

**Patient Information**

Name: Donor N4007  
 Date of Birth: [REDACTED]  
 Sema4 ID: 22148678  
 Client ID: SEATSB-S467234380  
 Indication: Carrier Screening

**Specimen Information**

Specimen Type: Blood  
 Date Collected: 07/26/2022  
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**Referring Provider**

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## Expanded Carrier Screen (502 genes) with Personalized Residual Risk

### SUMMARY OF RESULTS AND RECOMMENDATIONS

⊕ Positive	⊖ Negative
<p style="text-align: center;"><b>Carrier of Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency (AR)</b>            Associated gene(s): <i>CYP21A2</i>            Variant(s) Detected: c.1444C&gt;T, p.P482S, Pathogenic, Heterozygous (one copy)</p> <p style="text-align: center;"><b>Carrier of Gaucher Disease (AR)</b>            Associated gene(s): <i>GBA</i>            Variant(s) Detected: c.1604G&gt;A, p.R535H, Pathogenic, Heterozygous (one copy)</p> <p style="text-align: center;"><b>Carrier of Non-Syndromic Hearing Loss (GJB2-Related) (AR)</b>            Associated gene(s): <i>GJB2</i>            Variant(s) Detected: c.35delG, p.G12VfsX2, 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.

## Interpretation of positive results

### Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency (AR)

#### Results and Interpretation

*CYP21A2* copy number: 2

No pathogenic copy number variants detected

*CYP21A2* sequencing: c.1444C>T, p.P482S, Pathogenic, Heterozygous (one copy)

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

Inheritance: Autosomal Recessive

A heterozygous (one copy) pathogenic missense variant, c.1444C>T, p.P482S, was detected in the *CYP21A2* gene (NM\_000500.6). Please note that this variant is typically causative for the non-classic form of congenital adrenal hyperplasia (PMID: 29450859). Variants associated with the non-classic form usually cause non-classic congenital adrenal hyperplasia when found in trans with a pathogenic allele, regardless of whether the second variant is associated with classic or non-classic disease (PMID: 29450859). Therefore, this individual is expected to be at least a carrier for non-classic congenital adrenal hyperplasia. Heterozygous carriers are not expected to exhibit symptoms of this disease.

#### What is congenital adrenal hyperplasia (due to 21-hydroxylase deficiency)?

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders resulting from deficiency in the enzymes involved in cortisol biosynthesis. The majority (95%) of CAH cases are due to 21-hydroxylase deficiency (21-OHD CAH), which is caused by homozygous or compound heterozygous pathogenic variants in the gene *CYP21A2*. Approximately 20% of mutant alleles have deletions of 30 kb that have been generated by unequal meiotic crossing-over between the two genes. Another 75% of mutant alleles are due to gene conversion events, where an inactivating mutation from the *CYP21A1P* pseudogene is introduced into one copy of the *CYP21A2* gene, thus making the gene non-functional. Three different forms of 21-OHD CAH have been reported: a classic salt wasting form, a classic simple virilizing form, and a non-classic form.

- The classic salt wasting form results from a nonfunctional enzyme and is the most severe. The phenotype includes prenatal onset of virilization and inadequate adrenal aldosterone secretion that can result in fatal salt-wasting crises.
- The classic simple virilizing form results from low levels of functional enzyme and involves prenatal virilization but no salt-wasting.
- The non-classic form, which results from a mild enzyme deficiency, occurs postnatally and involves phenotypes associated with hyperandrogenism, such as hirsutism, delayed menarche, and infertility.

Treatment for the classic forms of the disorder include glucocorticoid and mineralocorticoid replacement therapy, as well as the possibility of feminizing genitoplasty, while patients with the non-classic form usually do not require treatment. The life expectancy for this disorder can be normal with treatment, however the occurrence of salt-wasting crises can be fatal.

### Gaucher Disease (AR)

#### Results and Interpretation

A heterozygous (one copy) pathogenic missense variant, c.1604G>A, p.R535H, was detected in the *GBA* gene (NM\_001005741.2). When this variant is present in trans with a pathogenic variant, it is considered to be causative for Gaucher disease. Therefore, this individual is expected to be at least a carrier for Gaucher disease. Heterozygous carriers are not expected to exhibit symptoms of this disease, but have an increased risk of developing Parkinson's disease. This risk is approximately five times higher than the general population in heterozygous carriers and 10-20 times higher than the general population in homozygous carriers (PMID: 31010158).

#### What is Gaucher Disease?

Gaucher disease is an autosomal recessive disease caused by pathogenic variants in the gene *GBA*. While it is found in populations worldwide, it is most prevalent in individuals of Ashkenazi Jewish descent. Gaucher disease has variable clinical features and can be divided into the following subtypes.

- Type 1 is characterized by bone disease and the lack of neurological involvement. The bone disease can vary in severity from asymptomatic to destruction of bone tissue and painful "bone crises". Patients often have anemia and abnormal blood cell counts and may have lung disease. Some patients may be asymptomatic.
- Type 2 is a severe form that begins in infancy and usually results in death by the age of 2 years. It is characterized by severe neurologic deterioration, seizures, anemia, poor feeding and failure to thrive.

- The perinatal-lethal form is a more severe subtype of type 2, where accumulation of fluid in the fetus results in death in utero, or in the first several days of life. Some patients do not have the excess fluid, but die within three months.
- Type 3 is characterized by neurologic deterioration, as with type 2, but onset may be anywhere from childhood to adulthood, and progresses more slowly. Patients develop seizures and declining intelligence. Patients also experience the bone disease and anemia seen in type 1.
- The cardiovascular form is a subtype of type 3 that is characterized by calcification of the heart valves during adolescence. Patients may also have problems controlling their eye movements. The cardiac manifestations are usually fatal.

Some pathogenic variants are associated with a specific type of Gaucher disease. However, there is significant variability in the phenotypes, even between identical twins. Therefore, it is not always possible to predict the severity of disease based on genotype.

### Non-Syndromic Hearing Loss (*GJB2*-Related) (AR)

#### Results and Interpretation

A heterozygous (one copy) pathogenic frameshift variant, c.35delG, p.G12VfsX2, was detected in the *GJB2* gene (NM\_004004.5). When this variant is present in trans with a pathogenic variant, it is considered to be causative for non-syndromic hearing loss (*GJB2*-related). Therefore, this individual is expected to be at least a carrier for non-syndromic hearing loss (*GJB2*-related). Heterozygous carriers are not expected to exhibit symptoms of this disease.

#### What is Non-Syndromic Hearing Loss (*GJB2*-Related)?

Non-syndromic hearing loss (*GJB2*-related) is an autosomal recessive disorder that is caused by pathogenic variants in the gene *GJB2*. It is found in individuals of many different ethnicities, but it more prevalent in individuals of Ashkenazi Jewish descent, as well as Caucasians and Asians. Patients with this form of hearing loss do not experience any other disease manifestations. Hearing loss is usually present from birth and does not progress in severity over time. The level of hearing loss can vary between patients from mild to profound. Patients with two inactivating variants are more likely to have profound hearing loss, whereas patients with two non-inactivating variants are more likely to have mild hearing loss. However, the variability that exists between patients means that it may not be possible to predict the severity of an individual's hearing loss based on their genotype. Life expectancy is not reduced.

## 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](http://go.sema4.com/residualrisk). Only variants determined to be pathogenic or likely pathogenic are reported in this carrier screening test.



**Wei Kelly, M.D., Ph.D., DABMGG, Assistant Director**

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>Positive</b>				
Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency	<i>CYP21A2</i>	AR	Carrier	<i>CYP21A2</i> copy number: 2 No pathogenic copy number variants detected <i>CYP21A2</i> sequencing: c.1444C>T, p.P482S, Pathogenic, Heterozygous (one copy)
Gaucher Disease	<i>GBA</i>	AR	Carrier	c.1604G>A, p.R535H, Pathogenic, Heterozygous (one copy)
Non-Syndromic Hearing Loss ( <i>GJB2</i> -Related)	<i>GJB2</i>	AR	Carrier	c.35delG, p.G12VfsX2, Pathogenic, Heterozygous (one copy)
<b>Negative</b>				
2-Methylbutyrylglycinuria	<i>ACADSB</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,800
3-Beta-Hydroxysteroid Dehydrogenase Type II Deficiency	<i>HSD3B2</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,300
3-Methylcrotonyl-CoA Carboxylase Deficiency ( <i>MCCC1</i> -Related)	<i>MCCC1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,400
3-Methylcrotonyl-CoA Carboxylase Deficiency ( <i>MCCC2</i> -Related)	<i>MCCC2</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,200
3-Methylglutaconic Aciduria, Type III	<i>OPA3</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 50,000
3-Phosphoglycerate Dehydrogenase Deficiency	<i>PHGDH</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 63,000
6-Pyruvoyl-Tetrahydropterin Synthase Deficiency	<i>PTS</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,800
<i>CD59</i> -Mediated Hemolytic Anemia	<i>CD59</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 415,000
Abetalipoproteinemia	<i>MTTP</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,200
Achalasia-Addisonianism-Alacrimia Syndrome	<i>AAAS</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,500
Achromatopsia ( <i>CNGA3</i> -Related)	<i>CNGA3</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 830
Achromatopsia ( <i>CNGB3</i> -related)	<i>CNGB3</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 8,600
Acrodermatitis Enteropathica	<i>SLC39A4</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 12,000
Acute Infantile Liver Failure	<i>TRMU</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 9,400
Acyl-CoA Oxidase I Deficiency	<i>ACOX1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 39,000
Adams-Oliver Syndrome 4	<i>EOGT</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 44,000
Adenosine Deaminase Deficiency	<i>ADA</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,100
Adrenocorticotrophic Hormone Deficiency	<i>TBX19</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 35,000
Adrenoleukodystrophy, X-Linked	<i>ABCD1</i>	XL	Reduced Risk	Personalized Residual Risk: 1 in 19,000
Agammaglobulinemia	<i>BTK</i>	XL	Reduced Risk	Personalized Residual Risk: 1 in 250,000
Agenesis of the Corpus Callosum	<i>FRMD4A</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,393,000
Aicardi-Goutieres Syndrome ( <i>RNASEH2C</i> -Related)	<i>RNASEH2C</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 11,000
Aicardi-Goutieres Syndrome ( <i>SAMHD1</i> -Related)	<i>SAMHD1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 10,000
Aicardi-Goutieres Syndrome ( <i>TREX1</i> -Related)	<i>TREX1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,200
Albinism, Oculocutaneous, Type III	<i>TYRP1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,500
Alkaptonuria	<i>HGD</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,100
Alpha-Mannosidosis	<i>MAN2B1</i>	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 454,000</b>
Asparagine Synthetase Deficiency	ASNS	AR	Reduced Risk	<b>Personalized Residual Risk: 1 in 202,000</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 7,900
Cerebral Dysgenesis, Neuropathy, Ichthyosis, and Palmoplantar Keratoderma Syndrome	<i>SNAP29</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,730,000
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 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	<i>MPL</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,100
Congenital Bile Acid Synthesis Defect (AKR1D1-Related)	<i>AKR1D1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,900
Congenital Bile Acid Synthesis Defect (HSD3B7-Related)	<i>HSD3B7</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 8,900
Congenital Disorder of Deglycosylation	<i>NGLY1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 14,000

Congenital Disorder of Glycosylation, Type Ia	<i>PMM2</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 540
Congenital Disorder of Glycosylation, Type Ib	<i>MPI</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,600
Congenital Disorder of Glycosylation, Type Ic	<i>ALG6</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,100
Congenital Disorder of Glycosylation, Type Im	<i>DOLK</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 134,000
Congenital Dyserythropoietic Anemia Type 2	<i>SEC23B</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,000
Congenital Dyserythropoietic Anemia, Type Ia	<i>CDAN1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 470
Congenital Ichthyosis 4A and 4B	<i>ABCA12</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,100
Congenital Insensitivity to Pain with Anhidrosis	<i>NTRK1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,700
Congenital Muscular Dystrophy ( <i>LAMA2</i> -Related)	<i>LAMA2</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 640
Congenital Myasthenic Syndrome ( <i>CHAT</i> -Related)	<i>CHAT</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,100
Congenital Myasthenic Syndrome ( <i>CHRNE</i> -Related)	<i>CHRNE</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,100
Congenital Myasthenic Syndrome ( <i>DOK7</i> -Related)	<i>DOK7</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,200
Congenital Myasthenic Syndrome ( <i>RAPSN</i> -Related)	<i>RAPSN</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,900
Congenital Neutropenia ( <i>HAX1</i> -Related)	<i>HAX1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 82,000
Congenital Neutropenia ( <i>VPS45</i> -Related)	<i>VPS45</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 163,000
Congenital Nongoitrous Hypothyroidism 1	<i>TSHR</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,000
Congenital Nongoitrous Hypothyroidism 4	<i>TSHB</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 118,000
Congenital Secretory Chloride Diarrhea 1	<i>SLC26A3</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,400
Corneal Dystrophy and Perceptive Deafness	<i>SLC4A11</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,600
Corticosterone Methyloxidase Deficiency	<i>CYP11B2</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,500
Cystic Fibrosis	<i>CFTR</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 440
Cystinosis	<i>CTNS</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 7,700
Cystinuria ( <i>SLC3A1</i> -Related)	<i>SLC3A1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 590
Cytochrome C Oxidase Deficiency / Leigh Syndrome ( <i>COX15</i> -Related)	<i>COX15</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,300
D-Bifunctional Protein Deficiency	<i>HSD17B4</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,000
Deafness, Autosomal Recessive 3	<i>MYO15A</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 240
Deafness, Autosomal Recessive 59	<i>PJVK</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 57,000
Deafness, Autosomal Recessive 7	<i>TMC1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,200
Deafness, Autosomal Recessive 76	<i>SYNE4</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 43,000
Deafness, Autosomal Recessive 77	<i>LOXHD1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,700
Deafness, Autosomal Recessive 8/10	<i>TMPRSS3</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 510
Deafness, Autosomal Recessive 9	<i>OTOF</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,400
Desbuquois Dysplasia 1	<i>CANT1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 24,000
Desmosterolosis	<i>DHCR24</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 27,000
Diaphanospondylydysostosis	<i>BMPER</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 18,000
Distal Renal Tubular Acidosis and other <i>SLC4A1</i> -related Disorders	<i>SLC4A1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,000
Duchenne Muscular Dystrophy / Becker Muscular Dystrophy	<i>DMD</i>	XL	Reduced Risk	Personalized Residual Risk: 1 in 10,000
Dyskeratosis Congenita ( <i>DKC1</i> -related)	<i>DKC1</i>	XL	Reduced Risk	Personalized Residual Risk: 1 in 9,259,000
Dyskeratosis Congenita ( <i>RTEL1</i> -Related)	<i>RTEL1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 9,800
Dystrophic Epidermolysis Bullosa	<i>COL7A1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 900
Ehlers-Danlos Syndrome, Type VI	<i>PLOD1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 20,000
Ehlers-Danlos Syndrome, Type VIIC	<i>ADAMTS2</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 243,000
Ellis-Van Creveld Syndrome ( <i>EVC2</i> -Related)	<i>EVC2</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,300
Ellis-van Creveld Syndrome ( <i>EVC</i> -Related)	<i>EVC</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,200
Emery-Dreifuss Myopathy 1	<i>EMD</i>	XL	Reduced Risk	Personalized Residual Risk: 1 in 833,000
Enhanced S-Cone Syndrome	<i>NR2E3</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,600



Ethylmalonic Encephalopathy	<i>ETHE1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,400
Fabry Disease	<i>GLA</i>	XL	Reduced Risk	Personalized Residual Risk: 1 in 7,700
Factor IX Deficiency	<i>F9</i>	XL	Reduced Risk	Personalized Residual Risk: 1 in 5,100
Factor VII Deficiency	<i>F7</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 450
Factor XI Deficiency	<i>F11</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,500
Familial Autosomal Recessive Hypercholesterolemia	<i>LDLRAP1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 136,000
Familial Dysautonomia	<i>IKBKAP</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 51,000
Familial Hypercholesterolemia	<i>LDLR</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 280
Familial Hyperinsulinemic Hypoglycemia 4 / 3-Hydroxyacyl-CoA Dehydrogenase Deficiency	<i>HADH</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 9,200
Familial Hyperinsulinism (ABCC8-Related)	<i>ABCC8</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 450
Familial Hyperinsulinism (KCNJ11-Related)	<i>KCNJ11</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,300
Familial Hyperphosphatemic Tumoral Calcinosis	<i>GALNT3</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 7,800
Familial Mediterranean Fever	<i>MEFV</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,200
Fanconi Anemia, Group A	<i>FANCA</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,100
Fanconi Anemia, Group C	<i>FANCC</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 12,000
Fanconi Anemia, Group G	<i>FANCG</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 28,000
Fanconi-Bickel Syndrome	<i>SLC2A2</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,000
Fragile X Syndrome	<i>FMR1</i>	XL	Reduced Risk	<i>FMR1</i> CGG repeat sizes: Not Performed <i>FMR1</i> 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	<i>FBP1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,600
Fucosidosis	<i>FUCA1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 9,200
Fumarase Deficiency	<i>FH</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,500
Fundus Albipunctatus	<i>RDH5</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,000
Galactokinase Deficiency	<i>GALK1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,700
Galactose Epimerase Deficiency	<i>GALE</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,600
Galactosemia	<i>GALT</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,200
Galactosialidosis	<i>CTSA</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 7,900
Generalized Thyrotropin-Releasing Hormone Resistance	<i>TRHR</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 104,000
Geroderma Osteodysplasticum	<i>GORAB</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 70,000
Citellman Syndrome	<i>SLC12A3</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 290
Glanzmann Thrombasthenia (ITGA2B-Related)	<i>ITGA2B</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,800
Glanzmann Thrombasthenia (ITGB3-Related)	<i>ITGB3</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,600
Glutaric Acidemia, Type I	<i>GCDH</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,700
Glutaric Acidemia, Type IIa	<i>ETFA</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,700
Glutaric Acidemia, Type IIb	<i>ETFB</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,900
Glutaric Acidemia, Type IIc	<i>ETFDH</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,700
Glutathione Synthetase Deficiency	<i>GSS</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,500
Glycine Encephalopathy (AMT-Related)	<i>AMT</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,700
Glycine Encephalopathy (GLDC-Related)	<i>GLDC</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 760
Glycogen Storage Disease, Type 0	<i>GYS2</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,200
Glycogen Storage Disease, Type Ia	<i>G6PC</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,300
Glycogen Storage Disease, Type Ib	<i>SLC37A4</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 7,300
Glycogen Storage Disease, Type II	<i>GAA</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 520
Glycogen Storage Disease, Type III	<i>AGL</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,600
Glycogen Storage Disease, Type IV / Adult Polyglucosan Body Disease	<i>GBE1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,400



Glycogen Storage Disease, Type IXb	<i>PHKB</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,600
Glycogen Storage Disease, Type V	<i>PYGM</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,200
Glycogen Storage Disease, Type VI	<i>PYGL</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,600
Glycogen Storage Disease, Type VII	<i>PFKM</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,300
GRACILE Syndrome and Other <i>BCS1L</i> -Related Disorders	<i>BCS1L</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,900
Gray Platelet Syndrome	<i>NBEAL2</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,800
Growth Hormone Deficiency, Type IB	<i>GHRHR</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,900
Hemochromatosis, Type 2A	<i>HFE2</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 12,000
Hemochromatosis, Type 3	<i>TFR2</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 11,000
Hereditary Fructose Intolerance	<i>ALDOB</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,900
Hereditary Spastic Paraparesis 49	<i>TECPR2</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 116,000
Hermansky-Pudlak Syndrome, Type 1	<i>HPS1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,500
Hermansky-Pudlak Syndrome, Type 3	<i>HPS3</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 49,000
Hermansky-Pudlak Syndrome, Type 4	<i>HPS4</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 35,000
Hermansky-Pudlak Syndrome, Type 6	<i>HPS6</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 9,400
HMG-CoA Lyase Deficiency	<i>HMGCL</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,700
Hmg-CoA Synthase 2 Deficiency	<i>HMGCS2</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,000
Holocarboxylase Synthetase Deficiency	<i>HLCS</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,500
Homocystinuria ( <i>CBS</i> -Related)	<i>CBS</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,400
Homocystinuria due to <i>MTHFR</i> Deficiency	<i>MTHFR</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,300
Homocystinuria, cblE Type	<i>MTRR</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 9,600
Homocystinuria-Megaloblastic Anemia, Cobalamin G Type	<i>MTR</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,100
Hydrocephalus	<i>L1CAM</i>	XL	Reduced Risk	Personalized Residual Risk: 1 in 40,000
Hydrolethals Syndrome	<i>HYLS1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 52,000
Hyper-Igm Syndrome	<i>CD40LG</i>	XL	Reduced Risk	Personalized Residual Risk: 1 in 1167,000
Hyperornithinemia-Hyperammonemia-Homocitrullinuria Syndrome	<i>SLC25A15</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,700
Hyperuricemia, Pulmonary Hypertension, Renal Failure, and Alkalosis	<i>SARS2</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 23,000
Hypohidrotic Ectodermal Dysplasia 1	<i>EDA</i>	XL	Reduced Risk	Personalized Residual Risk: 1 in 22,000
Hypomagnesemia 1	<i>TRPM6</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 11,000
Hypomyelinating Leukodystrophy 3	<i>AIMP1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 341,000
Hypomyelinating Leukodystrophy 12	<i>VPS11</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 72,000
Hypoparathyroidism-Retardation-Dysmorphic Syndrome	<i>TBCE</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 21,000
Hypophosphatasia	<i>ALPL</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 790
Hypophosphatemic Rickets with Hypercalciuria	<i>SLC34A3</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,200
Hypotrichosis 8 / Autosomal Recessive Woolly Hair 1	<i>LPAR6</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 27,000
Immunodeficiency 18	<i>CD3E</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 73,000
Immunodeficiency 19	<i>CD3D</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 46,000
Inclusion Body Myopathy 2	<i>GNE</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,000
Infantile Cerebral and Cerebellar Atrophy	<i>MED17</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 129,000
Infantile Neuroaxonal Dystrophy 1 and other <i>PLA2G6</i> -Related Disorders	<i>PLA2G6</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 690
Intellectual Disability, Autosomal Recessive 3	<i>CC2D1A</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 220,000
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 152,000
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	RPGRIPL	AR	Reduced Risk	Personalized Residual Risk: 1 in 32,000
Junctional Epidermolysis Bullosa (COL17A1-Related)	COL17A1	AR	Reduced Risk	Personalized Residual Risk: 1 in 25,000
Junctional Epidermolysis Bullosa (ITGA6-Related)	ITGA6	AR	Reduced Risk	Personalized Residual Risk: 1 in 125,000
Junctional Epidermolysis Bullosa (ITGB4-Related)	ITGB4	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,400
Junctional Epidermolysis Bullosa (LAMA3-Related)	LAMA3	AR	Reduced Risk	Personalized Residual Risk: 1 in 21,000
Junctional Epidermolysis Bullosa (LAMB3-Related)	LAMB3	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,900
Junctional Epidermolysis Bullosa (LAMC2-Related)	LAMC2	AR	Reduced Risk	Personalized Residual Risk: 1 in 77,000
Kohlschutter-Tonz Syndrome	ROGDI	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,300
Krabbe Disease	GALC	AR	Reduced Risk	Personalized Residual Risk: 1 in 860
Lamellar Ichthyosis, Type 1	TGM1	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,500
Laron Dwarfism	GHR	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,700
Leber Congenital Amaurosis 10 and Other CEP290-Related Ciliopathies	CEP290	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,100
Leber Congenital Amaurosis 13	RDH12	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,500
Leber Congenital Amaurosis 15 / Retinitis Pigmentosa 14	TULP1	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,800
Leber Congenital Amaurosis 2 / Retinitis Pigmentosa 20	RPE65	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,500
Leber Congenital Amaurosis 4	AIP1	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,100
Leber Congenital Amaurosis 5	LCA5	AR	Reduced Risk	Personalized Residual Risk: 1 in 14,000
Leber Congenital Amaurosis 8 / Retinitis Pigmentosa 12 / Pigmented Paravenous Chorioretinal Atrophy	CRB1	AR	Reduced Risk	Personalized Residual Risk: 1 in 990
Leigh Syndrome (NDUFS7-Related)	NDUFS7	AR	Reduced Risk	Personalized Residual Risk: 1 in 26,000
Leigh Syndrome (SURF1-Related)	SURF1	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,400
Leigh Syndrome, French-Canadian Type	LRPPRC	AR	Reduced Risk	Personalized Residual Risk: 1 in 32,000
Lethal Congenital Contracture Syndrome 1 / Lethal Arthrogyposis with Anterior Horn Cell Disease	GLE1	AR	Reduced Risk	Personalized Residual Risk: 1 in 10,000
Lethal Congenital Contracture Syndrome 2	ERBB3	AR	Reduced Risk	Personalized Residual Risk: 1 in 96,000
Lethal Congenital Contracture Syndrome 3	PIP5K1C	AR	Reduced Risk	Personalized Residual Risk: 1 in 318,000
Leukoencephalopathy with Vanishing White Matter	EIF2B5	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,300
Limb-Girdle Muscular Dystrophy, Type 2A	CAPN3	AR	Reduced Risk	Personalized Residual Risk: 1 in 960
Limb-Girdle Muscular Dystrophy, Type 2B	DYSF	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,100
Limb-Girdle Muscular Dystrophy, Type 2C	SGCG	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,900
Limb-Girdle Muscular Dystrophy, Type 2D	SGCA	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,500
Limb-Girdle Muscular Dystrophy, Type 2E	SGCB	AR	Reduced Risk	Personalized Residual Risk: 1 in 31,000
Limb-Girdle Muscular Dystrophy, Type 2F	SGCD	AR	Reduced Risk	Personalized Residual Risk: 1 in 52,000
Limb-Girdle Muscular Dystrophy, Type 2H	TRIM32	AR	Reduced Risk	Personalized Residual Risk: 1 in 10,000
Limb-Girdle Muscular Dystrophy, Type 2I	FKRP	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,400
Limb-Girdle Muscular Dystrophy, Type 2L	ANO5	AR	Reduced Risk	Personalized Residual Risk: 1 in 660
Lipoamide Dehydrogenase Deficiency	DLD	AR	Reduced Risk	Personalized Residual Risk: 1 in 14,000
Lipoid Adrenal Hyperplasia	STAR	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,600
Lipoprotein Lipase Deficiency	LPL	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	<i>BCKDHB</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1100
Maple Syrup Urine Disease, Type 2	<i>DBT</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,600
Meckel Syndrome 1 / Bardet-Biedl Syndrome 13	<i>MKS1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,700
Medium Chain Acyl-CoA Dehydrogenase Deficiency	<i>ACADM</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,800
MEDNIK Syndrome	<i>AP1S1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 211,000
Megalencephalic Leukoencephalopathy with Subcortical Cysts	<i>MLC1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,300
Megaloblastic Anemia 1	<i>AMN</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,300
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 1,000
Methionine Adenosyltransferase I/III Deficiency	<i>MAT1A</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,900
Methylmalonic Acidemia (MMAA-Related)	<i>MMAA</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 15,000
Methylmalonic Acidemia (MMAB-Related)	<i>MMAB</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 12,000
Methylmalonic Acidemia (MUT-Related)	<i>MUT</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,300
Methylmalonic Aciduria and Homocystinuria, Cobalamin C Type	<i>MMACHC</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,800
Methylmalonic Aciduria and Homocystinuria, Cobalamin D Type	<i>MMADHC</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 219,000
Methylmalonic Aciduria and Homocystinuria, Cobalamin F Type	<i>LMBRD1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,600
Methylmalonyl-CoA Epimerase Deficiency	<i>MCEE</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 98,000
Microphthalmia / Anophthalmia	<i>VSX2</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 40,000
Mitochondrial Complex I Deficiency (ACAD9-Related)	<i>ACAD9</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,800
Mitochondrial Complex I Deficiency (NDUFA11-Related)	<i>NDUFA11</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 414,000
Mitochondrial Complex I Deficiency (NDUFAF5-Related)	<i>NDUFAF5</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 9,800
Mitochondrial Complex I Deficiency (NDUFS6-Related)	<i>NDUFS6</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 353,000
Mitochondrial Complex I Deficiency (NDUFV1-Related)	<i>NDUFV1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 870
Mitochondrial Complex I Deficiency / Leigh Syndrome (FOXRED1-Related)	<i>FOXRED1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 13,000
Mitochondrial Complex I Deficiency / Leigh Syndrome (NDUFAF2-Related)	<i>NDUFAF2</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 168,000
Mitochondrial Complex I Deficiency / Leigh Syndrome (NDUFS4-Related)	<i>NDUFS4</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 41,000
Mitochondrial Complex IV Deficiency (COX20-related)	<i>COX20</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 42,000
Mitochondrial Complex IV Deficiency (COX6B1-related)	<i>COX6B1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,116,000
Mitochondrial Complex IV Deficiency (APOPT1-Related)	<i>APOPT1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 9,200
Mitochondrial Complex IV Deficiency (PET100-Related)	<i>PET100</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 469,000
Mitochondrial Complex IV Deficiency (SCO1-related)	<i>SCO1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 13,000
Mitochondrial Complex IV Deficiency / Leigh Syndrome (COX10-Related)	<i>COX10</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 9,200
Mitochondrial DNA Depletion Syndrome 2	<i>TK2</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,900
Mitochondrial DNA Depletion Syndrome 3	<i>DGUOK</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,200
Mitochondrial DNA Depletion Syndrome 4A and 4B and other POLG-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 (HADHB-Related)	HADHB	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,000
Molybdenum Cofactor Deficiency A	MOCS1	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,700
Mucopolidosis II / IIIA	GNPTAB	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,100
Mucopolidosis III Gamma	GNPTG	AR	Reduced Risk	Personalized Residual Risk: 1 in 68,000
Mucopolidosis IV	MCOLN1	AR	Reduced Risk	Personalized Residual Risk: 1 in 9,400
Mucopolysaccharidosis Type I	IDUA	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,300
Mucopolysaccharidosis Type II	IDS	XL	Reduced Risk	Personalized Residual Risk: 1 in 76,000
Mucopolysaccharidosis Type IIIA	SGSH	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,700
Mucopolysaccharidosis Type IIIB	NAGLU	AR	Reduced Risk	Personalized Residual Risk: 1 in 950
Mucopolysaccharidosis Type IIIC	HGSNAT	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,200
Mucopolysaccharidosis Type IIID	GNS	AR	Reduced Risk	Personalized Residual Risk: 1 in 137,000
Mucopolysaccharidosis Type IVa	GALNS	AR	Reduced Risk	Personalized Residual Risk: 1 in 690
Mucopolysaccharidosis Type IVb / GM1 Gangliosidosis	GLB1	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,700
Mucopolysaccharidosis type IX	HYAL1	AR	Reduced Risk	Personalized Residual Risk: 1 in 149,000
Mucopolysaccharidosis type VI	ARSB	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,300
Mucopolysaccharidosis VII	GUSB	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,600
Mulibrey Nanism	TRIM37	AR	Reduced Risk	Personalized Residual Risk: 1 in 31,000
Multiple Congenital Anomalies-Hypotonia-Seizures Syndrome 1	PIGN	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,800
Multiple Pterygium Syndrome	CHRNA3	AR	Reduced Risk	Personalized Residual Risk: 1 in 9,900
Multiple Sulfatase Deficiency	SUMF1	AR	Reduced Risk	Personalized Residual Risk: 1 in 69,000
Muscle-Eye-Brain Disease and Other POMGNT1-Related Congenital Muscular Dystrophy-Dystroglycanopathies	POMGNT1	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,200
Myoneurogastrointestinal Encephalopathy	TYMP	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,100
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 3,200
Nemaline Myopathy 2	NEB	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,400
Nephrogenic Diabetes insipidus (AVPR2-related) / Nephrogenic Syndrome of Inappropriate Antidiuresis	AVPR2	XL	Reduced Risk	Personalized Residual Risk: 1 in 471,000
Nephrogenic Diabetes Insipidus, Type II	AQP2	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,400
Nephronophthisis 2	INVS	AR	Reduced Risk	Personalized Residual Risk: 1 in 56,000
Nephrotic Syndrome (NPHS1-Related) / Congenital Finnish Nephrosis	NPHS1	AR	Reduced Risk	Personalized Residual Risk: 1 in 920
Nephrotic Syndrome (NPHS2-Related) / Steroid-Resistant Nephrotic Syndrome	NPHS2	AR	Reduced Risk	Personalized Residual Risk: 1 in 780
Neurodegeneration due to Cerebral Folate Transport Deficiency	FOLR1	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,300
Neurodevelopmental Disorder with Progressive Microcephaly, Spasticity, and Brain Anomalies	PLAA	AR	Reduced Risk	Personalized Residual Risk: 1 in 229,000
Neuronal Ceroid-Lipofuscinosis (CLN3-Related)	CLN3	AR	Reduced Risk	Personalized Residual Risk: 1 in 9,200
Neuronal Ceroid-Lipofuscinosis (CLN5-Related)	CLN5	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,300
Neuronal Ceroid-Lipofuscinosis (CLN6-Related)	CLN6	AR	Reduced Risk	Personalized Residual Risk: 1 in 8,600
Neuronal Ceroid-Lipofuscinosis (CLN8-Related)	CLN8	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,100
Neuronal Ceroid-Lipofuscinosis (MFSD8-Related)	MFSD8	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,200
Neuronal Ceroid-Lipofuscinosis (PPT1-Related)	PPT1	AR	Reduced Risk	Personalized Residual Risk: 1 in 7,500
Neuronal Ceroid-Lipofuscinosis (TPP1-Related)	TPP1	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,300
Niemann-Pick Disease (SMPD1-Related)	SMPD1	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,800
Niemann-Pick Disease, Type C (NPC1-Related)	NPC1	AR	Reduced Risk	Personalized Residual Risk: 1 in 690
Niemann-Pick Disease, Type C (NPC2-Related)	NPC2	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,600
Nijmegen Breakage Syndrome	NBN	AR	Reduced Risk	Personalized Residual Risk: 1 in 14,000

Oculocutaneous Albinism, Type IA / IB	TYR	AR	Reduced Risk	Personalized Residual Risk: 1 in 240
Oculocutaneous Albinism, Type IV	SLC45A2	AR	Reduced Risk	Personalized Residual Risk: 1 in 830
Odonto-Onycho-Dermal Dysplasia / Schopf-Schulz-Passarge Syndrome	WNT10A	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,900
Omenn Syndrome (RAG2-Related)	RAG2	AR	Reduced Risk	Personalized Residual Risk: 1 in 17,000
Omenn Syndrome / Severe Combined Immunodeficiency, Athabaskan-Type	DCLRE1C	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,500
Omenn Syndrome and other RAG2-Related Disorders	RAG1	AR	Reduced Risk	Personalized Residual Risk: 1 in 850
Ornithine Aminotransferase Deficiency	OAT	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,400
Ornithine Transcarbamylase Deficiency	OTC	XL	Reduced Risk	Personalized Residual Risk: 1 in 103,000
Osteogenesis Imperfecta, Type XI	FKBP10	AR	Reduced Risk	Personalized Residual Risk: 1 in 9,500
Osteopetrosis 1	TCIRG1	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,700
Osteopetrosis 8	SNX10	AR	Reduced Risk	Personalized Residual Risk: 1 in 16,000
Otospondylomegapiphyseal Dysplasia / Deafness / Fibrochondrogenesis 2	COL11A2	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,700
Papillon-Lefevre Syndrome	CTSC	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,000
Pendred Syndrome	SLC26A4	AR	Reduced Risk	Personalized Residual Risk: 1 in 390
Peroxisome Biogenesis Disorder 3A and 3B	PEX12	AR	Reduced Risk	Personalized Residual Risk: 1 in 30,000
Peroxisome Biogenesis Disorder 7A and 7B	PEX26	AR	Reduced Risk	Personalized Residual Risk: 1 in 70,000
Phenylalanine Hydroxylase Deficiency	PAH	AR	Reduced Risk	Personalized Residual Risk: 1 in 340
Polycystic Kidney Disease, Autosomal Recessive	PKHD1	AR	Reduced Risk	Personalized Residual Risk: 1 in 450
Polyglandular Autoimmune Syndrome, Type 1	AIRE	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,300
Pontocerebellar Hypoplasia, Type 1A	VRK1	AR	Reduced Risk	Personalized Residual Risk: 1 in 25,000
Pontocerebellar Hypoplasia, Type 1B	EXOSC3	AR	Reduced Risk	Personalized Residual Risk: 1 in 10,000
Pontocerebellar Hypoplasia, Type 2A and Type 4	TSEN54	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,700
Pontocerebellar Hypoplasia, Type 2E	VPS53	AR	Reduced Risk	Personalized Residual Risk: 1 in 139,000
Pontocerebellar Hypoplasia, Type 6	RARS2	AR	Reduced Risk	Personalized Residual Risk: 1 in 8,600
Primary Carnitine Deficiency	SLC22A5	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,500
Primary Ciliary Dyskinesia (CCDC103-Related)	CCDC103	AR	Reduced Risk	Personalized Residual Risk: 1 in 27,000
Primary Ciliary Dyskinesia (CCDC151-Related)	CCDC151	AR	Reduced Risk	Personalized Residual Risk: 1 in 59,000
Primary Ciliary Dyskinesia (CCDC39-Related)	CCDC39	AR	Reduced Risk	Personalized Residual Risk: 1 in 12,000
Primary Ciliary Dyskinesia (DNAH5-Related)	DNAH5	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,500
Primary Ciliary Dyskinesia (DNAI1-Related)	DNAI1	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,000
Primary Ciliary Dyskinesia (DNAI2-Related)	DNAI2	AR	Reduced Risk	Personalized Residual Risk: 1 in 76,000
Primary Ciliary Dyskinesia (RSPH9-Related)	RSPH9	AR	Reduced Risk	Personalized Residual Risk: 1 in 253,000
Primary Coenzyme Q10 Deficiency 7	COQ4	AR	Reduced Risk	Personalized Residual Risk: 1 in 12,000
Primary Congenital Glaucoma 3A	CYP1B1	AR	Reduced Risk	Personalized Residual Risk: 1 in 880
Primary Hyperoxaluria, Type 1	AGXT	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,900
Primary Hyperoxaluria, Type 2	GRHPR	AR	Reduced Risk	Personalized Residual Risk: 1 in 11,000
Primary Hyperoxaluria, Type 3	HOGA1	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,400
Progressive Cerebello-Cerebral Atrophy	SEPSECS	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,400
Progressive Familial Intrahepatic Cholestasis, Type 2	ABCB11	AR	Reduced Risk	Personalized Residual Risk: 1 in 950
Progressive Myoclonic Epilepsy, Type 1B	PRICKLE1	AR	Reduced Risk	Personalized Residual Risk: 1 in 98,000
Progressive Pseudorheumatoid Dysplasia	WISP3	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,600
Prolidase Deficiency	PEPD	AR	Reduced Risk	Personalized Residual Risk: 1 in 30,000
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 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	<i>PNPO</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 10,000
Pyridoxine-Dependent Epilepsy	<i>ALDH7A1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,100
Pyruvate Carboxylase Deficiency	<i>PC</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 8,000
Pyruvate Dehydrogenase E1-Alpha Deficiency	<i>PDHA1</i>	XL	Reduced Risk	Personalized Residual Risk: 1 in 139,000
Pyruvate Dehydrogenase E1-Beta Deficiency	<i>PDHB</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 15,000
Renal Tubular Acidosis and Deafness	<i>ATP6V1B1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,600
Retinitis Pigmentosa 25	<i>EYS</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,800
Retinitis Pigmentosa 26	<i>CERKL</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 13,000
Retinitis Pigmentosa 28	<i>FAM161A</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 34,000
Retinitis Pigmentosa 36	<i>PRCD</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 304,000
Retinitis Pigmentosa 59	<i>DHDDS</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 601,000
Retinitis Pigmentosa 64 / Bardet-Biedl Syndrome 21 / Cone-Rod Dystrophy 16	<i>C8ORF37</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 168,000
Rh Deficiency Syndrome	<i>RHAG</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 46,000
Rhizomelic Chondrodysplasia Punctata, Type 1	<i>PEX7</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 10,000
Rhizomelic Chondrodysplasia Punctata, Type 3	<i>AGPS</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 620,000
Roberts Syndrome	<i>ESCO2</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 139,000
Salla Disease	<i>SLC17A5</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 8,400
Salt and Pepper Developmental Regression Syndrome	<i>ST3GAL5</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 25,000
Sandhoff Disease	<i>HEXB</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,800
Schimke Immunoosseous Dysplasia	<i>SMARCAL1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,800
Seckel Syndrome 5 / Microcephaly 9	<i>CEP152</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,700
Segawa Syndrome	<i>TH</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,100
Sepiapterin Reductase Deficiency	<i>SPR</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 35,000
Severe Combined Immunodeficiency ( <i>IL7R</i> -Related)	<i>IL7R</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 20,000
Severe Combined Immunodeficiency ( <i>JAK3</i> -Related)	<i>JAK3</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,100
Severe Combined Immunodeficiency ( <i>PTPRC</i> -Related)	<i>PTPRC</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 8,500
Severe Congenital Neutropenia 4	<i>G6PC3</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 10,000
Severe Neonatal Hyperparathyroidism	<i>CASR</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,700
Short Stature, Onychodysplasia, Facial Dysmorphism, and Hypotrichosis	<i>POC1A</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 108,000
Short-Chain Acyl-CoA Dehydrogenase Deficiency	<i>ACADS</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 660
Shwachman-Diamond Syndrome	<i>SBDS</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,700
Sialidosis, Type I and Type II	<i>NEU1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,000
Sjogren-Larsson Syndrome	<i>ALDH3A2</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,500
Smith-Lemli-Opitz Syndrome	<i>DHCR7</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 750
Spastic Paraplegia 15	<i>ZFYVE26</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 46,000
Spastic Tetraplegia, Thin Corpus Callosum, and Progressive Microcephaly	<i>SLC1A4</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 855,000
Spherocytosis, Type 5	<i>EPB42</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,200
Spinal Muscular Atrophy	<i>SMN1</i>	AR	Reduced Risk	<i>SMN1</i> copy number: 2 <i>SMN2</i> copy number: >=3 c.*3>80T>G: Negative <i>SMN1</i> Sequencing: Negative Personalized Residual Risk: 1 in 1,107
Spinal Muscular Atrophy with Respiratory Distress 1 / Charcot-Marie-Tooth Disease, Type 2S	<i>IGHMBP2</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,200
Spinocerebellar Ataxia with Axonal Neuropathy 3	<i>COA7</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 12,000
Spondylocostal Dysostosis 1	<i>DLL3</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 7,200



Spondylometaepiphyseal 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%: 60.0% (Non-carrier : 55.0 - 72.0%; Carrier: &lt;50%)</li> <li>Total hexosaminidase activity: 1816 nmol/hr/mg</li> </ul> <p>Plasma: Non-carrier</p> <ul style="list-style-type: none"> <li>Hex A%: 60.0 (Non-carrier : 58.0 - 72.0%; Carrier: &lt;54%)</li> <li>Total hexosaminidase activity: 978 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 45,000
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 4,200
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-Sakati 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
X-Linked Severe Combined Immunodeficiency	IL2RG	XL	Reduced Risk	Personalized Residual Risk: 1 in 250,000
Xeroderma Pigmentosum (POLH-Related)	POLH	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,900

Xeroderma Pigmentosum, Group A	<i>XPA</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 11,000
Xeroderma Pigmentosum, Group C	<i>XPC</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 12,000
Xeroderma Pigmentosum, Group G	<i>ERCC5</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,000
Zellweger Syndrome Spectrum ( <i>PEX10</i> -Related)	<i>PEX10</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,300
Zellweger Syndrome Spectrum ( <i>PEX1</i> -Related)	<i>PEX1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,000
Zellweger Syndrome Spectrum ( <i>PEX2</i> -Related)	<i>PEX2</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 77,000
Zellweger Syndrome Spectrum ( <i>PEX6</i> -Related)	<i>PEX6</i>	AR	Reduced Risk	Personalized Residual Risk: 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. 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 2+0 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.\*3+80T>G (chr5:70,247,901T>G) variant allele in an individual with Ashkenazi Jewish or Asian ancestry is typically indicative of a duplication of *SMN1*. When present in an Ashkenazi Jewish or Asian individual with two copies of *SMN1*, c.\*3+80T>G is likely indicative of a silent (2+0) carrier. In individuals with two copies of *SMN1* with African American, Hispanic or Caucasian ancestry, the presence or absence of c.\*3+80T>G significantly increases or decreases, respectively, the likelihood of being a silent 2+0 carrier.

MLPA for Gaucher disease (*GBA*), cystic fibrosis (*CFTR*), and non-syndromic hearing loss (*GJB2/GJB3*) 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 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<sup>®</sup> 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; *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 chr19:3637602-3637616 (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 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%)

Th 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.

#### **Tay-Sachs Disease (TSD) Enzyme Analysis (Analytical Detection Rate $\geq$ 98%)**

Hexosaminidase activity and Hex A% activity were measured by a standard heat-inactivation, fluorometric method using artificial 4-MU- $\beta$ -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 these tests were developed and their performance characteristics were determined by Sema4 Opco, 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.

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### **Spinal Muscular Atrophy:**

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

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### **Duchenne Muscular Dystrophy:**

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### **Variant Classification:**

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Additional disease-specific references available upon request.



Patient Information	Specimen Information	Client Information
<b>N4007, DONOR</b>  <b>DOB:</b> ████████ <b>AGE:</b> ████ Gender: M Phone: NG Patient ID: LP2790837	Specimen: CF868526C Requisition: 3268251 Lab Ref #: 22813721SPB  Collected: 07/26/2022 Received: 07/27/2022 / 20:43 EDT Reported: 08/05/2022 / 01:03 EDT	Client #: 48041578 NYNJMAIL GENOMICS, SEMA4 SEMA4 62 SOUTHFIELD AVE STAMFORD, CT 06902-7229

Ward: SEATSB
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**Cytogenetic Report**

**CHROMOSOME ANALYSIS, BLOOD - 14596** **Lab:EZ**

**CHROMOSOME ANALYSIS, BLOOD**

Order ID: 22-312890  
 Specimen Type: Blood  
 Clinical Indication: Encounter of male for testing for disease carrier status for procrea management.

**RESULT:**  
 NORMAL MALE KARYOTYPE

**INTERPRETATION:**  
 Chromosome analysis revealed normal G-band patterns within the limits of standard cytogenetic analysis.

Please expect the results of any other concurrent study in a separate report.

**NOMENCLATURE:**  
 46,XY

**ASSAY INFORMATION:**

Method: G-Band (Digital Analysis: MetaSyst)  
 Cells Counted: 20  
 Band Level: 450  
 Cells Analyzed: 5  
 Cells Karyotyped: 5

This test does not address genetic disorders that cannot be detected by standard cytogenetic methods or rare events such as low level mosaicism or subtle rearrangements.

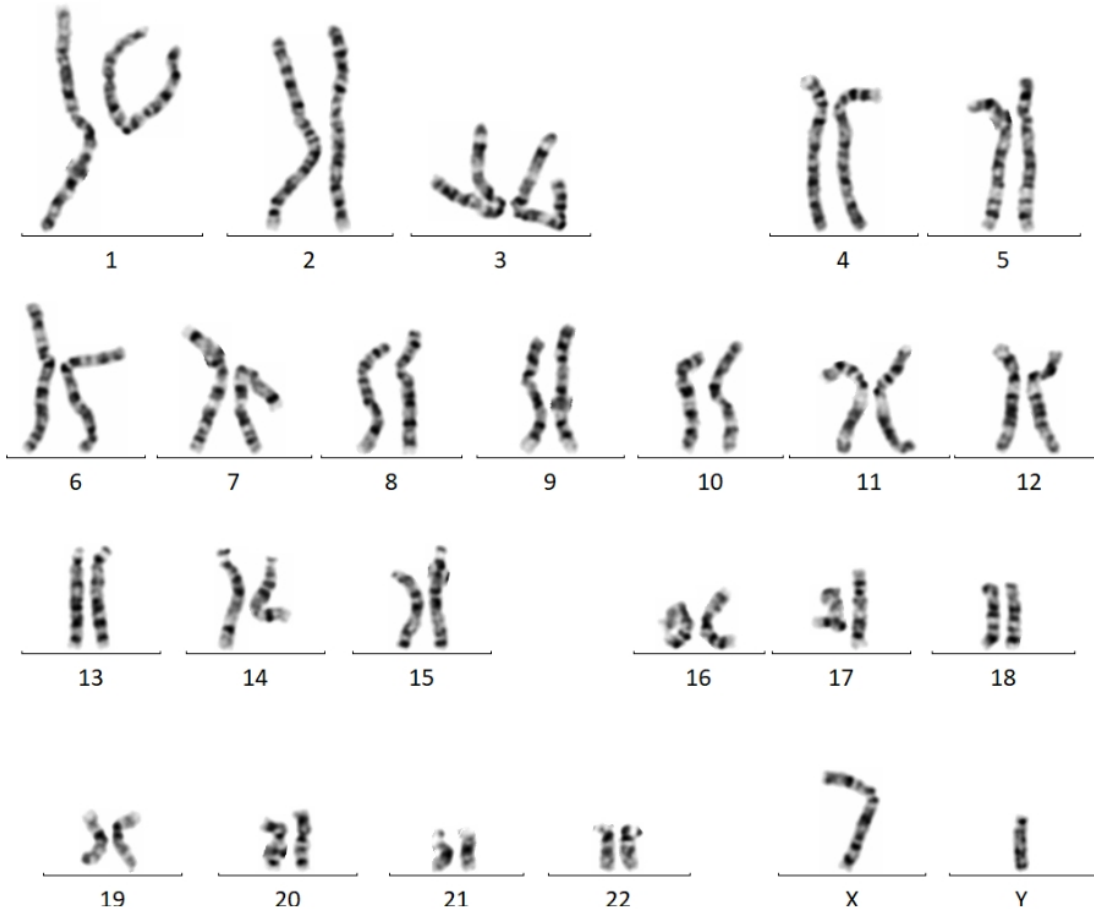
Lakshmi J. Nemana, Ph.D., FACMG

Electronic Signature: 8/4/2022 11:44 PM





Patient Information	Specimen Information	Client Information
<p><b>N4007, DONOR</b></p> <p>DOB: ████████ AGE: █</p> <p>Gender: M</p> <p>Patient ID: LP2790837</p>	<p>Specimen: CF868526C</p> <p>Collected: 07/26/2022</p> <p>Received: 07/27/2022 / 20:43 EDT</p> <p>Reported: 08/05/2022 / 01:03 EDT</p>	<p>Client #: 48041578</p> <p>GENOMICS, SEMA4</p>



**PERFORMING SITE:**

EZ QUEST DIAGNOSTICS/NICHOLS SJC, 33608 ORTEGA HWY, SAN JUAN CAPISTRANO, CA 92675-2042 Laboratory Director: IRINA MARAMICA, MD, PHD, MBA, CLIA: 05D0643352