

**Patient Information**

Name: Donor 16031  
 Date of Birth: [REDACTED]  
 Sema4 ID: 22227362  
 Client ID: SEATSB-S484330735  
 Indication: Carrier Screening

**Specimen Information**

Specimen Type: Blood  
 Date Collected: 11/08/2022  
 Date Received: 11/09/2022  
 Final Report: 11/29/2022

**Referring Provider**

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Expanded Carrier Screen (502 genes)  
 with Personalized Residual Risk

**SUMMARY OF RESULTS AND RECOMMENDATIONS**

⊕ Positive	⊖ Negative
<p><b>Carrier of <i>WNT10A</i>-Related Ectodermal Dysplasia (AR)</b>            Associated gene(s): <i>WNT10A</i>            Variant(s) Detected: c.682T&gt;A, p.F228I, Pathogenic,            Heterozygous (one copy)</p> <p><b>Carrier of Cystic Fibrosis (AR)</b>            Associated gene(s): <i>CFTR</i>            Variant(s) Detected: c.3107C&gt;T, p.T1036I, Likely Pathogenic,            Heterozygous (one copy)</p> <p><b>Carrier of Mucopolysaccharidosis IV (AR)</b>            Associated gene(s): <i>MCOLN1</i>            Variant(s) Detected: c.406-2A&gt;G, Pathogenic, Heterozygous            (one copy)</p>	<p><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</p>

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. 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.

## Interpretation of positive results

### ***WNT10A*-Related Ectodermal Dysplasia (AR)**

#### **Results and Interpretation**

A heterozygous (one copy) pathogenic missense variant, c.682T>A, p.F228I, was detected in the *WNT10A* gene (NM\_025216.2). Please note that this variant has been associated with reduced penetrance and variable expressivity, and therefore some individuals with a pathogenic variant on the opposite allele may not exhibit any clinical symptoms (PMID:19559398). Individuals with the p.F228I variant in homozygosity or compound heterozygosity have been reported to exhibit highly variable phenotypes, with most symptomatic patients described as having isolated tooth agenesis, and a smaller fraction also exhibiting one or more additional ectodermal-related symptoms including nail dysplasia, fragile and/or sparse hair, hypohidrosis and dry skin or eczema (PMID: 34228861, 34593752, 33383702, 30046887, 28976000, 23401279, 20979233). An analysis of the reported literature suggested that of the symptomatic homozygotes reported, the majority have isolated tooth agenesis, and up to 25% may exhibit additional ectodermal features. When this variant is observed in compound heterozygosity with a second variant, up to 15% of patients that display any symptoms may exhibit features of the more severe clinical syndromes odonto-onycho-dermal dysplasia or Schopf-Schulz-Passarge syndrome. However, individuals with the same genotype, even within the same family, may display milder symptoms or be asymptomatic (PMID: 19559398, 22581971). Please note that individuals who harbor this variant are 2-3 times more likely than individuals in the general population to have hypodontia (PMID: 29364747). When this variant is present in trans with a pathogenic variant, it is considered to be causative for *WNT10A*-related ectodermal dysplasia. Therefore, this individual is expected to be at least a carrier for *WNT10A*-related ectodermal dysplasia. Approximately half of individuals with a heterozygous *WNT10A* variant have been reported to exhibit minor disease-associated symptoms, including abnormalities of several permanent teeth, dry skin, and sparse scalp hair, eyelashes, and/or eyebrows.

#### **What is *WNT10A*-Related Ectodermal Dysplasia?**

*WNT10A*-related ectodermal dysplasia represents a group of related conditions characterized by differences in the development of skin, hair, nails, teeth and sweat glands. Patients with *WNT10A*-related ectodermal dysplasia may exhibit a broad spectrum of symptoms affecting one or more of these tissue types with variable severity. The spectrum may range from isolated (nonsyndromic) findings affecting just one tissue type, through milder syndromic phenotypes to comparatively more severe syndromic phenotypes affecting multiple tissue types including odonto-onycho-dermal dysplasia and Schopf-Schulz-Passarge syndrome.

- Nonsyndromic tooth agenesis is characterized by the absence of one or more teeth without other significant symptoms of ectodermal dysplasia. Missing less than 6 teeth is called hypodontia whereas agenesis of 6 or more teeth is called oligodontia.
- Odonto-onycho-dermal dysplasia (OODD) is characterized by thickening of the skin on the palms of the hand and soles of the feet, and misshapen or missing nails and teeth. Some patients may have dry, thin hair and sparse eyebrows, and may have a smooth tongue with missing taste buds.
- Schopf-Schulz-Passarge syndrome (SSPS) is characterized by missing teeth and cysts at the corners of the eyes, misshapen nails or nails that separate from the nailbed, and an increased risk of basal cell and squamous cell carcinomas.

It is not possible to predict which phenotype a patient may have based on the genotype. In many cases the same genotypes have been found in patients with different clinical presentations, even among patients from the same family. Lifespan has not been reported to be shortened.

### **Cystic Fibrosis (AR)**

#### **Results and Interpretation**

A heterozygous (one copy) likely pathogenic missense variant, c.3107C>T, p.T1036I, was detected in the *CFTR* gene (NM\_000492.3). When this variant is present in trans with a pathogenic variant, it is considered to be causative for cystic fibrosis. Therefore, this individual is expected to be at least a carrier for cystic fibrosis. The majority of individuals heterozygous for a variant in this gene are not expected to exhibit symptoms of *CFTR*-related disorders. However, several studies suggest that carrying a heterozygous *CFTR* variant may confer an increased risk for certain health conditions including chronic or recurrent pancreatitis. Recent studies estimate the relative risk for chronic pancreatitis is approximately 5-9 times greater in heterozygous carriers compared to the general population (PMID: 31882447).

#### **What is Cystic Fibrosis?**

Cystic fibrosis is an autosomal recessive disorder caused by pathogenic variants in the gene *CFTR*. It may be diagnosed in individuals worldwide, but has the highest prevalence in the Caucasian population, in individuals with Northern European ancestry. The clinical presentation includes thick mucus accumulation in the lungs leading to breathing difficulties and infection, poor digestion, and male infertility.

The average life expectancy is in the 30s. Although some genotype-phenotype correlations exist, individuals with two classic pathogenic variants in *CFTR* are expected to present with a more severe disease phenotype. Non-classic variants in *CFTR* may lead to less severe forms of disease or specific phenotypes, such as male infertility as a result of congenital absence or hypoplasia of the vas deferens.

## Mucopolipidosis IV (AR)

### Results and Interpretation

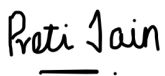
A heterozygous (one copy) pathogenic splice site variant, c.406-2A>G, was detected in the *MCOLN1* gene (NM\_020533.2). When this variant is present in trans with a pathogenic variant, it is considered to be causative for mucopolipidosis IV. Therefore, this individual is expected to be at least a carrier for mucopolipidosis IV. Heterozygous carriers are not expected to exhibit symptoms of this disease.

### What is Mucopolipidosis IV?

Mucopolipidosis IV is an autosomal recessive disorder caused by pathogenic variants in the gene *MCOLN1*. It is predominantly diagnosed in individuals of Ashkenazi Jewish descent, although it has also been reported in patients of other ethnicities. The typical form of the disease is characterized by a severe motor delay (which halts at the level of a 1 or 2 year old) and vision loss as a result of retinal degeneration and corneal clouding. Most patients do not learn to speak or walk, but may learn some sign language or be able to sit independently. Patients are intellectually disabled and have difficulty controlling their movements. Approximately 15% of patients experience deterioration of neurological symptoms over time, but the neurologic deficits do not change in the remainder of patients. About 5% of patients have a milder, atypical form characterized by progressive ataxia and eye abnormalities, and they may learn to walk. Most patients live into adulthood, although life expectancy is shorter than normal. Specific variants have been associated with typical or atypical disease, and therefore it may be possible to predict the severity of disease based on the genotype. The pathogenic variant common in the Ashkenazi Jewish population is associated with the more severe form.

## 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.



Preti Jain, Ph.D., FACMG, DABMGG, Director - Molecular Genetics

## 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>Positive</b>				
WNT10A-Related Ectodermal Dysplasia	WNT10A	AR	Carrier	c.682T>A, p.F228I, Pathogenic, Heterozygous (one copy)
Cystic Fibrosis	CFTR	AR	Carrier	c.3107C>T, p.T1036I, Likely Pathogenic, Heterozygous (one copy)
Mucopolipidosis IV	MCOLN1	AR	Carrier	c.406-2A>G, Pathogenic, Heterozygous (one copy)
<b>Negative</b>				
2-Methylbutyrylglycinuria	ACADSB	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,800
3-Beta-Hydroxysteroid Dehydrogenase Type II Deficiency	HSD3B2	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,300
3-Methylcrotonyl-CoA Carboxylase Deficiency (MCCC1-Related)	MCCC1	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,400
3-Methylcrotonyl-CoA Carboxylase Deficiency (MCCC2-Related)	MCCC2	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,200
3-Methylglutaconic Aciduria, Type III	OPA3	AR	Reduced Risk	Personalized Residual Risk: 1 in 50,000
3-Phosphoglycerate Dehydrogenase Deficiency	PHGDH	AR	Reduced Risk	Personalized Residual Risk: 1 in 63,000
6-Pyruvoyl-Tetrahydropterin Synthase Deficiency	PTS	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,800
CD59-Mediated Hemolytic Anemia	CD59	AR	Reduced Risk	Personalized Residual Risk: 1 in 415,000
Abetalipoproteinemia	MTTP	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,200
Achalasia-Addisonianism-Alacrimia Syndrome	AAAS	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,500
Achromatopsia (CNGA3-Related)	CNGA3	AR	Reduced Risk	Personalized Residual Risk: 1 in 830
Achromatopsia (CNGB3-related)	CNGB3	AR	Reduced Risk	Personalized Residual Risk: 1 in 8,600
Acrodermatitis Enteropathica	SLC39A4	AR	Reduced Risk	Personalized Residual Risk: 1 in 12,000
Acute Infantile Liver Failure	TRMU	AR	Reduced Risk	Personalized Residual Risk: 1 in 9,400
Acyl-CoA Oxidase I Deficiency	ACOX1	AR	Reduced Risk	Personalized Residual Risk: 1 in 39,000
Adams-Oliver Syndrome 4	EOGT	AR	Reduced Risk	Personalized Residual Risk: 1 in 44,000
Adenosine Deaminase Deficiency	ADA	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,100
Adrenocorticotrophic Hormone Deficiency	TBX19	AR	Reduced Risk	Personalized Residual Risk: 1 in 10,000
Adrenoleukodystrophy, X-Linked	ABCD1	XL	Reduced Risk	Personalized Residual Risk: 1 in 19,000
Agammaglobulinemia	BTK	XL	Reduced Risk	Personalized Residual Risk: 1 in 250,000
Agenesis of the Corpus Callosum	FRMD4A	AR	Reduced Risk	Personalized Residual Risk: 1 in 348,000
Aicardi-Goutieres Syndrome (RNASEH2C-Related)	RNASEH2C	AR	Reduced Risk	Personalized Residual Risk: 1 in 11,000
Aicardi-Goutieres Syndrome (SAMHD1-Related)	SAMHD1	AR	Reduced Risk	Personalized Residual Risk: 1 in 10,000
Aicardi-Goutieres Syndrome (TREX1-Related)	TREX1	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,200
Albinism, Oculocutaneous, Type III	TYRP1	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,500
Alkaptonuria	HGD	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,100
Alpha-Mannosidosis	MAN2B1	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,200

Condition	Gene	Inheritance	Risk	Notes
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 <b>Personalized Residual Risk: 1 in 490</b>
Alpha-Thalassemia Intellectual Disability Syndrome	ATRX	XL	Reduced Risk	<b>Personalized Residual Risk: 1 in 48,000</b>
Alport Syndrome (COL4A3-Related)	COL4A3	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 1,800</b>
Alport Syndrome (COL4A4-Related)	COL4A4	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 1,800</b>
Alport Syndrome (COL4A5-Related)	COL4A5	XL	Reduced Risk	<b>Personalized Residual Risk: 1 in 150,000</b>
Alstrom Syndrome	ALMS1	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 3,800</b>
Andermann Syndrome	SLC12A6	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 151,000</b>
Antley-Bixler Syndrome (POR-Related)	POR	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 4,000</b>
Argininemia	ARG1	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 6,500</b>
Argininosuccinic Aciduria	ASL	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 1,200</b>
Aromatase Deficiency	CYP19A1	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 5,400</b>
Arthrogryposis, Intellectual Disability, and Seizures	SLC35A3	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 37,000</b>
Asparagine Synthetase Deficiency	ASNS	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 21,000</b>
Aspartylglycosaminuria	AGA	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 13,000</b>
Ataxia With Isolated Vitamin E Deficiency	TTPA	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 61,000</b>
Ataxia-Telangiectasia	ATM	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 1,300</b>
Ataxia-Telangiectasia-Like Disorder 1	MRE11	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 5,500</b>
Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay	SACS	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 2,600</b>
Bardet-Biedl Syndrome (ARL6-Related)	ARL6	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 29,000</b>
Bardet-Biedl Syndrome (BBS10-Related)	BBS10	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 2,700</b>
Bardet-Biedl Syndrome (BBS12-Related)	BBS12	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 9,900</b>
Bardet-Biedl Syndrome (BBS1-Related)	BBS1	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 6,400</b>
Bardet-Biedl Syndrome (BBS2-Related)	BBS2	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 1,200</b>
Bardet-Biedl Syndrome (BBS4-Related)	BBS4	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 22,000</b>
Bare Lymphocyte Syndrome, Type II	CIITA	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 35,000</b>
Barth Syndrome	TAZ	XL	Reduced Risk	<b>Personalized Residual Risk: 1 in 183,000</b>
Bartter Syndrome, Type 3	CLCNKB	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 740</b>
Bartter Syndrome, Type 4A	BSND	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 91,000</b>
Bernard-Soulier Syndrome, Type A1	GP1BA	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 42,000</b>
Bernard-Soulier Syndrome, Type C	GP9	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 3,300</b>
Beta-Globin-Related Hemoglobinopathies	HBB	AR	Reduced Risk	<b>Personalized Residual Risk (Beta-Globin-Related Hemoglobinopathies): 1 in 2,000</b> <b>Personalized Residual Risk (Beta-Globin-Related Hemoglobinopathies: HbS Variant): 1 in 11,000</b> <b>Personalized Residual Risk (Beta-Globin-Related Hemoglobinopathies: HbC Variant): 1 in 42,000</b>
Beta-Ketothiolase Deficiency	ACAT1	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 5,400</b>
Beta-Mannosidosis	MANBA	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 9,100</b>
BH4-Deficient Hyperphenylalaninemia C	QDPR	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 3,100</b>
BH4-Deficient Hyperphenylalaninemia D	PCBD1	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 8,000</b>
Bilateral Frontoparietal Polymicrogyria	GPR56	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 203,000</b>
Biotinidase Deficiency	BTBD	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 500</b>
Bloom Syndrome	BLM	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 7,400</b>
Canavan Disease	ASPA	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 4,000</b>
Carbamoylphosphate Synthetase I Deficiency	CPS1	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 1,100</b>

Carnitine Acylcarnitine Translocase Deficiency	<i>SLC25A20</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,100
Carnitine Palmitoyltransferase IA Deficiency	<i>CPT1A</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 24,000
Carnitine Palmitoyltransferase II Deficiency	<i>CPT2</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 670
Carpenter Syndrome	<i>RAB23</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 21,000
Cartilage-Hair Hypoplasia	<i>RMRP</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 960
Catecholaminergic Polymorphic Ventricular Tachycardia	<i>CASQ2</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,900
Central Hypothyroidism and Testicular Enlargement	<i>IGSF1</i>	XL	Reduced Risk	Personalized Residual Risk: 1 in 781,000
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 2,100
Cerebral Creatine Deficiency Syndrome 3	<i>GATM</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 7900
Cerebral Dysgenesis, Neuropathy, Ichthyosis, and Palmoplantar Keratoderma Syndrome	<i>SNAP29</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 383,000
Cerebrotendinous Xanthomatosis	<i>CYP27A1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,900
Charcot-Marie-Tooth Disease, Type 4D	<i>NDRG1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 730,000
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
Chediak-Higashi Syndrome	<i>LYST</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 7,100
Chondrodysplasia Punctata	<i>ARSE</i>	XL	Reduced Risk	Personalized Residual Risk: 1 in 862,000
Choreoacanthocytosis	<i>VPS13A</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 13,000
Choroideremia	<i>CHM</i>	XL	Reduced Risk	Personalized Residual Risk: 1 in 125,000
Chronic Granulomatous Disease (CYBA-Related)	<i>CYBA</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,000
Chronic Granulomatous Disease (CYBB-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 12,000
Citrullinemia, Type 1	<i>ASS1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,500
Cockayne Syndrome, Type A	<i>ERCC8</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 8,900
Cockayne Syndrome, Type B and other ERCC6-Related Disorders	<i>ERCC6</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 8,100
Cohen Syndrome	<i>VPS13B</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,400
Combined Factor V and VIII Deficiency	<i>LMAN1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 102,000
Combined Malonic and Methylmalonic Aciduria	<i>ACSF3</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,400
Combined Oxidative Phosphorylation Deficiency 1	<i>GFM1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 13,000
Combined Oxidative Phosphorylation Deficiency 3	<i>TSMF</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 27,000
Combined Pituitary Hormone Deficiency 1	<i>POU1F1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,900
Combined Pituitary Hormone Deficiency 2	<i>PROP1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,800
Combined Pituitary Hormone Deficiency 3	<i>LHX3</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 140,000
Combined SAP Deficiency	<i>PSAP</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 44,000
Cone-Rod Dystrophy 6 / Leber Congenital Amaurosis 1	<i>GUCY2D</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,200
Congenital Adrenal Hyperplasia due to 11-Beta-Hydroxylase Deficiency	<i>CYP11B1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 520
Congenital Adrenal Hyperplasia due to 17-Alpha-Hydroxylase Deficiency	<i>CYP17A1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,800
Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency	<i>CYP21A2</i>	AR	Reduced Risk	CYP21A2 copy number: 2 CYP21A2 sequencing: Negative <b>Personalized Residual Risk (Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency (Non-Classic)):</b> 1 in 200 <b>Personalized Residual Risk (Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency (Classic)):</b> 1 in 1,300
Congenital Adrenal Hypoplasia (NR0B1-Related)	<i>NR0B1</i>	XL	Reduced Risk	Personalized Residual Risk: 1 in 353,000
Congenital Adrenal Insufficiency (CYP11A1-Related)	<i>CYP11A1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,100



Congenital Amegakaryocytic Thrombocytopenia	MPL	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,100
Congenital Bile Acid Synthesis Defect (AKR1D1-Related)	AKR1D1	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,900
Congenital Bile Acid Synthesis Defect (HSD3B7-Related)	HSD3B7	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,200
Congenital Disorder of Deglycosylation	NGLY1	AR	Reduced Risk	Personalized Residual Risk: 1 in 14,000
Congenital Disorder of Glycosylation, Type Ia	PMM2	AR	Reduced Risk	Personalized Residual Risk: 1 in 540
Congenital Disorder of Glycosylation, Type Ib	MPI	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,600
Congenital Disorder of Glycosylation, Type Ic	ALG6	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,100
Congenital Disorder of Glycosylation, Type Im	DOLK	AR	Reduced Risk	Personalized Residual Risk: 1 in 134,000
Congenital Dyserythropoietic Anemia Type 2	SEC23B	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,000
Congenital Dyserythropoietic Anemia, Type Ia	CDAN1	AR	Reduced Risk	Personalized Residual Risk: 1 in 470
Congenital Ichthyosis 4A and 4B	ABCA12	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,100
Congenital Insensitivity to Pain with Anhidrosis	NTRK1	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,700
Congenital Muscular Dystrophy (LAMA2-Related)	LAMA2	AR	Reduced Risk	Personalized Residual Risk: 1 in 640
Congenital Myasthenic Syndrome (CHAT-Related)	CHAT	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,100
Congenital Myasthenic Syndrome (CHRNE-Related)	CHRNE	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,100
Congenital Myasthenic Syndrome (DOK7-Related)	DOK7	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,200
Congenital Myasthenic Syndrome (RAPSN-Related)	RAPSN	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,900
Congenital Neutropenia (HAX1-Related)	HAX1	AR	Reduced Risk	Personalized Residual Risk: 1 in 82,000
Congenital Neutropenia (VPS45-Related)	VPS45	AR	Reduced Risk	Personalized Residual Risk: 1 in 43,000
Congenital Nongoitrous Hypothyroidism 1	TSHR	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,000
Congenital Nongoitrous Hypothyroidism 4	TSHB	AR	Reduced Risk	Personalized Residual Risk: 1 in 118,000
Congenital Secretory Chloride Diarrhea 1	SLC26A3	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,400
Corneal Dystrophy and Perceptive Deafness	SLC4A11	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,600
Corticosterone Methyloxidase Deficiency	CYP11B2	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,500
Cystinosis	CTNS	AR	Reduced Risk	Personalized Residual Risk: 1 in 7,700
Cystinuria (SLC3A1-Related)	SLC3A1	AR	Reduced Risk	Personalized Residual Risk: 1 in 590
Cytochrome C Oxidase Deficiency / Leigh Syndrome (COX15-Related)	COX15	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,300
D-Bifunctional Protein Deficiency	HSD17B4	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,000
Deafness, Autosomal Recessive 3	MYO15A	AR	Reduced Risk	Personalized Residual Risk: 1 in 240
Deafness, Autosomal Recessive 59	PJVK	AR	Reduced Risk	Personalized Residual Risk: 1 in 57,000
Deafness, Autosomal Recessive 7	TMC1	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,200
Deafness, Autosomal Recessive 76	SYNE4	AR	Reduced Risk	Personalized Residual Risk: 1 in 43,000
Deafness, Autosomal Recessive 77	LOXHD1	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,700
Deafness, Autosomal Recessive 8/10	TMPPRS3	AR	Reduced Risk	Personalized Residual Risk: 1 in 510
Deafness, Autosomal Recessive 9	OTOF	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,400
Desbuquois Dysplasia 1	CANT1	AR	Reduced Risk	Personalized Residual Risk: 1 in 24,000
Desmosterolosis	DHCR24	AR	Reduced Risk	Personalized Residual Risk: 1 in 27,000
Diaphanospondylodysostosis	BMPER	AR	Reduced Risk	Personalized Residual Risk: 1 in 18,000
Distal Renal Tubular Acidosis and other SLC4A1-related Disorders	SLC4A1	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,000
Duchenne Muscular Dystrophy / Becker Muscular Dystrophy	DMD	XL	Reduced Risk	Personalized Residual Risk: 1 in 10,000
Dyskeratosis Congenita (DKC1-related)	DKC1	XL	Reduced Risk	Personalized Residual Risk: 1 in 9,259,000
Dyskeratosis Congenita (RTEL1-Related)	RTEL1	AR	Reduced Risk	Personalized Residual Risk: 1 in 9,800
Dystrophic Epidermolysis Bullosa	COL7A1	AR	Reduced Risk	Personalized Residual Risk: 1 in 900
Ehlers-Danlos Syndrome, Type VI	PLOD1	AR	Reduced Risk	Personalized Residual Risk: 1 in 20,000

Ehlers-Danlos Syndrome, Type VIIC	ADAMTS2	AR	Reduced Risk	Personalized Residual Risk: 1 in 16,000
Ellis-Van Creveld Syndrome (EVC2-Related)	EVC2	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,300
Ellis-van Creveld Syndrome (EVC-Related)	EVC	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,200
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 1,600
Ethylmalonic Encephalopathy	ETHE1	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,400
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 VII Deficiency	F7	AR	Reduced Risk	Personalized Residual Risk: 1 in 450
Factor XI Deficiency	F11	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,500
Familial Autosomal Recessive Hypercholesterolemia	LDLRAP1	AR	Reduced Risk	Personalized Residual Risk: 1 in 136,000
Familial Dysautonomia	IKBKAP	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,400
Familial Hypercholesterolemia	LDLR	AR	Reduced Risk	Personalized Residual Risk: 1 in 280
Familial Hyperinsulinemic Hypoglycemia 4 / 3-Hydroxyacyl-CoA Dehydrogenase Deficiency	HADH	AR	Reduced Risk	Personalized Residual Risk: 1 in 9,200
Familial Hyperinsulinism (ABCC8-Related)	ABCC8	AR	Reduced Risk	Personalized Residual Risk: 1 in 450
Familial Hyperinsulinism (KCNJ11-Related)	KCNJ11	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,300
Familial Hyperphosphatemic Tumoral Calcinosis	GALNT3	AR	Reduced Risk	Personalized Residual Risk: 1 in 7,800
Familial Mediterranean Fever	MEFV	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,200
Fanconi Anemia, Group A	FANCA	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,100
Fanconi Anemia, Group C	FANCC	AR	Reduced Risk	Personalized Residual Risk: 1 in 12,000
Fanconi Anemia, Group G	FANCG	AR	Reduced Risk	Personalized Residual Risk: 1 in 28,000
Fanconi-Bickel Syndrome	SLC2A2	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,000
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 19,000
Fructose-1,6-Bisphosphatase Deficiency	FBP1	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,600
Fucosidosis	FUCA1	AR	Reduced Risk	Personalized Residual Risk: 1 in 9,200
Fumarase Deficiency	FH	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,500
Fundus Albipunctatus	RDH5	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,000
Galactokinase Deficiency	GALK1	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,700
Galactose Epimerase Deficiency	GALE	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,600
Galactosemia	GALT	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,200
Galactosialidosis	CTSA	AR	Reduced Risk	Personalized Residual Risk: 1 in 7,900
Gaucher Disease	GBA	AR	Reduced Risk	Personalized Residual Risk: 1 in 280
Generalized Thyrotropin-Releasing Hormone Resistance	TRHR	AR	Reduced Risk	Personalized Residual Risk: 1 in 104,000
Geroderma Osteodysplasticum	GORAB	AR	Reduced Risk	Personalized Residual Risk: 1 in 70,000
Gitelman Syndrome	SLC12A3	AR	Reduced Risk	Personalized Residual Risk: 1 in 290
Glanzmann Thrombasthenia (ITGA2B-Related)	ITGA2B	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,800
Glanzmann Thrombasthenia (ITGB3-Related)	ITGB3	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,600
Glutaric Acidemia, Type I	GCDH	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,700
Glutaric Acidemia, Type IIa	ETFA	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,700
Glutaric Acidemia, Type IIb	ETFB	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,900
Glutaric Acidemia, Type IIc	ETFDH	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,700
Glutathione Synthetase Deficiency	GSS	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,500
Glycine Encephalopathy (AMT-Related)	AMT	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,700
Glycine Encephalopathy (GLDC-Related)	GLDC	AR	Reduced Risk	Personalized Residual Risk: 1 in 760
Glycogen Storage Disease, Type 0	GYS2	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,200



Glycogen Storage Disease, Type Ia	G6PC	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,300
Glycogen Storage Disease, Type Ib	SLC37A4	AR	Reduced Risk	Personalized Residual Risk: 1 in 7,300
Glycogen Storage Disease, Type II	GAA	AR	Reduced Risk	Personalized Residual Risk: 1 in 520
Glycogen Storage Disease, Type III	AGL	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,600
Glycogen Storage Disease, Type IV / Adult Polyglucosan Body Disease	GBE1	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,400
Glycogen Storage Disease, Type IXb	PHKB	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,600
Glycogen Storage Disease, Type V	PYGM	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,200
Glycogen Storage Disease, Type VI	PYGL	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,600
Glycogen Storage Disease, Type VII	PFKM	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,300
GM3 Synthase Deficiency	ST3GAL5	AR	Reduced Risk	Personalized Residual Risk: 1 in 25,000
GRACILE Syndrome and Other BCS1L-Related Disorders	BCS1L	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,900
Gray Platelet Syndrome	NBEAL2	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,800
Growth Hormone Deficiency, Type IB	GHRHR	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,900
Hemochromatosis, Type 2A	HFE2	AR	Reduced Risk	Personalized Residual Risk: 1 in 12,000
Hemochromatosis, Type 3	TFR2	AR	Reduced Risk	Personalized Residual Risk: 1 in 11,000
Hereditary Fructose Intolerance	ALDOB	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,900
Hereditary Spastic Paraparesis 49	TECPR2	AR	Reduced Risk	Personalized Residual Risk: 1 in 15,000
Hermansky-Pudlak Syndrome, Type 1	HPS1	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,500
Hermansky-Pudlak Syndrome, Type 3	HPS3	AR	Reduced Risk	Personalized Residual Risk: 1 in 49,000
Hermansky-Pudlak Syndrome, Type 4	HPS4	AR	Reduced Risk	Personalized Residual Risk: 1 in 35,000
Hermansky-Pudlak Syndrome, Type 6	HPS6	AR	Reduced Risk	Personalized Residual Risk: 1 in 9,400
HMG-CoA Lyase Deficiency	HMGCL	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,700
Hmg-CoA Synthase 2 Deficiency	HMGCS2	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,000
Holocarboxylase Synthetase Deficiency	HLCS	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,500
Homocystinuria (CBS-Related)	CBS	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,400
Homocystinuria due to MTHFR Deficiency	MTHFR	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,300
Homocystinuria, cblE Type	MTRR	AR	Reduced Risk	Personalized Residual Risk: 1 in 9,600
Homocystinuria-Megaloblastic Anemia, Cobalamin G Type	MTR	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,100
Hydrocephalus	L1CAM	XL	Reduced Risk	Personalized Residual Risk: 1 in 40,000
Hydrolethalus Syndrome	HYLS1	AR	Reduced Risk	Personalized Residual Risk: 1 in 52,000
Hyper-Igm Syndrome	CD40LG	XL	Reduced Risk	Personalized Residual Risk: 1 in 1,167,000
Hyperornithinemia-Hyperammonemia-Homocitrullinuria Syndrome	SLC25A15	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,700
Hyperuricemia, Pulmonary Hypertension, Renal Failure, and Alkalosis	SARS2	AR	Reduced Risk	Personalized Residual Risk: 1 in 23,000
Hypohidrotic Ectodermal Dysplasia 1	EDA	XL	Reduced Risk	Personalized Residual Risk: 1 in 22,000
Hypomagnesemia 1	TRPM6	AR	Reduced Risk	Personalized Residual Risk: 1 in 11,000
Hypomyelinating Leukodystrophy 3	AIMP1	AR	Reduced Risk	Personalized Residual Risk: 1 in 341,000
Hypomyelinating Leukodystrophy 12	VPS11	AR	Reduced Risk	Personalized Residual Risk: 1 in 72,000
Hypophosphatasia	ALPL	AR	Reduced Risk	Personalized Residual Risk: 1 in 790
Hypophosphatemic Rickets with Hypercalciuria	SLC34A3	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,200
Hypotrichosis 8 / Autosomal Recessive Woolly Hair 1	LPAR6	AR	Reduced Risk	Personalized Residual Risk: 1 in 27,000
Immunodeficiency 18	CD3E	AR	Reduced Risk	Personalized Residual Risk: 1 in 73,000
Immunodeficiency 19	CD3D	AR	Reduced Risk	Personalized Residual Risk: 1 in 46,000
Inclusion Body Myopathy 2	GNE	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,000
Infantile Cerebral and Cerebellar Atrophy	MED17	AR	Reduced Risk	Personalized Residual Risk: 1 in 129,000
Infantile Neuroaxonal Dystrophy 1 and other PLA2G6-Related Disorders	PLA2G6	AR	Reduced Risk	Personalized Residual Risk: 1 in 690
Intellectual Disability, Autosomal Recessive 3	CC2D1A	AR	Reduced Risk	Personalized Residual Risk: 1 in 21,000

Intrahepatic Cholestasis	<i>ATP8B1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,400
Isovaleric Acidemia	<i>IVD</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,000
Joubert Syndrome 2	<i>TMEM216</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 14,000
Joubert Syndrome 4 / Senior-Loken Syndrome 1 / Juvenile Nephronophthisis 1	<i>NPHP1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 21,000
Joubert Syndrome 7 / Meckel Syndrome 5 / COACH Syndrome	<i>RPGRIPL</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 9,000
Junctional Epidermolysis Bullosa ( <i>COL17A1</i> -Related)	<i>COL17A1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 25,000
Junctional Epidermolysis Bullosa ( <i>ITGA6</i> -Related)	<i>ITGA6</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 125,000
Junctional Epidermolysis Bullosa ( <i>ITGB4</i> -Related)	<i>ITGB4</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,400
Junctional Epidermolysis Bullosa ( <i>LAMA3</i> -Related)	<i>LAMA3</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 21,000
Junctional Epidermolysis Bullosa ( <i>LAMB3</i> -Related)	<i>LAMB3</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,900
Junctional Epidermolysis Bullosa ( <i>LAMC2</i> -Related)	<i>LAMC2</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 77,000
Kohlschutter-Tonz Syndrome	<i>ROGDI</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,300
Krabbe Disease	<i>GALC</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 860
Lamellar Ichthyosis, Type 1	<i>TGM1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,500
Laron Dwarfism	<i>GHR</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,700
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 5,500
Leber Congenital Amaurosis 15 / Retinitis Pigmentosa 14	<i>TULP1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,800
Leber Congenital Amaurosis 2 / Retinitis Pigmentosa 20	<i>RPE65</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,500
Leber Congenital Amaurosis 4	<i>AIPL1</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 14,000
Leber Congenital Amaurosis 8 / Retinitis Pigmentosa 12 / Pigmented Paravenous Chorioretinal Atrophy	<i>CRB1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 990
Leigh Syndrome ( <i>NDUFS7</i> -Related)	<i>NDUFS7</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 26,000
Leigh Syndrome ( <i>SURF1</i> -Related)	<i>SURF1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,400
Leigh Syndrome, French-Canadian Type	<i>LRPPRC</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 32,000
Lethal Congenital Contracture Syndrome 1 / Lethal Arthrogyposis with Anterior Horn Cell Disease	<i>GLE1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 10,000
Lethal Congenital Contracture Syndrome 2	<i>ERBB3</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 96,000
Lethal Congenital Contracture Syndrome 3	<i>PIP5K1C</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 318,000
Leukoencephalopathy with Vanishing White Matter	<i>EIF2B5</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,300
Limb-Girdle Muscular Dystrophy, Type 2A	<i>CAPN3</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 960
Limb-Girdle Muscular Dystrophy, Type 2B	<i>DYSF</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,100
Limb-Girdle Muscular Dystrophy, Type 2C	<i>SGCG</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,900
Limb-Girdle Muscular Dystrophy, Type 2D	<i>SGCA</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,500
Limb-Girdle Muscular Dystrophy, Type 2E	<i>SGCB</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 31,000
Limb-Girdle Muscular Dystrophy, Type 2F	<i>SGCD</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 52,000
Limb-Girdle Muscular Dystrophy, Type 2H	<i>TRIM32</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 10,000
Limb-Girdle Muscular Dystrophy, Type 2I	<i>FKRP</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,400
Limb-Girdle Muscular Dystrophy, Type 2L	<i>ANO5</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 660
Lipoamide Dehydrogenase Deficiency	<i>DLD</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 14,000
Lipoid Adrenal Hyperplasia	<i>STAR</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,600
Lipoprotein Lipase Deficiency	<i>LPL</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,400

Long-Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency	HADHA	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,900
Lowe Syndrome	OCRL	XL	Reduced Risk	Personalized Residual Risk: 1 in 1,375,000
Lysinuric Protein Intolerance	SLC7A7	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,000
Malonyl-CoA Decarboxylase Deficiency	MLYCD	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,800
Maple Syrup Urine Disease, Type 1a	BCKDHA	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,100
Maple Syrup Urine Disease, Type 1b	BCKDHB	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,100
Maple Syrup Urine Disease, Type 2	DBT	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,600
Meckel Syndrome 1 / Bardet-Biedl Syndrome 13	MKS1	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,700
Medium Chain Acyl-CoA Dehydrogenase Deficiency	ACADM	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,800
MEDNIK Syndrome	AP1S1	AR	Reduced Risk	Personalized Residual Risk: 1 in 211,000
Megalencephalic Leukoencephalopathy with Subcortical Cysts	MLC1	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,300
Megaloblastic Anemia 1	AMN	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,300
Menkes Disease	ATP7A	XL	Reduced Risk	Personalized Residual Risk: 1 in 172,000
Metachromatic Leukodystrophy	ARSA	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,000
Methionine Adenosyltransferase I/III Deficiency	MAT1A	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,900
Methylmalonic Acidemia (MMAA-Related)	MMAA	AR	Reduced Risk	Personalized Residual Risk: 1 in 15,000
Methylmalonic Acidemia (MMAB-Related)	MMAB	AR	Reduced Risk	Personalized Residual Risk: 1 in 12,000
Methylmalonic Acidemia (MUT-Related)	MUT	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,300
Methylmalonic Aciduria and Homocystinuria, Cobalamin C Type	MMACHC	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,800
Methylmalonic Aciduria and Homocystinuria, Cobalamin D Type	MMADHC	AR	Reduced Risk	Personalized Residual Risk: 1 in 219,000
Methylmalonic Aciduria and Homocystinuria, Cobalamin F Type	LMBRD1	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,600
Methylmalonyl-CoA Epimerase Deficiency	MCEE	AR	Reduced Risk	Personalized Residual Risk: 1 in 98,000
Microphthalmia / Anophthalmia	VSX2	AR	Reduced Risk	Personalized Residual Risk: 1 in 40,000
Mitochondrial Complex I Deficiency (ACAD9-Related)	ACAD9	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,800
Mitochondrial Complex I Deficiency (NDUFA11-Related)	NDUFA11	AR	Reduced Risk	Personalized Residual Risk: 1 in 414,000
Mitochondrial Complex I Deficiency (NDUFAF5-Related)	NDUFAF5	AR	Reduced Risk	Personalized Residual Risk: 1 in 9,800
Mitochondrial Complex I Deficiency (NDUFS6-Related)	NDUFS6	AR	Reduced Risk	Personalized Residual Risk: 1 in 353,000
Mitochondrial Complex I Deficiency (NDUFV1-Related)	NDUFV1	AR	Reduced Risk	Personalized Residual Risk: 1 in 870
Mitochondrial Complex I Deficiency / Leigh Syndrome (FOXRED1-Related)	FOXRED1	AR	Reduced Risk	Personalized Residual Risk: 1 in 13,000
Mitochondrial Complex I Deficiency / Leigh Syndrome (NDUFAF2-Related)	NDUFAF2	AR	Reduced Risk	Personalized Residual Risk: 1 in 168,000
Mitochondrial Complex I Deficiency / Leigh Syndrome (NDUFS4-Related)	NDUFS4	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,800
Mitochondrial Complex IV Deficiency (COX20-related)	COX20	AR	Reduced Risk	Personalized Residual Risk: 1 in 42,000
Mitochondrial Complex IV Deficiency (COX6B1-related)	COX6B1	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,116,000
Mitochondrial Complex IV Deficiency (APOPT1-Related)	APOPT1	AR	Reduced Risk	Personalized Residual Risk: 1 in 9,200
Mitochondrial Complex IV Deficiency (PET100-Related)	PET100	AR	Reduced Risk	Personalized Residual Risk: 1 in 469,000
Mitochondrial Complex IV Deficiency (SCO1-related)	SCO1	AR	Reduced Risk	Personalized Residual Risk: 1 in 13,000
Mitochondrial Complex IV Deficiency / Leigh Syndrome (COX10-Related)	COX10	AR	Reduced Risk	Personalized Residual Risk: 1 in 9,200
Mitochondrial DNA Depletion Syndrome 2	TK2	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,900
Mitochondrial DNA Depletion Syndrome 3	DGUOK	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,200

Mitochondrial DNA Depletion Syndrome 4A and 4B and other <i>POLG</i> -Related Disorders	<i>POLG</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 320
Mitochondrial DNA Depletion Syndrome 5	<i>SUCLA2</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 78,000
Mitochondrial DNA Depletion Syndrome 6 / Navajo Neurohepatopathy	<i>MPV17</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,400
Mitochondrial Myopathy and Sideroblastic Anemia 1	<i>PUS1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 449,000
Mitochondrial Trifunctional Protein Deficiency ( <i>HADHB</i> -Related)	<i>HADHB</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,000
Molybdenum Cofactor Deficiency A	<i>MOCS1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,700
Mucopolipidosis II / IIIA	<i>GNPTAB</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,100
Mucopolipidosis III Gamma	<i>GNPTG</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 68,000
Mucopolysaccharidosis Type I	<i>IDUA</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,300
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 2,700
Mucopolysaccharidosis Type IIIB	<i>NAGLU</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 950
Mucopolysaccharidosis Type IIIC	<i>HGSNAT</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,200
Mucopolysaccharidosis Type IIID	<i>GNS</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 137,000
Mucopolysaccharidosis Type IVa	<i>GALNS</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 690
Mucopolysaccharidosis Type IVb / GM1 Gangliosidosis	<i>GLB1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,700
Mucopolysaccharidosis type IX	<i>HYAL1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 149,000
Mucopolysaccharidosis type VI	<i>ARSB</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,300
Mucopolysaccharidosis VII	<i>GUSB</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,600
Mulibrey Nanism	<i>TRIM37</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 31,000
Multiple Congenital Anomalies-Hypotonia-Seizures Syndrome 1	<i>PIGN</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,800
Multiple Pterygium Syndrome	<i>CHRNA3</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 9,900
Multiple Sulfatase Deficiency	<i>SUMF1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 69,000
Muscle-Eye-Brain Disease and Other <i>POMGNT1</i> -Related Congenital Muscular Dystrophy-Dystroglycanopathies	<i>POMGNT1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,200
Myoneurogastrointestinal Encephalopathy	<i>TYMP</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,100
Myotubular Myopathy 1	<i>MTM1</i>	XL	Reduced Risk	Personalized Residual Risk: 1 in 192,000
N-Acetylglutamate Synthase Deficiency	<i>NAGS</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,200
Nemaline Myopathy 2	<i>NEB</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 660
Nephrogenic Diabetes insipidus ( <i>AVPR2</i> -related) / Nephrogenic Syndrome of Inappropriate Antidiuresis	<i>AVPR2</i>	XL	Reduced Risk	Personalized Residual Risk: 1 in 471,000
Nephrogenic Diabetes Insipidus, Type II	<i>AQP2</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,400
Nephronophthisis 2	<i>INVS</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 56,000
Nephrotic Syndrome ( <i>NPHS1</i> -Related) / Congenital Finnish Nephrosis	<i>NPHS1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 920
Nephrotic Syndrome ( <i>NPHS2</i> -Related) / Steroid-Resistant Nephrotic Syndrome	<i>NPHS2</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 780
Neurodegeneration due to Cerebral Folate Transport Deficiency	<i>FOLR1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,300
Neurodevelopmental Disorder with Progressive Microcephaly, Spasticity, and Brain Anomalies	<i>PLAA</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 229,000
Neuronal Ceroid-Lipofuscinosis ( <i>CLN3</i> -Related)	<i>CLN3</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 9,200
Neuronal Ceroid-Lipofuscinosis ( <i>CLN5</i> -Related)	<i>CLN5</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,300
Neuronal Ceroid-Lipofuscinosis ( <i>CLN6</i> -Related)	<i>CLN6</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 8,600
Neuronal Ceroid-Lipofuscinosis ( <i>CLN8</i> -Related)	<i>CLN8</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,100
Neuronal Ceroid-Lipofuscinosis ( <i>MFSD8</i> -Related)	<i>MFSD8</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,200
Neuronal Ceroid-Lipofuscinosis ( <i>PPT1</i> -Related)	<i>PPT1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 7,500
Neuronal Ceroid-Lipofuscinosis ( <i>TPP1</i> -Related)	<i>TPP1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,300

<b>Niemann-Pick Disease (SMPD1-Related)</b>	<i>SMPD1</i>	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 1,800</b>
<b>Niemann-Pick Disease, Type C (NPC1-Related)</b>	<i>NPC1</i>	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 690</b>
<b>Niemann-Pick Disease, Type C (NPC2-Related)</b>	<i>NPC2</i>	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 6,600</b>
<b>Nijmegen Breakage Syndrome</b>	<i>NBN</i>	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 14,000</b>
<b>Non-Syndromic Hearing Loss (GJB2-Related)</b>	<i>GJB2</i>	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 600</b>
<b>Oculocutaneous Albinism, Type IA / IB</b>	<i>TYR</i>	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 240</b>
<b>Oculocutaneous Albinism, Type IV</b>	<i>SLC45A2</i>	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 830</b>
<b>Omenn Syndrome (RAG2-Related)</b>	<i>RAG2</i>	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 17,000</b>
<b>Omenn Syndrome / Severe Combined Immunodeficiency, Athabaskan-Type</b>	<i>DCLRE1C</i>	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 5,500</b>
<b>Omenn Syndrome and other RAG1-Related Disorders</b>	<i>RAG1</i>	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 850</b>
<b>Ornithine Aminotransferase Deficiency</b>	<i>OAT</i>	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 6,400</b>
<b>Ornithine Transcarbamylase Deficiency</b>	<i>OTC</i>	XL	Reduced Risk	<b>Personalized Residual Risk: 1 in 103,000</b>
<b>Osteogenesis Imperfecta, Type XI</b>	<i>FKBP10</i>	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 9,500</b>
<b>Osteopetrosis 1</b>	<i>TCIRG1</i>	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 4,700</b>
<b>Osteopetrosis 8</b>	<i>SNX10</i>	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 16,000</b>
<b>Otospondylomegaepiphyseal Dysplasia / Deafness / Fibrochondrogenesis 2</b>	<i>COL11A2</i>	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 2,700</b>
<b>Papillon-Lefevre Syndrome</b>	<i>CTSC</i>	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 5,000</b>
<b>Pendred Syndrome</b>	<i>SLC26A4</i>	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 390</b>
<b>Peroxisome Biogenesis Disorder 3A and 3B</b>	<i>PEX12</i>	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 30,000</b>
<b>Peroxisome Biogenesis Disorder 7A and 7B</b>	<i>PEX26</i>	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 70,000</b>
<b>Phenylalanine Hydroxylase Deficiency</b>	<i>PAH</i>	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 340</b>
<b>Polycystic Kidney Disease, Autosomal Recessive</b>	<i>PKHD1</i>	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 450</b>
<b>Polyglandular Autoimmune Syndrome, Type 1</b>	<i>AIRE</i>	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 5,300</b>
<b>Pontocerebellar Hypoplasia, Type 1A</b>	<i>VRK1</i>	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 25,000</b>
<b>Pontocerebellar Hypoplasia, Type 1B</b>	<i>EXOSC3</i>	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 10,000</b>
<b>Pontocerebellar Hypoplasia, Type 2A and Type 4</b>	<i>TSEN54</i>	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 4,700</b>
<b>Pontocerebellar Hypoplasia, Type 2E</b>	<i>VPS53</i>	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 139,000</b>
<b>Pontocerebellar Hypoplasia, Type 6</b>	<i>RARS2</i>	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 8,600</b>
<b>Primary Carnitine Deficiency</b>	<i>SLC22A5</i>	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 1,500</b>
<b>Primary Ciliary Dyskinesia (CCDC103-Related)</b>	<i>CCDC103</i>	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 27,000</b>
<b>Primary Ciliary Dyskinesia (CCDC151-Related)</b>	<i>CCDC151</i>	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 59,000</b>
<b>Primary Ciliary Dyskinesia (CCDC39-Related)</b>	<i>CCDC39</i>	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 12,000</b>
<b>Primary Ciliary Dyskinesia (DNAH5-Related)</b>	<i>DNAH5</i>	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 1,500</b>
<b>Primary Ciliary Dyskinesia (DNAI1-Related)</b>	<i>DNAI1</i>	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 5,000</b>
<b>Primary Ciliary Dyskinesia (DNAI2-Related)</b>	<i>DNAI2</i>	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 8,000</b>
<b>Primary Ciliary Dyskinesia (RSPH9-Related)</b>	<i>RSPH9</i>	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 253,000</b>
<b>Primary Coenzyme Q10 Deficiency 7</b>	<i>COQ4</i>	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 12,000</b>
<b>Primary Congenital Glaucoma 3A</b>	<i>CYP1B1</i>	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 880</b>
<b>Primary Hyperoxaluria, Type 1</b>	<i>AGXT</i>	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 1,900</b>
<b>Primary Hyperoxaluria, Type 2</b>	<i>GRHPR</i>	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 11,000</b>
<b>Primary Hyperoxaluria, Type 3</b>	<i>HOGA1</i>	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 2,400</b>
<b>Progressive Cerebello-Cerebral Atrophy</b>	<i>SEPSECS</i>	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 6,400</b>
<b>Progressive Familial Intrahepatic Cholestasis, Type 2</b>	<i>ABCB11</i>	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 950</b>
<b>Progressive Myoclonic Epilepsy, Type 1B</b>	<i>PRICKLE1</i>	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 98,000</b>
<b>Progressive Pseudorheumatoid Dysplasia</b>	<i>WISP3</i>	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 5,600</b>
<b>Prolidase Deficiency</b>	<i>PEPD</i>	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 30,000</b>
<b>Propionic Acidemia (PCCA-Related)</b>	<i>PCCA</i>	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 2,600</b>



Propionic Acidemia (PCCB-Related)	PCCB	AR	Reduced Risk	Personalized Residual Risk: 1 in 12,000
Pulmonary Surfactant Dysfunction	ABCA3	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,200
Pycnodysostosis	CTSK	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,100
Pyridoxamine 5'-Phosphate Oxidase Deficiency	PNPO	AR	Reduced Risk	Personalized Residual Risk: 1 in 10,000
Pyridoxine-Dependent Epilepsy	ALDH7A1	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,100
Pyruvate Carboxylase Deficiency	PC	AR	Reduced Risk	Personalized Residual Risk: 1 in 8,000
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 1,000
Renal Tubular Acidosis and Deafness	ATP6V1B1	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,600
Retinitis Pigmentosa 25	EYS	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,800
Retinitis Pigmentosa 26	CERKL	AR	Reduced Risk	Personalized Residual Risk: 1 in 13,000
Retinitis Pigmentosa 28	FAM161A	AR	Reduced Risk	Personalized Residual Risk: 1 in 34,000
Retinitis Pigmentosa 36	PRCD	AR	Reduced Risk	Personalized Residual Risk: 1 in 304,000
Retinitis Pigmentosa 59	DHDDS	AR	Reduced Risk	Personalized Residual Risk: 1 in 9,900
Retinitis Pigmentosa 64 / Bardet-Biedl Syndrome 21 / Cone-Rod Dystrophy 16	C8ORF37	AR	Reduced Risk	Personalized Residual Risk: 1 in 168,000
Rh Deficiency Syndrome	RHAG	AR	Reduced Risk	Personalized Residual Risk: 1 in 46,000
Rhizomelic Chondrodysplasia Punctata, Type 1	PEX7	AR	Reduced Risk	Personalized Residual Risk: 1 in 10,000
Rhizomelic Chondrodysplasia Punctata, Type 3	AGPS	AR	Reduced Risk	Personalized Residual Risk: 1 in 620,000
Roberts Syndrome	ESCO2	AR	Reduced Risk	Personalized Residual Risk: 1 in 139,000
Salla Disease	SLC17A5	AR	Reduced Risk	Personalized Residual Risk: 1 in 8,400
Sandhoff Disease	HEXB	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,800
Sanjad-Sakati Syndrome	TBCE	AR	Reduced Risk	Personalized Residual Risk: 1 in 21,000
Schimke Immunoosseous Dysplasia	SMARCAL1	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,800
Seckel Syndrome 5 / Microcephaly 9	CEP152	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,700
Segawa Syndrome	TH	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,100
Sepiapterin Reductase Deficiency	SPR	AR	Reduced Risk	Personalized Residual Risk: 1 in 35,000
Severe Combined Immunodeficiency (IL7R-Related)	IL7R	AR	Reduced Risk	Personalized Residual Risk: 1 in 20,000
Severe Combined Immunodeficiency (JAK3-Related)	JAK3	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,100
Severe Combined Immunodeficiency (PTPRC-Related)	PTPRC	AR	Reduced Risk	Personalized Residual Risk: 1 in 8,500
Severe Congenital Neutropenia 4	G6PC3	AR	Reduced Risk	Personalized Residual Risk: 1 in 10,000
Severe Neonatal Hyperparathyroidism	CASR	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,700
Short Stature, Onychodysplasia, Facial Dysmorphism, and Hypotrichosis	POC1A	AR	Reduced Risk	Personalized Residual Risk: 1 in 108,000
Short-Chain Acyl-CoA Dehydrogenase Deficiency	ACADS	AR	Reduced Risk	Personalized Residual Risk: 1 in 660
Shwachman-Diamond Syndrome	SBDS	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,700
Sialidosis, Type I and Type II	NEU1	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,000
Sjogren-Larsson Syndrome	ALDH3A2	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,500
Smith-Lemli-Opitz Syndrome	DHCR7	AR	Reduced Risk	Personalized Residual Risk: 1 in 750
Spastic Paraplegia 15	ZFYVE26	AR	Reduced Risk	Personalized Residual Risk: 1 in 46,000
Spastic Tetraplegia, Thin Corpus Callosum, and Progressive Microcephaly	SLC1A4	AR	Reduced Risk	Personalized Residual Risk: 1 in 11,000
Spherocytosis, Type 5	EPB42	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,200
Spinal Muscular Atrophy	SMN1	AR	Reduced Risk	SMN1 copy number: 2 SMN2 copy number: >=3 c.3>80T>G: Negative SMN1 Sequencing: Negative Personalized Residual Risk: 1 in 1,107
Spinal Muscular Atrophy with Respiratory Distress 1 / Charcot-Marie-Tooth Disease, Type 2S	IGHMBP2	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,200



Spinocerebellar Ataxia with Axonal Neuropathy 3	COA7	AR	Reduced Risk	Personalized Residual Risk: 1 in 12,000
Spondylocostal Dysostosis 1	DLL3	AR	Reduced Risk	Personalized Residual Risk: 1 in 7,200
Spondylometaphyseal Dysplasia (DDR2-Related)	DDR2	AR	Reduced Risk	Personalized Residual Risk: 1 in 236,000
Spondylothoracic Dysostosis	MESP2	AR	Reduced Risk	Personalized Residual Risk: 1 in 382,000
Steel Syndrome	COL27A1	AR	Reduced Risk	Personalized Residual Risk: 1 in 93,000
Stuve-Wiedemann Syndrome	LIFR	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,000
Sulfate Transporter-Related Osteochondrodysplasia	SLC26A2	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,800
Tay-Sachs Disease	HEXA	AR	Reduced Risk	<p>Tay-Sachs disease enzyme: Non-carrier</p> <p>White blood cells: Non-carrier</p> <ul style="list-style-type: none"> <li>Hex A%: 69.2% (Non-carrier : 55.0 - 72.0%; Carrier: &lt;50%)</li> <li>Total hexosaminidase activity: 1381 nmol/hr/mg</li> </ul> <p>Plasma: Non-carrier</p> <ul style="list-style-type: none"> <li>Hex A%: 71.7 (Non-carrier : 58.0 - 72.0%; Carrier: &lt;54%)</li> <li>Total hexosaminidase activity: 519 nmol/hr/ml</li> </ul> <p>HEXA Sequencing: Negative</p> <p>Personalized Residual Risk: 1 in 1,400</p>
Thiamine-Responsive Megaloblastic Anemia Syndrome	SLC19A2	AR	Reduced Risk	Personalized Residual Risk: 1 in 11,000
Thyroid Dysmorphogenesis 1	SLC5A5	AR	Reduced Risk	Personalized Residual Risk: 1 in 7,400
Thyroid Dysmorphogenesis 2A	TPO	AR	Reduced Risk	Personalized Residual Risk: 1 in 910
Thyroid Dysmorphogenesis 3	TG	AR	Reduced Risk	Personalized Residual Risk: 1 in 850
Thyroid Dysmorphogenesis 4	IYD	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,800
Thyroid Dysmorphogenesis 5	DUOXA2	AR	Reduced Risk	Personalized Residual Risk: 1 in 29,000
Thyroid Dysmorphogenesis 6	DUOX2	AR	Reduced Risk	Personalized Residual Risk: 1 in 190
Trichohepatoenteric Syndrome 1	TTC37	AR	Reduced Risk	Personalized Residual Risk: 1 in 14,000
Tyrosinemia, Type I	FAH	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,900
Tyrosinemia, Type II	TAT	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,800
Tyrosinemia, Type III	HPD	AR	Reduced Risk	Personalized Residual Risk: 1 in 15,000
Usher Syndrome, Type IB	MYO7A	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,000
Usher Syndrome, Type IC	USH1C	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,600
Usher Syndrome, Type ID	CDH23	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,400
Usher Syndrome, Type IF	PCDH15	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,800
Usher Syndrome, Type IIA	USH2A	AR	Reduced Risk	Personalized Residual Risk: 1 in 290
Usher Syndrome, Type III	CLRN1	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,300
Very Long Chain Acyl-CoA Dehydrogenase Deficiency	ACADVL	AR	Reduced Risk	Personalized Residual Risk: 1 in 920
Vitamin D-Dependent Rickets, Type I	CYP27B1	AR	Reduced Risk	Personalized Residual Risk: 1 in 7,900
Vitamin D-Resistant Rickets, Type IIA	VDR	AR	Reduced Risk	Personalized Residual Risk: 1 in 17,000
Walker-Warburg Syndrome and Other FKTN-Related Dystrophies	FKTN	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,200
Werner Syndrome	WRN	AR	Reduced Risk	Personalized Residual Risk: 1 in 9,200
Wilson Disease	ATP7B	AR	Reduced Risk	Personalized Residual Risk: 1 in 350
Wiskott-Aldrich Syndrome (WAS-Related)	WAS	XL	Reduced Risk	Personalized Residual Risk: 1 in 1,203,000
Wolcott-Rallison Syndrome	EIF2AK3	AR	Reduced Risk	Personalized Residual Risk: 1 in 22,000
Wolman Disease / Cholesteryl Ester Storage Disease	LIPA	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,200
Woodhouse-Sakatani Syndrome	DCAF17	AR	Reduced Risk	Personalized Residual Risk: 1 in 81,000
X-Linked Juvenile Retinoschisis	RS1	XL	Reduced Risk	Personalized Residual Risk: 1 in 40,000

<b>X-Linked Severe Combined Immunodeficiency</b>	<i>IL2RG</i>	XL	Reduced Risk	<b>Personalized Residual Risk:</b> 1 in 250,000
<b>Xeroderma Pigmentosum (POLH-Related)</b>	<i>POLH</i>	AR	Reduced Risk	<b>Personalized Residual Risk:</b> 1 in 5,900
<b>Xeroderma Pigmentosum, Group A</b>	<i>XPA</i>	AR	Reduced Risk	<b>Personalized Residual Risk:</b> 1 in 11,000
<b>Xeroderma Pigmentosum, Group C</b>	<i>XPC</i>	AR	Reduced Risk	<b>Personalized Residual Risk:</b> 1 in 12,000
<b>Xeroderma Pigmentosum, Group G</b>	<i>ERCC5</i>	AR	Reduced Risk	<b>Personalized Residual Risk:</b> 1 in 3,000
<b>Zellweger Syndrome Spectrum (PEX10-Related)</b>	<i>PEX10</i>	AR	Reduced Risk	<b>Personalized Residual Risk:</b> 1 in 6,300
<b>Zellweger Syndrome Spectrum (PEX1-Related)</b>	<i>PEX1</i>	AR	Reduced Risk	<b>Personalized Residual Risk:</b> 1 in 2,000
<b>Zellweger Syndrome Spectrum (PEX2-Related)</b>	<i>PEX2</i>	AR	Reduced Risk	<b>Personalized Residual Risk:</b> 1 in 9,700
<b>Zellweger Syndrome Spectrum (PEX6-Related)</b>	<i>PEX6</i>	AR	Reduced Risk	<b>Personalized Residual Risk:</b> 1 in 1,600

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. AmplideX<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\_020734.6.2) 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<sup>®</sup> 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™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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Additional disease-specific references available upon request.