# Donor 6387

# Genetic Testing Summary

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

Last Updated:03/24/22

Donor Reported Ancestry: Columbian

Jewish Ancestry: No

| Genetic Test* | Result | Comments/Donor's Residual Risk** |
|---|---|---|
| Chromosome analysis (karyotype) | Normal male karyotype | No evidence of clinically significant chromosome abnormalities |
| Hemoglobin evaluation | Normal hemoglobin fractionation and MCV/MCH results | Reduced risk to be a carrier for sickle cell anemia, beta thalassemia, alpha thalassemia trait (aa/-- and a-/a-) and other hemoglobinopathies |
| Expanded Genetic Disease Carrier Screening Panel attached- **502** diseases by gene sequencing | Carrier: Retinitis Pigmentosa 28 (FAM161A)<br><br>Carrier: Tay-Sachs Disease (HEXA)<br><br>Negative for other genes sequenced | Partner testing recommended before using this donor. |

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

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

**Patient Information**
Name: Donor 6387
Date of Birth: [redacted]
Sema4 ID: [redacted]
Client ID [redacted]
Indication: Carrier Screening

**Specimen Information**
Specimen Type: Blood
Date Collected: 02/10/2022
Date Received: 02/11/2022
Final Report: 02/28/2022

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

# Expanded Carrier Screen (502 genes)

with Personalized Residual Risk

## SUMMARY OF RESULTS AND RECOMMENDATIONS

| ⊕ Positive | ⊖ Negative |
|---|---|
| **Carrier of Retinitis Pigmentosa 28 (AR)**<br>Associated gene(s): *FAM161A*<br>Variant(s) Detected: c.1355_1356delCA, p.T452SfsX3, Pathogenic, Heterozygous (one copy)<br><br>**Carrier of Tay-Sachs Disease (AR)**<br>Associated gene(s): *HEXA*<br>Variant(s) Detected: c.1444G>A, p.E482K, Pathogenic, Heterozygous (one copy) and c.533G>A, p.R178H, Pathogenic, Heterozygous (one copy)<br>Enzyme results in the carrier range | **Negative for all other genes tested**<br>To view a full list of genes and diseases tested please see Table 1 in this report |

*AR=Autosomal recessive; XL=X-linked*

### Recommendations

- Testing the partner for the above positive disorder(s) and genetic counseling are recommended.
- Please note that for female carriers of X-linked diseases, follow-up testing of a male partner is not indicated.
- CGG repeat analysis of *FMR1* for fragile X syndrome is not performed on males as repeat expansion of premutation alleles is not expected in the male germline.
- Individuals of Asian, African, Hispanic and Mediterranean ancestry should also be screened for hemoglobinopathies by CBC and hemoglobin electrophoresis.
- Consideration of residual risk by ethnicity after a negative carrier screen is recommended for the other diseases on the panel, especially in the case of a positive family history for a specific disorder.

# Interpretation of positive results

### Retinitis Pigmentosa 28 (AR)

**Results and Interpretation**

A heterozygous (one copy) pathogenic frameshift variant, c.1355_1356delCA, p.T452SfsX3, was detected in the *FAM161A* gene (NM_032180.2). When this variant is present in trans with a pathogenic variant, it is considered to be causative for retinitis pigmentosa 28. Therefore, this individual is expected to be at least a carrier for retinitis pigmentosa 28. Heterozygous carriers are not expected to exhibit symptoms of this disease.

**What is Retinitis Pigmentosa 28?**

Retinitis pigmentosa 28 is an autosomal recessive disorder caused by pathogenic variants in the gene *FAM161A* . While it has been reported in populations worldwide, it is more prevalent in Ashkenazi and Sephardic Jewish individuals. Retinitis pigmentosa begins with the onset of night blindness in either childhood, adolescence or young adulthood, and progresses to tunnel vision and blindness. Age of onset and severity of vision loss may vary between patients. Life expectancy is not reduced. No genotype-phenotype correlation has been reported.

### Tay-Sachs Disease (AR)

**Results and Interpretation**

*HEXA* Sequence Analysis:

A heterozygous (one copy) pathogenic missense variant, c.1444G>A, p.E482K, was detected in the *HEXA* gene (NM_000520.4). A second heterozygous (one copy) pathogenic missense variant, c.533G>A, p.R178H, was detected in the *HEXA* gene (NM_000520.4). Please note that this variant is known as a B1 variant. B1 variants have higher residual activity than other known variants, and may appear as negative by enzymatic testing. This variant generally causes juvenile Tay-Sachs disease when found in trans with a severe allele, and chronic Tay-Sachs disease if homozygous. When this variant is present in trans with a pathogenic variant, it is considered to be causative for Tay-Sachs disease. Therefore, this individual is expected to be at least a carrier for Tay-Sachs disease. Heterozygous carriers are not expected to exhibit symptoms of this disease.

Hexosaminidase Enzyme Activity:

White blood cells: Carrier

- Hex A%: 44.6% (Non-carrier : 55.0 - 72.0%; Carrier: <50%)
- Total hexosaminidase activity: 1889 nmol/hr/mg

Plasma: Carrier

- Hex A%: 45.1 (Non-carrier : 58.0 - 72.0%; Carrier: <54%)
- Total hexosaminidase activity: 405 nmol/hr/ml

*HEXA* Sequencing: c.1444G>A, p.E482K, Pathogenic, Heterozygous (one copy) and c.533G>A, p.R178H, Pathogenic, Heterozygous (one copy)

The patient's Hex A% activity is within the **CARRIER** range. This result and positive mutation status are consistent with the patient being a carrier for Tay-Sachs disease. Testing of the reproductive partner and genetic counseling are recommended.

**What is Tay-Sachs Disease?**

Tay-Sachs disease is an autosomal recessive disorder resulting from pathogenic variants in the *HEXA* gene. It has been reported in individuals from different ethnicities, but there is an increased prevalence of the disease in people of Ashkenazi Jewish, French Canadian, and Irish descent. Pathogenic *HEXA* variants result in loss of function of the beta-hexosaminidase A enzyme, causing accumulation of GM2 gangliosides in body tissues. Several different forms of the disease exist, including the infantile and later-onset variants.

- The infantile form, which is the most common, has an onset of symptoms around 6 months of age. Clinical features include progressive loss of coordination, seizures, difficulty swallowing and poor pulmonary function. Affected individuals eventually become blind, severely intellectually disabled, paralyzed and unaware of their surroundings. Death usually occurs at 3 to 5 years of age.
- The subacute (or juvenile) form usually has an age of onset between 2 and 10 years. The progression of the disease is similar to that of the infantile form, and death occurs between 10 and 15 years of age.
- In the chronic form, age of onset is similar to that of the juvenile form, but the symptoms progress more slowly. The clinical presentation is one of ataxia and dystonia. Survival is long-term.
- The adult-onset form is characterized by progressive muscle loss, weakness and difficulty speaking. Age of onset, symptoms and severity are variable among individuals. Survival is long-term.

A genotype-phenotype correlation has been observed, where specific variants can be predicted to cause a later-onset form of the disease. Later-onset forms of the disease result when the residual beta-hexosaminidase A enzyme activity is between 5% and 15%. However, more than 90% of all pathogenic *HEXA* variants result in the infantile form of Tay-Sachs disease.

# 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**. Only variants determined to be pathogenic or likely pathogenic are reported in this carrier screening test.

**Christie Buchovecky, Ph.D., Assistant Director, Reproductive Genomic**
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**

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

| Disease | Gene | Inheritance Pattern | Status | Detailed Summary |
|---|---|---|---|---|
| **Positive** | | | | |
| **Retinitis Pigmentosa 28** | *FAM161A* | AR | Carrier | c.1355_1356delCA, p.T452SfsX3, Pathogenic, Heterozygous (one copy) |
| **Tay-Sachs Disease** | *HEXA* | AR | Carrier | Tay-Sachs disease enzyme: Carrier by enzyme<br><br>White blood cells: Carrier<br>• Hex A%: 44.6% (Non-carrier : 55.0 - 72.0%; Carrier: <50%)<br>• Total hexosaminidase activity: 1889 nmol/hr/mg<br><br>Plasma: Carrier<br>• Hex A%: 45.1 (Non-carrier : 58.0 - 72.0%; Carrier: <54%)<br>• Total hexosaminidase activity: 405 nmol/hr/ml<br><br>*HEXA* Sequencing: c.1444G>A, p.E482K, Pathogenic, Heterozygous (one copy) and c.533G>A, p.R178H, Pathogenic, Heterozygous (one copy) |
| **Negative** | | | | |
| **2-Methylbutyrylglycinuria** | *ACADSB* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 1,000 |
| **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 8,300 |
| **3-Phosphoglycerate Dehydrogenase Deficiency** | *PHGDH* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 4,200 |
| **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 150 |
| **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 |
| **Adrenocorticotropic Hormone Deficiency** | *TBX19* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 35,000 |
| **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 420,000 |

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|---|---|---|---|---|
| **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 1,500 |
| **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 5,200 |
| **Alpha-Thalassemia** | *HBA1/HBA2* | AR | Reduced Risk | *HBA1* Copy Number: 2<br>*HBA2* Copy Number: 2<br>No pathogenic copy number variants detected<br>*HBA1/HBA2* Sequencing: Negative<br>**Personalized Residual Risk:** 1 in 490 |
| **Alpha-Thalassemia Intellectual Disability Syndrome** | *ATRX* | XL | Reduced Risk | **Personalized Residual Risk:** 1 in 48,000 |
| **Alport Syndrome (*COL4A3*-Related)** | *COL4A3* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 1,600 |
| **Alport Syndrome (*COL4A4*-Related)** | *COL4A4* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 1,800 |
| **Alport Syndrome (*COL4A5*-Related)** | *COL4A5* | XL | Reduced Risk | **Personalized Residual Risk:** 1 in 150,000 |
| **Alstrom Syndrome** | *ALMS1* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 3,800 |
| **Andermann Syndrome** | *SLC12A6* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 76,000 |
| **Antley-Bixler Syndrome (*POR*-Related)** | *POR* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 4,000 |
| **Argininemia** | *ARG1* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 1,100 |
| **Argininosuccinic Aciduria** | *ASL* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 1,200 |
| **Aromatase Deficiency** | *CYP19A1* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 5,400 |
| **Arthrogryposis, Intellectual Disability, and Seizures** | *SLC35A3* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 336,000 |
| **Asparagine Synthetase Deficiency** | *ASNS* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 21,000 |
| **Aspartylglycosaminuria** | *AGA* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 13,000 |
| **Ataxia With Isolated Vitamin E Deficiency** | *TTPA* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 61,000 |
| **Ataxia-Telangiectasia** | *ATM* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 1,300 |
| **Ataxia-Telangiectasia-Like Disorder 1** | *MRE11* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 5,500 |
| **Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay** | *SACS* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 2,600 |
| **BH4-Deficient Hyperphenylalaninemia C** | *QDPR* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 3,100 |
| **BH4-Deficient Hyperphenylalaninemia D** | *PCBD1* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 8,000 |
| **Bardet-Biedl Syndrome (*ARL6*-Related)** | *ARL6* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 20,000 |
| **Bardet-Biedl Syndrome (*BBS10*-Related)** | *BBS10* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 2,700 |
| **Bardet-Biedl Syndrome (*BBS12*-Related)** | *BBS12* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 9,900 |
| **Bardet-Biedl Syndrome (*BBS1*-Related)** | *BBS1* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 6,400 |
| **Bardet-Biedl Syndrome (*BBS2*-Related)** | *BBS2* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 1,200 |
| **Bardet-Biedl Syndrome (*BBS4*-Related)** | *BBS4* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 15,000 |
| **Bare Lymphocyte Syndrome, Type II** | *CIITA* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 35,000 |
| **Barth Syndrome** | *TAZ* | XL | Reduced Risk | **Personalized Residual Risk:** 1 in 183,000 |
| **Bartter Syndrome, Type 3** | *CLCNKB* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 350 |
| **Bartter Syndrome, Type 4A** | *BSND* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 91,000 |
| **Bernard-Soulier Syndrome, Type A1** | *GP1BA* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 42,000 |
| **Bernard-Soulier Syndrome, Type C** | *GP9* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 3,300 |
| **Beta-Globin-Related Hemoglobinopathies** | *HBB* | AR | Reduced Risk | **Personalized Residual Risk (Beta-Globin-Related Hemoglobinopathies):** 1 in 2,000<br>**Personalized Residual Risk (Beta-Globin-Related Hemoglobinopathies: HbS Variant):** 1 in 23,000<br>**Personalized Residual Risk (Beta-Globin-Related Hemoglobinopathies: HbC Variant):** 1 in 215,000 |
| **Beta-Ketothiolase Deficiency** | *ACAT1* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 4,200 |

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|---|---|---|---|---|
| **Beta-Mannosidosis** | *MANBA* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 9,100 |
| **Bilateral Frontoparietal Polymicrogyria** | *GPR56* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 15,000 |
| **Biotinidase Deficiency** | *BTD* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 500 |
| **Bloom Syndrome** | *BLM* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 7,400 |
| **Canavan Disease** | *ASPA* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 4,000 |
| **Carbamoylphosphate Synthetase I Deficiency** | *CPS1* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 1,100 |
| **Carnitine Acylcarnitine Translocase Deficiency** | *SLC25A20* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 1,600 |
| **Carnitine Palmitoyltransferase IA Deficiency** | *CPT1A* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 5,500 |
| **Carnitine Palmitoyltransferase II Deficiency** | *CPT2* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 670 |
| **Carpenter Syndrome** | *RAB23* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 21,000 |
| **Cartilage-Hair Hypoplasia** | *RMRP* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 960 |
| **Catecholaminergic Polymorphic Ventricular Tachycardia** | *CASQ2* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 5,900 |
| **Central Hypothyroidism and Testicular Enlargement** | *IGSF1* | XL | Reduced Risk | **Personalized Residual Risk:** 1 in 781,000 |
| **Cerebral Creatine Deficiency Syndrome 1** | *SLC6A8* | XL | Reduced Risk | **Personalized Residual Risk:** 1 in 208,000 |
| **Cerebral Creatine Deficiency Syndrome 2** | *GAMT* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 2,100 |
| **Cerebral Creatine Deficiency Syndrome 3** | *GATM* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 7,900 |
| **Cerebral Dysgenesis, Neuropathy, Ichthyosis, and Palmoplantar Keratoderma Syndrome** | *SNAP29* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 210,000 |
| **Cerebrotendinous Xanthomatosis** | *CYP27A1* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 3,900 |
| **Charcot-Marie-Tooth Disease, Type 4D** | *NDRG1* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 693,000 |
| **Charcot-Marie-Tooth Disease, Type 5 / Arts Syndrome** | *PRPS1* | XL | Reduced Risk | **Personalized Residual Risk:** 1 in 114,000 |
| **Charcot-Marie-Tooth Disease, X-Linked** | *GJB1* | XL | Reduced Risk | **Personalized Residual Risk:** 1 in 11,000 |
| **Chediak-Higashi Syndrome** | *LYST* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 7,100 |
| **Chondrodysplasia Punctata** | *ARSE* | XL | Reduced Risk | **Personalized Residual Risk:** 1 in 862,000 |
| **Choreoacanthocytosis** | *VPS13A* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 2,500 |
| **Choroideremia** | *CHM* | XL | Reduced Risk | **Personalized Residual Risk:** 1 in 125,000 |
| **Chronic Granulomatous Disease (*CYBA*-Related)** | *CYBA* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 5,000 |
| **Chronic Granulomatous Disease (*CYBB*-Related)** | *CYBB* | XL | Reduced Risk | **Personalized Residual Risk:** 1 in 294,000 |
| **Citrin Deficiency** | *SLC25A13* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 12,000 |
| **Citrullinemia, Type 1** | *ASS1* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 2,500 |
| **Cockayne Syndrome, Type A** | *ERCC8* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 8,900 |
| **Cockayne Syndrome, Type B and other *ERCC6*-Related Disorders** | *ERCC6* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 8,100 |
| **Cohen Syndrome** | *VPS13B* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 6,400 |
| **Combined Factor V and VIII Deficiency** | *LMAN1* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 102,000 |
| **Combined Malonic and Methylmalonic Aciduria** | *ACSF3* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 2,400 |
| **Combined Oxidative Phosphorylation Deficiency 1** | *GFM1* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 13,000 |
| **Combined Oxidative Phosphorylation Deficiency 3** | *TSFM* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 27,000 |
| **Combined Pituitary Hormone Deficiency 1** | *POU1F1* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 3,900 |
| **Combined Pituitary Hormone Deficiency 2** | *PROP1* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 2,800 |
| **Combined Pituitary Hormone Deficiency 3** | *LHX3* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 140,000 |
| **Combined SAP Deficiency** | *PSAP* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 44,000 |
| **Cone-Rod Dystrophy 6 / Leber Congenital Amaurosis 1** | *GUCY2D* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 1,200 |
| **Congenital Adrenal Hyperplasia due to 11-Beta-Hydroxylase Deficiency** | *CYP11B1* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 520 |
| **Congenital Adrenal Hyperplasia due to 17-Alpha-Hydroxylase Deficiency** | *CYP17A1* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 1,800 |

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|---|---|---|---|---|
| **Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency** | *CYP21A2* | AR | Reduced Risk | *CYP21A2* copy number: 2<br>*CYP21A2* sequencing: Negative<br>**Personalized Residual Risk (Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency (Non-Classic)):** 1 in 200<br>**Personalized Residual Risk (Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency (Classic)):** 1 in 1,200 |
| **Congenital Adrenal Hypoplasia (*NR0B1*-Related)** | *NR0B1* | XL | Reduced Risk | **Personalized Residual Risk:** 1 in 353,000 |
| **Congenital Adrenal Insufficiency (*CYP11A1*-Related)** | *CYP11A1* | 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 8,900 |
| **Congenital Disorder of Deglycosylation** | *NGLY1* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 5,400 |
| **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 163,000 |
| **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 2,100 |
| **Corticosterone Methyloxidase Deficiency** | *CYP11B2* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 1,500 |
| **Cystic Fibrosis** | *CFTR* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 440 |
| **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 15,000 |
| **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** | *TMPRSS3* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 510 |
| **Deafness, Autosomal Recessive 9** | *OTOF* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 630 |
| **Desbuquois Dysplasia 1** | *CANT1* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 7,700 |

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| **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 15,000 |
| **Ehlers-Danlos Syndrome, Type VIIC** | *ADAMTS2* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 243,000 |
| **Ellis-Van Creveld Syndrome (*EVC2*-Related)** | *EVC2* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 5,100 |
| **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 370 |
| **Factor XI Deficiency** | *F11* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 1,200 |
| **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 51,000 |
| **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 4,000 |
| **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 4,100 |
| **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 1,500 |
| **Fragile X Syndrome** | *FMR1* | XL | Reduced Risk | *FMR1* CGG repeat sizes: Not Performed<br>*FMR1* Sequencing: Negative<br>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.<br>**Personalized Residual Risk:** 1 in 19,000 |
| **Fructose-1,6-Bisphosphatase Deficiency** | *FBP1* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 1,600 |
| **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 |
| **GRACILE Syndrome and Other *BCS1L*-Related Disorders** | *BCS1L* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 3,900 |
| **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 1,200 |
| **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 |

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| **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 1,400 |
| **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 920 |
| **Glycine Encephalopathy (*GLDC*-Related)** | *GLDC* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 660 |
| **Glycogen Storage Disease, Type 0** | *GYS2* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 1,200 |
| **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 700 |
| **Glycogen Storage Disease, Type Ia** | *G6PC* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 3,100 |
| **Glycogen Storage Disease, Type Ib** | *SLC37A4* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 7,300 |
| **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 |
| **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 |
| **HMG-CoA Lyase Deficiency** | *HMGCL* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 2,700 |
| **Hemochromatosis, Type 2A** | *HFE2* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 3,300 |
| **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 116,000 |
| **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 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 5,200 |
| **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 |
| **Hypoparathyroidism-Retardation-Dysmorphic Syndrome** | *TBCE* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 8,100 |

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| **Hypophosphatasia** | *ALPL* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 790 |
| **Hypophosphatemic Rickets with Hypercalciuria** | *SLC34A3* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 780 |
| **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 16,000 |
| **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 92,000 |
| **Intrahepatic Cholestasis** | *ATP8B1* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 1,400 |
| **Isovaleric Acidemia** | *IVD* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 2,000 |
| **Joubert Syndrome 2** | *TMEM216* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 152,000 |
| **Joubert Syndrome 4 / Senior-Loken Syndrome 1 / Juvenile Nephronophthisis 1** | *NPHP1* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 21,000 |
| **Joubert Syndrome 7 / Meckel Syndrome 5 / COACH Syndrome** | *RPGRIP1L* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 13,000 |
| **Junctional Epidermolysis Bullosa (*COL17A1*-Related)** | *COL17A1* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 5,200 |
| **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 2,600 |
| **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 1,400 |
| **Leber Congenital Amaurosis 4** | *AIPL1* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 2,100 |
| **Leber Congenital Amaurosis 5** | *LCA5* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 4,200 |
| **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 Arthrogryposis with Anterior Horn Cell Disease** | *GLE1* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 2,800 |
| **Lethal Congenital Contracture Syndrome 2** | *ERBB3* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 36,000 |
| **Lethal Congenital Contracture Syndrome 3** | *PIP5K1C* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 151,000 |
| **Leukoencephalopathy with Vanishing White Matter** | *EIF2B5* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 2,000 |
| **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 |

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| **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 550 |
| **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 3,300 |
| **Lipoid Adrenal Hyperplasia** | *STAR* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 2,400 |
| **Lipoprotein Lipase Deficiency** | *LPL* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 1,000 |
| **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 |
| **MEDNIK Syndrome** | *AP1S1* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 211,000 |
| **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 1,300 |
| **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 2,400 |
| **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 7,900 |
| **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 41,000 |
| **Mitochondrial Complex IV Deficiency (*COX20*-related)** | *COX20* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 42,000 |

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| **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 3,400 |
| **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 *POLG*-Related Disorders** | *POLG* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 320 |
| **Mitochondrial DNA Depletion Syndrome 5** | *SUCLA2* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 45,000 |
| **Mitochondrial DNA Depletion Syndrome 6 / Navajo Neurohepatopathy** | *MPV17* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 4,400 |
| **Mitochondrial Myopathy and Sideroblastic Anemia 1** | *PUS1* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 320,000 |
| **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 1,900 |
| **Mucolipidosis II / IIIA** | *GNPTAB* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 2,100 |
| **Mucolipidosis III Gamma** | *GNPTG* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 68,000 |
| **Mucolipidosis IV** | *MCOLN1* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 4,100 |
| **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 1,600 |
| **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 VII** | *GUSB* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 1,600 |
| **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 |
| **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** | *CHRNG* | 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 2,200 |
| **Nephrogenic Diabetes Insipidus, Type II** | *AQP2* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 3,400 |
| **Nephrogenic Diabetes insipidus (*AVPR2*-related)/ Nephrogenic Syndrome of Inappropriate Antidiuresis** | *AVPR2* | XL | Reduced Risk | **Personalized Residual Risk:** 1 in 471,000 |
| **Nephronophthisis 2** | *INVS* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 53,000 |
| **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 |

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| **Neurodegeneration due to Cerebral Folate Transport Deficiency** | *FOLR1* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 3,700 |
| **Neurodevelopmental Disorder with Progressive Microcephaly, Spasticity, and Brain Anomalies** | *PLAA* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 217,000 |
| **Neuronal Ceroid-Lipofuscinosis (*CLN3*-Related)** | *CLN3* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 5,400 |
| **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 5,100 |
| **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 |
| **Non-Syndromic Hearing Loss (*GJB2*-Related)** | *GJB2* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 600 |
| **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 *RAG1*-Related Disorders** | *RAG1* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 850 |
| **Ornithine Aminotransferase Deficiency** | *OAT* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 4,100 |
| **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 |
| **Otospondylomegaepiphyseal 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 5,300 |
| **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 2,300 |
| **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 63,000 |
| **Primary Ciliary Dyskinesia (*RSPH9*-Related)** | *RSPH9* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 15,000 |

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| **Primary Coenzyme Q10 Deficiency 7** | *COQ4* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 5,300 |
| **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 2,400 |
| **Progressive Familial Intrahepatic Cholestasis, Type 2** | *ABCB11* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 910 |
| **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 5,100 |
| **Propionic Acidemia (*PCCA*-Related)** | *PCCA* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 1,100 |
| **Propionic Acidemia (*PCCB*-Related)** | *PCCB* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 3,200 |
| **Pulmonary Surfactant Dysfunction** | *ABCA3* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 1,200 |
| **Pycnodysostosis** | *CTSK* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 2,000 |
| **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 15,000 |
| **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 36** | *PRCD* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 304,000 |
| **Retinitis Pigmentosa 59** | *DHDDS* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 422,000 |
| **Retinitis Pigmentosa 64 / Bardet-Biedl Syndrome 21 / Cone-Rod Dystrophy 16** | *C8ORF37* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 50,000 |
| **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 7,200 |
| **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 5,300 |
| **Salt and Pepper Developmental Regression Syndrome** | *ST3GAL5* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 15,000 |
| **Sandhoff Disease** | *HEXB* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 1,400 |
| **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 25,000 |
| **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 |

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| **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 80,000 |
| **Spherocytosis, Type 5** | *EPB42* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 2,500 |
| **Spinal Muscular Atrophy** | *SMN1* | AR | Reduced Risk | *SMN1* copy number: 2<br>*SMN2* copy number: 1<br>c.*3+80T>G: Negative<br>*SMN1* Sequencing: Negative<br>**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 6,400 |
| **Spondylocostal Dysostosis 1** | *DLL3* | 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 233,000 |
| **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 |
| **Thiamine-Responsive Megaloblastic Anemia Syndrome** | *SLC19A2* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 5,200 |
| **Thyroid Dyshormonogenesis 1** | *SLC5A5* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 4,300 |
| **Thyroid Dyshormonogenesis 2A** | *TPO* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 790 |
| **Thyroid Dyshormonogenesis 3** | *TG* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 850 |
| **Thyroid Dyshormonogenesis 4** | *IYD* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 1,800 |
| **Thyroid Dyshormonogenesis 5** | *DUOXA2* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 29,000 |
| **Thyroid Dyshormonogenesis 6** | *DUOX2* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 190 |
| **Trichohepatoenteric Syndrome 1** | *TTC37* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 7,700 |
| **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 690 |
| **Usher Syndrome, Type IF** | *PCDH15* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 2,000 |
| **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 810 |
| **Vitamin D-Dependent Rickets, Type I** | *CYP27B1* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 5,000 |
| **Vitamin D-Resistant Rickets, Type IIA** | *VDR* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 14,000 |
| **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 240 |
| **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 2,100 |
| **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 |

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| **Xeroderma Pigmentosum (*POLH*-Related)** | *POLH* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 5,900 |
| **Xeroderma Pigmentosum, Group A** | *XPA* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 11,000 |
| **Xeroderma Pigmentosum, Group C** | *XPC* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 12,000 |
| **Xeroderma Pigmentosum, Group G** | *ERCC5* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 3,000 |
| **Zellweger Syndrome Spectrum (*PEX10*-Related)** | *PEX10* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 6,300 |
| **Zellweger Syndrome Spectrum (*PEX1*-Related)** | *PEX1* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 2,000 |
| **Zellweger Syndrome Spectrum (*PEX2*-Related)** | *PEX2* | AR | Reduced Risk | **Personalized Residual Risk:** 1 in 63,000 |
| **Zellweger Syndrome Spectrum (*PEX6*-Related)** | *PEX6* | 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. AmplideX® *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® 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® 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 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$^{TM}$XT Low Input technology was used with a custom capture library to target the exonic regions and intron/exon splice junctions of the relevant genes, as well as a number of UTR, intronic or promoter regions that contain previously reported mutations. Libraries were pooled and sequenced on the Illumina NovaSeq 9000 platform, using paired-end 100 bp reads. The sequencing data was analyzed using a custom bioinformatics algorithm designed and validated in house.

The coding exons and splice junctions of the known protein-coding RefSeq genes were assessed for the average depth of coverage (minimum of 20X) and data quality threshold values. Most exons not meeting a minimum of >20X read depth across the exon are further analyzed by Sanger sequencing. Please note that several genomic regions present difficulties in mapping or obtaining read depth >20X. These regions, which are described below, will not be reflexed to Sanger sequencing if the mapping quality or coverage is poor. Any variants identified during testing in these regions are confirmed by a second method and reported if determined to be pathogenic or likely pathogenic. However, as there is a possibility of false negative results within these regions, detection rates and residual risks for these genes have been calculated with the presumption that variants in these exons will not be detected, unless included in the MassARRAY® 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 ΔΔCt 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$^{TM}$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$^{th}$ "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 ≥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 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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Additional disease-specific references available upon request.