The Informed Consent Process

The benefits and risks of the Genomic Unity® test are explained 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 sequences the entire DNA using a PCR-free protocol that produces comprehensive and consistent coverage of all exons and non-coding regions. When applicable to familial samples, whole exome protocols that target exons may be 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). The Genomic Unity® Whole Genome Analysis test considers mitochondrial variants from the mitochondrial genome as well as most variant types overlapping the exome traditionally reported using other methodologies, excluding technically challenging variants listed in the limitations of testing. The Genomic Unity® Exome Analysis test considers most variant types overlapping the exome traditionally reported using other methodologies, excluding technically challenging variants listed in the limitations of testing. The Genomic Unity® Constitutional Genome-Wide Copy Number Variant Analysis test considers structural variants only. The Genomic Unity® Mitochondrial Genome Analysis test considers mitochondrial variants from the mitochondrial genome only, and therefore does not include nuclear encoded genes. All other tests consider variants in or overlapping a subset of genes which are described in brief in the Targeted Analyses section of the test requisition form and in more detail on the individual test information web page indicated. When a Custom Analysis is specified, only variants in or overlapping the listed gene(s) specified is/are considered and only for small sequence changes, deletion/duplications and short tandem repeats as applicable to the gene. All tests are focused on rare variants. When noted for the specified analysis, this test uniquely assesses tandem repeats in genes involved in early-onset intellectual disability (*AFF2, AFF3, DIP2B, FMR1*), adult-onset movement disorders with or without cognitive involvement (*AR, ATN1, ATXN1, ATXN2, ATXN3, ATXN7, ATXN8OS, ATXN10, C9ORF72, CACNA1A, CNBP, CSTB, DMPK, FMR1, FXN, NOP56, NOTCH2NLC, PPP2R2B, TBP*) and/or other disorders (*PHOX2B, TCF4*). Full and pre-mutation alleles will be reported for these genes when relevant to the patient's clinical symptoms. Based on recommendations by the ACMG, the *JPH3* and *HTT* genes are excluded from this analysis by default, but may be included if a specialized consent form has been signed by the patient/guardian and ordering clinician. Access the form at https://www.variantyx.com/HTT-JPH3-Consent/.

The positive predictive value of this test ranges from 0.99676 to 0.99931 depending upon the specific assay selected. Additional information about Genomic Unity® 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. Requests for predictive, carrier and other non-diagnostic genetic testing are available by ordering the Genomic Inform® 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 repeat expansions has not been determined for the following genes: *AFF2, AFF3, ATXN10, CNBP, CSTB, DIP2B, JPH3, NOP56, NOTCH2NLC, PHOX2B, TBP, TCF4*. Not all expansions are reported with specific allele counts. The following genes can be assessed for normal repeat ranges only: *AFF3, DIP2B, JPH3, NOTCH2NLC, TCF4*. Repeat counts falling outside the normal range will be reported as indeterminate. When exome protocols are applied to familial samples, repeat expansions and most deletions, duplications and copy number variants will not be detected. Any additional test specific limitations are noted on the individual test information web page indicated. 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 adequate. 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 mutations.

Possible Test Results

Test results will be issued as a single clinical report for the patient. When parental samples are submitted they are used in the evaluation of the patient only. No specific parental results are issued individually or under the family member's name. If the patient chooses to receive secondary or other incidental findings as described below, those findings will be included in a separate section of the clinical report. Incidental findings will not be provided for parental samples. Possible results of this test include:

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 / Variant of uncertain significance (VUS) - 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 there is uncertainty as to 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.

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.

Reporting of Unrelated Findings

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, as listed below, 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.

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 incidental and secondary findings.

Unavoidable incidental findings (typically reported if present)
Some incidental findings are unavoidable and 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 ageing (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. Patients for whom the Genomic Unity® Whole Genome Analysis or Genomic Unity® Exome Analysis test is ordered have the choice to opt-in to two additional sets of findings:

Secondary (ACMG) findings (OPTION 1)
The American College of Medical Genetics and Genomics (ACMG) recommends reporting pathogenic, expected pathogenic variants, or both in a list of 59 genes in a gene-specific manner. 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. These genes are primarily related to cancer and cardiac conditions. 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 (VUS) are not reported in these genes. If a variant is a VUS and later is considered pathogenic, that cannot be determined without a reanalysis of the data.

Other incidental findings (OPTION 2)
Other incidental findings are discovered in genes unrelated to the patient's present symptoms, but may have some actionability such as monitoring for possible cardiac implications, increased cancer screening, monitoring of iron levels, have a dietary impact or are diseases for which possible treatment is available (e.g. cardiovascular diseases predisposing to sudden cardiac death). These are genes not on the ACMG list but are similar in that they could impact medical management and decision making.

The option to receive Secondary (ACMG) Findings and/or Other Incidental Findings is not available for tests other than Genomic Unity® Whole Genome Analysis or Genomic Unity® Exome Analysis and is not available to relatives (limited to the proband only).

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 (familial samples) may be used to improve the interpretation of genetic variants identified in the patient's DNA. Variantyx will determine the method (exome or genome) of sequencing used for the familial samples based on the 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. This test reports the inheritance of genetic variants when parental samples are 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.

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. Personnel at Variantyx will not release test results directly to patients and will not discuss the test results with anyone except the medical professional who ordered the test or has been authorized to receive the results. 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, Variantyx may contact you or your healthcare provider for research purposes.

Turnaround Time

The turnaround time (TAT) of this test is 6 to 8 weeks starting from the time of sample receipt. For trio (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 beyond 6 to 8 weeks: (1) when the DNA sample fails QC and is determined to be insufficient for testing, requiring collection of a new sample; (2) when a repeat expansion has been identified and sent for orthogonal confirmation at an outside laboratory. In the second scenario, the turnaround time can be expected to be extended by the turn around time of the outside laboratory plus 1 week.

Sample Retention

DNA extracted from submitted samples may be stored for at least 3 months following completion of testing and will be discarded thereafter, unless there is a consent for retention. 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.

Patient Consent

I have read the contents of this document. I have discussed Genomic Unity® test with my healthcare provider including the purpose and procedure, risks, benefits and alternatives. I have been given an opportunity to ask questions about the test, and any questions I had were answered to my satisfaction. I acknowledge that I have sufficient information and understanding to give this informed consent.

1. I give permission to Variantyx and their affiliates to extract and sequence my DNA and perform genetic testing as described.

2. I give permission for my anonymized DNA to be used by Variantyx and their affiliates for test development or improvement, internal validation, orthogonal variant confirmation at an outside referral laboratory and/or quality assurance and training purposes.

3. I give permission for my anonymized sample and clinical information to be included in variant and allele frequency databases and publications. My name or other personal identifying information will not be used in or linked to any databases or publications.

4. In the case of direct insurance billing: I acknowledge that the information provided by me is true and correct. I authorize my healthcare provider and/or insurer to share medical information with Variantyx related to my condition, diagnosis and treatment as relevant to my genetic testing, as well as information about my healthcare plan benefits. I authorize Variantyx to release my medical information concerning my testing to my insurer. I authorize Variantyx to be my designated representative for purposes of appealing any denial of benefits as needed and to request additional medical records for this purpose. I understand that Variantyx will notify me if my out of pocket costs are determined to exceed $100. I authorize my insurance benefits to be paid directly to Variantyx. I understand that I am responsible for sending Variantyx any and all of the money that I receive directly from my insurer in payment for this test.

5. In the case that independent pre-test and/or post-test genetic counseling is required by my insurance provider and/or referring institution, I agree, by signing this consent form, to have DNAVisit, a third party, facilitate the genetic counseling services. By signing this consent form, I authorize Variantyx to release my contact information and any medical information necessary to DNAVisit, as well as authorize communication and sharing of information between DNAVisit and my referring physician, in order to complete pre-test and/or post-test genetic counseling. Information about DNAVisit is available at https://www.dnavisit.com/.

6. **I ☐ give / ☐ do not give permission** for Variantyx to contact me or my healthcare provider about research studies. If no option is selected, no contact will be made.

7. Regarding Secondary Findings and Other Incidental Findings (only available with the Genomic Unity® Whole Genome Analysis and Genomic Unity® Exome Analysis tests, and only for the patient):

I choose ☐ to receive / ☐ not to receive Secondary (ACMG) Findings

I choose ☐ to receive / ☐ not to receive Other Incidental Findings

No selection above will default to an opt-out option and findings in these categories will not be returned to you.

8. For NY state residents : ☐ **By checking this box I give permission** for Variantyx and their affiliates to retain any remaining sample longer than 60 days for testing completion, test development/improvement, internal validation, orthogonal variant confirmation at an outside referral laboratory and/or quality assurance and training purposes.

Patient first name

Patient last name

Patient (or authorized individual) signature

Date

Authorized individual first name

Authorized individual last name

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