variantyx

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Genomic Unity®
Informed Consent

Patient Name		Affix barcode label of Patient's sample here
Date of Birth		

Form instructions:

✓ Review the information on pages 1-4
✓ The patient or legal guardian must sign on page 1
✓ When submitting comparator samples, the relative(s) must sign on page 5

Patient Consent

I have discussed the 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 physician, 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 (or authorized individual) first name	**Last name**
Patient (or authorized individual) signature	**Date**

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Website: www.variantyx.com

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Test Information

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 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 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 and small sequence changes intersecting reportable copy number variants when requested. 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 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, 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, PABPN1, PPP2R2B, TBP)* and/or other disorders (*PHOX2B, TCF4*). Expanded 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 the 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, ATXN10, CNBP, CSTB, DIP2B, JPH3, NOP56, NOTCH2NLC, PHOX2B, TBP, TCF4*. The following genes can be assessed for normal repeat ranges only: *DIP2B, NOTCH2NLC, TCF4*. Repeat counts above 45 will be reported as indeterminate. For dominant repeat expansion disorders parental inheritance will not be reported on the initial report. 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 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

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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.

Reporting of Unrelated Findings

Secondary (ACMG) Findings and/or Other Incidental Findings are only available for Genomic Unity® Whole Genome Analysis, Genomic Unity® Exome Plus Analysis and Genomic Unity® Exome 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 or other incidental findings, those findings will be included in a separate section of the clinical report.

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 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 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, Genomic Unity® Exome Plus Analysis or Genomic Unity® Exome Analysis test is ordered have the choice to opt-in to two additional sets of 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. Variantyx evaluates the secondary findings list of genes, the version of which will be listed in the report and can be found on the Variantyx website, www.variantyx.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.

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Other Incidental Findings
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.

Special Consent
To receive results on select genes that are not included in the above, a special consent form is required.
In general the Genomic Unity® tests are for diagnostic purposes and are not offered for predictive testing such as identifying adult onset disorders in an individual who is too young for disease manifestation. In addition, certain genes require additional genetic counseling for the patient and family due to the complexity of the clinical implications and psychological consequences of receiving such results. Therefore, for individuals seeking these results an additional consent is required.

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. 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. 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 counselling for the parents may be recommended prior to reporting parental inheritance of the repeat expansion.

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, Variantyx may contact you or your healthcare provider for research purposes.

Turnaround Time

The turnaround time (TAT) of this test can be found on the Variantyx website, which begins at the time of 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 QC and 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.

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Biological Mother's Information

First Name	Last Name	DOB
Sample Collection Date	Sample Type ◯ Blood ◯ Saliva ◯ Genomic DNA	If affected by the same disorder as the patient please list the clinical symptoms:

Biological Father's Information

First Name	Last Name	DOB
Sample Collection Date	Sample Type ◯ Blood ◯ Saliva ◯ Genomic DNA	If affected by the same disorder as the patient please list the clinical symptoms:

Other Relative's Information

First Name	Last Name	DOB
Sample Collection Date	Sample Type ◯ Blood ◯ Saliva ◯ Genomic DNA	If affected by the same disorder as the patient please list the clinical symptoms:

Relationship to Patient

Brother: Sister: Other:

Family Member Consent

I have discussed the 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/my relative's DNA and perform genetic testing for the purpose of improving the interpretation of genetic variants identified in the patient's DNA.

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.

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Biological mother's first name	Last name
Biological mother's signature	Date
Biological father's first name	Last name
Biological father's signature	Date
Other relative's first name	Last name
Other relative's (or authorized individual) signature	Date