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Report to Congress
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Report on Confirmatory Genetic Diagnostic Test Activity

UNITED STATES
PATENT AND TRADEMARK OFFICE



REPORT ON CONFIRMATORY GENETIC DIAGNOSTIC TEST ACTIVITY

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EXECUTIVE SUMMARY

The USPTO respectfully submits to Congress this report on the availability to patients of confirmatory genetic diagnostic testing and on the respective impacts that the patent system and cost and insurance have upon that availability. Section 27 of the Leahy Smith America Invents Act directs the Director of the USPTO to study these issues and to provide Congress with recommendations on effective ways to provide confirmatory genetic diagnostic testing where patents and exclusive licenses exist that cover the genetic diagnostic tests. Through *Federal Register* notices and public hearings and roundtables, the USPTO received testimony and written comments from fifty organizations and individuals. Respondents included U.S. intellectual property organizations, federal agencies, academic institutions, companies and other organizations, patent practitioners, and members of the public. The USPTO also conducted a review of prior reports, studies, and scientific and medical opinion.

In all, the evidence is unsatisfactory in providing clear findings to Congress on the items enumerated in Section 27. The evidence associated with genetic diagnostic testing is sparse, and the evidence available on confirmatory genetic testing is even more so. Demand for confirmatory genetic testing is small, with only about 1–5% of patients who have undergone a primary genetic test needing a confirmatory test. Where verification is sought, it is often available from the primary testing provider itself if not from alternative providers. The effect of exclusivity on test quality is mixed. On one hand, aggregated data residing with a single provider offers the most reliable results whereas data fragmented and unshared among multiple providers is less reliable. However, data exclusivity also raises questions about a single provider's incentives to improve the quality of its testing, with no clear answers. Similarly unclear is the evidence on whether exclusive rights in genetic diagnostics may impede follow-on innovation, including university research that is academic in nature versus commercial.

Regardless of the degree to which patenting and licensing practices may impact the availability of confirmatory testing, creating a mechanism that would allow independent providers to perform confirmatory tests would likely have little negative effect on the exclusive providers of the initial test, with one potentially important exception. Providers authorized to provide only confirmatory tests may enter the market unlawfully to provide primary testing in order to recoup the investments necessary to enter the market at all. This risk could impose on primary testing providers the cost and burden of monitoring the confirmatory testing practices of others.

As to the broader question of what effect patents have on the practice of medicine itself, they incentivize innovation and require beneficial public disclosure of scientific and technological advances. It is also apparent that widespread infringement increases the motivation of patent holders to combat violations of their rights. Moreover, high demand, clinical acceptance, and available insurance coverage are correlated both with the value of the exclusive right and with the incidence of enforcement efforts. In this situation, availability of confirmatory testing may be severely limited or nonexistent. The little evidence presented to the USPTO indicated that doctors may order confirmatory genetic tests in only 1 to 5% of cases, presumably even when those tests are available from multiple providers. From this evidence, it is difficult to draw conclusions about the perceived medical need for confirmatory tests.

As for the role of cost and insurance, the limited evidence is unclear as to whether exclusivity drives the cost of a given test markedly higher than if the test were offered on a non-exclusive basis. The evidence does suggest that the availability of insurance plays an important role in the decision to have or not have a test done, especially when the cost of the test is substantial. Governmental and private coverage policies do not generally cover confirmatory

genetic testing. It is possible but unknown if individuals who may seek confirmation of a specific test result forgo it due to cost, even if it is available from multiple independent providers.

Although the evidence on each of these points was limited in its scope and mixed in its implications, recent Supreme Court decisions make it unlikely that exclusive provision of a diagnostic test, whether for an original diagnosis or to confirm the original result, will be possible based on patenting and licensing behavior. Patients seeking independent confirmation of diagnostic results will almost certainly be able to find it as long as the demand level for the test (or research interest in the particular gene or condition) supports a market for multiple test providers. For this reason, much of the USPTO's factual findings may now be superseded by intervening judicial decisions. In view of the altered legal landscape, the USPTO's recommendations to Congress are limited in scope.

The first recommendation is to proceed cautiously, monitoring changes in the actual availability of gene-based diagnostic tests from multiple providers. The second recommendation is to consider creating mechanisms to facilitate sharing data on diagnostic correlations in order to build robust databases of the relationships between genetic mutations and the presence, absence, or likelihood of acquiring the relevant medical condition. Data sharing of this kind would promote the most rapid advances in the diagnostic accuracy of individual tests. The third recommendation is to consider the role of cost and insurance. However, because the USPTO does not have the institutional expertise to make specific recommendations regarding insurance coverage for gene-related diagnostic tests, this report can only emphasize that insurance coverage does appear to play significant a role in access to testing and should be taken into consideration when issues of access are examined.

I. INTRODUCTION

Section 27 of the Leahy-Smith “America Invents Act” (AIA) directs the United States Patent and Trademark Office (“USPTO” or “Office”) to gather information and report on several questions related to the ability of patients to obtain independent, confirmatory gene-based diagnostic tests. Interest in these questions was spurred primarily (but not solely) by the perception that one company has used exclusively-licensed patents to prevent any other test provider from offering tests for deleterious mutations in the breast and ovarian cancer genes, BRCA1 and BRCA2. A patient with breast cancer who tests positive for one of these mutations has a very high risk of a recurring breast cancer or ovarian cancer, and the only remedy that has been shown to be effective is life-changing surgery. Because of that, many positive-testing patients have a strong desire to have the test result validated independently. The study ordered in Section 27 of the AIA is not limited to a consideration of BRCA1 and BRCA2, but the existence of gene-based tests such as BRCA1/BRCA2, that are offered only by a single entity and the use of patents on human genes to promote or enforce that exclusivity, created a high level of public interest and discussion and prompted the study. The ability of the company that holds the rights to the BRCA1 and BRCA2 gene patents to prevent others from offering the test also created the environment that led to those patents being challenged in the courts, resulting in decisions that have profoundly changed the landscape of gene-based diagnostics.

Based on data in the NIH Genetic Testing Registry¹, there are currently no fewer than 5,800 genetic diseases for which diagnostic tests have been developed, with hundreds of laboratories in the United States providing these tests. From these many sources, there are

¹ The NIH Genetic Testing Registry can be accessed at: <http://www.ncbi.nlm.nih.gov/gtr/>

different arrangements for providing both primary and confirmatory tests, many licensing and business models, and significant variation in the manner that testing results are ultimately made available to both patients and caregivers. This study is mainly focused on the situation where a test or the underlying information needed to perform the test is patented and licensed exclusively to a single provider.

There have been several important studies and reports covering issues related to genetic diagnostic testing in recent years. However, the items listed in Section 27 of the AIA, which relate to independent, confirmatory genetic diagnostic testing, have generally been given little attention or left unaddressed by policymakers. That is not to suggest that these items are unimportant. To the contrary, having adequate evidence to formulate responses to these items can meaningfully inform the current debate about how genetic diagnostic testing is made available to patients by physicians and insurers, and the role that patenting may play in the availability, affordability and reliability of these tests.

The AIA charged the Director of the USPTO with studying and providing Congress with recommendations on effective ways to provide confirmatory genetic diagnostic testing where patents and exclusive licenses that cover the genetic diagnostic tests exist.² Section 27 is primarily focused on “confirming genetic diagnostic test activity,” which is defined in the legislation as follows:

the performance of a genetic diagnostic test, by a genetic diagnostic test provider, on an individual solely for the purpose of providing the individual with an independent confirmation of results obtained from another test provider’s prior performance of the test on the individual.³

² Leahy-Smith America Invents Act, Pub. L. No. 112-29, § 27, 125 Stat 284, 338–39 (2011), *available at* <http://www.gpo.gov/fdsys/pkg/BILLS-112hr1249enr/pdf/BILLS-112hr1249enr.pdf>.

³ *Id.*

In this context, Congress directed the USPTO to examine the following:⁴

- (1) The impact that the current lack of independent second opinion testing has had on the ability to provide the highest level of medical care to patients and recipients of genetic diagnostic testing, and on inhibiting innovation to existing testing and diagnoses.
- (2) The effect that providing independent second opinion genetic diagnostic testing would have on the existing patent and license holders of an exclusive genetic test.
- (3) 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.
- (4) The role that cost and insurance coverage have on access to and provision of genetic diagnostic tests.

Confirmatory testing has been defined in multiple ways. These include *replication or retesting*, whereby the primary test is repeated on the same sample using the same methodology; *validation testing*, whereby selected positive test results (such as a single deleterious mutation) are confirmed by a second laboratory; and *independent confirmatory testing*, whereby an independent provider either re-administers the same test using the same methodology as the original test or uses a different methodology that is designed to detect the same genetic alteration if the alteration does, indeed, exist. This report is concerned mainly with independent confirmatory testing to include either (1) an independent provider's re-administration of the primary test using the same methods that were used for the primary testing or (2) an independent provider's administration of a different procedure designed to detect the same genetic alteration that was detected by the original test.

DNA-related patents that affect genetic diagnostic testing generally fall into two categories: (1) those that claim compositions of matter or manufactures in isolated nucleic acid

⁴ *Id.*

molecules; or (2) those that claim methods of analyzing or detecting DNA sequences or particular mutations.⁵

II. BACKGROUND

Recognizing the diversity and complexity of the public policy issues surrounding genetic diagnostic testing, the USPTO conducted a thorough review of the academic and scientific literature, took notice of several published reports, and actively sought diverse input from the public. The Office published a *Federal Register* notice seeking written comments and announcing two public hearings for this study.⁶ The Office also provided the public with a dedicated e-mail address and a contact person in the USPTO to receive comments and answer questions. As announced, the Office held two public hearings dedicated to taking public comment for this report. The first was held at the USPTO headquarters in Alexandria, Virginia, on Thursday, February 16, 2012, and the second was held at the University of San Diego School of Law in San Diego, California, on Friday, March 9, 2012. At both hearings, witnesses provided testimony, and a panel of USPTO representatives actively questioned witnesses. At each hearing, the USPTO panel also accepted unscheduled prepared testimony from those in attendance and allowed informal commenting and questioning from members of the public.

In the final days before the deadline for written comments, the Supreme Court issued two rulings with potential ramifications for the present study. The first was the decision in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012) and the second

⁵ For examples of each of these types of claims, see Secretary's Advisory Committee on Genetics, Health, and Society, *Gene Patents and Licensing Practices and Their Impact on Patent Access to Genetic Testing* at A-8 (Apr. 2010), available at http://oba.od.nih.gov/oba/sacghs/reports/SACGHS_patents_report_2010.pdf [hereinafter "SACGHS Report"] pages 12-13.

⁶ Request for Comments and Notice of Public Hearings on Genetic Diagnostic Testing, 77 Fed. Reg. 3748 (Jan. 25, 2012), available at http://www.uspto.gov/aia_implementation/2012-1481_genetic-testing-hearing-notice.pdf.

was an order in *Association for Molecular Pathology v. Myriad Genetics, Inc.*, 132 S.Ct. 1794 (2012) granting the petition for a writ of certiorari, vacating the decision of the Federal Circuit, and remanding the case to the Federal Circuit for reconsideration in light of the *Mayo* decision. Accordingly, the USPTO published a notice on its dedicated AIA implementation website seeking public input, within ten calendar days, regarding the Supreme Court's actions as they might affect confirmatory genetic diagnostic testing.⁷ Representatives from the USPTO also attended the annual meeting of the American College of Medical Genetics and Genomics in Charlotte, North Carolina, on March 21, 2012. In informal sessions during this meeting, the USPTO heard from approximately a dozen physicians, clinicians, and scientists working in the genetics and genomics field.⁸ The USPTO subsequently determined that the complexity and diversity of the collected opinions, comments and suggestions warranted further review, discussion, and analysis. Accordingly, the USPTO informed Congress of plans to hold an additional public roundtable, review the comments received, and then finalize its recommendation to Congress. The Office published a *Federal Register* notice announcing this roundtable,⁹ and the roundtable itself was held at the USPTO headquarters in Alexandria, Virginia, on Thursday, January 10, 2013. Participants at the roundtable also received the opportunity to expand on their remarks through written comments by February 9, 2013.

Through the *Federal Register* notices, hearings, and roundtable, the Office received testimony and written comments from fifty organizations and individuals.¹⁰ Respondents

⁷ USPTO, AIA Studies and Reports, available at http://www.uspto.gov/aia_implementation/aia_studies_reports.jsp.

⁸ The USPTO thanks the Center for Genome Ethics, Law & Policy at Duke University for facilitating these meetings.

⁹ Notice of Public Roundtable on Genetic Diagnostic Testing, 77 Fed. Reg. 71170 (Nov. 29, 2012), available at http://www.uspto.gov/aia_implementation/genetic-testing-federal-register-notice-roundtable_2012nov16.pdf.

¹⁰ See Public Comments and Notice of Public Hearings on Genetic Diagnostic Testing, available at http://www.uspto.gov/aia_implementation/genetic-testing-comments.jsp,

included six U.S. intellectual property organizations, two U.S. government agencies, two academic research institutions, twenty U.S. companies and organizations, eight U.S. patent practitioners, and twelve members of the public speaking as individuals.

Since the AIA was enacted, the law that governs the patent-eligibility of inventions related to genetic diagnostic testing has changed considerably due to two Supreme Court patent decisions, *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012), and *Association for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107 (2013). In *Myriad*, the Court held that isolated naturally-occurring DNA segments are not patent-eligible subject matter under 35 U.S.C. § 101. The Court's invalidation of patent claims to isolated genomic DNA in *Myriad* lifted a potential obstacle to confirmatory genetic diagnostic testing. This was a significant change notwithstanding that the Court also confirmed the patent-eligibility of cDNA, a laboratory-made complementary copy of the protein-encoding messenger RNA containing only the actual protein-coding sequence without non-coding internal sequence blocks found in almost all human genes.

The Court in *Myriad* emphasized that the relevant difference between genomic DNA and cDNA is that in cDNA, the non-coding regions of naturally-occurring genomic DNA have been removed. Strictly speaking, then, cDNA does not occur in nature and so does not fall into the “product of nature” exception to subject matter eligibility under § 101. By contrast, observed the Court, genomic DNA does occur in nature and so does fall into the “product of nature” exception. Relatedly in *Mayo*, the Court addressed the patent-eligibility of method claims reciting “natural phenomena” or “law of nature” and concluded that (1) a newly discovered law

Transcript of Public Hearing on Genetic Diagnostic Testing (Feb. 16, 2012) [hereinafter “Alexandria Hearing”], available at http://www.uspto.gov/aia_implementation/120216-genetic_transcript.pdf, and Transcript of Public Hearing on Genetic Diagnostic Testing (Mar. 9, 2012) [hereinafter “San Diego Hearing”], available at http://www.uspto.gov/aia_implementation/120309-genetic_transcript.pdf.

of nature is itself unpatentable and (2) the application of that newly discovered law is also normally unpatentable if the application merely relies upon elements already well understood, routine, and conventional in the art. The Court explained that to transform an unpatentable law of nature into a patent-eligible application of the law, it must contain other elements or a combination of elements—an “inventive concept”—sufficient to ensure that the claim amounts to significantly more than the natural law itself, i.e., it must limit its reach to a particular inventive application of the law.

More recently, several decisions have issued in the federal district courts and the United States Court of Appeals for the Federal Circuit demonstrating the extent to which patent-eligible subject matter has been limited in this area. In *PerkinElmer, Inc. v. Intema Ltd.*, 496 Fed. Appx. 65 (Fed. Cir. 2012), a non-precedential decision, the Federal Circuit found that claims directed to a non-invasive prenatal test for Down’s Syndrome that involves measuring levels of specific screening markers were ineligible for patent protection because the methods did not constitute an “inventive concept” as defined in *Mayo*. The United States District Court for the Northern District of California found in *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 19 F. Supp. 3d 938 (N.D. Cal. 2013), that claims directed to a non-invasive prenatal test for identifying and characterizing paternal fetal DNA in blood from a pregnant woman were ineligible because they contained only conventional and existing detection steps and, thus, lacked the “inventive concept” required by *Mayo*. This decision was upheld on appeal by the Federal Circuit in *Ariosa Diagnostics, Inc. v. Sequenom, Inc.* (Fed Cir, 2014-1139, 2014-1144, 6/12/2015). The District Court of Delaware, in *Genetic Technologies Ltd. v. Laboratory Corp. of America Holdings*, 2014 WL 4379587 (D. Del. Sept. 3, 2014), evaluated claims directed to a method of predicting athletic performance based on the presence in an individual of particular alleles of the α -actinin-3 gene.

The court determined, again based on *Mayo*, that the claimed steps of analyzing, detecting, and predicting did not constitute a patent-eligible application of the natural correlation. Finally, the Federal Circuit in *University of Utah Research Foundation v. Ambry Genetics Corp.*, 774 F.3d 755 (Fed. Cir. 2014), invalidated a number of composition-of-matter and diagnostic-method claims that were not addressed by the Supreme Court in *Myriad* and that were then asserted by Myriad Genetics against Ambry Genetics in an effort to prevent Ambry from offering BRCA testing. The court held that the claims at issue were directed to products of nature or applications of laws of nature with insufficient inventive concept to be patent-eligible.

Taken together, these cases dramatically affect the landscape of diagnostic testing, whether gene-based or not. To be sure, patents may continue to be obtained on non-naturally occurring or significantly modified natural substances such as cDNA, on compositions or products containing such modified substances, and on diagnostic test methods which are limited to a particular inventive application of a law of nature that incorporates an inventive concept. However, especially with respect to most gene-based diagnostics that rely on a correlation between the presence or absence of a particular genetic marker or mutation, almost always there are numerous well-known and effective ways to detect the marker which could not be encompassed by a patent claim. Once the key correlation is published, a third party could exploit any of the well-known methods to use the correlation in a diagnostic test in competition with the patent holder. Unless and until the legal environment shifts again, it is difficult to conceive of a gene-based diagnostic correlation that could be exclusively protected by a patented means of determining the correlation owned by single provider.

III. DISCUSSION

While genetic testing has been extensively studied and reported upon, prior fact-gathering on confirmatory genetic diagnostic testing has been much more limited. That should not suggest

that confirmatory genetic tests are unimportant to those who desire them. To the contrary, although USPTO is not the clinical expert in this area, the USPTO's research suggests that such confirmatory tests can be important for Americans suffering from disorders for which genetic diagnostics are playing an important preventative and screening role. Patients and physicians have expressed concerns about how widely available genetic diagnostic testing is, how the private and public sectors deliver genetic diagnostic testing when available, and how the complex medical innovation system in the United States delivers these new testing methods to consumers. So far, these concerns have focused on primary testing.

It is in this context that the Supreme Court's decisions in *Mayo* and *Myriad* and later federal cases interpreting those two decisions must be understood. The legal landscape has changed to the extent that it is now very unlikely that patents can impose significant barriers to the availability from multiple independent testing entities of alternative gene-based diagnostic tests that detect the same condition. The USPTO presents the following findings, conclusions, and recommendations with the understanding that they may remain generally applicable to the issue of access to gene-based diagnostic tests. The USPTO also cautions, however, that factors not related to patents and exclusive licensing, such as geographic availability, market demand and cost, may also affect the extent of availability and the quality of diagnostic tests.

A. Prior Literature and Evidence Relating to the Items Presented

To guide the USPTO's findings of fact, Congress directed the USPTO specifically to study four issues:

- (1) The impact that the current lack of independent second opinion testing has had on the ability to provide the highest level of medical care to patients and recipients of genetic diagnostic testing, and on inhibiting innovation to existing testing and diagnoses.
- (2) The effect that providing independent second opinion genetic diagnostic testing would have on the existing patent and license holders of an exclusive genetic test.

- (3) 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.
- (4) The role that cost and insurance coverage have on access to and provision of genetic diagnostic tests.

In order to understand the issues surrounding confirmatory genetic diagnostic testing activity, and to collect evidence, the Office conducted a review of prior reports, studies, and scientific and medical opinion. In general, the results of this review were unsatisfactory in terms of discovering clear responses to these items. While the evidentiary record associated with genetic diagnostic testing tends to be light, the record available on confirmatory genetic testing is even more so. We review here by issue the relevant existing evidence.

1. Relating to the impact that the current lack of independent second opinion testing has had on the ability to provide the highest level of medical care to patients and recipients of genetic diagnostic testing, and on inhibiting innovation to existing testing and diagnoses.

The first item posed by Section 27 concerns “the impact that the current lack of independent second opinion testing has had on the ability to provide the highest level of medical care to patients and recipients of genetic diagnostic testing, and on inhibiting innovation to existing testing and diagnoses.”¹¹ The core of this item concerns whether doctors were unable to gain access to meaningful confirmatory genetic testing when they believed such testing was needed or otherwise in the interest of their patients. The evidence offered on this issue was sparse. Where evidence was available, it was often not of the magnitude, quality, or rigor that scientists generally consider reliable in drawing conclusions. Much of the evidence was anecdotal and, what is worse, often contradictory. For confirmatory diagnostic genetic tests, there was insufficient evidence of clinical utility (the impact of testing on medical management

¹¹ AIA § 27(b)(1).

and patient outcomes), and medical or scientific consensus on the value of confirmatory testing is unsettled.

A prime example of this evidence is the 2010 report of the Secretary's Advisory Committee on Genetics, Health and Society (SACGHS).¹² According to several researchers active in studying public policy issues relating to the patenting of genetic materials and techniques:

[SACGHS], after careful study of current knowledge on the effects of patenting genes on research and accessibility to genetic tests, found that there is no convincing evidence that patents either facilitate or accelerate the development and accessibility of such tests. On the other hand, the Committee found that there was some, albeit limited, evidence that patents had a negative effect on clinical research and on the accessibility of genetic tests by patients.¹³

It is notable that the limited evidence uncovered in the extensive fact gathering performed by the SACGHS included case studies and not primarily studies of large, randomly-drawn samples. Some of the difficulty of evidence-gathering on this issue relates to the understandable reluctance of doctors and patients to discuss health issues, and to legal impediments against reporting private health information.

An important threshold issue to consider is the extent of a market for confirmatory genetic diagnostic testing at all. Some evidence from clinicians who are experienced in prescribing genetic diagnostic tests suggested that demand for confirmatory genetic testing may be small, with only about 1–5% of patients who have undergone a primary genetic test needing a secondary, confirmatory genetic test. For some tests, this need could be easily met because the tests are available from several sources. Other tests could not be independently verified because

¹² Secretary's Advisory Committee on Genetics, Health, and Society, *Gene Patents and Licensing Practices and Their Impact on Patent Access to Genetic Testing* at A-8 (Apr. 2010), available at http://oba.od.nih.gov/oba/sacghs/reports/SACGHS_patents_report_2010.pdf.

¹³ Julia Carbone et al, *DNA Patents and Diagnostics: Not a Pretty Picture*, 28 NATURE BIOTECH. 784 (2010), available at <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3026778/pdf/nihms-218168.pdf>.

they may have been available only from a single provider. Confirmatory genetic testing from the primary provider, although not independent, could still serve to confirm or refute the initial findings. Furthermore, it was not clear that licensing of these techniques was generally unavailable. For instance, Myriad Genetics testified that it had licensed one of its BRCA tests to at least three university laboratories.¹⁴ Myriad also licensed Labcorp to perform the “Ashkenazi panel” test, which detects the three deleterious BRCA mutations that are most common to Ashkenazi Jews. It was also unclear from the evidence whether the availability of these alternative services was widely known to the physicians and patients who would wish to access independent confirmatory genetic tests.¹⁵

Also important is the effect of competition on test quality. There was mixed evidence about the effect that being an exclusive provider has on the quality and accuracy of diagnostic tests.¹⁶ An exclusive provider, by being the sole recipient of patient data, can amass a more extensive dataset of test-to-patient outcomes, and this more comprehensive data coverage will tend to produce more accurate diagnostic results.¹⁷ If two or more entities provide the same test, however, the data will be fragmented among them—absent some mechanism and incentive for sharing—reducing the ability of each to make accurate correlations between mutations and outcomes. Because data that correlate test results to patient outcomes are crucial to improving the interpretation of results, an effective mechanism to facilitate sharing data across providers would be useful to ensure quality testing and analytics. Otherwise, each competitor would have

¹⁴ San Diego Hearing at 52 (testimony of Richard Marsh, General Counsel, Myriad Genetics).

¹⁵ San Diego Hearing at 85 and 89 (Myriad Genetics General Counsel Richard Marsh responding to then USPTO Deputy Director Teresa Rea).

¹⁶ Some respondents have claimed that high error rates result from patent exclusivity. *See, e.g.*, Comments of Knowledge Ecology International at 3–4. Other respondents, even those who otherwise oppose exclusivity in genetic diagnostic testing, have described error rates as low: “The commonly quoted error rate for most clinical labs is 1 percent, but in practice, it is likely much lower.” *See, e.g.*, Comments of National Society of Genetic Counselors at 3–4.

¹⁷ Comments of Myriad Genetics at 20–21.

fewer data points on which to evaluate its testing procedure. Some commenters also suggested that, absent competition, exclusive providers may not have the proper incentives to report and decrease error rates, although others noted that exclusive providers tend to decrease error rates over time in response to monitoring in the research environment and marketplace.¹⁸ However, this monitoring is also difficult when data access is fragmented.

The effect on test quality of being available only from a single provider is ambiguous. A survey performed over a decade ago at clinical laboratories reported that the quality of testing, as perceived by laboratory personnel, was only modestly affected by the presence of gene patents in the space.¹⁹ In another study, several researchers used methodology different from that used by an exclusive provider to analyze the BRCA1 and BRCA2 genes that acts as a marker for breast cancer risk. The researchers reported several large genetic rearrangements in BRCA1 and BRCA2 genes that were not detected by the exclusive provider's test method. The study estimated as many as 12% of women with breast cancer or with a severe family history of cancer and who had tested negative for BRCA1 and BRCA2 mutations could be expected to carry one of the genomic rearrangements.²⁰ The exclusive provider countered that changes in its testing in 2002 would have picked up one third of the failures reported in the first study, and that it has subsequently introduced newer testing to identify more deletions. These findings may suggest that more competition would allow for higher-quality products, but they could also suggest that market and research activity is appropriately monitoring exclusive providers and creating opportunities for test improvement. In all, it is unclear that competition in this space

¹⁸ Comments of Wendy Chung at 1–2.

¹⁹ Mildred K. Cho et. al., *Effect of Patents and Licenses on the Provision of Clinical Genetic Testing Services*, 5 J. MOLECULAR DIAGNOSTICS 3 (2003), available at <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1907368/>.

²⁰ Tom Walsh et. al., *Spectrum of Mutations in BRCA1, BRCA2, CHEK2, and TP53 in Families at High Risk of Breast Cancer*, 295 J. AM. MED. ASS'N 1379 (2006), available at <http://jama.jamanetwork.com/article.aspx?articleid=202583>.

would necessarily induce higher quality. For example, competitive pressure could lead to introduction of a test before it is fully developed and validated, or it could lead to cost-cutting that would affect the quality of the test.

Beyond the static effects of exclusivity upon the provision of existing tests, it is also important to consider dynamic effects that exclusivity may have on follow-on innovation. Some surveys of those involved in the field carried out 10 to 15 years ago, suggest that exclusivity may reduce follow-on innovation in diagnostic tests for genetic diseases. In one study, authors reported that 53% of laboratory directors said they had decided not to develop or perform a test because of a patent, and 67% stated that patents have decreased their ability to do research.²¹ According to the results of a survey of members of the American Society of Human Genetics, 49% of respondents indicated that the existence of patents have at some time delayed or limited their research, while 46% indicated that such patents have never delayed or limited their research.²² Yet another study found that biomedical research in general was not significantly impeded by gene patents (with only 1% reporting having to delay a project, and none abandoning projects due to patents).²³ However, where gene patents cover a diagnostic test, researchers have reported more instances of patent owners asserting exclusive rights or asking for what they believed to be unreasonable licensing conditions. Thirty percent of clinical laboratories reported not developing or abandoning a test for hereditary hemochromatosis, for example, because of

²¹ Mildred K. Cho et al, *supra* note 19.

²² Isaac Rabino, *How Human Geneticists in US View Commercialization of the Human Genome Project*, 29 NATURE GENETICS 15 (2002), available at <http://www.nature.com/ng/journal/v29/n1/pdf/ng0901-15.pdf>.

²³ Timothy Caulfield et al, *Evidence and Anecdotes: An Analysis of Human Gene Patenting Controversies*, 24 NATURE BIOTECHNOLOGY 1091 (2006), available at <http://www.nature.com/nbt/journal/v24/n9/pdf/nbt0906-1091.pdf>; Jon F. Merz et al, *Diagnostic Testing Fails the Test: The Pitfalls of Patents Are Illustrated by the Case of Hemochromatosis*, 415 NATURE 577 (2002), available at http://repository.upenn.edu/cgi/viewcontent.cgi?article=1047&context=bioethics_papers.

patents held by others.²⁴ Not surprisingly, while evidence suggesting that patents impede biomedical research generally is sparse,²⁵ some evidence does suggest that patents have inhibited research laboratories that are engaged in commercial activity.²⁶

In 2006, the National Research Council of the National Academies surveyed university researchers and found that gene patents are unlikely to cause scientists to either abandon projects or fail to undertake them. The study committee did observe a significant barrier to research due to a prevalent and likely increasing reluctance among research labs to exchange proprietary research materials, whether patented or not.²⁷ The study concluded that the apparent lack of research inhibition by patents stems from a combination of researchers' lack of awareness of IP rights and patent holders refraining from pursuing infringement litigation against universities—either of which, the study indicated, could change with time.

When assessing the effect of the patenting of genetic diagnostic testing materials and methods upon confirmatory genetic testing, it was relevant to determine whether, and to what extent, patents have been enforced against the unauthorized practice of confirmatory genetic tests. While there have not been studies on confirmatory genetic testing per se, one researcher studied the incidence of human gene patents being asserted in court cases and, as of April 2007, found 31 cases in which the infringement of a human gene patent was asserted.²⁸ Among these

²⁴ Timothy Caulfield et al, *Evidence and Anecdotes: An Analysis of Human Gene Patenting Controversies*, 24 NATURE BIOTECHNOLOGY 1091 (2006), available at <http://www.nature.com/nbt/journal/v24/n9/pdf/nbt0906-1091.pdf>; Jon F. Merz et al, *Diagnostic Testing Fails the Test: The Pitfalls of Patents Are Illustrated by the Case of Hemochromatosis*, 415 NATURE 577 (2002), available at http://repository.upenn.edu/cgi/viewcontent.cgi?article=1047&context=bioethics_papers.

²⁵ John P. Walsh et al, *View from the Bench: Patents and Material Transfers*, 309 SCIENCE 2002 (2005), available at <http://www.sciencemag.org/content/309/5743/2002.full.pdf>.

²⁶ Mildred K. Cho et al, *supra* note 20; J.F. Merz et al, *supra* note 24.

²⁷ Nat'l Res. Council, REAPING THE BENEFITS OF GENOMIC AND PROTEOMIC RESEARCH: INTELLECTUAL PROPERTY RIGHTS, INNOVATION, AND PUBLIC HEALTH (2006), available at http://www.nap.edu/catalog.php?record_id=11487.

²⁸ Christopher M. Holman, *The Impact of Human Gene Patents on Innovation and Access: A Survey of Human Gene Patent Litigation*, 76 UMKC L. REV. 295 (2007), available at http://heinonline.org/HOL/Page?handle=hein.journals/umkc76&div=17&g_sent=1&collection=journals.

cases, only five concerned diagnostic testing for genetic conditions. The author concluded that gene patents have a relatively small impact because they are so rarely litigated. Overall, he estimated that only 0.4% of human gene patents are litigated as compared to 1–2% of all patents, and upwards of 4% of pharmaceutical patents generally. According to one study, “no exclusive license in this field has been deemed to be of such importance for anyone to take to court.”²⁹ Indeed, the Myriad patents appear to be the first challenged in court.³⁰

Notwithstanding actual litigation, a substantial amount of enforcement activity can take place in the shadow of a litigation threat but without actually initiating litigation. For instance, one study identified nine instances in which the exclusive licensee of the BRCA1 and BRCA2 breast cancer patents enforced its rights against presumed infringing activities.³¹ It is also likely that once the threat of enforcement against some entities becomes known, others who might have become providers would decide not to offer the test to avoid the risk of litigation. The impact of an exclusively-licensed patent cannot be determined only on litigation statistics, and as with other issues examined in the USPTO’s fact-finding, evidence on these impacts is limited and mixed.

2. Relating to the effect that providing independent second opinion genetic diagnostic testing would have on the existing patent and license holders of an exclusive genetic test.

The second item posed by Section 27 concerns “the effect that providing independent confirmatory genetic diagnostic testing would have on the existing patent and license holders of an exclusive genetic test.”³² This question relates to whether the availability of independent confirmatory genetic tests would negatively affect the profits, or competitive position, of

²⁹ Julia Carbone et. al., *supra* note 13.

³⁰ *Id.*

³¹ Mildred K. Cho et al, *supra* note 20.

³² AIA § 27(b)(2).

authorized diagnostics companies that would otherwise be the sole test provider. There was little data on this issue, though it is unlikely that confirmatory testing by a second entity would have a significant negative impact on exclusive licensees. One reason is that only a subset of those who are tested would need or request confirmatory testing, and that subset is likely to be limited. The subset may include not only those who test positive but also those who test negative but are members of a high-risk group. Because demand for confirmatory testing is likely to be small relative to the demand for initial testing, the lost profits associated with confirmatory genetic testing conducted by other laboratories would appear not to be a major inconvenience for commercial entities that provide primary testing. Another reason is that where an exclusive licensee had the right to exclude others from doing the first test, there would be little or no economic harm done by an independent entity doing a second, confirmatory genetic test. Indeed, one major provider of primary genetic diagnostic testing testified that, in theory, “second opinion confirmatory genetic testing should have no appreciable impact on existing patent and license holders of an exclusive license”³³—with one caveat.

The caveat is that providers may unlawfully enter the market for primary testing under the guise of providing confirmatory testing, creating significant concerns for current primary testing providers. Once a competitor has made the investments in personnel, physical plant, and equipment that are necessary to conduct confirmatory genetic tests, economic pressure to recoup those investments and only a relatively small demand for confirmatory tests may drive the competitor to offer primary tests unlawfully.³⁴ The very possibility of this situation would

³³ San Diego Hearing at 57–58 (testimony of Richard Marsh) (discussing the impact upon rights holder of allowing confirmatory genetic diagnostic testing).

³⁴ See Second Written Statement of Robert Cook-Deegan at 9; San Diego Hearing at 144 (testimony of Bernard Greenspan) (discussing reasons against deliberately segmenting genetic diagnostic testing into primary and secondary markets, including concerns of cost recovery for a laboratory providing only secondary testing).

impose a burden upon the licensed primary provider to monitor not only whether others are performing the test, but also in what sequence— primary and secondary—those others are performing the test. Similarly, a supposedly limited transfer of the technology could introduce uncertainty over the future income stream of the primary testing company, thus making it more difficult to adequately raise investment capital for further growth.³⁵ While evidence on this point is sparse, it suggests that the existence of a market for independent confirmatory genetic testing generally may not substantially harm patent owners or exclusive licensees who provide initial testing so long as the market for confirmatory testing is properly regulated and monitored.

3. Relating to 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.

The third item posed by Section 27 concerns “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.”³⁶ There was little evidence that the interpretation of reliable test results is affected by patents and exclusive licensing practice. One commenter during the comment period suggested that interpretation was unimpeded,³⁷ and that confirmatory genetic tests were a relatively simple matter,³⁸ and another affirmed this point with regard to multiple mutations.³⁹ Another commenter suggested that, from a patient health standpoint, the most important element of interpretation that may lead to a need for confirmatory genetic testing is when a negative test result is obtained and the doctor has

³⁵ *See id.*

³⁶ AIA § 27(b)(3).

³⁷ *See* Comments of Roche Molecular Systems and Abbott Laboratories, Inc. at 2–3 (noting that patents pose no barrier at all to the review and interpretation of test results).

³⁸ *See* Comments of Roche Molecular Systems and Abbott Laboratories, Inc. at 2 (comparing the greater value of follow-on innovation through the proliferation of competing tests to “the simple repetition of an existing test”).

³⁹ *See* Comments of Prometheus Laboratories at 2 (citing Brenda Richards et al, Multiplex PCR Amplification from the CFTR Gene Using DNA Prepared from Buccal Brushes/Swabs, 2 HUMAN MOLECULAR GENETICS 159 (1993)).

reason to believe that the primary test results showing no anomalies may be in error due to other patient characteristics, including other genetic factors that may be available from more comprehensive, independent tests.⁴⁰

Regarding the performance of testing, the question is whether exclusive licensing of patents limits the ability of diagnostic testing centers to provide confirmatory results. On this point, one survey reported that 65% of responding diagnostic testing center directors had been contacted by a patent or license holder about potential infringement, and that 25% of the directors avoided providing a genetic testing service as a result.⁴¹ This report also found that, of the 461 tests potentially available at the time, twelve had been the subject of patent enforcement activity. Interestingly, all twelve tests were offered by eleven or more laboratories (the category of most widely available service point offerings).⁴² Widespread infringement of patents covering genetic tests clearly increases the likelihood of enforcement by patentees to combat the violation of their patents and protect the rights of their authorized licensees. It is also likely that the factors that may lead to multiple labs offering a test for changes in a particular gene—such as large demand, clinical acceptance and available insurance coverage—increase the value of the exclusive right and drive enforcement efforts of the patent owners and exclusive licensees authorized to bring patent infringement lawsuits against infringers.

It is unclear whether those findings, which related to laboratories engaged in potentially infringing activities by conducting primary genetic diagnostic tests, would apply equally to the provision of confirmatory results. Commentary and testimony provided to the USPTO suggested that the market for confirmatory genetic tests is small relative to primary tests, and so it may be

⁴⁰ Comments of James Evans at 1.

⁴¹ Mildred K. Cho et al, *supra* note 20.

⁴² *Id.*

that confirmatory genetic testing goes undetected. The USPTO found no evidence about whether, and how often, doctors order confirmatory genetic tests even when multiple test providers are available.

It is also likely following *Mayo* and *Myriad*, that the natural correlations that underlie gene-based diagnostic tests can now be detected using non-infringing methods and materials, regardless of the presence of patents on specific, patent-eligible forms of a test for any particular targeted condition.

4. Relating to the role of cost and insurance in genetic diagnostic testing.

The fourth item posed by Section 27 concerns “the role that cost and insurance coverage have on access to and provision of genetic diagnostic tests.”⁴³ An important basic inquiry in this regard is whether insurance companies cover or would be likely to cover the costs of confirmatory genetic tests. Evidence from insurance policies indicated that the cost of confirmatory genetic testing is generally currently not covered.

In general, Medicare does not cover the cost of “duplicate testing.”⁴⁴ The Medicare policy manual advises that “[m]ultiple tests to identify the same analyte, marker, or infectious agent should not be reported separately.”⁴⁵ Insurance expert Dr. Bruce Quinn, one of the respondents to the USPTO’s requests for information, identified an exception that allows “measuring the same analyte in two materially different tissues,” e.g., a possible cancer on the left arm versus the right arm, but noted that such an exception “would not apply to germline

⁴³ AIA § 27(b)(4).

⁴⁴ Ctrs. for Medicare & Medicaid Svcs., National Correct Coding Initiative Policy Manual for Medicare Services, Ch. 10, at X-20 (2013), available at <http://www.cms.gov/Medicare/Coding/NationalCorrectCodInitEd/index.html>.

⁴⁵ *Id.*

genetic tests which would give the same results regardless what part of the body a sample was taken from.”⁴⁶

Major private insurers, too, presume that a genetic test for a particular inherited disorder should be conducted only once in the lifetime of a patient: for example, this is the case for Aetna,⁴⁷ WellCare,⁴⁸ and Capital Blue Cross.⁴⁹

Another important inquiry is whether exclusive patent protection results in higher costs, and whether the costs of genetic tests are so high that the price inhibits patients from requesting confirmatory tests or doctors from prescribing them. Costs do play a role in whether patients choose to undergo treatments,⁵⁰ and commenters suggest that insurance coverage, in turn, plays a major role in whether testing services are sought,⁵¹ especially where the cost of the service is high. There is little evidence, however, to suggest that prices for exclusively-licensed genetic tests are significantly inflated relative to what they would be if they did not hold an exclusive position in the marketplace. To the contrary, the SACGHS report found “little consistent price effect of the BRCA patents” based on a comparison of “intra-laboratory cost per amplicon for Myriad’s testing of BRCA versus colon cancer genes” and of “Myriad’s price for full-sequence testing of colon cancer genes compared to other (competitor) services.”⁵² In another study

⁴⁶ Statement of Bruce Quinn at 6.

⁴⁷ Aetna Inc., Clinical Policy Bulletin No. 0140: Genetic Testing at 3 (Jan. 18, 2013), available at http://www.aetna.com/cpb/medical/data/100_199/0140.html.

⁴⁸ WellCare, Policy No. HS-021: Diagnostic and Predictive Testing at 2 (June 7, 2012), available at https://www.wellcare.com/WCAssets/corporate/assets/HS021_Genetic_Testing.pdf.

⁴⁹ Capital BlueCross, Medical Policy No. MP-2.232: Genetic Testing for Inheritable Disease at 2 (July 1, 2012), available at <https://www.capbluecross.com/NR/rdonlyres/251A974E-2846-43FF-9F2C-1873080CD7DA/0/GeneticTestingforInheritableDiseaseMinorReviewcoded122012sb.pdf>.

⁵⁰ See, e.g., Aaron B. Caughey et al, *Assessment of Demand for Prenatal Diagnostic Testing Using Willingness to Pay*, 103 OBSTET. GYNECOL. 539 (2004), available at http://journals.lww.com/greenjournal/fulltext/2004/03000/assessment_of_demand_for_prenatal_diagnostic.22.aspx.

⁵¹ See, e.g., Comments of Cancer Legal Resource Center at 1–2 and Comments of Lori Pressman at 16.

⁵² Robert Cook-Deegan et al, *Impact of Patents and Licensing Practices on Access to Genetic Testing for Inherited Susceptibility to Cancer: Comparing Breast and Ovarian Cancers to Colon Cancers*, Case Study in SACGHS REPORT at A-5–A-6.

related to pricing, a group of researchers compared the prices charged for genetic tests for breast and colorectal cancers, one of which is exclusively licensed (breast cancer) and the other of which is not (colorectal cancer), and found that the exclusive licensee charged less for its test than the non-exclusive licensee did for its test.⁵³

While exclusivity may not drive the cost of a given test markedly higher than if the test were offered on a non-exclusive basis, it is clear that the availability of insurance plays an important role in the decision to have a test done, especially when the cost of the test is substantial. One report includes a case study, finding that nearly 70% of women who were eligible for free BRCA1 testing chose to undergo the testing, whereas only 22% of those women without coverage elected to undergo the test.⁵⁴ The exclusive provider of testing using the BRCA1 and BRCA2 gene mutation for breast cancer reports that 95% of those requesting testing have insurance coverage, which pays 90% of the charges.⁵⁵ Another study reports that, out of 450 women whom genetics professionals had counseled regarding breast/ovarian cancer risk, 42% of women who declined BRCA testing had insurance that provided no coverage for such testing; that 25% had insurance offering partial coverage; and that 33% had full coverage.⁵⁶ The same study reports that women who could not afford full or partial payment of BRCA genetic testing for breast cancer were 5.5 times less likely to elect to have the test.⁵⁷

⁵³ Robert Cook-Deegan et al, *supra* note 54.

⁵⁴ Soo-Chin Lee et al, *Utilization of BRCA1/2 Genetic Testing in the Clinical Setting*, 94 *CANCER* 1876 (2002), available at <http://onlinelibrary.wiley.com/doi/10.1002/cncr.10420/pdf>. Aside from access to free testing, “prior diagnosis of breast or ovarian carcinoma and Ashkenazi Jewish heritage were the only [other] factors associated with genetic testing on both univariate and multivariate analysis.”

⁵⁵ Robert Cook-Deegan et al, *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*, 12 *GENETICS MEDICINE* 215 (2010), available at <http://fds.duke.edu/db/attachment/1368>.

⁵⁶ Shannon Kieren et al, *The Role of Financial Factors in Acceptance of Clinical BRCA Genetic Testing*, 1 *GENETIC TESTING* 101 (2007), available at <http://online.liebertpub.com/doi/pdfplus/10.1089/gte.2006.9999>.

⁵⁷ *Id.*

Insurance coverage plays a central role in making primary genetic tests accessible to patients. Because insurance coverage policies, both governmental and private, do not generally cover confirmatory genetic testing, a significant number of individuals who may seek confirmation of a specific test result will likely forgo it due to cost, even if it is available from independent providers. Accordingly, while the USPTO does not find sufficient evidence to recommend specific changes to insurance coverage for gene-related diagnostic tests, such coverage should be considered in any discussion of access to confirmatory genetic diagnostic testing.

B. A Further Statistical Consideration Regarding Preventative Screening

Currently, gene-based tests are performed primarily when there is a medical indication that warrants them. In the case of BRCA1 and BRCA2, the indication would be a diagnosis of breast cancer or being in a family with a history of breast, ovarian or other BRCA-related cancer. An Ashkenazi Jewish ancestry is also associated with a markedly higher risk of a deleterious BRCA mutation than occurs in the general population. The tests are not done as part of large-scale screening exercises to detect disease in a general population. In this situation, a test result will be most questionable if it is negative when the combination of indications would lead one to expect a positive result. False negatives would likely be caught, and false positives would be quite rare. If a situation arose in which it was advantageous to administer a gene-based test as part of a wide screening program, the need for confirmatory testing would be greatly amplified. Confirmatory genetic tests can and will uncover the inevitable errors that occur in any kind of diagnostic testing. Errors due to mishandling of samples or the inherent error rate of any test, for example, are very likely to be uncovered by repeating the test on a different sample from the tested individual. To assess how important confirmatory genetic testing can be, it is helpful

to consider that deleterious mutations often occur at much higher rates in certain populations than in the general population.

For example, a genetic test may give false-positive results 2 times out of 10,000 tests on average due to an inherent error rate. In such a case, testing an at-risk population that has an occurrence of a deleterious mutation in gene A of 150 out of 10,000 will have a false-positive probability of approximately 1.3 percent ($100 \times (2 \text{ false positives}/152 \text{ total positives})$). However, if a general population for whom the likelihood of a deleterious mutation in gene A is 2 out of 10,000 were tested, then the probability that any one of those positive results will be false increases to 50 percent ($100 \times (2 \text{ false positives}/4 \text{ total positives})$). In other words, if large-scale screening were performed on populations for rare deleterious mutations, then confirmatory genetic testing of positive results would be very important.⁵⁸ Moreover, when the presence of a deleterious mutation prompts life-changing treatment decisions, the possibility of error may lead individuals to seek assurance about the result.

C. Recommendations

When the AIA was enacted in 2011, Congress asked the USPTO to examine and report on several aspects of the availability of confirming, or confirmatory, gene-based diagnostic tests, particularly where patents and exclusive licensing regimes were involved. While the USPTO was engaged in fact-finding and preparation of this report, several court cases were decided by the Supreme Court, the Federal Circuit and U.S. District Courts that fundamentally altered the patentability of medical diagnostic tests of all types, but especially gene-based tests. As discussed in the Background section above, the decisions in *Mayo* and *Myriad*, as well as several more recent decisions that interpret those cases, have made it very unlikely that new patents will

⁵⁸ Such large-scale screenings are not presently conducted in the United States, but offer an important illustration of the value of confirmatory genetic diagnostic testing.

be issued or that existing patents will be sustained by the courts if they claim naturally occurring products or methods using a natural phenomenon broadly enough to preclude all ways of carrying out a diagnostic test for the condition related to the particular product or natural phenomenon. Claims to natural correlations with well-understood, routine and conventional steps for detecting the correlation, as well as claims to DNA molecules which include a natural form of a particular coding sequence (i.e., genomic DNA), will be ineligible under the patent laws as being directed to a law of nature or a natural product. Conversely, any patent that does issue on a gene-based diagnostic method will necessarily not cover all methods of detecting the condition, nor will it cover the basic sequence that is the target of the test. Third parties will be free to perform the test by using conventional methods and naturally-occurring materials that the patented claims cannot cover. The ability of multiple parties to provide tests directed to the same mutation or gene creates the opportunity for any individual to obtain a confirmatory test (albeit, one that uses a different methodology than a patented primary test) by an independent testing provider, should such a provider be available. Although some evidence suggests that academic research has not been overly affected by gene or diagnostic method patents, the absence of broad, exclusive rights to testing any given diagnostic target further reduces even the threat that patent enforcement may interfere with gene-related diagnostic research.

In view of this watershed change in the legal environment surrounding gene-based diagnostic tests, the USPTO makes the following limited recommendations.

- 1. Continue to Monitor Confirmatory Testing for any Barriers to Access.**

The USPTO recommends that Congress monitor changes in the availability of gene-based diagnostic tests from multiple providers. Lawsuits by Myriad Genetics against several companies attempting to provide BRCA1/BRCA2 testing have recently been settled, and these

settlements strongly suggest that exclusive provision of gene-based tests is a thing of the past. Should this prove not to be the case, then any exclusivity will likely be due to factors that are related not to patents or to licensing practices but to other considerations.

2. Consider Creating a Mechanism to Facilitate Sharing of Test Results.

Some gene-based diagnostic tests involve situations where multiple different changes to the same gene may be deleterious, but many other changes may occur that have little or no effect on the individual carrying those mutations. Indeed, this is the case with BRCA1 and BRCA2. In these cases, the mere finding of a mutation is not, by itself, a meaningful or interpretable result unless there is a known correlation between that mutation and a deleterious or neutral effect. Such correlations, in turn, can be determined accurately only by an accumulation of independent results that reinforces the correlation. It would be advantageous to develop a mechanism for encouraging test providers to share their results in order to build a robust database of correlations between genetic alterations and the presence, absence, or statistical probability of acquiring the condition related to the gene being tested. Already existing NIH databases ClinVar⁵⁹ and/or ClinGen⁶⁰ could provide the basis for such a mechanism. Data sharing of this kind could promote the most rapid advances in the accuracy of individual tests.

3. Consider the Importance of Cost and Insurance in any Policy Discussion of Confirmatory Genetic Diagnostic Testing.

Congress specifically required an exploration in this study of the role that cost and insurance play in access and test provision.⁶¹ Comments throughout the USPTO's evidentiary

⁵⁹ ClinVar: <http://www.ncbi.nlm.nih.gov/clinvar/>

⁶⁰ ClinGen: <http://clinicalgenome.org/about/>

⁶¹ AIA § 27(b)(4).

record identify insurance coverage of genetic diagnostic testing as a key issue in patient access.⁶² There are two major concerns in this regard. The first is that exclusive providers may not accept some insurance carriers. The second is that insurance carriers do not generally cover confirmatory tests. The first of these concerns is minimal when there are multiple providers. .

In determining Medicare coverage for genetic diagnostic tests, the Centers for Medicare and Medicaid Services (CMS) and its contractors look to whether an item or service is reasonable and necessary as required by the Medicare statute.⁶³ CMS findings of reasonableness and necessity are usually made through the national coverage determination process, or by Medicare contractors who may develop local coverage determinations or make case-by-case determinations. Confirmatory tests, especially for germline gene mutations, are currently considered to be a form of duplicate testing and, as a result, medically unnecessary. This policy, in one form or another, appears to hold true for the insurance industry as a whole. An individual patient or a physician wishing to confirm a questionable or frightening result must now do so knowing the patient will have to cover costs out of pocket.

Societally, this may be a reasonable tradeoff, given that insurance rates may be pressured upward for all if confirmatory testing were widely covered, and a significant amount of unnecessary testing may occur. If in the future, based on considerations such as those discussed in Part III B above, situations arise where it is deemed advisable to screen allele the general population and not just individuals known or suspected to be at risk for a rare allele, then confirmatory testing of positive results may be necessary. This could be an area Congress may

⁶² See, e.g., Comments of Christine Gritzmacher at 2; Comments of Myriad Genetics at 24; Comments of National Society of Genetic Counselors at 3; Comments of Pharmaceutical Research and Manufacturers of America at 4-5; Comments of Roche Molecular Systems at 34; Comments of Suzannah K. Sundby at 1.

⁶³ Title XVIII of the Social Security Act, Section 1862 (a)(1)(A), enacted as 42 U.S.C. § 1395y, available at http://www.ssa.gov/OP_Home/ssact/title18/1862.htm.

have to consider in the future, although the dramatic decrease in costs of gene sequencing over the past several years may mitigate this concern to a large degree.

The USPTO has neither the authority nor the expertise to assess whether it would be appropriate for broader scale confirmatory testing to become more common for screening purposes in the future or to recommend specific actions that Congress may wish to consider should that occur. Therefore, this report can only emphasize that insurance coverage does appear to play significant a role in access to testing and should be taken into consideration should such a potential issue be examined.

IV. CONCLUSION

The findings presented in this report demonstrate foremost that much of the debate surrounding the role and impact of patents and exclusivity in genetic diagnostic testing has taken place in the absence of hard data and rigorous analysis, with little empirical support for the often far-reaching changes proposed in legal, economic, or regulatory policy. As the landscape of gene-related patents and exclusive licensing evolves in light of the Supreme Court's *Mayo* and *Myriad* decisions, the USPTO concludes that with respect specifically to confirmatory, gene-based diagnostic testing, Congress need take no immediate action.

It is also worth noting that the changing legal landscape will provide an opportunity for many potential providers, including many relatively small university-based molecular pathology laboratories, to enter the business of providing gene-based tests. A possible consequence of this entry may be that larger-scale commercial entities will not develop and market tests because of the risk that they cannot recoup their investments. The availability of tests on a small-scale or even local basis by a number of providers may have several potentially negative consequences. First, the quality of these "home-grown" tests may be highly variable, with some labs providing high-quality tests and others developing and providing lower quality tests. Second, results may

be shared only as individual laboratories see fit to publish them in journals, and the rapidity of bringing results to publication may vary significantly from one laboratory to another. Third, the availability of tests in a fragmented market may be limited even when there are good mechanisms for publicizing what tests are being done and by whom. While many tests are offered now on a national basis, by virtue of being licensed to national providers, university-based molecular pathology laboratories may not have the resources or desire to cater to a broad, or nationwide patient population. As Congress considers the many issues surrounding diagnostic testing in general, including quality and regulation, it should keep these considerations in mind.

The U.S. market system requires an ongoing balance to be struck between supporting incentives for innovation and achieving effective access for consumers. As an agency charged with continually channeling knowledge and discovery into the marketplace for the long-term benefit of society, the USPTO appreciates first-hand the value of appropriately striking this balance. For this reason, the USPTO urges Congress to proceed cautiously in formulating legislative reforms.



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