# Data Analysis and Variant Classification Process

Every variant identified at GeneDx goes through a comprehensive review process as described below. Additionally, we support the community by consistently sharing our data in publically available variant databases and are the largest commercial laboratory contributor to ClinVar.

## Technical Data Analysis

- Technical review of raw data
- Confirmation of identified variants by Sanger sequencing, microarray, MLPA or other appropriate method
- Determine nomenclature and technical parameters (e.g. coverage, mosaicism, heteroplasmy)

## Clinical Review

- In-depth analysis of the variant within clinical context in literature (e.g. segregation, case-control studies, co-occurrence with a known pathogenic variant) and patients' clinical information
- Consultation and collaboration with recognized scientific experts
- Performed by board-certified/eligible genetic counselors

## Reporting

- Results summarized in clear, concise and thoughtfully written reports customized to the patient tested
- Reports include clinical references, as well as appropriate medical management, patient educational material and other resources, when available
- Written and signed by genetic counselors and board-certified medical and molecular geneticists


## Literature and Database Review

- Comprehensive database and literature review, including Human Gene Mutation Database, ClinVar, as well as gene-specific, population and internal databases
- Review of output from *in-silico* protein and splicing prediction models, as well as evolutionary conservation data
- Analysis of functional impact, including assessing structural/functional domain and predicted effect on protein
- Performed by PhD-level analysts trained in molecular genetics and/or biochemistry

## Final Review

- Detailed review of cumulative evidence and final classification of variants in line with 2015 ACMG guidelines: Pathogenic, Likely Pathogenic, Variant of Uncertain Significance (VUS), Likely Benign and Benign
- Performed by board-certified medical and molecular geneticists with specific expertise in the disease area and testing platform

## Variant Follow-Up

- Complimentary Variant Testing Program available to eligible families to aid in variant classification
- Re-evaluation of variants incorporates literature and database review, segregation and clinical data, when available
- Applies to variants identified in a new patient or upon client request, when it has been more than 6 months since the variant was last vetted or pertinent, new data is available
- Updated results report provided to the ordering healthcare provider for any one-step classification change involving a VUS, Likely Pathogenic Variant or Positive
- Continued communication with clients to discuss cases and results