

**Patient Information**

Name: Donor 10709  
 Date of Birth: [REDACTED]  
 Sema4 ID: [REDACTED]  
 Client ID: SEATSB-S476566151  
 Indication: Carrier Screening

**Specimen Information**

Specimen Type: Blood  
 Date Collected: 09/29/2022  
 Date Received: 09/30/2022  
 Final Report: 10/12/2022

**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 Retinitis Pigmentosa 25 (AR)</b></p> <p style="text-align: center;">Associated gene(s): <i>EYS</i></p> <p style="text-align: center;">Variant(s) Detected: c.9405T&gt;A, p.Y3135X, Pathogenic, Heterozygous (one copy)</p> <p style="text-align: center;"><b>Carrier of Sandhoff Disease (AR)</b></p> <p style="text-align: center;">Associated gene(s): <i>HEXB</i></p> <p style="text-align: center;">Variant(s) Detected: c.851G&gt;A, p.R284Q, Likely Pathogenic, Heterozygous (one copy)</p> <p style="text-align: center;">Enzyme results in the carrier range for Sandhoff Disease</p>	<p style="text-align: center;"><b>Negative for all other genes tested</b></p> <p style="text-align: center;">To view a full list of genes and diseases tested please see Table 1 in this report</p>

AR=Autosomal recessive; XL=X-linked

**Recommendations**

- Testing the partner for the above positive disorder(s) and genetic counseling are recommended.
- Please note that for female carriers of X-linked diseases, follow-up testing of a male partner is not indicated.
- CGG repeat analysis of *FMR1* for fragile X syndrome is not performed on males as repeat expansion of premutation alleles is not expected in the male germline.
- Individuals of Asian, African, Hispanic and Mediterranean ancestry should also be screened for hemoglobinopathies by CBC and hemoglobin electrophoresis.
- Consideration of residual risk by ethnicity after a negative carrier screen is recommended for the other diseases on the panel, especially in the case of a positive family history for a specific disorder. Please note that residual risks for X-linked diseases (including full repeat expansions for Fragile X syndrome) may not be accurate for males and the actual residual risk is likely to be lower.
- As genetic technologies may improve and variant classifications may change over time, it is recommended to obtain a new carrier screening test or reanalysis when a new pregnancy is being considered.

## Interpretation of positive results

**Retinitis Pigmentosa 25 (AR)**

**Results and Interpretation**

A heterozygous (one copy) pathogenic premature stop codon, c.9405T>A, p.Y3135X, was detected in the *EYS* gene (NM\_001142800.1). When this variant is present in trans with a pathogenic variant, it is considered to be causative for retinitis pigmentosa 25. Therefore, this individual is expected to be at least a carrier for retinitis pigmentosa 25. Heterozygous carriers are not expected to exhibit symptoms of this disease.

### What is Retinitis Pigmentosa 25?

Retinitis pigmentosa 25 is an autosomal recessive disorder caused by pathogenic variants in the gene *EYS*. While it has been reported in populations worldwide, it is more prevalent in Spain and Sephardic Jewish populations from Morocco. Retinitis pigmentosa begins with the onset of night blindness in childhood, and progresses to tunnel vision and blindness in adulthood. Age of onset and severity of vision loss may vary between patients. Life expectancy is not reduced. No genotype-phenotype correlation has been reported.

### Sandhoff Disease (AR)

#### Results and Interpretation

##### HEXB Sequence Analysis:

A heterozygous (one copy) likely pathogenic missense variant, c.851G>A, p.R284Q, was detected in the *HEXB* gene (NM\_000521.3). When this variant is present in trans with a pathogenic variant, it is considered to be causative for Sandhoff disease. Therefore, this individual is expected to be at least a carrier for Sandhoff disease. Heterozygous carriers are not expected to exhibit symptoms of this disease.

##### Hexosaminidase Enzyme Activity:

White blood cells: Sandhoff?

- Hex A%: 77.2% (Non-carrier : 55.0 - 72.0%; Carrier: >75%)
- Total hexosaminidase activity: 82g nmol/hr/mg

Plasma: Sandhoff?

- Hex A%: 87.0 (non-carrier range: (Non-carrier : 58.0 - 72.0%; Carrier: >75%))
- Total hexosaminidase activity: 332 nmol/hr/ml

*HEXB* Sequencing: c.851G>A, p.R284Q, Likely Pathogenic, Heterozygous (one copy)

The patient's Hex A% activity is within the non-carrier range for Tay-Sachs disease. This finding is consistent with the patient being a non-carrier for Tay Sachs disease. **Please note:** The Hex A% activity is high in this specimen. This result and positive HEXB mutation are consistent with the patient being a **CARRIER** for Sandhoff disease. Testing of the reproductive partner for Sandhoff disease and genetic counseling are recommended.

### What is Sandhoff Disease?

Sandhoff disease is an autosomal recessive disorder resulting from pathogenic variants in the *HEXB* gene. It has been reported in individuals from different ethnicities, but there is an increased prevalence of the disease in specific isolated groups, including the Metis of Northern Saskatchewan and Argentinian Creoles. Pathogenic *HEXB* variants result in loss of function of the hexosaminidase B 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 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 4 and 25 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 the presence of one allele with residual enzyme activity is likely to result in a later-onset phenotype. However, it may not be possible to predict the age of onset in all patients.



## Test description

This patient was tested for a panel of diseases using a combination of sequencing, targeted genotyping and copy number analysis. Please note that negative results reduce but do not eliminate the possibility that this individual is a carrier for one or more of the disorders tested. Please see Table 1 for a list of genes and diseases tested with the patient's personalized residual risk. If personalized residual risk is not provided, please see the complete residual risk table at [go.sema4.com/residualrisk](https://go.sema4.com/residualrisk). Only variants determined to be pathogenic or likely pathogenic are reported in this carrier screening test.

*Hongli Zhan*

Hongli Zhan, Ph.D., Director

## Genes and diseases tested

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

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

Disease	Gene	Inheritance Pattern	Status	Detailed Summary
<b>Positive</b>				
Retinitis Pigmentosa 25	<i>EYS</i>	AR	Carrier	c.9405T>A, p.Y3135X. Pathogenic, Heterozygous (one copy) Hex A enzyme: Possible Sandhoff carrier White blood cells: Sandhoff? <ul style="list-style-type: none"> <li>Hex A%: 77.2% (Non-carrier : 55.0 - 72.0%; Carrier: &gt;75%)</li> <li>Total hexosaminidase activity: 829 nmol/hr/mg</li> </ul>
Sandhoff Disease	<i>HEXB</i>	AR	Carrier	Plasma: Sandhoff? <ul style="list-style-type: none"> <li>Hex A%: 87.0 (non-carrier range: (Non-carrier : 58.0 - 72.0%; Carrier: &gt;75%))</li> <li>Total hexosaminidase activity: 332 nmol/hr/ml</li> </ul> <i>HEXB</i> Sequencing: c.851G>A, p.R284Q. Likely 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 (MCCC1-Related)	<i>MCCC1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,400
3-Methylcrotonyl-CoA Carboxylase Deficiency (MCCC2-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
CD59-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 (CNGA3-Related)	<i>CNGA3</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 830
Achromatopsia (CNGB3-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>ACO1</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
Alpha-Thalassemia	<i>HBA1/HBA2</i>	AR	Reduced Risk	<i>HBA1</i> Copy Number: 2 <i>HBA2</i> Copy Number: 2 No pathogenic copy number variants detected <i>HBA1/HBA2</i> Sequencing: Negative Personalized Residual Risk: 1 in 10,000
Alpha-Thalassemia Intellectual Disability Syndrome	<i>ATRX</i>	XL	Reduced Risk	Personalized Residual Risk: 1 in 48,000
Alport Syndrome ( <i>COL4A3</i> -Related)	<i>COL4A3</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,800
Alport Syndrome ( <i>COL4A4</i> -Related)	<i>COL4A4</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,800
Alport Syndrome ( <i>COL4A5</i> -Related)	<i>COL4A5</i>	XL	Reduced Risk	Personalized Residual Risk: 1 in 150,000
Alstrom Syndrome	<i>ALMS1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,800
Andermann Syndrome	<i>SLC12A6</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 151,000
Antley-Bixler Syndrome ( <i>POR</i> -Related)	<i>POR</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,000
Argininemia	<i>ARG1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,500
Argininosuccinic Aciduria	<i>ASL</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,200
Aromatase Deficiency	<i>CYP19A1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,400
Arthrogryposis, Intellectual Disability, and Seizures	<i>SLC35A3</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 454,000
Asparagine Synthetase Deficiency	<i>ASNS</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 202,000
Aspartylglycosaminuria	<i>AGA</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 13,000
Ataxia With Isolated Vitamin E Deficiency	<i>TTPA</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 61,000
Ataxia-Telangiectasia	<i>ATM</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,300
Ataxia-Telangiectasia-Like Disorder 1	<i>MRE11</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,500
Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay	<i>SACS</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,600
Bardet-Biedl Syndrome ( <i>ARL6</i> -Related)	<i>ARL6</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 29,000
Bardet-Biedl Syndrome ( <i>BBS10</i> -Related)	<i>BBS10</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,700
Bardet-Biedl Syndrome ( <i>BBS12</i> -Related)	<i>BBS12</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 9,900
Bardet-Biedl Syndrome ( <i>BBS1</i> -Related)	<i>BBS1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,400
Bardet-Biedl Syndrome ( <i>BBS2</i> -Related)	<i>BBS2</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,200
Bardet-Biedl Syndrome ( <i>BBS4</i> -Related)	<i>BBS4</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 22,000
Bare Lymphocyte Syndrome, Type II	<i>CIITA</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 35,000
Barth Syndrome	<i>TAZ</i>	XL	Reduced Risk	Personalized Residual Risk: 1 in 183,000
Bartter Syndrome, Type 3	<i>CLCNKB</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 740
Bartter Syndrome, Type 4A	<i>BSND</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 91,000
Bernard-Soulier Syndrome, Type A1	<i>GPIBA</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 42,000
Bernard-Soulier Syndrome, Type C	<i>GP9</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,300
Beta-Globin-Related Hemoglobinopathies	<i>HBB</i>	AR	Reduced Risk	Personalized Residual Risk (Beta-Globin-Related Hemoglobinopathies): 1 in 2,000 Personalized Residual Risk (Beta-Globin-Related Hemoglobinopathies: HbS Variant): 1 in 790,000 Personalized Residual Risk (Beta-Globin-Related Hemoglobinopathies: HbC Variant): 1 in 2,107,000
Beta-Ketothiolase Deficiency	<i>ACAT1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,400
Beta-Mannosidosis	<i>MANBA</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 9,100
BH4-Deficient Hyperphenylalaninemia C	<i>QDPR</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,100

BH4-Deficient Hyperphenylalaninemia D	<i>PCBD1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 8,000
Bilateral Frontoparietal Polymicrogyria	<i>GPR56</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 203,000
Biotinidase Deficiency	<i>BTD</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 500
Bloom Syndrome	<i>BLM</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 7,400
Canavan Disease	<i>ASPA</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,000
Carbamoylphosphate Synthetase I Deficiency	<i>CPS1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,100
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 Hyperplasia due to 21-Hydroxylase Deficiency	<i>CYP21A2</i>	AR	Reduced Risk	<i>CYP21A2</i> copy number: 2 <i>CYP21A2</i> sequencing: Negative Personalized Residual Risk (Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency (Non-Classic)): 1 in 200 Personalized Residual Risk (Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency (Classic)): 1 in 1,300
Congenital Adrenal Hypoplasia ( <i>NR0B1</i> -Related)	<i>NR0B1</i>	XL	Reduced Risk	Personalized Residual Risk: 1 in 353,000
Congenital Adrenal Insufficiency ( <i>CYP11A1</i> -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 ( <i>AKR1D1</i> -Related)	<i>AKR1D1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,900
Congenital Bile Acid Synthesis Defect ( <i>HSD3B7</i> -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>MPL</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 ( <i>ABCC8</i> -Related)	<i>ABCC8</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 450
Familial Hyperinsulinism ( <i>KCNJ11</i> -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
Gaucher Disease	<i>GBA</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,300
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
Gitelman Syndrome	<i>SLC12A3</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 290
Glanzmann Thrombasthenia ( <i>ITGA2B</i> -Related)	<i>ITGA2B</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,800

Glanzmann Thrombasthenia ( <i>ITGB3</i> -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 ( <i>AMT</i> -Related)	<i>AMT</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,700
Glycine Encephalopathy ( <i>GLDC</i> -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 87,000
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
Hydroletharus 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	ALPL	AR	Reduced Risk	Personalized Residual Risk: 1 in 790
Hypophosphatemic Rickets with Hypercalciuria	SLC34A3	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,200
Hypotrichosis 8 / Autosomal Recessive Woolly Hair 1	LPAR6	AR	Reduced Risk	Personalized Residual Risk: 1 in 27,000
Immunodeficiency 18	CD3E	AR	Reduced Risk	Personalized Residual Risk: 1 in 73,000
Immunodeficiency 19	CD3D	AR	Reduced Risk	Personalized Residual Risk: 1 in 46,000
Inclusion Body Myopathy 2	GNE	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,000
Infantile Cerebral and Cerebellar Atrophy	MED17	AR	Reduced Risk	Personalized Residual Risk: 1 in 129,000
Infantile Neuroaxonal Dystrophy 1 and other PLA2G6-Related Disorders	PLA2G6	AR	Reduced Risk	Personalized Residual Risk: 1 in 690
Intellectual Disability, Autosomal Recessive 3	CC2D1A	AR	Reduced Risk	Personalized Residual Risk: 1 in 220,000
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 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 Arthrogyrosis 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	BCKDHB	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,100
Maple Syrup Urine Disease, Type 2	DBT	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,600
Meckel Syndrome 1 / Bardet-Biedl Syndrome 13	MKS1	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,700
Medium Chain Acyl-CoA Dehydrogenase Deficiency	ACADM	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,800
MEDNIK Syndrome	AP1S1	AR	Reduced Risk	Personalized Residual Risk: 1 in 211,000
Megalencephalic Leukoencephalopathy with Subcortical Cysts	MLC1	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,300
Megaloblastic Anemia 1	AMN	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,300
Menkes Disease	ATP7A	XL	Reduced Risk	Personalized Residual Risk: 1 in 172,000
Metachromatic Leukodystrophy	ARSA	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,000
Methionine Adenosyltransferase I/III Deficiency	MAT1A	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,900
Methylmalonic Acidemia (MMAA-Related)	MMAA	AR	Reduced Risk	Personalized Residual Risk: 1 in 15,000
Methylmalonic Acidemia (MMAB-Related)	MMAB	AR	Reduced Risk	Personalized Residual Risk: 1 in 12,000
Methylmalonic Acidemia (MUT-Related)	MUT	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,300
Methylmalonic Aciduria and Homocystinuria, Cobalamin C Type	MMACHC	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,800
Methylmalonic Aciduria and Homocystinuria, Cobalamin D Type	MMADHC	AR	Reduced Risk	Personalized Residual Risk: 1 in 219,000
Methylmalonic Aciduria and Homocystinuria, Cobalamin F Type	LMBRD1	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,600
Methylmalonyl-CoA Epimerase Deficiency	MCEE	AR	Reduced Risk	Personalized Residual Risk: 1 in 98,000
Microphthalmia / Anophthalmia	VSX2	AR	Reduced Risk	Personalized Residual Risk: 1 in 40,000
Mitochondrial Complex I Deficiency (ACAD9-Related)	ACAD9	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,800
Mitochondrial Complex I Deficiency (NDUFA11-Related)	NDUFA11	AR	Reduced Risk	Personalized Residual Risk: 1 in 414,000
Mitochondrial Complex I Deficiency (NDUFAF5-Related)	NDUFAF5	AR	Reduced Risk	Personalized Residual Risk: 1 in 98,000
Mitochondrial Complex I Deficiency (NDUFS6-Related)	NDUFS6	AR	Reduced Risk	Personalized Residual Risk: 1 in 353,000
Mitochondrial Complex I Deficiency (NDUFV1-Related)	NDUFV1	AR	Reduced Risk	Personalized Residual Risk: 1 in 870
Mitochondrial Complex I Deficiency / Leigh Syndrome (FOXRED1-Related)	FOXRED1	AR	Reduced Risk	Personalized Residual Risk: 1 in 13,000
Mitochondrial Complex I Deficiency / Leigh Syndrome (NDUFAF2-Related)	NDUFAF2	AR	Reduced Risk	Personalized Residual Risk: 1 in 168,000
Mitochondrial Complex I Deficiency / Leigh Syndrome (NDUFS4-Related)	NDUFS4	AR	Reduced Risk	Personalized Residual Risk: 1 in 41,000
Mitochondrial Complex IV Deficiency (COX20-related)	COX20	AR	Reduced Risk	Personalized Residual Risk: 1 in 42,000

Mitochondrial Complex IV Deficiency ( <i>COX6B1</i> -related)	<i>COX6B1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,116,000
Mitochondrial Complex IV Deficiency ( <i>APOPT1</i> -Related)	<i>APOPT1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 9,200
Mitochondrial Complex IV Deficiency ( <i>PET100</i> -Related)	<i>PET100</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 469,000
Mitochondrial Complex IV Deficiency ( <i>SCO1</i> -related)	<i>SCO1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 13,000
Mitochondrial Complex IV Deficiency / Leigh Syndrome ( <i>COX10</i> -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 <i>POLG</i> -Related Disorders	<i>POLG</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 320
Mitochondrial DNA Depletion Syndrome 5	<i>SUCLA2</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 78,000
Mitochondrial DNA Depletion Syndrome 6 / Navajo Neurohepatopathy	<i>MPV17</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,400
Mitochondrial Myopathy and Sideroblastic Anemia 1	<i>PUS1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 449,000
Mitochondrial Trifunctional Protein Deficiency ( <i>HADHB</i> -Related)	<i>HADHB</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,000
Molybdenum Cofactor Deficiency A	<i>MOCS1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,700
Mucopolipidosis II / IIIA	<i>GNPTAB</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,100
Mucopolipidosis III Gamma	<i>GNPTG</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 68,000
Mucopolipidosis IV	<i>MCOLN1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 9,400
Mucopolysaccharidosis Type I	<i>IDUA</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,300
Mucopolysaccharidosis Type II	<i>IDS</i>	XL	Reduced Risk	Personalized Residual Risk: 1 in 76,000
Mucopolysaccharidosis Type IIIA	<i>SGSH</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,700
Mucopolysaccharidosis Type IIIB	<i>NAGLU</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 950
Mucopolysaccharidosis Type IIIC	<i>HGSNAT</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,200
Mucopolysaccharidosis Type IIID	<i>GNS</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 137,000
Mucopolysaccharidosis Type IVa	<i>GALNS</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 690
Mucopolysaccharidosis Type IVb / GM1 Gangliosidosis	<i>GLB1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,700
Mucopolysaccharidosis type IX	<i>HYAL1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 149,000
Mucopolysaccharidosis type VI	<i>ARSB</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,300
Mucopolysaccharidosis VII	<i>GUSB</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,600
Mulibrey Nanism	<i>TRIM37</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 31,000
Multiple Congenital Anomalies-Hypotonia-Seizures Syndrome 1	<i>PIGN</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,800
Multiple Pterygium Syndrome	<i>CHRNA3</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 9,900
Multiple Sulfatase Deficiency	<i>SUMF1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 69,000
Muscle-Eye-Brain Disease and Other <i>POMGNT1</i> -Related Congenital Muscular Dystrophy-Dystroglycanopathies	<i>POMGNT1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,200
Myoneurogastrointestinal Encephalopathy	<i>TYMP</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,100
Myotubular Myopathy 1	<i>MTM1</i>	XL	Reduced Risk	Personalized Residual Risk: 1 in 192,000
N-Acetylglutamate Synthase Deficiency	<i>NAGS</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,200
Nemaline Myopathy 2	<i>NEB</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,400
Nephrogenic Diabetes insipidus ( <i>AVPR2</i> -related) / Nephrogenic Syndrome of Inappropriate Antidiuresis	<i>AVPR2</i>	XL	Reduced Risk	Personalized Residual Risk: 1 in 471,000
Nephrogenic Diabetes Insipidus, Type II	<i>AQP2</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,400
Nephronophthisis 2	<i>INVS</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 56,000
Nephrotic Syndrome ( <i>NPHS1</i> -Related) / Congenital Finnish Nephrosis	<i>NPHS1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 920
Nephrotic Syndrome ( <i>NPHS2</i> -Related) / Steroid-Resistant Nephrotic Syndrome	<i>NPHS2</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 780

Neurodegeneration due to Cerebral Folate Transport Deficiency	<i>FOLR1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,300
Neurodevelopmental Disorder with Progressive Microcephaly, Spasticity, and Brain Anomalies	<i>PLAA</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 229,000
Neuronal Ceroid-Lipofuscinosis ( <i>CLN3</i> -Related)	<i>CLN3</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 9,200
Neuronal Ceroid-Lipofuscinosis ( <i>CLN5</i> -Related)	<i>CLN5</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,300
Neuronal Ceroid-Lipofuscinosis ( <i>CLN6</i> -Related)	<i>CLN6</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 8,600
Neuronal Ceroid-Lipofuscinosis ( <i>CLN8</i> -Related)	<i>CLN8</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,100
Neuronal Ceroid-Lipofuscinosis ( <i>MFSD8</i> -Related)	<i>MFSD8</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,200
Neuronal Ceroid-Lipofuscinosis ( <i>PPT1</i> -Related)	<i>PPT1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 7,500
Neuronal Ceroid-Lipofuscinosis ( <i>TPP1</i> -Related)	<i>TPP1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,300
Niemann-Pick Disease ( <i>SMPD1</i> -Related)	<i>SMPD1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,800
Niemann-Pick Disease, Type C ( <i>NPC1</i> -Related)	<i>NPC1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 690
Niemann-Pick Disease, Type C ( <i>NPC2</i> -Related)	<i>NPC2</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,600
Nijmegen Breakage Syndrome	<i>NBN</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 14,000
Non-Syndromic Hearing Loss ( <i>GJB2</i> -Related)	<i>GJB2</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 600
Oculocutaneous Albinism, Type IA / IB	<i>TYR</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 240
Oculocutaneous Albinism, Type IV	<i>SLC45A2</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 830
Odonto-Onycho-Dermal Dysplasia / Schopf-Schulz-Passarge Syndrome	<i>WNT10A</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,900
Omenn Syndrome ( <i>RAG2</i> -Related)	<i>RAG2</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 17,000
Omenn Syndrome / Severe Combined Immunodeficiency, Athabaskan-Type	<i>DCLRE1C</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,500
Omenn Syndrome and other <i>RAG1</i> -Related Disorders	<i>RAG1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 850
Ornithine Aminotransferase Deficiency	<i>OAT</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,400
Ornithine Transcarbamylase Deficiency	<i>OTC</i>	XL	Reduced Risk	Personalized Residual Risk: 1 in 103,000
Osteogenesis Imperfecta, Type XI	<i>FKBP10</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 9,500
Osteopetrosis 1	<i>TCIRG1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,700
Osteopetrosis 8	<i>SNX10</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 16,000
Otospondylomegapiphyseal Dysplasia / Deafness / Fibrochondrogenesis 2	<i>COL11A2</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,700
Papillon-Lefevre Syndrome	<i>CTSC</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,000
Pendred Syndrome	<i>SLC26A4</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 390
Peroxisome Biogenesis Disorder 3A and 3B	<i>PEX12</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 30,000
Peroxisome Biogenesis Disorder 7A and 7B	<i>PEX26</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 70,000
Phenylalanine Hydroxylase Deficiency	<i>PAH</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 340
Polycystic Kidney Disease, Autosomal Recessive	<i>PKHD1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 450
Polyglandular Autoimmune Syndrome, Type 1	<i>AIRE</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,300
Pontocerebellar Hypoplasia, Type 1A	<i>VRK1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 25,000
Pontocerebellar Hypoplasia, Type 1B	<i>EXOSC3</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 10,000
Pontocerebellar Hypoplasia, Type 2A and Type 4	<i>TSEN54</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 4,700
Pontocerebellar Hypoplasia, Type 2E	<i>VPS53</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 139,000
Pontocerebellar Hypoplasia, Type 6	<i>RARS2</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 8,600
Primary Carnitine Deficiency	<i>SLC22A5</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,500
Primary Ciliary Dyskinesia ( <i>CCDC103</i> -Related)	<i>CCDC103</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 27,000
Primary Ciliary Dyskinesia ( <i>CCDC151</i> -Related)	<i>CCDC151</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 59,000
Primary Ciliary Dyskinesia ( <i>CCDC39</i> -Related)	<i>CCDC39</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 12,000
Primary Ciliary Dyskinesia ( <i>DNAH5</i> -Related)	<i>DNAH5</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,500
Primary Ciliary Dyskinesia ( <i>DNAI1</i> -Related)	<i>DNAI1</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,000
Primary Ciliary Dyskinesia ( <i>DNAI2</i> -Related)	<i>DNAI2</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 76,000
Primary Ciliary Dyskinesia ( <i>RSPH9</i> -Related)	<i>RSPH9</i>	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	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 26	CERKL	AR	Reduced Risk	Personalized Residual Risk: 1 in 13,000
Retinitis Pigmentosa 28	FAM161A	AR	Reduced Risk	Personalized Residual Risk: 1 in 34,000
Retinitis Pigmentosa 36	PRCD	AR	Reduced Risk	Personalized Residual Risk: 1 in 304,000
Retinitis Pigmentosa 59	DHDDS	AR	Reduced Risk	Personalized Residual Risk: 1 in 601,000
Retinitis Pigmentosa 64 / Bardet-Biedl Syndrome 21 / Cone-Rod Dystrophy 16	C8ORF37	AR	Reduced Risk	Personalized Residual Risk: 1 in 168,000
Rh Deficiency Syndrome	RHAG	AR	Reduced Risk	Personalized Residual Risk: 1 in 46,000
Rhizomelic Chondrodysplasia Punctata, Type 1	PEX7	AR	Reduced Risk	Personalized Residual Risk: 1 in 10,000
Rhizomelic Chondrodysplasia Punctata, Type 3	AGPS	AR	Reduced Risk	Personalized Residual Risk: 1 in 620,000
Roberts Syndrome	ESCO2	AR	Reduced Risk	Personalized Residual Risk: 1 in 139,000
Salla Disease	SLC17A5	AR	Reduced Risk	Personalized Residual Risk: 1 in 8,400
Salt and Pepper Developmental Regression Syndrome	ST3GAL5	AR	Reduced Risk	Personalized Residual Risk: 1 in 25,000
Schimke Immunoosseous Dysplasia	SMARCAL1	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,800
Seckel Syndrome 5 / Microcephaly 9	CEP152	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,700
Segawa Syndrome	TH	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,100
Sepiapterin Reductase Deficiency	SPR	AR	Reduced Risk	Personalized Residual Risk: 1 in 35,000
Severe Combined Immunodeficiency (IL7R-Related)	IL7R	AR	Reduced Risk	Personalized Residual Risk: 1 in 20,000
Severe Combined Immunodeficiency (JAK3-Related)	JAK3	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,100
Severe Combined Immunodeficiency (PTPRC-Related)	PTPRC	AR	Reduced Risk	Personalized Residual Risk: 1 in 8,500
Severe Congenital Neutropenia 4	G6PC3	AR	Reduced Risk	Personalized Residual Risk: 1 in 10,000
Severe Neonatal Hyperparathyroidism	CASR	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,700
Short Stature, Onychodysplasia, Facial Dysmorphism, and Hypotrichosis	POC1A	AR	Reduced Risk	Personalized Residual Risk: 1 in 108,000
Short-Chain Acyl-CoA Dehydrogenase Deficiency	ACADS	AR	Reduced Risk	Personalized Residual Risk: 1 in 660
Shwachman-Diamond Syndrome	SBDS	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,700
Sialidosis, Type I and Type II	NEU1	AR	Reduced Risk	Personalized Residual Risk: 1 in 2,000
Sjogren-Larsson Syndrome	ALDH3A2	AR	Reduced Risk	Personalized Residual Risk: 1 in 5,500
Smith-Lemli-Opitz Syndrome	DHCR7	AR	Reduced Risk	Personalized Residual Risk: 1 in 750

Spastic Paraplegia 15	ZFYVE26	AR	Reduced Risk	Personalized Residual Risk: 1 in 46,000
Spastic Tetraplegia, Thin Corpus Callosum, and Progressive Microcephaly	SLC1A4	AR	Reduced Risk	Personalized Residual Risk: 1 in 85,000
Spherocytosis, Type 5	EPB42	AR	Reduced Risk	Personalized Residual Risk: 1 in 3,200
Spinal Muscular Atrophy	SMN1	AR	Reduced Risk	SMN1 copy number: 2 SMN2 copy number: 2 c.3+80T>G: Negative SMN1 Sequencing: Negative Personalized Residual Risk: 1 in 1,107
Spinal Muscular Atrophy with Respiratory Distress 1 / Charcot-Marie-Tooth Disease, Type 2S	IGHMBP2	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,200
Spinocerebellar Ataxia with Axonal Neuropathy 3	COA7	AR	Reduced Risk	Personalized Residual Risk: 1 in 12,000
Spondylocostal Dysostosis 1	DLL3	AR	Reduced Risk	Personalized Residual Risk: 1 in 7,200
Spondylometaphyseal Dysplasia (DDR2-Related)	DDR2	AR	Reduced Risk	Personalized Residual Risk: 1 in 236,000
Spondylothoracic Dysostosis	MESP2	AR	Reduced Risk	Personalized Residual Risk: 1 in 382,000
Steel Syndrome	COL27A1	AR	Reduced Risk	Personalized Residual Risk: 1 in 93,000
Stuve-Wiedemann Syndrome	LIFR	AR	Reduced Risk	Personalized Residual Risk: 1 in 6,000
Sulfate Transporter-Related Osteochondrodysplasia	SLC26A2	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,800
Tay-Sachs Disease	HEXA	AR	Reduced Risk	For Tay Sachs disease enzyme results, please refer to Sandhoff disease results above HEXA Sequencing: Negative Personalized Residual Risk: 1 in 1,400
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 266,000
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	<i>RS1</i>	XL	Reduced Risk	Personalized Residual Risk: 1 in 40,000
X-Linked Severe Combined Immunodeficiency	<i>IL2RG</i>	XL	Reduced Risk	Personalized Residual Risk: 1 in 250,000
Xeroderma Pigmentosum ( <i>POLH</i> -Related)	<i>POLH</i>	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* premutations and full mutations greater than 90 CGG repeats in length were further analyzed by Southern blot analysis or methylation PCR to assess the size and methylation status of the *FMR1* CGG repeat. Additional testing to determine the status of AGG interruptions within the *FMR1* CGG repeat will be automatically performed for premutation alleles ranging from 55 to 90 repeats. These results, which may modify risk for expansion, will follow in a separate report.

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

Multiplex PCR amplification and 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 *SMN2* is performed in association with short-read sequencing of exons 2a-7, followed by confirmation using long-range PCR (described below).

In individuals with two copies of *SMN1* with Ashkenazi Jewish, East Asian, African American, Native American or Caucasian ancestry, the presence or absence of c.3+80T>G significantly increases or decreases, respectively, the likelihood of being a silent 2+0 silent carrier.

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

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

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

Agilent SureSelect<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; *F5* (NM\_000130.4) chr1:169,551,662-169,551,679 (partial exon 2); *FH* (NM\_000143.3) exon 1; *GAMT* (NM\_000156.5) exon 1; *GLDC* (NM\_000170.2) exon 1; *GNPTAB* (NM\_024312.4) chr17:4,837,000-4,837,400 (partial exon 2); *GNPTG* (NM\_032520.4) exon 1; *GHR* (NM\_000163.4) exon 3; *GYS2* (NM\_021957.3) chr12:21,699,370-21,699,409 (partial exon 12); *HGSNAT* (NM\_152419.2) exon 1; *IDS* (NM\_000202.6) exon 3; *ITGB4* (NM\_000213.4) chr17:73,749,976-73,750,060 (partial exon 33); *JAK3* (NM\_000215.3) chr19:17,950,462-17,950,483 (partial exon 10); *LIFR* (NM\_002310.5) exon 19; *LMBRD1* (NM\_018368.3) chr6:70,459,226-70,459,257 (partial exon 5), chr6:70,447,828-70,447,836 (partial exon 7) and exon 12; *LYST* (NM\_000081.3) chr1:235,944,158-235,944,176 (partial exon 16) and chr1:235,875,350-235,875,362 (partial exon 43); *MLYCD* (NM\_012213.2) chr16:83,933,242-83,933,282 (partial exon 1); *MTR* (NM\_000254.2) chr1:237,024,418-237,024,439 (partial exon 20) and chr1:237,038,019-237,038,029 (partial exon 24); *NBEAL2* (NM\_015175.2) chr3:47,021,385-47,021,407 (partial exon 1); *NEB* (NM\_001271208.1) exons 82-105; *NPC1* (NM\_000271.4) chr18:21,123,519-21,123,538 (partial exon 14); *NPHP1* (NM\_000272.3) chr2:110,937,251-110,937,263 (partial exon 3); *OCRL* (NM\_000276.3) chrX:128,674,450-128,674,460 (partial exon 1); *PHKB* (NM\_000293.2) exon 1 and chr16:47,732,498-47,732,504 (partial exon 30); *PIGN* (NM\_176787.4) chr18:59,815,547-59,815,576 (partial exon 8); *PIP5K1C* (NM\_012398.2) exon 1 and chr19:3637602-3637616 (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 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. Deletions and duplications near the lower limit of detection may not be detected due to run variability.

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

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

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

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

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

Long-range PCR was performed to generate locus-specific amplicons for *CYP21A2*, *HBA1* and *HBA2* and *GBA*. The PCR products were then prepared for short-read NGS sequencing and sequenced. Sequenced reads were mapped back to the original genomic locus and run through the bioinformatics pipeline. If indicated, copy number from MLPA was correlated with the sequencing output to analyze the results. Please note that in rare cases, allele drop-out may occur, which has the potential to lead to false negative results. For *CYP21A2*, a certain percentage of healthy individuals carry a duplication of the *CYP21A2* gene, which has no clinical consequences. In cases where multiple copies of *CYP21A2* are located on the same chromosome in tandem, only the last copy will be amplified and assessed for potentially pathogenic variants, due to size limitations of the PCR reaction. However, because these alleles contain at least two copies of the *CYP21A2* gene in tandem, it is expected that this patient has at least one functional gene in the tandem allele and this patient is therefore less likely to be a carrier. A *CYP21A1P/CYP21A2* hybrid gene detected only by MLPA but not by long-range PCR will not be reported when the long-range PCR indicates the presence of two full *CYP21A2* gene copies (one on each chromosome), as the additional hybrid gene is nonfunctional. Classic 30-kb deletions are identified by MLPA and are also identified by the presence of multiple common pathogenic *CYP21A2* variants by long-range PCR. Since multiple pseudogene-derived variants are detected in all cases with the classic 30kb deletion, we cannot rule out the possibility that some variant(s) detected could be present in trans with the chimeric *CYP21A1P/CYP21A2* gene created by the 30kb deletion. When an individual carries both a duplication allele and a pathogenic variant, or multiple pathogenic variants, the current analysis may not be able to determine the phase (cis/trans configuration) of the *CYP21A2* alleles identified. Family studies may be required in certain scenarios where phasing is required to determine the carrier status.

#### Residual Risk Calculations

Carrier frequencies and detection rates for each ethnicity were calculated through the combination of internal curations of >30,000 variants and genomic frequency data from >138,000 individuals across seven ethnic groups in the gnomAD database. Additional variants in HGMD and novel deleterious variants were also incorporated into the calculation. Residual risk values are calculated using a Bayesian analysis combining the *a priori* risk of being a pathogenic mutation carrier (carrier frequency) and the detection rate. They are provided only as a guide for assessing approximate risk given a negative result, and values will vary based on the exact ethnic background of an individual. This report does not represent medical advice but should be interpreted by a genetic counselor, medical geneticist or physician skilled in genetic result interpretation and the relevant medical literature.

#### Personalized Residual Risk Calculations

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

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

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

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

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

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

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

This test was developed, and its performance characteristics determined by Sema4 Opco, Inc. It has not been cleared or approved by the US Food and Drug Administration. FDA does not require this test to go through premarket FDA review. This test is used for clinical purposes. It should not be regarded as investigational or for research. This laboratory is certified under the Clinical Laboratory Improvement Amendments (CLIA) as qualified to perform high complexity clinical laboratory testing. These analyses generally provide highly accurate information regarding the patient's carrier or affected status. Despite this high level of accuracy, it should be kept in mind that there are many potential sources of diagnostic error, including misidentification of samples, polymorphisms, or other rare genetic variants that interfere with analysis. Families should understand that rare diagnostic errors may occur for these reasons.

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**Variant Classification:**

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

Additional disease-specific references available upon request.



Patient Information	Specimen Information	Client Information
<b>10709, DONOR</b>  <b>DOB:</b> ██████ <b>AGE:</b> ████ Gender: M Phone: NG Patient ID: ██████	Specimen: CF228560G Requisition: 6384568 Lab Ref #: 22816867SPB  Collected: 09/29/2022 Received: 09/30/2022 / 21:51 EDT Reported: 10/08/2022 / 19:39 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: 22-414949  
 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

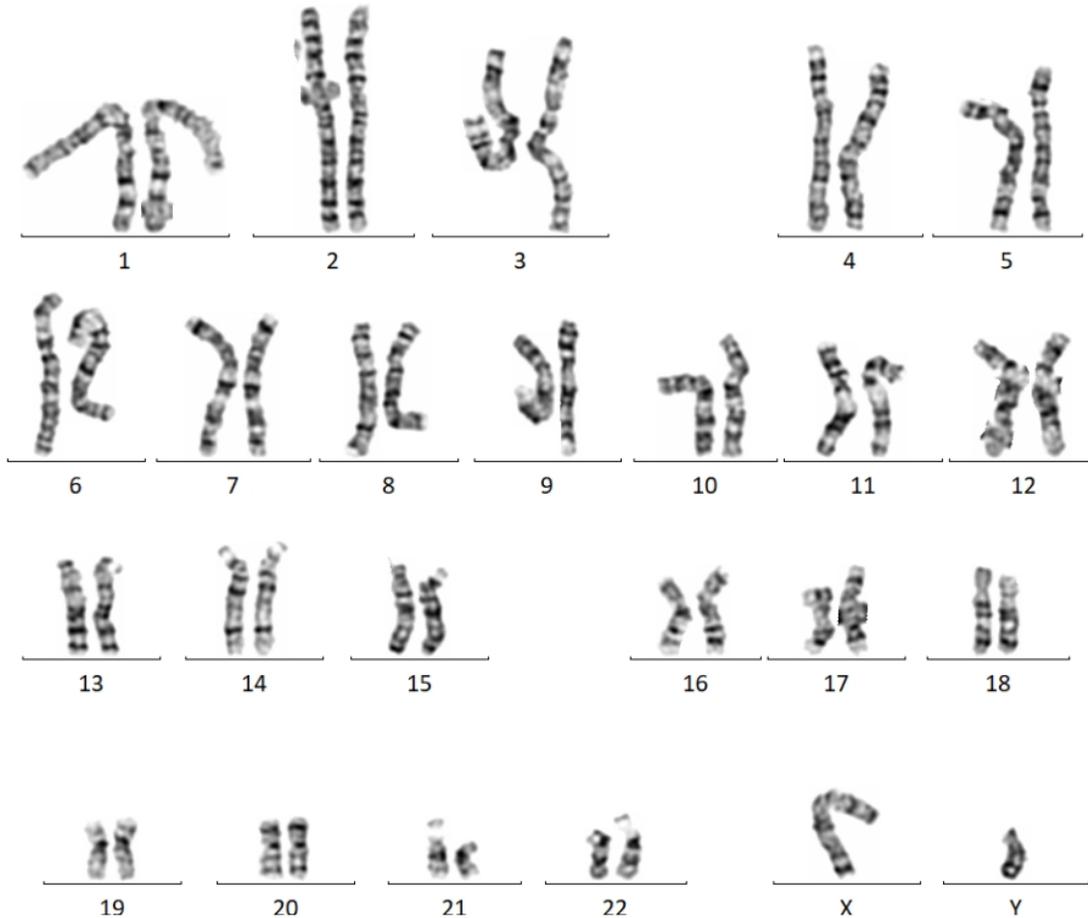
This test does not address genetic disorders that cannot be detected by standard cytogenetic methods or rare events such as low level mosaicism or subtle rearrangements.

Mark A. Micale, PhD, FACMG

Electronic Signature: 10/8/2022 6:53 PM



Patient Information	Specimen Information	Client Information
<b>10709, DONOR</b>  <b>DOB:</b> ████████ <b>AGE:</b> ████ Gender: M Patient ID: ████████	Specimen: CF228560G Collected: 09/29/2022 Received: 09/30/2022 / 21:51 EDT Reported: 10/08/2022 / 19:39 EDT	Client #: 48041578 GENOMICS, SEMA4



**PERFORMING SITE:**

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