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Genetic Testing Summary

Enclosed are the genetic testing results for

CB 497

No amount of genetic testing can guarantee that a child will not be affected with a genetic condition. Genetic testing can inform you of the likelihood of passing on the genetic conditions that are tested for, but it cannot eliminate the risk of passing on any genetic condition.

The genetic conditions Cryobio tests for are inherited in an autosomal recessive manner. This means that the child would have to inherit a genetic mutation from both the sperm source and the egg source to be affected with the condition. When both the sperm source and the egg source have undergone genetic carrier screening and the test results are negative, the risk of a child being affected with the conditions tested for is significantly reduced, but it cannot be completely eliminated.

All recipients should discuss both or their own risk for passing on genetic conditions and whether would benefit from genetic counseling and testing with their health care provider. Before using a donor that is a carrier for a specific recessive genetic condition or conditions, we strongly recommend that the recipient (or egg source, if different) consider genetic counseling and testing to determine if they are a carrier for the same genetic condition or conditions as the donor.

Screening and testing have changed dramatically over the years, and so the screening and testing done on each donor may very depending on the testing that was in place when he was actively in Cryobio's donor program. Earlier donors may not have had as extensive testing as later donors. Screening and testing may change again in the future, so please review the results each time before ordering as both the testing done and the results may change.

Patient Information
Name: Cb 497
Date of Birth: [redacted]
Sema4 ID: [redacted]
Client ID: [redacted]
Indication: Carrier Testing

Specimen Information
Specimen Type: Blood
Date Collected: [redacted]
Date Received: [redacted]
Final Report: [redacted]

Referring Provider
David Prescott, M.D.
Cryobiology, Inc.
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Columbus, OH, 43214
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Expanded Carrier Screen (283)

Number of genes tested: 283

SUMMARY OF RESULTS AND RECOMMENDATIONS

⊕ Positive	⊖ Negative
Carrier of Congenital Disorder of Glycosylation, Type Ia (AR) Associated gene(s): *PMM2* Variant(s) Detected: c.422G>A, p.R141H, 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

Congenital Disorder of Glycosylation, Type Ia (AR)

Results and Interpretation

A heterozygous (one copy) pathogenic missense variant, c.422G>A, p.R141H, was detected in the *PMM2* gene (NM_000303 2). When this variant is present in trans with a pathogenic variant, it is considered to be causative for congenital disorder of glycosylation, type Ia. Therefore, this individual is expected to be at least a carrier for congenital disorder of glycosylation, type Ia. Heterozygous carriers are not expected to exhibit symptoms of this disease.

What is Congenital Disorder of Glycosylation, Type Ia?

Congenital disorder of glycosylation, type Ia is an autosomal recessive syndrome caused by pathogenic variants in the gene *PMM2* . While patients have been reported from multiple ethnicities, this disease is more common in the Ashkenazi Jewish and Caucasian populations. This disease may present in infancy, childhood or adolescence, and the clinical manifestations are highly variable. In infants, the disease may present as failure to thrive as a result of feeding problems; later, the disease may manifest as encephalopathy, hypotonia, delayed language and motor development, intellectual disability, stroke-like episodes, and retinitis pigmentosa. Severely affected individuals may die in early childhood, but more mildly affected individuals may survive into adulthood with variable intellectual disability, spinal abnormalities, endocrine dysfunction and coagulopathy. Several specific variants have been associated with milder or more severe disease, and therefore the disease severity may be predicted in some patients.

Test description

This patient was tested for a panel of diseases using a combination of sequencing, targeted genotyping and copy number analysis. Please note that negative results reduce but do not eliminate the possibility that this individual is a carrier for one or more of the disorders tested. Please see Table 1 for a list of genes and diseases tested, 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.

Wanqiong Qiao Ph.D. Assistant Lab 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**				
Congenital Disorder of Glycosylation, Type Ia	*PMM2*	AR	Carrier	c.422G>A, p.R141H, 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 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 Transcarbomylase 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
Smith-Lemli-Opitz Syndrome	*DHCR7*	AR	Reduced Risk

Spinal Muscular Atrophy	*SMN1*	AR	Reduced Risk	*SMN1* copy number: 2 *SMN2* copy number: 2 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	Tay-Sachs disease enzyme: Non-carrier White blood cells: Non-carrier • Hex A%: 60.1% (Non-carrier : 55.0 - 72.0%; Carrier: <50%) • Total hexosaminidase activity: 1559 nmol/hr/mg Plasma: Non-carrier • Hex A%: 66.0 (Non-carrier : 58.0 - 72.0%; Carrier: <54%) • Total hexosaminidase activity: 730 nmol/hr/mL *HEXA* Sequencing: Negative
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 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 due to unequal meiotic crossing-over between *CYP21A2* and the pseudogene *CYP21A1P* . These 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 with SMA have an *SMN1* mutation that occurred *de novo* . Typically in these cases, only one parent is an SMA carrier.

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.

Pathogenic or likely pathogenic sequence variants in exon 7 may be detected during testing for the c.*3+80T>G variant allele; these will be reported if confirmed to be located in SMN1 using locus-specific Sanger primers

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}QXT 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. Samples were pooled and sequenced on the Illumina HiSeq 2500 platform in the Rapid Run mode or the Illumina NovaSeq platform in the Xp workflow, using 100 bp paired-end 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. The exons contained within these regions are noted within Table 1 (as "Exceptions") and 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.

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.

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 through the combination of internal curations of >28,000 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.

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

Please note these tests were developed and their performance characteristics were determined by 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.

5 Integrated
fJ GENETICS
LabCorp Specialty Testing Group

Cystic Fibrosis Mutation Analysis

Patient Name: GB 497..
,-.ferring Physician: David Prescott, MD
Jcimen #:
Patient ID: [redacted]

Client #: [redacted]
Case #: [redacted]

DOB: -
Sex:M
SSN:-

Date Collected: [redacted]
Date Received:
LABID:
Hospital ID:
Specimen Type: BLDPER

[redacted]
Cryoblology, Inc.
4830-D Knightsbridge Boulevard
Columbus, OH 43214

Ethnicity: Ashkenazi Jewish

Indication: Carrier Test/ Gamete donor

RESULTS: Negative for the 97 mutations analyzed

INTERPRETATION:

This individual is negative for the mutations analyzed. This result reduces but does not eliminate the risk to be a CF carrier. See Comments for ethnic-specific risk reductions based on a negative family history.

COMMENTS:

Mutations Detection Ratn among Ethnic; Group — Detection Rates are based on mutation f19quencies In patients affected with cystic fibrosis. Among indivlduala with an atypical or mlld presentation (e.g. congenllal absence of the vas deferens, pancreatitis) detection rates may vary from tt,ose provided here.

Icily	Carrier rlak reduction when no family hlatory	Detection rate	ReferencH
African American	1/61 to 11316	81%	ACOG Committee Opinion 486 PMID: 21422883; Helm PMID: 11388766
Ashkenazl Jewish	1/24 to 1/767	97%	ACOG CommKtee Opinion 466 PMID: 21422883
Asian American	1/94 to <1/183	49-55%	ACOG Committee Opinion 486 PMIO: 21422883; Watson PMID: 1384328
Caucasian	1125 lo 11343	93%	ACOO Commtttee Opinion 486 PMIO: 21422883; Helm PMIO: 11388766; Palomaki PMIO: 11682786
Hispanic	1/58 to 1/260	78%	ACOG Committee Opinion 488 PMIO: 21422883; Heim PMID: 11388756; catifomla Database: (http://WWW,cdph.ca.gov/programs/GDSP/Documents/CFTabelCurrent.pdf)
Jawlsh, non•Ashkenazi		Varies by country of origin	Orgad PMID: 11336401; Kerem PMID:10464623
Mixed or Other		Not Provided	For counseling, consider using the ethnic background with the most conservative risk estimates.

This interpretation is based on the clinical and family relationship information provided and the current understanding of the molecular genetics of this condition.

METHOD/ LIMITATIONS:

CFTR gene regions are amplified enzymatically. The 97 CF mutations are tested by multiplex allele-specific primer extension, bead array hybridization, and fluorescence detection. The test discriminates between p.F608del and three polymorphisms (p.1S06V, p.1507V and p.F508C). Numbering and nomenclature follow Human Genome Variation Society recommendations. Mutations and their legacy names are listed at www.integratedgenetics.com/CFplus. The DNA reference sequence Is NG_O16465.1. False positive or negative results may occur for reasons that Include genetic variants, blood transfusions, bone marrow transplantation, erroneous representation of family relationships, or maternal contamination of a fetal sample.

Integrated Genetics Is a bullnen unit of Eaoterlx Genetle Laboratorlea, LLC, a wholly-owned 1Ub81dary of Laboratory Corporation of America Holdings.

Electronically Signed By: Lynne S Rosenblum, Ph.D., FACMG, on -

Counsyl

RESULTS RECIPIENT
CRYOBIOLOGY, INC.
Attn: Dr. David Prescott
4830-D Knightsbridge Blvd.
Columbus, OH 43214
Phone: (614) 451-4375
Fax: (614) 451-5284
NPI: [redacted]
Report Date: [redacted]

MALE
CB 497
DOB: [redacted]
Ethnicity: Ashkenazi Jewish
Sample Type: EDTA Blood
Date of Collection: [redacted]
Date Received: [redacted]
Date Tested: [redacted]
Barcode: [redacted]
Indication: Egg or sperm donor

FEMALE
N/A

Foresight™ Carrier Screen

NEGATIVE

ABOUT THIS TEST

The **Counsyl Foresight Carrier Screen** utilizes sequencing, maximizing coverage across all DNA regions tested, to help you learn about your chance to have a child with a genetic disease.

RESULTS SUMMARY

Risk Details	CB 497	Partner
Panel Information	Foresight Carrier Screen Ashkenazi Jewish Panel **(19 conditions tested)**	N/A
All conditions tested A complete list of all conditions tested can be found on page 4.	⊖ **NEGATIVE** No disease-causing mutations were detected.	N/A

CLINICAL NOTES

- None

NEXT STEPS

- If necessary, patients can discuss residual risks with their physician or a genetic counselor.

Counsyl has renamed its products effective July 19, 2017. The Family Prep Screen is now the Foresight Carrier Screen. The new names now appear on all communications from Counsyl. If you have any questions, please contact Counsyl directly.

Methods and Limitations

CB 497 [Foresight Carrier Screen]: sequencing with copy number analysis, spinal muscular atrophy, and analysis of homologous regions.

Sequencing with copy number analysis

High-throughput sequencing and read depth-based copy number analysis are used to analyze the listed exons, as well as selected intergenic and intronic regions, of the genes in the Conditions Tested section of the report. The region of interest (ROI) of the test comprises these regions, in addition to the 20 intronic bases flanking each exon. In a minority of cases where genomic features (e.g., long homopolymers) compromise calling fidelity, the affected intronic bases are not included in the ROI. The ROI is sequenced to high coverage and the sequences are compared to standards and references of normal variation. More than 99% of all bases in the ROI are sequenced at greater than the minimum read depth. Mutations may not be detected in areas of lower sequence coverage. Small insertions and deletions may not be as accurately determined as single nucleotide variants. Genes that have closely related pseudogenes may be addressed by a different method. *CFTR* and *DMD* testing includes analysis for both large (exon-level) deletions and duplications with an average sensitivity of 99%, while other genes are only analyzed for large deletions with a sensitivity of >75%. However, the sensitivity may be higher for selected founder deletions. If *GJB2* is tested, two large upstream deletions which overlap *GJB6* and affect the expression of *GJB2*, del(*GJB6*-D13S1830) and del(*GJB6*-D13S1854), are also analyzed. Mosaicism or somatic variants present at low levels may not be detected. If detected, these may not be reported.

Detection rates are determined by using literature to estimate the fraction of disease alleles, weighted by frequency, that the methodology is unable to detect. Detection rates only account for analytical sensitivity and certain variants that have been previously described in the literature may not be reported if there is insufficient evidence for pathogenicity. Detection rates do not account for the disease-specific rates of de novo mutations.

All variants that are a recognized cause of the disease will be reported. In addition, variants that have not previously been established as a recognized cause of disease may be identified. In these cases, only variants classified as "likely" pathogenic are reported. Likely pathogenic variants are described elsewhere in the report as "likely to have a negative impact on gene function". Likely pathogenic variants are evaluated and classified by assessing the nature of the variant and reviewing reports of allele frequencies in cases and controls, functional studies, variant annotation and effect prediction, and segregation studies. Exon level duplications are assumed to be in tandem and are classified according to their predicted effect on the reading frame. Benign variants, variants of uncertain significance, and variants not directly associated with the intended disease phenotype are not reported. Curation summaries of reported variants are available upon request.

Spinal muscular atrophy

Targeted copy number analysis is used to determine the copy number of exon 7 of the *SMN1* gene relative to other genes. Other mutations may interfere with this analysis. Some individuals with two copies of *SMN1* are carriers with two *SMN1* genes on one chromosome and a *SMN1* deletion on the other chromosome. This is more likely in individuals who have 2 copies of the *SMN1* gene and are positive for the g.27134T>G SNP, which affects the reported residual risk; Ashkenazi Jewish or Asian patients with this genotype have a high post-test likelihood of being carriers for SMA and are reported as carriers. The g.27134T>G SNP is only reported in individuals who have 2 copies of *SMN1*.

Analysis of homologous regions

A combination of high-throughput sequencing, read depth-based copy number analysis, and targeted genotyping is used to determine the number of functional gene copies and/or the presence of selected loss of function mutations in certain genes that have homology to other regions. The precise breakpoints of large deletions in these genes cannot be determined, but are estimated from copy number analysis. High numbers of pseudogene copies may interfere with this analysis.

If *CYP21A2* is tested, patients who have one or more additional copies of the *CYP21A2* gene and a loss of function mutation may not actually be a carrier of 21-hydroxylase-deficient congenital adrenal hyperplasia (CAH). Because the true incidence of non-classic CAH is unknown, the residual carrier and reproductive risk numbers on the report are only based on published incidences for classic CAH. However, the published prevalence of non-classic CAH is highest in individuals of Ashkenazi Jewish, Hispanic, Italian, and Yugoslav descent. Therefore, the residual and reproductive risks are likely an underestimate of overall chances for 21-hydroxylase-deficient CAH, especially in the aforementioned populations, as they do not account for non-classic CAH. If *HBA1/HBA2* are tested, some individuals with four alpha globin genes may be carriers, with three genes on one chromosome and a deletion on the other chromosome. This and similar, but rare, carrier states, where complementary changes exist in both the gene and a pseudogene, may not be detected by the assay.

Limitations

In an unknown number of cases, nearby genetic variants may interfere with mutation detection. Other possible sources of diagnostic error include sample mix-up, trace contamination, bone marrow transplantation, blood transfusions and technical errors. This test is designed to detect and report germline alterations. While somatic variants present at low levels may be detected, these may not be reported. If more than one variant is detected in a gene, additional studies may be necessary to determine if those variants lie on the same chromosome or different chromosomes. The test does not fully address all inherited forms of intellectual disability, birth defects and genetic disease. A family history of any of these conditions may warrant additional evaluation. Furthermore, not all mutations will be identified in the genes analyzed and additional testing may be beneficial for some patients. For example, individuals of African, Southeast Asian, and Mediterranean ancestry are at increased risk for being carriers for hemoglobinopathies, which can be identified by CBC and hemoglobin electrophoresis or HPLC (*ACOG Practice Bulletin No. 78. Obstet.Gynecol. 2007;109:229-37*).

This test was developed and its performance characteristics determined by Counsyl, Inc. It has not been cleared or approved by the US Food and Drug Administration (FDA). The FDA does not require this test to go through premarket 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 of 1988 (CLIA) as qualified to perform high-complexity clinical testing. These results are adjunctive to the ordering physician's evaluation. CLIA Number: **#05D1102604**.

LAB DIRECTORS

Hyunseok Kang

H. Peter Kang, MD, MS, FCAP

Conditions Tested

ABCC8-related Hyperinsulinism - Gene: ABCC8. Autosomal Recessive. Sequencing with Copy Number Analysis. **Exons:** NM_000352:1-39. **Detection Rate:** Ashkenazi Jewish >99%.

Bloom Syndrome - Gene: BLM. Autosomal Recessive. Sequencing with Copy Number Analysis. **Exons:** NM_000057:2-22. **Detection Rate:** Ashkenazi Jewish >99%.

Canavan Disease - Gene: ASPA. Autosomal Recessive. Sequencing with Copy Number Analysis. **Exons:** NM_000049:1-6. **Detection Rate:** Ashkenazi Jewish 98%.

Cystic Fibrosis - Gene: CFTR. Autosomal Recessive. Sequencing with Copy Number Analysis. **Exons:** NM_000492:1-27. IVS8-5T allele analysis is only reported in the presence of the R117H mutation. **Detection Rate:** Ashkenazi Jewish >99%.

Familial Dysautonomia - Gene: IKBKAP. Autosomal Recessive. Sequencing with Copy Number Analysis. **Exons:** NM_003640:2-37. **Detection Rate:** Ashkenazi Jewish >99%.

Fanconi Anemia Type C - Gene: FANCC. Autosomal Recessive. Sequencing with Copy Number Analysis. **Exons:** NM_000136:2-15. **Detection Rate:** Ashkenazi Jewish >99%.

FKTN-related Disorders - Gene: FKTN. Autosomal Recessive. Sequencing with Copy Number Analysis. **Exons:** NM_001079802:3-11. **Detection Rate:** Ashkenazi Jewish >99%.

Gaucher Disease - Gene: GBA. Autosomal Recessive. Analysis of Homologous Regions. **Variants (10):** D409V, D448H, IVS2+1G>A, L444P, N370S, R463C, R463H, R496H, V394L, p.L29Afs*18. **Detection Rate:** Ashkenazi Jewish 95%.

Glycogen Storage Disease Type Ia - Gene: G6PC. Autosomal Recessive. Sequencing with Copy Number Analysis. **Exons:** NM_000151:1-5. **Detection Rate:** Ashkenazi Jewish >99%.

Hexosaminidase A Deficiency (Including Tay-Sachs Disease) - Gene: HEXA. Autosomal Recessive. Sequencing with Copy Number Analysis. **Exons:** NM_000520:1-14. **Detection Rate:** Ashkenazi Jewish >99%.

Joubert Syndrome 2 - Gene: TMEM216. Autosomal Recessive. Sequencing with Copy Number Analysis. **Exons:** NM_001173990:1-5. **Detection Rate:** Ashkenazi Jewish >99%.

Lipoamide Dehydrogenase Deficiency - Gene: DLD. Autosomal Recessive. Sequencing with Copy Number Analysis. **Exons:** NM_000108:1-14. **Detection Rate:** Ashkenazi Jewish >99%.

Maple Syrup Urine Disease Type 1B - Gene: BCKDHB. Autosomal Recessive. Sequencing with Copy Number Analysis. **Exons:** NM_183050:1-10. **Detection Rate:** Ashkenazi Jewish >99%.

Mucolipidosis IV - Gene: MCOLN1. Autosomal Recessive. Sequencing with Copy Number Analysis. **Exons:** NM_020533:1-14. **Detection Rate:** Ashkenazi Jewish >99%.

NEB-related Nemaline Myopathy - Gene: NEB. Autosomal Recessive. Sequencing with Copy Number Analysis. **Exons:** NM_001271208:3-80,117-183. **Detection Rate:** Ashkenazi Jewish >99%.

Niemann-Pick Disease, SMPD1-associated - Gene: SMPD1. Autosomal Recessive. Sequencing with Copy Number Analysis. **Exons:** NM_000543:1-6. **Detection Rate:** Ashkenazi Jewish >99%.

PCDH15-related Disorders - Gene: PCDH15. Autosomal Recessive. Sequencing with Copy Number Analysis. **Exons:** NM_033056:2-33. **Detection Rate:** Ashkenazi Jewish 93%.

Spinal Muscular Atrophy - Gene: SMN1. Autosomal Recessive. Spinal Muscular Atrophy. **Variant (1):** SMN1 copy number. **Detection Rate:** Ashkenazi Jewish 94%.

Usher Syndrome Type 3 - Gene: CLRN1. Autosomal Recessive. Sequencing with Copy Number Analysis. **Exons:** NM_174878:1-3. **Detection Rate:** Ashkenazi Jewish >99%.

Counsyl

RESULTS RECIPIENT
CRYOBIOLOGY, INC.
Attn: Dr. David Prescott
NPI: [redacted]
Report Date: [redacted]

MALE
CB 497
DOB: [redacted]
Ethnicity: Ashkenazi Jewish
Barcode: [redacted]

FEMALE
N/A

Risk Calculations

Below are the risk calculations for all conditions tested. Since negative results do not completely rule out the possibility of being a carrier, the **residual risk** represents the patient's post-test likelihood of being a carrier and the **reproductive risk** represents the likelihood the patient's future children could inherit each disease. These risks are inherent to all carrier screening tests, may vary by ethnicity, are predicated on a negative family history and are present even after a negative test result. Inaccurate reporting of ethnicity may cause errors in risk calculation. The reproductive risk presented is based on a hypothetical pairing with a partner of the same ethnic group.

Disease	CB 497 Residual Risk	Reproductive Risk
ABCC8-related Hyperinsulinism	1 in 6,700	< 1 in 1,000,000
Bloom Syndrome	1 in 11,000	< 1 in 1,000,000
Canavan Disease	1 in 3,300	1 in 720,000
Cystic Fibrosis	1 in 2,700	1 in 290,000
Familial Dysautonomia	1 in 3,000	1 in 370,000
Fanconi Anemia Type C	1 in 8,900	< 1 in 1,000,000
FKTN-related Disorders	1 in 15,000	< 1 in 1,000,000
Gaucher Disease	1 in 310	1 in 19,000
Glycogen Storage Disease Type Ia	1 in 7,000	< 1 in 1,000,000
Hexosaminidase A Deficiency (Including Tay-Sachs Disease)	1 in 3,000	1 in 350,000
Joubert Syndrome 2	1 in 9,100	< 1 in 1,000,000
Lipoamide Dehydrogenase Deficiency	1 in 9,300	< 1 in 1,000,000
Maple Syrup Urine Disease Type 1B	1 in 9,600	< 1 in 1,000,000
Mucolipidosis IV	1 in 10,000	< 1 in 1,000,000
NEB-related Nemaline Myopathy	1 in 11,000	< 1 in 1,000,000
Niemann-Pick Disease, SMPD1-associated	1 in 10,000	< 1 in 1,000,000
PCDH15-related Disorders	1 in 2,000	< 1 in 1,000,000
Spinal Muscular Atrophy	Negative for g.27134T>G SNP SMN1: 2 copies	1 in 94,000
Usher Syndrome Type 3	1 in 580 1 in 12,000	< 1 in 1,000,000

BAYLOR GENETICS

www.bmgl.com | genetictest@bmgl.com
Ph 1-800-411-4363 I Fx 713-798-2787
2450 Holcombe Blvd, Houston, TX 77021

Name: DONOR CB 497
Date of birth: [redacted]
Gender: M
Hospital/MR #:
Accession #:
Sample Type: BLOOD
Test Code: 8600
Indication: Sperm Donor

Lab Number:
Family #:
Date Collected:
Date Received:
Date Reported:
[redacted]

Sendouts-Cryobiology
Cryobiology
Tel. No.: 614-451-4375
Fax No: 614-451-5284
CC: Prescott David Fax # 614-451-5284

Chromosome Analysis - Blood

METHOD OF ANALYSIS:
GTG-Banding

[redacted]

Cultures:	2	***No. of images:***	7
Cells counted:	30	***Cells karyotyped:***	3
Cells analyzed:	5	***Band resolution:***	550

RESULTS:
46,XY

INTERPRETATION :
Normal male chromosome analysis. Analysis of 30 cells rules out 10% mosaicism at the 95% confidence level.

DISCLAIMER:
The resolution of analysis for this standard cytogenetic methodology does not routinely detect subtle rearrangements (<5Mb) or low-level mosaicism. Standard cytogenetic analysis cannot detect microdeletions/microduplications that might be diagnosed with Chromosomal Microarray Analysis. These results do not rule out the possibility of genetic conditions not detectable by cytogenetic analysis. Depending upon the clinical indication, additional testing may be warranted.

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Medical Director

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Assistant Laboratory Director