Written Comments on

Genetic Diagnostic Testing Study

Myriad Genetics, Inc.

Before United States Patent and Trademark Office (USPTO)

Submitted March 26, 2012

Pursuant to The United States Patent and Trademark Office ("USPTO") Request for Comments and Notice of Public Hearings on Genetic Diagnostic Testing, Fed. Reg. Vol. 77, No. 16, January 25, 2012 ("Federal Register Notice"), Myriad Genetics, Inc. ("Myriad") submits the following comments.

I. INTRODUCTION

The Federal Register Notice reiterated the four questions mandated in Section 27 of the America Invents Act ("AIA"), as well as posing 14 additional questions. These questions focus, to varying degrees, on "second opinion […] genetic diagnostic testing." Myriad will respond to each of the four statutory questions and several of the additional questions posed in the Federal Register Notice in the following remarks.

The USPTO held two public hearings to collect testimony for the present study, one on February 16, 2012 in Alexandria, VA ("Alexandria hearing") and another on March 9, 2012 in San Diego, CA ("San Diego hearing"). Most of the individuals who gave testimony at both hearings discussed Myriad and its testing services by name and at length.[1]

In view of this, and based on the fact that the present study is motivated by alleged deficiencies in second opinion testing for the BRCA genes, a brief background on Myriad, its testing, and the molecular diagnostics industry is appropriate. Widespread problems of access to genetic diagnostic testing, including second opinion testing, have been alleged and, in many cases, accepted as true without any proof. Myriad believes our experience as a world-wide leader in premium genetic diagnostics shows that there are no such access problems.

[1] Myriad itself provided testimony at the San Diego hearing.

II. BACKGROUND

Myriad is a leading molecular diagnostic company located in Salt Lake City, Utah. We are focused on developing and commercializing novel predictive medicine, personalized medicine and prognostic medicine tests. As a central reference laboratory, Myriad performs all of the molecular diagnostic testing and analysis for our own tests. We believe that the future of medicine lies in a shift from a trial and error paradigm to a prevention and personalized medicine paradigm. By understanding the underlying genetic basis of disease, it has been well documented that individuals who have a greater risk of developing disease can be identified, and physicians can use this information to improve patient outcomes and better manage patient healthcare. In addition, by understanding the genetic differences in each individual, personalized medicine tests can be used to predict whether someone will respond favorably to a particular drug therapy and what drug dose will produce the best treatment results. Myriad's goal is to provide physicians with critical information that can be used to more precisely guide the healthcare management of their patients.

Myriad's molecular diagnostic tests are designed to analyze molecular markers (such as genes) in order to assess an individual's risk for developing disease later in life, determine a patient's likelihood of responding to a particular drug, assess a patient's risk of disease progression and disease recurrence, and measure a patient's exposure to drug therapy to ensure optimal dosing and reduced drug toxicity. To date, Myriad has launched nine commercial molecular diagnostic tests. Two representative genetic testing services Myriad offers are the BRAC*Analysis*® test and the COLARIS® test:

- Our BRAC*Analysis* test is a comprehensive analysis of the *BRCA1* and *BRCA2* genes for assessing a woman's risk of developing hereditary breast and ovarian cancer. A woman who tests positive for a deleterious mutation with the BRAC*Analysis* test has up to an 87% risk of developing breast cancer and up to a 44% risk of developing ovarian cancer during her lifetime. Pre-symptomatic individuals who have a high risk of developing breast cancer can reduce their risk by approximately 50% with appropriate preventive therapies.[2] Additionally, pre-symptomatic individuals who carry gene mutations can lower their risk of developing ovarian cancer by approximately 60% with appropriate preventive therapies.[3]

- Our COLARIS test is a comprehensive analysis of the MLH1, MSH2, MSH6 and PMS2 genes for assessing a person's risk of developing colorectal cancer or uterine cancer. Individuals who carry a deleterious mutation in one of the colon cancer genes in the COLARIS test have a greater than 80% lifetime risk of developing colon cancer and women have up to a 71% lifetime chance of developing uterine cancer. Highly effective preventive measures for colon cancer include colonoscopy and the removal of precancerous polyps and for uterine cancer includes hysterectomy.

Myriad employs a number of proprietary technologies, including patented technologies owned or licensed by Myriad, to better understand the genetic basis of human disease and the role that genes and other molecular markers may play in the onset and progression of disease. This intellectual property plays a critical and

[2] Fisher *et al., Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study*, J. NATL. CANCER INST. (1998) 90:1371-1388.

[3] Kauff, *et al., Risk-reducing salpingo-oophorectomy in women with a* BRCA1 *or* BRCA2 *mutation*, N. ENG. J. MED. (2002) 346:1609-1615.

vital role in driving the investment of capital, both human and financial, in the research, development, and commercialization of molecular diagnostic tests.

It is important to recognize the substantial risks and significant investment necessary for a molecular diagnostic test to be successful. To be successful and beneficial to the general public, a genetic test must go through various stages of development: First, the initial research and discovery effort; followed by the process of validating the clinical test to be done in a clinical laboratory at commercial scale; next, commercially launching the new test, which includes developing all of the associated medical support literature, patient education materials, and marketing materials; additional clinical trials must then be undertaken to generate peer-reviewed publications on the medical necessity and importance of the new testing; medical societies must then be educated on the new testing and encouraged to adopt new guidelines regarding testing; and finally, great effort is needed to gain insurance reimbursement for testing which includes demonstrating the positive pharmacoeconomics of testing. Myriad's development of the BRAC*Analysis* test illustrates well these stages and the importance of patent protection at each stage.

The first step is discovery. Twenty years ago Myriad was a small, start-up biotechnology company with the goal to discover and characterize the genes associated with hereditary breast and ovarian cancer. Initial funding for Myriad's research and development efforts came largely from outside venture capital and collaborative research contracts with pharmaceutical partners, based on the promise of a limited period of exclusivity for the fruits, if any, of our research and discovery efforts.

While the discovery of the *BRCA1* and *BRCA2* genes was monumental, our success and the invaluable benefit delivered to patients have far more to do with the ensuing phases of product development. Great discoveries can languish in academic laboratories and scientific publications, and never fully benefit the public, without significant efforts to develop and commercialize them appropriately for public consumption. This was the foundation of the Bayh-Dole Act, a transformative law aimed at ensuring discoveries reach their full potential to benefit the public. Molecular diagnostics, like genetic tests, require an enormous commitment of capital to be developed and launched, and then additional sustained and significant financial support to reach a level of commercial viability at which point patients may benefit. The risk and reward inherent in the ability to obtain exclusive license rights within the U.S. patent system is the driving force behind investment in genetic tests, and hence their development and commercialization to the general public.

Myriad's story again well illustrates these principles. Myriad spent over $500 million and 17 years in the research, development and ensuing commercialization and operational support of the BRAC*Analysis* test before achieving financial break-even. Myriad would not have been able to make this capital investment without the promise of exclusive patent rights and the then hoped-for, but unknown, positive return on investment. Hence, patents drive innovation, product introductions, product commercialization, and societal adoption of new genetic testing.

III. STATUTORY TOPIC 1

The first study topic mandated by Section 27 of the AIA reads as follows: "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."

A. What Does "Second Opinion" Mean?

First, an important term to clarify is "**second opinion testing**" in the context of genetic testing and the Federal Register Notice. The ability of patients to seek a second opinion is an important part of medical care. However, there is a big difference between repeating a diagnostic test to confirm the initial test results on the one hand, and getting a second opinion as to what to do with the result of such a test on the other. For example, if a patient's MRI shows a cancerous lesion in her breast, and her doctor recommends a lumpectomy, the patient may seek the "second opinion" of another doctor to consider an alternative or confirmatory treatment. However, the patient is much less likely to ask for, and insurance will generally not pay for, a repeated MRI; there is most likely not a need. In such an instance, it is not the accuracy of the test that the patient likely questions, but the plan of action presented by the doctor.

In this respect, second opinions are no less available in genetic testing than in any other field. Patients are free to seek the medical advice and counsel of any healthcare practitioner as to an appropriate medical treatment plan following a genetic test result. This is an important point to clarify since many in the general public react strongly to rhetoric claiming they cannot get a "second opinion." They likely interpret this term in its conventional sense rather than the unusual way it is being used in these proceedings. Given this caveat, Myriad will use the term "second opinion testing" in this unusual way—referring to conducting a second

test to confirm the results of the initial laboratory diagnostic test that was performed.

B. There Is No "Current Lack of Independent Second Opinion Testing"

Statutory Topic 1 asks about the impact of "the current lack of independent second opinion testing" on medical care, which *assumes* there is a lack of such testing. With respect to Myriad's BRAC*Analysis* test, however, this assumption is wrong as second opinion testing is available. In fact, since 1999, multiple laboratories have performed testing to confirm the reported identification of a deleterious mutation in the *BRCA1* or *BRCA2* gene. Today, for example, NCBI's Genetic Testing Registry[4] lists seven laboratories in the U.S. other than Myriad that conduct a clinical "confirming genetic diagnostic test" on the *BRCA1* gene and six labs that test the *BRCA2* gene.[5] To name a few: UCLA Diagnostic Molecular Pathology Laboratory, the University of California San Francisco Molecular Diagnostic Laboratory and University of Chicago Genetic Services Laboratory.

In addition, in 2002, Myriad licensed LabCorp the right to conduct single site and multi-site (Ashkenazi Jewish Panel) testing.[6] This license remains in effect today. LabCorp was and remains one of the largest reference laboratory

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[4] NCBI's Genetic Test Registry was relatively recently launched. *See* NIH Press Release of February 29, 2012 (*available at* http://www.nih.gov/news/health/feb2012/od-29.htm). However, it was preceded by a similar, freely available Internet resource at www.genetests.org.

[5] For *BRCA1*: http://www.ncbi.nlm.nih.gov/gtr/tests/?condition=C2676676&methods=2:19&locations=840:102,112,117,125,129,136,143&test_type=Clinical&term=BRCA1[gene] (last accessed March 23, 2012)

For *BRCA2*: http://www.ncbi.nlm.nih.gov/gtr/tests/?condition=C2675520&methods=2:19&locations=840:102,112,117,125,136,143&test_type=Clinical&term=BRCA2[gene] (last accessed March 23, 2012)

[6] LabCorp-Myriad Joint Press Release of June 5, 2002 (*available at* http://www.prnewswire.com/news-releases/myriad-genetics-and-labcorp-form-exclusive-predictive-medicine-marketing-alliance-74475582.html).

companies in the world; at the time Myriad granted the license, LabCorp had over 200,000 physician customers and a 600-person sales force in the U.S. Again, it is difficult to conclude there is any lack of availability of second opinion testing.[7]

So, if a patient received a BRAC*Analysis* report of a deleterious mutation, several laboratories in the U.S., independent of Myriad, could perform a confirmatory test for that reported mutation before the patient makes any treatment decisions. Therefore, in the case of BRCA1/2 testing there has been no adverse impact on medical care due to any supposed absence of second opinion testing because there is no such absence—second opinion testing is, and has been, available.

C. Why Might it not Be Well-Known that Second Opinion Genetic Testing Is Available?

It appears that some stakeholders, even those who have studied issues surrounding genetic testing in great detail, were not aware of the various U.S. labs offering BRCA1/2 confirmatory testing.[8] This is regrettable, but it is a problem of dissemination of information rather than availability of testing. This also invites the question of why there is such a lack of information and education. Myriad sees two possible reasons, neither of which points to a problem attributable to the existence of patents covering genetic tests.

First, there is no significant need for second opinion testing. Myriad's initial BRCA testing is of the highest quality and, while Myriad's testing services lead the

[7] A search of LabCorp's current test menu (*available at* https://www.labcorp.com/wps/portal/provider/testmenu) shows that LabCorp is apparently no longer offering single-site BRCA testing despite having a license. If this is true, it only further adds to the evidence that there is no significant level of demand for confirmatory testing. *See* Section III.C., *infra*.

[8] *See, e.g.*, oral testimony of Misha Angrist at San Diego hearing.

industry, we have seen no evidence that genetic testing offered by others is significantly lacking in quality.[9]

A second reason, which is closely related to the first, is the problem of incentives. Several parties gave testimony pointing to the fact health insurers are unlikely to reimburse duplicative confirmatory testing.[10] Hence, none of the labs offering confirmatory testing has the incentive to educate doctors or patients on the merits of or need for such testing. In this way, Myriad submits it is not the existence of patent exclusivity, but perhaps the lack of such exclusivity, that reduces the prevalence of second opinion testing by reducing the incentive to promote such testing.

D. There Is No Significant Need for Second Opinion Testing

Even assuming, for argument's sake, second opinion testing was not available, Myriad does not believe it would have an adverse impact on patient medical care. CLIA-approved laboratories such as Myriad's must have quality systems that are highly regulated and regularly audited to confirm proficiency in testing.[11] As a result of the high quality of testing provided by Myriad, there has not been a significant need for second opinion BRCA testing. We have no reason to believe this is not the case for the rest of the genetic diagnostic testing industry. This is at least evidenced by the fact that Myriad has never received a request by a patient or health care practitioner for permission for a third party to conduct a second confirmatory test. It has only been on an extremely rare occasion that we

[9] *See* Section III.D, *infra*.

[10] *See, e.g.*, oral testimony of Mary Williams at Alexandria hearing, oral testimony of Hans Sauer at Alexandria hearing, and oral testimony of Bernard Greenspan at San Diego hearing. *See also*, Section III.D., *infra*.

[11] *See, e.g.*, oral testimony of Bernard Greenspan at San Diego hearing.

have received, which we have always granted, a request from a patient for Myriad to conduct a confirmatory test. To our knowledge, the volume of testing performed by the several U.S. labs offering confirmatory BRCA testing is quite low.[12]

The lack of demand for confirmatory testing is supported by the testimony of AMP in the Alexandria hearing. The executive director of AMP noted that a patent safe-harbor for confirmatory testing would not result in increased access to confirmatory testing because labs will seldom invest the significant resources needed to develop a test merely for duplicative purposes and health insurers and Medicare will likely not reimburse the cost of the test as it will be viewed as duplicative.

Second, there is no need for a second, confirmatory test due to the degree of accuracy and rigor of Myriad's testing process. Today, Myriad's genetic testing is highly regarded and generally recognized as the gold standard for diagnostic testing.[13] One example of the rigor of our testing is that before reporting out any deleterious mutation, we will retest the sample to confirm the result. Hence, technically, a second confirmatory test is already run by Myriad on every positive report.

In this regard, a very important observation is made in the Statement of Dissent to the Secretary's Advisory Committee on Genetics, Health and Society report ("SACGHS Report"), released in 2010, by three of the committee members with respect to the quality of testing by sole source providers such as Myriad:

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[12] *See, e.g., supra*, n.7. Perhaps patients desiring such a test either (1) contact one of the labs offering confirmatory testing, *see* Section III.B., *supra*; or (2) don't know testing is available, *see* Section III.C., *supra*.

[13] *See, e.g.*, Section III.E., *infra*.

> We do not believe … that there is any credible evidence that the quality of testing performed in sole source laboratories is routinely or demonstrably subpar in any way to that which is done in multiple laboratories. Nor do we believe that data indicate that modifying the gene patent system and protections it offers through exclusive license agreements would result in multiple laboratories performing proprietary tests with better quality than generated by current and developing oversight of quality assurance undertaken by these agencies and the laboratories themselves.[14]

Others, including several prominent academics, have similarly called for evidence rather than rhetoric and anecdotes in assessing the impact of patents on genetic testing.[15] Indeed, even the anecdotal examples of alleged problems with patents in genetic testing do not hold up under scrutiny.[16]

This Statement of Dissent is found at the end of the SACGHS Report. Myriad encourages the USPTO to review the entire Statement of Dissent as it makes several very important observations about the SACGHS Report. In particular, Myriad echoes the Statement of Dissent in urging extreme caution in approaching the Report's recommendations. As we stated in our oral testimony at

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[14] SACGHS Report, p.391-392 (*available at* http://oba.od.nih.gov/oba/SACGHS/reports/SACGHS_patents_report_2010.pdf).

[15] *See, e.g.*, Caulfield *et al*., *Evidence and anecdotes: an analysis of human gene patenting controversies*, 24 NATURE BIOTECHNOL. 1091 (2010) ("When it comes to gene patenting, policy makers may be responding more to high-profile media controversies than to systematic data about the issues."); Christopher M. Holman, *The Impact of Human Gene Patents on Innovation and Access: A Survey of Human Gene Patent Litigation*, 76 UKMC L.R. 295, 300 (2006) ("The paucity of documented examples in which the fears surrounding gene patents have manifested themselves is striking, particularly when one considers the high level of public concern and the extraordinary nature of the proposed legislative fix.").

[16] For example, some point to Myriad as an example of patents functioning badly in genetic testing. The evidence shows this to be false. *See, e.g.*, Section III.B., *supra*, Section V, *infra*, and Holman, *supra*, n.15, at 299 ("Even the Myriad example is based primarily on anecdotal reports of laboratories voluntarily curtailing their genetic testing services involving the BRCA gene due to fears of patent liability, fears which are based on subjective assessments of risk by laboratory directors").

the San Diego hearing, the underlying studies commissioned by the Committee offer valuable data and insights that may be very useful in the present study.[17] However, many find the recommendations proffered by the SACGHS Report are not supported by, and in some cases are clearly contrary to, the findings of these underlying studies.[18] This Statement of Dissent provides, what Myriad believes, are fair observations and comments regarding the SACGHS Report.

E. There Is No Evidence of Any Inhibitory Impact on Innovation in Testing and Diagnosis

The second half of the first statutory topic asks whether the supposed lack of second opinion testing has any inhibitory impact on innovation to existing testing and diagnosis. Myriad does not believe so, and has not seen any evidence of a negative impact with respect to BRCA testing. One obvious reason for this is found in the very purpose of a second opinion confirmatory test: to duplicate the original testing in order to confirm or deny its results. Thus, by definition, this category of testing cannot be expected to expand or attempt to create alternative or new innovative testing. It is hard to imagine that any lack of second opinion confirmatory testing would inhibit innovation when the presence of confirmatory

[17] For example, 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 with colon cancers*, GENET. MED. (2010) 12:S15-38. This study corresponds to pages A2-A51 of the SACGHS Report.

[18] *See, e.g.*, *US HHS advisory group SACGHS' proposals to limit gene patent draws fire from industry*, thepharmaletter.com (Feb. 8, 2010) ("At a BIO-sponsored press conference in Washington DC, former SACGHS committee member Brian Stanton said that the committee had not found significant evidence of problems to date to support such proposed changes, that it had over-reached its original task, and that the rules would have unintended consequences, such as squelching private sector research."), *available at* http://www.thepharmaletter.com/file/68022/us-hhs-advisory-group-sacghs-proposals-to-limit-gene-patent-draws-fire-from-industry.html; *id.* ("Also at the BIO press meeting, former US Senator Birch Bayh said that the legislation he co-sponsored with former Senator Bob Dole came at a time when the federal government owned all the inventions that came from federally funded research and US innovation was stagnating and investment in R&D was not growing. He attacked the proposed rules as an 'attempt to roll back the clock to implement the failed policies of the past.'").

testing would not promote innovation. Rather innovation is spurred by basic research, and by incentives for commercialization which are largely driven by the patent system. Innovation is not fueled by running the same test to merely confirm a prior result.

Accordingly, Myriad has seen no evidence of inhibition of innovation for existing tests and diagnoses. Our experience in large rearrangement BRCA1/2 testing is instructive on this point. Some, including several who provided testimony in the public hearings for the present study, have argued that Myriad's testing is incomplete or deficient, saying that it does not detect up to 12% of known mutations.[19] This allegation is based on a publication in the spring of 2006 studying large rearrangements in BRCA1/2 that were not being tested at the time.[20] This is then typically coupled with the assertion that it was only this publication that spurred Myriad to begin developing large rearrangement testing. The full story is quite different.

Myriad strives to develop and implement the most accurate and up-to-date testing for variations in the BRCA genes. This is evidenced by the developments and improvements made to our *BRCA1* and *BRCA2* test over the years. Our development work and improvements surrounding large rearrangements in the BRCA genes is, contrary to the testimony given in the Alexandria and San Diego hearings, an excellent illustration of Myriad's commitment to the highest quality testing for our patients.

[19] *See, e.g.*, oral testimony of Mary Williams at Alexandria hearing, oral testimony of Lisa Schlager at Alexandria hearing.

[20] Walsh *et al.*, *Spectrum of Mutations in* BRCA1, BRCA2, CHEK2, *and* TP53 *in Families at High Risk of Breast Cancer*, J. AM. MED. ASSOC. (2006) 295:1379-1388.

Large rearrangements are DNA alterations that involve the duplication or deletion of large (generally >1000 base pair) pieces of genomic DNA. Due to the size and type of these DNA changes, large rearrangements are generally not detectable by standard PCR-based sequencing. Other laboratory techniques are required to identify the presence of large rearrangements.

When Myriad first initiated testing of the BRCA genes in 1996, the general scientific belief was that there would be few large rearrangements in the BRCA genes. This was before the frequency and underlying mechanisms of genomic copy number variants were better understood. However, as further research was undertaken, it became apparent that there were some common large rearrangements.[21]

Myriad subsequently determined the presence of five recurrent large rearrangements in the *BRCA1* gene based on literature reports and our own internal research. In 2002 we launched clinical testing for a large rearrangement panel of these five recurrent *BRCA1* large rearrangements for all patients ordering *BRCA1* and *BRCA2* gene sequencing.[22]

Myriad's continued research led us to believe there were additional large rearrangements that were not detected by this test. We assessed existing technologies at the time and realized that there were no commercially available

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[21] *See, e.g.*, Gad *et al.*, *Significant contribution of large BRCA1 gene rearrangements in 120 French breast and ovarian cancer families*, ONCOGENE (2002) 21:6841-6847; Frans *et al.*, *Large Genomic Deletions and Duplications in the BRCA1 Gene Identified by a Novel Quantitative Method*, CANCER RES. (2003) 63: 1449–1453.

[22] Hendrickson *et al.*, *Prevalence of five previously reported and recurrent BRCA1 genetic rearrangement mutations in 20,000 patients from hereditary breast/ovarian cancer families*, GENES CHROMOSOMES CANCER (2005) 43:309-313; *see also*, Myriad Press Release of August 1, 2006 (*available at* http://investor.myriad.com/releasedetail.cfm?ReleaseID=325803) (announcing launch of BART and mentioning release of LRP in 2002).

assays that could meet the stringent quality parameters for a clinical test, especially a Myriad test. Therefore, we started to develop our own robust, commercial scale test to identify large rearrangements in both *BRCA1* and *BRCA2* in 2003. We named this new sophisticated assay BART (BRAC*Analysis* Rearrangement Test).

The BART assay provides high analytical sensitivity and specificity in detecting large rearrangements, and incorporates multiple features for quality control and robustness. We presented technical details and preliminary results of this work in the form of two poster presentations at the American Society of Human Genetics (ASHG) annual meeting in October 2004,[23] a year and a half before the publication of the Walsh *JAMA* paper. This development and validation work resulted in our launch of BART as a clinical service in August 2006.[24] The cumulative results of BART clinical testing have been presented as posters at the Association for Molecular Pathology (AMP) annual meeting in 2006,[25] the American Society for Clinical Oncology (ASCO) annual meeting in 2007,[26] at the ASHG annual meetings in 2007 and 2011,[27] and as an invited platform

[23] Judkins *et al.*, *Detection of large rearrangement mutations in BRCA1 and BRCA2 in 528 high risk families from North America by quantitative PCR based gene dose analysis*, ASHG 54th Annual Meeting, Toronto, Canada (October 2004); Hendrickson *et al.*, *Improved quantitative PCR-based gene dose analysis for the clinical laboratory: Assay design parameters and quality assurance metrics*, ASHG 54th Annual Meeting, Toronto, Canada (October 2004).

[24] Myriad Press Release of August 1, 2006, *supra*, n.22.

[25] Thaddeus Judkins *et al.*, *Clinical Testing for Gene Rearrangements in* BRCA1 *and* BRCA2, Association for Molecular Pathology, Orlando, FL (November 2006).

[26] Richard Wenstrup *et al.*, *Molecular Genetic Testing for Large Genomic Deletion and Duplication Mutations in the* BRCA1 *and* BRCA2 *Genes for Hereditary Breast and Ovarian Cancer*, American Society of Clinical Oncology (2007).

[27] Spence *et al.*, *Clinical testing experience for large genomic rearrangements in the* BRCA1 *and* BRCA2 *genes for hereditary breast and ovarian cancer*, ASHG 57th Annual Meeting, San Diego, California (October 2007); Roa *et al.*, BRCA1 *and* BRCA2 *large genomic rearrangement testing in a large cohort of hereditary breast/ovarian cancer patients: prevalence and mutation profiles in risk-stratified patient groups of different ethnicities*, ASHG 61st Annual Meeting, Montreal, Canada (October 2011).

presentation at the AMP annual meeting in 2007.[28] We currently have a paper in press at the journal *Cancer* that describes interesting findings on the prevalence and mutation profiles of *BRCA1* and *BRCA2* large rearrangements in our laboratory testing cohort.

Detractors recount the BRCA large rearrangement story, with several of the critical details above omitted, as evidence of supposed problems caused by patents in genetic testing. Instead, the above illustrates the patent system working as it should and Myriad making extraordinary efforts to bring the best possible test to patients.

Myriad took the initiative to develop large rearrangement testing not because of the Walsh *JAMA* paper, but began work years earlier based on a desire to provide patients the best possible testing and backed by the incentive provided by our patent position. Myriad's multi-million dollar investment in large rearrangement technologies is due in large part to being the exclusive licensee of the BRCA patents, allowing Myriad to dedicate the time, talent and resources on these development and commercialization efforts.

Further, the story of large rearrangement testing in BRCA1/2 shows how patents in genetic testing do not prevent research or technological advance. Clearly Myriad's patents didn't prevent Walsh *et al.* from conducting their study and publishing the results. Patents don't prevent technological advance and patent-holders still have a strong incentive to improve their testing.

IV. STATUTORY TOPIC 2

[28] *Quantitative Multiplex PCR Analysis for Large Gene Rearrangements*, Invited Speaker, Technical Topics Workshop, Association for Molecular Pathology Annual Meeting, November 8, 2007, Los Angeles, California.

The second study topic mandated by Section 27 of the AIA reads as follows: "The effect that providing independent second opinion genetic diagnostic testing would have on the existing patent and license holders of an exclusive genetic test."

Over the past decade, second opinion genetic diagnostic testing has occurred while Myriad has offered BRAC*Analysis*.[29] In theory, such confirmatory testing should have no appreciable impact on existing patent and license holders of an exclusive genetic test,[30] provided that second opinion testing in no way circumvents the initial testing conducted by the patent and license holders. Such exclusive providers will have already derived the benefit of their patent rights from the initial test.

However, the real danger to exclusive providers and patent and license holders is "grey market" erosion of their rights resulting from initial tests performed by unauthorized third parties. If a lab ostensibly offers confirmatory testing under a statutory license, but is not required to verify that an initial test has been performed by the exclusive provider, this can effectively eviscerate the exclusive provider's patent position by allowing the other lab to perform unauthorized *initial* testing under the guise of statutorily *second opinion* sanctioned testing. Even if the second lab is statutorily required to verify authorized initial testing before performing a confirmatory test, there must be a mechanism for the exclusive provider to easily confirm this.

While Myriad believes there is no need for a statutory scheme to authorize confirmatory testing, these and many other issues would need to be publicly addressed if Congress were to determine there was a need to intervene. Any

[29] *See* Section III.B., *supra*.

[30] Indeed Myriad has experienced no negative effects of the currently available second opinion testing.

proposed "solution" must adequately protect the intellectual property rights driving innovation in molecular diagnostics. As a general principle, and with Myriad as an exemplar, we believe protecting IP rights in molecular diagnostics incentivizes innovation and ultimately benefits patients.

V. STATUORY TOPIC 3

The third study topic mandated by Section 27 of the AIA reads as follows: "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."

By any objective measure, the standard of medical care for the diagnosis, treatment and reimbursement of hereditary breast and ovarian cancer (HBOC) syndrome in the United States is unparalleled anywhere in the world. Today, a woman with a personal or family history of cancer, who meets medical society criteria, can be tested for the HBOC syndrome, and receive timely and accurate test results, through her health care practitioner, to guide medical management and treatment decisions; all at an affordable cost based on insurance reimbursement. This standard of care has been accomplished based on the patenting of BRCA isolated DNA and the exclusive licensing of such rights to Myriad by the NIH and several academic and research institutions who participated in the discovery effort. The incentives of the patent system enabled the raising of investment capital that allowed Myriad to make the research, development and commercial investments to bring accurate, reliable and affordable HBOC testing to the general population.

Myriad's exclusive licensing of the BRCA patents and our commercialization of the BRAC*Analysis* test have led to advancements in research,

medical care, testing practices, patient access and insurance coverage. For example,

- Over 9,000 research papers have been published relating to *BRCA1* and *BRCA2* and predisposition testing for hereditary breast and ovarian cancer
- Over 18,000 different authors have published on the BRCA genes
- The number of patients who have received BRCA testing is approaching one million
- Approximately 40,000 health care providers have ordered BRCA testing
- 95% of patients have access to BRAC*Analysis* testing through private, public or financial assistance programs
- Over 2,500 distinct insurance payers (companies) have paid for BRCA testing
- 80,000 individual group plans have paid for BRCA testing

There are also additional benefits of having a single entity exclusively providing particular test results. Such benefits include:

- Uniformity of testing results and procedures
- Increased volume of test cases for greatly enhanced interpretation of test results
- Ability and incentive to fund and pursue, at no cost to patient or family, family member testing of novel variants of uncertain significance ("VUS") results for subsequent classification
- Ability to identify subgroups of populations with testing anomalies

- Better ability to adopt new testing standards whether developed internally or by third party research
- Better ability to negotiate and obtain insurance reimbursement for testing. Myriad has private insurance coverage for BRAC*Analysis* for over 200 million covered lives. In addition, for those covered by public insurance, BRAC*Analysis* is reimbursed by Medicare and a majority of state Medicaid plans.
- Dedicated customer support groups to work with insurance companies to facilitate patient reimbursement. Myriad employs over 160 individuals who interact daily with patients and insurance companies to help patients work through the complexities of insurance coverage.
- Funding of financial assistance programs for the uninsured or underinsured. In the last four years Myriad has performed free testing for over 4,000 low-income or underinsured patients.
- Ability and incentive to undertake and provide patient and physician education. Myriad organizes hundreds of educational meetings for physicians to learn about hereditary breast and ovarian cancer.

Some may argue that patents are not necessary for the research and discovery effort, citing to the work of academic institutions. However, academic institutions do not have the organization, the infrastructure, the capital, or the mandate to commercialize products. Rather, such institutions rely on licensing their discoveries to commercial entities who will continue with the investment of capital and commercialization of products. Since the passage of the Bayh-Dole Act, there has been tremendous growth in the licensing of intellectual property for commercialization with remarkable success both in terms of revenue return to the

academic institutions as well as a development of new and innovative medical products, and in particular molecular diagnostic products.

Others may suggest that exclusive rights to genetic tests hinder research, restrict innovation, restrict patient access, result in higher pricing, and restrict access to confirmatory testing, amongst other allegations. In the case of BRCA diagnostic testing, this is patently false. In fact the opposite is true and was noted in a recent study published by the Duke Institute for Genome Sciences & Policy which found:

> It is, therefore, difficult to attribute reduced access to BRCA testing to patents. We cannot exclude the possibility that [Myriad's] investments in education about hereditary breast and ovarian cancer and testing have actually had the opposite effect of increasing access to testing. […]Prices for BRCA1 and 2 testing do not reflect an obvious price premium attributable to exclusive patent rights compared with colorectal cancer testing, and indeed, Myriad's per unit costs are somewhat lower for BRCA1/2 testing than testing for colorectal cancer susceptibility.[31]

In the area of personalized medicine, exclusive patents rights do not hinder research or innovation. On the contrary, in order to successfully commercialize a personalized medicine product, there must be medical society guidelines instructing health care practitioners to undertake testing as a standard of medical care. Society guidelines are based on research and peer reviewed publications; exclusive patent holders wanting to commercialize a product are incentivized to promote research and clinical testing of a product to yield such publications.

[31] Cook-Deegan *et al.*, *supra*, n.17.

Equally so, insurance reimbursement will only occur once the payer community is convinced of the medical necessity and positive pharmacoeconomics of testing. Once again, costly research and clinical trials are needed and will be encouraged and conducted by patent holders. In Myriad's case, we have collaborated with over 440 outside researchers and participated in more than 110 research programs and studies through outside researchers' clinical trials. Myriad provided research testing services at a fraction of the commercial testing price to researchers conducting research funded by the National Cancer Institute ("NCI") or other Institute under the National Institutes of Health ("NIH"). During this program, 178 scientists received the discounted research testing services and approximately 6,000 individuals received subsidized testing for *BRCA* mutations through the NIH to research the BRCA genes. This resulted in prolific research and publication concerning the BRCA genes.

By way of comparison, full sequence BRCA testing is offered exclusively by Myriad in the U.S., but by a number of different laboratories in Europe. Based on market research conducted by a leading consultant in the diagnostic market with over 200 European laboratories, it is clear that the current service provided in the United States has advantages inherent in this single-source model. There is wider availability to patients in the US, especially those that are unaffected, who can use test results to prevent cancer. There are faster turnaround times for results in the US due to the economy of scale of a single lab – 2 weeks versus 6 months in Europe. And, there is a significantly lower rate of uncertain test results in the US - 3% versus 20% in Europe. Additionally, we observe that pricing for full sequence

BRCA1/2 analysis in Europe is consistent with the pricing in the US, despite the fact that it is available from multiple laboratories in Europe.[32]

VI. STATUTORY TOPIC 4

The fourth study topic mandated by Section 27 of the AIA reads as follows: "The role that cost and insurance coverage have on access to and provision of genetic diagnostic tests."

Although genetic testing is costly, the information provided through the testing can provide substantial savings to both the individual patient and the overall health care system. With respect to our specific molecular diagnostic tests, Myriad has made substantial investments to educate the payer community on the positive pharmacoeconomics of predisposition testing. This has taken much time, effort, energy, and capital for us to assemble and train a workforce to compile the necessary pharmacoeconomic data and negotiate with payers for reimbursement of BRAC*Analysis* testing, and other molecular diagnostic tests. As a result, insurance companies almost universally cover molecular diagnostic testing. In addition, government health programs like Medicare also provide coverage of BRCA testing and other proven genetic tests. With payer reimbursement, genetic testing is affordable to the individual patient. For the vast majority of BRCA patients, the cost of testing and availability of insurance coverage do not create barriers to testing.

Myriad is committed to continuing our efforts to ensure broad access to testing. However, inherent aspects of the U.S. health care system can lead to gaps in access. For example, in order to ensure patients are able to access the test ordered by their physician, Myriad performs free testing for certain patients based

[32] Again reinforcing the findings of Cook-Deegan *et al.*, *supra*, n.17.

on financial and medical criteria, but *by law* we cannot directly offer free testing to an otherwise qualified patient who is a Medicare or Medicaid beneficiary.

There have been some allegations, overstated in the ACLU lawsuit against Myriad and even referenced in testimony at both the Alexandria and San Diego hearings, that Myriad has rejected or will not provide testing to certain individuals due to their insurance coverage. The specific allegation is that Myriad rejected the insurance coverage of one of the ACLU plaintiffs who resided in Massachusetts. However, the facts are that this individual was covered by Massachusetts Medicaid, and Myriad and this insurer had not yet entered into an agreement for coverage of BRAC*Analysis* testing. Hence, Myriad did not reject her insurance coverage; rather, it was not yet a covered benefit. When Myriad realized this, it sought to provide free testing to this individual under Myriad's patient financial assistance plan (well before the ACLU lawsuit was filed), but was precluded from doing so due to Medicare and Medicaid beneficiary laws. The good news is two-fold; first, the Plaintiff in question did get tested through free testing provided by Myriad to an unrelated non-profit organization, and second Massachusetts Medicaid now covers BRCA testing.

Hence, the allegations against Myriad were unfounded. Rather, the underlying cause of this individual's difficulty in getting tested was due to the application of general health care laws and the insurance coverage environment. The Statement of Dissent to the SACGHS Report also mentions this oft-overlooked reality, noting the need for the evaluation of:

> … relevant laws, regulations and policies, such as anti-kick-back, health care fraud statutes, and government reimbursement policies, that are overly burdensome or result in practical barriers on diagnostic companies who

would otherwise elect to offer tests at little or no cost based on financial need.

It is important to note, however, that payer acceptance of new medical treatments does not happen overnight. To the contrary, payers can be apprehensive in adopting new technologies without extensive education and supporting scientific evidence. In fact, in the mid to late 1990's, there was much apprehension and opposition to conducting genetic testing in general, and specifically BRCA testing. We refer the USPTO to a case study undertaken by the Stanford Graduate School of Business, Case BME-3, dated May 5, 2005, which documents and discusses the opposition to genetic testing and the difficulty in developing BRCA testing. Myriad has spent a great deal of time and resources to ensure payers and physicians are educated on the latest technologies and their benefits to patients and the overall health care system.

We believe everyone can benefit from a health care system that values getting the right treatment to the right patient at the right time. Therefore, payers must continue to support coverage and appropriate reimbursement of personalized medicine products like BRAC*Analysis*. The extensive resources Myriad commits to ensuring access to BRCA testing for patients is made possible through the promise of some exclusivity of testing rendered by patents in an effort to ensure a positive return on the large investment. Without a positive return, companies and venture capitalists will not make the investment, and the market will not develop or will be much delayed.

VII. CONCLUSION

In summary, Myriad believes that the medical care, access and affordability of genetic testing has been tremendously advanced to the benefit of all in the U.S.

as a result of the patenting and exclusive licensing of the BRCA genes. Myriad strongly supports the patent system as a means to bring new innovative medical treatments to patients while providing jobs, revenue and opportunities to the biotechnology sector in specific and the economy in general.

We also believe the USPTO must ensure the rights of the patent holder, and exclusive licensee where applicable, as well as the underlying purposes of the patent system are respected and preserved as detailed in its mission anchored in Article 1, Section 8, Clause 8 of the Constitution. To undermine this proven system would deprive patients and the medical community of new and innovative products which aim to bring the promise of personalized medicine to fruition. We encourage the USPTO to base its findings concerning genetic testing patents not on anecdotal stories or allegations, but on well structured, unbiased studies which Myriad believes will support the conclusion that the quality of patient care has been significantly advanced through the patent system, and that any changes thereto should be carefully measured, if any.