Ambry Genetics
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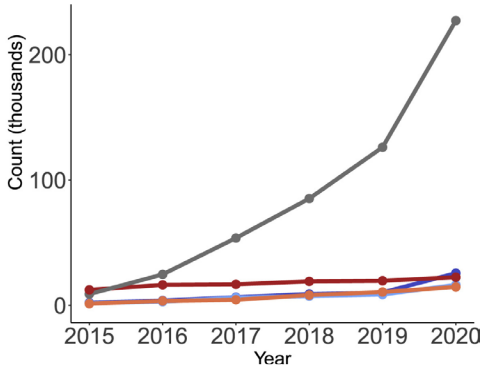
Research For Your Practice

Transforming Genetic Testing with MAVEs: High-Throughput Variant Interpretation for Improved Patient Care

INTRODUCTION

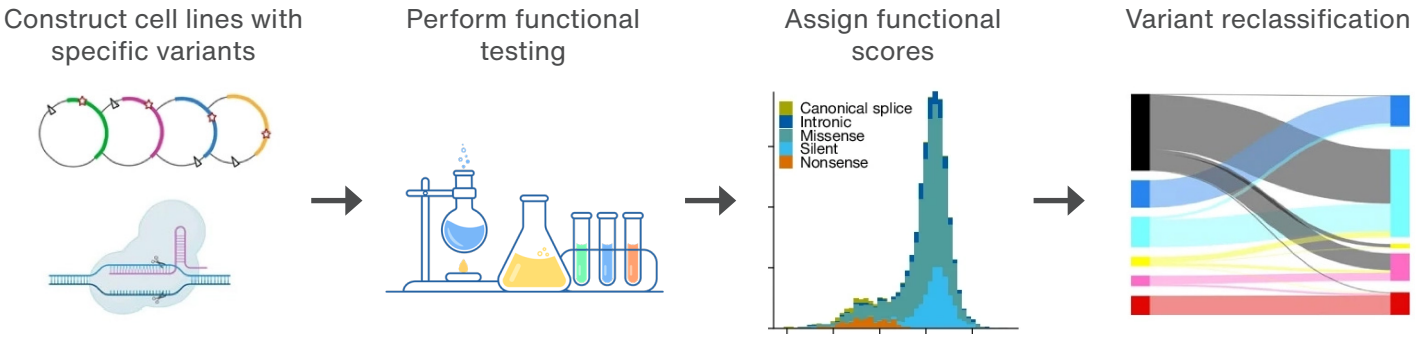
As the adoption of genetic testing has increased, so have the number of inconclusive results (Figure 1). To keep up with the pace of testing, the ability to accurately interpret the vast number of variants must become scalable. Multiplexed Assays of Variant Effects (MAVEs) have transformed the testing landscape by enabling high-throughput, functional assessment of thousands of genetic variants at the same time (Figure 2). Scores are assigned based on the outcomes of functional testing for each variant and can be used as evidence towards variant classification. In addition to performing at high volume, MAVEs produce novel evidence—even for rare variants—which makes them an especially useful tool to improve interpretation in understudied racial and ethnic groups.

Figure 1. ClinVar variant entries by classification



Fayer et al. *Am J Hum Genet*. 2021. Modifications to figure include cropping. Used under CC-BY.

Figure 2. Typical MAVE workflow



Huang et al. *Nature*. 2025. Changes to figure include addition of original content and cropping. Used under CC-BY.

NEW INSIGHTS FOR *BRCA2* VARIANT INTERPRETATION

In a recent study led by Fergus Couch, PhD, et al published in *Nature*, we can see the impact of a MAVE in action. Approximately 7,000 variants in *BRCA2* were evaluated simultaneously using an ultra-high-throughput cell survival assay—generating evidence that can contribute to classifications for 91% of variants studied. This includes proposed classifications of over 3,000 novel variants proactively, before they have even been observed in a patient.

Interested in Learning More?

Watch “The Use of MAVES in Genetic Testing” webinar with Dr. Couch.

The success of this study was driven by several key factors (Figure 3).

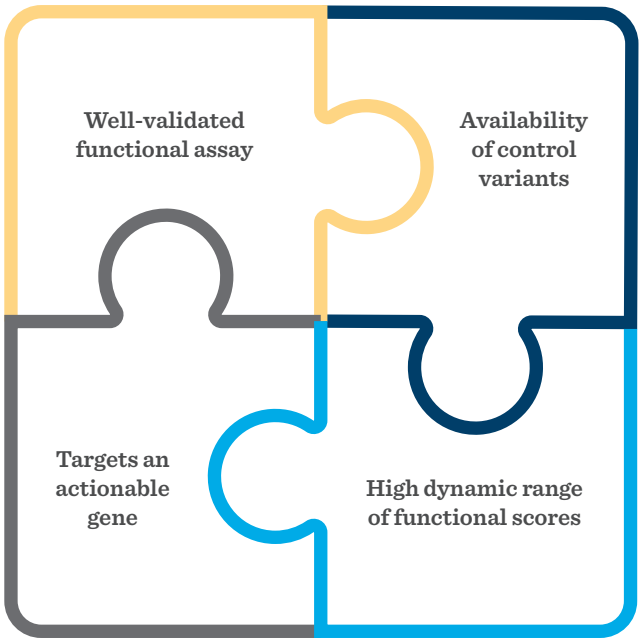
1. A well-validated, high-throughput functional assay demonstrated strong correlation with clinical phenotypes.

2. The inclusion of well-characterized positive and negative control variants (encompassing both known pathogenic and benign variants) ensured robust assay performance.

3. The assay exhibited a high dynamic range, allowing for clear separation between functional and non-functional variant scores.
   - Ambry Genetics' data contributed to the clinical validation of the functional and non-functional variant categories.

4. The study focused on an actionable gene (*BRCA2*), where reclassification of variants has direct implications for patient management, underscoring the clinical utility of this approach.

Figure 3. MAVE components that contribute to clinical utility



SUCCESS BY THE NUMBERS

- Theoretical classifications were made in 91% of studied variants
- Proposed classifications of >3,000 novel variants
- Theoretical reduction in VUS rate of studied variants, from 50% to 8%

SUMMARY

By integrating high-throughput functional data with clinical classification frameworks, we can refine variant interpretation, enhance diagnostic accuracy, and improve patient care and equity. Translating these findings into clinical practice requires seamless collaboration between laboratories maintaining robust variant databases and researchers conducting functional assays.

Definitive and novel variant classifications can have life-saving implications, such as increased surveillance, prophylactic interventions, or targeted therapies. Ambry takes pride in advancing the understanding of genetic variants and informing both providers and patients about relevant variant classifications and reclassifications, empowering them to make more informed health decisions.

1. Fayer et al. *Am J Hum Genet*. 2021. PMID: 34793697
2. Gelman et al. *Genome Med*. 2019. PMID: 31862013
3. Huang et al. *Nature*. 2025. PMID: 39779857

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