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

Specimen Information
Specimen Type: Blood
Date Collected: 11/08/2022
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Expanded Carrier Screen (502 genes)

with Personalized Residual Risk

SUMMARY OF RESULTS AND RECOMMENDATIONS

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

WNT10A-Related Ectodermal Dysplasia (AR)

Results and Interpretation

A heterozygous (one copy) pathogenic missense variant, c.682T>A, p.F228I, was detected in the *WNT10A* gene (NM_025216.2). Please note that this variant has been associated with reduced penetrance and variable expressivity, and therefore some individuals with a pathogenic variant on the opposite allele may not exhibit any clinical symptoms (PMID:19559398). Individuals with the p.F228I variant in homozygosity or compound heterozygosity have been reported to exhibit highly variable phenotypes, with most symptomatic patients described as having isolated tooth agenesis, and a smaller fraction also exhibiting one or more additional ectodermal-related symptoms including nail dysplasia, fragile and/or sparse hair, hypohidrosis and dry skin or eczema (PMID: 34228861, 34593752, 33383702, 30046887, 28976000, 23401279, 20979233). An analysis of the reported literature suggested that of the symptomatic homozygotes reported, the majority have isolated tooth agenesis, and up to 25% may exhibit additional ectodermal features. When this variant is observed in compound heterozygosity with a second variant, up to 15% of patients that display any symptoms may exhibit features of the more severe clinical syndromes odonto-onycho-dermal dysplasia or Schopf-Schulz-Passarge syndrome. However, individuals with the same genotype, even within the same family, may display milder symptoms or be asymptomatic (PMID: 19559398, 22581971). Please note that individuals who harbor this variant are 2-3 times more likely than individuals in the general population to have hypodontia (PMID: 29364747). When this variant is present in trans with a pathogenic variant, it is considered to be causative for *WNT10A*-related ectodermal dysplasia. Therefore, this individual is expected to be at least a carrier for *WNT10A*-related ectodermal dysplasia. Approximately half of individuals with a heterozygous *WNT10A* variant have been reported to exhibit minor disease-associated symptoms, including abnormalities of several permanent teeth, dry skin, and sparse scalp hair, eyelashes, and/or eyebrows.

What is *WNT10A*-Related Ectodermal Dysplasia?

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

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

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

Cystic Fibrosis (AR)

Results and Interpretation

A heterozygous (one copy) likely pathogenic missense variant, c.3107C>T, p.T1036I, was detected in the *CFTR* gene (NM_000492.3). When this variant is present in trans with a pathogenic variant, it is considered to be causative for cystic fibrosis. Therefore, this individual is expected to be at least a carrier for cystic fibrosis. The majority of individuals heterozygous for a variant in this gene are not expected to exhibit symptoms of *CFTR*-related disorders. However, several studies suggest that carrying a heterozygous *CFTR* variant may confer an increased risk for certain health conditions including chronic or recurrent pancreatitis. Recent studies estimate the relative risk for chronic pancreatitis is approximately 5-9 times greater in heterozygous carriers compared to the general population (PMID: 31882447).

What is Cystic Fibrosis?

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

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

Mucolipidosis IV (AR)

Results and Interpretation

A heterozygous (one copy) pathogenic splice site variant, c.406-2A>G, was detected in the *MCOLN1* gene (NM_020533.2). When this variant is present in trans with a pathogenic variant, it is considered to be causative for mucolipidosis IV. Therefore, this individual is expected to be at least a carrier for mucolipidosis IV. Heterozygous carriers are not expected to exhibit symptoms of this disease.

What is Mucolipidosis IV?

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

Test description

This patient was tested for a panel of diseases using a combination of sequencing, targeted genotyping and copy number analysis. Please note that negative results reduce but do not eliminate the possibility that this individual is a carrier for one or more of the disorders tested. Please see Table 1 for a list of genes and diseases tested with the patient's personalized residual risk. If personalized residual risk is not provided, please see the complete residual risk table at **go.sema4.com/residualrisk**. 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				
***WNT10A*-Related Ectodermal Dysplasia**	*WNT10A*	AR	Carrier	c.682T>A, p.F228I, Pathogenic, Heterozygous (one copy)
Cystic Fibrosis	*CFTR*	AR	Carrier	c.3107C>T, p.T1036I, Likely Pathogenic, Heterozygous (one copy)
Mucolipidosis IV	*MCOLN1*	AR	Carrier	c.406-2A>G, 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 50,000
3-Phosphoglycerate Dehydrogenase Deficiency	*PHGDH*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 63,000
6-Pyruvoyl-Tetrahydropterin Synthase Deficiency	*PTS*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,800
***CD59*-Mediated Hemolytic Anemia**	*CD59*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 415,000
Abetalipoproteinemia	*MTTP*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 3,200
Achalasia-Addisonianism-Alacrimia Syndrome	*AAAS*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 4,500
Achromatopsia (*CNGA3*-Related)	*CNGA3*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 830
Achromatopsia (*CNGB3*-related)	*CNGB3*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 8,600
Acrodermatitis Enteropathica	*SLC39A4*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 12,000
Acute Infantile Liver Failure	*TRMU*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 9,400
Acyl-CoA Oxidase I Deficiency	*ACOX1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 39,000
Adams-Oliver Syndrome 4	*EOGT*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 44,000
Adenosine Deaminase Deficiency	*ADA*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 5,100
Adrenocorticotropic Hormone Deficiency	*TBX19*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 10,000
Adrenoleukodystrophy, X-Linked	*ABCD1*	XL	Reduced Risk	**Personalized Residual Risk:** 1 in 19,000
Agammaglobulinemia	*BTK*	XL	Reduced Risk	**Personalized Residual Risk:** 1 in 250,000
Agenesis of the Corpus Callosum	*FRMD4A*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 348,000
Aicardi-Goutieres Syndrome (*RNASEH2C*-Related)	*RNASEH2C*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 11,000
Aicardi-Goutieres Syndrome (*SAMHD1*-Related)	*SAMHD1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 10,000
Aicardi-Goutieres Syndrome (*TREX1*-Related)	*TREX1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 3,200
Albinism, Oculocutaneous, Type III	*TYRP1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 3,500
Alkaptonuria	*HGD*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,100
Alpha-Mannosidosis	*MAN2B1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 6,200

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 6,500
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 37,000
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 11,000 **Personalized Residual Risk (Beta-Globin-Related Hemoglobinopathies: HbC Variant):** 1 in 42,000
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 203,000
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 24,000
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 383,000
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 13,000
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 Hyperplasia due to 21-Hydroxylase Deficiency	*CYP21A2*	AR	Reduced Risk	*CYP21A2* copy number: 2 *CYP21A2* 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 (*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 1,200
Congenital Disorder of Deglycosylation	*NGLY1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 14,000
Congenital Disorder of Glycosylation, Type Ia	*PMM2*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 540
Congenital Disorder of Glycosylation, Type Ib	*MPI*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 5,600
Congenital Disorder of Glycosylation, Type Ic	*ALG6*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 4,100
Congenital Disorder of Glycosylation, Type Im	*DOLK*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 134,000
Congenital Dyserythropoietic Anemia Type 2	*SEC23B*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,000
Congenital Dyserythropoietic Anemia, Type Ia	*CDAN1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 470
Congenital Ichthyosis 4A and 4B	*ABCA12*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 5,100
Congenital Insensitivity to Pain with Anhidrosis	*NTRK1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 5,700
Congenital Muscular Dystrophy (*LAMA2*-Related)	*LAMA2*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 640
Congenital Myasthenic Syndrome (*CHAT*-Related)	*CHAT*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 3,100
Congenital Myasthenic Syndrome (*CHRNE*-Related)	*CHRNE*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 4,100
Congenital Myasthenic Syndrome (*DOK7*-Related)	*DOK7*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,200
Congenital Myasthenic Syndrome (*RAPSN*-Related)	*RAPSN*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 2,900
Congenital Neutropenia (*HAX1*-Related)	*HAX1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 82,000
Congenital Neutropenia (*VPS45*-Related)	*VPS45*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 43,000
Congenital Nongoitrous Hypothyroidism 1	*TSHR*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,000
Congenital Nongoitrous Hypothyroidism 4	*TSHB*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 118,000
Congenital Secretory Chloride Diarrhea 1	*SLC26A3*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 2,400
Corneal Dystrophy and Perceptive Deafness	*SLC4A11*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 4,600
Corticosterone Methyloxidase Deficiency	*CYP11B2*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,500
Cystinosis	*CTNS*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 7,700
Cystinuria (*SLC3A1*-Related)	*SLC3A1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 590
Cytochrome C Oxidase Deficiency / Leigh Syndrome (*COX15*-Related)	*COX15*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 3,300
D-Bifunctional Protein Deficiency	*HSD17B4*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 5,000
Deafness, Autosomal Recessive 3	*MYO15A*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 240
Deafness, Autosomal Recessive 59	*PJVK*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 57,000
Deafness, Autosomal Recessive 7	*TMC1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,200
Deafness, Autosomal Recessive 76	*SYNE4*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 43,000
Deafness, Autosomal Recessive 77	*LOXHD1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 6,700
Deafness, Autosomal Recessive 8/10	*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 16,000
Ellis-Van Creveld Syndrome (*EVC2*-Related)	*EVC2*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 6,300
Ellis-van Creveld Syndrome (*EVC*-Related)	*EVC*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 4,200
Emery-Dreifuss Myopathy 1	*EMD*	XL	Reduced Risk	**Personalized Residual Risk:** 1 in 833,000
Enhanced S-Cone Syndrome	*NR2E3*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,600
Ethylmalonic Encephalopathy	*ETHE1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 3,400
Fabry Disease	*GLA*	XL	Reduced Risk	**Personalized Residual Risk:** 1 in 7,700
Factor IX Deficiency	*F9*	XL	Reduced Risk	**Personalized Residual Risk:** 1 in 5,100
Factor VII Deficiency	*F7*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 450
Factor XI Deficiency	*F11*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,500
Familial Autosomal Recessive Hypercholesterolemia	*LDLRAP1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 136,000
Familial Dysautonomia	*IKBKAP*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 3,400
Familial Hypercholesterolemia	*LDLR*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 280
Familial Hyperinsulinemic Hypoglycemia 4 / 3-Hydroxyacyl-CoA Dehydrogenase Deficiency	*HADH*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 9,200
Familial Hyperinsulinism (*ABCC8*-Related)	*ABCC8*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 450
Familial Hyperinsulinism (*KCNJ11*-Related)	*KCNJ11*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 5,300
Familial Hyperphosphatemic Tumoral Calcinosis	*GALNT3*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 7,800
Familial Mediterranean Fever	*MEFV*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,200
Fanconi Anemia, Group A	*FANCA*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,100
Fanconi Anemia, Group C	*FANCC*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 12,000
Fanconi Anemia, Group G	*FANCG*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 28,000
Fanconi-Bickel Syndrome	*SLC2A2*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 4,000
Fragile X Syndrome	*FMR1*	XL	Reduced Risk	*FMR1* CGG repeat sizes: Not Performed *FMR1* Sequencing: Negative Fragile X CGG triplet repeat expansion testing was not performed at this time, as the patient has either been previously tested or is a male. **Personalized Residual Risk:** 1 in 19,000
Fructose-1,6-Bisphosphatase Deficiency	*FBP1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 2,600
Fucosidosis	*FUCA1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 9,200
Fumarase Deficiency	*FH*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 2,500
Fundus Albipunctatus	*RDH5*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 2,000
Galactokinase Deficiency	*GALK1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 2,700
Galactose Epimerase Deficiency	*GALE*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 5,600
Galactosemia	*GALT*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 3,200
Galactosialidosis	*CTSA*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 7,900
Gaucher Disease	*GBA*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 280
Generalized Thyrotropin-Releasing Hormone Resistance	*TRHR*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 104,000
Geroderma Osteodysplasticum	*GORAB*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 70,000
Gitelman Syndrome	*SLC12A3*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 290
Glanzmann Thrombasthenia (*ITGA2B*-Related)	*ITGA2B*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,800
Glanzmann Thrombasthenia (*ITGB3*-Related)	*ITGB3*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,600
Glutaric Acidemia, Type I	*GCDH*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 2,700
Glutaric Acidemia, Type IIa	*ETFA*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 4,700
Glutaric Acidemia, Type IIb	*ETFB*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 5,900
Glutaric Acidemia, Type IIc	*ETFDH*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,700
Glutathione Synthetase Deficiency	*GSS*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 3,500
Glycine Encephalopathy (*AMT*-Related)	*AMT*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 5,700
Glycine Encephalopathy (*GLDC*-Related)	*GLDC*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 760
Glycogen Storage Disease, Type 0	*GYS2*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,200

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

Intrahepatic Cholestasis	*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 14,000
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 9,000
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	*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 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 9,800
Mitochondrial Complex I Deficiency (*NDUFS6*-Related)	*NDUFS6*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 353,000
Mitochondrial Complex I Deficiency (*NDUFV1*-Related)	*NDUFV1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 870
Mitochondrial Complex I Deficiency / Leigh Syndrome (*FOXRED1*-Related)	*FOXRED1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 13,000
Mitochondrial Complex I Deficiency / Leigh Syndrome (*NDUFAF2*-Related)	*NDUFAF2*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 168,000
Mitochondrial Complex I Deficiency / Leigh Syndrome (*NDUFS4*-Related)	*NDUFS4*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 4,800
Mitochondrial Complex IV Deficiency (*COX20*-related)	*COX20*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 42,000
Mitochondrial Complex IV Deficiency (*COX6B1*-related)	*COX6B1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,116,000
Mitochondrial Complex IV Deficiency (*APOPT1*-Related)	*APOPT1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 9,200
Mitochondrial Complex IV Deficiency (*PET100*-Related)	*PET100*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 469,000
Mitochondrial Complex IV Deficiency (*SCO1*-related)	*SCO1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 13,000
Mitochondrial Complex IV Deficiency / Leigh Syndrome (*COX10*-Related)	*COX10*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 9,200
Mitochondrial DNA Depletion Syndrome 2	*TK2*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 4,900
Mitochondrial DNA Depletion Syndrome 3	*DGUOK*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 5,200

Mitochondrial DNA Depletion Syndrome 4A and 4B and other *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
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 660
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 70,000
Phenylalanine Hydroxylase Deficiency	*PAH*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 340
Polycystic Kidney Disease, Autosomal Recessive	*PKHD1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 450
Polyglandular Autoimmune Syndrome, Type 1	*AIRE*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 5,300
Pontocerebellar Hypoplasia, Type 1A	*VRK1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 25,000
Pontocerebellar Hypoplasia, Type 1B	*EXOSC3*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 10,000
Pontocerebellar Hypoplasia, Type 2A and Type 4	*TSEN54*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 4,700
Pontocerebellar Hypoplasia, Type 2E	*VPS53*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 139,000
Pontocerebellar Hypoplasia, Type 6	*RARS2*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 8,600
Primary Carnitine Deficiency	*SLC22A5*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,500
Primary Ciliary Dyskinesia (*CCDC103*-Related)	*CCDC103*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 27,000
Primary Ciliary Dyskinesia (*CCDC151*-Related)	*CCDC151*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 59,000
Primary Ciliary Dyskinesia (*CCDC39*-Related)	*CCDC39*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 12,000
Primary Ciliary Dyskinesia (*DNAH5*-Related)	*DNAH5*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,500
Primary Ciliary Dyskinesia (*DNAI1*-Related)	*DNAI1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 5,000
Primary Ciliary Dyskinesia (*DNAI2*-Related)	*DNAI2*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 8,000
Primary Ciliary Dyskinesia (*RSPH9*-Related)	*RSPH9*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 253,000
Primary Coenzyme Q10 Deficiency 7	*COQ4*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 12,000
Primary Congenital Glaucoma 3A	*CYP1B1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 880
Primary Hyperoxaluria, Type 1	*AGXT*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,900
Primary Hyperoxaluria, Type 2	*GRHPR*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 11,000
Primary Hyperoxaluria, Type 3	*HOGA1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 2,400
Progressive Cerebello-Cerebral Atrophy	*SEPSECS*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 6,400
Progressive Familial Intrahepatic Cholestasis, Type 2	*ABCB11*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 950
Progressive Myoclonic Epilepsy, Type 1B	*PRICKLE1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 98,000
Progressive Pseudorheumatoid Dysplasia	*WISP3*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 5,600
Prolidase Deficiency	*PEPD*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 30,000
Propionic Acidemia (*PCCA*-Related)	*PCCA*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 2,600

Propionic Acidemia (*PCCB*-Related)	*PCCB*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 12,000
Pulmonary Surfactant Dysfunction	*ABCA3*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,200
Pycnodysostosis	*CTSK*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 5,100
Pyridoxamine 5'-Phosphate Oxidase Deficiency	*PNPO*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 10,000
Pyridoxine-Dependent Epilepsy	*ALDH7A1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,100
Pyruvate Carboxylase Deficiency	*PC*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 8,000
Pyruvate Dehydrogenase E1-Alpha Deficiency	*PDHA1*	XL	Reduced Risk	**Personalized Residual Risk:** 1 in 139,000
Pyruvate Dehydrogenase E1-Beta Deficiency	*PDHB*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,000
Renal Tubular Acidosis and Deafness	*ATP6V1B1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 6,600
Retinitis Pigmentosa 25	*EYS*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,800
Retinitis Pigmentosa 26	*CERKL*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 13,000
Retinitis Pigmentosa 28	*FAM161A*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 34,000
Retinitis Pigmentosa 36	*PRCD*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 304,000
Retinitis Pigmentosa 59	*DHDDS*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 9,900
Retinitis Pigmentosa 64 / Bardet-Biedl Syndrome 21 / Cone-Rod Dystrophy 16	*C8ORF37*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 168,000
Rh Deficiency Syndrome	*RHAG*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 46,000
Rhizomelic Chondrodysplasia Punctata, Type 1	*PEX7*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 10,000
Rhizomelic Chondrodysplasia Punctata, Type 3	*AGPS*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 620,000
Roberts Syndrome	*ESCO2*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 139,000
Salla Disease	*SLC17A5*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 8,400
Sandhoff Disease	*HEXB*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,800
Sanjad-Sakati Syndrome	*TBCE*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 21,000
Schimke Immunoosseous Dysplasia	*SMARCAL1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 3,800
Seckel Syndrome 5 / Microcephaly 9	*CEP152*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,700
Segawa Syndrome	*TH*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 6,100
Sepiapterin Reductase Deficiency	*SPR*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 35,000
Severe Combined Immunodeficiency (*IL7R*-Related)	*IL7R*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 20,000
Severe Combined Immunodeficiency (*JAK3*-Related)	*JAK3*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 2,100
Severe Combined Immunodeficiency (*PTPRC*-Related)	*PTPRC*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 8,500
Severe Congenital Neutropenia 4	*G6PC3*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 10,000
Severe Neonatal Hyperparathyroidism	*CASR*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 2,700
Short Stature, Onychodysplasia, Facial Dysmorphism, and Hypotrichosis	*POC1A*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 108,000
Short-Chain Acyl-CoA Dehydrogenase Deficiency	*ACADS*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 660
Shwachman-Diamond Syndrome	*SBDS*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,700
Sialidosis, Type I and Type II	*NEU1*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 2,000
Sjogren-Larsson Syndrome	*ALDH3A2*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 5,500
Smith-Lemli-Opitz Syndrome	*DHCR7*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 750
Spastic Paraplegia 15	*ZFYVE26*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 46,000
Spastic Tetraplegia, Thin Corpus Callosum, and Progressive Microcephaly	*SLC1A4*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 11,000
Spherocytosis, Type 5	*EPB42*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 3,200
Spinal Muscular Atrophy	*SMN1*	AR	Reduced Risk	*SMN1* copy number: 2 *SMN2* copy number: >=3 c.*3+80T>G: Negative *SMN1* Sequencing: Negative **Personalized Residual Risk:** 1 in 1,107
Spinal Muscular Atrophy with Respiratory Distress 1 / Charcot-Marie-Tooth Disease, Type 2S	*IGHMBP2*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 1,200

Spinocerebellar Ataxia with Axonal Neuropathy 3	*COA7*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 12,000
Spondylocostal Dysostosis 1	*DLL3*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 7,200
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%: 69.2% (Non-carrier : 55.0 - 72.0%; Carrier: <50%) • Total hexosaminidase activity: 1381 nmol/hr/mg Plasma: Non-carrier • Hex A%: 71.7 (Non-carrier : 58.0 - 72.0%; Carrier: <54%) • Total hexosaminidase activity: 519 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 7,400
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 1,200
Werner Syndrome	*WRN*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 9,200
Wilson Disease	*ATP7B*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 350
Wiskott-Aldrich Syndrome (*WAS*-Related)	*WAS*	XL	Reduced Risk	**Personalized Residual Risk:** 1 in 1,203,000
Wolcott-Rallison Syndrome	*EIF2AK3*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 22,000
Wolman Disease / Cholesteryl Ester Storage Disease	*LIPA*	AR	Reduced Risk	**Personalized Residual Risk:** 1 in 3,200
Woodhouse-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 9,700
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 duplications are confirmed by a second method. Analysis of *DMD* is performed in association with sequencing of the coding regions.

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

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

de novo, therefore cannot be picked up by carrier screening in the parents. Analysis of *SMN1* is performed in association with short-read sequencing of exons 2a-7, followed by confirmation using long-range PCR (described below).

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

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

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

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

Agilent SureSelect^{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^{TM}XT Low-Input technology was utilized in order to create whole-genome libraries for each patient sample. Libraries were then pooled and sequenced on the Illumina NovaSeq platform. Each sequencing lane was multiplexed to achieve 0.4-2x genome coverage, using paired-end 100 bp reads. The sequencing data underwent ancestral analysis using a customized, licensed bioinformatics algorithm that was validated in house. Identified sub-ethnic groupings were binned into one of 7 continental-level groups (African, East Asian, South Asian, Non-Finnish European, Finnish, Native American, and Ashkenazi Jewish) or, for those ethnicities that matched poorly to the continental-level groups, an 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
16031, DONOR **DOB:** [redacted] **AGE:** [redacted] Gender: M Phone: NG Patient ID: LP2899995	Specimen: CF217648J Requisition: 8116650 Lab Ref #: 22818756SPB Collected: 11/08/2022 Received: 11/10/2022 / 22:35 EST Reported: 11/18/2022 / 01:14 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: 22-476891
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: 500
Cells Analyzed: 5
Cells Karyotyped: 5

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

Lakshmi J. Nemana, Ph.D., FACMG

Electronic Signature: 11/17/2022 11:59 PM

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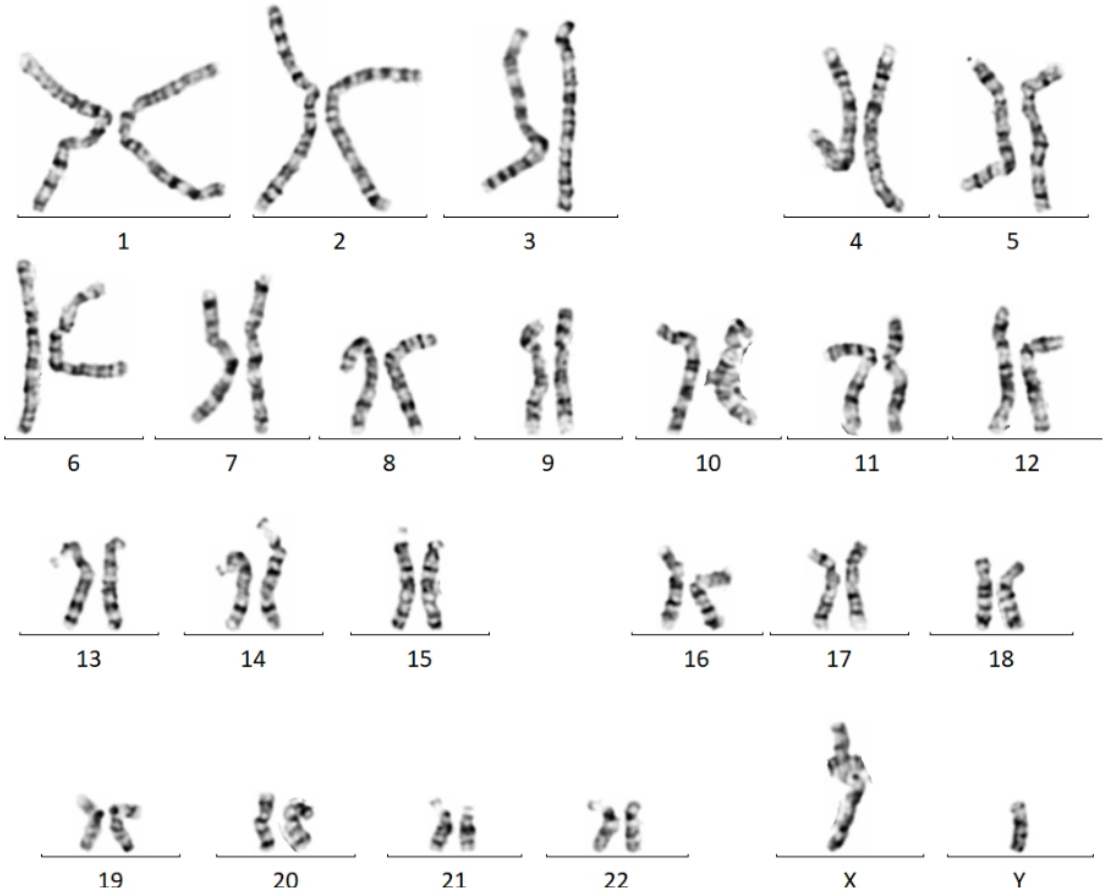
Patient Information	Specimen Information	Client Information
16031, DONOR **DOB:** [redacted] **AGE:** [redacted] Gender: M Patient ID: LP2899995	Specimen: CF217648J Collected: 11/08/2022 Received: 11/10/2022 / 22:35 EST Reported: 11/18/2022 / 01:14 EST	Client #: 48041578 GENOMICS, SEMA4



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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

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