Reproductive Technologies, Inc.
THE SPERM BANK OF CALIFORNIA
2115 MILVIA STREET, BERKELEY 94704 PHONE 510.841.1858 www.thespermbankofca.org A 501(C)(3) CORPORATION

Acknowledgement of Positive Carrier Screening Results: Donor 5773

I, the undersigned recipient, understand that this donor has tested **POSITIVE** as a carrier for the following condition. More information regarding these conditions can be found in his Invitae Expanded Carrier Screening results.

- **WNT10-A Related Conditions**

I intend to use sperm samples from this donor for insemination or other assisted conception procedure(s).

I acknowledge that The Sperm Bank of California (TSBC) has made the donor's genetic testing results available to me and my medical providers, and that I have reviewed these results. I understand that TSBC **strongly recommends** that I review these genetic testing results with a Genetic Counselor and my medical providers. I understand that TSBC can refer me to genetic counseling services if desired.

I understand that recipient testing is strongly recommended when a donor has positive carrier screening results and that such testing can reduce but not eliminate risks.

- I acknowledge that I personally assume all risks associated with use of semen samples provided by a donor who has tested **POSITIVE as a carrier for WNT10-A Related Conditions**.
- I further acknowledge that I understand that **WNT10A-related Conditions** are inherited in both an autosomal **recessive** and autosomal **dominant** pattern**.**

On behalf of myself and my spouse, heirs, representatives, I hereby release and forever hold harmless TSBC and its current and former officers, directors, employees, attorneys, insurers, consultants, agents, and representatives (collectively "Releases") from any liability or responsibility whatsoever for any and all outcomes, and hereby release and forever discharge Releases from any and all actions, causes of action, demands, damages, losses, liabilities, suits, expenses, including attorneys' fees and costs, of whatever character, in law or in equity, whether currently known, suspected, unknown or unsuspected, matured or unmatured, arising out of my use of sperm donated by a donor who has tested **POSITIVE as a carrier for WNT10-A Related Conditions that are inherited in both an autosomal recessive and autosomal dominant pattern.**

This release involves the waiver of all rights and benefits that I may have under California Civil Code section 1542, which states: "A general release does not extend to claims that the creditor or releasing party does not know or suspect to exist in his or her favor at the time of executing the release and that, if known by him or her, would have materially affected his or her settlement with the debtor or released party."

Please select one of the following:

☐ I have been tested for the above named condition(s) and/or I plan to be tested prior to using the samples.

☐ I understand that TSBC **strongly recommends** that I discuss these results with a Genetic Counselor and my medical providers and consider testing for the above named condition(s). At this time I have **declined** testing and/or **do not anticipate being tested**.

I understand that if I transfer my vials (or embryos if applicable) to any other person, including my spouse, that TSBC requires that person (1) register with TSBC and (2) complete an **Acknowledgement of Positive Carrier Screening Results**.

I understand that any and all questions as to the legal interpretation, validity or any other aspect of this agreement shall be determined by the laws of the State of California, regardless of the location or residence of any of the parties.

Recipient's signature	Recipient's printed name	Date

Reproductive Technologies, Inc.
THE SPERM BANK OF CALIFORNIA
2115 Milvia Street, Berkeley Ca 94704 Phone 510.841.1858 Fax: 510.841.0332 Email: staff@tsbca.org

GENETIC TESTING: POSITIVE CARRIER STATUS

This donor tested **POSITIVE** as a carrier for one or more autosomal recessive conditions as described on the prior page and in the attached genetic testing results.

What does it mean to be a carrier?

All people carry genetic mutations in their DNA. Genetic testing can help to identify some, but not all, of these mutations. While this donor carries a mutation for one or more recessively inherited condition(s), **offspring from this donor are not expected to be at risk of developing these condition(s) unless the recipient (or egg provider if different from the recipient) also carries a genetic mutation for the same condition(s).** For this reason, we strongly encourage you to discuss carrier screening for yourself (or your egg provider) with your physician and a genetic counselor. Genetic testing can reduce but not eliminate risks.

***NOTE: Some recessive conditions may also have increased risks for people who only have one copy of the gene. Children who inherit one copy the WNT10-A Related Conditions gene variant from 5773 may be affected with a common condition called isolated tooth agenesis. Tooth agenesis is the absence of one or more teeth. This variant has reduced penetrance - people who carry it may not be affected but are more likely than others to have it. It's estimated people who carry the variant are 2-3 times more likely to have isolated tooth agenesis than the general population where it occurs in 2-8% of people. See "Reclassification of a genetic variant in the WNT10A gene" from Invitae attached to the ECS results for more information.**

What are my next steps?

1. **Download the genetic test results and review with your medical providers**
   We **strongly recommend** that you discuss this donor's genetic test results with your physician **PRIOR TO SCHEDULING A SHIPMENT OR PICK-UP**, to confirm the donor is suitable for your use. Vials retrieved from the building cannot be exchanged or refunded. The donor's genetic test results are available for free download on the donor's page at https://www.thespermbankofca.org/donor-catalog.

2. **We recommend scheduling a genetic counseling session.**
   A genetic counselor can explain the results in detail including the inheritance pattern, potential risks to your children, and the available testing options that you may want to consider for yourself (or your egg provider). Phone or in person consultations are available for a fee with TSBC's Genetic Counselors at San Francisco Genetic Counseling (https://www.sfgenetics.org/) or you can locate a genetic counselor at www.findageneticcounselor.com.

3. **Complete and return the Acknowledgement of Positive Carrier Screening Results**
   TSBC requires that all recipients selecting this donor complete this acknowledgement form **PRIOR TO SCHEDULING A SHIPMENT OR PICK-UP**. Completing this form documents that you have been informed about this donor's genetic test results and that you are aware of TSBC's recommendation to discuss the genetic test results with your medical providers as noted above.

DATE: 12/14/2021

Reproductive Technologies, Inc.

THE SPERM BANK OF CALIFORNIA

EXPANDED CARRIER SCREENING RESULTS DONOR 5773

Expanded carrier screening for 268 autosomal recessive conditions was completed by **Invitae** and reported on 10/08/2021.

The results were **POSITIVE** for **WNT10-A Related Conditions**. Donor 5773 is a carrier for these conditions.

It is strongly recommended recipients who use this donor's sperm undergo carrier screening for WNT10A-related conditions.

WNT10A-related conditions are inherited in both an autosomal recessive and autosomal dominant pattern. The variant detected in WNT10A (c.682A>T; p.Phe228Ile) can cause a common condition called isolated tooth agenesis, which affects 2-8% of the general population. Tooth agenesis, also called hypodontia, is the absence of one or more teeth. It's estimated people who carry the variant are 2-3 times more likely to have one or more missing teeth. All offspring of donor 5773 have a 50% chance to inherit the c.682A>T WNT10A variant and be at increased risk for isolated tooth agenesis/hypodontia.

Testing was negative for the remainder of genes screened. **Please refer to the donor's Invitae expanded carrier test report for more information on WNT10A conditions, the testing completed and the donors test results.**

Disease	Result	Residual risk to be a carrier (based on Northern European ancestry)
WNT10A-related conditions	POSITIVE (low penetrance)	n/a
Cystic Fibrosis	Negative	1 in 2700
Spinal Muscular Atrophy	Negative: 2 copies exon 7 c.*3+80T>G variant not detected	1 in 880
HBB Hemoglobinopathies & Thalassemia	Negative	1 in 37200
Alpha Thalassemia	Negative	Reduced

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.

At the request of another recipient, screening for the following recessive conditions was performed by **LabCorp** and reported on 11/17/2021.

This testing was performed through LabCorp 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
Ataxia-telangiectasia	Negative	1 in 7,700
Joubert syndrome and related disorders, AHI1 including Meckel-Gruber syndrome	Negative	1 in 7,600
Mucopolysaccharidosis, Type I (IDUA)	Negative	1 in 11,000
Primary carnitine deficiency (SLC22A5)	Negative	1 in 12,000

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 LabCorp 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

INVITAE

INVITAE CARRIER SCREEN RESULTS

Patient name:	5773 DONOR	**Sample type:**	Saliva	**Report date:**	10/08/2021
DOB:		**Sample collection date:**	09/27/2021	**Invitae #:**	RQ2470617
Sex assigned at birth:	Male	**Sample accession date:**	09/30/2021	**Clinical team:**	Janine Mash Lorraine Bonner, MD
Gender:		**MRN:**			

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: POSITIVE

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 shows the presence of clinically significant genetic change(s) in this individual in the gene(s) indicated below. No other clinically significant changes were identified in the remaining genes evaluated with this test.

RESULTS	GENE	VARIANT(S)	INHERITANCE	PARTNER TESTING RECOMMENDED
Carrier: WNT10A-related conditions	WNT10A	c.682T>A (p.Phe228Ile) §	Autosomal recessive	Yes

§ This variant is known to have low penetrance. See Clinical summary and/or Variant details on following pages for more information.

Next steps

- See the table above for recommendations regarding testing of this individual's reproductive partner.
- 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.
- Genetic counseling is recommended to further explain the implications of this test result and assess family health history, which may point to health information that merits additional consideration.
- 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.

Laboratory Director: Kristin Gibson, PhD, FACMG, NYCQ, CGMB, ErCLG
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Clinical summary

RESULT: CARRIER

WNT10A-related conditions

A single Pathogenic (low penetrance) variant, c.682T>A (p.Phe228Ile), was identified in WNT10A. See "What are WNT10A-related conditions?" and Variant details for additional information.

What are WNT10A-related conditions?

WNT10A-related conditions include autosomal recessive odonto-onycho-dermal dysplasia (OODD) and Schöpf-Schulz-Passarge syndrome (SSPS) and autosomal dominant isolated tooth agenesis. Individuals with a clinically significant variant in this gene are carriers for the autosomal recessive conditions and may be at risk to develop the autosomal dominant condition associated with this gene.

Autosomal recessive WNT10A-related conditions, OODD and SSPS, refer to a spectrum of features associated with ectodermal dysplasia (ED), which causes abnormal development of the skin, hair, nails, teeth, and sweat glands. OODD is characterized by dental abnormalities including either fewer teeth than normal (hypodontia) or in more severe cases, the absence of six or more teeth (oligodontia), as well as a smooth tongue, malformed nails (onychodysplasia), clusters of enlarged blood vessels on the face (facial telangiectasias), and thickened skin (hyperkeratosis) with excessive sweating (hyperhidrosis) of the palms of the hands and soles of the feet. SSPS shares the same features as OODD, and is also associated with an increased risk of skin tumors which may be benign (non-cancerous) or malignant, and multiple eyelid cysts. Symptoms and severity of autosomal recessive WNT10A-related conditions are variable. Intellect and life span are not impacted.

Isolated tooth agenesis is a condition that affects the development of the teeth. It can be caused by changes in different genes. Isolated tooth agenesis is the congenital absence of one or more teeth, most commonly the permanent (secondary) teeth. Additional dental abnormalities may include small and/or irregular shaped teeth. Some individuals with WNT10A-related tooth agenesis have also been reported to have mild symptoms of ectodermal dysplasia (ED), which is a condition associated with abnormal development of the skin, hair, nails, teeth, and sweat glands. The severity of WNT10A-related tooth agenesis is variable, and some affected individuals may not have obvious symptoms (incomplete penetrance). Intellect and life span are not impacted.

Please note, the c.682T>A (p.Phe228Ile) variant identified in this individual is known to have low penetrance for both the associated autosomal recessive and autosomal dominant conditions. This means that not all individuals with this genetic change will show signs or symptoms of the condition.

Follow-up depends on each affected individual's specific situation, and discussion with a healthcare provider should be considered.

Next steps

Carrier testing for the reproductive partner is recommended.

Due to the potential for personal health risk for this individual associated with this result, follow-up with a medical provider may be warranted.

If your partner tests positive:

The WNT10A gene is associated with conditions that are inherited in both an autosomal recessive and autosomal dominant fashion. In autosomal recessive inheritance, an individual must have disease-causing genetic changes in each copy of the WNT10A gene to be affected. Carriers, who have a disease-causing genetic change in only one copy of the gene, typically do not have symptoms of the autosomal recessive condition. When both reproductive partners are carriers of an autosomal recessive condition, there is a 25% chance for each child to have the condition. In autosomal dominant inheritance, an individual with a disease-causing change in one copy of the WNT10A gene is at risk to be affected with autosomal dominant isolated tooth agenesis. When one parent has a change in the WNT10A gene, there is a 50% chance for each child to inherit the change and be at risk to be affected with the autosomal dominant condition.

If your partner tests negative:

A negative carrier test result reduces, but does not eliminate, the chance that a person may be a carrier. The risk that a person could still be a carrier, even after a negative test result, is called a residual risk. See the table below for your partner's hypothetical residual risk after testing negative for WNT10A-related conditions. These values are provided only as a guide, are based on the detection rate for the condition as tested at Invitae, and assume a negative family history, the absence of symptoms, and vary based on the ethnic background of an individual. For genes associated with both dominant and recessive inheritance, the numbers provided apply to the recessive condition(s) associated with the gene.

DISORDER (INHERITANCE)	GENE	ETHNICITY	CARRIER FREQUENCY BEFORE SCREENING	CARRIER RESIDUAL RISK AFTER NEGATIVE RESULT
WNT10A-related conditions (AR) NM_025216.2	WNT10A	Pan-ethnic	1 in 305	1 in 30400

Results to note

Pseudodeficiency allele

Benign change, c.1685T>C (p.Ile562Thr), known to be a pseudodeficiency allele, identified in the GALC gene. Pseudodeficiency alleles are not known to be associated with disease, including Krabbe disease.

The presence of a pseudodeficiency allele does not impact this individual's risk to be a carrier. Individuals with pseudodeficiency alleles may exhibit false positive results on related biochemical tests, including newborn screening; however, pseudodeficiency alleles are not known to cause disease, including Krabbe disease. Carrier testing for the reproductive partner is not indicated.

Pseudodeficiency alleles

Benign changes, c.*96A>G (Non-coding), known to be pseudodeficiency alleles, identified in the ARSA gene. Pseudodeficiency alleles are not known to be associated with disease, including metachromatic leukodystrophy (ARSA-related).

The presence of a pseudodeficiency allele does not impact this individual's risk to be a carrier. Individuals with pseudodeficiency alleles may exhibit false positive results on related biochemical tests, including newborn screening; however, pseudodeficiency alleles are not known to cause disease, including metachromatic leukodystrophy (ARSA-related). Carrier testing for the reproductive partner is not indicated.

Variant details

WNT10A, Exon 3, c.682T>A (p.Phe228Ile), heterozygous, Pathogenic (low penetrance)

- This sequence change replaces phenylalanine with isoleucine at codon 228 of the WNT10A protein (p.Phe228Ile). The phenylalanine residue is highly conserved and there is a small physicochemical difference between phenylalanine and isoleucine.
- This variant is present in population databases (rs121908120, ExAC 2.0%), including at least one homozygous and/or hemizygous individual.
- This variant has been observed in many individuals with autosomal recessive forms of ectodermal dysplasia (PMID: 19559398, 28976000, 30974434, Invitae). It has been found in trans (on the opposite chromosome) from many different pathogenic variants. Based on an internal analysis, this variant is associated with reduced penetrance for autosomal recessive disease (15% when in homozygosity and 30-60% when present with another pathogenic variant) compared to other pathogenic or likely pathogenic variants, which have a penetrance of 70-80% (Invitae). In addition, in a large meta-analysis, this variant conferred a 2.25-3.42-fold increased risk (95% CI: 1.39-4.10) for isolated tooth agenesis, the autosomal dominant condition associated with WNT10A (PMID: 29364747).
- ClinVar contains an entry for this variant (Variation ID: 4462).
- Algorithms developed to predict the effect of missense changes on protein structure and function are either unavailable or do not agree on the potential impact of this missense change (SIFT: "Deleterious"; PolyPhen-2: "Probably Damaging"; Align-GVGD: "Class C0").
- In summary, this variant is reported to cause disease. However, because this variant is associated with a lower penetrance form of disease than other pathogenic alleles in the WNT10A gene, and because it is found in homozygosity in healthy individuals, it has been classified as Pathogenic (low penetrance).

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
Alport syndrome (COL4A3-related) (AR) NM_000091.4	COL4A3	Ashkenazi Jewish	1 in 192	1 in 19100
		Caucasian	1 in 284	1 in 28300
		Pan-ethnic	1 in 354	1 in 35300
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
Dihydrolipoamide 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 Ib (AR) NM_001164277.1	SLC37A4	Pan-ethnic	1 in 354	1 in 7060
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

DISORDER (INHERITANCE)	GENE	ETHNICITY	CARRIER FREQUENCY BEFORE SCREENING	CARRIER RESIDUAL RISK AFTER NEGATIVE RESULT
		Sephardic Jewish (Iranian)	1 in 10	1 in 900
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 (RPGRIP1L-related) (AR) NM_015272.2	RPGRIP1L *	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 DNA depletion syndrome-6 (AR) NM_002437.4	MPV17	Navajo	1 in 20	1 in 475
		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
Mucolipidosis type III gamma (AR) NM_032520.4	GNPTG	Pan-ethnic	≤1 in 500	Reduced
Mucolipidosis 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
Pontocerebellar hypoplasia type 2D (AR) NM_016955.3	SEPSECS	Pan-ethnic	≤1 in 500	Reduced
		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
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
		Southern European	1 in 83	1 in 8200
Spastic paraplegia type 15 (AR) NM_015346.3	ZFYVE26	Pan-ethnic	≤1 in 500	Reduced
Spastic paraplegia type 49 (AR) NM_014844.3	TECPR2	Pan-ethnic	≤1 in 500	Reduced
		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	1 in 59	1 in 342
		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 (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
		Sephardic Jewish	1 in 125	1 in 12400
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
Very long-chain acyl-CoA dehydrogenase deficiency (AR) NM_000018.3	ACADVL	Pan-ethnic	1 in 100	1 in 9900

DISORDER (INHERITANCE)	GENE	ETHNICITY	CARRIER FREQUENCY BEFORE SCREENING	CARRIER RESIDUAL RISK AFTER NEGATIVE RESULT
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
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 -α3.7

subtypes, and all -α3.7 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), NR2E3 (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), PROP1 (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

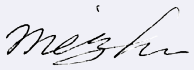
DNA studies do not constitute a definitive test for the selected condition(s) in all individuals. It should be realized that there are possible sources of error. Errors can result from trace contamination, rare technical errors, rare genetic variants that interfere with analysis, recent scientific developments, 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.
- COL27A1: Deletion/duplication analysis is not offered for exons 46-47. NBN: Deletion/duplication analysis is not offered for exons 15-16. GALC: Deletion/duplication analysis is not offered for exon 6. MMADHC: Deletion/duplication analysis is not offered for exons 5-6. 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. USH1C: Deletion/duplication analysis is not offered for exons 5-6. 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. 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. ALG6: Deletion/duplication analysis is not offered for exons 11-12. 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". 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. OAT: Deletion/duplication analysis is not offered for exon 2. TSFM: Sequencing analysis is not offered for exon 5. FAH: Deletion/duplication analysis is not offered for exon 14. RPGRIP1L: Sequencing analysis is not offered for exon 23. 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. VPS13A: Deletion/duplication analysis is not offered for exons 2-3, 27-28.

This report has been reviewed and approved by:



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

Reclassification of a genetic variant in the *WNT10A* gene:

What it means for patients and their families

Why am I receiving this amended report?

Millions of tiny differences exist between the DNA sequences of any two individuals. Although some of these changes, known as variants, can cause disease, most of them do not. Genetic test results, including your carrier screening results, do not mention these "benign" variants because they are not expected to cause health issues.

Yet the scientific community's understanding of which variants do and do not cause disease can change with time.

You are receiving this amended report because the understanding of a variant that we identified in your DNA—the c.682T>A (p.Phe228Ile) variant in the *WNT10A* gene—has changed and is now classified as "pathogenic (low penetrance)."

Why did the understanding of this variant change?

As you may know, as more people undergo genetic testing, we learn more about how genes vary from person to person. Sometimes this new information will change our understanding of a particular DNA variant. In rare cases, variants thought likely to cause disease may eventually be shown not to cause disease and, conversely, variants thought unlikely to cause disease may be shown to cause disease. When our understanding of a variant changes, we call this a variant reclassification. When this happens at Invitae, all reports that include that variant are automatically updated, and the updated reports are released to the healthcare provider who ordered the test.

Why are you sharing this information with me?

At Invitae, we feel that providing variant reclassifications to healthcare providers and patients is important for a variety of reasons. For carrier screening, the new information may change the reproductive risks for current or future pregnancies or may impact your or your family members' personal risk for disease. Providing amended reports also reduces the need for you to repeat the testing at a later time. Invitae's philosophy is that if we become aware of new medically important information that is relevant to you, that information should not be withheld.

What condition is the c.682T>A (p.Phe228Ile) variant in the *WNT10A* gene associated with?

The *WNT10A* gene, where your variant is located, is known to be associated with two conditions.

The first condition is autosomal recessive, which means that a child has to inherit two disease-causing variants—one from each biological parent—to be affected. In this scenario, the child would have a type of **ectodermal dysplasia**, which means abnormal growth of tissues arising from a tissue layer called the ectoderm. Forms of ectodermal dysplasia include odonto-onycho-dermal dysplasia and Schöpf-Schulz-Passarge syndrome, both of which can involve dental anomalies (extra, missing, or malformed teeth), weak hair and nails, and excessive sweating due to abnormal development of sweat glands.[1,2] Treatment is focused on managing symptoms. With early diagnosis and adequate management, many children with these conditions can have a normal life.

The second condition is autosomal dominant, meaning that a child needs to inherit only one disease-causing genetic change to be affected. Some patients with a single variant in *WNT10A* may have a few missing teeth, though others show no observable signs or symptoms of disease.[3–5]

What does pathogenic (low penetrance) mean?

Pathogenic means that a variant is capable of causing disease. Low penetrance means that only some people with the pathogenic variant will show signs and symptoms of the disease. The c.682T>A (p.Phe228Ile) variant is a pathogenic (low penetrance) variant in the *WNT10A* gene. This means that not all individuals with this specific genetic change will show the signs or symptoms of a *WNT10A*-related condition.

Individuals who carry one copy of the c.682T>A (p.Phe228Ile) variant and have no other disease-causing genetic changes typically do not have symptoms, although they may have been missing one or more teeth since birth.[6]

Individuals who carry the c.682T>A (p.Phe228Ile) variant along with another disease-causing variant in the *WNT10A* gene show signs and symptoms of ectodermal dysplasia somewhere between 15% and 60% of the time.

What does this reclassification mean for me?

If you have a single copy of this variant and no other changes in this gene, it is possible that you may have some mild dental differences, such as missing or underdeveloped teeth. However, not all people with a single variant have noticeable signs or symptoms. If you have a single copy of the variant, we encourage you to inform your doctor. Although it is unlikely to affect your medical care, it's important for your doctor to be aware.

What does the reclassification mean if I am pregnant?

The risk that your child will be affected with a *WNT10A*-related condition depends on multiple factors, including the number of variants you and your partner carry and the number of variants the child inherits. If you are pregnant, carrier testing for your reproductive partner is recommended, if it has not yet been completed.

If your partner does not have a change in the *WNT10A* gene, there is a 50% chance that your child will inherit the change. As described above, this typically results in mild dental differences or no signs or symptoms at all.

If your partner does have a change in the *WNT10A* gene, there is a 25% chance that the child will inherit two disease-causing variants. In this case, they may have a form of ectodermal dysplasia but, as described above, they may or may not show signs or symptoms of the disease, given the low penetrance of your *WNT10A* variant. However, there are other scenarios to consider. If your partner carries a *WNT10A* variant, you should consult a genetic counselor or another qualified healthcare provider to discuss these implications.

What does it mean if I am not pregnant?

If you or any of your children have signs or symptoms of a *WNT10A*-related condition, you may benefit from a clinical evaluation by a healthcare provider. If you are considering a pregnancy in the future, carrier testing for your reproductive partner is recommended.

Should my family members be tested?

Your biological relatives may wish to consider genetic testing, especially if they have any signs or symptoms of ectodermal dysplasia or are planning a pregnancy themselves. If they are planning a pregnancy and genetic testing shows that they carry the *WNT10A* variant, carrier testing for their reproductive partners should be considered.

What if I have more questions?

Please send us an email at clientservices@invitae.com or contact Client Services at (800) 436-3037.
We are available to discuss any further questions you may have.

References

1. Castori M, *et al.* Two families confirm Schöpf-Schulz-Passarge syndrome as a discrete entity within the *WNT10A* phenotypic spectrum. *Clin Genet.* 2011;79(1):92–5.
2. Plaisancié J, *et al.* Mutations in *WNT10A* are frequently involved in oligodontia associated with minor signs of ectodermal dysplasia. *Am J Med Genet A.* 2013;161A(4):671–8.
3. Song S, *et al. WNT10A* variants are associated with non-syndromic tooth agenesis in the general population. *Hum Genet.* 2014;133(1):117–24.
4. Van den Boogaard M-J, *et al.* Mutations in *WNT10A* are present in more than half of isolated hypodontia cases. *J Med Genet.* 2012;49(5):327–31.
5. Ruiz-Heiland G, *et al.* Prevalence of *WNT10A* gene mutations in non-syndromic oligodontia. *Clin Oral Investig.* 2019;23(7):3103–13.
6. Jonsson L, *et al.* Rare and common variants conferring risk of tooth agenesis. *J Dent Res.* 2018;97(5):515–22.

Integrated GENETICS
LabCorp Specialty Testing Group

GeneSeq® PLUS

Specimen ID: 27449481890 **Container ID:** L8041
Control ID: **Acct #:** LCA-SO **Phone:**

Donor, 5773

Patient Details		Specimen Details		Physician Details	
DOB:		**Date Collected:**	10/01/2021 12:00 (Local)	**Ordering:**	
Age (yyy/mm/dd):		**Date Received:**	10/06/2021	**Referring:**	
Gender:	Male	**Date Entered:**	10/06/2021	**ID:**	
Patient ID:	27449481890	**Date Reported:**	11/17/2021 17:44 (Local)	**NPI:**	
Ethnicity:	Not provided	Specimen Type:	Blood	Lab ID:	MNEGA
Indication:	Carrier screening			Genetic Counselor:	

SUMMARY: NEGATIVE

NEGATIVE RESULTS

DISORDER *(GENE)*	RESULTS	INTERPRETATION
Ataxia-telangiectasia (*ATM*) NMID: NM_000051	NEGATIVE	This result reduces, but does not eliminate the risk to be a carrier. **Risk**: NOT at an increased risk for an affected pregnancy.
Mucopolysaccharidosis type I (*IDUA*) NMID: NM_000203	NEGATIVE	This result reduces, but does not eliminate the risk to be a carrier. **Risk**: NOT at an increased risk for an affected pregnancy.
Primary carnitine deficiency (*SLC22A5*) NMID: NM_003060	NEGATIVE	This result reduces, but does not eliminate the risk to be a carrier. **Risk**: NOT at an increased risk for an affected pregnancy.
Joubert syndrome and related disorders, including Meckel-Gruber syndrome (*CPLANE1*) NMID: NM_023073	NEGATIVE	This result reduces, but does not eliminate the risk to be a carrier. **Risk**: NOT at an increased risk for an affected pregnancy.

Genetic counseling is recommended to discuss the potential clinical and/or reproductive implications of positive results, as well as recommendations for testing family members and, when applicable, this individual's partner. Genetic counseling services are available. To access Integrated Genetics Genetic Counselors please visit www.integratedgenetics.com/genetic-counseling or call (855) GC-CALLS (855-422-2557).

ADDITIONAL CLINICAL INFORMATION

Ataxia-telangiectasia: Ataxia-telangiectasia is an autosomal recessive disorder with variable severity and age at onset. Signs and symptoms may include early-onset progressive cerebellar ataxia, telangiectasia of the conjunctivae, recurrent infections, radiation hypersensitivity, and cancer susceptibility. Treatment is supportive. Carriers of ataxia-telangiectasia may be at increased risk for malignancies, particularly breast cancer in females. (Gatti, PMID:20301790).

Reported by: S. Hussain Askree, MBBS PhD

Reports electronically released under the direction of Geraldine A. McDowell. PhD FACMG. Laboratory Director. Medical Neurogenetics. LLC

Testing Performed at Medical Neurogenetics, LLC, 5424 Glenridge Drive. Atlanta, GA 30342. Geraldine A. McDowell, PhD FACMG, Laboratory Director 1-800-255-7357

Patient: Donor, 5773
DOB: **Patient ID:** 27449481890 **Control ID:**
Specimen ID: 27449481890
Container ID: L8041
Date Collected: 10/01/2021

Mucopolysaccharidosis type I: Mucopolysaccharidosis type I, also known as Hurler syndrome, is an autosomal recessive lysosomal storage disorder with variable severity and age at onset. Signs and symptoms may include distinctive facial features, hepatosplenomegaly, skeletal dysplasia, corneal clouding causing vision loss, cardiac disease, and progressive intellectual disability. Life expectancy ranges from the 20s or 30s to a usual lifespan. Treatment is primarily supportive. Bone marrow or stem cell transplantation, or enzyme replacement therapy, may be available. (Clarke, PMID:20301341).

Primary carnitine deficiency: Systemic primary carnitine deficiency is an autosomal recessive disorder of fatty acid oxidation with variable severity and age at onset. Metabolic episodes may be triggered by fasting or common illness starting in infancy or early childhood. Signs and symptoms may include vomiting, irritability, lethargy, hypotonia, hepatomegaly, hypoglycemia, encephalopathy, and cardiomyopathy. Pregnant women with the disorder require close monitoring of plasma carnitine levels and increased carnitine supplementation. Treatment focuses on prevention of complications and management of symptoms. Cardiac failure and sudden death may occur without treatment. (El-Hattab, PMID 22420015).

Joubert syndrome and related disorders, including Meckel-Gruber syndrome: Joubert syndrome and related disorders (JSRD) are ciliopathies caused by at least 30 genes with varied inheritance patterns. Autosomal recessive genes are included in this analysis. Signs and symptoms are of variable severity and age at onset. Symptoms of classic Joubert syndrome may include the molar tooth sign, hypotonia, cerebellar ataxia, developmental delay, intellectual disability of variable severity, hyperpnea or apnea, ocular motor apraxia, and distinctive facial features. Additional signs and symptoms may include retinal dystrophy, renal disease, ocular colobomas, occipital encephalocele, hepatic fibrosis, polydactyly, and endocrine abnormalities. Meckel-Gruber syndrome can be fatal in the prenatal or perinatal period. Treatment is supportive. (Brancati, PMID:20615230; Valente, PMID:20512146; Parisi, PMID:20301500).

COMMENTS

This interpretation is based on the clinical information provided and the current understanding of the molecular genetics of the disorder(s) tested. References and additional information about the disorders tested are available at www.integratedgenetics.com.

METHODS/LIMITATIONS

Single Nucleotide Polymorphism and Small Indel Sequencing Assessment: Genomic regions of interest are selected using a custom capture reagent for target enrichment (Twist Bioscience) and sequenced via the Illumina® next generation sequencing platform. Sequencing reads are aligned with the human genome reference GRCh37/hg19 build. Regions of interest include all exons and intron/exon junctions (+/- 20 nucleotides) for each gene analyzed. A minimum of 99% of bases are covered at >15X. Analytical sensitivity is estimated to be >99% for single nucleotide variants, >97% for insertions/deletions less than six base pairs, and >95% for insertions/deletions between six and fifteen base pairs. Uncovered regions with known pathogenic variants are sequenced in a targeted manner (List based on ClinVar Database: November 7, 2020 release).

Copy Number Variant Assessment: Next Generation Sequencing is performed and the data are assessed with Illumina's DRAGEN (Dynamic Read Analysis for GENomics) Bio-IT Platform. Genes listed in ClinVar with pathogenic deletions less than 10 exons in size are padded with additional intronic probes to allow single exon resolution CNV detection (List based on ClinVar Deletion Database: January 2019 release; see list below). For other genes, large deletions (>10 exons) can be detected. The resolution of this analysis can vary depending on region-specific features. Reported variants are confirmed by a second method. Analytical sensitivity is estimated to be >95%. Padded genes: *ABCA12, ABCD1, ACADM, ACOX1, ADAMTS2, ADGRV1, AGL, AGPAT2, AGXT, AHI1, AIRE, ALDOB, ALMS1, AP3B1, ARL6, ARSA, ARSB, ATM, ATP7A, ATRX, BBS1, BBS2, BBS4, BBS5, BBS7, BBS9, BCKDHB, BLM, BRIP1, CAPN3, CBS, CDH23, CFTR, CLCN5, CLN3, CLN5, CLN8, CNTNAP2, COL4A5, CP, CPT1A, CTNS, CYBB, DBT, DCLRE1C, DHCR7, DMD, DOCK8, DOK7, DYSF, EIF2B5, ELP1, EMD, ERCC4, ETHE1, EYS, FA2H, FAM126A, FANCA, FANCC, FANCD2, FANCI, FKRP, FKTN, GAA, GALC, GALNS, GALT, GBE1, GLDC, GNE, GNPTAB, GUSB, HBB, HEXA, HEXB, HINT1, HJV, HPD, HSD17B4, IDS, IFT140, IL2R, ITPA, KCTD7, L1CAM, LAMA2, LAMP2, MCOLN1, MEGF8, MKKS, MKS1, MLC1, MMAB, MTM1, NBN, NCF2, NDUFAF2, NDUFS6, NEB, NPHP1, NROB1, NTRK1, OAT, OCRL, OTC, PAH, PANK2, PCCA, PCDH15, PDHX, PEX1, PEX6, PHKA1, PHKA2, PHKB, PKHD1, PLA2G6, PMM2, POLH, POMGNT1, RAPSN, RDH12, RPGRIP1, RPS6KA3, SGCD, SGCG, SLC25A20, SLC26A4, SLC2A10, SLC35A3, SLC7A7, SPG11, STX11, SYNE4, TAZ, TMEM231, TMEM237, TMEM38B, TMEM70, TRIM32, USH2A, VLDLR, VPS13B, VRK1, WRN.*

Reported by: S. Hussain Askree, MBBS PhD

Reports electronically released under the direction of Geraldine A. McDowell, PhD FACMG, Laboratory Director, Medical Neurogenetics, LLC

Testing Performed at Medical Neurogenetics, LLC, 5424 Glenridge Drive, Atlanta, GA 30342. Geraldine A. McDowell, PhD FACMG, Laboratory Director 1-800-255-7357

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Patient: Donor, 5773
DOB:
Patient ID: 27449481890
Control ID:
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Container ID: L8041
Date Collected: 10/01/2021

Reported Variants: Pathogenic variants, likely pathogenic variants, and variants of uncertain significance are reported. *NEB* variants occurring in exons 82-105 may not be reliably detected by this analysis and are not reported. Nondeletion variants are specified using the numbering and nomenclature recommended by the Human Genome Variation Society (HGVS, http://www.hgvs.org/). Benign and likely benign variants are not reported. Variant classification is consistent with ACMG standards and guidelines (Richards, PMID:25741868). Detailed variant classification information is available upon request.

Limitations: Technologies used do not detect germline mosaicism and do not rule out the presence of large chromosomal aberrations, including rearrangements, variants in regions or genes not included in this test, or possible inter/intragenic interactions between variants. Variant classification and/or interpretation may change over time if more information becomes available. False positive or negative results may occur for reasons that include: genetic variants, sex chromosome abnormalities, pseudogene interference, blood transfusions, bone marrow transplantation, somatic or tissue-specific mosaicism, mislabeled samples, or erroneous representation of family relationships.

This test was developed and its performance characteristics determined by Medical Neurogenetics, LLC. It has not been cleared or approved by the Food and Drug Administration.

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