

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.

AC GT Technical Data Analysis

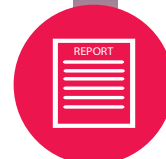
- Technical review of raw data
- Confirmation of identified variants by Sanger sequencing, microarray, MLPA or other appropriate method
- Determine nomenclature and technical parameters (e.g. coverage, mosaicism, heteroplasmy)

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