ACMG
American College of Medical Genetics and Genomics
Translating Genes Into Health®

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To the Editor:

As the Board of the American College of Medical Genetics and Genomics (ACMG), a professional organization representing clinical geneticists, clinical laboratory geneticists, and genetic counselors, we read with compassion and concern, Amy Dockser Marcus' December 20th article entitled "A Genetic Test Led Seven Women in One Family to Have Major Surgery. Then the Odds Changed". Many families like the Mathes family face the uncertainty that can sometimes accompany genetic testing. The only way to reduce that uncertainty and, hopefully, someday to eradicate it, is for genetic testing laboratories to share their variant classification information. This is readily done through a public database established by the National Institutes of Health. Sharing of variant classifications allows all patients to benefit from the most up to date evidence when they make the difficult medical decisions associated with genetic testing results.

Myriad Genetics is an outlier among large testing laboratories in that it has refused to share its variant classification data. As a patient-centered organization, the ACMG calls on Myriad Genetics to end its practice of maintaining a proprietary classification database and to join the international community of genetic testing laboratories who share classifications in the best interests of all patients.

Identifying and addressing genetic risks to health is a complicated task. Humans have 20,000 genes and these genes are spelled out in millions of letters of DNA code using a four-letter alphabet. The *BRCA2* gene in question in the Mathes family has over 11,000 letters of code. There are tens of thousands of possible variants. Some of us have no variation in the 11,000 plus letters when compared to the normal reference. When a laboratory identifies a variant, it is classified into one of five groups: benign, likely benign, variant of uncertain significance, likely pathogenic or pathogenic.

The process of determining whether a variant is disease causing or "pathogenic" is based on established criteria and evolving evidence. The fulfillment of the criteria rely largely on what is reported in the medical literature and in public databases. For some variants in *BRCA2* the evidence is overwhelming due to the number of cases described, however for others the evidence is less strong because relatively few cases have been described. For any given variant, the conclusions arising from the evidence review improves with increased data. It is for this reason that the sharing of clinical genomic data among clinical laboratories is critical.

The DNA variant in *BRCA2* that is in question for the Mathes family was not only found by Myriad genetics as described in the *WSJ* article. It also was found in testing done by Ambry Genetics, Color, GeneDx, Laboratory Corporation of America, Mendelics, and Quest

Diagnostics. We know that this international group of laboratories have found this variant because they have shared their variant classifications and supporting evidence via the publicly available ClinVar database www.ncbi.nlm.nih.gov/clinvar/. Collectively, they interpreted the variant as "likely pathogenic," meaning that they believe there is a greater than 90% chance, based on the evidence available to them, that this variant is capable of causing disease.

In 2017, the ACMG published a position statement on "Laboratory and clinical genomic data sharing is crucial to improving genetic health care". We strongly endorse sharing of variant interpretation level data in the public ClinVar database for three reasons (1) it improves patient care, (2) it is done in a manner that presents little or no risk to individual privacy, and (3) when we explain the risk:benefit ratio to our patients they are in favor of such sharing in order to benefit themselves and others.

The December 20th *WSJ* article reveals that, at some point prior to May 2019, Myriad had information that was used to re-classify Ms. Mathes' *BRCA2* variant. However, Myriad chose not to share this information through the ClinVar database. Myriad's chief medical officer acknowledged in a 2016 interview that Myriad's proprietary database can be a selling point for its tests, and "we don't want to cut ourselves off at the knees." https://www.statnews.com/2016/11/29/brca-cancer-myriad-genetic-tests/ If Myriad maintains this position, going forward, patients around the world could be placed in a similar position as the Mathes family was in 2016. To prevent this from happening, it is incumbent that all laboratories share their information for the public good.

The genetic testing market is a competitive business space. In this market, ACMG encourages innovation as well as competition that improves patient care and access. However, we believe no company should put their interest above best patient care. To prevent patient harm and ensure all patients benefit equally from accurate and reliable genetics and genomics information, ACMG calls on Myriad and all laboratories to share their variant classification data.

Board of Directors, American College of Medical Genetics and Genomics