Heritable genetic changes in the open

To correctly interpret human genetic variation in hereditary disorders, researchers and clinicians should populate databases that distribute aggregated information on the clinical significance of these variants.

Closely linked to the recent Supreme Court decision (docket 12-398) limiting the scope of patenting human genes, discussion has been growing about whether anonymized data collected by genetic testing laboratories should be freely available. The perceived unwillingness by some companies, who often are the sole provider of a particular test, to share such anonymized data on genetic variants has drawn sharp criticism from researchers and clinicians.

Myriad Genetics provides a good illustration for how big the difference between what is known by a company and what is available to the community can be. Until the court decision, the company held the monopoly on testing for hereditary mutations in the DNA repair proteins BRCA1 and BRCA2; some of these mutations confer a high risk for breast and ovarian cancer. With data from an estimated 1 million tested patients, Myriad's database allows high-accuracy classification of a patient's variants as one of four classes indicating the degree of pathogenicity. Only 3% of the variants Myriad encounters in the United States fall into a fifth class, that of variants of unknown significance (VUSs).

In contrast, with freely accessible databases, an average of 15% of BRCA1 and BRCA2 variants cannot be classified and remain VUSs, says Alvaro Monteiro, who is part of the Evidence-based Network for the Interpretation of Germline Mutant Alleles (ENIGMA) consortium focused on classifying BRCA mutations.

This puts researchers outside of Myriad, as well as clinicians, at a considerable disadvantage with respect to fully understanding the impact that changes in these genes can have.

Myriad's and other companies' hands may be tied when it comes to data sharing. According to a company spokesperson, Myriad is subject to oversight from the Clinical Laboratory Improvement Amendments and the US Food and Drug Administration. "Consistent with these regulations, we are not allowed to distribute our variant databases, as they may only be used to interpret clinical test results for patients tested in our laboratories." The company does, however, collaborate with researchers, given their appropriate institutional approval, to help classify VUSs in the context of a specific study and allows the results to be published.

This is a laudable, if small, step that may narrow the knowledge gap, but scientists want to bring information on all variants into the public domain on a much larger scale and are organizing efforts to that end. These efforts will stand or fall depending on community support.

Robert Nussbaum from the University of California, San Francisco, started a grassroots effort, the Sharing Clinical Reports Project (SCRP), appealing to patients and clinicians to share data on BRCA testing in appropriately anonymized form. The aggregated data are submitted to open databases such as the Breast Cancer Information Core (BIC) or ClinVar. SCRP is ready to submit its first 1,885 variants, including 351 that are new to BIC, according to Lawrence Brody, who founded BIC in 1995. These numbers show that the project resonates with people and is gaining traction.

ClinVar strives to be the most comprehensive of such databases. Founded in 2012 and hosted by the US National Center for Biotechnology Information, it aims to collect information on variation in any gene that affects human health, together with phenotypic information for such variants. It currently hosts around 38,000 variants (in about 3,000 genes) from about 90 different submitters, including genetic-testing laboratories from industry and academia.

ClinVar does not provide recommendations for medical diagnosis to patients or physicians. It is meant to be a resource for scientists, clinicians and genetic counselors who want to investigate a particular variant and its clinical implications in more detail.

Hopefully community support to expand the number of genes that ClinVar covers will increase. To ensure high data quality, ClinVar will need independent confirmatory submissions on each gene variant. More detailed phenotypic description of the conditions associated with each variant and the likely pathogenicity, where appropriate, would further enhance value.

It is hard to forecast whether genetic testing will increase in the wake of the Supreme Court decision. Lawsuits filed by Myriad Genetics and other plaintiffs against Ambry Genetics and Gene by Gene on 9 and 10 July, respectively, indicate looming legal battles. Regardless, efforts such as SCRP and ClinVar need support to ensure that genetic information is shared in appropriate forms to benefit not only individual patients but the research community at large.