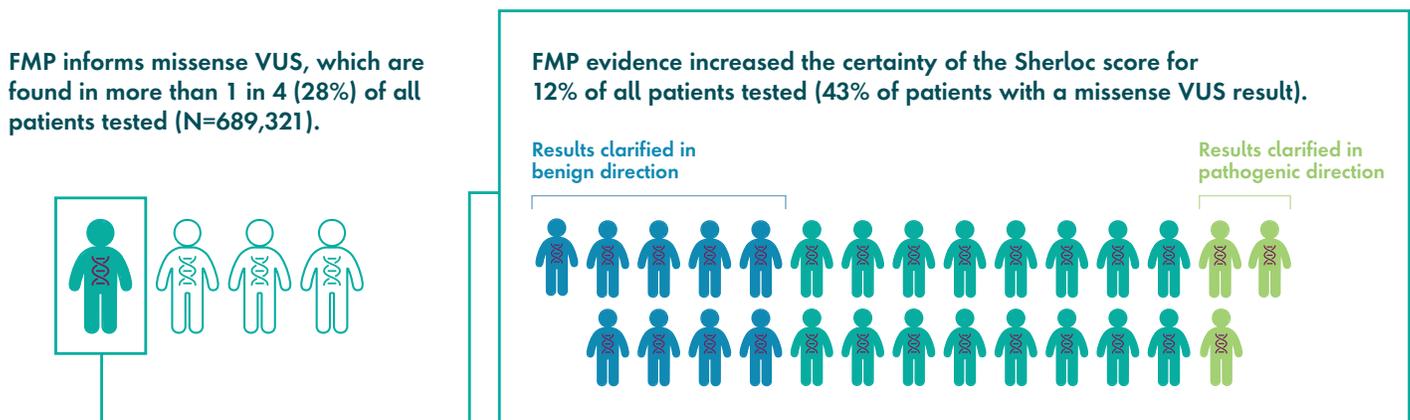# The impact of functional analysis on variant interpretation

Invitae is committed to providing patients with high-quality genetic test results. In accordance with the American College of Medical Genetics (ACMG) guidelines, our experienced variant interpretation team of scientists and genetic counselors utilize a framework called Sherloc to critically evaluate the latest scientific evidence to interpret genetic variants and provide healthcare providers and their patients with the information needed to help make important medical decisions.

In some instances, a genetic variant may be classified as a variant of uncertain significance (VUS) due to a lack of publicly available high-quality functional data to assess the impact that variant may have on disease. This may pose significant challenges for clinicians and their patients, especially when that information may help guide therapeutic interventions.

Invitae recognizes the value of RNA studies. However, only a small proportion of patients have variants that may affect splicing, which may be clarified through RNA analysis. The vast majority of patients with VUSs have missense variants, which require diverse functional evidence to assess impact on disease.

In order to address this need, Invitae has invested in state-of-the-art computational and cellular approaches for functional modeling to explore important biological questions about an observed genetic variant. Housed within the Functional Modeling Platform (FMP), these technologies enable Invitae to generate, quality control, and apply high-quality cellular (in vitro) and computational (in silico) data within a validated framework. With additional clinical and functional evidence evaluated within Sherloc, the FMP helps to resolve VUSs across all clinical areas in accordance with ACMG guidelines.

FMP informs missense VUS, which are found in more than 1 in 4 (28%) of all patients tested (N=689,321).

FMP evidence increased the certainty of the Sherloc score for 12% of all patients tested (43% of patients with a missense VUS result).

Results clarified in benign direction

Results clarified in pathogenic direction

Invitae's FMP has the potential to offer clarity for more than 1 in 4 patients— significantly higher than the 1 in 43 patients that may benefit from RNA analysis.