variantyx



# Genomic Unity® Prenatal Analysis Test Requisition Form

| | | |
|---|---|---|
| Patient Name (fetus of) | | Affix barcode label of fetal sample here |
| Patient Date of Birth | | |

## Required Information Checklist:

- ❍ Pregnancy and parent demographics
- ❍ ICD-10 codes
- ❍ Healthcare provider signature
- ❍ Signed informed consents
- ❍ Clinical & genetic counseling notes with pedigree (please include all family history of known chronic and inherited disease and copies of genetic test results if available)
- ❍ Ultrasound report(s)
- ❍ Completed TRF and all clinical notes faxed to 617-433-5024

## Test Order

| | |
|---|---|
| ◯ Genomic Unity® Prenatal Analysis | Provides whole genome sequencing to identify genetic variants that correlate with prenatal findings and/or are predicted to result in severe, early onset genetic disorders. The genetic changes identified in the test include: sequence analysis (single nucleotide variants, deletions/insertions, characterized intronic variants); copy number variants, duplications/deletions, regions of homozygosity (ROH), mobile element insertions, inversions, and aneuploidy; mitochondrial genome sequence analysis and large deletions; and short tandem repeat expansion analysis in 4 selected genes. |
| ◯ Opt-In Variants of Uncertain Significance (for trios only) | No selection will default to an opt-out option. Variants of uncertain significance (VUS) may be reported if correlated with the provided clinical symptoms of the fetus, the pregnancy and/or the family history. For more information see page 4. |
| ◯ Opt-In ACMG Secondary Findings | No selection will default to an opt-out option and findings in this category will not be returned. For more information see page 5. |
| ◯ Opt-In Fluorescent *In-Situ* Hybridization (FISH) | No selection will default to an opt-out option. Rapid FISH includes analysis for the common aneuploidies (13, 18, 21, X and Y). For more information see page 3. |

## Ordering Healthcare Provider

| | | | |
|---|---|---|---|
| First Name | Last Name | Title | NPI # |
| Facility Name | | | Phone |
| Facility Address | | | Fax |
| City | State | Zip Code / Country | Email |

## Additional Report Recipients

| | | | |
|---|---|---|---|
| Full Name | Phone | Fax | Email |
| Full Name | Phone | Fax | Email |

## Healthcare Provider's Statement

By my signature below, I attest that I am the referring physician, an authorized healthcare provider for the patient, or procurator thereof and this testing is medically necessary for diagnosis and/or treatment of the patient. I attest that the patient (or guardian) has been appropriately consented about the test including possible results and outcomes, has been given the opportunity to ask questions about the testing and/or seek genetic counseling, and agrees to allow an independent genetic counselor facilitated through a third party, DNAVisit, to provide pre-test and/or post-test genetic counseling, if required by the insurer and/or referring institution. I attest that the patient (or guardian) has voluntarily consented to testing performed by Variantyx for diagnostic purposes through both oral and written consent.

Healthcare provider signature _____ Date _____

## Billing Information

ICD-10 Code(s)*

*ICD-10 codes must be specified here and/or in attached clinical notes

◯ Insurance Billing

| | | |
|---|---|---|
| Insurance Company | Policy # | Group # |
| Policy Holder First Name | Policy Holder Last Name | Policy Holder DOB |

Who is the Policy Holder? ◯ Patient ◯ Spouse ◯ Parent

| | |
|---|---|
| Policy Holder's Employer | Employer's Address |

◯ Institutional Billing — An invoice will be sent to the institution listed above. Please contact us for alternate billing.

◯ Patient Payment — An invoice will be sent to the patient email provided. Insurance will not be billed.

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## Patient Information (fetus of)

| | | | |
|---|---|---|---|
| First Name | Last Name | MI | DOB |
| Address | | | ID/MR# |
| City | State | Country | Zip Code |
| Phone | | Email | |
| Sample Type ◯ Blood ◯ Other | | Sample Collection Date | |

## Biological Maternal Information (if egg donor or gestational carrier)

| | | | |
|---|---|---|---|
| First Name | Last Name | MI | DOB |
| Sample Type ◯ Blood ◯ Other | | Sample Collection Date | |

## Biological Paternal Information

| | | | |
|---|---|---|---|
| First Name | Last Name | MI | DOB |
| Sample Type ◯ Blood ◯ Other | | Sample Collection Date | |

## Pregnancy History - Please attach detailed clinical notes (with pedigree if available)

G _____ P _____ A _____

| | | |
|---|---|---|
| Sample Type ◯ Amniotic fluid ◯ Cultured cells ◯ Genomic DNA | | Collection Date* |
| Gestational Age at Collection<br>W _____ D _____ | Expected Delivery Date | Predicted Fetal Sex<br>◯ Male ◯ Female<br>◯ Unknown ◯ Ambiguous |
| Multiple Pregnancy?<br>◯ Twin ◯ Triplet ◯ Other _____ | Sperm Donation?<br>◯ Yes ◯ No | Egg Donation?<br>◯ Yes ◯ No |

Abnormal Findings in Previous Pregnancies

Testing Previously Performed in Current Pregnancy

◯ FISH ◯ Karyotype ◯ Microarray ◯ Maternal Serum Screening ◯ Non-Invasive Prenatal Screening ◯ Other _____

Results:

*Note that the collection date is not the same as the date of service for test billing purposes. For more information, please see CMS guidelines.

Genomic Unity® Prenatal Analysis
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## Test Information

The benefits and risks of the Genomic Unity® Prenatal Analysis test are explained below. It is recommended that you receive genetic counseling from a licensed and/or certified 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 Genomic Unity® Prenatal Analysis is a whole genome sequence based test designed to identify genetic variants that correlate with prenatal findings and/or are predicted to result in severe, early onset genetic disorders. This test includes sequence analysis (single nucleotide variants, deletions/insertions, characterized intronic variants); copy number variants, duplications/deletions, regions of homozygosity (ROH), mobile element insertions, inversions, and aneuploidy; mitochondrial genome sequence analysis and large deletions; and short tandem repeat expansion analysis in select genes.

**Test Process**
The referring medical provider will coordinate collection of the amniotic fluid sample and the parental blood samples. The collected amniotic fluid sample will be shipped to and cultured by the Center for Human Genetics (CHG). Fetal DNA, derived from cultured embryonic cells, will be extracted and undergo quality control by CHG including determination of maternal cell contamination (MCC). If elected, the cells will also be processed for fluorescence *in situ* hybridization (FISH) for common aneuploidies. For more information on MCC or FISH analyses please visit https://chginc.org/. Extracted fetal DNA will be shipped to Variantyx and its affiliates for sequencing and interpretation.

The test is offered as a “trio" test, which compares the fetus’ DNA sequence to its biological parents' samples. Fetal sex is determined from the sequencing data and displayed in the analysis report. Parental blood samples will be shipped separately to Variantyx and its affiliates for DNA extraction and sequencing.

A report with the test results will be delivered to the referring clinician and it is their responsibility to provide post-test genetic counseling and follow-up, if necessary. In certain cases, confirmatory testing may be required to verify the test results obtained, and may take several weeks to complete.

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 require the extraction to be performed in a CLIA/CAP accredited laboratory. Variantyx is not responsible for specimen errors (e.g. labeling, extraction) for samples received that may have occurred prior to our receipt.

Maternal cell contamination (MCC) will be determined and may influence the confidence of the results or the ability to proceed with testing. In the case of a sample failing the CHG evaluation of MCC but still passing the Variantyx quality control (QC), testing will proceed but may lead to an indeterminate result. In the case of a sample failing the Variantyx QC, testing will not proceed and an additional sample will be requested, extending the turnaround time.

**Turnaround Time**
The turnaround time (TAT) of this test is 20-30 days. If elected, the turnaround time for FISH testing is 3-5 days. For trio 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 fetal 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.

**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. The raw data files containing the DNA sequences (BAM files) can be transferred to the tested individuals at no additional charge, upon request, for a minimum of two years. Cultured amniocytes may be maintained for up to two weeks following the completion of testing. During this limited time period, cultures may be made available to the clinician, upon written request, for confirmatory testing such as chromosome analysis and/or (FISH).

New York 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.

**Possible Test Results**
This test will report genetic variants with evidence in the medical literature reported to be disease causing, or that are computationally predicted to be disease causing, and are classified as likely pathogenic or pathogenic in accordance with the ACMG (American College of Medical Genetics and Genomics) classification guidelines, in the genes and regions tested. Optionally, variants of uncertain clinical significance (VUS) may be reported with this test in cases of abnormal findings or medical history strongly correlated with the provided clinical symptoms of the fetus, the pregnancy and/or the family history. Result types 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 clinical symptoms or findings 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 clinical symptoms or findings was identified by this test. This reduces the likelihood of, but does not exclude a genetic cause.

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**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 a disorder. The variant could be a normal genetic difference that does not cause a 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 (if selected) 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 fetal 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 fetus. 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. Interpretation of results is limited by the current medical understanding of disease and available scientific information. Variants may not be reported if they are not associated with a disease in the OMIM database.

Regions of homozygosity (ROH) are detectable with this analysis. These regions may be indicative of segmental uniparental disomy or identity by descent. ROH is reported for regions greater than or equal to 5 megabases (Mb) for imprinted chromosomes (6, 7, 11, 14, 15 and 20). ROH for non-imprinted autosomal chromosomes is reported for regions greater than or equal to 10 Mb, which may include multiple regions. ROH is not reported for the sex chromosomes. The results of ROH are not interpreted. Additional testing may aid in diagnosis.

Variants of uncertain significance (VUS) identified in genes correlated with the reported fetal phenotype and severe early onset disorders, and that meet specific reporting criteria, will be reported only if the ordering clinician opts in to receive these results. Reporting criteria for VUSs include:

A VUS in gene with strong clinical correlation to the reported abnormal ultrasound findings and/or the pregnancy, medical or family history, and is: *de novo* VUS associated with an autosomal dominant disorder, compound heterozygous variants (single VUS in *trans* with a known pathogenic/likely pathogenic variant) associated with an autosomal recessive disease, single VUS in an autosomal dominant disorder if correlated with reported fetal phenotype, structural variants > 1 Mb if a deletion or >2 Mb if a duplication.

A VUS in gene associated with highly penetrant early onset disease and is: *de novo* VUS associated with an autosomal dominant disorder, compound heterozygous variants (single VUS in trans with a known pathogenic/likely pathogenic variant) associated with an autosomal recessive disease, structural variants > 1 Mb if a deletion or >2 Mb if a duplication.

**Single Nucleotide Variants**
Genome-wide single nucleotide variants and small deletion/insertions (<50 bp) are reported if they are known to be pathogenic or likely pathogenic and sufficient to cause severe early onset disease. Variants of uncertain significance (if selected) may be reported if there is strong clinical correlation to the fetus' reported medical findings or family history.

**Structural Variants**
Structural variants are considered genome-wide and are reported if the genes contained within the structural region have clinical correlation with the reported phenotype or are predicted to result in severe early onset disease. Structural variants are not orthogonally confirmed. Parental inheritance will be reported for structural variants when both parents are available for testing.

**Short Tandem Repeats**
Short tandem repeats in the *FMR1, AR, DMPK,* and *FXN* genes will be reported if the repeat is in a range associated with juvenile onset. Repeat expansions are not orthogonally confirmed in the *DMPK* and *FXN* genes prior to reporting. Repeat expansions will be orthogonally confirmed in the *FMR1* and *AR* genes prior to reporting. The *FXN, DMPK,* and *FMR1* expanded alleles are reported without the allele size. Methylation status is not included in this analysis. Repeat expansions are reported without reference to interrupting repeat status. Parental inheritance will be identified for reportable repeat expansions, which may reveal a risk to a parent. Reporting expansions in the *FXN* gene requires trio analysis.

**Mitochondrial Variants**
Mitochondrial variants are reported in the mitochondrial genome if they are pathogenic or likely pathogenic, previously reported in the MITOMAP database, and homoplasmic. Homoplasmic large deletions are reported; however, duplications are not. Heteroplasmy can be identified above 2%;

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## Test Information

however, the significance of variants with low level heteroplasmy is uncertain in interpretation.

**ACMG Secondary Findings**
The American College of Medical Genetics and Genomics (ACMG) recommends reporting pathogenic and likely pathogenic variants in a list of genes. Patients for whom the Genomic Unity® Prenatal Analysis test is ordered have the choice to opt-in to 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 (ACMG Secondary Findings). These variants are not typically reviewed during routine processing of fetal 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.

The option to receive Secondary (ACMG) Findings is not available to relatives, with the exception of the reported parental inheritance of the variants identified in the fetus. No specific parental results are issued as a separate report under the family member's name.

**Technical Limitations**
This assay evaluates the genome sequence within the scope described for the test. While whole genome sequencing is the most sensitive sequencing technology available today, there are a few limitations that may prevent detection of some types of DNA changes. Variant types that may not be detectable include aberrations not caused by variants in DNA sequence such as methylation abnormalities or other epigenetic modifications, fusions, chromosome conformational changes, X-linked recessive variants in females who manifest disease due to skewed X-inactivation, variants that are not uniquely mappable as in regions homologous to pseudogenes (e.g. *CYP21A2*), are of low coverage or are otherwise determined to be of low quality, or other unknown abnormalities. Uncommon 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. Mosaic aneuploidy is detectable at levels, in general, above 15%; however, the occurrence of both trisomy and monosomy for the same chromosome may not be detected. Any additional test specific limitations are noted on the individual test information web page indicated. The test sensitivity, specificity, accuracy and positive predictive value for different variant types are available upon request.

**Reporting Limitations**
This test will only report variants that correlate with prenatal findings, family history, and/or are predicted to result in severe, early onset genetic disorders. This test will not report variants related to infertility, carrier status of autosomal recessive disease, carrier status of X-linked recessive diseases, or variants that increase statistical risk for a disease, variants for late-onset conditions (including but not limited to neurological diseases, etc.) and variants associated with low penetrance diseases. Variants are not confirmed unless stated and confirmations are not part of the test turn-around time. Additional testing may be recommended to assist in the clinical correlation of results.

If there are abnormal findings in the pregnancy, interpretation will be done with reference to the provided personal medical and family history; therefore, it is important to provide accurate and complete medical notes.

Parental samples are used as reference for the fetus' test interpretation only. Parental inheritance will be listed for variants reported in the fetus, but no specific reports are issued in the parent's name. Findings in parents alone will not be reported, and therefore this test is not intended to identify diseases or carrier status in parents. However, positive findings in the fetus may disclose parental genotype, or reveal a risk to a parent.

Due to the time sensitive nature of the test, in the event that a parent is not a biological parent, mosaicism is discovered in one of the parents, or one of the parent's DNA samples has low quality, the assay will be processed without the parent and the report will contain only positive or likely positive results (i.e. no variants of uncertain clinical significance).

**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.

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Genomic Unity® Prenatal Analysis Supplement

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|---|---|---|
| Patient Name (fetus of) | | Affix barcode label of fetal sample here |
| Patient Date of Birth | | |

## Fetus Phenotypes

| | | Phenotype |
|---|---|---|
| Growth | ○ | Cystic hygroma |
| | ○ | Hydrops fetalis |
| | ○ | Increased nuchal translucency |
| | ○ | Intrauterine growth restriction (IUGR) |
| | ○ | Large for gestational age (Macrosomia) |
| | ○ | Oligohydramnios Placental abnormality |
| | ○ | Polyhydramnios |
| | ○ | Single umbilical artery |
| | ○ | Other: |
| Neurological | ○ | Abnormal posterior cranial fossa morphology |
| | ○ | Anencephaly |
| | ○ | Aplasia/hypoplasia of the corpus callosum |
| | ○ | Cerebellar hypoplasia |
| | ○ | Choroid plexus cysts |
| | ○ | Dandy-Walker malformation |
| | ○ | Decreased fetal movement |
| | ○ | Holoprosencephaly |
| | ○ | Hydrocephalus |
| | ○ | Lissencephaly |
| | ○ | Spina bifida |
| | ○ | Ventriculomegaly |
| | ○ | Other: |
| Craniofacial | ○ | Cleft lip |
| | ○ | Cleft palate |
| | ○ | Hypertelorism |
| | ○ | Hypotelorism |
| | ○ | Macrocephaly |
| | ○ | Microcephaly |
| | ○ | Micrognathia |
| | ○ | Pierre-Robin sequence |
| | ○ | Other: |
| Pulmonary | ○ | Abnormality of the thoracic cavity |
| | ○ | Congenital cystic adenomatoid malformation of lung (CCAM) |
| | ○ | Congenital diaphragmatic hernia |
| | ○ | Diaphragmatic eventration |
| | ○ | Pleural effusion |
| | ○ | Other: |
| Gastrointestinal | ○ | Abnormal stomach morphology |
| | ○ | Choanal atresia |
| | ○ | Duodenal atresia |
| | ○ | Echogenic fetal bowel |
| | ○ | Gastroschisis |
| | ○ | Omphalocele |
| | ○ | Tracheoesophageal fistula |
| | ○ | Other: |

| | | Phenotype |
|---|---|---|
| Cardiac | ○ | Aortic valve atresia |
| | ○ | Atrial septal defect (ASD) |
| | ○ | Atrioventricular canal defect |
| | ○ | Coarctation of aorta |
| | ○ | Dextrocardia |
| | ○ | Ebstein anomaly |
| | ○ | Echogenic intracardiac focus |
| | ○ | Hypoplastic left heart |
| | ○ | Hypoplastic right heart |
| | ○ | Pericardial effusion |
| | ○ | Pulmonary valve atresia |
| | ○ | Tetralogy of Fallot |
| | ○ | Transposition of the great arteries |
| | ○ | Truncus arteriosus |
| | ○ | Ventricular septal defect (VSD) |
| | ○ | Other: |
| Genitourinary | ○ | Ambiguous genitalia |
| | ○ | Fetal pyelectasis |
| | ○ | Hydronephrosis |
| | ○ | Hypogonadism |
| | ○ | Hypospadias |
| | ○ | Megacystis |
| | ○ | Polycystic kidneys |
| | ○ | Renal agenesis |
| | ○ | Urethral obstruction |
| | ○ | Ureteral obstruction |
| | ○ | Other: |
| Musculoskeletal | ○ | Abnormal vertebral morphology |
| | ○ | Abnormality of the lower limb |
| | ○ | Abnormality of the upper limb |
| | ○ | Arthrogryposis multiplex congenita |
| | ○ | Contractures |
| | ○ | Clubfoot |
| | ○ | Polydactyly |
| | ○ | Rocker bottom foot |
| | ○ | Scoliosis |
| | ○ | Short long bone |
| | ○ | Skeletal dysplasia |
| | ○ | Syndactyly |
| | ○ | Other: |

Other

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**Website**: www.variantyx.com