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	Female	*Provider*
Name:	KIRA DINEEN	Mitera
DOB:	[redacted]	Kataneh Salari
Lab #:	[redacted]	[redacted]
Family #:		[redacted]
MRN #:	[redacted]	
Ethnicity:	Northern European Caucasian (Scandinavian, UK, Germany)	
Test Code:	[redacted]	
Indication:		

CARRIER

Results Summary

Disease / Gene / Risk Details	KIRA DINEEN	Partner
CONGENITAL MYASTHENIC SYNDROME, RAPSN-RELATED	CARRIER	Not Submitted
RAPSN - Reproductive Risk: 1 in 1000	c.1174C>T (p.Q392*)	
Inheritance Pattern: Autosomal recessive	Heterozygous	

This individual is a heterozygous carrier for the c.1174C>T (p.Q392*) likely pathogenic variant, which is associated with classical presentation.

Additional Comments

No likely pathogenic or pathogenic variants were detected in the remaining genes analyzed in this test. Please see the Diseases/Disorders Tested table for a list of all genes analyzed by this test code. A negative result does not rule out the rare possibility of a variant in other regions of the tested gene or in other genes causing a very similar disease. In addition, a negative test result does not rule out germ-line mosaicism in the tested parents or de novo pathogenic variants that occur in the offspring.

Comments and Recommendations:

- This test is intended to identify couples with high reproductive risk. Thus, concurrent testing of both prospective parents is highly recommended. With newer expanded carrier testing using full gene sequencing, supplemented with CNV analysis for genes with frequent deletions, detection rates are expected to be 90-99%. Consequently, an individual has a negligible reproductive risk for genes that are screen negative. Therefore, reproductive risks are only provided when a pathogenic variant is detected in one or both prospective parents. We recommend testing the partner if the patient is a carrier for an autosomal recessive disease.
- We recommend that you discuss these results with your physician. Your physician can determine if any additional testing is indicated. You may also discuss these results with a GeneAware genetic counselor at no additional charge. Please call 1-800-411-GENE (4363) for a telephone appointment.
- We recommend sharing this information with family members. Testing for at risk relatives is available.
- Please see methodology for details of this analysis, which includes full gene sequencing and copy number analysis of genes included in panel, excluding FMR1 (only CGG analysis performed). For a list of genes tested, see table at the end of this report.

Christine M. Eng, M.D.
Medical Director

Jennifer Scull, Ph.D.
Laboratory Co-Director

CONGENITAL MYASTHENIC SYNDROME, RAPSN-RELATED

Disease / Gene / Risk Details	KIRA DINEEN	Partner
RAPSN - CONGENITAL MYASTHENIC SYNDROME, RAPSN-RELATED	CARRIER	Not Submitted
Inheritance Pattern: Autosomal recessive	c.1174C>T (p.Q392*)	
	Heterozygous	

What is Congenital Myasthenic Syndrome?

Congenital myasthenic syndrome (CMS) is a group of inherited disorders characterized by skeletal muscle weakness and fatigue, including facial muscles and muscles controlling swallowing and sucking. Onset is usually at birth, but disease symptoms can begin in childhood and, rarely, adulthood. Severity of the disorder is variable, but generally, the earlier the symptoms appear, the more pronounced the disease is likely to be. Affected infants may be delayed in learning to crawl or walk and later on display difficulty running or climbing stairs. They may also have joint deformities and breathing problems. There is no cure for CMS; however there are drugs available for some types of CMS that help to improve muscle strength and endurance. Also, medical surveillance and care may help to improve some symptoms and overall condition of life. CMS is caused by pathogenic variants in multiple genes, including RAPSN, CHAT, DOK7, and CHRNE, which accounts for the majority of CMS cases.

How is Congenital Myasthenic Syndrome inherited?

CMS is usually inherited in an autosomal recessive manner. This type of inheritance requires the presence of two copies of a pathogenic variant in the gene for a person to have the genetic disease. Both parents must be carriers of a pathogenic variant in the gene in order to be at risk to have an affected child. The child must inherit a pathogenic variant from each carrier parent in order to be affected. There is a 1 in 4 chance that a baby will inherit two mutated copies of the gene and be affected when both parents are carriers.

What does it mean to be a carrier?

There are generally no signs or symptoms associated with being a carrier for CMS. However, the risk to have a child affected with CMS is increased. Testing of reproductive partners is recommended for carriers of CMS.

How common is Congenital Myasthenic Syndrome?

It is unknown exactly how often CMS occurs worldwide, although it is estimated to occur in 1 in 500,000 newborns in Europe.

Family References and Resources

Genetics Home Reference: Congenital Myasthenic Syndrome (http://ghr.nlm.nih.gov/)
Orphanet: Congenital Myasthenic Syndrome (http://www.orpha.net/consor/cgi-bin/index.php?lng=EN)

Clinician References

OMIM [Congenital Myasthenic Syndrome: 608931] (http://www.ncbi.nlm.nih.gov/omim)
GeneReviews: Congenital Myasthenic Syndrome (http://www.ncbi.nlm.nih.gov/books/NBK1116/)

Fragile-X Syndrome: Normal Result

Patient Repeat Sizes: 30 and 31

This patient has normal allele sizes indicating that there is no increased risk for a repeat expansion that would cause Fragile-X syndrome

Disease	Gene	Inheritance Pattern	KIRA DINEEN	Risk Summary
Fragile X	FMR1	X-linked	Normal	NOT at an increased risk for expansion

*Males are not tested for Fragile-X Syndrome as part of this carrier screen.

Methodology:

Normal alleles: 5-44 CGG repeats
Intermediate alleles: 45-54 CGG repeats. May expand to premutations through maternal transmission, but not to full mutations.
Premutation: 55-200 CGG repeats. Not associated with fragile X syndrome, but increases risk for premature ovarian failure in females and for ataxia/tremor in either sex.
Full penetrance alleles: 200 or more CGG repeats are associated with a disease phenotype.
The CGG repeat region at the FMR1 5'-untranslated region is amplified by fluorescent PCR followed by capillary electrophoresis. Allele sizes up to 200 repeats are analyzed by GeneMapper software. Reflex Southern blot analysis will be performed and reported in an addendum for samples with premutations and full penetrance alleles in order to assess size and methylation status for larger repeats.
This analysis does not detect deletions or point mutations, which comprises less than one percent of the FMR1 pathogenic variants.

SMN1 COPY NUMBER ANALYSIS: NONCARRIER

Results Summary

Disease / Gene / Risk Details	KIRA DINEEN	Partner
Spinal Muscular Atrophy	Noncarrier	Not Submitted
SMN1 - Reproductive Risk: 1 in 120000	2 copies; g.27134T>G absent	
Inheritance Pattern: Autosomal recessive		

SMA Carrier Testing

SMA carrier testing is performed using the massively parallel sequencing read depth analysis (see "Copy Number Analysis" in the Methodology section). An individual with a two-copy result may or may not be an SMN1 deletion carrier. Some individuals with a twocopy result will be silent carriers ("2+0" configuration), having an SMN1 duplication on a single allele and no copies of SMN1 on the homologous chromosome. A novel single nucleotide polymorphism (g.27134T>G) in intron 7 of SMN1 helps assess the chance that an individual is a silent carrier of an SMN1 deletion. Both the frequency of silent carriers and the degree to which the benign g.27134T>G polymorphism is associated with silent carrier status varies by ethnicity. The table below provides the chance for a two copy result to correspond to a "2+0" genotype based on ethnicity and on the presence or absence of the g.27134T>G polymorphism. This assay does not report SMN2 copy number or sequence changes other than the g.27134T>G variant.

SMA Carrier Risk

	Untested	Tested				
		0 SMN1 copies	1 SMN1 copies	2 SMN1 copies		≥ 3 SMN1 copies
				g.27134T>G Absent	g.27134T>G Present	
African American	1 in 72	POSSIBLY AFFECTED	CARRIER	1 in 360	1 in 38	≤ 1 in 4300
Ashkenazi Jewish	1 in 67	POSSIBLY AFFECTED	CARRIER	1 in 630	LIKELY CARRIER	≤ 1 in 4800
Asian	1 in 59	POSSIBLY AFFECTED	CARRIER	1 in 580	1 in 61	≤ 1 in 4800
Caucasian	1 in 47	POSSIBLY AFFECTED	CARRIER	1 in 650	1 in 69	≤ 1 in 4900
General Population	1 in 54	POSSIBLY AFFECTED	CARRIER	1 in 520	1 in 44	≤ 1 in 4800
Hispanic American	1 in 68	POSSIBLY AFFECTED	CARRIER	1 in 630	1 in 98	≤ 1 in 4800

References: Feng Y et al. The next generation of population-based spinal muscular atrophy carrier screening: competitive pan-ethnic SMN1 copy-number and sequence variant analysis by massively parallel sequencing (PMID 28125085). Luo M et al. An Ashkenazi Jewish SMN1 haplotype specific to duplication alleles improves pan-ethnic carrier screening for spinal muscular atrophy (PMID 23788250). Sugarman EA at al. Pan-ethnic carrier screening and prenatal diagnosis for spinal muscular atrophy: clinical laboratory analysis of ≥ 72,400 specimens (PMID 21811307). Carrier risks are current as of the report issue date.

TERMINOLOGY

- Residual and Reproductive Risk
  Residual Risk is the chance that an individual with negative screening results is a carrier of a non-examined pathogenic variant in this gene.

  Reproductive risk is the chance that a single pregnancy will result in an affected child as the result of inherited mutations in this gene. For autosomal recessive conditions, both partner's carrier risks are multiplied and then divided by 4. When the partner has not been screened, the carrier risk for an unrelated partner of the same ethnicity with a negative family history is used. Testing both partners improves the estimate of reproductive risk and is recommended. Genetic counseling is strongly recommended for carriers or anyone with a family history of the condition.

- Detection Rates and Carrier Frequencies
  Detection rates are obtained through the analysis of affected individuals. For most ethnic groups, actual measurements of the detection rate are unavailable due to insufficient numbers of affected individuals having being studied. When detection rates are unknown, the carrier frequency may be used to set an upper bound on carrier risk.

  Carrier frequencies are obtained from either the incidence of the disease or from the study of large numbers of random individuals from the target population. If carrier frequencies are unknown for the patient's ethnic group, then the carrier frequency of the general population will be utilized.

- Variant Reporting Information
  Benign variants, variants of uncertain significance, and variants not directly associated with the intended disease phenotype will not be reported.

  Carrier (for variants ranked as pathogenic or likely pathogenic) - there is high confidence that this variant is pathogenic or likely pathogenic. This includes inactivating/loss-of-function variants and missense variants where there is significant evidence that the variant has caused the disease in 3 or more families or is consistent with ACMG guidelines for the interpretation of sequence variants. Data from well-established clinical and functional assays will also be considered.

DISEASES SCREENED

Below is a list of all diseases screened and the result. Certain conditions have unique patient-specific numerical values, therefore, results for those conditions are fomatted differently.

1
17-BETA-HYDROXYSTEROID DEHYDROGENASE TYPE III DEFICIENCY (*HSD17B3*): **negative**

3
3-BETA-HYDROXYSTEROID DEHYDROGENASE DEFICIENCY, TYPE II (*HSD3B2*): **negative**
3-HYDROXY-3-METHYLGLUTARYL-COA LYASE DEFICIENCY (*HMGCL*): **negative**
3-METHYLCROTONYL-COA CARBOXYLASE 1 DEFICIENCY (*MCCC1*): **negative**
3-METHYLCROTONYL-COA CARBOXYLASE 2 DEFICIENCY (*MCCC2*): **negative**
3-METHYLGLUTACONIC ACIDURIA, TYPE III (*OPA3*): **negative**
3-PHOSPHOGLYCERATE DEHYDROGENASE DEFICIENCY (*PHGDH*): **negative**

6
6-PYRUVOYL-TETRAHYDROPTERIN SYNTHASE (PTPS) DEFICIENCY (*PTS*): **negative**

A
ABETALIPOPROTEINEMIA (*MTTP*): **negative**
ACHROMATOPSIA, CNGB3-RELATED (*CNGB3*): **negative**
ACRODERMATITIS ENTEROPATHICA (*SLC39A4*): **negative**
ACTION MYOCLONUS RENAL FAILURE SYNDROME (SCARB2) (*SCARB2*): **negative**
ACUTE INFANTILE LIVER FAILURE (*TRMU*): **negative**
ACYL-COA OXIDASE I DEFICIENCY (*ACOX1*): **negative**
ADENOSINE DEAMINASE DEFICIENCY (*ADA*): **negative**
ADRENAL HYPERPLASIA, CONGENITAL, DUE TO 11-BETA-HYDROXYLASE DEFICIENCY (*CYP11B1*): **negative**
ADRENOLEUKODYSTROPHY, X-LINKED (*ABCD1*): **negative**
AGAMMAGLOBULINEMIA, X-LINKED (*BTK*): **negative**
AICARDI-GOUTIERES SYNDROME 2 (*RNASEH2B*): **negative**
AICARDI-GOUTIERES SYNDROME 3 (*RNASEH2C*): **negative**
AICARDI-GOUTIERES SYNDROME 4 (*RNASEH2A*): **negative**
AICARDI-GOUTIÈRES SYNDROME, SAMHD1-RELATED (*SAMHD1*): **negative**
ALPHA-1 ANTITRYPSIN DEFICIENCY (*SERPINA1*): **negative**
ALPHA-MANNOSIDOSIS (*MAN2B1*): **negative**
ALPHA-THALASSEMIA (*HBA1/HBA2*): **negative**
ALPHA-THALASSEMIA INTELLECTUAL DISABILITY SYNDROME, X-LINKED (*ATRX*): **negative**
ALPORT SYNDROME, COL4A3-RELATED (*COL4A3*): **negative**
ALPORT SYNDROME, COL4A4-RELATED (*COL4A4*): **negative**
ALPORT SYNDROME, COL4A5-RELATED, X-LINKED (*COL4A5*): **negative**
ALSTROM SYNDROME (*ALMS1*): **negative**
AMISH INFANTILE EPILEPSY SYNDROME (*ST3GAL5*): **negative**
ANDERMANN SYNDROME (HEREDITARY MOTOR AND SENSORY NEUROPATHY WITH AGENESIS OF THE CORPUS CALLOSUM) (*SLC12A6*): **negative**
ARGININEMIA (*ARG1*): **negative**
ARGININOSUCCINATE ACIDURIA (*ASL*): **negative**
AROMATASE DEFICIENCY (*CYP19A1*): **negative**
ARTHROGRYPOSIS, MENTAL RETARDATION, AND SEIZURES (*SLC35A3*): **negative**
ARTS SYNDROME (*PRPS1*): **negative**
ASPARAGINE SYNTHETASE DEFICIENCY (*ASNS*): **negative**
ASPARTYLGLYCOSAMINURIA (*AGA*): **negative**
ATAXIA WITH VITAMIN E DEFICIENCY (*TTPA*): **negative**
ATAXIA-TELANGIECTASIA (*ATM*): **negative**
ATAXIA-TELANGIECTASIA-LIKE DISORDER (*MRE11*): **negative**
AUTOIMMUNE POLYGLANDULAR SYNDROME, TYPE 1 (*AIRE*): **negative**
AUTOSOMAL RECESSIVE POLYCYSTIC KIDNEY DISEASE (*PKHD1*): **negative**

B
BARDET-BIEDL SYNDROME 4 (*BBS4*): **negative**
BARDET-BIEDL SYNDROME 6 (*MKKS*): **negative**
BARDET-BIEDL SYNDROME 7 (*BBS7*): **negative**
BARDET-BIEDL SYNDROME 8 (*TTC8*): **negative**
BARDET-BIEDL SYNDROME 9 (*BBS9*): **negative**
BARDET-BIEDL SYNDROME, BBS10-RELATED (*BBS10*): **negative**
BARDET-BIEDL SYNDROME, BBS12-RELATED (*BBS12*): **negative**
BARDET-BIEDL SYNDROME, BBS1-RELATED (*BBS1*): **negative**
BARDET-BIEDL SYNDROME, BBS2-RELATED (*BBS2*): **negative**
BARE LYMPHOCYTE SYNDROME, TYPE II (*CIITA*): **negative**
BARTH SYNDROME (*TAZ*): **negative**
BARTTER SYNDROME, TYPE IV (*BSND*): **negative**
BERNARD-SOULIER SYNDROME TYPE A1 (*GP1BA*): **negative**
BERNARD-SOULIER SYNDROME, TYPE C (*GP9*): **negative**
BETA HEMOGLOBINOPATHIES (*HBB*): **negative**
BETA-KETOTHIOLASE DEFICIENCY (*ACAT1*): **negative**
BETA-UREIDOPROPIONASE DEFICIENCY (*UPB1*): **negative**
BILATERAL FRONTOPARIETAL POLYMICROGYRIA (*ADGRG1*): **negative**
BIOTINIDASE DEFICIENCY (*BTD*): **negative**
BLOOM SYNDROME (*BLM*): **negative**

C
CANAVAN DISEASE (*ASPA*): **negative**
CARBAMOYL PHOSPHATE SYNTHETASE I DEFICIENCY (*CPS1*): **negative**
CARNITINE DEFICIENCY, SYSTEMIC PRIMARY (*SLC22A5*): **negative**
CARNITINE PALMITOYLTRANSFERASE I DEFICIENCY (*CPT1A*): **negative**
CARNITINE PALMITOYLTRANSFERASE II DEFICIENCY (*CPT2*): **negative**
CARNITINE-ACYLCARNITINE TRANSLOCASE DEFICIENCY (*SLC25A20*): **negative**

C

CARPENTER SYNDROME (*RAB23*): **negative**
CARTILAGE-HAIR HYPOPLASIA (*RMRP*): **negative**
CEREBROOCULOFACIOSKELETAL SYNDROME 1 (COFS1) (*ERCC6*): **negative**
CEREBROTENDINOUS XANTHOMATOSIS (*CYP27A1*): **negative**
CEROID LIPOFUSCINOSIS, NEURONAL, 10 (*CTSD*): **negative**
CHARCOT-MARIE-TOOTH DISEASE, GJB1-RELATED, X-LINKED (*GJB1*): **negative**
CHARCOT-MARIE-TOOTH DISEASE, TYPE 4D (*NDRG1*): **negative**
CHEDIAK-HIGASHI SYNDROME (*LYST*): **negative**
CHOLESTASIS, BENIGN RECURRENT INTRAHEPATIC (*ATP8B1*): **negative**
CHOLESTASIS, PROGRESSIVE FAMILIAL INTRAHEPATIC 4 (*TJP2*): **negative**
CHOLESTERYL ESTER STORAGE DISEASE (*LIPA*): **negative**
CHOREOACANTHOCYTOSIS (*VPS13A*): **negative**
CHOROIDEREMIA, X-LINKED (*CHM*): **negative**
CHRONIC GRANULOMATOUS DISEASE, CYTOCHROME B-NEGATIVE (*CYBA*): **negative**
CHRONIC GRANULOMATOUS, X-LINKED (*CYBB*): **negative**
CILIOPATHIES, RPGRIP1L-RELATED (*RPGRIP1L*): **negative**
CITRIN DEFICIENCY (*SLC25A13*): **negative**
CITRULLINEMIA, TYPE I (*ASS1*): **negative**
COCKAYNE SYNDROME: TYPE A (*ERCC8*): **negative**
COHEN SYNDROME (*VPS13B*): **negative**
COMBINED MALONIC AND METHYLMALONIC ACIDURIA (*ACSF3*): **negative**
COMBINED OXIDATIVE PHOSPHORYLATION DEFICIENCY 3 (*TSFM*): **negative**
COMBINED OXIDATIVE PHOSPHORYLATION DEFICIENCY 4 (*GFM1*): **negative**
COMBINED OXIDATIVE PHOSPHORYLATION DEFICIENCY 6 (*AIFM1*): **negative**
COMBINED PITUITARY HORMONE DEFICIENCY 3 (*LHX3*): **negative**
CONGENITAL ADRENAL HYPERPLASIA, 17-ALPHA-HYDROXYLASE DEFICIENCY (*CYP17A1*): **negative**
CONGENITAL ADRENAL HYPERPLASIA, 21-HYDROXYLASE DEFICIENCY (*CYP21A2*): **negative**
CONGENITAL AMEGAKARYOCYTIC THROMBOCYTOPENIA (*MPL*): **negative**
CONGENITAL DISORDER OF GLYCOSYLATION, TYPE IA (*PMM2*): **negative**
CONGENITAL DISORDER OF GLYCOSYLATION, TYPE IB (*MPI*): **negative**
CONGENITAL DISORDER OF GLYCOSYLATION, TYPE IC (*ALG6*): **negative**
CONGENITAL ICHTHYOSIS: ABCA12 RELATED (*ABCA12*): **negative**
CONGENITAL INSENSITIVITY TO PAIN WITH ANHIDROSIS (CIPA) (*NTRK1*): **negative**
CONGENITAL LIPOID ADRENAL HYPERPLASIA (*STAR*): **negative**
CONGENITAL MUSCULAR DYSTROPHY-DYSTROGLYCANOPATHY WITH BRAIN AND EYE ANOMALIES TYPE A1 (*POMT1*): **negative**
CONGENITAL MYASTHENIC SYNDROME, CHAT-RELATED (*CHAT*): **negative**
CONGENITAL MYASTHENIC SYNDROME, CHRNE-RELATED (*CHRNE*): **negative**
CONGENITAL MYASTHENIC SYNDROME, DOK7-RELATED (*DOK7*): **negative**
CONGENITAL MYASTHENIC SYNDROME, RAPSN-RELATED (*RAPSN*): **positive**
CONGENITAL NEUTROPENIA, HAX1-RELATED (*HAX1*): **negative**
CONGENITAL NEUTROPENIA, VPS45-RELATED (*VPS45*): **negative**
CORNEAL DYSTROPHY AND PERCEPTIVE DEAFNESS SYNDROME (*SLC4A11*): **negative**
CORTICOSTERONE METHYLOXIDASE DEFICIENCY (*CYP11B2*): **negative**
CRASH SYNDROME (*L1CAM*): **negative**
CRB1-RELATED RETINAL DYSTROPHIES (*CRB1*): **negative**
CREATINE TRANSPORTER DEFECT, SLC6A8-RELATED, X-LINKED (*SLC6A8*): **negative**
CYSTIC FIBROSIS (*CFTR*): **negative**
CYSTINOSIS (*CTNS*): **negative**

D

D-BIFUNCTIONAL PROTEIN DEFICIENCY (*HSD17B4*): **negative**
DEAFNESS, AUTOSOMAL RECESSIVE 48 (*CIB2*): **negative**
DEAFNESS, AUTOSOMAL RECESSIVE 77 (*LOXHD1*): **negative**
DENT DISEASE (*CLCN5*): **negative**
DESBUQUOIS DYSPLASIA, TYPE I (*CANT1*): **negative**
DEVELOPMENTAL DELAY AND MICROENCEPHALY (SLC1A4-RELATED) (*SLC1A4*): **negative**
DIHYDROLIPOAMIDE DEHYDROGENASE DEFICIENCY (*DLD*): **negative**
DIHYDROPYRIMIDINE DEHYDROGENASE DEFICIENCY (*DPYD*): **negative**
DUCHENNE / BECKER MUSCULAR DYSTROPHY, X-LINKED (*DMD*): **negative**
DYSKERATOSIS CONGENITA, RTEL1-RELATED (*RTEL1*): **negative**
DYSKERATOSIS CONGENITA, X-LINKED (*DKC1*): **negative**
DYSTROPHIC EPIDERMOLYSIS BULLOSA, COL7A1-RELATED (*COL7A1*): **negative**

E

EHLERS-DANLOS SYNDROME, TYPE VIIC (*ADAMTS2*): **negative**
ELLIS-VAN CREVELD SYNDROME (*EVC*): **negative**
ELLIS-VAN CREVELD SYNDROME (*EVC2*): **negative**
EMERY-DREIFUSS MUSCULAR DYSTROPHY, X-LINKED (*EMD*): **negative**
ENHANCED S-CONE SYNDROME (*NR2E3*): **negative**
ERCC2 (*ERCC2*): **negative**
ETHYLMALONIC ENCEPHALOPATHY (*ETHE1*): **negative**

F

FABRY DISEASE, X-LINKED (*GLA*): **negative**
FACTOR XI DEFICIENCY (*F11*): **negative**
FAMILIAL DYSAUTONOMIA (*ELP1*): **negative**
FAMILIAL HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (*PRF1*): **negative**
FAMILIAL HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS-4 (*STX11*): **negative**
FAMILIAL HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS-5 (*STXBP2*): **negative**
FAMILIAL HYPERCHOLESTEROLEMIA, LDLRAP1-RELATED (*LDLRAP1*): **negative**
FAMILIAL HYPERCHOLESTEROLEMIA, LDLR-RELATED (*LDLR*): **negative**

F

FAMILIAL HYPERINSULINEMIC HYPOGLYCEMIA-4 (*HADH*): **negative**
FAMILIAL HYPERINSULINISM, ABCC8-RELATED (*ABCC8*): **negative**
FAMILIAL HYPERINSULINISM, KCNJ11-RELATED (*KCNJ11*): **negative**
FAMILIAL MEDITERRANEAN FEVER (*MEFV*): **negative**
FANCONI ANEMIA, COMPLEMENTATION GROUP B (*FANCB*): **negative**
FANCONI ANEMIA, COMPLEMENTATION GROUP D2 (*FANCD2*): **negative**
FANCONI ANEMIA, COMPLEMENTATION GROUP E (*FANCE*): **negative**
FANCONI ANEMIA, COMPLEMENTATION GROUP F (*FANCF*): **negative**
FANCONI ANEMIA, COMPLEMENTATION GROUP I (*FANCI*): **negative**
FANCONI ANEMIA, COMPLEMENTATION GROUP L (*FANCL*): **negative**
FANCONI ANEMIA, TYPE A (*FANCA*): **negative**
FANCONI ANEMIA, TYPE C (*FANCC*): **negative**
FANCONI ANEMIA, TYPE G (*FANCG*): **negative**
FARBER LIPOGRANULOMATOSIS (*ASAH1*): **negative**
FRAGILE X SYNDROME (*FMR1*): **negative**
FUMARASE DEFICIENCY (*FH*): **negative**

G

GABA-TRANSAMINASE DEFICIENCY (*ABAT*): **negative**
GALACTOKINASE DEFICIENCY (*GALK1*): **negative**
GALACTOSEMIA (*GALT*): **negative**
GALACTOSIALIDOSIS (*CTSA*): **negative**
GAUCHER DISEASE (*GBA*): **negative**
GITELMAN SYNDROME (*SLC12A3*): **negative**
GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY, X-LINKED (*G6PD*): **negative**
GLUTARIC ACIDEMIA, TYPE I (*GCDH*): **negative**
GLUTARIC ACIDEMIA, TYPE IIA (*ETFA*): **negative**
GLUTARIC ACIDEMIA, TYPE IIC (*ETFDH*): **negative**
GLUTARIC ACIDEMIA: TYPE IIB; MULTIPLE ACYL-COA DEHYDROGENASE DEFICIENCY; MADD (*ETFB*): **negative**
GLYCINE ENCEPHALOPATHY, AMT-RELATED (*AMT*): **negative**
GLYCINE ENCEPHALOPATHY, GLDC-RELATED (*GLDC*): **negative**
GLYCOGEN STORAGE DISEASE, TYPE IA (*G6PC*): **negative**
GLYCOGEN STORAGE DISEASE, TYPE IB (*SLC37A4*): **negative**
GLYCOGEN STORAGE DISEASE, TYPE II (*GAA*): **negative**
GLYCOGEN STORAGE DISEASE, TYPE III (*AGL*): **negative**
GLYCOGEN STORAGE DISEASE, TYPE IV (*GBE1*): **negative**
GLYCOGEN STORAGE DISEASE, TYPE V (*PYGM*): **negative**
GLYCOGEN STORAGE DISEASE, TYPE VII (*PFKM*): **negative**
GM1 GANGLIOSIDOSIS (*GLB1*): **negative**
GRACILE SYNDROME (*BCS1L*): **negative**
GUANIDINOACETATE METHYLTRANSFERASE DEFICIENCY (*GAMT*): **negative**

H

HEMOPHILIA B, X-LINKED (*F9*): **negative**
HEPATOCEREBRAL MITOCHONDRIAL DNA DEPLETION SYNDROME, MPV17-RELATED (*MPV17*): **negative**
HEREDITARY FRUCTOSE INTOLERANCE (*ALDOB*): **negative**
HEREDITARY HEMOCHROMATOSIS, HJV-RELATED (*HJV*): **negative**
HEREDITARY HEMOCHROMATOSIS, TFR2-RELATED (*TFR2*): **negative**
HEREDITARY SPASTIC PARAPARESIS, TYPE 49 (*TECPR2*): **negative**
HERMANSKY-PUDLAK SYNDROME 2 (*AP3B1*): **negative**
HERMANSKY-PUDLAK SYNDROME, HPS1-RELATED (*HPS1*): **negative**
HERMANSKY-PUDLAK SYNDROME, HPS3-RELATED (*HPS3*): **negative**
HOLOCARBOXYLASE SYNTHETASE DEFICIENCY (*HLCS*): **negative**
HOMOCYSTINURIA DUE TO DEFICIENCY OF MTHFR (*MTHFR*): **negative**
HOMOCYSTINURIA, CBS-RELATED (*CBS*): **negative**
HOMOCYSTINURIA, TYPE CBLE (*MTRR*): **negative**
HPS4 (*HPS4*): **negative**
HYDROLETHALUS SYNDROME (*HYLS1*): **negative**
HYPERPHOSPHATEMIC FAMILIAL TUMORAL CALCINOSIS (*GALNT3*): **negative**
HYPOHIDROTIC ECTODERMAL DYSPLASIA, X-LINKED (*EDA*): **negative**
HYPOPHOSPHATASIA (*ALPL*): **negative**

I

IMMUNODYSREGULATION, POLYENDOCRINOPATHY, AND ENTEROPATHY, X-LINKED (*FOXP3*): **negative**
INCLUSION BODY MYOPATHY 2 (*GNE*): **negative**
INFANTILE CEREBRAL AND CEREBELLAR ATROPHY (*MED17*): **negative**
INFANTILE NEUROAXONAL DYSTROPHY 1 (*PLA2G6*): **negative**
INFANTILE X-LINKED SPINAL MUSCULAR ATROPHY (*UBA1*): **negative**
ISOVALERIC ACIDEMIA (*IVD*): **negative**

J

JOHANSON-BLIZZARD SYNDROME (*UBR1*): **negative**
JOUBERT SYNDROME 1 (*INPP5E*): **negative**
JOUBERT SYNDROME 15 (*CEP41*): **negative**
JOUBERT SYNDROME 2 (*TMEM216*): **negative**
JOUBERT SYNDROME 21 (*CSPP1*): **negative**
JOUBERT SYNDROME 25 (*CEP104*): **negative**
JOUBERT SYNDROME 27 (*B9D1*): **negative**
JOUBERT SYNDROME 3 (*AHI1*): **negative**
JOUBERT SYNDROME 31 (*CEP120*): **negative**

J
JOUBERT SYNDROME 34 (*B9D2*): **negative**
JOUBERT SYNDROME 8 (*ARL13B*): **negative**
JUNCTIONAL EPIDERMOLYSIS BULLOSA, LAMA3-RELATED (*LAMA3*): **negative**
JUNCTIONAL EPIDERMOLYSIS BULLOSA, LAMB3-RELATED (*LAMB3*): **negative**
JUNCTIONAL EPIDERMOLYSIS BULLOSA, LAMC2-RELATED (*LAMC2*): **negative**
JUVENILE NEPHRONOPHTHISIS (*INVS*): **negative**
JUVENILE NEPHRONOPHTHISIS (*NPHP1*): **negative**
JUVENILE RETINOSCHISIS, X-LINKED (*RS1*): **negative**

K
KRABBE DISEASE (*GALC*): **negative**

L
LAMELLAR ICHTHYOSIS, TYPE I (*TGM1*): **negative**
LEBER CONGENITAL AMAUROSIS, CEP290-RELATED (*CEP290*): **negative**
LEBER CONGENITAL AMAUROSIS, LCA5-RELATED (*LCA5*): **negative**
LEBER CONGENITAL AMAUROSIS, RPE65-RELATED (*RPE65*): **negative**
LEBER CONGENTIAL AMAUROSIS, RDH12-RELATED (*RDH12*): **negative**
LEIGH SYNDROME, FRENCH-CANADIAN (*LRPPRC*): **negative**
LESCH-NYHAN SYNDROME (*HPRT1*): **negative**
LETHAL CONGENITAL CONTRACTURE SYNDROME 1 (*GLE1*): **negative**
LEUKOENCEPHALOPATHY WITH VANISHING WHITE MATTER (*EIF2B5*): **negative**
LIMB-GIRDLE MUSCULAR DYSTROPHY, TYPE 2A (*CAPN3*): **negative**
LIMB-GIRDLE MUSCULAR DYSTROPHY, TYPE 2B (*DYSF*): **negative**
LIMB-GIRDLE MUSCULAR DYSTROPHY, TYPE 2C (*SGCG*): **negative**
LIMB-GIRDLE MUSCULAR DYSTROPHY, TYPE 2D (*SGCA*): **negative**
LIMB-GIRDLE MUSCULAR DYSTROPHY, TYPE 2E (*SGCB*): **negative**
LIMB-GIRDLE MUSCULAR DYSTROPHY, TYPE 2F (*SGCD*): **negative**
LIMB-GIRDLE MUSCULAR DYSTROPHY, TYPE 2I (*FKRP*): **negative**
LIPOPROTEIN LIPASE DEFICIENCY (*LPL*): **negative**
LISSENCEPHALY, X-LINKED 2 (*ARX*): **negative**
LONG CHAIN 3-HYDROXYACYL-COA DEHYDROGENASE DEFICIENCY (*HADHA*): **negative**
LOWE SYNDROME, X-LINKED (*OCRL*): **negative**
LYSINURIC PROTEIN INTOLERANCE (*SLC7A7*): **negative**

M
MALONYL-COA DECARBOXYLASE DEFICIENCY (*MLYCD*): **negative**
MAPLE SYRUP URINE DISEASE, TYPE 1A (*BCKDHA*): **negative**
MAPLE SYRUP URINE DISEASE, TYPE 1B (*BCKDHB*): **negative**
MAPLE SYRUP URINE DISEASE, TYPE 2 (*DBT*): **negative**
MECKEL SYNDROME 6 (*CC2D2A*): **negative**
MEDIUM CHAIN ACYL-COA DEHYDROGENASE DEFICIENCY (*ACADM*): **negative**
MEDNIK SYNDROME (*AP1S1*): **negative**
MEGALENCEPHALIC LEUKOENCEPHALOPATHY WITH SUBCORTICAL CYSTS (*MLC1*): **negative**
MEROSIN-DEFICIENT CONGENITAL MUSCULAR DYSTROPHY TYPE 1A (*LAMA2*): **negative**
METACHROMATIC LEUKODYSTROPHY, ARSA-RELATED (*ARSA*): **negative**
METACHROMATIC LEUKODYSTROPHY, PSAP-RELATED (*PSAP*): **negative**
METHYLMALONIC ACIDURIA, MMAA-RELATED (*MMAA*): **negative**
METHYLMALONIC ACIDURIA, MMAB-RELATED (*MMAB*): **negative**
METHYLMALONIC ACIDURIA, TYPE CBLC (*MMACHC*): **negative**
METHYLMALONIC ACIDURIA, TYPE CBLD (*MMADHC*): **negative**
MICROPTHALMIA / ANOPTHALMIA (*VSX2*): **negative**
MITOCHONDRIAL COMPLEX 1 DEFICIENCY, NDUFAF5-RELATED (*NDUFAF5*): **negative**
MITOCHONDRIAL COMPLEX 1 DEFICIENCY, NDUFS6-RELATED (*NDUFS6*): **negative**
MITOCHONDRIAL COMPLEX I DEFICIENCY, NUCLEAR TYPE 1 (*NDUFS4*): **negative**
MITOCHONDRIAL COMPLEX I DEFICIENCY, NUCLEAR TYPE 17 (*NDUFAF6*): **negative**
MITOCHONDRIAL COMPLEX IV DEFICIENCY (*PET100*): **negative**
MITOCHONDRIAL MYOPATHY AND SIDEROBLASTIC ANEMIA (*PUS1*): **negative**
MITOCHONDRIAL TRIFUNCTIONAL PROTEIN DEFICIENCY: HADHB RELATED (*HADHB*): **negative**
MKS1-RELATED DISORDERS (*MKS1*): **negative**
MOLYBDENUM COFACTOR DEFICIENCY OF COMPLEMENTATION GROUP A (*MOCS1*): **negative**
MUCOLIPIDOSIS III GAMMA (*GNPTG*): **negative**
MUCOLIPIDOSIS, TYPE II / III ALPHA / BETA (*GNPTAB*): **negative**
MUCOLIPIDOSIS, TYPE IV (*MCOLN1*): **negative**
MUCOPOLYSACCHARIDOSIS TYPE IVA (MPS4A) (*GALNS*): **negative**
MUCOPOLYSACCHARIDOSIS VII (*GUSB*): **negative**
MUCOPOLYSACCHARIDOSIS, TYPE I (HURLER SYNDROME) (*IDUA*): **negative**
MUCOPOLYSACCHARIDOSIS, TYPE II (HUNTER SYNDROME), X-LINKED (*IDS*): **negative**
MUCOPOLYSACCHARIDOSIS, TYPE IIIA (SANFILIPPO A) (*SGSH*): **negative**
MUCOPOLYSACCHARIDOSIS, TYPE IIIB (SANFILIPPO B) (*NAGLU*): **negative**
MUCOPOLYSACCHARIDOSIS, TYPE IIIC (SANFILIPPO C) (*HGSNAT*): **negative**
MUCOPOLYSACCHARIDOSIS, TYPE IIID (*GNS*): **negative**
MUCOPOLYSACCHARIDOSIS, TYPE IX (*HYAL1*): **negative**
MUCOPOLYSACCHARIDOSIS, TYPE VI (MAROTEAUX-LAMY) (*ARSB*): **negative**
MULIBREY NANISM (*TRIM37*): **negative**
MULTIPLE PTERYGIUM SYNDROME, LETHAL TYPE (*CHRNG*): **negative**
MULTIPLE SULFATASE DEFICIENCY (*SUMF1*): **negative**
MUSCLE-EYE-BRAIN DISEASE, POMGNT1-RELATED (*POMGNT1*): **negative**
MUSCULAR DYSTROPHY-DYSTROGLYCANOPATHY (CONGENITAL WITH BRAIN AND EYE ANOMALIES), TYPE A, 6 (*LARGE1*): **negative**

M

MUSCULAR DYSTROPHY-DYSTROGLYCANOPATHY (CONGENITAL WITH MENTAL RETARDATION), TYPE B, 2 (*POMT2*): **negative**
MUSCULAR DYSTROPHY-DYSTROGLYCANOPATHY (LIMB-GIRDLE), TYPE C, 7 (*ISPD*): **negative**
MYASTHENIC SYNDROME, CONGENITAL, 5 (*COLQ*): **negative**
MYONEUROGASTROINTESTINAL ENCEPHALOPATHY (MNGIE) (*TYMP*): **negative**
MYOTUBULAR MYOPATHY, MTM1-RELATED, X-LINKED (*MTM1*): **negative**

N

N-ACETYLGLUTAMATE SYNTHASE DEFICIENCY (*NAGS*): **negative**
NEMALINE MYOPATHY 2 (*NEB*): **negative**
NEPHROGENIC DIABETES INSIPIDUS (*AQP2*): **negative**
NEPHROTIC SYNDROME (*PLCE1*): **negative**
NEPHROTIC SYNDROME, TYPE 1 (*NPHS1*): **negative**
NEURONAL CEROID LIPOFUSCINOSIS, CLN3-RELATED (*CLN3*): **negative**
NEURONAL CEROID LIPOFUSCINOSIS, CLN5-RELATED (*CLN5*): **negative**
NEURONAL CEROID LIPOFUSCINOSIS, CLN6-RELATED (*CLN6*): **negative**
NEURONAL CEROID LIPOFUSCINOSIS, CLN8-RELATED (*CLN8*): **negative**
NEURONAL CEROID LIPOFUSCINOSIS, MFSD8-RELATED (*MFSD8*): **negative**
NEURONAL CEROID LIPOFUSCINOSIS, PPT1-RELATED (*PPT1*): **negative**
NEURONAL CEROID LIPOFUSCINOSIS, TPP1-RELATED (*TPP1*): **negative**
NIEMANN-PICK DISEASE, TYPE A / B (*SMPD1*): **negative**
NIEMANN-PICK DISEASE, TYPE CI / D (*NPC1*): **negative**
NIEMANN-PICK DISEASE, TYPE CII (*NPC2*): **negative**
NIJMEGEN BREAKAGE SYNDROME (*NBN*): **negative**
NONSYNDROMIC HEARING LOSS AND DEAFNESS: MYO15A RELATED (*MYO15A*): **negative**
NONSYNDROMIC HEARING LOSS, GJB2-RELATED (*GJB2*): **negative**

O

OCCIPITAL HORN SYNDROME (MOTOR NEUROPATHY, DISTAL), X-LINKED (*ATP7A*): **negative**
ODONTO-ONYCHO-DERMAL DYSPLASIA / SCHOPF-SCHULZ-PASSARGE SYNDROME (*WNT10A*): **negative**
OMENN SYNDROME (*DCLRE1C*): **negative**
OMENN SYNDROME, RAG2-RELATED (*RAG2*): **negative**
ORNITHINE AMINOTRANSFERASE DEFICIENCY (*OAT*): **negative**
ORNITHINE TRANSCARBAMYLASE DEFICIENCY, X-LINKED (*OTC*): **negative**
ORNITHINE TRANSLOCASE DEFICIENCY (*SLC25A15*): **negative**
OROFACIODIGITAL SYNDROME VI (*CPLANE1*): **negative**
OROFACIODIGITAL SYNDROME XIV (*C2CD3*): **negative**
OSTEOPETROSIS, INFANTILE MALIGNANT, TCIRG1-RELATED (*TCIRG1*): **negative**

P

PENDRED SYNDROME (*SLC26A4*): **negative**
PERLMAN SYNDROME (*DIS3L2*): **negative**
PEROXISOME BIOGENESIS DISORDER 3A (ZELLWEGER) (*PEX12*): **negative**
PHENYLALANINE HYDROXYLASE DEFICIENCY (*PAH*): **negative**
POLG-RELATED DISORDERS (*POLG*): **negative**
PONTOCEREBELLAR HYPOPLASIA (*EXOSC3*): **negative**
PONTOCEREBELLAR HYPOPLASIA TYPE 2B (*TSEN2*): **negative**
PONTOCEREBELLAR HYPOPLASIA TYPE 4 (*TSEN54*): **negative**
PONTOCEREBELLAR HYPOPLASIA, RARS2-RELATED (*RARS2*): **negative**
PONTOCEREBELLAR HYPOPLASIA, TYPE 2E (*VPS53*): **negative**
PONTOCEREBELLAR HYPOPLASIA, VRK1-RELATED (*VRK1*): **negative**
PRIMARY CILIARY DYSKINESIA, DNAH5-RELATED (*DNAH5*): **negative**
PRIMARY CILIARY DYSKINESIA, DNAI1-RELATED (*DNAI1*): **negative**
PRIMARY CILIARY DYSKINESIA, DNAI2-RELATED (*DNAI2*): **negative**
PRIMARY CONGENITAL GLAUCOMA (*CYP1B1*): **negative**
PRIMARY HYPEROXALURIA, TYPE I (*AGXT*): **negative**
PRIMARY HYPEROXALURIA, TYPE II (*GRHPR*): **negative**
PRIMARY HYPEROXALURIA, TYPE III (*HOGA1*): **negative**
PROGRESSIVE CEREBELLO-CEREBRAL ATROPHY (*SEPSECS*): **negative**
PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS, TYPE II (*ABCB11*): **negative**
PROLIDASE DEFICIENCY (*PEPD*): **negative**
PROP1-RELATED COMBINED PITUITARY HORMONE DEFICIENCY (*PROP1*): **negative**
PROPIONIC ACIDEMIA, PCCA-RELATED (*PCCA*): **negative**
PROPIONIC ACIDEMIA, PCCB-RELATED (*PCCB*): **negative**
PSEUDOCHOLINESTERASE DEFICIENCY (*BCHE*): **negative**
PSEUDOXANTHOMA ELASTICUM (*ABCC6*): **negative**
PYCNODYSOSTOSIS (*CTSK*): **negative**
PYRIDOXINE-DEPENDENT EPILEPSY (*ALDH7A1*): **negative**
PYRUVATE CARBOXYLASE DEFICIENCY (*PC*): **negative**
PYRUVATE DEHYDROGENASE DEFICIENCY, PDHA1-RELATED, X-LINKED (*PDHA1*): **negative**
PYRUVATE DEHYDROGENASE DEFICIENCY, PDHB-RELATED (*PDHB*): **negative**

R

RECURRENT METABOLIC CRISES WITH RHABDOMYOLYSIS, CARDIAC ARRHYTHMIAS, AND NEURODEGENERATION (*TANGO2*): **negative**
REFSUM DISEASE (*PHYH*): **negative**
RENAL TUBULAR ACIDOSIS (*SLC4A4*): **negative**
RENAL TUBULAR ACIDOSIS AND DEAFNESS, ATP6V1B1-RELATED (*ATP6V1B1*): **negative**
RENAL-HEPATIC-PANCREATIC DYSPLASIA 1 (*NPHP3*): **negative**
RETINITIS PIGMENTOSA 25 (*EYS*): **negative**

R
RETINITIS PIGMENTOSA 26 (*CERKL*): **negative**
RETINITIS PIGMENTOSA 28 (*FAM161A*): **negative**
RETINITIS PIGMENTOSA 59 (*DHDDS*): **negative**
RHIZOMELIC CHONDRODYSPLASIA PUNCTATA, TYPE 2 (*GNPAT*): **negative**
RHIZOMELIC CHONDRODYSPLASIA PUNCTATA, TYPE I (*PEX7*): **negative**
RHIZOMELIC CHONDRODYSPLASIA PUNCTATA, TYPE III (*AGPS*): **negative**
RIBOFLAVIN RESPONSIVE COMPLEX 1 DEFICIENCY (ACYL-COENZYME DEHYDROGENASE 9 DEFICIENCY) (*ACAD9*): **negative**
ROBERTS SYNDROME (*ESCO2*): **negative**

S
SALLA DISEASE (*SLC17A5*): **negative**
SANDHOFF DISEASE (*HEXB*): **negative**
SCHIMKE IMMUNOOSSEOUS DYSPLASIA (*SMARCAL1*): **negative**
SENIOR-LOKEN SYNDROME 4 (*NPHP4*): **negative**
SENIOR-LOKEN SYNDROME 5 (*IQCB1*): **negative**
SEVERE COMBINED IMMUNODEFICIENCY, IL2RG-RELATED, X-LINKED (*IL2RG*): **negative**
SHWACHMAN-DIAMOND SYNDROME (*SBDS*): **negative**
SIALIDOSIS, TYPE II (*NEU1*): **negative**
SJOGREN-LARSSON SYNDROME (*ALDH3A2*): **negative**
SLC26A2-RELATED SKELETAL DYSPLASIAS (*SLC26A2*): **negative**
SMITH-LEMLI-OPITZ SYNDROME (*DHCR7*): **negative**
SPASTIC ATAXIA OF CHARLEVOIX-SAGUENAY (ARSACS) (*SACS*): **negative**
SPASTIC PARAPLEGIA TYPE 15 (*ZFYVE26*): **negative**
SPINAL MUSCULAR ATROPHY (*SMN1*): **negative**
SPINOCEREBELLAR ATAXIA-12 (*WWOX*): **negative**
SPONDYLOTHORACIC DYSOSTOSIS (*MESP2*): **negative**
STEEL SYNDROME (*COL27A1*): **negative**
STEROID RESISTANT NEPHROTIC SYNDROME (*NPHS2*): **negative**
STUVE-WIEDEMANN SYNDROME (*LIFR*): **negative**

T
T CELL-NEGATIVE (T-), B CELL-NEGATIVE (B-), NATURAL KILLER CELL-POSITIVE (NK +) SEVERE COMBINED IMMUNODEFICIENCY (*RAG1*): **negative**
TAY-SACHS DISEASE (*HEXA*): **negative**
TRICHOHEPATOENTERIC SYNDROME 1 (*TTC37*): **negative**
TRIPLE A SYNDROME (*AAAS*): **negative**
TYROSINE HYDROXYLASE DEFICIENCY (*TH*): **negative**
TYROSINEMIA, TYPE I (*FAH*): **negative**
TYROSINEMIA, TYPE II (*TAT*): **negative**

U
USHER SYNDROME, TYPE 2C (*ADGRV1*): **negative**
USHER SYNDROME, TYPE IB (*MYO7A*): **negative**
USHER SYNDROME, TYPE IC (*USH1C*): **negative**
USHER SYNDROME, TYPE ID (*CDH23*): **negative**
USHER SYNDROME, TYPE IF (*PCDH15*): **negative**
USHER SYNDROME, TYPE IIA (*USH2A*): **negative**
USHER SYNDROME, TYPE III (*CLRN1*): **negative**

V
VERY LONG-CHAIN ACYL-COA DEHYDROGENASE DEFICIENCY (*ACADVL*): **negative**
VITAMIN D-DEPENDENT RICKETS, TYPE I (*CYP27B1*): **negative**

W
WALKER-WARBURG SYNDROME, FKTN-RELATED (*FKTN*): **negative**
WERNER SYNDROME (*WRN*): **negative**
WILSON DISEASE (*ATP7B*): **negative**
WISKOTT-ALDRICH SYNDROME, X-LINKED (*WAS*): **negative**
WOLCOTT-RALLISON SYNDROME; EPIPHYSEAL DYSPLASIA, MULTIPLE WITH EARLY-ONSET DIABETES MELLITUS (*EIF2AK3*): **negative**

X
XERODERMA PIGMENTOSUM, GROUP A (*XPA*): **negative**
XERODERMA PIGMENTOSUM, GROUP C (*XPC*): **negative**
X-LINKED CHONDRODYSPLASIA PUNCTATA 1 (*ARSE*): **negative**
X-LINKED CONGENITAL ADRENAL HYPOPLASIA (*NR0B1*): **negative**
X-LINKED HETEROTAXY-1 AND MULTIPLE TYPES OF CONGENITAL HEART DEFECTS-1 (*ZIC3*): **negative**
X-LINKED HYPER IGM SYNDROME (*CD40LG*): **negative**
X-LINKED LISSENCEPHALY-1 (*DCX*): **negative**

Z
ZELLWEGER SPECTRUM DISORDERS, PEX10-RELATED (*PEX10*): **negative**
ZELLWEGER SPECTRUM DISORDERS, PEX1-RELATED (*PEX1*): **negative**
ZELLWEGER SPECTRUM DISORDERS, PEX2-RELATED (*PEX2*): **negative**
ZELLWEGER SPECTRUM DISORDERS, PEX6-RELATED (*PEX6*): **negative**
ZELLWEGER SYNDROME (*PEX26*): **negative**

METHODOLOGY

Next-generation sequencing (NGS)

1. For the paired-end pre-capture library procedure, genomic DNA is fragmented by sonication and ligated to the Illumina multiplexing PE adapters with sequencing barcodes (indexes). The adapter-ligated DNA is then PCR amplified using primers. For the target enrichment capture procedure, the pre-capture libraries are pooled as a 47-plex and enriched by hybridizing to biotin- labeled probe (smallUTCv3) in-solution at 56C or 47C for 16-48 hours. The post-capture library DNA is subjected to massively parallel sequencing on the Illumina HiSeq 2500 platform for 100 bp paired-end reads. The following quality control metrics of the sequencing data are generally achieved: >98% target bases covered at >20X, >95% target bases covered at >40X, mean coverage oftarget bases at >120X. SNP concordance to genotype array: >95%. This test may not provide detection of a portion of the gene due to local sequence characteristics or the presence of closely related pseudogenes. Terminal deletions and duplications may not be fully delineated. Partial exonic copy number changes and sequences present in repetitive sequences may not be identified by this methodology.
2. As a quality control measure, analysis includes a genotyping assay performed by the Fluidigm SNPtype platform using the SNPTrace Panel. The SNPTrace Panel consists of 90 autosomal loci and 6 allosome loci (3 SNPs each on chrX and chrY). Samples and assays are transferred to a 96 Fluidigm Dynamic array, loaded to reaction chambers by an integrated fluidic circuit (IFC) controller, thermal cycled, and endpoint-imaged on the BioMark HD System (Fluidigm). The SNP data are first analyzed by SNP Genotyping Analysis Software (Fluidigm) and then by comparison with the genotype calls made from the Dragen BioIT Platform for NGS data to ensure correct sample identification. Once an assessment of identity match is established, contamination analysis is performed by using homozygous sites and computational inspection of BAM data.
3. Data analysis and interpretation are performed by the Baylor Genetics analytics pipeline. The output data from the Illumina HiSeq are converted from BCL files to FastQ files according to each sample's specific adapter sequence using Illumina's recommended procedure. FastQ data are aligned to the human reference genome using the Dragen BioIT Platform (Illumina). The output of the alignment is a BAM file; QC metrics of the map-align process are recorded for quality review. QC statistics include coverage for target genes and known pathogenic variant sites, mate-pair alignment information as well as number of total and duplicate reads. Variant calling on the BAM file is performed using the Dragen haplotype-based variant calling system. The variant calling step generates a "raw" VCF file containing a list of detected variants, which are then annotated using a locally installed annotation system. The annotation platform leverages the GenomOncology Knowledge Management System API and provides annotations using open source data sets such as ExAC, EVS, and ClinVar and professional resources such as HGMD Pro. The API also provides HGVS nomenclature built using the Biocommons open-source suite of tools: HGVS python library, the UTA transcript repository, and SeqRepo sequence database. This annotation system reports zygosity as well as inference of mutation types including nonsense, missense, synonymous, splicing and frameshift, among others. Synonymous variants, intronic variants not affecting splicing sites, and common benign variants are excluded from interpretation unless previously reported as pathogenic variants. It should be noted that the data interpretation is based on our current understanding of the gene and variants at the time of reporting. The sequence alignment, variant calling and annotation algorithms may be updated periodically with validated improvements and increments to the knowledgebase.
4. Copy number variants (CNV) are analyzed by the Baylor Genetics analytics pipeline. CNV analysis is limited to deletions involving more than one exon for most genes in the panel, except specific known recurrent deletion events, and exonic deletion and multi-exonic duplication events of CFTR, DMD, and HBB. The method does not detect gene inversions, most single-exonic deletions, and duplications. Additionally, the method does not define the exact deletion/duplication boundaries of detected CNV events. Confirmation testing for copy number variation is performed by specific PCR, Multiplex Ligation-dependent Probe Amplification (MLPA), next generation sequencing, or other methods for confirmation and variant sizing; additional information.
5. SMN1 exon 7 deletion and g.27134T>G SNP analysis is performed by the Baylor Genetics analytics pipeline. The SMN1 analysis does not identify a carrier who has an exon 7 deletion on one chromosome and two copies of the SMN1 gene on the other chromosome.
6. If CYP21A2 is tested, CYP21A2 deletion and sequencing variant analysis is performed by the Baylor Genetics analytics pipeline. Specific enhancement on variant detection is applied to c.92C>T (p.P31L), c.293-13C>G, c.332_339delGAGACTAC (p.G111Vfs*21), c.518T>A (p.I173N), c.(710T>A;713T>A)(I237N;V238E), c.844G>T (p.V282L), c.923dupT (p.L308Ffs*6), c.955C>T (p.Q319*), c.1069C>T (p.R357W), c.1360C>T (p.P454S). CYP21A2 duplication will be reflexed if c.955C>T (p.Q319*) is detected. Sequencing variants outside these regions might be detected as well.

Reflex Testing

If the CFTR R117H variant is detected, reflex testing of the polythymidine variations (5T, 7T and 9T) at the intron 9 (legacy intron number 8) branch/acceptor site of the CFTR gene will be performed. The polythymidine variations (5T, 7T and 9T) are analyzed by Sanger sequencing.

Sanger Sequencing

A PCR-based assay is used to amplify the region(s) of interest in the gene. Direct sequence analysis of PCR products is performed in both the forward and reverse directions using automated fluorescence dideoxy sequencing methods.

Fragile X

The CGG repeat region at the FMR1 5'-untranslated region is amplified by fluorescent PCR followed by capillary electrophoresis. Allele sizes up to 200 repeats are analyzed by GeneMapper software. Reflex Southern blot analysis will be performed for samples with full mutation allele in order to assess size and methylation status for larger repeats. This analysis does not detect deletions or point mutations, which comprises less than one percent of the FMR1 pathogenic variants.

Spinal Muscular Atrophy

The total combined copy number of SMN1 and SMN2 exon 7 is quantified based on NGS read depth. The ratio of SMN1 to SMN2 is calculated based on the read-depth of a single nucleotide that distinguishes these two genes in exon 7. In addition to copy number analysis, testing for the presence of absence of a single nucleotide polymorphism (g.27134T>G in intron 7 of SMN1) associated with the presence of a SMN1 duplication allele is performed using NGS.