ClinVar Is a Critical Resource to Advance Variant Interpretation

The recent article by Gradishar et al. [1] compared *BRCA1* and *BRCA2* variant interpretations between ClinVar and Myriad, finding 27% of variants at least partially discordant, arguing that ClinVar and other public databases may add "undue ambiguity and error in management decisions." The conclusions drawn from this study are flawed, based on the following arguments:

1. The bulk of the analysis in the Gradishar et al. study was based on ClinVar data from February 2015; however, concordance has greatly increased since then. As of May 2017, only 856/12,809 (6.7%) of *BRCA1/2* variants are flagged as discordant. Additionally, in assessing discordance, the authors neglected to differentiate between ClinVar star status and interpretation differences that do or do not affect medical management. Limiting analysis to "criteria provided, single submitter," consistent with clinical practice, lowers *BRCA1/2* conflict counts to 3.9% of *BRCA1/2* variants, and only 0.4% of variants have differences that would affect patient management.
2. The Gradishar et al. study assumes the Myriad interpretations are correct. However, there is no scientific proof for these interpretations, and the authors have not shared their data for peer review, a practice unacceptable by current scientific review standards.
3. The authors conclude that, for clinicians, "it is unclear whether any additional benefit is gleaned over receipt of the laboratory test result alone." Clearly, if there are conflicts between laboratories today, and if knowledge changes over time, then a physician should not blindly trust a single laboratory report. ClinVar is a means to obtain second opinions and variant interpretation updates with little cost to the health care system. Obtaining second opinions is routinely considered best practice in medicine, yet many patients do not have the resources or time to obtain these second opinions or updates, and experts are often inaccessible. ClinVar solves this problem if laboratories share their data.
4. The authors point out several variants in conflict in ClinVar and provide alternate interpretations of the data. Instead of highlighting the problems with ClinVar, these variants provide excellent examples in which sharing knowledge allows for more community scrutiny of these variants, improving clinical practice. As an additional example, the Partners Healthcare Laboratory for Molecular Medicine (LMM) has been well-recognized as a leader in the field of cardiomyopathy testing, having launched the first clinical test in 2003 and cornering the market for several years. Instead of hoarding data and trying to maintain full market share, LMM released its data to the community. The laboratory is now routinely contacted by clinicians observing variants LMM deposited in ClinVar and sharing their own patient data, and this exchange has continually helped clarify the clinical significance of variants. It would be naïve to think that LMM, operating in a silo without this exchange, would be better.

In summary, we are deeply concerned that the misrepresentation of ClinVar and of how laboratories and clinicians use the database is detrimental to encouraging community data sharing, a critical step in providing the safest and most informed use of genomic data in the care of patients.

Heidi L. Rehm

Steven M. Harrison

Partners Healthcare and Harvard Medical School, Boston, Massachusetts, USA

Christa L. Martin

Geisinger Health System, Danville, Pennsylvania, USA

Disclosures

The authors indicated no financial relationships.

Reference

1. Gradishar W, Johnson K, Brown K et al. Clinical variant classification: A comparison of public databases and a commercial testing laboratory. ***The Oncologist*** 2017;22:797–803.

http://dx.doi.org/10.1634/theoncologist.2017-0246