motor memory), agnosia (sensory recognition), and executive functioning (complex behavior sequencing). Laboratory tests may be used to rule out other disorders like hypothyroidism that can cause symptoms of dementia.[76]

EOAD

While not diagnostic, analysis of cerebrospinal fluid for the 42 amino acid form of β-amyloid may be suggestive of early AD.[77] (Tau levels are also measured. This is relevant to all AD, not just early onset.)

Role of Genetic Testing

As noted above, with the exception of EOAD in descendants of affected individuals in high-risk, early-onset families, genetic testing for AD is not recommended at this time. Even for the small percentage of cases of EOAD, detection does not lead to reversal of the disease since there is no known cure for any form of AD. However, diagnosis can aid in increasing a patient's quality of life and facilitating planning for life care and financial needs. In addition, a positive genetic test can end the quest for a specific diagnosis. There is some indication that APOE ε4 is an indicator of poor response, especially in women, to acetylcholinesterase treatments, which has obvious implications for drug prescriptions.[78]

Life Management

Diagnosis, especially in the earlier stages of AD, allows patients to make informed decisions about long-term finances, nursing care options, living wills, etc. Non-medical treatments to improve quality of life such as support groups and increased exposure to music and art can help substantially on the individual level.

"Personalized genomics" and AD testing

Patents and intellectual property concerns could influence the direct-to-consumer "personal genomics" services that are springing up, although we have limited specific information about this. Two examples of how patents might emerge as important can help illustrate the possible future complexities: (1) patents on multiplex genetic testing (or "genomic profiling"), and (2) enforcement of existing patents against

[75] Santacruz KS, Swagerty D. Early Diagnosis of Dementia. *American Family Physician* 2001. 63, (4): 703-13.
[76] Ibid.
[77] Ibid.
[78] Liddell MB, Lovestone S, Owen MJ. Genetic risk of Azlehimer's disease: advising relatives. *British Journal of Psychiatry* 2001. (178): 7-11.

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multiplex testing. The Perlegen patent application noted above (US 2006/0228728 A1/WO060838354A2) indicates that multi-locus genetic testing is being contemplated commercially. It is also possible that existing patents on genes, mutations, and methods pertinent to genetic tests of many DNA variants associated with AD could be a future legal battleground, if new uses are found to infringe such patents (or if those wanting to use new methods choose to challenge the validity of claims in existing patents).

It is clear that some risk information about Alzheimer's disease is being disclosed to at least some of those who use "personal genomics" testing services. The April 14, 2008, feature story in the *Los Angeles Times* opens with the author's receipt of APOE risk information about AD from Navigenics in the service that became available that week.[79] The test was based on a DNA base change linked to the APOE ε4 allele.[80] We have asked both Duke and Athena about sublicenses for risk assessment consumer testing but have received no reply. Navigenics has a page on its website with its "Gene Patent Policy," stating its willingness to license patents, with a formula for specifying royalties.[81] If there were a license, then presumably Athena and Duke would receive a royalty stream. If there were no such license, then the Duke patents might be enforced against the testing firms, which would either lead to settlement or litigation. Athena might choose not to enforce its patents against personalized genomics firms, however, if it judged that personal genomics services would drive business to their AD testing service for confirmation in a CLIA-certified laboratory. It is also unclear whether multiplex testing along the lines implied by the Perlegen patent application would require a license for the AD-associated genes and mutations covered by patents.

One interesting sidelight on the personal genomics business models is AD risk assessment by deCODEme. The Duke patent was licensed to Athena with worldwide exclusive rights, but Duke did not secure patent rights in Iceland. DeCODE is therefore not infringing the patent by carrying out the tests there, and courts would have to decide if importation of ***information*** (test results) back to the United States would constitute infringement of patent claims.

Lessons Learned

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[79] Gosline A, "Genome Scans Go Deep into Your DNA," *Los Angeles Times* April 14 2008.

[80] The wording of the relevant claims of the Duke patents is highly convoluted and its interpretation would require legal expertise and might entail disagreement that would be settled definitively only if litigated to completion.

[81] Navigenics, Inc. *Gene Patent Policy*. See http://www.navigenics.com/policies/GenePatents/ [accessed June 6, 2008]. A crucial paragraph in that policy explains:

> "Because our service uses multiple SNPs to assess your genetic risk for a variety of conditions, it requires a new kind of licensing approach for gene patents. For example, if we obtain licenses from third parties to 10 patents, each covering the use of one SNP included in our service, and each subject to a royalty of between 1 percent and 5 percent of our net sales of the service, we would be required to pay between 10 percent and 50 percent of our net sales revenue — just for gene patent licenses! Now consider that the whole genome scanning platform currently utilized in the Navigenics Health Compass service analyzes approximately 900,000 SNPs, and that for certain health conditions included in our service we look at more than 10 SNPs. Also note that this example does not include any up-front or milestone fees or annual minimum royalties, which make the traditional gene patent licensing approach even more untenable for this type of service."

Their royalty model is specified as:

> "We have developed, with input from third parties, a universal royalty model for licensing gene patents for services such as the Navigenics Health Compass. In this model, royalties payable to a hypothetical Party X for a license to patents covering one or more SNPs used by the service to assess risk for hypothetical Condition Y would be calculated as follows:

$$5\% \text{ of Net Sales} \times \frac{\left(\frac{\#\text{ licensed SNPs for Condition Y}}{\text{total }\#\text{ SNPs for Condition Y}}\right)}{\#\text{ conditions in service}}$$ "

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EOAD is important in those families at risk but such families are rare, and thus the market for such testing is small. During the period when it was not clear whether testing for PSEN2 and APP were even being offered, families faced an access problem, but not one specifically attributable to patent status. Rather, the limitation was absence of a CLIA-approved testing service for genetic testing. We are not aware of enforcement actions for EOAD testing.

The most recent developments in late-onset AD genetic testing are its use in those with mild cognitive impairment and the new availability of direct-to-consumer testing. APOE testing has been considered for use in clinical trials that involve those with mild cognitive impairment, as a way to identify those most at risk of progressing to dementia. APOE genotype is also available direct-to-consumer through some genetic testing services and, as noted, using indirect markers of APOE status, through some "personal genomics" services.

Basic Research

On one hand, an argument can be made that patents were part of the mix of motivations that spurred innovation in Alzheimer's research. Two books, Daniel Pollen's *Hannah's Heirs* and Rudolph E. Tanzi's *Decoding Darkness,* document the hyper-competitive races to trace the genetic origins of Alzheimer's Disease. Some of the major competitors in these races found their way to the patent office with claims covering EOAD, transgenic models of AD, and other inventions related to the research.[82] From various accounts, there was intense animosity among the different research teams, and competition to discover and publish findings motivated the speed of AD research.[83] Both publications and patents were pursued by the various competing laboratories. At least in the initial period of discovery, the patenting landscape encouraged research, or at least did not dramatically hinder it. Dr. Tanzi expressed concern about Athena's patent control of the A-beta protein patents in connection with AD.[84]

Most of the researchers we interviewed expressed ambivalence about patenting, and none attributed the intensity of the races to patent priority. Rather, they stated that the races were driven by wanting priority of scientific discovery, prestige, scientific credit, and the ability to secure funding for additional research based on scientific achievement. If patents added "the fuel of interest to the fire of genius," in Abraham Lincoln's famous phrase, it was here at best a tiny pile of kindling at the outer margin of a large conflagration.

Having not found patents to be a significant impediment to research on AD, are patent benefits any clearer? Here again, it is difficult to argue that patents added much fuel to a fire that was already raging to hypercompetition. Indeed, Dr. Roses corrected us in the interview when we asked if one reason he sought a patent was to verify priority of his discovery associating APOE ε4 with elevated risk of AD. He said it was not ***a*** reason, but it was the ***only*** reason he sought a patent.[85] According to those who were in the race, research would not have slowed without a patent incentive.

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[82] Inventors on various patents include Dr. Peter St. George-Hyslop of the Toronto group, Dr. Tanzi of Massachusetts General, Drs. Thomas Bird and Jerry Schellenberg of the University of Washington; Dr. Christine van Broekhoven (then of Antwerp; US 5525714 claiming an APP mutation), Dr. John Hardy (then of Imperial College, London; US 5877015, another APP mutation), and Dr. Allen Roses of Duke University concentrated on APOE for LOAD, as well as co-inventors on their respective teams.
[83] Interview with Dr. Allen Roses, Duke University, July 26, 2007.
Phone interview with Dr. Tom Bird, University of Washington, July 26, 2007
Phone conference with Dr. Rudolph Tanzi, Massachusetts General Hospital, July 3, 2007.
Phone conference with David Galas (formerly of Darwin Molecular, currently at Battelle Memorial Institute; Dr. Galas was chief scientist at Darwin when it collaborated with Drs. Schellenberg and Bird to sequence EOAD-associated genes) July 3, 2007.
[84] Phone interview with Dr. Tanzi, July 3, 2007.
[85] Interview with Dr. Allen Roses, July 5, 2007.

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Patents did, however, provide a mechanism for academic research institutions to convey rights to Athena Diagnostics, which aggregated patent rights from disparate academic groups to become the main testing service for AD in the United States. Athena Diagnostics' business interests cover the United States, Canada and Japan, and it also does some testing for Europe. In several jurisdictions including the United States, Athena has collected rights to genetic tests for many neurological conditions, and it has a sales force that keys to neurologists and other brain disease specialists. Where Athena enforced its exclusively licensed patents against other diagnostic services, it is clear that alternative providers were reduced in number.[86] It is impossible to judge, however, whether this has had an impact on clinical access, or even whether it has affected price (with the exception of APOE testing in Canada, which is listed for considerably less than Athena's price from two providers).

The role of patents in AD testing is thus clear in the sense that it has enabled Athena Diagnostics to consolidate the testing market in the United States. Whether this is optimal for the US health system as a whole is less clear.

Development and Commercialization

Appendix 4 shows a pricing chart of all available AD testing in the U.S. and Canada. With the exception of preimplantation genetic diagnosis, Athena Diagnostics has been the only company offering APOE and PSEN1 screening since it became available, except the 8-month period when Smart Genetics operated with a sublicense. We found no indication that Graceful Earth has a license for APOE genotyping to assess AD risk, and ambiguity about APOE testing for cardiovascular disease (which would not infringe the patents) may enable some AD genetic testing for APOE without a license. Cardiovascular testing would be completely legitimate, while interpreting AD risk assessment or diagnosis from APOE genotyping would be difficult to detect. Within the past year, the Saint Louis center has offered APOE testing for cardiovascular purposes.[87]

It remains to be seen if Duke or Athena will enforce the Duke patents against Graceful Earth or personal genomics firms. Unlike academic centers to which Athena has previously sent cease-and-desist letters, Graceful Earth is not transparent about its process of AD testing, makes no mention of CLIA laboratory certification, and alongside its APOE screening also offers pet hair analysis and herbal supplements.[88] Graceful Earth is not therefore a major clinical service provider, and its direct-to-consumer model raises questions about regulation of direct-to-consumer companies, which are outside this case study's scope.[89]

Compared to prices in the Canadian centers, prices for APOE genetic testing at Athena and at the Saint Louis Center are higher. If the Canadian laboratories' prices accurately reflect production costs, then testing for APOE can be performed at a lower cost. Prices for health goods and services are lower in Canada across the board, however, so APOE testing is not an exception, but conforms to the rule.

Athena is the only available avenue for PSEN1, PSEN2, and APP testing. The $1675 price for PSEN1 is high relative to APOE genotyping, but it entails genomic sequencing, and this price is comparable to other full-sequence tests for BRCA, colon cancer genes, and spinocerebellar ataxias cited in other case

[86] Cho M, Illangasekare S, Weaver M, Leonard D, Merz J. Effects of Patents and Licenses on Provision of Clinical Genetic Testing Services. *Journal of Molecular Diagnostics* 2003. 5, (1): 3-8.
[87] Phone interview with St. Louis University Health Science Center representative, June 19, 2007.
[88] *Graceful Earth, Inc.* See http://www.gracefulearth.com/ [accessed November 14, 2008].
[89] The recent actions by the New York State and California Departments of Health to regulate direct-to-consumer genetic testing are directly relevant. Graceful Earth was not, however, among the 13 laboratories that got letters from California, and we do not know if they got a letter from New York.

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studies. The cost of this testing is out of the financial range of many patients, especially when insurers will not cover "experimental" tests. We simply cannot judge the degree to which threat of patent enforcement explains other laboratories not offering testing for the very rare families with APP, PSEN1, and PSEN2 mutations, but it is likely that patent status is just one factor among others such as set-up costs, CLIA certification, ensuring reimbursement, and building a referral network.

Marketing

AD screening in the general population is not recommended at this time. Until recently, *any* testing for either EOAD or LOAD needed to be done by physician referral, so marketing directly to consumers was a nonissue. Patents do appear to have an effect on marketing to physicians, as Athena has a sales force focused on neurologists for its AD tests, which are just a few among many genetic tests it offers for brain, muscle, endocrine, and nervous system disorders.

Patenting also affected health professional marketing indirectly, by using licensing as a tool for constraining clinical use. Dr. Roses said that a major reason Duke University decided to license exclusively to Athena was to ensure that APOE testing was done in compliance with professional standards.[90] While neither Athena nor Duke's Office of Licensing and Ventures has responded to questions about the licensing terms,[91] the end result of the exclusive patenting did ensure that testing complied with professional standards, at a time when concern was high that genetic screening for AD could cause fatalism and commercial incentives would militate to overutilization. This fear of widespread testing does not appear to have materialized, as research suggested that "consumers from our focus groups were not interested in testing that could provide neither predictive data nor a reasonably precise answer about their individual risk of developing AD at a particular age."[92] This suggests that demand would have been low in any event, but Athena's policy of requiring physician corroboration of dementia before genetic testing, as Duke University stipulated, was an additional check on testing outside professional standards.

More recently, companies like Graceful Earth, Inc. and Smart Genetics began to offer testing directly to consumers. Smart Genetics is a unique case, since the firm transiently sublicensed from Athena.[93] Athena has always been a reference lab only available to physicians.[94] Sublicensing to Smart Genetics marked a departure from this policy of ensuring that only individuals with a high likelihood of AD were tested. Both Smart Genetics and Athena received significant press and media coverage from many audiences, including *CBS-3*, *FOX-29*, *Parade* magazine, *USA Today*, and *Science*.[95] Smart Genetics relied on research published in 2005 and conducted by the REVEAL study, which found that "preliminary analyses suggest that risk assessment and genotype disclosure did not adversely affect the psychological well-being of participants."[96]

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[90] Interview with Dr. Allen Roses, July 5, 2007.
[91] Email correspondence with Michael W. Henry, VP of Business Development of Athena Diagnostics, Inc., November 20, 2007. Email correspondence with Rose Ritts and Bob Taber, Office of Licensing & Ventures, Duke University, February 10, 2008.
[92] Post SG, Whitehouse PJ, Binstock RH, Bird TD, Eckert SK, Farrer LA, Fleck LM, Gaines AD, Juengst ET, Karlinsky H, Miles S, Murray TH, Quaid KA, Relkin NR, Roses AD, St George-Hyslop PH, Sachs GA, Steinbock B, Truschke EF, Zinn AB. The clinical introduction of genetic testing for Alzheimer disease. An ethical perspective. *JAMA* 1997. 277, (10): 832-6.
[93] We have sought confirmation that terms of the Duke license precluded sublicensing for risk assessment, and those terms were brought to the attention of Athena as a result of action by Allen Roses, the first inventor on the relevant Duke patents.
[94] *About Athena Diagnostics*. See http://www.athenadiagnostics.com/content/about/ [accessed November 14, 2008].
[95] *Welcome To The Smart Genetics Press Room*. See http://www.smartgenetics.com/index.php/News/Latest/news.html [accessed November 14, 2008].
[96] J. Scott Roberts P, L. Adrienne Cupples, Norman R Relkin, Peter J. Whitehouse, and Robert C. Green,. Genetic Risk Assessment for Adult Children of People With Alzheimer's Disease: The Risk Evaluation and Education for Alzheimer's Disease (REVEAL) Study. *Journal of Geriatric Psychiatry and Neurology* 2005. 18, (4): 250-55.

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Adoption by Third-Party Payers

For AD, patents have not detectably helped or hindered the decisions by insurance companies to cover LOAD diagnosis using APOE genotype. Almost all major insurers and payers consider APOE testing experimental. In this situation, patents are irrelevant because the service is not covered as medically necessary.

One case where patents might have an impact is with EOAD. Based on its coverage policy for APP and PSEN1, CIGNA Healthcare would likely also cover PSEN2 in "Volga German" family members at risk. Other payers do not have clear policies. Other case studies suggest, however, that so long as prices fall in the range of other genetic tests, patent status would affect access little (and in other cases, pricing has not been clearly associated with patent status).

The main effect of patents is that it enables a sole-provider consolidation of testing, which thereby indirectly links access to coverage and reimbursement (because access is then restricted to the contracts that a sole provider has with payers). If Athena has contracts for payment, then patients would pay a co-payment rather than full cost. If not, patients would bear full costs unless Athena covers them through Athena Access (essentially free or very low cost testing) or its Patient Protection Program (with 20 percent payment up front, but no further direct charges to patients, and refunds if third-party payers later reimburse more than 80 percent). The effect of patents is to block other services from filling in if Athena's own programs do not meet patient needs, precluding alternative laboratories from testing due to fear of patent infringement liability.

Consumer Utilization

In the case of AD genetic testing, consumer utilization is complicated. Athena does not publicly report utilization rates for APOE, PSEN1, PSEN2, or APP testing.[97] Since no academic group is in a position to track those tested, this means Athena is in the best position to inform genetic epidemiology of EOAD and genetic risk of late-onset AD, but unlike Myriad Genetics for BRCA testing, it does not contribute much to the scientific or clinical literature.

The recent rise in direct-to-consumer testing and availability of personal genomics and eventually the broader use of sequencing are likely to increase the number of people who undergo testing, although it will often not be specifically about AD. As *Science* reported, APOE status was "the only genetic information that James Watson, the DNA discoverer who recently had his entire genome sequenced, kept secret."[98] Stanley Lapidus adopted this same stance for his "full genome" analysis as part of the Personal Genome Project,[99] as did Steven Pinker in his January 2009 feature in the New York Times Magazine.[100] It appears that at least for upper income white males past middle age with conspicuous public personae, APOE risk status is a special case.

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[97] Email correspondence with Michael W. Henry, VP of Business Development of Athena Diagnostics, Inc., 20 November 2007. Athena does report ApoE genotyping utilization to Duke, and presumably reports PSEN1, PSEN2 and APP testing use to the licnesors as part of its royalty agreements.

[98] Couzin J. Once Shunned, Test for Alzheimer's Risk Headed to Market. *Science* 2008. 319, (5866): 1022-33. Watson's stated purpose was to avoid learning this information himself.

[99] Lapidus SN. Interpreting the genome (video). *Technology Review* 2009 (January/February). See http://www.technologyreview.com/Video/?vid=187 [accessed January 21, 2009].

[100] Pinker S. My genome, my self. *New York Times Magazine* 2009 (January 7). See http://www.nytimes.com/2009/01/11/magazine/11Genome-t.html?_r=1&scp=1&sq=pinker&st=cse [accessed January 21, 2009].

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The extent of testing is highly unpredictable, and will likely depend in part on cost and in part on whether treatments are developed that might reasonably delay the onset of the disease. Patenting could affect access both through price and through single-provider status. And any litigation may also indirectly affect access by limiting the number of providers (but as noted, this does not necessarily imply loss of access). A single provider has strong incentives to advertise and expand market to the point of saturation. A single provider also benefits from establishing an informed network of users (both health professionals and those seeking testing) and securing payment agreements to cover testing with insurers and health plans.

Finally, increased consumer utilization may have an impact on long-term care insurance. In research to find the effect of AD on insurance-purchasing behavior, "Almost 17 percent of those who tested positive subsequently changed their long-term care insurance coverage in the year after APOE disclosure, compared with approximately 2 percent of those who tested negative and 4 percent of those who did not receive APOE disclosure."[101] If more people do decide to screen for APOE with the direct-to-consumer companies, long-term care insurance could be affected. The market may stratify according to APOE genotype (with those having an ε4 allele paying more, especially ε4/ε4 homozygotes). This effect, however, is not attributable to patents, but rather to how many people are tested and informed of their AD risk. Any patent effects would be mediated by price or access constraints.

Acknowledgements

Drs. Michael Hopkins, Allen Roses, Thomas Bird, Robert Green, and Colm Lawler all kindly reviewed this report. The work was carried out under grant P50 HG03391 from the National Human Genome Research Institute and US Department of Energy.

[101] Cathleen D. Zick , J. Scott Roberts, Robert Cook-Deegan, Robert J. Pokorski, and Robert C. Green. Genetic Testing for Alzhimer's Disease and Its Impact on Insurance Purchasing Behavior. *Health Affairs* 2005. 24, (2): 483-90.

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Appendix 1

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Appendix 2: Criteria for clinical diagnosis of Alzheimer's disease

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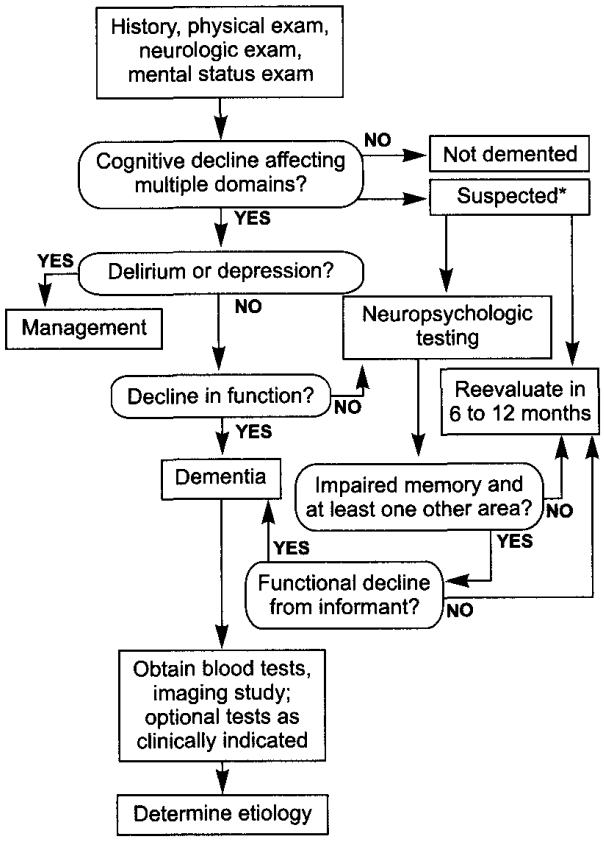
Appendix 3

FIGURE 3.1 — ALGORITHM FOR DEMENTIA EVALUATION AND DIAGNOSIS



* Worrisome history without obvious mental status deficit or impaired memory only, suggesting mild cognitive impairment (see Chapter 6, *Natural History*).

Modified from: Corey-Bloom J, et al. *Neurology*. 1995;45:211-218.

Reproduced with publisher's permission from Green, RC. *Diagnosis and Management of Alzheimer's Disease and Other Dementias*, 2nd ed. West Islip, NY: Professional Communications, 2005, 24.

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Appendix 4

Gene	Institution	Cost**	Type	Patents
APOE	Athena	$475	SISAR	5508167 5716828 6027896
	Smart Genetics*	$399 initially, then $249	SISAR	Sublicensed from Athena*
	Saint Louis University Health Science Center	$365	Targeted Mutation Analysis	
	Graceful Earth, Inc.	$280	NA	
	Sunnybrook Molecular Genetics Laboratory (Canada)	$120 (CD$)***	Targeted Mutation Analysis	
	McGill University Health Center (Canada)	$100	Targeted Mutation Analysis	
APP	Athena		Sequence Analysis	None listed
	Reproductive Genetics Institute	~$5,000	PGD	
PSEN1	Athena	$1,675	Sequence Analysis	6194153
	Genesis Genetics Institute	$2,750	PGD	
PSEN2	Athena		Sequence Analysis	5840540

*Smart Genetics ceased operations October 2008
**All prices in US $ unless otherwise noted
***Price in Canadian dollars, approximately $97 in US dollars at exchange rate of $1 Canadian per $.81 US

SISAR: Serial Invasive Signal Amplification Reaction (a method to detect short, targeted sequence variants)
PGD: Preimplantation Genetic Diagnosis

Compiled by authors.

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Appendix 5: Email sent by Dr. Robert Cook-Deegan to Rose Ritts, Director of Duke's Office of Licensing and Ventures, on 10 February 2008 (repeated 18 October 2008)

"Given the potential for confusion here, I think we should resort to formal written questions and answers, so I don't get anything wrong, and so it's all a matter of public record. The federal advisory committee may well want to follow our trail. Feel free to share with your licensee.

I have prepared a list of questions below that will be shared with the Secretary's Advisory Committee on Genetics, Health and Society (SACGHS) on the record. We will share either your reply or we will explain that we got no reply.

The Committee has a task force addressing the impact of patenting and licensing on access to clinical genetic testing, which includes ex officio members from NIH, FDA, CDC, the USPTO and other agencies. You may need to say some information is confidential. That is fine, but being as open as possible would no doubt be welcomed, since this is a federal advisory committee tasked with making recommendations about policy. The more information they have, the more informed their recommendations will be. The responses from Duke and Athena will presumably be interpreted as indicative of how open federal grantees and their licensees are in responding when a researcher requests information pertinent to licensing federally funded inventions, when such research is being carried out on behalf of a federal advisory committee.
Some questions it would be helpful for the task force to answer:

1. Does Athena Diagnostics report the number of ApoE genotyping tests it does each year? [This query was addressed. The answer was 'yes.']

2. Do those data include aggregated (anonymized) results of those tests that might be relevant to gathering data about allele frequencies in populations tested, or other data relevant to public health?

3. Will Duke or Athena share those data with the SACGHS task force?

4. Alan Roses said in his interview that one major reason for licensing exclusively to Athena Diagnostics was to ensure compliance with professional standards emerging at the time, from neurologists' professional organizations and the Stanford group, suggesting ApoE genotyping should only be done in the context of (1) research, or (2) a part of the diagnostic work-up of someone with symptoms of dementia. Was compliance with professional guidelines built into the licensing? How?

5. If so, what diligence provisions were included in the license? How does Duke monitor compliance with such terms?

6. The Duke licenses were negotiated in the mid-1990s. A 2005 National Research Council report recommended licensing of genetic diagnostics to permit verification testing, so that exclusive licensees could not block such verification. Did Duke anticipate such a possibility and include provisions in its license? In the wake of the 2005 recommendation, have Duke and Athena discussed bringing this license into agreement with this NRC recommendation?

7. Now that professional standards are relaxing to use ApoE genotyping for minimal cognitive impairment and for risk profiling without symptoms of dementia, are there mechanisms to adjust the licensing terms to accommodate those changes? Or are the terms of the of the license general enough to permit those changes without renegotiating the license?

8. Smart Genetics announced last week that it will be offering a risk profile service, with a sublicense from Athena. What arrangements has Smart Genetics made with Athena vis a vis the licensing of APOE testing to asymptomatic individuals, if this was stipulated in the Duke-Athena license (see item 4 above)?

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9. What is the posture of Athena or Smart Genetics with regard to APOE testing being offered as a stand alone test for AD risk by a company like DNADirect or as part of multi-gene panels by DTC companies such as 23andMe, deCODEme, Navigenics, SeqWright, etc.?

10. If gene panels identify risk markers that are in linkage disequilibrium with ApoE, such as in this article: <http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17474819&ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum> is that considered testing for ApoE requiring a license from Duke or sublicense from Athena?"

Dr. Michael Henry of Athena Diagnostics spoke with Dr. Cook-Deegan on February 25, 2008, and several times in October and November 2008 about other matters. Answers to these questions (except the partial answer to question 1) have not been received as of 19 January 2009.

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Impact of Gene Patents and Licensing Practices on Access to Genetic Testing for Cystic Fibrosis

Subhashini Chandrasekharan, PhD,[1] Christopher Heaney, BA, [2] Tamara James,[3] Chris Conover, PhD, [4] and Robert Cook-Deegan, MD[5]

Introduction

Approximately 30,000 Americans have cystic fibrosis (CF). It is the most common severe recessive genetic disorder among Caucasians.[6] The disease is caused by mutations in the *CFTR* gene, which encodes a transmembrane chloride ion channel. One mutation, ΔF508, causes approximately 70% of CF cases (~50% of CF patients are homozygous for this mutation) in Caucasian populations. Other mutations are far rarer. Mutation and carrier rates vary by ethnicity. *CFTR* mutations lead to excessively thick and sticky mucus and, as a result, to frequent infections in the lungs. Approximately 90% of CF patients die from obstructive lung disease.[7] As of 2006, half of all CF patients were expected to survive to 36.9 years of age.[8]

Presently there is no cure for CF. Therapies to treat the disease's symptoms include movement and clearing of mucus in the lungs, antibiotic treatment of infections, and diet and pancreatic enzyme replacement to improve nutrition.[9] Lung transplants are an option for adult and pediatric patients, although the procedure's utility for children is unclear.[10] Early detection through newborn screening can reduce CF deaths and alert parents and doctors to the need for disease management.[11] Carrier screening also has implications for reproductive decisions. Hence, the American College of Medical Genetics (ACMG) endorses carrier screening based on testing for *CFTR* mutations and newborn screening that uses DNA testing if high levels of the enzyme immunoreactive trypsinogen (IRT) are detected.[12]

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[1] Center for Public Genomics, Center for Genome Ethics, Law & Policy, Institute for Genome Sciences & Policy, Duke University
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[4] Center for Health Policy, Terry Sanford Institute of Public Policy, Duke University
[5] Center for Public Genomics, Center for Genome Ethics, Law & Policy, Institute for Genome Sciences & Policy, Duke University
[6] Cutting G. Modifier genetics: cystic fibrosis. *Annual Review of Genomics and Human Genetics* 2005. 6: 237-260.
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[8] Cystic Fibrosis Foundation. *Patient Registry 2006 Annual Report*. Bethesda, Maryland. See http://www.cff.org/UploadedFiles/research/ClinicalResearch/2006%20Patient%20Registry%20Report.pdf [accessed July 21, 2008].
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[12] American College of Medical Genetics. Cystic fibrosis population carrier screening: 2004 revision of American College of Medical Genetics mutation panel. 2004. See http://www.acmg.net/resources/policies/CF_mutation_8-2004.pdf [accessed April 15, 2007]. American College of Medical Genetics. Immunoreactive Trypsinogen (IRT Elevated). 2006. See http://www.acmg.net/resources/policies/ACT/Visio-IRT(4-17-06).pdf [accessed July 29, 2008].

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CF was chosen as a case study specifically because non-exclusive licensing practices for the gene and its mutations allow for a rough comparison to other genes that are exclusively licensed. The University of Michigan, The Hospital for Sick Children in Toronto (HSC), and Johns Hopkins University (JHU) hold patents covering *CFTR* mutations and methods for detecting them. The University of Michigan's patent portfolio includes the important ΔF508 mutation. Currently, 63 labs in the United States test the *CFTR* gene.[13] This is possible in part because the University of Michigan, HSC, and JHU license their respective patents non-exclusively.

A survey of laboratories' prices for CF genetic testing, a review of literature on CF tests' cost effectiveness, and the developing market for testing for CF provide no evidence that patents have significantly hindered access to genetic tests for CF or prevented financially cost-effective screening. Current licensing practices appear to facilitate both academic research and commercialization of products.

Background

Approximately 30,000 Americans have cystic fibrosis (CF), making it the most common severe recessive genetic disorder among Caucasians.[14] Carrier rates vary by ethnicity. According to the American College of Obstetricians and Gynecologists:

- 1/24 Ashkenazi Jews are carriers
- 1/25 Non-Hispanic Caucasians are carriers
- 1/46 Hispanic Americans are carriers
- 1/65 African Americans are carriers
- 1/94 Asian Americans are carriers[15]

The cystic fibrosis transmembrane conductance regulator (*CFTR*) gene encodes a transmembrane chloride ion channel, mutations of which result in defective movements of materials through membranes and excessively thick and sticky mucus throughout the body. CF affects multiple bodily functions including breathing, digestion and reproduction. Symptoms include chronic pulmonary disease, pancreatic exocrine insufficiency, reproductive disorders, and elevated sweat chloride levels. Because CF patients cannot adequately clear their airways of the mucus build-up associated with CF, they wheeze, cough, and suffer from repeated lung infections and other pulmonary pathologies. Approximately 90% of CF patients die because of obstructive lung disease. The thick, sticky mucus found in CF patients also accumulates in the pancreas, thus preventing digestive enzymes from reaching the small intestine and leading to poor digestion, retarded growth, and persistent diarrhea.[16] "Almost all males with CF are infertile due to congenital malformation of the reproductive tract."[17]

According to a consensus panel convened by the Cystic Fibrosis Foundation, "the diagnosis of CF should be based on the presence of one or more characteristic phenotypic features, a history of CF in a sibling, or a positive newborn screening test result plus laboratory evidence of a *CFTR* abnormality as documented by elevated sweat chloride concentration, or identification of mutations in each *CFTR* gene known to

[13] Moskowitz S et al. *CFTR-Related Disorders*. See http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=cf#cf.References [accessed July 21, 2008].
[14] Cutting G. Op. cit.
[15] American College of Obstetricians and Gynecologists. Op. cit.
[16] Cutting G. Op. cit.
Moskowitz S et al. Op. cit.
[17] Welsh et al. Op. cit. at 5121.

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cause CF or in vivo demonstration of characteristic abnormalities in ion transport across the nasal epithelium."[18]

Though few children born with cystic fibrosis in the 1950's could expect to survive to attend school, by 2006 half of all CF patients were expected to survive to 36.9 years.[19] 71% of patients are diagnosed within one year of birth; 92% of patients are diagnosed by the time they are ten years old.[20]

Presently there is no cure for CF, although research into normalizing the mutated ΔF508 *CFTR* protein product using small molecule pharmaceuticals continues. Physical therapy and medications can enhance patients' length and quality of life. Current therapies include movement and clearing of mucus in the lungs, pharmaceutical treatment of infections, and diet and pancreatic enzyme replacement to improve nutrition.[21] Lung transplants are an option (but not a cure) for adult patients with damaged lungs.[22] Lung transplants for children are performed, but their clinical utility is unclear.[23] Early detection through newborn screening can reduce deaths due to CF and alert parents and doctors to the need for disease management.[24] Carrier screening also informs prospective parents about their risks of having an affected child. Screening and diagnostic methods, including genetic tests, are discussed in more detail below.

Gene Discovery

Researchers have used a plethora of gene identification methodologies to search for and map the CF gene. The nearly forty-year hunt for the CF gene began in the 1950's. Using linkage analysis, researchers studied whether the CF gene was linked to blood groups but were unsuccessful.[25] A major difficulty in identifying the cystic fibrosis gene was the lack of cytologically detectable chromosome rearrangements or deletions. Such large-scale and DNA changes greatly facilitated the positional cloning of some other human disease genes.

In the 1980's, new technologies were applied to search for the CF gene. Researchers used RFLP's (restriction fragment length polymorphisms, which reflect sequence differences in DNA sites that can be cleaved by restriction enzymes) for linkage analysis to establish the approximate chromosomal location of genes. In 1985, Lap Chee Tsui and colleagues reported that an uncharacterized RFLP marker, DOCRI-917, was linked to the CF gene in 39 families with CF-affected children.[26] It took four years of intensive effort by many laboratories to move from this initial linkage to find the mutated gene. Wainright et al. reported a tight linkage between the CF locus and another chromosome 7 probe, pJ3.11.[27]. Ray White and colleagues independently mapped the gene to chromosome 7.[28] Lap-Chee Tsui and colleagues, using genetic linkage analysis, further localized the DOCRI-917 on human chromosome 7, but additional

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[25] Steinberg A et al. Linkage studies with cystic fibrosis of the pancreas. *American Journal of Human Genetics* 1956. 8(3): 162-76.
Steinberg A et al. Sequential test for linkage between cystic fibrosis of the pancreas and the MNS locus. *American Journal of Human Genetics* 1956. 8(3):177-89.
[26] Tsui L et al. Cystic fibrosis locus defined by a genetically linked polymorphic DNA marker. *Science* 1985. 230(4729): 1054-1057.
[27] Wainwright BJ et al. Localization of cystic fibrosis locus to human chromosome 7cen-q22. *Nature* 1985. 318: 384-5.
[28] White R et al. A closely linked genetic marker for cystic fibrosis. *Nature* 1985. 318: 382-384.

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studies were needed to determine the exact location of the gene.[29],[30] Zengerling and colleagues in 1987, used human-mouse cell hybrids to narrow the search to a small segment of chromosome 7.[31] Shortly afterward, Estivill et al. reported a potential break-through in disclosing a candidate cDNA for the CF gene,[32] but individuals with CF did not have mutations in that candidate gene. Rommens et al. closed the gap further, mapping two more probes (D78122 and D7S340) to a location between two markers known to flank the CF gene, MET and D7S38.[33] Finally, in 1989, Drs. Tsui and John Riordan and colleagues from The Hospital for Sick Children in Toronto and Dr. Francis Collins and fellow researchers, then at the University of Michigan, identified the gene encoding the cystic fibrosis transmembrane conductance regulator or *CFTR*.[34],[35],[36]

This was the first time a human disease gene had been identified solely on the basis of its chromosomal location, without biochemical clues or the availability of visible cytogenetic rearrangements to guide the search. Although the identification of markers that flanked the gene did not indicate the gene's exact location, the discovery of these markers did provide a starting point for novel DNA-cloning strategies specifically developed to locate the *CFTR* gene. These strategies included chromosome jumping from the flanking markers, cloning of DNA fragments from a defined physical region, a combination of somatic cell hybrid and molecular cloning techniques designed to isolate DNA fragments, chromosome micro-dissection and cloning, and saturation cloning of a large number of DNA markers from the 7q31 region. These techniques were pioneered in the hunt for the CF gene because it was a relatively common disease known to have a single-gene cause, and because the gene's location was approximately known.

The *CFTR* Gene

The *CFTR* gene encodes a protein that regulates the flow of chloride ions through membranes. Mutations in *CFTR* alter protein function, which in turn causes the symptoms of CF in afflicted patients. Because different mutations alter protein function in different ways and to different degrees, there are wide variations in the severity of the clinical syndrome. To date, scientists have found over 1,500 mutations in the *CFTR* gene.[37] ΔF508, a deletion of three nucleotides in DNA causes the protein to lack the amino acid phenylalanine (F) at position 508. That one mutation accounts for 70% of CF chromosomes worldwide, and 90% of CF patients in the United States. Individuals homozygous for ΔF508 (about 50% of patients) have the most severe form of cystic fibrosis.[38]

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[29] Knowlton RG et al. A polymorphic DNA marker linked to cystic fibrosis is located on chromosome 7. *Nature* 1985. 318(6044):380-2

[30] Tsui L et al. Genetic analysis of cystic fibrosis using linked DNA markers. *American Journal of Human Genetics* 1986. 39:720-728.

[31] Zengerling S et al. Mapping of DNA markers linked to the cystic fibrosis locus on the long arm of chromosome 7. *American Journal of Human Genetics* 1987. 40:228-236.

[32] Estivill X et al. A candidate for the cystic fibrosis locus isolated by selection for methylation-free islands. *Nature* 1987. 326:840-845.

[33] Rommens J et al. Identification and regional localization of DNA markers on chromosome 7 for the cloning of the cystic fibrosis gene. *American Journal of Human Genetics* 1988. 43(5):645–663.

[34] Rommens J et al. Identification of the cystic fibrosis gene: chromosome walking and jumping." *Science* 1989. 245(4922): 1059-65.

[35] Riordan JR et al. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA." *Science* 1989. 245(4922):1066 – 1073

[36] Kerem B et al. Identification of the cystic fibrosis gene: genetic analysis. *Science* 1989. 245(4922):1073–1080.

[37] Cutting G. Op. cit.
Grody W, Cutting GR, Watson MS. The cystic fibrosis mutation 'arms race': when less is more. *Genetics in Medicine* 2007. 9(11):739.

[38] Johansen H et al. Severity of cystic fibrosis in patients homozygous and heterozygous for delta F508 mutation. *Lancet* 1991. 337(8742): 631-4.
Welsh MJ et al. Op. cit.

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Differences in the frequency of various mutations among ethnic groups complicate analysis of genetic testing. The Foundation for Blood Research reports: "A different mutation [than ΔF508] is the main cause of cystic fibrosis in Ashkenazi Jews. Half of Ashkenazi Jewish carriers of cystic fibrosis have the W1282X mutation (rarely found in non-Jewish carriers), whereas less than one-third have the [ΔF508] mutation. In other populations, no single mutation accounts for a dominant proportion."[39]

Certain *CFTR* mutations are known to result in a milder clinical syndrome. Some of these spare the pancreatic involvement (and are thus called "pancreatic sufficient"), and even milder mutations may result in just isolated male infertility, due to congenital bilateral absence of the vas deferens. But the severity of lung disease is not entirely predictable on the basis of genotype. As Grody et al. note, "It has been clear since the cloning of the gene that *CFTR* is a very complex genetic element, replete with an ever-growing number of identified mutations and variants and subject to modification in its phenotypic effects by internal polymorphisms and distant gene loci. It has been a major undertaking just to characterize the molecular and functional effects of the more common mutations. When it comes to rare variants… much less is known… The potential for misattribution of effects and for false assumptions is manifest."[40] Thus, there is much to be learned that may affect how tests are licensed or conducted, making the relationship between the intellectual property and clinical data described below subject to continual revision.

Patents

Drs. Francis Collins and colleagues at The University of Michigan, and Drs. Lap-Chee Tsui, John Riordan, and colleagues at The Hospital for Sick Children (HSC) in Toronto, Canada, jointly determined the nucleotide sequence of the *CFTR* gene. Tsui, Collins, and their colleagues were the first to identify the ΔF508 mutation and to then link this mutation with symptomatic CF. According to Dr. Francis Collins, all parties including the CF Foundation and the Howard Hughes Medical Institute,[41] which partially funded their research (along with NIH), agreed that it was important to seek patent protection for the *CFTR* gene and the ΔF508 mutation because of the implications for diagnosis and potential therapies (e.g., gene therapy).[42] Dr. David Ritchie, Senior Technology Licensing Specialist at the University of Michigan's Office of Technology Transfer, recalls that there were extended discussions about whether patents should be applied for in foreign jurisdictions. However, given the possibility of commercial interest in both therapeutic and diagnostic applications, patent applications were eventually filed in the US, the European Patent Office, Japan, Australia, Ireland, and Canada just prior to publication in *Science* on September 8, 1989.[43] This family of US and foreign patent applications covered the sequence of the normal and ΔF508 mutant cDNAs, genetic testing, the normal and mutant *CFTR* proteins, and vectors and cell lines expressing the normal and mutant *CFTR* genes.

The USPTO declared a patent interference after receiving a patent application from Genzyme Corporation, with Richard Gregory as the first inventor. The Genzyme application claimed the sequence of the *CFTR* cDNA, as well as rights to the *CFTR*-containing vector, which overlapped with claims in the Michigan-HSC patent applications. Subsequently, Genzyme argued that Tsui *et al.* failed to provide a written description of the manner and process for their inventions (USPTO interferences 103,882, 103,933, and 104,228). The interference proceedings went on for ten years and were resolved in part in

[39] National Office of Public Health Genomics, CDC, and Foundation for Blood Research. *ACCE Review of CF/Prenatal: Clinical Utility*. 2002. See http://www.cdc.gov/genomics/gtesting/file/print/FBR/CFDisSet.pdf [accessed July 29, 2008 at], at 7.
[40] Grody W et al. The cystic fibrosis mutation 'arms race': when less is more. Op. cit. at 741.
[41] Dr. Francis Collins was a Howard Hughes Medical Institute investigator at the time.
[42] Phone interview with Dr. Francis Collins by Subhashini Chandrasekharan and Christopher Heaney, September 10, 2008.
[43] Priority date of patent application August 22, 1989, versus the acceptance of the manuscript "Identification of the Cystic Fibrosis Gene: Cloning and Characterization of Complementary DNA" on August 18, 1989 (Riordan JR et al. Op. cit.).

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Tsui's favor in 2002.[44] The Tsui patents covering both the wild-type *CFTR* cDNA sequence and ΔF508 mutant sequences (US 6,984,487) and the *CFTR* protein sequence (US 6,730,777) were granted. Genzyme was granted patent US 5,876,974, which covers methods for producing the *CFTR* cDNA. In 2006, Genzyme was granted US 7,118,911, which covers vectors for producing the *CFTR* cDNA (See Appendix B). Dr. Ritchie confirmed that the interference was a time consuming and expensive process. However, a licensee that was developing a CF therapeutic funded a majority of the interference costs for the University of Michigan and HSC. Importantly, one of the Tsui patent applications covering genetic testing methods for the ΔF508 mutation was not included in this interference and issued as US Patent No. 5,776,677 on July 7, 1998. Thus, licensing of this particular patent was not affected by the interference.

Licensing

The University of Michigan and HSC choose to license the '677 patent non-exclusively, with University of Michigan managing patent rights in the US and HSC managing patent rights for the rest of the world. Dr. Ritchie indicated that the decision to license non-exclusively was made primarily in keeping with NIH licensing guidelines.[45] According to Dr. Francis Collins, the CF Foundation actively participated in discussions about licensing and provided an important patient advocacy perspective. He recalls that the scientists involved in the discovery of *CFTR* had extensive discussions with technology licensing officers. These highlighted the uncertainty about the number of additional mutations that might be discovered later, the contribution of mutations to disease pathology (ΔF508 accounts for only ~70% of cases worldwide), and which technology platform would be best suited for high-sensitivity carrier detection. The Foundation and scientists were concerned that without complete knowledge of the mutation spectrum, or of future diagnostic testing platforms, an exclusive license to a single provider could impede long-term research and development of diagnostic tools. Dr. Collins stated that the decision made by the University of Michigan and HSC to license the '677 patent non-exclusively grew out of these discussions and concerns.[46] In 1992, the year before the first license for the patent was granted, the NIH's guidelines followed Part 404 of the Code of Federal Regulations, which dealt with licensing of government owned inventions and stated that exclusive licensing is only acceptable if non-exclusive licensing would impede the development of products and not be in the public's best interests.[47] Dr. Ritchie stated that current licensing practices are designed to follow the National Institutes of Health's 1999 Principles and Guidelines, which urge "wide distribution on a nonexclusive basis."[48] Licensing practices are also in accordance with three relevant guidance documents that came out later, the 2004 "Best Practices for Licensing Genomic Inventions" from the National Institutes of Health[49], the 2006 Organisation for Economic Co-Operation and Development's (OECD) "Guidelines for the Licensing of Genetic Inventions,"[50] and the March 2007 "Nine Points" statement later endorsed by the Association of University Technology Managers.[51] Dr. Ritchie shared a template of the non–exclusive license agreement

[44] USPTO Interference Nos 103,882, 103,933 and 104,228 Gregory vs. Tsui, et al. January 4, 2002.
[45] Phone interview with Dr. David Ritchie, Office of Technology Transfer and Corporate Research, University of Michigan, by Subhashini Chandrasekharan and Christopher Heaney, July 3, 2008.
[46] Phone interview with Dr. Francis Collins by Subhashini Chandrasekharan and Christopher Heaney, September 10, 2008.
[47] 37 CFR 404. 1992.
[48] Email from Dr. David Ritchie to Christopher Heaney, July 22, 2008. Email references *Guidance to Campuses on NIH 'Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources*. 1999. See http://www.cogr.edu/docs/ResearchTools.htm [accessed July 29, 2008].
[49] Best practices for the licensing of genomic inventions. *Federal Register* 2005 (April 11). 70(68):18413 – 18415. See http://ott.od.nih.gov/pdfs/70FR18413.pdf [accessed November 18, 2008].
[50] Organisation for Economic Co-operation and Development. *Guidelines for the Licensing of Genetic Inventions*. 2006. See http://www.oecd.org/dataoecd/39/38/36198812.pdf [accessed 6 October 2008]. Email from Arlene Yee and Dr. David Ritchie to Yvette Seger, Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) staff.
[51] Association of University Technology Managers. *In the Public Interest: Nine Points to Consider in Licensing University Technology*. March 6, 2007. See http://www.autm.net/aboutTT/Points_to_Consider.pdf [accessed November 18, 2008].

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for CF testing "kit" developers (see Appendix A)[52] that enables companies to develop and sell genetic CF testing kits that include the ΔF508 mutation. A second non-exclusive license is also available for companies that wish to develop their own "in-house" CF assays for testing patient samples at a "single site" laboratory.

The initial license fee for kit licenses is $25,000, which has not changed in over 15 years. The annual fees too have remained unchanged since the initial license was granted in 1993. The initial license fee for the in-house commercial test is $15,000.[53] As indicated in section 4.2 of the "Kit" License Agreement (Appendix A), licensees must agree to pay a 6% royalty on their net sales of products. However, as Dr. Ritchie explained, these licenses also take into account "a licensee's need to add additional technologies (i.e., mutations) to a final product by allowing this royalty rate to be reduced by 40%. Thus, the actual royalty percentage generally is agreed to be 3.6%, which does not impede a licensee from entering the marketplace."[54] Revenue obtained from these fees and royalties have gone, in large part, toward covering the costs for international patent protection.

Detailed information about current licensing of the US 5,776,677 patent was initially gathered from The University of Michigan as part of a study of university licensing practices,[55] and then supplemented with their permission. According to Dr. Ritchie, all licenses are non-exclusive. The first license for a therapeutic product was granted in 1993 for gene therapy; the first license for a diagnostic kit was granted in 1996. [56] As of 2008, the University of Michigan and HSC have 21 active licenses covering the ΔF508 mutation. [57] As of 2002, licenses generated between $1 and $10 million in revenue. [58] Currently, 63 American laboratories perform CF testing. The majority of those labs are academic medical centers or hospital-based genetic testing laboratories that use CF test kits developed under these licensees.[59]

Dr. Ritchie recalled only one instance in the past ten years that dealt with potentially infringing activity. A licensee advised the University of Michigan of an unlicensed company advertising CF diagnostic services to consumers. Dr. Ritchie contacted the company and verbally informed it of the '677 patent and asked if the company was interested in taking a license. Because the company in question "dropped it," and presumably ceased offering diagnostic services, the matter was not taken to the level of formal, written communication or legal action. [60]

Licensing practices are especially important because CF tests are essential in newborn screening and population screening for carriers. As Grody et al. state, "Perceiving a large market as CF screening was declared standard of care for the entire population, the first of any commercial consequence in the history of molecular genetics, reagent and equipment vendors quickly developed and began marketing test platforms. Indeed, virtually overnight CF became the flagship test product offered by many established and start-up companies."[61] Currently, the FDA has approved at least two diagnostic "kits" for cystic

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[52] Email from Dr. David Ritchie to Subhashini Chandrasekharan, July 8, 2008.
[53] Phone interview with Dr. David Ritchie, Office of Technology Transfer and Corporate Research, University of Michigan, by Subhashini Chandrasekharan, April 24, 2007, and April 30, 2007.
[54] Email from Dr. David Ritchie to Subhashini Chandrasekharan, July 8, 2008.
[55] Pressman L et al. The licensing of DNA patents by US academic institutions: an empirical survey. *Nature Biotech* 2006. 24(1):31–39.
[56] Email from Dr. David Ritchie to Subhashini Chandrasekharan, July 17, 2008.
[57] Email from Dr. David Ritchie to Subhashini Chandrasekharan, July 17, 2008.
[58] Licensing Revenue Information disclosed with permission of University of Michigan and HSC. Email from Dr. David Ritchie and Lori Pressman to Subhashini Chandrasekharan, October 2007.
[59] *CFTR-Related Disorders*. See www.genetests.org [accessed July 2, 2008].
[60] Phone interview with Dr. David Ritchie by Subhashini Chandrasekharan and Christopher Heaney, July 3, 2008.
[61] Grody W et al. The cystic fibrosis mutation 'arms race': when less is more. Op. cit. at 739.

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fibrosis, and other companies are proceeding through the regulatory process for producing and selling diagnostic devices.

For example, one FDA-approved diagnostic kit is the Luminex Kit, which includes intellectual property held by HSC and Johns Hopkins.[62] The HSC and Hopkins patents cover mutations other than the ΔF508 mutation (See Appendix B). Two of the four mutations covered by Hopkins patent U.S. Patent No. 5,407,796 are included in the American College of Medical Genetics' (ACMG's) currently recommended list of mutations to test. Laboratories that test for the ΔF508 mutation as well as the mutations patented by HSC and Hopkins presumably must obtain licenses from all three patent-holding institutions (Michigan-HSC, HSC, and Johns Hopkins) since "valuation" of each of the mutations is always a negotiable topic and each institution is best able to defend its valuation philosophy.

Another major player in CF testing is Ambry Genetics, which advertises several proprietary CF tests. The advertisements state that Ambry has "analyzed the complete CF gene for more than 10,000 patient samples."[63] Ambry's most extensive test is CF Amplified, which Ambry promotes as "the most comprehensive CF test available, detecting approximately 99% of mutations in patients of all ethnicities."[64] Unlike Luminex's Tag-It kit that tests for 39 mutations and 4 variants, the CF Amplified test sequences "the full *CFTR* gene as well as surrounding critical introns" and includes rearrangement testing.[65] Presumably Ambry had to license the same patents as Luminex. Johns Hopkins offers non-exclusive licenses to its patent to kit developers, judging from the fact that both Ambry and Luminex offer tests that cover mutations claimed in the Hopkins patent.[66]

Other manufacturers are preparing FDA approved diagnostic tests to compete in the CF testing and screening markets, further increasing the probable number of licensees of the University of Michigan, HSC, and Hopkins patents. In spring 2007, Nanogen announced that "it has submitted the 510(K) [premarket notification] to FDA for its Cystic Fibrosis Kit and NanoChip 400 microarray system."[67] The kit tests for the ACMG-recommended 23 mutations.[68] In January 2007, Third Wave also submitted a 510(K) form for its CF test, which is "intended to provide information to determine CF carrier status in adults, as an aid in newborn screening and in confirmatory diagnostic testing in newborns and children."[69] The FDA has since approved the test for diagnostic use. [70] On June 9, 2008, Third Wave and Hologic announced Hologic's purchase of Third Wave for $580 million cash. In a conference call, Hologic's Chairman said that one reason for the acquisition was that the CF test "will be a natural complement to our full-term preterm birth product which is sold by our OB/Gyn sales force."[71] Although genetic tests for Human Papilloma Virus were described as a more important reason for the acquisition than the CF testing platform, it seems that Third Wave's ability to license and use intellectual property including CF mutations was an asset.

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[62] Luminex licenses cystic fibrosis gene patent from Johns Hopkins. *BIOTECH Patent News* 2007 (March). See http://www.entrepreneur.com/tradejournals/article/164609425.html [accessed July 29, 2008].
[63] Ambry Genetics. *Cystic Fibrosis*. See http://www.ambrygen.com/ts/ts_cf.aspx [accessed July 29, 2008].
[64] Ibid.
[65] Ibid.
[66] JHU confirmed that its cystic fibrosis patent is licensed non-exclusively for commercial *CFTR* testing. Email from Leigh A. Penfield, Associate Director, Johns Hopkins Technology Transfer, Johns Hopkins University to Christopher Heaney, August 4, 2008.
[67] *Nanogen Submits 510 for Cystic Fibrosis Genetic Assay and NanoChip 400 System*. Business Wire 2007 (April 17). See http://findarticles.com/p/articles/mi_m0EIN/is_2007_April_17/ai_n27203429 [accessed July 29, 2008].
[68] Ibid.
[69] *Third Wave Submits 510(k) to FDA for InPlex™ Cystic Fibrosis Molecular Test*. See http://www.medicalnewstoday.com/articles/60125.php [accessed July 29, 2008].
[70] *Transcript of a Conference Call Held by Hologic, Inc on June 9, 2008. Exhibit 99.1*. See http://www.secinfo.com/d14D5a.t3vh8.d.htm [accessed November 18, 2008].
[71] Ibid.

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More recently, several nonprofit institutions that fund for-profits doing either CF research or drug development for developing world chronic conditions such as diarrhea have approached the University of Michigan and HSC about licensing rights in order to develop and use screening assays for the discovery of small molecule drugs useful for treating patients with the ΔF508 mutation, or for drug development to treat diarrhea (which also involves the *CFTR* protein). Because much of the original research leading to the discovery of the *CFTR* gene was funded by two nonprofit organizations, the Cystic Fibrosis Foundation and the Howard Hughes Medical Institute, specific licenses were developed for both The Cystic Fibrosis Foundation Therapeutics, Inc. (CFFT), and for One World Health, whose missions, in part, are to ensure broad access to medical technologies. This is a new type of "research" license for the use of *CFTR*-related patents and grants both CFFT and One World Health rights to sub-license appropriate patents covering research tools such as the *CFTR* gene sequence and cell lines containing either the native gene or ΔF508 mutation to for-profit companies conducting research. Applicable research includes screening small-molecule libraries to produce therapeutic CF or anti-diarrheal drugs.[72] The parties developed this promising licensing strategy to reduce transaction costs and facilitate research on new therapeutic drugs for treating these devastating conditions. Success could be especially beneficial in resource-poor regions of the world where diarrheal diseases are endemic. According to Dr. Ritchie, the University of Michigan and HSC will receive a small sublicense fee whenever a sublicense is granted but will not receive any royalties from sales of the final drug products. In other words, this license does not give the University of Michigan or HSC any "reach through" rights since they have only licensed access to research tools.

The table below shows the test panel currently recommended by the ACMG with annotations describing how the relevant intellectual property is distributed.[73] The clinical importance of the chart is discussed below. The mutation list below is a current standard of care that the test market aims to meet or exceed.

Recommended Core Mutation Panel for Cystic Fibrosis Carrier Screening in the General Population

Standard Mutation Panel	R560T, ΔF508[a], R553X[b], R1162X, ΔI507, 2184delA, G542X, G551D[b], W1282X, N1303K, 621+1GΔT, R117H, 1717-1GΔA, A455E, G85E, R334W, R347P, 711+1GΔT, 1898+1GΔA, 3849+10kbCΔT, 2789+5GΔA, 3659delC, 3120+1GΔA
Additional Testable Mutations	I506V,[c] I507V,[c] F508C[c], 5T/7T/9T[d]

[a]Univ of Michigan/HSC Patent No. U.S. 5,776,677
[b]Johns Hopkins University U.S. Patent No. 5,407,796
[c]Benign variants. This test distinguishes between a CF mutation and these benign variants. I506V, I507V, and F508C are performed only as reflex tests for unexpected homozygosity for ΔF508 and/or ΔI507.
[d]5T in *cis* can modify R117H phenotype or alone can contribute to congenital bilateral absence of vas deferens (CBAVD); 5T analysis is performed only as a reflex test for R117H positives.

[72] Phone interview with Dr. David Ritchie by Subhashini Chandrasekharan, April 24, 2007, and April 30, 2007.
[73] American College of Medical Genetics. *Cystic fibrosis population carrier screening: 2004 revision of American College of Medical Genetics mutation panel*. 2004. See http://www.acmg.net/resources/policies/CF_mutation_8-2004.pdf [accessed April 15, 2007].

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Testing Practices for CF

Newborn Screening

Early detection of CF is important to improve disease management. Farrell et al. found that "early diagnosis of CF through neonatal screening combined with aggressive nutritional therapy can result in significantly enhanced long-term nutritional status."[74] In 2005 the CDC released recommendations on newborn screening for cystic fibrosis and indicated several benefits from newborn screening both for disease management and improving quality of life.[75] In a review in 2006, Grosse et al. found that newborn screening can reduce childhood mortality from CF.[76]

In May 2006, the ACMG published a report from its Newborn Screening Expert Group, which included academic experts, government officials, professional medical organization representatives, and patient advocates. The report recommended that newborns undergo testing for CF and twenty-eight other conditions in state newborn screening programs. The report considered the model of initial screening for unusually high levels of the enzyme immunoreactive trypsinogen (IRT), followed by a second IRT test and then a DNA test if necessary.[77] In a letter to DHHS Secretary Leavitt, the Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Children (SACHDGDC) "strongly and unanimously recommends that the Secretary initiate appropriate action to facilitate adoption of the ACMG recommended screening panel [which includes CF] by every State newborn screening program."[78]

The ACMG's guidelines for newborn screening call for testing of levels of the IRT enzyme which if unusually high are indicative of CF, followed by a repeat IRT test, or DNA testing, and a sweat test for elevated chloride levels that will confirm indicate a diagnosis of CF. In the screening protocol either a positive repeat of the IRT test or a positive DNA test for one of 23 mutations leads to a sweat chloride test for confirmation.[79]

Although comprehensive data about states' testing practices are not available, some information is available from the National Newborn Screening Information System. According to their 2008 report on cystic fibrosis screening, at least 28 states include cystic fibrosis in their newborn screening programs. All of those states test IRT in the first round of testing; 17 of them use a DNA test if IRT levels indicate a second round of testing is required. At least 7 of those DNA tests are based on testing for 38 to 43

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[74] Farrell PM et al. Early diagnosis of cystic fibrosis through neonatal screening prevents severe malnutrition and improves long-term growth. *Pediatrics* 2001. 107(1):1-13, at 2. See http://pediatrics.aappublications.org/cgi/content/abstract/107/1/1 [accessed July 28, 2008].

[75] Neff MJ. CDC releases recommendations for state newborn screening programs for cystic fibrosis. *American Family Physician* 2005 (April 15). See http://www.aafp.org/afp/20050415/practice.html [accessed January 22, 2009].
Grosse SD, Boyle CA, Botkin JR, Comeau AM, Kharrazi M, Rosenfeld M, Wilfond BS. Newborn screening for cystic fibrosis: evaluation of benefits and risks and recommendations for state newborn screening programs. *MMWR Recommendations and Reports* 2004 (October 15). 53(RR-13):1-36.

[76] Grosse SD et al. Potential impact of newborn screening for cystic fibrosis on child survival: a systematic review and analysis. *Journal of Pediatrics* 2006. 149(3):362 – 6.

[77] Watson MS et al. American College of Medical Genetics' Newborn Screening Expert Group. *Newborn Screening: Toward a Uniform Screening Panel and System*. See http://www.acmg.net/resources/policies/NBS/NBS-sections.htm [accessed January 13, 2009].

[78] Howell RR. Chairperson, Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children. Letter to Secretary Michael Leavitt. Undated. See ftp://ftp.hrsa.gov/mchb/genetics/correspondence/ACHDGDNCletterstoSecretary.pdf [accessed July 8, 2008].

[79] American College of Medical Genetics. Immunoreactive Trypsinogen (IRT Elevated). 2006. See http://www.acmg.net/resources/policies/ACT/Visio-IRT(4-17-06).pdf [accessed July 29, 2008].

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mutations.[80] The Cystic Fibrosis Foundation lists all states but Nevada, Utah, Texas, Tennessee, North Carolina, Pennsylvania, and Connecticut as screening all newborns for CF, and except for North Carolina all of the other state governments are considering or preparing comprehensive state programs.[81] Given the spate of recommendations on CF testing, this situation seems likely to continue evolving rapidly.

Carrier Testing

ACMG Guidelines and Update (2001 and 2004). Current guidelines for genetic testing for CF mutation carriers were developed in response to a 1997 National Institutes of Health (NIH) report, which stated, "Genetic testing for CF should be offered to adults with a positive family history of CF, to partners of people with CF, to couples currently planning a pregnancy, and to couples seeking prenatal care."[82] In 2001, the ACMG published recommendations on cystic fibrosis carrier screening. In 2001,The American College of Obstetricians and Gynecologists (ACOG), the ACMG and the NIH Steering Committee incorporated those recommendations into a set of clinical guidelines and educational material sent to clinicians. The ACMG called for screening to be offered to a more specific population of "non-Jewish Caucasians and Ashkenazi Jews."[83] The ACMG recommended using a pan-ethnic *CFTR* panel of twenty-five *CFTR* mutations, all of which occurred in at least 0.1% in the general U.S. population. In 2004, additional data on the rarity of two mutations persuaded the ACMG to remove them from the panel.[84] The updated panel will detect mutations in 94% of Ashkenazi Jewish carriers, 88% of non-Hispanic Caucasian carriers, 72% of Hispanic Americans, 65% of African Americans, and 49% of Asian Americans.[85] As of 2006, the ACMG still endorses the updated panel of twenty-three mutations.[86]

In its 2001 recommendations, the ACMG advised providers that they should not routinely offer testing for additional mutations. However, providers could disclose the existence of such extended panels to inquiring patients and use such panels on an *ad hoc* basis. Couples in which one or both partners are positive, those with family history of CF, or males found to have mutations associated with infertility require further genetic counseling or additional testing strategies. In those cases, the ACMG encouraged clinicians to direct patients to visit genetics centers. Also, "patients diagnosed with CF… should be referred [directly] to a genetics center for appropriate testing and counseling."[87] While acknowledging that "testing will often occur in the prenatal setting," the ACMG urged "preconception testing… whenever possible."[88]

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[80] National Newborn Screening Information System Database. *Cystic Fibrosis (CF) – Laboratory Testing in 2008*. See http://www2.uthscsa.edu/nnsis/ [accessed on July 22, 2008].
[81] Cystic Fibrosis Foundation. *Newborn Screening for Cystic Fibrosis*. http://www.cff.org/GetInvolved/Advocate/WhyAdvocate/NewbornScreening/#What_states_do_newborn_screening_for_CF? [accessed July 29, 2008].
[82] National Institutes of Health Consensus Development Conference Statement on Genetic Testing for Cystic Fibrosis. Genetic testing for cystic fibrosis. *Archives of Internal Medicine* 1999. 159:1529 –1539, at 1529.
[83] Grody W et al. Laboratory standards and guidelines for population-based cystic fibrosis carrier screening. *Genetics in Medicine* 2001. 3(2):149–154, at 150.
[84] Ibid., 150 – 151.
Watson MS et al. Cystic fibrosis population carrier screening: 2004 revision of American College of Medical Genetics mutation panel. *Genetics in Medicine* 2004. 6(5):387–391. See http://www.eurogentest.org/cfnetwork/files/public/doc/artikels/Cystic%20fibrosis%20population%20carrier%20screening%202004.pdf [accessed July 8, 2008].
[85] American College of Obstetricians and Gynecologists. Op. cit.
[86] Amos J et al. American College of Medical Genetics. *Technical Standards and Guidelines for CFTR Mutation Testing 2006 Edition*. See http://www.acmg.net/Pages/ACMG_Activities/stds-2002/cf.htm [accessed July 22, 2008].
[87] Grody W et al. Laboratory standards and guidelines for population-based cystic fibrosis carrier screening. Op. cit. at 149.
[88] Ibid., 150.

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The ACMG also recommended that providers make carrier testing available to couples whose ethnic background reduces their risk for CF but also might have CF mutations of lower frequency in existing databases, because current data are based primarily on Caucasian population studies. The ACMG specifically indicated that "Asian-Americans and Native-Americans without significant Caucasian admixture should be informed of the rarity of the disease and the very low yield of the test in their respective populations."[89] Likewise, the ACMG recommend that "testing should be made available [but not offered] to African-Americans, recognizing that only about 50% of at-risk couples will be detected."[90] The corollary is that CF screening and testing in populations outside Europe and North American might require better data about *CFTR* mutations in non-Caucasian populations.

For Ashkenazi Jewish and Caucasian couples of Northern European descent, the ACMG recommended couple-based testing. In couple-based testing, or concurrent testing, the lab collects and tests a sample from each partner and fully discloses the results to each partner. In populations in which individuals are less likely to be CF mutation carriers, or in cases where testing both partners simultaneously is difficult, providers can consider testing one person and then only testing the second if the first has a mutation (sequential testing). "In general, the individual provider or center should choose whichever method they feel most appropriate or practical."[91]

ACOG Screening Recommendations (2005). In December 2005, the American College of Obstetricians and Gynecologists (ACOG) updated its recommendations. ACOG expressed concern that "most obstetricians are offering [CF] carrier screening to their pregnant patients… [but] significantly fewer obstetrician-gynecologists offer nonpregnant patients [CF] carrier screening unless a patient requests the information or has a family history."[92] Noting how "difficult [it] is to assign a single ethnicity" to a patient, the ACOG nonetheless recommended increasing the scope of carrier testing. "It is reasonable to offer CF Carrier screening to all couples regardless of race or ethnicity as an alternative to selective screening."[93] This recommendation comes with the caveat that providers should be clear about the impact of ethnicity on carrier risk and test sensitivity. Further, "Cystic fibrosis carrier screening should be offered before conception or early in pregnancy when both partners are of Caucasian, European, or Ashkenazi Jewish ethnicity. Patients may elect to use either sequential or concurrent carrier screening; the latter option may be preferred if there are time constraints for decisions regarding prenatal diagnostic testing or termination of the affected pregnancy. Individuals who have a reproductive partner with cystic fibrosis or congenital bilateral absence of the vas deferens may benefit from screening with an expanded panel of mutations or, in some cases, a complete analysis of the *CFTR* gene by sequencing." [94]

Prenatal Diagnostic Testing

ACMG Guidelines and Update (2002 and 2006). The 2006 updated ACMG Standards and Guidelines for *CFTR* Mutation Testing state that prenatal *CFTR* mutation testing is indicated if there is a "positive family history," "a CF mutation in both partners," or an "echogenic bowel in fetus during second trimester."[95] The test can be performed using "both direct and cultured amniotic fluid cells (AFC) and chorionic villus samples."[96] The parents should both be tested before the fetus. Because of the results' significance, "The laboratory must… provide referring professionals with appropriate instructions.

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[89] Ibid.
[90] Ibid.
[91] Ibid.
[92] American College of Obstetricians and Gynecologists. Op. cit. at 1465.
[93] Ibid., 1466.
[94] Ibid., 1466 – 1467.
[95] Amos J. et al. Op. cit.
[96] Ibid.

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Laboratories must have a prenatal follow-up program in place to verify diagnostic accuracy."[97] The 2006 recommendations also note that prenatal diagnostic testing typically requires a larger mutation panel than carrier screening. "A larger number of mutations (>23) is generally appropriate for diagnostic testing in order to achieve the highest possible clinical sensitivity, but care should be taken to ensure that the penetrance of tested mutations is known."[98] Finally, "A positive prenatal diagnostic test result is considered to be definitive rather than predictive since the penetrances for these 23 mutations are known to be high."[99]

Preimplantation Genetic Diagnosis

ACMG Guidelines and Update (2002 and 2006). In October 2002, the ACMG Laboratory Quality Assurance Committee released *Standards and Guidelines for CFTR Mutation Testing,*[100] intended as an educational resource for clinical laboratory geneticists. Preimplantation testing is indicated for CF in the 2002 guidelines and the 2006 updated version.[101] Despite lingering technical concerns about performing DNA assays using a relatively small sample, preimplantation diagnosis for CF was first reported in 1992 and has continued to occur.[102]

Diagnostic Testing

The updated 2006 ACMG Standards and Guidelines for *CFTR* Mutation Testing note that CF mutation testing is indicated for diagnostic purposes when there is a possible or definite clinical diagnosis of CF, when an infant presents with meconium ileus (excessively thick bowel movements immediately after birth), or when a male presents with congenital bilateral absence of the vas deferens. Because this mutation testing is done for diagnostic rather than screening purposes, laboratories may need to expand the mutation panel beyond the core twenty-three mutations used in carrier testing.[103] The ACOG adds that while gene sequencing "is not appropriate for routine carrier screening," it is acceptable "for patients with cystic fibrosis, a family history of cystic fibrosis, infertile males with congenital bilateral absence of the vas deferens, or a positive newborn screening test result when mutation testing using an expanded panel of mutations has a negative result."[104]

More recently, Grody and others involved in the ACMG statements have expressed personal concern about the use of rapidly increasing number of mutations and gene sequencing options. This trend is not necessarily in patients' best interest because of limited knowledge about the CF's genetic basis. "[A] large number of mutations selected for expanded panels… were chosen because the testing laboratory happened to stumble upon one, or read about it in a research or clinical paper whose researcher or clinician author had likewise stumbled upon it. In other words, these are very rare events, arbitrary almost to the point of randomness."[105] Given the frequency with which guidelines have been released and debated, medical consensus and guidelines for diagnostic testing as well as other testing forms seem likely to evolve.

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[97] Ibid.
[98] Ibid.
[99] Ibid.
[100] Richards CR et al. Standards and guidelines for *CFTR* mutation testing. *Genetics in Medicine* 2002. 4(5):379-391.
[101] Amos J et al. Op. cit.
[102] Keymolen K et al. Clinical outcome of preimplantation genetic diagnosis for cystic fibrosis: the Brussels' experience. *European Journal of Human Genetics* 2007. 15:752 – 758.
[103] Amos J. et al. Op. cit.
[104] American College of Obstetricians and Gynecologists. Op. cit. at 1466.
[105] Grody et al. The cystic fibrosis mutation 'arms race': when less is more. Op. cit. at 741.

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Cost of CF Genetic Tests

Prices for CF genetic tests were obtained from twelve laboratories. All tests refer to the *CFTR* gene. Prices are those charged to insurance companies, except for Quest Diagnostics and Johns Hopkins University DNA Diagnostic Laboratory, which chose to provide out-of-pocket costs for patients who do not use insurance to cover the test. Sequencing prices are discussed below. The cost of mutation analysis is discussed in "Cost Effectiveness of CF Screening."

Non-Profit Laboratories

ARUP Laboratories[106]

- Full gene sequencing: $1,200
- Gene deletion/duplication analysis: $525

Baylor College of Medicine[107]:

- Full gene sequencing: $1800
- Full gene sequencing (prenatal): $1500

Boston University Center for Human Genetics[108]

- 40 mutation panel (including ACMG recommended 23 mutations): $195
- 100 mutation panel (including ACMG recommended 23 mutations): $295

City of Hope Molecular Diagnostic Laboratory[109]

- Full gene sequencing: $2,586.96

Harvard[110]

- Gene sequencing: $1,650
- Gene sequencing (prenatal testing): $2,600 ($1,650 + $950 for maternal cell contamination testing)

Johns Hopkins University DNA Diagnostic Laboratory[111]

- Full gene sequencing: $2,298

Mayo Clinic Molecular Genetics Laboratory[112]

- Full gene sequencing: $1,500

For-Profit Laboratories

Ambry Genetics[113]

- CF Amplified (Full gene sequencing and deletion/duplication testing): $3,358
- CF Amplified (Full gene sequencing without deletion/duplication testing): $2,762

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[106] ARUP Laboratories, via phone, Feburary 11, 2008. ARUP Laboratories is a non-profit enterprise owned by the University of Utah.

[107] Baylor College of Medicine. Medical Genetics Laboratories. *Prices and CPT Codes.* July 25, 2008. See http://www.bcm.edu/geneticlabs/pricesandCPTcodes.pdf [accessed July 28, 2008].

[108] Boston University Center for Human Genetics. *Direct DNA Tests.* June 9, 2008. See http://www.bumc.bu.edu/Dept/Content.aspx?DepartmentID=118&PageID=2194 [accessed July 28, 2008].
Alison Nicoletti. Boston University Center for Human Genetics, via phone July 28, 2008.

[109] Email from Dr. Juan-Sebastian Saldivar, City of Hope Clinical Molecular Diagnostic Laboratory, to Christopher Heaney, July 8, 2008. Prices are effective as of August 1, 2008.

[110] Harvard Medical School – Partners Healthcare Center for Genetics and Genomics. *CFTR Sequencing Assay for Cystic Fibrosis and CBAVD*. See http://www.hpcgg.org/LMM/comment/Cystic%20Fibrosis%20Info%20Sheet.jsp?name=LMM&subname=genetictests [accessed July 28, 2008].
Samantha Baxter, Harvard Medical School – Partners Healthcare Center for Genetics and Genomics, via phone, July 28, 2008.

[111] Johns Hopkins University DNA Diagnostic Laboratory, via phone February 11, 2008, and 10 September, 2008.

[112] Mayo Clinic Molecular Genetics Laboratory, via phone February 11, 2008.

[113] Lori Ross, Ambry Genetics, via phone, July 28, 2008.
Ambry Genetics. *Cystic Fibrosis Testing*. See http://www.ambrygen.com/ts/ts_cf.aspx [accessed July 28, 2008].

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- 508 First (ΔF508 mutations only): $84

CytoGenX[114]

- 39 mutation panel (23 ACMG recommended mutations and 16 others): $2,100

Genzyme Genetics[115]

- Full gene sequencing: $2,004

Quest Diagnostics[116]

- Gene deletion/duplication analysis: $420.00
- Full gene sequencing: $2,485.00
- Screen for ACMG 23 recommended mutations: $595.00
- DNA Analysis, Fetus (23 ACMG recommended mutations and 8 others): $660 ($335 + $325 for maternal cell contamination testing)

Prevention Genetics[117]

- Full gene sequencing: $1,290

Laboratory	Amplicons*	Gene sequencing price	Cost per amplicon**
ARUP Laboratories	30	$1,200	$40
Baylor College of Medicine	29	$1,800	$62.07
City of Hope Molecular Diagnostic Laboratory	30	$2,586.96	$86.23
Harvard	29	$1,650	$56.90
Johns Hopkins University DNA Diagnostic Laboratory	31	$2,298	$74.13
Mayo Clinic	N/A***	$1,500	
Ambry Genetics	50	$2,762	$55.24
Prevention Genetics	29	$1,290	$44.48
Quest Diagnostics	32	$2,485	$77.66

* Number of nucleic acid sequences targeted for amplification (according to number of times CPT billing code 83898 is used)
**Gene sequencing price divided by number of times CPT 83898 billed
***CPT code 83898 is not listed on the Mayo Clinic Molecular Genetics Laboratory's technical specifications (See http://216.245.161.151/TestView.aspx?testID=12286 [accessed January 14, 2009]).

Comparing the prices of CF genetic testing is difficult. First, none of the labs surveyed offered identical mutation panels. Second, although CPT codes provide some standardization, at least for full sequencing analysis tests, they do not necessarily indicate that techniques and procedures are identical. The contribution of different techniques and procedures (usually billed under different CPT codes for each test) is not always known. Even after comparing pricing based on CPT codes, which are not always consistent among labs, the labs surveyed have different overhead costs and ways of accounting for such costs.

[114] Dr. Dunn, CytoGenX, via phone, July 28, 2008.
CytoGenX. *Cystic Fibrosis Collection*. See http://www.cytogenx.com/cystic_fibrosis.asp [accessed July 28, 2008].
[115] Genzyme Genetics, via phone, February 11, 2008.
[116] Email from Sam Garetano, Quest Diagnostics, to Christopher Heaney, July 28, 2008.
[117] Prevention Genetics, via phone February 11, 2008.

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With those caveats noted, the price range for *CFTR* gene sequencing among non-profit institutions ($40 to $86.23 for each sequence targeted for amplification or amplicon) is higher than the per amplicon price range for non-profits' sequencing the colorectal cancer gene *APC* ($28.57 to $ 39.88). However the price per amplicon for *CFTR* sequencing is comparable to that of non-profit labs' price ($30.00 to $77.44/amplicon) for sequencing *MLH1*, *MSH2*, and *MSH6* genes.[118] This comparison between the prices of sequencing different genes is only an approximation. The fact that Baylor College of Medicine, City of Hope, and Harvard perform both colorectal cancer and CF testing and that colorectal cancer genes are also licensed non-exclusively by non-profits makes the comparison worth noting. Specifically, the same labs performing these two tests presumably incur similar overhead costs. Also, because JHU has patents on certain *CFTR* mutations as well as *APC* and *MSH2*, there is at least one common actor involved in licensing intellectual property associated with colorectal cancer testing and CF testing. Sequencing the colorectal cancer genes and *CFTR*, on a price per amplicon basis, is comparable to sequencing the *BRCA1* and *BRCA2* genes, for which the sole provider Myriad Genetics charges $38.05 per amplicon.[119] That is, CF and colorectal cancer genes cost slightly more to PCR-amplify and then sequence at non-profit academic institutions than *BRCA1* and *BRCA2* genes at Myriad Genetics, the single for-profit provider.[120]

Cost Effectiveness of CF Screening Tests

Cost effectiveness of CF testing is a concern for payers and consumers. If testing is cost effective at a certain price and CF tests that analyze patented mutations are available at or below that price, then CF licensing practices at least do not preclude cost effective testing. As the CF testing market continues to develop, licensing practices may also have to evolve, although changes are contingent on current licensing terms until they expire or are renegotiated.

The first step in analyzing cost effectiveness for CF testing is to determine the financial cost of treating the disease. According to the 1997 NIH Consensus Development Conference Report:

> Using data from 1989, the Office of Technology Assessment estimated in 1992 that the annual treatment costs for CF were approximately $10,000 per year per individual. Current estimates are over $40,000 per year in direct medical costs and $9,000 per year in other related costs. Using a 3% annual inflation rate, an estimated total of $800,000 [in 1996 dollars] can be assumed for each CF birth. [121]

Other studies give varying U.S. estimates of the lifetime financial cost of medical care for a CF patient, ranging from $220,000 to $844,000 (1996 dollars). [122]

The next step is to compare that cost to the cost of various tests. Evidence is available for carrier and prenatal screening and, to a much lesser extent, preimplantation genetic diagnosis (PGD).

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[118] Cook-Deegan R et al. *Impact of Gene Patents on Access to Genetic Testing for Inherited Susceptibility to Cancer: Comparing Breast and Ovarian Cancers to Colon Cancers*. Peer-reviewed case study submitted to the Secretary's Advisory Committee on Genetics, Health, and Society, 2008.
[119] Ibid.
[120] Ibid.
[121] NIH Consensus Development Conference Statement. Genetic testing for cystic fibrosis. *Archives of Internal Medicine* 1997. 159: 1529-1539.
[122] Haddow JE et al. *Population-Based Prenatal Screening for Cystic Fibrosis via Carrier Testing: ACCE Review Clinical Utility*. Scarborough, ME: Foundation for Blood Research. June 2002:4-61. See http://www.cdc.gov/genomics/gtesting/file/print/FBR/CFClilUti.pdf [accessed August 17, 2007].

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Carrier and Prenatal Screening

When analyzing cost effectiveness of CF carrier testing, costs beyond providing the actual test include obtaining informed consent, providing educational and counseling services, and other administrative costs. To assess the cost effectiveness of universal prenatal screening, a number of additional factors must be considered including the number of participants, the population rate of CF carriers, the number of couples with an affected fetus who would choose to terminate the pregnancy, the number of children couples may desire, and the testing method used.

In one study by Asch et al., the costs and clinical outcomes of sixteen strategies for CF carrier screening were evaluated using a model of 500,000 pregnancies in a population of only European descent.[123] Asch et al. found that a sequential screening approach minimized the cost of averting CF births. With this approach, the first partner was screened with a test for the ΔF508 mutation and five other common mutations known at the time. This panel, covering fewer mutations than the ACMG now recommends, was modeled as identifying 85% of carriers in the population. If the first partner tested positive, the second partner was screened with an expanded test of another twenty to thirty mutations estimated to identify 90% of carriers. In the end, such an approach identified 75% of anticipated CF births at a cost of $367,000 (1995 dollars) per averted birth. However, this estimate only holds true if "all couples who identify a fetus as high risk choose to terminate the pregnancy. If only half of couples will proceed to abortion under these circumstances, the cost per CF birth avoided would increase to $734,000 per CF birth avoided."[124] Also, "for couples planning two pregnancies, the cost effectiveness ratios for CF screening are roughly half those of the single-pregnancy case," meaning that the cost per CF birth avoided is roughly halved.[125]

In 2007, Wei et al. analyzed data collected between 2001 and 2005 on more than 6,000 women screened for CF carrier status at the Henry Ford Health System in Detroit, Michigan.[126] Wei's study complements Asch's work by providing a more ethnically diverse cohort that was 45% African American, 35% non-Jewish Caucasian, 10% Arab American, 5% Hispanic, 5% Asian and 1% Ashkenazi Jewish. The study excluded "patients with a family history of CF, a known/possible diagnosis of CF, males with infertility, and fetuses with echogenic bowels."[127] 98.5% of her cohort received sequential screening that included the 25 ACMG recommended mutations in addition to another seven to seventeen mutations. Over four years and at a total cost of $334,000 (2005 dollars),[128] testing identified six positive couples and one (subsequently aborted) fetus with mutations from both parents. Comparing this to a lifetime care cost of $1 million per CF patient, which is within the range indicated by other studies, Wei et al. concluded that population-based carrier screening is cost-effective even when it includes a high number of non-Caucasians. Wei's cost per CF birth averted is less than Asch et al.'s best-case scenario of $367,000 per averted birth even before the two studies are normalized to same-year dollars.

Rowley et al. used data from a trial of CF carrier screening to analyze cost effectiveness.[129] 4,879 women were tested, 124 of whom were CF carriers but none of whom had pregnancies diagnosed with CF through prenatal testing. Costs (given below) were based on surveys, data from the US Congress's Office

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[123] Asch DA et al. Carrier screening for cystic fibrosis: costs and clinical outcomes. *Medical Decision Making* 1998. 18:202–212. Model cohort ethnicity according to email from David Asch to Christopher Heaney, July 24, 2008.
[124] Ibid., 209.
[125] Ibid.
[126] Wei S et al. Is cystic fibrosis carrier screening cost effective? *Community Genetics* 2007. 10(2):103-9.
[127] Ibid., 104.
[128] Year for dollars from email from K. Monaghan to Christopher Heaney, July 29, 2008.
[129] Rowley P et al. Prenatal screening for cystic fibrosis carriers: an economic evaluation. *American Journal of Human Genetics* 1998. 63(4):1160-74.

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of Technology Assessment, and personal communications. Based on those figures and the behaviors observed in the carrier screening trial, Rowley et al. determined the cost effectiveness of screening a hypothetical cohort of a 100,000 women. In their model, at a total cost of $11.1 million, 8.4 CF affected pregnancies were terminated. This translated to $1.322 million to $1.396 million per averted birth, depending on whether parents choose to have another child. Assuming a lifetime care cost of $1.574 million per CF patient, Rowley et al. concluded that "the averted medical-care cost resulting from choices freely made are estimated to offset ~74%-78% of the costs of a screening program."[130] The study added that "the cost of prenatal CF carrier screening could fall to equal the averted costs of CF patient care if the cost of carrier testing were to fall to $100."[131] Assuming that a pregnancy is terminated because of CF and the family does not have another pregnancy, there is no gain in terms of aggregate family quality-adjusted life-years. If the family has another pregnancy, the marginal cost for prenatal CF carrier screening is estimated to be $8,290 per quality-adjusted life-year (QALY). This figure "is comparable to that for newborn screening for phenylketonuria and is more advantageous than the ratios for many widely advocated preventive interventions."[132] Neither Asch et al. nor Wei et al. included QALY in their metrics, precluding a QALY-based comparison.

Other reports were considered in an extensive review produced by the Foundation for Blood Research in cooperation with the CDC.[133] Although the review's discussion of previous studies is too extensive to describe here, the review did produce a relevant summary of the financial costs of testing. Using 1996 dollars, the review concluded that diagnosing one case of CF by population screening would cost approximately $400,000 for Ashkenazi Jewish descendants, $500,000 among non-Hispanic Caucasians, and $19 million among Asian Americans. The $19 million figure reflects the low rate of detecting CF in Asian Americans.

Boston University's panel of 40 mutations (including the ACMG's recommended mutations) for $195 and Ambry's test for ΔF508 mutations for $85 both show that the market is at least approaching Rowley's threshold cost of $100 for a cost-effective carrier screening test. Although we cannot estimate overall costs from our price survey, the empirical evidence and empirically derived models discussed above suggest that licensing practices for *CFTR* at least do not preclude cost-effective screening for CF.

Summary of Cost Estimates			
Study	Asch *et al.* (1995 Dollars)	Wei *et al.* (2005 dollars)	ACCE (1996 Dollars)
Costs	• Testing for 6 mutations: $50 • Testing for approx. 30 mutations: $100 • Genetic counselor's time per hour w/benefits: $26 • Patient time per hour w/ benefits: $15 • Amniocentesis (excluded karotyping): $200	• DNA mutation testing (including reagents, disposables, technical time, professional interpretation): $50 • 1 hour counseling with genetics counselor and MD or PhD: $175 • Chorionic villus sampling with karotyping: $1,200 • Amniocentesis with karotyping: $900	• Providing education and information to the entire population: $1 to $3 • Obtaining informed consent: $5 to $10 • Collecting and transporting the sample: $10 (blood);$4 (buccal) • Performing the DNA

[130] Ibid., 1160.
[131] Ibid.
[132] Ibid., 1168.
[133] National Office of Public Health Genomics, CDC, and Foundation for Blood Research. *ACCE Review of CF/Prenatal: Clinical Utility*. 2002. See http://www.cdc.gov/genomics/gtesting/file/print/FBR/CFDisSet.pdf [accessed July 29, 2008].

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	• Microvillar intestinal enzyme analysis (to verify CF diagnosis): $100 • Miscarriage: $260 • Midtrimeseter abortion: $2,800 • Delivery: $3,120 • Travel (per office visit): $5 • Lifetime medical and nonmedical direct costs of CF: $351,278		test: $80 to $100 • Reporting negative results: $2 by mail/fax/electronic • Reporting positive results: $20 (individual); $50 (couple) • Performing diagnostic testing: $400 to $600 (w/o karotype) • Accounting for procedure-related fetal losses: $400
Cost per CF affected birth prevented	• $367,000	• $334,000	• $400,000 (Ashkenazi Jewish) • $500,000 (non-Hispanic Caucasians) • $4,000,000 (Hispanic Caucasians) • $7,000,000 African Americans • $19,000,000 (Asian Americans)

Preimplantation Genetic Diagnosis (PGD)

Although PGD has been used to detect CF in embryos for more than a decade, there is very limited evidence for its cost effectiveness. In an oral presentation supported by the Reproductive Genetics Institute and reported in *Fertility and Sterility*, the cost of performing PGD on 11,511 embryos ($235 million) was compared to the cost of treating CF patients who have been born had PGD not been used to avoid implanting CF affected embryos (est. total $50 million annually, based on $55,537 annual direct care costs per patient).[134] The presenters concluded, "Offering IVF-PGD to all CF carrier couples… is highly cost effective and will save hundreds of millions of direct health care dollars annually." Working in Taiwan, Tsai performed PGD "without using fluorescent primers and expensive automatic instrumentation," which was an improvement over previous techniques and a reduction in financial cost.[135] Neither of those sources gives as much empirical evidence as the studies discussed above, leaving PGD's cost effectiveness open to further research.

[134] Tur-Kaspa et al. Preimplanation genetic diagnosis (PGD) for all cystic fibrosis (CF) carrier couples: strategy and cost analysis. *Fertility & Sterility* 2006. 86(3):S59.
[135] Tsai YH. Cost-effective one-step PCR amplification of cystic fibrosis delta F508 fragment in a single cell for preimplanation genetic diagnosis." *Prenatal Diagnosis* 1999. 19(11):1048–1051.

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Lessons Learned About the Patent Process

Research

There is no direct evidence that the patent process affected the research that ultimately led to *CFTR* gene discovery. The prospect of patents was not reported as an important incentive to do the research, which was largely funded by government and nonprofit entities hoping to understand the disease. Though linkage analysis of the *CFTR* gene was not successful throughout the 1950's,[136] RFLP (restriction fragment length polymorphism) mapping enabled genetic linkage to chromosome 7 to be established in the 1980's. Researchers identified the first linkage between a marker and the CF phenotype in 1985 and identified the *CFTR* gene and its most common mutation, ΔF508, in 1989.[137]

Multiple individuals and institutions applied for patents at the same time and the discovery of the *CFTR* gene was characterized as a "race."[138] However, academic competition more than the prospect of patents incited the intense hunt for the *CFTR* gene and innovation in techniques for gene mapping and positional cloning of genes, at least among the several academic groups involved. Two primary academic groups (Francis Collins and colleagues, University of Michigan and John Riordan, Lap-Chee Tsui and colleagues at The HSC) combined their complementary approaches to advantage and were successful in beating the competition and discovering the *CFTR* gene in June 1989. Collins, Riordan and Tsui published their findings simultaneously in three back to back papers in September 1989 in *Science*. As mentioned earlier, they also jointly filed for patents. We have not found any evidence that CF gene patents impeded subsequent basic or clinical research.

Development

There is no evidence that the patent process affected the speed of genetic test development. The CF patent interferences were ultimately resolved in 2002, largely in the favor of Tsui and Collins. The interference process took several years to resolve at significant expense. However, it does not appear that the interference proceeding added time to the commercial test development process. It did add costs that were largely borne by one of the patent licensees (who had licensed for therapeutic use such as gene therapy) and not the academic research institutions. During patent inference proceedings, the University of Michigan and The Hospital for Sick Children practiced broad, nonexclusive licensing of patents covering mutations including the ΔF508 mutation. The fact that the NIH Consensus Conference (1997) guidelines recommended genetic testing for all "adults with a positive family history of CF, to partners of people with CF, to couples currently planning a pregnancy, and to couples seeking prenatal testing" and that the 2001 ACMG statement made a similarly broad recommendation for carrier screening suggests that CF genetic test was widely available by the time these reports were released.[139]

Commercialization

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[136] Steinberg A et al. Linkage studies with cystic fibrosis of the pancreas. Op. cit.
Steinberg A et al. Sequential test for linkage between cystic fibrosis of the pancreas and the MNS locus. Op. cit.
[137] Tsui L et al. Cystic fibrosis locus defined by a genetically linked polymorphic DNA marker. Op. cit.
Tsui L et al. Genetic analysis of cystic fibrosis using linked DNA markers. Op. cit.
[138] Davies K. The search for the cystic fibrosis gene. *New Scientist* 1989 (21 October). See http://www.newscientist.com/article/mg12416873.900-the-search-for-the-cystic-fibrosis-gene-for-nearly-adecade-several-teams-of-molecular-biologists-h [accessed September 17, 2008].
[139] National Institutes of Health Consensus Development Conference Statement on Genetic Testing for Cystic Fibrosis. Op. cit.
Grody W et al. Laboratory standards and guidelines for population-based cystic fibrosis carrier screening. Op. cit.

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Development and commercialization of new test techniques and technologies continue for CF genetic testing. Laboratories use several test methods, platforms and kits or analyte specific reagents (ASRs). It is likely that broad and non-exclusive licensing practiced by the University of Michigan, HSC, and Johns Hopkins University has facilitated commercial kit development by lowering IP-related barriers to entry. To date, 64 labs across the country offer CF testing.[140] Patents do not appear to limit overall commercial availability.

Communication/Marketing

Direct-to-consumer marketing has not been practiced for CF testing. Marketing and education for CF testing is provided by health professionals within professional associations, among primary care physicians, and among pediatricians. Most laboratories will not perform tests without a doctor's referral. However, as guidelines have called for widespread use of the test, the number of test providers has risen.[141] Although this may increase access, it also means that companies have an incentive to prepare marketing material for patients. In any case, patents and licensing practices have not prevented marketing and publicizing CF testing to date. Non-exclusive licensing may have facilitated growth of the CF genetic testing market.

Adoption

There is no evidence that patents reduced adoption of CF tests by laboratories, healthcare providers, or third party payers.

Consumer Utilization

There is no evidence that *CFTR* gene patents and licensing have limited consumer utilization.

Conclusions

Cystic Fibrosis was selected as a case study for this report to the SACGHS as an example of broad non-exclusive licensing of patented genetic tests. Some providers note that gene patents can limit their practice of medicine and specifically their ability to provide genetic tests. However, Dr. Debra Leonard notes that "[i]f every license or every patent was being licensed like this cystic fibrosis Delta F508 mutation," then such constraints on medical practitioners and the associated controversies would be greatly reduced.[142] Our research shows how patenting and licensing decisions by the University of Michigan, The Hospital for Sick Children and Johns Hopkins University allow for significant research without unduly hindering patient access or commercial markets. These practices also preserve strong patent protection and the accompanying investment incentives for possible therapeutic discoveries arising from the same DNA patents. Our study also suggests that the active participation of the CF Foundation (which funded part of the research)[143] in discussions about intellectual property and licensing allowed patient perspectives to be included and may have significantly influenced decisions about licensing. In addition, scientists' perspectives on uncertainties associated with genetic testing in the long term,

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[140] *CFTR-Related Disorders*. See www.genetests.org [accessed July 2, 2008].
[141] Cutting G. Op. cit.
Grody W et al. The cystic fibrosis mutation 'arms race': when less is more. Op. cit.
[142] Secretary's Advisory Committee on Genetics, Health, and Society (2006). SACGHS Meeting Transcript, June 26-27, 2006. See http://oba.od.nih.gov/oba/SACGHS/meetings/June2006/transcripts/Patents_Licensing-Leonard.pdf [accessed January 14, 2009].
[143] Davies K. Op. cit.

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especially in light of future discoveries and technological evolution, also helped inform decisions about optimal commercialization strategies. Indeed, the broad, non-exclusive diagnostic licensing practices associated with the patents surrounding CF allow for competition as well as innovation.

Acknowledgements

This case study was reviewed by Francis Collins, Arlene Yee, David Ritchie, and Leigh Hopkins for the Secretary's Advisory Committee on Genetics, Health, and Society.

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Appendix A: License Agreement

LICENSE AGREEMENT
MICHIGAN FILE 492p2 TECHNOLOGY
DIAGNOSTIC PRODUCT DISTRIBUTION LICENSE

This License Agreement, effective as of the _ day of _____, 2008 (the "Effective Date"), entered into by _____, a corporation incorporated in the State of _____, located at _____ ("LICENSEE"), the Regents of the University of Michigan, a constitutional corporation of the State of Michigan ("MICHIGAN"), and HSC Research and Development Limited Partnership, a partnership organized and subsisting under the laws of the Province of Ontario, Canada ("RDLP"). LICENSEE, MICHIGAN and RDLP agree as follows:

1. BACKGROUND.

1.1 Michigan (in part in the Howard Hughes Medical Institute ("HHMI") laboratories at MICHIGAN) and the Research Institute of The Hospital for Sick Children of Toronto, Ontario, Canada, ("HSC") have conducted research relating to cystic fibrosis. As a result of that research, MICHIGAN and RDLP have developed rights in the "Licensed Patent(s)" defined below.

1.2 LICENSEE desires to obtain, and MICHIGAN and RDLP, consistent with their missions of education and research, desire to grant a license of the "Licensed Patent(s)" on the terms and conditions listed below.

1.3 MICHIGAN and RDLP have entered into a Memorandum of Agreement covering the Licensed Patent(s), consistent with which MICHIGAN and RDLP are entering into this License Agreement jointly as the licensor of the Licensed Patents.

2. DEFINITIONS.

2.1 "TECHNOLOGY", as used in this Agreement, shall mean the information, manufacturing techniques, data, designs or concepts developed by MICHIGAN and HSC, covering the gene for cystic fibrosis and uses thereof as covered by the claims of U.S. Patent No. 5,776,677 entitled "Cystic Fibrosis Gene."

2.2 "Parties", in singular or plural usage as required by the context, shall mean LICENSEE, MICHIGAN and/or RDLP.

2.3 "Affiliate(s)" shall mean any individual, corporation, partnership, proprietorship or other entity controlled by, controlling, or under common control with LICENSEE through equity ownership, ability to elect directors, or by virtue of a majority of overlapping directors, and shall include any individual, corporation, partnership, proprietorship or other entity directly or indirectly owning, owned by or under common ownership with LICENSEE to the extent of thirty percent (30%) or more of the voting shares, including shares owned beneficially by such party.

2.4 "Licensed Patents" shall mean U.S. Patent No. 5,776,677, a divisional of U.S. Patent No. 6,984,487, entitled "Cystic Fibrosis Gene" and all foreign equivalent patent applications and Patent Cooperation Treaty filings, and all patents issuing therefrom in which Michigan and/or RDLP has or acquires a property interest (currently including the applications listed in the Appendix [AI] attached to this Agreement [see below]). "Licensed Patent(s)" shall also include any divisional, continuation (excluding continuations-in-part), reissue, reexamination or

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extension of the above-described patent applications and resulting patents, along with any extended or restored term, and any confirmation patent, registration patent, or patent of addition.

2.5 "Valid Claim(s)" means any claim(s) in an unexpired patent or pending in a patent application included within the Licensed Patents which has not been held unenforceable, unpatentable, or invalid by a decision of a court or other governmental agency of competent jurisdiction, unappealable or unappealed within the time allowed for appeal, and which has not been admitted to be invalid or unenforceable through reissue or disclaimer. If in any country there should be two or more such decisions conflicting with respect to the validity of the same claim, the decision of the higher or highest tribunal shall thereafter control; however, should the tribunals be of equal rank, then the decision or decisions upholding the claim shall prevail when the conflicting decisions are equal in number, and the majority of decisions shall prevail when the conflicting decisions are unequal in number.

2.6 "Product(s)" shall mean any product(s) whose manufacture, use or sale in any country would, but for this Agreement, comprise an infringement, including contributory infringement, of one or more Valid Claims.

2.7 "Field of Use" shall refer to the field for which Products may be designed, manufactured, used and/or marketed under this Agreement, and shall mean solely Products to be used for the research of, diagnosis of and screening for the disease cystic fibrosis.

2.8 "Net Sales" shall mean the sum, over the term of this Agreement, of all amounts received and all other consideration received (or, when in a form other than cash or its equivalent, the fair market value thereof when received) by LICENSEE and its Affiliates from persons or entities due to or by reason of the sale or other distribution of Products, or the use of Products, including any use by LICENSEE and Affiliates in the performance of services for their customers; less the following deductions and offsets, but only to the extent such sums are otherwise included in the computation of Net Sales, or are paid by LICENSEE and not otherwise reimbursed: refunds, rebates, replacements or credits actually allowed and taken by purchasers for return of Products; customary trade, quantity and cash discounts actually allowed and taken; excise, value-added, and sales taxes actually paid by LICENSEE for Products; and shipping and handling charges actually paid by LICENSEE for Products.

2.9 "Royalty Quarter(s)" shall mean the three month periods ending on the last day of March, June, September and December of each year.

2.10 "Territory" means all countries of the world.

2.11 "First Diagnostic Sale" shall mean the first sale of any Product (including any sale of a service using a Product in the Field of Use) by LICENSEE or an Affiliate, other than for use in clinical trials being conducted to obtain FDA or other governmental approvals to market Products.

3. GRANT OF LICENSE.

3.1 MICHIGAN and RDLP hereby grant to LICENSEE a non-exclusive license under the Licensed Patents to make, have made, use (including use in the performance of services for its customers), market and sell, in the Territory, Products designed and marketed solely for use in the Field of Use.

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3.2 MICHIGAN and RDLP reserve the right to license and use all aspects of the TECHNOLOGY and the Licensed Patents for any use or purpose, including the right to develop and produce Products.

3.3 The license granted to LICENSEE herein shall be without the right to sublicense, except that LICENSEE may sublicense Affiliate(s) who agree to be and are bound in writing to the terms and conditions of this Agreement to the same extent as LICENSEE. LICENSEE agrees to strictly monitor and enforce compliance with the terms and conditions of this Agreement by all Affiliate sublicensees.

4. CONSIDERATION.

4.1 LICENSEE shall pay to MICHIGAN a one-time, non-creditable license issue fee of U.S. $25,000.00, forthwith following the Effective Date. Notwithstanding any other terms of this Agreement, this Agreement and the license granted hereunder shall not become effective until such issue fee is received by MICHIGAN.

4.2 LICENSEE shall also pay MICHIGAN, with respect to each Royalty Quarter, a royalty equal to six percent (6%) of the Net Sales of Products of LICENSEE and Affiliates during such Royalty Quarter.

4.3 The obligation to pay MICHIGAN a royalty under this Article 4 is imposed only once with respect to the same unit of Product regardless of the number of Valid Claims or Licensed Patents covering the same; however, for purposes of determination of payments due hereunder, whenever the term "Product" may apply to a property during various stages of manufacture, use or sale, Net Sales, as otherwise defined, shall be derived from the sale, distribution or use of such Product by LICENSEE or Affiliates at the stage of its highest invoiced value to unrelated third parties.

4.4 LICENSEE shall pay to MICHIGAN an annual license maintenance fee. This annual fee shall accrue in the Royalty Quarter ending in March of the years specified below, and shall be due and payable and included with the report for that quarter.

If LICENSEE defaults in the payment of any annual license maintenance fee, and fails to remedy that default within sixty (60) days after written notice of it by MICHIGAN, then this Agreement and the license rights conveyed herein shall terminate.

The annual license maintenance fees shall be as follows:

(1) In 2005, and in each year thereafter during the term of this Agreement up to and including the year in which LICENSEE first obtains FDA approval or other governmental approval to distribute or use Products in the Field of Use: U.S. $18,000.00;

Also, notwithstanding (1) above (and in place of the amounts therein listed, when applicable):

(2) In the first calendar year following the year in which LICENSEE obtains the approval described in (1) above, and in each year thereafter during the term of this Agreement up to and including the year in which the First Diagnostic Sale occurs: U.S. $20,000.00;

Also, notwithstanding (1-2) above (and in place of the amounts therein listed, when applicable):

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(3) In the first calendar year following the First Diagnostic Sale: U.S. $20,000.00;

(4) In the second year following the First Diagnostic Sale: U.S. $22,500.00;

(5) In the third year following the First Diagnostic Sale: U.S. $25,000.00; and

(6) In the fourth year following the First Diagnostic Sale, and in each year thereafter during the term of this Agreement; U.S. $30,000.00.

Each annual fee paid under (3-6) above may be credited by LICENSEE in full against all earned royalties otherwise to be paid to MICHIGAN under Paragraph 4.2 for the calendar year in which the specific annual fee is paid. The year for which such credits against royalties may be taken includes the Royalty Quarter in which the annual fee accrues and the next three Royalty Quarters.

Each annual fee paid under (1-2) above may be credited by LICENSEE in full against all earned royalties otherwise to be paid to MICHIGAN under Paragraph 4.2 after such annual fee is paid.

4.5 If LICENSEE takes any license(s), in a given country, under valid third party patents which would be infringed by the manufacture, use or sale of Products in that country, then LICENSEE can deduct up to forty percent (40%) of the royalties otherwise due and payable in each Royalty Quarter under Paragraph 4.2 above for Net Sales in that country, until such time as LICENSEE has recovered an amount equal to forty percent (40%) of the royalty paid to such third parties; provided that in no event shall such deducted amounts be applied to reduce or require reimbursement of the annual fees required under Paragraph 4.4. This Paragraph is not intended to imply an obligation upon MICHIGAN or RDLP to reimburse LICENSEE's above-described third-party royalties; the rights granted to LICENSEE in this Paragraph shall not exceed the ability of the above-described mechanism (i.e., a deduction of 40% of royalties due upon Net Sales in the country in question) to reimburse such expenses. LICENSEE shall make an accounting to MICHIGAN of all such third-party royalties, and all resulting deductions from royalties otherwise due and payable to MICHIGAN, as part of its reporting obligations under Article 5 below.

4.6 If MICHIGAN and RDLP grant a license under the Licensed Patents and in the Field of Use to any third party which is substantially the same as the license granted to LICENSEE under Article 3 above, for all or any part of the Territory, but which requires a royalty rate or license maintenance fees lower than those required of LICENSEE under this Agreement, then MICHIGAN and RDLP shall offer those terms to LICENSEE for that part of the Territory, to be effective as of the effective date of the license to that third party.

5. REPORTS.

5.1 Within sixty (60) days after the close of (i) any Royalty Quarter in which a fee under Paragraph 4.4 accrues, and (ii) each Royalty Quarter following the First Diagnostic Sale during the term of this Agreement (including the close of any Royalty Quarter immediately following any termination of this Agreement), LICENSEE shall report to MICHIGAN all royalties accruing to MICHIGAN during such Royalty Quarter. Such quarterly reports shall indicate for each Royalty Quarter the gross sales and Net Sales of Products by LICENSEE and Affiliates, and any other revenues with respect to which payments are due, and the amount of such payments, as well as the various calculations used to arrive at said amounts, including the quantity, description

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(nomenclature and type designation), country of manufacture and country of sale of Products. In case no payment is due for any such period, LICENSEE shall so report.

5.2 LICENSEE covenants that it will promptly establish and consistently employ a system of specific nomenclature and type designations for Products so that various types can be identified and segregated, where necessary; LICENSEE and Affiliates shall consistently employ such system when rendering invoices thereon and henceforth agree to inform MICHIGAN, or its auditors, when requested as to the details concerning such nomenclature system as well as to all additions thereto and changes therein.

5.3 LICENSEE shall keep, and shall require its Affiliates to keep, true and accurate records and books of account containing data reasonably required for the computation and verification of payments to be made as provided by this Agreement, which records and books shall be open for inspection upon reasonable notice during business hours by an independent certified accountant selected by MICHIGAN, for the purpose of verifying the amount of payments due and payable. Said right of inspection will exist for six (6) years from the date of origination of any such record, and this requirement and right of inspection shall survive any termination of this Agreement. MICHIGAN shall be responsible for all expenses of such inspection, except that if such inspection reveals an underpayment of royalties to MICHIGAN in excess of ten percent (10%) for any year, then said inspection shall be at LICENSEE's expense and such underpayment shall become immediately due and payable to MICHIGAN.

5.4 The reports provided for hereunder shall be certified by an authorized representative of LICENSEE to be correct to the best of LICENSEE's knowledge and information.

6. TIMES AND CURRENCIES OF PAYMENTS.

6.1 Payments accrued during each Royalty Quarter shall be due and payable in Ann Arbor, Michigan on the date each quarterly report is due (as provided in Paragraph 5.1), shall be included with such report and shall be paid in United States dollars. LICENSEE agrees to make all payments due hereunder to MICHIGAN by check made payable to "The Regents of The University of Michigan," and sent by prepaid, certified or registered mail, return receipt requested, to the address for notices set forth in Article 19 herein.

6.2 On all amounts outstanding and payable to MICHIGAN, interest shall accrue from the date such amounts are due and payable at two percentage points above the prime lending rate as established by the Chase Manhattan Bank, N.A., in New York City, New York, or at such lower rate as may be required by law.

6.3 Where Net Sales are generated in foreign currency, such foreign currency shall be converted into its equivalent in United States dollars at the exchange rate of such currency as reported (or if erroneously reported, as subsequently corrected) in the Wall Street Journal on the last business day of the Royalty Quarter during which such payments are received by LICENSEE or Affiliates (or if not reported on that date, as quoted by the Chase Manhattan Bank, N.A., in New York City, New York).

6.4 Except as provided in the definition of Net Sales, all royalty payments to MICHIGAN under this Agreement shall be without deduction for sales, use, excise, personal property or other similar taxes or other duties imposed on such payments by the government of any country or any political

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subdivision thereof; and any and all such taxes or duties shall be assumed by and paid by LICENSEE.

7. COMMERCIALIZATION.

7.1 It is understood that LICENSEE has the responsibility to do all that is necessary for any governmental approvals to manufacture and/or sell Products.

7.2 LICENSEE agrees to use reasonable efforts to develop Products, obtain any government approvals necessary, and manufacture and sell Products at the earliest possible date; and to effectively exploit, market and manufacture in sufficient quantities to meet anticipated customer demand and to make the benefits of the Products reasonably available to the public.

7.3 Within fifteen (15) days of the First Diagnostic Sale, LICENSEE shall report by written letter to MICHIGAN the date and general terms of that sale.

8. PATENT APPLICATIONS AND MAINTENANCE.

8.1 MICHIGAN and RDLP shall control all aspects of filing, prosecuting, and maintaining Licensed Patents, including foreign filings and Patent Cooperation Treaty filings. MICHIGAN and RDLP may in their sole discretion decide to refrain from or to cease prosecuting or maintaining any of the Licensed Patents, including any foreign filing or any Patent Cooperation Treaty filing.

8.2 MICHIGAN shall notify LICENSEE of any issuance of any Licensed Patent(s) and the Valid Claims included therein, and any lapse, revocation, surrender, invalidation or abandonment of any Licensed Patent or Valid Claim.

9. INFRINGEMENT.

9.1 If LICENSEE becomes aware of or reasonably suspects infringement of Licensed Patents by third parties, LICENSEE agrees to promptly notify MICHIGAN of such alleged infringement.

9.2 MICHIGAN and RDLP, at their sole discretion and at their own expense, may initiate proceedings in response to alleged infringement of Licensed Patents, but are under no obligation to do so.

10. NO WARRANTIES; LIMITATION ON MICHIGAN'S and RDLP'S LIABILITY.

10.1 MICHIGAN and RDLP, including their fellows, directors, officers, employees and agents, make no representations or warranties that any Licensed Patent is or will be held valid, or that the manufacture, use, sale or other distribution of any Products will not infringe upon any patent or other rights not vested in MICHIGAN or RDLP.

10.2 **MICHIGAN**, **HSC** AND **RDLP**, INCLUDING THEIR FELLOWS, DIRECTORS, OFFICERS, EMPLOYEES AND AGENTS, MAKE NO REPRESENTATIONS, EXTEND NO WARRANTIES OF ANY KIND, EITHER EXPRESS OR IMPLIED, INCLUDING BUT NOT LIMITED TO THE IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, AND ASSUME NO RESPONSIBILITIES WHATEVER WITH RESPECT TO DESIGN, DEVELOPMENT, MANUFACTURE, USE, SALE OR OTHER DISPOSITION BY **LICENSEE** OR **AFFILIATES** OF **PRODUCTS**.

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10.3 THE ENTIRE RISK AS TO THE DESIGN, DEVELOPMENT, MANUFACTURE, OFFERING FOR SALE, SALE OR OTHER DISPOSITION, AND PERFORMANCE OF **PRODUCTS** IS ASSUMED BY **LICENSEE** AND **AFFILIATES**. In no event shall MICHIGAN, RDLP or HSC, including their fellows, directors, officers, employees and agents, be responsible or liable for any direct, indirect, special, incidental, or consequential damages or lost profits to LICENSEE, Affiliates or any other individual or entity regardless of legal theory. The above limitations on liability apply even though MICHIGAN, RDLP, or HSC, including their fellows, directors, officers, employees or agents, may have been advised of the possibility of such damage.

10.4 LICENSEE shall not, and shall require that its Affiliates do not, make any statements, representations or warranties or accept any liabilities or responsibilities whatsoever to or with regard to any person or entity which are inconsistent with any disclaimer or limitation included in this Article 10.

10.5 Regardless of any research or testing that may have been done at HSC or MICHIGAN (including HHMI laboratories), HSC, MICHIGAN, and RDLP make no representations regarding how Products can or should be used in the diagnosis of and screening for the disease cystic fibrosis.

10.6 IT IS UNDERSTOOD THAT THE **TECHNOLOGY** AND THE **LICENSED PATENTS** DO NOT IDENTIFY THE PRESENCE OF THE CYSTIC FIBROSIS DISEASE IN ALL CASES.

11. <u>INDEMNITY; INSURANCE</u>.

11.1 LICENSEE shall defend, indemnify and hold harmless and shall require its Affiliates licensed hereunder to defend, indemnify and hold harmless MICHIGAN, RDLP and HSC, as well as their fellows, officers, trustees, directors, employees and agents, from and against any and all claims, demands, damages, losses, and expenses of any nature (including attorneys' fees and other litigation expenses), resulting from, but not limited to, death, personal injury, illness, property damage, economic loss or products liability arising from or in connection with, any of the following:

(1) Any manufacture, use, sale or other disposition by LICENSEE, Affiliates or transferees of Products;

(2) The direct or indirect use by any person of Products made, used, sold or otherwise distributed by LICENSEE or Affiliates;

(3) The use by LICENSEE or Affiliates of any invention related to the TECHNOLOGY or the Licensed Patents.

11.2 MICHIGAN and RDLP shall be entitled to participate at their option and expense through counsel of their own selection, and may join in any legal actions related to any such claims, demands, damages, losses and expenses under Paragraph 11.1 above.

11.3 HHMI and its trustees, officers, employees, and agents (collectively, “HHMI Indemnitees”), will be indemnified, defended by counsel acceptable to HHMI, and held harmless by the LICENSEE from and against any claim, liability, cost, expense, damage, deficiency, loss, or obligation, of any kind or nature (including, without limitation, reasonable attorneys’ fees and other costs and expenses of defense) (collectively, “Claims”), based upon, arising out of, or otherwise relating to this Agreement, including without limitation any cause of action relating to product liability. The

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previous sentence will not apply to any Claim that is determined with finality by a court of competent jurisdiction to result solely from the gross negligence or willful misconduct of an HHMI Indemnitee.

11.4 LICENSEE shall purchase and maintain in effect a policy of product liability insurance covering all claims with respect to diagnostic testing for cystic fibrosis using a Product and any Products manufactured, sold, licensed or otherwise distributed by LICENSEE and Affiliates. Such insurance policy must specify MICHIGAN, HHMI, RDLP and HSC, including their fellows, officers, trustees, directors, Regents, agents and employees, as an additional insureds. LICENSEE shall furnish certificate(s) of such insurance to MICHIGAN, upon request.

12. TERM AND TERMINATION.

12.1 Upon any termination of this Agreement, and except as provided herein to the contrary, all rights and obligations of the Parties hereunder shall cease, except as follows:

(1) Obligations to pay royalties and other sums accruing hereunder up to the day of such termination;

(2) MICHIGAN's rights to inspect books and records as described in Article 5, and LICENSEE's obligations to keep such records for the required time;

(3) Obligations of defense and indemnity under Article 11;

(4) Any cause of action or claim of LICENSEE or MICHIGAN or RDLP accrued or to accrue because of any breach or default by another Party hereunder;

(5) The general rights, obligations, and understandings of Articles 2, 10, 15, 17, 26 and 27; and 28;

(6) All other terms, provisions, representations, rights and obligations contained in this Agreement that by their sense and context are intended to survive until performance thereof.

12.2 This Agreement will become effective on its Effective Date and, unless terminated under another, specific provision of this Agreement, will remain in effect until and terminate upon the last to expire of Licensed Patents.

12.3 If LICENSEE shall at any time default in the payment of any royalty or the making of any report hereunder, or shall make any false report, or shall commit any material breach of any covenant or promise herein contained, and shall fail to remedy any such default, breach or report within sixty (60) days after written notice thereof by MICHIGAN specifying such default, then MICHIGAN and RDLP may, at their option, terminate this Agreement and the license rights granted herein by notice in writing to such effect. Any such termination shall be without prejudice to any Party's other legal rights for breach of this Agreement.

12.4 LICENSEE may terminate this Agreement by giving MICHIGAN a notice of termination, which shall include a statement of the reasons, whatever they may be, for such termination and the termination date established by LICENSEE, which date shall not be sooner than ninety (90) days after the date of the notice. Such notice shall be deemed by the Parties to be final.

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12.5 In the event LICENSEE shall at any time during the term of this Agreement deal with the TECHNOLOGY or Products in any manner which violates the laws, regulations or similar legal authority of any jurisdiction including, but not limited to, the public health requirements relating to the TECHNOLOGY or Products or the design, development, manufacture, offering for sale, sale or other disposition of Products, the license granted herein shall terminate immediately with respect to such Products within the territory encompassed by such jurisdiction.

13. ASSIGNMENT.

Due to the unique relationship between the Parties, this Agreement shall not be assignable by LICENSEE without the prior written consent of MICHIGAN and RDLP. Any attempt to assign this Agreement without such consent shall be void from the beginning. MICHIGAN and RDLP shall not unreasonably withhold consent for LICENSEE to assign this Agreement to a purchaser of all or substantially all of LICENSEE's business. No assignment shall be effective unless and until the intended assignee agrees in writing with RDLP and MICHIGAN to accept all of the terms and conditions of this Agreement. Further, LICENSEE shall refrain from pledging any of the license rights granted in this Agreement as security for any creditor.

14. REGISTRATION AND RECORDATION.

14.1 If the terms of this Agreement, or any assignment or license under this Agreement are or become such as to require that the Agreement or license or any part thereof be registered with or reported to a national or supranational agency of any area in which LICENSEE or Affiliates would do business, LICENSEE will, at its expense, undertake such registration or report. Prompt notice and appropriate verification of the act of registration or report or any agency ruling resulting from it will be supplied by LICENSEE to MICHIGAN.

14.2 Any formal recordation of this Agreement or any license herein granted which is required by the law of any country, as a prerequisite to enforceability of the Agreement or license in the courts of any such country or for other reasons, shall also be carried out by LICENSEE at its expense, and appropriately verified proof of recordation shall be promptly furnished to MICHIGAN.

15. LAWS AND REGULATIONS OF THE UNITED STATES AND CANADA; EXPORT.

15.1 Activities under this Agreement shall be subject to all appropriate United States and Canadian laws and regulations now or hereafter applicable.

15.2 LICENSEE shall comply, and shall require its Affiliates to comply, with all provisions of any applicable laws, regulations, rules and orders relating to the license herein granted and to the testing, production, transportation, export, packaging, labeling, sale or use of Products, or otherwise applicable to LICENSEE's or its Affiliates' activities hereunder.

15.3 LICENSEE shall obtain, and shall require its Affiliates to obtain, such written assurances regarding export and re-export of technical data (including Products made by use of technical data) as may be required by the United States Office of Export Administration Regulations, and LICENSEE hereby gives such written assurances as may be required under those Regulations to MICHIGAN.

15.4 LICENSEE shall obtain, and shall require its Affiliates to obtain, such authorization regarding export and re-export of technical data (including Products made by use of technical data) as may be required by the Department of External Affairs, Export Controls Division, or any authorization

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necessary for export from or import into Canada, and LICENSEE hereby gives written assurances as may be required under those regulations to RDLP.

16. BANKRUPTCY.

If during the term of this Agreement, LICENSEE shall make an assignment for the benefit of creditors, or if proceedings in voluntary or involuntary bankruptcy shall be instituted on behalf of or against LICENSEE, or if a receiver or trustee shall be appointed for the property of LICENSEE, MICHIGAN and RDLP may, at their option, terminate this Agreement and revoke the license herein granted by written notice to LICENSEE.

17. PUBLICITY.

LICENSEE agrees to refrain from using and to require Affiliates to refrain from using the name of MICHIGAN, HHMI, RDLP and HSC in publicity or advertising without the prior written approval of that entity.

18. PRODUCT MARKING.

LICENSEE agrees to mark, and to require Affiliates to mark, Products with the appropriate patent notice as approved by MICHIGAN or RDLP (when appropriate), such approval not to be unreasonably withheld.

19. NOTICES.

Any notice, request, report or payment required or permitted to be given or made under this Agreement by a Party shall be given by sending such notice by certified or registered mail, return receipt requested, to the address set forth below or such other address as such Party shall have specified by written notice given in conformity herewith. Any notice not so given shall not be valid unless and until actually received, and any notice given in accordance with the provisions of this Paragraph shall be effective when mailed.

To LICENSEE:

Attn.:

To MICHIGAN:
The University of Michigan
Technology Management Office
Wolverine Tower, Room 2071
3003 South State Street
Ann Arbor, MI 48109-1280
U.S.A.

Attn.: File No. 492p2

with a copy to:
HSC Research and Development
Limited Partnership
555 University Avenue,
Toronto, Ontario M5G 1X8
CANADA
Attn.: President

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20. INVALIDITY.

In the event that any term, provision, or covenant of this Agreement shall be determined by a court of competent jurisdiction to be invalid, illegal or unenforceable, that term will be curtailed, limited or deleted, but only to the extent necessary to remove such invalidity, illegality or unenforceability, and the remaining terms, provisions and covenants shall not in any way be affected or impaired thereby.

21. ENTIRE AGREEMENT AND AMENDMENTS.

This Agreement contains the entire understanding of the Parties with respect to the matter contained herein. The Parties may, from time to time during the continuance of this Agreement, modify, vary or alter any of the provisions of this Agreement, but only by an instrument duly executed by authorized officials of all Parties hereto.

22. WAIVER.

No waiver by a Party of any breach of this Agreement, no matter how long continuing or how often repeated, shall be deemed a waiver of any subsequent breach thereof, nor shall any delay or omission on the part of a Party to exercise any right, power, or privilege hereunder be deemed a waiver of such right, power or privilege.

23. ARTICLE HEADINGS.

The Article headings herein are for purposes of convenient reference only and shall not be used to construe or modify the terms written in the text of this Agreement.

24. NO AGENCY RELATIONSHIP.

The relationship between the Parties is that of independent contractor and contractees. LICENSEE shall not be deemed to be an agent of MICHIGAN or RDLP in connection with the exercise of any rights hereunder, and shall not have any right or authority to assume or create any obligation or responsibility on behalf of MICHIGAN or RDLP.

25. FORCE MAJEURE.

No Party hereto shall be deemed to be in default of any provision of this Agreement, or for any failure in performance, resulting from acts or events beyond the reasonable control of such Party, such as Acts of God, acts of civil or military authority, civil disturbance, war, strikes, fires, power failures, natural catastrophes or other "force majeure" events.

26. GOVERNING LAW.

This Agreement and the relationship of LICENSEE to the other Parties shall be governed in all respects by the law of the State of Michigan or the Province of Ontario (notwithstanding any provisions governing conflict of laws under such law to the contrary), depending upon the jurisdiction in which any action relating to the Agreement is brought; except that questions affecting the construction and effect of any patent shall be determined by the law of the country in which the patent has been granted.

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27. JURISDICTION AND FORUM.

LICENSEE hereby consents to the jurisdiction of the courts of the State of Michigan over any dispute concerning this Agreement or the relationship of the Parties. Should LICENSEE bring any claim, demand or other action against MICHIGAN or RDLP, including their fellows, officers, employees or agents, arising out of this Agreement or the relationship between the Parties, LICENSEE agrees to bring said action only in an appropriate court of the State or Province of that Party.

28. HHMI THIRD PARTY BENEFICIARY STATUS

HHMI is not a party to this Agreement and has no liability to any licensee, sublicensee, or user of anything covered by this License Agreement, but HHMI is an intended third-party beneficiary of this License Agreement and certain its provisions are for the benefit of HHMI and are enforceable by HHMI in it own name.

IN WITNESS WHEREOF, the Parties hereto have executed this Agreement in triplicate originals by their duly authorized officers or representatives.

FOR LICENSEE

By_____
(authorized representative)

Typed Name_____

Title_____

Date_____

FOR HSC RESEARCH AND DEVELOPMENT LIMITED PARTNERSHIP

By_____
(authorized representative)

Typed Name_____

Title_____

Date_____

FOR THE REGENTS OF THE UNIVERSITY OF MICHIGAN

By_____
(authorized representative)

Typed Name_____

Title_____

Date_____

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Appendix [AI]: Patents and Pending Patent Applications

July 28, 2005

Title: Cystic Fibrosis Gene

Inventors: Tsui, Riordan, Collins, Rommens, Iannuzzi, Kerem, Drumm, Buchwald,

Abstract: The cystic fibrosis gene and its gene product are described for both the normal and mutant forms. The genetic and protein information is used in developing DNA diagnosis, protein diagnosis, carrier and patient screening, drug and gene therapy, cloning of the gene and manufacture of the protein, and development of cystic fibrosis affected animals.

Patent Applications Pending:

Country	Number	Date Filed
United States	07/396,894	abandoned
United States	07/399,945	abandoned
United States	07/401,609	31/08/89
US Continuation (6)	08/123,864	20/09/93
US Divisional (7)	08/252,778	2/06/94
US Divisional (3)	08/446,866	6/06/95
US Divisional	08/471,654	abandoned
US Divisional	08/466,897	abandoned
US Divisional (5)	08/469,630	6/06/95
US Divisional (4)	08/469,617	6/06/95
Ireland (8)	3024/90	21/08/90
PCT	CA90/00267	20/08/90
	WO 91/02796	7/03/91
EPO (1)	90912428.1	20/08/90
Japan	511424/90	20/08/90
Japan Divisional	029998/04	5/03/04
Canada	2066204-2	20/08/90
Australia (2)	61616/90	20/08/90
		Date Issued
(1) EPO*	0489058	5/11/03
(2) Australia granted	647,408	25/01/94
(3) US issued	5,766,677	7/07/98
(4) US issued	6,201,107	13/03/01
(5) US issued	6,730,777	4/05/04
(6) US allowed on 6/04/05		
(7) US issued	6,902,907	7/06/05
(8) Ireland granted	83911	6/05/05

* Designated States include the following countries: Austria, Belgium, Switzerland, Liechtenstein, Germany, Denmark, Spain, France, United Kingdom, Italy, Luxembourg, Netherlands, Sweden

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Appendix B: Patents Related to Discovery of Cystic Fibrosis Gene

Patent No.	Date Filed and Issued	Inventors	Patent Holder	First Independent Claim
W09102796A1 (WIPO)	03/07/1991	Tsui et al.	HSC Research and University of Michigan	(Pending Claim:) A DNA molecule comprising an intronless DNA sequence selected from the group consisting of: (a) DNA sequences which correspond to the DNA sequence of Figure 1 from amino acid residue position 1 to position 1480; (b) DNA sequences encoding normal *CFTR* polypeptide having the sequence according to Figure 1 for amino acid residue positions from 1 to 1480; (c) DNA sequences which correspond to a fragment of the sequence of Figure 1 including at least 16 sequential nucleotides between amino acid residue positions 1 and 1480; (d) DNA sequences which comprise at least 16 nucleotides and encode a fragment of the amino acid sequence of Figure 1; and (e) DNA sequences encoding an epitope encoded by at least 18 sequential nucleotides in the sequence of Figure 1 between amino acid residue positions 1 and 1480.
U.S. 5876974	08/30/1994 03/02/1999	Gregory	Genzyme Corporation	A method of producing a DNA molecule encoding wild type human cystic fibrosis transmembrane conductance regulator protein (*CFTR*), said method comprising: growing E. coli cells comprising a purified and isolated DNA molecule encoding wild type human *CFTR*; and recovering said DNA from said cells
U.S. 5,407,796	01/04/1991 04/18/1995	Cutting et al.	Johns Hopkins University	A nucleic acid probe which is complementary to a mutant allele of the *CFTR* gene said allele being selected from the group consisting of: Asn549, Asp551, Stop553, and Thr559.
U.S. 5776677	06/06/1995 07/07/1998	Tsui et al.	HSC Research and University of Michigan	A method for screening a subject to determine if said subject is a CF carrier or a CF patient, comprising: (a) providing a biological sample of the subject to be screened, said sample containing a mutant or a normal *CFTR* gene; and (b) assaying said biological sample for the mutant or the normal *CFTR* gene, wherein the assay includes: (i) assaying for the presence of a normal *CFTR* gene by hybridization comprising: (A) an oligonucleotide probe which specifically binds to a normal DNA molecule

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				encoding a normal *CFTR* polypeptide, wherein the normal DNA molecule comprises a DNA sequence selected from the group consisting of: (1) a DNA sequence encoding a normal *CFTR* protein having the amino acid sequence depicted in FIG. 1; (2) a DNA sequence which hybridizes under stringent conditions to at least 16 contiguous nucleotides of the DNA sequence of (1); and (3) a DNA sequence complementary to the DNA sequence of (1) or (2), and (B) providing at least one reagent for detecting the hybridization of the oligonucleotide probe to said normal DNA molecule; or (ii) assaying for the presence of a mutant *CFTR* gene by hybridization comprising: (A) an oligonucleotide probe which specifically binds to a mutant DNA molecule encoding a mutant *CFTR* polypeptide, wherein the mutant DNA molecule comprises a DNA sequence selected from the group consisting of: (1) a DNA sequence encoding a mutant *CFTR* protein having the amino acid sequence depicted in FIG. 1 with a .DELTA.F508 CF mutation as a three base pair deletion of the codon encoding phenylalanine at amino acid position 508 in FIG. 1; (2) a DNA sequence which hybridizes under stringent conditions to at least 16 contiguous nucleotides of the DNA sequence of (1), said DNA sequence containing said .DELTA.F508 CF mutation; and (3) a DNA sequence complementary to the DNA sequence of (1) or (2); and (B) providing at least one reagent for detecting the hybridization of the oligonucleotide probe to said mutant DNA molecule, wherein the probe and the reagent in (i) and (ii) are each present in amounts effective to perform the hybridization assay.
U.S. 6001588	07/13/1992 12/14/1999	Tsui et al.	HSC Research	A DNA molecule comprising an intronless DNA sequence encoding a mutant *CFTR* polypeptide, said intronless DNA sequence varying from that of SEQ ID NO:1 in having nucleotide sequence variants resulting in a deletion or alteration of an amino acid in the encoded *CFTR* polypeptide, so that the sequence of said encoded *CFTR* polypeptide varies from that of SEQ ID NO:2 in an amino acid residue position selected from the group consisting of amino acid residues 85, 178, 455, 493, 507, 542, 549, 560, and 1092 of SEQ ID NO:2, and wherein an alteration at position 549 is either S549R or S549I.
U.S. 6201107	06/06/1995 03/13/2001	Tsui et al.	HSC Research and University of Michigan	An anti-*CFTR* polyclonal or monoclonal antibody specific for a normal *CFTR* polypeptide (SEQ ID NO:17), wherein said antibody is specific for an epitope of the sequence of SEQ ID NO:17 between amino acid residue positions 1 and 1480.
U.S. 6730777	06/06/1995	Tsui et al.	HSC Research	An isolated polypeptide comprising an amino acid sequence

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	05/04/2004		and University of Michigan	(a) according to FIGS. 1A-1H for amino acid residue positions from 1 to 1480 comprising a normal *CFTR* polypeptide.
U.S. 6902907	06/02/1994 06/07/2005	Tsui et al.	HSC Research and University of Michigan	A recombinant vector containing a purified DNA molecule comprising a normal cystic fibrosis transmembrane conductance regulator (*CFTR*) DNA sequence encoding an amino acid sequence depicted in FIGS. 1A-1H selected from the group consisting of amino acid positions: (a) 28 to 45; (b) 58 to 75; (c) 104 to 117; (d) 139 to 153; (e) 204 to 249; (f) 279 to 294; (g) 347 to 698; (h) 500 to 512; (i) 710 to 757; (l) 725 to 739; (k) 758 to 796; (l) 933 to 946; (m) 1066 to 1084; and (n) 1188 to 1480.
U.S. 6984487	09/20/1993 01/10/2006	Tsui et al.	HSC Research and University of Michigan	A purified DNA molecule, comprising a cystic fibrosis transmembrane conductance regulator (*CFTR*) DNA sequence selected from the group consisting of: (a) a DNA sequence encoding a normal *CFTR* protein having the amino acid sequence depicted in FIG. 1; (b) a DNA sequence which hybridizes under stringent conditions to at least 16 contiguous nucleotides of the DNA sequence depicted in FIG. 1; and (c) a DNA sequence complementary to the DNA sequence of (a) or (b), wherein said DNA sequence of (a), (b) or (c), when present as part of a coding sequence of a normal *CFTR* gene, is expressed in human epithelial cells as a normal *CFTR* protein which is not characterized as having cystic fibrosis associated activity.

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Impact of Gene Patents and Licensing Practices on Access to Genetic Testing for Hearing Loss

Subhashini Chandrasekharan, Ph.D. and Melissa Fiffer

Introduction

Inherited DNA mutations account for over half of all hearing loss cases. Genetic hearing loss can be classified as "syndromic" or "nonsyndromic," depending on whether there are associated clinical features (syndromic) or not (nonsyndromic). Mutations in a multitude of individual genes have been implicated in genetic hearing loss. In some cases, a single mutated gene is associated with hearing loss (dominant) and in others, symptoms occur when both parental genes an individual inherits are mutated (recessive) or a mutation occurs on the X chromosome (X-linked). Mutations in a few genes are the most common: GJB2/Connexin 26, GJB6/Connexin 30, SLC26A4/PDS, MTRNR1, and MTTS1. Those mutations are most commonly tested in the US.

Genetic testing for hearing loss can be controversial. Deafness and acquired hearing loss are disabilities, and whether or not to classify them as medical conditions is contested. Beliefs, lived experiences, and attitudes of individuals, both in the hearing and the Deaf Community differ widely. Whether genetic testing is useful or valuable is not a point of consensus. The complexities of when, whether, and how to classify deafness or hearing loss as a medical condition are beyond the scope of this case study. This case study is about testing for inherited mutations that can cause loss of hearing, but with no particular view about whether such testing is valuable or whether it is a medical service.

The diverse perspectives on whether hearing loss is a disease or a disability influence consumer utilization of tests.[1,2] This complicates the notion of "access," because consumer values and preferences affect utilization. For those who deliberately choose not to use tests, lack of utilization does not indicate lack of access but rather expression of a choice. While this is true in general for all genetic testing, the fact that many in the Deaf Community contest the understanding of deafness as a disability is particularly relevant to this particular case study. Statistics on utilization are always only an indirect measure of access, but for hearing loss utilization rates are particularly suspect. Access is about how many people who want information and could benefit from it can get it; how hearing loss and deafness are regarded directly affects how many people actually want to know the cause, and consequently how many people want testing. Hereafter our analysis will proceed on assumption that we are addressing the use of genetic testing among those who want it and can benefit from it, while recognizing that some would not seek testing even if it were freely available at no cost, and access were not an issue.

Clinical guidelines from the American College of Medical Genetics (ACMG) recommend incorporating genetic testing into the diagnosis of congenital hearing loss.[3] The benefits of genetic testing in diagnostic evaluation of hearing loss include:

(i) Reducing additional time-consuming and expensive testing;

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[1] Burton S, Withrow K, Arnos KS, Kalfoglou AL, Pandya A. A focus group study of consumer attitudes toward genetic testing and newborn screening for deafness. *Genet Med* 2006. 8(12):779-783.
[2] Taneja PR, Pandya A, Foley DL, Nicely LV, Arnos KS. Attitudes of deaf individuals towards genetic testing. *Am J Med Genet* 2004. 130(1):17-21.
[3] American College of Medical Genetics (ACMG). Genetics evaluation guidelines for the etiologic diagnosis of congenital hearing loss. *Genet Med* 2002. 4(3): 162-171.

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(ii) Facilitating early interventions such as hearing aids, cochlear implants, or sign language that significantly improve language ability;

(iii) Understanding disease progression;

(iv) Monitoring associated clinical manifestations and complications, particularly for syndromic hearing loss; and

(v) Providing accurate information on the chance of recurrence that some may choose to use in making decisions about having children (and others may not).

Patent Issues Concerning A Multi-Gene, Multi-Mutation Condition

Hearing loss provides an opportunity to investigate how the patenting of different genes, mutations, and methods by multiple parties can affect access to genetic testing. Patents on multiple DNA sequences (both normal genes and mutations) owned by many parties have raised concerns about "patent thickets" or "anticommons." An *anticommons* can occur when it becomes difficult to offer a service because the intellectual property is dispersed, making it difficult to accumulate all the permissions needed to offer genetic tests for the mutations that might cause hearing loss. This problem was characterized most famously in May 1998 by Heller and Eisenberg.[4]

The related notion of a patent *thicket* is that there is so much intellectual property that needs to be accumulated that it becomes difficult to cut through it all. This is a problem of density and profusion. The two concepts are distinct, but travel together in the real world, in areas where many patents have been granted to many players.

Another concern about patents is "*blocking*," where a single patent owner with claims pertaining to common variants (or to a key method) can block others from doing genetic testing. Blocking can happen from just one or a few patents on key sequences, key methods, or other inventions, if they are difficult or impossible to invent around. This is a concern for hearing loss genes because patents on one or a few common variants might enable those who hold the relevant patents to prevent others from testing for other hearing loss genes.

One concept in intellectual property that requires aggregation of many patent rights is the incentive for *hold-out*. This was not highlighted in our case study, but is a possibility in the future, depending on how the tests evolve. The fact that different mutations have different frequencies (and therefore explain different fractions of cases) means that the potential commercial value of a mutation patent varies. Patents covering common variants should, therefore, generally be more valuable for clinical testing than rare ones. This makes patent pooling more complicated, because many pools simply count patents rather than try to weigh their value, and this may not work for genetic testing even if all the other issues about setting up patent pools were to get resolved. The hold-out incentive appears when a pool has started to form, but a key patent lies outside the pool, and the patent-holder perceives he or she has bargaining advantage and gets a disproportionate benefit (a "hold-out premium") for joining the pool compared to others already in. This is not distinctive to gene patents, but it could surface as a problem if patent pools begin to emerge.

The blocking effect is related to the somewhat different phenomenon of a "penumbra" effect. We characterize a penumbra as activities by a patent holder that are not strictly speaking infringing activities but that in practice result from controlling one or a few patents. This phenomenon appears in this case

[4] Heller MA, Eisenberg RS. Can patents deter innovation? The anticommons in biomedical research. *Science* 1998 (May 1). 280(5364):698-701.

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study because having rights to some common variants can in effect force those who want genetic testing to go to a particular single provider, even though no one can know in advance whether the mutations for which that provider has exclusive rights are actually the ones that cause symptoms in that individual.

One important purpose of seeking genetic testing for hearing loss is to identify the precise molecular cause of the symptoms. So if one testing service retains exclusive rights to test for a common variant, then everyone will of course need to test for that variant, and therefore will send samples to that service, even though the patient may actually have some other mutation—whether unpatented, discovered by someone else and patented, or that no one has ever before discovered. By having rights to one common variant, therefore, a service can force all who seek genetic testing for an entire clinical syndrome to come to it, even if its intellectual property covers only a fraction of all possible mutations. The owner of the key patent thereby controls not only his or her own intellectual property, but collateral space. This enables the holder to accumulate knowledge and expand its intellectual property. All those with hearing loss and seeking genetic testing will come to this service, and new mutations will thus be found by it, leading to more patents for mutations for that condition. By this mechanism, a monopoly on the original discovery is leveraged to future discoveries and future patents on new mutations that no one has discovered before, in the clinical penumbra of the originally patented test.

The penumbra effect in effect expands the intellectual property controlled by the initial patent holder, but it can also create some perverse incentives for subsequent inventions falling in the penumbra of the original patent. Those discovering a hearing loss mutation may think about simply leaving the discovery in the public domain. This might even be socially optimal by making the discovery available for both scientific progress and also making it easy for any testing service to incorporate the new discovery into ongoing testing. But if one service is controlling the testing because it has patent rights to common variants, then leaving the discovery unpatented merely fuels that service's advantage. The institution making the new discovery will thus face several choices: (1) patent and license to the dominant provider, getting a piece of the action (and thus increasing costs in general, both transaction costs of getting and licensing the patent, but also the pass-through costs to the provider and even higher pass-through costs to end-users—this is the option taken by many institutions in this case study); (2) patent and nonexclusively license; (3) don't patent and forego royalties (true for several in this case study); or (4) patent and license to an entirely different provider, setting up a mutual-blocking situation among service providers. To our knowledge mutual blocking has not occurred in this case, but it does appear to be developing for Long-QT syndrome in a separate case study. All of these options are socially suboptimal by one criterion or another (fairness, efficiency, or both). The penumbra effect is one of the reasons that diagnostic licensing will be a difficult policy problem to solve.

Finally, when a clinical condition requires testing for mutations or uses methods covered by many patents, this can increase costs due to *royalty stacking* (because payments to many patent owners are required). This is a common problem in technology licensing, and not distinctive to diagnostics. The solutions include having a cap on total royalties, clauses in licenses that permit royalty reduction if further licenses become necessary to practice an invention, patent pools, and renegotiation rules. These solutions are all dependent on licensing terms. Because licensing is largely opaque—those out-licensing in-licensing technologies have no obligation to share terms of licensing with us—we do not know the extent to which these issues have been addressed in patent licenses that affect genetic testing for hearing loss.

In this case study, we assess the patent status of hearing loss genes and go as far as we can in judging whether or not they pose the potential for a patent thicket, or anticommons, and also the possibility of blocking patents and the penumbra effect. To our knowledge, royalty stacking was not identified as a major problem, although some have wondered about it in interviews. Our main findings are:

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- Most hearing loss genes identified to date are not patented. It does not follow that testing for mutations in these genes is freely available, because of the penumbra effect.
- Testing for Connexin 26 gene mutations, which account for up to half of all non-syndromic recessive hearing loss cases, is patented.
- Of the five most commonly tested hearing loss genes, three (GJB6, SLC26A4, and MTTS1) are not patented. Clinical testing is offered for each of these genes by several providers listed on the GeneTests.org website.
- Testing for mutations in genes involved in less common forms of hearing loss is predominantly offered on a research basis, if it is available at all. Laboratories doing genetic testing for research purposes are generally not CLIA-certified.
- The Institut Pasteur holds two patents (US 5,998,147 and 6,485,908) for the GJB2/ Connexin 26 gene and for detecting its most common deletion mutation 35delG.
- GJB2 patents have been exclusively licensed, apparently with territory of use restrictions, to the for-profit company Athena Diagnostics for testing in the United States, Canada, and Japan. (The documents that specify terms of licensing, including territorial restrictions, are not public, so we can only infer such terms.)
- Cedars-Sinai Medical Center holds a patent (US 5,506,101) that covers MTRNR1 mutation testing, specifically testing for the most common A1555G mutation. This patent is also exclusively licensed to Athena Diagnostics.

Lessons Learned

Research

Research on both rare and common forms of hearing loss appears to have progressed independently of patenting status. There is no evidence that patents have had any positive or negative impact on hearing loss genetics research.

- Research on microarray and chip-based diagnostics for hearing loss is being performed by multiple groups. These diagnostics include patented genes and mutations and are currently offered on a research-only basis in the U.S.
- Concerns about increased patent enforcement have been raised by some researchers, who worry about both research and clinical access.

Development and Commercialization

- We found no evidence that patents accelerated or inhibited hearing loss test development.
- Diagnostic tests for both patented (GJB2, MTRNR1) and unpatented genes (SLC26A4, GBJ6, and MTTS1) have been developed and are offered as a clinical service by several providers. Demand for testing and the extent of research on hearing loss appear to be the primary factors that determine whether diagnostic testing for a particular hearing loss gene is offered as a clinical service at that institution.
- Several providers offer testing panels that include both patented and unpatented tests, e.g., GJB2/Cx26 and GJB6/Cx 30 and MTRNR1 and MTTS1.

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- Testing for GJB2 mutations, which is licensed exclusively to Athena Diagnostics in the U.S., was offered as early as 1998. At least 19 providers offered the test in the U.S in January 2009, a majority of which are academic medical centers. However there have been intermittent enforcement efforts by Athena Diagnostics and some laboratories have stopped testing. In August 2008 one provider (Boston University's Center for Human Genetics) stopped offering Connexin 26 and MTRNR1 testing following Athena's enforcement actions. The recent discontinuation of ASRs offered by Third Wave Technologies[5] to detect the 35delG mutation has increased concern about inability to circumvent patents covering 35delG mutation detection controlled by Athena. This may change the number of providers offering GJB2 testing. Laboratories previously using a two-tiered approach for GJB2 testing, first detecting the 35delG mutation with the ThirdWave Invader™ assay, followed by full sequencing, especially if the sample is negative for 35delG mutations, may now be prevented from reporting out 35delG mutations. This may limit providers from performing clinically meaningful testing since 35delG is the most common GJB2 mutation and some providers may stop offering the test altogether, especially if Athena steps up enforcement activity.
- The price of genetic tests for hearing loss does not appear to correlate with patent status alone. The most expensive test is for Pendred Syndrome, and involves full sequence analysis of SLC26A4. There are no patents associated with the SLC26A4 gene and average test price is ~$1,700. In contrast, testing for GJB2, which is patented, has a list price ranging from $336 to $818. However the price per amplicon for full sequence analysis of GJB2 ($140.8- $430/per amplicon) appears to be higher than SLC26A4 sequencing prices, which range from $55.00-$125.25/per amplicon. This price differential cannot be attributed to patents or licensing, however, because most providers of GJB2 testing probably do not have sublicenses from Athena. (Athena states it has not issued sublicenses.) Factors such as how labor and fixed costs are distributed in test pricing may contribute to this price difference.
- The cost for GJB2 full sequence analysis offered by Athena Diagnostics ($575) is nearly $100 more than the average price of the same test offered by the other providers. Athena's price is nonetheless in the middle of the price range for full-sequence analysis offered by universities, hospitals and academic medical centers ($290-$816). The price per amplicon for GJB2 sequence analysis offered by several non-profit providers (range $140.8- $430) is comparable to Athena's price ($287.50)
- The cost of the MTRNR1 test offered by Athena Diagnostics ($365) is higher than the price of the test offered by universities and hospitals ($150-$285,average price $210). Athena's higher price is not necessarily due to patents, however, and other factors may also contribute to price difference.
- Testing for the MTTS1gene, which is not patented, is offered at prices comparable (average price $238) to MTRNR1 by universities and hospital-based providers. The test is not offered by any commercial testing providers, including Athena Diagnostics.
- The SoundGene™ diagnostic panel developed by Pediatrix includes testing for the most common mutations associated with hearing loss, including GJB2/Connexin 26. Athena Diagnostics has negotiated a sublicense with Pediatrix for Connexin 26 testing. A guaranteed royalty stream from high volume of testing associated with newborn screening follow-up was a likely motivator of this agreement.

[5] Third Wave Technologies Inc was acquired by HoloLogics Inc. in June 2008 and has discontinued marketing several ASRs for genetic testing , including Connexin 26 mutation testing, for business reasons.

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Communication and Marketing

- Patents on hearing loss genes and related genetic tests appear to have little to no impact on dissemination of information about genetic testing or on how tests are marketed.
- Athena Diagnostics does not engage in direct-to-consumer marketing. Athena markets primarily through a sales force keyed to clinical specialists. Athena does not have a sales force dedicated to the marketing of hearing loss tests to pediatricians or hearing loss specialists, rather its sales representatives address many neurological and neuromuscular conditions.

Adoption by Clinical Providers

- To date, exclusive US licenses to patents on Connexin 26 and MTRNR1 testing do not appear to have secured Athena Diagnostics sole provider status. While Athena Diagnostics is the reference provider, a number of additional providers, most of which are academic medical centers, are listed as providers of clinical testing at GeneTests.org. However, Athena has intermittently enforced its patents, and laboratories remain concerned about future enforcement activity.
- Negative effects of patents and licensing practices on adoption of genetic tests for hearing loss by providers are not readily apparent, although concerns were expressed in interviews. As early as 1998, ten providers offered GJB2 testing. The number of providers listed on GeneTests.org has risen to 18 since then. Nine providers for MTRNR1 testing are listed on GeneTests.org. However, there has been intermittent enforcement, and some providers have ceased offering some patented tests. We cannot determine how many laboratories decided against offering tests in the first place due to concerns about patent enforcement.
- Athena Diagnostics has sent at least three "cease and desist" letters to other providers. In one instance, the UCLA Diagnostic Molecular Pathology Laboratory (non-profit) stopped offering a test (Connexin26 GJB2 and GJB6 as part of the panel) and did not negotiate a sublicense, citing substantial up-front payment as an impediment. GeneDx (for-profit) continues to perform full sequence analysis for Connexin 26 to identify mutations associated with a rare skin condition, KID, and agreed not to report hearing loss-associated mutations that are discovered during its full sequence analysis. In August 2008, the Center for Human Genetics of Boston University agreed to stop offering GJB2 testing, along with many other tests for which Athena Diagnostics holds an exclusive license.[6]
- Providers of GJB2 and MTRNR1 testing presumably either collect samples and send them to Athena or offer the service without a sublicense from Athena Diagnostics. Athena states that no sublicenses for hearing loss testing have been negotiated with universities or academic medical centers to date.

Consumer Utilization

- We found no evidence that consumer utilization of these tests is impeded by patents.
- A large number of providers offer these tests with a wide price range.
- Athena Diagnostics does not engage in direct to consumer marketing. There is no evidence that tests may be over utilized by consumers.

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[6] Biomedicine News. See http://www.bio-medicine.org/medicine-technology-1/Boston-University-and-The-Center-for-Human-Genetics--Inc--Announce-Change-in-Testing-Services-2851-1/ [accessed November 14, 2008].

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- Given the lack of clear correlation between the costs of these tests and patent or license status, there is no evidence that patenting or licensing has hindered consumer utilization in the U.S. because of test price.
- Some consumers (such as those covered by MediCal) may not have tests such as Connexin 26 testing covered by their insurance or health plan, because the reference provider Athena Diagnostics does not have a contract with that program. Access for these consumers therefore depends on the availability of additional providers who may have contracts with Medicaid or entails direct out-of-pocket payment by consumers. Uncertainty surrounding whether these alternate providers will face enforcement or will stop testing creates an unstable situation.

Adoption by third party payers

- In our informal phone survey, test providers indicated that genetic tests for hearing loss are usually covered by insurance.
- While comprehensive data on the coverage position of all major insurers for all hearing loss tests are not available, it is unlikely that patents have had significant impact on the adoption of tests. CIGNA health care, for example, covers testing for GJB2 (patented) and GJB6 (unpatented).

Clinical and Scientific Background

Hearing loss refers to the permanent, bilateral or unilateral, sensory or conductive, loss of hearing averaging 30 decibels or more in the frequency region important for speech recognition.[7] Hearing loss can present at different stages in life, and therefore can be classified as prelingual (before learning to speak) or postlingual (after having learned a language). Prelingual hearing loss may be congenital or late-onset. Profound congenital hearing loss occurs in 1.8 per 1,000 live births in the U.S. The prevalence increases to 2.7 per 1,000 among those below five years of age. During the teenage years, prevalence increases to 3.5 per 1,000.[8] The lifetime societal costs for childhood hearing loss are estimated at $1.1 million per person, including lost productivity, special education, vocational rehabilitation, medical costs, and assistive devices attributable to deafness. Universal audiological newborn hearing screening programs have been introduced in the U.S. to reduce speech, social and emotional development problems experienced by children through early detection and intervention. At least 37 states have universal newborn hearing screening legislation and every state has early hearing detection and intervention programs, which screen approximately 93% of all infants.

As a heterogeneous trait, hearing loss has many environmental and genetic causes. Its incidence varies over time and across populations (see Figure 1).[9] Environmental causes, such as infections, account for approximately half of hearing loss cases. Congenital cytomegalovirus (CMV) infection, in particular, is responsible for as much as 10 percent of congenital hearing loss.[10] Genetic causes account for the other half of hearing loss cases. Hearing loss typically occurs due to abnormalities in single genes or sometimes gene pairs. A multitude of different genes and gene pairs (at least 65 genes and 110 choromosomal locations) have been implicated. Many others may yet be discovered.[11]

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[7] American College of Medical Genetics (ACMG). Genetics evaluation guidelines for the etiologic diagnosis of congenital hearing loss. Op. cit.
[8] Morton C, Nance WE. Newborn hearing screening - a silent revolution. *NEJM* 2006. 354:2151-2164.
[9] Ibid.
[10] Ibid.
[11] Ibid.

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Genetic hearing loss can be further classified as "syndromic" and "non-syndromic," depending on whether it is associated with other clinical features (syndromic) or not (non-syndromic).[12] Syndromic cases represent about 30 percent of genetic hearing loss cases overall and encompass at least 400 syndromes and a similar number of genes. Non-syndromic hearing loss or impairment (NSHL or NSHI) comprises the other 70 percent of genetic hearing loss cases and involves at least 100 loci, which can further be broken down by pattern of inheritance. NSHL loci include 55 autosomal recessive (AR), 41 autosomal dominant (AD), 4 X-linked (XL), and two mitochondrial loci. Different mutations at the same locus (chromosomal location, usually a gene) can present as either non-syndromic or syndromic hearing loss.[13] Mutations in different genes may also result in the similar phenotypes (clinical symptoms and signs).[14] A listing of non-syndromic and syndromic hearing loss disorders and loci, including genes, genetic tests, and associated patents, is presented in the appendix (Appendix I and II).

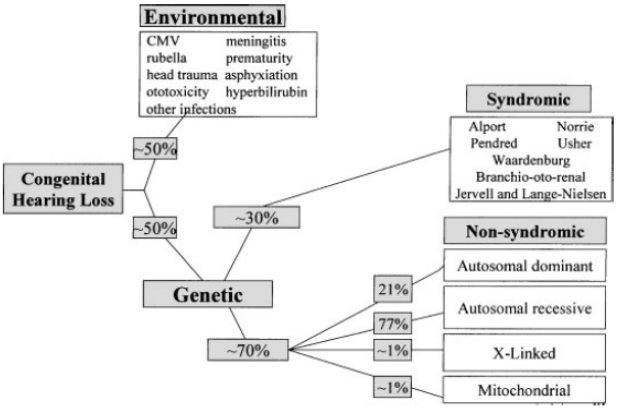

Figure 1. Causes of Hearing Loss (White K. Early hearing detection and intervention programs: opportunities for genetic services. *Am J Med Genet* 2004. 130A(1):29-36.**)**
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Five most Common Genetic Tests for Hearing Loss

Given the numerous hearing loss genes, we have chosen to focus on the five genes most commonly tested for, based on population frequency: GJB2/Connexin 26, GJB6/Connexin 30, SLC26A4/PDS, MTRNR1, and MTTS1.[15]

GJB2

Mutations in GJB2, or Gap Junction Protein Beta-2, have by far the highest frequency among genetic causes of deafness and hearing loss, accounting for up to 50 percent of cases of profound deafness caused by DNA mutations (Table 1)[16]. GJB2 encodes Connexin 26 (Cx26), a hexameric gap junction protein widely expressed in the cells and tissues of the cochlea.[17] The link between GJB2 and non-syndromic

[12] Ibid.
[13] American College of Medical Genetics (ACMG). Genetics evaluation guidelines for the etiologic diagnosis of congenital hearing loss. Op. cit.
[14] Morton C, Nance WE. Op. cit.
[15] The five most common hearing loss genes are also the most frequently tested genes. Authors' email and phone correspondence with Dr. Michael Watson, Director, American College of Medical Genetics, March, 2007.
[16] American College of Medical Genetics (ACMG). (2002). Genetics evaluation guidelines for the etiologic diagnosis of congenital hearing loss. *Genet Med*, 4(3):162-171.
[17] Morton C, Nance WE. Op. cit.

deafness at the DFNB1 locus[18] was first published in a 1997 *Nature* article by D.P. Kelsell and colleagues at St. Bartholomew's and the Royal London School of Medicine and Dentistry, Queen Mary and Westfield College.[19] That same year at the Institut Pasteur, Christine Petit and colleagues discovered the most prevalent GJB2 mutation, 35delG.[20] The Institut Pasteur holds two patents (US 5,998,147 and 6,485,908) for the GJB2/Connexin 26 gene and detection of its common deletion mutation. Patent applications were filed in August 1997 and granted in 1999 and 2002. The Institut Pasteur also holds patents for Connexin 26 in Canada and Japan. We have found no granted patents in Europe, although applications appear to have been filed. Patents have been exclusively licensed to Athena Diagnostics, and we infer these were licensed for use in the U.S., Canada, and Japan. In Europe, the exclusive license for Connexin 26 testing went to Nanogen, a provider of molecular diagnostic services.[21] As of February 2008, "Molecular Diagnostics for Prelingual Hearing" was still listed as a diagnostic technology available for licensing at the Institut Pasteur technology transfer website. This suggests either that existing licenses to Nanogen and Athena do not exhaust all territories worldwide or that provisions for particular fields of use have been retained by Institut Pasteur.[22] We have no direct information about whether Institut Pasteur has granted any additional licenses in Europe or the US.[23]

Based on data gathered through our telephone survey of providers (identified through GeneTests.org), testing for GJB2/Connexin 26 in the United States began as early as 1998. Kenneson et al. surveyed Connexin 26 testing providers in the U.S. in 1999 and 2000 (10 eligible providers in 1999 and 8 providers in 2000).[24] Based on provider information at GeneTests.org, 19 U.S. providers (18 non-profit and 1 for-profit) offered full sequence analysis, which is the most common type of GJB2 testing. PCR-based sequence analysis has been facilitated by the relatively small size of the single GJB2 coding exon.[25] Full sequence analysis is appropriate given that more than 195 GJB2 mutations have been identified,[26] which vary in frequency by race/ethnicity and family history.[27] The average price of the GJB2 full sequence test among non-profit providers is $472.35 compared to the list prices of $575 quoted by Athena Diagnostics, the reference provider (Table 1).

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[18] Nonsyndromic hearing loss loci are classified "DFNB" for recessive, "DFNA" for dominant, "DFN" for X-linked, and "DFNM" if they modify the expression of other genetic forms. The loci within each class are then numbered (Morton C, Nance WE. Op. cit.).

[19] Kelsell D, Dunlop J, Stevens HP, Lench NJ, Liang JN, Parry G et al. Connexin 26 mutations in hereditary non-syndromic sensorineural deafness. *Nature* 1997. 387:80-83.

[20] Denoyelle F, Weil D, Maw MA, Wilcox SA, Lench NJ, Allen-Powell DR et al. Prelingual deafness: high prevalence of 30delG mutation in the connexin 26 gene. *Hum Mol Genet* 1997. 6:2173-2177.

[21] Fresh News. Nanogen licenses rights to gene linked to hereditary deafness. 2003. See http://www.freshnews.com/news/biotech-biomedical/article_15724.html?Nanogen [accessed March 10, 2007].

[22] Institut Pasteur Technology Transfer. See http://www.pasteur.fr/ip/easysite/go/03b-000024-0ap/licensing-opportunities/list-of-technologies-available-for-licencing-or-transfer [accessed January 16, 2009]. Currently the technology is listed under Genomics (ID 98.30); however, it is unclear if the technology listed relates to testing for GJB2 specifically. Previous versions of the site accessed in February 2008 indicated that the technology listed was GJB2 testing.

[23] The Institut Pasteur was contacted by email to clarify the status of licenses but has not responded.

[24] Kenneson A, Myers MF, Lubin IM, Boyle C. Genetic laboratory practices related to testing of the GJB2 (connexin 26) gene in the United States in 1999 and 2000. *Genetic Testing* 2003. 7(1):49-56.

[25] Pandya A, Arnos KS, Xia XJ, Welch KO, Blanton SH, Friedman TB et al. Frequency and distribution of GJB2 (connexin 26) and GJB6 (connexin 30) mutations in a large North American repository of deaf probands. *Genet Med* 2003. 5(4):295-303.

[26] Morton C, Nance WE. Op. cit.
University of Cardiff. *Human Gene Mutation Database*. See http://www.hgmd.cf.ac.uk/ac/gene.php?gene=GJB2 [accessed 19 November 2008].

[27] Pandya, A., Arnos KS, Xia XJ, Welch KO, Blanton SH, Friedman TB, et al. Op. cit.

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Table 1 Prices of Genetic Tests for the five most commonly tested Hearing Loss Gene

Gene Name	Type of hearing loss	Prevalence in affected	Patent holder	Type of Test	No of providers[a]		Price of Test ($)[b]	
					NonProfit	For Profit	NonProfit	For Profit
GJB2	Non syndromic	>50% [i]	Institut Pasteur US 5998147 US 6485908	Full sequence Analysis	18	1	472.35 [c] (362-818)	Athena 575 Prevention[d] 290 Diagnostics
GJB6	Non syndromic	7-16% [j]	N/A	Deletion Analysis	6	1	300.25 [e] (161-534)	295
SLC26A4	Syndromic	4-10% [k]	N/A	Full sequence Analysis	6	0	1686 [f] (1100-2507)	N/A
MTRNR1	Mitochondrial Non syndromic	<1% [i]	Cedars-Sinai US 5506101	Targeted mutation	8	2	210 [g] (150-285)	248 [h] 365
MTTS1	Mitochondrial Non syndromic	<1% [i]	N/A	Targeted mutation	4	0	238 (150-285)	N/A

[a] Providers for specific test type identified from Genetests (see http://www.genetests.org) are current as of January 2009.
[b] List prices of tests obtained from phone survey March 2007 or test laboratory web site
[c] Average list price for 14 out of 17 providers offering full sequence analysis
[d] Prices of 2 separate for-profit providers in 2008. Preventions Diagnostics is no longer listed on GeneTests as of January 2009.
[e] Average list price for 4 out of 7 providers
[f] Average list price for 4 out of 6 providers, not including NIH which offers testing free of charge to research participants
[g] Average list price for 6 out of 8 providers
[h] Prices of 2 separate for-profit providers
[i] American College of Medical Genetics (ACMG). Genetics evaluation guidelines for the etiologic diagnosis of congenital hearing loss. *Genet Med* 2002. 4(3): 162-171.
[j] del Castillo et al. Prevalence and evolutionary origins of the del(GJB6-D13S1830) mutation in the DFNB1 locus in hearing-impaired subjects: a multicenter study**.** *Am J of Human Genet* 2003. 73(6):1452-8.
[k] Morton C, Nance WE. Newborn hearing screening - a silent revolution. *NEJM* 2006. 354:2151-2164.

Table 2 Comparison of Prices for Connexin 26 full sequence analysis

Laboratory	Amplicons*	Gene sequencing price	Cost per amplicon**
Athena Diagnostics (for profit)	2	$575	$287.5
Case Western University	5	$704	$140.8
Emory University	3	$490	$163.33
Univ of Chicago	2	$430	$215.
Cincinnati Childrens Medical Center	2	$533	$266.50
Baylor College	1	$430	$430
Harvard Partners	2	$400	$200
Greenwood Genetics	2	$500	$250
Univ of Washington	2	$362.54	$181.27

* Number of nucleic acid sequences targeted for amplification (according to number of times CPT billing code 83898 is used)
**Gene sequencing price divided by number of times CPT 83898 billed

Prices for full sequence analysis of *Connexin 26*, when normalized for number of amplicons, are also quite variable among providers. The unit price for the test offered by Athena Diagnostics is in the middle of the price range of non-profit providers (Table 2). The average price per amplicon of tests offered by non-profit providers is ~$231 and is comparable to Athena's unit price for full-sequence analysis ($287.5). Although diagnostic billing codes provide some standardization for full-sequence tests,

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techniques and procedures are not identical among laboratories. Beyond comparing prices based on CPT codes for amplification and the same billing codes are not always used the labs surveyed also likely have different overhead costs.

While it appears that the number of U.S. providers offering Connexin 26 testing has increased to 19 from the 10 identified by Kenneson et al. in 2000 (19 providers listed on Genetests.org offered full sequence analysis in January 2009),[28] it is unclear whether the Institut Pasteur's exclusive license to Athena Diagnostics for Connexin 26 testing has deterred other laboratories from testing. Some listed services may send samples to Athena or to offshore providers. To date, it appears that Athena Diagnostics has not granted sublicenses to any other providers listed on GeneTests.org.[29] It is also not clear whether patents and exclusive licensing have contributed to a pricing differential or monopoly pricing by a sole provider. The 14 non-profit institutions we surveyed offer the test at varying prices, some comparable to the price of Athena Diagnostics, as shown in Tables 1 and 2.

GJB6

A significant portion (30-50%) of nonsyndromic genetic hearing loss is attributed to mutations in GJB6, or Gap Junction Protein Beta-6. Like GJB2, GJB6 is expressed in the cochlea and contributes to DFNB1 hearing loss. The GJB6 gene encodes Connexin 30 (Cx 30), a heteromeric gap junction protein that can form channels with Connexin 26, resulting in cases of digenic transmission (that is, the condition results from two different affected genes).[30] The link between the > 300kb GJB6 deletion and nonsyndromic DFNB1 hearing loss was first published in January 2002 in the *New England Journal of Medicine* by Ignacio del Castillo and colleagues at the Unidad de Genética Molecular, Hospital Ramón y Cajal, Madrid, Spain.[31] Genetic testing for GJB6 deletions in patients with hearing loss is linked to the genetic diagnosis of GJB2. GJB6 deletions are found in trans (that is, the genes are located on different chromosomes, suggesting the effect is mediated by a protein produced by the genes, rather than regulation of the genes themselves) with a mutant GJB2 allele and contribute to the same subtype of genetic deafness, DFNB1. The joint contribution of mutations in these two genes to non-syndromic recessive hearing loss is about 30-50%. While prevalence varies across populations, one North American study found a 2.57% prevalence of GJB2/GJB6 digenic cases among deaf individuals, with more severe hearing loss than is typical for GJB2 alone.[32] However a more recent study by Putcha et al. reported that the frequency of a >300Kb deletion in individuals bearing compound GJB2 and GJB6 mutations was only 1% in a large North American cohort. Putcha et al.'s data suggest that this mutation may be quite rare.[33] No U.S. patents or applications associated with the Connexin 30 gene or mutation testing were identified in our patent searches. Dr. Ignacio del Castillo, who first reported the GJB6 deletion mutation, confirmed that he had not applied for patents.[34] To date, seven (six non-profit and one for-profit) providers offer Connexin 30 deletion analysis in the U.S. The test appears to have been offered in the U.S. as early as 2002, based on our telephone survey of providers listed on GeneTests.org. The list price for GJB6/Connexin 30 testing averages $300 at non-profit institutions and is $295 at the one for-profit laboratory.

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[28] Kenneson A, Myers MF, Lubin IM, Boyle C. Op. cit.
[29] Author's personal communications by phone with Dr. Michael Henry, Business Development, Athena Diagnostics, March 2007.
[30] Morton C, Nance WE. Op. cit.
[31] del Castillo I, Villamar M, Moreno-Pelayo MA, del Castillo FJ, Alvarez A, Telleria D et al. A deletion involving the connexin 30 gene in nonsyndromic hearing impairment. *NEJM* 2002. 346:243-249.
[32] Pandya, A., Arnos KS, Xia XJ, Welch KO, Blanton SH, Friedman TB, et al. Op. cit.
[33] Putcha GV et al. A multicenter study for the frequency and distribution of GJB2 and GJB6 mutations in a large North American cohort. *Gen in Med* 2007. 9:413-426.
[34] Authors' email correspondence with Dr. Ignacio del Castillo, June 2007.

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SLC26A4

In 1997, Eric Green and colleagues at the National Human Genome Research Institute (NHGRI) identified the SLC26A4, or PDS gene, which encodes the protein pendrin, a transporter of chloride, bicarbonate and iodide.[35] Mutations in SLC26A4 are implicated in a form of syndromic deafness (Pendred syndrome), as well as a form of nonysndromic deafness DFNB4. Pendred syndrome is the most common form of syndromic deafness, and accounts for up to 10 percent of deafness. Pendred syndrome has an incidence of 7.15-10 per 100,000 births.[36]

While both Pendred syndrome and DFNB4 involve severe hearing loss and an enlarged vestibular aqueduct, Pendred syndrome is also associated with thyroid goiter.[37] The severity of goiter is variable, and thyroid symptoms may not occur until late childhood or even adolescence. Pendred syndrome typically has a prelingual age of onset (before the critical period for language development), whereas nonsyndromic DFNB4-associated deafness tends to be postlingual.[38] No U.S. patents relating to SLC26A4 were identified.[39]

Based on our informal phone survey of providers, testing for SLC26A4 has been available since at least 2002. The most commonly offered test, full-sequence analysis, can detect disease-causing mutations in about half of multiplex and one-fifth of simplex cases.[40] All six U.S. providers of full sequence analysis SLC26A4 testing are non-profit institutions, and the average price is $1,686. The relatively high price of SLC26A4 full sequence analysis cannot be attributed to the existence of a patent or exclusive licensing. Rather, it appears that the cost of full sequence analysis relates to SLC26A4 being a large gene (~77 Kb) with twenty-one exons encoding a 4.93 Kb transcript. Therefore, testing requires testing methods comparable in complexity and price to testing for inherited susceptibility to colon and breast cancer.[41] The price/per amplicon for sequencing the SLC26A4 gene ranges from $55.00- $125.25 when standardized for the number of PCR amplifications reactions performed.[42] Four providers offer SLC26A4 analysis for specific mutations at lower costs ($635) than the full sequence analysis. Targeted mutation analysis has a sensitivity of 70% for heterozygotes and 91% for those homozygous for a mutation.[43]

MTRNR1 and MTTS1

Mitochondrial forms of moderate to profound nonsyndromic hearing loss result from mutations in either the MTRNR1 or MTTS1 genes in mitochondrial DNA, each of which accounts for fewer than 1% of hearing loss cases. MTRNR1 encodes 12S ribosomal RNA (12S rRNA), while MTTS1 encodes transfer

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[35] Everett L, Glaser B, Beck JC, Idol JR, Buchs A, Heyman M et al. Pendred syndrome is caused by mutations in a putative sulphate transporter gene (PDS). *Nat Genet* 1997. 17:411-422.
[36] Ibid.
[37] Smith R, Van Camp G. *Pendred Syndrome/DFNB4.* 2008. See http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=pendred [retrieved April 15, 2007]. In the absence of goiter, Pendred syndrome is classified by an abnormal perchlorate discharge test.
[38] Morton C, Nance WE. Op. cit.
[39] Requires independent verification by Dr. Eric Green, the senior author on the publication reporting the discovery of the PDS gene and mutations.
[40] Smith R, Van Camp G. Op. cit.
[41] Morton C, Nance WE. Op. cit.
Cook-Deegan R et al. *Impact of Gene Patents on Access to Genetic Testing for Inherited Susceptibility to Cancer: Comparing Breast and Ovarian Cancers to Colon Cancers.* Peer-reviewed case study submitted to the Secretary's Advisory Committee on Genetics, Health, and Society, 2008.
[42] The number of amplicons for SLC26A4 gene sequencing is 20, the number of nucleic acid sequences targeted for amplification (base on the number of times CPT billing code 83898 is used by the provider).
[43] Ibid.

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RNA for serine (tRNA Ser[UCN]).[44] The most common MTRNR1 mutation, A1555G, occurs with a 0.3% frequency in the United States.[45] Prezant et al., from Cedars-Sinai Medical Center in Los Angeles, California, first reported the association between A1555G mutations and aminoglycoside-induced and nonsyndromic deafness in *Nature Genetic*s in July 1993.[46,47]

MTRNR1 mutations may contribute to permanent, non-progressive hearing loss either through: (1) susceptibility to aminoglycoside (antibiotic) ototoxicity, irrespective of dose, or (2) late onset hearing loss in the absence of aminoglycoside exposure. MTTS1-related hearing loss, in contrast, has a characteristic progression first appearing during childhood and with penetrance that varies by individual mutational load (more numerous mutations accompany earlier onset and more severe deafness).[48] Higher mutation loads of some MTTS1 mutations also correlate with the manifestation of other clinical signs, such as palmoplantar keratoderma, or ataxia and myoclonus.

The association between mutations in MTTS1 (tRNA –Ser [UCN]) and sensorineural deafness was first reported in 1994 by F.M. Reid and colleagues at the University of Glasgow in Scotland, UK.[49]

Cedars-Sinai Medical Center holds a patent (US 5,506,101) that covers MTRNR1 mutation testing, specifically testing for the A1555G mutation. The patent application was filed in June 1993 and granted in April 1996. Athena Diagnostics acquired an exclusive license for mutation testing for MTRNR1 from Cedars-Sinai Medical Center. Cedars-Sinai Medical Center also holds patents in Japan and Canada for MTRNR1 A1555G mutation and testing. No patents were filed in Europe.

Our searches found no patents covering the MTTS1 sequence or genetic testing for its mutations.

MTRNR1 testing first became available in the U.S in 2000. Targeted mutational analysis is now offered by ten U.S. providers. The two for-profit providers average a higher list price ($355) than the six non-profit (university hospitals and medical center based) providers (average $210) (See Table 1). Information about sublicenses from Athena Diagnostics for MTRNR1 mutation testing is not publicly available. (If SACGHS sends a list of queries to Athena Diagnostics, licensing status of MTRNR1 testing could be included.) In contrast, MTTS1 targeted mutation analysis has been available since 2004 and is offered by four non-profit providers for an average price of $238 (see Table 1). In addition, a subset of non-profit providers also offers testing for a panel of mitochondrial mutations, including both MTRNR1 and MTTS1, for an average price of $438.

Newborn Hearing Screening

Because of the potential for language, social, emotional, and other developmental consequences in children whose hearing loss is detected after six months of age, a 1993 National Institutes of Health (NIH)

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[44] Pandya A. *Nonsyndromic Hearing Loss and Deafness, Mitochondrial*. 2007. See http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=mt-deafness [accessed January 15, 2008].
[45] Pandya A. *Nonsyndromic Hearing Loss and Deafness, Mitochondrial*. 2007. See http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=mt-deafness [accessed January 15, 2008].
[46] Prezant T, Agapian JV, Bohlman MC, Bu X, Oztas S, Qiu WQ et al. Mitochondrial ribosomal RNA mutation associated with both antibiotic-induced and non-syndromic deafness. *Nat Genet* 1993. 4:289-294.
[47] Estivill X, Govea N, Barcelo A, Perello E, Badenas C, Romero E et al. Familial progressive sensorineural deafness is mainly due to the mtDNA A1555G mutation and is enhanced by treatment with aminoglycosides. *Am J Hum Genet* 1998. 62:27-35.
[48] Pandya A. Op. cit.
[49] Reid F, Vernham GA, Jacobs HT. A novel mitochondrial point mutation in a maternal pedigree with sensorineural deafness. *Hum Mutat* 1994. 3(3):243-247.

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Consensus Development Conference endorsed universal newborn hearing screening.[50] In 1999, the Health Resources and Services Administration (HRSA) and Centers for Disease Control and Prevention (CDC) began funding state Early Hearing Detection and Intervention (EHDI) programs.[51] At least 37 states have legislation for universal newborn screening for hearing. Today, EHDI programs exist in every state, providing screening for approximately 93% of all infants.[52] The goals of EHDI programs are three-fold: (1) to screen all newborns before one month; (2) to diagnose newborns before three months; and (3) to coordinate intervention before six months[53] (see Appendix III for detailed flowchart). EHDI programs have reduced the average age for confirming hearing loss from 20 to 30 months (before the program), to 2 to 3 months (after implementation).

The EHDI programs miss some hearing loss cases, however, because prelingual hearing loss does not always present during infancy. SLC26A4 and A1555G-related hearing loss can appear after infancy, for example. Some cases of GJB2 deafness cannot be detected at birth. With an estimated non-penetrance rate of 3.8%,[54] EHDI programs are seen by some as an opportunity for more genetic testing as part of the evaluation process.[55,56] Practical obstacles remain in screening programs for hearing loss, including uncertainty about the appropriate timing and role of genetic testing in the EHDI process.[57] Survey data show that 20% of professionals who administer EHDI programs lack genetics training, which fuels concern about ordering and interpreting complex genetic tests.[58]

Clinical Guidelines for Genetic Testing

In 2002, the American College of Medical Genetics (ACMG) published clinical guidelines that incorporate genetic testing into the diagnosis of congenital hearing loss.[59] The Cincinnati Children's Hospital Medical Center's testing paradigm exemplifies how hearing loss genetic test providers approach genetic evaluation (see Appendix IV). A pre-test session to explain the causes and types of deafness, along with testing options and modes of inheritance, is important. After the pre-test session, the next step entails getting a family history and an individual patient history and conducting a physical examination to determine whether or not a diagnosis is apparent. If syndromic hearing loss is suspected, the ACMG recommends gene-specific mutation tests. The diagnosis of non-syndromic cases is more complex, and relies on details of family history and individual symptoms. Individuals with hearing-impaired first-degree relatives, or two deaf parents, are also candidates for GJB2 testing. As the most common genetic cause of hearing loss, GJB2 is the first in a series of recommended tests.

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[50] *Early Identification of Hearing Impairment in Infants and Young Children. NIH Consensus Development Conference Statement*. March 1 – 3, 1993. See http://consensus.nih.gov/1993/1993HearingInfantsChildren092html.htm [accessed January 16, 2009].
[51] White KR. The current status of EHDI programs in the United States. *Ment Retard Disabil Res Rev* 2003. 9:79-88.
[52] National Resource Center for Early Hearing Detection and Intervention. See http://www.infanthearing.org/tas/index.html [accessed August 2007].
[53] White KR. The current status of EHDI programs in the United States. Op. cit.
[54] Norris V, Arnos KS, Hanks WD, Xia X, Nance WE, Pandya A. Does universal newborn hearing screening identify all children with GJB2 (connexin 26) deafness? Penetrance of GJB2 deafness. *Ear & Hearing* 2006. 27:732-741.
[55] Arnos K. The implications of genetic testing for deafness. *Ear & Hearing* 2003. 24:324-331.
[56] White K. Early hearing detection and intervention programs: opportunities for genetic services. *Am J Med Genet* 2004. 130A(1):29-36.
[57] Schimmenti L, Martinez A, Fox M, Crandall B, Shapiro N, Telatar M et al. Genetic testing as part of the early hearing detection and intervention (EHDI) process. *Genet Med* 2004. 6(6):521-525.
[58] Burton S, Withrow K, Arnos KS, Kalfoglou AL, Pandya A. A focus group study of consumer attitudes toward genetic testing and newborn screening for deafness. *Genet Med* 2006. 8(12):779-783.
[59] American College of Medical Genetics (ACMG). Genetics evaluation guidelines for the etiologic diagnosis of congenital hearing loss. Op. cit.

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If a GJB2 test reveals that an individual is a heterozygote, Cincinnati Children's conducts a follow-up GJB6 deletion screen. If the GJB2 test is negative, the ACMG calls for non-syndromic mitochondrial testing, specifically for the A1555G and A7445G mutations. Cincinnati Children's distinguishes among the types of mitochondrial testing, suggesting MTRNR1 testing only in the presence of aminoglycoside exposure, and a full mitochondrial panel otherwise. Following these initial rounds of genetic testing for GJB2 and mitochondrial mutations, the ACMG recommends post-test counseling and education. Given that 10% of deaf infants have culturally deaf parents, the availability of interpreters and the culturally sensitive interpretation of hearing loss test results are critical.[60]

After parents are informed of their options, follow-up and additional genetic testing may be recommended. Imaging studies may be ordered to consider the possibility of DFNB4 or Pendred syndrome, particularly for progressive hearing loss. Such imaging studies may include temporal bone imaging, to look for an enlarged vestibular aqueduct and/or cochlear dysplasia. If imaging studies have positive findings, mutation screening of SLC26A4 would be recommended.

Clinical Utility of Genetic Testing for Hearing Loss

Genetic tests offer several advantages over conventional hearing loss evaluation without genetic testing. The benefits anticipated from genetic testing include:[61,62,63]

1) Reduction of additional time consuming, invasive, and expensive testing;
2) Choice of early interventions such as hearing aids, cochlear implants , or sign language that significantly improve language ability and quality of life outcomes;
3) Information on the progression of the condition;
4) Ability to monitor associated clinical manifestations and complications, particularly for certain syndromic forms of hearing loss;
5) Information on the chance of recurrence in the family that can inform reproductive decisions; and
6) Information pertinent to risks and health care decisions (e.g., avoiding aminoglycoside antibiotics among those with MTRNR1 mutations).

Genetic testing may be more sensitive and specific than traditional evaluation. A study at Cincinnati Children's Hospital found that 80% of hearing loss patients remained undiagnosed after traditional evaluation. Furthermore, genetic tests may facilitate earlier detection of hearing loss. Despite widespread newborn screening for hearing loss, a recent analysis showed that "current newborn hearing screening does not identify all infants with two GJB2 mutations."[64] The age at which the hearing loss was identified ranged from 12-60 months. A delay in detecting hearing loss has important implications for language acquisition and limits subsequent choices among management strategies. A study about cochlear implants reports, "There seems to be a substantial benefit for both speech and vocabulary outcomes when children receive their implant before the age of 2.5 years."[65] A white paper addressing the societal costs of hearing loss concludes that "early identification of deafness or hearing loss is critical in preventing or

[60] Ibid.
[61] White K. Early hearing detection and intervention programs: opportunities for genetic services. Op. cit.
[62] Schimmenti, L., Martinez A, Fox M, Crandall B, Shapiro N, Telatar M et al. Op. cit.
[63] Robin N, Prucka SK, Woolley AL, Smith RJH. The use of genetic testing in the evaluation of hearing impairment in a child. *Curr Opin Pediatr* 2005. 17:709-712.
[64] Norris V, Arnos KS, Hanks WD, Xia X, Nance WE, Pandya A. Op. cit.
[65] Connor CM, Craig HK, Raudenbush SW, Heavner K, Zwolan TA. The age at which young deaf children receive cochlear implants and their vocabulary and speech-production growth: is there an added value for early implantation? *Ear Hear* 2006. 27(6):628-44.

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ameliorating language delay or disorder in children who are deaf or hard of hearing and allows for appropriate intervention or rehabilitation. Early identification and intervention have lifelong implications for language development."[66] The present value of lifetime societal costs for prelingual hearing loss is estimated as $1.1 million, which includes lost productivity, special education, vocational rehabilitation, medical costs, and assistive devices attributable to deafness.[67]

Cost Effectiveness of Genetic Testing for Hearing Loss

We found no comprehensive cost effectiveness analyses of genetic testing for hearing loss. GJB2 testing may preclude the need for more expensive or invasive tests and provide the emotional benefit of knowing the cause as well as the clinical benefit of predictive information about progression and treatment options.[68] A recent study at the Cincinnati Children's Hospital Medical Center demonstrated that when compared to "simultaneous testing, which comprises a battery of tests including standard laboratory work-up, or diagnostic evaluation by imaging--a diagnostic algorithm with GJB2 genetic testing as the first step--resulted in a possible savings of $20,180 in imaging costs and $34,000 in laboratory test costs per 100 children screened."[69] The data on test-specific savings are:[70]

Table 2. Cost estimates of alternative SNHL evaluation approaches based on diagnostic yields

Testing yields	Bilateral			Unilateral	Overall
	Mild to moderate	Moderately severe	Severe to profound		
GJB2 screen (N = 161)	15.5% (N= 45)	5.0% (N=20)	37.7% (N= 71)	0.0% (N= 25)	18.0%
Imaging (N = 616)	21.2% (N=144)	24.7% (N=81)	29.9% (N=241)	35.7% (N=150)	27.3%
Laboratory test	0.0%	0.0%	0.3%	0.0%	0.07%
Cost estimates (per 100 children)					
Simultaneous evaluation	$193,200	$193,200	$193,200	$193,200	$193,200
GJB2 paradigm*	$141,096	$152,005	$121,530	n/a	$139,020
Imaging paradigm†	$145,900	$144,034	$144,763	$103,900	$145,766

*Our proposed diagnostic algorithm (*GJB2* paradigm) suggests that children with positive *GJB2* screens do not require further testing. Overall, an 18% yield, as seen in our cohort, would entail savings of up to $20,180 in imaging costs and nearly $34,000 in laboratory costs per 100 children.

†In cases of bilateral SNHL, it could be argued that imaging should be obtained prior to *GJB2* screening (Imaging paradigm). Estimates across SNHL groups, however, generally show cost savings when *GJB2* screening is performed as an initial step.

Reprinted from Otolaryngology – Head and Neck Surgery, Vol. 131, num. 6, Diego A. Preciado, Lynne H.Y. Lim, Aliza P. Cohen, Colm Madden, David Myer, Chris Ngo, John K. Bradshaw, Louise Lawson, Daniel I. Choo and John H. Greinwald Jr, "A diagnostic paradigm for childhood idiopathic sensorineural hearing loss," pp. 804-809, at p. 809, Copyright 2004 American Academy of Otolaryngology – Head and Neck Surgery Foundation, Inc., with permission from Elsevier.

Another study at Children's Hospital of Alabama assessed the cost of a battery of laboratory tests to evaluate hearing loss, including thyroid function, congenital infection, electrocardiograms, urine analysis, and serum phytanic acid levels, weighed in at more than $1,300, compared to the one-time $425 cost of a GJB2 genetic test.[71]

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[66] *A White Paper Addressing the Societal Costs of Hearing Loss and Issues in Third Party Reimbursement*. 2004. See http://www.audiologyonline.com/articles/article_detail.asp?article_id=1204 [accessed January 16, 2009].
[67] Mohr PE, Feldman JJ, Dunbar JL, McConkey-Robbins A, Niparko JK, Rittenhouse RK, Skinner MW. The societal costs of severe to profound hearing loss in the United States. *Int J Technol Assess Health Care* 2000.16(4):1120-35.
[68] Arnos K. Op. cit.
[69] Preciado D, Lim LHY, Cohen AP, Madden C, Myer D, Ngo C et al. A diagnostic paradigm for childhood idiopathic hearing loss. Otolaryngol Head Neck Surg 2004. 131:804-809.
[70] Ibid.
[71] Robin N, Prucka SK, Woolley AL, Smith RJH. Op. cit.

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While the benefits of GJB2 testing have yet to be quantified, researchers note the ability of GJB2 tests to define chance of recurrence, i.e., if a child is GJB2 positive, a hearing couple knows that there is a 25 percent chance they will have a deaf child in each future pregnancy, and a deaf couple (each with GJB2 deafness) can learn that there is a 100% chance they will have deaf children.[72] GJB2 testing may also be important given the success of cochlear implants among GJB2 positive individuals. A GJB2-positive individual may develop the same speech skills as an individual with normal hearing if the hearing loss is diagnosed and the cochlear implants are prescribed at a young enough age.[73]

In the case of non-syndromic mitochondrial testing, quantitative data are scarce. The benefits, however, are significant, considering that a positive A1555G test could prevent an infant from being exposed to aminoglycoside antibiotics, thereby preventing hearing loss. Another consideration associated with testing for these mutations is that aminoglycosides are often given before genetic testing has been performed because the infectious process has to be treated without delay. So in reality, the test is only beneficial if conducted prior to the onset of infection, or if test results can be turned around within a few hours. Due to increased numbers of premature births and widespread use of gentamycin in neonatal intensive care units, neonatologists have been particularly concerned about A1555G mutations and aminoglycoside exposure. However, in the absence of point-of-care testing, it would require screening parents prior to delivery or testing newborns to identify those at high risk of hearing loss from aminoglycoside use. For an individual with an A1555G substitution and no exposure to aminoglycosides, the probability of developing hearing loss by age 30 drops from 100% to 40%.[74] Given the lifetime cost associated with prelingual hearing loss of $1.1 million, that amount could be averted by each case of deafness avoided. Since aminoglycosides are only prescribed in the event of severe in-hospital infections, the number of individuals prescribed aminoglycosides and estimates of the increased risk of untreated infection would have to be factored into any cost-effectiveness calculation.[75]

The limitations of genetic testing for hearing loss also have to be taken into account in cost effectiveness analysis. Since genetic deafness is population- and ethnicity-specific, relative frequencies should first be refined to best represent the population being studied. While GJB2 testing may confer large benefits for individuals who test positive, those benefits also have to be measured against the costs for individuals who test negative. Individuals who test negative for GJB2 mutations may have to undergo additional medical and/or genetic testing or may experience emotional difficulty when attempting to comprehend the meaning of the confusing and inconclusive test results.[76]

Molecular Testing for Hearing Loss: New Developments and Technologies

If recommendations to include genetic testing as part of expanded EHDI[77,78] programs and clinical follow up of infants identified by universal newborn hearing loss screening are followed, then the volume of genetic testing for hearing loss could rise dramatically. Testing for mutations associated with the most common forms of syndromic and non-syndromic hearing loss plus congenital CMV infection can determine the cause of hearing loss in most cases of congenital hearing loss. Preciado et al. conclude that

[72] Ibid.
[73] Ibid.
[74] Pandya A, Arnos KS, Xia XJ, Welch KO, Blanton SH, Friedman TB et al. Op. cit.
[75] Fischel-Ghodsian N. Mitochondrial mutations and hearing loss: paradigm for mitochondrial genetics. *Am J Hum Genet* 1998. 62:15-19.
[76] Robin N, Prucka SK, Woolley AL, Smith RJH. Op. cit.
[77] White K. Early hearing detection and intervention programs: opportunities for genetic services. Op. cit.
[78] Joint Committee on Infant Hearing (JCIH). Year 2000 position statement: principles and guidelines for early hearing detection and intervention programs. *Pediatrics* 2000. 106(4):798-817.

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introduction of genetic testing (specifically GJB2 testing) for hearing loss in the clinical evaluation paradigm is cost effective.[79]

Recently Pediatrix introduced genetic testing services for hearing loss. Pediatrix is one of the largest providers of newborn metabolic screening and newborn hearing loss screening services in the U.S. Pediatrix's SoundGene™ Screening panel includes mutations associated with the most common forms of nonsyndromic and syndromic hearing loss. It also includes testing for common mutations in the mitochondrial MTTS1 gene, as well as testing for CMV infection (determined by measurement of copies of viral DNA, and therefore also, in essence, another genetic test). CMV infections account for up to 25% of congenital hearing loss caused by pathogenic agents. The SoundGene™ panel includes:

The SoundGene™ Screening Panel[80]

Connexin 26 (Cx26) GJB2 mutations:
35delG 167delT
235delC M34T

Connexin 30 (Cx30) GJB6 large deletion
309 kb large deletion

Mitochondrial mutations:
7445A>C (A7445C) 961T>C (T961C)
7445A>G (A7445G) 961T>G (T961G)
7444G>A (G7444A) 961 delT + C(n)ins

Pendred SLC26A4 mutations:
L236P 1001+1G>A
E384G T416P

CMV DNA

The SoundGene™ Screening Panel was introduced in December 2006. The list price is $ 95.00.[81] A U.S. patent application for the SoundGene™ Screening Panel is pending (Application U.S. 20040038266A filed in 2003, see Appendix V). SoundGene™ has also been trademarked. The test is described as a "quick and cost-effective alternative" and has an average turnaround time of 48 hours. Genetic counseling services for interpretation of test results and consultation are available through Pediatrix. Pediatrix has acquired a sublicense from Athena Diagnostics for testing of the Connexin 26 35delG mutation, which is included in the SoundGene™ panel. Pediatrix is the only provider to which Athena reports having issued a sublicense for Connexin 26 testing in the U.S. Although we do not have details of the licensing agreement and royalties, it is likely that the anticipation of high testing volume by Pediatrix as part of its newborn hearing loss screening services was an incentive for this agreement. Interestingly, however, the SoundGene™ panel does not include testing for the common A1555G mutation in the mitochondrial MTRNR1 gene (Patent no: US 5,506,101) that is also exclusively licensed to Athena Diagnostics.

[79] Preciado D, Lim LHY, Cohen AP, Madden C, Myer D, Ngo C et al. Op. cit.
[80] See http://www.pediatrix.com/body.cfm?id=2889 [accessed January 16, 2009].
[81] Information obtained from Pediatrix by phone inquiry, March 2007.

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High-throughput molecular diagnostics for hearing loss

With over 90 percent of newborns currently being screened for hearing loss and the potential for expanded EHDI programs to include molecular screening, genetic testing may shift to newer platform technologies for high-throughput genetic testing. Microarray-based genetic testing is being actively pursued as an efficient, reliable and potentially cost-effective tool when many mutations in a gene or numerous different genes must be tested. Hearing loss could be such a case. Since hundreds of loci are involved in the biology of hearing loss and additional genes and mutations may yet be discovered, microarray chips that can readily add new genes or mutations might help address both research and clinical needs. Microarray-based diagnostic testing for hearing loss might make it more flexible, less expensive, and more comprehensive while being as sensitive and specific as existing genetic tests.

Several groups report working on microarray-based diagnostic testing for hearing loss. Henrik Dahl and colleagues from the University of Melbourne and Children's Royal Hospital in Australia have developed a hearing loss microarray that detects 15 common mutations in the Connexin 26/GJB2, SLC26A4, USH2A genes and mitochondrial 12S rRNA.[82] This array-based chip was validated using DNA from 250 patients diagnosed with sensorineural hearing loss. It detected the mutations for which it was designed with 100% accuracy, and Siemering et al. report that no false positives or negatives were detected.[83] Commercial development of the hearing loss biochip is suggested by U.S. patent application US20070009887A1, "Genotyping of deafness by oligonucleotide microarray analysis," which was filed in November 2003, listing Victoria Siemering and Henrik Dahl as the inventors (Appendix V).

Another microarray diagnostic chip was recently reported by Iris Schrijver, Andres Metspalu, and colleagues in September 2006.[84] Their diagnostic panel includes 198 mutations in 8 genes most commonly associated with non-syndromic sensorineural hearing loss. A patent application US20070134691A1 for this diagnostic has been filed by Schrijver and colleagues (Appendix V). The chip uses arrayed primer extension (APEX) technology, first developed by J. M. Shumaker and C.T. Caskey (Baylor College of Medicine, Houston Texas) and A. Metspalu (University of Tartu, Estonia).[85,86] Patents covering this technology, US 6,153,379 and US 7,001,722, were granted in 2000 and 2006.

The hearing loss chip tests for mutations in Connexin 26/GJB2, Connexin 30/GJB6, GJB3, GJA1, SLC26A4, SLC26A5, and mitochondrial 12S rRNA and tRNA Ser[UCN] and includes the commonly tested Connexin 26 35delG and A1555G MTRNR1 mutations, both of which are licensed exclusively to Athena Diagnostics. Currently this diagnostic assay is being offered on a "research only" basis at the Molecular Pathology Laboratory at Stanford University by Dr. Schrijver and colleagues.[87] Genetic testing for hearing loss using this diagnostic chip is being offered by Asper Biotech.[88] Asper Biotech, located in Tartu, Estonia, was founded in 1999 with Dr. Andres Metspalu as its scientific advisor, and has expertise in developing and validating highly customized SNP/mutation screening assays. Asper Biotech also offers genetic testing services for diseases including cystic fibrosis, Usher Syndrome, retinitis pigmentosa,

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[82] Siemering K, Manji SS, Hutchison WM, Du Sart D, Phelan D, Dahl HH. Detection of mutations in genes associated with hearing loss using a microarray-based approach. *J Mol Diagn* 2006. 8(4):483-489.
[83] Ibid.
[84] Gardner P, Oitmaa E, Messner A, Hoefsloot L, Metspalu A, Schrijver I. Simultaneous multigene mutation detection in patients with sensorineural hearing loss through a novel diagnostic microarray: a new approach for newborn screening follow-up. *Pediatrics* 2006. 118(3):985-994.
[85] Shumaker J, Metspalu A, Caskey CT. Mutation detection by solid phase primer extension. *Hum Mutat* 1996. 7(4):346-354.
[86] Kurg A, Tonisson N, Georgiou I, Shumaker J, Tollett J, Metspalu A. Arrayed primer extension: solid-phase four-color DNA resequencing and mutation detection technology. *Genet Test* 2000. 4(1):1-7.
[87] Personal communication, Phone Conversation with Iris Schrijver, March 07
[88] Asper Biotech. *Hereditary Hearing Loss Testing*. See http://www.asperbio.com/HHL.htm [accessed March 10, 2007].

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thalassemia, and a panel of genetic disorders common in the Ashkenazi Jewish population.[89] Dr. Andres Metspalu at University of Tartu, Estonia, confirmed that the testing services offered by Asper Biotech are for research. The hearing loss test and other genetic tests offered by Asper Biotech are used by some academic medical centers and hospitals in the U.S in clinical research studies, often as part of collaborative projects.[90] It is not clear that any licenses have been negotiated by Asper Biotech with Institut Pasteur or Nanogen for the use of Connexin 26 mutation testing or with Cedars Sinai Medical Center for MTRNR1 mutation testing, but a license might not be required because they are not patented in Estonia. (Patent applications covering Connexin 26 and MTRNR1 mutations and diagnostic testing were never filed in Estonia.) Dr Metspalu confirmed that there is no patent protection for Connexin 26 and MTRNR1 mutations and testing in Estonia. However, he indicated that if Asper Biotech did decide to market the hearing loss test in the US, it would have to acquire sublicenses for all the relevant intellectual property and would have to factor royalty payments into its business plan. (We are not sure we concur with this judgment if the test itself were conducted in Estonia.)

Additional groups in the U.S. (shown in Appendix V) are exploring the use of kits and microarray diagnostics for high-throughput, comprehensive, and cost-effective molecular screening. Dr. John Greinwald and colleagues at the Cincinnati Children's Hospital previously reported that a diagnostic paradigm incorporating genetic testing during clinical evaluation of hearing loss proved more cost effective than standard simultaneous laboratory work-up.[91,92] Dr. Greinwald's group is now testing a microarray-based diagnostic gene chip that includes 13 genes associated with hearing loss. This collaborative project between Cincinnati Children's Hospital Medical Center and the University of Cincinnati Medical Center is being carried out at the Computational Medicine Center and is in an early phase of integrity and validation studies.[93] Dr. Greinwald and colleagues have also filed U.S. patent applications US20050112598A1 and US20040166495A1, "Microarray-based diagnosis of pediatric hearing impairment-construction of a deafness gene chip," based on the development of this gene chip (Appendix V). In a recent paper, Li et al. reported using a multiplex allele-specific PCR-based universal array (ASPUA), which combines Amplification Refractory Mutation System (ARMS) with array technology for clinical diagnostic testing of hearing loss mutations in parallel.[94]

Several groups have thus developed high-throughput diagnostic testing for hearing loss. U.S. patent applications filed by at least two of these groups on microarray-based gene chips suggest the potential for future commercialization of these diagnostic tests. However, we do not know if these tests will be adopted by clinical providers. Factors including test sensitivity, clinical utility and cost of the test are likely to significantly affect their uptake.

We also do not know whether the chip makers and testing service providers have licensed patents for mutations and methods associated with genetic tests for hearing loss. Neither have we studied whether use of short DNA probes on these chips would infringe existing patents, as this would require detailed analysis of claims and deep knowledge of the testing methods.

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[89] Asper Biotech. *Hereditary Hearing Loss Tests Supplement*. Seewww.asperbio.com/supplement.pdf [accessed March 10, 2007].
[90] Authors' phone conversation with Dr. Andres Metspalu, University of Tartu, Estonia (founder of Asper Biotech), April 14, 2008.
[91] Preciado D, Lim LHY, Cohen AP, Madden C, Myer D, Ngo C et al. Op. cit.
[92] Preciado D, Lawson L, Madden C, Myer D, Ngo C, Bradshaw JK, Choo DI, Greinwald JH Jr. Improved diagnostic effectiveness with a sequential diagnostic paradigm in idiopathic pediatric sensorineural hearing loss. *Otol Neurotol* 2005. 26(4):610-615
[93] Computational Medicine Center. *Gene chip diagnostic test for pediatric hearing impairment*. 2005. See http://www.computationalmedicine.org/project/hearing_loss.htm [March 10, 2007].
[94] Cai-Xia i, Qian P et al. Construction of a multiplex allele-specific PCR-based universal array (ASPUA) and its application to hearing loss screening. *Human Mutation* 2008. 29:306-314.

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Finally, we note that full-genome sequencing technologies are progressing apace, and if such analysis became possible, then the basis for genetic testing would be individual genomic sequencing and comparing that sequence to known mutations associated with all genetic forms of hearing loss, rather than tests specifically keyed to hearing loss. The intellectual property implications are unclear, as they are for genetic testing of other clinical conditions.

Lessons Learned about impact of Patents on Access to Hearing Loss Testing

Research

We found no evidence about positive or negative effects of hearing loss gene patents on research in the field of hearing loss genetics. Basic research to determine the associations between candidate genes and their roles in various forms of hereditary hearing loss has steadily progressed. Research appears to be proceeding rapidly on rare forms of deafness that offer the prospect of a small market for diagnostic testing and are therefore unlikely to provide significant monetary incentives for genetic testing. Most genes associated with different forms of syndromic and non-syndromic deafness are not patented (Appendix I and II). Even among the five most commonly tested hearing loss genes, which are presumably of greatest commercial interest, three genes are not patented. It is unclear whether patents or the potential for commercialization provided an incentive for the research. At least two research groups at non-profit institutions were engaged in studies to identify Connexin 26 gene mutations. Publications reporting the identification of mutations in Connexin 26 by Kelsell at al (Queen Mary and Westfield College, UK) and Christine Petit et al (Institut Pasteur) were submitted in January (published in May) and August (published in November) of 1997 to *Nature* and *Human Molecular Genetics*, respectively. While the UK group does not appear to have applied for a patent, Christine Petit and Institut Pasteur secured US patents on GJB2/Connexin 26 and its mutations in December 1999. Petit and colleagues applied for a patent in August 1997, the same month they submitted their findings for publication. Dr. Fischel-Ghodsian and colleagues at Cedars-Sinai Medical Center submitted their report on the MTRNR1 A1555G mutation to *Nature Genetics* in February 1993 (published July 1993). The corresponding patent application on detection of A1555G mutation was filed on June 30, 1993, four months after submitting for publication, and granted to Cedars-Sinai in April 1996. While these chronologies suggest that scientific publication and patenting activities proceeded in parallel, we cannot determine if journal submissions were in fact delayed in the first place to prepare patent applications for parallel filing.

Without information on the royalties Institut Pasteur and Cedars-Sinai Medical Center receive from the licenses to Athena Diagnostics for Connexin 26 and MTRNR1 testing, it is also difficult to comment on the impact these patents have had on supporting subsequent basic research at these institutions. Such support would be one of the positive effects of patents.

A substantial amount of clinical research has been performed, for example on the prevalence of Connexin 26 mutations in different populations, and on new methods for diagnostic testing including array-based diagnostics. Such studies include genetic testing for mutations covered by patents and licensed exclusively to Athena Diagnostics (Connexin 26, MTRNR1). However, researchers at academic medical centers remain concerned about the consequences of future enforcement activity by Athena Diagnostics on the clinical testing and clinical research.[95] They warn that uncertainty about whether an academic medical center or reference lab may be required to stop testing and the absence of a clearly stated policy about research use from Athena Diagnostics may have chilling effects on clinical research.

[95] Comments provided during external review, August 22, 2008.

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Development and Commercialization

Genetic tests for Connexin 26 and MTRNR1 which are patented, and for GJB6, SLC24A6, and MTTS1, which are not covered by patents, have been developed and are offered by several providers at similar prices. Several providers have in fact developed test panels that include both the patented Connexin 26/MTRNR1 as well as the unpatented Connexin 30/MTTS1 tests. The acquisition of an exclusive license for Connexin 26 diagnostic testing in the US was presumably integral to Athena Diagnostics' plan to commercialize these tests. GJB2 testing was offered by at least 9 providers in the U.S. as early as 1998. The number of providers listed at GeneTests.org has doubled since 1999-2000.[96] Testing for the patented genes GJB2 and MTRNR1 and their most common mutations is offered by more U.S. providers than testing for the unpatented genes SLC26A4, GJB6, and MTTS1. This is not entirely surprising given that GJB2 mutations account for up to 50% of cases of non-syndromic hearing loss. The majority of laboratories listing the tests are academic health centers.

Clinical testing for MTRNR1 in the U.S. may have been delayed. The association of MTRNR1 mitochondrial mutations to hearing loss was published as early as 1993, yet clinical testing appears to have become available only in 2000. In our telephone survey, many laboratories were unable to provide data on when they first made this test available. A more systematic and detailed survey of providers might help determine if patents impeded or deterred providers from developing these tests, as we did not query providers specifically about this issue.

It is difficult to assess exactly how much of a price premium the exclusive license provides Athena Diagnostics, or what impact the patent licenses have on volume. According to Athena Diagnostics, to date only one sublicense for Connexin 26 testing has been granted (to Pediatrix). Thus, the list price of the other providers must not include royalty or licensing fees. The price range can be attributed to factors such as overhead costs at different institutions. In the case of testing for MTRNR1, the price offered by both for-profit providers is on average $145 more than the price of the test provided by non-profit institutions. The $365 list price of the test offered by Athena Diagnostics is nearly 73 percent higher than the average list price offered by other university and hospital-based providers. In contrast, testing for the unpatented MTTS1 gene is offered by only four non-profit providers and at prices comparable to MTRNR1 testing services offered by these providers. MTTS1 testing is not offered by Athena Diagnostics.

Costs of hearing loss tests do not appear to correlate strongly with patent status. For instance, the price of the most expensive test--SLC26A4 full sequence analysis--can be attributed mostly to the costs of sequencing a large gene. The relatively high cost of the SLC26A4 testing also affects fewer consumers, since Pendred's syndrome accounts for a small fraction of hearing loss cases and testing is recommended only to follow up on positive imaging findings.

Communication/ Marketing

It appears that patents on DNA sequences and platforms for hearing loss genetic testing have had little impact on the dissemination of information about such tests or how they are marketed. We found no evidence of direct-to-consumer marketing. In the course of a phone conversation, Dr. Michael Henry, Vice President of Business Development at Athena Diagnostics, clearly stated the company's commitment to refrain from direct-to-consumer marketing and emphasized that Athena relies primarily on physician-prescribed testing. He also indicated that while Athena Diagnostics does have sales representatives who communicate information about genetic testing for neurological conditions to

[96] Kenneson A, Myers MF, Lubin IM, Boyle C. Op. cit.

neurologists and medical practices, there is no sales force specifically committed to marketing hearing loss genetic testing to pediatricians and specialists (e.g., otolaryngologists and audiologists).

Adoption by Clinical Providers and Testing Laboratories

Any effects of patents on adoption of hearing impairment genetic tests by clinical providers are not readily apparent.
The exclusive license procured by Athena Diagnostics for Connexin 26 and MTRNR1 testing does not appear to have established Athena Diagnostics as the sole provider. However, the number of providers currently available may not fully capture the effects of patents on provider adoption. According to Dr. Michael Watson, Director of the ACMG, "Athena aggressively enforced their IP for many years but were increasingly irritating practitioners and made them an example in the press of bad IP behavior. Around 2000, they [Athena] stopped enforcing and tried to develop their 'Academic Partnership Program.' Although the intent was to allow laboratories to retain some volume for research and training of clinical laboratorians, it ultimately failed largely because if a lab did more than 100 cases in a year, the licensing fees made the lab noncompetitive."[97]

We have clearly identified three instances of patent enforcement by Athena Diagnostics for Connexin 26 testing against other providers. The first of these proved to be a case of non-infringing use that has been resolved.[98,99] GeneDx currently continues to perform full sequence analysis for Connexin 26 to identify the GJB2 D50N mutation and other mutations associated with a rare skin condition KID, which is not covered by the patents licensed to Athena. We understand the matter reached amicable resolution with GeneDx agreeing not to report hearing loss mutations and referring to Athena if they are found (See Appendix VII). Athena Diagnostics, which holds the exclusive license to GJB2 mutation testing in the U.S., expressed willingness to grant sublicenses. [100] However, according to Dr Sherri Bale, Athena refused to grant a sublicense when GeneDx attempted to acquire one in the context of KID testing.[101] This case also raises concerns about withholding of useful clinical information and increased costs, as another blood draw and test by Athena would be required if GeneDx identified a potential hearing loss mutation in a sample sent to them for KID testing, although this is clinically unlikely.

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[97] Comments provided by Dr Michael Watson, during external review. Email from Dr Watson to SACGHS staff, September 10, 2008.
[98] Authors' email communication with Richard Flaherty (BioReference Laboratories, CIO, Director of Technology and Investor Relations) and Sherri Bale, Clinical Director, GeneDx. February 22, 2008.
[99] In testimony before the House Judiciary Subcommittee on Courts, the Internet and Intellectual Property, on October 30, 2007, Marc Grodman, CEO of Bio-Reference Laboratory, Inc., indicated that while GeneDx (a company acquired by BRLI) was performing a genetic test for a rare skin condition by full sequence analysis of the gene in question, it "received a letter from another laboratory claiming that within the sequence being analyzed was another sequence associated with hearing loss." Athena Diagnostics' letter indicated that since testing for this hearing loss gene was patented, performing the test might be an act of infringement. Attempts by GeneDx to perform the test by paying a royalty to the other company were unsuccessful. We have confirmed by personal communication with Dr. Grodman and Dr. Sherri Bale, Clinical Director at GeneDx, that the genetic test in question involved sequencing the Connexin 26 gene for mutations associated with a rare skin condition Keratitis Ichthyosis Deafness (KID). Dr. Bale confirmed that Athena Diagnostics sent a "cease and desist letter" and indicated that the matter has been resolved. "We accepted a letter from Athena that instructed us to not report the 35delG mutation. However, what we've done is: if we find the deletion, we call the referring MD, tell them the results and that we can't report them, and then suggest they redraw the patient and send the sample to Athena for testing." This requires a second visit to the patient's physician, another blood draw, and payment, this time to Athena Diagnostics, to repeat the GJB2 test. (See Appendix VI Letter from Sherri Bale, GeneDx to Athena Diagnostics.)
[100] Authors' phone conversation with Michael Henry, Vice President Business Development, Athena Diagnostics Inc. March 2007.
[101] Authors' email communication with Richard Flaherty (BioReference Laboratories, CIO, Director of Technology and Investor Relations) and Sherri Bale, Clinical Director, GeneDx. February 22, 2008.

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In another instance, the Diagnostic Molecular Pathology Laboratory at the University of California Los Angeles stopped offering testing for Connexin 26/GJB2 over two years ago, after receiving a "cease and desist letter" from Athena Diagnostics. According to Dr. Wayne Grody,[102] Director of the Laboratory, the terms of the sublicense offered by Athena Diagnostics "were unreasonable, with an upfront fee of $50,000 per year plus a significant per test fee" and not economically viable for the laboratory, given the relatively low volume of testing for hearing loss at UCLA. Attempts to negotiate terms of a sublicense were not successful. It is unclear to what extent cessation of testing at UCLA has affected patient access to hearing loss testing. Dr. Grody indicated that samples are now sent to Athena Diagnostics for clinical testing. His laboratory considered using an alternate test methodology, namely custom ASRs from Third Wave Technologies for Connexin 26 mutation testing. This method reportedly allows laboratories to avoid infringing the Connexin 26 patents licensed to Athena. It is unclear if this is because a sublicense acquired from Athena Diagnostics comes attached to the purchase of the ASRs or because the test methodology (Invader™ assay) offers "workarounds" of the patents (US5998147, 6485908). However, these ASRs are no longer being offered since HoloLogics Inc acquired Third Wave Technologies in June 2008.[103]

Dr. Grody indicated that even if the alternate methodology could help overcome the problem of patent infringement, it is not ideal because ASRs for the 235delC Connexin 26 mutation, found commonly in Asian populations, are not available from Third Wave. Testing for this mutation is particularly relevant at UCLA given the high Asian and Asian American population in California. Dr. Grody also noted that shipping samples to Athena Diagnostics is problematic for indigent patient populations covered by the California MediCaid program (MediCal). MediCal only reimburses laboratories with which it has a contract, which Athena does not have.

We also recently became aware that Athena Diagnostics sent a "cease and desist" letter to the Center for Human Genetics at Boston University regarding testing for a number of genetic conditions including hearing loss.[104] In August 2008, the Center for Human Genetics ceased testing for hearing loss and several other conditions for which Athena has exclusive IP rights.

Athena confirmed that no sublicenses have been given to university and academic or medical centers.[105]

The SoundGene™ panel offered by Pediatrix is performed under a sublicense from Athena Diagnostics for GJB2/Connexin 26 testing. To our knowledge, Pediatrix is the only provider that has received a sublicense from Athena Diagnostics to date. Presumably, this will lead to a steady royalty stream for Athena from genetic testing done by Pediatrix as part of newborn hearing loss screening, and a flow of patients for diagnostic follow up.

Microarray chip-based diagnostics for hearing loss are currently not available as a clinical service in the U.S. However, if chip based diagnostics do become commercialized, and if use of DNA probes on those microarrays infringe the patents that Athena has licensed, Athena Diagnostics could choose to demand a license for testing that includes patented sequences of Connexin 26 and MTRNR1. Simultaneous multi-gene testing also seems to be a departure from the current ACMG clinical guidelines, which call for a systematic utilization of genetic tests based on relative frequencies, family histories, patient symptoms

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[102] Authors' phone conversation with Dr. Wayne Grody, March 21, 2008.
[103] See transcript of HoloLogics press conference about Third Wave Technologies acquisition at http://www.secinfo.com/d14D5a.t3vh8.d.htm [last accessed January 8, 2009].
[104] Authors' phone Communication with Dr. Aubrey Milunsky, Director, Center for Human Genetics, Boston University, May 29, 2008.
[105] Authors' phone conversation with Michael Henry, Vice President Business Development, Athena Diagnostics Inc., March 2007.

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and apparent diagnosis. Those guidelines might change, however, if microarray testing proved equally sensitive, specific, and accurate, while being faster and cheaper and identifying many mutations in different genes in a single test.

Consumer Utilization

This case study finds limited effects on patient access to genetic testing for hearing loss that can be directly attributed to patenting. The availability of genetic testing for hearing loss in California may be limited for MediCal patients because the patent-holder, Athena Diagnostics, lacks a contract with MediCal and is out-of-state. The issue here is not patents per se, but patents preventing other laboratories from offering the test under MediCal contract. The laboratories with MediCal contracts do not have sublicenses from Athena and Athena apparently does not have a contract with MediCal.

We were unable to identify systematic evidence beyond the MediCal situation noted above, that the patents have impeded utilization of hearing loss tests by people who are interested in or require testing. Testing for the genes licensed exclusively to Athena Diagnostics is not marketed directly to consumers by Athena or by other direct-to-consumer providers like DNAdirect. Sixteen providers other than Athena Diagnostics are listed on GeneTests.org as offering Connexin 26 testing. Nine providers in addition to Athena Diagnostics are listed for MTRNR1 testing. Many of these provider websites have detailed information on the availability and cost of both patented and unpatented hearing loss genetic tests. Although several providers for these tests have emerged, we found no information about usage of the tests by consumers.

While we did not query test providers about their testing volume or the number of patients requesting each test, a future survey could assess utilization of hearing loss tests by consumers. It would also be valuable to determine how frequently reimbursement for such tests is denied by insurers and payers, as coverage and reimbursement of genetic testing are likely to affect consumer use.

Finally, patient access may be affected, as much or more by factors other than patents, such as the lack of knowledge about the genetics of hearing loss, particularly among primary care physicians, and their low propensity to refer cases for genetic testing as follow-up.[106] A recent survey by Duncan et al. noted that while 86% of pediatric otolaryngologists reported having easy access to genetic testing services for referral, many also identified "discomfort with various aspects of genetic testing" as a reason for not ordering genetic tests.[107] Lack of knowledge about genetic testing or about interpretation of test results may be a more significant barrier to test adoption by healthcare providers than patents.

Coverage and reimbursement by third party payers

We have no evidence that gene patents have directly affected third party payer coverage and reimbursement decisions for hearing loss tests. Laboratories report that insurers have generally adopted genetic testing for some hearing loss genes, as illustrated below by the coverage position from CIGNA HealthCare on "Genetic Testing for Congenital Profound Deafness."[108]

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[106] Moeller MP, White KR, Shisler L. Primary care physicians' knowledge, attitudes, and practices related to newborn hearing screening. *Pediatrics* 2006. 118(4):1357-70.
[107] Duncan RD, Prucka S, Wiatrak BJ, Smith RJ, Robin NH. Pediatric otolaryngologists' use of genetic testing. *Arch Otolaryngol Head Neck Surg* 2007. 133(3):231-6.
[108] See http://www.cigna.com/customer_care/healthcare_professional/coverage_positions/medical/mm_0254_coveragepositioncriteria_genetic_test_congenital_profound_deafness.pdf [accessed January 16, 2009].

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Coverage Position

CIGNA HealthCare covers genetic testing for congenital, nonsyndromic, sensorineural, mild to profound deafness (DFNB1) as medically necessary for ANY of the following indications:

- For diagnostic testing when the clinical examination and conventional studies suggest a diagnosis of congenital, nonsyndromic, sensorineural, mild to profound deafness (DFNB1)
- For carrier testing in EITHER of the following situations:
  - when the patient has a first- or second-degree relative* with a GJB2 or GJB6 gene mutation
  - when the patient is the reproductive partner of a known carrier (deafness-causing mutation of gene GJB2 or GJB6) and the couple has the capacity and intention to reproduce
- For prenatal testing when both parents are known carriers of deafness-causing mutation of gene GJB2 or GJB6 mutation.

CIGNA HealthCare does not cover genetic screening for congenital, nonsyndromic, sensorineural, mild to profound deafness (DFNB1) in the general population because such screening is considered not medically necessary or of unproven benefit.

All individuals undergoing genetic testing for any reason should have both pre- and post-test genetic counseling with a licensed or certified genetic counselor or physician trained in genetics and genetic counseling.

Aetna covers full sequence and targeted mutation analysis of GJB2/Connexin 26 and deletion analysis for GJB6/Connexin 30, but it excludes pre-implantation genetic diagnosis (PGD) for DFNB1, which is deemed an "unproven benefit at this time." We have not verified whether other commercial insurers have a similar position, except through the interviews with testing laboratories. Indirect effects that patents may have on price might lead to a higher level of scrutiny by insurance providers if the tests are priced above other genetic tests, but hearing loss genetic test prices are in the same range as other case studies. Decisions about coverage for SLC26A4, MTRNR1 and MTTS1 may be case by case, because these conditions are not common enough to warrant an explicit coverage policy. These tests are likely handled similarly to tests for other rare conditions, covering tests in a routine price range and requiring special justification for expensive testing. During the informal phone survey, most test providers indicated that hearing loss genetic tests were mostly covered by insurance. However, we have no direct evidence about how often consumers are denied coverage for hearing loss testing, pay for them out of pocket, face high co-pay fees because of reimbursement limits, or encounter other factors that affect their choice to get such tests.

Athena Diagnostics has a policy of directly billing insurance providers for services when Athena is the contracted provider for that particular plan. However, when Athena is not a contracted provider and the insurer does not cover the testing in part or full, Athena guarantees as part of its Patient Protection Plan that "an eligible, enrolled patient's liability will be limited to 20% of the cost of the test, even if the patient's insurance plan pays nothing. (These programs are discussed at greater length in the spinocerebellar ataxia case study.) For patients enrolled in the Patient Protection Plan, any amount collected from the insurance company in excess of 80% of the amount billed will be refunded to the patient."[109] The Patient Protection Plan is not, however, available in all states, does not apply to government health programs (Medicare and Medicaid, for example) and does not apply to most insurers and health plans. Florida and Maryland are excluded, for example.

Athena Diagnostics does not participate in Medicaid but it does offer discounts to Medicaid patients through its financial assistance programs. If the test of interest is not covered by Medicare carriers, the patient will be required to pay for the test in advance. In such cases, if the Medicare carrier denies coverage of the test, the patient may have to pay the entire cost out of pocket, since Medicare patients are ineligible for Athena's Patient Protection Plan. Thus insurance coverage, independent of the patenting status of the test, may limit patient access in some cases, specifically Medicaid patients, most Medicare patients, and those covered by health plans with which Athena does not have a contract. However, even in

[109] See http://www.athenadiagnostics.com/content/ordering/ [accessed August 2007].

these cases, patients have the option of using other providers who may accept Medicaid, at least as long as those providers continue to offer the service.

Conclusion

Patents do not appear to have significantly impeded patient or clinical access for hearing loss genetic testing. Many institutions provide tests, even those covered by patents exclusively licensed to Athena Diagnostics, presumably without a sublicense. While Athena Diagnostics has sent out some "cease and desist" letters, enforcement is apparently incomplete, as several other testing services are listed on GeneTests.org. It is possible that the volume of testing at most institutions, even for Connexin 26, is not large enough to warrant more aggressive enforcement by Athena Diagnostics.

Given that experts have recommended incorporation of genetic tests into EHDI programs, use of genetic tests for hearing loss is likely to increase. The recent introduction of the SoundGene™ diagnostic panel by Pediatrix Screening is indicative of this trend. However concerns have been raised that a small panel such as SoundGene™ may not be ideal. For example, patients with GJB2 related hearing loss may be missed because they do not carry the mutations represented on the panel. More recent literature suggests it is not sufficient to test only the four common mutations associated with Pendred syndrome included in the panel. This is one reason many labs now sequence the entire SLC26A4 gene because targeted mutation testing misses many mutations. Multi-gene, chip-based tests may help address problems in diagnosing individuals who develop hearing loss as children or adolescents, and potentially reduce the cost and duration of diagnostic testing. These new diagnostics, although likely to detect a much broader range of mutations and gene variants, may also miss rare and novel mutations, especially for genes like GJB2 and SLC26A4, as patients often have new or private mutations. The clinical utility and analytical validity of such array-based tests also needs to be demonstrated. It remains to be seen whether patents on genes and mutations for hearing loss will impede development of multi-allele methods.

This case study illustrates the complexity of assessing the impact of patents on access to genetic testing. This is in part because of the number of genes and mutations involved, but also depends on patents and their enforcement. Aggressive patent enforcement might reduce the number of outlets for genetic testing, and for those not covered by health plans covering payment to Athena Diagnostics, this would reduce access. It therefore appears that access depends on an unstable intellectual property regime and the vicissitudes of payment contracts between health insurers and health care plans, on one hand, and different testing labs, on the other.

Genetic testing for hearing loss also illustrates several other features of intellectual property and genetic testing. Most of the patents for commonly tested genes are owned by academic institutions and licensed to Athena Diagnostics. The patenting and licensing practices of academic institutions are therefore linked to both the benefits and problems associated with having a single major provider. The case also illustrates the penumbra effect of exclusive rights to some mutations leveraging testing for others, although it is also clear from this case that the effect is incomplete since multiple providers are offering tests.

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Appendix I. ***Nonsyndromic Loci: Known Genes, Genetic Tests, and Patents***

Locus	Pattern of Inheritance	Genes	Age of Onset	Relative Frequency	Test Avalablei	Patent Holder
DFNB61	AR	PRES (SLC26A5)		higher among Caucasians		Northwestern (6602992)
DFNB1	AR	GJB2 (Cx 26), GJB6 (Cx 30)	Prelingual	Up to 50%	GJB2 (Cx 26), GJB6 (Cx 30)	Institut Pasteur (5998147, 6485908)
DFNB2	AR	MYO7A	Prelingual		MY07A	
DFNB3	AR	MYO15A	Prelingual	2% incidence in Benkala, Bali		
DFNB4	AR	SLC26A4	Postlingual	4-10%	SLC26A4	
DFNB6	AR	TMIE	Prelingual			
DFNB7/11	AR	TMC1	Prelingual			
DFNB8/10	AR	TMPRSS3	DFNB8-Prelingual, DFNB10-Postlingual			
DFNB9	AR	OTOF	Prelingual		OTOF	
DFNB112	AR	CDH23				
DFNB16	AR	STRC	Postlingual			
DFNB18	AR	USH1C	Prelingual			
DFNB21	AR	TECTA	Postlingual		TECTA	
DFNB22	AR	OTOA	Prelingual			
DFNB23	AR	PCDH15	Prelingual			
DFNB28	AR	TRIOBP	Prelingual			
DFNB29	AR	CLDN14	Prelingual			
DFNB30	AR	MYO3A	Prelingual			
DFNB31	AR	WHRN	Prelingual			
DFNB36	AR	ESPN	Prelingual			
DFNB37	AR	MYO6	Prelingual			
DFNB67D FNB59	AR	TMHSDFNB59 (pejvakin)				
DFNA1	AD	DIAPH1	Postlingual			
DFNA2	AD	GJB3 (Cx 31), KCNQ4	Postlingual		KQCN4	NeuroSearch A/S (6794161)
DFNA3	AD	GJB2 (Cx 26),	Prelingual	GJB2 >50%	GJB2 (Cx 26), GJB6 (Cx 30)	Institut Pasteur (5998147, 6485908)

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		GJB6 (Cx 30)				
DFNA4	AD	MYH14	Varies	1%		
DFNA5	AD	DFNA5	Postlingual			
DFNA6/14/38	AD	WFS1	Prelingual		WFS1	Washington University School of Medicine (WOO18787A1)
DFNA8/12	AD	TECTA	Pre or postlingual		TECTA	
DFNA9	AD	COCH	Postlingual		COCH5B2	Brigham and Women's Hospital (7030235), Brigham and Women's Hospital & U-Antwerp (6730475)
DFNA10	AD	EYA4	Postlingual		EYA4	
DFNA11	AD	MYO7A	Postlingual			
DFNA13	AD	COL11A2	Postlingual		COL11A2	
DFNA15	AD	POU4F3	Postlingual			
DFNA17	AD	MYH9	Postlingual		MYH9	
DFNA20/26	AD	ACTG1	Postlingual			
DFNA22	AD	MY06O	Postlingual			
DFNA28	AD	TFCP2L3	Postlingual			
DFNA36	AD	TMC1	Postlingual			
						Wash U. School of Medicine (WOO18787A1)
DFNA44	AD	CCDC50	Postlingual			
DFNA48	AD	MYO1A	Postlingual			
None Listed	AD	CRYM	Prelingual			
DFN3	XL	POU3F4	Prelingual			
Aminoglycoside Ototoxicity	Mitochondrial	MTRNR-1 (A1555G), MTTS-1	Prelingual	A1555G <1% (1/20-40,000 births)	MTRNR-1, MTTS-1	Cedars-Sinai (5506101) MTRNR1
None Listed		TDC-1, TDC-2			TDC-1, TDC-2	Griffith, Kurima, Wilcox & Friedman (20040249139A1)
Dentinogenesis imperfecta type II (DGI-II)		DSPP			DSPP	Kong, Xiao, Zhao, Yu & Hu (2003018020A1)

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Appendix II. ***Syndromic Disorders: Known Genes, Genetic Tests, and Patents***

Disorder	Type	Pattern of Inheritance	Genes	Age of Onset	Relative Frequency	Prevalence	Test Available?	Patent Holder (Patent Number)
Pendred's Syndrome	Syndromic	AR	SLC26A4	Prelingual	4-10%		SLC26A4	
Type 4 Barter'st Syndrome	Syndromic	AR or digenic	BSND, CLCNKA, CLCNKB		con-sanguineous Middle Easterners			
Branchio-oto-renal (BOR) Syndrome	Syndromic	AD	EYA1, SIX1		1 in 40,000		EYA1, SIX1	
Alport Syndrome	Syndromic	AD	MYH9, COL4A5, COL4A3, COL4A4		Rare		MYH9, COL4A5, COL4A3, COL4A4	
Fechtner's Syndrome	Syndromic	AD	MYH9		Rare			
Sebastian Syndrome	Syndromic	AD	MYH9		Rare			
(DFNA22)	Syndromic	AD	MYO6	Postlingual	Rare			
Renal Tubular Acidosis	Syndromic	AR, consanguinity	ATP6B1, ATP6N1B		con-sanguineous North Africans			
Waardenburg's Syndrome	Syndromic	AD or AR	PAX3, MITF, SOX10, EDN3, EDNRB		1-4%			
Wolfram Syndrome	Syndromic	AD	WFS1	Prelingual			WFS1	Washington University School of Medicine (WOO18787A1)
Meniere's Disease	Syndromic	AD	COCH	Postlingual			COCH5B2	Brigham and Women's Hospital (7030235), Brigham and Women's Hospital & U-Antwerp (6730475)
Cockayne Syndrome Type A	Syndromic		ERCC8	Prelingual			ERCC8	
Cockayne Syndrome Type B	Syndromic		ERCC6	Prelingual			ERCC6	
Diabetes-Deafness	Syndromic		MTND5, MTTL1				MTTL1	

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Syndrome								
Charcot-Marie Tooth Neuropathy Type 1A	Syndromic	AD	PMP22				PMP22	
Charcot-Marie Tooth Neuropathy Type 1B	Syndromic	AD	MPZ				MPZ	
Charcot-Marie Tooth Neuropathy Type 1C	Syndromic	AD	LITAF				LITAF	
Charcot-Marie Tooth Neuropathy Type 1D	Syndromic	AD	EGR2				EGR2	
Charcot-Marie Tooth Neuropathy Type 1E	Syndromic	AD	PMP22				PMP22	Athena (5691144), Athena (6001576)
Charcot-Marie Tooth Neuropathy Type 1F/2E	Syndromic	AD	NEFL				NEFL	
Isolated Renal Hypomagnesemia	Syndromic		CLDN16				CLDN16	
Urticaria-Deafness-Amyloidosis (UDA) Syndrome	Syndromic		CIAS1, NLRP3				CIAS1, NLRP3	
Long QT Syndromes and Deafness	Syndromic		KVLQT1, SCN5A				KVLQT1, SCN5A	U-Utah Research Foundation (20020061524 A1), U-Utah Research Foundation and Genzyme, Inc (6582913), U-Utah Research Foundation (6787309)
Jervell and Lange Nielsen (JLN) Syndrome	Syndromic	AR	KLVQT1, KCNQ1 (JLN1), KCNE1 (JLN2)	Prelingual	Rare		KLVQT1, KCNQ1 (JLN1), KCNE1 (JLN2)	U-Utah Research Foundation (6150104)
Stickler Syndrome	Syndromic	AD	COL11A2, COL2A1, COL11A1, COL9A1				COL11A1, COL11A2, COL2A1, COL9A1	
Epstein Syndrome	Syndromic	AD	MYH9				MYH9	

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Norrie Disease	Syndromic		NDP				NDP	
Treacher Collins Syndrome	Syndromic		TCOF1				TCOF1	
Usher Syndrome Type I (USH1)	Syndromic	AR	MY07A,O USH1C, CDH23, PCDH15, SANS	Prelingual	all Usher combined 3-6% of child deafness	all Usher combined 4.4/100,000	MY07A, PCDH15	
Usher Syndrome Type II (USH2)	Syndromic	AR	USH2A, VLGR1, WHRN	Prelingual	all Usher combined 3-6% of child deafness	all Usher combined 4.4/100,001	USH2A	
Usher Syndrome Type III (USH3)	Syndromic	AR	USH3	Postlingual	all Usher combined 3-6% of child deafness	all Usher combined 4.4/100,002	USH3A (CLRN1)	
Kearns-Sayre Syndrome	Syndromic	Mitochondrial					mtDNA deletion syndromes	
Pearson Syndrome	Syndromic	Mitochondrial					mtDNA deletion syndromes	
Progressive External Ophthalmoplegia	Syndromic	Mitochondrial					mtDNA deletion syndromes	
Leigh Syndrome	Syndromic	Mitochondrial	MTATP6, MTTL1, MTTK, MTND1, MTND3, MTND4, MTND5, MTND6, MTCO3, MTTW, and MTTV				MT-ATP6, MT-CO3 , MT-ND1, MT-ND3, MT-ND4 , MT-ND5 , MT-ND6, MT-TK , MT-TL1, MT-TV, MT-TW	
NARP	Syndromic	Mitochondrial	MTATP6				MT-ATP6	
MELAS	Syndromic	Mitochondrial	MTTL1, MTND5, MT-TC, MT-TV, MT-TF, and MT-TS1				MTTL1, MTND5	
MERRF	Syndromic	Mitochondrial	MTTK				MTTK	
Vohwinkel Syndrome	Syndromic		GJB2 (Cx 26)		GJB2 >50%		GJB2 (Cx 26)	Institut Pasteur (5998147, 6485908)
Deafness-Dystonia Syndrome (DDON)	Syndromic	XL	TIMM8A	Varies				
Hypoparathyroidism,	Syndromic		GATA3				GATA3	

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Sensorineural Deafness, and Renal (HDR) Disease								
Ichthyosis, Hystrix-like, with Deafness	Syndromic		GJB2 (Cx 26)				GJB2 (Cx 26)	Institut Pasteur (5998147, 6485908)

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Appendix III: Universal Newborn Hearing Screening EHDI Guidelines for Pediatric Medical Home Providers

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Appendix IV: Cincinnati Children's Hospital Hearing Loss Genetic Evaluation Clinical Guidelines

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Appendix V: Patent Applications for high throughput hearing loss diagnostic testing

Patent/ Application No.	Assignee	Inventors	Publication/ File Date	Title
US20070009887A1	None	Victoria Siemering, Henrik Dahl	2007-01-11 / 2003-11-18	Genotyping of deafness by oligonucleotide microarray analysis
US20070134691A1	None	Iris Schrijver et al. (Stanford Univ, CA)	2007-06-14 / 2006-11-14	Methods & compositions for determining whether a subject carries a gene mutation associated with hearing loss.
US20050112598A1 US20040166495A1	None	Greinwald, John H. Wenstrup, Richard J Aronow, Bruce J.	2005-05-26 / 2004-02-24 2004-08-26 / 2003-02-24	Microarray-based diagnosis of pediatric hearing impairment-construction of a deafness gene chip
US20040038266A1[a]	None	Dobrowolski, Steven F Lin, Zhili	2004-02-26 / 2003-05-22	Advancing the detection of hearing loss in newborns through parallel genetic analysis
US20050059041A1	None	Johnson, Robert C. Mohammed, Mansoor Kim, Jae Weon Lu, Xan-Yan	2005-03-17 / 2004-05-17	Nucleic acids arrays and methods of use therefore
US20040203035A1	Third Wave Technologies, Inc.	Mast, Andrea L. Dorn, Erin; Kwiatkowski, Robert J Accola, Molly Wigdal, Susan S	2004-10-14 / 2004-01-09	Connexin allele detection assays

[a] Inventors Steven F.Dobrowolski and Zhili Lin were employees of NeoGen Screening Inc which was acquired by Pediatrix Medical Group and renamed Pediatrix Screening in 2003.

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Appendix VI: Letter from GeneDx to Athena Diagnostics regarding Connexin 26 sequencing.

Michael W. Henry
VP, Business Development
Athena Diagnostics, Inc.
Four Biotech Park
377 Plantation Street
Worcester, MA 01605

October 11, 2006

Re: GeneDx testing in GJB2 gene

Dear Mr. Henry:
I am in receipt of your letter dated September 11, 2006 regarding Athena Diagnostics being the exclusive licensee of two US Patents. You noted that a letter had been sent to John Compton on November 11, 2002 regarding this issue. That letter was never received at GeneDx or by John Compton. We had moved to 207 Perry Parkway the previous month and our mail was not being forwarded by the post office.

We have reviewed the two patents to which your letter of September 11, 2006 refer (5,998,147 and 6,485,908). These two patents specifically make claims regarding detecting mutations in the Connexin 26 gene comprising a deletion of a nucleotide from nucleotides 30 to 32 or a deletion of 38 base pairs beginning at position 30 (mutations described as being involved in autosomal recessive prelingual non-syndromic deafness).

GeneDx provides GJB2 (Connexin 26) gene testing for the ectodermal dysplasia known as Keratitis-Ichthyosis-Deafness syndrome, a severe and sometimes lethal autosomal dominant syndromic disorder. KID syndrome is considered an ultra-rare disorder, with only about 100 cases reported in the literature. Nearly 80% of patients with KID syndrome have a mutation, D50N, in the GJB2 gene. The mutation spectrum in KID syndrome and other rare dominant syndromic disorders involving the GJB2 gene have been published by the principals of GeneDx (see below).
You can find the details of the testing we offer on our website (www.genedx.com) and in the information sheet that can be downloaded from the site. Should you have any further questions, please do not hesitate to contact us.

Sincerely,
Sherri J. Bale, Ph.D., FACMG
Clinical Director
GeneDx

Richard G, White TW, Smith LE, Bailey RA, Compton JG, Paul DL, Bale SJ. Functional defects of Cx26 resulting from a heterozygous missense mutation in a family with dominant deaf-mutism and palmoplantar keratoderma. Hum Genet. 1998 Oct;103(4):393-9.
Richard G, Rouan F, Willoughby CE, Brown N, Chung P, Ryynanen M, Jabs EW, Bale SJ, DiGiovanna JJ, Uitto J, Russell L. Missense mutations in GJB2 encoding connexin-26 cause the ectodermal dysplasia keratitis-ichthyosis-deafness syndrome.
Am J Hum Genet. 2002 May;70(5):1341-8. Epub 2002 Mar 22.
Richard G, Brown N, Ishida-Yamamoto A, Krol A. Expanding the phenotypic spectrum of Cx26 disorders: Bart-Pumphrey syndrome is caused by a novel missense mutation in GJB2. J Invest Dermatol. 2004 Nov;123(5):856-63.

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Appendix VII: Email response from Athena Diagnostics to Gene Dx shared with permission of Dr. Sherri Bale, Clinical Director, GeneDx

Delivered-To: sherrib@genedx.com
Tue, 31 Oct 2006 15:31:28 -0500

Dear Sherri:
Thank you for your attached letter of October 11 regarding Cx26 (GJB2).
I understand that you test for the GJB2 D50N mutation for Keratitis-Icthyosis-Deafness (KID) syndrome.

Please confirm that GeneDx GJB2 testing does not include testing for the following mutations:
Deletion of nucleotides 27-35
Deletion of 38 base pairs starting at position 30
Deletion at position 30
Deletion of a nucleotide from nucleotide 30 to nucleotide 32

If GeneDx does not test for these GJB2 mutations, then I will consider this matter closed.

Regards,
Mike
Michael W. Henry
Vice President, Business Development
Athena Diagnostics, Inc.
377 Plantation Street
Worcester, MA 01605
(508) 756-2886 x3100
(508) 752-7421 fax
mhenry@athenadiagnostics.com

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Impact of Gene Patents and Licensing Practices on Access to Genetic Testing for Hereditary Hemochromatosis

Subhashini Chandrasekharan, Ph.D., Emily Pitlick, J.D., Christopher Heaney and Robert Cook-Deegan, M.D.[1]

Introduction

Hereditary hemochromatosis (HH) is an autosomal recessive disorder that results most often from mutations in the *HFE* gene,[2,3,4] which regulates iron absorption. HH caused by functional mutations in the *HFE* gene is commonly referred to as HH type 1. Mutations in the *HFE* gene place the individual at an increased risk for developing symptomatic HH, an iron metabolism disorder that leads to excess iron absorption from the diet, particularly in males. Since the body lacks a natural way to rid itself of the excess iron, it accumulates over time, resulting in organ damage, particularly in the heart, liver, and pancreas. In extreme cases, hemochromatosis can even lead to death, usually due to heart or liver failure.

Early detection of the disorder, and thus earlier treatment by phlebotomy (repeated blood draws), can greatly mitigate its effects and allow HH patients to live normal, healthy lives.[5] *HFE* testing in combination with a patient's family history and physical health record can provide guidance for clinical interventions or lifestyle changes that a patient would not have without genetic testing. Testing for the presence of *HFE* gene mutations can also help physicians to identify patients experiencing characteristic symptoms of the disorder, clarifying their diagnosis, and sometimes preventing irreversible organ damage.

HH is a candidate for genetic screening for many reasons. First, the mutations associated with HH are present at birth, whereas characteristic symptoms of hemochromatosis as a disease usually do not develop until mid-adulthood, beginning in an individual's 40s and 50s. In addition, the variability and non-specific nature of symptoms can make diagnosis difficult, raising the possibility that patients, especially those with no family history, may be diagnosed too late. Therefore, an early, specific diagnosis allows for an effective treatment plan. Secondly, unlike some hereditary disorders, a limited number of genes are associated with HH that can be tested for mutations to determine a patient's risk. Finally, HH is among the most common recessive genetic traits[6] in some populations of Northern European descent, resulting in a relatively high carrier frequency. Between 1 in 200 and 1 in 400 people of Northern European descent, or 0.5% of this population, is homozygous for the *HFE* mutation and thus at high risk of developing

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[1] Center for Public Genomics, Center for Genome Ethics, Law & Policy, Institute for Genome Sciences and Policy, Duke University (and Duke School of Law, for Emily Pitlick)

[2] *Hemochromatosis.* See http://digestive.niddk.nih.gov/ddiseases/pubs/hemochromatosis/index.htm [accessed November 10, 2008].

[3] Schmitt B, Aronson M, Fitterman N, Snow V, Weiss KV, Owens DK. Screening primary care patients for hereditary hemochromatosis with trasnferrin saturation and serum ferritim level: systematic review for the American College of Physicians. *Ann Intern Med* 2005. 143:522-536.

[4] Olynyk JK, Trinder D, Ramm GA, Britton RS, Bacon BR, Hereditary hemocromatosis in the post-*HFE* era. *Hepatology* 2008. 48(3): 991- 1001.

[5] Crawford DH, Hickman P. Screening for hemochromatosis. *Hepatology* 2000. 31(5):1192-93.

[6] The reason for higher population frequency in Northern Europe is not known. One intriguing, but still speculative, theory posits a survival advantage among those with HH mutations in resisting infections causing plague and other diseases prevalent in Europe. (See, for example, Moalen S, Weinberg ED, Percy ME. Hemochromatosis and the enigma of misplaced iron: implications for infectious disease and survival. *Biometals* 2004. 17(2):135-139.) Another hypothesis, which is not incompatible, is co-selection of hemochromatosis and certain major histocompatibility loci involved in immune function. (See, for example, Cardozo CS, Alves H, Mascarenhas M, Goncalves R, Oliveira P, Rodrigues P, Cruz E, de Sousa M, Porto G. Co-selection of the C64D mutation and HLA-A29 allele: a new paradigm of linkage disequilibrium? *Immunogenetics* 2002. 53:1002-1008.)

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clinical hemochromatosis.[7] The estimated carrier frequency of *HFE* mutation is 1 in every 8 to 10 individuals of Northern European ancestry.[8]

Despite this, universal genetic screening has not been recommended for several reasons. First, presence of the mutation does not mean that the individual will develop HH. While testing may assist physicians in diagnosing HH when a patient is presenting characteristic symptoms, presence of the mutation merely indicates one's susceptibility to iron overload and not the certainty of disease for those who are asymptomatic. The symptoms of HH are highly variable among homozygotes (those in whom both chromosomal copies of the HFE gene have hemochromatosis-associated mutations). Some are completely asymptomatic, others are severely affected. Several studies provide evidence that the penetrance of the *HFE* mutations, or the chance that those with the mutations will have HH symptoms, is lower than first estimated and highly variable.[9] The disease is also rarer in non-white populations. Homozygous mutation levels are 0.27 homozygotes per 1,000 Hispanic individuals, less than .0001 homozygotes per 1,000 Asian American individuals, 0.12 homozygotes per 1,000 in Pacific Islanders, and an estimated .14 homozygotes per 1,000 in African–American individuals.[10] The American College of Physicians does not recommend genetic or phenotypic (using biochemical tests) screening for HH in the asymptomatic general population.[11] The U.S. Preventive Services Task Force (USPTF) similarly found insufficient evidence to support broad population genetic screening.[12] Finally, the current price of the genetic diagnostic tests also makes their use as an initial screening procedure for HH prohibitive. Current practice is to identify symptomatic individuals utilizing non-genetic tests that measure iron overload, followed by genetic testing for specific diagnosis and to detect cases in families once an HH proband is identified.

Hereditary hemochromatosis is a natural case study for studying the impact of intellectual property (IP) on patient access to genetic testing. Patents exist on the *HFE* gene, its related protein, genetic screening test methods, and related testing kits.[13] Additional genes linked to rarer forms of HH are also patented.

The impact of these patents and their licensing on access to testing for HH type 1 is complicated by the generally subordinate role of clinical genetic testing in hemochromatosis, but also by the complex history of ownership of these patents. Despite an initial controversy about patenting, *HFE* genetic testing appears to have been adopted in clinical practice and much of the heat may have drained from the public debate. The path to the current state, however, involved transitional periods of turbulence that centered on exclusive licensing of a genetic diagnostic test.

One distinctive feature of this case is how *HFE* testing has evolved over time. *HFE* genetic testing illustrates how patent ownership and use by different patent-holders can affect licensing. *HFE* patent rights were transferred many times, and use and licensing policies changed over time. A 2002 *Nature* article, written when the licensing schema was based on exclusive licensing and a single-provider model, judged that *HFE* genetic testing "failed the test" of socially optimal access. In 2007 and 2008, compared to 2002, we found little controversy surrounding *HFE* genetic testing, and the licensing model has evolved to include several providers and sublicensing for use on different platform technologies. The past

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[7] Qaseem A, Aronson M, Fitterman N, Snow V, Weiss KB, Owens DK. Screening for hereditary hemochromatosis: a clinical practice guideline from the American College of Physicians. *Ann Intern Med* 2005. 143:517-521.
[8] *GeneReviews HFE-Associated Hemochromatosis.* See http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=hemochromatosis [accessed November 10, 2008].
[9] Olynyk JK, Trinder D, Ramm GA, Britton RS, Bacon BR. Op. cit.
[10] Whitlock EP, Garlitz BA, Harris EL, Beil TL, Smith PR. Screening for hereditary hemochromatosis: a systematic review for the U.S. Preventative Services Task Force. *Ann Intern Med* 2006. 145:209-223.
[11] Qaseem A, Aronson M, Fitterman N, Snow V, Weiss KB, Owens DK. Op. cit.
[12] Whitlock EP, Garlitz BA, Harris EL, Beil TL, Smith PR. Op. cit.
[13] See Appendix A for a list of patents and their claims.

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licensing practices of SmithKline Beecham Clinical Laboratories (SBCL) (exclusive licensing model) were controversial, but the current owner of patent rights, Bio-Rad Ltd., appears to have adopted a broad sub-licensing model that has resulted in broader clinical and patient access and less public conflict.

HFE genetic testing in the context of HH also shows how genetic testing is part of a larger set of diagnostic tools addressing a clinical syndrome. The clinical utility of those tools, including genetic testing, evolves over time. Growing knowledge about the uncertain penetrance of *HFE* mutations required additional research to determine the clinical significance of different *HFE* mutations, and other factors influencing expression of disease. These studies demonstrated a much lower clinical penetrance of *HFE* mutations than first expected, suggesting that the mutations alone were poor predictors of developing clinically significant hemochromatosis. Population screening was more likely to be pursued, if at all, by chemical or protein assays rather than genetic testing—with genetic tests finding more limited use in confirmatory diagnosis and family risk assessment once an index case is found. This most likely had a significant impact on interest in investing in patent enforcement, since the market for HFE genetic testing became much smaller when general population use seemed highly unlikely.

Lessons Learned

Research

- The Mercator Genetics business plan was centered on the identification of candidate genes for a number of complex diseases including asthma, schizophrenia, cardiovascular disease and prostate cancer, all of which presumably had a diagnostic market. The prospects of patents and revenue from diagnostic testing for HH probably stimulated research at Mercator Genetics. However, Dr. Dennis Drayna, co-founder of Mercator Genetics, notes that the company was conceived and initially funded on an agenda much broader than hemochromatosis gene discovery or diagnostic testing alone. Discovery of the *HFE* gene was nonetheless Mercator's signature success.
- The "race" for the HH gene was won by Mercator Genetics with the publication of an August 1996 *Nature Genetics* article. Two additional groups (one in France and another in Australia, which were both in non-profit institutions) were pursuing similar approaches to candidate gene identification and would likely have been successful in their efforts within months. However, the scale and focus of the positional cloning effort at Mercator, enabled by private R&D investment, probably gave their research group a competitive advantage.
- The patent applications filed by Mercator Genetics predated the submission of related manuscripts by nearly a year.[14] It is unclear, however, if this delay resulted from scientific issues, patenting activities, corporate strategy, or commercialization efforts by Mercator. It remains possible that such a delay may be the consequence of factors unrelated to patenting, such as the need for additional research or data prior to submission to peer reviewed journals, journal requests for additional data and experiments, delays in peer review, etc. Dr. Dennis Drayna, a senior author of the *Nature Genetics* paper, indicated that the latter was in fact true, and that Mercator Genetics made every attempt to expedite simultaneous paper submissions and patent filings.
- Concerns regarding inhibition of research due to the *HFE* gene patents do not seem to be supported. Substantial basic research, including identification of genes and mutations associated with other types of hemochromatosis has continued. Similarly, research on improved methods for detection of *HFE* mutations has also progressed. The adoption of broad sublicensing practices by

[14] Merz JF, Kriss AG, Leonard DGB, Cho MK. Diagnostic testing fails the test. *Nature* 2002. 415: 577-79.

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Bio-Rad, Ltd., has facilitated commercial research and development efforts focused on alternative methods for *HFE* mutation detection.

Development

- Mercator Genetics announced that it was developing a blood test for *HFE* genotyping within a year of publication of results. It is likely that the prospect of revenues from population wide screening may have served as an incentive for test development. However, no test was marketed before Mercator went out of business and merged with Progenitor.
- Intellectual property ownership alone did not provide incentive for test development. As reported by Merz et al., laboratories were able to develop in-house testing and offer it as clinical service soon after information of the gene sequence and its associated mutation had been made public and well before the patents were granted.

Commercialization

- *HFE* patents were potentially valuable assets for Mercator in facilitating its merger with Progenitor. Exclusive licensing of the *HFE* patents to SmithKline Beecham Clinical Laboratories (SBCL) resulted in significant and guaranteed revenue for Progenitor.
- Until it was sold to Quest Diagnostics, SBCL offered the test as part of its commercial diagnostics services. SBCL also undertook enforcement activities, including sending "cease and desist" letters to clinical laboratories.
- Similarly, the *HFE* patents were perceived as valuable assets when Bio-Rad acquired them subject to the exclusive clinical testing license and all pending patents from Progenitor in 1999. Quest transferred the license to Bio-Rad under undisclosed terms.
- Acquisition of the *HFE* patents was integral to Bio-Rad's business plans to develop and market analyte-specific reagents (ASRs) for *HFE* testing. *HFE* ASRs became available in 2001.
- *HFE* patents do not appear to have blocked commercial development of additional methods of *HFE* testing utilizing different platform technologies. For instance, Bio-Rad Ltd. granted a non-exclusive license to Nanogen Ltd for detection of the C282Y and H63D mutations using the NanoChip™ System. We cannot assess whether alternatives were unimpeded in all cases, but at least some alternatives have developed. The patent-associated fees may have discouraged some laboratories from entering the market,[15] but testing is widely available from multiple sources.
- Several non-profit and for-profit laboratories offer *HFE* testing for a fee. It is unknown how many providers have acquired a sublicense from Bio-Rad for tests developed in-house or use the Bio-Rad analyte specific reagents (ASRs) (in which case a sublicense is built into the purchase).
- It is unclear how much of the price variability among different providers (list price for mutation analysis ranges from approximately $150 to $500) can be attributed to license/royalty fees as opposed to variable overhead costs or costs associated with different testing methodology/platforms.

Communication and Marketing

- Patents have had little to no impact on the communication and marketing of *HFE* testing.

[15] One external reviewer of an early draft of this case study noted he was aware of at least one potential HFE test developer who decided not to develop a test because of the up-front payments to BioRad.

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- There is no evidence that *HFE* mutation testing was ever marketed directly to consumers by Mercator Genetics or subsequent holders of *HFE* patent rights.
- Information on promotion of *HFE* testing by Mercator Genetics among clinicians and other medical professionals is also unavailable. Similarly, it is unclear if SBCL and Bio-Rad Ltd. engaged in specific marketing activities to increase utilization of the test by consumers or health care providers.
- Independent campaigns by the Hemochromatosis Foundation, the American Hemochromatosis Society, the American Liver Foundation and the CDC[16] have sought to increase awareness of HH screening and *HFE* genetic testing among patients and medical professionals. The organizations promoting awareness are not the patent-holders, and the motivation appears to be public health awareness.
- Direct-to-consumer testing is also available from DNADirect.

Clinical Adoption

- Adoption of testing was rapid. As reported by Merz et al., adoption began nearly 17 months before the first patent was issued.[17]
- In a survey of testing providers, Merz et al. reported that 5 of 58 clinical laboratories offering the test in January 1998 elected to stop testing after receiving "cease and desist" letters from SBCL. Out of 31 other laboratories that had not developed the test, 22 indicated patents were the primary reason for not doing so. SBCL began patent enforcement ("cease and desist" letters) approximately two years after the patents were issued, by which time there had been significant adoption of the test.
- Although the number of laboratories offering *HFE* testing decreased, the majority of clinical providers (53) continued *HFE* genetic testing services. Therefore, it is unclear if the reduction in laboratories offering the test directly reduced clinical access to *HFE* testing.
- As of May 2007, 37 laboratories were listed as providers of *HFE* testing on the Genetests.org website. In addition, the test is offered directly to consumers by DNADirect.

Adoption by third party payers

- Patents do not appear to have had a direct or significant effect on decisions to cover the test by public or private insurance providers. A number of insurance companies cover genetic testing for HH when "medically necessary."

Consumer utilization

- There is little evidence bearing on the impact of patents on consumer utilization.
- Patent enforcement activities by SBCL led to the discontinuation of testing in some laboratories. Other laboratories reported being deterred from developing an *HFE* test by patent enforcement activities. However, most laboratories did continue offering the test as a

[16] Information about the American Hemochromatosis Society can be found at http://www.americanhs.org/. Efforts by the CDC to improve early detection and promote diagnosis of Hemochromatosis in the US are summarized in McDonnell SM, Witte DL, Cogswell ME, McIntyre R. Strategies to increase detection of hemochromatosis. *Ann Inter Med* 1998. 129:987-992.
[17] Merz JF, Kriss AG, Leonard DGB, Cho MK. Op. cit.

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service. The effects that the reduction in number of laboratories had on patient access or consumer utilization cannot be determined.

- *HFE* testing currently appears to be widely available. A large number of clinical laboratories offer the test in the price range of $160- $500. Consumers can also access testing independent of physicians through DNAdirect. The price offered by DNAdirect ($199) is less than that listed by many clinical laboratories and includes genetic counseling services.
- The test is covered by several insurance providers when patients meet the eligibility criteria for testing. In the absence of quantitative data on how many tests are ordered per year and when and how often insurance coverage is denied, it is unclear to what extent third party adoption affects consumer utilization. The effect of patents on such coverage decisions, if any, was not mentioned by those offering tests or seeking reimbursement for them, and was not noted in payer coverage or reimbursement policies.

Background

The clinical syndromes of HH relate to the excessive deposition of iron in various organs. While healthy people usually absorb about 10 percent of the iron contained in their diet to meet their bodies' needs, those with HH absorb more. Chronic iron absorption may lead to a variety of symptoms. The most common symptoms include joint pain, fatigue, lack of energy, abdominal pain, loss of sex drive, and heart problems (including both arrhythmia and cardiomyopathy, or loss of cardiac muscle function). Men are more likely to experience symptoms and experience them earlier in life, between the ages of 30 and 50. Women affected by HH are usually symptomatic after the age of 50. The lower rates of HH in younger women are attributed to the protective effect of physiological blood loss associated with menstruation.[18]

HH begins as mere iron overload, but over time this overload can result in more serious disease through organ failure. Without early detection, the accumulated iron in various tissues may lead to:

- Arthritis (due to joint damage)
- Liver failure and cirrhosis (death of liver cells followed by scarring)
- Pancreatic damage that can possibly include diabetes[19]
- Problems with digestion (due to loss of pancreatic enzymes and paucity of fat-absorbing bile pigments produced by the liver)
- Heart abnormalities such as irregular heart rhythms or congestive heart failure
- Impotence
- Early menopause
- Abnormal pigmentation causing the skin to appear gray or bronze
- Thyroid deficiency

[18] Yen AW, Fancher TL, Bowlus CL. Revisiting hereditary hemochromatosis: current concepts and progress. *Am J Med* 2006. 119(5):391-399.

[19] Dr. Paul Adams cautions "that this area remains controversial since screening studies have not shown an increase in prevalence of diabetes. Several metabolic studies have suggested that the diabetes seen in hemochromatosis is more often insulin resistance of cirrhosis." Email from Paul Adams to SACGHS staff. September 9, 2008.

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- Damage to the adrenal gland, and infrequently
- Liver cancer

There are several known types of HH.[20] The most common form, Type 1, affects adults and is usually caused by a defect in the *HFE* gene. Type 2 or juvenile hemochromatosis, which is not associated with the *HFE* gene, leads to severe iron overload and liver and heart disease in young adults between the ages of 15 and 30. Unlike adult-onset HH, juvenile HH affects males and females equally. Similarly, Types 3 and 4 of hereditary hemochromatosis are not associated with *HFE* mutations and they are much rarer.

Since the symptoms of HH can arise from many causes, doctors often focus on treating the individual symptoms and may not identify the underlying HH. Many cases of HH are therefore undiagnosed. This problem of effective diagnosis could be partially solved by genetic screening tests that would easily detect the *HFE* mutation in symptomatic persons and through a systematic screening process that identifies those presymptomatic individuals with iron overload. Individuals with signs of iron overload could then be evaluated with genetic testing and other means for determining causes of iron overload. In most cases, either an environmental source of overwhelming iron intake (e.g., vitamin overdose, dietary practice, water supply, or environmental exposure) or a known genetic mutation would explain the iron overload.

Genes Associated with Hemochromatosis

The gene most commonly associated with Type1 HH is *HFE*, located in the region of the gene *HLA-A* on chromosome 6.[21] There are two known mutations of the *HFE* gene that are most commonly linked to HH. The C282Y mutation is caused by a single base change, resulting in tyrosine replacing the normal cystine at position 282 of the *HFE* protein. C282Y accounts for almost 90 percent of HH cases.[22] Most patients are homozygous for the mutation, which is transmitted in an autosomal recessive manner.[23] Environmental factors and other genotypes also contribute to HH.[24] Another mutation, H63D, is the result of the substitution of an aspartic acid for a histidine at position 63. It is still unclear exactly how the H63D mutation is associated with HH. When H63D is inherited from one parent, it usually causes little increase in iron absorption and rarely leads to the development of hemochromatosis. Although most patients with a clinical diagnosis of HH are homozygous for the C282Y mutation, approximately 10% are compound heterozygotes carrying a single copy each of the C282Y and H63D mutations.[25] S65C is an *HFE* gene mutation tentatively linked to a mild form of iron overload. Other mutations with less frequency and/or low penetrance have also been described, including V53M, V59M, H63H, Q127H, Q283P, P168X, E168Q, E168X, and W168X.[26]

Juvenile hemochromatosis, also called HH type 2, (subtypes 2A and 2B), is an autosomal recessive disorder not caused by a defect in the *HFE* gene. *HJV*, a gene located on chromosome 1q, was recently identified as the cause of HH type 2A. Juvenile HH type 2B is caused by mutation in the *HAMP* gene coding for hepcidin, a peptide hormone that has a key role in human iron metabolism.[27] The hepcidin

[20] Olynyk JK, Trinder D, Ramm GA, Britton RS, Bacon BR. Op. cit.
[21] Whitlock EP, Garlitz BA, Harris EL, Beil TL, Smith PR. Op. cit
[22] Qaseem A, Aronson M, Fitterman N, Snow V, Weiss KB, Owens DK. Op. cit.
[23] Schmitt B, Golub RM, Green R. Op. cit.
[24] Wood M, Powell LW, Ramm GA. Environmental and genetic modifiers of the progression to fibrosis and cirrhosis in hemochromatosis. *Blood* 2008. 111:4456-4462.
[25] Yen AW, Fancher TL, Bowlus CL. Op. cit.
[26] Franchini M, Veneri D. Hereditary hemochromatosis. *Hematology* 2005. 10(2):145-49.
[27] Ibid.

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protein hormone was initially called "Liver-Expressed Anti-microbial Protein"[28] because its function appeared to be related to fighting fungal and bacterial infections (iron is essential to the inflammatory response to certain pathogens). HH type 3 is an autosomal recessive disease caused by mutations in the transferrin receptor 2 gene, *TRF2*.[29] HH type 4, which is an autosomal dominant disease, is caused by mutations in the *SLC40A1* gene. *SLC40A1* encodes for a protein implicated in iron intestinal export, ferroportin.[30]

The remainder of this case study focuses on *HFE,* the gene most commonly associated with Type 1 HH, and for which the patenting and licensing stories are best documented.

Genetic Tests for Hemochromatosis

Several genetic tests are currently available for hemochromatosis. Targeted mutation analysis is the most common form of clinical genetic testing. This process tests for the presence of the two most common known disease-causing alleles in the *HFE* gene, C282Y and H63D.[31] Different laboratories use different methods. Several common testing methods for the presence of the C282Y and H63D mutations were used by 90 U.S. laboratories in 2002. These include electrophoresis for restriction fragment length polymorphisms (RFLPs) and size analysis (64% of labs), allele-specific oligonucleotide assay (ASO) (11% of labs), allele-specific polymerase chain reaction and Amplification Refractory Mutation System (PCR/ARMS) (6% of labs), LightCycler (8% of labs), DNA sequencing (3% of labs), and other/unspecified methods (8% of labs).[32] Linked linear amplification (LLA) is another means of amplification of DNA to detect *HFE* mutations.

Some methods are more labor intensive than others, making them suitable only for research rather than diagnostic laboratories. Other methods accommodate the needs of large numbers of specimens requiring short turn-around times. In Canada and Europe, commercial suppliers can provide "kits" to clinical laboratories. However, since such kits used for clinical testing in the United States are regulated by the FDA, increasing the costs associated with development, and analyte specific reagents (ASR) rather than test kits are routinely developed and marketed by biotech companies. Four biotechnology companies, Bio-Rad, Nanogen, LightCycler (a subsidiary of Roche), and Orchid Cellmark, provide reagents for the most commonly used methods of large-scale HH gene testing. A full sequence analysis can also be performed, usually to identify mutant alleles associated with HH that are not C282Y or H63D.

Non-Genetic-Based Means of Diagnosing Hemochromatosis

Currently, diagnosis of HH is often based on first-level biochemical tests, followed by second-level genetic testing. Biochemical methods are simple, fast, and inexpensive. The standard test is transferrin saturation (TS). This test determines how much iron is bound to transferrin, the protein that carries iron in the blood. Measuring a morning fasting TS level eliminates 80 percent of false-positive results. Values of 60% or greater in men and 50% or greater in women have an approximate sensitivity of 92%, specificity

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[28] Krausse A et al. LEAP-1 a novel highly disulphide-bonded human peptide, exhibits antimicrobial activity. *FEBS Letters* 2000. 480:147-150. Park CH, Valore EV, Waring AJ, Ganz T. Hepcidin, a urinary antimicrobial peptide synthesized in the liver. *J Biol Chem* 2001. 276:7806-7810.
[29] Ibid.
[30] Ibid.
[31] Roughly 60 – 90% of the persons tested with an *HFE* mutation will have two C282Y alleles. While 3 – 8% will have one C282Y mutation and one H63D mutation, the rarest combination, roughly 1 % of those with *HFE* mutations will have two H63D mutations present. See Appendix D for more information.
[32] *ACC Review of HHC/General Adult Population Analytic Validity.* Centers for Disease Control and Prevention. Version 2003.6 (archived 2002). See http://www.cdc.gov/genomics/gtesting/ACCE/FBR/HH/HHAnaVal_17.htm [accessed January 12, 2009].

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of 93%, and positive predictive value of 86% for detecting homozygous individuals with HH.[33] The above data are primarily from referral studies in which the TS test is embedded in the clinical diagnosis. In general population screening studies, where there is no referral for testing, the sensitivity of TS is much less. There is also a wide biological variability in the test. Fasting TS has also been shown to be of no increased value over random testing.[34,35] The lack of a uniform cutoff percentage for the optimal detection of disease lowers the specificity and positive predictive value of the TS test. Another limitation of TS is that it is a two-step test and therefore more prone to error.

A second possible test is serum ferritin (SF). This test estimates the total body iron stores. Ferritin values greater than 300 µg/L in men and 200 µg/L in women, suggest iron overload. However, ferritin can be falsely elevated as an acute phase reactant and does not become abnormal until iron loading has advanced due to liver involvement.[36] Therefore, doctors should consider non-HH causes behind a patient's high serum ferritin levels if transferrin saturation is not elevated.

A more recent biochemical method used to test for HH is unbound iron-binding capacity (UIBC). UIBC is a one-step assay that has high sensitivity and has been suggested as a reliable and potentially inexpensive diagnostic test for HH.[37] Prior to the availability of mutation analysis, liver biopsy was the most common second-level diagnostic test for HH. Liver biopsy helps determine the extent of iron accumulation in the liver. However, the biopsy is more often used as a prognostic tool, to review the level of damage in the liver.[38,39] Another non-genetic test used to diagnose HH is quantitative phlebotomy,[40] in which specified amounts of blood are drawn. Removing "4 g or more of mobilizable iron stores (16 phlebotomies, each removing 500 mL of blood [250 mg of iron per 500 mL]) before the development of iron-limited erythropoiesis confirms the presence of primary iron overload due to hemochromatosis."[41] If any of the tests described above suggest iron overload, *HFE* genotype testing is strongly suggested.

Treatment of Hemochromatosis

Unlike many other serious genetic disorders, hemochromatosis may be treated simply, safely, and inexpensively. The most common treatment for HH is phlebotomy, a process used to rid the body of excess iron. In phlebotomy, doctors remove a pint of blood once or twice a week for several months or more, depending on the iron levels. Phlebotomy has been widely adopted because it is inexpensive and safe, and has clear face validity as a common-sense treatment for iron overload. Recent studies have demonstrated a reversal of liver fibrosis with phlebotomy treatment.[42,43] Treatment for those who already

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[33] Yen AW, Fancher TL, Bowlus CL. Op. cit.
[34] Adams PC, Reboussin DM, Press RD, Barton JC, Acton RT, Moses GC, Leiendecker-Foster C, McLaren G, Dawkins F, Gordeuk V, Lovato L, Eckfeldt J. Biological variability of transferrin saturation and unsaturated iron binding capacity. *Am J Med* 2007. 120:999.e1.-e7.
[35] Adams PC, Reboussin DM, Eckfeldt JH, Moses GC, Leiendecker-Foster C, McLaren CE, McLaren GD, Dawkins FW, Kasvosve I, Acton RT, Barton JC, Zaccaro D, Harris EL, Press R, Chang H. A comparison of the unsaturated iron binding capacity to transferrin saturation as a screening test to detect C282Y homozygotes for hemochromatosis in 101,168 participants in the HEIRS study. *Clinical Chemistry* 2005. 51:1048-1052.
[36] Ibid.; Franchini M, Veneri D. Op. cit.
[37] Murtagh LJ, Whiley M, Wilson S, Tran H, Bassett ML. Unsaturated iron binding capacity and transferrin saturation are equally reliable in detection of *HFE* hemochromatosis. *Am J Gastroenterol* 2002. 97(8):2093-9.
[38] Whitlock EP, Garlitz BA, Harris EL, Beil TL, Smith PR. Op. cit.
[39] Adams PC, Kertesz AE, McLaren CE, Barr R, Bamford A, Chakrabarti S. Population screening for hemochromatosis: a comparison of unbound iron-binding capacity, transferrin saturation, and C282Y genotyping in 5,211 voluntary blood donors. *Ann Intern Med* 2000. 31(5):1160-64.
[40] Powell LW, George DK, McDonnell SM, Kowdley KV. Diagnosis of hemochromatosis. *Ann Intern Med* 1998. 129:925-931.
[41] Ibid.
[42] Falize L, Guillygomarch A, Perrin M, Laine F, Guyader D, Brissot P, Turlin B, Deugnier Y. Reversibility of hepatic fibrosis in treated genetic hemochromatosis: a study of 36 cases. *Hepatology* 2006. 44:472-7.

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have organ damage is more complicated. While phlebotomy may stop the progression of liver disease in its early stages, those with more severe cases may need to seek a specialist. Phlebotomy will not cure other conditions associated with hemochromatosis, but it will help most of them, with the exception of arthritis, for which removal of excess iron has little effect.

Current Guidelines for Genetic Testing

Clinical uses of genetic testing include confirmatory diagnostic testing, predictive testing for at-risk relatives, carrier testing to identify heterozygotes, and prenatal diagnosis (technically available but rarely performed)[44]. The American College of Physicians (ACP) clinical practice guidelines for the screening of HH state evidence is insufficient to recommend for or against screening for HH in the general population.[45] They recognize that the C282Y mutation is the most common predictor of whether the patient will develop HH but note that there is still no way of predicting which homozygous patients will develop HH.[46] For these reasons, the ACP leaves the decision whether or not to perform tests for HH to clinical judgment, based on: whether patients exhibit symptoms of the associated disorders; whether patients exhibit serum ferritin levels of more than 200 µg/L in women and more than 300 µg/L in men combined with transferrin saturation greater than 55%; or whether the individual has a family history of HH. Each factor increases the risk for developing the disease compared to the general population.[47]

The ACP also encourages doctors to discuss the risks and benefits of genetic testing with their patients. This should include a discussion of the available treatment and its efficacy, as well as the social impact of disease labeling, insurability, psychological well-being, and as-yet-unknown genotypes associated with HH.[48] For example, asymptomatic persons found homozygous or not for the C282Y mutation may develop unnecessary stress or false reassurance.[49] The ACP does acknowledge that the lack of information on the natural history of HH makes it difficult to manage patients with the disorder,[50] and considers future technological developments and genetic screening as potential aids in the management of the disease.[51] Finally, the ACP recommends more uniform diagnostic criteria.

The American Association for the Study of Liver Disease recommends genetic testing for all patients in whom there is a strong suspicion for iron overload. Such patients should have C282Y and H63D mutation analysis completed.[52,53]

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[43] Powell L, Dixon J, Ramm G, Purdie D, Lincoln D, Anderson G, Subramaniam, VN, Hewett DG, Searle JW, Fletcher LM, Crawford DH, Rodgers H, Allen KJ, Cavanaugh JA, Bassett ML. Screening for hemochromatosis in asymptomatic subjects with or without a family history. *Arch Intern Med* 2006. 166:294-301.
[44] See http://www.geneclinics.org/profiles/hemochromatosis/details.html [accessed January 13, 2009].
[45] Qaseem A, Aronson M, Fitterman N, Snow V, Weiss KB, Owens DK. Op. cit.
[46] Ibid.
[47] Ibid.
[48] Ibid. See also Anderson RT, Wenzel L, Walker AP, Ruggiero A, Acton RT, Tucker DC, Thomson E, Harrison B, Howe E, Holup J, Leiendecker-Foster C, Power T, Adams P. Impact of hemochromatosis screening in patients with indeterminate results: the hemochromatosis and iron overload screening study. *Genet Med* 2006. 8(11):681-87. The observational study found that notification of indeterminate results from screening might pose a potential participant risk. Asymptomatic individuals who underwent *HFE* genotype testing, or were tested for HH using the SF or FT methods and were found to have elevated levels of uncertain clinical significance. It found that compared to normal controls, those persons reported diminished general health and mental wellbeing, and more health worries.
[49] Qaseem A, Aronson M, Fitterman N, Snow V, Weiss KB, Owens DK. Op. cit.
[50] Environmental factors often modify the natural expression of iron accumulation and disease. These factors include blood loss from menstruation or donation, alcohol intake, diet, and co-morbid disease including viral hepatitis. Whitlock, E.P.; Garlitz, B.A.; Harris, E.L.; Beil, T.L.; Smith, P.R. Screening for hereditary hemochromatosis: a systematic review for the U.S. Preventative Services Task Force. *Ann Intern Med* 2006. 145:209-223.
[51] Qaseem A, Aronson M, Fitterman N, Snow V, Weiss KB, Owens DK. Op. cit.
[52] See Appendix C.
[53] Yen AW, Fancher TL, Bowlus CL. Op. cit..

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Patenting of HH Genes

Bio-Rad Laboratories, Inc., is the owner and licensee of most of the patents relating to HH genetic testing and the *HFE* gene. In 1999, Bio-Rad bought many of those rights from Progenitor, which had retained the rights to HH genetic testing following the Mercator-Progenitor merger. Mercator was the initial patent owner and assignee.

Mercator scientists first identified the *HFE* gene in 1995–96, along with the two mutations, C282Y and H63D, which were present in over 80 percent of people suffering from HH.[54] In 1995 and 1996, Mercator applied for patents related to *HFE* and its mutations. The patents were issued at various times between 1998 and 2000 and covered the whole *HFE* gene sequence, a method for diagnosing the C282Y and H63D mutations within the *HFE* sequence, a method of analyzing C282Y and H63D *HFE* mutations, and a method of analyzing the mutation using a kit. Other patents in the same patent family and with the same group of inventors issued between 2000 and 2006 and were assigned to Bio-Rad. These patents included diagnostic methods for a panel of less prevalent mutations, which did not include C282Y or H63D. They also cover polypeptides related to the *HFE* gene, and the associated proteins. Another patent covers a method of diagnosis for TRF2, another gene related to HH.[55]

Some other patents pertinent to HH are not controlled by Bio-Rad, but they are far fewer in number. Billups-Rothenberg, Inc., (BRI), in San Diego, California owns a gene patent, US 6,355,425 "Mutations Associated with Iron Disorders," which covers a diagnostic method for a panel of *HFE* mutations including S65C, 193T, G93R, 277C, 105T, 314C but does not include C282Y and H63D. BRI has exclusively licensed this patent to Nanogen. The one HH gene patent owned by a non-profit organization is assigned to Erasmus University in Rotterdam, Netherlands. This patent claims a method of diagnosis for SCL11A3, a mutation of the ferroportin 1 gene. We have been unable to determine if this patent was ever licensed. However, these patents may be less relevant to the case study because the predominant tests related to HH genotyping involve the mutations C282Y and H63D that are covered by the Bio-Rad patents.

We know of no litigation over the DNA sequence patents associated with HFE or other genetic forms of hemochromatosis, although given exclusive licenses to Nanogen for several mutations, this is a conceivable prospect.

Licensing of HH Genes

Merz et al. published a report in 2002 highlighting the patenting of the *HFE* gene and the licensing practices of the Mercator/Bio-Rad patents. The authors argued that gene patents had a negative on clinical practice because of the high prices the patent owners commanded.[56] According to the article, in the late 1990s, Progenitor exclusively licensed the patent rights to perform clinical testing of the HH mutations to SmithKline Beecham Clinical Laboratories (SBCL) for an up-front payment and guaranteed continuing fees worth roughly $3 million.[57] The licensing agreement guaranteed that SBCL's exclusive license and payments to Progenitor would continue until a kit became available for use by clinical laboratories.[58] In June 1998, after SBCL obtained the exclusive licensing for the clinical testing component of HH, it began informing laboratories of their possible infringement activities and offering sublicenses for an up-front fee

[54] Feder JN et al. A novel MHC class-I like gene is mutated in patients with hereditary hemochromatosis. *Nat Genet* 1996. 13:399-408.
[55] See Appendix A.
[56] Merz JF, Kriss AG, Leonard DGB, Cho MK. Op. cit.
[57] Ibid.
[58] Ibid.

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of $25,000 to academic licensees and for 5 to 10 times that amount to commercial laboratories (Appendix E). It also sought royalties as high as $20 per test.[59] After the sale of SBCL and the patent rights for clinical testing to Quest Diagnostics in 1999, the IP was not enforced again until Bio-Rad began offering analyte-specific reagents (ASRs) in 2001.

When Bio-Rad acquired the portfolio of pending and issued patents covering *HFE* and its mutations from Progenitor in April 1999, it acquired them subject to the exclusive clinical-testing license held by SBCL.[60] Quest transferred the clinical-testing license it acquired from SBCL to Bio-Rad.[61] The terms and conditions of that license agreement were not made public. Bio-Rad obtained other patents related to HH gene products. It began offering analyte-specific reagents (ASR) for testing of the C282Y and H63D alleles in 2001.

Today, Bio-Rad offers two HH test kits, the mDx Hereditary Hemochromatosis ASR kit and mDx Hereditary Hemochromatosis LLA ASR test kit. Both kits provide for 24 tests at a cost of $2,016, or $84 per test. A purchase of the kit includes the purchase of a sublicense from Bio-Rad to perform the test. According to some providers, the sublicenses attached to Bio-Rad's kits are more cost efficient than the licenses it offers to laboratories that develop and offer their own mutation testing or "in-house" assays.[62] However, Dr Michael Watson at the American College of Medical Genetics indicates that, at least initially, the Bio-Rad test kit's inferior performance essentially forced laboratories to develop their own "in-house" tests, which would require paying the higher fee for a sublicense. Such a sub-license includes up-front payments that are inversely proportional to the testing volume of the laboratory plus a per test fee, which was $20 in 2002.[63] It is not known what sublicensing fees are currently paid by laboratories that offer tests they have developed in-house, also known as "home- brews". The CDC review of analytic validity of *HFE* testing [64] noted that since Bio-Rad owned the patent for hereditary hemochromatosis, no other commercially available manufactured reagents were available for this test. However, ASRs for mutation detection using other platform technologies have become available more recently. For example, ASRs are offered by Nanogen Inc,[65] with sublicenses from Bio-Rad and presumably BRI too.

Impact of IP and Licensing on Clinical Genetic Testing for HH

Despite the presence of IP on clinical testing methods, laboratories around the country were performing HH screening on patients before and after the Mercator patents issued.[66] In a study of 128 U.S. laboratories identified as capable of offering the *HFE* test, with 119 of those laboratories responding, 58 laboratories indicated that they were performing *HFE* testing by 1998.[67] Thirty-five of the 58 laboratories were conducting the testing after the *Nature Genetics* paper published in August 1996 identifying the mutation, but before the patent issued in January, 1998.[68] Fifty-four of the 58 laboratories

[59] Ibid.
[60] Ibid.
[61] Ibid.
[62] Merz JF, Kriss AG, Leonard DGB, Cho MK. Op. cit.
[63] Ibid.
[64] *ACC Review of HHC/General Adult Population Analytic Validity*. Op. cit.
[65] Non exclusive license between Nanogen Inc and BioRad for *HFE* C282Y and H63D testing .
See http://sec.edgar-online.com/2003/03/31/0001104659-03-005523/Section8.asp [accessed January 13, 2009]. Third Wave Technologies, which previously marketed custom HFE ASRs, was acquired by HoloLogics in June 2008. Custom ASRs for HFE testing are no longer marketed by HoloLogics.
[66] *ACC Review of HHC/General Adult Population Analytic Validity*. Op. cit.
[67] Cho MK. *Effects of Gene Patents and Licenses on Clinical Genetic Testing*. Presentation to Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS). 27 June 2008. See http://oba.od.nih.gov/oba/SACGHS/meetings/June2006/Cho.pdf [accessed November 12, 2008].
[68] Ibid.

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conducting the test received letters from SBCL informing them of the HH IP and offering a sublicense.[69] Ninety-one percent of the interviewed laboratories were aware of the *HFE* patents and 36 revealed that the patents contributed to their decisions not to offer the test.[70] Five laboratories out of the initial 128 sample, or 4 percent, chose to stop performing the test. Of these 5 labs, 2 stated that the reason to stop testing was patents. One laboratory stated that patents were one of several reasons for abandonment of the HH test. Two additional laboratories stated that patents were not a reason for their decision to abandon the test. Commercial reasons (e.g., lack of adequate volume to cover fixed costs) appeared to be the predominant reason why these laboratories stopped performing the test.[71],[72]

As of May 2007, the GeneTests database (www.genetest.org) listed 37 U.S. laboratories performing targeted mutation analysis for HH. A sampling of 17 of those 37 laboratories revealed a list price for targeted mutation analysis that fell between $125 and $467 [73] indicating a significant range in prices. This may be due to several factors, including variability in methods of mutation testing, reagents costs for each method, and potentially licensing fees to perform HH testing. Some laboratories may perform "home-brew" assays with relatively low reagent costs. In these cases, one must consider the cost of the technical time for reagent preparation and the Quality Control/Quality Assurance (QC/QA) costs. The costs of ASR can be relatively high compared to traditional biochemical assays. At the same time, savings in technical staff time for preparation and QC/QA can offset reagent costs. For screening, the relevant figure is the cost per patient tested, not the cost per mutation tested; a diagnostic test may entail running the test case as well as controls, which also consume reagents covered by the reagent kits.[74] The exact economics of *HFE* mutation testing for HH are therefore not completely transparent. The cost of the IP is a minimum of the $20 per test fee and could be higher, depending on how licensing fees are structured into reagent costs that come with associated patent licenses.

Cost Effectiveness of Screening for *HFE* Mutations

Several studies on the cost-effectiveness and benefits of genotypic screening for the common disease-causing alleles on the *HFE* gene have been performed. As recently reviewed by Phatak et al., these studies provide evidence that screening would improve health status. However, all the studies reviewed support the use of biochemical tests rather than genetic tests as the initial test.[75] In 1999, Adams et al. reported that the genotypic screening of voluntary blood donors and their siblings by genotyping would be less expensive than phenotypic screening with biochemical tests if the genetic test cost less than $28. However, if the genetic test cost $173, then it would cost nearly $110,000 to identify a homozygote with a potentially life-threatening disease. The cost per homozygote identified also increased with decreasing penetrance of the disease. A 10% penetrance (i.e., 10% of those individuals with the relevant mutation actually have HH) resulted in nearly $400,000 in costs per individual identified.[76]

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[69] Merz JF, Kriss AG, Leonard DGB, Cho MK. Op. cit.
[70] Ibid.
[71] Data provided by Jon Merz, September 5, 2008. Data provided during external review process.
[72] Cho MK. Op. cit.
[73] The sample was conducted by informal telephone conversations with laboratory staff on April 6, 2007. The providers were surveyed for their laboratory's "list price" for *HFE* testing. In some situations, staff offered both the individual list price and the insurance list price. See Appendix B. By way of comparison, a study noted that the cost of *HFE*-genotyping in Australia cost less than $28. Adams PC, Kertesz AE, McLaren CE, Barr R, Bamford A, Chakrabarti S. Population screening for hemochromatosis: a comparison of unbound iron-binding capacity, transferrin saturation, and C282Y genotyping in 5,211 voluntary blood donors. *Ann Intern Med* 2000. 31(5): 1160-64.
[74] *ACC Review of HHC/General Adult Population Analytic Validity*. Op. cit.
[75] Phatak PD, Bonkovsky HL, Kowdley KV. Hereditary hemochromatosis: time for targeted screening. *Ann Intern Med* 2008. 149(4):270-2.
[76] Adams PC, Valberg LS. Screening blood donors for hereditary hemochromatosis: decision analysis model comparing genotyping to phenotyping. *Am J Gastroenterology* 1999. 94:1593-1600.

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A literature review and synthesis conducted by Whitlock *et al*. for the U.S. Preventive Services Task Force provides some outline of the cost effectiveness of *HFE* screening. However, it could not determine the cost-effectiveness of screening because of uncertainties associated with penetrance of disease in individuals with C282Y mutations, poorly defined natural history of disease progression, and variable prevalence of *HFE* mutations in different ethnic populations.[77] HH testing would not be as effective as the control procedures without evidence establishing that the prevailing symptoms are caused directly by or associated with iron overload. The review outlined several studies suggesting that while members of the general population with symptoms or signs consistent with HH did not have higher levels of C282Y homozygosity, patients in a liver clinic prescreened for higher transferrin saturation levels, hospitalized diabetic patients, and patients referred to specialists for chronic fatigue and arthralgias did.[78] Studies have suggested that most individuals with the genetic abnormality do not have shortened life expectancy or progression of disease when compared with control groups.[79] Morbidity and mortality in HH are related to the presence of iron overload in the blood, tissue, and organ systems, not the *HFE* mutation, per se.[80] End organ damage is related to the severity of iron overload and reduces life expectancy.[81] One study suggests that *HFE* screening is cost effective *if* the proportion of C282Y homozygotes that develop end organ damage when left untreated is over twenty percent.[82] Allen *et al*. recently reported that nearly 28 % of men and 1 % of women with C282Y homozygosity will develop iron overload disease.[83]

To assess the cost-effectiveness of genotype screening for HH, a study would need to address: (1) the prevalence of HH; (2) the probability of developing disease manifestations and cost of managing them; (3) the cost of the screening test; (4) the cost offsets of screening and diagnosis compared to costs avoided by early detection or more effective management; and (5) the discount rate, to accommodate the separation in time from detection to health benefit.

In a recent comprehensive analysis, Gagne et al. evaluated the cost effectiveness of 165 population screening algorithms using biochemical and genetic tests in a simulated virtual population with user defined demographic characteristics including variable *HFE* mutation frequencies and penetrance. Biochemical penetrance was used as an intermediate phenotype in this study. In the 165 algorithms used in 91 virtual populations of a million individuals, biochemical screening tests were more cost effective than genetic tests when used as the initial test. Genetic testing was once again found to be most cost effective when performed as the final confirmatory step.[84]

HFE gene testing for the C282Y mutation is a cost-effective method of screening the siblings and children of patients with HH.[85] The authors incorporated serum iron studies among persons homozygous for C282Y and compared a no-screening strategy with four screening strategies for HH. All the strategies were developed for treating children and siblings of probands, except for one when the spouse was also given a genetic test. This exception strategy was only applied to children. The study recommended a four step clinical intervention: "(1) serum iron studies; (2) gene testing of the proband. If the proband is

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[77] Whitlock EP, Garlitz BA, Harris EL, Beil TL, Smith PR. Op. cit.
[78] Ibid.
[79] Waalen J, Nordestgaard BG, Beutler E. The penetrance of hereditary hemochromatosis. *Best Pract Res Clin Haematol* 2005. 18(2):203–220. Yen AW, Fancher TL, Bowlus CL. Op. cit.
[80] El-Serag HB, Inadomi JM, Kowdley KV. Screening for hereditary hemochromatosis in siblings and children of affected patients, a cost-effectiveness analysis. *Ann Intern Med* 2000. 132:261–269.
[81] Crawford DH, Hickman P. Op. cit.
[82] Ibid.
[83] Allen KJ et al. Iron-overload-related disease in *HFE* hereditary hemochromatosis. *N Engl J Med* 2008. 358(3):221-30.
[84] Gagne G, Reinharz D, Laflamme N, Adams PC, Rousseau F. Hereditary hemochromatosis: effect of mutation penetrance and prevalence on cost-effectiveness of screening modalities. *Clinical Genetics* 2007. 71: 46-58.
[85] El-Serag HB, Inadomi JM, Kowdley KV. Screening for hereditary hemochromatosis in siblings and children of affected patients, a cost-effectiveness analysis. *Ann Intern Med* 2000. 132:261–269.

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[without a C282Y mutation], the spouse undergoes gene testing; if he or she is heterozygous [for the C282Y mutation], the children undergo gene testing; (3) Gene testing of the proband; if he or she is homozygous, relatives undergo gene testing; (4) Direct gene testing of relatives."[86] The study concluded that "*HFE* gene testing of the proband was the most cost-effective strategy for screening one child," with an incremental cost-effectiveness ratio of $508 per life-year saved. For screening two or more children, the second most cost effective strategy was "*HFE* gene testing of the proband followed by testing of the spouse." There, the incremental cost-effectiveness ratio was $3665 per life-year saved. The study also concluded that "in siblings, all screening strategies were dominant compared with no screening" and that "strategies using *HFE* [genetic] testing were less costly than serum iron studies."[87] The greater cost-effectiveness of this sequential algorithm, which incorporates genetic testing but does not use genetic testing as the first step, is because the relatively high cost of genetic testing is incurred only in cases where risk is higher than average. The use of clinical genetic testing to confirm a diagnosis of HH among those with iron overload, in this conceptual framework, is an "indicated" preventive intervention targeted at asymptomatic individuals who have evidence of iron overload based on inexpensive biochemical screening tests. Here, we borrow from the terminology of Gordon's classification of preventive strategies, using genetic testing as one step in the prevention strategy.[88]

Phatak et al. recommend selective or "targeted" screening in groups whose risk is elevated such as adult men greater than 25 years of age of Northern European ancestry and first degree relatives of patients with known HH[89].

Lessons Learned

HH was selected for study to assess the impact of patenting and licensing practices on access to genetic testing. Using the conceptual framework developed for a parallel literature synthesis, we now consider what lessons might be learned from this case.

Research

We considered whether the gene patents in question either accelerated or retarded the original discovery that ultimately led to the development of HH mutation analysis and genetic testing. Initially, the discovery of the HH-related genes was characterized as a "race," which was won by Roger K. Wolff and his colleagues of Mercator Genetics in Mountain View, California. The scientists knew that the gene for HH resided on chromosome 6, but were unable to pinpoint it. They suspected that most people with HH had the same mutations and invested heavily in research to find such mutations. Studying a group of 178 people with iron-overload disease from across the country, the researchers identified a segment of DNA that all patients had in common and used that information to scour that region of chromosome 6 in search of specific mutations. After a long search, they determined that two mutations accounted for 87 percent of iron-overload patients in the study and published their findings in the August 1996 issue of *Nature Genetics*.[90] French and Australian scientists verified these findings a few months later, publishing their findings in the November issue of that same journal.[91] There is no evidence that the patent retarded the

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[86] Ibid.
[87] Ibid.
[88] Gordon RS. An operational definition of disease prevention. *Public Health Reports* 1983. 98: 107-109.
[89] Phatak PD, Bonkovsky HL, Kowdley KV. Op. cit.
[90] Feder JN et al. Op. cit.
[91] Jazwinska EC et al. Hemochromatosis and HLA-H (Letter). *Nature Genetics* 1996. 14: 249-251.
Jouanolle AM et al. Hemochromatosis and HLA-H (Letter). *Nature Genetics* 1996. 14: 251-252.
Fackelmann K. Rusty origins: researchers identify the gene for iron-overload disease. *Science News* 1997 (January 18). 151(3): 46. See http://findarticles.com/p/articles/mi_m1200/is_n3_v151/ai_19056180/pg_1?tag=artBody;col1 [accessed January 12, 2009].

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original discovery. On the contrary, the potential of revenues from diagnostic testing may have provided added incentive for basic research linking *HFE* mutations to HH by drawing Mercator into the race. Of Mercator's four original patents, the first was filed on May 8, 1995 and the last was filed May 23, 1996.[92] The May 1995 patent application pre-dates the submission of the *Nature Genetics* article by over one year. While some speculated that patenting and commercial positioning might account for the delay, Dr. Dennis Drayna, who was a co-founder of Mercator Genetics and a senior author in the 1996 *Nature Genetics* paper, indicated that "there was no attempt to delay publication for commercial or competitive reasons".[93] He said that delay in publication simply resulted from the time taken for scientific review and subsequent efforts to address reviewers' comments and criticisms before resubmitting the manuscript. In fact he believes that the opposite was true and that it was in Mercator Genetics's best interest to publish their results as early as possible. In Dr. Drayna's opinion, "Early scientific discoveries are essential for raising subsequent rounds of funding from additional investors, and publication of scientific discoveries is paramount to the maintenance of an ongoing enterprise. Laboratory discoveries are trumpeted as loudly and quickly as possible, which is basically what Mercator Genetics did."[94]

Dr. Margit Krikker, medical director of the Hemochromatosis Foundation, opposed Mercator's approach to patenting in a 1996 AP story published in the *New York Times.* "[She] complained about the way Mercator was handling the discovery, saying that by filing a patent for the gene, Mercator had limited other scientists' research opportunities."[95] We found no evidence to corroborate this assertion. Substantial basic and clinical research on the genetics of hemochromatosis has continued since the discovery of *HFE*, including identification of genes and mutations associated with other types of hemochromatosis, suggesting patents have not blocked further research and development. We cannot eliminate the possibility of a "chilling effect" from fear of patent prosecution, but in 2007 and 2008 it did not emerge as a major controversy, as it appears to have been at the time of the patent and again in 2002.

However negotiating licenses for the use of *HFE* patents may have contributed to a several-month delay in initiating research conducted as part of the Hemochromatosis and Iron Overload Screening Study (HEIRS) sponsored by the NHLBI. The purpose of HEIRS is to determine the prevalence, genetic and environmental determinants, and potential clinical, personal, and societal impact of iron overload and hereditary hemochromatosis, in a multi-center, multiethnic, primary care-based sample of 100,000 adults. Dr. Michael Watson, Executive Director of the American College of Medical Genetics, indicated that "the study was delayed by nearly 6 months" because Third wave Technologies needed a sublicense from Bio-Rad Ltd for the use of patents covering *HFE* mutations (C282Y and H63D) for the Invader™ assay ASRs.[96] Dr. Eckfeldt, another prominent researcher in HEIRS, confirmed that the study was indeed delayed between 4-6 months but indicated that start-up logistics also contributed to this delay. A modified Invader™ assay was used for all *HFE* genotyping in the study[97]. NHLBI paid Bio-Rad a license fee to access *HFE* patents for genetic testing performed as part of HEIRS, since the study was designed to return test results to the nearly 100,000 patients enrolled and their physicians. Dr John Eckfeldt stated that the

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[92] See Appendix A.
[9393] Email from Dr. Dennis Drayna, Section Chief NIDCD/National Institutes of Health, September 11, 2008. Comments provided during external review process.
[94] Email from Dr. Dennis Drayna, Section Chief NIDCD/National Institutes of Health, September 11, 2008. Comments provided during external review process.
[95] Associated Press. Gene Found For Iron Buildup. *New York Times.* July 31, 1996. See http://query.nytimes.com/gst/fullpage.html?sec=health&res=9800E7DA1439F932A05754C0A960958260 [accessed November 13, 2008].
[96] Meeting with Dr. Michael Watson October 11, 2007.
[97] Adams PC, Reboussin DM, Barton JC, McLaren CE, Eckfeldt JH, McLaren GD, Dawkins FW, Acton RT, Harris EL, Gordeuk VR, Leiendecker-Foster C, Speechley M, Snively BM, Holup JL, Thomson E, Sholinsky P, Hemochromatosis and Iron Overload Screening (HEIRS) Study Research Investigators. Hemochromatosis and iron-overload screening in a racially diverse population. *N Engl J Med* 2005. 352(17):1769-78.

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royalty fee per test paid to Bio-Rad was reasonable, although the exact amount is confidential and protected by non-disclosure agreements. He also noted that "considering that 100,000 subjects were screened, the overall cost to NHLBI was quite substantial" despite a nominal fee per test. Bio-Rad subsequently granted a general sublicense to Third Wave Technologies. Until recently, Third Wave offered *HFE* custom ASRs as a service. Following the acquisition of Third Wave by Hologics Inc., in June 2008, custom ASRs for HFE are no longer being marketed.[98]

Development

Within one year of the *Nature Genetics* publication, Mercator announced that it was developing a blood test for HH genotype testing. The company pointed to the ultimate goal of population-wide screening for HH, whereby all persons, not just those at higher risk for the mutation, would be tested.[99] As demonstrated above, laboratories without IP rights on the *HFE* gene developed genetic tests for the mutations based on the *Nature Genetics* paper before the patent issued. This suggests that information on the gene sequence and its associated mutations was sufficient for other clinical providers to develop and offer genetic testing for HFE.[100]

Commercialization

Mercator Genetics, the company that first patented the *HFE* gene and its corresponding mutations, was founded by a group of doctors and genetic researchers from Stanford Medical School and the Silicon Valley biotechnology sector. Mercator Genetics described itself as a "gene discovery company" that focused on the identification of genes responsible for major diseases. Mercator's business model consisted of positional cloning to discover genes of interest and then capitalizing on the development of diagnostic tools associated with those genes.[101] Financial support was solicited from the pharmaceutical industry and venture capitalists like Robertson Stephens & Co., Interwest Partners, and Oak Investment Partners.[102] Investment was possibly tied to the prospect of patents. According to Dr. Dennis Drayna, "Mercator Genetics was conceived and raised funding on the basis of a far broader agenda. Hemochromatosis was never mentioned in any of the discussions that preceded funding of the company. HH was settled upon as a research and commercial target during later discussions with the Scientific Advisory Board. The choice of a diagnostic as a commercial target, as opposed to our competing genomics companies who mostly worked toward therapeutics as commercial targets, generated some discussion at the time, as the investors had already committed their funds."[103] Mercator was not only "racing" to clone the HH gene but also to search for genes linked with complex diseases like asthma, schizophrenia, prostate cancer, and cardiovascular disease.[104] However, Dr. Drayna said, "While the company did work in a number of other disease areas, these were either small exploratory efforts (such as Werner Syndrome and narcolepsy), or were the subject of primarily business transactions. There was never any work in the laboratory on asthma, schizophrenia, prostate cancer, or cardiovascular disease at Mercator Genetics." Mercator placed second or later and thus lost to Darwin Molecular Corporation in the "race" to patent the gene for the aging disorder Werner's syndrome.[105] Ultimately, the company's only successful entry in a patent race was the search for *HFE* and its mutations. Mercator Genetics's most

[98] Hologics Inc acquired Third Wave technologies in June 2008. See transcript of conference call held by Hologic Inc on 9 June 2008 at http://www.secinfo.com/d14D5a.t3vh8.d.htm [accessed January 13, 2009].
[99] Rusty origins: researchers identify the gene for iron-overload disease – hereditary hemochromatosis. Op. cit.
[100] Cho MK. Op. cit.
[101] Capitalizing on the Genome (Editorial). *Nat Gen* 1996. 13(1):1.
[102] Ibid.
[103] Email from Dr. Dennis Drayna, Section Chief NIDCD/National Institutes of Health, September 11, 2008. Comments provided during external review process.
[104] Rusty origins: Researchers identify the gene for iron-overload disease – hereditary hemochromatosis. Op. cit.
[105] Capitalizing on the genome (Editorial). Op. cit.

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valuable IP assets were patent rights to *HFE* and its mutations. In 1997, after expending $10 million on developing its method of positional cloning and discovering the association between *HFE* mutations and HH, Mercator went out of business and merged with Progenitor in 1997, which received rights to Mercator's pending and issued patents.[106] Dr. Drayna believes that "Mercator Genetics …. was a clear scientific success in the face of exceptionally widespread competition. It was less of a business success largely due to medical, social, and political factors surrounding the adoption of genetic testing on a widespread basis."[107]

Progenitor obtained rights to Mercator's *HFE* patents, and was readying its first initial public offering (IPO) when it was sold to SmithKline Beecham Laboratories, which received assets from both Mercator and Progenitor. Progenitor anticipated an IPO price between $10 and $12 per share and proposed funding its acquisition of Mercator with $22 million of Progenitor Common Stock, based upon an initial public offering price.[108] Again, the value of Progenitor was largely based upon the perceived value of its IP more than tangible assets.

Communication/Marketing

There is no evidence that the patented *HFE* mutation analysis test was ever marketed using direct-to-consumer marketing, although the idea was considered originally. For instance, there has been no ad campaign similar to the one launched by Myriad Genetics during the 2002 Super Bowl and test-marketed in Denver and Atlanta, or Myriad's 2007-2008 BRCA advertising in the Northeast.

Outside of Mercator's promotion activities, organizations committed to HH awareness have led their own marketing campaigns. Following the gene discovery in 1996, Margit Krikker of the Hemochromatosis Foundation bought an advertisement in the New York Times to alert the public to the deadliness of HH. The Foundation was frustrated over the lack of interest in HH displayed by federal officials and wanted to mount an awareness campaign. Another early and active proponent of communicating Mercator's discoveries was the American Liver Foundation.[109] The American Hemochromatosis Society (AHS) designated May 2007 as "National Hereditary Hemochromatosis Genetic Screening & Awareness Month." It asked its membership to contact local newspapers, TV and radio stations with AHS press releases that connected screening to saving lives.[110]

The CDC has also made detailed information available about diagnosis of hemochromatosis for physicians and the use of genetic testing in family based testing for hemochromatosis.[111] However, in the absence of family history, CDC recommends genetic testing for *HFE* mutations only as the confirmatory step of their testing protocol after the appropriate biochemical tests for iron overload (TS and serum

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[106] Merz JF, Kriss AG, Leonard DGB, Cho MK. Op. cit.
[107] Email from Dr. Dennis Drayna, Section Chief NIDCD/National Institutes of Health, September 11, 2008. Comments provided during external review process.
[108] Progenitor files registration statements for initial public offering of 2,750,000 shares and for acquisition of Mercator Genetics Inc. Business Wire. March 14, 1997.
[109] Email from Dr. Dennis Drayna, Section Chief NIDCD/National Institutes of Health, 11 September 2008. Comments provided during external review process.
[110] The American Hemochromatosis Society's homepage discusses HH awareness. American Hemochromatosis Society. See http://www.americanhs.org [accessed May 3, 2007].
[111] *Hemochromatosis for Health Care Professionals.* Centers for Disease Prevention and Control. November 1, 2007. See http://www.cdc.gov/ncbddd/hemochromatosis/training/family_detection/testing_and_counseling.htm [accessed November 12, 2008]. This program was run by Sharon McDonnell who is now in the Public Health Dept at Dartmouth University Medical School.

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ferritin) have been conducted.[112] The HH genetic test is currently also available directly to consumers through DNAdirect. Otherwise, HH testing is primarily offered to consumers by healthcare providers.

Adoption

Shortly following the *HFE* gene discovery, the CDC considered recommending widespread screening for HH and considered advising doctors to order a gene test for all patients 18 years or older. That recommendation has not been made because of inconclusive evidence on the penetrance of *HFE* mutations and cost-effectiveness of the test. Dr. Dennis Drayna, a Mercator co-founder and NIH molecular geneticist, argued enthusiastically for broad HH genetic screening at a 1997 Ethical, Legal and Social Issues (ELSI) meeting associated with the Human Genome Project.[113] Ethical, legal, and social concerns such as fear of genetic discrimination and questions over whether it made sense to "diagnose people based on genotype and not health" were raised as criticisms.[114] An account of this meeting suggested that the market would determine whether insurance companies and HMOs adopted the test to save money in HH complications like liver transplants.[115] A recent study, which measured the extent of employment and health insurance problems associated with population screening for hereditary hemochromatosis and iron overloads, found that at one year following genotypic and phenotypic screening, only 0.4% of individuals surveyed (3 out of 1154 individuals) reported any problems. Problems primarily involved life insurance and long term care insurance coverage. However, none of the affected individuals reported problems with health insurance coverage or employment. The outcome suggests that genetic discrimination concerns are much lower than originally anticipated.[116] It also suggests, however, that they occur in forms of insurance, long-term care and life insurance, that are not covered by the Genetic Information Nondiscrimination Act passed in 2008 (which begins to take effect in 2009 and 2010).

Insurance companies and at least one Medicare carrier have adopted HH genotype testing but not as the broad screening test initially conceived. Rather, HH genotyping is usually a second-level test conducted after less expensive biochemical tests suggest HH or to test family members of identified HH homozygotes. Insurance policies may cover HH testing if it comports with "medical necessity." To be eligible for testing, the insured individual will likely need to meet defined conditions for testing that in some plans are enforced by preauthorization requirements, such as: (1) prior blood test indicating iron overload; (2) family history of HH; or, (3) member of a family with a known HH mutation. Cost is not cited as an explicit criterion, and patents may not have a direct or significant effect on the decisions to cover the test by insurance providers. However, patents did affect which laboratories offered the test and which laboratories decided to cease testing after patent enforcement by SBCL.[117] Yet the majority of laboratories continued to offer the test either with or without a sublicense. As noted earlier, several providers offer these tests currently and presumably interact with a range of carriers for insurance reimbursement.

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[112] *Hemochromatosis for Health Care Professionals: Diagnostic Testing.* Centers for Disease Prevention and Control. November 1, 2007. See http://www.cdc.gov/ncbddd/hemochromatosis/training/diagnostic_testing/testing_protocol.htm [accessed November 12, 2008].
[113] Allen A. Policing the gene machine. *Lingua Franca*. March 1997. See http://linguafranca.mirror.theinfo.org/9703/Policing6.html [accessed May 2, 2007].
[114] Ibid.
[115] Ibid.
[116] Hall M, Barton JC, Adams PC, McLaren CE, Reiss J, Castro O, Ruggiero A, Acton R, Power T, Bent T. Genetic screening for iron overload: no evidence of discrimination at one year. *J Fam Practice* 2007. 56:829-833.
[117] Cho MK. Op. cit.

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Consumer Utilization

The *HFE* test is not available as an initial, universal screening test along the lines originally envisioned. Consumers typically access the tests through clinical laboratories via their physicians. Appendix B provides a sample of some laboratories, their services, and their costs. At least 37 laboratories offered HFE genetic testing as of May 2007. Additional providers not listed on Genetests.org may also offer this test. The test is also easily obtainable without physicians serving as the conduit for HH testing. DNAdirect, a direct-to-consumer genetic testing service, offers HH genetic testing for $199. Consumers using this service can thus choose to avoid involving a doctor or notifying their insurance company.[118] DNAdirect sends consumers a test collection kit in the mail that includes cotton swabs for cheek swabbing and a postage-paid envelope to mail the swabs back to the laboratory for DNA analysis. Unlike most direct-to-consumer testing outlets, DNAdirect offers genetic counseling with the test results. DNAdirect provides forms, CPT Codes, and Letters of Medical Necessity for consumers seeking reimbursement from insurance or health plans. The service also offers anonymity and explains why anonymity might be desirable due to the potential of genetic discrimination. Since the $199 price tag is less than several of the clinical laboratories offering the test,[119] consumers with or without a family history of HH but with some means can easily obtain results, provided that they do not seek insurance reimbursement (insurance coverage would generally be confined to high-risk individuals meeting iron overload or family history criteria). However, DNAdirect and its counterparts are not FDA-regulated, and there is no peer review of the tests' accuracy, although the tests themselves are performed in CLIA-approved laboratories.[120]

Our study does not provide information regarding the impact of patents on under- or over-utilization of the *HFE* genetic test. Test utilization would need to be ascertained more systematically by surveying providers about how frequently the test is ordered and matching clinical indication to test use.

We did not uncover evidence about whether consumers are denied coverage for HH genetic tests. Direct assessment of test utilization and the frequency of inability to receive testing due to insurance coverage problems will help address the issue of patient access more comprehensively.

Acknowledgements

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John Eckfeldt, Michael Hopkins, Dennis Drayna, Jon Merz, Michael Watson, and Paul Adams kindly reviewed this case study.

[118] DNA Direct. See http://www.dnadirect.com/web/article/testing-for-genetic-disorders/hemochromatosis/36/who-should-consider-testing
[accessed January 12, 2009].
[119] See Appendix B.
[120] Shute N. Unraveling your DNA's secret. *US News & World Report*. December 31, 2006.

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Appendix A US Patents related to Hemochromatosis testing.

Patent No. and Title	Date Filed/Issued	Inventors	Assignee	Claims
5705343, Method to Diagnose Hereditary Hemochromatosis	Feb. 9, 1996 / Jan. 6, 1998	Drayna et al.	Mercator Genetics Inc., Menlo Park, CA	Mutation analysis of *HFE* with kit
5712098, Hereditary Hemochromatosis Diagnostic Markers and Diagnostic Methods	Apr. 16, 1996/ Jan. 27, 1998	Tsuchihashi et al.	Mercator Genetics, Menlo Park, CA	Mutation analysis for *HFE*
5753438, Method to Diagnose Hereditary Hemochromatosis	May 8, 1995 / May 19, 1998	Drayna et al.	Mercator Genetics Inc., Menlo Park, CA	Method for diagnosing the mutation of an *HFE* sequence; mutation sequences, but not the whole gene.
6025130, Hereditary Hemochromatosis Gene	May 23, 1996 / Feb. 15, 2000	Thomas et al.	Mercator Genetics Inc., Menlo Park, CA	*HFE* gene and a diagnostic method; whole *HFE* gene sequence
6140305, Hereditary Hemochromatosis Gene Products	Apr. 4, 1997 / Oct. 31, 2000	Thomas et al.	Bio-Rad Laboratories, Inc., Hercules, CA	Polypeptides associated with *HFE*
6228594, Method for Determining the Presence or Absence of Hereditary Hemochromatosis Gene Mutation	Feb. 14, 2000 / May 8, 2001	Thomas et al.	Bio-Rab Laboratories, Hercules, CA	Diagnostic method for C282Y and H63D detection using DNA and RNA.
6355425, Mutations Associated With Iron Disorders	Mar. 26, 1999 / Mar. 12, 2002	Rothenberg et al.	Billups-Rothenberg, Inc., San Diego, CA	Diagnostic method for a panel of mutations in *HFE*,including : S65C, 193T, G93R, 277C, 105T, 314C
6762293, Diagnostics and Therapeutics for Autosomal Dominant Hemochromatosis	Oct. 10, 2001 / Jul, 13, 2004	van Duijn et al.	Erasmus University Rotterdam, Rotterdam (NL)	Ferroportin (SLC11A3) sequence and method of diagnosis for SLC11A3
6849399, Methods and Compositions for Diagnosis and Treatment of Iron Misregulation Diseases	Aug. 27, 1997 / Feb. 1, 2005	Feder et al.	Bio-Rab Laboratories, Hercules, CA	Diagnostic method for transferring receptor (TFR2) and mutation A424G
6955875, Mutations associated with iron disorders	Oct. 16, 2001/ Oct. 18, 2005	Rothberg et al.	Billups-othberg Inc.	Methods for diagnosing HFE by detecting mutations in nucleotide position 193
7067255, Hereditary Hemochromatosis Gene	May 2, 2002 / Jun 27, 2006	Thomas et al.	Bio-Rab Laboratories, Hercules, CA	Method for detecting three mutant alleles (24d1, 2 and 7)

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7078513, Plasmids Comprising Nucleic Acids from the Hereditary Hemochromatosis Gene	Feb. 4, 2000 / Jul. 18, 2006	Thomas et al.	Bio-Rab Laboratories, Hercules, CA	Plasmid containing HFE mutation 24d1
7026116, Polymorphisms in the Region of the Human Hemochromatosis Gene	May 7, 1997 / Apr. 11, 2006	Ruddy et al.	Bio-Rad Laboratories, Hercules, CA	Isolated polynucleotide of *HFE* gene sequence containing SNP variants, and a kit.

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Appendix B Price Comparison for *HFE* testing from a subset of providers.

Laboratory	Genetic Test[121]	List Price[122]		CPT Codes[123]
Arup Laboratory	*HFE* PCR	$225		83890, 83900, 83896 x 4, 83912
Baylor College of Medicine		$200		83914 x 3, 83912, 83898 x 2, 83891
Blood Center of Wisconsin	Allele-specific PCR	$175		83891, 83900, 83896 x 4, 83912
Boston University School of Medicine		$250		
Case Western Reserve Univ.		$275		83890, 83892 x 2, 83894 x 2, 83898 x 2, 83912 x 2
Cincinnati Children's Hosp. Medical Center		$337		83891, 83894, 83898, 83912, 83892
Duke Univ. Health System	ARMS	$467.25		
Greenwood Genetics Center		$250		83894, 83898, 83912
Kimball Genetics, Inc.	PCR analysis for both the C282Y and the H63D mutations	$190		
LabCorp		$297 cost w/o insurance	$229.50 with insurance	
Mayo Clinic	PCR-based assay (using LightCycler technology) used to test for 3 mutations in the *HFE* gene: C282Y, H63D, and S65C. S65C mutation is only reported when it is found with the C282Y mutation. (PCR utilized pursuant to a license agreement with Roche Molecular Systems, Inc.)	$411.20		83890, 83898 x 2, 83912
Michigan State Univ.	Extract DNA from the sample and amplified	$227		83890, 83898 x 2, 83892 x 2, 83894, 83912

[121] All the tests described are targeted mutation analysis, or allele-specific mutation analysis. The tests are for either (1) a nucleotide repeat expansion, or (2) one or more specific mutations. Some of the labs provided a more specific description of their services. The blank boxes indicate areas for which no information was obtained.
[122] List prices as of May 2007. Prices were obtained either by phone call or from information listed on provider website.
[123] CPT Code Interpretation: 83890 Molecular Isolation and Extraction; 83900 Amplification; 83891 Isolation and extraction of highly purified nucleic acid; 83894; 83896 Nucleic Acid Probes; 38398 Amplification of nucleic acid, each primer pair; 83900 Amplification of nucleic acid, first two sequences; 83912 Interpretation and report; 83914 Mutation identification by enzymatic ligation or primer extension, single segment, each segment (eg, oligonucleotide ligation assay (OLA), single base chain extension (SBCE), or allele-specific primer extension (ASPE)).

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	enzymatically then digested with the following restriction enzymes: Rsa I, Dpn II, and Hinf I. After digestion, the fragments are separated by electrophoresis. Testing can detect the C282Y, H63D, and S65C mutations in the *HFE* gene.		
NorDx	Linked Linear Amplification (LLA) with DNA probes	$372.50	83890 83896 x 4 83900 83912
SUNY Upstate Medical Univ.		$158	
Specialty Laboratories	Cleave-based Invader Assay Hemochromatosis GenotypeR	$345	83891, 83892x4, 83896 x 10, 83903 x 2, 83908 x 2, 83912
Spectrum Health		$205.50	8 CPT Codes
University of Alabama @ Birmingham	Detection of C282Y and H63D mutations in the *HFE* gene using multiplex PCR methods.	$200	83890 83898 83892 83894 83912
Univ. of Iowa Hospitals & Clinics		$395	

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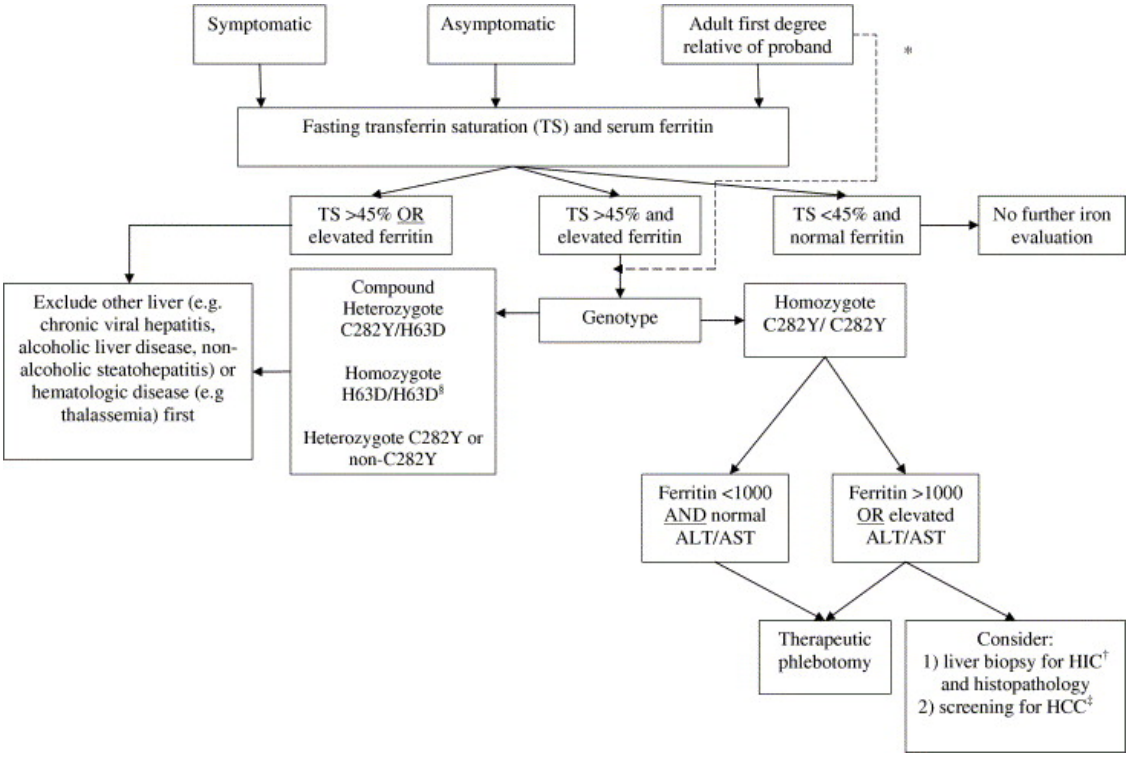
Appendix C Diagnostic Algorithm for Hereditary Hemochromatosis



Modified from the American Association for the Study of Liver Disease Diagnostic Algorithm, 2001.
*direct testing of first degree probands is an acceptable alternative
†hepatic iron concentration
‡hepatocellular carcinoma

§Although H63D homozygosity is thought to lead to hemochromatosis in some individuals, this is more the exception, rather than the rule. Since the H63D mutation has a higher prevalence than the C282Y mutation, but accounts for a significantly smaller portion of those with clinically relevant hemochromatosis, abnormal iron studies with H63D homozygosity should prompt further evaluation into other disease processes first, with a diagnosis of hereditary hemochromatosis only after other avenues have been explored.

Reprinted from the American Journal of Medicine, Volume 119, Number 5, Andrew W. Yen, Tonya L. Fancher and Christopher L. Bowlus, "Revisiting Hereditary Hemochromatosis: Current Concepts and Progress,," pp. 391-9, at p. 396, 2006, with permission from Elsevier.

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Appendix D Molecular Genetic Testing: Clinical methods and Testing Strategy[124]

There are various ways to detect hemochromatosis:

- Targeted mutation analysis: available on a clinical basis for two known disease-causing alleles in the *HFE* gene (C282Y and H63D). About 87% of individuals of European origin with *HFE*-HH are either homozygotes for the C282Y mutation or compound heterozygotes for the C282Y and H63D mutations. Most clinical laboratories do not routinely test for the S65C allele because it appears to account for only 1% of individuals affected clinically and its clinical significance is unclear.
- Sequence analysis: available in a limited number of clinical and research laboratories to identify other mutant alleles associated with *HFE*-HH laboratories

The table below summarizes molecular genetic testing for this disorder.[125]

Molecular Genetic Testing **Used in *HFE*-HHC**				
Test Method	**Mutations Detected**	**Mutation Detection Rate**		**Test Availability**
		% of Individuals with HHC [1, 2]	**Genotype**	
Targeted mutation analysis	*HFE* mutations: p.C282Y, p.H63D	~60%-90%	p.C282Y/p.C282Y	Clinical Testing
		3%-8%	p.C282Y/p.H63D	
		~1%	p.H63D/p.H63D [3]	
Sequence analysis	*HFE* sequence alterations	Unknown	Unknown [4]	

From Ramrakhiani & Bacon (1998)
1. In populations of European origin
2. Morrison et al 2003
3. There is no evidence that p.H63D/p.H63D is associated with a hemochromatosis phenotype in the absence of another cause of iron overload.
4. A few individuals who are compound heterozygotes for the p.C282Y allele, and one of a small number of rare *HFE* mutations, have the hemochromatosis phenotype.

Testing Strategy for a Proband

1. Adults with transferrin-iron saturation higher than 45% warrant targeted mutation analysis. Individuals homozygous for the C282Y mutation or compound heterozygous for the C282Y and H63D mutations can be diagnosed as having the genetic make-up to develop *HFE*-HHC.

2. Individuals who are not C282Y homozygotes generally represent a heterogeneous group who may suffer from liver disease unrelated to *HFE* or have other metabolic syndromes. These individuals should

[124] Adapted from Genetests.Org. See http://www.geneclinics.org/profiles/hemochromatosis/details.html [accessed May 3, 2007].
[125] Ibid. Copyright University of Washington, Seattle.

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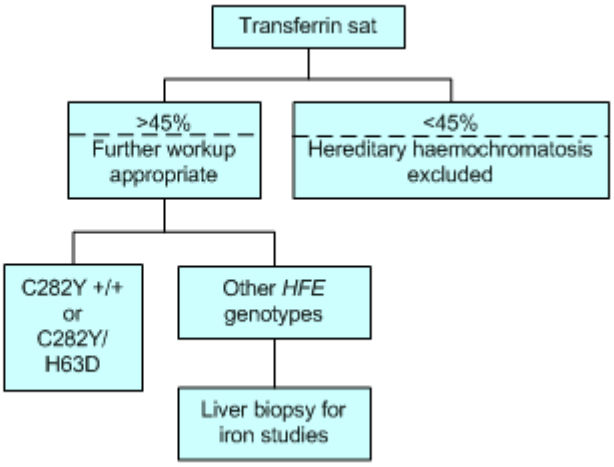
undergo liver biopsy with assessment of histology and measurement of hepatic iron concentration as a next diagnostic step.

The figure below represents the testing strategy to establish the diagnosis of *HFE*-HH for the two groups listed above.[126]



[126] Ibid. Copyright University of Washington, Seattle.

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Appendix E Sample letter of patent enforcement for *HFE* testing from SBCL[127]

June 24, 1998

Dr. Debra Leonard
University of Pennsylvania Medical Center
3400 Spruce Street
7103 Founders
Philadelphia, PA 19104-4283

Dear Dr. Leonard:

Hereditary Hemochromatosis Assay

I would like to bring to your attention three U.S. patents, 5,705,343; 5,712,098; and 5,753,438 all relating to an assay for hereditary hemochromatosis. The '098 patent may be of most interest to you and I have taken the liberty of enclosing a copy of it for your convenience. These patents are owned by Progenitor, Inc. and licensed exclusively to SmithKline Beecham Clinical Laboratories, Inc. for use in running a home-brew assay.

If you are offering a genetic test for hereditary hemochromatosis, please provide me with an assurance that the test procedure you are running is not covered by one or more of the three mentioned patents. If your test might be covered by these patents, SBCL is willing to make arrangements to insure that your clients have continued access to this gene-based HHC test discovered by Progenitor within the context of Progenitor's issued patents. I invite you to initiate such arrangements by contacting Rose Tricoski at SmithKline Beecham Clinical Laboratories, 1201 South Collegeville Road, Collegeville, PA 19426. Please feel free to call her at 610.454.6367, by fax at 610.983.2302 or by e-mail at rose.tricoski@sb.com. She and others at SBCL can assist you with making the necessary arrangements to avoid any inconvenience or interruption of services to your clients.

I ask that you follow up with Ms. Tricoski by July 24th. Thank you.

Sincerely,

David O'Bryan

David O'Bryan, Ph.D.
Vice President and Director,
Science and Technology

[127] Sample letter reproduced with permission from Dr. Debra Leonard.

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Impact of Gene Patents and Licensing Practices on Access to Genetic Testing for Long QT Syndrome

Misha Angrist, Ph.D., Subhashini Chandrasekharan, Ph.D., Christopher Heaney, B.A., and Robert Cook-Deegan, M.D.

Executive Summary

- Familial Long QT syndrome (LQTS) affects 1 in 3,000 newborns. It is a Mendelian condition in which patients' hearts do not recharge appropriately after heartbeats and can lead to life-threatening arrhythmias. It accounts for a small but significant fraction of sudden death in young people. Beta-blocker drugs and implantable cardioverter-defibrillators are the most common therapies. Patients and those close to them can also endeavor to avoid triggers for arrhythmias such as loud noises or physical or emotional stress.
- Mutations in 12 susceptibility genes account for some 75% of familial LQTS; of that 75%, mutations in three genes account for most cases. Genetic testing for LQTS is important because knowing which gene (and which part of that gene) is mutated can have a direct bearing on decisions regarding preventive measures and pharmacological therapies.
- The major LQTS susceptibility genes were discovered at the University of Utah in the mid-1990s. Their discovery was funded in part by the National Institutes of Health. The first LQTS gene patent was awarded in 1997.
- The University of Utah Research Foundation began licensing patents on LQTS susceptibility genes in the late 1990s. Until recently, at any one time there was never more than a single licensee of the major intellectual property (IP) attached to the three genes that predispose to the majority of familial LQTS. In 2008, Bio-Reference Laboratories (BRLI) obtained an exclusive license for one of those patents as well as two others giving it rights to test for LQT3, which accounts for approximately 10 to 15% of inherited LQTS. BRLI has also aggregated IP related to susceptibility genes for LQT1, LQT2, LQT5, LQT6, LQT7, and Jervell and Lange-Nielsen syndrome (JLNS). As a consequence the patent landscape for LQTS testing has become fragmented among different exclusive licensees. It remains to be seen what impact this turn of events will have on the LQTS genetic testing landscape.
- In 2002, before a commercial test of five genes was launched under the name FAMILION®, there were at least two other fee-for-service providers of genetic testing; however, they focused their sequencing on regions previously associated with mutations causing LQTS, which amounted to a minority of the five genes' combined coding sequence. Subsequent enforcement of the gene patents prompted at least one diagnostic provider, GeneDx (subsequently acquired by BRLI), to cease testing in 2002. We suggest, based on incomplete evidence, that this probably had a small but tangible negative effect on patient access to genetic testing for LQTS between 2002 and 2004. We believe this negative effect would likely have been larger had there been greater awareness, understanding and acceptance of genetic testing on the part of cardiologists and electrophysiologists at that time.
- From 2005-2008, most LQTS gene IP relevant to clinical genetic testing was controlled by Clinical Data, Inc., and its subsidiary, PGxHealth LLC. During that period the company did not sublicense its test to any other diagnostic services in the U.S., although it has granted international licenses in Australia, New Zealand and Europe. It has also granted a research license to a company in Utah.
- In general, clinicians we spoke to say that PGxHealth does a very good job of carrying out genetic testing of the five genes that account for ~ 75% of LQTS. Its turnaround time for a complex, sequence-based test is typically less than two months versus what is often a year or more for research-

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based testing. The company reports that its turnaround time has been substantially reduced since it began offering the test. PGxHealth's FAMILION® testing continues to be widely adopted by cardiologists and electrophysiologists, which the company attributes to its efforts to educate physicians and patients, its customer service, and diligent advocacy for reimbursement policies and payment agreement with insurers and health plans. It can be argued (and has been by PGxHealth parent Clinical Data) that an exclusive license has contributed to the company's skill at performing the test and allowed it to leverage economies of scale. GeneDx parent company BRLI attributes these improvements to the march of technology and the threat of competition.

- PGxHealth has been criticized for occasional laboratory errors (missed mutations and misinterpretations). It is not clear that the lab's error rate is outside acceptable norms, nor worse than its stated analytical accuracy of over 99 percent. PGxHealth says it implements process changes to ensure that any errors are not repeated, thus leading to improved accuracy over time. Misinterpretation, the company says, can be a subjective phenomenon in a complex disease such as LQTS. PGxHealth consults with experts in the field to review variants of questionable interpretation. It also issues amended reports when interpretations change due to new knowledge in the field.
- PGxHealth performs proficiency testing in conjunction with Michael Ackerman, a researcher and physician at the Mayo Clinic who has the sequencing facilities and diverse genetic samples and clinical profiles necessary to conduct such a program in accordance with the relatively nonspecific regulations set forth by the Clinical Laboratory Improvement Amendments (CLIA), the pertinent federal statute. By all accounts Dr. Ackerman is an outstanding clinician and researcher who has greatly advanced the cause and treatment of LQTS patients. His financial arrangements with Clinical Data and PGxHealth have been reported to and vetted by Mayo, and his service as a consultant to PGxHealth has been disclosed in publications.
- In 2005 PGxHealth reported allelic dropout in research laboratory screening of LQTS patients. This phenomenon, a technical issue associated with DNA amplification assays, can result in false negatives (that is, results that report no relevant mutation when in fact a deletion or genomic rearrangement has altered the relevant protein). The company's identification and publication of this problem ultimately increased the sensitivity of LQTS genetic testing.
- The overall yield of FAMILION® testing, as reported by PGxHealth in 2007, was 38 percent, versus 50 percent for the 1995-2004 era of research-based testing. This lower figure is likely due to an increase in surveillance of borderline cases resulting from the availability of large-scale commercial testing. Another possible factor reducing yield might be surveillance of fewer genes in the commercial test than in research laboratories.
- PGxHealth has been criticized by at least one clinician (Wendy Chung, who consults for would-be competitor BRLI) for its difficulty in processing paraffin-embedded samples from deceased individuals. Routine extraction of DNA from such samples remains a challenge. Based on the anecdotal accounts we have received from the company, referring physicians and potential competitors, we have no evidence that PGxHealth is less (or more) adept at performing this procedure than other commercial diagnostic laboratories.
- PGxHealth has thus far decided not to add genes to its LQTS testing panel, citing both minimal benefit in light of the rarity of mutations in the seven other genes known to predispose to LQTS, and possible misinterpretation and uncertainty for patients due to decreased clinical specificity resulting from uncharacterized background variants in these genes. Patients who are not found to have a mutation in the five genes included in the panel are referred to research laboratories for additional testing. Research laboratories, however, may take months or years to return results. While it is possible that sublicensing of the right to test the major genes would have made other providers more willing to assume the burden of testing the rarer loci, we cannot know this.

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- The recent acquisition of selected LQTS gene patent licenses by Bio-Reference Laboratories—for testing LQT3, LQT5, LQT6 and LQT7 susceptibility genes, as well as for testing several mutations predisposing to LQT1 and LQT2—may offer a real-world test of how prices respond to competition, and whether testing technology changes with competition, although the nature of the competition may not be head-to-head for the same mutations unless a cross-licensing arrangement is struck between the rival testing services.
- Newer technologies minimize the cost of adding new mutations, but without competition, the commercial incentive to find new platforms is reduced.
- PGxHealth does not offer prenatal genetic diagnosis for LQTS, effectively making it unavailable in the U.S. The company does not have an official policy governing prenatal diagnosis. It claims that there are technical difficulties in distinguishing maternal from fetal DNA; however, other clinicians and would-be LQTS genetic test providers argue that this technical issue is trivial. At least one other former competitor has claimed that the company has denied its request to offer prenatal testing. Given the treatable nature of LQTS and the highly variable phenotype, it is not clear how strong the demand would be for prenatal or preimplantation testing. We do know that at least one provider offered prenatal diagnosis in 2002 prior to patent enforcement actions.
- Since 2004, there have been three publications in peer-reviewed journals that feature PGxHealth scientists as co-authors; most data have been presented at various cardiology meetings. Given the availability of a European mutation database and an international registry containing thousands of LQTS genotypes and phenotypes, PGxHealth's decision not to publish its mutation data seems unlikely to have harmed patient care. Moreover, PGxHealth does not necessarily have access to the detailed phenotypic data that make mutation catalogs useful. One former provider and would-be competitor insisted to us, however, that a knowledge base of certain detailed, clinically useful phenotypic information is likely to come only from high-volume commercial diagnostic labs and not from research labs. In November 2008, PGxHealth announced that, in collaboration with other researchers at multiple institutions, it would make its LQTS mutation database public in 2009.
- FAMILION® LQTS testing costs $5400 per index case (a full-sequence test to look for mutations) and $900 per confirmatory test in additional family members (for identified mutations). For index cases, this breaks down to $74 per amplicon, nearly twice the $38-per-amplicon cost of hereditary breast cancer testing (albeit at a much lower volume), but significantly less expensive than the $129-per-amplicon partial test that was offered in 2002 and the per-amplicon price of some other tests (see case studies on hearing loss and Tay-Sachs/Canavan). Such a cost comparison does not take into account the more cost-effective technologies that have become available in recent years. Several independent cardiologists, researchers, patient advocates and patients with whom we communicated complained about the cost of the FAMILION® test. The cost will also be compared to the precipitous drop in the cost of full genomic sequencing in the foreseeable future. These complaints may have resulted in part from historically incomplete coverage by many payers. To date, the FAMILION LQTS test has received positive coverage decisions from 28 health plans. The company has also established simplified billing codes. Among government payers with favorable coverage policies are TRICARE and Medicaid in 38 states (the company has applied for Medicaid coverage in all 50 states). Insurance coverage of FAMILION® testing increased dramatically in 2007-2008, with the number of covered lives growing from seven million to 155 million lives.
- It's not entirely clear what effect multiple test providers would have had on payer reimbursement in the early years. Multiple providers may have hastened favorable coverage decisions, although all of the genetic testing providers we spoke with readily admitted that obtaining third-party payer coverage is a lengthy and difficult process. PGxHealth's would-be competitor, BRLI, believes that its own

recent aggregation of LQTS gene IP has prompted PGxHealth to more aggressively pursue insurance coverage.

- Having competitors may or may not have led to substantial improvements in quality and coverage, but we believe that a competitive presence could have accelerated the test to market and lowered the cost from its current $5400. BRLI, an admittedly biased party, asserts that competition would have forced providers to differentiate the test in order to survive, by developing newer platforms along with more patient and clinical support and education.
- Our understanding of LQTS genetics remains woefully incomplete. The same mutation in different members of the same family may lead to radically different phenotypes (or to no detectable signs or symptoms). This suggests the existence of yet-to-be discovered modifier genes and environmental factors. Meanwhile, some ten percent of familial LQTS patients are presumptive compound heterozygotes, that is, they carry two distinct variations in LQTS susceptibility genes. This raises difficult clinical questions about which of these variants are pathogenic and which are benign. We believe it is legitimate to ask if the field as a whole might not have made deeper inroads into understanding the clinical significance of those uncertain variants if there were one or more additional commercial entities focused on the same sorts of interpretive questions.
- The results of genetic testing may have profound downstream financial implications. Both cardiologists and manufacturers of implantable cardioverter-defibrillators stand to benefit from the implantation of such devices in actual or suspected LQTS patients.
- Conflicts of interest abound in this case study. These conflicts affect not only officers of PGxHealth and its primary consultant physician-scientist, but also former and would-be providers of LQTS genetic testing who would benefit if they were among the major LQTS gene-patent licensees.

Introduction: What is Long QT Syndrome?

Congenital long QT syndrome (LQTS) is an inherited cardiac disorder affecting about 1 in 3,000 to 1 in 5,000 people. LQTS patients may experience fainting ("syncope"), seizures or sudden death, although the phenotype can vary widely.[1] Most of the 1 in 2,000 people harboring mutations in LQTS susceptibility genes will remain silent carriers throughout their lives.[2] That is, there are more people who have mutations in relevant genes than people who actually have a clinical syndrome. Nevertheless, the disease appears to explain a small but significant fraction of sudden cardiac deaths in young people.[3] Moreover, some five percent of cases of sudden infant death syndrome (SIDS) are thought to be attributable to familial or sporadic LQTS.[4]

The "QT" in long QT refers to a telltale measurement seen on an electrocardiogram (ECG). The QT interval is the time it takes for the heart to recharge ("repolarize") after each beat. Depending on age and gender, when the corrected QT interval (QTc) exceeds ~ 440 to 470 milliseconds, it is considered to be

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[1] Goldenberg I, Moss AJ. Long QT syndrome. *J Am Coll Cardiol* 2008. 51, (24): 2291-300.
[2] Roden DM. Clinical practice. Long-QT syndrome. *N Engl J Med* 2008. 358, (2): 169-76.
[3] Ibid.
Goldenberg I, Moss AJ, Peterson DR, McNitt S, Zareba W, Andrews ML, Robinson JL, Locati EH, Ackerman MJ, Benhorin J, Kaufman ES, Napolitano C, Priori SG, Qi M, Schwartz PJ, Towbin JA, Vincent GM, Zhang L. Risk factors for aborted cardiac arrest and sudden cardiac death in children with the congenital long-QT syndrome. *Circulation* 2008. 117, (17): 2184-91.
Berul CI. Congenital long-QT syndromes: who's at risk for sudden cardiac death? *Circulation* 2008. 117, (17): 2178-80.
[4] Tester DJ, Ackerman MJ. Sudden infant death syndrome: how significant are the cardiac channelopathies? *Cardiovasc Res* 2005. 67, (3): 388-96.

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prolonged. A prolonged QT interval coupled with a clinical history of fainting and a family history of LQTS or unexplained sudden cardiac death strongly suggests a diagnosis of LQTS.[5]

Clinical manifestations of LQTS are the result of the heart "spinning out of control" into a characteristic tachycardia (speeding of the heart rate) called *torsades de pointes* (TdP). TdP causes an individual to faint; he or she may then wake up, experience seizures, or die. Survival then depends upon whether the heart spontaneously assumes its normal rhythm or an internal or external defibrillator stops the arrhythmia.[6]

High-risk patients are typically treated with beta-blocker drugs, which can reduce the risk of life-threatening cardiac events.[7] Implantable cardioverter-defibrillators (ICDs) may be used as a primary therapy in patients refractory to beta-blocker therapy or as a secondary measure in addition to beta-blockers.[8] Surgical denervation and pacemakers have also been used with some success.[9]

While LQTS with accompanying deafness (Jervell and Lange-Nielsen Syndrome) and the classical form of the disease (LQT1, Romano-Ward Syndrome) were described more than 40 years ago, the exact molecular basis of the disorder eluded investigators until 1995.[10] It was then that Mark Keating's NIH-funded group at the University of Utah isolated genes predisposing to LQT2 and LQT3. With the cloning of these genes and the isolation of the LQT1 gene the next year,[11] it became clear that defects in cellular sodium and potassium ion channels (or related proteins) caused LQTS: the window into the "cardiac channelopathies" was now open.[12] Currently there are 12 known LQTS susceptibility genes,[13] although

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[5] Goldenberg I, Moss AJ. Long QT syndrome. *J Am Coll Cardiol* 2008. 51, (24): 2291-300.
[6] Ackerman MJ. Cardiac channelopathies: it's in the genes. *Nat Med* 2004. 10, (5): 463-4.
[7] Goldenberg I, Moss AJ. Long QT syndrome. *J Am Coll Cardiol* 2008. 51, (24): 2291-300.
Moss AJ, Zareba W, Hall WJ, Schwartz PJ, Crampton RS, Benhorin J, Vincent GM, Locati EH, Priori SG, Napolitano C, Medina A, Zhang L, Robinson JL, Timothy K, Towbin JA, Andrews ML. Effectiveness and limitations of beta-blocker therapy in congenital long-QT syndrome. *Circulation* 2000. 101, (6): 616-23.
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[8] Choi GR, Porter CB, Ackerman MJ. Sudden cardiac death and channelopathies: a review of implantable defibrillator therapy. *Pediatr Clin North Am* 2004. 51, (5): 1289-303.
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Goldenberg I, Moss AJ. Long QT syndrome. *J Am Coll Cardiol* 2008. 51, (24): 2291-300.
[11] Wang Q, Curran ME, Splawski I, Burn TC, Millholland JM, VanRaay TJ, Shen J, Timothy KW, Vincent GM, de Jager T, Schwartz PJ, Toubin JA, Moss AJ, Atkinson DL, Landes GM, Connors TD, Keating MT. Positional cloning of a novel potassium channel gene: KVLQT1 mutations cause cardiac arrhythmias. *Nat Genet* 1996. 12, (1): 17-23.
[12] Marban E. Cardiac channelopathies. *Nature* 2002. 415, (6868): 213-8.
[13] Lehnart SE, Ackerman MJ, Benson DW, Jr., Brugada R, Clancy CE, Donahue JK, George AL, Jr., Grant AO, Groft SC, January CT, Lathrop DA, Lederer WJ, Makielski JC, Mohler PJ, Moss A, Nerbonne JM, Olson TM, Przywara DA, Towbin JA, Wang LH, Marks AR. Inherited arrhythmias: a National Heart, Lung, and Blood Institute

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the QTc phenotype can vary and mutations in several have been observed in only a few families. Of the 12 genes, mutations in those predisposing to LQT1 (potassium channel gene KCNQ1), LQT2 (potassium channel gene KCNH2) and LQT3 (sodium channel gene SCN5A) account for some 70% of congenital LQTS.[14]

Intellectual Property and LQTS Testing: Dramatis Personae

The following list (presented alphabetically) is intended to provide capsule descriptions of many of the important stakeholders in and narrators of the LQTS genetic IP story. Some may have a conflict of interest by virtue of past and/or present consultation with genetic diagnostic test providers and/or past, present or future provision of such testing themselves.

Dr. Michael J. Ackerman is Professor of Medicine, Pediatrics and Pharmacology at the Mayo Clinic. He directs the Mayo Clinic Windland Smith Rice Sudden Death Genomics Laboratory. He is Director of the Mayo Clinic's Long QT Syndrome Clinic and is active in clinical translational research efforts devoted to identifying individuals at greatest risk for sudden death. He served on the Genaissance Pharmaceuticals Advisory Board in 2004[15] and is a paid consultant to FAMILION® test provider PGxHealth.[16] He is a strong advocate of exclusive patent licenses for genetic diagnostics. Dr. Ackerman offers a charity waiver and conducts research-based genetic testing for patients unable to pay for FAMILION® testing.[17]

Dr. Charles Antzelevitch is the Executive Director of and Director of Research at the Masonic Medical Research Laboratory (MMRL). He also holds an academic appointment as Professor of Pharmacology at the SUNY Health Science Center at Syracuse and an endowed chair in Experimental Cardiology (Gordon K. Moe Scholar) at the MMRL. Dr. Antzelevitch provides free testing for hardship cases and enrolls patients in genetic research studies at the MMRL.[18] He opposes exclusive patent licenses in the realm of genetic diagnostics.[19]

Dr. Sherri J. Bale is co-founder, President and Clinical Director of GeneDx, a firm that specializes in genetic testing for rare hereditary disorders. Dr. Bale is a Board-certified Ph.D. Medical Geneticist and a

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and Office of Rare Diseases workshop consensus report about the diagnosis, phenotyping, molecular mechanisms, and therapeutic approaches for primary cardiomyopathies of gene mutations affecting ion channel function. *Circulation* 2007. 116, (20): 2325-45.
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[15] Genaissance Pharmaceuticals, *EX-99.1 of 8-K*, 11 May 2004. See: http://www.sec.gov/Archives/edgar/data/1110009/000110465904013687/a04-5741_1ex99d1.htm, [accessed 26 September 2008].

[16] Ackerman MJ, "Interview with Michael J. Ackerman, MD, PhD, director of the Sudden Death Genomics Laboratory at the Mayo Clinic," Rochester, Minnesota: 6 May 2008.

[17] Ibid.

[18] Antzelevitch C. Written comments from Charles Antzelevitch, Ph.D., F.A.C.C., F.A.H.A., Executive Director and Director of Research of the Masonic Medical Research Laboratory (MMRL) 18 November 2008.

[19] Antzelevitch C. Interview with Charles Antzelevitch, Ph.D., F.A.C.C., F.A.H.A., Executive Director and Director of Research of the Masonic Medical Research Laboratory (MMRL) 2 July 2008.

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founding member of the American College of Medical Genetics. GeneDx offered partial genetic testing for LQTS until 2002, when it was sued by then-LQTS-patent-licensee DNA Sciences. The two companies reached an agreement whereby GeneDx would refrain from offering LQTS testing (Appendix 7). In 2006, GeneDx was purchased by BioReference Laboratories, Inc. (BRLI), which has since sought to offer genetic testing for LQTS.[20] Dr. Bale is a strong opponent of exclusive licensing of gene patents for genetic diagnostic purposes, except as a tool to combat other exclusive licensing.

Congressman Howard L. Berman (D-CA) chaired the October 2007 Congressional hearing, "Stifling or Stimulating - The Role of Gene Patents in Research and Genetic Testing," under the auspices of his chairmanship of the House Judiciary Subcommittee on Courts, the Internet, and Intellectual Property.[21]

The Cardiac Arrhythmias Research and Education Foundation, Inc. (C.A.R.E.) is a 501(c)(3) nonprofit corporation based in Washington State. It advocates increased support for comprehensive scientific research and clinical trials; educates patients, the public and health professionals to increase awareness; and advances strategies to identify, protect and support at-risk individuals and their families. Its Board of Directors includes Dr. Arthur J. Moss. Its Scientific Advisory Board includes LQTS experts Dr. Michael J. Ackerman, Dr. Charles Antzelevitch, Dr. Mark T. Keating, Dr. Dan M. Roden, and Dr. Jeffrey A. Towbin, among others.

Dr. Wendy K. Chung is a clinical and molecular geneticist who directs the clinical genetics program at Columbia University and performs human genetic research. She directs research programs in human genetics of complex traits. Clinically, she directs programs in risk assessment for oncogenetics, cardiomyopathy, arrhythmias, and diabetes and develops novel molecular diagnostic methods to improve genetic testing. She was formerly a member of the PGxHealth FAMILION® Advisory Board.[22] She is now a paid consultant to BRLI.[23] She submitted written testimony to the October 2007 Congressional hearing, "Stifling or Stimulating - The Role of Gene Patents in Research and Genetic Testing." Dr. Chung is a strong critic of exclusive patent licenses in genetic diagnostics.[24]
Mr. Drew Fromkin has served as President and Chief Executive Officer of Clinical Data since 2006. Clinical Data is the parent company of PGxHealth, which, from 2005-2008 was—and as of February 2009, is—the exclusive provider of commercial genetic testing for LQTS. In April 2008, Mr. Fromkin submitted a letter to Congressman Berman[25] responding to the 2007 Congressional testimony presented

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[20] "Stifling or stimulating: the role of gene patents in research and genetic testing.," Subcommittee on Courts, the Internet, and Intellectual Property of the Committee on the Judiciary, One Hundred Tenth Congress; First Session ed. Washington, DC: 30 October 2007. Hearing records available online at http://judiciary.house.gov/hearings/hear_103007.html (accessed 24 January 2009).
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[21] "Stifling or stimulating: the role of gene patents in research and genetic testing.," Subcommittee on Courts, the Internet, and Intellectual Property of the Committee on the Judiciary, One Hundred Tenth Congress; First Session ed. Washington, DC: 30 October 2007.
[22] Reed C, Salisbury B, "Written comments of Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 14 November 2008.
[23] Chung W, "Interview with Wendy Chung, MD, PhD, pediatrician, geneticist and researcher at Columbia University " 7 May 2008.
[24] "Stifling or stimulating: the role of gene patents in research and genetic testing.," Subcommittee on Courts, the Internet, and Intellectual Property of the Committee on the Judiciary, One Hundred Tenth Congress; First Session ed. Washington, DC: 30 October 2007.
[25] Fromkin AJ, "Letter to the Honorable Howard L. Berman from Clinical Data CEO Andrew J. Fromkin." 1 April 2008.

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by Clinical Data's competitor BRLI.[26] Mr. Fromkin is a strong advocate of exclusive patent licenses for genetic diagnostics.[27]

Dr. Jorge Goldstein is an attorney at Sterne Kessler Goldstein & Fox. He has prepared and prosecuted patent applications before the U.S. and foreign patent offices in genomics, molecular and cell biology, recombinant DNA technology, immunology, transgenics and therapeutic methods, as well as organic synthesis, pharmaceuticals, and polymers. He has written about patents and genetic diagnostics.[28] He serves as outside counsel to BRLI.

Dr. Marc Grodman founded Bio-Reference Laboratories (BRLI) in 1981 and has remained its Chairman of the Board, President, Chief Executive Officer and a Director. Dr. Grodman is an Assistant Professor of Clinical Medicine at Columbia University's College of Physicians and Surgeons and Assistant Attending Physician at New York Presbyterian Hospital. He gave testimony at the October 2007 Congressional hearing, "Stifling or Stimulating - The Role of Gene Patents in Research and Genetic Testing."[29] BRLI has made inquiries about purchasing Clinical Data's laboratory operations and begun to aggregate LQTS gene IP.[30] Dr. Grodman is a strong critic of exclusive patent licenses in genetic diagnostics, except as a tool to combat other exclusive licensing.[31]

Dr. Richard Judson was Chief Science Officer at Genaissance Pharmaceuticals from 1999-2005 and oversaw the commercial launch of FAMILION® testing in 2004.

Dr. Mark T. Keating elucidated the genetic basis of LQTS in the mid-1990s at the University of Utah and is the principal inventor on several LQTS gene patents, including those covering the most common variants.

Mr. Steven Lehrer was CEO of DNA Sciences, the original licensee of the relevant LQTS gene IP, from 2001-2003. During his tenure as CEO, DNA Sciences filed suit against GeneDx for infringement of LQTS patents. Mr. Lehrer supports exclusive patent rights for genetic diagnostic tests.

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[26] "Stifling or stimulating: the role of gene patents in research and genetic testing.," Subcommittee on Courts, the Internet, and Intellectual Property of the Committee on the Judiciary, One Hundred Tenth Congress; First Session ed. Washington, DC: 30 October 2007.

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Dr. Aubrey Milunsky is Professor of Human Genetics, Pediatrics, Obstetrics and Gynecology, and Pathology, and Founding Director of the Center for Human Genetics at Boston University Medical Center. The Center for Human Genetics is an international referral center for commercial DNA diagnostics and prenatal genetic diagnosis. Dr. Milunsky is board-certified in Internal Medicine, Pediatrics and Clinical Genetics. BU began offering LQTS genetic testing in 2002. Since then Dr. Milunsky has sought to offer prenatal and other commercial genetic testing for LQTS. He is a strong critic of exclusive patent licenses for genetic diagnostics.[32]

Dr. Arthur J. Moss is Professor of Medicine and Professor of Community and Preventive Medicine at the University of Rochester Medical Center. He is Director of the Heart Research Follow-up Program. His clinical research relates to cardiac arrhythmias and heart failure complicating chronic ischemic heart disease due to coronary atherosclerosis. With Dr. Peter Schwartz, he co-founded the International Long QT Registry in 1979.[33] He was a member of the Genaissance Advisory Board[34] and consulted for the company prior to its sale to Clinical Data.[35] At one time he contemplated setting up commercial testing for LQTS at Rochester. He was later asked to consult by BRLI, but declined.[36] BRLI funds LQTS-related research at the University of Rochester. Dr. Moss believes that gene patent licensing exclusivity is not in the best interests of society.[37]

Dr. Silvia G. Priori is Director of Molecular Cardiology and Electrophysiology Laboratories, IRCCS Fondazione Salvatore Maugeri, Pavia, Italy. She is a clinical cardiologist specializing in the field of inherited arrhythmia syndromes. Much of Dr. Priori's research has focused on the genetic component of cardiac defects. She maintains a public database of LQTS mutations. In 2008 she began working at New York University Medical Center part-time. She has met with PGxHealth representatives and encouraged them to solicit input from additional physicians and scientists working in LQTS.[38]

Dr. Carol Reed is Executive Vice President and Chief Medical Officer for Clinical Data Inc. From 2003-2005, she served as Vice President of Medical Affairs for Genaissance Pharmaceuticals. Dr. Reed is a strong advocate for exclusive patent licenses in genetic diagnostics.

Dr. Heidi Rehm is Associate Molecular Geneticist at the Harvard Medical School-Partners Healthcare Center for Genetics and Genomics. She is also Instructor in Pathology (Brigham & Women's Hospital), Director of the Clinical Molecular Genetics Training Program (American Board of Medical Genetics/Harvard Medical School), and Associate Director of the Harvard Medical School Center for Hereditary Deafness. Her clinical role involves daily sign-out of hearing loss and cardiovascular disease testing for the Laboratory for Molecular Medicine in addition to an administrative role in overseeing the

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laboratory. We consulted with her on the evolution of commercial genetic testing for hypertrophic cardiomyopathy (HCM).

Dr. Hugh Y. Rienhoff founded DNA Sciences (originally Kiva Genetics) in 1998, serving as its Chairman and CEO until late 2001. He helped to negotiate the original LQTS gene patent licenses from the University of Utah. He is a clinical geneticist and holds an appointment in the Department of Molecular Biology and Genetics at the Johns Hopkins University School of Medicine. He is also the founder of MyDaughtersDNA.org, an organization dedicated to rare genetic conditions.

Dr. Dan M. Roden is Director of the Institute of Experimental Therapeutics, William Stokes Professor of Experimental Therapeutics, Professor of Medicine, and Professor of Pharmacology at Vanderbilt University. He has treated LQTS patients and carried out research on the disease for many years. He holds a patent on a variant associated with drug-induced LQTS that he and his co-inventor have licensed to Clinical Data Inc. He told us he would be "happy" to give up his royalties if it meant improved patient care.[39]

Dr. Benjamin A. Salisbury is Senior Director of Clinical Genetics for Clinical Data Inc. He previously served as Group Leader for Computational Genomics at Genaissance Pharmaceuticals.

The Sudden Arrhythmia Death Syndromes Foundation (SADS) is a 501(c)(3) nonprofit corporation dedicated to informing the general public (as well as families and medical professionals) about the effects of untreated/undiagnosed cardiac arrhythmias and the methods by which sudden death can be prevented. Initiatives include sponsoring public awareness meetings in local communities, providing educational videos on LQTS, and establishing media relationships to publicize information about arrhythmias. SADS receives financial support from Clinical Data Inc. Its Board of Trustees includes Drs. Michael J. Ackerman and Silvia G. Priori. Its Scientific Advisory Board includes Drs. Charles Antzelevitch, Dan M. Roden, Peter Schwartz, Jeffrey A. Towbin, Arthur Wilde, and Raymond Woosley.

Dr. Jeffrey A. Towbin is Professor in the Departments of Pediatrics (Cardiology), Cardiovascular Sciences, and Molecular and Human Genetics at Baylor College of Medicine. He is Chief of Pediatric Cardiology at Texas Children's Hospital, holds the Texas Children's Hospital Foundation Chair in Pediatric Cardiac Research, and is Director of the Phoebe Willingham Muzzy Pediatric Molecular Cardiology Laboratory. He is Medical Director of the John Welsh Cardiovascular Diagnostic Laboratory and of the Pediatric Heart Failure and Transplantation Service. He is Co-Director of the Cardiovascular Genetics Clinic at Texas Children's Hospital and Director of Research in the BCM Department of Pediatrics (Cardiology). For the last several years, Dr. Towbin's laboratory has offered fee-for-service cardiovascular genetic testing.[40] These services include testing for mutations in KCNJ2 (Andersen syndrome/LQT7 and Short QT syndrome) and Caveolin-3 (LQT9)[41], both of which are rare.[42]

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Dr. Towbin only offers testing for mutant genes that have been discovered by his laboratory; he has not patented any of these genes.[43]

The University of Utah Technology Commercialization Office owns the patent rights to the major LQTS susceptibility genes. Pursuant to the Bayh-Dole Act,[44] this office licensed rights to diagnostic testing of these genes to DNA Sciences in the late 1990s. Patent licenses were subsequently transferred to Genaissance Pharmaceuticals (circa 2003) and Clinical Data Inc. (circa 2005).[45] During 2006-2008, Utah began licensing patent rights to certain LQTS susceptibility genes to Clinical Data competitor BRLI, thereby creating a potential mutual-blocking situation.[46] Despite repeated requests, the University of Utah Technology Commercialization Office declined to speak with us (for this study or for the BRCA case study, in which it is also involved).

Why is Genetic Testing for LQTS Important?

Genetic testing for LQTS is clinically important for several reasons:

- For unequivocal diagnosis of LQTS, it remains the gold standard,[47] although the resting ECG is critical and a negative genetic test cannot rule out the presence of the disease.[48]

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- The consequences of relying solely on clinical history and sometimes-imprecise and difficult-to-interpret ECG measurements for diagnosis can be grave. 25 to 50% of genetically proven LQTS patients do not exhibit a pathologically prolonged QTc.[49] Without treatment, LQTS-mutation carriers not identified by ECG/clinical evaluation have a ten-percent risk of a serious cardiac event by age 40.[50] Conversely, a recent study suggests that LQTS may be overdiagnosed; among a cohort of 176 patients referred to the Mayo Clinic for LQTS, 40 percent left the clinic without such a diagnosis.[51] Such patients who do not truly have LQTS may be given unnecessary beta-blockers or worse, implanted with gratuitous ICDs.
- Management of LQTS can be genotype-dependent.[52] LQT1 mutation carriers are more likely to experience syncope or sudden death in response to emotional or physical stress.[53] For LQT2 patients, cardiac events can be triggered by sudden loud noises.[54] Women with LQT2 mutations are at higher risk for cardiac events during the postpartum period.[55] Thus, genotype-specific management of the environment can be critical. Mutation location within a gene can be an important correlate of severity.[56] Moreover, beta-blocker therapy appears to be more effective in LQT1 patients[57] and may be counterproductive in LQT3, in which the lower heart rate is

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associated with an increased risk of arrhythmias.[58] In LQT3, the trigger often occurs during rest, while both LQT3 and JLNS are more often associated with fatal outcomes.[59]

Despite these arguments in favor of genetic testing, our understanding of LQTS remains incomplete. First, it must be emphasized again that *a negative genetic test does not rule out a LQTS diagnosis*. Second, because it is not always clear that a given variant in a LQTS gene causes disease, the potential for false positive diagnoses remains.[60] Finally, within a family, the same mutation may be associated with radically different severity and type of symptoms.[61] At the moment, genetic testing for LQTS appears to be most useful: (1) when a clinical diagnosis is fairly certain and treatment strategies may depend on the nature of the mutation; or (2) to confirm or rule out the diagnosis in family members of an affected proband with a known mutation.[62] Clinical Data believes that testing may also clarify the clinical status of patients lacking a clear diagnosis,[63] although one clinician told us that the net effect of this approach can "open a can of worms" and leave patients without diagnoses and with variants of uncertain significance.[64]

The major European and American cardiology societies have issued joint guidelines for the care of patients at risk for sudden cardiac death, including those with LQTS.[65] Genetic testing is recommended for diagnosed LQTS patients.

The Sudden Arrhythmia Death Syndromes Foundation (SADS) suggests genetic testing for:

- All patients with a diagnosis of LQTS who have not had a genetic test;
- Anyone tested in a research study with family members yet to be tested; or
- Family members of a LQTS patient known to carry a mutation.[66]

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Finally, we note additional incentives for genetic testing. Both cardiologists and makers of ICDs may financially benefit from the implantation of defibrillators in actual or suspected LQTS patients. Data indicate that ICDs are a cost-effective means of preventing sudden cardiac death when clinically indicated.[67] The dollars involved in ICD procedures dwarf those associated with genetic testing. Final ICD costs in 2007 sometimes approached $40,000.[68]

Genetic Testing for LQTS: 1995-2004

Following the identification of the first LQTS susceptibility genes, academic laboratories began offering genetic testing on a research basis. Clinicians we spoke to said that research subjects would often not receive their LQTS genotypes for a year or more,[69] if at all.[70]

In 2001, GeneDx began offering commercial genetic testing for LQT1, LQT2, LQT3, LQT5 and LQT6. Boston University began testing the following year; both labs also offered prenatal testing. As described in Appendix 8, the GeneDx LQTS testing regime was incomplete: it covered about one-third of the combined coding regions of the five most important susceptibility genes.[71] BU's assay was similar but not identical: it covered 26 of 63 exons in the five genes.[72] At the time, there was a tacit assumption that LQTS would resemble cystic fibrosis with respect to mutation distribution, i.e., one or a few major

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According to its annual reports available online, SADS received funding from Genaissance Pharmaceuticals, the previous exclusive licensee of the major LQTS gene patents, prior to 2005. (See http://www.sads.org/index.php/Documents/Annual-Reports-Financials.html [accessed September 15, 2008].)

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mutations accounting for most of the disease burden plus a fair number of rarer mutations.[73] This turned out not to be the case; the overwhelming majority of LQTS mutations are "private" and not recurring.[74]

In an email, the Mayo Clinic's Dr. Michael J. Ackerman, LQTS expert clinician, researcher and consultant to PGxHealth, emphasized that during this period, there were a substantial number of mis-detections and a high false negative rate (that is, people with mutations causing LQTS but missed by genetic testing methods). He contends that BU, for example, marketed its test as equivalent to his own laboratory's research-based test, despite the former missing more than 30% of the mutations found by the latter. He believes that this confused doctors and patients because they thought the then-commercially available tests were equivalent to the Mayo test.[75] In his view, this period represented the "black hole" era in LQTS genetic diagnostics.[76]

Genetic Testing for LQTS: The Current Protocol

Since its commercial launch by Genaissance Pharmaceuticals[77] under the name FAMILION® in 2004 and through early 2009, the genetic testing protocol for LQTS has remained relatively unchanged.[78] As outlined in Appendix 1, a physician or laboratory collects a small blood sample (8 ml) from a LQTS or potential LQTS patient (the index case), and sends it to Clinical Data subsidiary PGxHealth in New Haven, CT. Upon arrival, genomic DNA is extracted from blood and the samples are bar-coded for tracking.

Using primers specific for the five genes, DNA samples are then amplified by polymerase chain reaction (PCR) for direct sequence analysis of the susceptibility genes for LQT1 (the KCNQ1 gene), LQT2 (KCNH2), LQT3 (SCN5A), LQT5 (KCNE1) and LQT6 (KCNE2). This analysis includes comprehensive sequence determination and variant detection in open reading frames and intronic sequences containing splice junction sites for the included exons. FAMILION® testing for LQTS covers approximately 13.4 kilobases of DNA divided among 73 amplicons.[79] Directed sequencing is performed in both directions, except where the DNA sequence constraints preclude this approach (those regions are amplified and sequenced twice in a single direction). The DNA fragments resulting from PCR are electrophoretically separated and sequenced. Sequence traces are analyzed for heterozygous or homozygous variants compared to public reference sequences that have been confirmed by sequencing several hundred healthy individuals of diverse ancestry. Two technologists independently score all traces for variants and a supervisor reconciles any discrepancies.

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[79] Salisbury B, "Email from Ben Salisbury regarding total coding sequence of five LQTS genes." 30 September 2008.

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Mutations in these five genes account for ~75% of clinically verified familial LQTS cases.[80] Actual yield from FAMILION® testing has been substantially lower.[81] This lower yield is likely due to the inclusion of patients with a lower pre-test probability of actually having LQTS.[82] Surveillance of fewer genes by FAMILION® testing versus research laboratories may have also played a role in determining yield.

As described in the FAMILION® Technical Specifications Sheet (Appendix 1), reported variants are divided into Classes I, II and III:

CLASS I: Deleterious and Probable Deleterious Mutations

1. Evidence of deleteriousness
2. Nonsense variant
3. Missense single-nucleotide variant not seen in the Reference Panel in transmembrane-spanning domain or pore
4. Insertion or deletion
    a. Frameshift variant
    b. In-frame variant in transmembrane-spanning domain or pore

CLASS II: Possible Deleterious Mutations (Variants of Uncertain Significance)

1. Missense single-nucleotide variant not seen in the Reference Panel and not in transmembrane-spanning domain or pore
2. Missense single-nucleotide variant seen in the Reference Panel with allelic frequency < 0.5%, but with published evidence of deleteriousness
3. In-frame insertion or deletion not in transmembrane-spanning domain or pore
4. Predicted splice-site variant

CLASS III: Polymorphisms (Variants Not Generally Expected to be Deleterious)

1. Protein-altering variant seen in the Reference Panel with either
    a. Common frequency (≥ 0.5%) or
    b. Rare frequency (< 0.5%) and without published evidence of deleteriousness

The final report is reviewed and signed by a CLIA-licensed Laboratory Director.[83] Results are returned to the physician, "usually within 6 weeks."[84] When a Class I or Class II mutation is found, a

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[80] Ackerman MJ. Genetic testing for risk stratification in hypertrophic cardiomyopathy and long QT syndrome: fact or fiction? *Curr Opin Cardiol* 2005. 20, (3): 175-81.
Goldenberg I, Moss AJ. Long QT syndrome. *J Am Coll Cardiol* 2008. 51, (24): 2291-300.
[81] Tester DJ, Salisbury BA, Carr JL, Harris-Kerr C, Reed CR, Ackerman MJ. Clinical phenotype and the yield of the Familion(TM) genetic test for congenital Long QT syndrome. *Abstract presented at Heart Rhythm Society Meeting* 2007.
[82] Reed C, Salisbury B, "Written comments of Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 14 November 2008.
Tester DJ, Salisbury BA, Carr JL, Harris-Kerr C, Reed CR, Ackerman MJ. The effect of mutation class on QTc in unrelated patients referred for the Familion(TM) genetic test for Long QT syndrome. *Abstract presented at Heart Rhythm Society Meeting* May 2007. Tester DJ, Will ML, Haglund CM, Ackerman MJ. Effect of clinical phenotype on yield of long QT syndrome genetic testing. *J Am Coll Cardiol* 2006. 47, (4): 764-8.
[83] CLIA stands for Clinical Laboratory Improvement Amendments of 1988 (see http://www.cms.hhs.gov/clia/ [accessed November 11, 2008]), which were designed to improve the quality and expand federal oversight of clinical laboratories in the United States.

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recommendation for clinical evaluation and genetic testing of first-degree blood relatives is included in the report (Appendices 2 and 3). Examples of a negative report and the accompanying letter sent to doctors are shown in Appendices 4 and 5, respectively. If the clinical interpretation of a reported variant changes, an amended test report is generated and provided to the referring physician when possible (Appendix 1).

The test costs $5400 for the index case and $900 to confirm/rule out a previously characterized mutation in each additional family member. PGxHealth maintains a customer service group that works with patients' insurance providers to pre-authorize services. PGxHealth is quoted an estimate of coverage from the insurance carrier but does not guarantee reimbursement.[85]

LQTS Genes: The Intellectual Property Chain of Custody

Insofar as we can tell, until recently the intellectual property attached to the major LQTS susceptibility genes was exclusively licensed by the University of Utah to a succession of corporate genetic testing firms, but at any given time, exclusive rights were held by a single firm.[86] DNA Sciences Inc. was the original sole licensee (1999-2003.)[87] In 2003, most of the assets of DNA Sciences, including patent licenses for the three major LQTS genes, were purchased out of bankruptcy by Genaissance Pharmaceuticals,[88] which, following renegotiation of the patent licenses, launched commercial LQTS testing in 2004 under the name FAMILION®.[89] In 2005, Genaissance was acquired by Clinical Data Inc.[90]

Since that time, Clinical Data subsidiary PGxHealth™ has overseen rapid growth in commercial testing for LQTS and other channelopathies. In fiscal 2008, sales of PGxHealth tests grew 41% year-over-year to $4.6 million. Judging from a recent company presentation,[91] the overwhelming source of this growth was FAMILION® testing (for LQTS, catecholaminergic polymorphic ventricular tachycardia [CPVT], and Brugada syndrome[92]). During the same year, the company launched a provider-focused sales force and customer-service staff to help drive FAMILION® test adoption,[93] to which much of the sales growth can be attributed, along with an increased focus by PGxHealth in working with physicians to convince reluctant insurers to cover genetic testing for LQTS. PGxHealth reported that it has also invested in

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[84] See http://www.pgxhealth.com/genetictests/familion/patients/index.cfm [accessed October 7, 2008].
[85] See http://www.pgxhealth.com/genetictests/familion/patients/faq.cfm [accessed October 7, 2008].
[86] The University of Utah Technology Commercialization Office declined to speak with us on the record, despite repeated requests.
[87] Rienhoff HY, "Interview with Hugh Y. Rienhoff, Jr., MD, founder and former CEO of DNA Sciences." 13 June 2008.
[88] Judson R, "Interview with Richard Judson, PhD, former CSO of Genaissance Pharmaceuticals." 9 July 2008. Company news - DNA sciences declares bankruptcy, sells assets to Genaissance. *Biotechnology Law Report* June 2003. 22, (3): 307.
[89] Genaissance Pharmaceuticals, *Genaissance Pharmaceuticals Launches its Proprietary FAMILION™ Test for Genetic Mutations Associated With Sudden Cardiac Death*, 2004. See: http://www.medscape.com/pages/editorial/pressreleases/pr-crm-genaissance2, September 17 2008].
[90] Genaissance Pharmaceuticals to merge with Clinical Data. *Pharmacogenomics* July 2005. 6, (5): 459.
[91] Clinical Data, *EX-99.1 of 8-K*, 9 July 2008. See: http://www.sec.gov/Archives/edgar/data/716646/000095013508004859/b71062cdexv99w1.htm, [accessed 17 September 2008].
[92] LQTS notwithstanding, Clinical Data has licensed rights to these other cardiac disorders on a non-exclusive basis. In May 2008 the company launched a test for hypertrophic cardiomyopathy.
[93] Clinical Data, *10-K*, 16 June 2008. See: http://www.sec.gov/Archives/edgar/data/716646/000095013508004390/b70423cde10vk.htm, [accessed 17 September 2008].

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enhancements in its laboratory operations to handle the increased volume and to reduce turnaround times.[94] According to BRLI CEO Dr. Marc Grodman, the intention of his company to enter the cardiac genetics market became well known by early 2007. He believes this potential competition played an important role in Clinical Data's marketing strategy.[95]

Genetic Testing for LQTS: At Issue

Questions about LQTS intellectual property came to the fore and achieved policy significance through the 2007 Congressional testimony of Bio-Reference Laboratories CEO Dr. Marc Grodman and Columbia University clinical geneticist Dr. Wendy Chung.[96] In their testimony they contended that:

- Competition in diagnostic testing is critical to the public health; because of exclusive licensing of the relevant gene patents, in LQTS there is effectively no competition and there has not been since 2002.
- The discovery of the LQTS genes was partly funded by NIH, yet the University of Utah had originally, and at the time of Dr. Grodman's testimony, only seen fit to license the patents to a single private-sector provider.
- By sending cease-and-desist letters to and/or suing the laboratories who were offering LQTS genetic testing prior to commercialization and refusing to sublicense to any other genetic test provider, DNA Sciences Inc (the exclusive patent licensee at the time) created a nearly-two-year period during which only research laboratory-based testing was available to LQTS patients and family members. During that period, DNA Sciences "cleared the market" of potential competitors, including nonprofit testing services, although DNA Sciences did not yet offer a test itself.
- LQTS genetic research has been stifled by Clinical Data's monopoly.
- There have been problems with quality and interpretation of results in Clinical Data's LQTS testing.
- Clinical Data has not developed the ability to reliably perform genetic testing on paraffin-embedded samples from deceased persons.
- Clinical Data's testing regime is incomplete.
- Clinical Data's turnaround time can be as long as six to eight weeks.
- Variants of unknown significance are disproportionately reported in minority populations.
- FAMILION® testing is $5400; a competitive laboratory could offer the test for about "a quarter of the price." The cost of the test is "not routinely covered by most insurance companies without a lengthy preauthorization process that frequently takes 3-12 months to complete." The test would be accessible to many more patients if it were "correctly" priced in a competitive marketplace.[97]

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[94] Reed C, Salisbury B, "Written comments of Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 14 November 2008.
[95] Grodman M, "Written comments of Marc Grodman, MD, CEO of Bio-Reference Laboratories." 12 November 2008.
[96] "Stifling or stimulating: the role of gene patents in research and genetic testing.," Subcommittee on Courts, the Internet, and Intellectual Property of the Committee on the Judiciary, One Hundred Tenth Congress; First Session ed. Washington, DC: 31 October 2007.
[97] Ibid...

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In an April 2008 letter to Howard L. Berman (D-CA), Chairman of the House Judiciary Subcommittee on Courts, the Internet, and Intellectual Property, Clinical Data CEO Drew Fromkin responded to the Grodman/Chung testimony.[98] In his letter Fromkin argued:

- The patent system and the availability of exclusive licensing spurs innovation and provides incentives for product development that can save lives. LQTS is a great example.
- Clinical Data is highly motivated to continually improve FAMILION testing: the company has reduced turnaround time from 6 weeks to 4.5 weeks. With or without competition, poor products stop selling.
- Clinical Data periodically considers adding LQTS mutations to its testing regime. Recently, the susceptibility gene for CPVT was added to the FAMILION® menu.
- In most cases so far, the inclusion of additional genes would add cost to the test with only minimal clinical benefit.
- Research has not been stifled: since the launch of FAMILION® testing, four new LQTS genes have been identified. In the event a FAMILION® test comes back negative, the patient is referred to a research laboratory for further testing.
- Clinical Data is ready to accommodate any common specimen type, including paraffin-embedded tissues.
- Clinical Data holds itself to the highest federal and corporate standards for the quality of its lab work: two clear sequencing reads are required for every sample. All variants are reviewed by three people, including a board-certified medical geneticist.
- Clinical Data responds immediately to reports of inconsistent or erroneous reports.
- Clinical Data regularly presents its LQTS data at national meetings. Additional publications are in preparation.
- Without exclusive patent rights in this and most other fields, competitive pressures would severely limit the disclosure of scientific discovery and harm the public interest.
- Of >1300 non-LQTS individuals tested, mutation information has been published on > 700 with more to come. This testing is done in order to quantify and specify background variation so that the test specificity is understood and so that fewer rare, benign variants are mistaken for pathogenic mutations.[99]
- Half of the healthy subjects who have been tested have come from non-Caucasian populations.
- Health plan coverage of FAMILION® LQTS testing has grown rapidly despite the fact that gaining insurance coverage is “a long and difficult road” that takes years.
- Exclusive licenses lead to higher quality genetic tests that in turn lead to better patient outcomes and a more cost-effective healthcare system. Non-exclusive rights lead to “commodity” and “me-too” tests that place pressures on profit margins that result in mediocrity and can ultimately harm patients and society.

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[98] Fromkin AJ, "Letter to the Honorable Howard L. Berman from Clinical Data CEO Andrew J. Fromkin." 1 April 2008.
[99] Reed C, Salisbury B, "Written comments of Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 14 November 2008.

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- Dr. Grodman has a financial interest in the non-exclusive licensing of LQTS gene patents. Moreover, he has approached Clinical Data in the past seeking: (1) a license to FAMILION® tests and (2) to acquire Clinical Data's laboratory operations as a whole. Clinical Data is surprised he "would so quickly be transformed from a suitor to a harsh critic."
- Dr. Grodman's words do not match his actions. In early 2008, Dr. Grodman's company acquired an exclusive license to the patent surrounding the LQT7 gene (KCNJ2). [100]

Given such highly polarized and seemingly contradictory assertions, LQTS is a natural case study for the effects of IP on access to genetic testing. Beyond the Grodman/Chung testimony and the Fromkin response, there are other reasons to undertake an examination of patenting in LQTS. First, with an incidence of 1 in 3000 to 1 in 5000, [101] it is a relatively common Mendelian disorder. Second, as in hereditary breast cancer testing, from the outset there has been a single exclusive licensee of the major LQTS genes (at least until recently). However, there was a period prior to 2003 when the LQTS gene patent rights were not enforced; thus, we are able to compare the pre- and post-enforcement landscapes, albeit in a highly limited way and with some very serious caveats.[102] Third, genetic testing in LQTS matters: undiagnosed cases may be at high risk for cardiac events,[103] which could potentially be avoided if these individuals were known to carry a mutation in one or more specific genes. Moreover, different mutations in different genes may suggest different therapeutic options.[104]

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[100] In October 2008, attorney Jorge Goldstein, counsel to BRLI, informed us that, since the time of the testimony of Dr Grodman (October 2007), his client had obtained licenses to several LQTS gene patents relating to LQT1, 2, 3, 5, 6, and 7. The patent landscape has therefore become divided between the licenses held by PGxHealth and those held by BRLI.

[101] Goldenberg I, Moss AJ. Long QT syndrome. *J Am Coll Cardiol* 2008. 51, (24): 2291-300.
Lehnart SE, Ackerman MJ, Benson DW, Jr., Brugada R, Clancy CE, Donahue JK, George AL, Jr., Grant AO, Groft SC, January CT, Lathrop DA, Lederer WJ, Makielski JC, Mohler PJ, Moss A, Nerbonne JM, Olson TM, Przywara DA, Towbin JA, Wang LH, Marks AR. Inherited arrhythmias: a National Heart, Lung, and Blood Institute and Office of Rare Diseases workshop consensus report about the diagnosis, phenotyping, molecular mechanisms, and therapeutic approaches for primary cardiomyopathies of gene mutations affecting ion channel function. *Circulation* 2007. 116, (20): 2325-45.
Roden DM. Clinical practice. Long-QT syndrome. *N Engl J Med* 2008. 358, (2): 169-76.

[102] BRLI's Dr. Grodman believes that because of advances in technology since the early 2000s, this "then-and-now" comparison unfairly favor current applications. For their part, Clinical Data's Drs. Reed and Salisbury believe that the recent advances in genetic diagnostic technology, the relative completeness of the current commercial test, and the greater awareness of clinicians and patients of genetic testing also casts serious doubt on the validity of this comparison.

[103] Napolitano C, Priori SG, Schwartz PJ, Bloise R, Ronchetti E, Nastoli J, Bottelli G, Cerrone M, Leonardi S. Genetic testing in the long QT syndrome: development and validation of an efficient approach to genotyping in clinical practice. *JAMA* 2005. 294, (23): 2975-80.
Priori SG, Schwartz PJ, Napolitano C, Bloise R, Ronchetti E, Grillo M, Vicentini A, Spazzolini C, Nastoli J, Bottelli G, Folli R, Cappelletti D. Risk stratification in the long-QT syndrome. *N Engl J Med* 2003. 348, (19): 1866-74.

[104] Saenen JB, Vrints CJ. Molecular aspects of the congenital and acquired Long QT Syndrome: clinical implications. *J Mol Cell Cardiol* 2008. 44, (4): 633-46.
Tan HL, Bardai A, Shimizu W, Moss AJ, Schulze-Bahr E, Noda T, Wilde AA. Genotype-specific onset of arrhythmias in congenital long-QT syndrome: possible therapy implications. *Circulation* 2006. 114, (20): 2096-103.
Schwartz PJ. The congenital long QT syndromes from genotype to phenotype: clinical implications. *J Intern Med* 2006. 259, (1): 39-47.

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LQTS Genes and Intellectual Property

Research, Databases, Publications, and Technical Issues

The field of LQTS genetics is young. As with hereditary breast cancer, the molecular basis of the major LQTS genes has only been known since the mid-1990s.[105] The prospect of a Bayh-Dole Act-inspired patent incentive,[106] however, did not appear to stimulate a LQTS gene race akin to the race for the hereditary breast cancer genes,[107] probably because of the relative rarity of LQTS and what was presumed to be a small market for LQTS testing. The principal inventor on the LQTS gene patents, Dr. Mark Keating, a cardiologist then at the University of Utah, was himself skeptical about the commercial value of testing, though his lab was inundated with requests from other physicians to perform genetic tests on their LQTS patients. Dr. Hugh Rienhoff, the founder of DNA Sciences and a friend of Dr. Keating's, thought there would be commercial value beyond diagnosing LQTS mutations, namely, that SIDS might also be a part of the spectrum of LQTS and that variants in certain genes combined with particular drugs might induce LQTS. Consequently DNA Sciences licensed the patents on LQTS genes and mutations with a view toward extending the research to include these new patients: SIDS victims and their families as well as individuals on drug regimens vulnerable to drug-induced LQTS resulting from certain genetic variants. The research into LQTS thus stemmed from Dr. Keating's very successful genetics research. DNA Sciences extended the LQTS paradigm into areas that Dr. Keating thought were likely to be more complicated and scientifically less productive. According to Dr. Rienhoff, Keating was "more or less right about that."[108] Dr. Rienhoff said there was also skepticism on the part of DNA Sciences investors as to whether genetic testing for "infrequent" (in commercial terms) congenital cardiac disorders would be a viable business.[109]

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[105] Curran ME, Splawski I, Timothy KW, Vincent GM, Green ED, Keating MT. A molecular basis for cardiac arrhythmia: HERG mutations cause long QT syndrome. *Cell* 1995. 80, (5): 795-803.
Wang Q, Shen J, Li Z, Timothy K, Vincent GM, Priori SG, Schwartz PJ, Keating MT. Cardiac sodium channel mutations in patients with long QT syndrome, an inherited cardiac arrhythmia. *Hum Mol Genet* 1995. 4, (9): 1603-7.
Wang Q, Shen J, Splawski I, Atkinson D, Li Z, Robinson JL, Moss AJ, Towbin JA, Keating MT. SCN5A mutations associated with an inherited cardiac arrhythmia, long QT syndrome. *Cell* 1995. 80, (5): 805-11.
Wang DW, Yazawa K, George AL, Jr., Bennett PB. Characterization of human cardiac Na+ channel mutations in the congenital long QT syndrome. *Proc Natl Acad Sci U S A* 1996. 93, (23): 13200-5.
Wang Q, Curran ME, Splawski I, Burn TC, Millholland JM, VanRaay TJ, Shen J, Timothy KW, Vincent GM, de Jager T, Schwartz PJ, Toubin JA, Moss AJ, Atkinson DL, Landes GM, Connors TD, Keating MT. Positional cloning of a novel potassium channel gene: KVLQT1 mutations cause cardiac arrhythmias. *Nat Genet* 1996. 12, (1): 17-23.
[106] Thursby JG, Thursby MC. Intellectual property. University licensing and the Bayh-Dole Act. *Science* 2003. 301, (5636): 1052.
Boettiger S, Bennett AB. Bayh-Dole: if we knew then what we know now. *Nat Biotechnol* 2006. 24, (3): 320-3.
[107] Williams-Jones B. History of a gene patent: tracing the development and application of commercial BRCA testing. *Health Law J* 2002. 10: 123-46.
[108] Rienhoff HY, "Written comments of Hugh Y. Rienhoff, Jr., founder and former CEO of DNA Sciences, Inc. ." 1 November 2008.
Tester DJ, Ackerman MJ. Sudden infant death syndrome: how significant are the cardiac channelopathies? *Cardiovasc Res* 2005. 67, (3): 388-96.
[109] Rienhoff HY, "Interview with Hugh Y. Rienhoff, Jr., MD, founder and former CEO of DNA Sciences." 13 June 2008.

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Through 2008, there was no corporate equivalent in LQTS to the extensive Myriad Genetics contributions to the public BRCA mutation database.[110] Dr. Silvia Priori maintains a public, online database in Italy that includes "a couple thousand" LQTS patients; its mutation data are culled mainly from the published literature.[111] Drs. Arthur Moss and Peter Schwartz founded the International Long-QT Syndrome Registry in 1979; today it includes 1276 families and ~3600 affecteds or borderline affecteds, with genetically confirmed diagnoses in ~2000 of those cases.[112] Most of the Registry's genotype information, however, was obtained from research labs and not from FAMILION® testing;[113] Drs. Reed and Salisbury suggested to us that this is because the Registry was closing around the time of the FAMILION® launch in 2004. According to Baylor's Dr. Towbin, access to the Registry is by application.[114] Prior to the FAMILION® launch, Genaissance and Dr. Michael Ackerman from the Mayo Clinic collaborated to establish an internal database of normal controls and LQTS mutations.[115] Without associated clinical data, it's not clear to us how helpful access to the FAMILION® mutation data would be. Dr. Towbin suggests that it is unreasonable to expect a non-research laboratory to acquire the necessary clinical data.[116] Boston University's Dr. Aubrey Milunsky, however, director of BU's clinical genetics diagnostic service and a former and would-be LQTS testing provider, believes that a knowledge base of certain clinically useful and detailed phenotypic information can come only from a commercial diagnostic lab and not from research labs. Drs. Reed and Salisbury believe such registries should be set up under the auspices of an independent institution with Institutional Review Board approval, as Dr. Moss and Dr. Priori have done. PGxHealth, they say, would support such an initiative.[117] In November 2008, Clinical Data announced that its LQTS mutation data would be made public in spring 2009.[118]

To the best of our knowledge, during the FAMILION® (Genaissance/Clinical Data) testing period from 2004-2008, there have been three full-length LQTS papers published in which scientists employed by the corporate patent licensees shared authorship.[119] The companies have also presented data at national

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[110] Frank TS, Deffenbaugh AM, Reid JE, Hulick M, Ward BE, Lingenfelter B, Gumpper KL, Scholl T, Tavtigian SV, Pruss DR, Critchfield GC. Clinical characteristics of individuals with germline mutations in BRCA1 and BRCA2: analysis of 10,000 individuals. *J Clin Oncol* 2002. 20, (6): 1480-90.

[111] Priori S, "Interview with Silvia G. Priori, MD, PhD, LQTS researcher and clinician in Pavia, Italy." 29 May 2008.

[112] Moss AJ, "Interview with Arthur J. Moss, MD, research physician at the University of Rochester " 28 August 2008.
Goldenberg I, Moss AJ. Long QT syndrome. *J Am Coll Cardiol* 2008. 51, (24): 2291-300.
Moss AJ, Schwartz PJ. 25th anniversary of the International Long-QT Syndrome Registry: an ongoing quest to uncover the secrets of long-QT syndrome. *Circulation* 2005. 111, (9): 1199-201.

[113] Moss AJ, "Interview with Arthur J. Moss, MD, research physician at the University of Rochester. " 28 August 2008.

[114] Towbin JA, "Interview with Jeffrey A. Towbin, MD, chief of pediatric cardiology, Baylor College of Medicine." 29 September 2008.

[115] Judson R, "Interview with Richard Judson, PhD, former CSO of Genaissance Pharmaceuticals." 9 July 2008.

[116] Towbin JA, "Interview with Jeffrey A. Towbin, MD, chief of pediatric cardiology, Baylor College of Medicine." 29 September 2008.

[117] Reed C, Salisbury B, "Written comments of Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 14 November 2008.

[118] Clinical Data Launches Genetic Test for Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC); Company to release its genetic databases for inherited cardiac conditions. *Business Wire* 10 November 2008.

[119] Ackerman MJ, Splawski I, Makielski JC, Tester DJ, Will ML, Timothy KW, Keating MT, Jones G, Chadha M, Burrow CR, Stephens JC, Xu C, Judson R, Curran ME. Spectrum and prevalence of cardiac sodium channel variants among black, white, Asian, and Hispanic individuals: implications for arrhythmogenic susceptibility and Brugada/long QT syndrome genetic testing. *Heart Rhythm* 2004. 1, (5): 600-7.
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meetings and published their findings in abstract form.[120] PGxHealth representatives informed us in June 2008 that the company had multiple manuscripts in progress.[121]

As noted in the *Dramatis Personae* section, Dr. Ackerman's group performs LQTS genetic research at the Mayo Clinic, as does Dr. Priori's in Pavia, Dr. Moss's in Rochester, Dr. Towbin's at Baylor, Dr. Roden's at Vanderbilt, and Dr. Chung's at Columbia University, among several others. It is clearly not in PGxHealth's interest to discourage or antagonize these investigators—the LQTS research community is

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Tester DJ, Cronk LB, Carr JL, Schulz V, Salisbury BA, Judson RS, Ackerman MJ. Allelic dropout in long QT syndrome genetic testing: a possible mechanism underlying false-negative results. *Heart Rhythm* 2006. 3, (7): 815-21.

[120] Salisbury BA, Carr JL, Harris-Kerr C, Ackerman MJ. Abstract 2215: Clinical genetic testing for congenital Long QT syndrome: spectrum of mutations discovered in the first two years. *Abstract presented at American Heart Association Meeting* 2006.

Tester DJ, Salisbury BA, Carr JL, Harris-Kerr C, Reed CR, Ackerman MJ. Should a minimum corrected QT interval (QTc) be a prerequisite for Long QT syndrome genetic testing? *Abstract presented at American Heart Association Meeting.* 6 November 2007.

Ackerman MJ, Tester DJ, Valdivia C, Salisbury BA, Wilde AAM, Makielski JC. Is A572-SCN5A a LQT3/sudden death susceptibility mutation or background genetic noise? *Abstract presented at Heart Rhythm Society Meeting* May 2008.

Johnson JN, Haglund CM, Tester DJ, Perry J, Salisbury BA, Reed CR, Ackerman MJ. Prevalence of early onset atrial fibrillation in congenital Long QT syndrome. *Abstract presented at Heart Rhythm Society Meeting* May 2007.

Kapa S, Tester DJ, Salisbury BA, Wilde AA, Ackerman MJ. Distinguishing Long QT Syndrome-causing mutations from "background" genetic noise. *Abstract presented at Heart Rhythm Society Meeting.* 16 May 2008.

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Tester DJ, Salisbury BA, Carr JL, Harris-Kerr C, Reed CR, Ackerman MJ. Clinical phenotype and the yield of the Familion(TM) genetic test for congenital Long QT syndrome. *Abstract presented at Heart Rhythm Society Meeting.* 2007.

Tester DJ, Salisbury BA, Carr JL, Harris-Kerr C, Reed CR, Ackerman MJ. The effect of mutation class on QTc in unrelated patients referred for the Familion(TM) genetic test for Long QT syndrome. *Abstract presented at Heart Rhythm Society Meeting.* 2007.

Tester DJ, Will ML, Salisbury BA, Carr JL, Schulz V, Judson RS, Ackerman MJ. Allelic drop-out in long QT syndrome genetic testing: a possible mechanism underlying false negative results. *Abstract presented at Heart Rhythm Society Meeting.* May 2005.

Will ML, Tester DJ, Salisbury BA, Carr JL, Schulz V, Judson RS, Ackerman MJ. Repeat long QT syndrome genetic testing of phenotype positive cases: prevalence and etiology of detection misses. *Abstract presented at Heart Rhythm Society Meeting.* May 2005.

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Pungliya M, Salisbury BA, Judson RS, Tester DJ, Will ML, Ackerman MJ. A comparison of mutation patterns in suspected cases of congenital long QT syndrome and controls. *Abstract presented at the American Society of Human Genetics Meeting.* 28 October 2005.

[121] Reed C, Salisbury B, "Interview with Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 12 June 2008.

Ackerman MJ, "Interview with Michael J. Ackerman, MD, director of the Sudden Death Genomics Laboratory at the Mayo Clinic." 2008.

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fairly small and these physicians are invaluable liaisons to patients. There has been productive collaboration between PGxHealth and these investigators, including in the interpretation of variants of unknown significance that may or may not cause disease.[122] In a few cases, however, test results and/or their interpretation appear to have differed.[123] This is not surprising: virtually all laboratories make occasional errors,[124] even in cases where they are screening for the same few mutations over and over again.[125] But in instances where discrepancies occur, it is conceivable, especially in a disease as challenging to understand as LQTS, that the availability of a second commercial provider held to the same CLIA standards, motivated by the same incentives, and subjected to the same competitive pressures could offer a second source of variant confirmation (and perhaps alternative interpretation).

Clinical Data's Dr. Reed: "We encourage our customers to inform us if there is any question or concern regarding a result or an interpretation. We fully annotate our reports and will work to resolve any concerns. If a mistake on our part is found, we will rectify it and improve any process that might have been faulty. In fact, if we are notified of a discrepancy we are obligated to resolve it."

"Re-interpreting a result would not require a second laboratory, just an expert and/or new information. Research labs are generally headed by exactly the expert individual capable of sorting out discrepancies and/or differences in interpretation."[126]

It is important to note again the existence of conflicts of interest on all sides. Those providing commercial testing (PGxHealth and its consultants) have an interest in maintaining the status quo. Many of those who would like to see other commercial providers and stand to benefit from becoming one of them (former providers, BRLI and its consultants) have an obvious interest in altering the current system.

The most important LQTS patents begin to expire in March 2015.[127] Until then, PGxHealth and recent licensee BRLI may exercise influence over the course of LQTS genetic research in the U.S.

Clinical Data suggested to us that FAMILION® testing might actually be facilitating research by identifying patients with known mutations, allowing research laboratories to focus their resources on

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[122] Dr. Ackerman is a paid consultant to Clinical Data. Dr. Chung is a paid consultant to diagnostic firm Bio-Reference Laboratories. Dr. Moss consulted for Genaissance in the past.

[123] Moss AJ, "Interview with Arthur J. Moss, MD, research physician at the University of Rochester. " 28 August 2008.
Chung W, "SACGHS Task Force on Gene Patents and Licensing Practices Interview with Wendy Chung, MD, PhD, pediatrician, geneticist and researcher at Columbia University. " 2008.
Chung W, "Interview with Wendy Chung, MD, PhD, pediatrician, geneticist and researcher at Columbia University" 7 May 2008.
"Stifling or stimulating: the role of gene patents in research and genetic testing.," Subcommittee on Courts, the Internet, and Intellectual Property of the Committee on the Judiciary, One Hundred Tenth Congress; First Session ed. Washington, DC: 31 October 2007.

[124] Ramsden SC, Deans Z, Robinson DO, Mountford R, Sistermans EA, Grody WW, McQuaid S, Patton SJ, Stenhouse SA. Monitoring standards for molecular genetic testing in the United Kingdom, the Netherlands, and Ireland. *Genet Test* 2006. 10, (3): 147-56.

[125] Hertzberg M, Neville S, McDonald D. External quality assurance of molecular analysis of haemochromatosis gene mutations. *J Clin Pathol* 2006. 59, (7): 744-7.

[126] Reed C, Salisbury B, "Written comments of Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 14 November 2008.

[127] US Patent No. 5,599,673 (4 February 1997).

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those without known mutations. The company also emphasized that it does not prevent research labs from conducting research.[128]

To date, while we cannot know with certainty what might have been had there been multiple providers, we have no evidence that the virtual LQTS monopoly from 2003-2008 has had a stifling effect on research, with the possible exception of interpretation of variants of unknown significance, which is discussed in subsequent sections.

Development and Commercialization

The University of Utah Research Foundation was granted three patents covering the major genes predisposing to LQT1, LQT2, LQT3 and LQT5 in 1997, 2001 and 2002.[129] DNA Sciences received exclusive licenses to these patents beginning in 1999, under a "fairly standard" royalty agreement with the University of Utah Research Foundation.[130] In 2003, Genaissance purchased most of the assets of DNA Sciences out of bankruptcy.[131] In the first quarter of 2004, Genaissance concluded agreements with the University of Utah and Yale University covering an estate of more than 50 issued and pending patents relating to the five known mutant genes predisposing to cardiac channelopathies.[132] These agreements included an exclusive license to patents pertaining to the three major LQTS susceptibility genes that had been licensed to DNA Sciences.[133] The LQTS patent landscape as we understand it is presented in Appendix 6.

The LQTS gene patents were key assets of both DNA Sciences[134] and then Genaissance.[135] Clearly there was perceived value in LQTS IP. Both Genaissance and Clinical Data appear to have made testing for LQTS a substantive part of their genetic testing business plans.[136] (Nota bene: Clinical Data has declined

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[128] Reed C, Salisbury B, "Written comments of Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 14 November 2008.
[129] US Patent No. 5,599,673 (4 February 1997).
US Patent No. 6,432,644 B1 (13 August 2002).
US Patent No. 6,207,383 B1 (27 March 2001).
[130] Rienhoff HY, "Interview with Hugh Y. Rienhoff, Jr., MD, founder and former CEO of DNA Sciences." 13 June 2008.
[131] Company news - DNA sciences declares bankruptcy, sells assets to Genaissance. *Biotechnology Law Report* June 2003. 22, (3): 307.
Judson R, "Interview with Richard Judson, PhD, former CSO of Genaissance Pharmaceuticals." 9 July 2008.
[132] Genaissance Pharmaceuticals, *EX-99.1 of 8-K*, 11 May 2004. See: http://www.sec.gov/Archives/edgar/data/1110009/000110465904013687/a04-5741_1ex99d1.htm, [accessed 26 September 2008].
[133] Judson R, "Interview with Richard Judson, PhD, former CSO of Genaissance Pharmaceuticals." 9 July 2008.
[134] Rienhoff HY, "Interview with Hugh Y. Rienhoff, Jr., MD, founder and former CEO of DNA Sciences." 13 June 2008.
DNA Sciences, *S-1*, 5 January 2001. See: http://www.sec.gov/Archives/edgar/data/1130013/000091205701000445/a2033717zs-1.htm, [accessed 22 September 2008].
[135] Judson R, "Interview with Richard Judson, PhD, former CSO of Genaissance Pharmaceuticals." 9 July 2008.
Genaissance Pharmaceuticals, "Event Transcript: GNSC - Q4 2003 Genaissance Pharmaceuticals, Inc. Earnings Conference Call," CCBN Street Events, 2004.
[136] Genaissance Pharmaceuticals, *10-K*, 30 March 2004. See: http://www.sec.gov/Archives/edgar/data/1110009/000104746904010049/a2131537z10-k.htm, [accessed 23 September 2008].

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to share its current or past LQTS-related intellectual property rights with us. We have partially deduced these holdings from interviews with former executives at DNA Sciences and Genaissance, from Securities and Exchange Commission filings, from litigation-related documents and cease-and-desist letters, and from an interview with BRLI's outside legal counsel.)

A patent infringement suit was brought by DNA Sciences against GeneDx[137] in 2002 (Appendix 7). Cease and desist letters were sent to one or more additional labs[138] at around the same time.[139] This suggests an effort by DNA Sciences to "clear the market" in 2002. According to DNA Sciences founder Dr. Rienhoff (who left the company in 2001), one of the stipulations of the company's license agreement with the University of Utah was that the company vigorously defend its IP; to not do so would have been a violation of that agreement.[140] The University of Utah Technology Commercialization Office declined to speak with us for this study.

Because DNA Sciences had not yet developed the test when financial difficulties necessitated the sale of its assets to Genaissance in 2003, commercial testing was not offered until May 2004 with Genaissance's launch of FAMILION®. Thus, it is likely that there was a period of 18 months or so during which genetic testing for LQTS testing was limited mostly to academic labs, whose turnaround time can be a year or more.[141]

Dr. Milunsky at BU reported Clinical Data's more recent efforts to prevent his laboratory from offering genetic testing for LQTS.[142] According to PGxHealth, this was because he had begun to offer the LQTS test more widely, versus only conducting LQTS research.[143]

Genaissance's launch of FAMILION® testing for LQTS in May 2004[144] came nine years after the first patent application was filed.[145] We speculate the delay was likely due to a combination of factors: the bursting of the biotech bubble in 2000,[146] the relative complexity and technical difficulty of the test,[147]

Clinical Data, *10-K*, 29 June 2006. See: http://www.sec.gov/Archives/edgar/data/716646/000095013506004150/b61410cie10vk.htm, [accessed 23 September 2008].

[137] GeneDx was acquired by Bio-Reference Laboratories, Inc. for $17 million in 2006 (http://phx.corporate-ir.net/phoenix.zhtml?c=84759&p=irol-newsArticle_Print&ID=900168&highlight=).

[138] Chung W, "SACGHS Task Force on Gene Patents and Licensing Practices Interview with Wendy Chung, MD, PhD, pediatrician, geneticist and researcher at Columbia University. " 2008.

[139] Lehrer S, "Interview with Steve Lehrer, former CEO of DNA Sciences." 27 June 2008.

[140] Rienhoff HY, "Written comments of Hugh Y. Rienhoff, Jr., founder and former CEO of DNA Sciences, Inc. " 1 November 2008.

[141] Moss AJ, "Interview with Arthur J. Moss, MD, research physician at the University of Rochester. " 28 August 2008.

[142] Butkus B. BU Genetics Center Stops Using Athena Dx Tests After Firm Tightens IP Restrictions. *Biotech Transfer Week* 20 August 2008.

[143] Reed C, Salisbury B, "Written comments of Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 14 November 2008.

[144] "Genaissance Pharmaceuticals Launches its Proprietary FAMILION(TM) Test for Genetic Mutations Associated With Sudden Cardiac Death, *PR Newswire,* 20 May 2004.

[145] US Patent No. 5,599,673 (4 February 1997).

[146] Rienhoff HY, "Interview with Hugh Y. Rienhoff, Jr., MD, founder and former CEO of DNA Sciences." 13 June 2008.

[147] Tester DJ, Cronk LB, Carr JL, Schulz V, Salisbury BA, Judson RS, Ackerman MJ. Allelic dropout in long QT syndrome genetic testing: a possible mechanism underlying false-negative results. *Heart Rhythm* 2006. 3, (7): 815-21.

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and perhaps exclusive IP (which may have created less external competitive pressure on the licensee to launch, although exclusivity also arguably increased investment up front, expediting product launch).

Genaissance (2004-2005) and Clinical Data subsidiary PGxHealth (2005-present) remained essentially the sole commercial providers from 2004-2008. Dr. Milunsky's nonprofit, university-based laboratory offered testing until 2006. From 2006-2008, Bio-Reference Laboratories acquired exclusive licenses from the University of Utah for 13 patents related to composition of matter and/or mutation detection in LQT1, LQT2, LQT3, LQT5, LQT6 and LQT7 (Appendix 6). Thus, the LQTS IP has begun to fragment, with two licensees of different patents covering different genes and mutations. We may be in the early stages of a mutual blocking situation. Those sending samples for testing cannot know in advance which mutations will be found, and yet neither testing service has rights to test for the full range of mutations.[148] As of early 2009, the three interested parties—BRLI, Clinical Data and the University of Utah—were discussing how to proceed.[149] It remains to be seen what impact this turn of events will have on LQTS genetic testing, particularly with respect to pricing and insurer coverage and the prospect of litigation, cross-licensing, or other negotiated legal agreements.

The price for complete sequence-based testing of five LQTS genes has remained $5400 since the 2004 Genaissance launch.[150] Payer coverage has increased significantly during these five years.[151] Clinical Data's Dr. Reed says that it is important to note that "…retail price does not directly correlate with revenue generated and cash received by a lab provider, including PGxHealth. Discounting to payers and inability to collect copayments/deductibles from patients leads to a notably lower value to the lab."[152]

In 2002, GeneDx offered partial testing for $2200. GeneDx claimed that it could detect 87% of the mutations present in the genes for LQT1, LQT2, LQT3, LQT5 and LQT6, and that the overall sensitivity of its test was 59% (see Appendix 8). Given what has been learned about LQTS mutations since—namely that most mutations are "private" and not recurring[153]—GeneDx's sensitivity was probably significantly lower than that estimate. By our calculations, GeneDx was screening about 33% of the five genes' approximately 13.4 kilobases of combined coding sequence.[154] PGxHealth charges — and has always

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[148] Ebersole T, Guthrie M, Goldstein JA. Patent Pools as a Solution to the Licensing Problems of Diagnostic Genetics. *IP and Technology Law Journal* 2005. 17, (1): 6-13.
Verbeure B, van Zimmeren E, Matthijs G, Van Overwalle G. Patent pools and diagnostic testing. *Trends Biotechnol* 2006. 24, (3): 115-20.
[149] Goldstein J, "Interview with Jorge Goldstein, JD, patent attorney at Sterne, Kessler, Goldstein & Fox, outside counsel to Bio-Reference Laboratories and GeneDx." 31 October 2008.
[150] Reed C, Salisbury B, "Interview with Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 12 June 2008.
[151] Clinical Data Launches Genetic Test for Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC); Company to release its genetic databases for inherited cardiac conditions. *Business Wire* 10 November 2008.
[152] Reed C, Salisbury B, "Written comments of Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 14 November 2008.
[153] Moss AJ, Shimizu W, Wilde AA, Towbin JA, Zareba W, Robinson JL, Qi M, Vincent GM, Ackerman MJ, Kaufman ES, Hofman N, Seth R, Kamakura S, Miyamoto Y, Goldenberg I, Andrews ML, McNitt S. Clinical aspects of type-1 long-QT syndrome by location, coding type, and biophysical function of mutations involving the KCNQ1 gene. *Circulation* 2007. 115, (19): 2481-9.
Roden DM. Clinical practice. Long-QT syndrome. *N Engl J Med* 2008. 358, (2): 169-76.
[154] Abbott GW, Sesti F, Splawski I, Buck ME, Lehmann MH, Timothy KW, Keating MT, Goldstein SA. MiRP1 forms IKr potassium channels with HERG and is associated with cardiac arrhythmia. *Cell* 1999. 97, (2): 175-87.
Larsen LA, Andersen PS, Kanters J, Svendsen IH, Jacobsen JR, Vuust J, Wettrell G, Tranebjaerg L, Bathen J, Christiansen M. Screening for mutations and polymorphisms in the genes KCNH2 and KCNE2 encoding the cardiac HERG/MiRP1 ion channel: implications for acquired and congenital long Q-T syndrome. *Clin Chem* 2001. 47, (8): 1390-5.

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charged — $900 to confirm a mutation in additional family members; the same service was reportedly $350 from GeneDx and $250 from Boston University in 2002.[155] The fact that GeneDx and BU both provided fee-for-service testing from ~2001-2002 before the patents were enforced suggests that a patent incentive was not required to develop a test.[156] Clinical Data's Dr. Reed argues that during this period there is no evidence that GeneDx or BU invested in physician education or expanded insurance coverage for their "inferior" tests.[157]

LQTS testing uptake has grown steadily since 2004. Genaissance reported FAMILION® revenues of $841,000 from the May 2004 launch through June 30, 2005.[158] Subsequently, the test has been a consistent source of growth for Clinical Data. FAMILION® sales grew from ~$2.7 million in fiscal 2007 to ~$4.5 million in fiscal 2008. In the first two quarters of fiscal 2009, FAMILION® generated an estimated $4.1 million. [159] Dr. Reed notes her company's "…significant investment in Clinical Data's sales and marketing efforts, infrastructure and payer contracting. Furthermore, this increase could not have happened without the intensive investment by PGxHealth and collaborations with academia and advocacy groups…"[160]

The fairness of the price of testing ($5400 or ~$74 per amplicon) is difficult to judge definitively given the exclusive license (and therefore no direct competitive comparison). It is worth noting that in 2002, if we assume one amplicon per exon, GeneDx charged ~ $129 per amplicon ($2200) for its partial primary screen of 17 exons selected from the five genes.[161] On the other hand, Myriad Genetics charges $38 per amplicon for its sequence-based testing of the BRCA1 and BRCA2 genes, for which it has exclusive rights (see BRCA case study) and a significantly higher test volume. In the course of preparing this case study, some patients, patient advocates and physicians complained to us about the high cost of the FAMILION® test and less than complete payer coverage, although incomplete coverage is not in Clinical

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Neyroud N, Richard P, Vignier N, Donger C, Denjoy I, Demay L, Shkolnikova M, Pesce R, Chevalier P, Hainque B, Coumel P, Schwartz K, Guicheney P. Genomic organization of the KCNQ1 K+ channel gene and identification of C-terminal mutations in the long-QT syndrome. *Circ Res* 1999. 84, (3): 290-7.
Salisbury B, "Email from Ben Salisbury regarding total coding sequence of five LQTS genes." 30 September 2008.
Splawski I, Shen J, Timothy KW, Vincent GM, Lehmann MH, Keating MT. Genomic structure of three long QT syndrome genes: KVLQT1, HERG, and KCNE1. *Genomics* 1998. 51, (1): 86-97.
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Milunsky A, "Email from Aubrey Milunsky, MB.B.Ch., D.Sc., F.R.C.P., F.A.C.M.G., D.C.H." 17 November 2008.

[156] Milunsky A, "Interview with Aubrey Milunsky, MB.B.Ch., D.Sc., F.R.C.P., F.A.C.M.G., D.C.H., Director of Boston University's Center for Human Genetics." 29 May 2008.
Bale S, "Interview with Sherri Bale, PhD, President and Clinical Director of GeneDx." 12 May 2008.

[157] Reed C, Salisbury B, "Written comments of Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 14 November 2008.

[158] Genaissance Pharmaceuticals, *10-Q*, 9 August 2005. See: http://www.sec.gov/Archives/edgar/data/1110009/000110465905037531/a05-13057_110q.htm, [accessed 24 September 2008].
Genaissance Pharmaceuticals, *10-K*, 15 March 2005. See: http://www.sec.gov/Archives/edgar/data/1110009/000104746905006537/a2152822z10-k.htm, [accessed 24 September 2008].

[159] See http://www.clda.com/uploads/CLDA_Q2-09%2011-3-08FINAL.pdf [accessed November 4, 2008].

[160] Reed C, Salisbury B, "Written comments of Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 14 November 2008.

[161] In patients and families known to have Jervell and Lange-Nielsen syndrome (JLNS), a rare autosomal recessive variant of LQTS that features profound congenital deafness, GeneDx screened for mutations in all exons of KCNQ1 and KCNE1, the two susceptibility genes known to cause JLNS (see Appendix 8).

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Data's interest, either. Dr. Rienhoff and Mr. Lehrer, both formerly of DNA Sciences, emphasized the complexity of the test that eventually became FAMILION® and said the price should be judged accordingly.[162]

In his rebuttal to the Grodman/Chung testimony, Clinical Data CEO Drew Fromkin pointed out that Grodman's firm had recently secured an exclusive license on KCNJ2, the susceptibility gene for hereditary LQTS7, a rare form of the disease,[163] thereby suggesting that Grodman was being hypocritical. Grodman told us that his licensing of the gene was strategic. "We have exclusive licensing [on KCNJ2 and some others], but we have not exercised it. We were approached by [Clinical Data] to do the [LQT7] test with them and we said we'd be happy to share IP. Part of that is strategic, it's not a belief in the process. It's not what you have, it's what you do with it."[164] Indeed, in the face of a pre-existing exclusive license to a competitor, absence of a patent or a nonexclusive license would not solve the problem, and an exclusive license may be the only legal tool to compel cross-licensing or other negotiated agreement. Securing an exclusive license is therefore not necessarily hypocritical, if it is a strategy to induce negotiation in the face of existing exclusive rights.

Dr. Reed regards this as "…an incomplete statement and somewhat self-serving. In fact, we approached Dr. Grodman to in-license his 'strategic' IP to run the test for this single gene ourselves, not with [BRLI]. Dr. Grodman would agree only if we cross-licensed the whole of our LQTS IP so [BRLI] could commercialize a directly competitive LQTS test. This was not an appealing proposition to us…[This is] a business dispute where one party simply wants rights to a market the other company has built diligently through entrepreneurial investment of time and resources."[165]

This dispute points up the market constraints of the current situation: given Clinical Data's unwillingness to sublicense to U.S. diagnostic labs, any laboratory interested in non-research-based testing for cardiac channelopathy genes must either restrict itself to genes that have not been patented and licensed exclusively[166] or try to gain leverage by amassing intellectual property on genes outside of Clinical Data's patent estate, but that account for a minority of LQTS.[167] BRLI's recent licensing of multiple LQTS gene patents, including patents for one of the three major genes (SCN5A, mutations in which can predispose to LQT3), will provide a real-time measure of the extent of this leverage.

This case is thus a stark illustration of two features of how exclusive licensing of patent rights can influence diagnostic testing: the potential for mutual blocking situations, and the "penumbra effect" (discussed in the hearing loss case study also) in which exclusive rights to one or a few common genetic variants can in effect drive business for all genetic testing—even for variations that have been discovered but not patented or that have never been discovered before—to the rights holder. That is, rights on one set of mutations can be leveraged to drive business for other mutations not covered by patent claims. This has been the practice until very recently for LQTS testing, and the situation is now unstable because BRLI

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[162] Lehrer S, "Interview with Steve Lehrer, former CEO of DNA Sciences." 27 June 2008.
Rienhoff HY, "Written comments of Hugh Y. Rienhoff, Jr., founder and former CEO of DNA Sciences, Inc. ." 1 November 2008.
[163] Fromkin AJ, "Letter to the Honorable Howard L. Berman from Clinical Data CEO Andrew J. Fromkin." 1 April 2008.
[164] Grodman M, "Interview with Marc Grodman, MD, CEO of Bio-Reference Laboratories, Inc." 21 August 2008.
[165] Reed C, Salisbury B, "Written comments of Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 14 November 2008.
[166] Towbin JA, "Interview with Jeffrey A. Towbin, MD, chief of pediatric cardiology, Baylor College of Medicine." 29 September 2008.
[167] Grodman M, "Interview with Marc Grodman, MD, CEO of Bio-Reference Laboratories, Inc." 21 August 2008.

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has obtained countervailing exclusive rights. This cannot be resolved by those seeking genetic test results because they cannot know in advance which mutations will be found.

In at least one instance, Clinical Data has sub-licensed its LQTS IP. In October 2007 the company announced that its PGxHealth subsidiary had entered into a non-exclusive sub-license agreement with the Victorian Clinical Genetics Services, a not-for-profit subsidiary of the Murdoch Children's Research Institute, for the provision of genetic testing for familial LQTS in Australia and New Zealand. [168] According to Dr. Reed, this shows Clinical Data's "…willingness to cede markets to others where we are not equipped to provide services."[169] This has minimal relevance, however, to the U.S. market, since it affects testing in a foreign jurisdiction covered by patent law in that jurisdiction.

PGxHealth has also availed itself of others' nonexclusive licenses. In May 2008 the company launched genetic testing for hypertrophic cardiomyopathy (HCM), which has been licensed by Harvard Medical School to multiple diagnostic providers. [170] Drs. Grodman and Chung contend that HCM is a better model for IP related to genetic testing because it fosters a system of competition and checks and balances. [171] Dr. Ackerman, on the other hand, pointed out that the test continued to lack both Medicare and Medicaid coverage in 2008 in most jurisdictions.[172] Dr. Heidi Rehm, Associate Molecular Geneticist at the Harvard Medical School-Partners Healthcare Center for Genetics and Genomics, confirmed this assertion (as did another provider off the record). She said that while Harvard launched the commercial HCM test in 2004, Harvard is proscribed from offering direct third-party billing.[173] The second provider, Correlagen Diagnostics, did not launch until July 2007.[174] Dr. Reed says that by offering HCM testing, Clinical Data is "…[building] on the investment justified by our LQTS test."[175]

Communication and Marketing

In 2004-2005, Dr. Ackerman wrote at least four articles in professional journals that noted the availability of commercial genetic testing for LQTS; his financial interest was disclosed in each case.[176] A 2005

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[168] See http://www.clda.com/uploads/LQTaustralia-draft%20press%20release10107FINAL.pdf [accessed October 6, 2008].
[169] Reed C, Salisbury B, "Written comments of Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 14 November 2008.
[170] See http://www.4hcm.org/WCMS/index.php?id=81,0,0,1,0,0 (accessed October 7, 2008].
[171] Chung W, "Interview with Wendy Chung, MD, PhD, pediatrician, geneticist and researcher at Columbia University. " 7 May 2008.
Grodman M, "Interview with Marc Grodman, MD, CEO of Bio-Reference Laboratories, Inc." 21 August 2008.
[172] Ackerman MJ, "Email from Michael J. Ackerman, MD, PhD; first response to case study." 27 October 2008.
[173] Rehm H, "Interview with Heidi Rehm, PhD, Associate Molecular Geneticist at the Harvard Medical School-Partners Healthcare Center for Genetics and Genomics." 17 November 2008.
[174] See http://www.correlagen.com/about/downloads/Correlagen_CAP_NewsRelease_030507.pdf [accessed November 19, 2008].
[175] Reed C, Salisbury B, "Written comments of Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 14 November 2008.
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Ackerman MJ. Genetic testing for risk stratification in hypertrophic cardiomyopathy and long QT syndrome: fact or fiction? *Curr Opin Cardiol* 2005. 20, (3): 175-81.
Ackerman MJ. Genotype-phenotype relationships in congenital long QT syndrome. *J Electrocardiol* 2005. 38, (4 Suppl): 64-8.
Tester DJ, Ackerman MJ. Genetic testing for cardiac channelopathies: ten questions regarding clinical considerations for heart rhythm allied professionals. *Heart Rhythm* 2005. 2, (6): 675-7.

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article partially funded by Genaissance concluded that genetic testing for familial LQTS was cost-effective.[177]

Clinical Data has undertaken efforts to market its services to physicians. In 2007, the company established a sales force to promote FAMILION® testing. This sales force makes calls on pediatric electrophysiologists and cardiologists and, increasingly, their adult equivalents. Based on the initial positive results of this effort, the company expanded the size of the sales force in 2008. Clinical Data has also recently added resources to focus on the provider and payer markets[178] and has a dedicated customer service group.[179]

PGxHealth also markets FAMILION® testing via patient advocacy groups and professional organizations that offer patient support and promote research and education. These include the Sudden Arrhythmia Death Syndromes Foundation, or SADS, and "The National Society of Clinical Geneticists."[180]

Examining Test Quality

In five cases, Dr. Chung, a paid consultant to BRLI and former consultant to PGxHealth, said she split samples and tried to confirm PGxHealth's results in her own laboratory. In two cases, she said there were discrepancies. In one case, there was a sequencing problem; in the other there was an informatics issue.[181]

In her 2007 statement to Congress and in interviews with us and the SACGHS Task Force on Gene Patents and Licensing Practices, Dr. Chung called PGxHealth's protocol for dealing with variants of unknown significance and other ambiguous results inadequate, especially given that five to ten percent of all results will be difficult to interpret.[182] "…it puts clinicians in a very awkward position [if] the patient has spent $5400 on this test…and [they] don't know how to interpret it…"[183] Dr. Chung has expressed particular concern about the interpretation of so-called "Class II variants," which PGxHealth calls "Variants of Uncertain Significance" and "Possible Deleterious Mutations." These include some missense variants, in-frame deletions/insertions, and predicted splice-site variants (see Appendix 1). Dr. Chung

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[177] Phillips KA, Ackerman MJ, Sakowski J, Berul CI. Cost-effectiveness analysis of genetic testing for familial long QT syndrome in symptomatic index cases. *Heart Rhythm* 2005. 2, (12): 1294-300.
[178] Clinical Data, *10-K*, 16 June 2008. See: http://www.sec.gov/Archives/edgar/data/716646/000095013508004390/b70423cde10vk.htm, [accessed 17 September 2008].
[179] Reed C, Salisbury B, "Written comments of Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 14 November 2008.
[180] To our knowledge, there is no "National Society of Clinical Geneticists." It's possible that this could be referring to the National Society of Genetic Counselors or the American College of Medical Genetics. Clinical Data, *10-K*, 16 June 2008. See: http://www.sec.gov/Archives/edgar/data/716646/000095013508004390/b70423cde10vk.htm, [accessed 17 September 2008].
[181] Chung W, "Interview with Wendy Chung, MD, PhD, pediatrician, geneticist and researcher at Columbia University " 7 May 2008.
[182] "Stifling or stimulating: the role of gene patents in research and genetic testing.," Subcommittee on Courts, the Internet, and Intellectual Property of the Committee on the Judiciary, One Hundred Tenth Congress; First Session ed. Washington, DC: 31 October 2007.
Chung W, "SACGHS Task Force on Gene Patents and Licensing Practices Interview with Wendy Chung, MD, PhD, pediatrician, geneticist and researcher at Columbia University. " 2008.
Chung W, "Interview with Wendy Chung, MD, PhD, pediatrician, geneticist and researcher at Columbia University." 7 May 2008.
[183] Chung W, "SACGHS Task Force on Gene Patents and Licensing Practices Interview with Wendy Chung, MD, PhD, pediatrician, geneticist and researcher at Columbia University." 2008.

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expressed fear that many cardiologists will interpret these as definitive disease-causing variants.[184] Dr. Chung also contended that there has not been robust vetting of these variants because the scientific community has not had access to PGxHealth's database.[185]

Dr. Chung believes that having only a single commercial provider denies clinicians the opportunity to solicit a second opinion. "…when you don't have the ability to get a second opinion, you have no idea where your errors or pitfalls are and [there is] no independent way for clinicians to be able to validate whatever they're seeing or, on the other hand, to be able to come up with [what] at the end is a correct diagnosis."[186] Dr. Milunsky, who is a past and would-be provider of commercial testing, shares this view.[187] Their assumption is that multiple providers would reach consensus interpretations, and alternative providers would be accompanied by more public availability of data and more open discussion of its interpretation.

Dr. Chung also criticizes PGxHealth for the incompleteness of FAMILION® LQTS testing. She takes issue with Clinical Data's contention that the addition of more genes to the FAMILION® panel will not add much value. She says that this cannot be known with certainty.[188]

In her 2007 testimony, Dr. Chung stated that PGxHealth is not able to reliably offer genetic testing on paraffin-embedded tissue samples, which is often the only tissue sample available from deceased persons.[189] She told us about a case in which a patient was receiving a heart transplant in which the donor heart had LQTS; she described an "ordeal" in order to get PGxHealth to extract DNA from frozen tissue.[190]

By its own admission, PGxHealth's results have not been perfect. In bi-annual proficiency testing, "there has been an occasional conflict,"[191] although Dr. Reed emphasizes that in every such case, "we have been right."[192]

Responses to Quality Concerns

Dr. Reed takes strong exception to Dr. Chung's claims: "…Dr. Chung [is] a paid consultant to a competitor company that desires access to the patents under discussion."

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[184] Chung W, "Interview with Wendy Chung, MD, PhD, pediatrician, geneticist and researcher at Columbia University. " 7 May 2008.
[185] Chung W, "SACGHS Task Force on Gene Patents and Licensing Practices Interview with Wendy Chung, MD, PhD, pediatrician, geneticist and researcher at Columbia University. " 2008.
[186] Ibid.
[187] Milunsky A, "Interview with Aubrey Milunsky, MB.B.Ch., D.Sc., F.R.C.P., F.A.C.M.G., D.C.H., Director of Boston University's Center for Human Genetics." 29 May 2008.
[188] Chung W, "Interview with Wendy Chung, MD, PhD, pediatrician, geneticist and researcher at Columbia University." 7 May 2008.
[189] "Stifling or stimulating: the role of gene patents in research and genetic testing.," Subcommittee on Courts, the Internet, and Intellectual Property of the Committee on the Judiciary, One Hundred Tenth Congress; First Session ed. Washington, DC: 31 October 2007.
[190] Ibid.
[191] Reed C, Salisbury B, "Interview with Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 12 June 2008.
[192] Reed C, Salisbury B, "Written comments of Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 14 November 2008.

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"…These variants are inherently ambiguous and 'problematic.' This has nothing to do with 'protocols,' rather it is a matter of biomedical science where even experts may disagree. Just because we don't interpret every mutation the way Dr. Chung might, does not make it wrong. We acknowledge that this is a difficult area. Thus, Dr. Chung's concerns are no surprise and are indicative of the state of the art." Dr. Reed also notes that as a former member of a FAMILION® Advisory Board, Dr. Chung has herself engaged in discussions with the company as to the difficulty in interpreting these variants. Dr. Reed also points out PGxHealth uses a reference population of >1300 controls to evaluate all variants (Appendix 1). This reference population, says Dr. Reed, plays a critical role in ensuring that variants are appropriately classified. Finally, with respect to including additional genes, Dr. Reed suggests that the lack of knowledge about these loci makes it "…premature to include these genes in a clinical test…[A]dding them could create more confusion for cardiologists and may decrease the clinical specificity of testing." Furthermore, she notes that Dr. Moss, as quoted in this report (see below), does not think it worthwhile to add genes with non-cardiac syndromic manifestations that can be fairly easily diagnosed by physical exam.[193]

For proficiency testing of the FAMILION® assay, Dr. Ackerman sends blinded, de-identified samples to PGxHealth every six months. According to him, since 2004 there has been only a single discordant result, which was attributable to his lab missing a non-synonymous variant that PGxHealth detected.[194] Dr. Reed notes that these results are available via Clinical Data's periodically audited proficiency testing records.[195]

Again, one difficulty in evaluating the quality and proficiency FAMILION® testing is the inherent conflict of interest of a number of the critical stakeholders. Dr. Ackerman, for example, is a paid consultant to Clinical Data. Dr. Chung is a paid consultant to Clinical Data competitor BRLI and former consultant to PGxHealth. Mr. Fromkin and Dr. Grodman are at the helms of the two competing companies.

Five current and former LQTS genetic researchers/clinicians we spoke to do not have any current and direct financial conflicts of interest related to genetic testing for variants in the five major genes predisposing to congenital LQTS. We asked them specifically to disclose any financial arrangements linked to LQTS patents and licensees. These experts offered their perspectives on the perceived quality of and/or rationale behind FAMILION® testing for LQTS mutations:

- Dr. Silvia Priori: "[M]y interpretation of the situation [is] that the company [PGxHealth] is definitely better than any research laboratory. It has to be better than any research laboratory in handling the samples and quickly performing the sequence analysis. Obviously the difference comes in the interpretation of the mutation…a research laboratory has a lot of time dedicated to studying the individual mutation. So if I have a patient with a new mutation I am also in the position of being the clinician taking care of that patient…I have told [PGxHealth] that I feel quite uncomfortable with the fact that they have been working with very limited input from the scientific community. They seem to be a company consulting with [only] one physician…it is

[193] Reed C, Salisbury B, "Written comments of Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 14 November 2008.
[194] Ackerman MJ, "Email from Michael J. Ackerman, MD, PhD." 2008.
[195] Reed C, Salisbury B, "Interview with Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 12 June 2008.
Reed C, Salisbury B, "Written comments of Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 14 November 2008.

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clear that [he] is skilled and competent but it is still only one [physician who] is being consulted."[196],[197]

- Dr. Arthur J. Moss[198]: "[PGxHealth has] more expensive equipment. They do a pretty good job in terms of turnaround [time], but Bio-Reference Laboratories would do the same thing…we have seen a moderate amount of inconsistency and errors. We have had several occasions where PGxHealth was wrong.[199] One occurred—off the top of my head—in a test that was run by Jeff Towbin. The physician sent a blood sample [to him and to] FAMILION® and the results were different. We tracked this down and repeated the test here. We got the same result as Dr. Towbin and reported this to FAMILION® and to the patient. I don't think [the error rate] is large."[200]

  "Complete [genetic] testing of other genes is not really necessary. LQT7 through LQT11 are based on one or two families each, or else based on neurological symptoms where the diagnosis is not very difficult. The Andersen-Tawil syndrome diagnosis is easy to make because of morphological changes in the jaw and face…Timothy syndrome is rare and those people [with the syndrome] have striking skeletal defects. Genetic testing is not critical [in those cases]..."[201]

- Dr. Charles Antzelevitch: "We repeated genetic analysis of the same genes screened by FAMILION® in only three patients using CLIA-approved methods and found an error in two of the three; the two were members of the same family. In this case FAMILION® missed detection of a G insertion in exon 12 of KCNH2, causing a frameshift and leading to a stop codon."

  "[M]y personal view is that FAMILION® is filling an important need and is doing a decent job of it, but that it is not in the best interest of science or medicine for any company to a have an absolute monopoly on genetic screening of LQTS. A little friendly competition may improve quality control and reduce prices, thus making it more affordable for all. This would facilitate the acquisition of additional data on genotype-phenotype correlation, thus leading to improved diagnosis, prognosis and a better approach to therapy of LQTS."[202]

- Dr. Jeffrey Towbin: "I think it would be valuable for PGxHealth to publish its data...[But to] make a genotype-phenotype correlation you have to have the [phenotypic information]. FAMILION® can't be expected to have that. I think that while their datasets would be extraordinarily useful if they had the clinical information necessary, I think that's a pipedream the way it's set up now."[203]

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[196] Dr. Reed notes that Clinical Data held a 19-member advisory board meeting in January 2008 and held a "similarly large" adult electrophysiologist advisory board meeting in the fall of 2008.
[197] Priori S, "Interview with Silvia G. Priori, MD, PhD, LQTS researcher and clinician in Pavia, Italy." 29 May 2008.
[198] Dr. Moss consulted with Genaissance when that firm held the license to LQTS IP. According to Dr. Moss, Dr. Grodman, CEO of BRLI, wanted to establish a consulting relationship; Dr. Moss declined and instead asked that Dr. Grodman direct funds to the University of Rochester, which it did.
[199] Dr. Reed says that she knows of only a single instance. "Again, without specific feedback from our customers, we cannot make test improvements if needed."
[200] Moss AJ, "Interview with Arthur J. Moss, MD, research physician at the University of Rochester " 28 August 2008.
[201] Ibid.
[202] Antzelevitch C. Written comments from Charles Antzelevitch, Ph.D., F.A.C.C., F.A.H.A., Executive Director and Director of Research of the Masonic Medical Research Laboratory (MMRL). 18 November 2008.
[203] Towbin JA, "Interview with Jeffrey A. Towbin, MD, chief of pediatric cardiology, Baylor College of Medicine." 29 September 2008.

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> "I have no [real] way of knowing FAMILION's quality. When you send a sample and you get a result you have no way of knowing unless you run parallel samples. Yes there have been discrepancies on occasion that we've seen. But I don't know who's right; I [might] argue that our labs are wrong—we all make mistakes. We don't get the right answer sometimes….On balance, I would say the approach they're taking is reasonable….They've been doing it long enough…. I think their system and their thought process make sense. They've done a good job and for some patients have done a real service. The research labs were never going to do that. I think [commercial testing is] a useful resource and I think [PGxHealth is] doing it pretty well….If you want a CLIA-approved test for LQTS looking at the standard five genes, it's a very good option….I think Art [Moss] is correct that there have been errors, but no one will meet the perfection standard. [PGxHealth is] good or very good….I think they provide a useful service. Could it be better? Yes. [But] I don't look at them as the bad guy. They're in business, they have standards for quality and turnaround time. That is the state of the art at the moment…"
>
> "[LQTS] is not going to get easier to understand. I don't think we should expect clinicians to understand exactly the meaning of what we're telling people [about their results]…. It's very hard in the early 21st century for the average clinician to know enough about genetics to really utilize a [genetic] test. But it's the sexy thing to do."[204]

- Dr. Hugh Rienhoff: "[Dr. Towbin's comments are] absolutely true and one of the reasons that the inventor, Dr. Keating, was so willing to 'unload' the responsibility of LQTS testing to DNA Sciences. He did not have a CLIA lab, there were no rigorous [standard operating procedures] for testing, no dedicated personnel, [no dedicated] space or devices for the work, and no way to charge for the work. It was regarded as a burden to his lab because it used up valuable technician [and] student time and resources. This is a very common set of circumstances in an academic lab that has made a discovery and has a unique set of reagents or capabilities."[205]

Dr. Rienhoff, a clinical geneticist and founder of DNA Sciences, elaborated further on the formidable challenge in interpreting the meaning of genetic variants in diseases such as LQTS:

> "This is a problem that is widespread and not specific to the particular parties at hand. New missense mutations will always pose a problem for interpretation. It is a challenge to show that any new variant in a gene has functional consequences [for] either mRNA stability or protein structure and function. It is unrealistic to think anyone could easily resolve the un-interpretability of these findings. Indeed, it simply underscores the fact that we are still early in our description of the human genome and the variants that can be found in it."[206]

In addition to the difficulty of finding experts who do not have a current or past conflict of interest, another impediment to making objective assessments regarding quality is the present inadequacy of CLIA oversight of genetic testing laboratories.[207] The Centers for Medicare & Medicaid Services (CMS) have yet to institute specific requirements for molecular or biochemical genetic testing laboratories. Thus, while CLIA requires laboratories to have quality assurance programs in place, most genetic testing

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[204] Ibid.
[205] Rienhoff HY, "Written comments of Hugh Y. Rienhoff, Jr., founder and former CEO of DNA Sciences, Inc. " 1 November 2008.
[206] Ibid.
[207] Hudson KL. Genetic testing oversight. *Science* 2006. 313, (5795): 1853.
Report of the Secretary's Advisory Committee on Genetics H, and Society, U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services. (Bethesda, MD, 2008).

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laboratories are not required by CLIA to perform proficiency testing with specific benchmarks.[208] Moreover, petitions to CMS to issue updated standards for genetic testing laboratories, including standards for proficiency testing, have thus far gone unheeded. [209] To its credit, PGxHealth has instituted its own proficiency testing program in conjunction with Dr. Ackerman.[210] When such proficiency testing is in place, however, there is no CLIA guidance about whether the conduct of such testing under auspices of a paid consultant is an acceptable practice. Clinical Data has opposed more stringent regulation of laboratory-developed tests such as FAMILION®.[211]

Allelic dropout is another issue that pertains to test quality. Allelic dropout is a technical problem in DNA amplification,[212] which likely contributed to the relatively low yield of LQTS mutations in the pre-Genaissance/PGxHealth era. A year after commercial launch, at a national meeting the company presented its experiences with discovery and avoidance of the allelic dropout problems present in assays used by research laboratories.[213] In late 2005, scientists from the Mayo Clinic and what was then still Genaissance submitted a paper on the allelic dropout phenomenon to a peer-reviewed journal, which appeared in 2006.[214] The recognition of allelic dropout ultimately improved the sensitivity of the test.

As for sample type, PGxHealth Chief Medical Officer Dr. Carol Reed told us via email that, "Our laboratory does and has always accepted paraffin-embedded tissue for testing, so long as it meets quality specifications."[215] Obtaining DNA from paraffin-embedded tissue can be challenging, however, because the DNA tends to be degraded. According to a recent paper from Dr. Ackerman's group, for example, DNA from such tissue should be considered "error prone and unreliable in comprehensive surveillance of sudden unexplained death-associated genes."[216] Some relatively successful protocols appear to exist, however, particularly for subsequent amplification of shorter DNA fragments,[217] although this may not be

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[208] Report of the Secretary's Advisory Committee on Genetics H, and Society, U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services. (Bethesda, MD, 2008).
[209] See http://www.geneticalliance.org/policy.clia.letter (last accessed on 7 October 2008)
[210] Reed C, "Email from Carol Reed, MD." 2008.
Ackerman MJ, "Email from Michael J. Ackerman, MD, PhD." 2008.
[211] Clinical Data, Inc. Reaffirms Support for Current Regulation of Laboratory-Developed Tests. *Business Wire* 16 December 2008.
[212] Johnson PC, Haydon DT. Maximum-likelihood estimation of allelic dropout and false allele error rates from microsatellite genotypes in the absence of reference data. *Genetics* 2007. 175, (2): 827-42.
[213] Tester DJ, Will ML, Salisbury BA, Carr JL, Schulz V, Judson RS, Ackerman MJ. Allelic drop-out in long QT syndrome genetic testing: a possible mechanism underlying false negative results. *Abstract presented at Heart Rhythm Society Meeting* May 2005.
[214] Tester DJ, Cronk LB, Carr JL, Schulz V, Salisbury BA, Judson RS, Ackerman MJ. Allelic dropout in long QT syndrome genetic testing: a possible mechanism underlying false-negative results. *Heart Rhythm* 2006. 3, (7): 815-21.
[215] Reed C, "Email from Carol Reed, MD." 2008.
[216] Carturan E, Tester DJ, Brost BC, Basso C, Thiene G, Ackerman MJ. Postmortem genetic testing for conventional autopsy-negative sudden unexplained death: an evaluation of different DNA extraction protocols and the feasibility of mutational analysis from archival paraffin-embedded heart tissue. *Am J Clin Pathol* 2008. 129, (3): 391-7.
[217] Dedhia P, Tarale S, Dhongde G, Khadapkar R, Das B. Evaluation of DNA extraction methods and real time PCR optimization on formalin-fixed paraffin-embedded tissues. *Asian Pac J Cancer Prev* 2007. 8, (1): 55-9.
Gillio-Tos A, De Marco L, Fiano V, Garcia-Bragado F, Dikshit R, Boffetta P, Merletti F. Efficient DNA extraction from 25-year-old paraffin-embedded tissues: study of 365 samples. *Pathology* 2007. 39, (3): 345-8.
Santos MC, Saito CP, Line SR. Extraction of genomic DNA from paraffin-embedded tissue sections of human fetuses fixed and stored in formalin for long periods. *Pathol Res Pract* 2008. 204, (9): 633-6.
Santos S, Sa D, Bastos E, Guedes-Pinto H, Gut I, Gartner F, Chaves R. An efficient protocol for genomic DNA extraction from formalin-fixed paraffin-embedded tissues. *Res Vet Sci* 2008.

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practical for all exons in LQTS susceptibility genes.[218] Nevertheless, as Dr. Ackerman's group has recommended, given the shortcomings associated with DNA extraction from paraffin-embedded tissue, standard autopsy procedures for sudden unexplained death should include archiving preserved blood or frozen tissue to facilitate postmortem genetic testing.[219]

Adoption by Clinical Providers

We suspect that relatively few LQTS genetic tests were performed before 2004. GeneDx President Sherri Bale told us that over the course of 2001-2002, her firm ran "about 20" tests.[220] In 2002-2003, Dr. Milunsky's lab did 42.[221] After its May 2004 launch, clinical embrace of FAMILION® testing started somewhat slowly but has grown substantially in the last five years. Extrapolating from Genaissance and Clinical Data filings with the Securities and Exchange Commission, FAMILION® LQTS test demand will have increased nearly ten-fold from its launch in 2004 through Clinical Data's fiscal 2009 (ending 31 March, 2009). Genaissance reported FAMILION® revenues of $841,000 from the May 2004 launch through June 30, 2005.[222] If we assume, as Clinical Data has during investor presentations,[223] that approximately 85.7% of the revenue derived from FAMILION LQTS tests are from initial $5400 tests and the remainder is from $900 confirmatory tests of other family members, then approximately 133 initial and 133 confirmatory tests were run in the first 14 months of FAMILION® availability. More recently, FAMILION® sales grew from ~$2.7 million in fiscal 2007 to ~$4.5 million in fiscal 2008. In the first two quarters of fiscal 2009, FAMILION generated an estimated $4.1 million. [224] Thus, as of early 2009, ignoring what we suspect are modest revenues from non-LQTS FAMILION® testing and no emergence of LQTS testing from any other commercial entity in the near term, our admittedly crude estimate is that the company is on pace to perform 1270 initial tests and approximately the same number of confirmatory tests through 31 March 2009.

In 2006 clinical guidelines published by the American College of Cardiology, the American Heart Association and the European Society of Cardiology,[225] genetic testing for LQTS was deemed "very

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[218] Reed C, Salisbury B, "Written comments of Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 14 November 2008.
[219] Carturan E, Tester DJ, Brost BC, Basso C, Thiene G, Ackerman MJ. Postmortem genetic testing for conventional autopsy-negative sudden unexplained death: an evaluation of different DNA extraction protocols and the feasibility of mutational analysis from archival paraffin-embedded heart tissue. *Am J Clin Pathol* 2008. 129, (3): 391-7.
[220] Bale S, "Email from Sherri Bale regarding GeneDx's LQTS prenatal diagnosis policy in 2002." 2008.
[221] Milunsky A, "Email from Aubrey Milunsky, MB.B.Ch., D.Sc., F.R.C.P., F.A.C.M.G., D.C.H." 17 November 2008.
[222] Genaissance Pharmaceuticals, *10-Q*, 9 August 2005. See: http://www.sec.gov/Archives/edgar/data/1110009/000110465905037531/a05-13057_110q.htm, [accessed 24 September 2008].
Genaissance Pharmaceuticals, *10-K*, 15 March 2005. See: http://www.sec.gov/Archives/edgar/data/1110009/000104746905006537/a2152822z10-k.htm, [accessed 24 September 2008].
[223] Clinical Data, *EX-99.1 of 8-K*, 18 January 2007. See: http://www.sec.gov/Archives/edgar/data/716646/000095013507000224/b63771cdexv99w1.htm, [accessed 6 June 2008].
[224] See http://www.clda.com/uploads/CLDA_Q2-09%2011-3-08FINAL.pdf [accessed November 4, 2008].
[225] Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, Gregoratos G, Klein G, Moss AJ, Myerburg RJ, Priori SG, Quinones MA, Roden DM, Silka MJ, Tracy C, Smith SC, Jr., Jacobs AK, Adams CD, Antman EM, Anderson JL, Hunt SA, Halperin JL, Nishimura R, Ornato JP, Page RL, Riegel B, Blanc JJ, Budaj A, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo JL, Zamorano JL. ACC/AHA/ESC 2006 Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: a report of the American College of Cardiology/American Heart

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important" for identifying all affected members within a family. In patients affected by LQTS, genetic analysis was considered "useful for risk stratification and for making therapeutic decisions." In an interview with us, Dr. Towbin thought the 2006 guidelines were somewhat inadequate given how new and poorly understood genetic testing was when those guidelines were written; he noted that the Heart Rhythm Society is preparing new guidelines.[226]

There is ample room for further growth in genetic testing for LQTS. In a January 2007 presentation to investors made by Clinical Data,[227] the company estimated there to be a $94.5-million market for initial LQTS genetic screening ($81 million) and subsequent mutation screening within families ($13.5 million).

Consumer Utilization

We can only speculate about whether the patent enforcement actions of the early 2000s adversely affected consumer access to commercial genetic testing for LQTS. The overall number of LQTS patients affected by the patent enforcement actions was probably small: According to Dr. Towbin, there was minimal awareness of genetic testing and poor understanding of LQTS genetics at the time. "In 2002, nobody took DNA Sciences or anyone else seriously as purveyors of a LQTS diagnostic test, in part because they themselves didn't: They weren't advertising, they didn't have buy-in, and [they] were talking about testing for *specific* mutations, which didn't make sense."[228]

PGxHealth does not offer prenatal diagnosis, thereby rendering it commercially unavailable in the U.S. When asked about the subject, PGxHealth's Drs. Reed and Salisbury cited "technical concerns" and "very little demand" given the treatable nature of LQTS. They said that while the company does not have an official policy regarding prenatal diagnosis, Drs. Reed and Salisbury's advice to the company would be "not to enforce the patent" for such uses.[229] GeneDx did offer prenatal testing for LQTS in 2002; however, it was offered only in cases where another family member was known to carry a mutation (Appendix 8).[230] In separate interviews, Drs. Moss and Antzelevitch (Masonic Medical Research Laboratory) cautioned us not to overstate the importance of prenatal diagnosis.[231] Both researchers said that prenatal diagnosis would be of limited usefulness given the highly variable phenotype: an infant may harbor a mutation and go on to live a long and healthy life.[232] Dr. Milunsky views the situation

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Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (writing committee to develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation* 2006. 114, (10): e385-484.

[226] Towbin JA, "Interview with Jeffrey A. Towbin, MD, chief of pediatric cardiology, Baylor College of Medicine." 29 September 2008.

[227] Clinical Data, *EX-99.1 of 8-K*, 18 January 2007. See: http://www.sec.gov/Archives/edgar/data/716646/000095013507000224/b63771cdexv99w1.htm, [accessed 6 June 2008].

[228] Towbin JA, "Interview with Jeffrey A. Towbin, MD, chief of pediatric cardiology, Baylor College of Medicine." 29 September 2008.

[229] Reed C, Salisbury B, "Interview with Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 12 June 2008.

[230] Bale S, "Email from Sherri Bale regarding GeneDx's LQTS prenatal diagnosis policy in 2002." 2008.

[231] Antzelevitch C. Interview with Charles Antzelevitch, Ph.D., F.A.C.C., F.A.H.A., Executive Director and Director of Research of the Masonic Medical Research Laboratory (MMRL) 2 July 2008. Moss AJ, "Interview with Arthur J. Moss, MD, research physician at the University of Rochester." 28 August 2008.

[232] Moss AJ, "Interview with Arthur J. Moss, MD, research physician at the University of Rochester." 28 August 2008.
Antzelevitch C. Interview with Charles Antzelevitch, Ph.D., F.A.C.C., F.A.H.A., Executive Director and Director of Research of the Masonic Medical Research Laboratory (MMRL) 2 July 2008.

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differently. He told us that: (1) some families are indeed interested in prenatal diagnosis; (2) distinguishing fetal from maternal DNA is a trivial technical issue that all prenatal diagnostic laboratories must contend with; (3) Clinical Data will not perform prenatal diagnosis; and (4) company representatives made it clear that Clinical Data will not permit his (Milunsky's) laboratory to perform it under any circumstances.[233] Dr. Bale (like Dr. Milunsky, a former and would-be competitor to PGxHealth) agrees with Dr. Milunsky that families are interested in prenatal diagnosis and that distinguishing maternal from fetal DNA is not a major technical barrier.[234]

Consumers pay different prices for FAMILION® testing based on what fraction of the $5400 cost of the test is covered by insurance. Research labs charge nothing; however, it may take many months or even years before patients receive their results from research labs.[235] In some cases, patients may never receive their results and the quality may be sub-standard.[236] Indeed, non-CLIA-certified laboratories are restricted by law from providing results of testing to the patient or referring physician.[237]

Our own informal collation of consumer views of LQTS testing culled from the online C.A.R.E. Cardiac Arrhythmias Support Community[238] suggests that LQTS patients want information about their condition, including genetic information. Many are understandably frightened by the prospect of sudden cardiac death and are concerned about potential triggers for such events. As far as we can tell, out-of-pocket cost is the most significant deterrent to consumer utilization, although several patients complained about the turnaround time and the time necessary to negotiate insurance coverage. A summary of our very preliminary findings from the C.A.R.E. forum appears below. It is important to note the caveats: all data are self-reported and the sample size is minimal. This is a convenience sample of motivated forum participants, not a representative sample of the general population. We take up the payment issue in the next section on *Adoption by third-party payers.*

C.A.R.E. Cardiac Arrhythmias Support Community LQTS Genetic Testing Data

1. When was your test performed?

Year:	2000	2006	2007	2008	Unknown
Number:	1	1	8	3	5

[233] Milunsky A, "Interview with Aubrey Milunsky, MB.B.Ch., D.Sc., F.R.C.P., F.A.C.M.G., D.C.H., Director of Boston University's Center for Human Genetics." 29 May 2008.
Milunsky A, "Interview with Aubrey Milunsky, MB.B.Ch., D.Sc., F.R.C.P., F.A.C.M.G., D.C.H., Director of Boston University's Center for Human Genetics: Review of case study." 2008.
[234] Bale S, "Written comments of Sherri Bale, PhD, President and co-founder of GeneDx." 12 November 2008.
[235] Priori S, "Interview with Silvia G. Priori, MD, PhD, LQTS researcher and clinician in Pavia, Italy." 29 May 2008.
Moss AJ, "Interview with Arthur J. Moss, MD, research physician at the University of Rochester." 28 August 2008.
[236] Towbin JA, "Interview with Jeffrey A. Towbin, MD, chief of pediatric cardiology, Baylor College of Medicine." 29 September 2008.
[237] Medicare and Medicaid programs; Medicare, Medicaid, and Clinical Laboratories Improvement Act (CLIA) patient confidentiality rules--PHS and HCFA. Final rule. *Fed Regist* 1988. 53, (232): 48645-8.
Schwartz MK. Genetic testing and the clinical laboratory improvement amendments of 1988: present and future. *Clin Chem* 1999. 45, (5): 739-45.
Rivers PA, Dobalian A, Germinario FA. A review and analysis of the clinical laboratory improvement amendment of 1988: compliance plans and enforcement policy. *Health Care Manage Rev* 2005. 30, (2): 93-102.
Bookman EB, Langehorne AA, Eckfeldt JH, Glass KC, Jarvik GP, Klag M, Koski G, Motulsky A, Wilfond B, Manolio TA, Fabsitz RR, Luepker RV. Reporting genetic results in research studies: summary and recommendations of an NHLBI working group. *Am J Med Genet A* 2006. 140, (10): 1033-40.
[238] See http://www.inspire.com/groups/care-cardiac-arrhythmias/ [accessed October 6, 2008].

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2. Who performed the test?

Lab:	PGxHealth	Research Lab	Ex-US (PGxHealth)	Unknown
Number:	12	1	2 (Canada)	3

3. How long did it take for you to receive your results?

Lab ▸	PGxHealth	Research Lab	Ex-US (PGxHealth)	Unknown
Time ▾				7
3 weeks*	2			
4 weeks	1			
5 weeks	1			
6 weeks	2		1	
7 weeks	1			
8 weeks	1			
9 weeks	2		1	
2 years		1		

*confirmation testing for additional family members

4. Was a mutation found?

Lab ▸	PGxHealth	Research Lab	Ex-US (PGxHealth)	Unknown
				8
Yes	5			
No	2	1	1	
Class III variant*	1			

*not expected to be deleterious

5. Who was your insurance carrier and what was your out-of-pocket expense for FAMILION testing*?

Insurer ▸	Blue Cross/Blue Shield	Humana	TriCare (US Military)	Canadian Provincial	Unknown
Percent coverage ▾					
100%	2		1	2	3
90%	1				
80%					1
63%					1
Unknown partial fraction	1	1			
0%	1				1

*FAMILION testing for LQTS costs $5400 for the index case and $900 to confirm the presence of a mutation in each family member.

6. Was cost a factor in your decision to get tested (or not get tested) with FAMILION?

No: 7

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Yes: 6
No answer/not clear: 5

The lone study that modeled the cost-effectiveness of genetic testing for LQTS concluded that it is indeed cost-effective when compared to no testing.[239] It should be noted, however, that some funding for this 2005 study was provided by Genaissance through independent consulting contracts to two co-authors, Drs. Phillips and Ackerman.[240] There has been no systematic study of either clinicians' or payers' considerations of cost as part of their LQTS diagnostic heuristics.

The insurance and employment provisions of the Genetic Information Nondiscrimination Act of 2008 will take effect in 2009 and 2010. This may affect utilization of genetic testing.[241]

Adoption by third party payers

According to the PGxHealth website, [242] there were ten commercial payers with coverage policies supportive of FAMILION® testing as of August 2008. These were Aetna, Harvard Pilgrim, BCBS in 16 states (AK, AL, AR, HI, ID, IL, MI, MS, NJ, NM, NY, OK, SD, TN, TX, WA), Cigna, Coventry Health Care, HIP Plan of NY, Health Net, Inc., Humana, Select Health, and Tufts Health. Among government payers with favorable coverage policies, on its website PGxHealth cited: (1) TRICARE[243]; and (2) Medicaid in 38 states and the District of Columbia (the company has applied for Medicaid coverage in all U.S. state and territorial Medicaid jurisdictions). FAMILION® testing was not covered by New York State Medicaid until the spring of 2008. Coverage followed a segment on *Good Morning America* highlighting the gap in coverage and its potentially adverse effect on a young LQTS patient of Dr. Chung's.[244] In October 2008, PGxHealth announced that it had become an in-network provider for Aetna's healthcare coverage of FAMILION® tests.[245]

Former Genaissance CSO Dr. Richard Judson told us that, at least initially, "Medicaid's reimbursement rate was so low that it would not begin to cover the cost of the test. It was unfortunate. This is a disease typically diagnosed in childhood and there are lots of children on Medicaid."[246] Dr. Milunsky's lab did accept Medicaid, though he called Medicaid payments "pathetic."[247]

Each of the patent licensees emphasized the difficulty in gaining payer acceptance of the test. At the time of the sale of DNA Sciences' assets to Genaissance, DNA Sciences was negotiating with several private insurers. This process included assembly of a 100- to 150-page package that was meant to justify the cost of the test to potential payers.[248] Dr. Judson said the bar was higher for new, complex tests. "Because

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[239] Phillips KA, Ackerman MJ, Sakowski J, Berul CI. Cost-effectiveness analysis of genetic testing for familial long QT syndrome in symptomatic index cases. *Heart Rhythm* 2005. 2, (12): 1294-300.
[240] Ibid.
[241] Slaughter LM. The Genetic Information Nondiscrimination Act: why your personal genetics are still vulnerable to discrimination. *Surg Clin North Am* 2008. 88, (4): 723-38, vi.
[242] See http://www.pgxhealth.com/genetictests/familion/patients/insurance.cfm [accessed October 6, 2008].
[243] TRICARE is the Department of Defense's health care program for members of the uniformed services, their families and survivors (see http://www.military.com/benefits/tricare [accessed January 12, 2009]).
[244] See http://abcnews.go.com/GMA/OnCall/story?id=4358619&page=1 [accessed October 22, 2008].
[245] Clinical Data, Inc. Signs Contract with Aetna for In-network Coverage of FAMILION® Genetic Tests for Inherited Cardiac Syndromes. *Business Wire* 27 October 2008.
[246] Judson R, "Interview with Richard Judson, PhD, former CSO of Genaissance Pharmaceuticals." 9 July 2008.
[247] Milunsky A, "Interview with Aubrey Milunsky, MB.B.Ch., D.Sc., F.R.C.P., F.A.C.M.G., D.C.H., Director of Boston University's Center for Human Genetics." 29 May 2008.
[248] Lehrer S, "Interview with Steve Lehrer, former CEO of DNA Sciences." 27 June 2008.

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there are hundreds of individual insurance companies in the U.S., novel tests can require hundreds of individualized cases to be made for initial acceptance. The more complex a test is (and hence the more expensive), the longer it takes for acceptance."[249] In his letter to Congressman Berman, Clinical Data CEO Drew Fromkin said that anyone providing diagnostic services knows that "…health insurer coverage for lab tests is a long and difficult road and it takes many years for any novel test to gain significant coverage."[250] According to Clinical Data, between January and October 2008 FAMILION® payer coverage increased from 55 million to 155 million lives, including Medicaid coverage increasing from 7 to 37 states during the same period.[251]

The clinicians and researchers we interviewed all said they try to make testing available to those who cannot afford it. Dr. Ackerman described a "gentleman's agreement" with PGxHealth whereby if an insurer denies payment, he will offer a charity waiver.[252] Dr. Priori provides free testing to patients from developing countries.[253] Drs. Moss and Antzelevitch will enroll patients in research studies.[254] Dr. Chung will try multiple strategies, including shopping around for insurance, pooling family resources, and enrolling patients in research studies.[255] It is important to note again that while the research option is free, it is also very likely to mean a lengthy wait for the patient. And Dr. Towbin worries that in the current fiscal environment, research laboratories will not be able to continue providing complimentary LQTS genetic testing *ad infinitum*.[256]

Summing Up

Genetic testing for LQTS is a complex story that illustrates several features relevant to clinical access to genetic testing in general. Some of the complexity is biological: the clinical syndrome is uncommon but not rare. The mutations causing it are found in a multitude of genes. Sequencing the five genes most commonly mutated accounts for an estimated 75% of cases, but beyond those, there are many variants that truly are rare.

The intellectual property overlay of this biological story is also complex. It started with aggregation of the three initial patents by a single firm that "cleared the market" of testing services offering partial LQTS testing, but went bankrupt before it offered a test itself. Its rights were acquired by a second firm that introduced FAMILION®, which was in turn sold to Clinical Data, Inc., which continues to offer it through its subsidiary, PGxHealth. This was, and for now remains, the main provider of testing in the

[249] Judson R, "Genetic Diagnostic Notes." 2008.
[250] Fromkin AJ, "Letter to the Honorable Howard L. Berman from Clinical Data CEO Andrew J. Fromkin." 1 April 2008.
[251] Clinical Data, Inc. Signs Contract with Aetna for In-network Coverage of FAMILION® Genetic Tests for Inherited Cardiac Syndromes. *Business Wire* 27 October 2008.
[252] Ackerman MJ, "Interview with Michael J. Ackerman, MD, director of the Sudden Death Genomics Laboratory at the Mayo Clinic." 2008.
[253] Priori S, "Interview with Silvia G. Priori, MD, PhD, LQTS researcher and clinician in Pavia, Italy." 29 May 2008.
[254] Moss AJ, "Interview with Arthur J. Moss, MD, research physician at the University of Rochester " 28 August 2008.
Antzelevitch C. Interview with Charles Antzelevitch, Ph.D., F.A.C.C., F.A.H.A., Executive Director and Director of Research of the Masonic Medical Research Laboratory (MMRL) 2 July 2008.
[255] Chung W, "Interview with Wendy Chung, MD, PhD, pediatrician, geneticist and researcher at Columbia University." 7 May 2008.
[256] Towbin JA, "Interview with Jeffrey A. Towbin, MD, chief of pediatric cardiology, Baylor College of Medicine." 29 September 2008.

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United States, although some research laboratories do offer testing for indigent patients, for those with rare variants not found by FAMILION®, and perhaps in other circumstances.

BioReference Laboratories, Inc. has quietly accumulated some exclusive patent rights of its own, and is explicit in wanting to use them strategically to change the market dynamics of LQTS testing. This legal situation is unstable, and so the clinical testing situation may change. This case shows both how exclusive licensing can enable a single provider to "own" genetic testing for an entire clinical syndrome by holding rights to the most common patented variants, and leveraging those rights to cover unpatented variants and variants never before discovered. Yet it also illustrates the vulnerability of this strategy to a competitor that acquires countervailing exclusive rights. That is the situation that was unfolding for LQTS testing as this case study was being prepared.

The case also illustrates the fact that coverage decisions by insurers and health plans, and the level of reimbursement payments are arguably larger and more pervasive problems for clinical access to genetic testing than patent status. On the other hand, exclusive patent rights appear also to have contributed to relatively high pricing for LQTS testing (the truth of this statement may become more apparent if more than one provider emerges, although oligopolistic pricing would also reflect a patent premium).

In some ways, this case is simpler than others that could follow. Most of the key patents were licensed by a single institution, the University of Utah, which has now exclusively licensed rights to different mutations to two different firms. If there were multiple patent-holders, then even more parties, with potentially different stakes, would be involved in the negotiations.

Finally, the case illustrates how complex and pervasive the financial connections are. The community of clinical experts is fairly small, and its members respect one anothers' clinical expertise. They disagree about best practices, particularly regarding exclusive licensing of university-based patents involved in genetic testing, and their positions do map to their financial arrangements (although causality could be in both directions—those most trusting of a company's practices are apt to consult for it). Those without financial ties acknowledge the value of commercial testing, but also worry about high prices limiting access and the importance of having alternative sources because even high-quality laboratories make mistakes, and the system needs to have checks and balances. We find no consensus among the clinical experts most familiar with the medical consequences of testing, dominated until very recently by a single-provider commercial model, whether the current model is a net social benefit or a problem.

Finally, the case study shows the technological instability of current protocols for genetic testing. If full-genome sequencing becomes feasible in the next few years, and if its price comes into the same range as the $5,400 FAMILION® test, as seems likely, then the intellectual property consequences will become even more complex. The question of patent infringement will turn on the precise language of relevant patents, how courts interpret those claims, and the business decisions of patent holders with claims on DNA sequences and their clinical interpretation. The choice of total genomic sequencing could be either an alternative to testing for a particular syndrome, or full-genome sequencing could become the first step in a clinical decision tree that reduces the role of boutique genetic testing to confirming mutations provisionally detected. This would be a profound perturbation of the current business models. More over genome sequencing will almost certainly lead to a dramatic increase in the number of reported variants in cardiac ion-channel genes that are deemed to be "of unknown significance". This is likely to exacerbate existing problems of variant interpretation by orders of magnitude.

The current mutually blocking IP of two competing firms has yet to be resolved, and the future promises to add further layers of uncertainty regarding both intellectual property and technological options for genetic testing.

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FAMILION®
GENETIC TESTS FOR INHERITED CARDIAC SYNDROMES

Technical Specifications August 2008

The results of these tests should be interpreted and utilized after review of the following specifications:

Indications

These tests are indicated for individuals with suspected Familial Long QT Syndrome (LQTS), Brugada Syndrome (BrS), Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT), Hypertrophic Cardiomyopathy (HCM), and related syndromes, or for family members of individuals who have tested positive for a genetic variant associated with one of these conditions. These tests identify genetic variants in genes in which mutations have been shown to cause or create susceptibility to these syndromes.

Description of Genetic Assays

The *FAMILION* tests include 5 testing options. The first 4 options are index tests, which include comprehensive sequence determination and variant detection in open reading frame and intronic sequences containing splice junction sites for the included exons.

1. LQTS Test. Provides analysis covering all exons (73 amplicons) of five genes associated with LQTS as follows and is indicated for cases of suspected Long QT Syndrome: *KCNQ1* (LQT1), *KCNH2* (LQT2), *SCN5A* (LQT3), *KCNE1* (LQT5), and *KCNE2* (LQT6) and other syndromes attributed to mutations in these genes.

2. BrS Test. Provides analysis covering all exons (34 amplicons) of the gene *SCN5A* (BrS1) and is indicated for cases of suspected Brugada Syndrome and other syndromes attributed to mutations in *SCN5A*.

3. CPVT Test. Provides analysis covering selected exons (41 amplicons) of the gene *RYR2* (CPVT1) and is indicated for cases of suspected Catecholaminergic Polymorphic Ventricular Tachycardia. The following 38 exons are covered, which includes all those in which CPVT-associated mutations have been reported as of April, 2008, and others that are adjacent: 3, 8-15, 37, 41, 44-50, 83, 87-105.

4. HCM Test. Provides analysis covering all exons (113 amplicons) of nine genes associated with HCM as follows and is indicated for cases of suspected Hypertrophic Cardiomyopathy: *ACTC, MYBPC3*, *MYH7*, *MYL2*, *MYL3*, *TNNT2*, *TNNI3*, *TNNC1*, and *TPM1*.

5. Family Specific Test. Provides analysis of one or more Class I or II variants (see below) found in an index case and is indicated for testing blood-relatives. Includes sequence determination and variant detection in the gene region(s) in which mutation(s) were detected in the index case for the family. If additional mutations or variants are found in the Family Specific Test, these will also be reported.

Description of Methods

1. Sample acquisition: An 8 ml blood sample in two (2) 4 ml EDTA tubes provided in the sample collection kit is required and shipped overnight at room temperature to the test laboratory. Genomic DNA is isolated from fresh whole blood. Bar codes on each tube provide sample tracking. DNA, frozen blood, and frozen and paraffin-embedded tissue samples are also accepted if they meet specific requirement criteria. Please contact our Customer Service Department to discuss these criteria.

2. DNA Sequence Analysis: DNA amplification by polymerase chain reaction (PCR) is used to generate templates for direct sequencing. A number of PCR amplicons are utilized to obtain coverage of the complete open reading frame, splice junction sites and flanking regions for the targeted regions of each gene. Directed sequencing is performed in both forward and reverse directions using dye-terminator chemistries for all regions except for those regions that, due to constraints within the particular DNA sequence, are amplified twice and then sequenced in a single direction. Automated electrophoretic separation of sequencing reactions is performed.

3. Variant Detection: Sequence traces are analyzed for heterozygous or homozygous variants with respect to public reference sequences that have been confirmed by sequencing hundreds of individuals of diverse ancestry. For each amplicon, the analysis employs reference traces that were generated using the same protocol as the patients' traces. Sequence traces are computationally and visually compared with reference traces to identify and validate variant calls. In order to be analyzed, each trace must meet rigorous quality standards. Two technologists independently score all traces for variants and a supervisor reconciles discrepancies.

4. Report Generation: Class I, II, and III variants, as defined below, are reported. The final report is reviewed and signed by a CLIA licensed Laboratory Director.

Performance Characteristics

1. Analytical Specificity (Index Tests): The chance of a falsely detected genetic variant is minimized by requiring that each variant be seen in independent sequence traces and that two trained technicians independently examine each trace. For each positive finding of a Class I or Class II variant (see definitions below), a second round of PCR amplification and sequencing is performed to confirm the initial finding. Chances of false positives are further minimized by using a validated sample tracking system involving robotics and barcodes.

2. Analytical Sensitivity (Index Tests): Failure to detect a variant in an analyzed amplicon could be due to an amplicon being refractory to analysis by direct DNA sequencing, sample mishandling, sample tracking errors or errors in data analysis. The rate of such errors is estimated to be < 1%.

3. Clinical Sensitivity: It is estimated that detectable variants in these gene panels respectively account for 60-80% of LQTS, 15-30% of Brugada Syndrome, 50-55% of CPVT, and 50-60% of HCM (Tester et al. Heart Rhythm 2:507-517, 2005; Napolitano and Priori. Heart Rhythm 4:675-678, 2007; Taggart et al. Circulation 115:2613-2620, 2007; Keren et al. Nature Clinical Practice Cardiovascular Medicine 5:158-68, 2008.).

4. Clinical Specificity: It is estimated that 5% of apparently unaffected individuals test positive for a possible or probable deleterious mutation in one of the five LQTS genes, approximately 3% in *SCN5A* alone, 3% for CPVT, and a few percent for HCM (Ackerman et al. Mayo Clinic Proceedings 78:1479-1487, 2003; Ackerman et al. Heart Rhythm 1:600-607,

2004; Tester et al. Circulation 112:II-516, 2005). Therefore, comprehensive clinical evaluation is strongly recommended to direct treatment decisions for both positive and negative test results.

5. Family Specific Test: The analytical sensitivity, analytical specificity, and clinical sensitivity of these analyses are all approximately 100%.

6. Limitations: There may be amplicons for which it is not possible to generate traces in both directions. These tests will not detect large DNA rearrangements or deletions and will not detect errors in RNA transcription or processing that are unrelated to coding sequence variants of DNA exons. The tests will not detect mutations in non-targeted exons, nor in exons that belong to alternate transcripts. For many of these syndromes, mutations in other genes have been rarely implicated as causative but are not tested in these analyses.

Variant Classification and Interpretation

DNA variants are identified and classified by comparison with reference sequences and the PGxHealth Variant Database. This database is produced through review of published literature and through results of PGxHealth's sequencing. This database also contains an extensive collection of common polymorphisms and rare variants in these genes that are not expected to confer susceptibility to congenital arrhythmia syndromes; these variants were found in comprehensive scanning of the genes in several hundred individuals of diverse race and ethnicity or from study of the literature, together referred to as the "Reference Panel", which differs in composition across the tested genes. The healthy individuals in the Reference Panel were not known to have inherited cardiac syndromes (Ackerman et al. Mayo Clin Proc 78:1479-1487, 2003; Ackerman et al. Heart Rhythm 1:600-607, 2004). An expert scientist ensures variant classification and interpretation reflect current, published information.

Each variant that is detected is categorized into one of 4 classes. These classes and classification rules are described below. Based on additional evidence, rare exceptions may be made and will be noted in the test report. *Note:* These classes should not be confused with the designations such as LQT1, LQT2, LQT3, etc., which relate to the syndrome and affected gene.

CLASS I: Deleterious and Probable Deleterious Mutations

LQTS and BrS Tests

1. Evidence of deleteriousness
2. Nonsense variant
3. Missense single nucleotide variant not seen in the Reference Panel in transmembrane-spanning domain or pore
4. Insertion or deletion
   a. Frameshift variant
   b. In-frame variant in transmembrane-spanning domain or pore

CPVT and HCM Tests

1. Evidence of deleteriousness
2. Nonsense variant
3. Insertion or deletion causing a frameshift

CLASS II: Possible Deleterious Mutations (Variants of Uncertain Significance)

LQTS and BrS Tests

1. Missense single nucleotide variant not seen in the Reference Panel and not in transmembrane-spanning domain or pore
2. Missense single nucleotide variant seen in the Reference Panel with allelic frequency < 0.5%, but with published evidence of deleteriousness
3. In-frame insertion or deletion not in transmembrane-spanning domain or pore
4. Predicted splice site variant

CPVT and HCM Tests

1. Missense single nucleotide variant not seen in the Reference Panel
2. Missense single nucleotide variant seen in the Reference Panel with allelic frequency < 0.5%, but with published evidence of deleteriousness
3. In-frame insertion or deletion
4. Predicted splice site variant

CLASS III: Polymorphisms (Variants Not Generally Expected to be Deleterious)

1. Protein-altering variant seen in the Reference Panel with either
   a. Common frequency (≥ 0.5%) or
   b. Rare frequency (< 0.5%) and without published evidence of deleteriousness

CLASS IV: Non-Protein-Altering Variants

All non-coding and synonymous variants (no changes in encoded amino acid) except those predicted to affect intron splicing, which are categorized as Class II Mutations (splice variants). These variants do not alter the protein coding sequence. Because of the lack of known or suspected clinical significance, these variants are not reported.

Recommendation for family member testing: In cases where a Class I or Class II mutation is found, a recommendation for clinical evaluation and genetic testing of first-degree blood relatives will be included in the report.

Change of interpretation and amended reports: If there is a change in the clinical interpretation of a reported variant, an amended test report will be generated and provided to the referring physician, when possible. A change in interpretation may be due to new evidence that indicates a variant is more or less likely to be deleterious than indicated by evidence existing at the time of initial reporting.

Laboratory: The *FAMILION* tests are performed by PGxHealth, LLC, 5 Science Park, New Haven, CT 06511. The U.S. Food and Drug Administration (FDA) has not approved these tests; however, FDA approval is not currently required for clinical use of these tests. These tests meet the requirements for high complexity tests under the Clinical Laboratory Improvement Amendments Act and its implementing regulations.

Appendix 2

FAMILION®
GENETIC TESTS FOR INHERITED CARDIAC SYNDROMES

LQTS Test Report
(CONFIDENTIAL)

PHYSICIAN	SPECIMEN	PATIENT
Physician's Name:	Specimen Type: Blood	Patient's Name:
Hospital/Institution:	Draw Date:	Date of Birth:
Mailing Address:	Receive Date:	Patient ID:
	Report Date:	Gender: M
		Requisition #:

TEST RESULTS

This individual is positive for the deleterious mutation KCNH2 Gly 657 Ser.

INTERPRETATION

KCNH2 Gly 657 Ser - Deleterious Mutation Found: This test result indicates the presence of the genetic mutation KCNH2 Gly 657 Ser. This mutation is a Class I variant, meaning it has either been functionally characterized as abnormal or is otherwise strongly expected to cause a familial arrhythmia-causing syndrome: Type 2 Long QT Syndrome (LQT2)(Hardman et al., J Biol Chem. 2007 Nov 2;282(44):31972-81. Epub 2007 Sep 6. (17823114)). Comprehensive clinical evaluation is strongly recommended to direct treatment decisions.

Based upon this test result, all first-degree relatives of this patient (offspring, siblings, parents) should undergo a careful clinical evaluation that includes a screening electrocardiogram and genetic testing to determine the presence or absence of this specific mutation. Evaluation, including genetic testing of extended relatives (second-degree relatives: grandparents /aunts /uncles /nieces /nephews; third-degree relatives such as cousins, great aunts/uncles, etc. and beyond), should be directed based upon the family history or guided by transmission pattern established following genetic test results of first-degree relatives. For example, if this mutation is detected in an affected individual's mother but not in the father, then all of the mother's first-degree relatives should receive thorough evaluation whereas the paternal side of the family would require no further evaluation.

To order the FAMILION Family Specific Test for family members of this patient, use the following Family Specific Code:

GPI-_____

This code must be included on the FAMILION Test Requisition/Payment Authorization Form (Form A) for the Family Specific Test.

Polymorphism(s) Found: This test result indicates identification of one or more genetic variants that have been identified previously in normal subjects and are considered polymorphisms (Class III variants). These variants are not likely arrhythmia syndrome-causing variants. Family screening for the presence of class III variants is not recommended.

PGxHealth 5 Science Park New Haven, Connecticut 06511 866.326.4546

Continuation of Report

Patient Name:

RESULTS SUMMARY

Num	Gene	Region(G)	Nucl. Change	A.A. Change	Genotype	Region(P)	Region Type(P)	Class
1	KCNH2	exon 8	1969 G>A	Gly 657 Ser	G/A	S6	Transmembrane	I
2	KCNE1	exon 4	112 G>A	Gly 38 Ser	G/A	N-Terminal	N-Terminal	III
3	KCNH2	exon 11	2690 A>C	Lys 897 Thr	C/C	C-Terminal	C-Terminal	III

All Regions of Interest (100%) were successfully sequenced in the FAMILION Comprehensive Test for the genes KCNQ1 (LQT1), KCNH2 (LQT2), SCN5A (LQT3), KCNE1 (LQT5), KCNE2 (LQT6). Class IV variants, those genetic variants that are not expected to have any effect on the encoded protein, are not reported.

Limitations: This assay will not detect large DNA rearrangements or deletions and will not detect all errors in the RNA transcription or processing which are unrelated to coding sequence variants of DNA exons. Interpretation and classification of variants are subject to change in light of new evidence.

Methods: Genomic DNA was amplified by polymerase chain reaction to generate templates for direct sequencing of the complete open reading frame, splice junctions, and flanking regions of the genes KCNQ1, KCNH2, SCN5A, KCNE1, and KCNE2. See technical specifications for details.

These test results should only be used in conjunction with the patient's clinical history and any previous analysis of the appropriate family members. It is strongly recommended that these test results be communicated to the patient in a setting that includes appropriate counseling. The results of this test are not intended to be used as the sole means for patient diagnosis or patient management decisions. The test was developed and its performance characteristics determined by Cogenics. The U.S. Food and Drug Administration (FDA) has not approved this test; however, FDA approval is not currently required for clinical use of this test. This test meets the requirements for high complexity tests under the Clinical Laboratory Improvement Amendments Act and its implementing regulations.

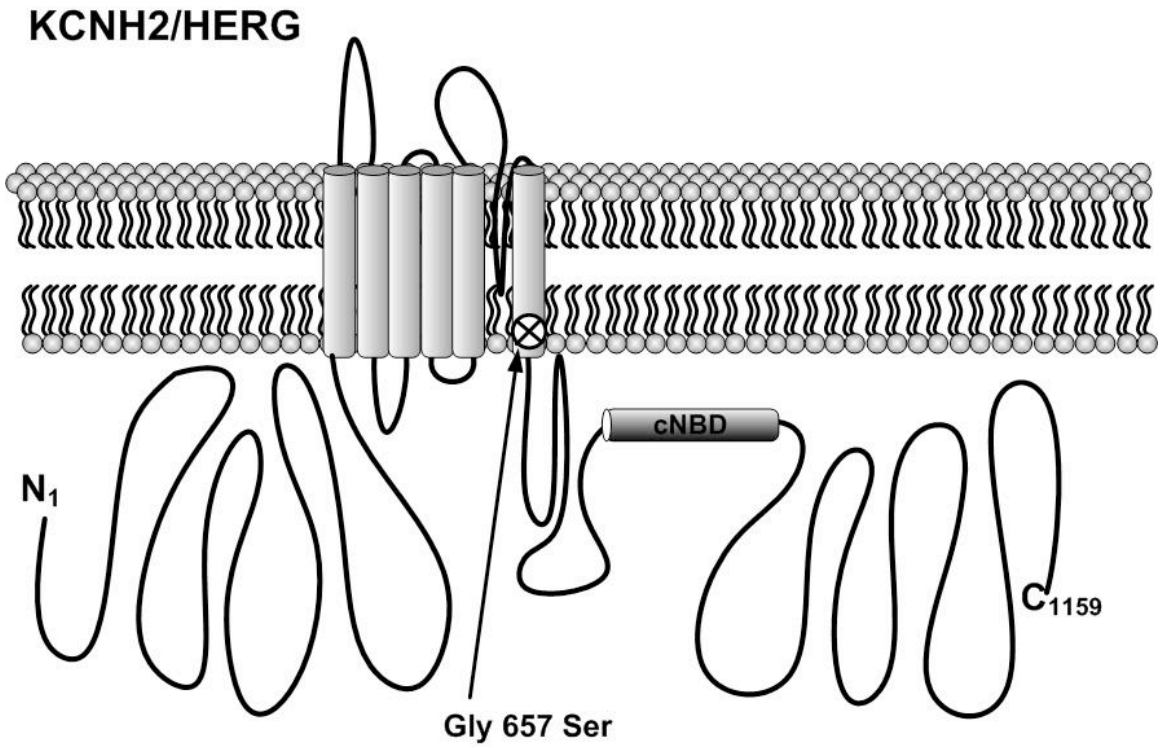
Authorized Signature:

Patricia D. Murphy, Ph.D., FACMG, Laboratory Director
Jessica K. Booker, Ph.D., FACMG, Associate Laboratory Director

X _____

This test is performed by Cogenics, Inc. , 5 Science Park, New Haven, CT 06511
CT License Number: CL-0633 CLIA Number: 07D0995237

Continuation of Report Patient Name:



PGxHealth 5 Science Park New Haven, Connecticut 06511 866.326.4546

Appendix 3

LQTS Test Report
(CONFIDENTIAL)

PHYSICIAN	SPECIMEN	PATIENT
Physician's Name:	Specimen Type: Blood	Patient's Name:
Hospital/Institution:	Draw Date:	Date of Birth:
	Receive Date:	Patient ID:
Mailing Address:	Report Date:	Gender: F
		Requisition #:

TEST RESULTS

This individual is positive for the possible deleterious mutation KCNQ1 Lys 362 Arg.

INTERPRETATION

KCNQ1 Lys 362 Arg - Possible Deleterious Mutation Found: This test result indicates the presence of the genetic mutation KCNQ1 Lys 362 Arg. This mutation is a Class II variant, meaning it is a type that may have the potential to cause a familial arrhythmia-causing syndrome: Type 1 Long QT Syndrome (LQT1) (Tester et al., Heart Rhythm. 2005 May;2(5):507-17 (15840476)). However, approximately 5% of reported healthy volunteers have been found to possess class II mutations. Therefore, extreme caution and comprehensive clinical evaluation are advised with respect to the incorporation of this variant information into treatment decisions.

Based upon this test result, all first-degree relatives of this patient (offspring, siblings, parents) should undergo a careful clinical evaluation that includes a screening electrocardiogram and genetic testing to determine the presence or absence of this specific mutation. Evaluation, including genetic testing of extended relatives (second-degree relatives: grandparents /aunts /uncles /nieces /nephews; third-degree relatives such as cousins, great aunts/uncles, etc. and beyond), should be directed based upon the family history or guided by transmission pattern established following genetic test results of first-degree relatives. For example, if this mutation is detected in an affected individual's mother but not in the father, then all of the mother's first-degree relatives should receive thorough evaluation whereas the paternal side of the family would require no further evaluation.

To order the FAMILION Family Specific Test for family members of this patient, use the following Family Specific Code:

GPI-_____

This code must be included on the FAMILION Test Requisition/Payment Authorization Form (Form A) for the Family Specific Test.

Polymorphism(s) Found: This test result indicates identification of one or more genetic variants that have been identified previously in normal subjects and are considered polymorphisms (Class III variants). These variants are not likely arrhythmia syndrome-causing variants. Family screening for the presence of class III variants is not recommended.

PGxHealth 5 Science Park New Haven, Connecticut 06511 866.326.4546

Continuation of Report

Patient Name:

RESULTS SUMMARY

Num	Gene	Region(G)	Nucl. Change	A.A. Change	Genotype	Region(P)	Region Type(P)	Class
1	KCNQ1	exon 8	1085 A>G	Lys 362 Arg	A/G	C-Terminal	C-Terminal	II
2	KCNE1	exon 4	112 G>A	Gly 38 Ser	A/A	N-Terminal	N-Terminal	III

All Regions of Interest (100%) were successfully sequenced in the FAMILION Comprehensive Test for the genes KCNQ1 (LQT1), KCNH2 (LQT2), SCN5A (LQT3), KCNE1 (LQT5), KCNE2 (LQT6). Class IV variants, those genetic variants that are not expected to have any effect on the encoded protein, are not reported.

Limitations: This assay will not detect large DNA rearrangements or deletions and will not detect all errors in the RNA transcription or processing which are unrelated to coding sequence variants of DNA exons. Interpretation and classification of variants are subject to change in light of new evidence.

Methods: Genomic DNA was amplified by polymerase chain reaction to generate templates for direct sequencing of the complete open reading frame, splice junctions, and flanking regions of the genes KCNQ1, KCNH2, SCN5A, KCNE1, and KCNE2. See technical specifications for details.

These test results should only be used in conjunction with the patient's clinical history and any previous analysis of the appropriate family members. It is strongly recommended that these test results be communicated to the patient in a setting that includes appropriate counseling. The results of this test are not intended to be used as the sole means for patient diagnosis or patient management decisions. The test was developed and its performance characteristics determined by Cogenics. The U.S. Food and Drug Administration (FDA) has not approved this test; however, FDA approval is not currently required for clinical use of this test. This test meets the requirements for high complexity tests under the Clinical Laboratory Improvement Amendments Act and its implementing regulations.

Authorized Signature:

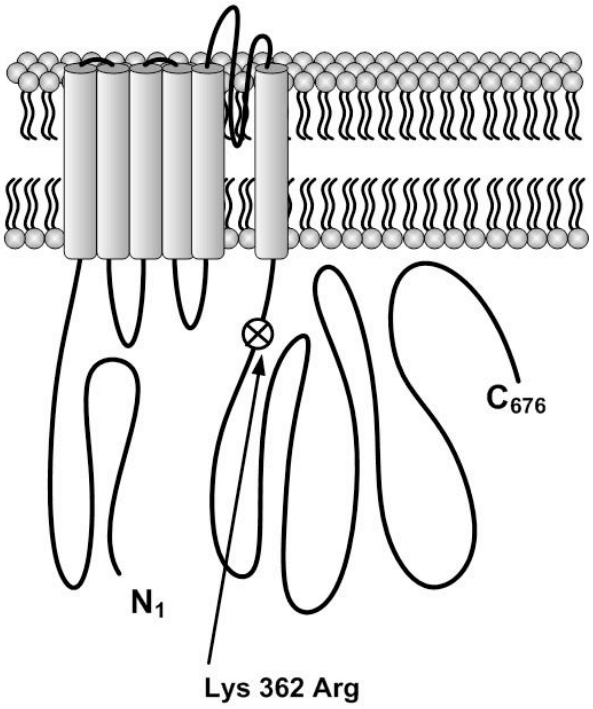
Patricia D. Murphy, Ph.D., FACMG, Laboratory Director
Jessica K. Booker, Ph.D., FACMG, Associate Laboratory Director

X _____

This test is performed by Cogenics, Inc. , 5 Science Park, New Haven, CT 06511
CT License Number: CL-0633 CLIA Number: 07D0995237

Continuation of Report Patient Name:

KCNQ1/KVLQT1



PGxHealth 5 Science Park New Haven, Connecticut 06511 866.326.4546

Appendix 4

LQTS Test Report
(CONFIDENTIAL)

PHYSICIAN	SPECIMEN	PATIENT
Physician's Name: Hospital/Institution: Mailing Address:	Specimen Type: Blood Draw Date: Receive Date: Report Date:	Patient's Name: Date of Birth: Patient ID: Gender: M Requisition #:

TEST RESULTS

This individual is negative for deleterious mutations.

INTERPRETATION

No deleterious mutations (Class I or Class II variants) were found. This result is inconclusive and DOES NOT EXCLUDE the presence of a heritable disorder predisposing to cardiac arrhythmias, as variants in genomic regions not included in this test may play a causative role in such disorders. Among patients with a high clinical index of suspicion of disease, up to 25% of patients with LQTS and 70% of patients with Brugada Syndrome do not have deleterious mutations that would be identified with this test but may have deleterious mutations in other genes or in other regions of these genes.

Polymorphism(s) Found: This test result indicates identification of one or more genetic variants that have been identified previously in normal subjects and are considered polymorphisms (Class III variants). These variants are not likely arrhythmia syndrome-causing variants. Family screening for the presence of class III variants is not recommended.

RESULTS SUMMARY

Num	Gene	Region(G)	Nucl. Change	A.A. Change	Genotype	Region(P)	Region Type(P)	Class
1*	KCNH2	exon 13	3140 G>T	Arg 1047 Leu*	G/T	C-Terminal	C-Terminal	III

**The variant Arg 1047 Leu may be a susceptibility variant in dofetilide-induced Torsades de Pointes (Sun, et al., J Mol Cell Cardiol. 2004 Nov;37(5):1031-9).*

All Regions of Interest (100%) were successfully sequenced in the FAMILION Comprehensive Test for the genes KCNQ1 (LQT1), KCNH2 (LQT2), SCN5A (LQT3), KCNE1 (LQT5), KCNE2 (LQT6). Class IV variants, those genetic variants that are not expected to have any effect on the encoded protein, are not reported.

Limitations: This assay will not detect large DNA rearrangements or deletions and will not detect all errors in the RNA transcription or processing which are unrelated to coding sequence variants of DNA exons. Interpretation and classification of variants are subject to change in light of new evidence.

PGxHealth 5 Science Park New Haven, Connecticut 06511 866.326.4546

Continuation of Report

Patient Name:

Methods: Genomic DNA was amplified by polymerase chain reaction to generate templates for direct sequencing of the complete open reading frame, splice junctions, and flanking regions of the genes KCNQ1, KCNH2, SCN5A, KCNE1, and KCNE2. See technical specifications for details.

These test results should only be used in conjunction with the patient's clinical history and any previous analysis of the appropriate family members. It is strongly recommended that these test results be communicated to the patient in a setting that includes appropriate counseling. The results of this test are not intended to be used as the sole means for patient diagnosis or patient management decisions. The test was developed and its performance characteristics determined by Cogenics. The U.S. Food and Drug Administration (FDA) has not approved this test; however, FDA approval is not currently required for clinical use of this test. This test meets the requirements for high complexity tests under the Clinical Laboratory Improvement Amendments Act and its implementing regulations.

Authorized Signature:

Patricia D. Murphy, Ph.D., FACMG, Laboratory Director
Jessica K. Booker, Ph.D., FACMG, Associate Laboratory Director

X _____

This test is performed by Cogenics, Inc. , 5 Science Park, New Haven, CT 06511
CT License Number: CL-0633 CLIA Number: 07D0995237

Appendix 5

5 Science Park
New Haven, CT 06511
P: 877.274.9432
F: 203.786.3418

March 3, 2008

Dr. XYZ
ADDRESS
CITY, STATE ZIP

Dear Dr. XYZ,

Thank you for referring your patient for the *FAMILION*® Test for cardiac ion channel mutations. Although the *FAMILION* Test did not identify any Class I or Class II mutations (see the *FAMILION* Technical Information Sheet for class definitions), this does not rule out a diagnosis of a cardiac channelopathy. In fact, based on current knowledge, approximately 25% of patients with a high index of suspicion for Long QT Syndrome (LQTS), 50% for Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) and 75% for Brugada Syndrome (BrS) will have a negative genetic test.

If your index of suspicion for an inherited heart rhythm disorder is high for this patient, research studies including mutational analysis for novel genetic mechanisms may be available. For information about current research genetic testing programs, please contact either of the following non-profit organizations that are dedicated to supporting and advocating for families with inherited heart rhythm disorders:

Cardiac Arrhythmias Research
and Education Foundation (CARE)
(800) 404-9500
STOP SADS
www.longqt.org

Sudden Arrhythmia Death
Syndromes (SADS) Foundation
(800) 786-7723 or (800)

www.sads.org

Respectfully,

Carol R. Reed, MD, FACP, FCCP
Executive Vice President and Chief Medical Officer for Clinical Data, Inc
cc: file

Patents and applications for Long QT Syndrome (LQTS) genetic testing

Syndrome**	Gene	US Patent/application No.	Assignee/ Inventor
LQT1, JLN1	KCNQ1	US6150104[&], US6277978[&], US6342357, US6451534, US6582913, US6972176[#]	University of Utah Research Foundation
LQT2	KCNH2	**US5599673**[#], **US6207383**[#], US7297489[#]	University of Utah Research Foundation
LQT3	SCN5A	US6787309, **US5599673**[#] US2004126787A1	University of Utah Research Foundation Inventors: Michael J Ackerman et al.
LQT5, JLN2	KCNE1	US6323026, **US6432644**[#], US7247436[#]	University of Utah Research Foundation
LQT6	KCNE2	US6864364	University of Utah Research Foundation
LQT7	KCNJ2	US7306911 US2005175995A1	University of Utah Research Foundation Inventors: Louis Ptacek et al. (University of Utah)
LQT8	CACNA1C	US2008118438A1*	Inventors: Charles Antzelevitch et al.

Search query sample: "long QT" <in> Claims. Additional patents and applications identified by gene names (for e.g. KCNJ2 or Kir 2.1 for LQT 7) as search terms. All patents highlighted in green are licensed to Bio-Reference Laboratories (BRLI)[1]. Patents in bold were subject of 2002 patent infringement lawsuit brought by DNA Sciences against GeneDx (see Appendix 7). **JLN1 and JLN2 = Jervell Lange-Nielsen syndrome variants; gene-syndrome correlations based on Saenen and Vrints, J Mol Cell Cardiol, 2008. 44(4): p. 633-46. [&] Patent claims are on mutations associated with JLN1 only. [#]Indicates patents that declare use of federal funds and government interest. *Indicates claims including use of microarrays for diagnostic detection.

[1]Data provided by Jorge Goldstein, Chief Counsel for BioReference Laboratories Inc. (Phone interview with Jorge Goldstein by Misha Angrist, Subhashini Chandrasekharan, Christopher Heaney, and Robert Cook-Deegan, 31 October 2008). In addition, BRLI has obtained licenses to US6274332 and US6420124 from the University of Utah Research Foundation. These patents claim methods for screening drugs that can be used to treat individuals with mutations in KCNE1 and KCNQ1 respectively. BRLI also has licensed US7208273 from the University of Utah. This patent covers the detection of SCN5A polymorphisms for diagnosing drug-induced ventricular fibrillation.

Syndromes	Genes included	Patent/ Application No.	Inventors	Title
LQTS 1, 2, 3,5,6	SCN5A,KCNQ1, KCNE1, KCNH2,	US7179597 US2005142591A1 **Error! Not a valid link.**	Raymond L Woosley (Georgetown Univ) Michael J Ackerman et al. (Mayo clinic)	Genetic diagnosis for qt prolongation related adverse drug reactions Method of genetic testing in heritable arrhythmia syndrome patient
LQT1,2,3,5, 6	SCN5A, KCNQ1, KCNE1, KCNH2, KCNE2	US7179597*	Raymond L Woosley (Georgetown Univ)	Genetic diagnosis for QT prolongation related adverse drug reactions
LQT2, LQT3, LQT1/JLN1	KCNH2, SCN5A,KCNQ1	US2005130190A1*	Charles Antzelevitch, Ramon Brugada et al. (Masonic Medical Research Lab)	Mutations in ion channel proteins associated with sudden cardiac death
LQT8 SCD	CACNA1C, CACNB2	US2008118438A1*	Charles Antzelevitch & Guido Pollevick. (Masonic Medical Research Lab)	Loss of function mutations in calcium channel polypeptides associated with sudden cardiac death
LQT3, LQT1/JLN1 LQT8	SCN5A,KCNQ1, CACNA1C	US2005287574A1	Medtronic Inc	Genetic diagnostic method for SCD risk stratification
SCD – Sudden Cardiac Death *Indicates applications and patents including claims on the use of microarrays for diagnostic detection.				

Appendix 7

Erie R. Lamison (State Bar No. 178262)
KIRKLAND & ELLIS
777 S. Figueroa Street
Los Angeles, California 90017
Telephone: (213) 680-8400
Facsimile: (213) 680-8500

MarkA.Pa1s
Lauren Hennessey Breit
KlRKLAND & ELLIS
200 East Rundolph Drive
Chicago,l1Iillois 60601
Telephone: (312) 861-2000
Facsimile: (312) 861-2200

FILED

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RICHARD W. WIEKING
CLERK, U.S. DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

E-filing

Attorneys for Plaintiff
DNA SCIENCES, INC.

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

SAN FRANCISCO DIVISION

eRR

DNA SCIENCES, INC.,	C 02	Civil Action No. 5578
Plaintiff,	)	COMPLAINT FOR PATENT INFRINGEMENT; DEMAND FOR JURY TRIAL; CERTIFICATION OF INTERESTED PARTIES OR PERSONS
vs.	)	
GENEDX, INC.,	)	
Defendant.	)	

Plaintiff, DNA Sciences, Inc., by its undersigned attomeys, for its Complaint against GeneDX, Inc., demands ajury trial and alleges follows:

NATURE OFTRE ACTION

1. This is action for patent inflingement arising under the patenllaws of the United States, 35 U.S.C. §§ I *et seq.*

THE PARTIES

2. Plaintiff, DNA Sciences, Inc. Sciences") is incorporated under the laws of the State of Dclaware, having its principal place of business at 6540 Kaiser Drive, Fremont, 94555.

3. On information and belief, Defendant GeneDX, Inc. ("GcncDX") is incorporated under the laws of the State of Maryland and has its principal place of business at 207 PelTY Parkway, Gaithersburg, Maryland 20877.

JURISDICTION AND VENUE

4. This Court has subject matter jurisdiction over this action pursuant to 28 U.S.c. §§ 1331 and 1338(a).

5. This Court has personal jurisdiction oYer Defendant GeneDX as it has substantial contacts with the state of Calitornia and has conunitted of infringement within this district.

6. Venue properly lies in this District pursulIn! to 28 U.S.C. §§ 1391 and

TNTRADISTRICT TRANSFER

7. This *ease* is an Intellectual Property Action under Local Rule 3-2(c), excepted [rom the categories providing for assignment by the Clerk to particular coullty Courthouses.

FACTS COMMON **TO** ALL COUNTS

8. DNA Sciences is an applied genetics company focused on the discovery and commercialization of tests for diagnosis and treatment of disease based upon variations in DNA sequence.

9. On information and belief, GeneDX provides DNA diagnostic services, including genetic testing for the purpose of diagnosis, carrier detection, and prenatal testing.

10. On infonnation and belief, GeneDX has offered and continues to offer genetic testing for Long QT Syndrome, also known as Romano syndrome (dominant) and Jervell, Lange-Nielsen syndrome (autosomal recessive), *inter alia* via its interactive website at

11. DNA Sciences is the exclusive licensee of, has the right to enforce, U.s. Patent No 6,432,644 '644 Patent"), entitled "MUTATIONS IN THE KCNEI GENE ENCODING MINK WHICH CAUSE ARRHYfHMIA SUSCEPTIBILITY THEREBY ESTABLISHING KCNE1 AS AN LQT GENE," duly and issued on August 13,2002 (attached hereto as exhibit A).

12. DNA Sciences is the exclusive licensee of, and has the right to enforce, U.S. Patent 6,207,383 '383 Patent"), entitled "MUTATIONS IN AND GENOMIC STRUCTURE OF

HERG-A LONG QT SYNDROME GENE," duly and lega\Jy issued on March 27,2001 (attached hereto exhibit B).

13. DNA Sciences is the exclusive licensee of, and has the right to enforce, U.S. Patcnt No. 5,599,673 ("the '673 Patent"), entitled "LONG QT SYNDROME GENES," duly and legally issued on February 4, 1997 (attached hereto as exhibit C).

14. On inJi.rmation and belief, GeneDX hilS actual notice oflhe existence of the above mentioned patents.

COUNT 1 - INFRINGEMENT OF THE '644 PATENT

15. DNA Sciences repents rea the nllegations of pnraBrnphs I through 1·1 as though fully set forth herein.

16. On information and belief, GeneDX has infringed, and is still infringing, either or under the doctrine of equivalents, one or more claims of the '644 Patent by making, using, importing, offering for sale, and/or selling genetic testing for Long QT syndrome using methods covered by the '644 patent.

17. On information and belief, GeneDX's infringement has injured or will injure DNA Sciences and DNA Sciences is or will be entitled to recover damages adequate to compensate it for GeneDX's infringement.

18. On information and be1ief, GeneDX's infringement has been deliberate, willful, intentional, and with full knowledge of the existence of the '644 patent.

19. GeneDX has caused DNA Sciences substantial damage and irreparable injury by its continuing infringement of the '644 Patent and DNA Sciences will continue to suffer damage and irreparable injury unless and until GeneDX is enjoined by this Court from continuing such infringement.

20. DNA Sciences entitled to injunctive and compensatory relief, including attorneys' fe.es, under 35 U.S.C. §§ 271, 281, and 283-285.

COUNT II - INFRINGEMENT OF THE '383 PATENT

21. DNA Sciences repeats and realleges the allegations of paragraphs 1 through 14 as though fully set forth herein.

22. Ou infonnation and belief, GeneDX has infringed, and is still infringing, either literally or under the doctrine of equivalents, one or more claims of '383 Patent by making, using, importing, offering for sale, and/or selling genetic testing for Long QT syndrome using methods covered by the '383

23. On information and belief, GeneDX's infringement has injured or will injure DNA Sciences and DNA is or will be entitled to recover adequate to compensate it for GeneDX's infringement.

24. On information and belief, GeneDX's infringement has been deliberate, willful, intentional, and with knowledge of the existence of the '383 palent.

25. GeneDX has caused DNA Sciences substantial damage and irreparable injury by its continuing infringement of the '383 Patent and DNA Sciences will continue to suffer and irreparable injury unless and until GeneDX is enjoined by this Courl [roIll continuing such infringement.

26. DNA Sciences is entitled to injunctive and compensatory relief, including attorneys' fees, under 35 U.S.C. §§ 271, 281, 283-285.

COUNT 1Il- INFRINGEMENT OF THE '673 PATENT

27. DNA Sciences repeats and realleges the allegations of paragraphs 1 through 14 as fully set forth herein.

28. On information and belief, GeneDX has infringed, and is still infringing, either literal!; or under the doclrine of equivalents, one or more claims of the '673 Patent by using, importing, offering sale, and/or selling genetic testing for Long QT syndrome using methods covered by the '673 patent.

29. On information and belief, GeneDX's infringement has injured or will injure DNA Sciences and DNA Sciences is or will be entitled to recover adequate to compensate it for GeneDX's infringement.

30. On information and belief, GcncDX's infringement been deliberate, willful, intentional, and with full knowledge of the existence of '673 patent.

31. GeneDX has caused DNA Sciences damage and irreparable injury by its of the '673 Patent and DNA Sciences will continue to suffer damage and irreparable injury and until GeneDX is enjoined by this Court from continuing infringement.

32. DNA Sciences is entitled to injunctive and compensatory relief, including attorneys' undcr 35 U.S.C. §§ 211,281, and 283-285

PAAYER FOR RELIEF

WHEREFORE, DNA Sciences respectfully requests that Judgment be in favor of DNA Scicnccs GCllcDX and that DNA Sciences be the foll\lwing

(i.) A declaration that GeneDX has infringed and is infringing the '644, '383, and '673 Patents;

(ii.) A that the aforementioned infringement afthc '644, '383, '613 Patents been and is willful;

(iii.) Entry of a permanent injunction rcstraining GeneDX, its officers, agents, employees, attorneys, all others in active concert or participation with GencDX from further acts of infringement of the '644, '383, and '673 Patents, pursuant to 35 § 283;

(iv.) An award of damages sufficient to compensate DNA Sciences for GcneDX's infringement of the '644, '383, '673 Patents, pursuant to 35 U.S.C. § 284;

(v.) An award of prejudgment and post judgment interest, pursuant to 35 U.S.C. § 284;

(vi.) An award of increased damages in an amount not less than three times the amount of found by the jury assessed by court for GeneDX's Willful pursuant to 35 U.S.C. § 284;

(vii.) A declaration that this case is "exceptional" undcr 35 U.s.C. § 285 and awarding Sciences its reasonable attorney's fees, expenses, and costs incurred in this action, pursuant to 35 U.S.C. § and

(viii.) Such other and further relief as this COUIt shall deem appropriate.

DATED: November 21.2002

KIRKLAND & ELLIS

By: _____

Eric R. Lamison
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777 S. Figueroa Street
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MerkA.
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KlRKLAND & ELLIS
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Chicago, IL 60601
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Attorneys For Plaintiff
DNA SCIENCES, INC

DEMAND FOR TRIAL BY JURY

Plaintiff DNA Sciences, Inc. hereby demands a jury trial of all issues triable to a jury in this action

DATED: November 21, 2002

KIRKLAND & ELLIS

By. _____

Eric R. Lamison
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Telephone: (312) -1000
Facsimile: (312) 861-2200

Attorneys For Plaintiff
DNA SCIENCES, INC

CERTIFiCATION OF iNTERESTED ENTITiES **OR** PERSONS

Pursuant to Ci viI L.R. 3-16, the undersigned certifies that the following listed persons, associations of persons, finns, partnerships, corporations (inclUding parent corporations) or other entities (i) have a financial interest in the subject matter in controversy or in a party to the proceeding. or (ii) have a non-financial interest in that matter or in a party that could be substantially affected by the outcome of this

1. University of Utah Research Foundation

This entity has a financial and non-financial interest in the subject malter in controvcrsy as the assignee of record fOI the patents being asserted liccnsor of the underlying to I)NA Sciences, Inc.

2. Yale University

This entity a non-financial interest in the maller in controversy liccllsor or related patent rights to DNA Sciences, Inc.

3. WebMD Corporation

This entity has a financial interest in DNA Sciences, Inc. a shareholder.

4. Pharmaceutical Product Development, Inc. (PPD, Inc.)

This entity has a financial interest in DNA Sciences, Inc. as a shareholder.

DATED: November 21, 2002

KIRKLAND & ELLIS

By: _____

Eric R. Lamison
KIRKLAND & ELLIS
777 S. Figueroa Street
Los Angeles, CA 90017
Telephone: (213) 680-8400
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A. Pals
Lauren Hennessey Breit
KIRKLAND & ELLIS
200 East Randolph Drive
Chicago, IL 60601
Telephone: (312) 861-2000
Facsimile: (312) 861-2200

Attorneys For Plaintiff
DNA SCIENCES, INC

AGREEMENT

This Agreement is made on this day of December, 2002 (the "Effective Date") by and between DNA Sciences, Inc., a Delaware corporation having its principal place of business at 6540 Kaiser Drive, Fremont, California 94555 ("DNA Sciences"), and GeneDX, Inc., a Maryland corporation having its principal place of business at 207 Perry Parkway, Gaithersburg, Maryland 20877 ("GeneDX").

RECITALS

WHEREAS, DNA Sciences initiated litigation against GeneDX under U.S. Patent Nos. 6,432,644,6,207,383, and 5,599,673 Patents") in the Northern District of California, Case No. C 02-5578 CRB (the "Patent Litigation"), and the parties now wish to resolve their differences at issue in the Patent Litigation.

NOW THEREFORE, in consideration of the foregoing and the mutual covenants and obligations herein undertaken, the parties agree as follows:

1. Within ten (10) days of the Effective Date, DNA Sciences shall voluntarily dismiss the Patent Litigation, without prejudice.

2. GeneDX admits that its manufacture, use, offer to sell, or sale of tests or services relating to the diagnosis of Long QT syndrome, Romano Ward syndrome (dominant), and Jervell, Lange-Nielsen syndrome (autosomal recessive), infringes at least one claim of at least one of the Patents.

3. GeneDX shall immediately cease to make, use, offer for sale and sell: (i) tests or services relating to the diagnosis of Long QT syndrome, Romano Ward syndrome (dominant), and Jervell, Lange-Nielsen syndrome (autosomal recessive) and (ii) any other test or any services relating to diagnosis of Long QT syndrome using methods that would be covered by a claim of any of the Patents.

4. With respect to any samples that arrive or arrived at GeneDX for any such testing or service after November 25, 2002, GeneDX, to the extent it has not already done so prior to the Effective Date, shall refuse all such samples and/or shall refuse to perfoml such testing or service.

5. Within two (2) days of the Effective Date, GeneDX shall remove or cause to be removed all mention of its tests or services for detecting mutations associated with Long QT syndrome, Romano syndrome, and Jervell, Lange-Nielsen syndrome from its website, GeneTest's website, and any other website to which GeneDX provides content or offers its services.

6. GeneDX admits that the Patents are valid and enforceable, and agrees that it will not, directly or indirectly, aid, assist or participate in any action contesting the validity or enforceability of any Patent or any claims thereof.

7. Nothing herein shall be interpreted as DNA Sciences, directly or indirectly, granting GeneDX any right or license, express or implied, to any of the Patents.

8. DNA Sciences hereby releases and discharges GeneDX from any damages arising from GeneDX's infringement of the Patents occurring prior to the Effective Date, but only so long as GeneDX abides by the terms of this Agreement.

9. Each party consents to the jurisdiction of the United States federal courts for the Northern District of California and, if applicable, the state courts located in San Francisco County, California, U.S.A. for any legal action, suit, or proceeding arising under or relating to this Agreement or any future infringement claim by DNA Sciences under any of the Patents, and agrees that any such action, suit, or proceeding may be brought only in such courts. Each party further waives any objection to the laying of venue for any such suit, action, or proceeding in such courts.

10. The terms of this Agreement shall be binding upon GeneDX and its respective directors, officers, agents, employees, representatives, controlled affiliates, subsidiaries, successors and assigns.

11. This Agreement constitutes the entire agreement between DNA Sciences and GeneDX with respect to the subject matter discussed herein, and supersedes all prior agreements, negotiations and understandings relating to such subject matter. This Agreement shall not be modified, altered, or amended unless in writing signed by both parties. This Agreement shall be governed by the laws of the state of California.

IN WITNESS WHEREOF, the parties hereto, by and through their dilly authorized undersigned representatives, have executed this Agreement on the dates indicated below.

DNA SCIENCES, INC.	**GENEDX, INC.**
By: _____	By: _____
Name:	Name: _____
Title: _____	Title: _____
Date: December _____, 2002	Date: December _____, 2002

Appendix 8

GeneDx, Inc.
207 Perry Parkway
Gaithersburg, MD 20877
Phone (301) 519-2100
Fax (301) 519-2892
E-mail: genedx@genedx.com
www.genedx.com

Information Sheet

Genetic testing for Long QT Syndrome (LQTS)

Also known as: Romano Ward syndrome (RWS), dominant; Jervell, Lange-Nielsen syndrome (JLNS), autosomal recessive

Mendelian Inheritance in Man Number: RWS, 192500; JLNS, 220400

Clinical features:
Cardiovascular disorder characterized by an abnormality in cardiac repolarization leading to a prolonged QT interval on the surface ECG. LQTS causes syncope and sudden death usually in young, otherwise healthy individuals. Romano-Ward syndrome is the most common form. Jervell, Lange-Nielsen syndrome is associated with congenital sensorineural deafness.

Inheritance pattern:
Two inherited forms of LQTS exist. Romano-Ward syndrome is inherited in a dominant manner and has variable penetrance. The offspring of an affected individual has a 50% risk of also being affected. Jervell, Lange-Nielsen syndrome is inherited in an autosomal recessive manner, with both parents carrying a mutation. The risk of inheritance of the Jervell, Lange-Nielsen syndrome to the offspring of such parents is 25%. However, the risk of inheriting just one abnormal gene from one parent, and having autosomal dominant (Romano-Ward) syndrome without deafness is 50%.

Indications for direct DNA testing:
1. Confirmation of clinical diagnosis
2. Genetic counseling for affected individuals
3. Pre-symptomatic testing of family members
4. Development of a medical surveillance plan and prophylaxis for mutation carriers
5. Prenatal diagnosis

Test methods:
Using genomic DNA obtained from buccal (cheek) swabs, the most frequently mutated exons of the five genes associated with this disorder are screened as follows: 8 exons of KCNQ1, (also known as KVLQT1) (exons 3, 5, 6, 7, 8, 12, 13, 15), five exons of HERG (exons 2, 6, 7, 9, 10), two exons of SCN5A (exons 26 and 28), the single coding exons of KCNE1 and KCNE2. In families where several affected individuals are available for study, linkage analysis is available to identify or rule-out the

involvement of specific genes prior to sequence analysis. JLN clinical features would dictate a primary screen in KCNQ1 (all 10 exons) and the single coding exon of KCNE1.

Test sensitivity:

Published data shows that 42% of the total mutations identified in the disorder occur in KCNQ1 (KVLQT1), 45% in HERG, 8% in SCN5A, 3% in KCNE1, and 2% in KCNE2. Using our screening approach described above, **we would detect 87% of the LQTS mutation that occur in these genes**. However, only about 68% of patients with LQTS have been found to have a mutation in one of these five genes, suggesting that there are other genes yet to be identified. We thus calculate **the overall sensitivity of our test methods to detect an LQTS-associated mutation to be 59%.**

Mutational spectrum:

Most LQTS mutations occur in KCNQ1 and HERG, accounting equally for a total of almost 90% of identifiable mutations. A large majority of the mutations are missense mutations that disrupt the activity of the potassium or sodium channel ventricular repolarization of the heart.

Costs and turn-around time:

Mutation detection in a new patient is $2200 for all five LQTS genes to be screened. Charges are assessed only for the LQTS genes actually screened. For testing a new patient, turn-around time is approximately 6-8 weeks, but will be longer if the entire set of 5 genes must be screened.

KCNQ1 and KCNE1 are preferentially screened if the patient has a Jervell, Lange-Nielsen clinical diagnosis, for a fee of $1300.

Pre-natal diagnosis using two samples (CVS, fresh amniocytes and/or cultured amniocytes) is $700. There may be an additional cost for ruling out maternal contamination of the fetal sample, in some cases. For pre-natal diagnoses, where the mutation in the family is known, turn-around time is approximately 2 weeks. Fees are subject to change without notice.

CPT codes for LQTS-associated gene mutation tests in Long QT Syndrome (full gene screen)

83891	x 20 units =	$ 180
83898	x 20 units =	$ 500
83894	x 20 units =	$ 200
83904	x 40 units =	$1200
83892	x 4 units =	$ 40
83912	x 4 units =	$ 80

TOTAL = $2200

Possible ICD9 Codes

Cardiac dysrhythmia, NOS	427.9
Ventricular fibrillation	427.41
Syncope and collapse	780.2

Spinocerebellar Ataxia: Patient and Health Professional Perspectives on Whether and How Patents Affect Access to Clinical Genetic Testing

Ashton Powell, Ph.D.,[1] Subhashini Chandrasekharan, Ph.D.,[2] and Robert Cook-Deegan, M.D.[2]

Abstract

Views of patients and health professionals about the impact of patents on access to genetic testing for spinocerebellar ataxia (SCA) were sampled via a web forum. Questions about access to genetic testing were posted on the website of the National Ataxia Foundation (NAF), which agreed to host the web forum. The web forum was supplemented by interviews with three neurologists and a laboratory director. Both the web forum and interviews focused on perceptions of whether patents impede neurological patients from using diagnostic tests for the most common autosomal dominant forms of spinocerebellar ataxia.

SCA is not a single condition, but a group of progressive neurological genetic disorders with common symptoms and disparate genetic causes. Genetic testing plays a direct role in identifying the molecular defect in some cases.

Patents were generally not perceived to be a major direct impediment in most cases, although they reduced access to the degree they increased the cost of testing borne directly by patients. Most SCA genetic testing in the United States is carried out by Athena Diagnostics, which has in-licensed exclusive patent rights from various holders of SCA patents, mainly universities and nonprofit research institutions. Some genes involved in SCA testing are not patented at all.

Price and concern about genetic discrimination both appear to reduce patient use of genetic tests. The decision not to get tested holds even for those who have progressed far into a diagnostic workup. SCA is a relatively rare syndrome and many genes are involved. The cost of testing can be as high as $7300, and only six out of fourteen patients surveyed who sought testing received reimbursement for testing from their insurance carriers. Yet clinical testing requires CLIA certification and testing for many genes, so patients are generally grateful there is a test provider.

Athena offers a "Patient Protection Program" that caps out-of-pocket payments at 20% of the price for cases where Athena directly bills the patient's insurer. However, this likely covers only a small minority (10-15%) of patients tested by Athena. Some patients who availed themselves of Athena's Patient Protection Program appreciated the out-of-pocket payment caps. Under this program, Athena takes responsibility for seeking reimbursement from payers and insurers for the other 80%. Athena also has an "Athena Access" program for those who cannot afford the 20% copay, which entails case-by-case review by Athena; analysis of SEC filings suggests that this covers relatively few patients. The 20% copay cap for patient outlays under the Patient Protection Program is a standard option, although many patients appear not to know about it, and those in certain health programs are not eligible for it. Athena did not provide statistics on the percentage of patients covered by these two programs, so we are unable to estimate their actual impact. Since the program is discretionary and operated by Athena, independent data about how many people use it, which insurers and health programs are covered, and other details are

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not available. SACGHS might consider requesting details about both the Patient Protection Program and Athena Access from the company, since these details were not shared with us.

We cannot estimate the population prevalence or magnitude of the effects because of the highly selected nature of our sample. The website respondents, however, do indicate the two main reasons that patients with rare genetic conditions may not use genetic tests even when they would like to have the results of them: fear of discrimination and cost.

Background

Spinocerebellar ataxia (SCA) is a designation given to a rare subset of autosomal dominant cerebellar diseases characterized by loss of cerebellar cells. (Spinocerebellar ataxia is also associated with other patterns of inheritance, both autosomal recessive [SCAR] and X-linked (SCAX), but these are even more rare and less well characterized and therefore less relevant for commercial genetic testing.) Symptoms include ataxia, or irregular movement due to loss of neural control, and often also other symptoms attributable to loss of brainstem and spinal cord function.[3] Ataxia is a common symptom found in conditions from chronic alcoholism to stroke. SCA accounts for less than 5% of the ataxic population, an estimated prevalence of 1-5:100,000.[4] While accounting for only one in twenty cases of ataxia, the autosomal dominant SCA syndromes are nonetheless much more common than the other genetic forms, which are quite rare.

The severity and types of symptoms vary among the cerebellar ataxias. Diagnosis often takes years and may entail many visits to a succession of physicians and other health professionals, especially when it is a "proband case," or the first known case in a family cluster. Once a first case is found in a family and confirmed as an inherited condition, genealogical tracing may identify other cases in the family. There are currently more than 30 identified variants of SCA (named SCA1-8, and 10-25 see Table 1), a number that is constantly expanding. Each variant has the symptom of ataxia, however the secondary symptoms can differ greatly. The symptoms associated with variants of SCA have significant overlap, so purely clinical symptom clusters rarely specify a particular mutation without DNA or protein testing. The vagueness with which each variant is described can make purely clinical diagnosis without genetic testing difficult, although there have been many attempts to design clinical scales using symptom correlations to hone in on a diagnosis (Figure 1).[5] There is no known cure for any subtype of SCA, and treatment often involves addressing individual symptoms as they appear.

Before 1982, symptoms that now distinguish the various subtypes of SCA were diagnosed as olivopontine cerebellar atrophy (OPCA), a classification that encompassed a host of cerebellar diseases.[6] Later, a clinical classification was proposed for a subset of these diseases based on mode of inheritance and

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[3] Schols L, Bauer P, Schmidt T, Schulte T, Riess O. Autosomal dominant cerebellar ataxias: clinical features, genetics, and pathogenesis. *Lancet Neurol* 2004. 3(5): 291-304.
Taroni F, DiDonato S. Pathways to motor incoordination: the inherited ataxias. *Nat Rev Neurosci* 2004. 5(8): 641-655.
[4] Moseley ML, Benzow KA, Schut LJ, Bird TD, Gomez CM et al. Incidence of dominant spinocerebellar and Friedreich triplet repeats among 361 ataxia families. *Neurology* 1998. 51(6): 1666-1671.
Mori M, Adachi Y, Kusumi M, Nakashima K. A genetic epidemiological study of spinocerebellar ataxias in Tottori prefecture, Japan. *Neuroepidemiology* 2001. 20(2): 144-149.
van de Warrenburg BP, Sinke RJ, Verschuuren-Bemelmans CC, Scheffer H, Brunt ER et al. Spinocerebellar ataxias in the Netherlands: prevalence and age at onset variance analysis. *Neurology* 2002. 58(5): 702-708.
[5] Maschke M, Oehlert G, Xie TD, Perlman S, Subramony SH et al. Clinical feature profile of spinocerebellar ataxia type 1-8 predicts genetically defined subtypes. *Mov Disord* 2005. 20(11): 1405-1412.
Schmitz-Hubsch T, du Montcel ST, Baliko L, Berciano J, Boesch S et al. Scale for the assessment and rating of ataxia: development of a new clinical scale. *Neurology* 2006. 66(11): 1717-1720.
[6] Konigsmark BW, Weiner LP. The olivopontocerebellar atrophies: a review. *Medicine* (Baltimore) 1970. 49(3): 227-241.

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secondary neurological symptoms not associated with the cerebellum.[7] These classifications, known as the autosomal dominant cerebellar ataxias (ADCAs), were subdivided into classes I, II, and III. This diagnostic refinement allowed neurologists to distinguish ataxias according to their accompanying symptoms, among those being: peripheral nerve damage and dementia (ADCA I), macular and retinal degeneration (ADCA II), and an especially severe late-onset pure form of ataxia (ADCA III).

Eventually, as genetic research was incorporated into the classification along with symptoms, these conditions were divided further into the more than 30 conditions now known as SCA (Harding 1982; Manto 2005; Maschke et al. 2005).[8] ADCA I was supplanted by SCA1-3, ACDA II was replaced with SCA7, and ACDA III was divided into SCA4-6 and 11. The classification has "gone molecular." It is now based on mutations in genes that encode proteins affecting nerve function. Some mutations are associated with changes in proteins that conduct charged particles through cell membranes ("channel" proteins), receptors, or other surface proteins on nerve cells. Despite the increased specificity in diagnosis, treatment has changed little. Progress in understanding the molecular details has not yet translated to better treatment. The primary benefits of SCA genetic testing for a patient are precision of prognosis, some reassurance from an accurate characterization of the molecular defect, an ability to diagnose those who are affected or presymptomatic among relatives, and the ability to test for a known mutation during preimplantation diagnosis or prenatal diagnosis in the progeny of an affected person.

We focus on the six most common forms, SCA1-3 & SCA 6-8.

Symptoms and Pathology Of SCA Subtypes

SCA1 has pan-cerebellar symptoms that typically begins in a patient's fourth decade, with an average duration of fifteen years (Table 1). Cerebellar symptoms include an atrophy of Purkinje cells, loss of afferent projections into the cerebellar cortex, and atrophy of dentatorubral pathways. Non-cerebellar symptoms include signs associated with damage to the dorsal columns and cranial nerve nuclei. SCA1 maps to chromosome 6p23 in the ataxin-1 gene and is a CAG trinucleotide repeat disorder (i.e., caused by expanded number of those three base pairs inserted as repeats into the gene's DNA). SCA1 is estimated to represent 5.6% of autosomal dominant SCA ataxias.[9]

SCA2, in addition to cerebellar symptoms found with olivopontocerebellar atrophy, is associated with marked loss or slowing of saccadic eye movements, dementia, and other peripheral neuropathy. Patients with SCA2 can show their first symptoms from age 2 to age 65, a huge range in age of onset, with an average duration of 10-15 years from onset to death.[10] SCA2 maps to chromosome 12q24.1 in the ataxin-2 gene and is a CAG trinucleotide repeat disorder. SCA2 is one of the most common of the autosomal dominant cerebellar ataxias accounting for an estimated 15.2% of SCA occurrences.[11]

SCA3, also known as Machado-Joseph disease, is characterized by cerebellar signs including degeneration of the dentate and vestibular nuclei, with no degeneration of the cerebellar cortex. Additional symptoms include extrapyramidal, motor cranial nerve, anterior horn, posterior root ganglion,

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[7] Harding AE. The clinical features and classification of the late onset autosomal dominant cerebellar ataxias. A study of 11 families, including descendants of the 'the Drew family of Walworth'. *Brain* 1982. 105(Pt 1): 1-28.
[8] Ibid.
Manto MU. The wide spectrum of spinocerebellar ataxias (SCAs). *Cerebellum* 2005. 4(1): 2-6.
Maschke M, Oehlert G, Xie TD, Perlman S, Subramony SH et al. Op. cit.
[9] Moseley ML, Benzow KA, Schut LJ, Bird TD, Gomez CM et al. Op. cit.
[10] Auburger G, Orozco Diaz, G, Capote RF, Sanchez SG, Perez MP, Estrada del Cueto M, Meneses MG, Farrall M, Williamson R, Chamberlain S, Baute LH. Autosomal dominant ataxia: genetic evidence for locus heterogeneity from a Cuban founder-effect population. *Am J Hum Genet* 1990. 46: 1163-1177.
[11] Moseley ML, Benzow KA, Schut LJ, Bird TD, Gomez CM et al. Op. cit.

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and spinopontine symptoms. SCA3 symptoms begin in the fourth decade with a typical duration of ten to fifteen years. SCA3 maps to chromosome 14q24.3-q32.2 in the ataxin-3 gene and is also a CAG trinucleotide repeat disorder. First described as Machado-Joseph disease, SCA3 accounts for 84% of autosomal dominant ataxias in ethnic Portuguese and 50% in ethnic German populations. In the US, SCA3 accounts for approximately 21% of dominant ataxias. The severity of symptoms correlates with the number of CAG repeats.[12]

SCA6 is an autosomal dominant ataxia that has a variable presentation, classified as three separate syndromes. The SCA6 syndromes are episodic ataxia, cerebellar ataxia plus brainstem or long tract degeneration, or pure cerebellar ataxia. Additional symptoms include a coarse gaze-evoked nystagmus, downbeat nystagmus on lateral gaze, and poor suppression of eye movement by vision.[13] SCA6 is a slowly progressing late-onset version of SCA that begins in the fifth or sixth decade with a typical duration of more than 25 years. The SCA6 mutation has been identified as a CAG expansion located at 19p13, a subunit of the voltage-gated calcium channel CACNL1A4. SCA6 accounts for approximately 15% of autosomal dominant ataxias in the US.

In addition to cerebellar symptoms and ataxia, SCA7 is associated with retinopathy or blindness. Beginning in the third or fourth decade, SCA7 is a slowly progressive ataxia, lasting an average of twenty years. Mapped to 3p21.1-p12, which encodes ataxin-7, SCA7 is a CAG repeat disorder as well. SCA7 accounts for roughly 5% of dominantly inherited ataxias in the United States. It is sometimes associated with genetic anticipation (earlier onset in successive generations, usually indicative of expansions of trinucleotide repeats) and severe childhood onset.

SCA8 is a less severe form of SCA, with symptoms including hyperreflexia, decreased sense of vibration, ataxic dysarthria (lack of control of joints), impaired smooth-pursuit eye movement, horizontal nystagmus, and atrophy of the cerebellar vermis and hemispheres. SCA8 begins in the fourth decade and is not associated with shortened lifespan. SCA8 has been mapped to 13q21, which encodes ataxin-8 and is a CAG/CTG repeat disorder. SCA8 accounts for 2-5% of autosomal dominant ataxias in the US.

Diagnosing Spinocerebellar Ataxia

When first diagnosing or treating an ataxic patient, one of the first lines of evidence is family history. Like many diseases with known genetic causes, a family history that reveals multiple family members afflicted with similar clinical conditions can indicate that diagnosis of SCA should be considered.

While an ataxic patient whose family history includes a genetically confirmed diagnosis of a SCA subtype is an ideal candidate for genetic testing, such cases are unusual. Most family histories contain no results from genetic testing because it is a relatively new technology. If ataxic symptoms exist in a family record, a previous diagnosis is likely to reflect a classification given to the disease at the time of diagnosis. Despite a dated classification, these histories are still valuable for diagnosing hereditary ataxias (Figure 2).

Family history is unavailable in many cases. A patient may be adopted, where heredity is impossible to trace through standard pedigree tracing. A patient may come from a family that has had little exposure to modern medicine and record keeping or adoption. Due to the late onset of some hereditary ataxias

[12] Onodera O, Idezuka J, Igarashi S, Takiyama Y, Endo K et al. Progressive atrophy of cerebellum and brainstem as a function of age and the size of the expanded CAG repeats in the MJD1 gene in Machado-Joseph disease. *Ann Neurol* 1998. 43(3): 288-296.
[13] Gomez CM, Thompson RM, Gammack JT, Perlman SL, Dobyns WB et al. Spinocerebellar ataxia type 6: gaze-evoked and vertical nystagmus, Purkinje cell degeneration, and variable age of onset. *Ann Neurol* 1997. 42(6): 933-950.

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(Harding 1982), not all families have had life expectancies long enough for symptoms to be observed.[14] Many die without a definitive diagnosis, and stigma associated with uncontrollable movement can lead to cases being "hidden" from family discussion and result in incomplete pedigrees.

An initial neurological consultation is also intended to resolve whether the ataxia is acquired (e.g., related to alcohol use, infection, or other known syndromes) or sporadic. Acquired ataxia refers to cases with no known genetic component. These can be highly variable from case to case.[15] Common causes of acquired ataxia include chronic alcoholism, stroke, multiple sclerosis, vitamin deficiency, and metabolic deficiencies.[16] In some cases, identifying the source of an acquired ataxia can lead to a relief or even reversal of symptoms.

Sporadic ataxia is a diagnosis given to a subset of patients who have ataxia with no known hereditary or acquired components. This residual classification is broken into either pure cerebellar or 'cerebellar plus,' depending on whether there are symptoms in addition to ataxia.[17] Regardless of whether the ataxia appears to be hereditary, sporadic or acquired upon an initial evaluation, an ataxic patient will generally undergo a complete neurological evaluation and an MRI scan.

After one or several MRI scans, the neurologist may observe cerebellar atrophy, or loss of cerebellar tissue. In addition to atrophy, the neurologist may observe signs and symptoms of a progressive loss of function in systems associated with the cerebellum. Symptoms can include gait disruption, nystagmus, vertigo, or general lack of coordination. Secondary non-cerebellar symptoms including impaired cognition, memory, and vision can also point to SCA.

Intellectual Property Landscape – Athena Diagnostics

Many genetic tests for SCA are available only from Athena Diagnostics, including the most commonly used SCA genetic tests. There are currently 15 variants of SCA for which genetic testing is available. Athena Diagnostics holds the patent or has exclusive license to 12 patents that identify 6 SCA variants (SCA1-3 & 6-8) and two other hereditary ataxias (Friedreich's Ataxia and Early Onset Ataxia) included in their Complete Ataxia Panel (Table 3). These variants are the most commonly occurring, accounting for roughly 60-80% of known SCA cases, depending on the patient's country of origin (Tang et al. 2000; Lee et al. 2003; Bauer et al. 2005).[18] Athena was also granted a nonexclusive license by Baylor Medical

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[14] Harding AE. Op. cit.
[15] Ibid.
Manto MU. Op. cit.
[16] Gordon N. Cerebellar ataxia and gluten sensitivity: a rare but possible cause of ataxia, even in childhood. *Dev Med Child Neurol* 2000. 42(4): 283-286.
Hadjivassiliou M, Grunewald R, Sharrack B, Sanders D, Lobo A et al. Gluten ataxia in perspective: epidemiology, genetic susceptibility and clinical characteristics. *Brain* 2003. 126(Pt 3): 685-691.
Zumrova A. Problems and possibilities in the differential diagnosis of syndrome spinocerebellar ataxia. *Neuro Endocrinol Lett* 2005. 26(2): 98-108.
[17] Koeppen AH. The pathogenesis of spinocerebellar ataxia. *Cerebellum* 2005. 4(1): 62-73.
Manto MU. Op. cit.
Maschke M, Oehlert G, Xie TD, Perlman S, Subramony SH et al. Op. cit.
[18] Tang B, Liu C, Shen L, Dai H, Pan Q et al. Frequency of SCA1, SCA2, SCA3/MJD, SCA6, SCA7, and DRPLA CAG trinucleotide repeat expansion in patients with hereditary spinocerebellar ataxia from Chinese kindreds. *Arch Neurol* 2000. 57(4): 540-544.
Lee WY, Jin DK, Oh MR, Lee JE, Song SM et al. Frequency analysis and clinical characterization of spinocerebellar ataxia types 1, 2, 3, 6, and 7 in Korean patients. *Arch Neurol* 2003. 60(6): 858-863.
Bauer PO, Zumrova A, Matoska V, Marikova T, Krilova S et al. Absence of spinocerebellar ataxia type 3/Machado-Joseph disease within ataxic patients in the Czech population. *Eur J Neurol* 2005. 12(11): 851-857.

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College for US6855497, which covers methods for detecting SCA-10,[19] and Athena also does testing for SCA5, 13, 14 and 17.

Of the 12 patents listed by Athena, half are licensed from the University of Minnesota. Three others are from academic institutions (two through Research Foundation, one from Baylor) and only one is assigned to Athena itself. It thus appears that at least 9 of 12 (75%) are licensed from academic institutions and one arose from in-house R&D at Athena.

Athena Diagnostics has enforced its exclusive licenses and is widely assumed to be the sole laboratory for the above tests.[20] Athena's legal department has sent "cease and desist" letters to some laboratories performing SCA genetic tests for which Athena has exclusive patent rights (Figure 3). In another instance, the Diagnostic Molecular Pathology Laboratory at the University of California Los Angeles stopped offering testing for SCA over two years ago, after receiving a "cease and desist" letter from Athena Diagnostics. According to Dr. Wayne Grody,[21] Director of the Laboratory, the terms of the sublicense offered by Athena Diagnostics were not economically viable for the laboratory. Attempts to negotiate terms of a sublicense have not been successful to date. It is unclear to what extent cessation of testing at UCLA has affected patient access to SCA testing. Dr. Grody indicated that samples are now sent to Athena Diagnostics for clinical testing. Several other laboratories are also listed on GeneTests.org for adult SCA diagnoses. Comprehensive Genetics Services offers a complete panel of SCA tests (Table 4) but did not respond to questions about patents or licensing in phone interviews. We recently became aware that Boston University reached a settlement with Athena Diagnostics regarding testing for SCA[22] and several other conditions and no longer offers SCA testing.

Athena Diagnostics does not list prenatal or preimplantation genetic diagnosis. Several labs listed on GeneTests.org perform these tests. We did not verify or otherwise pursue questions about prenatal or pre-implantation genetic testing for SCA.

SCA genetic tests can be performed individually for as little as $400, for the least expensive single-locus test, or as much as $2,335 for full-sequence analysis of the most expensive full-sequence gene test. The lower cost tests are for known mutations in the second or subsequent members of a family, once a proband case in that family is characterized. Athena also offers the Complete Ataxia Panel, a compilation of 18 tests that cover the most commonly identified SCA mutations for the price of $7,300. This cost includes PCR tests and tests requiring sequencing (Table 2 & 4). The Athena price for the five most common SCA's (1, 2, 3, 6 and 7) is $2,300 (if ordered individually, which is the only option). A University genetics laboratory can reportedly perform the same 5 SCA tests for $750 (or $1,500 if ordered individually).[23]

Most of Athena Diagnostic's testing revenue comes from direct billing to hospital and commercial laboratories that send samples to Athena for patients seen or tested within their health-care systems. In a public filing with the Securities and Exchange Commission, Athena indicated that 85% of their revenue comes from this source.[24] This is widely known in the clinical laboratory industry as the most profitable

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[19] Email and phone correspondence with Teresa L. Rakow, Sr. Licensing Associate Baylor Licensing Group Baylor College of Medicine, April 9 2008.
[20] Schissel A, Merz JF, Cho MK. Survey confirms fears about licensing of genetic tests. *Nature* 1999. 402(6758): 118.
Cho MK, Illangasekare S, Weaver MA, Leonard DG, Merz JF. Effects of patents and licenses on the provision of clinical genetic testing services. *J Mol Diagn* 2003. 5(1): 3-8.
[21] Phone conversation with Dr. Wayne Grody, March 21, 2008
[22] Phone conversation with Dr. Aubrey Milunsky, Director, Center for Human Genetics, Boston University, May 29, 2008.
[23] Laboratory director, name withheld at request.
[24] Athena Diagnostics. *S-1*. October 31, 2001. Table on page 39. See www.secinfo.com/dsvrt.4fD5f.f.htm [accessed 14 January, 2009].

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type of billing arrangement: the sending facility is obligated to pay the full contractual price of testing directly to Athena regardless of insurance coverage or patient ability to pay; the sending facility then bills the patient and/or the patient's third party payer for the cost of testing. Since reimbursement for this type of testing is often low or absent, the financial burden of poorly reimbursed testing is thus transferred from Athena to the sending healthcare facility and thence to the patient.

Athena has a formal policy that limits out-of-pocket expenditures for some patients for whom Athena directly bills the insurer. Athena's Patient Protection Plan (PPP), charges the patient 20% of the test fee (the usual copayment for most insurance programs) up front. After completing the test, if insurance covers the cost of the test, Athena will reimburse the patient for any payment their insurance makes above 80% of the total bill. Such patients must have private insurance. If the patient's insurance does not cover the genetic test, Athena will limit the patient's liability to the 20% already paid. This plan requires preapproval by Athena. There is an additional plan for low-income families, Athena Access. This is for those who may find the 20% co-pay prohibitive. Athena, upon receiving a request for a test, will attempt to contact the patient by mail and phone three times in order to enroll them into the PPP. Athena did not provide specific numbers regarding enrollment percentages into the PPP. It is also not clear whether this program includes persons whose only coverage is Medicare or Medicaid. However, the information in the SEC filing cited above would indicate that this program could apply to no more than 15% of the sources of revenue for testing at Athena in 2001. The PPP will not provide relief to a patient being billed by a health-care facility for testing sent to Athena under the common direct billing arrangement accounting for 85% of Athena's revenues. There is no way from public sources to estimate how much of the remaining 15% of revenue might have been reduced by the company's PPP or Athena Access programs.

Athena also has a repeat customer program that can also reduce costs borne by patients. If a patient has a genetic test performed by Athena and receives a positive result, subsequent family members who request the same test have a greatly reduced price. However, the impact of this program is probably small because of the low rate of positivity for SCA testing (only 6% for patients without a known family history of SCA.)[25]

The benefit of Athena's licensing SCA patents from several different academic institutions and combining them with their own patent is that this enables a single laboratory to test for many variants, and protects the company's investment in CLIA certification, laboratory proficiency testing, a sales force to educate neurologists about the tests, and staff to manage the complex coverage and reimbursement policies of a dizzying array of disparate payers, insurers, and health plans. The syndromes are relatively rare, and it is possible that this full range of tests would not be available without the patent incentive.

The counter-argument is that Athena has consolidated IP into an effective temporary monopoly for genetic testing of the SCA syndromes. It has been vigilant in enforcing its patent rights, and this has led several laboratories to avoid SCA testing who otherwise might have offered a testing alternative. As with all patented inventions, this reduces price competition, means all samples must be sent to an external laboratory, limits alternatives for verification of test results, and reduces the incentive to introduce cheaper and faster tests because the current technology is protected by patents. This could, for example, reduce incentives to develop a chip-based or microarray-bead or sequence-based test using alternative technologies, because the patents apply to any technology for assessing patented mutations or diagnostic methods that entail sequencing or sampling a patented sequence. Sole provider status also means that Athena effectively becomes the only testing service for mutations never yet detected (or patented) because the nature of the mutation is not known when a sample is sent. The means a single private firm

[25] Edlefsen KL, Tait JF, Wener MH, Astion M. Utilization and diagnostic yield of neurogenetic testing at a tertiary care facility. *Clin Chem* 2007. 53(6): 1016-1022.

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becomes the repository for data needed to determine if a discovered DNA change is actually a disease causing pathogenic mutation or a benign polymorphism, information that is critically important to clinical interpretation. Yet Athena does not appear to publish or report such data, leaving reporting to the disparate groups sending samples to their central laboratory.

Many of these tests were developed through federally funded research and licensed to Athena. The ultimate payer is often the federal government (through Medicare, Medicaid, Federal Employee Health Benefit Plan, Tricare, Veterans Health Administration, military health systems, Indian Health Service, etc.). The patents arising from federally funded research are subject to Bayh-Dole government use rights. Those government use rights are clearly not being interpreted to cover even payments channeled through the same federal Department of Health and Human Services that houses the National Institutes of Health (NIH) that funded the research (such DHHS payers include Medicare and federal components of Medicaid, the Indian Health Service and any genetic services covered by the Health Resources and Services Administration). We do not know if there is a price reduction for NIH-funded clinical trials and clinical research, because none of the respondents in the web forum specifically noted participation in such trials and the physicians interviewed did not mention this. SACGHS could ask Athena if it offers price reduction for genetic testing associated with federally funded research or allows unlicensed testing for clinical and/or basic research.

Physician Utilization and Access (Interviews with Neurologists)

To get clinicians' perspectives on access to genetic testing, we interviewed three neurologists with varying degrees of expertise with SCA, and a laboratory director. The neurologists we interviewed are Dr. Octavio de Marchena from the Neurology Associates of Lynchburg, Dr. James Burke from Duke University Hospital, and Dr. Thomas Bird from the University of Washington. The laboratory director requested that his/her name be withheld, and that interview is protected by a certificate of confidentiality (as are others, except when they were explicitly "on the record") under the IRB-approved interview protocol we followed.

Dr. de Marchena is a general neurologist at a regional hospital; he treats all types of neurological patients and refers cases of ataxia to a subspecialist as needed. Confirmed cases of hereditary ataxia treated by the Dr. de Marchena are rare, but he has had patients for whom he has established a positive diagnosis of SCA using genetic testing.

Dr. James Burke is a neurologist who specializes in neurodegenerative diseases at Duke, a private hospital and clinical outpatient service that is part of a major regional academic medical center. Dr. Burke does not solely treat patients with movement disorders, but does have ataxic patients referred to him from both inside and outside Duke. Cases of SCA are also rare for Dr. Burke, although he orders an estimated 5-10 genetic tests for SCA per year.

Dr. Thomas Bird is a researcher and clinician at the University of Washington and VA Puget Sound Health Care System, an academic health center with a long and distinguished history of medical genetics. His research includes the genetics of neurodegenerative diseases. His patients are often referred to him from all over the country, and many come with the expectation that they will have genetic tests performed as part of their visit. Compared to the other neurologists, Dr. Bird's patients are more often prescreened as candidates for genetic testing. Many patients referred to him have been seeking a specific diagnosis for some time. Many become involved in research studying trinucleotide repeat neurological diseases. Dr. Bird uses genetic tests much more often than most other neurologists. He estimated that in a given year he prescribes genetic testing for 35-45 ataxic patients, most patients receiving testing for multiple

variants. When itemized by SCA variant, the number of individual tests that he orders comes to well over 200 per year. He is also a consultant to Athena. That is, he is an international expert on SCA.
We asked all three neurologists to describe their use of genetic testing for SCA and the medical factors most responsible for prescribing tests. We asked them about how they interact with Athena Diagnostics. In addition, we asked them to describe their interactions with insurance companies and how insurance and health plan factors affect their use of genetic testing for SCA. Finally, we asked whether and how reducing the price of testing to $100 might change their use of genetic testing for SCA.

Clinical Guidelines and Utility of Genetic Testing

Achieving a diagnosis of SCA is more a complex process than a formal algorithm. The primary reasons for this are that ataxia is a common symptom associated with many disorders and because there are numerous forms of SCA. It takes substantial evidence from multiple methodologies (family history, brain imaging and blood tests) over several visits, often documented in medical records from different providers, before a neurologist considers a genetic test for SCA. The only time this is not the case is if the family history contains a specific SCA diagnosis in another family member. (In these cases, while a test will come earlier, there is still no guarantee of a positive result.)

Considering that genetic testing provides the sole confirming diagnosis of SCA, we probed further the rationale for delaying genetic tests until after significant clinical evaluation. The primary reason is low likelihood that genetic testing will be informative in symptomatic ataxia that is not fully characterized (by ruling out alcohol use, stroke, or multiple sclerosis, for example). Even the most common form of SCA in US populations (SCA3)[26] is likely to test negative more than 99% of the time in a patient displaying ataxia without a family history. If a neurologist can follow disease progression long enough, he or she can discern whether it follows any of the identified classifications of SCA, increasing likelihood of a positive genetic test. Clinical heterogeneity even among patients afflicted with the same variant of SCA can make it difficult for a neurologist to identify the SCA genes that should be tested.

Cost and cost-effectiveness enter into decisions about genetic testing for SCA, but not in a simple way. While positive results on genetic tests for SCA subtypes provide definitive diagnosis for ataxia in a patient, the interpretation of a negative result is much less well defined, and yet negative results are common, even among well-screened patients. Many patients with clinical ataxia do not have a mutation in any of the genes known to be associated with SCA. In such cases, the diagnosis will be a clinical, descriptive, or anatomical one, such as olivopontine cerebellar atrophy.

Cost Effectiveness of Genetic Testing

The primary issue associated with genetic testing for SCA is the low rate of positive results. The 30 identified spinocerebellar ataxias only account for an estimated 5% of all diagnosed ataxias.[27] Genetic tests are available for 12 of the genetic subtypes, representing an estimated 65-80% of SCA cases (Table 1). Edlefsen et al. compared the cost effectiveness of genetic tests.[28] In this study, 162 patients were given a total of 282 neurogenetic tests. The patients were referred for genetic testing by a neurologist based upon family history and symptoms. The tests included mutations associated with chorea, neuropathy, muscle weakness, and ataxia. In all, 30.2% of patients received a positive result on a genetic test or panel of tests corresponding to their symptoms. When only looking at probands, patients for

[26] Moseley ML, Benzow KA, Schut LJ, Bird TD, Gomez CM et al. Op. cit.
[27] Ibid.
Mori M, Adachi Y, Kusumi M, Nakashima K. Op. cit.
van de Warrenburg BP, Sinke RJ, Verschuuren-Bemelmans CC, Scheffer H, Brunt ER et al. Op. cit.
[28] Edlefsen KL, Tait JF, Wener MH, Astion M. Op. cit.

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whom there is no known family history, the positive rate goes down to 21.5%. For tests related to SCA (SCA1-3, 6-8, 10, 12, 17) the total positive rate for patients was 11% (2/18), and only 5.9% (1/18) for probands without known family history of other SCA cases. This "hit" rate for SCA was the lowest of all genetic tests surveyed.

One way to assess testing cost is to estimate the cost per positive test result. The genetic test for Huntington's disease costs $300. With a positive result in 71.2% of tests the cost per positive is $440. For the HD test, the symptoms, family history of chorea, and need to test only a single locus makes selection of a genetic test straightforward. For the SCA tests, the cost of the test itself varied from $225 for a single-locus test (for a known mutation in a second or subsequent family member) to $2,335 for a test requiring sequencing.[29] Twenty-seven genetic tests for SCA, ordered for 18 patients, were either for single variants (17 of 27; SCA3, 7, 8, 10, 12, 14, 17) or as a panel (10 of 27; SCA1-3, & 6-7). With a positive result rate of 11%, the cost per positive test for SCA was $7,620, the most expensive cost-per-positive-test studied. Edlefsen et al. note that this cost would increase to over $50,000 if all tests were sent to Athena Diagnostics.[30]

Adoption by Clinical Providers

When asked how they obtained SCA genetic testing for a patient, the neurologists said they simply check a box on a requisition form. A blood sample goes with the form to the pathology department of their institution. From there, the in-house laboratory either ships the sample to Athena Diagnostics or performs tests, depending on the test. All three neurologists stated the testing from Athena was generally consistent and reliable. The neurologists all stated their personal preference was that the laboratory of their own institution would perform these tests, especially those that are PCR-based and do not require sequencing.

Neurologists judged that the price of the test was sometimes problematic, mainly because insurance would not always reimburse all costs, and patients were not always able to cover the remaining costs. They considered cost a factor but focused primarily on the clinical value of genetic testing. The patient might decide to forego testing, but while these neurologists considered costs, they saw their main task as explaining the clinical value of a genetic test, and left final determinations about whether a test was worth the cost to their patients.

To probe price sensitivity, the neurologists were asked a question about whether a decrease in test pricing to $100 would increase test prescriptions. All three neurologists reiterated their stance that the limitations of current SCA genetic testing panels place genetic testing for this condition low on the diagnostic tree and late in the process, so such testing is not common and therefore not a major cost driver for diagnosis overall. They indicated that lowering the price to $100 would have little effect on their prescribing pattern. Dr. de Marchena stated that, "any neurologist would call for testing when the symptoms and family history call for it, regardless of price." Price is not the main factor in deciding whether to test, although it is a factor they consider. Dr. Bird noted that any neurologist must take into account "what value is this to a patient and his family, just giving the test without thought will not benefit them." On further reflection, however, Dr. Bird believed he would order more tests if the cost were substantially lower.

Lowering the price of testing would not affect the informational value of the test, as neurologists focus on "benefit to the patient," and indeed it may be appropriate for patients to decide for themselves the value of the genetic test, since there are no clinical treatments that follow from specific genetic diagnosis. The

[29] Ibid.
[30] Ibid., 1021.

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neurologists order the test to provide clinically relevant information; the patients then must decide the personal value of that information to them, compared to their out-of-pocket costs and any other costs (needing to deal with applying for the Patient Protection program, Athena Access, etc.). The benefits of testing are mainly that the diagnostic work-up can end with a definitive result, a genetic diagnosis enables more precise prognosis, and it enables risk evaluation and a much more efficient diagnostic strategy for others related to that person.

The Edelfsen et al. article notes that testing for ataxia is among the most expensive areas for genetic testing, and that costs would be even higher if patents were enforced rigorously. They conclude:

> For example, the cost per positive result for ataxia testing would increase nearly 7-fold, to >$50 000, if all tests had been obtained from the laboratory [NB: clearly referring to Athena Diagnostics] that claims exclusive patent rights for many of these tests. This increase reflects both higher per-test cost and test packaging that encourages the ordering of larger panels of tests. Thus, policymakers should be aware that many of the costs per positive result found in this study may be greatly increased in the future because of intellectual property restrictions.[31]

Adoption by 3rd Party Payers

While price does not appear to have a strong effect on the number of tests ordered by neurologists, the contribution of insurance may influence whether patients go ahead and get genetic testing. When insurance does cover costs for Athena's Complete Ataxia Panel, generally leaving an estimated 20%, or $1,500 co-pay, almost all patients who were not personally opposed to the test would take it. If insurance refused coverage, and patients were required to pay Athena the full price of $7,300 for the Complete Ataxia Panel, both Dr. Bird and Dr. Burke report that patients were likely to pay for the test less than half the time. Additionally, Dr. Burke stated that, "for individual tests for a specific SCA variant, insurance often covered the request because the evidence of its utility was much greater." Dr Bird noted that $7,300 self-pay is prohibitive for most patients.

The neurologists all concurred about the inconsistency in insurance companies deciding to cover a genetic test. The uncertainty surrounding insurance decisions sometimes led to their postponing genetic testing while awaiting insurer pre-approval and often having to write time-consuming letters of justification. All these factors tend to reinforce a two-tiered health system, with full use of genetic testing by the wealthy and many others foregoing SCA genetic tests.

Patient Perspectives

We solicited direct patient input through a web forum. The mission of the National Ataxia Foundation (NAF, www.ataxia.org) is to improve the lives of those suffering from ataxia by offering information, support, and resources. The NAF maintains a bulletin board forum with over 700 users, many of whom have an ataxia or are family members of someone who does. The forum supplies information about where to go for diagnosis and how to cope with the effects of disease. With the cooperation of the NAF, we established a discussion thread on this forum and asked users to discuss their personal stories regarding genetic testing for ataxia.

We began the discussion with a list of questions about genetic testing, about prices, about the involvement of insurance and health plans, and how the results of the tests affected the patients. The

[31] Ibid.

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questions are listed below, followed by a discussion of the responses. The participants were fully aware they were participating in a public forum. The entire discussion through 17 October 2007 is Appendix A. One purpose of the web survey and online forum was to convey information about patient perspectives to the SACGHS task force. The survey remains online and may expand due to the patient interest in this topic.

The response was impressive, with 30 responses and 450 views of the website over several weeks. The responses indicated that patients were passionate about the issue of access to genetic testing, and their comments provided insight into complexities of genetic testing that complemented the issues raised by the neurologists, the laboratory director, insurance companies, and policy makers.

Who responded?

Among the 16 forum users who responded to our questionnaire, there were two major groups: those diagnosed with a variant of SCA, and others (many of them caregivers or family members). This is almost surely a highly biased, relatively well-informed and therefore unrepresentative sample. For our purposes of getting knowledgeable and informed patient perspectives, however, it was an excellent convenience sample. Of the 16 respondents, 11 had a SCA genetic test performed. Of the 5 without a test, 1 abstained for fear of genetic discrimination, 1 would have a test performed soon, and the other 3 were not covered by their insurance and could not pay for the testing themselves. Of the 11 responders that took the test, 6 were covered by their insurance carrier, the others paid out of pocket. The users who had a diagnosis achieved it through genetic testing by Athena Diagnostics. Those without an SCA diagnosis either took the test and had negative or inconclusive results, or did not take a genetic test.

Responses regarding insurance deciding on coverage sounded a consistent theme: inconsistency in coverage and reimbursement decisions by payers (insurers and health plans):

> Dancingpoodle wrote "*The insurance company said they wouldn't cover the genetic testing since there was no family history and the cost was so high.*"
>
> Jonab wrote, "*I have called my insurer to see if I am covered, and they have told me that I am covered, if it's 'medically necessary'.*"
>
> Rrose wrote, "*My insurance company did not cover the cost of the test. The cost to me was $2500. They told me at the time it was because Athena was not one of their preferred providers. I was required to pay the entire amount upfront, directly to Athena Labs.*"

Should genetic testing have been prescribed earlier?

Users were generally well informed about the various diseases presenting as ataxia and the limitations surrounding current diagnostic methodology. Most users had ataxia or lived with someone who did. They understood that over two dozen variants of SCA had been identified, 12 of which could be genetically tested. They also understood and agreed that these tests should not be prescribed as a screening test for ataxia because a substantial clinical threshold needed to be crossed before a genetic test was warranted. When asked if their neurologist should have prescribed a genetic test earlier, three patients responded that while they would prefer to have the diagnosis made clear earlier, their neurologist ordered genetic testing at the appropriate time. Two patients stated they went through multiple neurologists to get genetic testing ordered, although both came up negative for a known SCA variant.

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How has genetic testing for SCA affected you?

Having an undiagnosed progressive neurological condition is frightening and disheartening, yet the users on the forum seemed patient. Diagnosis was an important uncertainty in the lives of many forum participants. Many had been seeking a diagnosis of their symptoms for years. Many did not have a diagnosis for their ataxia and other symptoms despite having undergone extensive diagnostic evaluation, including genetic testing. Despite this, patients encouraged one another regularly to continue the quest for precise diagnosis. In their view, a positive or negative result on a diagnostic test helped and also advanced medical practice for future patients. They fully understood the lack of cure or prevention for any type of SCA and viewed their participation as essential to changing this.

For participants who received a positive result on a genetic test for SCA, many described complex emotions. A positive result can give knowledge about the disease and its prognosis, but there is no cure.

> Marjorienye wrote, "*First, when I was diagnosed and then more so as my symptoms have worsened, I've felt more and more helpless to fight what is happening to me. I like to at least be somewhat knowledgeable about the disease that's wringing the freedom out of my life, since there's very little I can do to fight it. There's no surgery I can have, no experimental drugs, and rehabilitative techniques will only slow things down, not cure me. Sometimes it seems like knowledge is all I can depend on.*"

Many of the positive results came from users who had a relative with a specific form of SCA already diagnosed through genetic testing. The result was particularly difficult if the patient was asymptomatic (meaning that the test was presymptomatic) or if they had children of their own.[32]

> Rrose stated, "*Having a definite diagnosis is helpful is some ways, as I tend to focus my research, but troubling in other ways with respect to my children. They know I have the same thing as their grandmother, but the whole question of when to tell them they can be tested is very difficult. How do you tell three young men 20, 18 and 16 with no symptoms, to have testing done that might change the course of their life decisions? I'm not sure I have the answer to that.*"

The benefits of a positive result included certainty of diagnosis, clearer prognosis, and information relevant to family planning decisions. The variable severity of SCA among subtypes meant that knowing which type a patient has could have a significant impact on almost every aspect of their life. For example, a patient with SCA6 can expect slow deterioration with relatively mild secondary symptoms.[33] The SCA6 patient may be able to continue working a job not requiring much physical exertion. A diagnosis of SCA3, however, carries a much worse prognosis. A patient can expect to lose mobility in 5-10 years and face rapid progression of secondary symptoms that often leave the patient unable to work. For a younger or asymptomatic patient, a diagnosis of SCA3 may change long-term life planning. Dr. Burke reflected that some patients reevaluate their lives based upon the expected years of functionality. Some patients ask him, "W*hy should I go to college if I know that in 20 years I'll be in a wheelchair?*"

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[32] de Villiers C, Weskamp K, Bryer A. The sword of Damocles: the psychosocial impact of familial spinocerebellar ataxia in South Africa. *Am J Med Genet* 1997. 74(3): 270-274.
Smith CO, Lipe HP, Bird TD. Impact of presymptomatic genetic testing for hereditary ataxia and neuromuscular disorders. *Arch Neurol* 2004. 61(6): 875-880.
[33] Maschke M, Oehlert G, Xie TD, Perlman S, Subramony SH et al. Op. cit.

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Do you feel you have access to genetic testing taking into consideration financial constraints?

A majority of the responses from the forum stated that even with genetic tests costing as much as $7,300, genetic testing was accessible. In some cases patients only required a single genetic test for a specific SCA variant. These tests, when performed by Athena, cost the patients from $88 to $440 depending on insurance reimbursement and Patient Protection Program (PPP) enrollment. Four of five patients who had a single test performed felt the price was reasonable even if the out-of-pocket expense was the full $480 cost of the test, that is, without insurance coverage or price reduction through the PPP.

For a patient who did not have a positive diagnosis in their family history, the Complete Ataxia Panel, with its $7,300 price tag, might be the prescribed diagnostic test. If insurance covered the test or the patient successfully enrolls in the PPP, the patient responsibility was $1,500. There were relatively few complaints about the price on the forum. Some comments, however, implied that $1,500 would inflict hardship on their family, especially considering the likely negative result.

> Dancingpoodle wrote, "*I suppose if I felt the test would help cure me if I knew what I had, I would take out a loan to have it done, but since there are no cures at the moment, I don't see a reason for putting that financial burden on my family.*"

Some paid for a complete ataxia panel without any contribution from insurance or the PPP. Such patients included some who got testing from sources other than Athena. Another group of people appeared to be eligible for Athena's PPP but were unaware of the price reduction available. They assumed that denial by insurance was the end of the story, and both the patient and neurologist were unaware of the possibility of negotiating with Athena. In these cases the price of $7,300 reduced testing, with 5 of 9 patients who were rejected by their insurer deciding to forego it. This indicates that both patients and Athena could benefit from greater coverage and reimbursement, and more knowledge about payment assistance and forgiveness programs.

The perceived risk of genetic discrimination is one unfortunate feature of SCA genetic testing. The survey was done before the Genetic Information Nondiscrimination Act passed in May 2008 (and it will not begin to take effect until mid-2009, in any event).

Some who sought testing and might have been eligible for Athena's PPP abstained from using their insurance because they did not want their insurance company to know they were being tested for SCA. These patients voluntarily decided to pay for testing out of pocket and therefore did not qualify for the PPP and often did not qualify for financial hardship reductions through Athena Access either. While respondents on the forum surely did not reflect the general public, but highly selected individuals, it appeared the number foregoing genetic testing might be a significant number among those who would have found clinical value in the information available from the test. Of patients surveyed who had genetic testing and had insurance coverage for the testing, 4 out of 7 patients chose not to notify their insurer (to avoid genetic discrimination for themselves or others in their family). In such cases, the $7,300 price did appear to result in some people choosing not to get tested. Whether or not genetic discrimination actually occurred, as no one reported an actual case of it, perceptions of the risk clearly did lead to decisions not to seek genetic testing. Several respondents were hopeful that GINA, the Genetic Information Nondiscrimination Act, could alleviate health insurance and employment discrimination based on genetic testing if it became law, as it did in May 2008.

Following are the experiences of two respondents describing their hesitation about getting genetic testing. One patient (poolgirl) had the testing covered by insurance, then wished she had not done so due to the possible repercussions if she had tested positive for a SCA variant.

> Poolgirl wrote, "*I had the genetic tests done at a very vulnerable point in my work-up and thankfully they were negative. Given the implications a positive test could have on my children, had I been thinking clearly, I would not have done the tests or would have considered paying for them myself to avoid having them on record. I will not do any tests that become available in the future unless one of my children specifically requests it be done to help guide them if/when they are thinking of having children and if so, I would probably do it off the record. I have no problems with my medical insurance but my personal interaction with my disability company has made me very cynical about trusting any insurance carrier to do the right thing.*"

Another story shows how one patient did not seek insurance reimbursement for her genetic test out of fear that her family would be labeled as a result. The loss of insurance for future generations was a major concern.[34]

> SunnyKay wrote, "*My mother requested that Athena not bill Medicare because she wanted to keep the results private for numerous reasons. That is why a payment plan was arranged instead. My mother not only did not want the health insurance company/Medicare to know about possible SCA results, she did not want to apply for a handicapped license plate with a diagnosis of some form of ataxia either. This is in addition to other things she did to keep anyone from the government or any other unnecessary place from finding out about my Dad's medical history, which of course becomes our and her children's family medical history for life.*"

Conclusions

- Both neurologists and patients stressed that inconsistency in coverage and reimbursement by payers was as a common problem that has real consequences for patients and their families by reducing access to genetic tests for SCA.
- All three neurologists interviewed agreed that a prescription for SCA genetic testing was based primarily on best medical practice, and the clinical value of information, not price. Despite their belief that Athena's prices are higher than if SCA were available in their home institution's laboratory, they did not describe any reduction in recommending genetic testing, and it was unclear whether lowering the price of testing to $100 would increase the number of tests they ordered. They noted, however, that price did affect their patients, who must decide if the value of the genetic testing information is worth the cost, and so high price reduces utilization (and if this information is deemed clinically useful, then also access).
- The neurologists emphasized the care they must take to ensure they never give a diagnosis of SCA lightly, either positive or negative. An incorrect diagnosis can have devastating consequences. From the neurologists' perspective, one advantage of sending samples to Athena for testing is that the liability risks associated with the tests themselves are then borne by Athena.

[34] We note that in this case, health insurance discrimination from a Medicare carrier is unlikely because Medicare is an entitlement and does not entail medical underwriting. This response may reflect an incomplete understanding of Medicare. It is possible, however, that sunnyKay was worried about how a Medicare reimbursement record might affect insurance status of a younger member of the family not in Medicare. It is unlikely, however, that a specific Medicare genetic testing reimbursement decision would affect underwriting, independent of other information potentially in the medical record and available for any medical underwriting involving another family member. This perception of high risk of genetic discrimination is therefore probably not an accurate assessment or real risk, but it also shows that perception of risk can heavily influence the choice to get a genetic test.

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However, this transfer of liability would apply equally to testing sent to any clinical laboratory facility, and is not unique to Athena.

- When applicable, Athena's "Patient Protection Program" can reduce the financial outlay out-of-pocket, and Athena Access is also available for case-by-case review of hardship. This feature was cited in the patient forum as valuable and may help explain the relative dearth of complaints about Athena's pricing. The actual use of this program is unknown, but statistics from Athena's 2001 stock offering suggest 85% of revenues derive hospital and other facility billing, rather than direct patient or insurance payments. Not all patients know about Athena's Patient Protection Program, which can reduce patient out-of-pocket outlays to 20% of test price. Some who do know about it choose not to avail themselves of it for fear of losing health insurance. However, Athena's reported financial data suggest this program is likely applicable to only a small part of Athena's revenue stream (10-15%), and proably a roughly comparable fraction of patients. It is also possible that some patients may not complain about test costs because most of the unreimbursed cost of testing is absorbed by the institutions that are billed directly for testing by Athena.
- From the patient perspective, the main benefit of in-house testing would be any decrease in cost and direct connection between the clinician ordering the tests and the laboratory performing them. Unlike some other case studies, we do not have lists of prices for test providers other than Athena. One published study (Edlefsen et al. 2007) estimated the cost of ataxia testing at an institution would increase nearly seven-fold if all patented tests were referred to Athena rather than being performed by the institution's laboratory. Another estimate of testing price for the five most common SCA mutations was $1,500 for a university laboratory compared to $2,300 for Athena.
- Use of genetic testing is reduced by fear of genetic discrimination by insurers, health plans and employers, which leads some not to seek third-party reimbursement for genetic tests. This was a factor for roughly half those who had insurance coverage, and clearly led to some choices to not get genetic testing despite valuing the clinical information that would result from the tests.
- We cannot discern in most cases whether this fear of genetic discrimination is warranted or merely perceived. Given the long search for a diagnosis in most cases, and thus the accumulation of medical records that would in theory be available to insurers and employers, it could be that the risk attributed to genetic testing specifically is lower than perceived—not necessarily because the risk is not there, but because risks of exclusion from health insurance, disability insurance, employment, or long-term care insurance are present even without the specific action of taking a genetic test. Seeking reimbursement does trigger payer scrutiny, and so the risk of genetic discrimination that some respondents attributed to genetic testing could still be real. Patients expressed a desire for GINA to become law, echoing the calls from the Genetic Alliance and other groups. Passage of the Act, however, will affect employment and health insurance, but not other forms of insurance for disability, life, and long-term care.
- Not all patients know about Athena's Patient Protection Program, which can reduce patient out-of-pocket outlays to 20% of test price. Some who do know about it choose not to avail themselves of it for fear of losing health insurance. GINA's provisions for health insurance may ameliorate this problem when they begin to take effect in 2009.
- The laboratory director believed that exclusive licensing of patented tests created significant barriers to patient access. He believed that academic institutions exclusively licensing patents to single-source providers were short-sighted and did not take into account that a university can achieve an equivalent royalty stream without giving exclusive control of their patents to a single company. He asserted that academic institutions should not accept an exclusive license bid for

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technologies that can readily enter the market. He believed this was especially true for patents on many diagnostic tests, where the scientific advance may simply be a new combination of nucleotides used as a primer for a previously unidentified gene.

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Tables & Figures

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Table 1. Classification of SCA variants

There are currently 24 genetically distinct forms of SCA. The trinucleotide repeat disorders, SCA1-8, comprise 65-80% of diagnosed patients. The classifications labeled in grey are those tested for in Athena Diagnostic's Complete Ataxia Panel ($7,300). Adapted from Zumrova A. Problems and possibilities in the differential diagnosis of syndrome spinocerebellar ataxia. *Neuro Endocrinol Lett* 2005. 26(2): 98-108.

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Genetic Test	Utility	Reference Value	CPT Codes
SCA1	Detects CAG triplet repeat expansion in the SCA1 gene	Normal: < 35 CAG trinucleotide repeats	83891(1), 83898(1), 83904(1), 83909(1), 83912(1)
SCA2	Detects CAG triplet repeat expansion in the SCA2 gene	Normal: < 31 CAG trinucleotide repeats	83891(1), 83898(1), 83909(1), 83912(1)
SCA3	Detects CAG triplet repeat expansion in the SCA3 gene	Normal: < 40 CAG trinucleotide repeats	83891(1), 83898(1), 83909(1), 83912(1)
SCA5	Detects sequence variations in three exons in the Spectrin (SPTBN2) gene known to cause SCA5	No sequence variations detected	83891(1), 83898(3), 83904(3), 83912(1)
SCA6	Detects CAG triplet repeat expansion in the SCA6 gene	Normal: < 18 CAG trinucleotide repeats	83891(1), 83898(1), 83909(1), 83912(1)
SCA7	Detects CAG triplet repeat expansion in the SCA7 gene	Normal: <18 CAG trinucleotide repeats	83891(1), 83898(1), 8909(1), 83912(1)
SCA8	Detects CTA/CTG triplet repeat expansions in the SCA8 gene	Normal: < 50 CTA/CTG trinucleotide repeats	83891(1), 83898(1), 83909(1), 83912(1)
SCA10	Detects ATTCT pentanucleotide expansions in the SCA10 gene	Normal: < 22 ATTCT pentanucleotide repeats detected	83891(1), 83898(1), 83909(1), 83912(1)
SCA13	Detects sequence variations in all of exon 2 and 20 bp of intronic sequence	No sequence variations detected	83891(1), 83898(4), 83904(4), 83909(1), 83912(1)
SCA14	Detects mutations in the SCA14 gene	No sequence alteration detected	83891(1), 83898(15), 83904(16), 83909(1), 83912(1)
SCA17	Detects CAG/CAA triplet repeat expansions in the SCA17 gene	Normal: < 42 CAG/CAA trinucleotide repeats	83891(1), 83898(1), 83909(1), 83912(1)
Frataxin	Detects GAA triplet repeat expansion in the Frataxin gene	Normal: < 33 GAA trinucleotide repeats	83891(1), 83894(1), 83898(1), 83912(1)
Aprataxin	Detects mutations in the aprataxin gene	No sequence alteration detected	83891(1), 83898(7), 83904(7), 83909(1), 83912(1)

Table 2. Description of Genetic Tests on Athena's Complete Ataxia Panel

The Complete Ataxia Panel test for 11 subtypes of SCA, as well as Friedreich's Ataxia and Early Onset Ataxia. Listed are the utility of the test and the reference value of normal for each test. CPT codes are also provided.

This paper was prepared for SACGHS by the Duke U. Center for Genome Ethics, Law & Policy. Any views expressed do not necessarily represent those of SACGHS.

Genetic Test	US Patents	Assignee
SCA-1	**5741645, 5834183**	Regents of the University of Minnesota, Minneapolis, MN
SCA-2	**6251589**	SRL, Inc., Tachikawa, Japan
SCA-3	**5840491**	Akira Kakizuka, Kyoto, Japan
SCA-6	**5853995**, **6303307, 7329487**	Research Development Foundation, Carson City, NV
SCA-7	**6280938, 6514755**, **7118893**	Regents of the University of Minnesota, Minneapolis, MN
SCA-8	6524791	Regents of the University of Minnesota, Minneapolis, MN
SCA-10	6855497	Baylor College of Medicine, Houston, TX
Friedrichs Ataxia (Frataxin)	6150091	Baylor College of Medicine, Houston, TX, INSERM, Paris, France
Aprataxin	**7119186**	Athena Diagnostics, Inc., Worcester, MA

Table 3. Patents associated with Athena's Complete Ataxia Panel

Athena Diagnostics controls 11 patents (in bold) for 6 tests for hereditary ataxia by exclusive licenses. It also holds a non-exclusive license to US6855497 for SCA-10 testing.
Additional patents for SCA-2 (US6623927, US6673535 and US6844431) were found in our search that Athena does not appear to have licensed.

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Provider	Applied Genomics Center at Samaritan	Athena Diagnostics	Baylor College of Medicine	Boston University	Comprehensive Genetic Services, SC	Johns Hopkins University	Reproductive genetics Instutute	US Air Force DNA Diagnostic Laboratory
Lab Name	Genesis Genetics Institute	Reference Lab	Molecular Genetics Laboratories	Center for Human Genetics	Molecular Diagnostic Laboratory	Neurogenetic Testing Laboratory		
Website/ Email	www.genesisgenetics.org	www.athenadiagnostics.com	www.bcm.edu/geneticlabs/	www.bumc.bu.edu	www.compgene.com/	aagarw11@jhmi.edu	www.reproductivegenetics.com/	julie.mccleliangr@keesler.af.mil
Phone	1-313-544-4006	1-800-394-4493	1-800-411-4363	1-617-638-7083	(877) - COMPGENE	(410) 955-1349	773-472-4900	(228) 377-6727
Notes	Prenatal	Adult	Adult and Prenatal	Adult and Prenatal	Adult and Prenatal	Research Only	Prenatal	Military only
Adult Pricing	N/A	PCR=$440 Sequencing=$2,335	$335	SCA1=$310 Others $175	$208	N/A	N/A	N/A
Test								
Method								
SCA1	Targeted Mutation Analysis (PCR)	X	X	X	X			X
SCA2	Targeted Mutation Analysis (PCR)	X	X	X	X		X	X
SCA3	Targeted Mutation Analysis (PCR)	X	X	X	X		X	X
SCA5	Sequence analysis of entire coding region		X					
SCA6	Targeted Mutation Analysis (PCR)		X	X	X	X	X	X
SCA7	Targeted Mutation Analysis (PCR)	X	X	X	X		X	X
SCA8	Targeted Mutation Analysis (PCR)		X	X	X			
SCA10	Targeted Mutation Analysis (PCR)		X	X	X			
SCA12	Targeted Mutation Analysis (PCR)			X		X		
SCA13	Sequence analysis of entire coding region		X					
SCA14	Sequence analysis of entire coding region		X					
SCA17	Targeted Mutation Analysis (PCR)		X	X				
Frataxin	Targeted Mutation Analysis (PCR)		X	X	X			
Aprataxin	Sequence analysis of entire coding region		X	X				

Table 4. Summary of Genetests.org laboratory directory for SCA testing

Patented tests are labeled in grey. Both tests performed by Johns Hopkins are used for research purposes only.

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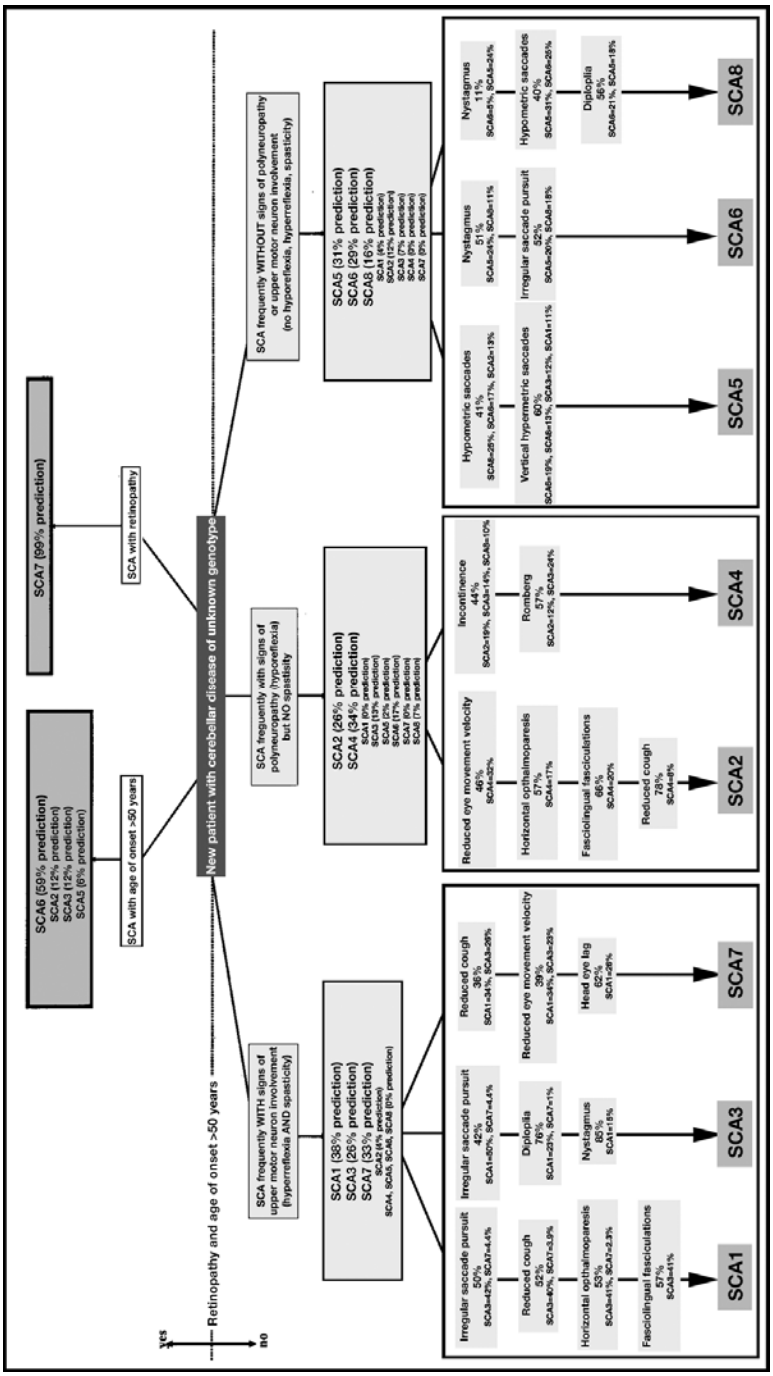

Figure 1. Clinical scales used to determine SCA variants

Many neurologists have attempted to create neurological tests that can increase SCA diagnose accuracy before attempting genetic testing. From Mashke M et al. Clinical feature profile of spinocerebellar ataxia type 1-8 predicts genetically defined subtypes. *Movement Disorders* 2005. 20(11):1405-1412, at 1410.

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Figure 2. Diagnostic tree for Spinocerebellar Ataxia

The diagnostic tree for SCA relies on many different tools. The most powerful remains family history, as this can quickly bring a patient to genetic testing. Because most ataxias are sporadic (not due to known inheritable factors), genetic testing does not occur early in the tree. From Zumrova A. Problems and possibilities in the differential diagnosis of syndrome spinocerebellar ataxia. *Neuro Endocrinol Lett* 2005. 26(2): 98-108.

This paper was prepared for SACGHS by the Duke U. Center for Genome Ethics, Law & Policy. Any views expressed do not necessarily represent those of SACGHS.

athena diagnostics™

Athena Diagnostics, Inc.
Four Biotech Park
377 Plantation Street
Worcester, MA 01605
Tel 508 756 2886 Fax 508 753 5601

October 16, 1998

RE: U.S. Patent Number 5,741,645

Dear Dr. Leonard:

I would like to advise you that Athena Diagnostics is the licensee to a recently issued U.S. patent 5,741,645, which is directed Spinocerebellar Ataxia type 1 (SCA1). A copy of the patent is enclosed for your convenience.

The patent covers methods of identifying whether an individual is or is not at risk for developing SCA1 disease by analyzing whether the SCA1 gene has an increased or normal number of CAG repeats.

We understand that University of Pennsylvannia may be offering a diagnostic test covered by this patent. Any such testing would infringe on the above patent under which Athena has exclusively licensed.

This diagnostic testing service is available through Athena's facilities, and it is only by using Athena's facilities that other laboratories can offer this patented diagnostic test without infringing the patent.

If University of Pennsylvannia is interested in continuing to offer this patented testing service to its customers, Athena would be pleased to perform the service on University of Pennsylvannia behalf.

Very truly yours,

Mike Boss

Michael A. Boss, Ph.D.
Vice President, Operations

Adapted from a presentation by Dr. Debra Leonard, June 21, 2007

Figure 3. Example of a Cease and Desist Letter

Athena Diagnostics has protected their intellectual property rights using letters like the above.

This paper was prepared for SACGHS by the Duke U. Center for Genome Ethics, Law & Policy. Any views expressed do not necessarily represent those of SACGHS.

From: Ashton Powell <Ashton_Powell@med.unc.edu>
Subject: **Patient Survey - Ataxia.org**
Date: October 11, 2007 6:15:47 PM EDT

5 Attachments, 2.3 KB

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Navigation » **National Ataxia Foundation - ENAF BB** » **All About Ataxia** » **Request for help from Ataxia Forum members** » Skin: Standard

Current Replies for Request for help from Ataxia Forum members

[1] 2 3 Next>

Request for help from Ataxia Forum members (Ashton)
Posted: 2:08:37 pm on 8/16/2007 **Modified:** Never

Greetings,

My name is Ashton Powell. I am graduate student at the University of North Carolina at Chapel Hill currently engaged in a fellowship at Duke University at the Genome Ethics, Law & Policy (GELP) Center.

If you are unfamiliar with GELP, we are a research center that attempts to achieve societal consensus on how advances in genome science affect the health, individual rights, and distributive justice of the public. This summer GELP was asked by the US Department of Health and Human Services to provide background and case studies for the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS). More information regarding SACHGS can be found at the following link:

http://www4.od.nih.gov/oba/sacghs.htm

One topic GELP has been researching is to identify the affects, if any, of patents on clinical/patient access to genetic testing. My role in this report is to provide a case study for Spinocerebellar Ataxia, which as you may know has an interesting story regarding genetic testing.

For this case study, I feel I would be remiss if those affected by ataxia were not given the ability to have their voices and experiences included in our analysis. In particular, I am hoping to gain the perspective of those affected by ataxia on the role genetic testing has on their lives, their health, and their wallets.

With that in mind, I am writing to ask if you on this message board would be willing to aid me by answering some issues surrounding genetic testing. Using this forum, I hope a dialogue will form that in addition to providing me with your viewpoint will give the members of the SACGHS a dialogue they can view online.

I have already found many compelling stories on your forum regarding these issues, but creating a single accessible thread for the SACGHS will enable your voices to be heard as one. Committee members are not likely to search for keywords like "Athena" in your forum, they will probably only follow a single link.

Like on your forum, all persons who care to post a comment will remain anonymous. Also, please keep the identity hidden of MDs, or institutions that may have performed SCA tests without permission from Athena as legal action may be taken against them.

Some questions may reflect ignorance, but remember these are questions that may be asked by those completely unfamiliar with SCA, or ataxia in general.

While there are many issues that can be discussed about genetic testing, there are 11 topics in particular I am interested in:

1. Has your neurologist referred you for genetic testing for SCA? How long/how many visits did it take before this test requested? Do you feel this test should have been requested earlier? What was the diagnostic regiment you received prior to and after genetic testing?

2. Does your insurance cover genetic testing for ataxia? Does your insurance cover other, non-genetic testing for SCA?

3. Was/Is the out of pocket price for genetic testing prohibitive to your taking the test?

4. If you have had a genetic test for your ataxia, how did the result affect your treatment?

5. If you have had a genetic test for your ataxia, how did the result affect you feelings or understanding of your symptoms? What was the personal result of the genetic test?

6. For those who have had a genetic test, how many have come back negative? Did insurance tell you if they would cover the test before the results were received?

7. Have you tried to receive genetic testing outside of the US? Have you found labs other than Athena to provide SCA testing? (Please do not name them as it may lead to Athena taking legal action towards them). What were their prices like compared to Athena?

8. Have you been given any differential diagnoses (misdiagnoses) that genetic testing aided?

9. Do you feel that genetic testing for SCA is clinically relevant? How does genetic testing compare to other diagnostic methods?

10. Do you feel you have access to genetic testing? Do you think Athena's licensing monopoly on many of the SCA genetic tests alters the rate of prescription, and does this make the price too great for you to use them?

11. Have you ever used Athena's Patient Protection Plan, which claims to limit patient liability for the cost of a test to 20% as long as they meet cirtain insurance related criteria? Did Athena hold up their part of the bargain, and did this make the test accessible to you?
The plan is described in brief here:

http://www.athenadiagnostics.com/content/ordering/billing

Thank you for your time.

I hope this makes a difference, even if just a small one,

Ashton Powell

Graduate Student

Curriculum in Neurobiology
UNC - Chapel Hill
Polleux Lab

Research Fellow
Genome Ethics, Law & Policy Center
Duke University

Re: Request for help from Ataxia Forum members (dancingpoodle)
Posted: 3:44:47 pm on 8/16/2007 **Modified:** Never

I saw a Movement Specialist at UVA eight months after my initial diagnosis of ataxia. She suggested genetic testing, but my insurance would not cover it, since I don't have a family history of SCA. I cannot afford it out-of-pocket.

I think that Athena having sole ownership of this testing is unethical, and puts it out of reach of many people who may be helped by having this test. The Movement Specialist voiced her opinion on this as well and said it is so frustrating to her since the test could be easily done by more labs at less a cost, and then help her in diagnosing her patients.

Don't know if that helps at all, but that's how things have gone for me. I suppose if I felt the test would help cure me if I knew what I had, I would take out a loan to have it done, but since there are no cures at the moment, I don't see a reason for putting that financial burden on my family.

Cheryl

Re: Request for help from Ataxia Forum members (Ashton)
Posted: 3:58:41 pm on 8/16/2007 **Modified:** Never

Thank you Cheryl,

Your post is exactly what we need.

If you don't mind, I have some follow up questions:

Did your insurance reject you when you asked for a genetic test, or are they never covered?

May I ask you if your Movement Specialist requested a specific SCA test or the Complete Ataxia Panel?

Did you attempt to enroll in Athena's Patient Protection Plan (PPP)? If so, were you accepted?

And forgive me if this is crass, but assuming you were to have the Complete Ataxia Panel performed and were enrolled in the PPP, would the 20% cost to you of $1,460 (down from the $7,300 list price) still place this out of reach?

Thank you again, Cheryl.

Ashton

Re: Request for help from Ataxia Forum members (pawlayer)
Posted: 8:17:33 pm on 8/16/2007 **Modified:** Never

I didn't realize that only Athena Labs could perform this type of genetic testing. Why is this?

Re: Request for help from Ataxia Forum members (Ashton)
Posted: 9:03:15 pm on 8/16/2007 **Modified:** Never

Hi pawlayer,

Thank you for your question.

As of now, Athena Diagnostics holds the licenses to use the patents for genetic testing of SCA-1,2,3,6,7, and EAOH. These comprise the genetic tests estimated 60-80% of known SCA mutations.

It is not clear which ones are exclusive only to Athena, they won't release that information. However, Athena has been known to send laboratories performing these patented methods cease and desist letters. This action has caused several labs to stop performing the test; they now ship the sample to Athena.

As of now, Athena legally has the right to be the only company to perform the tests for the above SCA subtypes, they also have the right to sue anyone who performs them without obtaining a sub-license (which would be very expensive).

The question we are trying to ask is if allowing people to patent genes, methods to test for genes, or methods used for diagnostic genetic tests are keeping patients from using them.

Athena may be jacking up the price and controlling the market, but are they keeping patients from the test?

While any input on whether genes should be patented is welcome, my goal is to try and see the if our current patent system affects patient care, not if patients like how that care gets to them (This is important as well but is another topic).

Thanks,

Ashton

Re: Request for help from Ataxia Forum members (pawlayer)
Posted: 9:23:11 pm on 8/16/2007 **Modified:** Never

Do you know when the patent will expire? My mother used Athena in 1987, 20 years ago.

And from what I have read on this forum, many who suspect they might have some form of ataxia are unable to afford the cost of having the testing done.

I have not yet been tested for SCA 6. I don't know if my insurance will even cover it as I have not been referred for testing.

To answer one of your questions, I would pay for being tested for SCA 6 only, if my insurance did not cover it. However, it would be cost prohibitive for me for anything additional.

Athena set up a payment plan for my sister. She really could not afford it even though insurance paid 80% of the cost. I believe she is still paying for the testing.

Yes, it is unconscionable that other labs are prohibited from doing this. But then again, Botox offers pain relief for people suffering from back pain but it is cost prohibitive because insurance won't cover it, and the company that developed Botox has a patent as well.

So, is Athena preventing people from getting the test? How many responses would you need in the affirmative? There are just over 500 of us signed on to this forum.

Re: Request for help from Ataxia Forum members (Ashton)
Posted: 10:03:21 pm on 8/16/2007 **Modified:** Never

Hi pawlayer,

Thank you for you input, it too is very helpful. Athena does provide testing for SCA-6 individually and if you qualify for the Patient Protection Program, the price you will have to pay may go down to around $100. It may be useful to give Athena a ring to check out the pricing and your eligibility.

I should be clear that Athena will not keep a patient from getting a test, but they may stop a specific lab from performing the test. They want to perform the test themselves. Athena will always give you the test if you have the means to pay for it.

But is the price, despite Athena's allegedly patient friendly payment plans, inhibitive?

The patents controlled by Athena are:

5,741,645 & 5,834,183 SCA-1 Filed: 1995, 1994

6,251,589 SCA-2 Filed: 1998

5,840,491 SCA-3 (MJD) Filed: 1995

5,853,995 & 6,303,307 SCA-6 Filed: 1997, 1999

6,280,938 & 6,514,755 & 7,118,893 SCA-7 Filed:1998, 2000, 2003

7,119,186 EAOH Filed: 2002

They should each expire 17-20 years from their filing date, depending on the laws at the time.

You can find more info on each of these by searching for them at:

freepatentsonline.com/

I'm not sure how your mother's test fits into this picture, but the methodology used my not have incorperated the same techniques at those above.

Ashton

Re: Request for help from Ataxia Forum members (BobJ)
Posted: 8:11:47 am on 8/17/2007 **Modified:** Never

I'll try to answer your questions in exactly the order that you gave them:

1. Yes, but I had to ask him to do it; he didn't "offer" it or suggest it. I requested this test after seeing him for about 4 years!! YES, he should have suggested this test MUCH earlier.

2. So far, my insurance has covered all the testing, but I haven't yet gotten the EOB on the genetic tests - and they were performed back in December of last year (9 months ago!!). I haven't gotten any bill from Athena yet either.

3. Don't know yet (see above answer).

4. All results (results were back by March) were "normal" - no apparent genetic causes.

5. See above . . .

6. See above . . .

7. No, and No

8. No

9. Yes, if it would have revealed a genetic type that there was a treatment for. As it turned out, it did eliminate some possibilities, so that was a "positive" outcome of sorts.

10. Don't know how to answer this one.

11. No, and N/A.

HTH

Will be glad to answer any other questions you may have (that is, IF I can).

BJ

" Start every day with a smile and get it over with. " W.C. Fields

Re: Request for help from Ataxia Forum members (dancingpoodle)
Posted: 10:18:54 am on 8/17/2007 **Modified:** Never

In response to your questions:

The insurance company said they wouldn't cover the genetic testing since there was no family history and the cost was so high.

The doctor wanted a complete panel and was willing to make a case to the insurance company for the need of the test, but because of no family history, there wasn't anything to base the argument on.

I wasn't aware of the PPP, but at this moment the cost would still be prohibitive since I've had to quit working full-time. Just like the insurance company, I guess I don't feel there is enough justification to pay for a test that has a high chance of coming back negative for anything specific.

I really can't complain about the insurance company as they have been great at paying for a lot of MRIs and other tests that have added up. I wonder if the overall cost of the test was reduced for the insurance companies as well, if they would be more willing to pay. After all, they have paid for numerous other tests that have come back negative. The odds of finding an answer with this $7500 tests (and I was told it was closer to $10,000) I suppose make the insurance companies less willing to cover it.

I also just have a personal issue with a company holding a patent for a test that could help more people if is was more readily available. The same as I have problems with companies holding a patent for a vaccine that could save lives and be made in greater quantities if not solely held by one company. I suppose that also makes me less willing to pay the money, but that's just a personal feeling. I'm sure many aren't even aware of the politics behind the testing. It's my own personal boycott, although not really effective, it does make me feel better knowing I'm not supporting a company who is in it for the money instead of the benefit of the people.

Cheryl

Re: Request for help from Ataxia Forum members (jonab)
Posted: 1:42:53 pm on 8/17/2007 **Modified:** Never

Hi there Ashton. Would you please refer to the "Administration" section, where I responded to these questions from a post by Atilla. I intend to take advantage of the Athena Patient Protection Plan.

The problem, as I see it, other than the high cost, is that I have called my insurer to see if I am covered, and they have told me that I am covered, if it's "medically necessary". Well, I sure think that it's medically necessary, and I'm sure that my neuro does, also; but, will the Insurer think so? I'll let the group know how I make out. I'm going to have the Complete Ataxia Evaluation. I do not have a definite diagnosis yet, after 4 years, but I do realize the difficulty of this. The best we have come up with is "sporadic ataxia with nystagmus".

I found this also of interest. My neuro gave me a brochure re Athena, who I already knew about through my neuro, and told me to call Athena and have them call my insurer to see if I'm covered. Athena told me to have my neuro make the call. My neuro then told me to make the call. This is not the way the medical profession was meant to be administered, as we all know.

Thak you,
Best,
Jonab

Re: Request for help from Ataxia Forum members (Atilla)
Posted: 3:25:33 pm on 8/17/2007 **Modified:** 4:07:54 pm on 8/17/2007

We posted all your questions under the Administration forum several days ago. There is even a link to it on the NAF homepage. The reason I started it there was that subjects "sink" rapidly in this forum and may become hard to find.
ATILLA

Mrs. ATILLA still loves me

Re: Request for help from Ataxia Forum members (Ashton)
Posted: 3:26:24 pm on 8/17/2007 **Modified:** Never

Here are several posts that were made from a duplicate of my initial questions. I didn't realize the duplication, so sorry for any confusion. If you could only respond to this thread, Id appreciate it.

I've moved the other posts over to this thread so we can read them all at in one place.

Thank you for bringing this to my attention, jonab and thanks to Attilla, Rhana1, Christina and SunnyKay for your help!

Ashton

Re: Your input please (Rhana1)
Posted: 10:02:57 pm on 8/15/2007 Modified: Never

1. yes. took 1 yr. i don't feel it should have been requested sooner. no diagnostic regimen before or after.

2. my ins does not cover genetic testing.

3. the cost was high, but I still had it done.

4. didn't affect treatment, as i have no treatment.

5. i was disappointed. As i have no diagnosis.

6. neg.

7. no

8. no

9. yes

10. yes

Re: Your input please (clr)
Posted: 10:09:30 am on 8/16/2007 Modified: Never

Hi there,
Here are some of my thoughts:
1. Yes. Three months after my neuro app't., Athena came directly to my house to do the blood draw. I was a bit surprised that my neuro was requesting the complete panel for me, since my mother had previously been tested for SCA1, SCA2 and SCA3 already...I was also sent for a swallowing evaluation and a brain MRI prior to genetic testing.
2. No, genetic testing is not covered by my insurance. Yes, they do cover standard diagnostic testing, such as MRI's, swallow evaluation, etc.
3. No, the pricing of the genetic testing was not prohibitive.
4. Since the results came up negative, my neuro and I agreed to monitor periodically via MRI and perhaps undergo any new genetic testing which becomes commercially available. And in the meantime, I decided to get a second opinion from an Ataxia specialist to confirm my partial diagnosis of SCA, type unknown. Additionally, we have discussed other potentials...
5. See above. Also, my extended family does not completely "buy" into the diagnosis of SCA, type unknown -- they still question past neurological diagnoses, particularly MS. It's very frustrating to me.
6. Yes, mine was negative.
7. No, I have not sought genetic testing outside of the US -- should I?
8. Once again, the genetic testing was supposed to put the MS diagnosis to rest for my family -- but that is still TBD, in some of my family's minds...even though I have tried to explain time and time again that the lesions presence and location is the deciding factor for our diagnosis, as I understand.
9. Yes, I feel that genetic testing for SCA is clinically relevant. However, and using my particular case as an example, other diagnostic methods such as neurological exam results, family history and MRI results are just as, if not even more, significant and revealing.
10. Yes, I have access to genetic testing.

Take care,
Christina

Re: Your input please (SunnyKay)
Posted: 11:03:24 am on 8/16/2007 Modified: Never

Answering as a representative of my family...My Father had Ataxia and died Dec 2004:
1. Yes. Five Years. No. My father had Ataxia for a long time. My parents changed neurologists twice. The third neuro was excellent. He wanted to wait until the genetic testing had improved to a certain level. My family agreed. Prior: Symmetrel, Aricept (d/c'd), physical therapy, home stretching program, cane to rollator to companion chair, participation in research studies. After: My father died within 2 weeks.
2. No. Yes.
3. Yes, but I arranged for my mother to get a payment plan.
4. Too late to have any affect as my father died. The testing was done more for our family than my father at that point.
5. The results were negative with one finding of "undetermined significance". Feelings of family were disappointment.
6. Basically all (see above).
7. No.
8. No.
9. Absolutely. Especially with known hereditary Ataxias.
10. Yes, but it causes financial hardship.

SunnyKay

Everyone Deserves A Great Doc!!!

Re: Your input please (jonab)
Posted: 12:13:12 pm on 8/16/2007 Modified: Never

Atilla:

Thank you. This is very timely and very important.

1.I first saw my neuro in 12/03. He referred me for genetic testing (Athena's Full Ataxia Evaluation) in 11/06. I did not have it done because of the uncertainty of insurance coverage for the $ 7,500 cost.

No, I do not think the test should have been requested earlier.

I have changed insurance and have requested the same testing from Athena, this week, as the new insurance rep said that I was covered as long ass "it is medically necessary". I'll be happy if I only have to pay a 20% co-pay. I will not know, for sure, if I am covered until it's all over.

I have a tentative diagnosis of sporadic ataxia with nystagmus, but my neuro and I understand that this is not final.

2.See above. If the insurance company agrees that if is "medically necessary" then I am covered with a 20% co pay. Yes,I think that my insurance covers non genetic testig for SCA.

3.$7,500 is prohibitive to me. However, I have no choice but to try anything out there, as my condition is deteriorating rapidly.

4. I have not had the genetic testing yet.

5.See 4. above. However, I expect that the tests will prove negative from what I have read of the experience of others.

6.i'll have to get back to you in several weeks, when the tests should be complete.

7.No, I have not tried outside the USA, simply because I hadn't thought of it.

8.No. I haven't had the genetic test yet.

9.Yes. I think that genetic testing for SCA is "the future". I just don't know what there is for us poor.....sho may not have any genetic basis for our "ataxic disorders", as Dr. Perkamn calls them.

10. Yes, I have access to genetic testing thru my neuro. I only know of Athena labs, though.

Thank you, Atilla.

PS My neuro and I agreed that I will see Dr. Perlman, UCLA. Yea! (See my earlier posts)

Best,
Jonab

Re: Request for help from Ataxia Forum members (Rhana1)
Posted: 8:14:32 pm on 8/17/2007 **Modified:** Never

I also already answered these questions, under the Admin section. But if I can be of further help, let me know.

Rhana

Re: Request for help from Ataxia Forum members (pawlayer)
Posted: 12:00:41 pm on 8/18/2007 **Modified:** Never

Here's the response I got from Athena:

"Thank you for your inquiry. All testing must be ordered by a physician.
Athena Diagnostics offers a test called the Familial Mutation Analysis Evaluation. This test is available for family member of patients that have previously been tested by Athena and received a positive result. We will evaluate only the mutation detected in the proband. If we bill a commercial insurance plan with which Athena is not a contracted provider the Patient Protection Plan would limit the out-of-pocket expense to $117. If we are to bill an insurance plan with which we are a contracted provider, the normal co-pay and deductible obligations would apply. Would you need to contact the insurance directly for that information."

I won't be able to fully participate in your questionnaire until I have been tested. I hope this will be ongoing as I will not even meet with the neurologist until November.

Patricia

Re: Request for help from Ataxia Forum members (Ashton)
Posted: 4:19:06 pm on 8/20/2007 **Modified:** Never

Hi Rhana,

Does your insurance not cover any genetic testing or just the SCA testing?

Where you able to enroll in the Patient Protection Program that Athena has?

If the Complete Ataxia Panle were now $1500 out of pocket, would you be willing or able to have it performed?

Thanks you for your help,

Ashton

Re: Request for help from Ataxia Forum members (SunnyKay)
Posted: 8:21:00 pm on 8/20/2007 **Modified:** Never

Ashton,

As far as I know, Medicare does not cover SCA testing. My mother requested that Athena NOT BILL MEDICARE because she wanted to keep the results PRIVATE for numerous reasons. That is why a payment plan was arranged instead.
SunnyKay

Everyone Deserves A Great Doc!!!

Re: Request for help from Ataxia Forum members (Ashton)
Posted: 8:42:28 pm on 8/20/2007 **Modified:** Never

As an addition to this topic, how many of you feel the need to get a diagnosis for SCA outside the knowledge of your insurance carrier?

It appears the pricing Athena gives assumes that insurance will be involved and will pay the massive price of the tests. If insurance REFUSES to pay, then Athena's Patient Protection Plan will cover most of the costs. However, if a patient

CHOOSES not want to use insurance, it then they have to take the entire cost themselves.

Unfortunately this leaves one heck of a bill.

Is the genetic test the only diagnostic test you all choose to take outside of insurance?

Do you fear discrimination from the insurance companies?

Have any of you encountered discrimination from an insurance company due to a genetic test?

Thank you,
Ashton

Re: Request for help from Ataxia Forum members (Ashton)
Posted: 9:40:05 am on 8/21/2007 **Modified:** Never

Re: Your input please (mmhogan)
Posted: 10:30:43 am on 8/18/2007 Modified: Never

1. No because the results for other members of my family with Ataxia have shown negative to all known SCA's. No, because it would not be cost effective to spend money testing for something that will almost certainly show negative as well. Diagnostic regiment included neurological exam and MRI, in depth record of family history.

2. Yes, we are an active duty military family...health insurance is free.

3. No

4. N/A

5. N/A

6. N/A

7. No

8. Previously misdiagnosed w/ eye problems due to altitude.

9. Yes. It's the only way to know if you have one of the known testable Ataxias.

10. Yes.

Mary

Re: Request for help from Ataxia Forum members (clr)
Posted: 9:59:16 am on 8/21/2007 **Modified:** Never

Hi Ashton,
Isn't this where GINA may come in handy, when finally passed?

Take care,
Christina

Re: Request for help from Ataxia Forum members (Ashton)
Posted: 10:42:45 am on 8/21/2007 **Modified:** Never

Hi Christina,

Well, Genetic Non-discrimination laws have been brought up in congress every year for the past ten years, but none have yet to pass. This year looks like it may pass, but you never know. There are many states that have passed nondiscrimination laws regarding genetics, but a federal law is way past due.

It would do nothing but help get this passed if there is more evidence of how patients use genetic testing (among other medical treatments) based upon real or perceived risks of discrimination by their insurance carriers.

It appears that in the case of SCA, there are quite a few patients who want to know the result of the test without their insurance knowing. I can only assume this is due to a fear of what an insurance company may do to them or their family members with this information.

Any information/stories about the "risks" of diagnosis would be quite interesting.

Thanks,
Ashton

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Re: Request for help from Ataxia Forum members (SunnyKay)
Posted: 1:02:14 pm on 8/21/2007 **Modified:** Never

SunnyKay here again...See above...
My mother not only did not want the health insurance company/Medicare to know about possible SCA results, she did not want to apply for a handicapped license plate with a diagnosis of some form of Ataxia either. This is in addition to other things she did to keep anyone from the government or any other unnecessary place from finding out about my Dad's medical history (which of course becomes OUR, her children's, family medical history for life...life insurance, Long Term Care, disability, employment, health insurance, etc., etc.).
SunnyKay

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Re: Request for help from Ataxia Forum members (marjorienye)
Posted: 2:53:07 pm on 8/21/2007 **Modified:** Never

Ashton-

1. My research neuro at Johns Hopkins asked that I request the test from my local treating neuro, who was happy to comply. I was diagnosed with "An hereditary form of Cerebellar Ataxia" based on my history and the physical exam. I was negative for all but an SETX mutation of unknown significance after the Athena tests.

2. It paid 80%, so I had to pay like $1,500.

3. Yes.

4. I suppose it didn't. My neuro pretty much just documents my degeneration and I have to find my own rehabilitation techniques. I tell him and he says "Hm. That's a good idea."

5. I felt a lot better having a clearer picture of my Ataxia. It also greatly helped my research neurologist.

6. There wasn't a problem with my insurance. All but the SETX mutation were negative.

7. No.

8. I think for awhile neurologists treating my family were thinking we probably had SCA6- it's helped a lot to be able to rule that out.

9. SCAs vary too much to rely on anything other than genetic testing. And unless we separate out the different genetic mutations, how could we ever hope to fix them?

10. Definitely. If more ataxians could be genetically tested, I think it would further Ataxia research. The cost and inavailability keeps a lot of people from digging deeper into the cause of their neurological problems.

11. I think so, but my insurance plan was very good, so I think that was mainly why I didn't have many problems dealing with them.

If there's anything else I can do to help, Ashton, just say the word. I live in Roanoke, which is pretty close to you. My email is marjorie.nyeATgmail.com

-Marjorie

"Onward we stagger, and if the tanks come, may God help the tanks."
—William O. Darby

Re: Request for help from Ataxia Forum members (marjorienye)
Posted: 2:54:00 pm on 8/21/2007 **Modified:** Never

Ashton-
1. My research neuro at Johns Hopkins asked that I request the test from my local treating neuro, who was happy to comply. I was diagnosed with "An hereditary form of Cerebellar Ataxia" based on my history and the physical exam. I was negative for all but an SETX mutation of unknown significance after the Athena tests.

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4. I suppose it didn't. My neuro pretty much just documents my degeneration and I have to find my own rehabilitation techniques. I tell him and he says "Hm. That's a good idea."

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If there's anything else I can do to help, Ashton, just say the word. I live in Roanoke VA, which is pretty close to you. My email is marjorie.nyeATgmail.com
-Marjorie
"Onward we stagger, and if the tanks come, may God help the tanks."
—William O. Darby

Re: Request for help from Ataxia Forum members (Happy Christian)
Posted: 12:56:30 am on 8/22/2007 **Modified:** Never

I AM NEW TO THIS FORUM. I JUST RECENTLY LEARNED ABOUT NAF. I DON'T WANT TO APPEAR STUPID, BUT WHAT IS ATHENA?

I HAVE NOT HAD ANY GENETIC TESTING, BECAUSE I KNEW RIGHT FROM THE BEGINNING OF MY DIAGNOSE THAT MY INSURANCE WOULD NOT COVER GENETIC TESTING. I WAS DIAGNOSED WITH SPINOCEREBELLAR DEGENERATION IN 2002. I HAVE LIVED WITH ATAXIA SINCE MY EARLY 30'S (AND IAM NOW 64) BUT MY PREVIOUS DOC (BEFORE 2002) WAS ONLY LOOKING FOR MS.

WHERE IS THE GENETIC TESTING DONE? I LIVE IN NORTH EAST OHIO

ANSWERS TO MY QUESTIONS WOULD BE APPRECIATED. THANK YOU

HAPPY CHRISTIAN

Re: Request for help from Ataxia Forum members (pawlayer)
Posted: 9:11:14 am on 8/22/2007 **Modified:** Never

Hi and Welcome:

Athena is a lab that conducts the testing for diagnosing diseases, more importantly, in this instance the testing for the different types of ataxias. I believe it is located in Mass., but it operates all over the country (my understanding). They have a web site which will give you a lot more information. Just Google Athena Diagnostics, and its official site will come up. They have a lot of information about the company on its site.

Re: Request for help from Ataxia Forum members (Ashton)
Posted: 11:05:17 am on 8/22/2007 **Modified:** Never

Hi Happy Christian,

Welcome to our discussion. Don't feel stupid at all, especially when our discussion is to ask whether the system we are working with is stupid.

As pawlayer said, you can find much information regarding the genetic testing Athena offers, and has legal rights to be the sole provider for at:

athenadiagnostics.com

Some of the issues we are attempting to figure out are if the prices Athena uses for these tests, which are expensive even if done at cost, are preventing patients from using them according to best medical practice. The real goal is to ask whether current patent law, which allows them to dictate price is affecting patient access to the tests.

There is an interesting relationship however between Athena, insurance companies, and MD/patients that is coming from this. Athena charges a large sum for testing, but has a Patient Protection Program (PPP) that limits the patient's liability to 20% of the total cost of the test. This brings the cost of the test down to what is generally the co-pay required if you insurance decides against coverage for the test.

However, it appears that many of you are not attempting to see if you are eligible for the PPP because you already know your insurance does not cover these tests. I am not 100% sure, but you may still be eligible for the reduced rate from Athena, it wouldn't hurt to ask.

The other interesting topic is that many patients choose to keep insurance out of the picture for a variety of personal reasons, but this ensures the price of testing will remain the massive $7,300. In other words, the requirement of insurance has reared its ugly head in this discussion.

Thanks for any input you have,

Ashton

Re: Request for help from Ataxia Forum members (Poolgirl)
Posted: 3:19:33 am on 8/23/2007 **Modified:** Never

Hi Ashton,
Answers to questions:
1. Yes. several years after first symptoms and ordered by 6th Neurologist I saw (to be fair to others, my exam changed significantly during that time).

2.Insurance covers all my testing

3. see #2

4. No

5. Ataxia panel negative. Only real benefit for me was less worry that I might have passed something on to my children (althought I am well aware that just means I don't have one of the already identified genetic ataxias).

6. Tests negative

7. No

8. No

9. I feel testing is indicating if the history strongly suggests the test will be positive. Having an ataxia specialist narrow down the most likely disease may help cut down on blindly running full ataxia panels. I am not sure if it is more cost effective to run specific test or the whole panel. Sometimes labs bundle tests and it ends up being cheaper to run the panel(maybe you already anwered this but if not, could you please address running for example, 3 variants versus panel. I personally feel the other tests to look for treatable causes of ataxia are more important and should be done first.

10. tests were covered

11. tests were covered

Note: I had the genetic tests done at a very vulnerable point in my work up and thankfully they were negative. Given the implications a positive test could have on my children, had I been thinking clearly, I would not have done the test or would have considered paying for them myself to avoid having them on record. I will not do any tests that become available in the future unless one of my children specifically requests it be done to help guide them if/when they are thinking of having children and if so, I would probably do it off the record. I have no problems with my medical insurance but my personal interaction with my disability company has made me very cynical about trusting any "insurance" carrier to " do the right thing".

PG

Re: Request for help from Ataxia Forum members (Atilla)
Posted: 9:06:30 am on 8/23/2007 **Modified:** 1:17:58 pm on 8/23/2007

If you haven't already, you may want to contact Dr. Marsha Nance. She is the NAF "expert" on genetic testing.
ATILLA

Mrs. ATILLA still loves me

Re: Request for help from Ataxia Forum members (rrose)
Posted: 2:03:08 pm on 8/23/2007 **Modified:** Never

Ashton...I have SCA6 which was confirmed by testing at Athena Labs. I will try to answer your questions.

1. My neurologist suggested testing after my first visit in 2004. He is a movement specialist that I was referred to by another neurologist who suspected some type of dominant Ataxia. I sought out treatment after experiencing similiar symptoms to my mother, who at that time had been told she had "some troubling signs" on an MRI, but was not offered any genetic testing. Her neurologist told her it was very expensive and it would not change anything in her prognosis as there was nothing that could be done for her. I had a full panel of tests done and was initially told the results were inconclusive. Athena requested another blood sample to re-run the tests, but for some reason my doctor failed to communicate this to me until March of 2007. He then sent new samples to Athena (at no additional cost to me) and I received a definite diagnosis of SCA6.

2. My insurance company did not cover the cost of the test. The cost to me was $2500. They told me at the time it was because Athena was not one of their preferred providers. I was required to pay the entire amount upfront, directly to Athena Labs.

3. No, but I only paid $2500, not the $7500 mentioned in the posts on this forum.

4. Only that I stopped the worrying about gluten, and the possibility that I might have gluten ataxia.

5. Having a definite diagnosis is helpful is some ways, as I tend to focus my research, but troubling in other ways with respect to my children. They know I have the same thing as their grandmother, but the whole question of when to tell them they can be tested is very difficult. How do you tell three young men 20,18 and 16 with no symptoms, to have testing done that might change the course of their life decisions? I'm not sure I have the answer to that.

6. My initial results were inconclusive, but eventually were confirmed as SCA6. I had to pay for the tests out of pocket.

7. No

8. No, just confirmation when the final results came back.

9. Yes. Because I now have a definite diagnosis, the other members of my extended family who have been misdiagnosed, can request testing be done for SCA6 only, at a greatly reduced price. Many of which, could not otherwise afford the tests.

10. Yes. Just a little hiccup with the results, but appears to have been on the part of my neurologist, not Athena.

11. N/A

I hope this information is helpful. Thanks for your efforts.

RRose

Re: Request for help from Ataxia Forum members (jonab)
Posted: 5:19:41 pm on 8/23/2007 **Modified:** Never

Hi RROSE;

Just one small point of possible clarification. The Athena Complete Ataxia Evaluation is more than one test, and cost about $7500. It may be that the $2500 that you mentioned was for one test only.

Best,
Jonab

Re: Request for help from Ataxia Forum members (SunnyKay)
Posted: 7:37:52 pm on 8/23/2007 **Modified:** Never

Jonab and All,
When my Dad was tested in the fall of 2004, there were less available tests in Athena's Complete Ataxia Panel, and the cost was much less than $7500 as I recall...
SunnyKay

Everyone Deserves A Great Doc!!!

Re: Request for help from Ataxia Forum members (Steph74)
Posted: 10:38:28 pm on 8/23/2007 **Modified:** Never

1. No - I got tested on my own and went to a genetic counselor, after my father was diagnosed, I'm currently asymptomatic. It took me almost 2 months to get my results, since Athena had to run the test twice due to a lab "error". My genetic counselor failed to tell me, so I showed up awaiting the results and then was told I would have to come back again.

2. Yes BCBS - but I paid for it out of pocket so they were unaware.

3. No

4. I was shown to have the expansion for SCA1, but no treatment since I have no sysmtoms as of yet.

5. I was pretty upset, but I knew I had a 50% chance.

6. N/A

7. No

8. No

9. N/A

10. N/A

11. No

* I'm not that happy with Athena - first it took FOREVER to get my results, and second, I asked them to run my father and I's blood next to each other (we had gotten our samples done years apart) so I could look at repeat differential - I even offered to pay, but they refused.

Re: Request for help from Ataxia Forum members (Ashton)
Posted: 7:57:15 pm on 8/24/2007 **Modified:** Never

Hi Steph74,

Thank you for helping me out with this project. I'm sorry to hear about about your results considering you are asymptomatic. I hope your experiences will help us move towards some true cures in the near future.

If you don't mind, may I ask you some specific questions about your testing?

How much did the single SCA-1 test cost you?

Do you consider this price reasonable, especially with insurance not being part of the equation?

Since your father been tested by Athena before and came back positive, were you given a discount?

What do you feel, or know would happen with your insurance if they were involved in this testing?

Thank you Steph,

Ashton

Re: Request for help from Ataxia Forum members (rrose)
Posted: 8:08:26 pm on 8/24/2007 **Modified:** Never

Hi Jonab,

Actually I did have the complete Ataxia panel done. I was under the impression that I was covering the entire cost, but with the information I am reading in this forum, my insurance company may have in fact paid for a portion of it. My testing was done several years ago, and at the time my neurologist was not hopeful that insurance would cover it. But possibly they did. That would be a surprise!

Re: Request for help from Ataxia Forum members (Steph74)
Posted: 8:53:41 pm on 8/24/2007 **Modified:** Never

1) Somewhere around $600 (I really can't remember specifics) - this was in 2006.

2) Yes, I would consider this price reasonable.

3) No, I wasn't given a discount.

4) I have not experienced any negative results with BCBS. They are now aware of my status of SCA (even asymtomatic) because I had a child and disclosed it during my pregnancy, due to risks related to labor/delivery. There has been full payment for everything. I even had my child tested in utero for SCA and they paid for it in full. I've also been to an ataxia neuro to make sure I wasn't showing any symptoms and they paid for that consultation as well.

Re: Request for help from Ataxia Forum members (Ashton)
Posted: 9:05:45 pm on 8/24/2007 **Modified:** Never

Hi Marjorie,

Thanks for your input,

I have a question for you that is not as much about the pricing of the tests, but the human desire to learn more about themselves.

Before medical research was able to differentiate between the genetic subtypes of SCA, the diagnosis for many of the "ataxians" would have been Olivopontine cerebellar atrophy (OPCA). Later the classification of these hereditary ataxias was

divided into autosomal dominant cerebellar ataxia classes (ADCA) I, II, and III. We now know that ADCA I encompasses SCA1, 2, and 3, ADCA II is SCA7, and ADCA III is SCA4, 5, 6, and 11.

Do you feel that your desire to search for a diagnosis would have been quenched if OPCA was your diagnosis and research was where it was 20 years ago? Would that satisfy you today?

If a new SCA designation is identified genetically do you think it would change any satisfaction you may have with this hypothetical diagnosis of OPCA? Does the search begin anew whenever there is a possible refinement of diagnosis?

Anyone else who has any thoughts on this, please feel free to write. In some ways this may help describe whether the patient demand for genetic introspection may coax people into paying fees for tests that well above their true value.

Thanks Marjorie,
Ashton

Re: Request for help from Ataxia Forum members (Ashton)
Posted: 9:18:24 pm on 8/24/2007 **Modified:** Never

Hi Poolgirl,

Thanks for your answers, they are quite helpful.

Did you have any co-pay for the test?

You write a bit about cynicism toward insurance companies and a positive result (a feeling shared by many of us I'm sure!)

The standard fear is that a company may now drop you or make it difficult for your children if the result is positive, but does an insurance company treat you any differently if you come back negative? Have you noticed a difference in how responsible an insurance company feels in regard to covering treatment for an undiagnosed vs. negatively diagnosed client?

As for different panels for the tests, I agree it would make sense for a company to offer "combo meals" depending on common symptoms or diagnostic procedure. I will discuss it in my report.

Thanks for the ideas,
Ashton

Re: Request for help from Ataxia Forum members (mariorienye)
Posted: 10:43:59 pm on 8/24/2007 **Modified:** Never

Ashton-

My granddad and his brother were originally diagnosed with OPCA. The general feeling in my family for the past 200+ years we've passed this along is that you can't do anything about it, so why bother thinking too much about it. But I myself feel driven to find out as much about it as I can.

First when I was diagnosed and then more so as my symptoms have worsened, I've felt more and more helpless to fight what is happening to me. I like to at least be somewhat knowledgeable about the disease that's wringing the freedom out of my lives, since there's very little I can do to fight it. There's no surgery I can have, no experimental drugs, and rehabilitative techniques will only slow things down, not cure me. Sometimes it seems like knowledge is all I can depend on.

So yes, I think I will continue to be dissatisfied and will continue to get all the testing I can to find out more about my Ataxia.

-Marjorie

"Onward we stagger, and if the tanks come, may God help the tanks."
—William O. Darby

Re: Request for help from Ataxia Forum members (smitties5)
Posted: 10:16:52 am on 8/29/2007 **Modified:** Never

I was diagnosed in June 2006, I am 54. i talk to a lady in Georgia who's had ataxia for 20 years or more. So I asked my dr.(neurologist at Jefferson) if it was to my benfit that I was diagnosed later in life, and he said yes.

Any comment or suggestions?

Beverly Smith

Re: Request for help from Ataxia Forum members (SunnyKay)
Posted: 7:15:53 pm on 8/29/2007 **Modified:** Never

Ashton,

My mother donated my father's brain for research "to help the future". I personally want to know an exact diagnosis as soon as it is determined, discovered, named, etc. We were given 2 potential diagnoses but they were not any identified SCAs and I personally disagree with them. (They seem to be even more rare than some of the SCAs!) I'm a family doc, and they just don't match what my Dad had.
SunnyKay

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Re: Request for help from Ataxia Forum members (greekmom81)
Posted: 2:26:23 pm on 9/3/2007 **Modified:** Never

Hi Ashton,

I don't know if my story qualifies for your study, but you can be the judge. Well after we came back from a long vacation to Europe, I noticed that I couldn't balance on my right foot. I mentioned to our doctor who assured me that it happens to everybody one time or another. I was 49 years old. I let it go and I mentioned again after a year because it wasn't getting any better. He sent me to a neurologist who after examined me, and a MRI, he found nothing wrong. To make the long story short after him I visited a lot of other neurologists who they suspected Parkinson or MS but nothing concrete. In 2000 I went to UT SOUTHWEST where with a MRI I was diagnosed with 'sporadic OPCA'. Since we didn't know what was it , we didn't panic even though he told us there is no cure for it.
Since then I saw a lot of doctors in Houston, Galveston, Dallas, but none of them suggested genetic testing. I participated in a clinical trial in NIH for IVIG but even though I got the right medicine they stopped the trial because the drug wasn't doing any good to the majority of the people. I tried acupuncture, gluten diet, vitamins, chiropractor, alternative medicine, without success. So I am going to try to answer your questions as good as I can.
1. NO
2. NO/NO
3. YES
4. IT DEPENDS (A LOT OF STUDIES ARE ONLY FOR GENETIC TYPES)
5. I DON'T KNOW. I HAD NO SYMPTOMS
6. N/A
7. NO, NO
8. A LITTLE ABOU MS OR PARKINSON
9. YES, I THINK IS MORE ACCURATE
10. YES
11. NO, AND I DON'T THINK I AM QUALIFY
IF THE INS. CAN NOT USE THE RESULTS AND DROP ANY OF US
GREEKMOM81

Re: Request for help from Ataxia Forum members (chyann)
Posted: 11:00:58 pm on 9/3/2007 **Modified:** Never

1. Has your neurologist referred you for genetic testing for SCA? Yes

How long/how many visits did it take before this test requested? This was a new neurologist but he did it on the first visit. It had never been done before.

Do you feel this test should have been requested earlier? Probably, but it was not until 16 years ago.

What was the diagnostic regiment you received prior to and after genetic testing? As a child I had spinal taps, x-rays, brain scans, touch-your-finger-to-your-nose-with-your-eyes-closed, stand with your eyes closed, walk this line, etc. type of tests but it had come down to 'do you think it has gotten worse' questions as an adult. Since the tests could not pinpoint wha kind of ataxia it is, the treatments were megadoses of vitamin E, coQ10 and suggestions that 'swimming will help your muscle tone so you will have more control' type of treatments.

2. Does your insurance cover genetic testing for ataxia? Yes

Does your insurance cover other, non-genetic testing for SCA? MRI, and physical therapy to train me to use a walker and now a scooter.

3. Was/Is the out of pocket price for genetic testing prohibitive to your taking the test? I only paid for the office visits but it has been years since the last test.

4. If you have had a genetic test for your ataxia, how did the result affect your treatment? No effect because it did not pinpoint the KIND of ataxia.

5. If you have had a genetic test for your ataxia, how did the result affect you feelings or understanding of your symptoms? No effect, nothing new.

What was the personal result of the genetic test? No result

6. For those who have had a genetic test, how many have come back negative? It is definitely not something else.

Did insurance tell you if they would cover the test before the results were received? No

7. Have you tried to receive genetic testing outside of the US? No

Have you found labs other than Athena to provide SCA testing? No
(Please do not name them as it may lead to Athena taking legal action towards them).

What were their prices like compared to Athena?

8. Have you been given any differential diagnoses (misdiagnoses) that genetic testing aided? No, by the time genetic testing was done I was grown and I was diagnosed at age 10

9. Do you feel that genetic testing for SCA is clinically relevant? Yes, ataxia has terrible consequences. If they can find the cause and fix it, many people would be spared much suffering.

How does genetic testing compare to other diagnostic methods? I don't know, I'm not a doctor.

10. Do you feel you have access to genetic testing? I've been tested several times in the last few years.

Do you think Athena's licensing monopoly on many of the SCA genetic tests alters the rate of prescription, and does this make the price too great for you to use them? No

11. Have you ever used Athena's Patient Protection Plan, which claims to limit patient liability for the cost of a test to 20% as long as they meet cirtain insurance related criteria? Insurance always paid because I have a definite diagnosis.

Did Athena hold up their part of the bargain, and did this make the test accessible to you? No problems

Re: Request for help from Ataxia Forum members (lacams)
Posted: 2:04:18 am on 9/5/2007 **Modified:** Never

1. Has your neurologist referred you for genetic testing for SCA? YES How long/how many visits did it take before this test requested? ONGOING, AS NEW TESTS WERE DEVELOPED Do you feel this test should have been requested

earlier? YES What was the diagnostic regiment you received prior to and after genetic testing? THE GENERAL SCA DX WAS CLEARLY INHERITED

2. Does your insurance cover genetic testing for ataxia? SOME Does your insurance cover other, non-genetic testing for SCA? YES

3. Was/Is the out of pocket price for genetic testing prohibitive to your taking the test? YES, ABSOLUTELY!

4. If you have had a genetic test for your ataxia, how did the result affect your treatment? ONLY NEGATIVE RESULTS SO FAR, BUT MANY TESTS HAVE YET TO BE DONE

5. If you have had a genetic test for your ataxia, how did the result affect you feelings or understanding of your symptoms? FRUSTRATION What was the personal result of the genetic test? THE FEW TESTS DONE SO FAR WERE ALL NEGATIVE

6. For those who have had a genetic test, how many have come back negative? SEVEN Did insurance tell you if they would cover the test before the results were received? PARTIALLY

7. Have you tried to receive genetic testing outside of the US? NO Have you found labs other than Athena to provide SCA testing? NO (Please do not name them as it may lead to Athena taking legal action towards them). What were their prices like compared to Athena? I DON¡¡T KNOW. IT¡¡D BE NICE IF SOMEBODY WOULD SLIP AN ANONYMOUS REFERRAL INTO THIS FORUM.

8. Have you been given any differential diagnoses (misdiagnoses) that genetic testing aided? NO

9. Do you feel that genetic testing for SCA is clinically relevant? TOTALLY! How does genetic testing compare to other diagnostic methods? IT WOULD BE AWESOME, ESP SINCE WE HAVE KIDS AND OTHER RELATIVES WHO COULD BE AFFECTED

10. Do you feel you have access to genetic testing? NOT AT THE MOMENT Do you think Athena's licensing monopoly on many of the SCA genetic tests alters the rate of prescription, and does this make the price too great for you to use them? ABSOLUTELY!

11. Have you ever used Athena's Patient Protection Plan, which claims to limit patient liability for the cost of a test to 20% as long as they meet cirtain insurance related criteria? THEY ARE CURRENTLY DEMANDING AN EXHORBITANT COPAY UP FRONT Did Athena hold up their part of the bargain, and did this make the test accessible to you? IT PROBABLY WILL BE INACCESSIBLE. ƒ¼
The plan is described in brief here:

http://www.athenadiagnostics.com/content/ordering/billing

Re: Request for help from Ataxia Forum members (jonab)
Posted: 1:01:16 pm on 9/9/2007 **Modified:** Never

Hi there Ashton:

I have already responded to your questionnaire, but I have not completed the Athena testing yet. Presently, my blood samples are at Athena being tested and I expect the results in a another week or two. They are doing the Complete Ataxia Evaluation (Panel).

I did want to inform you though that Athena said that I was not eligible for the Patient Protection Plan since they have a contract with my insurance company.

I can only hope that this means that I'll only be responsible for the co-payment. I'll let you know the end results.

I hope that your system can handle piecemeal data like this.

Best,
Jonab

<Previous 1 2 **[3]**

There are currently 600 members registered on National Ataxia Foundation - ENAF BB.

Impact of Gene Patents and Licensing Practices on Access to Genetic Testing and Carrier Screening for Tay-Sachs and Canavan Disease

Alessandra Colaianni, B.A., Subhashini Chandrasekharan, Ph.D., and Robert Cook-Deegan, M.D.*

Introduction

Tay-Sachs and Canavan disease are both neurological conditions that predominantly but not exclusively affect the Ashkenazi Jewish population. Carrier screening and genetic diagnosis for Tay-Sachs are mainly through enzyme assay, with DNA-based testing for ambiguous cases or for diagnostic confirmation. DNA-based analysis is the mainstay for both screening and diagnostic confirmation of Canavan disease. Nonprofit research institutions obtained patents on both relevant genes, first the gene that when mutated cause Tay-Sachs (the HEXA gene encoding the enzyme hexosaminidase A) and later for Canavan disease (the ASPA gene encoding aspartoacylase). The inventor for the HEXA patent worked at the National Institutes of Health, a government laboratory, and her Tay-Sachs patent was never licensed. That discovery is, therefore, effectively in the public domain. The patents relevant to Canavan disease, in contrast, were licensed by Miami Children's Hospital. The patents were eventually nonexclusively licensed at least 20 times. Patenting and licensing were initially highly controversial and led to litigation. Because the two diseases are similar pathologically and affect the same population, this difference in licensing history created a natural experiment to assess the impact of licensing practices on patients' and physicians' clinical access to genetic tests.

Background

Tay-Sachs disease (TSD) is a progressive disease that destroys brain function. TSD is caused by inheriting two mutated copies of the HEXA gene (one from each parent), which produces the hexosaminidase A subunit of an enzyme-protein complex. In an unaffected individual, the enzyme is part of a pathway that degrades Gm2 gangliosides, complex protein-carbohydrate molecules. In an individual affected by TSD, the absence or reduced activity of the enzyme causes the Gm2 gangliosides to build up in the brain—the metabolic pathway is blocked. This causes progressive destruction of the central nervous system. There are three types of TSD, differentiated by age of onset: acute infantile, juvenile, and late-onset. Infantile onset is the most common. In the classic progression of acute infantile TSD, the infant gets progressively weaker and loses motor skills between the ages of six months and three years. The infant has progressively diminished attentiveness and an exaggerated startle response. As TSD continues to destroy the brain, the infant suffers seizures, blindness, and eventually death, which usually occurs before four years of age. Death is painful for its victim and agonizing for parents and family. There is no cure for TSD, and treatment is limited to supportive care.[1]

Canavan disease also causes progressive deterioration of the brain. It is caused by inheriting two mutated copies of the ASPA gene, which encodes the aspartoacylase enzyme. In a normal individual, aspartoacylase breaks down *N*-acetylaspartic acid (NAA). In Canavan disease, the lack of aspartoacylase leads to a buildup of NAA in the brain, which causes demyelination and degeneration.[2] Symptoms of

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[1] Kaback, M. *Hexosaminidase A Deficiency*. See http://www.genetests.org/servlet/access?db=geneclinics&site=gt&id=8888891&key=aMeTZgBKBQcB9&gry=&fcn=y&fw=mD3m&filename=/profiles/tay-sachs/index.html [accessed February 22, 2008].

[2] Matalon R, Michals K, Kaul R. Canavan disease: from spongy degeneration to molecular analysis. *The Journal of Pediatrics*1995. 127(4):511-517, at 511, 512.

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Canavan disease are macrocephaly (larger-than-normal head size), lack of head control, developmental delays by the age of three to five months, and loss of muscle control. As the brain continues to deteriorate, the affected child suffers from muscle spasms and seizures. Individuals with Canavan disease are expected to live into their teens.[3] Like TSD, there is no cure for Canavan disease, and treatment is limited to supportive care.

	Tay-Sachs disease	**Canavan disease**
Mode of Inheritance	Autosomal Recessive[4*]	Autosomal Recessive[5]
Cause	Hexosaminidase A deficiency, leading to buildup of Gm2 gangliosides in neuronal cells[6]	Aspartoacylase deficiency leading to buildup of N-acetylaspartic acid, leading to demyelination and spongy degeneration of the brain[7]
Symptoms	Weakness, loss of motor skills, decreased attentiveness, increased startle response, death usually before age four[8]	Macrocephaly (large head), lack of head control, hypotonia (lack of muscle tone), seizures, spasticity, failure to achieve independent sitting, ambulation, or speech, death usually before teenage years[9]
Treatment	Supportive	Supportive
Carrier Rate (Ashkenazim)[10]	1:31	1:41
Natural Incidence[11]	1:3000	1:6400

*In an autosomal recessive inheritance pattern, if both parents are carriers of a mutation that reduces the activity of the resulting enzyme protein, each offspring has a one in four chance of receiving the mutated gene from both parents, and thus being affected by the condition.

Because there is no official disease registry for either TSD or Canavan disease, it is difficult to estimate how many children in the US are affected per year by each disease. However, Kim Crawford, the Director of Member Services at the National Tay-Sachs and Allied Diseases Foundation (NTSAD) estimated, based on the Foundation's best data, that there are 12-15 new infantile diagnoses of Tay-Sachs disease a year, and approximately 50 children currently living in the US with Tay-Sachs.[12] NTSAD is the primary support community for families affected by Tay-Sachs, so their estimates are likely as accurate as can be found. Estimates for Canavan disease are more difficult to find because data for the Canavan community is divided among three major centers: NTSAD, the United Leukodystrophy Foundation, and the Canavan Foundation. However, Drs. Paola Leone (University of Medicine & Dentistry of New Jersey) and Edwin Kolodny (New York University Medical Center) estimate that they see an average of 15-30 new cases a

[3] Matalon R. *Canavan Disease*. See http://www.genetests.org/servlet/access?db=geneclinics&site=gt&id=8888891&key=aMeTZgBKBQcB9&gry=&fcn=y&fw=6vhk&filename=/profiles/canavan/index.html [accessed February 22, 2008].
[4] Kaback M. *Hexosaminidase A Deficiency*. Op. cit.
[5] Matalon R. *Canavan Disease*. Op. cit.
[6] Kabac, M. *Hexosaminidase A Deficiency*. Op. cit.
[7] American College of Obstetricians and Gynecologists Committee on Genetics. Committee opinion number 212: screening for canavan disease. *International Journal of Gynecology & Obstetrics* 1998. 65: 91-92, at 91.
[8] Kaback M. *Hexosaminidase A Deficiency*. Op. cit.
[9] Matalon R. *Canavan Disease*. Op. cit.
[10] Monaghan KG, Feldman GL, Palomaki GE, Spector EB, Ashkenazi Jewish Reproductive Screening Working Group, and Molecular Subcommittee of the ACMG Laboratory Quality Assurance Committee. Technical standards and guidelines for reproductive screening in the Ashkenazi Jewish population. *Genetics in Medicine* 2008. 10(1):57-72, at 69.
[11] Based on a carrier rate of 1:30 and 1:40, respectively, described in: American College of Obstetricians and Gynecologists. Committee opinion 298: prenatal and preconceptional carrier screening for genetic diseases in individuals of Eastern European Jewish descent. *Obstetrics & Gynecology* 2004. 104(2):425-8, at 426.
[12] Ms. Crawford's estimates also include cases of Sandhoff's disease, a clinically similar disorder.

year.[13] Lois Neufeld, past president of the Canavan Foundation, estimated in a phone interview that there are at least 500 children in the US living with Canavan disease.[14]

Genetic Tests for Tay-Sachs and Canavan Disease, and Associated Patents

For a summary, see the timeline in the appendix below.

Tay-Sachs

There are two basic types of tests used to screen people for Tay-Sachs disease: one is an enzyme assay, and the other is a DNA-based test. The enzyme test, which was the basis of many carrier screening campaigns in the US, is still widely used for carrier screening and diagnosis. The DNA-based test can be used to confirm an inconclusive enzyme test, to identify the specific mutation in an individual, to evaluate an individual for a pseudodeficiency[15] allele (a sequence variant that does not alter protein function sufficiently to cause disease), for carrier testing, and for prenatal testing, including pre-implantantation genetic diagnosis (PGD).[16] Some members of the Ashkenazi population use the HEXA DNA test for carrier screening, before an enzyme test.[17] Because the enzyme test will detect all those affected while the DNA test will detect only those affected by known mutations,[18] some carriers may not be identified by the DNA test alone.

Enzyme Test

Drs. John O'Brien and Shintaro Okada developed the first enzyme test in the early 1970's.[19] Dr. Michael Kaback modified O'Brien's enzyme test and used it to spearhead a Tay-Sachs carrier screening campaign in Washington and Baltimore in the 1970's.[20] As a result of the Baltimore/Washington screening campaign, more than 100 cities began their own Tay-Sachs screening campaigns, which resulted in a greater than 90 percent reduction in the disease incidence.[21] The Dor Yeshorim screening program for members of the orthodox Jewish community, led by Rabbi Josef Ekstein, also used this enzymatic test for its carrier screening campaigns.[22] The enzyme test detects enzyme function: carriers (people with one normal and one abnormal allele) have 50 percent normal enzyme function, and those with the disease

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[13] Author's e-mail communication with Dr. Edwin Kolodny, Bernard A. and Charlotte Marden Professor of Neurology, and Department of Neurology, New York University. August 29, 2007. Author's telephone conversation with Dr. Paola Leone, Associate Professor, Department of Cell Biology, University of Medicine and Dentistry of New Jersey, July 12, 2007.
[14] Phone interview with Lois Neufeld, President, Canavan Foundation, by Catherine Alessandra Colaianni, June 27, 2007.
[15] Individuals with one or two copies of the pseudodeficiency alleles (R247W or R249W) falsely appear to be TSD carriers based on enzyme analysis. This is caused because the hexosaminidase enzyme in these individuals has reduced activity towards the artificial substrate used in the biochemical screening method. Individuals with the pseudodeficiency alleles are not carriers (Monaghan KG et al. Op. cit. at 62.)
[16] Monaghan KG, Feldman GL, Palomaki GE, Spector EB, Ashkenazi Jewish Reproductive Screening Working Group, and Molecular Subcommittee of the ACMG Laboratory Quality Assurance Committee. Op. cit. at 61.
[17] Kaback M. *Hexosaminidase A Deficiency*. Op. cit.
[18] Monaghan et al. put the sensitivity of the enzyme test at 97-98 percent, and the DNA test at 95 percent (op. cit. at 58, 62).
[19] Ross LF. Heterozygote carrier testing in high schools abroad: what are the lessons for the U.S.? *Journal of Law, Medicine & Ethics* 2006. 34(4):753-764.
[20] Kaback MM, Desnick RJ. Tay-Sachs Disease: from clinical description to molecular defect. *Advanced Genetics* 2001. 44:1-9, at 4.
[21] Kaback MM. Screening and prevention in Tay-Sachs Disease: origins, update, and impact. *Advanced Genetics* 2001. 44:253-265, at 257, 259.
[22] Wailoo K, Pemberton S. Eradicating a 'Jewish Gene': promise and pitfalls in the fight against Tay-Sachs Disease. In: *The Troubled Dream of Genetic Medicine: Ethnicity and Innovation in Tay-Sachs, Cystic Fibrosis, and Sickle Cell Disease*. Baltimore: The Johns Hopkins University Press, 2006, 14-61, at 41.

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have less than 10 percent enzymatic function.[23] The enzyme test detects approximately 97-98 percent of carriers, no matter their specific mutation.[24] Versions of this enzyme test are still widely used today. According to Dr. Kaback, there was never any effort to patent the original Tay-Sachs enzyme test.[25]

DNA Test

Dr. Rachel Myerowitz was working as a postdoctoral fellow at the NIH under Dr. Elizabeth F. Neufeld when she decided to clone the defective Tay-Sachs gene. She had previously done her biochemistry thesis at the University of Michigan on GM1 gangliosidosis, another rare lysosomal disorder. When she began in Dr. Neufeld's lab, she worked on Hurler syndrome, another lysosomal disorder caused by defective iduronidase enzyme,[26] and decided that she wanted to clone the iduronidase gene. However, material from Tay-Sachs patients was easier to obtain, so she switched to cloning the genes for hexosaminidase.[27] Dr. Myerowitz isolated a cDNA clone of the HEXA gene in 1983 and published these results in 1984. [28] In 1984, Dr. Neufeld, moved from NIH to UCLA. Dr. Myerowitz remained at the NIH and looked for mutations in the HEXA gene that were present in the Ashkenazi Jewish population.

Patenting the gene had never occurred to her, but, as she put it, "… in the late 1980's, NIH was very interested in patenting stuff. They would come around to your lab and say, 'Do you have anything that you think is patentable?'"[29] Myerowitz was approached by a lawyer from NIH who advised her to file a patent application. NIH filed a patent application in 1986[30] and was granted two patents: the first, US 5,217,865 "Screening for Tay-Sachs disease with cloned DNA for beta-hexosaminidase," issued in 1993, which covers diagnostic testing; and the second, US 5,475,095 "Nucleic acid compositions for the alpha chain of beta-hexosaminidase," issued in 1995, which covers the HEXA gene itself.[31]

Myerowitz left the NIH in 1993 for a position at St. Mary's College of Maryland. In 2000, she contacted the NIH legal department to ask about developments with the patents. The legal department told her that although they knew the DNA test based on the patents was widely used, they had never drafted a license because going after infringers was "more trouble than it [was] worth."[32] Thus, although the Tay-Sachs gene was patented, the patents were never licensed, and never enforced.

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[23] Ross LF. Op. cit.
[24] Monaghan KG, Feldman GL, Palomaki GE, Spector EB, Ashkenazi Jewish Reproductive Screening Working Group, and Molecular Subcommittee of the ACMG Laboratory Quality Assurance Committee. Op. cit. at 58.
[25] Email from Michael Kaback, Professor of Pediatrics, University of California San Diego, to Catherine Alessandra Colaianni, September 17, 2007.
[26] Clarke LA. *Mucopolysaccharidosis Type 1*. See http://www.genetests.org/servlet/access?db=geneclinics&site=gt&id=8888891&key=pwy2S875SvRNh&gry=&fcn=y&fw=-hHx&filename=/profiles/mps1/index.html [accessed February 22, 2008].
[27] Interview with Dr. Rachel Myerowitz, Professor, Department of Biology, St. Mary's College of Maryland, by Catherine Alessandra Colaianni, July 31, 2007.
[28] Myerowitz R, Proia RL. cDNA clone for the alpha-chain of human beta-hexosaminidase: deficiency of alpha-chain mRNA in Ashkenazi Tay-Sachs fibroblasts. *Proc Natl Acad Sci USA* 1984. 81(17):5394-8.
[29] Interview with Dr. Rachel Myerowitz. Op. cit.
[30] US patent 5,217,865 has a filing date of 10/31/88 and US 5,475,095 has a filing date of 12/7/93; however, both stemmed from one original application 889,502, filed 7/5/86. During the patent prosecution process, the original application's claims were split into two separate patents.
[31] US patents 5,217,865 and 5,475,095.
[32] Interview with Dr. Rachel Myerowitz. Op. cit.

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Canavan Disease

The gene for Canavan disease, called *ASPA*, was discovered and patented by Dr. Reuben Matalon and co-inventors. Dr. Matalon is now at the University of Texas Medical Branch (UTMB) Center for Metabolic Diseases; at the time the gene was discovered and patented, Matalon was affiliated with Miami Children's Hospital (MCH). Matalon had been recruited in May 1987 to search for the cause of Canavan disease while he was a professor at the University of Illinois at Chicago, by Daniel and Deborah Greenberg, a Chicago-based family that had two children, Jonathan and Amy, born with Canavan disease.[33] By 1988, Matalon had discovered and published an article in the *American Journal of Medical Genetics* about the aspartoacylase deficiency that causes Canavan disease.[34] In 1989, Matalon took a position as director of research at the MCH.[35]

In 1990, Matalon published a paper in the *Journal of Inherited Metabolic Diseases* detailing a prenatal enzymatic screening test that could diagnose Canavan disease using amniocytes (cells taken from the amniotic fluid of a gestating pregnancy) or chorionic villus sampling (CVS; cells taken from the placenta).[36] However, the enzymatic testing method proved to be unreliable: it resulted in the births of four babies with Canavan disease, who had been prenatally screened and pronounced free of the disease.[37] At least two lawsuits against MCH resulted, which were settled out of court.[38] It was later determined that Matalon's enzymatic test did not work because the amniocytes and CVS did not have enough enzymatic activity to provide an accurate screen.[39] Matalon's enzymatic test also could not distinguish adult Canavan carriers from non-carriers.[40] Matalon did not receive a patent on this test. In 1993, Bennett et al. published results that suggested that prenatal diagnosis using an enzyme assay of amniotic fluid (rather than amniocytes or CVS) provided more reliable results.[41] However, complications with the amniotic fluid assay were reported: it was only reliable at the extremes, and mid-range levels of enzyme activity were inconclusive.[42] According to the National Tay-Sachs and Allied Diseases Association (NTSAD), only two or three laboratories in the US offer that test.[43] One study recommended that DNA sequencing should accompany amniotic fluid screening wherever possible.[44] The Bennett et al. test was not patented.[45] Unlike Tay-Sachs disease, then, the only way to provide carrier screening for Canavan disease was through DNA-based testing, and DNA-based prenatal diagnosis would be an easier and more reliable method than amniotic fluid analysis.

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[33] Hahn L. Owning a piece of Jonathan. *Chicago Magazine* 2003 (May). Pp. 83-87, 104-106, at 86.
[34] Matalon R, Michals K, Sebasta D, Deanching M, Gashkoff P, Casanova J. Aspartoacylase deficiency and N-acetylaspartic aciduria in patients with Canavan disease. *American Journal of Medical Genetics* 1988. 29: 463-471.
[35] Hahn L. Op. cit. at 87.
[36] Matalon R, Michals K, Gashkoff P, Kaul R. Prenatal diagnosis of Canavan Disease. *Journal of Inherited Metabolic Diseases* 1992. 15:392-394.
[37] Winerip M. Fighting for Jacob. *The New York Times Magazine* 1998 (December 6). Pp. 56-63, 78-82, 112, at 59.
[38] Hahn L. Op. cit. at 87.
[39] Matalon R, Kaul R, Gao GP, Michaels K, Gray GF, Bennett-Briton S, Norman A, Smith M, Jakobs C. Prenatal diagnosis for Canavan disease: the use of DNA markers. *Journal of Inherited Metabolic Diseases* 1995. 18:215-217, at 215.
[40] American College of Obstetricians and Gynecologists Committee on Genetics. Committee opinion number 212: screening for Canavan disease. Op. cit. at 91.
[41] Bennett MJ, Gibson KM, Sherwood WG, Divry P, Rolland MO, Elpeleg ON, Rinaldo P, Jakobs, C. Reliable prenatal diagnosis of Canavan Disease (aspartoacylase deficiency): comparison of enzymatic and metabolite analysis. *Journal of Inherited Metabolic Disease* 1993. 16:831-6.
[42] Besely GNT, Elpeleg ON, Shaag A, Manning NJ, Jakobs C, Walter JH. Prenatal diagnosis of Canavan disease—problems and dilemmas. *Journal of Inherited Metabolic Disease* 1999. 22: 263-266, at 265.
[43] National Tay-Sachs and Allied Diseases Association, Inc. *What is Canavan Disease*? See www.ntsad.org [accessed February 26, 2008].
[44] Besely GNT, Elpeleg ON, Shaag A, Manning NJ, Jakobs C, Walter JH. Op. cit. at 263.
[45] Author's email communication with Dr. Michael J. Bennett, Professor of Pathology and Laboratory Medicine, University of Pennsylvania. February 13, 2008.

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On October 1, 1993, Matalon and his researchers published exciting results in *Nature Genetics*: they isolated and sequenced the aspartoacylase gene, and found a common mutation that causes Canavan disease.[46] This made a DNA-based Canavan test possible, and the Ashkenazi population leapt into action. Rabbi Josef Ekstein, who had spearheaded the Dor Yeshorim Tay-Sachs screening campaign in the 1980's, screened approximately 13,000 people that year for Canavan disease, and in 1996 the Canavan Foundation offered free testing at New York's Mount Sinai Hospital.[47]

Matalon filed a patent application on September 29, 1993,[48] and was granted two US patents, US 5,679,635 in October 1997, and US 7,217,547 in May 2007, both entitled "Aspartoacylase gene, protein, and methods of screening for mutations associated with Canavan disease."[49] The 1997 patent covered the DNA sequence of the gene, mutated sequences associated with Canavan disease, use of the sequence in DNA testing, and test kits for Canavan disease. The 2007 patent claimed mutated versions of the aspartoacylase protein. The patents were assigned to the Miami Children's Hospital Research Institute, Inc.

After the first patent was granted, MCH's chief financial officer, David Carroll, sent letters to laboratories and hospitals, advising them that MCH had received the patent, and that those doing Canavan's tests would have to take out a license or risk an infringement lawsuit. One such letter, received by Debra Leonard in 1999, stated: "We intend to enforce vigorously our intellectual property rights relating to carrier, pregnancy, and patient DNA tests for Canavan Disease mutations."[50] The letter described a $12.50 royalty for each test (the price was marked down from a reported $25. According to one source, MCH had originally set the price at $50[51]).[52] The letter also set volume limitations, or a limit on the number of tests each individual laboratory could perform (100 tests per academic laboratory).[53]

The enforcement of the MCH patent (US 5,679,635) angered many in the Canavan community, including Rabbi Josef Ekstein, members of the Canavan Foundation, and the Greenberg family. In response, the Canavan Disease Screening Consortium was formed. The Consortium consisted of the Canavan Foundation, the National Tay-Sachs and Allied Diseases Association (NTSAD), the National Foundation for Jewish Genetic Diseases, and the Canavan Research Fund. On January 20, 2000, the Canavan Disease Screening Consortium, including Judith Tsipis (NTSAD), Michael Watson (American College of Medical Genetics), Jon Merz (University of Pennsylvania), Orren Alperstein Gelblum, Rosalind Poss Rosen (both of the Canavan Foundation), and Daniel Greenberg (NTSAD) made a presentation to officials from MCH, explaining that they believed the MCH's licensing policies were too restrictive. They wanted the Canavan patent to be dedicated to the public good, as the University of Michigan's patent for the Cystic Fibrosis gene had been. If the patent could not be dedicated to the public good, they requested four actions from MCH:

(1) Remove the volume cap on testing;
(2) Charge a royalty no more than 1-5 percent of the test price;

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[46] Kaul R, Gao GP, Balamurugan K, Matalon R. Cloning of the human aspartoacylase cDNA and a common missense mutation in Canavan disease. *Nature Genetics* 1993. 5: 118-123.
[47] Hahn L. Op. cit. at 104.
[48] US 5679635 has a filing date of September 9, 1994 and US 7217547 has a filing date of October 1, 2001. However, both patents' Parent Case Text show that they stemmed from the same application 08/128,020, filed September 29, 1993.
[49] US patents 5,679,635 and 7,217,547.
[50] Leonard D. Presentation to Secretary's Advisory Committee on Genetics, Health, and Society (2006). See http://oba.od.nih.gov/oba/SACGHS/meetings/June2006/Leonard3.pdf [accessed January 14, 2009].
[51] Joshua Greenberg, son of Daniel and Debbie Greenberg, remembers that the price MCH originally intended to charge was $50, not $25. (Author's communication with Joshua Greenberg, January 25, 2008).
[52] Hahn L. Op. cit. at 105.
[53] Author's interview with Dr. Michael Watson, American College of Medical Genetics, Executive Director, October 1, 2007.

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(3) Develop an educational outreach program to promote carrier screening; and
(4) Set up a fund to assist people unable to pay for screening or prenatal diagnosis.[54]

According to Dr. Michael Watson, Executive Director of the American College of Medical Genetics, who was present at the meetings, the representatives of MCH offered an undisclosed sum of money to be used for the proposed educational outreach program, but did not agree to the Consortium's other requests.[55] An article by Jon Merz, who was also present at the meetings, says the offered sum was $20,000 per year, with the further condition that the Consortium members not publicly criticize the MCH. [56] The Consortium welcomed the financial help but did not agree to the gag order.[57]

The MCH marketing plan had two phases: first, MCH would offer nonexclusive licenses to a limited number of academic laboratories, allowing them to perform a limited number of tests per year. Then, MCH would identify a "market leader"—a single, high-volume licensee such as Quest or LabCorp—and grant them an exclusive license on the remainder of the testing volume.[58] According to Dr. Michael Watson, MCH originally planned to offer seven unrestricted licenses to the Canavan patents.[59] The effort to find a single large-volume licensee failed, and in April 2000 MCH revised its licensing plan.[60]

In the meantime, Dr. Debra Leonard had been performing Canavan disease testing in her University of Pennsylvania laboratory since before the patent issued. On advice from counsel, she refused to sign the MCH's license agreement with volume limitations and the $12.50 royalty. However, MCH was owed back royalties from the tests that Leonard had previously performed without a license, and Marc Golden, MCH's advisor and consultant, drafted a settlement agreement that prohibited any University of Pennsylvania physician from "perform[ing] or hav[ing] other(s) perform, any Canavan Tests… without first obtaining a license."[61] This would not only prevent Canavan testing at the University of Pennsylvania, but would also prevent University of Pennsylvania physicians from collecting samples and sending them out to licensed laboratories, until the University of Pennsylvania itself obtained a license, which would be at the discretion of MCH. After negotiations, the University agreed to pay MCH past royalties and not infringe the patent in the future.[62]

In the meantime, tensions rose between the MCH, on one hand, and Leonard and the Consortium, on the other. Both Leonard and members of the Consortium tried to learn the names of the dozen or so laboratories that had taken licenses—Leonard, so that she could send samples to licensed laboratories, and the Consortium so that they could direct the community at risk to laboratories at which they could legally get tested. MCH stated that it would release the names of four laboratories, out of approximately twelve that had obtained licenses, to Dr. Leonard, and did not provide any information about licensed services to the Consortium.[63]

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[54] Various presentation materials from the Canavan Disease Screening Consortium, provided by Dr. Michael Watson, Executive Director of the American College of Medical Genetics, who was present at the Canavan Disease Screening Consortium meetings and presentations.
[55] Author's interview with Dr. Michael Watson. Op. cit.
[56] Merz JF. Discoveries: are there limits on what may be patented? In: Magnus D, Caplan A, McGee G, eds. *Who Owns Life?* Amherst, New York: Prometheus Press, 2002, 99-116, at 106.
[57] Ibid.
[58] Ibid., 103.
[59] Author's interview with Dr. Michael Watson. Op. cit.
[60] Merz JF. Op. cit. at 106.
[61] Ibid., 105.
[62] Ibid., 105.
[63] Ibid., 106.

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In October 2000, the *Greenberg v. Miami Children's Hospital* lawsuit was filed. MCH had alienated the groups that directly contributed clinical data and samples to help discover the gene associated with Canavan disease, and the constituencies most likely to use genetic testing. That is, the licensing scheme offended important and influential users of the Canavan genetic test. Daniel Greenberg, along with the Canavan Foundation, Dor Yeshorim, NTSAD, and three other plaintiffs who had children afflicted with Canavan disease, sued MCH, the Miami Children's Hospital Research Institute and Reuben Matalon. The plaintiffs filed a six-count complaint, alleging a lack of informed consent, breach of fiduciary duty, unjust enrichment, fraudulent concealment, conversion, and misappropriation of trade secrets.[64] On August 3, 2003, the case settled confidentially out-of-court, and a gag order prevents us from knowing the exact terms of the settlement. A press release from the Canavan Foundation characterized the agreement as follows:

> Canavan Foundation, National Tay-Sachs & Allied Diseases Association, Daniel Greenberg and David Green have agreed not to further challenge Miami Children's Hospital's ownership and licensing of the Canavan gene patent. Miami Children's Hospital will continue to license and collect royalty fees for clinical testing for the Canavan gene mutation. The Agreement also allows license-free use of the Canavan gene in research to cure Canavan disease, including in gene therapy research, genetic testing in pure research, and in mice used to research Canavan disease.[65]

A phone survey conducted in 2001 by Cho, et al., showed that as of September 2001, four Canavan test providers listed on Genetests.org had stopped performing that test, citing the MCH patent as the reason for stopping.[66] The Cho et al. study did not contain information on exactly how many laboratories were performing the Canavan test before 2001, so it is impossible to say what fraction of labs stopped performing the Canavan test due to patent enforcement.

Testing Facilities and Prices

A 2003 newspaper article reported that MCH had licensed the patent to 15 laboratories.[67] Genetests.org currently lists 37 facilities that provide Canavan disease testing, diagnosis, and/or carrier screening. Of these 37 facilities, 23 are listed as providing mutation analysis, full sequencing, carrier testing, and/or prenatal diagnosis. These are all DNA-based tests, so those labs have most likely taken a license with MCH. Fourteen labs are listed as providing analyte testing only, which does not include DNA analysis and would not require a license.

In June 2007, Genetests.org listed 37 U.S. laboratories providing Canavan testing, and 34 for Tay-Sachs testing. Of these, 26 labs were listed as performing both Tay-Sachs and Canavan testing. A telephone survey of all 45 laboratories offering Canavan testing, Tay-Sachs testing, or both was performed between June and August 2007.[68] In the figures that follow, the tests are divided into several different categories,

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[64] Federico A. Moreno, US District Judge, Opinion. 264 F. Supp 2d 1064; 2003 U.S. Dist LEXIS 8959; 121 A.L.R. 5th 687; 16 Fla. L. Weekly Fed. D 417.

[65] *Canavan Foundation Press Release*. September 29, 2003. See http://canavanfoundation.org/news/09-03_miami.php [accessed February 26, 2008].

[66] Cho M, Illangasekare S, Weaver MA, Leonard DGB, Merz JF. Effects of patents and licenses on the provision of clinical genetic testing services. *Journal of Molecular Diagnostics* 2003. 5(1): 3-8, at 6.

[67] Hahn L. Op. cit. at 105.

[68] Of the 45, six did not respond to repeated telephone calls. Of the 45, two stated that they no longer offered the Tay-Sachs test, and five no longer offered the Canavan test. In addition, 5 labs stated that they only provided the tests as part of a panel including other genetic tests, and these labs were excluded. Laboratory personnel, usually receptionists or billing staff, were asked for the list price of the test in question. When the tests were only available as part of a panel, we did not report the price of the test. Personnel were not asked whether they had a license for the MCH patents, as a negative answer to such a question could have

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based both on test category information available from Genetests.org, on the website of the testing service, or descriptions of the type of test performed. Tests were divided into categories of Full Sequence Analysis, Targeted Mutation Analysis, and Enzyme Assay/Analyte. Price per Amplicon for Full Sequence Analysis was calculated by dividing the price of the test by the number of amplicons the test sequences; for Tay-Sachs, full sequencing entails 14 amplicons (for the 14 exons in the gene), and for Canavan disease, full sequencing entails 6 amplicons (for the 6 exons in the gene).

Full Sequence Analysis

Laboratory	*TS Test Price*	*CD Test Price*
Ambry Genetics[69]	$1,695	$895
Emory University Department of Human Genetics	$1,488[70]	not offered
New York University School of Medicine Neurogenetics Laboratory[71]	$1500	$1500
Average test price:	**$1536**	**$1198**

Full Sequence Analysis, Price per Amplicon

Laboratory	*TS Test Price*	*CD Test Price*
Ambry Genetics[72]	$121.07	$149.17
Emory University Department of Human Genetics	$106.29[73]	not offered
New York University School of Medicine Neurogenetics Laboratory[74]	$107.14	$250
Average test price:	**$111.50**	**$199.58**

Targeted Mutation Analysis

Laboratory	*TS Test Price*	*CD Test Price*
ARUP Laboratories[75]	$300	$300
Baylor College of Medicine[76]	not offered	$125
Boston University Medical Center[77]	$135	$195
Children's Hospital and Regional Medical Center[78]	not offered	$428.40
Genzyme Genetics[79]	$284	$284

posed a liability to the laboratory. Personnel were not asked whether they had taken a license of the Tay-Sachs patent, as we knew from the NIH OTT staff that it was never licensed.

[69] Ambry Genetics Corp., via phone June 21, 2007. (866) 262-7943.

[70] See http://www.genetics.emory.edu/egl/test.php?test_id=148 [accessed January 21, 2009].

[71] New York University School of Medicine Neurogenetics Laboratory, via phone June 26, 2007. (212) 263-6628.

[72] 14 amplicons for TS, 6 amplicons for Canavan disease. Ambry Genetics Corp., via phone January 21, 2009. (866) 262-7943.

[73] 14 amplicons for TS. See http://www.genetics.emory.edu/egl/test.php?test_id=148 [accessed January 21, 2009].

[74] 14 amplicons for TS, 6 amplicons for Canavan disease. New York University School of Medicine Neurogenetics Laboratory, via phone January 21, 2009. (212) 263-6628.

[75] ARUP Laboratories, via phone June 21, 2007. (800) 522-2787.

[76] Baylor College of Medicine, via phone June 21, 2007. (800) 411-4363.

[77] Boston University Medical Center, via phone June 21, 2007. (617) 638-7083.

[78] Children's Hospital and Regional Medical Center, via phone June 20, 2007. (206) 987-2289.

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Kimball Genetics[80]	$315	not offered
LabCorp[81]	$334	$345
Mayo Clinic Biochemical Genetics Laboratory[82]	$315	$366.80
New Jersey Medical School[83]	$100	$100
New York University School of Medicine Medical Genetics Lab[84]	$252	$128
New York University School of Medicine Neurogenetics Laboratory	$600	$600
ProGene, Inc.[85]	$175	$175
Quest Diagnostics, Inc.[86]	$252	$355
Specialty Laboratories[87]	$440	$440
Wayne State University/Detroit Medical Center University Laboratories[88]	Only offered as part of panel	$325
Average price of test:	**291.84**	**297.66**

Enzyme Assay (Tay-Sachs)/Analyte Test (Canavan)*

Laboratory	*TS Test Price*	*CD Test Price*
Baylor College of Medicine	$128	not offered
Children's National Medical Center[89]	$119 (serum) $172 (white blood cells)	not offered
Duke University[90]	not offered	$260
Emory University Department of Human Genetics	$250[91]	not offered
Emory University Department of Human Genetics	$525[92]	not offered
Genzyme Genetics	$134	not offered
Greenwood Genetics Center[93]	not offered	$200 (analyte)
Kennedy Krieger Institute[94]	not offered	$150 (analyte)
Kimball Genetics, Inc.	$160	not offered

[79] Genzyme Genetics, via phone June 22, 2007. (800) 357-5744 ext. 29407.
[80] Kimball Genetics, Inc., via phone June 21, 2007. (800) 320-1807.
[81] LabCorp, via phone June 21, 2007. (919) 361-7700.
[82] Mayo Clinic Biochemical Genetics Laboratory, via phone June 21, 2007. (800) 533-1710.
[83] New Jersey Medical School, via phone June 22, 2007. (973) 972-4480.
[84] New York University School of Medicine Medical Genetics Laboratory, via phone June 22, 2007. (212) 263-5746.
[85] ProGene, Inc., via phone June 20, 2007. (818) 548-0999.
[86] Quest Diagnostics, Inc., via phone June 20, 2007. (800) 877-2515.
[87] Specialty laboratories, via phone June 26, 2007. (800) 421-7110.
[88] Wayne State University/Detroit Medical Center, via phone June 22, 2007. (3113) 993-0724.
[89] Children's National Medical Center, via phone June 21, 2007. (202) 884-3991.
[90] Duke University Medical Center Pediatric Biochemical Genetics Lab, via phone June 2007. (919) 549-0445.
[91] See http://www.genetics.emory.edu/egl/test.php?test_id=167 [accessed July 24, 2007].
[92] See http://www.genetics.emory.edu/egl/test.php?test_id=20 [accessed July 24, 2007].
[93] Greenwood Genetics Center, via phone June 21, 2007. (800) 473-9411.
[94] Kennedy Krieger Institute, via phone June 21, 2007, (443) 923-2788. Test prices on the order form also available http://www.genetics.kennedykrieger.org/forms/cmsform.pdf [accessed July 24, 2007].

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LabCorp	$347 (leukocyte) $175 (serum)	not offered
Mayo Clinic Biochemical Genetics Laboratory	$188.30 (serum) $277.70 (white blood cells)	not offered
New York State Institute of Basic Research in Developmental Disabilities[95]	$280 (leukocytes) $260 (plasma)	$168 (organic acids)
Oregon Health and Science University[96]	$119.44 $223.42 (rush)	not offered
University of Alabama at Birmingham Metabolic Disease Laboratory[97]	$300	not offered
UCSD Molecular Genetics Laboratory[98]	$116	not offered
University of Maryland Pediatric Biochemical Genetics Laboratory[99]	$90 (serum) $155 (leukocytes)	not offered
Wayne State University/Detroit Medical Center	$63	not offered
Average test price:	**$204**	**$195**

*Analyte tests for Canavan Disease, as discussed previously, are not DNA-based and therefore the MCH patent had no bearing on the price or availability of these tests. These data are included for comparison with the Tay-Sachs enzyme screen.

These data show that, despite the differences in intellectual property, the only significant pricing difference between Canavan and Tay-Sachs laboratory tests occurs in the average price per amplicon. Average test prices of the tests for Tay-Sachs and Canavan Disease were usually less than ten dollars apart. The exception is the Ambry full sequence analysis for Tay-Sachs, which is $800 more than the comparable Canavan test. It is unclear why the Ambry Tay-Sachs test would be so much more expensive than the Ambry Canavan test. One possible reason is that the hexosaminidase gene is longer than the aspartoacylase gene: the ASPA gene is 29kb and the HEXA gene is 35kb.[100] Based on the Ambry prices and the length of the respective genes, the price per base pair for the Ambry Canavan test is $0.031; the price per base pair for the Ambry Tay-Sachs test is $0.048. The average price per amplicon for Tay-Sachs, however, is $111.50 while the price per amplicon for Canavan disease is $199.58: a significant difference that could reflect a patent premium.

There are several confounding factors that may affect these data. First, the number of laboratories offering each test may be inaccurate, because some "labs" are only sample collection points, which then send the samples they collect to other laboratories that perform the test. This would affect both the number of labs offering the test, and the number of labs that have a sub-license of the MCH patents. Also, at least in the case of Tay-Sachs Disease, many schools, universities, and Jewish organizations (such as the Dor Yeshorim) offer free carrier screening throughout the year, which could significantly increase access but does not appear on genetests.org. For example, a branch of NTSAD in the Delaware Valley offered six

[95] New York State Institute of Basic Research in Developmental Disabilities, via phone June 22, 2007. (718) 494-5369.
[96] Oregon Health and Science University, via phone June 22, 2007. (503) 494-7703.
[97] University of Alabama at Birmingham Metabolic Disease Laboratory, via phone June 26, 2007. (205) 996-4992
[98] UCSD Molecular Genetics Laboratory, via phone June 21, 2007. (858) 534-1353
[99] University of Maryland Pediatric Biochemical Genetics Laboratory, via phone June 25, 2007. (401) 716-4065
[100] Monaghan KG, Feldman GL, Palomaki GE, Spector EB, Ashkenazi Jewish Reproductive Screening Working Group, and Molecular Subcommittee of the ACMG Laboratory Quality Assurance Committee. Op. cit.

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free Canavan and Tay-Sachs screening dates during the months of May and early June in 2007, and published a list of nine hospitals offering free screening throughout the month of May 2007.[101] Other examples of universities offering free Tay-Sachs screening included the University of Wisconsin-Madison (2003 and 2004),[102] Santa Monica College (2003),[103] University of California at Davis (2005),[104] and San Jose University (2001).[105]

One other confounding factor is the pricing of the tests themselves. Laboratory prices may reflect a change in licensing policy from MCH's original $12.50 royalty; however, because the *Greenberg v MCH* settlement was sealed, any agreed royalty rate may never be publicly available. Overhead costs may also contribute to pricing differences.

Screening for Tay-Sachs and Canavan Disease

In 1995, the American College of Obstetricians and Gynecologists (ACOG) published a committee opinion recommending carrier screening for Tay-Sachs disease before pregnancy if both parents are of Ashkenazi Jewish, French-Canadian, or Cajun descent.[106] That opinion was renewed and re-published in 2005: if both parents were carriers of a mutated HEXA gene, genetic counseling and prenatal diagnosis should be offered.

In 1998, ACOG issued a similar committee opinion for Canavan disease, recommending carrier screening for Canavan disease if both parents were of Ashkenazi Jewish descent.[107] If both parents were carriers of an ASPA functional mutation, prenatal diagnosis would use DNA-based ASPA testing.

Also in 1998, the American College of Medical Genetics (ACMG) issued a position statement that people of Ashkenazi Jewish descent should be offered screening for Canavan disease before becoming pregnant; ACMG also suggested that screening for Canavan disease could be combined with screening for Tay-Sachs, since both disorders were common among Ashkenazi Jewish people.[108]

In 2004, the ACOG issued another committee opinion reiterating recommendations that people of Ashkenazi Jewish descent should be offered carrier screening for Tay-Sachs and Canavan disease, as well as seven other diseases that are common to that group.[109]

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[101] National Tay-Sachs and Allied Diseases Association of Delaware Valley. See http://www.tay-sachs.org/centers.php [accessed February 26, 2008].
[102] UW-Madison News: Newslink. University Communications. November 17, 2004. See http://www.news.wisc.edu/newslink/17-Nov-2004 [accessed February 26, 2008].
[103] Santa Monica College Spring 2003 Cover Stories. See http://www.smc.edu/schedules/archives/profiles/2003/031/coverstories_031.htm [accessed February 26, 2008].
[104] Senkevich, K. Free Tay-Sachs screening offered on campus-front page. *The California Aggie.* See http://media.www.californiaaggie.com/media/storage/paper981/news/2005/01/27/FrontPage/Free-TaySachs.Screening.Offered.On.Campus-1319352.shtml [accessed February 26, 2008].
[105] Ruf SG. Center to offer free Tay-Sachs Screening. *The Spartan Daily.* See http://media.www.thespartandaily.com/media/storage/paper852/news/2001/11/13/CampusNews/Center.To.Offer.Free.TaySachs.Screening-1494445.shtml [accessed February 26, 2008].
[106] American College of Obstetricians and Gynecologists Committee on Genetics. Committee opinion number 318: screening for Tay-Sachs disease. *Obstetrics & Gynecology* 2005. 106(4):893-894.
[107] American College of Obstetricians and Gynecologists Committee on Genetics. Committee opinion number 212: screening for Canavan disease. Op. cit.
[108] American College of Medical Genetics. *Position Statement on Carrier Testing for Canavan Disease.* January 10, 1998. See http://www.acmg.net/StaticContent/StaticPages/Canavan.pdf [accessed February 26, 2008].
[109] American College of Obstetricians and Gynecologists. Committee opinion 298: prenatal and preconceptional carrier screening for genetic diseases in individuals of eastern European Jewish descent. *Obstetrics & Gynecology* 2004. 104(2):425-8.

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These ACOG and ACMG recommendations help set the standard of care for screening for Tay-Sachs and Canavan disease in the U.S.

Clinical Utility of Genetic Testing for Tay-Sachs and Canavan Disease

Tay-Sachs. The Tay-Sachs Hexosaminidase A enzyme activity assay is very sensitive, with a 97-98% detection rate.[110] DNA testing for three common mutations detects more than 98% of Jewish carriers[111] and 93% of Jewish carriers are identified by the enzyme assay.[112] One study identified DNA-based testing as the preferred carrier screening method in individuals of full Ashkenazi Jewish descent.[113] DNA-based testing is also the only method to do pre-implantation genetic diagnosis (PGD), to confirm which specific mutation an individual has, or to rule out the possibility of pseudodeficiency alleles. In general, the enzyme test is inexpensive, accurate, and easy to do. It is also the best method to detect carrier status in individuals who are not of Ashkenazi Jewish descent (because any mutations might not be known DNA changes detected in current DNA-based tests).

Canavan disease. DNA testing for Canavan disease is based on two common mutations that account for 97-98% of Ashkenazi Jewish carriers.[114] Another mutation accounts for approximately 1 percent of the Ashkenazi Jewish population and about 50 percent of the non-Ashkenazi Jewish population.[115] DNA testing for Canavan Disease is the only way to detect carrier status, because enzymatic screens often fail to distinguish carriers from non-carriers.[116] In addition, prenatal testing using amniotic fluid (not CVS or amniotic *cells*, as previously discussed) is available, but not widespread.[117]

Cost-Effectiveness of Screening for Tay-Sachs and Canavan Disease

We have been unable to find any cost-effective or cost-benefit analysis of genetic screening for Canavan Disease.

We have also been unable to find any cost-effective or cost-benefit analysis of DNA-based testing for Tay-Sachs disease.[118]

This may be because screening for such devastating, incurable diseases as Tay-Sachs and Canavan is considered to be worth whatever the screening program costs. A quote from the National Tay-Sachs and Allied Diseases Association, Inc., illustrates this:

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[110] Monaghan KG, Feldman GL, Palomaki GE, Spector EB, Ashkenazi Jewish Reproductive Screening Working Group, and Molecular Subcommittee of the ACMG Laboratory Quality Assurance Committee. Op. cit. at 58.
[111] An obligate carrier is one who does not show clinical symptoms but who must carry a defective copy of the gene based on family history. For example, if a child is born with Tay-Sachs disease, both parents are obligate carriers.
[112] Monaghan KG, Feldman GL, Palomaki GE, Spector EB, Ashkenazi Jewish Reproductive Screening Working Group, and Molecular Subcommittee of the ACMG Laboratory Quality Assurance Committee. Op. cit. at 58.
[113] Bach G, Tomczak J, Risch N, Ekstein J. Tay Sachs screening in the Jewish Ashkenazi population: DNA testing is the preferred procedure. *American Journal of Medical Genetics* 2001. 99: 70-75.
[114] Monaghan KG, Feldman GL, Palomaki GE, Spector EB, Ashkenazi Jewish Reproductive Screening Working Group, and Molecular Subcommittee of the ACMG Laboratory Quality Assurance Committee. Op. cit. at 58.
[115] Ibid.
[116] American College of Obstetricians and Gynecologists Committee on Genetics. Committee opinion number 212: screening for Canavan disease. Op. cit. at 91.
[117] Monaghan KG, Feldman GL, Palomaki GE, Spector EB, Ashkenazi Jewish Reproductive Screening Working Group, and Molecular Subcommittee of the ACMG Laboratory Quality Assurance Committee. Op. cit. at 60.
[118] There are a few studies that do address the cost-benefit or cost-effectiveness of the Tay-Sachs enzyme test; however, they do not address the economics of the DNA-based test.

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> It is important to note that while the [insurance] appeal process and potential out-of-pocket cost of genetic testing may seem daunting it is a drop in the bucket compared to caring for a child affected by Tay-Sachs, Canavan or another allied disease.[119]

Lessons Learned

Research

It is clear that the Tay-Sachs gene patent did not stifle research as it was never enforced.

The Canavan patent may or may not have stifled basic research until 2003, when the terms of settling *Greenberg v Miami Children's Hospital* were reached. Clinical research labs as well as commercial labs received cease-and-desist letters from MCH in 1998, which could have stopped them from sequencing the ASPA gene and thus have stifled basic research and some clinical research.[120] As discussed previously, one of the terms of the agreement allowed " license-free use of the Canavan gene in research to cure Canavan disease, including in gene therapy research, genetic testing in pure research, and in mice used to research Canavan disease."[121] Thus, though the Canavan patent could in theory have impeded research until 2003, it does not anymore.

Development and Commercialization

The Tay-Sachs patent neither helped nor hindered commercialization of the Tay-Sachs DNA test. One company approached Dr. Rachel Myerowitz before the patent issued to ask whether or not the gene would be patented. According to her, the company did not want to develop a test kit unless the gene was patented. Once the patent issued, however, NIH decided it would be too much trouble to enforce the patent, so it was never licensed. The presence of a reliable enzyme test may have been a deterrent for any commercial interest in a DNA test for Tay-Sachs. The enzyme test for Tay-Sachs was never patented and therefore patents did not help or hinder its development or commercialization.

The impact that the Canavan patent had on commercialization is unclear. The controversy happened at the level of Miami Children's Hospital, not in litigation among competing commercial testing services. The lawsuit was about fair access and distribution of benefits, not commercialization *per se*.

Adoption by Third-Party Payers

Adoption of Tay-Sachs and Canavan disease carrier and prenatal screening by third-party payers is varied. For example, CIGNA covers both carrier and prenatal screening for Tay-Sachs and Canavan if eligibility criteria are met. CIGNA considers carrier testing medically necessary for individuals who have either an affected family member, or a reproductive partner with confirmed adult-onset TSD. Prenatal testing or PGD is considered medically necessary if both parents are heterozygous and do not carry a

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[119] *Insurance Coverage.* See http://www.ntsad.org/S06/S06inscoverage.htm [accessed November 5, 2008].
[120] Flap erupting over royalty for Canavan: Miami Children's Hospital exercises patent for test. Forward staff. *The Jewish Daily Forward* 1999 (August 20). Pp. 15-16.
[121] *Canavan Foundation Press Release*. September 29, 2003. See http://canavanfoundation.org/news/09-03_miami.php [accessed February 26, 2008].

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pseudodeficiency allele; one parent is heterozygous and the other parent's test was inconclusive; the mother is heterozygous and the father's status is unobtainable; or one parent has adult-onset TSD.[122]

CIGNA considers carrier testing for Canavan Disease medically necessary when the ASPA mutation has been identified in a family member, and the patient has the capacity and desire to reproduce. Prenatal testing and PGD are considered necessary when both reproductive partners are of Ashkenazi Jewish descent, or when both disease-causing alleles have been identified in an affected family member, and one parent is known to be heterozygous.[123]

Aetna does not have a policy on carrier screening, but considers genetic counseling in connection with pregnancy management medically necessary in specific populations, including people of Ashkenazi Jewish descent. Aetna also considers genetic counseling medically necessary in situations where both parents are known carriers of an autosomal recessive disorder, such as Tay-Sachs or Canavan. [124] Aetna's policy on genetic testing does not include carrier screening: their policy position only applies to the establishment of a molecular diagnosis of an inheritable disease in an individual.[125]

For other insurance companies that do not cover genetic testing for people of Ashkenazi Jewish descent, the National Tay-Sachs and Allied Diseases organization offers to send help in the form of a letter to the insurer or health plan.[126]

Reflections

Though the Tay-Sachs and Canavan disease stories have much in common, a few salient differences make a direct comparison difficult. The first such difference is the relative clinical importance of the cloning of the aspartoacylase and hexosaminidase genes. The identification and cloning of the hexosaminidase gene by Dr. Rachel Myerowitz was a scientific and intellectual triumph; the cloning of the aspartoacylase gene by Dr. Reuben Matalon was a medical necessity for a community with very few options. Perhaps Dr. Myerowitz herself put it best:

> …Finding out the mutations [for the HEX genes] was fine… but they have a very fine enzymatic screen which is really far superior, and the reason it's superior is because it's an all-encompassing screen. If you have individual mutation screens, they're okay for ethnic groups, but what if there's an Ashkenazi Jew who has a new mutation, or his mother wasn't really Jewish? You would miss them. So really, my discovery of the mutations was intellectually interesting, but it wasn't like you had a community waiting for prenatal testing like I believe you did in Canavan.[127]

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[122] *Cigna Position Statement 0059, Genetic Testing for Tay-Sachs Disease*. See http://cigna.com/customer_care/healthcare_professional/coverage_positions/medical/mm_0059_coveragepositioncriteria_genetic_testing_for_taysachs_disease.pdf [accessed February 26, 2008].
[123] *Cigna Position Statement 0333, Genetic Testing for Canavan Disease.* See http://www.cigna.com/customer_care/healthcare_professional/coverage_positions/medical/mm_0333_coveragepositioncriteria_genetic_testing_for_canavan_disease.pdf [accessed February 26, 2008].
[124] *Aetna Clinical Policy Bulletin: Genetic Counseling Number 0189*. See http://www.aetna.com/cpb/medical/data/100_199/0189.html [accessed February 26, 2008].
[125] *Aetna Clinical Policy Bulletin: Genetic Testing Number 0140.* See http://www.aetna.com/cpb/medical/data/100_199/0140.html [accessed February 26, 2008].
[126] National Tay-Sachs and Allied Diseases Association, Inc. *Insurance Coverage*. See www.ntsad.org [accessed February 26, 2008].
[127] Interview with Dr. Rachel Myerowitz. Op. cit.

Dr. Myerowitz's modesty understates the importance of Tay-Sachs DNA tests in specific ethnic groups, especially the Ashkenazim. The DNA test for Tay-Sachs also has clinical utility: it is useful for determining the specific mutations in an individual, for confirming an inconclusive enzyme test, for identifying pseudodeficiency alleles, and for preimplantation genetic diagnosis (PGD). It is nonetheless true that DNA testing is much more clinically pervasive for Canavan disease than Tay-Sachs.

Another salient difference is patent status. Both genes were patented, but no attempt was made to commercialize a test based on the Tay-Sachs gene, and that patent was never licensed; in contrast, the Canavan gene was licensed with a relatively high royalty and with volume restrictions. One reason that the Tay-Sachs patent was never licensed is that there was already a working enzyme assay, which may have decreased commercial interest in licensing the DNA-based patent. Because the assay was already available, there would likely not be a market for an expensive DNA test. With Canavan's, in contrast, the market was open for prenatal screening based on a DNA test, and so the gene patent was more commercially significant.

One interesting fact that has come to light as a result of this study is that the availability and pricing of Tay-Sachs and Canavan Disease screening and DNA testing is similar, despite the difference in the intellectual property scenarios. This may indicate that using such a metric to compare patient access is inaccurate, although this seems unlikely given the similar population and screening scenarios for both conditions. It may also indicate a reduction in royalties as a part of the 2003 settlement of *Greenberg v MCH*.

Had MCH been able to enact the licensing terms they originally intended to pursue—a $25 or $50 royalty, volume limitations, a single high-volume provider, and refusing to name licensed laboratories—it may well have created an access problem for the Canavan community. This case highlights an instance in which members of a community and clinical providers serving that community took legal actions because of their concern over an access problem. The legal actions they pursued may have played a role in mitigating the long-term access problem that might have resulted from the MCH's original licensing scheme.

What has this got to do with patents?

*Patents are only a part of any story of health care innovation***.** This story clearly shows how patent policy is only one feature of a complex set of policies that influence innovation in health care, including introduction of a new genetic screening and testing procedure.

One solution is to eliminate DNA sequence patents, along lines of the Becerra-Weldon bill (HR 110-997). Without patents, the licensing controversy would not have been possible, so patents are part of the story. The implication that eliminating gene patents would resolve all issues, however, introduces other possible consequences. At the time it was discovered, the Canavan gene was considered a possible target for gene therapy; or the gene patent might have been important in producing aspartoacylase protein for therapeutic use, along the lines of treatment for Gaucher's disease, adenosine deaminase deficiency, or other enzyme deficiencies. The absence of a gene patent could have made inducing investment in the therapeutic developments difficult, a socially suboptimal outcome. Such treatments have not developed for Canavan disease, but patents on genes for other therapeutic proteins have proven important in the past and might do so in the future. So the policy option of eliminating DNA sequence patents, while avoiding Canavan-like controversies, also comes with a price.

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The main lesson of the Canavan case is that exclusive property rights can be used unwisely. Without the property right, the problems do go away, but so also do any benefits of intellectual property. The Canavan case could easily have been a story similar to cystic fibrosis or Huntington's disease, in which the constituencies that were involved in the discovery were at the table when decisions were made about patenting and licensing. The narrative in those cases is one of scientific success leading to broad availability not only of a genetic test, but also creating new pathways for scientific advance building on the discovery of mutations in a causative gene. Patents were also part of those stories, but patenting did not cause a shift in the CF or Huntington's narrative from heroic scientific discovery to secrecy, betrayal, and greed—the way the Canavan story played out in the public media. The difference was partly about licensing strategy, but more importantly, it was about human and organizational relationships.

One of the emerging frameworks for technology licensing is to see it more as a tool for building a collaborative framework to build relationships and foster innovation and less as a legalistic entitlement to be used as a weapon to extract revenue and overcome opposition.[128] MCH's patenting and licensing mistakes included failure to inform groups involved in the initial discovery about the decision to apply for a patent and then deciding to engage the organizations that had existing systems of testing Ashkenazi Jewish populations through legalistic "cease and desist" letters rather than involving them early and having them at the table when initial licensing decisions were being made. This is, again, a stark contrast with the much more successful introduction of genetic testing for Huntington's or cystic fibrosis, where analogous constituencies were involved early and directly as partners, rather than late and through legalistic tactics as adversaries.

The main conclusion from this case study is that patents matter, but they are tools, not ends in themselves. How they are used matters, as much or more than whether they exist at all. The story is both a travesty of poor management of intellectual property and a story of tort law and litigation leading to a settlement acceptable to the parties. If managed sensibly, and with involvement of stakeholders, patented technologies can generate revenues for research institutions without hindering research or clinical use and at least in this case ultimately with few discernible impacts on prices of or access to genetic testing; if mismanaged, patent licensing can cause controversy and disrupt systems of genetic testing and screening, and damage the reputations of scientists and research institutions.

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[128] International Expert Group in Biotechnology, Innovation and Intellectual Property. *Toward a New Era of Intellectual Property: From Confrontation to Negotiation.* 2008 (October). The Innovation Partnership, McGill Centre for Intellectual Property Policy. See http://www.theinnovationpartnership.org/en/ieg/report/ [accessed January 19, 2009].

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Patents and Licensing Events

1997 – US Patent 5,679,635, claiming methods of screening for Canavan disease

1998 – 1999 – Miami Children's Hospital (MCH) sends enforcement letters to hospitals and laboratories testing for Canavan disease

January 20, 2000 – Canavan Disease Screening Consortium and Canavan disease experts meet with MCH to discuss licensing patents
October 2000 – After MCH fails to find single, large-volume licensee for Canavan testing and only discloses information about 4 of 12 licensees to Canavan Disease Screening Consortium, the patient advocacy groups and families with Canavan disease sue MCH, MCH Research Hospital, and Reuben Matalon (Greenberg v. Miami Children's Hospital)
August 3, 2003 – Greenberg v. Miami Children's Hospital settled out of court on confidential terms

Technical and Professional Events

1971 – Drs. John O'Brien and Shintaro Okada develop first enzyme test for Tay-Sachs disease

1990 – Dr. Matalon publishes details of prenatal enzymatic screening test for Canavan Disease

1993 – Dr. Matalon and others publish sequence of normal and mutated aspartoacylase gene, allowing for DNA-based Canavan testing

1995 – American College of Obstetricians and Gynecologists (ACOG) recommend DNA-based carrier screening for Tay-Sachs disease before pregnancy if both parents of Ashkenazi Jewish, French-Canadian, or Cajun descent

1998 – ACOG recommends DNA-based carrier screening for Canavan disease if both parents are of Ashkenazi-Jewish descent and prenatal, DNA-based diagnostic if both parents are carriers
1998 – American College of Medical Genetics (ACMG) recommends that people of Ashkenazi Jewish descent be offered DNA-based carrier screening for Canavan disease prior to pregnancy and that DNA-based screening for Canavan disease and Tay-Sachs disease be combined because both diseases are common among Ashkenazi Jews

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