SAMPLE REPORT

Specimen ID: 00000000
Control ID:

Acct #:
Phone:

LASTNAME, FIRSTNAME

CLIENT ADDRESS

Patient Details
DOB: M/DD/YYYY
Age (yyy/mm/dd): YYY/MM/DD
Gender: Female
Patient ID: 00000000

Specimen Details
Date collected: M/DD/YYYY 00:00 AM
Date received: M/DD/YYYY 00:00 PM
Date entered: M/DD/YYYY 00:00 PM
Date reported: M/DD/YYYY 00:00 PM

Physician Details
Ordering: ORDERING PHYS. NAME
Referring:
ID:
NPI:

Ethnicity: Not Provided
Indication: not provided

Specimen Type: Whole Blood

Lab ID:

DISORDER *(GENE)*	RESULTS	INTERPRETATION
Spinal muscular atrophy *(SMN1)*	AT RISK	2 copies of *SMN1*; positive for c.*3+80T>G SNP. At risk to be a silent carrier (2+0). For ethnic-specific risk revisions see Information Table. Genetic counseling is recommended.
Fragile X syndrome *(FMR1)*	PCR: 30 and 31 repeats.	Negative: not a carrier of a fragile X expansion mutation. This result is not associated with fragile X syndrome.
All other disorders	NEGATIVE for the mutations analyzed.	These results reduce, but do not eliminate, the chance to be a carrier. See Information Tables.

All Inheritest carrier screening panels include disorders for which professional societies have provided guidelines, including cystic fibrosis and spinal muscular atrophy. Genetic counseling services are available. To access Integrated Genetics Genetic Counselors please visit www.integratedgenetics.com/genetic-counseling or call (855) GC-CALLS (855-422-2557).

ADDITIONAL CLINICAL INFORMATION

Spinal muscular atrophy: Spinal muscular atrophy (SMA) is an autosomal recessive neurodegenerative disorder with variable age at onset and severity, characterized by progressive degeneration of the lower motor neurons in the spinal cord and brain stem, leading to muscle weakness, and in its most common form, respiratory failure by age two. Complications of SMA may include poor weight gain, sleep difficulties, pneumonia, scoliosis, and joint deformities. In severely affected individuals, abnormal fetal ultrasound findings may include congenital joint contractures, polyhydramnios, and decreased fetal movement (Korinthenberg, PMID:9307259). Treatment is supportive. Targeted therapies may be available for some individuals. Approximately 94% of affected individuals have 0 copies of the *SMN1* gene; in these individuals an increase in the number of copies of the *SMN2* gene correlates with reduced disease severity (Feldkotter, PMID:11791208). Individuals with one copy of the *SMN1* gene are predicted to be carriers of SMA; those with two or more copies have a reduced carrier risk. For individuals with two copies of the *SMN1* gene, the presence or absence of the variant c.*3+80T>G correlates with an increased or decreased risk, respectively, of being a silent carrier (2+0) (Luo, PMID 23788250; Feng, PMID 28125085). Genetic counseling is recommended to discuss the potential clinical and/or reproductive implications of these results, as well as recommendations for testing family members and, when applicable, this individual's partner.

Fragile X syndrome: 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 mutations causing fragile X syndrome. 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 risk for a premutation allele of 55-90 repeats to expand 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

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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).

COMMENTS

This analysis provides carrier testing by analyzing 14 genes for more than 1200 pathogenic variants associated with more than 13 autosomal recessive or X-linked disorders. Interpretations and risk calculations, where applicable, are based on the ethnic information and clinical and family relationships provided, as well as the current understanding of the molecular genetics of the conditions tested. References and additional information about the disorders are available at www.integratedgenetics.com.

The standard of care for Tay-Sachs disease carrier detection in all ethnic groups is enzyme (hexosaminidase A) analysis. For maximum sensitivity and specificity, enzyme analysis should be performed in addition to DNA variant analysis (Schneider, PMID:19876898). If Tay-Sachs enzyme analysis was ordered, results are reported separately.

The standard of care for determining carrier status for sickle cell disease and other hemoglobinopathies is to combine information from clinical assessment, complete blood count, hemoglobin electrophoresis, and DNA testing (Traeger-Synodinos, PMID:25052315). If hemoglobin electrophoresis was ordered, results are reported separately.

METHOD/LIMITATIONS

Next generation sequencing (NGS): Genomic regions of interest are selected using the Agilent®SureSelectXT® hybridization capture method for target enrichment and sequenced via the Illumina® next generation sequencing platform. Sequencing reads are aligned with the human genome reference GRCh37/hg19 build. Targeted regions are sequenced to at least 200X mean base coverage with a minimum of 99% of bases at ≥20X coverage. Analytical sensitivity is estimated to be >99% for single nucleotide variants and small insertions/deletions (≤6 bp).

Alpha thalassemia: Analysis of the alpha-globin (*HBA*) gene cluster is performed by multiplex ligation-dependent amplification (MLPA). 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 MLPA 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 >99% for the targeted variants.

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. When no copies of *SMN1* are detected, the primer and probe binding sites are sequenced to rule out variants that could interfere with copy number analysis and *SMN2* copy number is assessed by digital droplet PCR analysis relative to an internal standard reference gene. For carrier screening, when two copies of *SMN1* are detected, allelic discrimination qPCR targeting c.*3+80T>G in *SMN1* is performed.

Fragile X syndrome: DNA is amplified by the polymerase chain reaction (PCR) to determine the size of the CGG repeat region within the *FMR1* gene. PCR products are generated using a fluorescence labeled primer and sized by capillary gel electrophoresis. If indicated, Southern blot analysis is performed by hybridizing the probe StB12.3 to EcoRI- and EagI-digested DNA. The analytical sensitivity of both Southern blot and PCR analyses is 99% for expansion mutations in the *FMR1* gene. Reported CGG repeat sizes may vary as follows: +/- one for repeats less than 60, and +/- two to four for repeats in the 60 - 120 range. For repeats greater than 120, the accuracy is +/- 10%. If 55-90 trinucleotide repeats are detected in females (excluding prenatal specimens), a PCR assay targeting AGG sequences within the CGG repeats is performed to assess the number and position of AGG interruptions.

Reported variants: Pathogenic and likely pathogenic variants are reported. Nondeletion variants are specified using the numbering and nomenclature

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recommended by the Human Genome Variation Society (HGVS, http://www.hgvs.org/). Variants of uncertain significance and benign variants are not reported. Variant classification and confirmation are consistent with ACMG standards and guidelines (Richards, PMID:25741868; Rehm, PMID:23887774). Detailed variant classification information is available upon request.

Limitations: Technologies used do not detect germline mosaicism and do not rule out the presence of large chromosomal aberrations, including rearrangements, or variants in regions or genes not included in this test, or possible inter/intragenic interactions between variants. 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.

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INFORMATION TABLES

SMA risk reductions for individuals with no family history

Disorder (*Gene*) Reference sequence	Population	Detection rate (Copy number + SNP)	Pre-test carrier risk	Post-test risk of being a carrier with 2 copies**		Post-test risk of being a carrier with 3 copies
				POSITIVE for the c.*3+80T>G SNP	NEGATIVE for the c.*3+80&>G SNP	
Spinal muscular atrophy (*SMN1*) NM_000344	African American	90.3%	1 in 72	1 in 34	1 in 375	1 in 4200
	Ashkenazi Jewish	92.8%	1 in 67	High risk	1 in 918	1 in 5400
	Asian	93.6%	1 in 59	High risk	1 in 907	1 in 5600
	Caucasian	95.0%	1 in 47	1 in 29	1 in 921	1 in 5600
	Hispanic	92.6%	1 in 68	1 in 140	1 in 906	1 in 5400
	Mixed or other ethnic background	For counseling purposes, consider using the ethnic background with the most conservative risk estimate				

** includes carriers who are silent carriers (2+0) and carriers with a pathogenic variant not detected in this assay
Feng, PMID 28125085; Luo, PMID 23788250; Sugarman, PMID 21811307

Gene-specific risk reductions for individuals with no family history

Disorder (*Gene*) Reference sequence	Population	Detection Rate	Pre-test carrier risk	Post-test carrier risk with negative result
Alpha-thalassemia (*HBA1*, *HBA2*) 16p13.3	African	90%	1 in 3	N/A
	American	90%	1 in 21	N/A
	Eastern Mediterranean	90%	1 in 5	N/A
	European	90%	1 in 44	N/A
	Southeast Asian	90%	1 in 2	N/A
	Western Pacific	90%	1 in 10	N/A
Beta hemoglobinopathy, beta thalassemias (*HBB*) NM_000518	African American	90%	1 in 75	1 in 741
	East Asian	93%	1 in 50	1 in 700
	Mediterranean	97%	1 in 20	1 in 634
	Middle Eastern	84%	1 in 30	1 in 182
	South Asian	95%	1 in 20	1 in 381
	Southeast Asian	90%	1 in 30	1 in 291
Beta hemoglobinopathy, hemoglobins C, D, E, and O (*HBB*) NM_000518	African American	>99%	1 in 46	Negligible
	Asian	>99%	1 in 119	Negligible
	Asian Indian	>99%	1 in 68	Negligible
	Middle Eastern	>99%	1 in 255	Negligible
	Native American	>99%	1 in 292	Negligible
	Southeast Asian	>99%	1 in 15	Negligible
Beta hemoglobinopathy, sickle cell disease (*HBB*) NM_000518	African American	>99%	1 in 14	Negligible
	Hispanic	>99%	1 in 183	Negligible
	Middle Eastern	>99%	1 in 360	Negligible
	Native American	>99%	1 in 176	Negligible

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Testing performed at Esoterix Genetic Laboratories, LLC, 3400 Computer Drive, Westborough, MA 01581 Bernice A. Allitto, PhD, FACMG, Laboratory Director 1-800-255-7357

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Disorder (*Gene*) Reference sequence	Population	Detection Rate	Pre-test carrier risk	Post-test carrier risk with negative result
Bloom syndrome (*BLM*) NM_000057	Ashkenazi Jewish	97%	1 in 134	1 in 4434
Canavan disease (*ASPA*) NM_000049	Ashkenazi Jewish	98%	1 in 55	1 in 2700
Cystic fibrosis (*CFTR*) NM_000492	African American Ashkenazi Jewish Asian American Caucasian Hispanic	>81% >97% >55% >93% >78%	1 in 61 1 in 24 1 in 94 1 in 25 1 in 58	1 in 316 1 in 767 1 in 208 1 in 343 1 in 260
Familial dysautonomia (*IKBKAP*) NM_003640	Ashkenazi Jewish	99%	1 in 31	1 in 3000
Fanconi anemia group C (*FANCC*) NM_000136	Ashkenazi Jewish	99%	1 in 100	1 in 9900
Gaucher disease (*GBA*) NM_001005741	Ashkenazi Jewish	98%	1 in 15	1 in 700
Mucolipidosis type IV (*MCOLN1*) NM_020533	Ashkenazi Jewish	96%	1 in 89	1 in 2200
Niemann-Pick disease types A and B (*SMPD1*) NM_000543	Ashkenazi Jewish Worldwide	97% 40%	1 in 116 1 in 250	1 in 3834 1 in 416
Tay-Sachs disease (*HEXA*) NM_000520	Ashkenazi Jewish US French Canadian Worldwide	96%* 47%* 46%*	1 in 27* 1 in 73* 1 in 300*	1 in 650 1 in 136 1 in 554

* Excludes pseudodeficiency alleles

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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Testing performed at Esoterix Genetic Laboratories, LLC, 3400 Computer Drive, Westborough, MA 01581 Bernice A. Allitto, PhD, FACMG, Laboratory Director 1-800-255-7357