Expert Article

Variant Interpretation Then and Now

Moving toward rigorous, consistent workflows

By Dan Richards

Variant interpretation has come a long way since the days when single-gene or even single-variant tests represented the cutting-edge in clinical labs. With the explosion of next-generation sequencing (NGS) and other multiplex-friendly technologies, variant analysts who could once easily perform manual review of every mutation, now face an onslaught of data.

That transformation made it necessary to find alternatives to the completely manual process of interpreting variants. Today, many clinical labs have established industrial-scale pipelines requiring advanced analytic and interpretation tools to streamline the reporting of results from hereditary disease testing.

One of the biggest changes for these labs has been expanding test menus and variants interpreted well beyond the disease-related expertise of clinical geneticists on the team. As many readers will remember, most labs used to specialize in one area of hereditary testing — say, cardiac disorders or diseases associated with hearing loss. The advent of NGS testing and subsequent adoption of exome or even whole-genome sequencing to diagnose disease led to a situation where no individual analyst could possibly be an expert on every variant encountered. Labs have risen to the challenge, using creative and innovative techniques that allow them to conduct variant interpretation even without having dedicated experts in every disease area.

Here, I'd like to explore several approaches that clinical labs can take to improve the standardization and reproducibility of their variant interpretation pipelines.

Follow ACMG guidelines

When it became clear that high-throughput variant interpretation had something of the Wild West feel to it, the American College of Medical Genetics and Genomics (ACMG) took the opportunity to conceive and release guidelines that have been instrumental in helping the clinical lab community interpret NGS results more consistently. The guidelines include about 30 criteria for how a variant should be assessed — such as whether it's observed in the general population or whether it is found in combination with other variants implicated in a particular disease. Evaluating so many points for each mutation is a lotof work, so a byproduct of the ACMG guidelines has been a noticeable increase in the number of software tools that can help variant scientists comply with them in an efficient manner.

Some of these tools also display the strength and applicability of known evidence related to each variant and the ACMG criteria, which can significantly reduce turnaround time for reporting variants. While most labs have already adopted these guidelines, we are seeing plenty of new labs entering this space, and not all of them are aware of community best practices.

Get to know your variants

One of the most useful pieces of information about a variant is whether it's been seen before. Variant databases such as gnomAD and HGMD are great places to start because they can provide that foundation-level information. This is especially important as the number of new variants detected increases, even among genes that are often thought

to be fully characterized such as BRCA1 and BRCA2. As more people undergo testing, the number of novel variants detected will continue to rise.

Establish the context

Once you know whether a variant has been reported before, the next step is determining all the known information about it and putting it into a clinical context. Using ClinVar, gnomAD, or the Allele Frequency Community can help determine the frequency of a particular variant in the general population. It's also imperative to gather all references to the variant in the scientific and clinical literature.

That's a time-consuming and tedious task when done manually, but clinical decision support tools and internal knowledge bases can make faster work of it so long as they are regularly updated with the latest information. For example, tools powered by manual curation can cull the most important data from a publication — how many affected individuals harbored the variant, whether the variant segregated with disease across family members, and so on — to give variant scientists an at-a-glance summary of relevant metrics.

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Ultimately, ensuring the most rigorous workflow and consistent results for physicians means adopting a robust, systematic method for interpreting variants. As a community, we must leave behind the subjective parts of manual review and embrace guideline-driven interpretation processes. That's not to say the interpretation process should be automated; clearly, the expertise of variant scientists and clinical geneticists in evaluating evidence has great value and must be brought to bear. But clinical labs can generate better results and scale more quickly by taking advantage of tools designed to streamline the accurate assessment of variants.

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Learn more about QIAGEN's variant interpretation solutions for clinical testing labs at **www.digitalinsights.qiagen.com/clinical-testing**