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The Laboratorian SM

Hereditary Breast and Ovarian Cancer:

Interpreting Genetic Data in the Post-Myriad BRCA World

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Regarding the title of this piece- Myriad, the company that originally offered BRCA and other inherited breast and ovarian cancer-related gene sequencing to the marketplace in 1996, has not locked its doors and shuttered its windows. However, the company's key patents on BRCA sequencing were invalidated by the United States Supreme Court in 2013. Since that time, at least a dozen competitors, including Medical Diagnostic Laboratories, have brought similar products to the marketplace. According to basic economics and common sense, competition is good for the product and the consumer. One should expect product quality or related service to advance while prices decrease. However, is this the case with hereditary breast and ovarian cancer testing? Here, I will discuss how Myriad's practices impact similar hereditary cancer-related gene sequencing products; in particular, the interpretation of genetic data and ultimately, patient care.

What did Myriad have that deserved patent protection? Why was it invalidated by the Supreme Court?

Myriad discovered the precise location and sequence of the BRCA1 and BRCA2 human genes, variants of which may substantially increase the risks of breast and ovarian cancer. The average American woman has a 12- to 13-percent risk of developing breast cancer, but for women with certain genetic variants, the risk can range between 50 and 80 percent for breast cancer and between 20 and 50 percent for ovarian cancer. Before Myriad's discovery of the BRCA1 and BRCA2 genes, scientists knew that heredity played a role in establishing a woman's risk of developing breast and ovarian cancer, but they did not know which genes were associated with those cancers. Therefore, Myriad obtained a number of patents based upon this discovery.

Myriad was not the only entity to offer BRCA testing after it discovered the BRCA1 and BRCA2 genes. The University of Pennsylvania's Genetic Diagnostic Laboratory (GDL) and others provided genetic testing services to women. Myriad sent letters to or filed patent infringement suits against them, resulting in agreements to stop the alleged infringing genetic testing. Some years later, medical patients, advocacy groups, and doctors filed a lawsuit seeking a declaration that Myriad's patents were invalid. This lawsuit circulated through District Court, Federal Circuit Court, and finally landed in the US Supreme Court (argued April 15, 2013 and decided June 13, 2013). The US Supreme Court held that "A naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated… Myriad's DNA claim falls within the law of nature exception." In other words, genes cannot be patented. Thus, Myriad lost its monopoly on BRCA testing and other labs began offering the tests at a fraction of Myriad's $4,000 price tag.

What did the "head start" provide Myriad?

Myriad may have lost their monopoly, but the years of being the sole company performing BRCA testing afforded them an advantage over competitors: all that data. During nearly two decades of BRCA testing, Myriad had data from more than 2 million patients in a proprietary, unpublicized database. Simplified, the Myriad database contains information on which BRCA variants cause cancer and which are benign or don't affect a gene's function. This data is critical for patient risk and disease management. The identification of a genetic variant holds little consequence for the patient unless it is coupled with this interpretation. Myriad probably does have an excellent database. In fact, the company uses it and their experience as selling points in the current competitive marketplace. However, science is a collaborative effort; Myriad's competitors and the scientific community at large were quickly amassing piles of their own data, and they decided to share them.

How do competitors manage without Myriad's proprietary data?

Competitors, which entered the BRCA testing market in 2013 or later, have much smaller databases and rely in part on public ones. The public databases get their information in different ways, but in general it comes from published studies, genetic testing labs, and committees of medical experts. As of December 8, 2016, ClinVar, a commonly used public database, had 395,525 records submitted and 625 total submitters, none of which are from Myriad. Myriad would like to consider these types of public databases "inferior". Granted, differences in interpretation within a single database as well as among the public databases exists; however, it does not necessarily indicate that interpretations of variants are wrong or that these databases are inferior. As they are public and routinely studied, many discrepancies may be addressed, and even resolved, by the scientific and medical community. But there is no easy recourse to

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examine Myriad's proprietary database; therefore, no way to evaluate their interpretations in an unbiased or cooperative manner. That is, unless you kindly ask Myriad's customers to share their results.

Ire over Myriad's refusal to publicize its database led some physicians, breast cancer patients, and scientists to devise a creative solution. In 2012, the University of California, San Francisco and others launched the Sharing Clinical Reports Project to gather BRCA reports that Myriad had sent to health care providers. This led to the Free the Data consortium, which encouraged patients to share their results from Myriad. Those results offered insight into the Myriad database. The effort has collected over 2,000 patients' BRCA results. The data has allowed Myriad's competitors to compare their variant interpretations with Myriad. Several companies reported agreement between 98.7 percent and 99.5 percent of variants. Most of the disagreements (27 found in one report) are in variants found in as few as 1 in 2,000 patients.

In 2015, scientists and physicians launched the BRCA Exchange, an online database of BRCA variants from multiple sources. As of now, it has over 8,000 BRCA1 variants and 9,000 BRCA2 variants. An expert panel, including representatives from competitors Ambry, GeneDx, and Color Genomics reviews the evidence and resolves differences in interpretation. Still, Myriad does not participate. Given the pace at which gene variants and their interpretation are being added to the BRCA Exchange, it may not be long before there is as much information as contained in Myriad's database.

All in all, it appears that the advantage that BRCA testing pioneer Myriad gets from its database of gene variants may be coming to an end. The ever growing, large-scale collaborative efforts to interpret genetic and clinical data will not only lead to advances in patient care, but also unexpected challenges and discoveries. These are the advances we may now expect in this new "competitive" marketplace.

References

- BRCA Exchange. http://brcaexchange.org. Accessed 12/9/2016
- ClinVar Submission Statistics. https://www.ncbi.nlm.nih.gov/clinvar/submitters. Accessed 12/9/2016.
- Free The Data. http://www.free-the-data.org. Accessed 12/8/2016.
- Association for Molecular Pathology *et al*. *v*. Myriad Genetics, Inc., *et al*. Opinion of Supreme Court of the United States. No. 12-398. Argued April 15, 2013 – Decided June 13, 2013.
- Sharing Clinical Reports Project. https://www.clinicalgenome.org/data-sharing/sharing-clinical-reports-project-scrp. Accessed 12/6/2016.
- Surveillance, Epidemiology, and End Results Program. Cancer Fact Sheets, Breast. http://seercancer.gov. Accessed 12/5/2016.

New Tests Released in 2016

Available on ***OneSwab***® & ThinPrep®:

178	*Ureaplasma parvum* by Real-Time PCR (Reflex to fluoroquinolone resistance by Pyrosequencing)
320	*Ureaplasma urealyticum* by Real-Time PCR (Reflex to fluoroquinolone resistance by Pyrosequencing)

Available on whole blood (yellow top ACD solution A):

178	*Ureaplasma parvum* by Real-Time PCR (Reflex to fluoroquinolone resistance by Pyrosequencing)
320	*Ureaplasma urealyticum* by Real-Time PCR (Reflex to fluoroquinolone resistance by Pyrosequencing)
1235	Breast Cancer High Risk Extended Panel Plus: 14 genes (*BRCA1, BRCA2, CDH1, PTEN, TP53, STK11, ATM, CHEK2, PALB2, BARD1, BRIP1, MUTYH, RAD51C, RAD51D*) by Gene Sequencing with BRCA1/2 Deletion/Duplication Analysis
1221	B*RCA1/2*: Comprehensive *BRCA* Analysis by Gene Sequencing with Deletion/Duplication Analysis
1240	Breast Cancer High Risk Extended Panel (No *BRCA1, BRCA2)*: 12 genes (*CDH1, PTEN, TP53, STK11, ATM, CHEK2, PALB2, BARD1, BRIP1, MUTYH, RAD51C, RAD51D*) by Gene Sequencing
1222	*BRCA1/2*: Ashkenazi Jewish 3-site Mutation Analysis
1223	*BRCA1/2*: Ashkenazi Jewish 3-site Mutation Analysis (Reflex to Comprehensive BRCA Analysis) (* If the Ashkenazi Jewish 3-site Mutation Analysis is negative, reflex to 1221.)
1224	Gene Specific Site Analysis:
1236	*BRCA1/2*: Ashkenazi Jewish 3-site Mutation Analysis (Reflex to Breast Cancer High Risk Extended Panel Plus) (* If the Ashkenazi Jewish 3-site Mutation Analysis is negative, reflex to 1235.)

Quality Assurance Q&A

Question:

I would like to order BRCAcare™ testing for my patients. What type of specimens do you accept?

Answer:

Acceptable specimens include mouthwash and whole blood yellow top tube (ACD solution A). Both of which are stable for transport at room temperature. In the State of New York, only mouthwash is acceptable.

If you have a question you would like addressed in future issues, please email your question(s) to QAQ&A@mdlab.com.

Friede K, Li J, Voora D. 2016. Use of Pharmacogenetic Information in the Treatment of Cardiovascular Disease. *Clin Chem* (62)12.

BACKGROUND:
In 1964, Robert A. O'Reilly's research group identified members of a family who required remarkably high warfarin doses (up to 145 mg/day, 20 times the average dose) to achieve appropriate anticoagulation. Since this time, pharmacogenetics has become a mainstay of cardiovascular science, and genetic variants have been implicated in several fundamental classes of medications used in cardiovascular medicine.

CONTENT:
In this review, we discuss genetic variants that affect drug response to 3 classes of cardiovascular drugs: statins, platelet P2Y12 inhibitors, and anticoagulants. These genetic variations have pharmacodynamic and pharmacokinetic effects and have been shown to explain differences in drug response such as lipid lowering, prevention of cardiovascular disease, and prevention of stroke, as well as incidence of adverse events such as musculoskeletal side effects and bleeding. Several groups have begun to implement pharmacogenetics testing as part of routine clinical care with the goal of improving health outcomes. Such strategies identify both patients at increased risk of adverse outcomes and alternative strategies to mitigate this risk as well as patients with "normal" genotypes, who, armed with this information, may have increased confidence and adherence to prescribed medications. While much is known about the genetic variants that underlie these effects, translation of this knowledge into clinical practice has been hampered by difficulty in implementing cost-effective, point-of-care tools to improve physician decision-making as well as a lack of data, as of yet, demonstrating the efficacy of using genetic information to improve health.

SUMMARY:
Many genetic variants that affect individual responses to drugs used in cardiovascular disease prevention and treatment have been described. Further study of these variants is needed before successful implementation into clinical practice.

Bayraktar S, Arun B. 2016. BRCA mutation genetic testing implications in the United States. *Breast* **5**(31):224-232.

Abstract
BRCA mutation carriers have a very high risk of breast and ovarian cancer by age 70, in the ranges 47%-66% and 40%-57%, respectively. Additionally, women with BRCA mutation-associated breast cancer also have an elevated risk of other or secondary malignancies. Fortunately, the breast and ovarian cancer outcome for BRCA1/2 mutation carriers is at least as good as for non-carriers with chemoprevention, prophylactic surgeries and appropriate use of therapies. Therefore, identification of those who might have a mutation is important so that genetic counseling, testing, screening and prevention strategies can be applied in a timely manner. This article reviews the impact of genetic testing in general, timing of genetic testing after diagnosis and prior knowledge of mutation status in BRCA carriers with newly diagnosed breast cancer. Additionally, risk-reducing surgeries including the prophylactic contralateral mastectomy, and bilateral salpingo-oophorectomy and the sensitivity of BRCA-defective breast cancer cell lines to differential chemotherapeutic agents will be discussed.

Recent Publications

Institute for Metabolic Disorders:

1. **Villasmil ML, Francisco J, Gallo-Ebert C, Donigan M, Liu HY, Brower M, and Nickels JT Jr.** 2016. Ceramide signals for initiation of yeast mating-specific cell cycle arrest. *Cell Cycle* **15(**3):441-54. PMID: 26726837

2. **McCourt P, Liu HY, Parker JE, Gallo-Ebert C, Donigan M, Bata A, Giordano C, Kelly SL, Nickels JT Jr.** 2016. Proper Sterol Distribution Is Required for *Candida albicans* Hyphal Formation and Virulence. *G3 (Bethesda)* 2016 Aug 31. *[Epub ahead of print]* PMID:27587298

Femeris Women's Health Research Center:

1. **Schuyler JA, Mordechai E, Adelson ME, Sobel JD, Gygax SE, and Hilbert DW.** 2016. Identification of intrinsically metronidazole-resistant clades of *Gardnerella vaginalis.* *Diagn Microbiol Infect Dis* **84**(1):1-3. PMID: 26514076

2. **Hilbert DW, Smith WL, Chadwick SG, Toner G, Mordechai E, Adelson ME, Sobel JD, and Gygax SE.** 2016. Development and validation of a highly accurate quantitative real-time PCR assay for the diagnosis of bacterial vaginosis. *J Clin Microbiol* **54**(4):1017-24. Erratum in: *J Clin Microbiol* 2016 Jul; **54**(7):1930.

3. **Hilbert DW, Smith WL, Paulish-Miller TE, Chadwick SG, Toner G, Mordechai E, Adelson ME, Sobel JD, and Gygax SE.** 2016. Utilization of molecular methods to identify prognostic markers for recurrent bacterial vaginosis. *Diagn Microbiol Infect Dis* **86**(2):231-42. PMID:27431434

4. **Schlabritz-Loutsevitch N, Gygax SE, Dick E Jr, Smith WL, Snider C, Hubbard G, Ventolini G**. 2016. Vaginal Dysbiosis from an Evolutionary Perspective. *Sci Rep* 2016 May 26; **6**:26817. PMID: 27226349

Oncoveda Cancer Research Center:

1. **Pusey M, Bail S, Buiakova O, Nestor M, Yang JJ, Rice LM.** 2016. Inhibition of protein methylesterase 1 decreased cancerous phenotypes in endometrial adenocarcinoma cell lines and xenograft tumor models. *Tumour Biol* [*Epub ahead of* print] PMID:27048286

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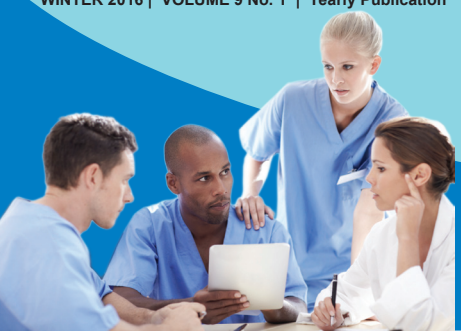

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