



## Donor 6440

### Genetic Testing Summary

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

Last Updated: 11/28/23

Donor Reported Ancestry: Chinese, Japanese

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	1/1400
Spinal Muscular Atrophy (SMA) carrier screening	Negative for deletions of exon 7 in the SMN1 gene	1/1115
Expanded Genetic Disease Carrier Screening Panel attached- 283 diseases by gene sequencing	<b>Carrier: Alstrom Syndrome (ALMS1)</b> Negative for other genes sequenced	Partner testing recommended before using this donor.
<b>Special Testing</b>		
Genes: GYS2, LAMA2, TYR	Negative by gene sequencing	See attached for residual risks

\*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 Information**

Name: Donor 6440

Date of Birth: [REDACTED]

Sema4 ID: [REDACTED]

Client ID: [REDACTED]

Indication: Carrier Screening

**Specimen Information**

Specimen Type: Blood

Date Collected: 08/25/2021

Date Received: 08/26/2021



Final Report: 09/10/2021

**Referring Provider**[REDACTED]  
Fairfax Cryobank, Inc.

## Expanded Carrier Screen Minus TSE (283 genes)

with Personalized Residual Risk

**SUMMARY OF RESULTS AND RECOMMENDATIONS**

 <b>Positive</b>	 <b>Negative</b>
<b>Carrier of Alstrom Syndrome (AR)</b> Associated gene(s): <i>ALMS1</i> Variant(s) Detected: c.430C>T, p.Q144X, Likely Pathogenic, Heterozygous (one copy)	<b>Negative for all other genes tested</b> To view a full list of genes and diseases tested please see Table 1 in this report

AR=Autosomal recessive; XL=X-linked

**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.
- 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 of positive results

**Alstrom Syndrome (AR)****Results and Interpretation**

A heterozygous (one copy) likely pathogenic premature stop codon, c.430C>T, p.Q144X, was detected in the *ALMS1* gene (NM\_015120.4). When this variant is present in trans with a pathogenic variant, it is considered to be causative for Alstrom syndrome. Therefore, this individual is expected to be at least a carrier for Alstrom syndrome. Heterozygous carriers are not expected to exhibit symptoms of this disease.

**What is Alstrom Syndrome?**

Alstrom syndrome is a pan-ethnic, autosomal recessive disorder caused by pathogenic variants in the gene *ALMS1*. Clinical features include short stature and obesity, progressive vision and hearing loss, and chronic inflammation of the liver and kidney, leading to more severe disease. Patients also have spinal abnormalities and endocrine disorders, including insulin-resistant diabetes, hypothyroidism, growth hormone deficiency and sex hormone disorders. While some developmental delay is present, patients are not intellectually disabled. Organ dysfunction may result in early death, and most patients do not live past the age of 50. It is not currently possible to predict the severity of the disease based on the genotype.

## Test description

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 with the patient's personalized residual risk. If personalized residual risk is not provided, please see the complete residual risk table at [go.sema4.com/residualrisk](https://go.sema4.com/residualrisk). Only variants determined to be pathogenic or likely pathogenic are reported in this carrier screening test.



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Laboratory Medical Consultant: George A. Diaz, M.D., Ph.D

## Genes and diseases tested

The personalized residual risks listed below are specific to this individual. The complete residual risk table is available at [go.sema4.com/residualrisk](https://go.sema4.com/residualrisk)

Table 1: List of genes and diseases tested with detailed results

Disease	Gene	Inheritance Pattern	Status	Detailed Summary
<b>+</b> Positive				
Alstrom Syndrome	ALMS1	AR	Carrier	c.430C>T, p.Q144X, Likely Pathogenic, Heterozygous (one copy)
<b>-</b> Negative				
3-Beta-Hydroxysteroid Dehydrogenase Type II Deficiency	HSD3B2	AR	Reduced Risk	Personalized Residual Risk: 1 in 181,000
3-Methylcrotonyl-CoA Carboxylase Deficiency (MCCC1-Related)	MCCC1	AR	Reduced Risk	Personalized Residual Risk: 1 in 930
3-Methylcrotonyl-CoA Carboxylase Deficiency (MCCC2-Related)	MCCC2	AR	Reduced Risk	Personalized Residual Risk: 1 in 500
3-Methylglutaconic Aciduria, Type III	OPA3	AR	Reduced Risk	Personalized Residual Risk: 1 in 29,000
3-Phosphoglycerate Dehydrogenase Deficiency	PHGDH	AR	Reduced Risk	Personalized Residual Risk: 1 in 123,000
6-Pyruvoyl-Tetrahydropterin Synthase Deficiency	PTS	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,800
Abetalipoproteinemia	MTTP	AR	Reduced Risk	Personalized Residual Risk: 1 in 7,500
Achromatopsia (CNGB3-related)	CNGB3	AR	Reduced Risk	Personalized Residual Risk: 1 in 21,000
Acrodermatitis Enteropathica	SLC39A4	AR	Reduced Risk	Personalized Residual Risk: 1 in 62,000
Acute Infantile Liver Failure	TRMU	AR	Reduced Risk	Personalized Residual Risk: 1 in 55,000
Acyl-CoA Oxidase I Deficiency	ACOX1	AR	Reduced Risk	Personalized Residual Risk: 1 in 59,000
Adenosine Deaminase Deficiency	ADA	AR	Reduced Risk	Personalized Residual Risk: 1 in 127,000
Adrenoleukodystrophy, X-Linked	ABCD1	XL	Reduced Risk	Personalized Residual Risk: 1 in 19,000
Aicardi-Goutieres Syndrome (SAMHD1-Related)	SAMHD1	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,700
Alpha-Mannosidosis	MAN2B1	AR	Reduced Risk	Personalized Residual Risk: 1 in 8,000
Alpha-Thalassemia	HBA1/HBA2	AR	Reduced Risk	HBA1 Copy Number: 2 HBA2 Copy Number: 2 No pathogenic copy number variants detected HBA1/HBA2 Sequencing: Negative Personalized Residual Risk: 1 in 380
Alpha-Thalassemia Intellectual Disability Syndrome	ATRX	XL	Reduced Risk	Personalized Residual Risk: 1 in 48,000
Alport Syndrome (COL4A3-Related)	COL4A3	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,700
Alport Syndrome (COL4A4-Related)	COL4A4	AR	Reduced Risk	Personalized Residual Risk: 1 in 510
Alport Syndrome (COL4A5-Related)	COL4A5	XL	Reduced Risk	Personalized Residual Risk: 1 in 150,000
Andermann Syndrome	SLC12A6	AR	Reduced Risk	Personalized Residual Risk: 1 in 287,000
Argininosuccinic Aciduria	ASL	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,000
Aromatase Deficiency	CYP19A1	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,200
Arthrogryposis, Mental Retardation, and Seizures	SLC35A3	AR	Reduced Risk	Personalized Residual Risk: 1 in 240,000
Asparagine Synthetase Deficiency	ASNS	AR	Reduced Risk	Personalized Residual Risk: 1 in 178,000
Aspartylglycosaminuria	AGA	AR	Reduced Risk	Personalized Residual Risk: 1 in 172,000
Ataxia With Isolated Vitamin E Deficiency	TTPA	AR	Reduced Risk	Personalized Residual Risk: 1 in 20,000
Ataxia-Telangiectasia	ATM	AR	Reduced Risk	Personalized Residual Risk: 1 in 540
Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay	SACS	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,100

Bardet-Biedl Syndrome ( <i>BBS10</i> -Related)	<i>BBS10</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,100
Bardet-Biedl Syndrome ( <i>BBS12</i> -Related)	<i>BBS12</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 287,000
Bardet-Biedl Syndrome ( <i>BBS1</i> -Related)	<i>BBS1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 10,000
Bardet-Biedl Syndrome ( <i>BBS2</i> -Related)	<i>BBS2</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,400
Bare Lymphocyte Syndrome, Type II	<i>CIITA</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 129,000
Bartter Syndrome, Type 4A	<i>BSND</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 69,000
Bernard-Soulier Syndrome, Type A1	<i>GP1BA</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 172,000
Bernard-Soulier Syndrome, Type C	<i>GP9</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,100
Beta-Globin-Related Hemoglobinopathies	<i>HBB</i>	AR	Reduced Risk	Personalized Residual Risk (Beta-Globin-Related Hemoglobinopathies): 1 in 1,200 Personalized Residual Risk (Beta-Globin-Related Hemoglobinopathies: HbS Variant): 1 in 11,000 Personalized Residual Risk (Beta-Globin-Related Hemoglobinopathies: HbC Variant): 1 in 42,000
Beta-Ketothiolase Deficiency	<i>ACAT1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,800
Bilateral Frontoparietal Polymicrogyria	<i>GPR56</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 143,000
Biotinidase Deficiency	<i>BTBD</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,800
Bloom Syndrome	<i>BLM</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 34,000
Canavan Disease	<i>ASPA</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,200
Carbamoylphosphate Synthetase I Deficiency	<i>CPS1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 690
Carnitine Palmitoyltransferase IA Deficiency	<i>CPT1A</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 143,000
Carnitine Palmitoyltransferase II Deficiency	<i>CPT2</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 930
Carpenter Syndrome	<i>RAB23</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 28,000
Cartilage-Hair Hypoplasia	<i>RMRP</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 450
Cerebral Creatine Deficiency Syndrome 1	<i>SLC6A8</i>	XL	Reduced Risk	Personalized Residual Risk: 1 in 208,000
Cerebral Creatine Deficiency Syndrome 2	<i>GAMT</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,300
Cerebrotendinous Xanthomatosis	<i>CYP27A1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 750
Charcot-Marie-Tooth Disease, Type 4D	<i>NDRG1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 225,000
Charcot-Marie-Tooth Disease, Type 5 / Arts Syndrome	<i>PRPS1</i>	XL	Reduced Risk	Personalized Residual Risk: 1 in 114,000
Charcot-Marie-Tooth Disease, X-Linked	<i>GJB1</i>	XL	Reduced Risk	Personalized Residual Risk: 1 in 11,000
Choreoacanthocytosis	<i>VPS13A</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,700
Choroideremia	<i>CHM</i>	XL	Reduced Risk	Personalized Residual Risk: 1 in 125,000
Chronic Granulomatous Disease ( <i>CYBA</i> -Related)	<i>CYBA</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,700
Chronic Granulomatous Disease ( <i>CYBB</i> -Related)	<i>CYBB</i>	XL	Reduced Risk	Personalized Residual Risk: 1 in 294,000
Citrin Deficiency	<i>SLC25A13</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,200
Citrullinemia, Type 1	<i>ASS1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 81,000
Cohen Syndrome	<i>VPS13B</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 13,000
Combined Malonic and Methylmalonic Aciduria	<i>ACSF3</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 23,000
Combined Oxidative Phosphorylation Deficiency 1	<i>GFM1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 8,100
Combined Oxidative Phosphorylation Deficiency 3	<i>TSFM</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 21,000
Combined Pituitary Hormone Deficiency 2	<i>PROP1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,300
Combined Pituitary Hormone Deficiency 3	<i>LHX3</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 121,000
Combined SAP Deficiency	<i>PSAP</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 78,000
Congenital Adrenal Hyperplasia due to 17-Alpha-Hydroxylase Deficiency	<i>CYP17A1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 840

Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency	CYP21A2	AR	Reduced Risk	CYP21A2 copy number: 2 CYP21A2 sequencing: Negative
				Personalized Residual Risk (Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency (Non-Classic)): 1 in 300 Personalized Residual Risk (Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency (Classic)): 1 in 1,200
Congenital Amegakaryocytic Thrombocytopenia	MPL	AR	Reduced Risk	Personalized Residual Risk: 1 in 68,000
Congenital Disorder of Glycosylation, Type Ia	PMM2	AR	Reduced Risk	Personalized Residual Risk: 1 in 550
Congenital Disorder of Glycosylation, Type Ib	MPI	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,100
Congenital Disorder of Glycosylation, Type Ic	ALG6	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,300
Congenital Insensitivity to Pain with Anhidrosis	NTRK1	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,000
Congenital Myasthenic Syndrome (CHRNA-Related)	CHRNA	AR	Reduced Risk	Personalized Residual Risk: 1 in 30,000
Congenital Myasthenic Syndrome (RAPSN-Related)	RAPSN	AR	Reduced Risk	Personalized Residual Risk: 1 in 47,000
Congenital Neutropenia (HAX1-Related)	HAX1	AR	Reduced Risk	Personalized Residual Risk: 1 in 126,000
Congenital Neutropenia (VPS45-Related)	VPS45	AR	Reduced Risk	Personalized Residual Risk: 1 in 110,000
Corneal Dystrophy and Perceptive Deafness	SLC4A11	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,200
Corticosterone Methyltransferase Deficiency	CYP11B2	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,700
Cystic Fibrosis	CFTR	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,400
Cystinosis	CTNS	AR	Reduced Risk	Personalized Residual Risk: 1 in 7,100
D-Bifunctional Protein Deficiency	HSD17B4	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,700
Deafness, Autosomal Recessive 77	LOXHD1	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,800
Duchenne Muscular Dystrophy / Becker Muscular Dystrophy	DMD	XL	Reduced Risk	Personalized Residual Risk: 1 in 10,000
Dyskeratosis Congenita (RTKL-Related)	RTKL	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,900
Dystrophic Epidermolysis Bullosa	COL7A1	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,400
Ehlers-Danlos Syndrome, Type VIIC	ADAMTS2	AR	Reduced Risk	Personalized Residual Risk: 1 in 63,000
Ellis-van Creveld Syndrome (EVC-Related)	EVC	AR	Reduced Risk	Personalized Residual Risk: 1 in 15,000
Emery-Dreifuss Myopathy 1	EMD	XL	Reduced Risk	Personalized Residual Risk: 1 in 833,000
Enhanced S-Cone Syndrome	NR2E3	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,700
Ethylmalonic Encephalopathy	ETHE1	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,600
Fabry Disease	GLA	XL	Reduced Risk	Personalized Residual Risk: 1 in 7,700
Factor IX Deficiency	F9	XL	Reduced Risk	Personalized Residual Risk: 1 in 5,100
Factor XI Deficiency	F11	AR	Reduced Risk	Personalized Residual Risk: 1 in 440
Familial Autosomal Recessive Hypercholesterolemia	LDLRAP1	AR	Reduced Risk	Personalized Residual Risk: 1 in 171,000
Familial Dysautonomia	IKBKAP	AR	Reduced Risk	Personalized Residual Risk: 1 in 78,000
Familial Hypercholesterolemia	LDLR	AR	Reduced Risk	Personalized Residual Risk: 1 in 260
Familial Hyperinsulinism (ABCC8-Related)	ABCC8	AR	Reduced Risk	Personalized Residual Risk: 1 in 240
Familial Hyperinsulinism (KCNJ11-Related)	KCNJ11	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,300
Familial Mediterranean Fever	MEFV	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,400
Fanconi Anemia, Group A	FANCA	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,700
Fanconi Anemia, Group C	FANCC	AR	Reduced Risk	Personalized Residual Risk: 1 in 34,000
Fanconi Anemia, Group G	FANCG	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,200
Fragile X Syndrome	FMR1	XL	Reduced Risk	FMR1 CGG repeat sizes: Not Performed FMR1 Sequencing: Negative 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.
				Personalized Residual Risk: 1 in 222,000
Fumarate Deficiency	FH	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,900
GRACILE Syndrome and Other BCS1L-Related Disorders	BCS1L	AR	Reduced Risk	Personalized Residual Risk: 1 in 82,000

Galactokinase Deficiency	<i>GALK1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,600
Galactosemia	<i>GALT</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 390
Gaucher Disease	<i>GBA</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,200
Gitelman Syndrome	<i>SLC12A3</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 230
Glutaric Acidemia, Type I	<i>GCDH</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 20,000
Glutaric Acidemia, Type IIa	<i>ETFA</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,100
Glutaric Acidemia, Type IIc	<i>ETFDH</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 260
Glycine Encephalopathy (AMT-Related)	<i>AMT</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 144,000
Glycine Encephalopathy (GLDC-Related)	<i>GLDC</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 240
Glycogen Storage Disease, Type II	<i>GAA</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 280
Glycogen Storage Disease, Type III	<i>AGL</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 55,000
Glycogen Storage Disease, Type IV / Adult Polyglucosan Body Disease	<i>GBE1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 64,000
Glycogen Storage Disease, Type Ia	<i>G6PC</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 410
Glycogen Storage Disease, Type Ib	<i>SLC37A4</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,900
Glycogen Storage Disease, Type V	<i>PYGM</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,400
Glycogen Storage Disease, Type VII	<i>PFKM</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 7,900
HMG-CoA Lyase Deficiency	<i>HMGCL</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 113,000
Hemochromatosis, Type 2A	<i>HFE2</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 740
Hemochromatosis, Type 3	<i>TFR2</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 275,000
Hereditary Fructose Intolerance	<i>ALDOB</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 35,000
Hereditary Spastic Paraparesis 49	<i>TECPR2</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 166,000
Hermansky-Pudlak Syndrome, Type 1	<i>HPS1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 286,000
Hermansky-Pudlak Syndrome, Type 3	<i>HPS3</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 22,000
Holocarboxylase Synthetase Deficiency	<i>HLCS</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,900
Homocystinuria (CBS-Related)	<i>CBS</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,200
Homocystinuria due to MTHFR Deficiency	<i>MTHFR</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,000
Homocystinuria, cblE Type	<i>MTRR</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 16,000
Hydroletharus Syndrome	<i>HYLS1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 296,000
Hyperornithinemia-Hyperammonemia-Homocitrullinuria Syndrome	<i>SLC25A15</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 30,000
Hypohidrotic Ectodermal Dysplasia 1	<i>EDA</i>	XL	Reduced Risk	Personalized Residual Risk: 1 in 22,000
Hypophosphatasia	<i>ALPL</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,200
Inclusion Body Myopathy 2	<i>GNB</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,600
Infantile Cerebral and Cerebellar Atrophy	<i>MED17</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 130,000
Isovaleric Acidemia	<i>IVD</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,200
Joubert Syndrome 2	<i>TMEM216</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 133,000
Joubert Syndrome 7 / Meckel Syndrome 5 / COACH Syndrome	<i>RPGRIP1L</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,100
Junctional Epidermolysis Bullosa (LAMA3-Related)	<i>LAMA3</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 49,000
Junctional Epidermolysis Bullosa (LAMB3-Related)	<i>LAMB3</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 8,600
Junctional Epidermolysis Bullosa (LAMC2-Related)	<i>LAMC2</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 28,000
Krabbe Disease	<i>GALC</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 340
Lamellar Ichthyosis, Type 1	<i>TGM1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,600
Leber Congenital Amaurosis 10 and Other CEP290-Related Ciliopathies	<i>CEP290</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,100
Leber Congenital Amaurosis 13	<i>RDH12</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 88,000
Leber Congenital Amaurosis 2 / Retinitis Pigmentosa 20	<i>RPE65</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,100
Leber Congenital Amaurosis 5	<i>LCA5</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,200



Leber Congenital Amaurosis 8 / Retinitis Pigmentosa 12 / Pigmented Paravenous Chorioretinal Atrophy	<i>CRB1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 960
Leigh Syndrome, French-Canadian Type	<i>LRPPRC</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 22,000
Lethal Congenital Contracture Syndrome 1 / Lethal Arthrogryposis with Anterior Horn Cell Disease	<i>GLE1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,900
Leukoencephalopathy with Vanishing White Matter	<i>EIF2B5</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 8,200
Limb-Girdle Muscular Dystrophy, Type 2A	<i>CAPN3</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,200
Limb-Girdle Muscular Dystrophy, Type 2B	<i>DYSF</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,000
Limb-Girdle Muscular Dystrophy, Type 2C	<i>SGCG</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 8,000
Limb-Girdle Muscular Dystrophy, Type 2D	<i>SGCA</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 8,400
Limb-Girdle Muscular Dystrophy, Type 2E	<i>SGCB</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 72,000
Limb-Girdle Muscular Dystrophy, Type 2I	<i>FKRP</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 460
Lipoamide Dehydrogenase Deficiency	<i>DLD</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 225,000
Lipoid Adrenal Hyperplasia	<i>STAR</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 36,000
Lipoprotein Lipase Deficiency	<i>LPL</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 800
Long-Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency	<i>HADHA</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,500
Lysinuric Protein Intolerance	<i>SLC7A7</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 72,000
Maple Syrup Urine Disease, Type 1a	<i>BCKDHA</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,000
Maple Syrup Urine Disease, Type 1b	<i>BCKDHB</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,100
Meckel Syndrome 1 / Bardet-Biedl Syndrome 13	<i>MKS1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 28,000
Medium Chain Acyl-CoA Dehydrogenase Deficiency	<i>ACADM</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,600
Megalencephalic Leukoencephalopathy with Subcortical Cysts	<i>MLC1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 171,000
Menkes Disease	<i>ATP7A</i>	XL	Reduced Risk	Personalized Residual Risk: 1 in 172,000
Metachromatic Leukodystrophy	<i>ARSA</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,600
Methylmalonic Acidemia (MMAA-Related)	<i>MMAA</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 216,000
Methylmalonic Acidemia (MMAB-Related)	<i>MMAB</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,700
Methylmalonic Acidemia (MUT-Related)	<i>MUT</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 830
Methylmalonic Aciduria and Homocystinuria, Cobalamin C Type	<i>MMACHC</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,300
Methylmalonic Aciduria and Homocystinuria, Cobalamin D Type	<i>MMADHC</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 172,000
Microphthalmia / Anophthalmia	<i>VSX2</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 83,000
Mitochondrial Complex I Deficiency (ACAD9-Related)	<i>ACAD9</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 9,100
Mitochondrial Complex I Deficiency (NDUFAF5-Related)	<i>NDUFAF5</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 770
Mitochondrial Complex I Deficiency (NDUFS6-Related)	<i>NDUFS6</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 211,000
Mitochondrial DNA Depletion Syndrome 6 / Navajo Neurohepatopathy	<i>MPV17</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 8,400
Mitochondrial Myopathy and Sideroblastic Anemia 1	<i>PUS1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 333,000
Mucopolidosis II / IIIA	<i>GNPTAB</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,100
Mucopolidosis III Gamma	<i>GNPTG</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 213,000
Mucopolidosis IV	<i>MCOLN1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,500
Mucopolysaccharidosis Type I	<i>IDUA</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 630
Mucopolysaccharidosis Type II	<i>IDS</i>	XL	Reduced Risk	Personalized Residual Risk: 1 in 76,000
Mucopolysaccharidosis Type IIIA	<i>SGSH</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 700
Mucopolysaccharidosis Type IIIB	<i>NAGLU</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 900
Mucopolysaccharidosis Type IIIC	<i>HGSNAT</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 42,000
Mucopolysaccharidosis Type IIID	<i>GNS</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 201,000



Mucopolysaccharidosis Type IVb / GM1 Gangliosidosis	GLB1	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,200
Mucopolysaccharidosis type IX	HYAL1	AR	Reduced Risk	Personalized Residual Risk: 1 in 63,000
Mucopolysaccharidosis type VI	ARSB	AR	Reduced Risk	Personalized Residual Risk: 1 in 144,000
Multiple Sulfatase Deficiency	SUMF1	AR	Reduced Risk	Personalized Residual Risk: 1 in 144,000
Muscle-Eye-Brain Disease and Other POMGNT1-Related Congenital Muscular Dystrophy-Dystroglycanopathies	POMGNT1	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,100
Myoneurogastrointestinal Encephalopathy	TYMP	AR	Reduced Risk	Personalized Residual Risk: 1 in 8,400
Myotubular Myopathy 1	MTM1	XL	Reduced Risk	Personalized Residual Risk: 1 in 192,000
N-Acetylglutamate Synthase Deficiency	NAGS	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,700
Nemaline Myopathy 2	NEB	AR	Reduced Risk	Personalized Residual Risk: 1 in 300
Nephrogenic Diabetes Insipidus, Type II	AQP2	AR	Reduced Risk	Personalized Residual Risk: 1 in 7,700
Nephrotic Syndrome (NPHS1-Related) / Congenital Finnish Nephrosis	NPHS1	AR	Reduced Risk	Personalized Residual Risk: 1 in 980
Nephrotic Syndrome (NPHS2-Related) / Steroid-Resistant Nephrotic Syndrome	NPHS2	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,700
Neuronal Ceroid-Lipofuscinosis (CLN3-Related)	CLN3	AR	Reduced Risk	Personalized Residual Risk: 1 in 59,000
Neuronal Ceroid-Lipofuscinosis (CLN5-Related)	CLN5	AR	Reduced Risk	Personalized Residual Risk: 1 in 75,000
Neuronal Ceroid-Lipofuscinosis (CLN6-Related)	CLN6	AR	Reduced Risk	Personalized Residual Risk: 1 in 91,000
Neuronal Ceroid-Lipofuscinosis (CLN8-Related)	CLN8	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,300
Neuronal Ceroid-Lipofuscinosis (MFSD8-Related)	MFSD8	AR	Reduced Risk	Personalized Residual Risk: 1 in 87,000
Neuronal Ceroid-Lipofuscinosis (PPT1-Related)	PPT1	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,300
Neuronal Ceroid-Lipofuscinosis (TPP1-Related)	TPP1	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,000
Niemann-Pick Disease (SMPD1-Related)	SMPD1	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,300
Niemann-Pick Disease, Type C (NPC1-Related)	NPC1	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,600
Niemann-Pick Disease, Type C (NPC2-Related)	NPC2	AR	Reduced Risk	Personalized Residual Risk: 1 in 12,000
Nijmegen Breakage Syndrome	NBN	AR	Reduced Risk	Personalized Residual Risk: 1 in 214,000
Non-Syndromic Hearing Loss (GJB2-Related)	GJB2	AR	Reduced Risk	Personalized Residual Risk: 1 in 280
Odonto-Onycho-Dermal Dysplasia / Schopf-Schulz-Passarge Syndrome	WNT10A	AR	Reduced Risk	Personalized Residual Risk: 1 in 900
Omenn Syndrome (RAG2-Related)	RAG2	AR	Reduced Risk	Personalized Residual Risk: 1 in 32,000
Omenn Syndrome / Severe Combined Immunodeficiency, Athabaskan-Type	DCLRE1C	AR	Reduced Risk	Personalized Residual Risk: 1 in 48,000
Ornithine Aminotransferase Deficiency	OAT	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,900
Ornithine Transcarbamylase Deficiency	OTC	XL	Reduced Risk	Personalized Residual Risk: 1 in 103,000
Osteopetrosis 1	TCIRG1	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,700
Pendred Syndrome	SLC26A4	AR	Reduced Risk	Personalized Residual Risk: 1 in 72
Phenylalanine Hydroxylase Deficiency	PAH	AR	Reduced Risk	Personalized Residual Risk: 1 in 150
Polycystic Kidney Disease, Autosomal Recessive	PKHD1	AR	Reduced Risk	Personalized Residual Risk: 1 in 350
Polyglandular Autoimmune Syndrome, Type 1	AIRE	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,100
Pontocerebellar Hypoplasia, Type 1A	VRK1	AR	Reduced Risk	Personalized Residual Risk: 1 in 215,000
Pontocerebellar Hypoplasia, Type 6	RARS2	AR	Reduced Risk	Personalized Residual Risk: 1 in 52,000
Primary Carnitine Deficiency	SLC22A5	AR	Reduced Risk	Personalized Residual Risk: 1 in 600
Primary Ciliary Dyskinesia (DNAH5-Related)	DNAH5	AR	Reduced Risk	Personalized Residual Risk: 1 in 19,000
Primary Ciliary Dyskinesia (DNAI1-Related)	DNAI1	AR	Reduced Risk	Personalized Residual Risk: 1 in 9,300
Primary Ciliary Dyskinesia (DNAI2-Related)	DNAI2	AR	Reduced Risk	Personalized Residual Risk: 1 in 144,000
Primary Hyperoxaluria, Type 1	AGXT	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,400
Primary Hyperoxaluria, Type 2	GRHPR	AR	Reduced Risk	Personalized Residual Risk: 1 in 68,000
Primary Hyperoxaluria, Type 3	HOGA1	AR	Reduced Risk	Personalized Residual Risk: 1 in 12,000
Progressive Cerebello-Cerebral Atrophy	SEPSECS	AR	Reduced Risk	Personalized Residual Risk: 1 in 247,000

Progressive Familial Intrahepatic Cholestasis, Type 2	ABCB11	AR	Reduced Risk	Personalized Residual Risk: 1 in 390
Propionic Acidemia (PCCA-Related)	PCCA	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,600
Propionic Acidemia (PCCB-Related)	PCCB	AR	Reduced Risk	Personalized Residual Risk: 1 in 920
Pycnodysostosis	CTSK	AR	Reduced Risk	Personalized Residual Risk: 1 in 7,200
Pyruvate Dehydrogenase E1-Alpha Deficiency	PDHA1	XL	Reduced Risk	Personalized Residual Risk: 1 in 139,000
Pyruvate Dehydrogenase E1-Beta Deficiency	PDHB	AR	Reduced Risk	Personalized Residual Risk: 1 in 8,300
Renal Tubular Acidosis and Deafness	ATP6V1B1	AR	Reduced Risk	Personalized Residual Risk: 1 in 7,800
Retinitis Pigmentosa 25	EYS	AR	Reduced Risk	Personalized Residual Risk: 1 in 580
Retinitis Pigmentosa 26	CERKL	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,000
Retinitis Pigmentosa 28	FAM161A	AR	Reduced Risk	Personalized Residual Risk: 1 in 145,000
Retinitis Pigmentosa 59	DHDDS	AR	Reduced Risk	Personalized Residual Risk: 1 in 201,000
Rhizomelic Chondrodysplasia Punctata, Type 1	PEX7	AR	Reduced Risk	Personalized Residual Risk: 1 in 55,000
Rhizomelic Chondrodysplasia Punctata, Type 3	AGPS	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,024,000
Roberts Syndrome	ESCO2	AR	Reduced Risk	Personalized Residual Risk: 1 in 95,000
Salla Disease	SLC17A5	AR	Reduced Risk	Personalized Residual Risk: 1 in 172,000
Sandhoff Disease	HEXB	AR	Reduced Risk	Personalized Residual Risk: 1 in 680
Schimke Immunoosseous Dysplasia	SMARCA1	AR	Reduced Risk	Personalized Residual Risk: 1 in 56,000
Segawa Syndrome	TH	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,000
Sjogren-Larsson Syndrome	ALDH3A2	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,100
Smith-Lemli-Opitz Syndrome	DHCR7	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,800
Spinal Muscular Atrophy	SMN1	AR	Reduced Risk	SMN1 copy number: 2 SMN2 copy number: 2 c.*3>80T>G: Negative SMN1 Sequencing: Negative Personalized Residual Risk: 1 in 1,115
Spondylothoracic Dysostosis	MESP2	AR	Reduced Risk	Personalized Residual Risk: 1 in 53,000
Steel Syndrome	COL27A1	AR	Reduced Risk	Personalized Residual Risk: 1 in 275,000
Stuve-Wiedemann Syndrome	LIFR	AR	Reduced Risk	Personalized Residual Risk: 1 in 172,000
Sulfate Transporter-Related Osteochondrodysplasia	SLC26A2	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,000
Tay-Sachs Disease	HEXA	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,700
Tyrosinemia, Type I	FAH	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,900
Usher Syndrome, Type IB	MYO7A	AR	Reduced Risk	Personalized Residual Risk: 1 in 180
Usher Syndrome, Type IC	USH1C	AR	Reduced Risk	Personalized Residual Risk: 1 in 400
Usher Syndrome, Type ID	CDH23	AR	Reduced Risk	Personalized Residual Risk: 1 in 880
Usher Syndrome, Type IF	PCDH15	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,100
Usher Syndrome, Type IIA	USH2A	AR	Reduced Risk	Personalized Residual Risk: 1 in 54
Usher Syndrome, Type III	CLRN1	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,800
Very Long Chain Acyl-CoA Dehydrogenase Deficiency	ACADVL	AR	Reduced Risk	Personalized Residual Risk: 1 in 380
Walker-Warburg Syndrome and Other FKTN-Related Dystrophies	FKTN	AR	Reduced Risk	Personalized Residual Risk: 1 in 390
Wilson Disease	ATP7B	AR	Reduced Risk	Personalized Residual Risk: 1 in 150
Wolman Disease / Cholesteryl Ester Storage Disease	LIPA	AR	Reduced Risk	Personalized Residual Risk: 1 in 32,000
X-Linked Juvenile Retinoschisis	RS1	XL	Reduced Risk	Personalized Residual Risk: 1 in 40,000
X-Linked Severe Combined Immunodeficiency	IL2RG	XL	Reduced Risk	Personalized Residual Risk: 1 in 250,000
Zellweger Syndrome Spectrum (PEX10-Related)	PEX10	AR	Reduced Risk	Personalized Residual Risk: 1 in 218,000
Zellweger Syndrome Spectrum (PEX1-Related)	PEX1	AR	Reduced Risk	Personalized Residual Risk: 1 in 740
Zellweger Syndrome Spectrum (PEX2-Related)	PEX2	AR	Reduced Risk	Personalized Residual Risk: 1 in 108,000
Zellweger Syndrome Spectrum (PEX6-Related)	PEX6	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,500

AR=Autosomal recessive; XL=X-linked

## 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 certain recurrent 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 typically due to unequal meiotic crossing-over between *CYP21A2* and the pseudogene *CYP21A1P*. Classic 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 20 carrier) or individuals that carry an intragenic mutation in *SMN1*. Please also note that 2% of individuals diagnosed with SMA have a causative *SMN1* variant that occurred *de novo*, and therefore cannot be picked up by carrier screening in the parents. Analysis of *SMN1* is performed in association with short-read sequencing of exons 2a-7, followed by confirmation using long-range PCR (described below).

The presence of the c.\*380T>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.\*380T>G is likely indicative of a silent (20) carrier. In individuals with two copies of *SMN1* with African American, Hispanic or Caucasian ancestry, the presence or absence of c.\*380T>G significantly increases or decreases, respectively, the likelihood of being a silent 20 carrier.

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).

#### 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<sup>TM</sup>XT Low Input 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. Libraries were pooled and sequenced on the Illumina NovaSeq 9000 platform, using paired-end 100 bp 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. These regions, which are described below, 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<sup>®</sup> 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.

#### Next Generation Sequencing for SMN1

Exonic regions and intron/exon splice junctions of *SMN1* and *SMN2* were captured, sequenced, and analyzed as described above. Any variants located within exons 2a-7 and classified as pathogenic or likely pathogenic were confirmed to be in either *SMN1* or *SMN2* using gene-specific long-range PCR analysis followed by Sanger sequencing. Variants located in exon 1 cannot be accurately assigned to either *SMN1* or *SMN2* using our current methodology, and so these variants are considered to be of uncertain significance and are not 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  $\Delta\Delta C_t$  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 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 >30,000 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.

#### Personalized Residual Risk Calculations

Agilent SureSelect<sup>TM</sup>XT Low-Input technology was utilized in order to create whole-genome libraries for each patient sample. Libraries were then pooled and sequenced on the Illumina NovaSeq platform. Each sequencing lane was multiplexed to achieve 0.4-2x genome coverage, using paired-end 100 bp reads. The sequencing data underwent ancestral analysis using a customized, licensed bioinformatics algorithm that was validated in house. Identified sub-ethnic groupings were binned into one of 7 continental-level groups (African, East Asian, South Asian, Non-Finnish European, Finnish, Native American, and Ashkenazi Jewish) or, for those ethnicities that matched poorly to the continental-level groups, an 8<sup>th</sup> "unassigned" group, which were then used to select residual risk values for each gene. For individuals belonging to multiple high-level ethnic groupings, a weighting strategy was used to select the most appropriate residual risk. For genes that had insufficient data to calculate ethnic-specific residual risk values, or for sub-ethnic groupings that fell into the "unassigned" group, a "worldwide" residual risk was used. This "worldwide" residual risk was calculated using data from all available continental-level groups.

#### 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.

## Exceptions:

Gene	Transcript	Exceptions
ABCD1	NM_000333	Exons 8 and 9
ADA	NM_000222	Exon 1
ADAMTS2	NM_014244.4	Exon 1
AGPS	NM_003659.3	chr2:178,257,512 - 178,257,649 (partial exon 1)
ALMS1	NM_015120.4	chr2:73,612,990 - 73,613,041 (partial exon 1)
CEP290	NM_025114.3	Exon 5, exon 7, chr12:88,519,017 - 88,519,039 (partial exon 13), chr12:88,514,049 - 88,514,058 (partial exon 15), chr12:88,502,837 - 88,502,841 (partial exon 23), chr12:88,481,551 - 88,481,589 (partial exon 32), chr12:88,471,605 - 88,471,700 (partial exon 40)
CFTCR	NM_000492.3	Exon 10
COL4A4	NM_000924	chr2:227,942,604 - 227,942,619 (partial exon 25)
CYP11B2	NM_000498.3	Exons 3 - 7
DNAI2	NM_023036.4	chr17:72,308,136 - 72,308,147 (partial exon 12)
EVC	NM_153717.2	Exon 1
FH	NM_000143.3	Exon 1
GA-MT	NM_000156.5	Exon 1
GLDC	NM_000170.2	Exon 1
GNPTAB	NM_024312.4	chr17:4,837,000 - 4,837,400 (partial exon 2)
GNPTG	NM_032520.4	Exon 1
HGSNAT	NM_152419.2	Exon 1
IDS	NM_000202.6	Exon 3
LIFR	NM_002310.5	Exon 19
NEB	NM_01271208.1	Exons 82 - 105

NPC 1	NM_00 0271.4	chr18:21,123,519 - 21,123,538 (partial exon 14)
PUS 1	NM_02 5215.5	chr12:132,414,446 - 132,414,532 (partial exon 2)
RPG RIP1 L	NM_01 5272.2	Exon 23
SGS H	NM_00 0199.3	chr17:78,194,022 - 78,194,072 (partial exon 1)
SLC 6A8	NM_00 5629.3	<p>Exons 3 and 4</p> <p><b>SELECTED REFERENCES</b></p> <p><b>Carrier Screening</b> Grody W et al. ACMG position statement on prenatal/preconception expanded carrier screening. <i>Genet Med</i>. 2013 15:482-3.</p> <p><b>Fragile X syndrome:</b> 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. <i>J Mol Diag</i> 2010 12:589-600.</p> <p><b>Spinal Muscular Atrophy:</b> Luo M et al. An Ashkenazi Jewish SMN1 haplotype specific to duplication alleles improves pan-ethnic carrier screening for spinal muscular atrophy. <i>Genet Med</i>. 2014 16:149-56.</p> <p><b>Ashkenazi Jewish Disorders:</b> Scott SA et al. Experience with carrier screening and prenatal diagnosis for sixteen Ashkenazi Jewish Genetic Diseases. <i>Hum. Mutat.</i> 2010 31:1-11.</p> <p><b>Duchenne Muscular Dystrophy:</b> Flanigan KM et al. Mutational spectrum of DMD mutations in dystrophinopathy patients: application of modern diagnostic techniques to a large cohort. <i>Hum Mutat.</i> 2009 30:1657-66.</p> <p><b>Variant Classification:</b> 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. <i>Genet Med</i>. 2015 May;17(5):405-24</p> <p>Additional disease-specific references available upon request.</p>



#### Patient Information

Name: Donor 6440  
Date of Birth: [REDACTED]  
Sema4 ID: [REDACTED]  
Client ID: [REDACTED]  
Indication: Carrier Screening

#### Specimen Information

Specimen Type: Blood  
Date Collected: 08/25/2021  
Date Received: 08/26/2021  
Final Report: 11/29/2022

#### Referring Provider

[REDACTED]  
Fairfax Cryobank, Inc.

## Unmask Additional Gene(s) (1 gene) with Personalized Residual Risk

### SUMMARY OF RESULTS AND RECOMMENDATIONS

 **Negative**

**Negative for all genes tested: GYS2**

To view a full list of genes and diseases tested  
please see Table 1 in this report

AR=Autosomal recessive; XL=X-linked

#### Recommendations

- 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. Please note that residual risks for X-linked diseases (including full repeat expansions for Fragile X syndrome) may not be accurate for males and the actual residual risk is likely to be lower.
- As genetic technologies may improve and variant classifications may change over time, it is recommended to obtain a new carrier screening test or reanalysis when a new pregnancy is being considered.

## Test description

This patient was tested for the genes listed above using one or more of the following methodologies: target capture and short-read sequencing, long-range PCR followed by short-read sequencing, targeted genotyping, and/or 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 with the patient's personalized residual risk. If personalized residual risk is not provided, please see the complete residual risk table at [go.sema4.com/residualrisk](https://go.sema4.com/residualrisk). Only known pathogenic or likely pathogenic variants are reported. This carrier screening test does not report likely benign variants and variants of uncertain significance (VUS). If reporting of likely benign variants and VUS are desired in this patient, please contact the laboratory at 800-298-6470, option 2 to request an amended report.




Anastasia Larmore, Ph.D., Associate Laboratory Director

## Genes and diseases tested

The personalized residual risks listed below are specific to this individual. The complete residual risk table is available at [go.sema4.com/residualrisk](https://go.sema4.com/residualrisk)

Table 1: List of genes and diseases tested with detailed results

Disease	Gene	Inheritance Pattern	Status	Detailed Summary
 Negative				
Glycogen Storage Disease, Type 0	GYS2	AR	Reduced Risk	Personalized Residual Risk: 1 in 29,000

AR=Autosomal recessive; XL=X-linked

## 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* premutations and full mutations greater than 90 CGG repeats in length were further analyzed by Southern blot analysis or methylation PCR to assess the size and methylation status of the *FMR1* CGG repeat. Additional testing to determine the status of AGG interruptions within the *FMR1* CGG repeat will be automatically performed for premutation alleles ranging from 55 to 90 repeats. These results, which may modify risk for expansion, will follow in a separate report.

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

Multiplex PCR amplification and single-base pair probe extension analyses using the Agena Bioscience iPLEX Pro chemistry on a MassARRAY<sup>®</sup> System were used to identify certain recurrent 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%)

Conventional MLPA and/or digitalMLPA<sup>®</sup> probe sets and reagents from MRC-Holland were used for copy number variations (CNVs) analysis of specific targets versus known control samples. digitalMLPA<sup>®</sup> is a semi-quantitative technique, based on the well-established conventional MLPA method, followed by Illumina based sequencing to determine read number for amplicon quantification. False positive or negative results may occur due to rare sequence variants in target regions detected by conventional MLPA or digitalMLPA<sup>®</sup> probes. Analytical sensitivity and specificity of both the conventional MLPA method and the digitalMLPA<sup>®</sup> method are greater than 99%.

For alpha thalassemia, the copy numbers of the *HBA1* and *HBA2* genes were analyzed. Alpha-globin gene deletions, duplications, 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 precisely specified without phase analysis. With the exception of duplications, 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 typically due to unequal meiotic crossing-over between *CYP21A2* and the pseudogene *CYP21A1P*. Classic 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. Depending on ethnicity, 6 - 29 % of carriers will not be identified by dosage sensitive methods as this testing cannot distinguish 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 identify intragenic mutation in *SMN1*. Please also note that 2% of individuals diagnosed with SMA have a causative *SMN1* variant that occurred de novo, therefore cannot be picked up by carrier screening in the parents. Analysis of *SMN1* is performed in association with short-read sequencing of exons 2a-7, followed by confirmation using long-range PCR (described below).

In individuals with two copies of *SMN1* with Ashkenazi Jewish, East Asian, African American, Native American 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 silent carrier.

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).

#### 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™XT Low Input 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. Libraries were pooled and sequenced on the Illumina NovaSeq 6000 platform, using paired-end 100 bp 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. These regions, which are described below, 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.

**Exceptions:** *ABCD1* (NM\_000033.3) exons 8 and 9; *ACADSB* (NM\_001609.3) chr10:124,810,695-124,810,707 (partial exon 9); *ADA* (NM\_000022.2) exon 1; *ADAMTS2* (NM\_014244.4) exon 1; *AGPS* (NM\_003659.3) chr2:178,257,512-178,257,649 (partial exon 1); *ALDH7A1* (NM\_001182.4) chr5:125,911,150-125,911,163 (partial exon 7) and chr5:125,896,807-125,896,821 (partial exon 10); *ALMS1* (NM\_015120.4) chr2:73,612,990-73,613,041 (partial exon 1); *APOPT1* (NM\_032374.4) chr14:104,040,437-104,040,455 (partial exon 3); *CDAN1* (NM\_138477.2) exon 2; *CEP152* (NM\_014985.3) chr15:49,061,146-49,061,165 (partial exon 14) and exon 22; *CEP290* (NM\_025114.3) exon 5, exon 7, chr12:88,519,017-88,519,039 (partial exon 13), chr12:88,514,049-88,514,058 (partial exon 15), chr12:88,502,837-88,502,841 (partial exon 23), chr12:88,481,551-88,481,589 (partial exon 32), chr12:88,471,605-88,471,700 (partial exon 40); *CFTR* (NM\_000492.3) exon 10; *COL4A4* (NM\_000092.4) chr2:227,942,604-227,942,619 (partial exon 25); *COX10* (NM\_001303.3) exon 6; *CYP11B1* (NM\_000497.3) exons 3-7; *CYP11B2* (NM\_000498.3) exons 3-7; *DNAI2* (NM\_023036.4) chr17:72,308,136-72,308,147 (partial exon 12); *DOK7* (NM\_173660.4) chr4:3,465,131-3,465,161 (partial exon 1) and exon 2; *DUOX2* (NM\_014080.4) exons 6-8; *EIF2AK3* (NM\_004836.5) exon 8; *EVC* (NM\_153717.2) exon 1; *F5* (NM\_000130.4) chr1:169,551,662-169,551,679 (partial exon 2); *FH* (NM\_000143.3) exon 1; *GAMT* (NM\_000156.5) exon 1; *GLDC* (NM\_000170.2) exon 1; *GNPTAB* (NM\_024312.4) chr17:4,837,000-4,837,400 (partial exon 2); *GNPTG* (NM\_032520.4) exon 1; *GHR* (NM\_000163.4) exon 3; *GYS2* (NM\_021957.3) chr12:21,699,370-21,699,409 (partial exon 12); *HGSNAT* (NM\_152419.2) exon 1; *IDS* (NM\_000202.6) exon 3; *ITGB4* (NM\_000213.4) chr17:73,749,976-73,750,060 (partial exon 33); *JAK3* (NM\_000215.3) chr19:17,950,462-17,950,483 (partial exon 10); *LIFR* (NM\_002310.5) exon 19; *LMBRD1* (NM\_018368.3) chr6:70,459,226-70,459,257 (partial exon 5), chr6:70,447,828-70,447,836 (partial exon 7) and exon 12; *LYST* (NM\_000081.3) chr1:235,944,158-235,944,176 (partial exon 16) and chr1:235,875,350-235,875,362 (partial exon 43); *MLYCD* (NM\_012213.2) chr16:83,933,242-83,933,282 (partial exon 1); *MTR* (NM\_000254.2) chr1:237,024,418-237,024,439 (partial exon 20) and chr1:237,038,019-237,038,029 (partial exon 24); *NBEAL2* (NM\_015175.2) chr3:47,021,385-47,021,407 (partial exon 1); *NEB* (NM\_001271208.1) exons 82-105; *NPC1* (NM\_000271.4) chr18:21,123,519-21,123,538 (partial exon 14); *NPHP1* (NM\_000272.3) chr2:110,937,251-110,937,263 (partial exon 3); *OCRL* (NM\_000276.3) chrX:128,674,450-128,674,460 (partial exon 1); *PHKB* (NM\_000293.2) exon 1 and chr16:47,732,498-47,732,504 (partial exon 30); *PIGN* (NM\_176787.4) chr18:59,815,547-59,815,576 (partial exon 8); *PIP5K1C* (NM\_012398.2) exon 1 and chr19:363,7602-363,7616 (partial exon 17); *POU1F1* (NM\_000306.3) exon 5; *PTPRC* (NM\_002838.4) exons 11 and 23; *PUS1* (NM\_025215.5) chr12:132,414,446-132,414,532 (partial exon 2); *RPGRIP1L* (NM\_015272.2) exon 23; *SGSH* (NM\_000199.3) chr17:78,194,022-78,194,072 (partial exon 1); *SLC6A8* (NM\_005629.3) exons 3 and 4; *ST3GAL5* (NM\_003896.3) exon 1; *SURF1* (NM\_003172.3) chr9:136,223,269-136,223,307 (partial exon 1); *TRPM6* (NM\_017662.4) chr9:77,362,800-77,362,811 (partial exon 31); *TSEN54*

(NM\_207346.2) exon 1; *TYR* (NM\_000372.4) exon 5; *VWF* (NM\_000552.3) exons 24-26, chr12:6,125,675-6,125,684 (partial exon 30), chr12:6,121,244-6,121,265 (partial exon 33), and exon 34.

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.

#### Next Generation Sequencing for *SMN1*

Exonic regions and intron/exon splice junctions of *SMN1* and *SMN2* were captured, sequenced, and analyzed as described above. Any variants located within exons 2a-7 and classified as pathogenic or likely pathogenic were confirmed to be in either *SMN1* or *SMN2* using gene-specific long-range PCR analysis followed by Sanger sequencing. Variants located in exon 1 cannot be accurately assigned to either *SMN1* or *SMN2* using our current methodology, and so these variants are not reported.

#### Copy Number Variant (CNV) Analysis (Analytical Detection Rate >98% for CNVs of 3 exons and larger, >90% for CNVs of 2 exons)

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. Deletions and duplications near the lower limit of detection may not be detected due to run variability. Genomic regions with high homology or highly repetitive sequences are excluded from this analysis.

#### Exon Array Comparative Genomic Hybridization (aCGH) (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 1,000,000 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 SYBR Green reagents on a LightCycler® 480 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  $\Delta\Delta C_t$  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. Please note that in rare cases, allele drop-out may occur, which has the potential to lead to false negative results. For *CYP21A2*, a certain percentage of healthy individuals carry a duplication of the *CYP21A2* gene, which has no clinical consequences. In cases where multiple copies of *CYP21A2* are located on the same chromosome in tandem, only the last 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. A *CYP21A1P/CYP21A2* hybrid gene detected only by MLPA but not by long-range PCR will not be reported when the long-range PCR indicates the presence of two full *CYP21A2* gene copies (one on each chromosome), as the additional hybrid gene is nonfunctional. Classic 30-kb deletions are identified by MLPA and are also identified by the presence of multiple common pathogenic *CYP21A2* variants by long-range PCR. Since multiple pseudogene-derived variants are detected in all cases with the classic 30kb deletion, we cannot rule out the possibility that some variant(s) detected could be present in trans with the chimeric *CYP21A1P/CYP21A2* gene created by the 30kb deletion. When an 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 >30,000 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.

#### Personalized Residual Risk Calculations

Agilent SureSelect<sup>TM</sup>XT Low-Input technology was utilized in order to create whole-genome libraries for each patient sample. Libraries were then pooled and sequenced on the Illumina NovaSeq platform. Each sequencing lane was multiplexed to achieve 0.4-2x genome coverage, using paired-end 100 bp reads. The sequencing data underwent ancestral analysis using a customized, licensed bioinformatics algorithm that was validated in house. Identified sub-ethnic groupings were binned into one of 7 continental-level groups (African, East Asian, South Asian, Non-Finnish European, Finnish, Native American, and Ashkenazi Jewish) or, for those ethnicities that matched poorly to the continental-level groups, an 8<sup>th</sup> "unassigned" group, which were then used to select residual risk values for each gene. For individuals belonging to multiple high-level ethnic groupings, a weighting strategy was used to select the most appropriate residual risk. For genes that had insufficient data to calculate ethnic-specific residual risk values, or for sub-ethnic groupings that fell into the "unassigned" group, a "worldwide" residual risk was used. This "worldwide" residual risk was calculated using data from all available continental-level groups.

Several genes have multiple residual risks associated to reflect the likelihood of the tested individual being a carrier for different diseases that are attributed to non-overlapping pathogenic variants in that gene. When calculating the couples' combined reproductive risk, the highest residual risk for each patient was selected.

#### 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.

#### Tay-Sachs Disease (TSD) Enzyme Analysis (Analytical Detection Rate ≥98%)

Hexosaminidase activity and Hex A% activity were measured by a standard heat-inactivation, fluorometric method using artificial 4-MU-β-N-acetyl glucosaminide (4-MUG) substrate. This assay is highly sensitive and accurate in detecting Tay-Sachs carriers and individuals affected with TSD. Normal ranges of Hex A% activity are 55.0-72.0 for white blood cells and 58.0-72.0 for plasma. It is estimated that less than 0.5% of Tay-Sachs carriers have non-carrier levels of percent Hex A activity, and therefore may not be identified by this assay. In addition, this assay may detect individuals that are carriers of or are affected with Sandhoff disease. False positive results may occur if benign variants, such as pseudodeficiency alleles, interfere with the enzymatic assay. False negative results may occur if both *HEXA* and *HEXB* pathogenic or pseudodeficiency variants are present in the same individual.

Please note that it is not possible to perform Tay-Sachs disease enzyme analysis on saliva samples, buccal swabs, tissue samples, semen samples, or on samples received as extracted DNA.

This test was developed, and its performance characteristics determined by Sema4 Opco, Inc. It has not been cleared or approved by the US Food and Drug Administration. FDA does not require this test to go through premarket FDA review. This test is used for clinical purposes. It should not be regarded as investigational or for research. This laboratory is certified under the Clinical Laboratory Improvement Amendments (CLIA) as qualified to perform high complexity clinical laboratory testing. 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.

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**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

Riggs ER, Andersen EF, Cherry AM, et al. Technical standards for the interpretation and reporting of constitutional copy-number variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics (ACMG) and the Clinical Genome Resource (ClinGen) [published correction appears in *Genet Med*. 2021 Nov;23(11):2230]. *Genet Med*. 2020;22(2):245-257.

Additional disease-specific references available upon request.





Patient Information:

**6440, Donor**

**DOB:** [REDACTED]

**Sex:** M

**MR#:** 6440

**Patient#:** [REDACTED]

Accession:

**Test#:** [REDACTED]

**Order#:** [REDACTED]

**Ext Test#:** [REDACTED]

**Ext Order#:** [REDACTED]

**Specimen Type:** DNA

**Collected:** Not provided

**Received Date:** Feb 09,2023

**Authorized Date:** Feb 13,2023

Physician:

**Seitz, Suzanne**

**ATTN:** Seitz, Suzanne

**Fairfax Cryobank**

**3015 Williams Drive**

**Fairfax, VA 22031**

**Phone:**

**Fax:**

Laboratory:

**Fulgent Genetics**

**CAP#:** 8042697

**CLIA#:** 05D2043189

**Laboratory Director:**

**Dr. Hanlin (Harry) Gao**

**Report Date:** Feb 28,2023

Final Report

TEST PERFORMED

**LAMA2 Single Gene**

(1 Gene Panel: *LAMA2*; gene sequencing with deletion and duplication analysis)

RESULTS:

**No clinically significant sequence or copy-number variants were identified in the submitted specimen.**

**A negative result does not rule out the possibility of a genetic predisposition nor does it rule out any pathogenic mutations of the sort not queried by this test or in areas not reliably assessed by this test.**

INTERPRETATION:

Notes and Recommendations:

- As requested, this report only includes variants classified as Pathogenic, Likely Pathogenic, or Risk Allele at the time of analysis. If detected, this report does not include variants classified as of uncertain significance.
- Gene specific notes and limitations may be present. See below.
- These results should be interpreted in the context of this individual's clinical findings, biochemical profile, and family history.
- Genetic counseling is recommended. Available genetic counselors and additional resources can be found at the National Society of Genetic Counselors (NSGC; <https://www.nsgc.org>)
- Guide to Interpreting Genomic Reports: A Genomics Toolkit (CSER Consortium; February 2017) (<https://www.genome.gov/For-Health-Professionals/Provider-Genomics-Education-Resources#hep>)

GENES TESTED:

**LAMA2 Single Gene**

1 genes tested (100.00% at >20x).

*LAMA2*

Gene Specific Notes and Limitations

No gene specific limitations apply to the genes on the tested panel.

METHODS:

**Patient:** 6440, Donor; **Sex:** M;  
**DOB:** [REDACTED] **MR#:** 6440

**Accession#:** [REDACTED]

**DocID:** [REDACTED]

**PAGE 1 of 3**





Genomic DNA was isolated from the submitted specimen indicated above (if cellular material was submitted). DNA was barcoded, and enriched for the coding exons of targeted genes using hybrid capture technology. Prepared DNA libraries were then sequenced using a Next Generation Sequencing technology. Following alignment to the human genome reference sequence (assembly GRCh37), variants were detected in regions of at least 10x coverage. For this specimen, 100.00% and 100.00% of coding regions and splicing junctions of genes listed had been sequenced with coverage of at least 10x and 20x, respectively, by NGS or by Sanger sequencing. The remaining regions did not have 10x coverage, and were not evaluated. Variants were interpreted manually using locus specific databases, literature searches, and other molecular biological principles. To minimize false positive results, any variants that do not meet internal quality standards are confirmed by Sanger sequencing. Variants classified as pathogenic, likely pathogenic, or risk allele which are located in the coding regions and nearby intronic regions (+/- 20bp) of the genes listed above are reported. Variants outside these intervals may be reported but are typically not guaranteed. When a single pathogenic or likely pathogenic variant is identified in a clinically relevant gene with autosomal recessive inheritance, the laboratory will attempt to ensure 100% coverage of coding sequences either through NGS or Sanger sequencing technologies ("fill-in"). All genes listed were evaluated for large deletions and/or duplications. However, single exon deletions or duplications will not be detected in this assay, nor will copy number alterations in regions of genes with significant pseudogenes. Putative deletions or duplications identified by NGS are confirmed by an orthogonal method (qPCR or MLPA), unless exceeding an internally specified and validated quality score, beyond which deletions and duplications are considered real without further confirmation. New York patients: diagnostic findings are confirmed by Sanger, MLPA, or qPCR; exception SNV variants in genes for which confirmation of NGS results has been performed  $\geq 10$  times may not be confirmed if identified with high quality by NGS. Bioinformatics: The Fulgent Germline v2019.2 pipeline was used to analyze this specimen.

#### LIMITATIONS:

These test results and variant interpretation are based on the proper identification of the submitted specimen, accuracy of any stated familial relationships, and use of the correct human reference sequences at the queried loci. In very rare instances, errors may result due to mix-up or co-mingling of specimens. Positive results do not imply that there are no other contributors, genetic or otherwise, to this individual's phenotype, and negative results do not rule out a genetic cause for the indication for testing. Official gene names change over time. Fulgent uses the most up to date gene names based on HUGO Gene Nomenclature Committee (<https://www.genenames.org>) recommendations. If the gene name on report does not match that of ordered gene, please contact the laboratory and details can be provided. Result interpretation is based on the available clinical and family history information for this individual, collected published information, and Alamut annotation available at the time of reporting. This assay is designed and validated for detection of germline variants only. It is not designed or validated for the detection of low-level mosaicism or somatic mutations. This assay will not detect certain types of genomic aberrations such as translocations, inversions, or repeat expansions (eg. trinucleotide or hexanucleotide repeat expansion). DNA alterations in regulatory regions or deep intronic regions (greater than 20bp from an exon) may not be detected by this test. Unless otherwise indicated, no additional assays have been performed to evaluate genetic changes in this specimen. There are technical limitations on the ability of DNA sequencing to detect small insertions and deletions. Our laboratory uses a sensitive detection algorithm, however these types of alterations are not detected as reliably as single nucleotide variants. Rarely, due to systematic chemical, computational, or human error, DNA variants may be missed. Although next generation sequencing technologies and our bioinformatics analysis significantly reduce the confounding contribution of pseudogene sequences or other highly-homologous sequences, sometimes these may still interfere with the technical ability of the assay to identify pathogenic alterations in both sequencing and deletion/duplication analyses. Deletion/duplication analysis can identify alterations of genomic regions which are two or more contiguous exons in size; single exon deletions or duplications may occasionally be identified, but are not routinely detected by this test. When novel DNA duplications are identified, it is not possible to discern the genomic location or orientation of the duplicated segment, hence the effect of the duplication cannot be predicted. Where deletions are detected, it is not always possible to determine whether the predicted product will remain in-frame or not. Unless otherwise indicated, deletion/duplication analysis has not been performed in regions that have been sequenced by Sanger.

#### SIGNATURE:

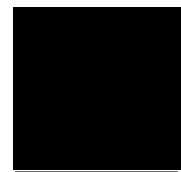
**Yan Meng, Ph.D., CGMB, FACMG** on 2/28/2023 11:00 AM PST  
Electronically signed



#### DISCLAIMER:

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This test was developed and its performance characteristics determined by **Fulgent Genetics**. It has not been cleared or approved by the FDA. The laboratory is regulated under CLIA as qualified to perform high-complexity testing. This test is used for clinical purposes. It should not be regarded as investigational or for research. Since genetic variation, as well as systematic and technical factors, can affect the accuracy of testing, the results of testing should always be interpreted in the context of clinical and familial data. For assistance with interpretation of these results, healthcare professionals may contact us directly at **(626) 350-0537** or **[info@fulgentgenetics.com](mailto:info@fulgentgenetics.com)**. It is recommended that patients receive appropriate genetic counseling to explain the implications of the test result, including its residual risks, uncertainties and reproductive or medical options.



Patient Information:

**6440, Donor**

**DOB:** [REDACTED]

**Sex:** M

**MR#:** 6440

**Patient#:** [REDACTED]

Accession:

**Test#:** [REDACTED]

**Order#:** [REDACTED]

**Ext Test#:** [REDACTED]

**Ext Order#:** [REDACTED]

**Specimen Type:** DNA

**Collected:** Not provided

**Received Date:** Feb 09, 2023

**Authorized Date:** Nov 21, 2023

Physician:

**Seitz, Suzanne**

**ATTN:** Seitz, Suzanne

**Fairfax Cryobank**

**3015 Williams Drive**

**Fairfax, VA 22031**

**Phone:**

**Fax:**

Laboratory:

**Fulgent Genetics**

**CAP#:** 8042697

**CLIA#:** 05D2043189

**Laboratory Director:**

**Dr. Hanlin (Harry) Gao**

**Report Date:** Nov 22, 2023

Final Report

TEST PERFORMED

**TYR Single Gene**

(1 Gene Panel: *TYR*; gene sequencing with deletion and duplication analysis)

RESULTS:

**No clinically significant sequence or copy-number variants were identified in the submitted specimen.**

**A negative result does not rule out the possibility of a genetic predisposition nor does it rule out any pathogenic mutations of the sort not queried by this test or in areas not reliably assessed by this test.**

INTERPRETATION:

Notes and Recommendations:

- As requested, this report only includes variants classified as Pathogenic, Likely Pathogenic, or Risk Allele at the time of analysis. If detected, this report does not include variants classified as of uncertain significance.
- Gene specific notes and limitations may be present. See below.
- These results should be interpreted in the context of this individual's clinical findings, biochemical profile, and family history.
- Genetic counseling is recommended. Available genetic counselors and additional resources can be found at the National Society of Genetic Counselors (NSGC; <https://www.nsgc.org>)
- Guide to Interpreting Genomic Reports: A Genomics Toolkit (CSER Consortium; February 2017) (<https://www.genome.gov/For-Health-Professionals/Provider-Genomics-Education-Resources#hep>)

GENES TESTED:

**TYR Single Gene**

1 genes tested (100.00% at >20x).

*TYR*

Gene Specific Notes and Limitations

*TYR*: Due to the interference by highly homologous regions, our current testing method has less sensitivity to detect variants in exons 4-5 of the *TYR* gene (NM\_000372.5).



## METHODS:

Genomic DNA was isolated from the submitted specimen indicated above (if cellular material was submitted). DNA was barcoded, and enriched for the coding exons of targeted genes using hybrid capture technology. Prepared DNA libraries were then sequenced using a Next Generation Sequencing technology. Following alignment to the human genome reference sequence (assembly GRCh37), variants were detected in regions of at least 10x coverage. For this specimen, 100.00% and 100.00% of coding regions and splicing junctions of genes listed had been sequenced with coverage of at least 10x and 20x, respectively, by NGS or by Sanger sequencing. The remaining regions did not have 10x coverage, and were not evaluated. Variants were interpreted manually using locus specific databases, literature searches, and other molecular biological principles. To minimize false positive results, any variants that do not meet internal quality standards are confirmed by Sanger sequencing. Variants classified as pathogenic, likely pathogenic, or risk allele which are located in the coding regions and nearby intronic regions (+/- 20bp) of the genes listed above are reported. Variants outside these intervals may be reported but are typically not guaranteed. When a single pathogenic or likely pathogenic variant is identified in a clinically relevant gene with autosomal recessive inheritance, the laboratory will attempt to ensure 100% coverage of coding sequences either through NGS or Sanger sequencing technologies ("fill-in"). All genes listed were evaluated for large deletions and/or duplications. However, single exon deletions or duplications will not be detected in this assay, nor will copy number alterations in regions of genes with significant pseudogenes. Putative deletions or duplications identified by NGS are confirmed by an orthogonal method (qPCR or MLPA), unless exceeding an internally specified and validated quality score, beyond which deletions and duplications are considered real without further confirmation. New York patients: diagnostic findings are confirmed by Sanger, MLPA, or qPCR; exception SNV variants in genes for which confirmation of NGS results has been performed  $\geq 10$  times may not be confirmed if identified with high quality by NGS. Bioinformatics: The Fulgent Germline v2019.2 pipeline was used to analyze this specimen.

## LIMITATIONS:

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## SIGNATURE:



**Yan Meng, Ph.D., CGMB, FACMG** on 11/22/2023 07:59 PM PST  
Electronically signed



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