Overview of Revised SACGHS Report *Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests*

James P. Evans, M.D., Ph.D.

[PowerPoint presentation.]

DR. EVANS: So while we're giving thanks, though, I do want to say this has been a five-year project really, as you'll see in a moment, and I want to highlight the contributions of the staff. I think that Sarah Carr, Darren Greninger, and Kathi Hanna have been absolutely indispensable, as they are regularly in these endeavors.

I also want to thank the members of the Task Force, who, in spite of having day jobs, were able to hang in there through interminable conference calls.

A note at the start here. We were never so delusional when we started this out as to expect unanimity in regard to this topic. This is an inherently contentious issue, and different stakeholders will understandably and naturally have different opinions. It's been a challenge to my conflict-averse personality, but I think that throughout our deliberations, we always tried to keep foremost in our minds the stakeholder that we ultimately all represent, and that is the patient.

In spite of some degree of, at times, very strong

dissent, the arguing and the vociferous debate was invaluable in shaping our conclusions. None of us got everything that we wanted, but it is fair to say, I think, that as a whole the Task Force is in firm support of the report and its recommendation.

So I am going to run through these slides at this point. We will have, it appears, ample time for discussion after public comments and lunch. So bear with me as I go through this rather rapidly, because we only have about 40 minutes now to get you to lunch.

This is the current composition of the Task Force with members, ad hoc experts, agency experts. I would give a special nod to Debra Leonard, who was the original chair of the Task Force when this first started, but her tenure came up a couple years ago and I took over.

The timeline is such that it was, again, about five years ago, or more than that, when we identified gene patents and licensing as a priority issue, but there was a National Academy of Sciences report that was in the works, and we deferred activity until after that report.

We formed a small group in the Fall of '05 to review that report, and in March '06, we endorsed the

report's general thrust, but there were significant limitations in terms of relevance to patient access. That was not their major focus. We felt that, from the standpoint of our charge as a committee, that more information regarding patient access was needed.

In June '06, we decided to move forward with an in-depth study. We established the Task Force, and in December of '06, Duke's Center for Genome Ethics, Law, and Policy was commissioned to assist in carrying out a variety of components of the study, most importantly the case studies.

In March '07, we organized a primer on gene patenting and licensing practices to establish a foundation of knowledge among members and in July '07, we had a Roundtable on International Perspectives and Gene Patents and Licensing Practices.

The Task Force continued the information-gathering process and began developing the report. About a year ago, we approved, after public consultation, a draft report for release and the public comment period went the standard time, this was from March 9th to May 15th, and we will hear some of the comments throughout this report to

you now.

The overview of this session, this next 40 minutes or so, is that we want to familiarize you with the process for having reviewed the comments and for creating the final draft report. We want to give you an overview of the report, a presentation of the proposed recommendations, and then we will, in the afternoon, have a discussion of findings and conclusions.

I would urge you all to read as much of the report as you can, especially the recommendations with the rationale that follows those recommendations towards the end of the report.

So we did receive a number of reports, some of them extraordinarily extensive, some with tables of contents and indexes, and there were 77 total reports. They came from a wide variety of different sources.

The review process for these public comments was extensive. Some of us read every single comment in detail, but the binder containing all of the comments was sent to each Task Force member for their review. Members of the Task Force were assigned comments to present for group discussion during the teleconferences and all comments were

discussed during conference calls, no matter how short or no matter how involved and lengthy.

The public comments were a critical supplement to case studies and literature. I think this is always an instructive process. I know that, for example, with the genetic discrimination process, the public comments were instrumental in forming our thinking and I think that, at least for many of us, the same can be said with regard to the public comments.

I would add that I think many of us on this Task Force very much started and ended the process in somewhat different places or very different places. It was very much a learning experience and the public comments were instrumental in that learning experience.

It was of note that the public comments confirmed that patient access issues that had been identified in the case studies were not isolated problems. These came up over and over again in public comments from a variety of sources, and the access problems appear to be the most problematic for the Medicaid population, as you'll see momentarily.

The public comments highlighted the problem of

exclusively-licensed sole providers and limitations on their ability to offer, for example, population-wide recommended carrier newborn screening and there were many comments that called for more discussion in the report and more discussion among the committee regarding the impact of patents on whole-genome sequencing, multiplex testing, and other emerging testing innovations.

After receiving all of the comments and going through them, I was actually pleasantly surprised to see that there were critical comments from really both ends of the spectrum, those that advocated dramatic and extensive changes and felt that there was extraordinarily problematic activities going on and those who felt that things really were great and that there should be no changes whatsoever.

I feel like we have tried to walk a balanced approach here, though I'm sure people, especially on the ends of the spectrum, will not agree with that.

Many that submitted public comments discussed their opinions and their perspectives on patents and that's certainly extraordinarily valid to do so. This is a subject that people have strong opinions and perspectives on. We especially appreciated, though, comments that had

concrete examples of benefits or harm, not platitudinous, not principle-based, but concrete examples.

Some of these concerned the impact, for example, of patents on test development. Some commentators thought that patents are not needed for test development, others thought that patents are needed for test development, and again we sought wherever we could to find evidence that illuminated those issues.

Regarding the process for producing this revised report, you'll notice, perhaps, that this report is much tighter. It's much shorter than the original report, and that was intentional. After reviewing and discussing the comments, we revisited our preliminary conclusions, and you'll remember that we took a somewhat unorthodox approach in our draft report, giving a range of possible recommendations to consider for recommendation to the Secretary.

What we were hoping and, indeed, I think, transpired was that following the public comment period and the extensive discussions we engaged in, we could then sort through those comments and decide as a task force which ones we felt were most appropriate to include in the final

report.

We revised the conclusions after considering all the evidence, the case studies, the articles, public comments, previous informational sessions, and public comments during meetings.

I would also point out that there was a wealth of expertise on the Task Force itself, people who do these tests, people who order and perform these tests, as well as those who deal with the consequences of them.

We discussed which policy options made sense as these final recommendations. The background sections of the draft report were revised to reflect the Task Force discussions, and the considerations, and it was reorganized according to the key questions that we addressed.

So here Is the summary of the report's main points.

First, we had to tackle what types of patents, or, more precisely, patent claims, are associated with genetic tests. It's important that we all be on the same page as we consider these issues. So there were patents claiming isolated nucleic acid molecules, and these in many ways are the oldest type of what is generically referred to

as "gene patents".

These patents claim an isolated nucleic acid whose sequence may correspond to a gene, to a mutated gene, to intergenic DNA, for example. These patents are sometimes called, loosely or colloquially, "gene patents," and for the sake of simplicity and accuracy, the report refers to these patents as "patent claims on genes."

There are other types of claims that really accomplish, in many ways, the same thing but have subtle and important differences. Patent claims to the act of simply associating a genotype with a phenotype is something that has gotten much, much activity and interest in recent years.

For example, a patent might claim "a method of determining a predisposition to disease X, comprising testing a body sample of a human for the presence of a mutation in gene A, wherein the presence of a mutation in gene A indicates a predisposition to disease X."

So what you can see with this type of claim is that, inherent in it is that association of genotype with phenotype. For the sake of simplicity, the report refers to these patents as "association patent claims." Again,

these are very much in the news now because of recent court rulings and pending court rulings.

There is another type of claim that is important to define so that we understand the different mechanisms for attempting to patent this type of information, and that is patent claims to processes for detecting specified genetic sequences.

So "a method," and I put that in quotes for important reasons, or process of detecting a particular sequence, including a particular mutation, using specific probes, specific primers, et cetera. In essence, this type of patent is attempting to claim a specific sequence, but you can see that it jumps through certain hoops to do so.

I think it's extraordinarily important to emphasize that this type of patent should not be confused with patents on innovative methods for general DNA analysis. What we are not talking about here at all today are methods patents. For example, PCR, a new type of sequencing, et cetera.

We are talking about laying claim, in some way, to a sequence through different avenues or to an association. Also, there are patent claims to test kits

for conducting a specific genetic test. So patents lead to exclusive rights. That is the intent of the patents. That is why we have patents in the first place.

Well, how a patent's claim can give exclusive rights to a genetic test is a multi-pronged mechanism. In addition to claiming an isolated gene molecule, these patents may claim, for example, primers for amplifying a gene and/or nucleic acids that are complementary to the gene. So that would be one way.

Because the typical methods of testing for a gene in a diagnostic setting involve either patented primers or complementary probes in such a situation, these methods, then, require the patented molecules in order to function. The patent holder's ability to exclude others from using the molecules, then, gives the patent holder exclusive rights to testing.

An association patent is a little different. It gives somebody exclusive rights to a test, but with an important, subtle difference. A patent of this sort does not claim the molecule itself, it claims the method -- again, I would put air quotes around that -- of testing humans for a particular genetic sequence and associating

that genotype with a phenotype. That "which" should not be there, and that "and" is very important.

So an association patent says we own the process for testing for this and associating it with a genotype, that thought step. The patent holder has exclusive rights to that process or method which involves the testing and the association of, for example, sequence A with disease X. Because genetic testing for disease X or its predisposition, for example, necessarily involves the patent process, the patent holder has exclusive rights to genetic testing in that setting.

There is another way that this can be done. Patent claims over a process for detecting a specific mutation through probe hybridization, primer-driven amplification and sequencing, or some other means. The patent holder then has exclusive rights to any genetic test that detects that specific mutation through that patented method.

So it's very important to keep in mind, as we go through this, the purpose of the patent system, and this goes back, of course, to the U.S. Constitution. Article II; Section 8, says that patents exist to promote progress

in the science and the useful arts.

There is a long history in U.S. legal tradition, founded originally in the Constitution, that the patent system has, very much, a utilitarian purpose in our country. Patents in the U.S. are not awarded as natural rights. They have a very utilitarian function in mind.

Patents are designed to stimulate scientific progress through a variety of mechanisms by offering the inventor an exclusive time-limited rights to use, make, or sell the invention. In other words, it grants a limited monopoly, and this is a trade-off.

Society has decided that this trade-off is a good thing for us, as a whole, and the trade-off is between benefits of patents and stimulating scientific progress, because as part of the deal when you receive a patent, for example, you divulge that information and now others are free to use it to build the next mouse trap. It has to balance that with the harms from the patent holder's ability to exclude others from an invention.

The report, from the outset, was intended, and we were charged with very clearly, the charge of examining both sides of this trade-off. So we were not charged

initially to, for example, just go out and find harms from patents. That would have been a presumptive and an unfair type of activity.

Not only would it have been presumptive and unfair, but it wouldn't take into account the basic, underlying rationale for patents in this country. Therefore, it was important that we kept in mind throughout the process that we were looking for both benefits and harms where we could find them.

So let's look, for a minute, at examination of benefits of patents in the genetic testing arena. The patent system, as I've said, is intended to promote scientific process, and economists recognize three main mechanisms for how such progress can be promoted in the scientific arena.

One, patents can promote progress by stimulating research for the purpose of making discoveries or inventions. This is what we think of, oftentimes, as the most overarching benefit to patents, but they also are meant to promote progress by stimulating disclosure of new discoveries and of adding to public knowledge.

Finally, patents promote progress by stimulating

investment in post-discovery development, especially in the realm of healthcare, as for example as Bayh-Dole recognized, we're not interested in just having discoveries, we're interested in implementing those discoveries.

So we want to drill down, and I think it's important to remember that our task force and this committee is charged with looking at a very narrow slice of patents, and that is in the realm of genetic diagnostics. So we want to frame these questions in the realm, in the context of gene testing.

So one question that we have to ask is, do patents stimulate genetic research leading to diagnostic tests. Regarding disclosure, we need to ask, do patents stimulate the disclosure of genetic discoveries that then lead to diagnostic tests; and finally, does stimulation of investment needs to be focused on whether patents stimulate investment and develop the discovery of a gene- disease association, for example, into a test.

Taking a look, for a moment, at this idea that we want to stimulate research and discovery for invention, the case studies were instructive here, and they revealed that

patents stimulate some private investors to fund genetic research.

However, there was also abundant evidence that academic scientists conduct research not because of patents but because of other motivations. In fact, academic researchers are oftentimes almost willfully ignorant of the patent situations.

Government provides vast amounts of funding for basic life sciences research, and this is an important piece of the equation when we're thinking about the stimulation of research in this field. There were no consistent findings, by case studies or public comments, that patents were necessary to stimulate research leading to the availability of genetic tests.

There were weak indicators here that there was never strong evidence that patents were necessary. In fact, many, many genetic tests exist out there in which patents were a complete side issue or non-existent as a consideration.

Disclosure is another issue which, of course, we are interested in. Researchers have, we felt, sufficient existing incentives to disclose genetic discoveries.

Academic ethos encourages open science and rewards publication of its first discovery, and the individual investigator in the academic environment where most of these discoveries are made is after other things that do not include patents in a typical situation.

Patents and genes, in fact, by some criteria, would appear to diminish public knowledge because they result in less follow-on research. In a study by Huang and Murray, we quote in the report that strict interpretation of our results suggest that follow-on genetic researchers forego about one in 10 research projects or, more precisely, research publications, hence, disclosure, through the causal negative impact on the gene patent grant.

Regarding the stimulation of investment to develop genetic tests, although patented discoveries are developed into tests, unpatented genetic discoveries are routinely developed into clinical genetic testing services, and I can't really emphasize this point too strongly.

The empirical data around this issue was a very persuasive point for many of us on the Task Force. What one sees in example after example, with regard to

development of genetic tests, is that the role of IP was primarily used to narrow the offerings out there for genetic testing.

Prior to the granting or implementation of patents and exclusive licenses for, again, example after example, many labs offered the tests, in that, there were numerous laboratory options for an individual to have a genetic test.

After IP was enforced, after exclusive licenses were negotiated, what one sees is a clearing of the market. This phenomenon is likely due to the fact that clinical need is sufficiently high and developmental costs are sufficiently low, so that genetic tests can be implemented when the knowledge is out there, and that therefore patents and IP considerations do not seem to play an important role in developing tests. In fact, again, what they seem to do in example after example is narrow the market.

Thus, the conclusion of most of us in the Task Force was that patents are not needed for the development of testing services. I think there was an instructive public comment from a director of a laboratory who specializes in rare disease, in which he very poignantly

said that when they are considering what new tests to develop, as soon as they see that there is IP, especially exclusive IP that is surrounding a particular test, it moves to the bottom of the list, in his quote.

Again, we will have plenty of time to talk about this in the discussion period. This was not a unanimous feeling among the Task Force, as I mentioned at the outset, but it was certainly the feeling of the majority of the Task Force.

So our overall conclusions concerning patents benefits are that patents do not serve as a powerful incentive to conduct genetic research, to disclose genetic discoveries, or to invest in the development of genetic tests. There exists sufficient incentives and funding for research and development and, as such, the benefits of patents in the area of genetic testing are limited.

We then turned to examining the costs, and when I say costs, I would always insert in your mind a slash "harms." We're not talking about just financial issues here, we're talking about harms or costs, in the universal sense, to patents in the genetic testing arena.

So the Task Force examined whether patents on

genes, on genotype/phenotype associations, on methods of detecting specified sequences, are causing (1) limitations on the availability of genetic tests at reasonable prices, and this could be through, for example, the combination of sole providers and a multipayer system; (2) limitations on the ability of researchers to develop new tests; and (3) whether one was seeing problems in the quality of genetic testing, because it must be remembered, of course, that access to genetic testing doesn't just mean access to any test, it means access to a quality test that is of the highest possible quality that we can reasonably expect.

We wanted to interject a quick licensing refresher here, because the issue of licensing is an important one when one discusses these issues.

So to evaluate the costs of patents and licensing practices, there is some background information that is required and a license is an agreement through which a patent holder agrees not to exclude a specific licensee from using the invention, and there are different types of licenses that exist.

On one hand and on one end of the spectrum, one has exclusive licenses. This creates a sole provider of a

genetic test. That is, only that licensee has the right to practice the invention.

There are less exclusive forms of licensing. There are, for example, non-exclusive licenses that are extraordinarily broad, co-exclusive licenses that permit multiple licensees to use the patented molecule or method to offer testing.

So one of the most surprising features or outcomes of the case studies was the impact on price for genetic tests, because I think most of us assumed at the outset that there would be some patent premium associated with the holding of a patent and exclusivity in the realm of a genetic test, and that did not turn out to be the case.

So there was not a pattern of overpricing for tests that were patented and exclusively licensed when compared with tests that were either unpatenteded or non-exclusively licensed. There were a number of instructive and interesting kind of experiments of nature here that focused, for example, on the BRCA testing. So Myriad Genetics, for example, as we all know, holds the patent on the BRCA test and excludes others from doing it.

When you compare the unit price for that test with either tests that they offer that are not exclusively owned by them or with tests that are performed by other entities, one does not see a patent premium.

Now, there is evidence or suggestion of a patent premium in the test for Canavan disease versus Tay-Sachs, which is a reasonable comparison that could reflect a patent premium, but overall, we did not see a pervasive increase in costs.

There was a public comment that was instructive, suggesting that Athena, who owns the exclusive licenses on a number of spinocerebellar ataxia-responsible genes is needlessly expensive, not because of a patent premium, per se, but because it necessitates bundled testing in some circumstances. So one has to think about the fact that we deal frequently with genetically heterogeneous diseases.

It may well be that a clinician would like to test gene A or gene B or gene C. If an exclusive licensee or an exclusive provider of such testing doesn't allow that type of testing and says no, you have to get the whole panel, that obviously can cause an increase in prices, is of a somewhat different mechanism than a traditional patent

premium.

So clinical access to genetic tests was judged by trying to review articles, case studies, public comments, and these indicated that overall patents and exclusive licenses have certainly limited the ability of clinical laboratories to offer genetic testing. This is a non-controversial statement, in that, one can show over and over again, of course, that laboratories are prohibited from doing testing when IP is invoked against them.

Now, licensing practices that limit the number of clinical labs that can offer a test do not necessarily result in patient access problems. However, patient access problems were certainly reported and arose when licensing creates a sole provider as, probably, the major type of context or situation in which problems occurred.

So going on to look at this process, these access problems have generally not occurred for patent-protected tests that are broadly licensed. Most problems seem to occur when tests are exclusively licensed and create, then, a sole provider.

For example, the case study of the Long QT syndrome. The Long QT syndrome is a lethal disorder in

which individuals have a genetic predisposition to lethal dysrythmias. Over a period of about 18 months, excessive exclusive licensees enforced patent rights, even though they were not yet offering a test, which, in the judgment of the case studies, "probably had a small but tangible negative effect on patient access."

So looking at the issue, an issue that was, again, highly instructive in the realm of public comments, and in talking to clinicians as well as patients who have dealt with these issues, is the issue of how the sole provider interacts with health insurance and how that changes or affects patient access.

What we saw over and over again and again, again, in the public comments, is that the combination of exclusive licensing to create a sole provider, combined in the context of a multiple payer system, like the U.S. healthcare system, often results in patient access problems. The meat of this type of scenario is the following.

Sole providers oftentimes fail to secure coverage from some major payers. This includes, for example, out-of-state Medicaid programs. As a result, some patients

can't obtain the covered testing and, of course, it's indigent patients, covered by Medicaid in particular, that do not obtain testing. The way this works, for example, is that a laboratory with exclusive rights to do this test, for example, doesn't have a contract with MediCal, the Medicaid program in California.

MediCal has numerous contracts with laboratories who have said, we would like to do this test; you have a contract with us, we would like to do this test. But they can't do it because of the exclusivity engendered by the patenting and licensing situation.

In the hearing loss example for Athena, which has exclusive license to a number of the genes that are involved in hearing loss, they have not been able to secure coverage from MediCal for Connexum-26 testing. Now Connexum-26 mutations account for the bulk of non-syndromic recessive hearing loss cases, and this quote is from the case studies:

"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."

So there are many different ways of dealing with this. If you're a lab and you have a contract with a state Medicaid agency, and yet you are prohibited from doing the test, one choice is, we won't do the test. That, of course, is what your legal counsel would tell you, typically, not to do. Other laboratories say, well, we're just going to do the test and hope that nobody enforces. So, as you can see, it's a rather unstable situation.

There are similar problems for SCA testing, which we have mentioned before. Sole providers offering testing for Alzheimer's disease and Long QTS have had problems, for example, securing coverage from particular payers.

Myriad Genetics had this problem at the outset but now has secured wide coverage from Medicare with very reasonable types of regulations about when it applies as well as private insurers, but it should be noted that Medicaid patients still cannot obtain such testing in at least most, if not all, states.

The information from public comments again

highlighted this issue. It arose in Georgia. We got several comments regarding this same issue going on in Georgia as going on in California with "the end result is that access to genetic tests can be largely influenced by patient's socioeconomic status and geographic location." In one state where there is a contract, you might be covered. If you're in another state, you won't.

A healthcare provider complained that some sole providers have not secured coverage and by this same mechanism there were problems in Montana. A parent complained of insurers not covering genetic testing for hearing loss. An advocacy group complained that Athena, the sole provider for dystrophin genetic testing, has not secured coverage from some payers, again resulting in access problems.

So observations from the public comments include that when there's a sole provider, patients can't obtain second opinion testing. So this is another issue that came out in the public comments and have actually been in the news of late because of the ACLU-orchestrated lawsuit against Myriad Genetics.

This issue of second opinion testing is seen as a

particularly-troubling one when one is in the context of a sole provider.

Recommended carrier and newborn screening is not possible at times when only one lab offers the test and it's thought that multiple labs are oftentimes needed to handle the kind of volume of testing as well as the temporal factors that are important in newborn screening in which this has to get done quickly in order for interventions to be enacted.

So our conclusions regarding patient access are for the most part patents covering genetic tests and related licensing practices do not appear to be causing wide or lasting barriers to patient access and this sentence is lifted out in a number of comments, that sometimes what is not lifted out is the subsequent sentences which are, "However, the case studies and public comments document several situations in which patient access to genetic tests has been impeded for segments of the population, especially indigent patients, when these tests are offered by an exclusive provider or a limited number of providers, a practice directly enabled by current patent and licensing practices."

Now, we struggled for a long time with the issue of quality. Again, as I mentioned, from the outset, our charge was to look at patient access to genetic testing and inherent in that charge was the genetic testing needed to be of high quality.

There were recurrent concerns regarding test quality, where a test is offered by a sole provider. Here, we relied to a considerable extent on the expertise of two members of the Task Force, Andrea Ferreira-Gonzalez and Debra Leonard, who do these tests and who are engaged, on a day-to-day basis, in quality control.

It was pointed out that proficiency testing, which undergirds quality control in this country for laboratory testing in general, requires that multiple labs offer a particular test.

In addition, there is concern that with samples becoming increasingly labile and smaller as we use biopsy techniques, for example, that are less invasive and produce smaller amounts of material, more local laboratories are needed to handle testing. Samples sent to a distant sole provider are subject, for example, to degradation.

The competition between multiple laboratories

offering a particular test, in addition, need innovation in the testing method for that test. So quality, I think, needs to be looked at from a rather expansive standpoint. We are not talking about just reproducibility, about did the right answer occur. Those are absolutely critical and are addressed optimally by multiple labs that can share samples and engage in proficiency testing.

In addition, when we think about quality, one needs to think about implementing new innovations in order to improve, for example, the sensitivity and specificity of a test. The most conical example of this that is brought out frequently is the Myriad Genetics example, where deletion testing lagged behind many calls for improved testing.

In the example of CF, which is instructive, you have a lack of exclusivity, and this has led to multiple, both private and non-private, labs, who all compete to offer a variety of things based on innovative testing, quality of testing, sensitivity, specificity, et cetera.

By having non-exclusivity, what one sees is basically a marketplace in which innovation and quality is enhanced. There is legitimate concern that exclusivity

undermines that process.

So the existence of a sole provider dictates, in addition, what method of testing is offered and the testing strategy. For example, bundling is common, as we discussed a moment ago, for heterogeneous conditions, but is not necessarily the most efficient or the most cost-effective way for a patient or a provider to proceed.

Again, in the setting of exclusivity, there is little pressure on a particular laboratory to offer a variety of modalities by which to do that test. Those methods are at the discretion of a single laboratory, and I mentioned the issue with Myriad and deletion testing.

One of the things you might notice, if you were able to get through both the draft report and the final report, is that we have spent more time in the final report discussing the implications of the current landscape in gene patents and licenses for the emerging world of genetic testing.

There were many comments from all across the spectrum that said, you guys need to consider this and that, which was a major driver in our deliberations over the last couple of months.

There is broad consensus, I think, in the medical arena, in the technological arena, that genetic testing will increasingly involve multiplex technologies. Genetic diseases, common diseases are genetically heterogeneous. That is, there are many genes that go into a predisposition for any given disease, and moreover, we are on the verge of whole-genome sequencing.

There is no question in anyone's mind, who is involved in this, that within the next few years, whole-genome sequencing will be readily available for prices that now certain bundles of testing, for example, SCA, will exceed in cost. So it will be cheaper to sequence the entire genome than to sequence at current costs, say, 11 genes responsible for a single disease.

The advent of multiplex testing is already an issue with regard to gene patents and access. Labs holding exclusive licenses are currently blocking labs that do multiplex testing from reporting full results pertaining to those patented genes, and we heard about this in public comments. The potential for a blocking situation in Long QT testing, we've discussed.

So the Task Force studied not only the costs or

harms of patents on existing tests but also the potential of existing patents to block the development of new tests, specifically multiplex tests, parallel sequencing of multiple genes, and clinical whole-genome sequencing.

I am going to need to go quickly here if people are going to get lunch.

There is no precise figure for the number of genes or associations protected by patents. Suffice it to say that the typical number bandied about is that about 20 percent of the human genome is under patent protection, and concerns have been raised that all of these existing patents on genes and disease phenotype associations have created a thicket of rights. A developer would need multiple licenses to develop a multigene test.

Patents on genes and associations cannot be invented around, an important point, and controversy exists regarding the legitimacy of patents on genes and associations. Some view patents on these as playing in products of nature, and view patents on association as claiming laws of nature.

So would these new methods actually infringe on patents on genes? Well, multiplex testing involves probed

molecules that would probably infringe corresponding patents and nucleic acid molecules. Multiple parallel sequencing typically involves aligo nucleotype molecules that again would probably infringe on patented nucleic acid molecules.

There is interesting uncertainty over whether whole-genome sequencing would infringe on such patents on genes. Association patent claims, on the other hand, are by definition quite broad. We've gone over the definition of an association patent. Claims, such as these, do not specify a particular method of testing, so any method of testing is protected, if one is making that association and, as such, any new form of testing would infringe claims of this breadth, assuming that the test included a gene referenced by the patent which, of course, whole-genome sequencing would by definition necessarily include all genes.

So delving into this a little more, would these new methods infringe patent claims? It really depends on the particular method and process claimed, and I'm going to go to the summary slide here.

New methods would probably infringe at least some

association patent claims. For example, parallel sequencing and multiple testing appear likely to infringe patent claims on genes and the methods for detecting specified sequences. Whole-genome sequencing may or may not infringe on patent claims to genes, and this is a matter of some debate amongst legal scholars in the area.

So test developers nevertheless would need multiple licenses to existing patents to develop most of these new innovations.

There are also challenges to obtaining licenses that has to do with the fact that the human genome has been staked out in many arenas. It is often unclear whether licensing rights are available. One way to learn of this is to look at existing licenses. However, license terms are often undisclosed. Even if one can obtain all needed licenses, all of these licenses can lead to royalty stacking. There are also transaction costs simply involved in having to separately negotiate each license.

A patent thicket may block or hinder the development of new innovations. There's costs involved in researching patents, separately negotiating each license and cumulative license fees that can then discourage

development, and even if these costs can be overcome, patent holders who refuse to license can prevent test developers from using a patented gene molecule or association, diminishing the value then of a multigene test, the blocking problem in which one individual laboratory says we've got this gene, it accounts for 11 percent of cases, and it's not going to be in this panel or that panel, and, moreover, patents on genes and associations, especially simply cannot be invented around.

There have been a variety of proposed solutions to patent thickets, including patent pools which are interesting and innovative agreements among multiple patent holders who license all patent rights as a packet, and those advantages include the ability to retain all the rights with one license. That solves the stacking problem. The disadvantages, however, are that patent pools are voluntary.

In biotechnology, patent holders have no real inherent incentive to join forces because again each holder of a gene can offer a single gene test as opposed to if one owns one necessary component of a chip, all right, you can't do anything with that, but you actually can do

something if you simply own a single gene. A hold-out's refusal to participate can limit the value of the pool and, most instructively, they've not proven useful in the genetic testing arena thus far. So questions remain as to the viability of these solutions.

Clearinghouses are another innovative solution that has promise. Patent holders join a collective that then charges a standard licensing fee for each patent and the advantages, again, are that you don't need to negotiate each license. You have license fees that are considered in bulk.

The disadvantages again are that clearinghouses are voluntary. There is the possibility of hold-outs and they've not proven useful in the genetic testing arena thus far. So again, there's significant questions as to whether this is a viable solution, and I think it would be awfully sketchy to rely on these as solutions.

There are additional challenges to the development of laboratory-developed tests or "home brews," in the colloquial. Research to create LDTs is not entitled to experimental use exemption. The Hatch-Waxman experimental use provision provides exemption from patent

infringement liability for using a patented invention for the purpose of developing and submitting information under federal law regulating drugs. Those using patented molecules during research to develop a CLIA lab-developed test couldn't invoke this exemption because CLIA is not a federal law that regulates drugs.

Conversely, to gain approval for a test kit, developers must submit information on analytic validity, clinical validity, under the FDCA, so any use of patented molecules, associations, et cetera, in a kit would likely be exempt from infringement.

Now, there are a variety of legal developments that are currently in flux. There are various ongoing cases that may well alter the patentability of genes associations and methods of detecting specific sequences.

We all probably know about the ACLU case in which a variety of plaintiffs are challenging the patentability of various claims, including the claim to BRCA1 and BRCA2, isolated gene molecules, the claim to association between BRCA2 and breast cancer, and claims to methods of detecting the mutations in these genes.

Bilski has just been granted certiorari by the

Supreme Court and will be heard and may well, it's almost certainly will, affect the patentability of processes for correlating a genotype with a phenotype, even though Bilski is not in its narrow sense about genes.

It was the feeling of the Task Force, however, that it is impossible to predict the outcome of these cases. It's better, then, to address problems that we see as pressing, through recommending policy changes and statutory changes.

We reviewed a few other pieces of material, including the Bayh-Dole Act. This established the uniform policy of allowing academic institutions to retain title to federally-funded inventions and the question arose during our Task Force deliberations over whether law gives agencies the authority to require non-exclusive licensing.

Clearly, even if it does, this is not the norm, and NIH best practices for the licensing of genomic inventions were reviewed. These have been promulgated to promote, for example, broad licensure.

The nine points have been promulgated to promote many of the same things. The OECD Guidelines for Licensing of Genetic Inventions, the NIH Policy of Sharing Data, et

cetera, et cetera. There is no shortage of promulgated suggestions and suggested rules that discourage exclusivity and, for example in this case, discourage genotype/phenotype association. However, these recommendations have existed for a long time and uptake is, to put it mildly, not universal.

Finally, before we get to the recommendations, I want to just remind people of something that I think the Task Force was cognizant of all along, and that is, there is a moral dimension to this question.

There were many comments that pointed out that moral and ethical issues are inherent to the consideration of gene patents and licenses. I think we all understand that at a basic level. You talk to anyone about this subject, people feel strongly about it.
There is a moral and ethical dimension.

There is strong sentiment in some quarters that exists that access to one's own genetic information should not be limited or proscribed by patents and, of course, that's what a diagnostic test is doing. It's achieving information about one's own genetic information, and this is at the root of the recent court case that's been brought

against Myriad.

I would also remind us, as we think about making changes to a system, that genetic tests are not equivalent to commodities. We're not talking about consumer electronics or kitchen appliances here. We're talking about human health, and these considerations are important to remember, in that they affect human lives and human health.

So to sum up, the patent system is designed to promote progress. That is the purpose of the patent system in the U.S., going back to the Constitution.

In the realm of therapeutics, for example drugs, strong arguments can be made that patents enable innovation, drive progress, and serve an important role because, for example, of the high, high upfront costs in investment that are required.

In the realm of diagnostics, patent-enabled exclusivity, primarily, demonstrably and empirically results in a narrowing of offering to patients and physicians.

If access, again, to kitchen appliances were the issue, I'm not sure that the situation would be anything

more than lamentable, and might not rise to the level which we might advocate change for, but what is at stake is patient access to important medical information and we, the Task Force, in general, with some dissent, felt that this warrants changes to the system.

Now, let me ask Sarah and Steve, since we're running late, do you want me to go through the recommendations, quickly?

DR. TEUTSCH: Yes. Can you briefly go through them?

DR. EVANS: Yes. I'll go through them very quickly, and then you can look at them.

DR. TEUTSCH: It would be helpful for everybody to have them.

DR. EVANS: We're going to go through these in detail afterwards.

So the overarching recommendations are really 1, 2, and perhaps 3. Number 1 advocates that the Secretary supports and works with the Secretary of Commerce to achieve the following statutory changes, and that would create an exemption from liability for infringement of patent claims on genes for those who make, use, order,

offer for sale, sell a test that is developed under the patent for patient care purposes.

What this seeks to do is, it seeks to narrowly dissect the diagnostic use of gene patents from other uses, and exempt that use in the medical context. This can be seen in some ways as analogous to the Ganski-Frist bill which exempts medical providers from infringement claims on a variety of procedures.

So Number 2 is, the creation of an exemption from infringement for those who use patent-protected genes in the pursuit of research. Number 3 is, the Secretary should discourage the seeking, granting, invoking of simple association patent claims, because it was the feeling of most of the Task Force that association patent claims represent basic laws of nature that cannot be invented around and should not be owned.

We are advocating recommendations that promote adherence to norms and we'll need to have a discussion, the major discussion being, should there be teeth put in regulations that seek to get, for example, fundees to adhere to norms of licensing, et cetera.

Enhancing transparency in licensing is important.

Again, it will be a matter of debate whether we want to put teeth [in the regulations] or simply suggest these things.

We have advocated an advisory board that would, in an ongoing way, assess problems in the realm of gene patents. I would add that we tailored these subsequent recommendations after 1, 2, and 3, because we recognize that statutory changes take awhile. The Secretary may not choose to implement them, and therefore we wanted some other recommendations as a fallback, basically.

Federal efforts to promote broad licensing and patient access, we've got recommendations that encourage these things. Again, we can have a discussion about whether this should be more than simple encouragement. Things like exploring whether approaches to addressing patent thickets, like patent pools and clearinghouses, may offer some solutions; whether the Bayh-Dole Act gives agencies authority to influence how grantees license patented inventions is not clear. We've asked for clarification about that particular point.

Finally -- I think this is the end -- it was felt that it might be helpful to the USPTO if an advisory committee were established to advise not only about ongoing

dilemmas with the fast clip of technology advancement but how to incorporate the legal decisions that are in the pipeline now into this changing landscape.

So we don't have a whole lot of time for lunch, but we'll come back, and then go through those recommendations and discussion in general.

DR. TEUTSCH: Thank you very much. It's a lot to cover and a lot to think about.

So we're going to break for lunch now. We are running late and it's going to be a little challenging to get everybody back since we're going to pretty much have to scatter to various eating places in the neighborhood, and you have a list in your packet, but we had allowed 45 minutes. That's probably going to be a little tight. So let's plan to start at 1:00. I think the public commenters are able to stay, so we can get all of your input, which we need.

So, why don't we break and see everybody back at 1:00.