

LASTNAME, FIRSTNAME

DOB: mm/dd/yyyy

Account Number: 00000000



Patient ID:

Age: 00

Specimen ID: 000-000-0000-0

Sex: Female

Ordering Physician:

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

Summary: ■ POSITIVE

SAMPLE REPORT

Variants Detected

Disorder (Gene)	Result	Interpretation
Fragile X syndrome (FMR1) NM_002024.6	POSITIVE: PREMUTATION CARRIER PCR repeats: 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_000049.4	NEGATIVE	This result reduces, but does not eliminate, the risk to be a carrier. Risk: NOT at an increased risk for an affected pregnancy.
Bloom syndrome (BLM) NM_000057.4	NEGATIVE	This result reduces, but does not eliminate, the risk to be a carrier. Risk: NOT at an increased risk for an affected pregnancy.
Cystic fibrosis (CFTR) NM_000492.4	NEGATIVE	This result reduces, but does not eliminate, the risk to be a carrier. Risk: NOT at an increased risk for an affected pregnancy.
Familial dysautonomia (ELP1) NM_003640.5	NEGATIVE	This result reduces, but does not eliminate, the risk to be a carrier. Risk: NOT at an increased risk for an affected pregnancy.
Fanconi anemia (FANCC) NM_000136.3	NEGATIVE	This result reduces, but does not eliminate, the risk to be a carrier. Risk: NOT at an increased risk for an affected pregnancy.
Gaucher disease (GBA1) NM_001005741.3	NEGATIVE	This result reduces, but does not eliminate, the risk to be a carrier. Risk: NOT at an increased risk for an affected pregnancy.
Beta-hemoglobinopathies, includes sickle cell disease and beta-thalassemias (HBB) NM_000518.5	NEGATIVE	This result reduces, but does not eliminate, the risk to be a carrier. Risk: NOT at an increased risk for an affected pregnancy.
Tay-Sachs disease (HEXA) NM_000520.6	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
Mucopolidosis type IV (<i>MCOLN1</i>) NM_020533.3	NEGATIVE	This result reduces, but does not eliminate, the risk to be a carrier. Risk: NOT at an increased risk for an affected pregnancy.
Spinal muscular atrophy (<i>SMN1</i>) NM_000344.4	NEGATIVE 2 copies of <i>SMN1</i> ; 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 (<i>SMPD1</i>) NM_000543.5	NEGATIVE	This result reduces, but does not eliminate, the risk to be a carrier. Risk: NOT at an increased risk for an affected pregnancy.

Recommendations

If the above result is positive, genetic counseling is recommended to discuss the potential clinical and/or reproductive implications, 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 hypochromic 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 (NGS): Genomic regions of interest are selected using the Twist Bioscience® hybridization capture method and sequenced via the Illumina® NGS platform. Sequencing reads are aligned to the human genome reference GRCh37/hg19 build. Regions of interest include coding exons, intron/exon junctions (typically +/- 20 nucleotides) and additional genomic regions with known significant pathogenic variants. Estimated analytical sensitivity is >99% for single nucleotide variants and insertions/deletions <45 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 or to the median read depth across the samples within the same NGS run. The overall analytical sensitivity for CNV detection in *CFTR* and *DMD* is >99% and, based on simulation studies, the estimated analytical sensitivity for single exon deletions is >97% and for single exon duplications is >82%. For all other genes, the assay is designed to detect CNVs with genomic size >10 kb and typically involving two or more consecutive coding exons with an overall analytical sensitivity of 96.7%. Large single-exon deletions or duplications may be detected. Precise breakpoints are not reported. Confirmatory testing by orthogonal technologies may include

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Methods/Limitations (Cont.)

Sanger sequencing, MLPA, gap PCR, or low coverage whole genome sequencing analysis.

If the following genes are included in this test, these analysis restrictions are applied: *F2* includes c.*97G>A variant only (also known as 20210G>A); *F5* includes the F5 Leiden c.1601G>A (p.Arg543Gln) variant only (also known as R506Q); *GJB2* analysis includes deletions involving the 5' end of *GJB6* and regulatory elements of *GJB2* that result in reduced *GJB2* expression; *HFE* includes full gene deletion and five variants: c.187C>G (p.His63Asp), c.502G>T (p.Glu168X), c.506G>A (p.Trp169X), c.845G>A (p.Cys282Tyr), c.1006+1G>A; *NEB* excludes exons 82-105; *TNXB* excludes exons 32-44. Regions not included in CNV analysis: *BBS9* exons 15-17, *CEP290* gene, *CORO1A* exon 11, *TMEM231* exons 2-3. Copy number gains cannot be detected in *PLN* and *RMRP*. Regions that may have lower analytical sensitivity due to intrinsic sequence properties: *ARX* exon 2, *RPGR* exon 13, *RPS6KA3* exon 20, *SELENON* exon1 and *SLC6A8* exon 1.

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 with fluorescent primers is used to amplify the CGG repeat region of the *FMR1* gene and Amelogenin loci on the X and Y chromosomes. PCR products are sized using capillary electrophoresis and GeneMapper fragment analysis software. The reportable CGG repeat ranges are: negative: <45; intermediate: 45-54; premutation: 55-200; full mutation: >200. Postnatal female samples with premutations of 55-90 repeats are reflexed to assess AGG interruptions within the CGG repeats. The predicted risk for the premutation to expand to a full mutation in the next generation is based on the size of the premutation and the number of AGG interruptions. If indicated, methylation PCR analysis using methylation-specific immunoprecipitation is performed. Relative amounts of methylated and unmethylated products are assessed to determine the methylation status: unmethylated, partially methylated, or completely methylated. 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 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: *GBA1*

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Patient ID:

Age: 00

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Specimen ID: 000-000-0000-0

Sex: Female

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Disorders Tested (Cont.)

Mucopolipidosis type IV (1 gene). Autosomal recessive: *MCOLN1*
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

This test was developed and its performance characteristics determined by Esoterix Genetic Laboratories, LLC. It has not been cleared or approved by the Food and Drug Administration.

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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: 0000000000

Control ID:

Alternate Control Number:

Date Collected: mm/dd/yyyy 0000 Local

Date Received: mm/dd/yyyy 0000 ET

Date Entered: mm/dd/yyyy 0000 ET

Date Reported: mm/dd/yyyy 0000 ET

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