variantyx

DCVXWLC03007Q

Genomic Inform®
Test Requisition Form

Patient Name		Affix barcode label here
Date of Birth	___ / ___ / _____	

Ordering Healthcare Provider

First Name	Last Name	Title	NPI #
Facility Name			Telephone / Fax
Facility Address			Email

Additional Report Recipients

Name	Telephone / Fax	Email
Name	Telephone / Fax	Email

Patient Information

First Name	Last Name	MI	Date of Birth ___ / ___ / _____	Gender ◯ Male ◯ Female
Address				Ethnicity ◯ African/African American ◯ Latino
Telephone	Email			◯ Ashkenazi Jewish ◯ East Asian ◯ Other:
Sample Collection Date ___ / ___ / _____	Sample Type ◯ Blood ◯ Genomic DNA ◯ Saliva			◯ European ◯ South Asian _____

Medical History

Please indicate if you have a history of any of the following:

Cancer

- ◯ Breast
- ◯ Colon
- ◯ Leukemia
- ◯ Lung
- ◯ Ovarian
- ◯ Pancreatic
- ◯ Prostate
- ◯ Skin
- ◯ Other _____

Diabetes

- ◯ Type I (Insulin dependent)
- ◯ Type II (Non-insulin dependent)

Cardiovascular

- ◯ Heart disease
- ◯ Heart attack
- ◯ Heart murmur / Arrhythmia
- ◯ High blood pressure
- ◯ High cholesterol level
- ◯ Stroke

Neurological

- ◯ Alzheimer's / Dementia
- ◯ Ataxia / Tremors
- ◯ Epilepsy / Seizures
- ◯ Migraines
- ◯ Parkinson's

Other

- ◯ Anxiety disorder
- ◯ Arthritis
- ◯ Asthma
- ◯ Depression
- ◯ Hearing loss
- ◯ Inflammatory bowel disorder
- ◯ Kidney disease
- ◯ Liver disease
- ◯ Lung / Respiratory disease
- ◯ Muscle weakness
- ◯ Osteoporosis
- ◯ Thyroid problems
- ◯ Vision loss

Please describe any additional significant health issues:

Please list all medications that you are currently taking:

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Family History

Please indicate if any of the listed family members have a history of any of the following:	Mother	Father	Maternal Grandmother	Maternal Grandfather	Paternal Grandmother	Paternal Grandfather	Brother / Sister (Circle one)	Brother / Sister (Circle one)	Brother / Sister (Circle one)	Brother / Sister (Circle one)
Cancer										
Breast	○	○	○	○	○	○	○	○	○	○
Colon	○	○	○	○	○	○	○	○	○	○
Leukemia	○	○	○	○	○	○	○	○	○	○
Lung	○	○	○	○	○	○	○	○	○	○
Ovarian	○	○	○	○	○	○	○	○	○	○
Pancreatic	○	○	○	○	○	○	○	○	○	○
Prostate	○	○	○	○	○	○	○	○	○	○
Skin	○	○	○	○	○	○	○	○	○	○
Other _____	○	○	○	○	○	○	○	○	○	○
Depression	○	○	○	○	○	○	○	○	○	○
Diabetes										
Type I (Insulin dependent)	○	○	○	○	○	○	○	○	○	○
Type II (Non-insulin dependent)	○	○	○	○	○	○	○	○	○	○
Neurological										
Alzheimer's / Dementia	○	○	○	○	○	○	○	○	○	○
Ataxia / Tremors	○	○	○	○	○	○	○	○	○	○
Epilepsy / Seizures	○	○	○	○	○	○	○	○	○	○
Parkinson's	○	○	○	○	○	○	○	○	○	○
Other										
Anxiety disorder	○	○	○	○	○	○	○	○	○	○
Arthritis	○	○	○	○	○	○	○	○	○	○
Asthma	○	○	○	○	○	○	○	○	○	○
Hearing loss	○	○	○	○	○	○	○	○	○	○
Heart disease	○	○	○	○	○	○	○	○	○	○
Inflammatory bowel disorder	○	○	○	○	○	○	○	○	○	○
Intellectual disability	○	○	○	○	○	○	○	○	○	○
Kidney disease	○	○	○	○	○	○	○	○	○	○
Liver disease	○	○	○	○	○	○	○	○	○	○
Lung / Respiratory disease	○	○	○	○	○	○	○	○	○	○
Muscle weakness	○	○	○	○	○	○	○	○	○	○
Osteoporosis	○	○	○	○	○	○	○	○	○	○
Stroke	○	○	○	○	○	○	○	○	○	○
Thyroid problems	○	○	○	○	○	○	○	○	○	○
Vision loss	○	○	○	○	○	○	○	○	○	○

Please describe any additional significant health issues within your family:

Patient Name		Affix barcode label here
Date of Birth	___ /___ /_____	

Informed Consent and Authorization

The benefits and risks of the Genomic Inform® 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, that increase the likelihood of an individual developing a condition and/or passing a condition on to offspring or that may affect an individual's response to certain drugs. This test sequences the entire genome using a PCR-free protocol that produces comprehensive and consistent coverage of all exons and non-coding regions. The resulting data is subjected to in-silico analyses optimized for small sequence changes, structural variants (including CNVs), short tandem repeats and mitochondrial variants. The positive predictive value of this test is 0.99713. Additional information about the Genomic Inform® test is available from your healthcare provider and on the Variantyx website at https://www.variantyx.com/.

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, 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. The false negative rate for repeat expansions has not been determined for the following genes: *AFF2*, *AFF3*, *ATXN10*, *CNBP*, *CSTB*, *DIP2B*, *NOTCH2NLC*, *PHOX2B*, *TBP*. Additionally, interpretation of the results is limited by the current medical understanding of disease and available scientific information. This test does not consider somatic mutations.

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.

Possible Test Results

Test results will be issued as a single clinical report for the patient. The following types of variants will be considered: variants in genes consistent with predisposition to cancer, variants in genes consistent with predisposition to select early- and late-onset conditions (see below), variants in genes consistent with predisposition to other conditions and variants in genes consistent with carrier risk.

This test uniquely assesses short tandem repeats in genes for a number of disorders. The genes are organized into four sets. To be included in the analysis you must opt in for the desired set(s).

The first set includes genes (*AFF2*, *AFF3*, *DIP2B*, *FMR1*) that are involved in early-onset intellectual disability. An example of a variant that could be identified through the analysis of this set of genes is an expansion of the *FMR1* gene which causes fragile X syndrome. Fragile X syndrome typically presents in very young children, so it is unlikely that a full mutation variant would be identified in a healthy adult. However, premutation variants which carry an increased risk of expanding to the full mutation size and causing disease in an individual's offspring are relatively prevalent in the general population, with an estimated 1 in 178 women being carriers of an *FMR1* premutation allele.

The second set includes genes (*AR*, *ATN1*, *ATXN1*, *ATXN2*, *ATXN3*, *ATXN7*, *ATXN8OS*, *ATXN10*, *C9ORF72*, *CACNA1A*, *CNBP*, *CSTB*, *DMPK*, *FMR1*, *FXN*, *NOP56*, *NOTCH2NLC*, *PPP2R2B,* TBP) that are involved in predominately late-onset movement disorders, with or without cognitive involvement. These include disorders such as ataxia, myotonic dystrophy and frontotemporal dementia and amyotrophic lateral sclerosis (FTD-ALS). Because these disorders typically present later in life, it is possible that a disease-causing full mutation could be identified in a healthy adult who does not yet display any symptoms of the disorder. Premutation variants which carry an increased risk of expanding to the full mutation size in offspring may also be identified.

The third set includes *PHOX2B*, a gene involved in congenital central hypoventilation syndrome, and *TCF4*, a gene involved in Fuchs endothelial corneal dystrophy.

The fourth set includes the *HTT* gene that is involved in Huntington disease (HD) and the *JPH3* gene that is involved in Huntington disease like 2 (HDL2). Because these disorders typically present later in life, it is possible that a disease-causing full mutation could be identified in a healthy adult who does not yet display any symptoms of the disorder. Based on recommendations by the American College of Medical Genetics and Genomics (ACMG), the *HTT* and *JPH3* genes are excluded from this analysis by default, but may be included if a specialized consent form has been signed by the patient and ordering healthcare provider. This form can be accessed at https://www.variantyx.com/HTT-JPH3-Consent. Premutation variants which carry an increased risk of expanding to the full mutation size in offspring may also be identified.

Possible results of this test include:

Positive result - A positive result indicates that one or more genetic variants were identified that are consistent with predisposition to one of the conditions described above or that are consistent with carrier risk.

Negative result - A negative result indicates that no genetic variants were identified that are consistent with predisposition to one of the conditions described above or that are consistent with carrier risk.

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 as a possible candidate for predisposition to one of the conditions described above, but based on available information in the medical literature and research and scientific databases it is not certain whether the variant is truly indicative of increased risk. The variant could be a normal genetic change that is not expected to increase risk to develop disease or it could be a variant that has not yet been definitively associated with disease. 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/). Short tandem repeat variants with an expanded number of repeats will be reported as full mutation or premutation. Variants with an intermediate number of repeats will not be reported unless specifically requested, or if the individual has a personal or family history related to the specific gene.

Even if this test finds DNA changes that are indicative of increased risk of developing a condition, the testing may not completely predict the severity of the condition, possible future problems, or response to treatment.

Patient Name		Affix barcode label here
Date of Birth	___ / ___ / _____	

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 discuss the test results with anyone except the healthcare provider(s) that you have 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.

Sample Retention

DNA extracted from submitted samples may be stored for at least 3 months following completion of testing and will 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.

Statement of Consent

I have read the Informed Consent and Authorization section of this document. I have discussed Genomic Inform® 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. I acknowledge that the information provided by me is true and correct.

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. Regarding opt in for testing for short tandem repeat variants:

- I ◯ choose / ◯ do not choose to include genes involved in early-onset intellectual disability (*AFF2*, *AFF3*, *DIP2B*, *FMR1*) as part of this test
- I ◯ choose / ◯ do not choose to include genes involved in late-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*) as part of this test
- I ◯ choose / ◯ do not choose to include the PHOX2B gene involved in congenital central hypoventilation syndrome and the TCF4 gene involved in Fuchs endothelial corneal dystrophy as part of this test.
- I ◯ choose / ◯ do not choose to include the *HTT* gene involved in Huntington disease (HD) and the *JPH3* gene involved in Huntington disease like 2 (HDL2) as part of this test (special consent required). The special consent form can be accessed at https://www.variantyx.com/HTT-JPH3-Consent.

For each of the above, if no option is selected, findings will not be reported.

5. I ◯ choose / ◯ do not choose to be contacted by a representative of the PeopleSeq Consortium to learn more about optional participation in a survey of healthy adults receiving genetic testing. Learn more about the PeopleSeq Consortium and their NIH funded longitudinal study at https://www.genomes2people.org/research/peopleseq/.

6. 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 or improvement, internal validation, orthogonal variant confirmation at an outside referral laboratory and/or quality assurance and training purposes.

Patient (or legal guardian*) first name _____ **Patient (or legal guardian) last name** _____

Patient (or legal guardian*) signature _____ **Date** _____

*** American Association of Pathologists (AAP) and American College of Medical Genetics and Genomics (ACMG) recommendations for testing of minors**

If you sign this consent as the legal guardian of a patient who is less than 18 years of age, you acknowledge that you are doing so against the recommendation of both the American Association of Pathologists (AAP) and the American Board of Medical Genetics and Genomics (ACMG) who do not support predictive or carrier testing of minors. Both support deferring testing for the future decisional autonomy of the minor, who will be able to make an informed choice about testing once he or she reaches the age of majority.

Healthcare Provider's Statement

By my signature below, I indicate that I am the referring physician or authorized healthcare provider. I have explained the purpose of the test described above. The patient has been given the opportunity to ask questions and/or seek genetic counseling. The patient has voluntarily decided to have the test performed by Variantyx for screening purposes.

Healthcare provider name _____

Healthcare provider signature _____ **Date** _____