Invitae's functional modeling platform: Reducing VUS rates in real time

When it comes to genetic test results, variants of uncertain significance (VUS) can be rough: they're complicated to explain and difficult for patients to understand. And when you test with larger, more comprehensive panels—which are more likely to provide answers—you often get more VUS.

How do you find balance? With Invitae's *functional modeling platform* (FMP), which reduces VUS rates when it is possible and responsible to do so.

FMP, the latest advancement to Invitae's trusted Sherloc variant classification framework, significantly reduces VUS rates in more than 1,100 genes across all clinical areas. By doing this in real-time, there's less need for reclassification at a later date: your patients get actionable answers, today.

Invitae is the only lab with FMP enhanced variant interpretation. We continually invest in state-of-the-art technology to help you confidently give more patients definitive results.

The combination of FMP and Sherloc enables:

- More comprehensive and accurate variant interpretation
- Decreased VUS rates
- Actionable information to inform medical management

FMP by the numbers

1,100+
genes modeled

FMP evidence has helped enable definitive results for

40,000+
patients since September 2019

A pilot study of FMP showed that FMP evidence changes classification for

2.5% (or 1 in 40) of all patients tested at Invitae

FMP is included, at no additional charge, for any patient undergoing testing at Invitae. No extra sample. No extra boxes to check. No extra cost to patients or payers.

Sherloc and the functional modeling platform

Clear. Actionable. Reliable. *And only available at Invitae.*

Invitae's functional modeling platform (FMP) accurately predicts how variants will affect protein function by integrating biophysical, molecular, cellular, and computational data, continuously incorporating the latest research and data.

FMP doesn't stand alone—rather, it's a line of evidence that is incorporated into Invitae's trusted Sherloc variant interpretation framework. Sherloc's systematic, point-based system is transparent, accountable, consistent, and adheres to expert guidelines.[1,2] FMP feeds information into two of Sherloc's evidence types: experimental studies and computational.

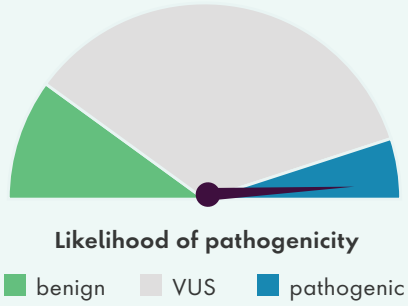
Sherloc: a set of **S**emiquantitative **h**ierarchical **e**vidence-based **r**ules for variant **loc**us interpretation

#1 Five types of evidence, considered in a hierarchical approach:

#2 Rule based scoring for each individual piece of evidence

	B (benign)	P (pathogenic)
Population data		*
Variant type		
Clinical observations		*
Experimental studies		
Indirect and computational		*

#3 Point score thresholds to determine final classification based on the ACMG suggested five-tier classification system



How does this compare to what other labs use?

Some other labs: Computational *(in silico)* evidence from publicly available models, such as PolyPhen2 and SIFT	**Invitae:** Computational *(in silico)* evidence from FMP incorporated into Sherloc
• Often outdated	• Dynamic and AI-enabled, continuously learning and improving with experience from Invitae's vast database of >2 million patients
• Single model for all genes: "one size fits all" approach	• Gene-specific: AI evaluates variants in each gene separately, taking gene-specific characteristics into account
• ~75-85% accuracy[3-5]	• >99% accuracy[6]

1. Nykamp K *et al. Genet Med.* 2017;19(10):1105-1117.
2. Richards S *et al. Genet Med.* 2015;17(5):405-424.
3. Sim NL *et al. Nucleic Acids Res.* 2012;40:W452-W457.
4. Adzhubei IA *et al. Nat Methods.* 2010;7(4):248-249.
5. Ioannidis NM *et al. Am J Hum Genet.* 2016;99(4):877-885.
6. Internal data on file - to be submitted for publication.

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