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

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on Process

Literature and
Database Review

Final Review

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About GeneDx

GeneDx was founded in 2000 by two scientists from the National Institutes of Health (NIH) to address the needs of patients diagnosed with rare disorders and the clinicians treating these conditions. Today, GeneDx has grown into a global industry leader in genomics, having provided testing to patients and their families in over 55 countries. Led by its world-renowned whole exome sequencing program, and an unparalleled comprehensive genetic testing menu, GeneDx has a continued expertise in rare and ultra-rare disorders. Additionally, GeneDx also offers a number of other genetic testing services, including: diagnostic testing for hereditary cancers, cardiac, mitochondrial, and neurological disorders, prenatal diagnostics, and targeted variant testing. At GeneDx, our technical services are backed by our unmatched scientific expertise and our superior customer support. Our growing staff includes more than 30 geneticists and 100 genetic counselors specializing in clinical genetics, molecular genetics, metabolic genetics, and cytogenetics who are just a phone call or email away to assist you with your questions and testing needs. We invite you to visit our website: www.genedx.com to learn more about us.

Reference:
Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, W. Grody W, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL. ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-24. (PMID: 25741868)

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