Donor 5596

Genetic Testing Summary

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

Last Updated: 03/04/22

Donor Reported Ancestry: German, Austrian, Irish, Welsh Jewish Ancestry: No

Genetic Test*	Result	Comments/Donor's Residual Risk**
Chromosome analysis (karyotype)	Normal male karyotype	No evidence of clinically significant chromosome abnormalities
Hemoglobin evaluation	Normal hemoglobin fractionation and MCV/MCH results	Reduced risk to be a carrier for sickle cell anemia, beta thalassemia, alpha thalassemia trait (aa/-- and a-/a-) and other hemoglobinopathies
Cystic Fibrosis (CF) carrier screening	Negative by gene sequencing in the CFTR gene	1/440
Spinal Muscular Atrophy (SMA) carrier screening	Negative for deletions of exon 7 in the SMN1 gene	1/894
Expanded Genetic Disease Carrier Screening Panel attached- 283 diseases by gene sequencing	Carrier: Smith-Lemli-Opitz Syndrome (DHCR7) Negative for other genes sequenced	Partner testing recommended before using this donor.

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

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

Patient Information

Name: Donor 5596
Date of Birth: [redacted]
Sema4 ID: [redacted]
Client ID: [redacted]
Indication: Carrier Testing

Specimen Information

Specimen Type: Blood
Date Collected: 12/15/2020
Date Received: 12/16/2020
Final Report: 01/05/2021

Referring Provider

[redacted]
Fairfax Cryobank, Inc.
[redacted]

Expanded Carrier Screen (283) Minus TSE

Number of genes tested: 283

SUMMARY OF RESULTS AND RECOMMENDATIONS

⊕ Positive	⊖ Negative
Carrier of Smith-Lemli-Opitz Syndrome (AR) Associated gene(s): *DHCR7* Variant(s) Detected: c.452G>A, p.W151X, 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.

Interpretation of positive results

Smith-Lemli-Opitz Syndrome (AR)

Results and Interpretation

A heterozygous (one copy) pathogenic premature stop codon, c.452G>A, p.W151X, 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, and **go.sema4.com/residualrisk** for specific detection rates and residual risk by ethnicity. With individuals of mixed ethnicity, it is recommended to use the highest residual risk estimate. Only variants determined to be pathogenic or likely pathogenic are reported in this carrier screening test.

Anastasia Larmore, Ph.D., Associate Laboratory Director
Laboratory Medical Consultant: George A. Diaz, M.D., Ph.D.

Genes and diseases tested

For specific detection rates and residual risk by ethnicity, please visit **go.sema4.com/residualrisk**

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

	Disease	Gene	Inheritance Pattern	Status	Detailed Summary
⊕	**Positive**				
	Smith-Lemli-Opitz Syndrome	*DHCR7*	AR	Carrier	c.452G>A, p.W151X, Pathogenic, Heterozygous (one copy)
⊖	**Negative**				

3-Beta-Hydroxysteroid Dehydrogenase Type II Deficiency	*HSD3B2*	AR	Reduced Risk	
3-Methylcrotonyl-CoA Carboxylase Deficiency (*MCCC1*-Related)	*MCCC1*	AR	Reduced Risk	
3-Methylcrotonyl-CoA Carboxylase Deficiency (*MCCC2*-Related)	*MCCC2*	AR	Reduced Risk	
3-Methylglutaconic Aciduria, Type III	*OPA3*	AR	Reduced Risk	
3-Phosphoglycerate Dehydrogenase Deficiency	*PHGDH*	AR	Reduced Risk	
6-Pyruvoyl-Tetrahydropterin Synthase Deficiency	*PTS*	AR	Reduced Risk	
Abetalipoproteinemia	*MTTP*	AR	Reduced Risk	
Achromatopsia (*CNGB3*-related)	*CNGB3*	AR	Reduced Risk	
Acrodermatitis Enteropathica	*SLC39A4*	AR	Reduced Risk	
Acute Infantile Liver Failure	*TRMU*	AR	Reduced Risk	
Acyl-CoA Oxidase I Deficiency	*ACOX1*	AR	Reduced Risk	
Adenosine Deaminase Deficiency	*ADA*	AR	Reduced Risk	
Adrenoleukodystrophy, X-Linked	*ABCD1*	XL	Reduced Risk	
Aicardi-Goutieres Syndrome (*SAMHD1*-Related)	*SAMHD1*	AR	Reduced Risk	
Alpha-Mannosidosis	*MAN2B1*	AR	Reduced Risk	
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
Alpha-Thalassemia Mental Retardation Syndrome	*ATRX*	XL	Reduced Risk	
Alport Syndrome (*COL4A3*-Related)	*COL4A3*	AR	Reduced Risk	
Alport Syndrome (*COL4A4*-Related)	*COL4A4*	AR	Reduced Risk	
Alport Syndrome (*COL4A5*-Related)	*COL4A5*	XL	Reduced Risk	
Alstrom Syndrome	*ALMS1*	AR	Reduced Risk	
Andermann Syndrome	*SLC12A6*	AR	Reduced Risk	
Argininosuccinic Aciduria	*ASL*	AR	Reduced Risk	
Aromatase Deficiency	*CYP19A1*	AR	Reduced Risk	
Arthrogryposis, Mental Retardation, and Seizures	*SLC35A3*	AR	Reduced Risk	
Asparagine Synthetase Deficiency	*ASNS*	AR	Reduced Risk	
Aspartylglycosaminuria	*AGA*	AR	Reduced Risk	
Ataxia With Isolated Vitamin E Deficiency	*TTPA*	AR	Reduced Risk	
Ataxia-Telangiectasia	*ATM*	AR	Reduced Risk	
Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay	*SACS*	AR	Reduced Risk	
Bardet-Biedl Syndrome (*BBS10*-Related)	*BBS10*	AR	Reduced Risk	
Bardet-Biedl Syndrome (*BBS12*-Related)	*BBS12*	AR	Reduced Risk	
Bardet-Biedl Syndrome (*BBS1*-Related)	*BBS1*	AR	Reduced Risk	
Bardet-Biedl Syndrome (*BBS2*-Related)	*BBS2*	AR	Reduced Risk	
Bare Lymphocyte Syndrome, Type II	*CIITA*	AR	Reduced Risk	
Bartter Syndrome, Type 4A	*BSND*	AR	Reduced Risk	
Bernard-Soulier Syndrome, Type A1	*GP1BA*	AR	Reduced Risk	
Bernard-Soulier Syndrome, Type C	*GP9*	AR	Reduced Risk	
Beta-Globin-Related Hemoglobinopathies	*HBB*	AR	Reduced Risk	
Beta-Ketothiolase Deficiency	*ACAT1*	AR	Reduced Risk	
Bilateral Frontoparietal Polymicrogyria	*GPR56*	AR	Reduced Risk	
Biotinidase Deficiency	*BTD*	AR	Reduced Risk	
Bloom Syndrome	*BLM*	AR	Reduced Risk	
Canavan Disease	*ASPA*	AR	Reduced Risk	
Carbamoylphosphate Synthetase I Deficiency	*CPS1*	AR	Reduced Risk	
Carnitine Palmitoyltransferase IA Deficiency	*CPT1A*	AR	Reduced Risk	
Carnitine Palmitoyltransferase II Deficiency	*CPT2*	AR	Reduced Risk	
Carpenter Syndrome	*RAB23*	AR	Reduced Risk	
Cartilage-Hair Hypoplasia	*RMRP*	AR	Reduced Risk	
Cerebral Creatine Deficiency Syndrome 1	*SLC6A8*	XL	Reduced Risk	
Cerebral Creatine Deficiency Syndrome 2	*GAMT*	AR	Reduced Risk	
Cerebrotendinous Xanthomatosis	*CYP27A1*	AR	Reduced Risk	
Charcot-Marie-Tooth Disease, Type 4D	*NDRG1*	AR	Reduced Risk	

Charcot-Marie-Tooth Disease, Type 5 / Arts Syndrome	*PRPS1*	XL	Reduced Risk	
Charcot-Marie-Tooth Disease, X-Linked	*GJB1*	XL	Reduced Risk	
Choreoacanthocytosis	*VPS13A*	AR	Reduced Risk	
Choroideremia	*CHM*	XL	Reduced Risk	
Chronic Granulomatous Disease (*CYBA*-Related)	*CYBA*	AR	Reduced Risk	
Chronic Granulomatous Disease (*CYBB*-Related)	*CYBB*	XL	Reduced Risk	
Citrin Deficiency	*SLC25A13*	AR	Reduced Risk	
Citrullinemia, Type 1	*ASS1*	AR	Reduced Risk	
Cohen Syndrome	*VPS13B*	AR	Reduced Risk	
Combined Malonic and Methylmalonic Aciduria	*ACSF3*	AR	Reduced Risk	
Combined Oxidative Phosphorylation Deficiency 1	*GFM1*	AR	Reduced Risk	
Combined Oxidative Phosphorylation Deficiency 3	*TSFM*	AR	Reduced Risk	
Combined Pituitary Hormone Deficiency 2	*PROP1*	AR	Reduced Risk	
Combined Pituitary Hormone Deficiency 3	*LHX3*	AR	Reduced Risk	
Combined SAP Deficiency	*PSAP*	AR	Reduced Risk	
Congenital Adrenal Hyperplasia due to 17-Alpha-Hydroxylase Deficiency	*CYP17A1*	AR	Reduced Risk	
Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency	*CYP21A2*	AR	Reduced Risk	*CYP21A2* copy number: 2 *CYP21A2* sequencing: Negative
Congenital Amegakaryocytic Thrombocytopenia	*MPL*	AR	Reduced Risk	
Congenital Disorder of Glycosylation, Type Ia	*PMM2*	AR	Reduced Risk	
Congenital Disorder of Glycosylation, Type Ib	*MPI*	AR	Reduced Risk	
Congenital Disorder of Glycosylation, Type Ic	*ALG6*	AR	Reduced Risk	
Congenital Insensitivity to Pain with Anhidrosis	*NTRK1*	AR	Reduced Risk	
Congenital Myasthenic Syndrome (*CHRNE*-Related)	*CHRNE*	AR	Reduced Risk	
Congenital Myasthenic Syndrome (*RAPSN*-Related)	*RAPSN*	AR	Reduced Risk	
Congenital Neutropenia (*HAX1*-Related)	*HAX1*	AR	Reduced Risk	
Congenital Neutropenia (*VPS45*-Related)	*VPS45*	AR	Reduced Risk	
Corneal Dystrophy and Perceptive Deafness	*SLC4A11*	AR	Reduced Risk	
Corticosterone Methyloxidase Deficiency	*CYP11B2*	AR	Reduced Risk	
Cystic Fibrosis	*CFTR*	AR	Reduced Risk	
Cystinosis	*CTNS*	AR	Reduced Risk	
D-Bifunctional Protein Deficiency	*HSD17B4*	AR	Reduced Risk	
Deafness, Autosomal Recessive 77	*LOXHD1*	AR	Reduced Risk	
Duchenne Muscular Dystrophy / Becker Muscular Dystrophy	*DMD*	XL	Reduced Risk	
Dyskeratosis Congenita (*RTEL1*-Related)	*RTEL1*	AR	Reduced Risk	
Dystrophic Epidermolysis Bullosa	*COL7A1*	AR	Reduced Risk	
Ehlers-Danlos Syndrome, Type VIIC	*ADAMTS2*	AR	Reduced Risk	
Ellis-van Creveld Syndrome (*EVC*-Related)	*EVC*	AR	Reduced Risk	
Emery-Dreifuss Myopathy 1	*EMD*	XL	Reduced Risk	
Enhanced S-Cone Syndrome	*NR2E3*	AR	Reduced Risk	
Ethylmalonic Encephalopathy	*ETHE1*	AR	Reduced Risk	
Fabry Disease	*GLA*	XL	Reduced Risk	
Factor IX Deficiency	*F9*	XL	Reduced Risk	
Factor XI Deficiency	*F11*	AR	Reduced Risk	
Familial Autosomal Recessive Hypercholesterolemia	*LDLRAP1*	AR	Reduced Risk	
Familial Dysautonomia	*IKBKAP*	AR	Reduced Risk	
Familial Hypercholesterolemia	*LDLR*	AR	Reduced Risk	
Familial Hyperinsulinism (*ABCC8*-Related)	*ABCC8*	AR	Reduced Risk	
Familial Hyperinsulinism (*KCNJ11*-Related)	*KCNJ11*	AR	Reduced Risk	
Familial Mediterranean Fever	*MEFV*	AR	Reduced Risk	
Fanconi Anemia, Group A	*FANCA*	AR	Reduced Risk	
Fanconi Anemia, Group C	*FANCC*	AR	Reduced Risk	
Fanconi Anemia, Group G	*FANCG*	AR	Reduced Risk	
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.

Fumarase Deficiency	*FH*	AR	Reduced Risk
GRACILE Syndrome and Other *BCS1L*-Related Disorders	*BCS1L*	AR	Reduced Risk
Galactokinase Deficiency	*GALK1*	AR	Reduced Risk
Galactosemia	*GALT*	AR	Reduced Risk
Gaucher Disease	*GBA*	AR	Reduced Risk
Gitelman Syndrome	*SLC12A3*	AR	Reduced Risk
Glutaric Acidemia, Type I	*GCDH*	AR	Reduced Risk
Glutaric Acidemia, Type IIa	*ETFA*	AR	Reduced Risk
Glutaric Acidemia, Type IIc	*ETFDH*	AR	Reduced Risk
Glycine Encephalopathy (*AMT*-Related)	*AMT*	AR	Reduced Risk
Glycine Encephalopathy (*GLDC*-Related)	*GLDC*	AR	Reduced Risk
Glycogen Storage Disease, Type II	*GAA*	AR	Reduced Risk
Glycogen Storage Disease, Type III	*AGL*	AR	Reduced Risk
Glycogen Storage Disease, Type IV / Adult Polyglucosan Body Disease	*GBE1*	AR	Reduced Risk
Glycogen Storage Disease, Type Ia	*G6PC*	AR	Reduced Risk
Glycogen Storage Disease, Type Ib	*SLC37A4*	AR	Reduced Risk
Glycogen Storage Disease, Type V	*PYGM*	AR	Reduced Risk
Glycogen Storage Disease, Type VII	*PFKM*	AR	Reduced Risk
HMG-CoA Lyase Deficiency	*HMGCL*	AR	Reduced Risk
Hemochromatosis, Type 2A	*HFE2*	AR	Reduced Risk
Hemochromatosis, Type 3	*TFR2*	AR	Reduced Risk
Hereditary Fructose Intolerance	*ALDOB*	AR	Reduced Risk
Hereditary Spastic Paraparesis 49	*TECPR2*	AR	Reduced Risk
Hermansky-Pudlak Syndrome, Type 1	*HPS1*	AR	Reduced Risk
Hermansky-Pudlak Syndrome, Type 3	*HPS3*	AR	Reduced Risk
Holocarboxylase Synthetase Deficiency	*HLCS*	AR	Reduced Risk
Homocystinuria (*CBS*-Related)	*CBS*	AR	Reduced Risk
Homocystinuria due to *MTHFR* Deficiency	*MTHFR*	AR	Reduced Risk
Homocystinuria, cblE Type	*MTRR*	AR	Reduced Risk
Hydrolethalus Syndrome	*HYLS1*	AR	Reduced Risk
Hyperornithinemia-Hyperammonemia-Homocitrullinuria Syndrome	*SLC25A15*	AR	Reduced Risk
Hypohidrotic Ectodermal Dysplasia 1	*EDA*	XL	Reduced Risk
Hypophosphatasia	*ALPL*	AR	Reduced Risk
Inclusion Body Myopathy 2	*GNE*	AR	Reduced Risk
Infantile Cerebral and Cerebellar Atrophy	*MED17*	AR	Reduced Risk
Isovaleric Acidemia	*IVD*	AR	Reduced Risk
Joubert Syndrome 2	*TMEM216*	AR	Reduced Risk
Joubert Syndrome 7 / Meckel Syndrome 5 / COACH Syndrome	*RPGRIP1L*	AR	Reduced Risk
Junctional Epidermolysis Bullosa (*LAMA3*-Related)	*LAMA3*	AR	Reduced Risk
Junctional Epidermolysis Bullosa (*LAMB3*-Related)	*LAMB3*	AR	Reduced Risk
Junctional Epidermolysis Bullosa (*LAMC2*-Related)	*LAMC2*	AR	Reduced Risk
Krabbe Disease	*GALC*	AR	Reduced Risk
Lamellar Ichthyosis, Type 1	*TGM1*	AR	Reduced Risk
Leber Congenital Amaurosis 10 and Other CEP290-Related Ciliopathies	*CEP290*	AR	Reduced Risk
Leber Congenital Amaurosis 13	*RDH12*	AR	Reduced Risk
Leber Congenital Amaurosis 2 / Retinitis Pigmentosa 20	*RPE65*	AR	Reduced Risk
Leber Congenital Amaurosis 5	*LCA5*	AR	Reduced Risk
Leber Congenital Amaurosis 8 / Retinitis Pigmentosa 12 / Pigmented Paravenous Chorioretinal Atrophy	*CRB1*	AR	Reduced Risk
Leigh Syndrome, French-Canadian Type	*LRPPRC*	AR	Reduced Risk
Lethal Congenital Contracture Syndrome 1 / Lethal Arthrogryposis with Anterior Horn Cell Disease	*GLE1*	AR	Reduced Risk
Leukoencephalopathy with Vanishing White Matter	*EIF2B5*	AR	Reduced Risk
Limb-Girdle Muscular Dystrophy, Type 2A	*CAPN3*	AR	Reduced Risk
Limb-Girdle Muscular Dystrophy, Type 2B	*DYSF*	AR	Reduced Risk

Limb-Girdle Muscular Dystrophy, Type 2C	*SGCG*	AR	Reduced Risk
Limb-Girdle Muscular Dystrophy, Type 2D	*SGCA*	AR	Reduced Risk
Limb-Girdle Muscular Dystrophy, Type 2E	*SGCB*	AR	Reduced Risk
Limb-Girdle Muscular Dystrophy, Type 2I	*FKRP*	AR	Reduced Risk
Lipoamide Dehydrogenase Deficiency	*DLD*	AR	Reduced Risk
Lipoid Adrenal Hyperplasia	*STAR*	AR	Reduced Risk
Lipoprotein Lipase Deficiency	*LPL*	AR	Reduced Risk
Long-Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency	*HADHA*	AR	Reduced Risk
Lysinuric Protein Intolerance	*SLC7A7*	AR	Reduced Risk
Maple Syrup Urine Disease, Type 1a	*BCKDHA*	AR	Reduced Risk
Maple Syrup Urine Disease, Type 1b	*BCKDHB*	AR	Reduced Risk
Meckel 1 / Bardet-Biedl Syndrome 13	*MKS1*	AR	Reduced Risk
Medium Chain Acyl-CoA Dehydrogenase Deficiency	*ACADM*	AR	Reduced Risk
Megalencephalic Leukoencephalopathy with Subcortical Cysts	*MLC1*	AR	Reduced Risk
Menkes Disease	*ATP7A*	XL	Reduced Risk
Metachromatic Leukodystrophy	*ARSA*	AR	Reduced Risk
Methylmalonic Acidemia (*MMAA*-Related)	*MMAA*	AR	Reduced Risk
Methylmalonic Acidemia (*MMAB*-Related)	*MMAB*	AR	Reduced Risk
Methylmalonic Acidemia (*MUT*-Related)	*MUT*	AR	Reduced Risk
Methylmalonic Aciduria and Homocystinuria, Cobalamin C Type	*MMACHC*	AR	Reduced Risk
Methylmalonic Aciduria and Homocystinuria, Cobalamin D Type	*MMADHC*	AR	Reduced Risk
Microphthalmia / Anophthalmia	*VSX2*	AR	Reduced Risk
Mitochondrial Complex I Deficiency (*ACAD9*-Related)	*ACAD9*	AR	Reduced Risk
Mitochondrial Complex I Deficiency (*NDUFAF5*-Related)	*NDUFAF5*	AR	Reduced Risk
Mitochondrial Complex I Deficiency (*NDUFS6*-Related)	*NDUFS6*	AR	Reduced Risk
Mitochondrial DNA Depletion Syndrome 6 / Navajo Neurohepatopathy	*MPV17*	AR	Reduced Risk
Mitochondrial Myopathy and Sideroblastic Anemia 1	*PUS1*	AR	Reduced Risk
Mucolipidosis II / IIIA	*GNPTAB*	AR	Reduced Risk
Mucolipidosis III Gamma	*GNPTG*	AR	Reduced Risk
Mucolipidosis IV	*MCOLN1*	AR	Reduced Risk
Mucopolysaccharidosis Type I	*IDUA*	AR	Reduced Risk
Mucopolysaccharidosis Type II	*IDS*	XL	Reduced Risk
Mucopolysaccharidosis Type IIIA	*SGSH*	AR	Reduced Risk
Mucopolysaccharidosis Type IIIB	*NAGLU*	AR	Reduced Risk
Mucopolysaccharidosis Type IIIC	*HGSNAT*	AR	Reduced Risk
Mucopolysaccharidosis Type IIID	*GNS*	AR	Reduced Risk
Mucopolysaccharidosis Type IVb / GM1 Gangliosidosis	*GLB1*	AR	Reduced Risk
Mucopolysaccharidosis type IX	*HYAL1*	AR	Reduced Risk
Mucopolysaccharidosis type VI	*ARSB*	AR	Reduced Risk
Multiple Sulfatase Deficiency	*SUMF1*	AR	Reduced Risk
Muscle-Eye-Brain Disease and Other *POMGNT1*-Related Congenital Muscular Dystrophy-Dystroglycanopathies	*POMGNT1*	AR	Reduced Risk
Myoneurogastrointestinal Encephalopathy	*TYMP*	AR	Reduced Risk
Myotubular Myopathy 1	*MTM1*	XL	Reduced Risk
N-Acetylglutamate Synthase Deficiency	*NAGS*	AR	Reduced Risk
Nemaline Myopathy 2	*NEB*	AR	Reduced Risk
Nephrogenic Diabetes Insipidus, Type II	*AQP2*	AR	Reduced Risk
Nephrotic Syndrome (*NPHS1*-Related) / Congenital Finnish Nephrosis	*NPHS1*	AR	Reduced Risk
Nephrotic Syndrome (*NPHS2*-Related) / Steroid-Resistant Nephrotic Syndrome	*NPHS2*	AR	Reduced Risk
Neuronal Ceroid-Lipofuscinosis (*CLN3*-Related)	*CLN3*	AR	Reduced Risk

Neuronal Ceroid-Lipofuscinosis (*CLN5*-Related)	*CLN5*	AR	Reduced Risk	
Neuronal Ceroid-Lipofuscinosis (*CLN6*-Related)	*CLN6*	AR	Reduced Risk	
Neuronal Ceroid-Lipofuscinosis (*CLN8*-Related)	*CLN8*	AR	Reduced Risk	
Neuronal Ceroid-Lipofuscinosis (*MFSD8*-Related)	*MFSD8*	AR	Reduced Risk	
Neuronal Ceroid-Lipofuscinosis (*PPT1*-Related)	*PPT1*	AR	Reduced Risk	
Neuronal Ceroid-Lipofuscinosis (*TPP1*-Related)	*TPP1*	AR	Reduced Risk	
Niemann-Pick Disease (*SMPD1*-Related)	*SMPD1*	AR	Reduced Risk	
Niemann-Pick Disease, Type C (*NPC1*-Related)	*NPC1*	AR	Reduced Risk	
Niemann-Pick Disease, Type C (*NPC2*-Related)	*NPC2*	AR	Reduced Risk	
Nijmegen Breakage Syndrome	*NBN*	AR	Reduced Risk	
Non-Syndromic Hearing Loss (*GJB2*-Related)	*GJB2*	AR	Reduced Risk	
Odonto-Onycho-Dermal Dysplasia / Schopf-Schulz-Passarge Syndrome	*WNT10A*	AR	Reduced Risk	
Omenn Syndrome (*RAG2*-Related)	*RAG2*	AR	Reduced Risk	
Omenn Syndrome / Severe Combined Immunodeficiency, Athabaskan-Type	*DCLRE1C*	AR	Reduced Risk	
Ornithine Aminotransferase Deficiency	*OAT*	AR	Reduced Risk	
Ornithine Transcarbamylase Deficiency	*OTC*	XL	Reduced Risk	
Osteopetrosis 1	*TCIRG1*	AR	Reduced Risk	
Pendred Syndrome	*SLC26A4*	AR	Reduced Risk	
Phenylalanine Hydroxylase Deficiency	*PAH*	AR	Reduced Risk	
Polycystic Kidney Disease, Autosomal Recessive	*PKHD1*	AR	Reduced Risk	
Polyglandular Autoimmune Syndrome, Type 1	*AIRE*	AR	Reduced Risk	
Pontocerebellar Hypoplasia, Type 1A	*VRK1*	AR	Reduced Risk	
Pontocerebellar Hypoplasia, Type 6	*RARS2*	AR	Reduced Risk	
Primary Carnitine Deficiency	*SLC22A5*	AR	Reduced Risk	
Primary Ciliary Dyskinesia (*DNAH5*-Related)	*DNAH5*	AR	Reduced Risk	
Primary Ciliary Dyskinesia (*DNAI1*-Related)	*DNAI1*	AR	Reduced Risk	
Primary Ciliary Dyskinesia (*DNAI2*-Related)	*DNAI2*	AR	Reduced Risk	
Primary Hyperoxaluria, Type 1	*AGXT*	AR	Reduced Risk	
Primary Hyperoxaluria, Type 2	*GRHPR*	AR	Reduced Risk	
Primary Hyperoxaluria, Type 3	*HOGA1*	AR	Reduced Risk	
Progressive Cerebello-Cerebral Atrophy	*SEPSECS*	AR	Reduced Risk	
Progressive Familial Intrahepatic Cholestasis, Type 2	*ABCB11*	AR	Reduced Risk	
Propionic Acidemia (*PCCA*-Related)	*PCCA*	AR	Reduced Risk	
Propionic Acidemia (*PCCB*-Related)	*PCCB*	AR	Reduced Risk	
Pycnodysostosis	*CTSK*	AR	Reduced Risk	
Pyruvate Dehydrogenase E1-Alpha Deficiency	*PDHA1*	XL	Reduced Risk	
Pyruvate Dehydrogenase E1-Beta Deficiency	*PDHB*	AR	Reduced Risk	
Renal Tubular Acidosis and Deafness	*ATP6V1B1*	AR	Reduced Risk	
Retinitis Pigmentosa 25	*EYS*	AR	Reduced Risk	
Retinitis Pigmentosa 26	*CERKL*	AR	Reduced Risk	
Retinitis Pigmentosa 28	*FAM161A*	AR	Reduced Risk	
Retinitis Pigmentosa 59	*DHDDS*	AR	Reduced Risk	
Rhizomelic Chondrodysplasia Punctata, Type 1	*PEX7*	AR	Reduced Risk	
Rhizomelic Chondrodysplasia Punctata, Type 3	*AGPS*	AR	Reduced Risk	
Roberts Syndrome	*ESCO2*	AR	Reduced Risk	
Salla Disease	*SLC17A5*	AR	Reduced Risk	
Sandhoff Disease	*HEXB*	AR	Reduced Risk	
Schimke Immunoosseous Dysplasia	*SMARCAL1*	AR	Reduced Risk	
Segawa Syndrome	*TH*	AR	Reduced Risk	
Sjogren-Larsson Syndrome	*ALDH3A2*	AR	Reduced Risk	
Spinal Muscular Atrophy	*SMN1*	AR	Reduced Risk	*SMN1* copy number: 2 *SMN2* copy number: 1 c.*3+80T>G: Negative
Spondylothoracic Dysostosis	*MESP2*	AR	Reduced Risk	
Steel Syndrome	*COL27A1*	AR	Reduced Risk	
Stuve-Wiedemann Syndrome	*LIFR*	AR	Reduced Risk	
Sulfate Transporter-Related Osteochondrodysplasia	*SLC26A2*	AR	Reduced Risk	
Tay-Sachs Disease	*HEXA*	AR	Reduced Risk	

Tyrosinemia, Type I	*FAH*	AR	Reduced Risk
Usher Syndrome, Type IB	*MYO7A*	AR	Reduced Risk
Usher Syndrome, Type IC	*USH1C*	AR	Reduced Risk
Usher Syndrome, Type ID	*CDH23*	AR	Reduced Risk
Usher Syndrome, Type IF	*PCDH15*	AR	Reduced Risk
Usher Syndrome, Type IIA	*USH2A*	AR	Reduced Risk
Usher Syndrome, Type III	*CLRN1*	AR	Reduced Risk
Very Long Chain Acyl-CoA Dehydrogenase Deficiency	*ACADVL*	AR	Reduced Risk
Walker-Warburg Syndrome and Other *FKTN*-Related Dystrophies	*FKTN*	AR	Reduced Risk
Wilson Disease	*ATP7B*	AR	Reduced Risk
Wolman Disease / Cholesteryl Ester Storage Disease	*LIPA*	AR	Reduced Risk
X-Linked Juvenile Retinoschisis	*RS1*	XL	Reduced Risk
X-Linked Severe Combined Immunodeficiency	*IL2RG*	XL	Reduced Risk
Zellweger Syndrome Spectrum (*PEX10*-Related)	*PEX10*	AR	Reduced Risk
Zellweger Syndrome Spectrum (*PEX1*-Related)	*PEX1*	AR	Reduced Risk
Zellweger Syndrome Spectrum (*PEX2*-Related)	*PEX2*	AR	Reduced Risk
Zellweger Syndrome Spectrum (*PEX6*-Related)	*PEX6*	AR	Reduced Risk

AR=Autosomal recessive; XL=X-linked

Test methods and comments

Genomic DNA isolated from this patient was analyzed by one or more of the following methodologies, as applicable:

Fragile X CGG Repeat Analysis (Analytical Detection Rate >99%)

PCR amplification using Asuragen, Inc. AmplideX® *FMR1* PCR reagents followed by capillary electrophoresis for allele sizing was performed. Samples positive for *FMR1* CGG repeats in the premutation and full mutation size range were further analyzed by Southern blot analysis to assess the size and methylation status of the *FMR1* CGG repeat.

Genotyping (Analytical Detection Rate >99%)

Multiplex PCR amplification and allele specific primer extension analyses using the MassARRAY® System were used to identify certain recurrent variants that are complex in nature or are present in low copy repeats. Rare sequence variants may interfere with assay performance.

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

MLPA® probe sets and reagents from MRC-Holland were used for copy number analysis of specific targets versus known control samples. False positive or negative results may occur due to rare sequence variants in target regions detected by MLPA probes. Analytical sensitivity and specificity of the MLPA method are both 99%.

For alpha thalassemia, the copy numbers of the *HBA1* and *HBA2* genes were analyzed. Alpha-globin gene deletions, triplications, and the Constant Spring (CS) mutation are assessed. This test is expected to detect approximately 90% of all alpha-thalassemia mutations, varying by ethnicity. carriers of alpha-thalassemia with three or more *HBA* copies on one chromosome, and one or no copies on the other chromosome, may not be detected. With the exception of triplications, other benign alpha-globin gene polymorphisms will not be reported. Analyses of *HBA1* and *HBA2* are performed in association with long-range PCR of the coding regions followed by short-read sequencing.

For Duchenne muscular dystrophy, the copy numbers of all *DMD* exons were analyzed. Potentially pathogenic single exon deletions and duplications are confirmed by a second method. Analysis of *DMD* is performed in association with sequencing of the coding regions.

For congenital adrenal hyperplasia, the copy number of the *CYP21A2* gene was analyzed. This analysis can detect large deletions typically due to unequal meiotic crossing-over between *CYP21A2* and the pseudogene *CYP21A1P*. Classic 30-kb deletions make up approximately 20% of *CYP21A2* pathogenic alleles. This test may also identify certain point mutations in *CYP21A2* caused by gene conversion events between *CYP21A2* and *CYP21A1P*. Some carriers may not be identified by dosage sensitive methods as this testing cannot detect individuals with two

copies (duplication) of the *CYP21A2* gene on one chromosome and loss of *CYP21A2* (deletion) on the other chromosome. Analysis of *CYP21A2* is performed in association with long-range PCR of the coding regions followed by short-read sequencing.

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

The presence of the c.*3+80T>G (chr5:70,247,901T>G) variant allele in an individual with Ashkenazi Jewish or Asian ancestry is typically indicative of a duplication of *SMN1*. When present in an Ashkenazi Jewish or Asian individual with two copies of *SMN1*, c.*3+80T>G is likely indicative of a silent (2+0) carrier. In individuals with two copies of *SMN1* with African American, Hispanic or Caucasian ancestry, the presence or absence of c.*3+80T>G significantly increases or decreases, respectively, the likelihood of being a silent 2+0 silent carrier.

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

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

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

Agilent SureSelect^{TM}XT Low Input technology was used with a custom capture library to target the exonic regions and intron/exon splice junctions of the relevant genes, as well as a number of UTR, intronic or promoter regions that contain previously reported mutations. Libraries were pooled and sequenced on the Illumina NovaSeq 9000 platform, using paired-end 100 bp reads. The sequencing data was analyzed using a custom bioinformatics algorithm designed and validated in house.

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

Exceptions: *ABCD1* (NM_000033.3) exons 8 and 9; *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); *ALMS1* (NM_015120.4) chr2:73,612,990 - 73,613,041 (partial exon 1); *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); *CYP11B2* (NM_000498.3) exons 3 - 7; *DNAI2* (NM_023036.4) chr17:72,308,136 - 72,308,147 (partial exon 12); *EVC* (NM_153717.2) exon 1; *FH* (NM_000143.3) exon 1; *GAMT* (NM_000156.5 exon 1; *GLDC* (NM_000170.2) exon 1; *GNPTAB* (NM_024312.4) chr17:4,837,000 - 4,837,400 (partial exon 2); *GNPTG* (NM_032520.4) exon 1; *HGSNAT* (NM_152419.2) exon 1; *IDS* (NM_000202.6) exon 3; *LIFR* (NM_002310.5) exon 19; *NEB* (NM_001271208.1) exons 82 - 105; *NPC1* (NM_000271.4) chr18:21,123,519 - 21,123,538 (partial exon 14); *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.

This test will detect variants within the exons and the intron-exon boundaries of the target regions. Variants outside these regions may not be detected, including, but not limited to, UTRs, promoters, and deep intronic areas, or regions that fall into the Exceptions mentioned above. This technology may not detect all small insertion/deletions and is not diagnostic for repeat expansions and structural genomic variation. In addition, a mutation(s) in a gene not included on the panel could be present in this patient.

Variant interpretation and classification was performed based on the American College of Medical Genetics Standards and Guidelines for the Interpretation of Sequence Variants (Richards et al, 2015). All potentially pathogenic variants may be confirmed by either a specific genotyping assay or Sanger sequencing, if indicated. Any benign variants, likely benign variants or variants of uncertain significance identified during this analysis will not be reported.

Next Generation Sequencing for SMN1

Exonic regions and intron/exon splice junctions of *SMN1* and *SMN2* were captured, sequenced, and analyzed as described above. Any variants located within exons 2a-7 and classified as pathogenic or likely pathogenic were confirmed to be in either *SMN1* or *SMN2* using gene-specific long-range PCR analysis followed by Sanger sequencing. Variants located in exon 1 cannot be accurately assigned to either *SMN1* or *SMN2* using our current methodology, and so these variants are considered to be of uncertain significance and are not reported.

Copy Number Variant Analysis (Analytical Detection Rate >95%)

Large duplications and deletions were called from the relative read depths on an exon-by-exon basis using a custom exome hidden Markov model (XHMM) algorithm. Deletions or duplications determined to be pathogenic or likely pathogenic were confirmed by either a custom arrayCGH platform, quantitative PCR, or MLPA (depending on CNV size and gene content). While this algorithm is designed to pick up deletions and duplications of 2 or more exons in length, potentially pathogenic single-exon CNVs will be confirmed and reported, if detected.

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

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

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

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

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

Long-range PCR was performed to generate locus-specific amplicons for *CYP21A2*, *HBA1* and *HBA2* and *GBA*. The PCR products were then prepared for short-read NGS sequencing and sequenced. Sequenced reads were mapped back to the original genomic locus and run through the bioinformatics pipeline. If indicated, copy number from MLPA was correlated with the sequencing output to analyze the results. For *CYP21A2*, a certain percentage of healthy individuals carry a duplication of the *CYP21A2* gene, which has no clinical consequences. In cases where two copies of a gene are located on the same chromosome in tandem, only the second copy will be amplified and assessed for potentially pathogenic variants, due to size limitations of the PCR reaction. However, because these alleles contain at least two copies of the *CYP21A2* gene in tandem, it is expected that this patient has at least one functional gene in the tandem allele and this patient is therefore less likely to be a carrier. When an individual carries both a duplication allele and a pathogenic variant, or multiple pathogenic variants, the current analysis may not be able to determine the phase (cis/trans configuration) of the *CYP21A2* alleles identified. Family studies may be required in certain scenarios where phasing is required to determine the carrier status.

Residual Risk Calculations

Carrier frequencies and detection rates for each ethnicity were calculated trough 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.

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.

Please note these tests were developed and their performance characteristics were determined by Mount Sinai Genomics, Inc. They have not been cleared or approved by the FDA. These analyses generally provide highly accurate information regarding the patient's carrier or affected status. Despite this high level of accuracy, it should be kept in mind that there are many potential sources of diagnostic error, including misidentification of samples, polymorphisms, or other rare genetic variants that interfere with analysis. Families should understand that rare diagnostic errors may occur for these reasons.

SELECTED REFERENCES

Carrier Screening

Grody W et al. ACMG position statement on prenatal/preconception expanded carrier screening. *Genet Med.* 2013 15:482-3.

Fragile X syndrome:

Chen L et al. An information-rich CGG repeat primed PCR that detects the full range of Fragile X expanded alleles and minimizes the need for Southern blot analysis. *J Mol Diag* 2010 12:589-600.

Spinal Muscular Atrophy:

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

Ashkenazi Jewish Disorders:

Scott SA et al. Experience with carrier screening and prenatal diagnosis for sixteen Ashkenazi Jewish Genetic Diseases. *Hum. Mutat.* 2010 31:1-11.

Duchenne Muscular Dystrophy:

Flanigan KM et al. Mutational spectrum of DMD mutations in dystrophinopathy patients: application of modern diagnostic techniques to a large cohort. *Hum Mutat.* 2009 30:1657-66.

Variant Classification:

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

Additional disease-specific references available upon request.