

22 December 2011

Amy P. Patterson
Associate Director for Science Policy
National Institutes of Health
Via gtr@od.nih.gov and OIRA_submission@omb.eop.gov



Duke Institute for
Genome Sciences & Policy

Center for Genome
Ethics, Law & Policy

Duke University
North Building, Research Drive
Box 90141
Durham, NC 27708

T 919-668-0793
F 919-668-0799

www.genome.duke.edu

Dear Dr. Patterson,

Thank you for the opportunity to comment on the proposed form that will be used to generate the Genetic Testing Registry (GTR), per *Federal Register* notice of 23 November 2011 (Vol. 76, No. 226, pp. 72424-5).

The test registry could replace genetests.org as the first place to go to determine who is offering genetic testing for a particular condition or locus. The OMB notice appropriately focuses on the potential burden on those submitting data. Only data essential to make sense of the list and not available more readily elsewhere should be included.

I have several concerns based on reviewing the proposed fields and mock-up entry. One is overinclusion of information for which the GTR is not the appropriate archival resource, and therefore not a good use of time for those submitting entries; another concern centers on patent and licensing elements that bear directly on the availability of tests but would not be included. My final comments will focus on overlap and coordination with the regulatory data required of testing services, so that the NIH database is integrated with rather than separate from data required for those tests (now and in the future) that will be regulated by the Food and Drug Administration (FDA; both Laboratory Developed Tests and In-Vitro Diagnostic Multi-Index Assays) and for regulation, coverage and reimbursement by the Centers for Medicare and Medicaid Services (CMS) under federally funded health programs and the Clinical Laboratories Improvement Amendments. There is a danger that three agencies will set up somewhat different databases for their different purposes and with extensively overlapping data requirements that are nonetheless not coordinated, so that those submitting data have to comply with these and any state and private health plan data needs separately. Explicit explanation of how data submitted to GTR will be used by FDA and CMS would be most welcome, so the system is not an added data burden but instead a single database serving multiple purposes and so streamlining federal data submission on genetic tests.

Overinclusion and redundancy

While it makes sense to list participation in proficiency testing and quality control national programs and to designate a contact person, the level of detail seems unduly high. The nature of quality control programs is constantly changing; moreover, many programs relate to multiple tests or by laboratory rather than by individual tests. Asking for exactly which QC program is used for each test will require a substantial effort centrally to generate an up-to-date set of pull-down items to select, and redundancy test-by-test for those submitting data. This test-by-test data entry format will be particularly burdensome for laboratories that do many tests; for them it would seem to make better sense to instead link to a page they make public that shows how they are complying with proficiency testing and CLIA certification requirements, which are done laboratory-by-laboratory rather than test-by-test. A single

entry per laboratory noting which QC programs it subscribes to might be more logical, obviating repeat entries for the laboratories that offer multiple tests. This suggests the option of organizing the data according to test and according to laboratory, with ability to connect between them, rather than only test-by-test.

Regarding the contact person, the level of specificity about certification, licensing, and specialty seems beyond the need of a list focused on what tests are available, and items associated with personnel are sure to require regular updating and thus often be out of date and inaccurate. I don't think I would use GTR to find an individual's medical certification, but I would use it to find out who is the laboratory director. Beyond an initial contact, however, I do not think GTR is the right place to list genetic counselors, physicians, or others except to the degree they are the primary contact for information about a particular test.

Regarding the details about which tissue samples, how samples are submitted, how linkage to counseling services is maintained, and exemplars of negative, VUS and positive reports, a central database seems a poor way to try to capture the information both because it will be constantly changing, and because in many cases, the same procedures will be used for multiple tests. Another option would be to require each laboratory offering a test to have a site that explains these details, and perhaps specify the data that must be available, but not to require data entry test-by-test. That is, require a link to a document that supplies stipulated information, but not directly incorporate the information centrally in the database. This would leave the control of updates in the hands of the laboratories, and require central management only of links rather than the constantly changing data.

The section on the condition tested (currently called "disease," but that is probably going to encounter some confusion for some testing, for example pharmacogenomic tests or broad screening tests). The option for detail here is welcome, but GTR seems unlikely to be the place that information about acronyms, mode of inheritance, disease mechanism, or prevalence are documented. A link out to OMIM, where possible, would be much more logical, but it does not appear that OMIM categories are cross-referenced here, so the data are apt to be redundant with OMIM, which is an actively archived and curated dataset and more likely to be current with the literature than GTR will be (as a database about what tests are available not about what is known about the diseases being tested). Explicit attention to MESH categories and OMIM categories might reduce the amount of data entered and also connect users to the relevant database. Finally, the information on individual mutations will be accumulating at databases such as MutaDATABASE, Breast Cancer Information Core, Human Gene Mutation Database, and Human Variome database. Linking to these rather than duplicating the information in them seems a wiser strategy, and these databases are much more appropriate archives for the basic data on which interpretation of tests will be based, whereas GTR will be the database of clinical tests and testing services.

In the section on "method," this seems likely to be especially fast moving and liable to change, and the categories will be shifting to a degree that may make a central database hard to maintain. And yet this information is exactly what someone contemplating ordering a test will want to know. My comments here are not apt to be as useful as those from active laboratory directors, but this does seem both very difficult and yet essential to have in a useful database. I will say that some of the level of detail implied by the mock-up (down to the level of reference sequences and which variants) seems impractical. In thinking of CF or BRCA testing, for example, there would be thousands of variants listed and it seems

unreasonable to expect that list to be maintained and up to date in a central database unless the database maps directly to one that is operational at the testing service, and automatically updated as test methods change. For sequence-based tests, the “all variants” item would work, but for multi-allele methods, there are many tests now that have dozens or even hundreds of variants. Is GTR the right place to try to keep track of this? The answer may be yes, but it may also be no. One solution might be to require a link to a page that would describe the test method that would be under control of the laboratory doing the testing, with specifications of the level of detail that those offering tests are expected to provide, but not trying to keep all this information in the central database.

The information about how VUS and other categories of interpretation would be most welcome to know, but seems more likely to arise more from other databases like the variome database, Mutadatabase, and human gene mutation database than from GTR. The part that would be essential to capture is how the lab bases its interpretation, and how to find the data and algorithms on which the interpretation is based. If there is an interpretive algorithm, then link to where that can be found. The questions about whether additional family members are invited for analysis (although right now, the only option is “without charge”) seems excellent, as well as information about recontact if interpretation changes. These answers of course have legal ramifications, but this seems like a reason to include, rather than exclude them.

There will surely be a debate, however, about whether GTR should be the place where such information is archived and documented. These are generally not laboratory-specific features, but about the nature of the test in general, and of course answers to such questions entail liability and spill over to regulatory compliance (under FDA, CLIA, New York State, etc.). The information about performance characteristics and clinical validity and utility are welcome, in part for these very reasons. Asking each laboratory to state utility and validity and cite the basis for it would go a long way towards accountability. These items would also mean the federal government would be able to readily note the conditions under which tests are being offered, including medical claims.

Missing elements about patents and licensing

Huys, et al., in their analysis of genetic testing for 22 commonly tested conditions, found at least one blocking claim in patents associated with genes for 16 of the conditions (*Nature Biotechnology* 29: 903-909, October 2009). Only a small fraction of claims were blocking, and most that were hard to work around were method claims, many of which may be invalid under shifting jurisprudence in the United States. But nonetheless, one fair interpretation of their findings is that patenting and licensing could affect availability of 73 percent of Mendelian conditions commonly tested.

Cho, et al., surveyed laboratories offering genetic tests a decade ago, and found that 65 percent had been contacted about patent enforcement (*J Molec Diagnostics* 5: 3-8, February 2003). Indeed, their sampling strategy started from genetests.org, indicating that GTR is the logical locus for identifying when intellectual property considerations might be relevant. In eight case studies of genetic testing for ten clinical conditions prepared for the Secretary’s Advisory Committee on Genetics, Health and Society, the evidence about effects of patenting and licensing on clinical access to tests was complex and often equivocal; but the evidence that patenting and licensing matter to which laboratories offer which tests was overwhelming and unequivocal. This work was summarized (*Nature* 458: 405-406, 26 March 2009; and *Nature Biotechnology* 28: 784-791, August 2010) and the case studies published (*Genetics in Medicine* 12 (Suppl): S1-S211, April 2010).

It is thus quite clear that one reason a test may or may not be offered is patent rights. Moreover the locus of responsibility for managing it will be at the level of laboratories. Just as other items on the list seem intended to assist in establishing accountability in genetic testing, it seems odd to leave licensing status entirely off the list of GTR data items.

The GTR is not the logical place to gather the detail information about patent status of relevant genes, or terms of licensing. It does seem appropriate to have an acknowledgement of and link to further information (where relevant) and patents and licensing. A simple check-box about whether patent rights are licensed, with a link to a laboratory-maintained page that lists patenting and licensing status when the box is checked (e.g., the list of patents, or public statement about licensing status) would both be simple to submit, would require only disclosure of information that a service offering a test should know about without undue research, and would greatly increase transparency and inconsistency in reporting that directly affects which tests are available from whom.

Since the function of intellectual property, like property, depends on defining metes and bounds, it seems remiss to leave out any mention of patents and licensing rights in a database of genetic tests given the evidence that such rights directly affect which tests are available from which laboratories. Indeed leaving such information out seems to signal acquiescence to patent-holders not disclosing their patents and laboratories continuing to indulge in wink-and-nod avoidance of intellectual property conditions for some genetic tests. At the least, if the decision is not to include such a check-box and link to further information, then an explicit reason for not doing so seems warranted, and this letter is an invitation to provide that justification.

This has obvious implications for infringement liability, but many other items being included in the database also have liability implications. The patenting and licensing situation for some tests can be murky, but this is in no small part because of failure in transparency for which GTR could be a partial remedy. To the degree that intellectual property considerations operate in the shadows, it breeds uncertainty and inefficiency. Patenting and licensing are at least as relevant to genetic testing as many other items on the list, and demonstrably relevant to whether genetic tests are available from a given laboratory. Moreover, if the legal regime under which genetic testing is to operate is to be both transparent and also respect intellectual property rights where they exist, the logical place to effect the transparency is where the test is publicly offered, i.e., the GTR. If a decision is made not to include this information, the reasons for the decision should be explicit and public.

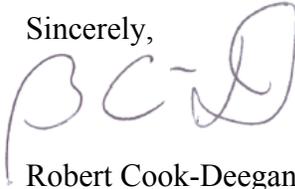
Coordination with other federal (and state) agencies that require data submission

CLIA certification seems essential. But presumably such CLIA certification comes with certain information submitted to CMS; will GTR be linked to such data, reducing the need to submit redundant information and keep it updated in two places? Regarding state licensing, it is not clear whether the information requested is for the lab or the lab director or both. And of course, the special requirements of New York State introduce yet another potential data redundancy. GTR could become the repository of relevant information for the federal government, serving this function for CMS as well as NIH, but it could also simply link to a separate CMS database (or the laboratories' own records of CLIA certification), but it would be good to avoid outright duplication.

The information about FDA status also seems essential, analogous to CLIA certification. The same issues of coordination arise. Asking if the test is FDA-approved as a kit, an IVDMA, or (in the future) LDT or is under investigational use or is research use only is a core element, and should be required. For tests that a laboratory administers but was not responsible for FDA review, however, there needs to be an option (e.g., if they offer a kit test manufactured elsewhere).

Again, thank you for the opportunity to comment. I can be reached at gelp@duke.edu; 919 668-0790 if I have been unclear or if you have questions or need more information.

Sincerely,

A handwritten signature in blue ink, appearing to read 'BC-D', with a stylized flourish at the end.

Robert Cook-Deegan, MD
Director, Center for Genome Ethics, Law & Policy,
Institute of Genome Sciences & Policy
Research Professor of Public Policy Studies and of Biology
Research Professor of Medicine
Duke University