Patient Information
Name: Donor 12946
Date of Birth: [redacted]
Sema4 ID: 22221897
Client ID: SEATSB-S451759305
Indication: Carrier Screening

Specimen Information
Specimen Type: Blood
Date Collected: 11/01/2022
Date Received: 11/02/2022
Final Report: 11/18/2022

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Expanded Carrier Screen (502 genes)

with Personalized Residual Risk

SUMMARY OF RESULTS AND RECOMMENDATIONS

⊕ Positive	⊖ Negative
Carrier of Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency (AR) Associated gene(s): *CYP21A2* Variant(s) Detected: c.841G>T, p.V281L, Pathogenic, Heterozygous (one copy) **Carrier of Methylmalonic Aciduria and Homocystinuria, Cobalamin C Type (AR)** Associated gene(s): *MMACHC* Variant(s) Detected: c.271dupA, p.R91KfsX14, Pathogenic, Heterozygous (one copy) **Carrier of Sepiapterin Reductase Deficiency (AR)** Associated gene(s): *SPR* Variant(s) Detected: c.751A>T, p.K251X, Pathogenic, Heterozygous (one copy) **Carrier of Smith-Lemli-Opitz Syndrome (AR)** Associated gene(s): *DHCR7* Variant(s) Detected: c.1228G>A, p.G410S, Pathogenic, Heterozygous (one copy)	**Negative for all other genes tested** 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. 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

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

Results and Interpretation

CYP21A2 copy number: 2
No pathogenic copy number variants detected
CYP21A2 sequencing: c.841G>T, p.V281L, Pathogenic, Heterozygous (one copy)

Genes analyzed: *CYP21A2* (NM_000500.6)

Inheritance: Autosomal Recessive

A heterozygous (one copy) pathogenic missense variant, c.841G>T, p.V281L, was detected in the *CYP21A2* gene (NM_000500.6). Please note that this variant is typically causative for the non-classic form of congenital adrenal hyperplasia (PMID: 29450859). Variants associated with the non-classic form usually cause non-classic congenital adrenal hyperplasia when found in trans with a pathogenic allele, regardless of whether the second variant is associated with classic or non-classic disease (PMID: 29450859). Therefore, this individual is expected to be at least a carrier for non-classic congenital adrenal hyperplasia. Heterozygous carriers are not expected to exhibit symptoms of this disease.

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

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

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

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

Methylmalonic Aciduria and Homocystinuria, Cobalamin C Type (AR)

Results and Interpretation

A heterozygous (one copy) pathogenic frameshift variant, c.271dupA, p.R91KfsX14, was detected in the *MMACHC* gene (NM_015506.2). When this variant is present in trans with a pathogenic variant, it is considered to be causative for methylmalonic aciduria and homocystinuria, cobalamin C type. Therefore, this individual is expected to be at least a carrier for methylmalonic aciduria and homocystinuria, cobalamin C type. Heterozygous carriers are not expected to exhibit symptoms of this disease.

What is Methylmalonic Aciduria and Homocystinuria, Cobalamin C Type?

Methylmalonic aciduria and homocystinuria, cobalamin C type is a pan-ethnic, autosomal recessive disease caused by pathogenic variants in the *MMACHC* gene. The clinical features are variable, and onset may be in infancy, childhood or adolescence. The most common presentation is during the first year of life. Affected infants are often born small and have a failure to thrive. Symptoms include lethargy, seizures and ataxia, and progressive encephalopathy. Affected infants also have characteristic facial features and may have cardiac malformations. Early-onset cases are associated with a poor prognosis and early death. Alternatively, onset may be in adolescence, where patients exhibit neuropsychiatric manifestations including psychosis and dementia. Several specific variants are associated with the development of either the early or later-onset form, but some variants do not have a known genotype-phenotype correlation.

Sepiapterin Reductase Deficiency (AR)

Results and Interpretation

A heterozygous (one copy) pathogenic premature stop codon, c.751A>T, p.K251X, was detected in the *SPR* gene (NM_003124 4). When this variant is present in trans with a pathogenic variant, it is considered to be causative for sepiapterin reductase deficiency. Therefore, this individual is expected to be at least a carrier for sepiapterin reductase deficiency. Heterozygous carriers are not expected to exhibit symptoms of this disease.

What is Sepiapterin Reductase Deficiency?

Sepiapterin reductase deficiency is an autosomal recessive disorder caused by pathogenic variants in the gene *SPR*. This disorder has infantile onset and is characterized by delayed growth, progressive psychomotor retardation, and involuntary and sustained muscle contractions, as well as muscle stiffness, tremors, oculogyric crises, ataxia, microcephaly, dystonic posture and falls, sleep disturbances, Parkinsonian features, behavioral abnormalities, and diurnal fluctuations of symptoms. The life expectancy for this disorder is currently unknown.

Smith-Lemli-Opitz Syndrome (AR)

Results and Interpretation

A heterozygous (one copy) pathogenic missense variant, c.1228G>A, p.G410S, was detected in the *DHCR7* gene (NM_001360 2). When this variant is present in trans with a pathogenic variant, it is considered to be causative for Smith-Lemli-Opitz syndrome. Therefore, this individual is expected to be at least a carrier for Smith-Lemli-Opitz syndrome. Heterozygous carriers are not expected to exhibit symptoms of this disease.

What is Smith-Lemli-Opitz Syndrome?

Smith-Lemli-Opitz syndrome is an autosomal recessive disease caused by pathogenic variants in the gene *DHCR7*. While it is a pan-ethnic disease, it is identified more frequently in people of Caucasian or Ashkenazi Jewish ancestry. Smith-Lemli-Opitz syndrome is characterized by impaired cholesterol synthesis, which results in congenital abnormalities including a small head, dysmorphic features, cleft palate, extra and/or fused fingers and toes, gastrointestinal anomalies and genital abnormalities in males. Intellectual deficits and behavioral problems, including autistic features, self-harm behaviors and hyperactivity may be present. While most patients have a severe phenotype and are identified at birth, more mildly affected patients who have been diagnosed in childhood or adolescence have been reported. It is thought that many conceptions affected with Smith-Lemli-Opitz syndrome are lost in early embryonic development, as the disease frequency is much rarer than what would be expected based on the frequency of carriers. Life expectancy varies with the severity of disease; it has been reported that approximately 25% of patients die in infancy, while others live to adulthood. A clear genotype-phenotype correlation has not been reported.

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.

Preti Jain

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

Genes and diseases tested

The personalized residual risks listed below are specific to this individual. The complete residual risk table is available at **go.sema4.com/residualrisk**

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

	Disease	Gene	Inheritance Pattern	Status	Detailed Summary
⊕	**Positive**				
	Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency	*CYP21A2*	AR	Carrier	*CYP21A2* copy number: 2 No pathogenic copy number variants detected *CYP21A2* sequencing: c.841G>T, p.V281L, Pathogenic, Heterozygous (one copy)
	Methylmalonic Aciduria and Homocystinuria, Cobalamin C Type	*MMACHC*	AR	Carrier	c.271dupA, p.R91KfsX14, Pathogenic, Heterozygous (one copy)
	Sepiapterin Reductase Deficiency	*SPR*	AR	Carrier	c.751A>T, p.K251X, Pathogenic, Heterozygous (one copy)
	Smith-Lemli-Opitz Syndrome	*DHCR7*	AR	Carrier	c.1228G>A, p.G410S, Pathogenic, Heterozygous (one copy)
⊖	**Negative**				
	2-Methylbutyrylglycinuria	*ACADSB*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 2,800
	3-Beta-Hydroxysteroid Dehydrogenase Type II Deficiency	*HSD3B2*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 3,300
	3-Methylcrotonyl-CoA Carboxylase Deficiency (*MCCC1*-Related)	*MCCC1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 3,400
	3-Methylcrotonyl-CoA Carboxylase Deficiency (*MCCC2*-Related)	*MCCC2*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,200
	3-Methylglutaconic Aciduria, Type III	*OPA3*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 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
	***WNT10A*-Related Ectodermal Dysplasia**	*WNT10A*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,900
	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 1,393,000
	Aicardi-Goutieres Syndrome (*RNASEH2C*-Related)	*RNASEH2C*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 11,000
	Aicardi-Goutieres Syndrome (*SAMHD1*-Related)	*SAMHD1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 10,000
	Aicardi-Goutieres Syndrome (*TREX1*-Related)	*TREX1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 3,200
	Albinism, Oculocutaneous, Type III	*TYRP1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 3,500
	Alkaptonuria	*HGD*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,100

Alpha-Mannosidosis	*MAN2B1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 6,200
Alpha-Thalassemia	*HBA1/HBA2*	AR	Reduced Risk	*HBA1* Copy Number: 2 *HBA2* Copy Number: 2 No pathogenic copy number variants detected *HBA1/HBA2* Sequencing: Negative **Personalized Residual Risk:** 1 in 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 1,800
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 151,000
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 454,000
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
Bardet-Biedl Syndrome (*ARL6*-Related)	*ARL6*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 29,000
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 22,000
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 740
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 **Personalized Residual Risk (Beta-Globin-Related Hemoglobinopathies: HbS Variant):** 1 in 23,000 **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 5,400
Beta-Mannosidosis	*MANBA*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 9,100
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
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 4,100
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 730,000
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
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 14,000
Congenital Disorder of Glycosylation, Type Ia	*PMM2*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 540
Congenital Disorder of Glycosylation, Type Ib	*MPI*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 5,600
Congenital Disorder of Glycosylation, Type Ic	*ALG6*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 4,100
Congenital Disorder of Glycosylation, Type Im	*DOLK*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 134,000
Congenital Dyserythropoietic Anemia Type 2	*SEC23B*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 1,000
Congenital Dyserythropoietic Anemia, Type Ia	*CDAN1*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 470
Congenital Ichthyosis 4A and 4B	*ABCA12*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 5,100
Congenital Insensitivity to Pain with Anhidrosis	*NTRK1*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 5,700
Congenital Muscular Dystrophy (*LAMA2*-Related)	*LAMA2*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 640
Congenital Myasthenic Syndrome (*CHAT*-Related)	*CHAT*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 3,100
Congenital Myasthenic Syndrome (*CHRNE*-Related)	*CHRNE*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 4,100
Congenital Myasthenic Syndrome (*DOK7*-Related)	*DOK7*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 1,200
Congenital Myasthenic Syndrome (*RAPSN*-Related)	*RAPSN*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 2,900
Congenital Neutropenia (*HAX1*-Related)	*HAX1*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 82,000
Congenital Neutropenia (*VPS45*-Related)	*VPS45*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 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 4,600
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 1,400
Desbuquois Dysplasia 1	*CANT1*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 24,000
Desmosterolosis	*DHCR24*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 27,000
Diaphanospondylodysostosis	*BMPER*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 18,000
Distal Renal Tubular Acidosis and other *SLC4A1*-related Disorders	*SLC4A1*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 4,000
Duchenne Muscular Dystrophy / Becker Muscular Dystrophy	*DMD*	XL	Reduced Risk	**Personalized Residual Risk**: 1 in 10,000
Dyskeratosis Congenita (*DKC1*-related)	*DKC1*	XL	Reduced Risk	**Personalized Residual Risk**: 1 in 9,259,000
Dyskeratosis Congenita (*RTEL1*-Related)	*RTEL1*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 9,800
Dystrophic Epidermolysis Bullosa	*COL7A1*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 900
Ehlers-Danlos Syndrome, Type VI	*PLOD1*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 20,000
Ehlers-Danlos Syndrome, Type VIIC	*ADAMTS2*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 243,000
Ellis-Van Creveld Syndrome (*EVC2*-Related)	*EVC2*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 6,300
Ellis-van Creveld Syndrome (*EVC*-Related)	*EVC*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 4,200
Emery-Dreifuss Myopathy 1	*EMD*	XL	Reduced Risk	**Personalized Residual Risk**: 1 in 833,000

Enhanced S-Cone Syndrome	*NR2E3*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,600
Ethylmalonic Encephalopathy	*ETHE1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 3,400
Fabry Disease	*GLA*	XL	Reduced Risk	**Personalized Residual Risk:** 1 in 7,700
Factor IX Deficiency	*F9*	XL	Reduced Risk	**Personalized Residual Risk:** 1 in 5,100
Factor VII Deficiency	*F7*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 450
Factor XI Deficiency	*F11*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,500
Familial Autosomal Recessive Hypercholesterolemia	*LDLRAP1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 136,000
Familial Dysautonomia	*IKBKAP*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 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 9,200
Familial Hyperinsulinism (*ABCC8*-Related)	*ABCC8*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 450
Familial Hyperinsulinism (*KCNJ11*-Related)	*KCNJ11*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 5,300
Familial Hyperphosphatemic Tumoral Calcinosis	*GALNT3*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 7,800
Familial Mediterranean Fever	*MEFV*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,200
Fanconi Anemia, Group A	*FANCA*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,100
Fanconi Anemia, Group C	*FANCC*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 12,000
Fanconi Anemia, Group G	*FANCG*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 28,000
Fanconi-Bickel Syndrome	*SLC2A2*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 4,000
Fragile X Syndrome	*FMR1*	XL	Reduced Risk	*FMR1* CGG repeat sizes: Not Performed *FMR1* Sequencing: Negative Fragile X CGG triplet repeat expansion testing was not performed at this time, as the patient has either been previously tested or is a male. **Personalized Residual Risk:** 1 in 19,000
Fructose-1,6-Bisphosphatase Deficiency	*FBP1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 2,600
Fucosidosis	*FUCA1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 9,200
Fumarase Deficiency	*FH*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 2,500
Fundus Albipunctatus	*RDH5*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 2,000
Galactokinase Deficiency	*GALK1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 2,700
Galactose Epimerase Deficiency	*GALE*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 5,600
Galactosemia	*GALT*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 3,200
Galactosialidosis	*CTSA*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 7,900
Gaucher Disease	*GBA*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,300
Generalized Thyrotropin-Releasing Hormone Resistance	*TRHR*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 104,000
Geroderma Osteodysplasticum	*GORAB*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 70,000
Gitelman Syndrome	*SLC12A3*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 290
Glanzmann Thrombasthenia (*ITGA2B*-Related)	*ITGA2B*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,800
Glanzmann Thrombasthenia (*ITGB3*-Related)	*ITGB3*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,600
Glutaric Acidemia, Type I	*GCDH*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 2,700
Glutaric Acidemia, Type IIa	*ETFA*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 4,700
Glutaric Acidemia, Type IIb	*ETFB*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 5,900
Glutaric Acidemia, Type IIc	*ETFDH*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,700
Glutathione Synthetase Deficiency	*GSS*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 3,500
Glycine Encephalopathy (*AMT*-Related)	*AMT*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 920
Glycine Encephalopathy (*GLDC*-Related)	*GLDC*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 760
Glycogen Storage Disease, Type 0	*GYS2*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,200
Glycogen Storage Disease, Type Ia	*G6PC*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 5,300
Glycogen Storage Disease, Type Ib	*SLC37A4*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 7,300
Glycogen Storage Disease, Type II	*GAA*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 520
Glycogen Storage Disease, Type III	*AGL*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 5,600

Glycogen Storage Disease, Type IV / Adult Polyglucosan Body Disease	*GBE1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 2,400
Glycogen Storage Disease, Type IXb	*PHKB*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 700
Glycogen Storage Disease, Type V	*PYGM*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,200
Glycogen Storage Disease, Type VI	*PYGL*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,600
Glycogen Storage Disease, Type VII	*PFKM*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 4,300
GM3 Synthase Deficiency	*ST3GAL5*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 25,000
GRACILE Syndrome and Other *BCS1L*-Related Disorders	*BCS1L*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 3,900
Gray Platelet Syndrome	*NBEAL2*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 6,800
Growth Hormone Deficiency, Type IB	*GHRHR*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 3,900
Hemochromatosis, Type 2A	*HFE2*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 12,000
Hemochromatosis, Type 3	*TFR2*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 11,000
Hereditary Fructose Intolerance	*ALDOB*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,900
Hereditary Spastic Paraparesis 49	*TECPR2*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 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 87,000
HMG-CoA Lyase Deficiency	*HMGCL*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 2,700
Hmg-CoA Synthase 2 Deficiency	*HMGCS2*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 2,000
Holocarboxylase Synthetase Deficiency	*HLCS*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 5,500
Homocystinuria (*CBS*-Related)	*CBS*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,400
Homocystinuria due to *MTHFR* Deficiency	*MTHFR*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,300
Homocystinuria, cblE Type	*MTRR*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 9,600
Homocystinuria-Megaloblastic Anemia, Cobalamin G Type	*MTR*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 2,100
Hydrocephalus	*L1CAM*	XL	Reduced Risk	**Personalized Residual Risk:** 1 in 40,000
Hydrolethalus Syndrome	*HYLS1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 52,000
Hyper-Igm Syndrome	*CD40LG*	XL	Reduced Risk	**Personalized Residual Risk:** 1 in 1,167,000
Hyperornithinemia-Hyperammonemia-Homocitrullinuria Syndrome	*SLC25A15*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 5,700
Hyperuricemia, Pulmonary Hypertension, Renal Failure, and Alkalosis	*SARS2*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 23,000
Hypohidrotic Ectodermal Dysplasia 1	*EDA*	XL	Reduced Risk	**Personalized Residual Risk:** 1 in 22,000
Hypomagnesemia 1	*TRPM6*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 11,000
Hypomyelinating Leukodystrophy 3	*AIMP1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 341,000
Hypomyelinating Leukodystrophy 12	*VPS11*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 72,000
Hypophosphatasia	*ALPL*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 790
Hypophosphatemic Rickets with Hypercalciuria	*SLC34A3*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,200
Hypotrichosis 8 / Autosomal Recessive Woolly Hair 1	*LPAR6*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 27,000
Immunodeficiency 18	*CD3E*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 73,000
Immunodeficiency 19	*CD3D*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 46,000
Inclusion Body Myopathy 2	*GNE*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 2,000
Infantile Cerebral and Cerebellar Atrophy	*MED17*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 129,000
Infantile Neuroaxonal Dystrophy 1 and other *PLA2G6*-Related Disorders	*PLA2G6*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 690
Intellectual Disability, Autosomal Recessive 3	*CC2D1A*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 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 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 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	*AIPL1*	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 Arthrogryposis 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 3,300
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 2,400
Methylmalonic Acidemia (*MUT*-Related)	*MUT*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,300
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 (*COX6B1*-related)	*COX6B1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,116,000
Mitochondrial Complex IV Deficiency (*APOPT1*-Related)	*APOPT1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 9,200
Mitochondrial Complex IV Deficiency (*PET100*-Related)	*PET100*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 469,000
Mitochondrial Complex IV Deficiency (*SCO1*-related)	*SCO1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 13,000
Mitochondrial Complex IV Deficiency / Leigh Syndrome (*COX10*-Related)	*COX10*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 9,200
Mitochondrial DNA Depletion Syndrome 2	*TK2*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 4,900
Mitochondrial DNA Depletion Syndrome 3	*DGUOK*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 5,200
Mitochondrial DNA Depletion Syndrome 4A and 4B and other *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 78,000
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 449,000
Mitochondrial Trifunctional Protein Deficiency (*HADHB*-Related)	*HADHB*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 3,000
Molybdenum Cofactor Deficiency A	*MOCS1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 4,700

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 9,400
Mucopolysaccharidosis Type I	*IDUA*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 3,300
Mucopolysaccharidosis Type II	*IDS*	XL	Reduced Risk	**Personalized Residual Risk:** 1 in 76,000
Mucopolysaccharidosis Type IIIA	*SGSH*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 2,700
Mucopolysaccharidosis Type IIIB	*NAGLU*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 950
Mucopolysaccharidosis Type IIIC	*HGSNAT*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 3,200
Mucopolysaccharidosis Type IIID	*GNS*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 137,000
Mucopolysaccharidosis Type IVa	*GALNS*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 690
Mucopolysaccharidosis Type IVb / GM1 Gangliosidosis	*GLB1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,700
Mucopolysaccharidosis type IX	*HYAL1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 149,000
Mucopolysaccharidosis type VI	*ARSB*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,300
Mucopolysaccharidosis VII	*GUSB*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,600
Mulibrey Nanism	*TRIM37*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 31,000
Multiple Congenital Anomalies-Hypotonia-Seizures Syndrome 1	*PIGN*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 2,800
Multiple Pterygium Syndrome	*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 2,400
Nephrogenic Diabetes insipidus (*AVPR2*-related)/ Nephrogenic Syndrome of Inappropriate Antidiuresis	*AVPR2*	XL	Reduced Risk	**Personalized Residual Risk:** 1 in 471,000
Nephrogenic Diabetes Insipidus, Type II	*AQP2*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 3,400
Nephronophthisis 2	*INVS*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 56,000
Nephrotic Syndrome (*NPHS1*-Related) / Congenital Finnish Nephrosis	*NPHS1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 920
Nephrotic Syndrome (*NPHS2*-Related) / Steroid-Resistant Nephrotic Syndrome	*NPHS2*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 780
Neurodegeneration due to Cerebral Folate Transport Deficiency	*FOLR1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 5,300
Neurodevelopmental Disorder with Progressive Microcephaly, Spasticity, and Brain Anomalies	*PLAA*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 229,000
Neuronal Ceroid-Lipofuscinosis (*CLN3*-Related)	*CLN3*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 9,200
Neuronal Ceroid-Lipofuscinosis (*CLN5*-Related)	*CLN5*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 4,300
Neuronal Ceroid-Lipofuscinosis (*CLN6*-Related)	*CLN6*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 8,600
Neuronal Ceroid-Lipofuscinosis (*CLN8*-Related)	*CLN8*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 3,100
Neuronal Ceroid-Lipofuscinosis (*MFSD8*-Related)	*MFSD8*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 6,200
Neuronal Ceroid-Lipofuscinosis (*PPT1*-Related)	*PPT1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 7,500
Neuronal Ceroid-Lipofuscinosis (*TPP1*-Related)	*TPP1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 6,300
Niemann-Pick Disease (*SMPD1*-Related)	*SMPD1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,800
Niemann-Pick Disease, Type C (*NPC1*-Related)	*NPC1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 690
Niemann-Pick Disease, Type C (*NPC2*-Related)	*NPC2*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 6,600
Nijmegen Breakage Syndrome	*NBN*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 14,000
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

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 6,400
Ornithine Transcarbamylase Deficiency	*OTC*	XL	Reduced Risk	**Personalized Residual Risk**: 1 in 103,000
Osteogenesis Imperfecta, Type XI	*FKBP10*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 9,500
Osteopetrosis 1	*TCIRG1*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 4,700
Osteopetrosis 8	*SNX10*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 16,000
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 5,300
Pontocerebellar Hypoplasia, Type 1A	*VRK1*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 25,000
Pontocerebellar Hypoplasia, Type 1B	*EXOSC3*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 10,000
Pontocerebellar Hypoplasia, Type 2A and Type 4	*TSEN54*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 4,700
Pontocerebellar Hypoplasia, Type 2E	*VPS53*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 139,000
Pontocerebellar Hypoplasia, Type 6	*RARS2*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 8,600
Primary Carnitine Deficiency	*SLC22A5*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 1,500
Primary Ciliary Dyskinesia (*CCDC103*-Related)	*CCDC103*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 27,000
Primary Ciliary Dyskinesia (*CCDC151*-Related)	*CCDC151*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 59,000
Primary Ciliary Dyskinesia (*CCDC39*-Related)	*CCDC39*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 12,000
Primary Ciliary Dyskinesia (*DNAH5*-Related)	*DNAH5*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 1,500
Primary Ciliary Dyskinesia (*DNAI1*-Related)	*DNAI1*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 5,000
Primary Ciliary Dyskinesia (*DNAI2*-Related)	*DNAI2*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 76,000
Primary Ciliary Dyskinesia (*RSPH9*-Related)	*RSPH9*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 15,000
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 5,100
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 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 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 25	*EYS*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 1,800
Retinitis Pigmentosa 26	*CERKL*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 13,000
Retinitis Pigmentosa 28	*FAM161A*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 34,000
Retinitis Pigmentosa 36	*PRCD*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 304,000
Retinitis Pigmentosa 59	*DHDDS*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 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
Sandhoff Disease	*HEXB*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 1,800
Sanjad-Sakati Syndrome	*TBCE*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 21,000
Schimke Immunoosseous Dysplasia	*SMARCAL1*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 3,800
Seckel Syndrome 5 / Microcephaly 9	*CEP152*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 1,700
Segawa Syndrome	*TH*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 6,100
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
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 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
Spondylometaepiphyseal Dysplasia (*DDR2*-Related)	*DDR2*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 236,000
Spondylothoracic Dysostosis	*MESP2*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 382,000
Steel Syndrome	*COL27A1*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 93,000
Stuve-Wiedemann Syndrome	*LIFR*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 6,000
Sulfate Transporter-Related Osteochondrodysplasia	*SLC26A2*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 1,800

Tay-Sachs Disease	*HEXA*	AR	Reduced Risk	Tay-Sachs disease enzyme: Non-carrier White blood cells: Non-carrier • Hex A%: 59.2% (Non-carrier : 55.0 - 72.0%; Carrier: <50%) • Total hexosaminidase activity: 2064 nmol/hr/mg Plasma: Non-carrier • Hex A%: 74.2 (Non-carrier : 58.0 - 72.0%; Carrier: <54%) • Total hexosaminidase activity: 458 nmol/hr/ml *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 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 910
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 14,000
Tyrosinemia, Type I	*FAH*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 1,900
Tyrosinemia, Type II	*TAT*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 4,800
Tyrosinemia, Type III	*HPD*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 15,000
Usher Syndrome, Type IB	*MYO7A*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 1,000
Usher Syndrome, Type IC	*USH1C*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 1,600
Usher Syndrome, Type ID	*CDH23*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 1,400
Usher Syndrome, Type IF	*PCDH15*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 3,800
Usher Syndrome, Type IIA	*USH2A*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 290
Usher Syndrome, Type III	*CLRN1*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 1,300
Very Long Chain Acyl-CoA Dehydrogenase Deficiency	*ACADVL*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 920
Vitamin D-Dependent Rickets, Type I	*CYP27B1*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 7,900
Vitamin D-Resistant Rickets, Type IIA	*VDR*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 17,000
Walker-Warburg Syndrome and Other *FKTN*-Related Dystrophies	*FKTN*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 4,200
Werner Syndrome	*WRN*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 9,200
Wilson Disease	*ATP7B*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 350
Wiskott-Aldrich Syndrome (*WAS*-Related)	*WAS*	XL	Reduced Risk	**Personalized Residual Risk**: 1 in 1,203,000
Wolcott-Rallison Syndrome	*EIF2AK3*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 22,000
Wolman Disease / Cholesteryl Ester Storage Disease	*LIPA*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 3,200
Woodhouse-Sakati Syndrome	*DCAF17*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 81,000
X-Linked Juvenile Retinoschisis	*RS1*	XL	Reduced Risk	**Personalized Residual Risk**: 1 in 40,000
X-Linked Severe Combined Immunodeficiency	*IL2RG*	XL	Reduced Risk	**Personalized Residual Risk**: 1 in 250,000
Xeroderma Pigmentosum (*POLH*-Related)	*POLH*	AR	Reduced Risk	**Personalized Residual Risk**: 1 in 5,900
Xeroderma Pigmentosum, Group A	*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 77,000

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

Genotyping (Analytical Detection Rate >99%)

Multiplex PCR amplification and single-base pair probe extension analyses using the Agena Bioscience iPlex Pro chemistry on a MassARRAY® System were used to identify certain recurrent variants that are complex in nature or are present in low copy repeats. Rare sequence variants may interfere with assay performance.

Multiplex Ligation-Dependent Probe Amplification (MLPA) (Analytical Detection Rate >99%)

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

For alpha thalassemia, the copy numbers of the *HBA1* and *HBA2* genes were analyzed. Alpha-globin gene deletions, duplications, and the Constant Spring (CS) mutation are assessed. This test is expected to detect approximately 90% of all alpha-thalassemia mutations, varying by ethnicity. Carriers of alpha-thalassemia with three or more *HBA* copies on one chromosome, and one or no copies on the other chromosome, may not be precisely specified without phase analysis. With the exception of duplications, other benign alpha-globin gene polymorphisms will not be reported. Analyses of *HBA1* and *HBA2* are performed in association with long-range PCR of the coding regions followed by short-read sequencing.

For Duchenne muscular dystrophy, the copy numbers of all *DMD* exons were analyzed. Potentially pathogenic single exon deletions and duplication are confirmed by a econd method Analy i of *DMD* i performed in a ociation with equencing of the coding region

For congenital adrenal hyperplasia, the copy number of the *CYP21A2* gene was analyzed. This analysis can detect large deletions typically due to unequal meiotic crossing-over between *CYP21A2* and the pseudogene *CYP21A1P*. Classic 30-kb deletions make up approximately 20% of *CYP21A2* pathogenic alleles. This test may also identify certain point mutations in *CYP21A2* caused by gene conversion events between *CYP21A2* and *CYP21A1P*. Some carriers may not be identified by dosage sensitive methods as this testing cannot detect individuals with two copies (duplication) of the *CYP21A2* gene on one chromosome and loss of *CYP21A2* (deletion) on the other chromosome. Analysis of *CYP21A2* is performed in association with long-range PCR of the coding regions followed by short-read sequencing.

For spinal muscular atrophy (SMA), the copy numbers of the *SMN1* and *SMN2* genes were analyzed. The individual dosage of exons 7 and 8 as well as the combined dosage of exons 1, 4, 6 and 8 of *SMN1* and *SMN2* were assessed. Copy number gains and losses can be detected. Depending on ethnicity, 6 - 29 % of carriers will not be identified by dosage sensitive methods as this testing cannot distinguish individuals with two copies (duplication) of the *SMN1* gene on one chromosome and loss of *SMN1* (deletion) on the other chromosome (silent 2+0 carrier) or identify intragenic mutation in *SMN1*. Please also note that 2% of individuals diagnosed with SMA have a causative *SMN1* variant that occurred de novo, therefore cannot be picked up by carrier screening in the parents. Analysis of *SMN1* is performed in association with short-read sequencing of exons 2a-7, followed by confirmation using long-range PCR (described below).

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

MLPA for Gaucher disease *(GBA)*, cystic fibrosis *(CFTR)*, and non-syndromic hearing loss *(GJB2/GJB6)* will only be performed if indicated for confirmation of detected CNVs. If *GBA* analysis was performed, the copy numbers of exons 1, 3, 4, and 6 - 10 of the GBA gene (of 11 exons total) were analyzed. If *CFTR* analysis was performed, the copy numbers of all 27 *CFTR* exons were analyzed. If *GJB2/GJB6* analysis was performed,

the copy number of the two *GJB2* exons were analyzed, as well as the presence or absence of the two upstream deletions of the *GJB2* regulatory region, del(*GJB6*-D13S1830) and del(*GJB6*-D13S1854).

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

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

Agilent SureSelect^{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 6000 platform, using paired-end 100 bp reads. The sequencing data was analyzed using a custom bioinformatics algorithm designed and validated in house.

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

Exceptions: *ABCD1* (NM_000033.3) exons 8 and 9; *ACADSB* (NM_ 001609.3) chr10:124,810,695-124,810,707 (partial exon 9); *ADA* (NM_000022 2) exon 1; *ADAMTS2* (NM_014244 4) exon 1; *AGPS* (NM_003659.3) chr2:178,257,512-178,257,649 (partial exon 1); *ALDH7A1* (NM_001182.4) chr5:125,911,150-125,911,163 (partial exon 7) and chr5:125,896,807-125,896,821 (partial exon 10); *ALMS1* (NM_015120.4) chr2:73,612,990-73,613,041 (partial exon 1); *APOPT1* (NM_ 032374.4) chr14:104,040,437-104,040,455 (partial exon 3); *CDAN1* (NM_138477.2) exon 2; *CEP152* (NM_014985.3) chr15:49,061,146-49,061,165 (partial exon 14) and exon 22; *CEP290* (NM_025114.3) exon 5, exon 7, chr12:88,519,017-88,519,039 (partial exon 13), chr12:88,514,049-88,514,058 (partial exon 15), chr12:88,502,837-88,502,841 (partial exon 23), chr12:88,481,551-88,481,589 (partial exon 32), chr12:88,471,605-88,471,700 (partial exon 40); *CFTR* (NM_000492.3) exon 10; *COL4A4* (NM_000092 4) chr2:227,942,604-227,942,619 (partial exon 25); *COX10* (NM_001303.3) exon 6; *CYP11B1* (NM_000497.3) exons 3-7; *CYP11B2* (NM_000498.3) exons 3-7; *DNAI2* (NM_023036 4) chr17:72,308,136-72,308,147 (partial exon 12); *DOK7* (NM_173660.4) chr4:3,465,131-3,465,161 (partial exon 1) and exon 2; *DUOX2* (NM_014080.4) exons 6-8; *EIF2AK3* (NM_004836.5 exon 8; *EVC* (NM_153717 2) exon 1; *F5*(NM_000130 4) chr1:169,551,662-169,551,679 (partial exon 2); *FH* (NM_000143.3) exon 1; *GAMT* (NM_000156.5 exon 1; *GLDC*(NM_000170 2) exon 1; *GNPTAB* (NM_024312 4) chr17:4,837,000-4,837,400 (partial exon 2); *GNPTG* (NM_032520 4) exon 1; *GHR* (NM_000163 4) exon 3; *GYS2* (NM_021957.3) chr12:21,699,370-21,699,409 (partial exon 12); *HGSNAT* (NM_152419.2) exon 1; *IDS* (NM_000202.6 exon 3; *ITGB4* (NM_000213 4) chr17:73,749,976-73,750,060 (partial exon 33); *JAK3* (NM_000215.3) chr19:17,950,462-17,950,483 (partial exon 10); *LIFR* (NM_002310.5 exon 19; *LMBRD1* (NM_018368.3) chr6:70,459,226-70,459,257 (partial exon 5), chr6:70,447,828-70,447,836 (partial exon 7) and exon 12; *LYST* (NM_000081.3) chr1:235,944,158-235,944,176 (partial exon 16) and chr1 235,875,350-235,875,362 (partial exon 43); *MLYCD* (NM_012213.2) chr16:83,933,242-83,933,282 (partial exon 1); *MTR* (NM_000254.2) chr1 237,024,418-237,024,439 (partial exon 20) and chr1:237,038,019-237,038,029 (partial exon 24); *NBEAL2* (NM_015175 2) chr3 47,021,385-47,021,407 (partial exon 1); *NEB* (NM_001271208.1 exons 82-105; *NPC1* (NM_000271 4) chr18:21,123,519-21,123,538 (partial exon 14); *NPHP1* (NM_000272.3)chr2:110,937,251-110,937,263 (partial exon 3); *OCRL* (NM_000276.3) chrX:128,674,450-128,674,460 (partial exon 1); *PHKB* (NM_000293 2) exon 1 and chr16:47,732,498-47,732,504 (partial exon 30); *PIGN* (NM_176787.4) chr18:59,815,547-59,815,576 (partial exon 8); *PIP5K1C* (NM_012398.2) exon 1 and chr19:3637602-3637616 (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 (CNV) Analysis (Analytical Detection Rate >98% for CNVs of 3 exons and larger, >90% for CNVs of 2 exons)

Large duplications and deletions were called from the relative read depths on an exon-by-exon basis using a custom exome hidden Markov model (XHMM) algorithm. Deletions or duplications determined to be pathogenic or likely pathogenic were confirmed by either a custom arrayCGH platform, quantitative PCR, or MLPA (depending on CNV size and gene content). While this algorithm is designed to pick up deletions and duplications of 2 or more exons in length, potentially pathogenic single-exon CNVs will be confirmed and reported, if detected. Deletions and duplications near the lower limit of detection may not be detected due to run variability. Genomic regions with high homology or highly repetitive sequences are excluded from this analysis.

Exon Array Comparative Genomic Hybridization (aCGH) (Confirmation method) (Accuracy >99%)

The customized oligonucleotide microarray (Oxford Gene Technology) is a highly-targeted exon-focused array capable of detecting medically relevant microdeletions and microduplications at a much higher resolution than traditional aCGH methods. Each array matrix has approximately 1,000,000 60-mer oligonucleotide probes that cover the entire genome. This platform is designed based on human genome NCBI Build 37 (hg19) and the CGH probes are enriched to target the exonic regions of the genes in this panel.

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

The relative quantification PCR is utilized on a Roche SYBR Green reagents on a LightCycler® 480 System, which relates the PCR signal of the target region in one group to another. To test for genomic imbalances, both sample DNA and reference DNA is amplified with primer/probe sets that specific to the target region and a control region with known genomic copy number. Relative genomic copy numbers are calculated based on the standard 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. 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 8th "unassigned" group, which were then used to select residual risk values for each gene. For individuals belonging to multiple high-level ethnic groupings, a weighting strategy was used to select the most appropriate residual risk. For genes that had insufficient data to calculate ethnic-specific residual risk values, or for sub-ethnic groupings that fell into the "unassigned" group, a "worldwide" residual risk was used. This "worldwide" residual risk was calculated using data from all available continental-level groups.

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

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

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

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

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

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

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

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Additional disease-specific references available upon request.

Patient Information	Specimen Information	Client Information
12946, DONOR **DOB:** [redacted] **AGE:** [redacted] Gender: M Phone: NG Patient ID: LP2892340	Specimen: CF796428H Requisition: 7751035 Lab Ref #: 22818447SPB Collected: 11/01/2022 Received: 11/02/2022 / 22:22 EST Reported: 11/10/2022 / 20:11 EST	Client #: 48041578 NYNJMAIL GENOMICS, SEMA4 SEMA4 62 SOUTHFIELD AVE STAMFORD, CT 06902-7229

Ward: SEATSB

Cytogenetic Report

CHROMOSOME ANALYSIS, BLOOD - 14596 Lab:EZ

CHROMOSOME ANALYSIS, BLOOD

Order ID: 22-463784
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:

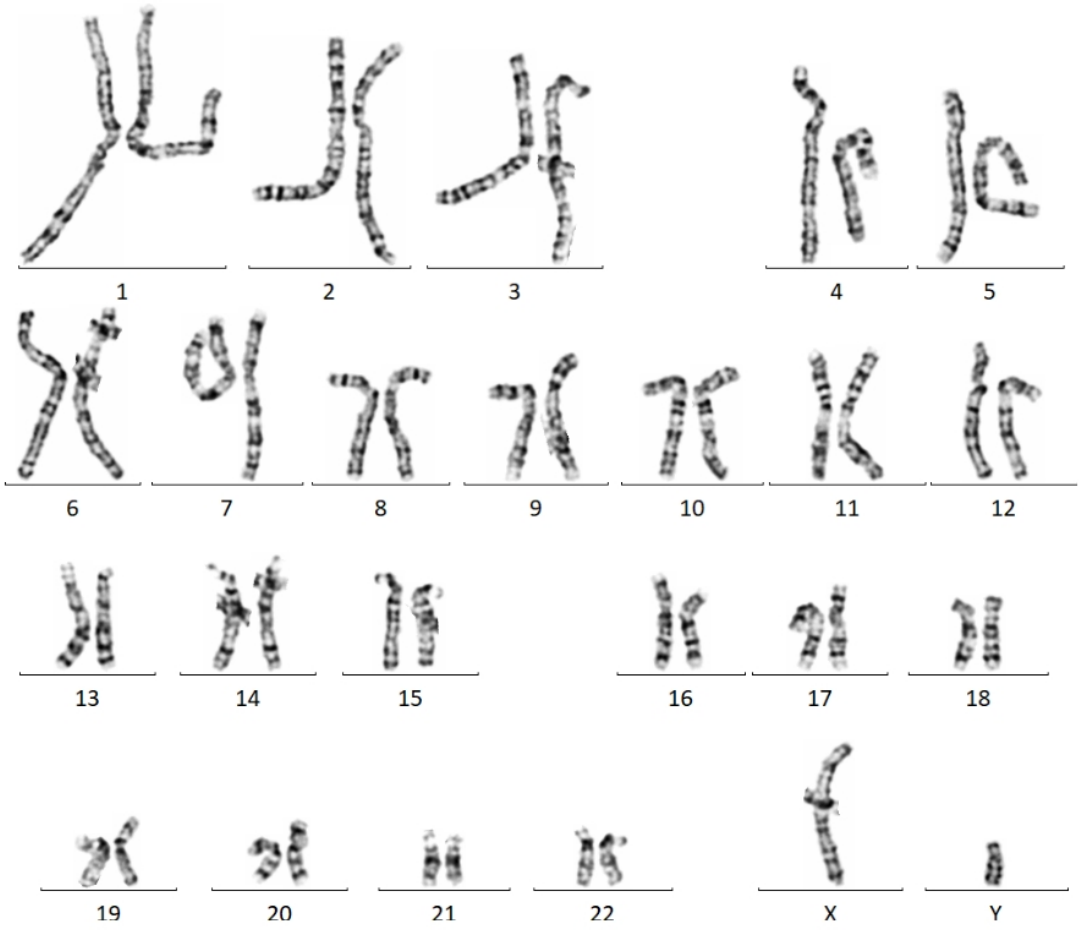
Method: G-Band (Digital Analysis: MetaSyst
Cells Counted: 20
Band Level: 450
Cells Analyzed: 5
Cells Karyotyped: 5

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.

Reha M. Toydemir, MD, PhD, FACMG

Electronic Signature: 11/10/2022 6:58 PM

Patient Information	Specimen Information	Client Information
12946, DONOR **DOB:** [redacted] **AGE:** [redacted] Gender: M Patient ID: LP2892340	Specimen: CF796428H Collected: 11/01/2022 Received: 11/02/2022 / 22:22 EST Reported: 11/10/2022 / 20:11 EST	Client #: 48041578 GENOMICS, SEMA4



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