Medical News & Perspectives

Quick Uptakes
Taking the Uncertainty Out of Interpreting *BRCA* Variants

Rebecca Voelker, MSJ

Interpreting genetic variants detected in *BRCA1* and *BRCA2* tests can be challenging. To help demystify the process, an international collaboration has developed a resource that may help guide clinical decision-making. Details of their work appeared recently in PLOS Genetics.

The Problem
Testing for *BRCA1* and *BRCA2* mutations identifies both benign and pathogenic genetic variants. But information about specific variants, particularly those of uncertain clinical significance (VUS), often isn't systematically curated, expertly reviewed, or easily searchable. In addition, different laboratories sometimes interpret test results differently.

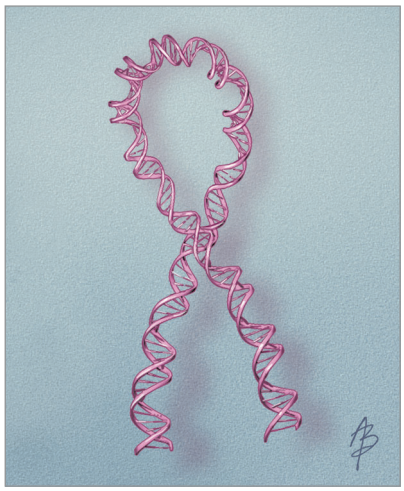
Downstream Risk
Some patients whose variants don't have a clear clinical meaning might seek or receive unnecessary care.

Statistically Speaking
About 3% of *BRCA1* and *BRCA2* findings on genetic tests are VUS. An estimated 15% to 20% of them are likely to be disease causing. As more people undergo genetic testing, clinicians will continue to see VUS.

Strategic Move
The Global Alliance for Genomics and Health in 2014 decided that "big data" could shine a spotlight on VUS in *BRCA1* and *BRCA2* genes. Plans emerged to launch an international effort aimed at creating a 1-stop shop to share information about *BRCA1* and *BRCA2* variants.

The Solution
Instead of wading through many databases with information that sometimes hasn't been properly vetted, the BRCA Exchange was created as a central repository for expertly reviewed genetic variation data. It's a web portal containing information from clinicians, clinical laboratories, and researchers around the world as well as existing clinical databases, including:

- ClinVar, a publicly available archive of genetic variants and their association with human phenotypes.
- Breast Cancer Information Core, an open access breast cancer mutation database.
- Leiden Open Variation Database—an open source database of gene variants.



Currently, the BRCA Exchange includes more than 20 000 unique *BRCA1* and *BRCA2* variants. The international Evidence-based Network for the Interpretation of Germline Mutant Alleles consortium provides expert classification of more than 6100 of those variants. So far, 3700 are classified as pathogenic.

Clinically Speaking
The BRCA Exchange is easy to use. "This is a website that you can go to, put in the variant, and it will give you the classification," said Susan Domchek, MD, a coauthor of the *PLOS Genetics* paper and director of the Basser Center for BRCA at Penn Medicine's Abramson Cancer Center in Philadelphia. "Anything that comes through as a variant of uncertain clinical significance in a commercial lab or things that are splice site or missense [mutations] are particularly valuable to have a second look at" in the BRCA Exchange.

Depending on the classification, clinicians and patients essentially have 3 options:

- A preventive approach such as breast or ovary removal for patients with a pathogenic variant.
- Targeted therapies for patients with a cancer diagnosis associated with a pathogenic variant.
- Periodically reappraising patients with variants of uncertain clinical significance.

"If the finding is a variant of unknown significance, we do not make management changes based on that classification," Domchek said. "We recommend that people with variants of unknown significance check in with us yearly so we can check all the data sources to see if anything has changed."

Welcome to the Global Village
When experts classify a variant, they consider not only its biological consequences, but also its prevalence in the general population and the phenotypic characteristics of any disease associated with it.

"These things are really important, especially in underrepresented minorities who are tested less and have a different spectrum of what is 'normal' in genetics," Domchek said. Clinicians have to be careful not to assume that these patients' VUS are pathogenic just because they're not seen in the general population.

That's why having an expansive international database with information from people of varying ethnic backgrounds from around the world is valuable. "The more times the variant is seen, the more precise the classification can be because you'll have personal and family history to guide you."

The Upshot
The BRCA Exchange may show that this type of data sharing—collaboration among

hundreds of organizations worldwide to determine the most efficient ways to make expertly reviewed information available—is feasible for other cancer-related genes and genes linked with other diseases.

With more widespread testing for genetic diseases on the horizon, Domchek said, "The more databases that we have that make it easy for individuals who may not live and breathe specific genetic changes…the better."

Yes, There's an App

It's free and is available for Android and Apple devices on Google Play and the App Store. ■

Note: Source references are available through embedded hyperlinks in the article text online.