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May 17, 2016

U.S. Department of Health and Human Services
Office for Civil Rights
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Washington, DC 20201

To Whom It May Concern:

I submit this letter in support of the HIPAA complaint filed by patients regarding patient access to genetic information.

I am the Director of the Laboratory for Molecular Medicine at Partners Healthcare Personalized Medicine and Associate Professor of Pathology at Harvard Medical School and Brigham & Women's Hospital. The CLIA accredited lab that I run offers a range of genetic sequencing services for both direct clinical use and to support research programs. I also am involved in a number of efforts aimed at public pooling of genetic data in order to facilitate research and clinical understanding of genetic variants, including ClinGen, the Clinical Genome Resource Program, funded by the National Institutes of Health. This involves laboratories submitting their variant interpretations to ClinVar, a free and open variant database allowing comparison of variant interpretations to identify and resolve differences, enabling improved care of patients. I am also involved in leading the Matchmaker Exchange program which facilitates sharing rare disease patient data to help identify new causes of disease.

I support the right of patients to access their genomic data. In our laboratory, we provide patients with access to their genetic information upon request. For patients who receive panel testing, where we are focusing on certain genes connected with particular diseases, we include all likely benign variants on the test report in case these variants are later reclassified as disease associated, and we also allow patients access upon request to a list of all of the genetic variants we identified, including benign variants. For those who receive whole genome sequencing, we typically provide the entire genetic sequence upon request.

While HIPAA makes clear that patients can access their data for any reason, there are at least three compelling, well-founded reasons why patients may want access. First, patients may want to confirm the interpretation of their genetic testing results. Second, patients may wish to retain a complete list of their genetic variants so they can monitor scientific findings related to those variants over time. Third, patients may want to share their data to advance research.

The process of genetic testing involves interrogating particular segments of a patient's DNA (or the entire sequence in the case of whole genome sequencing) to determine the sequence of nucleotides (A, C, T, and G) that make up the patient's genetic code. That sequence is then compared to a reference sequence, and where a patient's sequence differs, a genetic variant is identified. Each variant is then clinically interpreted. While there have been major advancements in deciphering the genetic bases of human disease, for the majority of the more

than 80 million genetic variants that have been uncovered in the human genome, we have no clear understanding of their role in human health and disease.

Every patient has numerous genetic variants, including in the BRCA1 and BRCA2 genes. Many of these variants are thought to be benign, or not connected to disease or susceptibility to disease, and some variants have been correlated with an increased risk of disease by scientists, but many others are of uncertain clinical significance.

The determination by a laboratory that a patient has particular variants but all are benign is typically reported as a "negative" test result, with no information provided to the patient that variants were identified and characterized as benign. In the context of testing the BRCA genes, this result generally leads a patient and the physician to conclude that there is no elevated risk for cancer and thus they need not pursue additional surveillance or prophylactic surgery.

Until recently there have been no standards for how genetic variants should be interpreted, and laboratories have developed their own systems and judgments. The American College of Medical Genetics and Genomics and the Association for Molecular Pathology recently published a set of guidelines for classifying variants as "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign."[1] However, application of the guidelines is not mandatory and even when applying such standards, labs still arrive at different conclusions given the subjectivity of applying the rules.[2] Laboratories also differ in the information they provide to patients in reporting their genetic test results. Some may choose to report only those variants that they believe are pathogenic, likely pathogenic, or of uncertain significance, while others may also report variants that are likely benign.

Laboratories can and do differ in interpreting variants, including variants thought to be benign or likely benign. As a result, our research has shown that in some cases, patients are receiving inconsistent and sometimes inaccurate information that can lead to patient harm. In a 2015 publication, we reported that 17% of variants interpreted by more than one laboratory were interpreted differently.[3] Patients therefore may want access to their genetic information in order to confirm a laboratory's clinical interpretation of their cancer risk.

Furthermore, variants are regularly re-classified. Sometimes variants initially classified as likely benign or benign can later be found to be risk factors for disease once data is combined across larger cohorts. Such variants have already been shown to be associated with increased risk for breast cancer.[4] Patients may wish to retain a copy of their complete list of variant calls so that they can monitor developments in scientific knowledge that may impact their risk.

Finally, patients may want access to their data so they can share it with the research community. Scientists rely on publicly available databases to inform how they interpret a genetic variant given that only a paucity of variant data is available through publications. A key factor in the ability of scientists to determine the clinical significance of a variant is whether they

[1] Richards et al., *Standards and guidelines for the interpretation of sequence variants*, Genetics in Medicine (Mar. 5, 2015).
[2] Amendola et al., *Performance of ACMG-AMP Variant Interpretation Guidelines among Nine Laboratories in the Clinical Sequencing Exploratory Research Consortium*, The Am. J. of Human Genetics (2016), http://dx.dol.org/10.1016/j.ahjg.2016.03.024.
[3] Heidi Rehm et al., *ClinGen – the Clinical Genome Resource* – N. Engl. J. Med. (May 27, 2015).
[4] Walsh et al., *Genomic Biomarkers for Breast Cancer Risk*, Adv. Exp. Med. Biol. 2016; 882:1-32. doi: 10.1007/978-3-319-22909-6_1.

can examine a large amount of data about that variant – including how often it has been identified in patients and whether they have experienced particular diseases, like cancer. Our lack of consistent, clear and clinically relevant annotation of human genetic variation is due, in part, to the so-called silo effect, in which various commercial and academic entities maintain isolated, sometimes proprietary, databases of variant interpretations. This prevents the sharing of critical knowledge that could benefit patients, families, health care providers, diagnostic laboratories, and payers.[5] It has been shown that comparing data to enable consensus efforts is the best approach to arrive at consistent variant interpretation.[6] Recognizing this issue, some healthcare providers have begun to only order services from laboratories who share their data and Aetna, a major health insurer, began requiring labs to submit to ClinVar if they wanted reimbursement for their BRCA tests.[7]

To the best of my knowledge, Myriad does not contribute genetic variant data to ClinVar and stopped contributing data about the BRCA1 and BRCA2 genes to the Breast Cancer Information Core more than a decade ago. It thus retains data about the BRCA1 and BRCA2 genetic variants it identifies in patients in its exclusive, proprietary database, even while acknowledging reliance on public databases in its own work.[8] In my opinion, Myriad's data exclusivity impoverishes the scientific and clinical understandings of the genes.

Myriad's website includes its "Policy on Genetic Information."[9] The Policy states: "Myriad's laboratory processes including variant classification and variant databases are subject to regulatory oversight from either CLIA (Clinical Laboratory Improvement Amendments) or the U.S. Food and Drug Administration. Consistent with this regulatory oversight, we are not allowed to release our variant databases because they may only be used to interpret clinical test results for patients tested in our laboratories." In my opinion and in consultation with FDA staff, this statement is incorrect and seriously misleading. Laboratories around the world, including my own, regularly contribute data about genetic variants to efforts like ClinVar and many others. Neither CLIA nor the FDA prohibits the release of variant data. Indeed, the federal government encourages and incentivizes genomic data-sharing.

Thank you for your consideration.

Sincerely,

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[5] Rehm et al., *supra* note 3.
[6] Amendola et al., *supra* note 2.
[7] Turna Ray, *Genomic variant data sharing gains support; Collaboration seen as key to interpretation challenge*, GenomeWeb, May 2, 2016.
[8] *See* J.M. Eggington et al., *A comprehensive laboratory-based program for classification of variants of uncertain significance in hereditary cancer genes*, Clinical Genetics 4 (Nov. 5, 2013) (discussing reliance on publicly available databases containing whole-exome sequencing data).
[9] https://www.myriad.com/myriad-cares-2/policy-on-genetic-information/.