LASTNAME, FIRSTNAME

Patient ID:

Specimen ID: **000-000-0000-0**

DOB: **mm/dd/yyyy**

Age: **00**

Sex: **Female**

Account Number: **00000000**

Ordering Physician:

labcorp

Date Collected: **mm/dd/yyyy**	Date Received: **mm/dd/yyyy**	Date Reported: **mm/dd/yyyy**	Date Entered: **mm/dd/yyyy**

Specimen Type: **Whole Blood**

Ethnicity: **Not Provided**

Indication: **Carrier Test / Screening**

Inheritest® 14-gene Panel

SAMPLE REPORT

Summary: ■ POSITIVE

Variants Detected

Disorder *(Gene)*	Result	Interpretation
Fragile X syndrome *(FMR1)* NM_002024.5	POSITIVE: PREMUTATION CARRIER PCR: 30 and 56 Premutation allele AGG interruption(s): 1 Haplotype:(CGG)25 AGG (CGG)31	Premutation carrier of fragile X syndrome. This individual may be at risk for primary ovarian insufficiency and late-onset fragile X-associated tremor/ataxia syndrome (FXTAS), and for having children with fragile X syndrome. **Risk:** AT INCREASED RISK FOR AFFECTED PREGNANCY. Risk of expansion to full mutation in offspring is <1% (Domniz, PMID:30619448). Genetic counseling is recommended.
Alpha-thalassemia *(HBA1/HBA2)* 16p13.3	POSITIVE: CARRIER Heterozygous for the -alpha3.7 deletion. (-alpha/alpha alpha)	Predicted to be a silent carrier of alpha-thalassemia. **Risk:** AT INCREASED RISK FOR AFFECTED PREGNANCY. If this individual's reproductive partner has alpha-0-thalassemia trait (--/alpha alpha), the risk for a fetus affected with HbH disease is 25%. Genetic counseling and reproductive partner carrier screening is recommended.

Negative Results

Disorder *(Gene)*	Result	Interpretation
Canavan disease *(ASPA)* NM_000049.2	NEGATIVE	This result reduces, but does not eliminate, the risk to be a carrier. **Risk:** NOT at an increased risk for an affected pregnancy.
Bloom syndrome *(BLM)* NM_000057.3	NEGATIVE	This result reduces, but does not eliminate, the risk to be a carrier. **Risk:** NOT at an increased risk for an affected pregnancy.
Cystic fibrosis *(CFTR)* NM_000492.3	NEGATIVE	This result reduces, but does not eliminate, the risk to be a carrier. **Risk:** NOT at an increased risk for an affected pregnancy.
Familial dysautonomia *(ELP1)* NM_003640.4	NEGATIVE	This result reduces, but does not eliminate, the risk to be a carrier. **Risk:** NOT at an increased risk for an affected pregnancy.
Fanconi anemia *(FANCC)* NM_000136.2	NEGATIVE	This result reduces, but does not eliminate, the risk to be a carrier. **Risk:** NOT at an increased risk for an affected pregnancy.
Gaucher disease *(GBA)* NM_001005741.2	NEGATIVE	This result reduces, but does not eliminate, the risk to be a carrier. **Risk:** NOT at an increased risk for an affected pregnancy.
Beta-hemoglobinopathies, includes sickle cell disease and beta-thalassemias *(HBB)* NM_000518.4	NEGATIVE	This result reduces, but does not eliminate, the risk to be a carrier. **Risk:** NOT at an increased risk for an affected pregnancy.
Tay-Sachs disease *(HEXA)* NM_000520.5	NEGATIVE	This result reduces, but does not eliminate, the risk to be a carrier. **Risk:** NOT at an increased risk for an affected pregnancy.

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Negative Results (Cont.)

Disorder *(Gene)*	Result	Interpretation
Mucolipidosis type IV *(MCOLN1)* NM_020533.2	NEGATIVE	This result reduces, but does not eliminate, the risk to be a carrier. **Risk:** NOT at an increased risk for an affected pregnancy.
Spinal muscular atrophy *(SMN1)* NM_000344.3	NEGATIVE 2 copies of *SMN1*; c.*3+80T>G risk variant not present.	This result reduces, but does not eliminate, the risk to be a carrier. **Risk:** NOT at an increased risk for an affected pregnancy.
Niemann-Pick disease types A and B *(SMPD1)* NM_000543.4	NEGATIVE	This result reduces, but does not eliminate, the risk to be a carrier. **Risk:** NOT at an increased risk for an affected pregnancy.

Recommendations

Genetic counseling is recommended to discuss the potential clinical and/or reproductive implications of positive results, as well as recommendations for testing family members and, when applicable, this individual's partner. Genetic counseling services are available. To access Labcorp Genetic Counselors please visit https://womenshealth.labcorp.com/genetic-counseling or call (855) GC-CALLS (855-422-2557).

Additional Clinical Information

Fragile X syndrome is an X-linked disorder of intellectual disability with variable severity. Expansions of CGG repeat sequences in the *FMR1* gene account for 99% of variants causing fragile X syndrome. The risk of expansion from a premutation allele of 55-90 repeats to a full mutation in offspring, when transmitted by a carrier female, is reduced with increasing number of AGG interruptions in the CGG repeat sequence (Yrigollen, PMID:22498846; Nolin, PMID:25210937). Greater than 99% of males and approximately 50% of females with the full mutation are intellectually disabled. Other signs and symptoms may include delayed speech and language skills, autism, hyperactivity, developmental delay, increased susceptibility to seizures, macroorchidism in males, a long, narrow face with prominent ears, and joint laxity. Individuals with a premutation do not have fragile X syndrome, but may have an increased risk for fragile X-related disorders. Females may have fragile X-associated primary ovarian insufficiency (FXPOI), which can cause infertility or early menopause. Most males with a premutation and some females are at risk for fragile X-associated tremor and ataxia syndrome (FXTAS), which can affect balance and is associated with tremor and memory problems in older individuals. Treatment is supportive and focuses on educational and behavioral support and management of symptoms. (Santoro, PMID:22017584).

Alpha-thalassemia, a disorder with variable severity, is usually inherited in an autosomal recessive manner. Individuals with alpha-thalassemia have a deficiency in the production of hemoglobin, which carries oxygen in the blood. Silent carriers of alpha-thalassemia are not expected to have related health problems. Individuals with alpha-thalassemia trait may have symptoms of mild anemia. The two clinically significant forms of alpha thalassemia are HbH disease and Hb Bart hydrops fetalis syndrome. Signs and symptoms of the less severe HbH disease usually appear in early childhood and may include mild to moderate hemolytic anemia, hepatosplenomegaly, mild jaundice, and bone changes. Signs and symptoms of the more severe Hb Bart hydrops fetalis syndrome appear before birth and may include generalized edema, severe hydrochromic anemia, hepatosplenomegaly, heart problems, and genitourinary abnormalities. Mothers of babies affected with Hb Bart hydrops fetalis syndrome may experience serious complications, including preeclampsia, premature delivery, or abnormal bleeding during pregnancy. Co-inheritance of alpha-thalassemia and other hemoglobinopathies, such as beta-thalassemia or sickle cell disease, may modify symptoms. In utero stem cell transplantation or fetal blood transfusions may be available for affected fetuses. Without treatment, most babies with Hb Bart syndrome are stillborn or die soon after birth. Individuals with HbH disease may survive to adulthood. Treatment is otherwise supportive and may include red blood cell transfusions. (Origa, PMID:20301599).

Comments

This interpretation is based on the clinical information provided and the current understanding of the molecular genetics of the disorder(s) tested. Information about the disorder(s) tested is available at https://womenshealth.labcorp.com.

Methods/Limitations

Next-generation Sequencing: Genomic regions of interest are selected using the Twist Biosciences® hybridization capture method and sequenced via the Illumina® next generation sequencing platform. Sequencing reads are aligned with the human genome reference GRCh37/hg19 build. Regions of interest include coding exons, intron/exon junctions (+/- 20 nucleotides) and additional genomic regions with known significant pathogenic variants. Analytical sensitivity at 30X coverage is estimated to be >99% for single nucleotide variants, >99% for insertions/deletions less than six base pairs and >96% for insertions/deletions between six and forty-five base pairs. Regions with low NGS coverage are selected for Sanger sequencing based on analytical sensitivity and probability of pathogenic variant(s). Qiagen CLC Genomics and in-house algorithms identify copy number variants (CNVs) by comparing normalized read depth for each target in the region of interest with a set of clinical control samples. Expected minimum size resolution for CNVs in *CFTR* and *DMD* is 200 bp. For all other genes, expected minimum size resolution for CNVs is 1000 bp. Precise breakpoints are not reported. Single-exon deletions or duplications are not detected in some cases due to the CNV size limitations, or due to isolated data quality variation or intrinsic sequence properties. Confirmatory testing by orthogonal technologies includes Sanger sequencing, MLPA, gap PCR and low coverage whole genome sequencing analysis.

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Methods/Limitations (Cont.)

If the following genes are included in this test, these analysis restrictions are applied: *F2* includes one variant: c.*97G>A (also known as 20210G>A); *F5* includes the F5 Leiden c.1601G>A (p.Arg543Gln) (also known as R506Q) variant only; *CORO1A* excludes exon 11; *GJB2* analysis includes deletions involving the 5' end of *GJB6* and regulatory elements of *GJB2,* which result in reduced *GJB2* expression; *HFE* includes five variants: c.187C>G (p.His63Asp), c.502G>T (p.Glu168X), c.506G>A (p.Trp169X), c.845G>A (p.Cys282Tyr), and c.1006+1G>A; *NEB* excludes exons 82-105.

The following regions may have lower analytical sensitivity due to intrinsic sequence properties: *ACAT1* exon 2, *ATP6V1B1* exon 1, *BBS9* exon7, *BRIP1* exon 17, *CRLF1* exon1, *GBE1* exon5, *HGSNAT* exon 1, *IDUA* exon1, *LIFR* exons 15 and 19, *PKHD1* exon 43, *PTPRC* exon 15, *SELENON* exons 1 and 3.

Reported variants: Pathogenic and likely pathogenic variants are reported for all tests. Benign and likely benign variants are typically not reported. Variants of uncertain significance are reported when included in the test specification. Variants are specified using the numbering and nomenclature recommended by the Human Genome Variation Society (HGVS, http://www.hgvs.org/). Variant classification and confirmation are consistent with ACMG standards and guidelines (Richards, PMID:25741868; Rehm, PMID:23887774). Detailed variant classification information and reevaluation are available upon request.

Alpha thalassemia: Analysis of the alpha-globin (HBA) gene cluster is performed by NGS. Positive results are confirmed by MLPA, gap PCR, or Sanger sequencing. There are two alpha-globin genes in the HBA gene cluster, *HBA1* and *HBA2*. Typically, an individual with a normal genotype has these two genes on each chromosome (alpha alpha/alpha alpha). A deletion that removes two of the genes on one of the chromosomes is described as - -/alpha alpha. Alpha-globin variants included in the analysis are the Constant Spring non-deletion variant and the following deletions: -alpha3.7, -alpha4.2, --alpha20.5, --SEA, --FIL, --THAI, --MED, and the HS-40 regulatory region. This analysis does not detect other variants in the alpha-globin genes or variants in the beta-globin gene and may not detect the co-occurrence of a deletion and a duplication. Analytical sensitivity is estimated to be >98% for the targeted variants.

Fragile X Syndrome: PCR analysis is used to detect the number of CGG repeats on each allele of the *FMR1* gene. The reportable range is 5-200 repeats. Alleles with expansions above 200 repeats are reported as >200. In females, excluding prenatal specimens, alleles between 55 and 90 repeats are assessed by a PCR assay to determine the number and position of AGG interruptions within the CGG repeats. If indicated, methylation status is determined by PCR analysis based on methylation-specific immunoprecipitation. Interpretation of repeat expansion results is based on the following ranges: Negative: < 45 repeats; intermediate: 45-54 repeats; premutation: 55-200 repeats; full mutation: >200 repeats. The analytical sensitivity of this assay for the detection of expanded alleles in the *FMR1* gene is estimated to be >99%. Reproducibility of repeat numbers is typically ±1 for alleles containing up to 60 repeats, ±3 for alleles with 61-119 repeats, and ±10 for alleles with >119 repeats. Low levels of mosaicism (<5%) and *FMR1* variants unrelated to trinucleotide expansion are not detected by this assay.

Spinal muscular atrophy: The copy number of *SMN1* exon 7 is assessed relative to internal standard reference genes by quantitative polymerase chain reaction (qPCR). A mathematical algorithm calculates 0, 1, 2 and 3 copies with statistical confidence. In fetal specimens and specimens with 0 or 1 copies, the primer and probe binding sites are sequenced to rule out variants that could interfere with copy number analysis. *SMN2* copy number is assessed by digital droplet PCR analysis relative to an internal standard reference gene in samples with no copies of *SMN1*. For carrier screening, when two copies of *SMN1* are detected, allelic discrimination qPCR targeting c.*3+80T>G in *SMN1* is performed.

Limitations: Technologies used do not detect germline mosaicism and do not rule out the presence of large chromosomal aberrations including rearrangements and gene fusions, or variants in regions or genes not included in this test, or possible inter/intragenic interactions between variants, or repeat expansions. Variant classification and/or interpretation may change over time if more information becomes available. False positive or false negative results may occur for reasons that include: rare genetic variants, sex chromosome abnormalities, pseudogene interference, blood transfusions, bone marrow transplantation, somatic or tissue-specific mosaicism, mislabeled samples, or erroneous representation of family relationships.

References

Gregg AR, Aarabi M, Klugman S *et al*. Screening for autosomal recessive and X-linked conditions during pregnancy and preconception: a practice resource of the American College of Medical Genetics and Genomics (ACMG). *Genet Med* 23, 1793 (2021). PMID: 34285390

Disorders Tested

Alpha-thalassemia (2 genes). Autosomal recessive: *HBA1/HBA2*
Beta-hemoglobinopathies, includes sickle cell disease and beta-thalassemias (1 gene). Autosomal recessive: *HBB*
Bloom syndrome (1 gene). Autosomal recessive: *BLM*
Canavan disease (1 gene). Autosomal recessive: *ASPA*
Cystic fibrosis (1 gene). Autosomal recessive: *CFTR*
Familial dysautonomia (1 gene). Autosomal recessive: *ELP1*
Fanconi anemia (1 gene). Autosomal recessive: *FANCC*
Fragile X syndrome (1 gene). X-linked: *FMR1*. Males are not tested for X-linked disorders.
Gaucher disease (1 gene). Autosomal recessive: *GBA*
Mucolipidosis type IV (1 gene). Autosomal recessive: *MCOLN1*

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Disorders Tested (Cont.)
Niemann-Pick disease types A and B (1 gene). Autosomal recessive: *SMPD1*
Spinal muscular atrophy (1 gene). Autosomal recessive: *SMN1*
Tay-Sachs disease (1 gene). Autosomal recessive: *HEXA*

Performing Labs

Component Type	Performed at	Laboratory Director
Technical component, processing	Esoterix Genetic Laboratories, LLC, 3400 Computer Drive, Westborough, MA 01581-1771	Hui Zhu, PhD, FACMG
Technical component, analysis	Esoterix Genetic Laboratories, LLC, 3400 Computer Drive, Westborough, MA 01581-1771	Hui Zhu, PhD, FACMG
Professional component	Esoterix Genetic Laboratories, LLC, 3400 Computer Drive, Westborough, MA 01581-1771	Hui Zhu, PhD, FACMG

For inquiries, the physician may contact the lab at 800-255-7357

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Patient Details
LASTNAME, FIRSTNAME

Phone:
Date of Birth: **mm/dd/yyyy**
Age: **00**
Sex: **Female**
Patient ID:
Alternate Patient ID:

Physician Details
CLIENT NAME
CLIENT ADDRESS

Phone: **000000000**
Account Number: **00000000**
Physician ID:
NPI:

Specimen Details
Specimen ID: **00000000000**
Control ID:
Alternate Control Number:
Date Collected: **mm/dd/yyyy 0000 Local**
Date Received: **mm/dd/yyyy 1426 ET**
Date Entered: **mm/dd/yyyy 1154 ET**
Date Reported: **mm/dd/yyyy 1657 ET**

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