Affix barcode label here	Patient Name		Requested Test	☐ Singleton ☐ Trio (family)
	Date of Birth	dd/mm/yyyy		

Patient Information

First Name	Last Name	ID / MR#		
		MI	Date of Birth dd/mm/yyyy	Gender ☐ Male ☐ Female
Address		Ethnicity ☐ African/African American ☐ Latino ☐ Ashkenazi Jewish ☐ East Asian ☐ Other: ☐ European ☐ South Asian _____		
Telephone	Email			

Summary of Clinical Information – Fill out for Proband Only

In addition to selecting from the phenotypes on page 2, please include a summary of current symptoms, age of onset, family history, medical history and previous testing. This information can also be submitted as a supplementary file(s).

Sample Information

Collection Date dd/mm/yyyy

Sample Type ☐ Amniotic Fluid ☐ Blood ☐ Saliva ☐ Genomic DNA

Family Relationship – Fill out for Family Members Only

Proband's name

Affected? ☐ Yes ☐ No

Relationship to Proband ☐ Father ☐ Mother ☐ Brother ☐ Sister ☐ Other: _____

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

Healthcare Provider's Statement

By my signature below, I indicate that I am the referring physician or authorized healthcare provider. This test is medically necessary for the diagnosis or detection of a disease, illness, impairment, symptom, syndrome or disorder. The results will determine my patient's medical management and treatment decisions. I have explained the purpose of the test described in this form. 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 diagnostic purposes.

Healthcare provider signature _____ **Date** dd/mm/yyyy

Billing Information – Fill out for Proband Only

☐ Insurance Billing	☐ Institutional Billing	☐ Patient Payment
Insurance Company	Facility Name	Contact Name
Policy # Group #	Contact Name	Telephone / Email
Patient Relation to Policy Holder? ☐ Self ☐ Spouse ☐ Child	Facility Address	☐ Check (Payable to Variantyx Inc) ☐ Credit Card (Call 617-209-2090) Visa, MasterCard, Amex and Discover are accepted
Name / D.O.B. of Policy Holder (if not self)	Telephone / Fax / Email	

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Phenotype(s) / History (check all that apply) – Fill out for Proband Only

Cognitive/Physical Development

- ☐ Developmental regression
- ☐ Global developmental delay
- ☐ Intellectual disability
- ☐ Fine motor delay
- ☐ Gross motor delay
- ☐ Speech articulation difficulties
- ☐ Speech delay

Behavioral

- ☐ Autism spectrum disorder
- ☐ Self-injurious behavior
- ☐ Stereotypic behavior

Brain Anomalies

- ☐ Abnormalities of basal ganglia
- ☐ Agenesis of the corpus callosum
- ☐ Brain atrophy
- ☐ Cerebellar hypoplasia
- ☐ Cortical dysplasia
- ☐ Dandy-Walker malformation
- ☐ Encephalocele
- ☐ Heterotopia
- ☐ Holoprosencephaly
- ☐ Hydrocephalus
- ☐ Lissencephaly
- ☐ Molar tooth sign
- ☐ Periventricular leukomalacia
- ☐ Polymicrogyria

Neurological

- ☐ Ataxia/Spasticity
- ☐ Chorea
- ☐ Dysmyelination
- ☐ Dystonia
- ☐ Foot drop
- ☐ Neurodegeneration
- ☐ Neurodevelopmental NOS
- ☐ Neuromuscular NOS
- ☐ Neuropathy
  - ☐ Distal motor neuropathy
  - ☐ Proximal motor neuropathy
- ☐ Pes cavus
- ☐ Pressure palsy
- ☐ Psychiatric
- ☐ Recurrent headache/migraine
- ☐ Reduced/absent deep tendon reflexes
- ☐ Seizures
- ☐ Sleep apnia
- ☐ Stroke-like episodes
- ☐ Tremor
- ☐ Vocal cord paresis
- ☐ Other movement disorder
- ☐ Abnormal CT
- ☐ Abnormal EEG
- ☐ Abnormal EMG
- ☐ Abnormal MRI
- ☐ Abnormal nerve biopsy
- ☐ Abnormal nerve conduction velocity

Muscular

- ☐ Dysphagia
- ☐ Exercise intolerance/easy fatigue
- ☐ Hypertonia
- ☐ Hypotonia
- ☐ Mobility limitations
- ☐ Muscle fasciculations
- ☐ Muscle wasting
- ☐ Muscle weakness
- ☐ Muscular dystrophy
- ☐ Myotonia
- ☐ Abnormal muscle biopsy

Endocrine

- ☐ Adrenal hyperplasia
- ☐ Adrenal insufficiency
- ☐ Cushing syndrome
- ☐ Hypothyroidism
- ☐ Hypoparathyroidism
- ☐ Hypogonadism
- ☐ Phaeochromocytoma/paraganglioma
- ☐ Type 1 Diabetes Mellitus
- ☐ Type 2 Diabetes Mellitus

Metabolic

- ☐ CPK abnormalities
- ☐ Elevated alanine
- ☐ Elevated pyruvate
- ☐ Ketosis
- ☐ Lactic acidosis
- ☐ Low plasma carnitine
- ☐ Organic acidura
- ☐ Abnormal metabolic testing: _____

Constitutional

- ☐ Dysmorphic features
  - ☐ Cleft lip/palate
  - ☐ Syndactyly
  - ☐ Polydactyly
- ☐ Failure to thrive
- ☐ Macrocephaly
- ☐ Microcephaly
- ☐ Obesity
- ☐ Overgrowth
- ☐ Short stature
- ☐ Tall stature

Opthamology/Auditory

- ☐ Blindness
- ☐ Cataracts
- ☐ CPEO (opthalmoplegia)
- ☐ Coloboma
- ☐ Optic atrophy
- ☐ Ptosis
- ☐ Retinitis pigmentosa
- ☐ Visual impairment
- ☐ External ear malformation
- ☐ Hearing loss/deafness
- ☐ Ototoxicity (aminoglycodside-induced)

Skin/Integument

- ☐ Abnormal hair or nails: _____
- ☐ Abnormal connective tissue
- ☐ Abnormal pigmentation
- ☐ Abnormal sweating
- ☐ Abnormal temperature regulation
- ☐ Icthyosis

Skeletal

- ☐ Club foot
- ☐ Craniosynostosis
- ☐ Multiple joint contractures
- ☐ Scoliosis
- ☐ Vertebral anomalies

Cardiac

- ☐ Arrhythmia
- ☐ Cardiomyopathy
- ☐ Pulmonary venous return
- ☐ Septal defect: _____
- ☐ Syncope
- ☐ Structural heart malformation
- ☐ Tetralogy of Fallot

Gastrointestinal

- ☐ Abdominal wall defect
- ☐ Chronic intestinal pseudo-obstruction
- ☐ Constipation
- ☐ Diarrhea
- ☐ Elevated hepatic transaminases
- ☐ Gastroesophageal reflux
- ☐ Gastroschisis/Omphalocele
- ☐ Hirschspring disease
- ☐ Pyloric stenosis
- ☐ Recurrent vomiting
- ☐ Tracheoesophageal fistula

Genitourinary

- ☐ Ambiguous genitalia
- ☐ Hydronephrosis
- ☐ Hypospadias
- ☐ Kidney malformation
- ☐ Renal agenesis
- ☐ Renal tubolopathy
- ☐ Undescended testis
- ☐ Other abnormality: _____

Prenatal Anomalies

- ☐ Intrauterine growth retardation
- ☐ Oligohydramnios
- ☐ Polyhydramnios
- ☐ Premature birth
- ☐ Cystic hygroma

Other

Variantyx Inc
1671 Worcester Rd, Suite 300
Framingham, MA 01701

Phone 617-209-2090 / Fax 617-433-5024
info@variantyx.com
www.variantyx.com

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Informed Consent and Authorization

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 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. Additional information about Genomic Unity™ 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. 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. 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 under the family member's name. If the patient chooses to receive incidental findings, those findings will be included in a separate section of the clinical report. 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.

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 medical problems, or it could be a variant causing an abnormality. Without further information, the effects of the variant cannot be known and an 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.

All 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 to be the sole genetic cause for the phenotype(s) in the patient and 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.

Incidental Findings

This test may identify genetic variants, called incidental findings, that are not directly related to the disorder or symptoms that prompted the test. Some incidental findings are unavoidable, such as when a phenotype-relevant variant or gene is associated with multiple disorders. In these cases the incidental finding will be reported. You may choose whether or not to receive a more extensive report of incidental findings. There are two classes to consider: ACMG recommended incidental findings and tandem repeat incidental findings.

The American College of Medical Genetics and Genomics (ACMG) has recommended that incidental/secondary findings identified in a subset of 59 medically-actionable genes associated with a variety of inherited disorders be reported for patients undergoing WES or WGS (for more information see: https://www.ncbi.nlm.nih.gov/pubmed/27854360). Only known pathogenic or likely/expected pathogenic variants in these genes will be reported. Whether pathogenic or expected pathogenic findings or both will be reported is per gene and based on the ACMG recommendations. The disorders strongly linked to variants in these genes include cancer predisposition risk, later-onset cardiac syndromes and connective tissue syndromes. The identification of incidental/secondary findings may result in the identification of a condition for which the individual has not yet experienced symptoms.

This test uniquely assesses tandem repeats in genes for disorders involving early-onset intellectual disability (AFF2, AFF3, DIP2B, FMR1) as well as disorders involving adult-onset movement with or without cognitive involvement (AR, ATN1, ATXN1, ATXN2, ATXN3, ATXN7, ATXN8OS, ATXN10, C9ORF72, CACNA1A, CNBP, CSTB, DMPK, FMR1, FXN, PP2R2B). Full and pre mutation alleles will be reported for these genes when relevant to the patient's clinical symptoms. A more extensive report of all alleles is available as tandem repeat incidental findings. 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.

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You may choose whether or not to have these incidental findings reported. If you do not specifically opt-in to receive incidental findings, none will be reported. If you choose to receive ACMG recommended incidental findings and/or tandem repeat incidental findings there may be implications for other family members. For example, identification of a genetic variant that indicates an increased risk for an individual of developing cancer may infer that other family members may also be at increased risk of developing cancer. Family members may need to pursue clinical genetic testing through their healthcare provider if concerned about their own risk. The absence of incidental findings does not mean that there are no disease-causing genetic variants in the 59 ACMG recommended genes or in other genes.

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. It is possible that this test may identify misattributed paternity, for example identifying that the stated father of the patient is not the true biological father, and that it may be necessary to report these findings. 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

Sample Retention

DNA extracted from submitted samples will 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 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. For proband only: 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/my child's condition, diagnosis and treatment as relevant to my/my child's genetic testing, as well as information about my healthcare plan benefits. I authorize Variantyx to release my/my child's medical information concerning my/my child's 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 $500. I authorize my insurance benefits to be paid directly to Variantyx.

5. For proband only: I ☐ give / ☐ do not give permission for Variantyx to contact me or my healthcare provider about available research studies.

6. For proband only: regarding incidental/secondary findings:
I choose ☐ to receive / ☐ not to receive ACMG recommended incidental/secondary findings
I choose ☐ to receive / ☐ not to receive tandem repeat incidental/secondary findings

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

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