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Stuart Graham, Ph.D.
Chief Economist
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Dear Dr. Graham,

In order to contribute to the USPTO's upcoming report on genetic verification testing under Sec. 27 of the America Invents Act, we collected information from individuals who could not attend the hearings, wished to remain anonymous, or preferred to contribute through an alternative channel. In this, we targeted a medically oriented subset of actors in order to get facts about and perspectives on the four points that are the subject of your study (we directly quoted the Federal Register notice with the statutory language from Section 27. Our respondents were all health professionals (physicians, laboratory directors, or genetic counselors) or patients.

Our methods for collection were as follows: We posted a form letter (available at: http://www.genome.duke.edu/centers/cpg/sec-27-study/) and also distributed it to a variety of groups: molecular pathologists, genetic counselors, clinical laboratory directors, and disease-oriented patient groups. These groups were free to circulate it within their networks. Respondents were then free to relay any information back to us via email, phone, or an alternative anonymous email pathway.

The attached document contains the material submitted to our center in response to our letter of solicitation for comments on genetic verification testing. Given our center's protection under a Certificate of Confidentiality, respondents submitted materials with the assurance that their identity and personal health information would be kept confidential. We hope that this material helps to inform your forthcoming report, and please feel free to follow up with us if any questions about the study, or the information that it generated, arise.

Sincerely,

Robert Cook-Deegan, M.D.
Principal Investigator, Center for Public Genomics (NIH grant P50 HG 003391)
Research Professor, Institute for Genome Sciences & Policy
Sanford School of Public Policy
Duke University

Lane Baldwin, B.A.
Center for Public Genomics

Attachment: Submissions to Duke Center for Public Genomics, responding to Section 27 of the America Invents Act

Materials submitted to the Center for Public Genomics

Responding to "open for comments" announcement pursuant to Section 27 of the America Invents Act, January-March 2012.

Oculomotor Ataxia, Athena Diagnostics

Genetic Counselor

I have a case that I think illustrates the issues of exclusive patents quite well. I will briefly outline the details below, but I can provide a much more comprehensive summary if this is the type of case you are looking for:

We have two adult siblings with childhood onset ataxia. They had the Athena "Complete ataxia profile" in 2005. The testing identified a single "variant of uncertain significance" in the *APTX* gene for autosomal recessive ataxia with oculomotor apraxia type 2 (AOA2). A second mutation was not identified.

These two siblings had classic findings of AOA1 (Ataxia-Oculomotor Apraxia, Type 1) and we strongly suspected that they had a second, undetected mutation. Copy number variation (i.e. exon deletions) had been reported in patients with AOA1, but Athena did not offer this testing. Because Athena held the patent, we were essentially not able to do this testing in the United States.

In 2008, I had the opportunity to meet a researcher from France who expressed interest in analyzing this family for copy number variation by MLPA (multiplex ligation-dependent probe analysis—essentially a way of doing many PCR-like amplifications at once, in this case used on a research basis). We submitted samples to his laboratory, and to our surprise, the researcher identified 2 point mutations. Both mutations were in areas of the gene that were covered by Athena Diagnostic's assay.

We informed Athena Diagnostics of this finding and re-submitted the samples from these siblings for re-analysis. The re-analysis came back with essentially the same results as our first test. This was problematic from two standpoints:

1. The repeat analysis failed to detect the second point mutation.
2. They still reported the one variant that they could detect as a "variant of uncertain significance" despite a body of published work about the specific mutation that was available in Pubmed clearly showing that it is a pathogenic mutation.

Because no other labs in the United States did this testing, we could not obtain a CLIA report with the two mutations. We decided to seek a second opinion using a "customized" mutation analysis at another lab. This lab verified the presence of the two point mutations and we had to go back to Athena and say that we now had two labs that had independently identified two mutations. The patient/insurance had to pay for this testing.

Athena re-analyzed the sample again and realized that their primers sat on top of a polymorphism, which led to "allele dropout." They subsequently re-designed their primers and finally on October 19, 2010 were able to issue us a CLIA report with the two mutations. This was 5 years after the initial analysis of the samples. This final report still listed the initial variant as "uncertain significance" despite my pointing out published evidence indicating otherwise.

BRCA testing, Myriad Genetics/Myriad Diagnostics

Genetic Counselor

I did have a patient that was very surprised by her positive results. She was Jewish on both sides and had breast cancer at 59, but had no family history of cancer in close relatives. She had a BRCA1 mutation (one of the Jewish founder mutations) and was very overwhelmed by the information. She requested a verification of this result because she didn't really believe it. Fortunately, because it was one of the Jewish founder mutations, other labs do offer testing for those 3 mutations and we were able to send it to Boston U for conformational testing (which also came back positive). She was very relieved to hear that it was confirmed and felt much more comfortable going forward with the prophylactic surgeries.

BRCA false positive, Myriad Diagnostics

Attorney on behalf of patient

I am an attorney in [state] who has been consulted by a [50+] year old woman who underwent BRCA testing in 2008 and was told that her BRCA mutation [specific mutation] was "deleterious." Based upon that interpretation, the woman was advised of an 87% chance of breast cancer and a 44% risk of ovarian cancer. Based upon those results she underwent bilateral mastectomies and a prophylactic oophorectomy.

About 6 months following the second of the prophylactic surgeries, the woman was contacted by Myriad, through her doctors, and was advised that the mutation was being reclassified from "deleterious" to "of uncertain significance."

My questions are is there some way, other than through Myriad, to confirm whether she is in fact BRCA1 positive? Secondly, we are trying to understand how this misclassification could have occurred. It obviously has had a profound impact on this woman.

BRCA Testing, Myriad Diagnostics

Patient

In a nutshell, about a year ago or so, my oncologist suggested that I consider receiving BRCA testing. He said that although everything pointed to my earlier chest

radiation as the cause of my breast cancer, the fact remains that I developed breast cancer at a young age and I'm of Ashkenazi Jewish heritage, 2 risk factors suggestive of a possible BRCA mutation. After thinking it over and doing some research, I decided to proceed, primarily for my family. My sister is almost 45 now, and ever since my BC diagnosis, her healthcare providers consider her at increased risk—meaning that she has to repeatedly point out that my cancer was secondary to radiation treatment and most likely not genetic. My hope was that my BRCA testing would be negative, giving my sister and my parents increased peace of mind that they were not at increased risk of cancer due to possible BRCA mutations.

So I met with my regional hospital's genetic counselor. Some of my first questions were about insurance and cost, and she assured me that the testing was covered by my insurance company. She then walked me through the possible pros and cons of the testing, considerations should the test be negative or positive, the fact that (as we know) negative BRCA testing does NOT rule out the possibility of non-BCRA genetic variations increasing the risk of cancer, and so on.

I decided to proceed, had a somewhat nerve-wracking month waiting for the results, and received the good news that my BRCA testing was negative. My entire family was thrilled with the news. About a month or so later, however, I received a letter from my insurance company. Based on what my genetic counselor had told me, I'd expected the letter to simply state that the testing had been approved and was covered. BUT that wasn't the case. My insurance company was claiming that the testing "was out of network" and therefore not covered—and I was responsible for the cost of the testing. My recollection was that the cost was about $2,000. Needless to say, I was very angry. How could my insurance company claim that my BRCA testing was "out of network" when Myriad Genetics performs ALL *BRCA1* and *BRCA2* testing in the United States? When I contacted my insurance company and explained this very obvious point, they responded by saying that I could contest it and go through the appeals process. This seemed absolutely ridiculous to me: why on earth should I be required to go through an appeal process when this had to be an error? Does my insurance company cover *BRCA* testing? Yes ... if it is "in network"? But this is not exactly a test where I can drive down to my local Quest or LabCorp and roll up my sleeve. I did go to my local hospital—which is very definitely "in network." The test was ordered by my oncologist, definitely in network. But if Myriad is the ONLY facility to perform the test—and as we know, has gone to great lengths to prevent any other facility in the country from doing so—how exactly can this be called "out of network"? (You can see that I'm still very annoyed by all this, more than a year later.)

So... after one phone call, another, and another, my insurance company finally conceded that this had indeed been an error, and they processed the claim. Thus, in my experience and that of my friends who have had or have considered *BRCA* testing, the concerns surrounding *BRCA* testing have not focused so much on the current lack of independent second opinion/confirmatory testing, but rather

regarding other areas that Congress has mandated the US Patient and Trade Office (USPTO) to report on this June, including:

- The role that cost and insurance coverage have on access to and provision of genetic diagnostic tests
- The impact that current exclusive licensing and patents on genetic testing activity has on the practice of medicine, including but not limited to: the interpretation of testing results and performance of testing procedures

In the *Federal Register*, the notice enumerated a series of questions to serve as a "preliminary guide to aid the USPTO in collecting relevant information." Again, in my and my friends' anecdotal experiences, our concerns have most focused on primary genetic diagnostic testing—i.e., access to *BRCA* testing in the first place, cost, insurance coverage, the privacy of results, assurance that genetic discrimination cannot result secondary to such testing, etc. The areas of access, cost, and insurance coverage are addressed with the following questions posed in the *Federal Register*:

- (1) "Currently, how widely available are primary genetic diagnostic tests? How often are such tests prescribed? What are the limitations, if any, on the availability of primary genetic diagnostic tests? If there are limitations on such availability, what are the consequences in terms of the quality of care, human health, and medical costs of such limitations? How has the practice of medicine, the quality of care that patients receive, and medical costs and insurance coverage been affected, if at all, by the availability of primary genetic diagnostic tests?"
- (2) "What is the amount and scope of patenting in the field of genetic diagnostic testing? What role, if any does patenting play in the availability of primary genetic testing?"
- (11) (a) "What effect does the cost of primary genetic testing have on the likelihood that patients will request such tests?" (b) "What effect does the cost of primary genetic diagnostic testing have on the likelihood that physicians will prescribe such tests?"
- (12) "How extensive is medical insurance for genetic diagnostic testing? What are the differences, if any, between the level of insurance coverage available for genetic diagnostic tests covered by patents and the level of insurance coverage of unpatented genetic diagnostic tests for the same diseases or disorders?"
- (13) "What effect does insurance coverage have on patient access to genetic diagnostic tests?" (a) "What effect does the insurance coverage of genetic diagnostic testing have on the likelihood that patients will request such tests?" (b) "What effect does the insurance coverage of genetic diagnostic testing have on the likelihood that physicians will prescribe such tests?"
- (14) "What effect do patents and exclusive licenses have on the availability of insurance coverage for genetic diagnostic tests?"

I sincerely hope that these crucial areas specific to primary genetic diagnostic testing are addressed in association with rational strategies to enable access to independent confirmatory genetic testing when needed, regardless of whether a diagnostic test is patented or exclusively licensed. For example, in researching these issues, I see that under the Bayh-Dole Act, the government can grant additional licenses to other applicants for a patented invention "if the patent holder or exclusive licensee fails to address the 'health and safety needs' of consumers."

Appendix

The 'open for comments' announcement pursuant to Section 27 of the America Invents Act, January-March 2012.

Verification Genetic Testing

We are seeking information about patient or provider experiences with verification of genetic tests

We are responding to the new patent law's request for information about what happens when patients or health professionals want a "second opinion," confirmation, or repetition of a genetic test result, but patent exclusivity limits the number of licensed providers of a genetic test.

"Verification testing" is genetic testing to confirm or repeat a genetic test result from a sole-source provider, such as Myriad Genetics (for BRCA1/2 testing), Athena Diagnostics (for neurological or endocrine conditions), or others offering genetic tests protected by exclusive patent rights.

On September 16, 2011, President Obama signed the America Invents Act (P.L. 112-29) into law. Section 27 of this law, a provision sponsored by Rep. Wasserman Schultz (D-FL), mandates a study by the US Patent and Trademark Office (USPTO) on patient access to verification testing.

Duke University's Center for Public Genomics (CpG) is gathering information about verification genetic testing to be relayed to Rep. Wasserman Schultz and the USPTO. This effort is intended to gather information from those who cannot attend upcoming USPTO-sponsored public hearings (additional information is provided below), those who wish to remain anonymous, or those who simply want to contribute data through this channel.

Individuals may wish to consider the following questions in order to decide whether they might have information relevant to this topic:

- Have you ever wanted to get (or order) a verification test? If so, have you encountered difficulties that may be attributable to patent exclusivity? Any details you can share?
- Do you offer verification testing under some circumstances? Do you worry about patent enforcement under those circumstances? Has it stopped you from offering a test?
- Have you ever received a notification letter, cease-and-desist letter, or other threat of patent enforcement about verification testing?
- If you order or perform verification testing, do you do it in a CLIA-certified laboratory?
- How did you find a laboratory willing to do verification testing? Was it made

easier or harder because of patent enforcement concerns?
- To your knowledge, have you benefited from patent incentives that have helped you develop a genetic test (as a provider) or get access to a genetic test (as a clinician or patient)?

There are several ways for you to contribute information pertinent to verification genetic testing:

1. Via the CpG Verification Genetic Testing website.
2. Contact Lane Baldwin at the Institute for Genome Sciences & Policy at Duke University (lane.baldwin@duke.edu, 704-641-8682).
3. To contribute information ***anonymously***, email gelp@duke.edu. Note that responding in this way does not allow us to contact you for clarification or follow-up. Our staff member will delete the header and "from" information from your email message, as well as any other identifying information, and then print out the message. Your original email message will then be deleted. We will make no effort to trace origins, and will cut the trail that would allow others to do so.
4. Use an anonymous email site or software (Anonymizer, Sendanonymousemail or other).

All data collected by these four response mechanisms will be reported in aggregate in a way that prevents identification of sources.

Duke's Center for Public Genomics (CpG) is funded by a P50 grant from the National Human Genome Research Institute and holds a Certificate of Confidentiality intended to protect the identity of those who submit information.[1]

USPTO will hold public hearings on the topic in Alexandria, Virginia on February 16, and in San Diego, California on March 9. Information on those hearings is available through the *Federal Register* (p. 3748, Vol. 77, No. 16, 25 January 2012).

The USPTO has been asked to report to Congress by June 2012, about the following:

1) The impact of current lack of independent second-opinion testing on providing the highest level of medical care to patients and recipients of genetic diagnostic testing, and on innovation related to existing testing and diagnoses
2) The effect of independent second-opinion genetic diagnostic testing on existing patent and exclusive license holders of a genetic test;
3) The impact of current exclusive licensing and patenting of genetic testing on the practice of medicine, including but not limited to interpretation of testing results and performance of testing procedures;
4) The role of cost and insurance coverage on access to and provision of genetic diagnostic tests.

[1] The Certificate of Confidentiality pertains to protocol 1277, approved by Duke's Institutional Review Board.