



## Donor 6715

### Genetic Testing Summary

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

Last Updated: 08/22/22

Donor Reported Ancestry: Italian, German

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: Usher Syndrome, Type ID (CDH23)  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 6715  
 Date of Birth: [REDACTED]  
 Sema4 [REDACTED]  
 Client ID: [REDACTED]  
 Indication: Carrier Testing

**Specimen Information**

Specimen Type: Blood  
 Date Collected: 06/08/2021  
 Date Received: 06/09/2021  
 Final Report: 06/23/2021

**Referring Provider**

[REDACTED]  
 Fairfax Cryobank, Inc.  
 [REDACTED]  
 [REDACTED]

## Expanded Carrier Screen (283) Minus TSE

Number of genes tested: 283

### SUMMARY OF RESULTS AND RECOMMENDATIONS

⊕ Positive	⊖ Negative
<p><b>Carrier of Usher Syndrome, Type ID (AR)</b>            Associated gene(s): <i>CDH23</i>            Variant(s) Detected: c.5237G&gt;A, p.R1746Q, Pathogenic,            Heterozygous (one copy)</p>	<p><b>Negative for all other genes tested</b>            To view a full list of genes and diseases tested            please see Table 1 in this report</p>

AR=Autosomal recessive; XL=X-linked

### Recommendations

- Testing the partner for the above positive disorder(s) and genetic counseling are recommended.
- Please note that for female carriers of X-linked diseases, follow-up testing of a male partner is not indicated.
- CGG repeat analysis of *FMR1* for fragile X syndrome is not performed on males as repeat expansion of premutation alleles is not expected in the male germline.
- Individuals of Asian, African, Hispanic and Mediterranean ancestry should also be screened for hemoglobinopathies by CBC and hemoglobin electrophoresis.
- Consideration of residual risk by ethnicity after a negative carrier screen is recommended for the other diseases on the panel, especially in the case of a positive family history for a specific disorder.

## Interpretation of positive results

### Usher Syndrome, Type ID (AR)

#### Results and Interpretation

A heterozygous (one copy) pathogenic missense variant, c.5237G>A, p.R1746Q, was detected in the *CDH23* gene (NM\_022124.5). When this variant is present in trans with a pathogenic variant, it is considered to be causative for Usher syndrome type ID. Therefore, this individual is expected to be at least a carrier for Usher syndrome type ID. Heterozygous carriers are not expected to exhibit symptoms of this disease.

#### What is Usher Syndrome, Type ID?

Usher syndrome type ID is an autosomal recessive, pan-ethnic disease caused by pathogenic variants in the gene *CDH23*. The disease is characterized by congenital bilateral sensorineural deafness, which may be treated by cochlear implants; hearing aids do not help. Progressive loss of vision due to retinitis pigmentosa begins in childhood. Retinitis pigmentosa first presents with night blindness, but progresses to tunnel vision and eventually blindness. Patients also have problems with their balance and therefore experience developmental delay. Some patients with missense variants, rather than null variants, may manifest only with deafness; however, it is not currently possible to predict a patient's phenotype based on genotype. Life expectancy is not reduced.



## 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](https://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.

**Xingwu Lu, Ph.D., FACMG, 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](https://go.sema4.com/residualrisk)

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

Disease	Gene	Inheritance Pattern	Status	Detailed Summary
<b>⊕ Positive</b>				
Usher Syndrome, Type ID	CDH23	AR	Carrier	c.5237G>A, p.R1746Q, Pathogenic, Heterozygous (one copy)
<b>⊖ Negative</b>				
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 Intellectual Disability 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	<i>HBB</i>	AR	Reduced Risk
Beta-Ketothiolase Deficiency	<i>ACAT1</i>	AR	Reduced Risk
Bilateral Frontoparietal Polymicrogyria	<i>GPR56</i>	AR	Reduced Risk
Biotinidase Deficiency	<i>BTD</i>	AR	Reduced Risk
Bloom Syndrome	<i>BLM</i>	AR	Reduced Risk
Canavan Disease	<i>ASPA</i>	AR	Reduced Risk
Carbamoylphosphate Synthetase I Deficiency	<i>CPS1</i>	AR	Reduced Risk
Carnitine Palmitoyltransferase IA Deficiency	<i>CPT1A</i>	AR	Reduced Risk
Carnitine Palmitoyltransferase II Deficiency	<i>CPT2</i>	AR	Reduced Risk
Carpenter Syndrome	<i>RAB23</i>	AR	Reduced Risk
Cartilage-Hair Hypoplasia	<i>RMRP</i>	AR	Reduced Risk
Cerebral Creatine Deficiency Syndrome 1	<i>SLC6A8</i>	XL	Reduced Risk
Cerebral Creatine Deficiency Syndrome 2	<i>GAMT</i>	AR	Reduced Risk
Cerebrotendinous Xanthomatosis	<i>CYP27A1</i>	AR	Reduced Risk
Charcot-Marie-Tooth Disease, Type 4D	<i>NDRG1</i>	AR	Reduced Risk
Charcot-Marie-Tooth Disease, Type 5 / Arts Syndrome	<i>PRPS1</i>	XL	Reduced Risk
Charcot-Marie-Tooth Disease, X-Linked	<i>GJB1</i>	XL	Reduced Risk
Choreoacanthocytosis	<i>VPS13A</i>	AR	Reduced Risk
Choroideremia	<i>CHM</i>	XL	Reduced Risk
Chronic Granulomatous Disease (CYBA-Related)	<i>CYBA</i>	AR	Reduced Risk
Chronic Granulomatous Disease (CYBB-Related)	<i>CYBB</i>	XL	Reduced Risk
Citrin Deficiency	<i>SLC25A13</i>	AR	Reduced Risk
Citrullinemia, Type 1	<i>ASS1</i>	AR	Reduced Risk
Cohen Syndrome	<i>VPS13B</i>	AR	Reduced Risk
Combined Malonic and Methylmalonic Aciduria	<i>ACSF3</i>	AR	Reduced Risk
Combined Oxidative Phosphorylation Deficiency 1	<i>GFM1</i>	AR	Reduced Risk
Combined Oxidative Phosphorylation Deficiency 3	<i>TSFM</i>	AR	Reduced Risk
Combined Pituitary Hormone Deficiency 2	<i>PROP1</i>	AR	Reduced Risk
Combined Pituitary Hormone Deficiency 3	<i>LHX3</i>	AR	Reduced Risk
Combined SAP Deficiency	<i>PSAP</i>	AR	Reduced Risk
Congenital Adrenal Hyperplasia due to 17-Alpha-Hydroxylase Deficiency	<i>CYP17A1</i>	AR	Reduced Risk
Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency	<i>CYP21A2</i>	AR	Reduced Risk <i>CYP21A2</i> copy number: 2 <i>CYP21A2</i> sequencing: Negative
Congenital Amegakaryocytic Thrombocytopenia	<i>MPL</i>	AR	Reduced Risk
Congenital Disorder of Glycosylation, Type Ia	<i>PMM2</i>	AR	Reduced Risk
Congenital Disorder of Glycosylation, Type Ib	<i>MPI</i>	AR	Reduced Risk
Congenital Disorder of Glycosylation, Type Ic	<i>ALG6</i>	AR	Reduced Risk
Congenital Insensitivity to Pain with Anhidrosis	<i>NTRK1</i>	AR	Reduced Risk
Congenital Myasthenic Syndrome (CHRNE-Related)	<i>CHRNE</i>	AR	Reduced Risk
Congenital Myasthenic Syndrome (RAPSN-Related)	<i>RAPSN</i>	AR	Reduced Risk
Congenital Neutropenia (HAX1-Related)	<i>HAX1</i>	AR	Reduced Risk
Congenital Neutropenia (VPS45-Related)	<i>VPS45</i>	AR	Reduced Risk
Corneal Dystrophy and Perceptive Deafness	<i>SLC4A11</i>	AR	Reduced Risk
Corticosterone Methyloxidase Deficiency	<i>CYP11B2</i>	AR	Reduced Risk
Cystic Fibrosis	<i>CFTR</i>	AR	Reduced Risk
Cystinosis	<i>CTNS</i>	AR	Reduced Risk
D-Bifunctional Protein Deficiency	<i>HSD17B4</i>	AR	Reduced Risk
Deafness, Autosomal Recessive 77	<i>LOXHD1</i>	AR	Reduced Risk
Duchenne Muscular Dystrophy / Becker Muscular Dystrophy	<i>DMD</i>	XL	Reduced Risk
Dyskeratosis Congenita (RTEL1-Related)	<i>RTEL1</i>	AR	Reduced Risk
Dystrophic Epidermolysis Bullosa	<i>COL7A1</i>	AR	Reduced Risk
Ehlers-Danlos Syndrome, Type VIIC	<i>ADAMTS2</i>	AR	Reduced Risk
Ellis-van Creveld Syndrome (EVC-Related)	<i>EVC</i>	AR	Reduced Risk
Emery-Dreifuss Myopathy 1	<i>EMD</i>	XL	Reduced Risk
Enhanced S-Cone Syndrome	<i>NR2E3</i>	AR	Reduced Risk
Ethylmalonic Encephalopathy	<i>ETHE1</i>	AR	Reduced Risk
Fabry Disease	<i>GLA</i>	XL	Reduced Risk

Factor IX Deficiency	<i>F9</i>	XL	Reduced Risk	
Factor XI Deficiency	<i>F11</i>	AR	Reduced Risk	
Familial Autosomal Recessive Hypercholesterolemia	<i>LDLRAP1</i>	AR	Reduced Risk	
Familial Dysautonomia	<i>IKBKAP</i>	AR	Reduced Risk	
Familial Hypercholesterolemia	<i>LDLR</i>	AR	Reduced Risk	
Familial Hyperinsulinism (ABCC8-Related)	<i>ABCC8</i>	AR	Reduced Risk	
Familial Hyperinsulinism (KCNJ11-Related)	<i>KCNJ11</i>	AR	Reduced Risk	
Familial Mediterranean Fever	<i>MEFV</i>	AR	Reduced Risk	
Fanconi Anemia, Group A	<i>FANCA</i>	AR	Reduced Risk	
Fanconi Anemia, Group C	<i>FANCC</i>	AR	Reduced Risk	
Fanconi Anemia, Group G	<i>FANCG</i>	AR	Reduced Risk	
Fragile X Syndrome	<i>FMR1</i>	XL	Reduced Risk	<i>FMR1</i> CGG repeat sizes: Not Performed <i>FMR1</i> Sequencing: Negative Fragile X CGG triplet repeat expansion testing was not performed at this time, as the patient has either been previously tested or is a male.
Fumarase Deficiency	<i>FH</i>	AR	Reduced Risk	
GRACILE Syndrome and Other <i>BCS1L</i> -Related Disorders	<i>BCS1L</i>	AR	Reduced Risk	
Galactokinase Deficiency	<i>GALK1</i>	AR	Reduced Risk	
Galactosemia	<i>GALT</i>	AR	Reduced Risk	
Gaucher Disease	<i>GBA</i>	AR	Reduced Risk	
Gitelman Syndrome	<i>SLC12A3</i>	AR	Reduced Risk	
Glutaric Acidemia, Type I	<i>GCDH</i>	AR	Reduced Risk	
Glutaric Acidemia, Type IIa	<i>ETFA</i>	AR	Reduced Risk	
Glutaric Acidemia, Type IIc	<i>ETFDH</i>	AR	Reduced Risk	
Glycine Encephalopathy (AMT-Related)	<i>AMT</i>	AR	Reduced Risk	
Glycine Encephalopathy (GLDC-Related)	<i>GLDC</i>	AR	Reduced Risk	
Glycogen Storage Disease, Type II	<i>GAA</i>	AR	Reduced Risk	
Glycogen Storage Disease, Type III	<i>AGL</i>	AR	Reduced Risk	
Glycogen Storage Disease, Type IV / Adult Polyglucosan Body Disease	<i>GBE1</i>	AR	Reduced Risk	
Glycogen Storage Disease, Type Ia	<i>G6PC</i>	AR	Reduced Risk	
Glycogen Storage Disease, Type Ib	<i>SLC37A4</i>	AR	Reduced Risk	
Glycogen Storage Disease, Type V	<i>PYGM</i>	AR	Reduced Risk	
Glycogen Storage Disease, Type VII	<i>PFKM</i>	AR	Reduced Risk	
HMG-CoA Lyase Deficiency	<i>HMGCL</i>	AR	Reduced Risk	
Hemochromatosis, Type 2A	<i>HFE2</i>	AR	Reduced Risk	
Hemochromatosis, Type 3	<i>TFR2</i>	AR	Reduced Risk	
Hereditary Fructose Intolerance	<i>ALDOB</i>	AR	Reduced Risk	
Hereditary Spastic Paraparesis 49	<i>TECPR2</i>	AR	Reduced Risk	
Hermansky-Pudlak Syndrome, Type 1	<i>HPS1</i>	AR	Reduced Risk	
Hermansky-Pudlak Syndrome, Type 3	<i>HPS3</i>	AR	Reduced Risk	
Holocarboxylase Synthetase Deficiency	<i>HLCS</i>	AR	Reduced Risk	
Homocystinuria (CBS-Related)	<i>CBS</i>	AR	Reduced Risk	
Homocystinuria due to <i>MTHFR</i> Deficiency	<i>MTHFR</i>	AR	Reduced Risk	
Homocystinuria, cblE Type	<i>MTRR</i>	AR	Reduced Risk	
Hydrolethalus Syndrome	<i>HYLS1</i>	AR	Reduced Risk	
Hyperornithinemia-Hyperammonemia-Homocitrullinuria Syndrome	<i>SLC25A15</i>	AR	Reduced Risk	
Hypohidrotic Ectodermal Dysplasia 1	<i>EDA</i>	XL	Reduced Risk	
Hypophosphatasia	<i>ALPL</i>	AR	Reduced Risk	
Inclusion Body Myopathy 2	<i>GNE</i>	AR	Reduced Risk	
Infantile Cerebral and Cerebellar Atrophy	<i>MED17</i>	AR	Reduced Risk	
Isovaleric Acidemia	<i>IVD</i>	AR	Reduced Risk	
Joubert Syndrome 2	<i>TMEM216</i>	AR	Reduced Risk	
Joubert Syndrome 7 / Meckel Syndrome 5 / COACH Syndrome	<i>RPGRIP1L</i>	AR	Reduced Risk	
Junctional Epidermolysis Bullosa (LAMA3-Related)	<i>LAMA3</i>	AR	Reduced Risk	
Junctional Epidermolysis Bullosa (LAMB3-Related)	<i>LAMB3</i>	AR	Reduced Risk	

Junctional Epidermolysis Bullosa ( <i>LAMC2</i> -Related)	<i>LAMC2</i>	AR	Reduced Risk
Krabbe Disease	<i>GALC</i>	AR	Reduced Risk
Lamellar Ichthyosis, Type 1	<i>TGM1</i>	AR	Reduced Risk
Leber Congenital Amaurosis 10 and Other CEP290-Related Ciliopathies	<i>CEP290</i>	AR	Reduced Risk
Leber Congenital Amaurosis 13	<i>RDH12</i>	AR	Reduced Risk
Leber Congenital Amaurosis 2 / Retinitis Pigmentosa 20	<i>RPE65</i>	AR	Reduced Risk
Leber Congenital Amaurosis 5	<i>LCA5</i>	AR	Reduced Risk
Leber Congenital Amaurosis 8 / Retinitis Pigmentosa 12 / Pigmented Paravenous Chorioretinal Atrophy	<i>CRB1</i>	AR	Reduced Risk
Leigh Syndrome, French-Canadian Type	<i>LRPPRC</i>	AR	Reduced Risk
Lethal Congenital Contracture Syndrome 1 / Lethal Arthrogyposis with Anterior Horn Cell Disease	<i>GLE1</i>	AR	Reduced Risk
Leukoencephalopathy with Vanishing White Matter	<i>EIF2B5</i>	AR	Reduced Risk
Limb-Girdle Muscular Dystrophy, Type 2A	<i>CAPN3</i>	AR	Reduced Risk
Limb-Girdle Muscular Dystrophy, Type 2B	<i>DYSF</i>	AR	Reduced Risk
Limb-Girdle Muscular Dystrophy, Type 2C	<i>SGCG</i>	AR	Reduced Risk
Limb-Girdle Muscular Dystrophy, Type 2D	<i>SGCA</i>	AR	Reduced Risk
Limb-Girdle Muscular Dystrophy, Type 2E	<i>SGCB</i>	AR	Reduced Risk
Limb-Girdle Muscular Dystrophy, Type 2I	<i>FKRP</i>	AR	Reduced Risk
Lipoamide Dehydrogenase Deficiency	<i>DLD</i>	AR	Reduced Risk
Lipoid Adrenal Hyperplasia	<i>STAR</i>	AR	Reduced Risk
Lipoprotein Lipase Deficiency	<i>LPL</i>	AR	Reduced Risk
Long-Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency	<i>HADHA</i>	AR	Reduced Risk
Lysinuric Protein Intolerance	<i>SLC7A7</i>	AR	Reduced Risk
Maple Syrup Urine Disease, Type 1a	<i>BCKDHA</i>	AR	Reduced Risk
Maple Syrup Urine Disease, Type 1b	<i>BCKDHB</i>	AR	Reduced Risk
Meckel Syndrome 1 / Bardet-Biedl Syndrome 13	<i>MKS1</i>	AR	Reduced Risk
Medium Chain Acyl-CoA Dehydrogenase Deficiency	<i>ACADM</i>	AR	Reduced Risk
Megalencephalic Leukoencephalopathy with Subcortical Cysts	<i>MLC1</i>	AR	Reduced Risk
Menkes Disease	<i>ATP7A</i>	XL	Reduced Risk
Metachromatic Leukodystrophy	<i>ARSA</i>	AR	Reduced Risk
Methylmalonic Acidemia ( <i>MMAA</i> -Related)	<i>MMAA</i>	AR	Reduced Risk
Methylmalonic Acidemia ( <i>MMAB</i> -Related)	<i>MMAB</i>	AR	Reduced Risk
Methylmalonic Acidemia ( <i>MUT</i> -Related)	<i>MUT</i>	AR	Reduced Risk
Methylmalonic Aciduria and Homocystinuria, Cobalamin C Type	<i>MMACHC</i>	AR	Reduced Risk
Methylmalonic Aciduria and Homocystinuria, Cobalamin D Type	<i>MMADHC</i>	AR	Reduced Risk
Microphthalmia / Anophthalmia	<i>VSX2</i>	AR	Reduced Risk
Mitochondrial Complex I Deficiency ( <i>ACAD9</i> -Related)	<i>ACAD9</i>	AR	Reduced Risk
Mitochondrial Complex I Deficiency ( <i>NDUFAF5</i> -Related)	<i>NDUFAF5</i>	AR	Reduced Risk
Mitochondrial Complex I Deficiency ( <i>NDUFS6</i> -Related)	<i>NDUFS6</i>	AR	Reduced Risk
Mitochondrial DNA Depletion Syndrome 6 / Navajo Neurohepatopathy	<i>MPV17</i>	AR	Reduced Risk
Mitochondrial Myopathy and Sideroblastic Anemia 1	<i>PUS1</i>	AR	Reduced Risk
Mucopolidosis II / IIIA	<i>GNPTAB</i>	AR	Reduced Risk
Mucopolidosis III Gamma	<i>GNPTG</i>	AR	Reduced Risk
Mucopolidosis IV	<i>MCOLN1</i>	AR	Reduced Risk
Mucopolysaccharidosis Type I	<i>IDUA</i>	AR	Reduced Risk
Mucopolysaccharidosis Type II	<i>IDS</i>	XL	Reduced Risk
Mucopolysaccharidosis Type IIIA	<i>SGSH</i>	AR	Reduced Risk
Mucopolysaccharidosis Type IIIB	<i>NAGLU</i>	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	SMARCA1	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: 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 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. AmpliX<sup>®</sup> *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<sup>®</sup> System were used to identify certain recurrent variants that are complex in nature or are present in low copy repeats. Rare sequence variants may interfere with assay performance.

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

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

For alpha thalassemia, the copy numbers of the *HBA1* and *HBA2* genes were analyzed. Alpha-globin gene deletions, triplications, and the Constant Spring (CS) mutation are assessed. This test is expected to detect approximately 90% of all alpha-thalassemia mutations, varying by

ethnicity, carriers of alpha-thalassemia with three or more *HBA* copies on one chromosome, and one or no copies on the other chromosome, may not be detected. With the exception of triplications, other benign alpha-globin gene polymorphisms will not be reported. Analyses of *HBA1* and *HBA2* are performed in association with long-range PCR of the coding regions followed by short-read sequencing.

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

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

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

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

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

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

Agilent SureSelect<sup>TM</sup>XT Low Input technology was used with a custom capture library to target the exonic regions and intron/exon splice junctions of the relevant genes, as well as a number of UTR, intronic or promoter regions that contain previously reported mutations. Libraries were pooled and sequenced on the Illumina NovaSeq 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<sup>®</sup> 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.

Variation 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  $\Delta\Delta C_t$  formula.

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

Long-range PCR was performed to generate locus-specific amplicons for *CYP21A2*, *HBA1* and *HBA2* and *GBA*. The PCR products were then prepared for short-read NGS sequencing and sequenced. Sequenced reads were mapped back to the original genomic locus and run through the bioinformatics pipeline. If indicated, copy number from MLPA was correlated with the sequencing output to analyze the results. 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 >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<sup>TM</sup>XT Low-Input technology was utilized in order to create whole-genome libraries for each patient sample. Libraries were then pooled and sequenced on the Illumina NovaSeq platform. Each sequencing lane was multiplexed to achieve 0.4-2x genome coverage,

using paired-end 100 bp reads. The sequencing data underwent ancestral analysis using a customized, licensed bioinformatics algorithm that was validated in house. Identified sub-ethnic groupings were binned into one of 7 continental-level groups (African, East Asian, South Asian, Non-Finnish European, Finnish, Native American, and Ashkenazi Jewish) or, for those ethnicities that matched poorly to the continental-level groups, an 8<sup>th</sup> "unassigned" group, which were then used to select residual risk values for each gene. For individuals belonging to multiple high-level ethnic groupings, a weighting strategy was used to select the most appropriate residual risk. For genes that had insufficient data to calculate ethnic-specific residual risk values, or for sub-ethnic groupings that fell into the "unassigned" group, a "worldwide" residual risk was used. This "worldwide" residual risk was calculated using data from all available continental-level groups.

#### **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.