Specimen ID:
Control ID:

Acct #:

Phone:

SAMPLE REPORT

Patient Details	Specimen Details	Physician Details
DOB: 00/00/0000	**Date collected:** 00/00/0000	**Ordering:**
Age (yyy/mm/dd): 000/00/00	**Date received:** 00/00/0000	**Referring:**
Gender: Female	**Date entered:** 00/00/0000	**ID:**
Patient ID: 00000000	**Date reported:** 00/00/0000	**NPI:**

Ethnicity: Ashkenazic Jewish
Indication: Screening

Specimen Type: Whole Blood

Lab ID:

DISEASE *(GENE)*	RESULTS	INTERPRETATION
Alpha-thalassemia *(HBA1/HBA2)*	POSITIVE. Heterozygous for the −alpha3.7 deletion (−alpha/alpha alpha)	Predicted to be a silent carrier of alpha-thalassemia. Genetic counseling is recommended. See Additional Clinical Information.
Spinal muscular atrophy *(SMN1)*	NEGATIVE.	*SMN1* copy number of two. This result reduces but does not eliminate the risk to be a carrier of SMA. For ethnic specific risk reduction see Information Table.
Fragile X syndrome *(FMR1)*	PCR: 29 and 30 repeats.	Negative: not a carrier of a fragile X expansion mutation. This result is not associated with fragile X syndrome.
All other diseases	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 call (855) GC-CALLS (855-422-2557).

ADDITIONAL CLINICAL INFORMATION

Alpha-thalassemia: 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. Genetic counseling and hemoglobinopathy testing are recommended for this individual's reproductive partner, when applicable, and family members. If this individual's reproductive partner has alpha-0-thalassemia trait (−− /alpha alpha), the risk for a fetus affected with HbH disease is 25%.

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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. 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. Approximately 94% of affected individuals have 0 copies of *SMN1*. In individuals with 0 copies of *SMN1* an increase in the number of copies of the *SMN2* gene correlates with reduced disease severity (Feldkotter M, PMID:11791208). 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.

Fragile X syndrome: Fragile X syndrome is an X-linked disorder of intellectual disability with variable severity. Expansions of CGG repeat sequences in the F*MR1* 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. 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).

COMMENTS

This analysis provides carrier testing by analyzing 48 genes for more than 2,300 pathogenic variants associated with more than 47 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,

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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: DNA is amplified by real-time polymerase chain reaction (PCR). The number of copies of exon 7 of *SMN1* is assessed relative to internal standard reference genes. A mathematical algorithm calculates 0, 1, 2 and 3 copies with statistical confidence. If one copy of *SMN1* is detected, primer and probe binding sites are sequenced to rule out variants that could interfere with copy number analysis. If no copies of *SMN1* are detected, *SMN2* copy number is assessed by digital PCR analysis relative to an internal standard reference gene. Copy number analysis cannot detect carriers with either 2 or, very rarely, 3 copies of *SMN1* on one chromosome and no copies of *SMN1* on the other chromosome.

Fragile X syndrome: DNA is amplified by the polymerase chain reaction (PCR) to determine the size of the CGG repeat 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%.

Reported variants: Pathogenic and likely pathogenic variants are reported after confirmation by Sanger sequencing or an appropriate technology. Non-deletion variants are specified using the numbering and nomenclature recommended by the Human Genome Variation Society (HGVS, http://www.hgvs.org/). Variants of uncertain significance and benign variants are not reported. Variant classification is consistent with ACMG standards and guidelines (Richards, PMID:25741868). 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**	**Pre-test carrier risk**	**Post-test carrier risk with 2 copy result**	**Post-test carrier risk with 3 copy result**
Spinal muscular atrophy *(SMN1)* NM_000344	African American	70.5%	1 in 72	1 in 130	1 in 4,200
	Ashkenazi Jewish	90.5%	1 in 67	1 in 611	1 in 5,400
	Asian	93.3%	1 in 59	1 in 806	1 in 5,600
	Asian Indian	90.2%	1 in 52	1 in 443	1 in 5,400
	Caucasian	94.8%	1 in 47	1 in 834	1 in 5,600
	Hispanic	90.0%	1 in 68	1 in 579	1 in 5,400
	Mixed or other ethnic background	For counseling purposes, consider using the ethnic background with the most conservative risk estimates			

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**
Abetalipoproteinemia (*MTTP*) NM_000253	Ashkenazi Jewish	N/A*	N/A	N/A
Alpha-thalassemia (*HBA1, HBA2*) 16p13.3	African American Eastern Mediterranean European Southeast Asian Western Pacific	90% 90% 90% 90% 90% 90%	1 in 3 1 in 21 1 in 5 1 in 44 1 in 2 1 in 10	N/A N/A N/A N/A N/A N/A
Alport syndrome, COL4A3-related (*COL4A3*) NM_000091	Ashkenazi Jewish	95%	1 in 183	1 in 3640
Arthrogryposis, mental retardation, and seizures (AMRS) (*SLC35A3*) NM_012243	Ashkenazi Jewish	N/A*	N/A	N/A
Ataxia-telangiectasia (*ATM*) NM_000051	Amish Costa Rican North African Jewish Norwegian Worldwide	99% 56% 97% 55% 40%	N/A* 1 in 100 1 in 81 1 in 197 1 in 100	N/A 1 in 226 1 in 2667 1 in 436 1 in 166
Bardet-Biedl syndrome, BBS2-related (*BBS2*) NM_031885	Ashkenazi Jewish	N/A*	1 in 136	N/A
Beta hemoglobinopathy, beta thalassemias (*HBB*) NM_000518	African American East Asian Mediterranean Middle Eastern South Asian Southeast Asian	90% 93% 97% 84% 95% 90%	1 in 75 1 in 50 1 in 20 1 in 30 1 in 20 1 in 30	1 in 741 1 in 700 1 in 634 1 in 182 1 in 381 1 in 291
Bloom syndrome (*BLM*) NM_000057	Ashkenazi Jewish	97%	1 in 134	1 in 4434

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Disorder (*Gene*) Reference sequence	Population	Detection Rate	Pre-test carrier risk	Post-test carrier risk with negative result
Canavan disease (*ASPA*) NM_000049	Ashkenazi Jewish	98%	1 in 55	1 in 2700
Carnitine palmitoyltransferase II deficiency (*CPT2*) NM_000098	Caucasian	72%	N/A*	N/A
Congenital amegakaryocytic thrombocytopenia (*MPL*) NM_005373	Ashkenazi Jewish	95%	1 in 75	1 in 1480
Congenital disorder of glycosylation type 1a (*PMM2*) NM_000303	Caucasian	89%	1 in 71	1 in 637
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
Cystinosis (*CTNS*) NM_004937	French Canadian Worldwide	70% 61%	1 in 39 1 in 158	1 in 127 1 in 403
Dihydrolipoamide dehydrogenase deficiency (*DLD*) NM_000108	Ashkenazi Jewish	95%	1 in 107	1 in 2121
Ehlers-Danlos syndrome type VIIC (*ADAMTS2*) NM_014244	Ashkenazi Jewish Worldwide	95% 80%	N/A* N/A*	N/A N/A
Familial dysautonomia (*IKBKAP*) NM_003640	Ashkenazi Jewish	99%	1 in 31	1 in 3000
Familial hyperinsulinism, ABCC8-related (*ABCC8*) NM_000352	Ashkenazi Jewish Finnish	97% 43%	1 in 52 1 in 101	1 in 1700 1 in 175
Familial Mediterranean fever (*MEFV*) NM_000243	Arab Armenian Ashkenazi Jewish North African Jewish Turkish	71% 78% 69% 94% 74%	1 in 5 1 in 5 1 in 81*** 1 in 7 1 in 5	1 in 14 1 in 19 1 in 259 1 in 100 1 in 16
Fanconi anemia group C (*FANCC*) NM_000136	Ashkenazi Jewish	99%	1 in 100	1 in 9900
Galactosemia, GALT-related (*GALT*) NM_000155	African American Ashkenazi Jewish Caucasian	65% 88% 81%	1 in 78 1 in 127 1 in 108	1 in 221 1 in 1050 1 in 564
Gaucher disease (*GBA*) NM_001005741	Ashkenazi Jewish	98%	1 in 15	1 in 700
Glycogen storage disease type Ia (*G6PC*) NM_000151	Ashkenazi Jewish Worldwide	99% 81%	1 in 64 1 in 177	1 in 6300 1 in 927
Glycogen storage disease type III (*AGL*) NM_000642	Faroese North African Jewish Worldwide	99% 99% 85%	1 in 30 1 in 37 1 in 159	1 in 2900 1 in 3600 1 in 1054
Joubert syndrome 2 (*TMEM216*) NM_001173990	Ashkenazi Jewish	99%	1 in 92	1 in 9100
Maple syrup urine disease type 1A (*BCKDHA*) NM_000709	Mennonite	99%	1 in 13	1 in 1200
Maple syrup urine disease type 1B (*BCKDHB*) NM_183050	Ashkenazi Jewish	95%	1 in 97	1 in 1921
Metachromatic leukodystrophy (*ARSA*) NM_000487	Caucasian Japanese	56% 50%	1 in 141 1 in 132	1 in 319 1 in 263

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Disorder (*Gene*) Reference sequence	Population	Detection Rate	Pre-test carrier risk	Post-test carrier risk with negative result
Mucolipidosis type IV (*MCOLN1*) NM_020533	Ashkenazi Jewish	96%	1 in 89	1 in 2200
Multiple sulphatase deficiency (*SUMF1*) NM_182760	Ashkenazi Jewish	N/A*	N/A	N/A
Nemaline myopathy, NEB-related (*NEB*) NM_001271208	Ashkenazi Jewish	95%	1 in 168	1 in 3341
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
Phenylalanine hydroxylase deficiency, includes phenylketonuria (PKU) (*PAH*) NM_000277	Caucasian Irish Turkish	57% 69% 55%	1 in 50 1 in 33 1 in 26	1 in 114 1 in 104 1 in 56
Phosphoglycerate dehydrogenase deficiency, PHGDH-related (*PHGDH*) NM_006623	Ashkenazi Jewish	N/A*	N/A	N/A
Polycystic kidney disease, autosomal recessive (*PKHD1*) NM_138694	Finnish Worldwide	79% 59%	1 in 70 1 in 70	1 in 329 1 in 169
Retinitis pigmentosa 59 (*DHDDS*) NM_024887	Ashkenazi Jewish	95%	1 in 322	1 in 6420
Smith-Lemli-Opitz syndrome (*DHCR7*) NM_001360	Worldwide	75%	1 in 71	1 in 281
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
Tyrosinemia type 1 (*FAH*) NM_000137	Ashkenazi Jewish Finnish French Canadian Worldwide	99% 95% 95% 72%	1 in 158 1 in 122 1 in 56 1 in 158	1 in 15,700 1 in 2421 1 in 1100 1 in 562
Usher syndrome type IF (*PCDH15*) NM_033056	Ashkenazi Jewish	75%	1 in 147	1 in 585
Usher syndrome type IIIA (*CLRN1*) NM_174878	Ashkenazi Jewish Finnish	98% 98%	1 in 120 1 in 134	1 in 5951 1 in 6650
Walker-Warburg syndrome, FKTN-related (*FKTN*) NM_001079802	Ashkenazi Jewish	99%	1 in 79	1 in 7800
Wilson disease (*ATP7B*) NM_000053	Asian Caucasian	39% 55%	1 in 50 1 in 90	1 in 81 1 in 199
Zellweger spectrum disorder, PEX2-related (*PEX2*) NM_000318	Ashkenazi Jewish	N/A*	1 in 123	N/A
Zellweger spectrum disorder, PEX6-related (*PEX6*) NM_000287	Worldwide	23%	1 in 280	1 in 363

* Not available: insufficient published data

**Excludes pseudodeficiency alleles

***The carrier frequency in healthy Ashkenazi Jewish individuals has been reported to be as high as 1 in 5; however, the carrier frequency of 1 in 81 is based on the observed incidence of the disorder

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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