

DATE: 3/3/2022



Reproductive Technologies, Inc.

THE SPERM BANK OF CALIFORNIA

EXPANDED CARRIER SCREENING RESULTS DONOR 5807

Expanded carrier screening for 268 autosomal recessive conditions was completed by Invitae and reported on 12/24/2021.

The results were **NEGATIVE** for all 268 conditions.

Disease	Result	Residual risk to be a carrier
Cystic Fibrosis	Negative	1 in 4,400
Spinal Muscular Atrophy	Negative - 2 copies exon 7 Negative for c.*3+80T>G variant in exon 7	1 in 784
HBB Hemoglobinopathies	Negative	1 in 1,600
Alpha thalassemia	Negative	1 in 241

Genetic tests can significantly reduce, but never completely eliminate, the chance that a person is a carrier for a particular disorder.

Please refer to the donor's Invitae expanded carrier test report for more information on the testing completed and the donor's results.

Please also see the Health Problems List for a summary of the information that this donor has provided to us regarding personal and family medical history.

Sincerely,

Janine Mash
LCGC Certified Genetic Counselor
San Francisco Genetic Counseling

At the request of another recipient, screening for the following recessive conditions was performed by Sema4 and reported on 02/15/2022.

This testing was performed through Sema4 because Invitae does not include these genes in their Expanded Carrier Screening panel.

The results were **NEGATIVE** for the conditions tested.

Disease	Result	Residual risk to be a carrier
Shwachman-Diamond Syndrome (SBDS)	Negative	1 in 1,700
Biotinidase Deficiency (BTD)	Negative	1 in 500

Genetic tests can significantly reduce, but never completely eliminate, the chance that a person is a carrier for a particular disorder.

Please refer to the donor's Sema4 test report for more information on the testing completed and the donor's results.

Please also see the Health Problems List for a summary of the information that this donor has provided to us regarding personal and family medical history.

Sincerely,

Janine Mash
 LCGC Certified Genetic Counselor
 San Francisco Genetic Counseling

Patient name: 5807 DONOR	Sample type: Saliva	Report date: 12/24/2021
DOB:	Sample collection date: 12/16/2021	Invitae #: RQ3010441
Sex assigned at birth: Male	Sample accession date: 12/17/2021	Clinical team: Janine Mash
Gender:	MRN:	Lorraine Bonner, MD

Reason for testing

Gamete donor

Test performed

Invitae Comprehensive Carrier Screen without X-linked Disorders

- Primary Panel (CF, SMA)
- Add-on Comprehensive Carrier Screen without X-linked Disorders genes


RESULT: NEGATIVE

This carrier test evaluated 268 gene(s) for genetic changes (variants) that are associated with an increased risk of having a child with a genetic condition. Knowledge of carrier status for one of these conditions may provide information that can be used to assist with family planning and/or preparation.

This test did not identify any genetic changes in the gene(s) analyzed that are currently recognized as clinically significant. This negative result reduces, but does not eliminate, the chance that this individual is a carrier for conditions caused by any of the genes tested. This individual may still be a carrier for a genetic condition that is not evaluated by this test.

Next steps

- Even for genes that have a negative test result, there is always a small risk that an individual could still be a carrier. This is called “residual risk.” See the table below for residual risks, which presumes a negative family history of the conditions listed.
- Discussion with a physician and/or genetic counselor is recommended to further review the implications of this test result and to understand these results in the context of any family history of a genetic condition.
- All patients, regardless of result, may wish to consider additional screening for hemoglobinopathies by complete blood count (CBC) and hemoglobin electrophoresis, if this has not already been completed.
- Individuals can register their tests at <https://www.invitae.com/patients/> to access online results, educational resources, and next steps.

Residual risk

This table displays residual risks after a negative result for each of the genes and corresponding disorders. The values provided assume a negative family history and the absence of symptoms for each disorder. For genes associated with both dominant and recessive inheritance, the numbers in this table apply to the recessive condition(s) associated with the gene. Residual risk values are provided for disorders when carrier frequency is greater than 1 in 500. For disorders with carrier frequency equal to, or less than, 1 in 500, residual risk is considered to be reduced substantially. When provided, residual risk values are inferred from published carrier frequencies, and estimated detection rates are based on testing technologies used at Invitae. Residual risks are provided only as a guide for assessing approximate risk given a negative result; values will vary based on the ethnic background of an individual. For individuals of mixed ethnicity, it is recommended to use the highest residual risk estimate. For any genes marked with an asterisk*, refer to the Limitations section below for detailed coverage information. In the case of a sample-specific limitation, "N/A" indicates that a residual risk value could not be calculated. AR = autosomal recessive, XL = X-linked, AD = autosomal dominant.

DISORDER (INHERITANCE)	GENE	ETHNICITY	CARRIER FREQUENCY BEFORE SCREENING	CARRIER RESIDUAL RISK AFTER NEGATIVE RESULT
3-hydroxy-3-methylglutaryl-CoA lyase deficiency (AR) NM_000191.2	HMGCL	Pan-ethnic	≤1 in 500	Reduced
		Portuguese	1 in 160	1 in 15900
ABCB11-related conditions (AR) NM_003742.2	ABCB11	Pan-ethnic	1 in 100	1 in 9900
ABCC8-related conditions (AR) NM_000352.4 When the mother is a noncarrier, but the father is a carrier, there is a residual risk for focal disease (1 in 540 for the Ashkenazi Jewish population; undetermined in other ethnic groups)	ABCC8	Ashkenazi Jewish	1 in 52	1 in 5100
		Finnish	1 in 100	1 in 9900
		Pan-ethnic	1 in 177	1 in 17600
Abetalipoproteinemia (AR) NM_000253.3	MTTP	Ashkenazi Jewish	1 in 131	1 in 13000
		Pan-ethnic	≤1 in 500	Reduced
Achromatopsia (CNGB3-related) (AR) NM_019098.4	CNGB3	Pan-ethnic	1 in 93	1 in 9200
ACOX1-related conditions (AR) NM_004035.6	ACOX1	Pan-ethnic	≤1 in 500	Reduced
Acrodermatitis enteropathica (AR) NM_130849.3	SLC39A4	Pan-ethnic	1 in 354	1 in 35300
Adenosine deaminase deficiency (AR) NM_000022.2	ADA	Pan-ethnic	1 in 224	1 in 2788
Aicardi-Goutieres syndrome 5 (AR) NM_015474.3	SAMHD1	Pan-ethnic	≤1 in 500	Reduced
Aldosterone synthase deficiency (AR) NM_000498.3	CYP11B2	Pan-ethnic	≤1 in 500	Reduced
		Sephardic Jewish (Iranian)	1 in 30	1 in 2900
Alpha-mannosidosis (AR) NM_000528.3	MAN2B1	Pan-ethnic	1 in 354	1 in 35300
Alpha-thalassemia (AR) NM_000517.4, NM_000558.4	HBA2/ HBA1 *	African-American	1 in 30	1 in 291
		Asian	1 in 20	1 in 191
		Caucasian	≤1 in 500	Reduced
		Pan-ethnic	1 in 25	1 in 241
		Ashkenazi Jewish	1 in 192	1 in 19100
Alport syndrome (COL4A3-related) (AR) NM_000091.4	COL4A3	Caucasian	1 in 284	1 in 28300
		Pan-ethnic	1 in 354	1 in 35300
		Ashkenazi Jewish	1 in 192	1 in 19100
Alport syndrome (COL4A4-related) (AR) NM_000092.4	COL4A4	Pan-ethnic	1 in 353	1 in 35200
Alström syndrome (AR) NM_015120.4	ALMS1	Pan-ethnic	≤1 in 500	Reduced
Arginase deficiency (AR) NM_000045.3	ARG1	Pan-ethnic	1 in 274	1 in 27300
Argininosuccinate lyase deficiency (AR) NM_000048.3	ASL	Pan-ethnic	1 in 133	1 in 1321
Aromatase deficiency (AR) NM_031226.2	CYP19A1	Pan-ethnic	≤1 in 500	Reduced
Asparagine synthetase deficiency (AR) NM_133436.3	ASNS	Pan-ethnic	≤1 in 500	Reduced

DISORDER (INHERITANCE)	GENE	ETHNICITY	CARRIER FREQUENCY BEFORE SCREENING	CARRIER RESIDUAL RISK AFTER NEGATIVE RESULT
		Sephardic Jewish (Iranian)	1 in 80	1 in 7900
Aspartylglucosaminuria (AR) NM_000027.3	AGA	Finnish	1 in 69	1 in 6800
		Pan-ethnic	≤1 in 500	Reduced
Ataxia with vitamin E deficiency (AR) NM_000370.3	TTPA	Italian	1 in 274	1 in 2731
		Pan-ethnic	≤1 in 500	Reduced
ATM-related conditions (AR) NM_000051.3	ATM	Pan-ethnic	1 in 100	1 in 9900
		Sephardic Jewish	1 in 69	1 in 6800
Autoimmune polyendocrinopathy with candidiasis and ectodermal dysplasia (AR) NM_000383.3	AIRE	Finnish	1 in 79	1 in 7800
		Pan-ethnic	1 in 150	1 in 14900
		Sardinian	1 in 60	1 in 5900
		Sephardic Jewish (Iranian)	1 in 48	1 in 4700
Autosomal recessive congenital ichthyosis (TGM1-related) (AR) NM_000359.2	TGM1	Norwegian	1 in 151	1 in 3000
		Pan-ethnic	1 in 224	1 in 4460
Autosomal recessive spastic ataxia of Charlevoix-Saguenay (AR) NM_014363.5	SACS	French Canadian (Saguenay-Lac-St-Jean)	1 in 21	1 in 2000
		Pan-ethnic	≤1 in 500	Reduced
Bardet-Biedl syndrome (BBS10-related) (AR) NM_024685.3	BBS10	Pan-ethnic	1 in 354	1 in 35300
Bardet-Biedl syndrome (BBS12-related) (AR) NM_152618.2	BBS12	Pan-ethnic	1 in 708	Reduced
BBS1-related conditions (AR) NM_024649.4	BBS1	Faroese	1 in 30	1 in 2900
		Pan-ethnic	1 in 330	1 in 32900
BBS2-related conditions (AR) NM_031885.3	BBS2	Ashkenazi Jewish	1 in 140	1 in 13900
		Pan-ethnic	1 in 560	Reduced
BCS1L-related conditions (AR) NM_004328.4	BCS1L	Caucasian	1 in 407	1 in 40600
		Finnish	1 in 108	1 in 10700
		Pan-ethnic	≤1 in 500	Reduced
Beta-ketothiolase deficiency (AR) NM_000019.3	ACAT1	Caucasian	1 in 354	1 in 35300
		Pan-ethnic	≤1 in 500	Reduced
Biopterin-deficient hyperphenylalaninemia (PTS-related) (AR) NM_000317.2	PTS	Chinese	1 in 122	1 in 12100
		Pan-ethnic	1 in 433	1 in 43200
Bloom syndrome (AR) NM_000057.3	BLM	Ashkenazi Jewish	1 in 100	1 in 9900
		Pan-ethnic	≤1 in 500	Reduced
BSND-related conditions (AR) NM_057176.2	BSND	Pan-ethnic	≤1 in 500	Reduced
Canavan disease (AR) NM_000049.2	ASPA	Ashkenazi Jewish	1 in 57	1 in 5600
		Pan-ethnic	1 in 159	1 in 15800
Carbamoyl phosphate synthetase I deficiency (AR) NM_001875.4	CPS1	Pan-ethnic	≤1 in 500	Reduced
Carnitine palmitoyltransferase I deficiency (AR) NM_001876.3	CPT1A	Hutterite	1 in 16	1 in 1500
		Pan-ethnic	≤1 in 500	Reduced
Carnitine palmitoyltransferase II deficiency (AR) NM_000098.2	CPT2	Ashkenazi Jewish	1 in 45	1 in 4400
		Pan-ethnic	1 in 182	1 in 18100
Carpenter syndrome (RAB23-related) (AR) NM_183227.2	RAB23	Pan-ethnic	≤1 in 500	Reduced
Cartilage-hair hypoplasia-anauxetic dysplasia spectrum disorders (AR) NR_003051.3	RMRP	Amish	1 in 10	1 in 900
		Finnish	1 in 76	1 in 7500
		Pan-ethnic	≤1 in 500	Reduced
CDH23-related conditions (AR) NM_022124.5	CDH23	Pan-ethnic	1 in 202	1 in 4020
CEP290-related conditions (AR) NM_025114.3	CEP290	Pan-ethnic	1 in 185	1 in 18400
Cerebrotendinous xanthomatosis (AR) NM_000784.3	CYP27A1	Pan-ethnic	1 in 112	1 in 5550
		Sephardic Jewish	1 in 76	1 in 3750
CERKL-related conditions (AR) NM_001030311.2	CERKL	Pan-ethnic	1 in 137	1 in 13600
		Sephardic Jewish	1 in 24	1 in 2300

DISORDER (INHERITANCE)	GENE	ETHNICITY	CARRIER FREQUENCY BEFORE SCREENING	CARRIER RESIDUAL RISK AFTER NEGATIVE RESULT
CFTR-related conditions (AR) NM_000492.3	CFTR	African-American - classic CF	1 in 61	1 in 6000
		Ashkenazi Jewish - classic CF	1 in 29	1 in 2800
		Asian - classic CF	1 in 88	1 in 8700
		Caucasian - classic CF	1 in 28	1 in 2700
		Pan-ethnic - classic CF	1 in 45	1 in 4400
		Pan-ethnic - classic CF and CFTR-related disorders	1 in 9	1 in 800
Charcot-Marie-Tooth disease type 4D (AR) NM_006096.3	NDRG1	Pan-ethnic	≤1 in 500	Reduced
		Roma	1 in 22	1 in 2100
Chorea-acanthocytosis (AR) NM_033305.2	VPS13A *	Pan-ethnic	≤1 in 500	Reduced
Chronic granulomatous disease (CYBA-related) (AR) NM_000101.3	CYBA	Pan-ethnic	≤1 in 500	Reduced
		Sephardic Jewish (Moroccan)	1 in 13	1 in 1200
Citrin deficiency (AR) NM_014251.2	SLC25A13	Chinese	1 in 65	1 in 6400
		Japanese	1 in 65	1 in 6400
		Korean	1 in 112	1 in 11100
		Pan-ethnic	1 in 313	1 in 31200
		Southern Chinese and Taiwanese	1 in 48	1 in 4700
Citrullinemia type 1 (AR) NM_000050.4	ASS1	Pan-ethnic	1 in 120	1 in 2975
CLN3-related conditions (AR) NM_001042432.1	CLN3	Pan-ethnic	1 in 230	1 in 22900
CLRN1-related conditions (AR) NM_174878.2	CLRN1	Ashkenazi Jewish	1 in 120	1 in 11900
		Pan-ethnic	1 in 533	Reduced
Cobalamin C deficiency (AR) NM_015506.2	MMACHC	Pan-ethnic	1 in 123	1 in 12200
Cobalamin D deficiency (AR) NM_015702.2	MMADHC *	Pan-ethnic	≤1 in 500	Reduced
Cockayne syndrome A (AR) NM_000082.3	ERCC8	Pan-ethnic	1 in 514	Reduced
Cockayne syndrome B (AR) NM_000124.3	ERCC6	Pan-ethnic	1 in 377	1 in 37600
Cohen syndrome (AR) NM_017890.4	VPS13B	Amish (Ohio)	1 in 12	1 in 1100
		Pan-ethnic	≤1 in 500	Reduced
Combined malonic and methylmalonic aciduria (AR) NM_174917.4	ACSF3	Pan-ethnic	1 in 87	1 in 8600
Combined oxidative phosphorylation deficiency 1 (AR) NM_024996.5	GFM1	Pan-ethnic	≤1 in 500	Reduced
Combined oxidative phosphorylation deficiency 3 (AR) NM_001172696.1	TSFM *	Finnish	1 in 80	1 in 1129
		Pan-ethnic	≤1 in 500	Reduced
Combined pituitary hormone deficiency (LHX3-related) (AR) NM_014564.4	LHX3	Pan-ethnic	≤1 in 500	Reduced
Combined pituitary hormone deficiency (PROP1-related) (AR) NM_006261.4	PROP1	Pan-ethnic	1 in 45	1 in 2200
Congenital adrenal hyperplasia due to 3-beta-hydroxysteroid dehydrogenase deficiency (AR) NM_000198.3	HSD3B2	Pan-ethnic	≤1 in 500	Reduced
Congenital adrenal hyperplasia due to 21-hydroxylase deficiency (AR) NM_000500.7	CYP21A2 *	Pan-ethnic	1 in 61	1 in 751
Congenital disorder of glycosylation (SLC35A3-related) (AR) NM_012243.2	SLC35A3	Ashkenazi Jewish	1 in 469	1 in 46800
		Pan-ethnic	≤1 in 500	Reduced
Congenital disorder of glycosylation type Ia (AR) NM_000303.2	PMM2	Ashkenazi Jewish	1 in 61	1 in 6000
		Caucasian	1 in 60	1 in 5900
		Pan-ethnic	1 in 190	1 in 18900
Congenital disorder of glycosylation type Ib (AR) NM_002435.2	MPI	Pan-ethnic	≤1 in 500	Reduced

DISORDER (INHERITANCE)	GENE	ETHNICITY	CARRIER FREQUENCY BEFORE SCREENING	CARRIER RESIDUAL RISK AFTER NEGATIVE RESULT
Congenital disorder of glycosylation type Ic (AR) NM_013339.3	ALG6 *	Pan-ethnic	≤1 in 500	Reduced
Congenital insensitivity to pain with anhidrosis (AR) NM_001012331.1	NTRK1	Pan-ethnic	≤1 in 500	Reduced
Congenital myasthenic syndrome (CHRNE-related) (AR) NM_000080.3	CHRNE	European Roma	1 in 25	1 in 2400
		Pan-ethnic	1 in 200	1 in 19900
Congenital nephrotic syndrome type 1 (AR) NM_004646.3	NPHS1	Finnish	1 in 46	1 in 4500
		Old Order Mennonite	1 in 12	1 in 1100
		Pan-ethnic	≤1 in 500	Reduced
Congenital nephrotic syndrome type 2 (AR) NM_014625.3	NPHS2	Pan-ethnic	≤1 in 500	Reduced
Corneal dystrophy and perceptive deafness (AR) NM_032034.3	SLC4A11	Pan-ethnic	≤1 in 500	Reduced
CRB1-related conditions (AR) NM_201253.2	CRB1	Pan-ethnic	1 in 112	1 in 11100
CYP11B1-related conditions (AR) NM_000497.3	CYP11B1	Pan-ethnic	1 in 194	1 in 19300
		Sephardic Jewish (Moroccan)	1 in 40	1 in 3900
CYP17A1-related conditions (AR) NM_000102.3	CYP17A1	Pan-ethnic	≤1 in 500	Reduced
Cystinosis (AR) NM_004937.2	CTNS	French Canadian (Saguenay-Lac-St-Jean)	1 in 39	1 in 3800
		Pan-ethnic	1 in 158	1 in 15700
		Sephardic Jewish (Moroccan)	1 in 100	1 in 9900
DHDDS-related conditions (AR) NM_024887.3	DHDDS	Ashkenazi Jewish	1 in 117	1 in 11600
		Pan-ethnic	≤1 in 500	Reduced
Dihydroipoamide dehydrogenase deficiency (AR) NM_000108.4	DLD	Ashkenazi Jewish	1 in 107	1 in 5300
		Pan-ethnic	≤1 in 500	Reduced
Distal renal tubular acidosis with deafness (ATP6V1B1-related) (AR) NM_001692.3	ATP6V1B1	Pan-ethnic	≤1 in 500	Reduced
		Sephardic Jewish	1 in 140	1 in 13900
DYSF-related conditions (AR) NM_003494.3	DYSF	Pan-ethnic	1 in 311	1 in 31000
		Sephardic Jewish (Libyan)	1 in 10	1 in 900
Dyskeratosis congenita spectrum disorders (RTEL1-related) (AR) NM_001283009.1	RTEL1	Ashkenazi Jewish	1 in 222	1 in 22100
		Pan-ethnic	≤1 in 500	Reduced
Dystrophic epidermolysis bullosa (AR) NM_000094.3	COL7A1	Pan-ethnic	1 in 370	1 in 12300
Ehlers-Danlos syndrome, dermatosparaxis type (AR) NM_014244.4	ADAMTS2	Ashkenazi Jewish	1 in 187	1 in 18600
		Pan-ethnic	≤1 in 500	Reduced
Ellis-van Creveld syndrome (EVC-related) (AR) NM_153717.2	EVC	Amish	1 in 8	1 in 700
		Pan-ethnic	1 in 220	1 in 21900
Ethylmalonic encephalopathy (AR) NM_014297.3	ETHE1	Pan-ethnic	≤1 in 500	Reduced
EVC2-related conditions (AR) NM_147127.4	EVC2	Pan-ethnic	1 in 199	1 in 19800
Familial chylomicronemia syndrome (AR) NM_000237.2	LPL	French Canadian (Saguenay-Lac-St-Jean)	1 in 46	1 in 4500
		Pan-ethnic	≤1 in 500	Reduced
Familial dysautonomia (AR) NM_003640.3	ELP1	Ashkenazi Jewish	1 in 36	1 in 3500
		Pan-ethnic	≤1 in 500	Reduced
Familial hypercholesterolemia (LDLR-related) (AD) NM_000527.4	LDLR	Afrikaner	1 in 72	1 in 7100
		Ashkenazi Jewish	1 in 69	1 in 6800
		French Canadian	1 in 270	1 in 26900
		Pan-ethnic	1 in 250	1 in 24900
Familial hypercholesterolemia (LDLRAP1-related) (AR) NM_015627.2	LDLRAP1	Pan-ethnic	≤1 in 500	Reduced
		Sardinian	1 in 143	1 in 14200
Fanconi anemia type A (AR) NM_000135.2	FANCA	Afrikaner	1 in 83	1 in 8200
		Pan-ethnic	1 in 345	1 in 34400

DISORDER (INHERITANCE)	GENE	ETHNICITY	CARRIER FREQUENCY BEFORE SCREENING	CARRIER RESIDUAL RISK AFTER NEGATIVE RESULT
		Sephardic Jewish	1 in 133	1 in 13200
		Spanish Roma	1 in 64	1 in 6300
Fanconi anemia type C (AR) NM_000136.2	FANCC	Ashkenazi Jewish	1 in 89	1 in 8800
		Pan-ethnic	1 in 417	1 in 41600
Fanconi anemia type G (AR) NM_004629.1	FANCG	African-American	1 in 100	1 in 9900
		Pan-ethnic	≤1 in 500	Reduced
FH-related conditions (AR) NM_000143.3	FH	Pan-ethnic	≤1 in 500	Reduced
Galactokinase deficiency galactosemia (AR) NM_000154.1	GALK1	Pan-ethnic	1 in 122	1 in 12100
		Roma	1 in 47	1 in 4600
Galactosemia (GALT-related) (AR) NM_000155.3	GALT	African-American	1 in 87	1 in 8600
		Ashkenazi Jewish	1 in 156	1 in 15500
		Irish Traveller	1 in 11	1 in 1000
		Pan-ethnic	1 in 100	1 in 9900
GBA-related conditions including Gaucher disease (AR) NM_001005741.2	GBA *	Ashkenazi Jewish	1 in 15	1 in 234
		Pan-ethnic	1 in 158	1 in 561
GBE1-related conditions (AR) NM_000158.3	GBE1	Ashkenazi Jewish	1 in 68	1 in 6700
		Pan-ethnic	1 in 387	1 in 38600
Gitelman syndrome (AR) NM_000339.2	SLC12A3	Pan-ethnic	1 in 100	1 in 9900
GJB2-related conditions (AR) NM_004004.5	GJB2	Ashkenazi Jewish	1 in 13	1 in 1200
		Pan-ethnic	1 in 50	1 in 4900
		Thai	1 in 9	1 in 800
GLB1-related conditions (AR) NM_000404.2	GLB1	Pan-ethnic	1 in 158	1 in 15700
		Roma	1 in 50	1 in 4900
		South Brazilian	1 in 58	1 in 5700
GLE1-related conditions (AR) NM_001003722.1	GLE1	Finnish	1 in 100	1 in 9900
		Pan-ethnic	≤1 in 500	Reduced
Glutaric acidemia type I (AR) NM_000159.3	GCDH	Amish	1 in 9	1 in 800
		Oji-Cree First Nations	1 in 9	1 in 800
		Pan-ethnic	1 in 87	1 in 8600
Glutaric acidemia type IIA (AR) NM_000126.3	ETFA	Pan-ethnic	≤1 in 500	Reduced
Glutaric acidemia type IIC (AR) NM_004453.3	ETFDH	Asian	1 in 87	1 in 8600
		Pan-ethnic	1 in 250	1 in 24900
Glycine encephalopathy (AMT-related) (AR) NM_000481.3	AMT	Finnish	1 in 142	1 in 14100
		Pan-ethnic	1 in 325	1 in 32400
Glycine encephalopathy (GLDC-related) (AR) NM_000170.2	GLDC	Caucasian	1 in 141	1 in 14000
		Pan-ethnic	1 in 165	1 in 16400
Glycogen storage disease type Ia (AR) NM_000151.3	G6PC	Ashkenazi Jewish	1 in 71	1 in 1400
		Pan-ethnic	1 in 177	1 in 3520
Glycogen storage disease type II (Pompe disease) (AR) NM_000152.3	GAA	African-American	1 in 60	1 in 5900
		Ashkenazi Jewish	1 in 58	1 in 5700
		Asian	1 in 112	1 in 11100
		Pan-ethnic	1 in 100	1 in 9900
Glycogen storage disease type III (AR) NM_000642.2	AGL	Faroese	1 in 28	1 in 540
		Pan-ethnic	1 in 159	1 in 3160
		Sephardic Jewish (Moroccan)	1 in 34	1 in 660
Glycogen storage disease type V (AR) NM_005609.3	PYGM	Caucasian	1 in 158	1 in 15700
		Pan-ethnic	1 in 171	1 in 17000
		Sephardic Jewish (Kurdish)	1 in 84	1 in 8300
Glycogen storage disease type VII (AR) NM_000289.5	PFKM	Ashkenazi Jewish	1 in 250	1 in 24900
		Pan-ethnic	≤1 in 500	Reduced
GNE-related conditions (AR) NM_001128227.2	GNE	Pan-ethnic	1 in 179	1 in 17800
		Sephardic Jewish (Iranian)	1 in 10	1 in 900

DISORDER (INHERITANCE)	GENE	ETHNICITY	CARRIER FREQUENCY BEFORE SCREENING	CARRIER RESIDUAL RISK AFTER NEGATIVE RESULT
GNPTAB-related conditions (AR) NM_024312.4	GNPTAB	Irish Traveller	1 in 15	1 in 1400
		Pan-ethnic	1 in 200	1 in 19900
Guanidinoacetate methyltransferase deficiency (AR) NM_000156.5	GAMT	Pan-ethnic	≤1 in 500	Reduced
		Portuguese	1 in 125	1 in 12400
Gyrate atrophy of the choroid and retina (AR) NM_000274.3	OAT *	Finnish	1 in 126	1 in 12500
		Pan-ethnic	≤1 in 500	Reduced
		Sephardic Jewish	1 in 177	1 in 17600
HADHA-related conditions (AR) NM_000182.4	HADHA	Caucasian	1 in 250	1 in 24900
		Finnish	1 in 125	1 in 12400
		Pan-ethnic	1 in 350	1 in 34900
HBB-related hemoglobinopathies (AR) NM_000518.4	HBB	African-American	1 in 8	1 in 700
		Asian	1 in 54	1 in 5300
		Caucasian	1 in 373	1 in 37200
		Hispanic	1 in 17	1 in 1600
		Mediterranean	1 in 28	1 in 2700
		Pan-ethnic	1 in 49	1 in 4800
Hereditary fructose intolerance (AR) NM_000035.3	ALDOB	African-American	1 in 226	1 in 22500
		Middle Eastern	1 in 97	1 in 9600
		Pan-ethnic	1 in 122	1 in 12100
Hereditary hemochromatosis type 2 (HJV-related) (AR) NM_213653.3	HJV	Pan-ethnic	≤1 in 500	Reduced
Hereditary hemochromatosis type 3 (AR) NM_003227.3	TFR2	Pan-ethnic	≤1 in 500	Reduced
Hermansky-Pudlak syndrome type 1 (AR) NM_000195.4	HPS1	Pan-ethnic	≤1 in 500	Reduced
		Puerto Rican (Northwestern)	1 in 21	1 in 2000
Hermansky-Pudlak syndrome type 3 (AR) NM_032383.4	HPS3	Ashkenazi Jewish	1 in 235	1 in 23400
		Pan-ethnic	≤1 in 500	Reduced
		Puerto Rican (Central)	1 in 63	1 in 6200
HGSNAT-related conditions (AR) NM_152419.2	HGSNAT	Pan-ethnic	≤1 in 500	Reduced
Holocarboxylase synthetase deficiency (AR) NM_000411.6	HLCS	Faroese	1 in 20	1 in 1900
		Japanese	1 in 158	1 in 15700
		Pan-ethnic	1 in 224	1 in 22300
Homocystinuria due to cobalamin E deficiency (AR) NM_002454.2	MTRR	Pan-ethnic	≤1 in 500	Reduced
Homocystinuria due to cystathionine beta-synthase deficiency (AR) NM_000071.2	CBS	Norwegian	1 in 40	1 in 3900
		Pan-ethnic	1 in 224	1 in 22300
		Qatari	1 in 21	1 in 2000
Homocystinuria due to MTHFR deficiency (AR) NM_005957.4	MTHFR *	Pan-ethnic	≤1 in 500	Reduced
		Sephardic Jewish (Bukharian)	1 in 39	1 in 3800
HSD17B4-related conditions (AR) NM_000414.3	HSD17B4	Pan-ethnic	1 in 158	1 in 15700
Hydrolethalus syndrome type 1 (AR) NM_145014.2	HYLS1	Finnish	1 in 40	1 in 3900
		Pan-ethnic	≤1 in 500	Reduced
Hyperornithinemia-hyperammonemia-homocitrullinuria syndrome (AR) NM_014252.3	SLC25A15	Metis (Saskatchewan)	1 in 19	1 in 1800
		Pan-ethnic	≤1 in 500	Reduced
Hypophosphatasia (AR) NM_000478.5	ALPL	Mennonite	1 in 25	1 in 480
		Pan-ethnic	1 in 150	1 in 2980
Isovaleric acidemia (AR) NM_002225.3	IVD	Pan-ethnic	1 in 250	1 in 24900
Joubert syndrome and related disorders (MKS1-related) (AR) NM_017777.3	MKS1	Finnish	1 in 47	1 in 920
		Pan-ethnic	1 in 260	1 in 5180
Joubert syndrome and related disorders (RPGRIPL-related) (AR) NM_015272.2	RPGRIPL *	Pan-ethnic	1 in 259	1 in 5160

DISORDER (INHERITANCE)	GENE	ETHNICITY	CARRIER FREQUENCY BEFORE SCREENING	CARRIER RESIDUAL RISK AFTER NEGATIVE RESULT
Joubert syndrome and related disorders (TMEM216-related) (AR) NM_001173990.2	TMEM216	Ashkenazi Jewish	1 in 92	1 in 9100
		Pan-ethnic	≤1 in 500	Reduced
Junctional epidermolysis bullosa (LAMC2-related) (AR) NM_005562.2	LAMC2	Pan-ethnic	≤1 in 500	Reduced
KCNJ11-related conditions (AR) NM_000525.3	KCNJ11	Pan-ethnic	≤1 in 500	Reduced
Krabbe disease (AR) NM_000153.3	GALC *	Druze	1 in 6	1 in 500
		Pan-ethnic	1 in 158	1 in 15700
LAMA2-related muscular dystrophy (AR) NM_000426.3	LAMA2	Pan-ethnic	1 in 87	1 in 8600
LAMA3-related conditions (AR) NM_000227.4	LAMA3	Pan-ethnic	≤1 in 500	Reduced
LAMB3-related conditions (AR) NM_000228.2	LAMB3	Pan-ethnic	1 in 317	1 in 31600
Leber congenital amaurosis 5 (AR) NM_181714.3	LCA5	Pan-ethnic	1 in 645	Reduced
Leukoencephalopathy with vanishing white matter (EIF2B5-related) (AR) NM_003907.2	EIF2B5	Pan-ethnic	≤1 in 500	Reduced
Limb-girdle muscular dystrophy (CAPN3-related) (AR) NM_000070.2	CAPN3	Pan-ethnic	1 in 134	1 in 13300
Limb-girdle muscular dystrophy type 2C (AR) NM_000231.2	SGCG	Caucasian	1 in 571	Reduced
		Japanese	1 in 374	1 in 37300
		Moroccan	1 in 250	1 in 24900
		Pan-ethnic	≤1 in 500	Reduced
		Roma	1 in 59	1 in 5800
Limb-girdle muscular dystrophy type 2D (AR) NM_000023.2	SGCA	Caucasian	1 in 286	1 in 28500
		Finnish	1 in 150	1 in 14900
		Pan-ethnic	≤1 in 500	Reduced
Limb-girdle muscular dystrophy type 2E (AR) NM_000232.4	SGCB	Caucasian	1 in 404	1 in 5038
		Pan-ethnic	≤1 in 500	Reduced
Lipoid congenital adrenal hyperplasia (AR) NM_000349.2	STAR	Korean	1 in 170	1 in 16900
		Pan-ethnic	≤1 in 500	Reduced
Lysinuric protein intolerance (AR) NM_001126106.2	SLC7A7	Finnish	1 in 120	1 in 2380
		Japanese	1 in 120	1 in 2380
		Pan-ethnic	≤1 in 500	Reduced
Lysosomal acid lipase deficiency (AR) NM_000235.3	LIPA	Caucasian	1 in 112	1 in 1850
		Pan-ethnic	1 in 359	1 in 5967
		Sephardic Jewish (Iranian)	1 in 33	1 in 534
Major histocompatibility complex class II deficiency (CIITA-related) (AR) NM_000246.3	CIITA	Pan-ethnic	≤1 in 500	Reduced
Maple syrup urine disease type 1A (AR) NM_000709.3	BCKDHA	Mennonite	1 in 10	1 in 900
		Pan-ethnic	1 in 373	1 in 37200
Maple syrup urine disease type 1B (AR) NM_183050.2	BCKDHB	Ashkenazi Jewish	1 in 97	1 in 9600
		Pan-ethnic	1 in 346	1 in 34500
Maple syrup urine disease type 2 (AR) NM_001918.3	DBT	Pan-ethnic	≤1 in 500	Reduced
Medium-chain acyl-CoA dehydrogenase deficiency (AR) NM_000016.5	ACADM	Northern European	1 in 40	1 in 3900
		Pan-ethnic	1 in 66	1 in 6500
Megalencephalic leukoencephalopathy with subcortical cysts 1 (AR) NM_015166.3	MLC1	Pan-ethnic	≤1 in 500	Reduced
		Sephardic Jewish (Libyan)	1 in 40	1 in 3900
Metachromatic leukodystrophy (ARSA-related) (AR) NM_000487.5	ARSA	Navajo	1 in 40	1 in 780
		Pan-ethnic	1 in 100	1 in 1980
		Sephardic Jewish	1 in 46	1 in 900
Methylmalonic acidemia (MMAA-related) (AR) NM_172250.2	MMAA	Pan-ethnic	1 in 316	1 in 10500

DISORDER (INHERITANCE)	GENE	ETHNICITY	CARRIER FREQUENCY BEFORE SCREENING	CARRIER RESIDUAL RISK AFTER NEGATIVE RESULT
Methylmalonic acidemia (MMAB-related) (AR) NM_052845.3	MMAB	Pan-ethnic	1 in 456	1 in 22750
Methylmalonic acidemia (MUT-related) (AR) NM_000255.3	MUT	Pan-ethnic	1 in 204	1 in 5075
MFSD8-related conditions (AR) NM_152778.2	MFSD8	Pan-ethnic	≤1 in 500	Reduced
Microcephaly, postnatal progressive, with seizures and brain atrophy (AR) NM_004268.4	MED17	Pan-ethnic	≤1 in 500	Reduced
		Sephardic Jewish	1 in 20	1 in 1900
Mitochondrial complex I deficiency 9 (AR) NM_004553.4	NDUFS6	Ashkenazi Jewish	1 in 290	1 in 28900
		Caucasus Jewish	1 in 24	1 in 2300
		Pan-ethnic	≤1 in 500	Reduced
Mitochondrial complex I deficiency 16 (AR) NM_024120.4	NDUFAF5	Ashkenazi Jewish	1 in 290	1 in 28900
		Pan-ethnic	≤1 in 500	Reduced
Mitochondrial complex I deficiency 20/ACAD9 deficiency (AR) NM_014049.4	ACAD9	Pan-ethnic	≤1 in 500	Reduced
Mitochondrial complex IV deficiency / Leigh syndrome, French Canadian type (AR) NM_133259.3	LRPPRC	French Canadian (Saguenay-Lac-St-Jean)	1 in 23	1 in 2200
		Pan-ethnic	≤1 in 500	Reduced
Mitochondrial neurogastrointestinal encephalomyopathy (AR) NM_001953.4	TYMP	Pan-ethnic	≤1 in 500	Reduced
		Sephardic Jewish	1 in 158	1 in 15700
MPL-related conditions (AR) NM_005373.2	MPL	Ashkenazi Jewish	1 in 57	1 in 5600
		Pan-ethnic	≤1 in 500	Reduced
MPV17-related conditions (AR) NM_002437.4	MPV17	Navajo	1 in 20	1 in 475
		Pan-ethnic	≤1 in 500	Reduced
Mucopolipidosis type III gamma (AR) NM_032520.4	GNPTG	Pan-ethnic	≤1 in 500	Reduced
Mucopolipidosis type IV (AR) NM_020533.2	MCOLN1	Ashkenazi Jewish	1 in 100	1 in 9900
		Pan-ethnic	≤1 in 500	Reduced
Mucopolysaccharidosis type I (AR) NM_000203.4	IDUA	Pan-ethnic	1 in 148	1 in 4900
Mucopolysaccharidosis type IIIA (AR) NM_000199.3	SGSH	Northern European	1 in 173	1 in 17200
		Pan-ethnic	1 in 215	1 in 21400
		Taiwanese	≤1 in 500	Reduced
Mucopolysaccharidosis type IIIB (AR) NM_000263.3	NAGLU	Pan-ethnic	1 in 224	1 in 22300
Mucopolysaccharidosis type IIID (AR) NM_002076.3	GNS	Pan-ethnic	≤1 in 500	Reduced
Mucopolysaccharidosis type IX (AR) NM_153281.1	HYAL1	Pan-ethnic	≤1 in 500	Reduced
Mucopolysaccharidosis type VI (AR) NM_000046.3	ARSB	Pan-ethnic	1 in 250	1 in 24900
Multiple sulfatase deficiency (AR) NM_182760.3	SUMF1	Pan-ethnic	≤1 in 500	Reduced
Muscular dystrophy-dystroglycanopathy (FKRP-related) (AR) NM_024301.4	FKRP	Norwegian	1 in 116	1 in 11500
		Pan-ethnic	1 in 158	1 in 15700
Muscular dystrophy-dystroglycanopathy (FKTN-related) (AR) NM_001079802.1	FKTN	Ashkenazi Jewish	1 in 80	1 in 7900
		Japanese	1 in 188	1 in 18700
		Pan-ethnic	≤1 in 500	Reduced
MYO7A-related conditions (AR) NM_000260.3	MYO7A	Pan-ethnic	1 in 200	1 in 3980
Myopathy, lactic acidosis, and sideroblastic anemia 1 (AR) NM_025215.5	PUS1	Pan-ethnic	≤1 in 500	Reduced
N-acetylglutamate synthase deficiency (AR) NM_153006.2	NAGS	Pan-ethnic	≤1 in 500	Reduced
Nemaline myopathy 2 (AR) NM_001271208.1	NEB *	Ashkenazi Jewish	1 in 108	1 in 10700
		Pan-ethnic	1 in 158	1 in 3140

DISORDER (INHERITANCE)	GENE	ETHNICITY	CARRIER FREQUENCY BEFORE SCREENING	CARRIER RESIDUAL RISK AFTER NEGATIVE RESULT
Nephrogenic diabetes insipidus (AQP2-related) (AR) NM_000486.5	AQP2	Pan-ethnic	1 in 1118	Reduced
Neuronal ceroid lipofuscinosis type 1 (AR) NM_000310.3	PPT1	Finnish	1 in 70	1 in 3450
		Pan-ethnic	1 in 199	1 in 9900
Neuronal ceroid lipofuscinosis type 2 (AR) NM_000391.3	TPP1	Newfoundland	1 in 53	1 in 1734
		Pan-ethnic	1 in 250	1 in 8300
Neuronal ceroid lipofuscinosis type 5 (AR) NM_006493.2	CLN5	Finnish	1 in 115	1 in 11400
		Pan-ethnic	≤1 in 500	Reduced
Neuronal ceroid lipofuscinosis type 6 (AR) NM_017882.2	CLN6	Pan-ethnic	≤1 in 500	Reduced
Neuronal ceroid lipofuscinosis type 8 (AR) NM_018941.3	CLN8	Finnish	1 in 135	1 in 13400
		Pan-ethnic	≤1 in 500	Reduced
Niemann-Pick disease type C (NPC1-related) (AR) NM_000271.4	NPC1	Pan-ethnic	1 in 183	1 in 18200
Niemann-Pick disease type C (NPC2-related) (AR) NM_006432.3	NPC2	Pan-ethnic	1 in 871	Reduced
Niemann-Pick disease types A and B (AR) NM_000543.4	SMPD1	Ashkenazi Jewish	1 in 90	1 in 1780
		Pan-ethnic	1 in 250	1 in 4980
Nijmegen breakage syndrome (AR) NM_002485.4	NBN *	Eastern European	1 in 155	1 in 15400
		Pan-ethnic	≤1 in 500	Reduced
Nonsyndromic deafness (LOXHD1-related) (AR) NM_144612.6	LOXHD1	Ashkenazi Jewish	1 in 180	1 in 17900
		Pan-ethnic	≤1 in 500	Reduced
NR2E3-related conditions (AR) NM_014249.3	NR2E3	Pan-ethnic	≤1 in 500	Reduced
OPA3-related conditions (AR) NM_025136.3	OPA3	Pan-ethnic	≤1 in 500	Reduced
		Sephardic Jewish (Iraqi)	1 in 10	1 in 900
Osteopetrosis (TCIRG1-related) (AR) NM_006019.3	TCIRG1	Ashkenazi Jewish	1 in 350	1 in 34900
		Chuvash	1 in 30	1 in 2900
		Pan-ethnic	1 in 317	1 in 31600
PCDH15-related conditions (AR) NM_033056.3	PCDH15	Ashkenazi Jewish	1 in 78	1 in 7700
		Pan-ethnic	1 in 400	1 in 39900
PEX7-related conditions (AR) NM_000288.3	PEX7	Pan-ethnic	1 in 157	1 in 15600
Phenylalanine hydroxylase deficiency (AR) NM_000277.1	PAH	African-American	1 in 111	1 in 11000
		Ashkenazi Jewish	1 in 225	1 in 22400
		East Asian	1 in 50	1 in 1225
		Finnish	1 in 225	1 in 22400
		Irish	1 in 33	1 in 3200
		Japanese	1 in 200	1 in 19900
		Pan-ethnic	1 in 58	1 in 5700
Turkish	1 in 26	1 in 2500		
Phosphoglycerate dehydrogenase deficiency (AR) NM_006623.3	PHGDH	Ashkenazi Jewish	1 in 400	1 in 39900
		Pan-ethnic	≤1 in 500	Reduced
Polycystic kidney disease (PKHD1-related) (AR) NM_138694.3	PKHD1	Pan-ethnic	1 in 70	1 in 6900
Polymicrogyria (ADGRG1-related) (AR) NM_005682.6	ADGRG1	Pan-ethnic	≤1 in 500	Reduced
POMGNT1-related conditions (AR) NM_017739.3	POMGNT1	Finnish	1 in 111	1 in 11000
		Pan-ethnic	≤1 in 500	Reduced
		Pan-ethnic	≤1 in 500	Reduced
Pontocerebellar hypoplasia type 2D (AR) NM_016955.3	SEPSECS	Sephardic Jewish (Moroccan and Iraqi)	1 in 43	1 in 4200
Pontocerebellar hypoplasia type 6 (AR) NM_020320.3	RARS2	Pan-ethnic	≤1 in 500	Reduced
Primary carnitine deficiency (AR) NM_003060.3	SLC22A5	Faroese	1 in 9	1 in 800
		Japanese	1 in 100	1 in 9900
		Pan-ethnic	1 in 71	1 in 7000

DISORDER (INHERITANCE)	GENE	ETHNICITY	CARRIER FREQUENCY BEFORE SCREENING	CARRIER RESIDUAL RISK AFTER NEGATIVE RESULT
Primary ciliary dyskinesia (DNAH5-related) (AR) NM_001369.2	DNAH5	Pan-ethnic	1 in 109	1 in 10800
Primary ciliary dyskinesia (DNAI1-related) (AR) NM_012144.3	DNAI1	Pan-ethnic	1 in 250	1 in 24900
Primary ciliary dyskinesia (DNAI2-related) (AR) NM_023036.4	DNAI2	Ashkenazi Jewish	1 in 200	1 in 19900
		Pan-ethnic	1 in 354	1 in 35300
Primary hyperoxaluria type 1 (AR) NM_000030.2	AGXT	Pan-ethnic	1 in 135	1 in 13400
Primary hyperoxaluria type 2 (AR) NM_012203.1	GRHPR	Pan-ethnic	≤1 in 500	Reduced
Primary hyperoxaluria type 3 (AR) NM_138413.3	HOGA1	Pan-ethnic	1 in 354	1 in 35300
Propionic acidemia (PCCA-related) (AR) NM_000282.3	PCCA	Arab	1 in 100	1 in 2475
		Pan-ethnic	1 in 224	1 in 5575
Propionic acidemia (PCCB-related) (AR) NM_000532.4	PCCB	Arab	1 in 100	1 in 9900
		Greenlandic Inuit	1 in 20	1 in 1900
		Pan-ethnic	1 in 224	1 in 22300
PSAP-related conditions (AR) NM_002778.3	PSAP	Pan-ethnic	≤1 in 500	Reduced
Pycnodysostosis (AR) NM_000396.3	CTSK	Pan-ethnic	1 in 438	1 in 43700
Pyruvate carboxylase deficiency (AR) NM_000920.3	PC	Algonquian Indian	1 in 10	1 in 180
		Pan-ethnic	1 in 250	1 in 4980
Pyruvate dehydrogenase complex deficiency (PDHB-related) (AR) NM_000925.3	PDHB	Pan-ethnic	≤1 in 500	Reduced
RAPSN-related conditions (AR) NM_005055.4	RAPSN	Pan-ethnic	1 in 283	1 in 28200
RDH12-related conditions (AR) NM_152443.2	RDH12	Pan-ethnic	1 in 460	1 in 45900
Retinitis pigmentosa 25 (AR) NM_001142800.1	EYS	Pan-ethnic	1 in 129	1 in 12800
		Sephardic Jewish	1 in 42	1 in 4100
Retinitis pigmentosa 28 (AR) NM_001201543.1	FAM161A	Ashkenazi Jewish	1 in 214	1 in 21300
		Pan-ethnic	1 in 289	1 in 28800
		Sephardic Jewish	1 in 41	1 in 4000
Rhizomelic chondrodysplasia punctata type 3 (AR) NM_003659.3	AGPS	Pan-ethnic	≤1 in 500	Reduced
Roberts syndrome (AR) NM_001017420.2	ESCO2	Pan-ethnic	≤1 in 500	Reduced
RPE65-related conditions (AR) NM_000329.2	RPE65	Pan-ethnic	1 in 228	1 in 22700
		Sephardic Jewish	1 in 90	1 in 8900
Sandhoff disease (AR) NM_000521.3	HEXB	Metis (Saskatchewan)	1 in 15	1 in 1400
		Pan-ethnic	1 in 180	1 in 17900
Schimke immuno-osseous dysplasia (AR) NM_014140.3	SMARCAL1	Pan-ethnic	≤1 in 500	Reduced
Severe combined immunodeficiency due to DCLRE1C (Artemis) deficiency (AR) NM_001033855.2	DCLRE1C	Navajo and Apache	1 in 10	1 in 900
		Pan-ethnic	≤1 in 500	Reduced
Severe combined immunodeficiency due to RAG2 deficiency (AR) NM_000536.3	RAG2	Pan-ethnic	≤1 in 500	Reduced
Severe congenital neutropenia due to HAX1 deficiency (AR) NM_006118.3	HAX1	Pan-ethnic	≤1 in 500	Reduced
Severe congenital neutropenia due to VPS45 deficiency (AR) NM_007259.4	VPS45	Pan-ethnic	≤1 in 500	Reduced
Sialic acid storage diseases (AR) NM_012434.4	SLC17A5	Finnish	1 in 100	1 in 9900
		Pan-ethnic	≤1 in 500	Reduced
Sjögren-Larsson syndrome (AR) NM_000382.2	ALDH3A2	Pan-ethnic	≤1 in 500	Reduced
		Swedish	1 in 250	1 in 24900

DISORDER (INHERITANCE)	GENE	ETHNICITY	CARRIER FREQUENCY BEFORE SCREENING	CARRIER RESIDUAL RISK AFTER NEGATIVE RESULT
SLC12A6-related conditions (AR) NM_133647.1	SLC12A6	French Canadian (Saguenay-Lac-St-Jean)	1 in 23	1 in 2200
		Pan-ethnic	≤1 in 500	Reduced
SLC26A2-related conditions (AR) NM_000112.3	SLC26A2	Finnish	1 in 75	1 in 1480
		Pan-ethnic	1 in 158	1 in 3140
SLC26A4-related conditions (AR) NM_000441.1	SLC26A4	Asian	1 in 74	1 in 7300
		Pan-ethnic	1 in 80	1 in 7900
SLC37A4-related conditions (AR) NM_001164277.1	SLC37A4	Pan-ethnic	1 in 354	1 in 7060
Smith-Lemli-Opitz syndrome (AR) NM_001360.2	DHCR7	African-American	1 in 339	1 in 33800
		Ashkenazi Jewish	1 in 41	1 in 4000
		Hispanic	1 in 135	1 in 13400
		Northern European	1 in 50	1 in 4900
		Pan-ethnic	1 in 71	1 in 7000
		Sephardic Jewish	1 in 68	1 in 6700
Spastic paraplegia type 15 (AR) NM_015346.3	ZFYVE26	Pan-ethnic	≤1 in 500	Reduced
		TECPR2	≤1 in 500	Reduced
Spastic paraplegia type 49 (AR) NM_014844.3	TECPR2	Sephardic Jewish - Bukharian	1 in 38	1 in 3700
		Spinal muscular atrophy (AR) NM_000344.3 SMN1: 2 copies c.*3+80T>G not detected Carrier residual risks listed are for 2 copy SMN1 results. Carrier residual risk for >2 copies are 5- to 10-fold lower.	SMN1 *	African-American
Ashkenazi Jewish	1 in 62			1 in 1017
Asian	1 in 50			1 in 701
Caucasian	1 in 45			1 in 880
Hispanic	1 in 48			1 in 784
Pan-ethnic	1 in 49			1 in 800
Spondylocostal dysostosis (MESP2-related) (AR) NM_001039958.1	MESP2	Pan-ethnic	1 in 224	1 in 22300
		Puerto Rican	1 in 55	1 in 5400
Steel syndrome (AR) NM_032888.3	COL27A1 *	Pan-ethnic	≤1 in 500	Reduced
		Puerto Rican	1 in 51	1 in 5000
Stüve-Wiedemann syndrome (AR) NM_002310.5	LIFR	Pan-ethnic	≤1 in 500	Reduced
Tay-Sachs disease (AR) NM_000520.4	HEXA	Ashkenazi Jewish	1 in 27	1 in 2600
		Asian	1 in 126	1 in 12500
		Caucasian	1 in 182	1 in 18100
		French Canadian	1 in 27	1 in 2600
		Irish	1 in 41	1 in 4000
		Pan-ethnic	1 in 250	1 in 24900
Transient infantile liver failure (AR) NM_018006.4	TRMU	Pan-ethnic	≤1 in 500	Reduced
		Sephardic Jewish (Yemenite)	1 in 34	1 in 3300
Tyrosine hydroxylase deficiency (AR) NM_199292.2	TH	Caucasian	1 in 224	1 in 22300
		Pan-ethnic	≤1 in 500	Reduced
Tyrosinemia type I (AR) NM_000137.2	FAH *	Ashkenazi Jewish	1 in 143	1 in 2840
		French Canadian	1 in 66	1 in 1300
		French Canadian (Saguenay-Lac-St-Jean)	1 in 16	1 in 300
		Pan-ethnic	1 in 125	1 in 2480
Tyrosinemia type II (AR) NM_000353.2	TAT	Pan-ethnic	1 in 250	1 in 24900
USH1C-related conditions (AR) NM_005709.3	USH1C *	French Canadian/Acadian	1 in 227	1 in 22600
		Pan-ethnic	1 in 353	1 in 3521
		Sephardic Jewish	1 in 125	1 in 1241
USH2A-related conditions (AR) NM_206933.2	USH2A	Caucasian	1 in 70	1 in 6900
		Pan-ethnic	1 in 112	1 in 11100
		Sephardic Jewish	1 in 36	1 in 3500

DISORDER (INHERITANCE)	GENE	ETHNICITY	CARRIER FREQUENCY BEFORE SCREENING	CARRIER RESIDUAL RISK AFTER NEGATIVE RESULT
Very long-chain acyl-CoA dehydrogenase deficiency (AR) NM_000018.3	ACADVL	Pan-ethnic	1 in 100	1 in 9900
VRK1-related conditions (AR) NM_003384.2	VRK1	Ashkenazi Jewish	1 in 225	1 in 22400
		Pan-ethnic	≤1 in 500	Reduced
VSX2-related conditions (AR) NM_182894.2	VSX2	Pan-ethnic	≤1 in 500	Reduced
		Sephardic Jewish	1 in 145	1 in 14400
Wilson disease (AR) NM_000053.3	ATP7B	Ashkenazi Jewish	1 in 67	1 in 3300
		Canary Islander	1 in 25	1 in 1200
		Pan-ethnic	1 in 90	1 in 4450
		Sardinian	1 in 50	1 in 2450
		Sephardic Jewish	1 in 65	1 in 3200
		WNT10A-related conditions (AR) NM_025216.2	WNT10A	Pan-ethnic
Xeroderma pigmentosum complementation group A (AR) NM_000380.3	XPA	Japanese	1 in 100	1 in 9900
		Pan-ethnic	1 in 1667	Reduced
Xeroderma pigmentosum complementation group C (AR) NM_004628.4	XPC	Pan-ethnic	1 in 763	Reduced
		Tunisian	1 in 50	1 in 4900
Zellweger spectrum disorder (PEX1-related) (AR) NM_000466.2	PEX1	Pan-ethnic	1 in 144	1 in 14300
Zellweger spectrum disorder (PEX2-related) (AR) NM_000318.2	PEX2	Ashkenazi Jewish	1 in 227	1 in 22600
		Pan-ethnic	≤1 in 500	Reduced
Zellweger spectrum disorder (PEX6-related) (AR) NM_000287.3	PEX6	French Canadian	1 in 55	1 in 5400
		Pan-ethnic	1 in 294	1 in 29300
		Sephardic Jewish	1 in 18	1 in 1700
Zellweger spectrum disorder (PEX10-related) (AR) NM_153818.1	PEX10	Pan-ethnic	1 in 606	Reduced
Zellweger spectrum disorder (PEX12-related) (AR) NM_000286.2	PEX12	Pan-ethnic	1 in 409	1 in 40800

Methods

- Genomic DNA obtained from the submitted sample is enriched for targeted regions using a hybridization-based protocol, and sequenced using Illumina technology. Unless otherwise indicated, all targeted regions are sequenced with ≥50x depth or are supplemented with additional analysis. Reads are aligned to a reference sequence (GRCh37), and sequence changes are identified and interpreted in the context of a single clinically relevant transcript, indicated below. Enrichment and analysis focus on the coding sequence of the indicated transcripts, 10bp of flanking intronic sequence, and other specific genomic regions demonstrated to be causative of disease at the time of assay design. Promoters, untranslated regions, and other non-coding regions are not otherwise interrogated. Exonic deletions and duplications are called using an in-house algorithm that determines copy number at each target by comparing the read depth for each target in the proband sequence with both mean read-depth and read-depth distribution, obtained from a set of clinical samples. Markers across the X and Y chromosomes are analyzed for quality control purposes and may detect deviations from the expected sex chromosome complement. Such deviations may be included in the report in accordance with internal guidelines. Invitae utilizes a classification methodology to identify next-generation sequencing (NGS)-detected variants that require orthogonal confirmation (Lincoln, et al. J Mol Diagn. 2019 Mar;21(2):318-329.). Pathogenic and Likely Pathogenic variants that do not meet the validated quality thresholds are confirmed. Confirmation technologies may include any of the following: Sanger sequencing, Pacific Biosciences SMRT sequencing, MLPA, MLPA-seq, Array CGH. Array CGH confirmation of NGS CNV calling performed by Invitae Corporation (1400 16th Street, San Francisco, CA 94103, #05D2040778). The following analyses are performed if relevant to the requisition. For GBA and CYP21A2, the reference genome has been modified to mask the sites of polymorphic paralog sequence variants (PSVs) in both the gene and pseudogene. If one or more reportable variants is identified (see Limitations), the gene is amplified by long-range PCR; PacBio sequencing of the long-range amplicons is used to confirm the variant. Gene conversion and fusion events are flagged by our NGS pipeline and reportable pseudogene-derived variants are identified by long-range PCR followed by PacBio sequencing of the long-range amplicons. In some cases, it may not be possible to disambiguate between the gene and pseudogene. For HBA1/2, the reference genome has been modified to force some

sequencing reads derived from HBA1 to align to HBA2, and variant calling algorithms are modified to support an expectation of 4 alleles in these regions. HBA1/2 copy number calling is performed by a custom hypothesis testing algorithm which generates diplotype calls. If sequence data for a sample does not support a unique high confidence match from among hypotheses tested, that sample is flagged for manual review. Copy number variation is only reported for coding sequence of HBA1 and HBA2 and the HS-40 region. This assay does not distinguish among the α 3.7 subtypes, and all α 3.7 variants are called as HBA1 deletions. This assay may not detect overlapping copy gain and copy loss events when the breakpoints of those events are similar. For FMR1, triplet repeats are detected by PCR with fluorescently labeled primers followed by capillary electrophoresis. Reference ranges: Normal: <45 CGG repeats, intermediate: 45-54 CGG repeats, premutation: 55-200 CGG repeats, full mutation: >200 CGG repeats. For alleles with 55-90 triplet repeats, the region surrounding the FMR1 repeat is amplified by PCR. The PCR amplicons are then processed through PacBio SMRTBell library prep and sequenced using PacBio long read technology. The number of AGG interruptions within the 55-90 triplet repeat is read directly from the resulting DNA sequences. Technical component of confirmatory sequencing is performed by Invitae Corporation (1400 16th Street, San Francisco, CA 94103, #05D2040778).

- The following transcripts were used in this analysis. If more than one transcript is listed for a single gene, variants were reported using the first transcript listed unless otherwise indicated in the report: ABCB11 (NM_003742.2), ABCC8 (NM_000352.4), ACAD9 (NM_014049.4), ACADM (NM_000016.5), ACADVL (NM_000018.3), ACAT1 (NM_000019.3), ACOX1 (NM_004035.6), ACSF3 (NM_174917.4), ADA (NM_000022.2), ADAMTS2 (NM_014244.4), ADGRG1 (NM_005682.6), AGA (NM_000027.3), AGL (NM_000642.2), AGPS (NM_003659.3), AGXT (NM_000030.2), AIRE (NM_000383.3), ALDH3A2 (NM_000382.2), ALDOB (NM_000035.3), ALG6 (NM_013339.3), ALMS1 (NM_015120.4), ALPL (NM_000478.5), AMT (NM_000481.3), AQP2 (NM_000486.5), ARG1 (NM_000045.3), ARSA (NM_000487.5), ARSB (NM_000046.3), ASL (NM_000048.3), ASNS (NM_133436.3), ASPA (NM_000049.2), ASS1 (NM_000050.4), ATM (NM_000051.3), ATP6V1B1 (NM_001692.3), ATP7B (NM_000053.3), BBS1 (NM_024649.4), BBS10 (NM_024685.3), BBS12 (NM_152618.2), BBS2 (NM_031885.3), BCKDHA (NM_000709.3), BCKDHB (NM_183050.2), BCS1L (NM_004328.4), BLM (NM_000057.3), BSND (NM_057176.2), CAPN3 (NM_000070.2), CBS (NM_000071.2), CDH23 (NM_022124.5), CEP290 (NM_025114.3), CERKL (NM_001030311.2), CFTR (NM_000492.3), CHRNE (NM_000080.3), CIITA (NM_000246.3), CLN3 (NM_001042432.1), CLN5 (NM_006493.2), CLN6 (NM_017882.2), CLN8 (NM_018941.3), CLRN1 (NM_174878.2), CNGB3 (NM_019098.4), COL27A1 (NM_032888.3), COL4A3 (NM_000091.4), COL4A4 (NM_000092.4), COL7A1 (NM_000094.3), CPS1 (NM_001875.4), CPT1A (NM_001876.3), CPT2 (NM_000098.2), CRB1 (NM_201253.2), CTNS (NM_004937.2), CTSK (NM_000396.3), CYBA (NM_000101.3), CYP11B1 (NM_000497.3), CYP11B2 (NM_000498.3), CYP17A1 (NM_000102.3), CYP19A1 (NM_031226.2), CYP21A2 (NM_000500.7), CYP27A1 (NM_000784.3), DBT (NM_001918.3), DCLRE1C (NM_001033855.2), DHCR7 (NM_001360.2), DHDDS (NM_024887.3), DLD (NM_000108.4), DNAH5 (NM_001369.2), DNAI1 (NM_012144.3), DNAI2 (NM_023036.4), DYSF (NM_003494.3), EIF2B5 (NM_003907.2), ELP1 (NM_003640.3), ERCC6 (NM_000124.3), ERCC8 (NM_000082.3), ESCO2 (NM_001017420.2), ETFA (NM_000126.3), ETFDH (NM_004453.3), ETHE1 (NM_014297.3), EVC (NM_153717.2), EVC2 (NM_147127.4), EYS (NM_001142800.1), FAH (NM_000137.2), FAM161A (NM_001201543.1), FANCA (NM_000135.2), FANCC (NM_000136.2), FANCG (NM_004629.1), FH (NM_000143.3), FKRP (NM_024301.4), FKTN (NM_001079802.1), G6PC (NM_000151.3), GAA (NM_000152.3), GALC (NM_000153.3), GALK1 (NM_000154.1), GALT (NM_000155.3), GAMT (NM_000156.5), GBA (NM_001005741.2), GBE1 (NM_000158.3), GCDH (NM_000159.3), GFM1 (NM_024996.5), GJB2 (NM_004004.5), GLB1 (NM_000404.2), GLDC (NM_000170.2), GLE1 (NM_001003722.1), GNE (NM_001128227.2), GNPTAB (NM_024312.4), GNPTG (NM_032520.4), GNS (NM_002076.3), GRHPR (NM_012203.1), HADHA (NM_000182.4), HAX1 (NM_006118.3), HBA1 (NM_000558.4), HBA2 (NM_000517.4), HBB (NM_000518.4), HEXA (NM_000520.4), HEXB (NM_000521.3), HGSNAT (NM_152419.2), HJV (NM_213653.3), HLCS (NM_000411.6), HMGCL (NM_000191.2), HOGA1 (NM_138413.3), HPS1 (NM_000195.4), HPS3 (NM_032383.4), HSD17B4 (NM_000414.3), HSD3B2 (NM_000198.3), HYAL1 (NM_153281.1), HYLS1 (NM_145014.2), IDUA (NM_000203.4), IVD (NM_002225.3), KCNJ11 (NM_000525.3), LAMA2 (NM_000426.3), LAMA3 (NM_000227.4), LAMB3 (NM_000228.2), LAMC2 (NM_005562.2), LCA5 (NM_181714.3), LDLR (NM_000527.4), LDLRAP1 (NM_015627.2), LHX3 (NM_014564.4), LIFR (NM_002310.5), LIPA (NM_000235.3), LOXHD1 (NM_144612.6), LPL (NM_000237.2), LRPPRC (NM_133259.3), MAN2B1 (NM_000528.3), MCOLN1 (NM_020533.2), MED17 (NM_004268.4), MESP2 (NM_001039958.1), MFSD8 (NM_152778.2), MKS1 (NM_017777.3), MLC1 (NM_015166.3), MMAA (NM_172250.2), MMAB (NM_052845.3), MMACHC (NM_015506.2), MMADHC (NM_015702.2), MPI (NM_002435.2), MPL (NM_005373.2), MPV17 (NM_002437.4), MTHFR (NM_005957.4), MTRR (NM_002454.2), MTTP (NM_000253.3), MUT (NM_000255.3), MYO7A (NM_000260.3), NAGLU (NM_000263.3), NAGS (NM_153006.2), NBN (NM_002485.4), NDRG1 (NM_006096.3), NDUFAF5 (NM_024120.4), NDUFS6 (NM_004553.4), NEB (NM_001271208.1), NPC1 (NM_000271.4), NPC2 (NM_006432.3), NPHS1 (NM_004646.3), NPHS2 (NM_014625.3), NRE3 (NM_014249.3), NTRK1 (NM_001012331.1), OAT (NM_000274.3), OPA3 (NM_025136.3), PAH (NM_000277.1), PC (NM_000920.3), PCCA (NM_000282.3), PCCB (NM_000532.4), PCDH15 (NM_033056.3), PDHB (NM_000925.3), PEX1 (NM_000466.2), PEX10 (NM_153818.1), PEX12 (NM_000286.2), PEX2 (NM_000318.2), PEX6 (NM_000287.3), PEX7 (NM_000288.3), PFKM (NM_000289.5), PHGDH (NM_006623.3), PKHD1 (NM_138694.3), PMM2 (NM_000303.2), POMGNT1 (NM_017739.3), PPT1 (NM_000310.3), PROPI (NM_006261.4), PSAP (NM_002778.3), PTS (NM_000317.2), PUS1 (NM_025215.5), PYGM (NM_005609.3), RAB23 (NM_183227.2), RAG2 (NM_000536.3), RAPSN (NM_005055.4), RARS2 (NM_020320.3), RDH12 (NM_152443.2), RMRP (NR_003051.3), RPE65 (NM_000329.2), RPGRIP1L (NM_015272.2), RTEL1 (NM_001283009.1), SACS (NM_014363.5), SAMHD1 (NM_015474.3), SEPSECS (NM_016955.3), SGCA (NM_000023.2), SGCB (NM_000232.4), SGCG (NM_000231.2), SGSH (NM_000199.3), SLC12A3 (NM_000339.2), SLC12A6 (NM_133647.1), SLC17A5 (NM_012434.4),

SLC22A5 (NM_003060.3), SLC25A13 (NM_014251.2), SLC25A15 (NM_014252.3), SLC26A2 (NM_000112.3), SLC26A4 (NM_000441.1), SLC35A3 (NM_012243.2), SLC37A4 (NM_001164277.1), SLC39A4 (NM_130849.3), SLC4A11 (NM_032034.3), SLC7A7 (NM_001126106.2), SMARCAL1 (NM_014140.3), SMN1 (NM_000344.3), SMPD1 (NM_000543.4), STAR (NM_000349.2), SUMF1 (NM_182760.3), TAT (NM_000353.2), TCIRG1 (NM_006019.3), TECPR2 (NM_014844.3), TFR2 (NM_003227.3), TGM1 (NM_000359.2), TH (NM_199292.2), TMEM216 (NM_001173990.2), TPP1 (NM_000391.3), TRMU (NM_018006.4), TSFM (NM_001172696.1), TTPA (NM_000370.3), TYMP (NM_001953.4), USH1C (NM_005709.3), USH2A (NM_206933.2), VPS13A (NM_033305.2), VPS13B (NM_017890.4), VPS45 (NM_007259.4), VRK1 (NM_003384.2), VSX2 (NM_182894.2), WNT10A (NM_025216.2), XPA (NM_000380.3), XPC (NM_004628.4), ZFYVE26 (NM_015346.3).

- Variants of uncertain significance are not included in this report; however, if additional evidence becomes available to indicate that a previously uncertain variant is clinically significant, Invitae will update this report and provide notification.
- A PMID is a unique identifier referring to a published, scientific paper. Search by PMID at <http://www.ncbi.nlm.nih.gov/pubmed>.
- An rsID is a unique identifier referring to a single genomic position, and is used to associate population frequency information with sequence changes at that position. Reported population frequencies are derived from a number of public sites that aggregate data from large-scale population sequencing projects, including ExAC (<http://exac.broadinstitute.org>) and dbSNP (<http://ncbi.nlm.nih.gov/SNP>).

Disclaimer

DNA studies do not constitute a definitive test for the selected condition(s) in all individuals. It should be realized that there are possible sources of error. Errors can result from trace contamination, rare technical errors, rare genetic variants that interfere with analysis, recent scientific developments, and alternative classification systems. This test should be one of many aspects used by the healthcare provider to help with a diagnosis and treatment plan, but it is not a diagnosis itself. This test was developed and its performance characteristics determined by Invitae. It has not been cleared or approved by the FDA. The laboratory is regulated under the Clinical Laboratory Improvement Act (CLIA) as qualified to perform high-complexity clinical tests (CLIA ID: 05D2040778). This test is used for clinical purposes. It should not be regarded as investigational or for research.

Limitations

- Based on validation study results, this assay achieves >99% analytical sensitivity and specificity for single nucleotide variants, insertions and deletions <15bp in length, and exon-level deletions and duplications. Invitae's methods also detect insertions and deletions larger than 15bp but smaller than a full exon but sensitivity for these may be marginally reduced. Invitae's deletion/duplication analysis determines copy number at a single exon resolution at virtually all targeted exons. However, in rare situations, single-exon copy number events may not be analyzed due to inherent sequence properties or isolated reduction in data quality. Certain types of variants, such as structural rearrangements (e.g. inversions, gene conversion events, translocations, etc.) or variants embedded in sequence with complex architecture (e.g. short tandem repeats or segmental duplications), may not be detected. Additionally, it may not be possible to fully resolve certain details about variants, such as mosaicism, phasing, or mapping ambiguity. Unless explicitly guaranteed, sequence changes in the promoter, non-coding exons, and other non-coding regions are not covered by this assay. Please consult the test definition on our website for details regarding regions or types of variants that are covered or excluded for this test. This report reflects the analysis of an extracted genomic DNA sample. While this test is intended to reflect the analysis of extracted genomic DNA from a referred patient, in very rare cases the analyzed DNA may not represent that individual's constitutional genome, such as in the case of a circulating hematolymphoid neoplasm, bone marrow transplant, blood transfusion, chimerism, culture artifact or maternal cell contamination.
- GBA: c.84dupG (p.Leu29Alafs*18), c.115+1G>A (Splice donor), c.222_224delTAC (p.Thr75del), c.475C>T (p.Arg159Trp), c.595_596delCT (p.Leu199Aspfs*62), c.680A>G (p.Asn227Ser), c.721G>A (p.Gly241Arg), c.754T>A (p.Phe252Ile), c.1226A>G (p.Asn409Ser), c.1246G>A (p.Gly416Ser), c.1263_1317del (p.Leu422Profs*4), c.1297G>T (p.Val433Leu), c.1342G>C (p.Asp448His), c.1343A>T (p.Asp448Val), c.1448T>C (p.Leu483Pro), c.1504C>T (p.Arg502Cys), c.1505G>A (p.Arg502His), c.1603C>T (p.Arg535Cys), c.1604G>A (p.Arg535His) variants only. Rarely, sensitivity to detect these variants may be reduced. When sensitivity is reduced, zygosity may be reported as "unknown". RPGRIP1L: Sequencing analysis is not offered for exon 23. CYP21A2: Analysis includes the most common variants (c.92C>T(p.Pro31Leu), c.293-13C>G (intronic), c.332_339delGAGACTAC (p.Gly111Valfs*21), c.518T>A (p.Ile173Asn), c.710T>A (p.Ile237Asn), c.713T>A (p.Val238Glu), c.719T>A (p.Met240Lys), c.844G>T (p.Val282Leu), c.923dupT (p.Leu308Phefs*6), c.955C>T (p.Gln319*), c.1069C>T(p.Arg357Trp), c.1360C>T (p.Pro454Ser) and the 30Kb deletion) as well as select rare HGMD variants only (list available upon request). Full gene duplications are reported only in the presence of a pathogenic variant(s). When a duplication and a pathogenic variant(s) is identified, phase (cis/trans) cannot be determined. Full gene deletion

analysis is not offered. Sensitivity to detect these variants, if they result from complex gene conversion/fusion events, may be reduced. NBN: Deletion/duplication analysis is not offered for exons 15-16. USH1C: Deletion/duplication analysis is not offered for exons 5-6. TSFM: Sequencing analysis is not offered for exon 5. FAH: Deletion/duplication analysis is not offered for exon 14. GALT: Deletion/duplication analysis is not offered for exon 6. HBA1/2: This assay is designed to detect deletions and duplications of HBA1 and/or HBA2, resulting from the -alpha20.5, --MED, --SEA, --FIL/--THAI, -alpha3.7, -alpha4.2, anti3.7 and anti4.2. Sensitivity to detect other copy number variants may be reduced. Detection of overlapping deletion and duplication events will be limited to combinations of events with significantly differing boundaries. In addition, deletion of the enhancer element HS-40 and the sequence variant, Constant Spring (NM_000517.4:c.427T>C), can be identified by this assay. HBA2: Sequencing analysis is not offered for exons 1-2. NEB: Deletion/duplication analysis is not offered for exons 82-105. NEB variants in this region with no evidence towards pathogenicity are not included in this report, but are available upon request. VPS13A: Deletion/duplication analysis is not offered for exons 2-3, 27-28. MMADHC: Deletion/duplication analysis is not offered for exons 5-6. OAT: Deletion/duplication analysis is not offered for exon 2. ALG6: Deletion/duplication analysis is not offered for exons 11-12. COL27A1: Deletion/duplication analysis is not offered for exons 46-47. MTHFR: The NM_005957.4:c.665C>T (p.Ala222Val) (aka 677C>T) and c.1286A>C (p.Glu429Ala) (aka 1298A>C) variants are not reported in our primary report. SMN1 or SMN2: NM_000344.3:c.*3+80T>G variant only. SMN1: Systematic exon numbering is used for all genes, including SMN1, and for this reason the exon typically referred to as exon 7 in the literature (PMID: 8838816) is referred to as exon 8 in this report. This assay unambiguously detects SMN1 exon 8 copy number. The presence of the g.27134T>G variant (also known as c.*3+80T>G) is reported if SMN1 copy number = 2.

This report has been reviewed and approved by:



Mei Zhu, Ph.D., FACMG
Clinical Molecular Geneticist



Carrier screening report
5807 Donor
 Date of Birth: [REDACTED]
 Sema4 ID: 22021472CS

Patient Information

Name: 5807 Donor
 Date of Birth: [REDACTED]
 Sema4 ID: 22021472CS
 Client ID: TSBCA-S4DONOR5807
 Indication: Carrier Screening

Specimen Information

Specimen Type: Saliva
 Date Collected: 02/01/2022
 Date Received: 02/02/2022
 Final Report: 02/15/2022

Referring Provider

Lorraine Bonner, M.D.
 The Sperm Bank of California
 2115 Milvia Street Suite 201
 Berkeley, CA. 94704
 Fax: 510-841-0332

Custom Carrier Screen (2 genes) with Personalized Residual Risk

SUMMARY OF RESULTS AND RECOMMENDATIONS

Negative

Negative for all genes tested: *BTD*, and *SBDS*
 To view a full list of genes and diseases tested
 please see Table 1 in this report

AR-Autosomal recessive; XL-X-linked

Recommendations

- 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.

Test description

This patient was tested for the genes listed above using one or more of the following methodologies: target capture and short-read sequencing, long-range PCR followed by short-read sequencing, targeted genotyping, and/or copy number analysis. Please note that negative results reduce but do not eliminate the possibility that this individual is a carrier for one or more of the disorders tested. Please see Table 1 for a list of genes and diseases tested with the patient's personalized residual risk. If personalized residual risk is not provided, please see the complete residual risk table at go.sema4.com/residualrisk. Only known pathogenic or likely pathogenic variants are reported. This carrier screening test does not report likely benign variants and variants of uncertain significance (VUS). If reporting of likely benign variants and VUS are desired in this patient, please contact the laboratory at 800-298-6470, option 2 to request an amended report.

Hongli Zhan, Ph.D., Director

Laboratory Medical Consultant: George A. Diaz, M.D., Ph.D



Carrier screening report
 5807 Donor
 Date of Birth [REDACTED]
 Sema4 ID: 220214/2CS

Genes and diseases tested

The personalized residual risks listed below are specific to this individual. The complete residual risk table is available at go.sema4.com/residualrisk

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

Disease	Gene	Inheritance Pattern	Status	Detailed Summary
Negative				
Biotinidase Deficiency	<i>BTBD</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 500
Shwachman-Diamond Syndrome	<i>SBDS</i>	AR	Reduced Risk	Personalized Residual Risk: 1 in 1,700

AR=Autosomal recessive; XL=X-linked

Test methods and comments

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

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

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

Genotyping (Analytical Detection Rate >99%)

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

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

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

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

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

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

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



Carrier screening report
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Date of Birth: [REDACTED]
Sema4 ID: 22021472CS

The presence of the c.73+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.73+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.73+80T>G significantly increases or decreases, respectively, the likelihood of being a silent 2+0 silent carrier.

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

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

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

Agilent SureSelect™XT Low Input technology was used with a custom capture library to target the exonic regions and intron/exon splice junctions of the relevant genes, as well as a number of UTR, intronic or promoter regions that contain previously reported mutations. Libraries were pooled and sequenced on the Illumina NovaSeq 6000 platform, using paired-end 100 bp reads. The sequencing data was analyzed using a custom bioinformatics algorithm designed and validated in house.

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

Exceptions: *ABCD1* (NM_000033.3) exons 8 and 9; *ACADSB* (NM_001609.3) chr10:124,810,695-124,810,707 (partial exon 9); *ADA* (NM_000022.2) exon 1; *ADAMTS2* (NM_014244.4) exon 1; *AGPS* (NM_003659.3) chr21:178,257,512-178,257,649 (partial exon 1); *ALDH7A1* (NM_001182.4) chr5:125,911,150-125,911,163 (partial exon 7) and chr5:125,896,807-125,896,821 (partial exon 10); *ALMS1* (NM_015120.4) chr2:73,612,990-73,613,041 (partial exon 1); *APOPT1* (NM_032374.4) chr14:104,040,437-104,040,455 (partial exon 3); *CDAN1* (NM_138477.2) exon 2; *CEP152* (NM_014985.3) chr15:49,061,146-49,061,165 (partial exon 14) and exon 22; *CEP290* (NM_025114.3) exon 5, exon 7, chr12:88,519,017-88,519,039 (partial exon 13), chr12:88,514,049-88,514,058 (partial exon 15), chr12:88,502,837-88,502,841 (partial exon 23), chr12:88,481,551-88,481,589 (partial exon 32), chr12:88,471,605-88,471,700 (partial exon 40); *CFTR* (NM_000492.3) exon 10; *COL4A4* (NM_000092.4) chr2:227,942,604-227,942,619 (partial exon 25); *COX10* (NM_001303.3) exon 6; *CYP11B1* (NM_000497.3) exons 3-7; *CYP11B2* (NM_000498.3) exons 3-7; *DNAI2* (NM_023036.4) chr1:772,308,136-72,308,147 (partial exon 12); *DOK7* (NM_173660.4) chr4:3,465,131-3,465,161 (partial exon 1) and exon 2; *DUOX2* (NM_014080.4) exons 6-8; *EIF2AK3* (NM_004838.5) exon 8; *EVC* (NM_153717.2) exon 1; *F5* (NM_000130.4) chr1:169,551,662-169,551,679 (partial exon 2); *FH* (NM_000143.3) exon 1; *GAMT* (NM_000156.5) exon 1; *GLDC* (NM_000170.2) exon 1; *GNPTAB* (NM_024312.4) chr17:4,837,000-4,837,400 (partial exon 2); *GNPTG* (NM_032520.4) exon 1; *GHR* (NM_000163.4) exon 3; *GYS2* (NM_021957.3) chr12:21,699,370-21,699,409 (partial exon 33); *HGSNAT* (NM_152419.2) exon 1; *IDS* (NM_000202.6) exon 3; *ITGB4* (NM_000213.4) chr17:73,749,976-73,750,060 (partial exon 33); *JAK3* (NM_000215.3) chr19:17,950,462-17,950,483 (partial exon 10); *LIFR* (NM_002310.5) exon 19; *LMBRD1* (NM_018368.3) chr6:70,459,226-70,459,257 (partial exon 5), chr6:70,447,828-70,447,836 (partial exon 7) and exon 12; *LYST* (NM_000081.3) chr1:235,944,158-235,944,176 (partial exon 16) and chr1:235,875,350-235,875,362 (partial exon 43); *MLYCD* (NM_012213.2) chr1:6,833,933,242-83,933,282 (partial exon 1); *MTR* (NM_000254.2) chr1:237,024,418-237,024,439 (partial exon 20) and chr1:237,038,019-237,038,029 (partial exon 24); *NBEAL2* (NM_015175.2) chr3:47,021,385-47,021,407 (partial exon 1); *NEB* (NM_001271208.1) exons 82-105; *NPC1* (NM_000271.4) chr18:21,123,519-21,123,538 (partial exon 14); *NPH1* (NM_000272.3) chr2:110,937,251-110,937,263 (partial exon 3); *OCRL* (NM_000276.3) chrX:128,674,450-128,674,460 (partial exon 1); *PHKB* (NM_000293.2) exon 1 and chr16:47,732,498-47,732,504 (partial exon 30); *PIGN* (NM_176787.4) chr18:59,815,547-59,815,576 (partial exon 8); *PIP5K1C* (NM_012398.2) exon 1 and chr9:363,7602-363,7616 (partial exon 17); *POU1F1* (NM_000306.3) exon 5; *PTPRC* (NM_002838.4) exons 11 and 23; *PUS1* (NM_025215.5) chr12:132,414,446-132,414,532 (partial exon 2); *RPGRIP1L* (NM_015272.2) exon 23; *SGSH* (NM_000199.3) chr17:78,194,022-78,194,072 (partial exon 1); *SLC6A8* (NM_005629.3) exons 3 and 4; *ST3GAL5* (NM_003896.3) exon 1; *SURF1* (NM_003172.3) chr9:138,223,269-138,223,307 (partial exon 1); *TRPM5* (NM_017662.4) chr9:77,362,800-77,362,811 (partial exon 31); *TSEN54* (NM_207346.2) exon 1; *TYR* (NM_000372.4) exon 5; *VWF* (NM_000552.3) exons 24-26, chr12:6,125,675-6,125,684 (partial exon 30), chr12:6,121,244-6,121,265 (partial exon 33), and exon 34.

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



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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 SureSelectTMXT Low-Input technology was utilized in order to create whole-genome libraries for each patient sample. Libraries were then pooled and sequenced on the Illumina NovaSeq platform. Each sequencing lane was multiplexed to achieve 0.4-2x genome coverage, using paired-end 100 bp reads. The sequencing data underwent ancestral analysis using a customized, licensed bioinformatics algorithm that was validated in house. Identified sub-ethnic groupings were binned into one of 7 continental-level groups (African, East Asian, South Asian, Non-Finnish European, Finnish, Native American, and Ashkenazi Jewish) or, for those ethnicities that matched poorly to the continental-level groups, an 8th "unassigned" group, which were then used to select residual risk values for each gene. For individuals belonging to multiple high-



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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.

Tay-Sachs Disease (TSD) Enzyme Analysis (Analytical Detection Rate >98%)

Hexosaminidase activity and Hex A% activity were measured by a standard heat-inactivation, fluorometric method using artificial 4-MU- β -N-acetylglucosaminide (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 Sema4 Opco, 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.

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Additional disease-specific references available upon request