



## Donor 5919

### Genetic Testing Summary

Fairfax Cryobank recommends reviewing this genetic testing summary with your healthcare provider to determine suitability.

Last Updated: 03/10/20

Donor Reported Ancestry: French Canadian, Austrian, Irish, Portuguese

Jewish Ancestry: No

Genetic Test*	Result	Comments/Donor's Residual Risk**
Chromosome analysis (karyotype)	Normal male karyotype	No evidence of clinically significant chromosome abnormalities
Hemoglobin evaluation	Normal hemoglobin fractionation and MCV/MCH results	Reduced risk to be a carrier for sickle cell anemia, beta thalassemia, alpha thalassemia trait (aa/-- and a-/a-) and other hemoglobinopathies
Cystic Fibrosis (CF) carrier screening	Negative by gene sequencing in the CFTR gene	1/440
Spinal Muscular Atrophy (SMA) carrier screening	Negative for deletions of exon 7 in the SMN1 gene	1/4900
Expanded Genetic Disease Carrier Screening Panel attached- 283 diseases by gene sequencing	<p><b>Carrier: Biotinidase Deficiency (BTD)</b></p> <p><b>Carrier: Niemann-Pick Disease (NPC1-Related)</b></p> <p>Negative for other genes sequenced.</p>	Partner testing is recommended before using this donor.

\*No single test can screen for all genetic disorders. A negative screening result significantly reduces, but cannot eliminate, the risk for these conditions in a pregnancy.

\*\*Donor residual risk is the chance the donor is still a carrier after testing negative.

Patient	Sample	Referring Doctor
<b>Patient Name:</b> Donor 5919 <b>Date of Birth:</b> [REDACTED] <b>Reference #:</b> [REDACTED] <b>Indication:</b> Carrier Testing <b>Test Type:</b> Expanded Carrier Screen (283) minus TSE	<b>Specimen Type:</b> Blood <b>Lab #:</b> [REDACTED] <b>Date Collected:</b> 5/9/2018 <b>Date Received:</b> 5/10/2018 <b>Final Report:</b> 5/30/2018	[REDACTED] <b>Fairfax Cryobank, Inc.</b> [REDACTED] [REDACTED] [REDACTED] [REDACTED]

## RESULT SUMMARY

### THIS PATIENT WAS TESTED FOR 283 DISEASES.

Please see Table 1 for list of diseases tested.

#### POSITIVE for biotinidase deficiency

A heterozygous (one copy) pathogenic variant, c.1330G>C, p.D444H, was detected in the *BTD* gene

#### POSITIVE for Niemann-Pick disease, type C (NPC1-related)

A heterozygous (one copy) likely pathogenic variant, c.688\_693delTCTGTG, p.S230\_V231del, was detected in the *NPC1* gene

#### NEGATIVE for the remaining diseases

#### Recommendations

Testing the partner for the above positive disorder(s) and genetic counseling are recommended.

Please note that for female carriers of X-linked diseases, follow-up testing of a male partner is not indicated. In addition, CGG repeat analysis of *FMR1* for fragile X syndrome is not performed on males as repeat expansion of premutation alleles is not expected in the male germline.

Individuals of Asian, African, Hispanic and Mediterranean ancestry should also be screened for hemoglobinopathies by CBC and hemoglobin electrophoresis.

Consideration of residual risk by ethnicity after a negative carrier screen is recommended for the other diseases on the panel, especially in the case of a positive family history for a specific disorder.

#### Interpretation for biotinidase deficiency

A heterozygous (one copy) missense variant, c.1330G>C, p.D444H, was detected in the *BTD* gene (NM\_000060.3). This variant is considered to be pathogenic and when present *in trans* with a pathogenic variant causative for biotinidase deficiency. Please note that this is a mild variant and is not expected to result in a

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disease phenotype when homozygous. If found in trans with a severe pathogenic variant, the individual is expected to develop partial biotinidase deficiency. Therefore, this individual is expected to be at least a carrier for biotinidase deficiency. Heterozygous carriers are not expected to exhibit symptoms of this disease.

### What is biotinidase deficiency?

Biotinidase deficiency is an autosomal recessive disorder caused by pathogenic variants in the gene *BTD*. This pan-ethnic disorder affects individuals within the first few months of life. Severe forms of the disorder cause children to experience neurological abnormalities such as seizures, hypotonia, developmental delay, and vision problems as well as hearing problems, respiratory problems, and cutaneous abnormalities. While effective treatment is available, symptoms such as vision problems, hearing loss, and developmental delay are irreversible. Several specific variants have been associated with full or partial biotinidase deficiency, and therefore the severity of the disease may be predicted based on the genotype.

### Interpretation for Niemann-Pick disease, type C (NPC1-related)

A heterozygous (one copy) inframe deletion, c.688\_693delTCTGTG, p.S230\_V231del, was detected in the *NPC1* gene (NM\_000271.4). This variant is considered to be likely pathogenic and when present *in trans* with a pathogenic variant causative for Niemann-Pick disease, type C (*NPC1*-related). Therefore, this individual is expected to be at least a carrier for Niemann-Pick disease, type C (*NPC1*-related). Heterozygous carriers are not expected to exhibit symptoms of this disease.

### What is Niemann-Pick disease, type C (NPC1-related)?

Niemann-Pick disease, type C (*NPC1*-related) is an autosomal recessive, pan-ethnic neurodegenerative disorder that is caused by pathogenic variants in the gene *NPC1*. The classic presentation includes spastic ataxia and seizures that begin between the ages of 2 and 4, often after a period of normal development. Progressive deterioration leads to the loss of previously learned speech, dystonia that eventually prevents oral feeding, and dementia. Most patients die in adolescence. Some patients may present in infancy with liver and lung problems, many of whom die in infancy. Occasionally, patients can present in adolescence or adulthood with neurologic manifestations. Several specific variants may be associated with the development of either the severe infantile or typical juvenile form, but some variants may not be associated with a known genotype-phenotype correlation.

This patient was tested for a panel of diseases using a combination of sequencing, targeted genotyping and copy number analysis. Please note that negative results reduce but do not eliminate the possibility that this individual is a carrier for one or more of the disorders tested. Please see Table 1 for a list of genes and diseases tested, and <http://sema4genomics.com/residualrisk> for specific detection rates and residual risk by ethnicity. With individuals of mixed ethnicity, it is recommended to use the highest residual risk estimate. Only variants determined to be pathogenic or likely pathogenic are reported in this carrier screening test.

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## TEST SPECIFIC RESULTS

### Alpha-thalassemia

#### **NEGATIVE for alpha-thalassemia**

*HBA1* copy number: 2

*HBA2* copy number: 2

No pathogenic copy number variants detected

*HBA1* and *HBA2* sequence analysis: No pathogenic or likely pathogenic variants identified

Reduced risk of being an alpha-thalassemia carrier (aa/aa)

**Genes analyzed:** *HBA1* (NM\_000558.4) and *HBA2* (NM\_000517.4)

**Inheritance:** Autosomal Recessive

### **Recommendations**

Individuals of Asian, African, Hispanic and Mediterranean ancestry should also be screened for hemoglobinopathies by CBC and hemoglobin electrophoresis.

### **Interpretation**

No pathogenic or likely pathogenic copy number variants or sequence variants were detected in this patient, suggesting that four copies of the alpha-globin gene are present (aa/aa). Typically, individuals have four functional alpha-globin genes: 2 copies of *HBA1* and 2 copies of *HBA2*, whose expression is regulated by a cis-acting regulatory element HS-40. Alpha-thalassemia carriers have three (silent carrier) or two (carrier of the alpha-thalassemia trait) functional alpha-globin genes with or without a mild phenotype. Individuals with only one functional alpha-globin gene have HbH disease with microcytic, hypochromic hemolytic anemia and hepatosplenomegaly. Loss of all four alpha-globin genes results in Hb Barts syndrome with the accumulation of Hb Barts in red blood cells and hydrops fetalis, which is fatal in utero or shortly after birth.

This individual was negative for all *HBA* deletions, duplications and variants that were tested. These negative results reduce but do not eliminate the possibility that this individual is a carrier. See *Table of Residual Risks Based on Ethnicity*. With individuals of mixed ethnicity, it is recommended to use the highest residual risk estimate.

### **Table of Residual Risks Based on Ethnicity**

<b>Ethnicity</b>	<b>Carrier Frequency</b>	<b>Detection Rate</b>	<b>Residual Risk</b>
Caucasian	1 in 500	95%	1 in 10,000
African American	1 in 30	95%	1 in 580
Asian	1 in 20	95%	1 in 380
Worldwide	1 in 25	95%	1 in 480

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**Congenital Adrenal Hyperplasia (21-Hydroxylase Deficiency)**

**NEGATIVE for congenital adrenal hyperplasia (due to 21-hydroxylase deficiency)**

CYP21A2 copy number: 2

No pathogenic copy number variants detected

No pathogenic sequence variants detected in CYP21A2

Reduced risk of being an congenital adrenal hyperplasia carrier

**Genes analyzed:** CYP21A2 (NM\_000500.6)

**Inheritance:** Autosomal Recessive

**Recommendations**

Consideration of residual risk by ethnicity (see below) after a negative carrier screen is recommended, especially in the case of a positive family history of congenital adrenal hyperplasia.

**Interpretation**

This individual was negative for all CYP21A2 deletions and duplications that were tested, and no pathogenic or likely pathogenic variants were identified by sequence analysis. These negative results reduce but do not eliminate the possibility that this individual is a carrier. See *Table of Residual Risks Based on Ethnicity*. With individuals of mixed ethnicity, it is recommended to use the highest residual risk estimate.

**Table of Residual Risk Based On Ethnicity - Classic Congenital Adrenal Hyperplasia Due to 21-Hydroxylase Deficiency**

Ethnicity	Carrier Frequency	Detection Rate	Residual Risk
Ashkenazi Jewish	1 in 40	>95%	1 in 781
Caucasian	1 in 67	>95%	1 in 1321
Worldwide	1 in 60	>95%	1 in 1181

**Table of Residual Risk Based On Ethnicity - Non-Classic Congenital Adrenal Hyperplasia Due to 21-Hydroxylase Deficiency**

Ethnicity	Carrier Frequency	Detection Rate	Residual Risk
Ashkenazi Jewish	1 in 7	>95%	1 in 121
Caucasian	1 in 11	>95%	1 in 201
Worldwide	1 in 16	>95%	1 in 301

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**Fragile X syndrome**

Fragile X CGG triplet repeat expansion testing was not performed at this time, as the patient has either been previously tested or is a male. Sequencing of the *FMR1* gene by next generation sequencing did not identify any clinically significant variants.

**Spinal Muscular Atrophy**

**NEGATIVE for spinal muscular atrophy**

*SMN1* Copy Number: >=3

*SMN2* Copy Number: 1

c.\*3+80T>G: Negative

**Negative copy number result**

**c.\*3+80T>G status does not modify residual risk (see *SMA Table*)**

**Genes analyzed:** *SMN1* (NM\_000344.3) and *SMN2* (NM\_017411.3)

**Inheritance:** Autosomal Recessive

**Recommendations**

Consideration of residual risk by ethnicity after a negative carrier screen is recommended, especially in the case of a positive family history for spinal muscular atrophy.

**Interpretation**

This patient is negative for loss of *SMN1* copy number. Complete loss of *SMN1* is causative in spinal muscular atrophy (SMA). Three or more copies of *SMN1* were detected in this individual, which is considered a negative copy number result. Parallel testing to assess the presence of an *SMN1* duplication allele was also performed to detect a single nucleotide polymorphism (SNP), c.\*3+80T>G, in intron 7 of the *SMN1* gene. This individual was found to be negative for this change; however, in individuals with three or more copies of *SMN1*, the absence or presence of this SNP does not modify residual risk.

**SMA Table: SMA Carrier detection and residual risk estimates**

Ethnicity	Carrier Frequency	Detection rate	Residual risk with 2 copies of <i>SMN1</i>	Residual risk with >3 copies of <i>SMN1</i> *
African American	1 in 85	71%	1 in 160	1 in 4,300
Ashkenazi Jewish	1 in 76	90%	1 in 672	1 in 4,800
East Asian	1 in 53	94%	1 in 864	1 in 4,900
Caucasian	1 in 48	95%	1 in 803	1 in 4,900
Latino	1 in 63	91%	1 in 609	1 in 4,800
South Asian	1 in 103	87%	1 in 637	1 in 4,700
Sephardic Jewish	1 in 34	96%	1 in 696	1 in 4,900

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\*The presence of three or more copies of *SMN1* reduces the risk of being an *SMN1* carrier between 5 - 10 fold, depending on ethnicity.  
*FOR INDIVIDUALS WITH MIXED ETHNICITY, USE HIGHEST RESIDUAL RISK ESTIMATE*

This case has been reviewed and electronically signed by Lisa Edelmann, Ph.D., FACMG, Co- Laboratory Director  
Laboratory Medical Consultant: George A. Diaz, M.D., Ph.D.

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## Test Methods and Comments

Genomic DNA isolated from this patient was analyzed by one or more of the following methodologies, as applicable:

### Fragile X CGG Repeat Analysis (Analytical Detection Rate >99%)

PCR amplification using Asuragen, Inc. AmpliX<sup>®</sup> *FMR1* PCR reagents followed by capillary electrophoresis for allele sizing was performed. Samples positive for *FMR1* CGG repeats in the premutation and full mutation size range were further analyzed by Southern blot analysis to assess the size and methylation status of the *FMR1* CGG repeat.

### Genotyping (Analytical Detection Rate >99%)

Multiplex PCR amplification and allele specific primer extension analyses using the MassARRAY<sup>®</sup> System were used to identify variants that are complex in nature or are present in low copy repeats. Rare sequence variants may interfere with assay performance.

### Multiplex Ligation-Dependent Probe Amplification (MLPA) (Analytical Detection Rate >99%)

MLPA<sup>®</sup> probe sets and reagents from MRC-Holland were used for copy number analysis of specific targets versus known control samples. False positive or negative results may occur due to rare sequence variants in target regions detected by MLPA probes. Analytical sensitivity and specificity of the MLPA method are both 99%.

For alpha thalassemia, the copy numbers of the *HBA1* and *HBA2* genes were analyzed. Alpha-globin gene deletions, triplications, and the Constant Spring (CS) mutation are assessed. This test is expected to detect approximately 90% of all alpha-thalassemia mutations, varying by ethnicity. Carriers of alpha-thalassemia with three or more *HBA* copies on one chromosome, and one or no copies on the other chromosome, may not be detected. With the exception of triplications, other benign alpha-globin gene polymorphisms will not be reported. Analyses of *HBA1* and *HBA2* are performed in association with long-range PCR of the coding regions followed by short-read sequencing.

For Duchenne muscular dystrophy, the copy numbers of all *DMD* exons were analyzed. Potentially pathogenic single exon deletions and duplications are confirmed by a second method. Analysis of *DMD* is performed in association with sequencing of the coding regions.

For congenital adrenal hyperplasia, the copy number of the *CYP21A2* gene was analyzed. This analysis can detect large deletions due to unequal meiotic crossing-over between *CYP21A2* and the pseudogene *CYP21A1P*. These 30-kb deletions make up approximately 20% of *CYP21A2* pathogenic alleles. This test may also identify certain point mutations in *CYP21A2* caused by gene conversion events between *CYP21A2* and *CYP21A1P*. Some carriers may not be identified by dosage sensitive methods as this testing cannot detect individuals with two copies (duplication) of the *CYP21A2* gene on one chromosome and loss of *CYP21A2* (deletion) on the other chromosome. Analysis of *CYP21A2* is performed in association with long-range PCR of the coding regions followed by short-read sequencing.

For spinal muscular atrophy (SMA), the copy numbers of the *SMN1* and *SMN2* genes were analyzed. The individual dosage of exons 7 and 8 as well as the combined dosage of exons 1, 4, 6 and 8 of *SMN1* and *SMN2* were assessed. Copy number gains and losses can be detected with this assay. Depending on ethnicity, 6 - 29 % of carriers will not be identified by dosage sensitive methods as this testing cannot detect individuals with two copies (duplication) of the *SMN1* gene on one chromosome and loss of *SMN1* (deletion) on the other chromosome (silent 2+0 carrier) or individuals that carry an intragenic mutation in *SMN1*. Please also note that 2% of individuals with SMA have an *SMN1* mutation that occurred *de novo*. Typically in these cases, only one parent is an SMA carrier.

The presence of the c.\*3+80T>G (chr5:70,247,901T>G) variant allele in an individual with Ashkenazi Jewish or Asian ancestry is typically indicative of a duplication of *SMN1*. When present in an Ashkenazi Jewish or Asian individual with two copies of *SMN1*, c.\*3+80T>G is likely indicative of a silent (2+0) carrier. In individuals with two copies of *SMN1* with African American, Hispanic or Caucasian ancestry, the presence or absence of c.\*3+80T>G significantly increases or decreases, respectively, the likelihood of being a silent 2+0 carrier.

Pathogenic or likely pathogenic sequence variants in exon 7 may be detected during testing for the c.\*3+80T>G variant allele; these will be reported if confirmed to be located in *SMN1* using locus-specific Sanger primers

MLPA for Gaucher disease (*GBA*), cystic fibrosis (*CFTR*), and non-syndromic hearing loss (*GJB2/GJB6*) will only be performed if indicated for confirmation of detected CNVs. If *GBA* analysis was performed, the copy numbers of exons 1, 3, 4, and 6 - 10 of the *GBA* gene (of 11 exons total) were analyzed. If *CFTR* analysis was performed, the copy numbers of all 27 *CFTR* exons were analyzed. If *GJB2/GJB6* analysis was performed, the copy number of the two *GJB2* exons were analyzed, as well as the presence or absence of the two upstream deletions of the *GJB2* regulatory region, del(*GJB6*-D13S1830) and del(*GJB6*-D13S1854).



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**Next Generation Sequencing (NGS) (Analytical Detection Rate >95%)**

NGS was performed on a panel of genes for the purpose of identifying pathogenic or likely pathogenic variants.

Agilent SureSelect™ QXT technology was used with a custom capture™ library to target the exonic regions and intron/exon splice junctions of the relevant genes, as well as a number of UTR, intronic or promoter regions that contain previously reported mutations. Samples were pooled and sequenced on the Illumina HiSeq 2500 platform in the Rapid Run mode or the Illumina NovaSeq platform in the Xp workflow, using 100 bp paired-end reads. The sequencing data was analyzed using a custom bioinformatics algorithm designed and validated in house.

The coding exons and splice junctions of the known protein-coding RefSeq genes were assessed for the average depth of coverage (minimum of 20X) and data quality threshold values. Most exons not meeting a minimum of >20X read depth across the exon are further analyzed by Sanger sequencing. Please note that several genomic regions present difficulties in mapping or obtaining read depth >20X. The exons contained within these regions are noted within Table 1 (as "Exceptions") and will not be reflexed to Sanger sequencing if the mapping quality or coverage is poor. Any variants identified during testing in these regions are confirmed by a second method and reported if determined to be pathogenic or likely pathogenic. However, as there is a possibility of false negative results within these regions, detection rates and residual risks for these genes have been calculated with the presumption that variants in these exons will not be detected, unless included in the MassARRAY® genotyping platform.

This test will detect variants within the exons and the intron-exon boundaries of the target regions. Variants outside these regions may not be detected, including, but not limited to, UTRs, promoters, and deep intronic areas, or regions that fall into the Exceptions mentioned above. This technology may not detect all small insertion/deletions and is not diagnostic for repeat expansions and structural genomic variation. In addition, a mutation(s) in a gene not included on the panel could be present in this patient.

Variant interpretation and classification was performed based on the American College of Medical Genetics Standards and Guidelines for the Interpretation of Sequence Variants (Richards et al, 2015). All potentially pathogenic variants may be confirmed by either a specific genotyping assay or Sanger sequencing, if indicated. Any benign variants, likely benign variants or variants of uncertain significance identified during this analysis will not be reported.

**Copy Number Variant Analysis (Analytical Detection Rate >95%)**

Large duplications and deletions were called from the relative read depths on an exon-by-exon basis using a custom exome hidden Markov model (XHMM) algorithm. Deletions or duplications determined to be pathogenic or likely pathogenic were confirmed by either a custom arrayCGH platform, quantitative PCR, or MLPA (depending on CNV size and gene content). While this algorithm is designed to pick up deletions and duplications of 2 or more exons in length, potentially pathogenic single-exon CNVs will be confirmed and reported, if detected.

**Exon Array (Confirmation method) (Accuracy >99%)**

The customized oligonucleotide microarray (Oxford Gene Technology) is a highly-targeted exon-focused array capable of detecting medically relevant microdeletions and microduplications at a much higher resolution than traditional aCGH methods. Each array matrix has approximately 180,000 60-mer oligonucleotide probes that cover the entire genome. This platform is designed based on human genome NCBI Build 37 (hg19) and the CGH probes are enriched to target the exonic regions of the genes in this panel.

**Quantitative PCR (Confirmation method) (Accuracy >99%)**

The relative quantification PCR is utilized on a Roche Universal Library Probe (UPL) system, which relates the PCR signal of the target region in one group to another. To test for genomic imbalances, both sample DNA and reference DNA is amplified with primer/probe sets that specific to the target region and a control region with known genomic copy number. Relative genomic copy numbers are calculated based on the standard  $\Delta\Delta Ct$  formula.

**Long-Range PCR (Analytical Detection Rate >99%)**

Long-range PCR was performed to generate locus-specific amplicons for *CYP21A2*, *HBA1* and *HBA2* and *GBA*. The PCR products were then prepared for short-read NGS sequencing and sequenced. Sequenced reads were mapped back to the original genomic locus and run through the bioinformatics pipeline. If indicated, copy number from MLPA was correlated with the sequencing output to analyze the results. For *CYP21A2*, a certain percentage of healthy individuals carry a duplication of the *CYP21A2* gene, which has no clinical consequences. In cases where two copies of a gene are located on the same chromosome in tandem, only the second copy will be amplified and assessed for potentially pathogenic variants, due to size limitations of the PCR reaction. However, because these alleles contain at least two copies of the *CYP21A2* gene in tandem, it is expected that this patient has at least one functional gene in the tandem allele and this patient is therefore less likely to be a carrier. When an

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individual carries both a duplication allele and a pathogenic variant, or multiple pathogenic variants, the current analysis may not be able to determine the phase (cis/trans configuration) of the *CYP21A2* alleles identified. Family studies may be required in certain scenarios where phasing is required to determine the carrier status.

#### Residual Risk Calculations

Carrier frequencies and detection rates for each ethnicity were calculated through the combination of internal curations of >28,000 variants and genomic frequency data from >138,000 individuals across seven ethnic groups in the gnomAD database. Additional variants in HGMD and novel deleterious variants were also incorporated into the calculation. Residual risk values are calculated using a Bayesian analysis combining the *a priori* risk of being a pathogenic mutation carrier (carrier frequency) and the detection rate. They are provided only as a guide for assessing approximate risk given a negative result, and values will vary based on the exact ethnic background of an individual. This report does not represent medical advice but should be interpreted by a genetic counselor, medical geneticist or physician skilled in genetic result interpretation and the relevant medical literature.

#### Sanger Sequencing (Confirmation method) (Accuracy >99%)

Sanger sequencing, as indicated, was performed using BigDye Terminator chemistry with the ABI 3730 DNA analyzer with target specific amplicons. It also may be used to supplement specific guaranteed target regions that fail NGS sequencing due to poor quality or low depth of coverage (<20 reads) or as a confirmatory method for NGS positive results. False negative results may occur if rare variants interfere with amplification or annealing.

Please note these tests were developed and their performance characteristics were determined by Mount Sinai Genomics, Inc. They have not been cleared or approved by the FDA. These analyses generally provide highly accurate information regarding the patient's carrier or affected status. Despite this high level of accuracy, it should be kept in mind that there are many potential sources of diagnostic error, including misidentification of samples, polymorphisms, or other rare genetic variants that interfere with analysis. Families should understand that rare diagnostic errors may occur for these reasons.

#### SELECTED REFERENCES

##### Carrier Screening

Grody W et al. ACMG position statement on prenatal/preconception expanded carrier screening. *Genet Med.* 2013 15:482-3.

##### Fragile X syndrome:

Chen L et al. An information-rich CGG repeat primed PCR that detects the full range of Fragile X expanded alleles and minimizes the need for Southern blot analysis. *J Mol Diag* 2010 12:589-600.

##### Spinal Muscular Atrophy:

Luo M et al. An Ashkenazi Jewish SMN1 haplotype specific to duplication alleles improves pan-ethnic carrier screening for spinal muscular atrophy. *Genet Med.* 2014 16:149-56.

##### Ashkenazi Jewish Disorders:

Scott SA et al. Experience with carrier screening and prenatal diagnosis for sixteen Ashkenazi Jewish Genetic Diseases. *Hum. Mutat.* 2010 31:1-11.

##### Duchenne Muscular Dystrophy:

Flanigan KM et al. Mutational spectrum of DMD mutations in dystrophinopathy patients: application of modern diagnostic techniques to a large cohort. *Hum Mutat.* 2009 30:1657-66.

##### Variant Classification:

Richards S et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med.* 2015 May;17(5):405-24

Additional disease-specific references available upon request.

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**Table 1. List of genes and diseases tested.**

Please see <http://go.sema4.com/residualrisk> for specific detection rates and residual by ethnicity.

Gene	Disease
<i>ACADM</i>	Medium Chain Acyl-CoA Dehydrogenase Deficiency
<i>ABCB11</i>	Progressive Familial Intrahepatic Cholestasis, Type 2
<i>ABCC8</i>	Familial Hyperinsulinism (ABCC8-Related)
<i>ABCD1</i>	Adrenoleukodystrophy, X-Linked
<i>ACAD9</i>	Mitochondrial Complex I Deficiency (ACAD9-Related)
<i>ACADVL</i>	Very Long Chain Acyl-CoA Dehydrogenase Deficiency
<i>ACAT1</i>	Beta-Ketothiolase Deficiency
<i>ACOX1</i>	Acyl-CoA Oxidase I Deficiency
<i>ACSF3</i>	Combined Malonic and Methylmalonic Aciduria
<i>ADA</i>	Adenosine Deaminase Deficiency
<i>ADAMTS2</i>	Ehlers-Danlos Syndrome, Type VIIC
<i>AGA</i>	Aspartylglycosaminuria
<i>AGL</i>	Glycogen Storage Disease, Type III
<i>AGPS</i>	Rhizomelic Chondrodysplasia Punctata, Type 3
<i>AGXT</i>	Primary Hyperoxaluria, Type 1
<i>AIRE</i>	Polyglandular Autoimmune Syndrome, Type 1
<i>ALDH3A2</i>	Sjogren-Larsson Syndrome
<i>ALDOB</i>	Hereditary Fructose Intolerance
<i>ALG6</i>	Congenital Disorder of Glycosylation, Type Ic
<i>ALMS1</i>	Alstrom Syndrome
<i>ALPL</i>	Hypophosphatasia
<i>AMT</i>	Glycine Encephalopathy (AMT-Related)
<i>AQP2</i>	Nephrogenic Diabetes Insipidus, Type II
<i>ARSA</i>	Metachromatic Leukodystrophy
<i>ARSB</i>	Mucopolysaccharidosis type VI
<i>ASL</i>	Argininosuccinic Aciduria
<i>ASNS</i>	Asparagine Synthetase Deficiency
<i>ASPA</i>	Canavan Disease
<i>ASS1</i>	Citrullinemia, Type 1
<i>ATM</i>	Ataxia-Telangiectasia
<i>ATP6V1B1</i>	Renal Tubular Acidosis and Deafness
<i>ATP7A</i>	Menkes Disease
<i>ATP7B</i>	Wilson Disease
<i>ATRX</i>	Alpha-Thalassemia Mental Retardation Syndrome
<i>BBS1</i>	Bardet-Biedl Syndrome (BBS1-Related)
<i>BBS10</i>	Bardet-Biedl Syndrome (BBS10-Related)
<i>BBS12</i>	Bardet-Biedl Syndrome (BBS12-Related)
<i>BBS2</i>	Bardet-Biedl Syndrome (BBS2-Related)
<i>BCKDHA</i>	Maple Syrup Urine Disease, Type 1a
<i>BCKDHB</i>	Maple Syrup Urine Disease, Type 1b
<i>BCS1L</i>	GRACILE Syndrome and Other BCS1L-Related Disorders
<i>BLM</i>	Bloom Syndrome
<i>BSND</i>	Bartter Syndrome, Type 4A
<i>BTD</i>	Biotinidase Deficiency
<i>CAPN3</i>	Limb-Girdle Muscular Dystrophy, Type 2A
<i>CBS</i>	Homocystinuria (CBS-Related)
<i>CDH23</i>	Usher Syndrome, Type ID
<i>CEP290</i>	Leber Congenital Amaurosis 10 and Other CEP290-Related Ciliopathies
<i>CERKL</i>	Retinitis Pigmentosa 26

Gene	Disease
<i>CFTR</i>	Cystic Fibrosis
<i>CHM</i>	Choroideremia
<i>CHRNE</i>	Congenital Myasthenic Syndrome (CHRNE-Related)
<i>CIITA</i>	Bare Lymphocyte Syndrome, Type II
<i>CLN3</i>	Neuronal Ceroid-Lipofuscinosis (CLN3-Related)
<i>CLN5</i>	Neuronal Ceroid-Lipofuscinosis (CLN5-Related)
<i>CLN6</i>	Neuronal Ceroid-Lipofuscinosis (CLN6-Related)
<i>CLN8</i>	Neuronal Ceroid-Lipofuscinosis (CLN8-Related)
<i>CLRN1</i>	Usher Syndrome, Type III
<i>CNGB3</i>	Achromatopsia
<i>COL27A1</i>	Steel Syndrome
<i>COL4A3</i>	Alport Syndrome (COL4A3-Related)
<i>COL4A4</i>	Alport Syndrome (COL4A4-Related)
<i>COL4A5</i>	Alport Syndrome (COL4A5-Related)
<i>COL7A1</i>	Dystrophic Epidermolysis Bullosa
<i>CPS1</i>	Carbamoylphosphate Synthetase I Deficiency
<i>CPT1A</i>	Carnitine Palmitoyltransferase IA Deficiency
<i>CPT2</i>	Carnitine Palmitoyltransferase II Deficiency
<i>CRB1</i>	Leber Congenital Amaurosis 8 / Retinitis Pigmentosa 12 / Pigmented Paravenous Chorioretinal Atrophy
<i>CTNS</i>	Cystinosis
<i>CTSK</i>	Pycnodysostosis
<i>CYBA</i>	Chronic Granulomatous Disease (CYBA-related)
<i>CYBB</i>	Chronic Granulomatous Disease (CYBB-related)
<i>CYP11B2</i>	Corticosterone Methyloxidase Deficiency
<i>CYP17A1</i>	Congenital Adrenal Hyperplasia due to 17-Alpha-Hydroxylase Deficiency
<i>CYP21A2</i>	Classic Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency
<i>CYP19A1</i>	Aromatase Deficiency
<i>CYP27A1</i>	Cerebrotendinous Xanthomatosis
<i>DCLRE1C</i>	Omenn Syndrome / Severe Combined Immunodeficiency, Athabaskan-Type
<i>DHCR7</i>	Smith-Lemli-Opitz Syndrome
<i>DHDDS</i>	Retinitis Pigmentosa 59
<i>DLD</i>	Lipoamide Dehydrogenase Deficiency
<i>DMD</i>	Duchenne Muscular Dystrophy / Becker Muscular Dystrophy
<i>DNAH5</i>	Primary Ciliary Dyskinesia (DNAH5-Related)
<i>DNAI1</i>	Primary Ciliary Dyskinesia (DNAI1-Related)
<i>DNAI2</i>	Primary Ciliary Dyskinesia (DNAI2-related)
<i>DYSF</i>	Limb-Girdle Muscular Dystrophy, Type 2B
<i>EDA</i>	Hypohidrotic Ectodermal Dysplasia 1
<i>EIF2B5</i>	Leukoencephalopathy with Vanishing White Matter
<i>EMD</i>	Emery-Dreifuss Myopathy 1
<i>ESCO2</i>	Roberts Syndrome
<i>ETFA</i>	Glutaric Acidemia, Type IIa
<i>ETFDH</i>	Glutaric Acidemia, Type IIc
<i>ETHE1</i>	Ethylmalonic Encephalopathy
<i>EVC</i>	Ellis-van Creveld Syndrome (EVC-Related)
<i>EYS</i>	Retinitis Pigmentosa 25
<i>F11</i>	Factor XI Deficiency
<i>F9</i>	Factor IX Deficiency
<i>FAH</i>	Tyrosinemia, Type I

**Patient:** Donor 5919

**DOB:** [REDACTED]

**Lab #:** [REDACTED]

Gene	Disease
<b>FAM161A</b>	Retinitis Pigmentosa 28
<b>FANCA</b>	Fanconi Anemia, Group A
<b>FANCC</b>	Fanconi Anemia, Group C
<b>FANCG</b>	Fanconi Anemia, Group G
<b>FH</b>	Fumarase Deficiency
<b>FKRP</b>	Limb-Girdle Muscular Dystrophy, Type 2I
<b>FKTN</b>	Walker-Warburg Syndrome and Other FKTN-Related Dystrophies
<b>FMR1</b>	Fragile X Syndrome
<b>G6PC</b>	Glycogen Storage Disease, Type Ia
<b>GAA</b>	Glycogen Storage Disease, Type II
<b>GALC</b>	Krabbe Disease
<b>GALK1</b>	Galactokinase Deficiency
<b>GALT</b>	Galactosemia
<b>GAMT</b>	Cerebral Creatine Deficiency Syndrome 2
<b>GBA</b>	Gaucher Disease
<b>GBE1</b>	Glycogen Storage Disease, Type IV / Adult Polyglucosan Body Disease
<b>GCDH</b>	Glutaric Acidemia, Type I
<b>GFM1</b>	Combined Oxidative Phosphorylation Deficiency 1
<b>GJB1</b>	Charcot-Marie-Tooth Disease, X-Linked
<b>GJB2</b>	Non-Syndromic Hearing Loss (GJB2-Related)
<b>GLA</b>	Fabry Disease
<b>GLB1</b>	Mucopolysaccharidosis Type IVb / GM1 Gangliosidosis
<b>GLDC</b>	Glycine Encephalopathy (GLDC-Related)
<b>GLE1</b>	Lethal Congenital Contracture Syndrome 1 / Lethal Arthrogyposis with Anterior Horn Cell Disease
<b>GNE</b>	Inclusion Body Myopathy 2
<b>GNPTAB</b>	Mucopolipidosis II / IIIA
<b>GNPTG</b>	Mucopolipidosis III Gamma
<b>GNS</b>	Mucopolysaccharidosis Type IIID
<b>GP1BA</b>	Bernard-Soulier Syndrome, Type A1
<b>GP9</b>	Bernard-Soulier Syndrome, Type C
<b>GPR56</b>	Bilateral Frontoparietal Polymicrogyria
<b>GRHPR</b>	Primary Hyperoxaluria, Type 2
<b>HADHA</b>	Long-Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency
<b>HAX1</b>	Congenital Neutropenia (HAX1-Related)
<b>HBA1/HBA2</b>	Alpha-Thalassemia
<b>HBB</b>	Beta-Globin-Related Hemoglobinopathies
<b>HEXA</b>	Tay-Sachs Disease
<b>HEXB</b>	Sandhoff Disease
<b>HFE2</b>	Hemochromatosis, Type 2A
<b>HGSNAT</b>	Mucopolysaccharidosis Type IIIC
<b>HLCS</b>	Holocarboxylase Synthetase Deficiency
<b>HMGCL</b>	HMG-CoA Lyase Deficiency
<b>HOGA1</b>	Primary Hyperoxaluria, Type 3
<b>HPS1</b>	Hermansky-Pudlak Syndrome, Type 1
<b>HPS3</b>	Hermansky-Pudlak Syndrome, Type 3
<b>HSD17B4</b>	D-Bifunctional Protein Deficiency
<b>HSD3B2</b>	3-Beta-Hydroxysteroid Dehydrogenase Type II Deficiency
<b>HYAL1</b>	Mucopolysaccharidosis type IX
<b>HYLS1</b>	Hydroletharus Syndrome
<b>IDS</b>	Mucopolysaccharidosis Type II

Gene	Disease
<b>IDUA</b>	Mucopolysaccharidosis Type I
<b>IKBKAP</b>	Familial Dysautonomia
<b>IL2RG</b>	X-Linked Severe Combined Immunodeficiency
<b>IVD</b>	Isovaleric Acidemia
<b>KCNJ11</b>	Familial Hyperinsulinism (KCNJ11-Related)
<b>LAMA3</b>	Junctional Epidermolysis Bullosa (LAMA3-Related)
<b>LAMB3</b>	Junctional Epidermolysis Bullosa (LAMB3-Related)
<b>LAMC2</b>	Junctional Epidermolysis Bullosa (LAMC2-Related)
<b>LCA5</b>	Leber Congenital Amaurosis 5
<b>LDLR</b>	Familial Hypercholesterolemia
<b>LDLRAP1</b>	Familial Autosomal Recessive Hypercholesterolemia
<b>LHX3</b>	Combined Pituitary Hormone Deficiency 3
<b>LIFR</b>	Stuve-Wiedemann Syndrome
<b>LIPA</b>	Wolman Disease / Cholesteryl Ester Storage Disease
<b>LOXHD1</b>	Deafness, Autosomal Recessive 77
<b>LPL</b>	Lipoprotein Lipase Deficiency
<b>LRPPRC</b>	Leigh Syndrome, French-Canadian Type
<b>MAN2B1</b>	Alpha-Mannosidosis
<b>MCCC1</b>	3-Methylcrotonyl-CoA Carboxylase Deficiency (MCCC1-Related)
<b>MCCC2</b>	3-Methylcrotonyl-CoA Carboxylase Deficiency (MCCC2-Related)
<b>MCOLN1</b>	Mucopolipidosis IV
<b>MED17</b>	Infantile Cerebral and Cerebellar Atrophy
<b>MEFV</b>	Familial Mediterranean Fever
<b>MESP2</b>	Spondylothoracic Dysostosis
<b>MFSD8</b>	Neuronal Ceroid-Lipofuscinosis (MFSD8-Related)
<b>MKS1</b>	Meckel syndrome 1 / Bardet-Biedl Syndrome 13
<b>MLC1</b>	Megalencephalic Leukoencephalopathy with Subcortical Cysts
<b>MMAA</b>	Methylmalonic Acidemia (MMAA-Related)
<b>MMAB</b>	Methylmalonic Acidemia (MMAB-Related)
<b>MMACHC</b>	Methylmalonic Aciduria and Homocystinuria, Cobalamin C Type
<b>MMADHC</b>	Methylmalonic Aciduria and Homocystinuria, Cobalamin D Type
<b>MPI</b>	Congenital Disorder of Glycosylation, Type Ib
<b>MPL</b>	Congenital Amegakaryocytic Thrombocytopenia
<b>MPV17</b>	Mitochondrial DNA Depletion Syndrome 6 / Navajo Neurohepatopathy
<b>MTHFR</b>	Homocystinuria due to MTHFR Deficiency
<b>MTM1</b>	Myotubular Myopathy 1
<b>MTRR</b>	Homocystinuria, cblE Type
<b>MTTP</b>	Abetalipoproteinemia
<b>MUT</b>	Methylmalonic Acidemia (MUT-Related)
<b>MYO7A</b>	Usher Syndrome, Type IB
<b>NAGLU</b>	Mucopolysaccharidosis Type IIIB
<b>NAGS</b>	N-Acetylglutamate Synthase Deficiency
<b>NBN</b>	Nijmegen Breakage Syndrome
<b>NDRG1</b>	Charcot-Marie-Tooth Disease, Type 4D
<b>NDUFAF5</b>	Mitochondrial Complex I Deficiency (NDUFAF5-Related)
<b>NDUFS6</b>	Mitochondrial Complex I Deficiency (NDUFS6-Related)
<b>NEB</b>	Nemaline Myopathy 2
<b>NPC1</b>	Niemann-Pick Disease, Type C (NPC1-Related)
<b>NPC2</b>	Niemann-Pick Disease, Type C (NPC2-Related)
<b>NPHS1</b>	Nephrotic Syndrome (NPHS1-Related) / Congenital Finnish Nephrosis

**Patient:** Donor 5919

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Gene	Disease
<b>NPHS2</b>	Nephrotic Syndrome (NPHS2-Related) / Steroid-Resistant Nephrotic Syndrome
<b>NR2E3</b>	Enhanced S-Cone Syndrome
<b>NTRK1</b>	Congenital Insensitivity to Pain with Anhidrosis
<b>OAT</b>	Ornithine Aminotransferase Deficiency
<b>OPA3</b>	3-Methylglutaconic Aciduria, Type III
<b>OTC</b>	Ornithine Transcarbamylase Deficiency
<b>PAH</b>	Phenylalanine Hydroxylase Deficiency
<b>PCCA</b>	Propionic Acidemia (PCCA-Related)
<b>PCCB</b>	Propionic Acidemia (PCCB-Related)
<b>PCDH15</b>	Usher Syndrome, Type IF
<b>PDHA1</b>	Pyruvate Dehydrogenase E1-Alpha Deficiency
<b>PDHB</b>	Pyruvate Dehydrogenase E1-Beta Deficiency
<b>PEX1</b>	Zellweger Syndrome Spectrum (PEX1-Related)
<b>PEX10</b>	Zellweger Syndrome Spectrum (PEX10-Related)
<b>PEX2</b>	Zellweger Syndrome Spectrum (PEX2-Related)
<b>PEX6</b>	Zellweger Syndrome Spectrum (PEX6-Related)
<b>PEX7</b>	Rhizomelic Chondrodysplasia Punctata, Type 1
<b>PFKM</b>	Glycogen Storage Disease, Type VII
<b>PHGDH</b>	3-Phosphoglycerate Dehydrogenase Deficiency
<b>PKHD1</b>	Polycystic Kidney Disease, Autosomal Recessive
<b>PMM2</b>	Congenital Disorder of Glycosylation, Type Ia
<b>POMGNT1</b>	Muscle-Eye-Brain Disease and Other POMGNT1-Related Congenital Muscular Dystrophy-Dystroglycanopathies
<b>PPT1</b>	Neuronal Ceroid-Lipofuscinosis (PPT1-Related)
<b>PROP1</b>	Combined Pituitary Hormone Deficiency 2
<b>PRPS1</b>	Charcot-Marie-Tooth Disease, Type 5 / Arts syndrome
<b>PSAP</b>	Combined SAP Deficiency
<b>PTS</b>	6-Pyruvoyl-Tetrahydropterin Synthase Deficiency
<b>PUS1</b>	Mitochondrial Myopathy and Sideroblastic Anemia 1
<b>PYGM</b>	Glycogen Storage Disease, Type V
<b>RAB23</b>	Carpenter Syndrome
<b>RAG2</b>	Omenn Syndrome (RAG2-Related)
<b>RAPSN</b>	Congenital Myasthenic Syndrome (RAPSN-Related)
<b>RARS2</b>	Pontocerebellar Hypoplasia, Type 6
<b>RDH12</b>	Leber Congenital Amaurosis 13
<b>RMRP</b>	Cartilage-Hair Hypoplasia
<b>RPE65</b>	Leber Congenital Amaurosis 2 / Retinitis pigmentosa 20
<b>RPGRIP1L</b>	Joubert Syndrome 7 / Meckel Syndrome 5 / COACH Syndrome
<b>RS1</b>	X-Linked Juvenile Retinoschisis
<b>RTEL1</b>	Dyskeratosis Congenita (RTEL1-Related)
<b>SACS</b>	Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay
<b>SAMHD1</b>	Aicardi-Goutières Syndrome (SAMHD1-Related)
<b>SEPSECS</b>	Progressive Cerebello-Cerebral Atrophy

Gene	Disease
<b>SGCA</b>	Limb-Girdle Muscular Dystrophy, Type 2D
<b>SGCB</b>	Limb-Girdle Muscular Dystrophy, Type 2E
<b>SGCG</b>	Limb-Girdle Muscular Dystrophy, Type 2C
<b>SGSH</b>	Mucopolysaccharidosis Type IIIA
<b>SLC12A3</b>	Gitelman Syndrome
<b>SLC12A6</b>	Andermann Syndrome
<b>SLC17A5</b>	Salla Disease
<b>SLC22A5</b>	Primary Carnitine Deficiency
<b>SLC25A13</b>	Citrin Deficiency
<b>SLC25A15</b>	Hyperornithinemia-Hyperammonemia-Homocitrullinuria Syndrome
<b>SLC26A2</b>	Sulfate Transporter-Related Osteochondrodysplasia
<b>SLC26A4</b>	Pendred Syndrome
<b>SLC35A3</b>	Arthrogyposis, Mental Retardation, and Seizures
<b>SLC37A4</b>	Glycogen Storage Disease, Type Ib
<b>SLC39A4</b>	Acrodermatitis Enteropathica
<b>SLC4A11</b>	Corneal Dystrophy and Perceptive Deafness
<b>SLC6A8</b>	Cerebral Creatine Deficiency Syndrome 1
<b>SLC7A7</b>	Lysinuric Protein Intolerance
<b>SMARCAL1</b>	Schimke Immunososseous Dysplasia
<b>SMN1</b>	Spinal Muscular Atrophy
<b>SMPD1</b>	Niemann-Pick Disease (SMPD1-Related)
<b>STAR</b>	Lipoid Adrenal Hyperplasia
<b>SUMF1</b>	Multiple Sulfatase Deficiency
<b>TCIRG1</b>	Osteopetrosis 1
<b>TECPR2</b>	Hereditary Spastic Paraparesis 49
<b>TFR2</b>	Hemochromatosis, Type 3
<b>TGM1</b>	Lamellar Ichthyosis, Type 1
<b>TH</b>	Segawa Syndrome
<b>TMEM216</b>	Joubert Syndrome 2
<b>TPP1</b>	Neuronal Ceroid-Lipofuscinosis (TPP1-Related)
<b>TRMU</b>	Acute Infantile Liver Failure
<b>TSFM</b>	Combined Oxidative Phosphorylation Deficiency 3
<b>TTPA</b>	Ataxia With Isolated Vitamin E Deficiency
<b>TYMP</b>	Myoneurogastrointestinal Encephalopathy
<b>USH1C</b>	Usher Syndrome, Type IC
<b>USH2A</b>	Usher Syndrome, Type IIA
<b>VPS13A</b>	Choreoacanthocytosis
<b>VPS13B</b>	Cohen Syndrome
<b>VPS45</b>	Congenital Neutropenia (VPS45-Related)
<b>VRK1</b>	Pontocerebellar Hypoplasia, Type 1A
<b>VSX2</b>	Microphthalmia / Anophthalmia
<b>WNT10A</b>	Odonto-Onycho-Dermal Dysplasia / Schopf-Schulz-Passarge Syndrome