



Genomic Unity® Lightning Genome Analysis

Test Information

The benefits and risks of the Genomic Unity® Lightning Genome Analysis test are described below. It is recommended that you receive genetic counseling from a licensed healthcare provider who can answer your questions about genetic testing and provide information about alternatives. Information about genetic counselors in your area is available at <https://www.nsgc.org/>.

Background

The purpose of genetic testing is to identify changes in the DNA sequence that are the cause of an affected individual's condition. This test uses a PCR-free protocol that produces comprehensive and consistent coverage of all exons and non-coding regions in an individual's genome. When applicable to familial samples, whole genome protocols are used for comparison to the proband. The resulting data is subjected to in-silico analyses optimized for small sequence changes (single nucleotide variants and deletion/insertions), structural variants in chromosomes (deletions, duplications, copy number variants), short tandem repeats (STRs) and mitochondrial variants (single nucleotide variants and small deletion/insertions and large deletions).

Additional information about the Genomic Unity® Lightning Genome Analysis test is available from your healthcare provider and on the Variantyx website at <https://www.variantyx.com/>. Adult-onset disorders not related to the indication for testing, and therefore representing predictive testing, are not reported with this test.

Technical Limitations

Genetic testing is accurate, but may not always identify a genetic variant even though one exists. This test attempts to evaluate the entire DNA sequence (within the scope described for the test), but may not be able to detect all DNA changes due to limitations in current technology. Certain regions of the DNA may not be well covered. Certain variant types may not be detectable such as methylation abnormalities, variants in genes with highly homologous pseudogenes and variants in regions that are difficult to assay based on current technology. Unusual circumstances including bone marrow transplantation, blood transfusion, and variants that exist in only a small fraction of cells (mosaicism) may interfere with variant identification. Deletions, duplications and copy number variants between 50 and 300 nucleotides are detected with a lower sensitivity. The false negative rate for mitochondrial large deletions has not been determined. The false negative rate for repeat expansions has not been determined for the following genes: *AFF2*, *ATXN10*, *CNBP*, *CSTB*, *DIP2B*, *JPH3*, *NOP56*, *NOTCH2NLC*, *PHOX2B*, *TBP*, *TCF4*. For dominant repeat expansion disorders parental inheritance will not be reported on the initial report. Additionally, interpretation of the results is limited by the current medical understanding of disease and available scientific information. This test requires high-quality DNA. In some cases, an additional sample may be needed if the volume, quality and/or condition of the initial sample is not sufficient. Samples submitted as genomic DNA will only be processed if the extraction was performed in a CLIA/CAP accredited laboratory. This test does not consider somatic variants.

Possible Test Results

Positive result - A positive result indicates that one or more genetic variants were identified that either explain or partially explain the cause of the disorder or indicate an increased risk of developing the disorder in the future. Individuals with positive results may wish to consider further independent testing and/or consultation with their physician or genetic counselor.

Negative result - A negative result indicates that no genetic variant explaining the disorder was identified by this test. This reduces the likelihood of, but does not exclude the possibility of, the disorder being genetic in nature.

Uncertain result - A variant of uncertain significance was identified by this test. This means that a genetic variant was identified, but based on available information in the medical literature and research and scientific databases it is not certain whether the variant may cause the disorder. The variant could be a normal genetic difference that does not cause the disorder. Without further information, the effects of the variant cannot be known and an "uncertain/clinically inconclusive" result may be reported. The uncertainty may be resolved over time if additional information becomes available. Periodic reanalysis of the sequence data or further analysis, including testing of additional family members, may be recommended.

Indeterminate result - An indeterminate result indicates that there were relevant genetic variant(s) identified in the analysis, but that it is uncertain whether they are true variants or artifacts. Furthermore, it is considered that a repeat test will not resolve the technical uncertainty and orthogonal confirmation is necessary to resolve the result.

Inconclusive result - A technically inconclusive result indicates that there was an issue with the patient sample that resulted in data that the lab cannot interpret. It is considered that a repeat test will likely resolve the technical uncertainty and therefore a repeat sample is recommended to complete the analysis.

Reporting Standards

All reportable variants in the clinical report will be categorized as pathogenic, likely pathogenic or a variant of uncertain significance (VUS) utilizing the American College of Medical Genetics and Genomics (ACMG)/Association for Molecular Pathology (AMP) guidelines as published by Richards et al. 2015 (for more information see: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4544753/>). Variants may have a strong phenotypic correlation with the reported patient phenotype(s) and be considered a strong causal candidate for the disorder or may have some phenotypic overlap with the reason for testing but not be considered the sole genetic cause for the phenotype(s) in the patient. Both types of variants may be reported. Even if this test finds DNA changes that are responsible for the reported symptoms, the testing may not completely predict the severity of the disorder, possible future problems, or response to treatment. Variants of uncertain clinical significance will only be reported if found to be associated with patient phenotype. Variants of uncertain clinical significance will not be reported in targeted analysis (phenotypic based analyses) unless sufficient clinical information was provided.

Variantyx reviews clinical notes provided with the test submission and may report results from other labs for: (a) detection of the variant on our platform, and inheritance, if applicable. This is possible if there is detailed information in the notes provided with the test requisition. Information required includes (but is not limited to): reference genome, chromosome location/gene name, variant change (c./p. or breakpoints), and transcript. It is recommended to include previous test results containing the required information.

Reporting of Unrelated Findings

Unrelated findings are findings obtained from genomic sequencing, usually whole genome or exome sequencing, and can be related to conditions that were not the primary reason for testing or findings that can allow one to deduce information as a result of testing that is not directly related to the test. Unrelated findings can be further defined into different types of secondary and incidental findings.



ACMG Secondary Findings

The American College of Medical Genetics and Genomics (ACMG) recommends reporting pathogenic and likely pathogenic variants in a list of genes in both a gene-specific and variant-specific manner. Variantx evaluates the secondary findings list of genes, the version of which will be listed in the report and can be found on the Variantx website, www.variantx.com/acmg-secondary-findings. These variants are not typically reviewed during routine processing of patient samples, but are actively sought and reported to the patient. The ACMG recommends reviewing variants in the genes in their recommended list because the genes are related to conditions that are considered 'actionable', meaning that there are steps that can be taken to mitigate the onset or severity of the clinical outcome. It is important to understand that it is possible to have a pathogenic variant but to have it not detected by the assay. In addition, variants of uncertain significance are not reported in these genes. If a variant is of uncertain significance, and later is considered pathogenic, it cannot be determined without a reanalysis of the data.

Unavoidable Incidental Findings (typically reported if present)

Some incidental findings are unavoidable and can be deduced from testing, such as discovering non-paternity when testing the parents of a child in trio analysis or discovering that a parent is a carrier for the condition identified in the child. Other incidental findings are variants in genes that may fit the patient's clinical phenotype but are also related to clinical symptoms unrelated or with a later onset. For example, more than 450 different pathogenic variants have been identified in the LMNA gene, which can cause a wide variety of distinct and disparate diseases involving striated muscle (dilated cardiomyopathy, skeletal myopathies), adipose tissue (lipodystrophy syndromes), peripheral nerve (Charcot-Marie-Tooth neuropathy) or multiple systems with accelerated aging (progerias). These results would likely be reported because they are integral to testing. The possibility of receiving unavoidable incidental findings should be discussed with the patient and family prior to testing, so they are aware that these results, if present, are likely to be returned to them. If the patient does not wish to receive these results, they can decide not to continue with testing.

With this test related findings are reported, such as genetic findings useful for the current diagnosis of the disease that initially led to the analysis and any clinically relevant genetic findings, which may have immediate benefits for the patient related to present diseases or clinical conditions. However, some unrelated findings may be reported as an option to receive with the report. While others such as, pharmacogenomic, high frequency risk alleles, carrier status (heterozygous pathogenic variants in genes associated with autosomal recessive conditions that are not associated with the patient's reported symptoms) and late onset disorders, etc., are outside the scope of testing and would not be typically reported. These different findings and options to receive results are described below.

Secondary Findings (ACMG) are available for Genomic Unity® Lightning Genome Analysis and are not available to relatives, with the exception of the reported parental inheritance of the variants identified in the patient. No specific parental results are issued as a separate report under the family member's name. If the patient chooses to receive secondary, those findings will be included in a separate section of the clinical report.

Testing of Family Samples

In the case of trio and/or larger cohort analysis, and for parental confirmation of singleton analysis, sequencing and analysis of family samples may be used to improve the interpretation of genetic variants identified in the patient's DNA. Accurate interpretation of test results requires accurate assignment of family relationships. Analysis of the sequenced DNA is performed with the assumption that correct family relationships have been provided. Parental samples that fail concordance with the patient (i.e. one parent does not share the expected number of variants with the child) will not be analyzed. Family samples are analyzed only with regard to the patient's condition. Parental inheritance is reported on variants if identifiable, this may include the inheritance of variants related to incidental or secondary findings. However for patients with repeat expansions, parental inheritance may not be reported. Additional counseling for the parents may be recommended prior to reporting parental inheritance of the repeat expansion.

Due to the urgency of this test, if the parental sample(s) fail quality control the test will be reported without the parental sample(s). Reports may be amended to include the parental samples at a later time when the quality issue(s) are resolved.

Patient Confidentiality

To maintain confidentiality, test results will only be released to the ordering healthcare provider or ordering laboratory, and upon your request, to additional healthcare provider(s) indicated on this test requisition form. Test results will only be disclosed to others by your written consent and/or if demanded by a court of competent jurisdiction. It is your responsibility to consider the possible impact of test results on insurance rates, the ability to obtain disability, life or long-term care insurance and employment. The Genetic Information Non-discrimination Act (GINA), enacted by the US Federal Government, provides some protection against discrimination by health insurance companies and employers based on genetic test results, but does not cover life, disability or long-term care insurance. Information about GINA is available at <https://www.genome.gov/10002328>.

Anonymized information obtained from the test may be included in variant and allele frequency databases used to help healthcare providers and scientists understand human disease, as well as in scientific publications. Names and personal identifying information will not be revealed. Separate from the above, if there are opportunities to participate in research relevant to your condition, and you have consented for recontact, Variantx may contact you or your healthcare provider for research purposes.

Turnaround Time

The turnaround time (TAT) of this test is five days, which begins at the time of completed requisition and sample receipt. For family testing, the timing starts when the last sample is received. Please note that the following scenarios will likely result in extension of the turnaround time (1) when the DNA sample fails quality control and/or is determined to be insufficient for testing, requiring collection of a new sample; (2) when the test is sent for orthogonal confirmation at an external laboratory. In the second scenario, the turnaround time can be expected to be extended by the turn around time of the external laboratory plus 1 week.

Sample Retention

DNA extracted from submitted samples may be stored for at least 3 months following completion of testing and may be discarded thereafter. Extracted DNA is not returned unless requested prior to testing (additional fees apply). After completion of testing, anonymized DNA may be used for test development and improvement, internal validation, quality assurance and training purposes before being discarded.

NY state residents: No other test shall be performed on this sample except the test ordered by the clinician, unless waived by the patient or authorized individual. In addition, the patient's biological sample will be destroyed within 60 days or upon the completion of testing, unless waived by the patient or authorized individual. Orthogonal confirmation of results at a reference lab cannot be performed unless the patient or authorized individual provides permission to do so.

24/7 customer support can be reached via Lightning@variantx.com, (tel) 1-508-834-3049, or (fax) 1-508-302-0528.