23andMe® Personal Genome Service® (PGS)
Carrier Status Tests Package Insert

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For *in-vitro* diagnostic use

Intended Use:

23andMe Carrier Status Tests for autosomal recessive conditions are qualitative in vitro molecular detection systems used for genotyping of clinically relevant variants in genomic DNA isolated from human saliva collected with the Oragene·Dx® model OGD-500.001. The tests are intended for adults, and not intended for copy number variation, cytogenetic, or biochemical testing.

Summary and explanation of the test:
23andMe Carrier Status Tests are tests you can order and use at home to learn about your DNA from a saliva sample collected using an FDA cleared collection device Oragene·Dx® model OGD-500.001. The tests work by detecting specific gene variants. Your genetic results are returned to you in a secure online account on the 23andMe website.

Indications for Use:
See test-specific information for each test.

Important:
- Please follow the instructions in the DNA Collection Kit to ensure your DNA results can be processed and connected to your online account.
- Some people feel a little anxious about getting genetic health results. This is normal. If you feel very anxious, you should speak to your doctor or a genetic counselor prior to collecting your sample for testing. You may also consider getting your test done by your doctor.
- Your ethnicity may affect whether certain tests are relevant for you. Your ethnicity also may affect how your genetic health results are interpreted.
- These tests are intended only for autosomal recessive carrier screening in adults.

- If you have a family history of a condition, or think you have symptoms of a condition, consult with your healthcare provider about appropriate testing.
- The absence of a variant tested does not rule out the presence of other variants that may be disease-related.
- These tests are not intended to diagnose a disease or tell you anything about the health of your fetus.
- These tests will not tell you or your newborn child the risk of developing a particular disease later in life.
- These tests are not a substitute for visits to a health care professional. It is recommended that you consult with a health care professional if you have any questions or concerns about your results.
- These tests do not diagnose any health conditions. Results should be used along with other clinical information for any medical purposes.
- As with every test, the possibility for a false positive or false negative result exists.

Limitations:

- These tests do not detect all genetic variants related to these diseases.
- The American College of Medical Genetics (ACMG) and American Congress of Obstetricians and Gynecologists (ACOG) have issued recommendations for carrier testing of certain health conditions. Some of our tests may not cover all of the variants recommended for testing.
- These tests do not always identify if a person has two copies of any variants.
- These tests may not be able to determine a result for all variants analyzed.
- The performance of these tests may be affected by the presence of rare mutations. The impact of potentially interfering mutations has not been evaluated.
- The laboratory may not be able to process your sample. The probability that the laboratory cannot process your saliva sample can be up to 3%. If this happens, we will notify you by email and you may request one free replacement kit to provide us with a new sample.

Test performance

The performance of these tests was assessed only for the detection of the specific gene variants analyzed by each test in adults. Samples were collected using the Oragene·Dx® saliva collection device (OGD-500.001). The samples were tested on the Illumina® Infinium BeadChip. Results were analyzed using the Illumina iScan System and GenomeStudio and Coregen software.

Clinical performance
The clinical performance and variants included for each test are supported by peer-reviewed scientific literature.

See test-specific information for each test.

Analytical performance

Accuracy
Accuracy studies were performed at two lab sites using samples with known variant status. Results of each 23andMe test were compared with sequencing results. Only samples that passed quality control and produced a genotype for both sequencing and the 23andMe test were included in the calculation for percent agreement. 23andMe test results demonstrated at least 99% agreement with sequencing.

Precision/Reproducibility
Precision studies were performed to understand the consistency of sample measurements when tested under different conditions. Human samples of known variant status were tested for precision. Testing was performed at two lab sites over five non-consecutive days with multiple operators. The testing used three lots of reagents and two sets of instruments at each lab site.

A total of 36 replicates were run for each sample tested. Any samples failing quality control acceptance criteria were retested per lab procedures. Only sample replicates that passed quality control and produced a genotype for the 23andMe test were included in the calculation for percent agreement.
All test results demonstrated at least 99% agreement between replicates.

Minimum DNA input
A minimum DNA input study was performed to understand the lowest concentration of DNA needed for at least 95% concordant test results. The study was performed using twenty human cell line samples and two lots of reagents at each of two lab sites. The study yielded concordant test results for samples with a DNA concentration of 15 ng/µL.

Interferences
Studies were performed to determine whether substances that may be present in saliva affect results of the PGS Carrier Status tests. Four proteins that may be found in human saliva were added to saliva samples. These proteins did not affect test performance.

Studies were also performed to determine whether foreign substances found in saliva affect results of the PGS Carrier Status tests. Saliva samples were collected from five people at three time points. First, a sample was collected before consuming a substance. Then, a sample was collected immediately after consumption. Finally, a sample was collected thirty minutes after consumption.

The following conditions were tested:
- Eating food containing beef
- Eating food other than beef
- Drinking
- Chewing gum
- Using mouthwash
- Smoking

The studies indicated that saliva samples should be collected at least thirty (30) minutes after eating, drinking, chewing gum, using mouthwash, or smoking.

Another study was performed to assess the effects of five microbes that may be found in human saliva. The microbial DNA had no effect on the accuracy of the PGS Carrier Status tests.

User studies

Saliva collection kit user study
User studies were performed to assess how well people understand the saliva collection kit instructions and to assess the ability of lay users to provide samples adequate for testing. Study participants represented a wide range of demographic characteristics. Participants were asked to collect and mail a saliva sample and answer an online survey about the collection kit instructions from home. Saliva samples were processed according to standard laboratory procedures.

The overall comprehension rate on the collection kit instructions was 92.1% and greater than 97% of samples met all laboratory quality criteria, demonstrating that users from diverse backgrounds can understand the collection kit instructions and provide adequate saliva samples.

PGS test report user comprehension study
User comprehension studies were performed to assess how well people understand the PGS Carrier Status test reports. A diverse group of people answered questions about test reports in a controlled lab-based setting. Comprehension was tested through a two-step process. First, participants' understanding of genetics was tested prior to viewing the educational module and test reports. Second, participants were shown the educational module and the test reports. Participants then completed the test report comprehension survey.

The Bloom Syndrome test report and Cystic Fibrosis test report were included in these studies. Overall comprehension rates per test report concept averaged 92% across all concepts in both studies. Comprehension of three out of five concepts tested was significantly improved following participants seeing the education module.

Specific test information
Agenesis of the Corpus Callosum with Peripheral Neuropathy
ARSACS
Autosomal Recessive Polycystic Kidney Disease
Beta Thalassemia and Related Hemoglobinopathies
Bloom Syndrome
Canavan Disease
Congenital Disorder of Glycosylation Type 1a (PMM2-CDG)
Cystic Fibrosis
D-Bifunctional Protein Deficiency
Dihydrolipoamide Dehydrogenase Deficiency

Familial Dysautonomia
Familial Hyperinsulinism (ABCC8-Related)
Familial Mediterranean Fever
Fanconi Anemia Group C
Gaucher Disease Type 1
Glycogen Storage Disease Type Ia
Glycogen Storage Disease Type Ib
GRACILE Syndrome
Hereditary Fructose Intolerance
Herlitz Junctional Epidermolysis Bullosa (LAMB3-related)
Leigh Syndrome, French Canadian Type
Limb-Girdle Muscular Dystrophy Type 2D
Limb-Girdle Muscular Dystrophy Type 2E
Limb-Girdle Muscular Dystrophy Type 2I
Maple Syrup Urine Disease Type 1B
MCAD Deficiency
Mucolipidosis Type IV
Neuronal Ceroid Lipofuscinosis (CLN5-Related)
Neuronal Ceroid Lipofuscinosis (PPT1-Related)
Niemann-Pick Disease Type A
Nijmegen Breakage Syndrome
Nonsyndromic Hearing Loss and Deafness, DFNB1 (GJB2-Related)
Pendred Syndrome and DFNB4 Hearing Loss (SLC26A4-Related)
Phenylketonuria and Related Disorders
Primary Hyperoxaluria Type 2
Rhizomelic Chondrodysplasia Punctata Type 1
Salla Disease
Sickle Cell Anemia
Sjögren-Larsson Syndrome
Tay-Sachs Disease
Tyrosinemia Type I
Usher Syndrome Type 1F
Usher Syndrome Type 3A
Zellweger Syndrome Spectrum (PEX1-Related)

Agenesis of the Corpus Callosum with Peripheral Neuropathy (ACCPN)

Indications for Use

The 23andMe PGS Carrier Status Test for Agenesis of the Corpus Callosum with Peripheral Neuropathy (ACCPN) is indicated for the detection of the T813fsX813 variant in the SLC12A6 gene. This test is intended to be used to determine carrier status for ACCPN in adults, but cannot determine if a person has two copies of a tested variant. The test is most relevant for people of French Canadian descent.

Special considerations

- There are currently no professional guidelines in the U.S. for carrier testing for this condition.

Clinical performance

The variant covered by this test is mainly found in people of French Canadian descent. About 1 in 23 people (4.3%) with this ancestry from the Charlevoix/Saguenay-Lac-St.-Jean region of Quebec carries this variant.

Frequency of SLC12A6 variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
T813fsX813	0.01%	0.00%	0.00%	0.00%	0.00%	0.00%

This test is expected to detect more than 99% of carriers of French Canadian descent for this condition.

Pre-test and post-test carrier risks for the 23andMe PGS Carrier Status Test for ACCPN

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result "0 Variants Detected"
French Canadian	>99%	1 in 23	1 in 22,000,000
Other ethnicities*	Unknown	Unknown	Unknown

*This condition is not well studied in other ethnicities.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 46 samples with known variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 92.3% to 100.0%.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 69 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Selected References

Dupre N et al. (2003). "Hereditary motor and sensory neuropathy with agenesis of the corpus callosum." Ann Neurol. 54(1):9-18.

Howard HC et al. (2002). “The K-Cl cotransporter KCC3 is mutant in a severe peripheral neuropathy associated with agenesis of the corpus callosum.” Nat Genet. 32(3):384-92.

Additional references included in the test report.

ARSACS

Indications for Use

The 23andMe PGS Carrier Status Test for Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (ARSACS) is indicated for the detection of the 6594delT variant in the SACS gene. This test is intended to be used to determine carrier status for ARSACS in adults, but cannot determine if a person has two copies of a tested variant. The test is most relevant for people of French Canadian descent.

Special considerations

- There are currently no professional guidelines in the U.S. for carrier testing for this condition.

Clinical performance

The 6594delT variant covered by this test is mainly found in people of French Canadian descent. About 1 in 22 people (4.55%) with this ancestry from the Charlevoix/Saguenay-Lac-St.-Jean region of Quebec carries this variant.

Frequency of SACS variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
6594delT	0.01%	0.00%	0.00%	0.00%	<0.01%	0.00%

This test is expected to detect 94% of carriers of French Canadian descent for this condition.

Pre-test and post-test carrier risks for the 23andMe PGS Carrier Status Test for ARSACS

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result “0 Variants Detected”
French Canadian	94%	1 in 22	1 in 340
Other ethnicities*	Unknown	Unknown	Unknown

*This condition is rare and not well studied in other ethnicities.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 54 samples with known variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 93.4% to 100.0%.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 68 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Selected References

De Braekeleer M et al. (1993). "Genetic epidemiology of autosomal recessive spastic ataxia of Charlevoix-Saguenay in northeastern Quebec." Genet Epidemiol. 10(1):17-25.

Dupré N et al. (2006). "Hereditary ataxia, spastic paraparesis and neuropathy in the French-Canadian population." Can J Neurol Sci. 33(2):149-57.

Mercier J et al. (2001). "Rapid detection of the sacsin mutations causing autosomal recessive spastic ataxia of Charlevoix-Saguenay." Genet Test. 5(3):255-9.

Additional references included in the test report.

Autosomal Recessive Polycystic Kidney Disease

Indications for Use

The 23andMe PGS Carrier Status Test for Autosomal Recessive Polycystic Kidney Disease (ARPKD) is indicated for the detection of 3 variants in the PKHD1 gene. This test is intended to be used to determine carrier status for ARPKD in adults, but cannot determine if a person has two copies of a tested variant.

Special considerations

- The test does not include a large fraction of variants that cause ARPKD in any ethnicity.
- There are currently no professional guidelines in the U.S. for carrier testing for ARPKD.

Clinical performance

The variants covered by this test are most common in people of Finnish descent. Worldwide, about 1 in 70 people (1.4%) is a carrier for ARPKD.

Frequency of PKHD1 variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
T36M	0.12%	0.04%	<0.01%	0.00%	0.05%	<0.05%
R496X	0.01%	<0.01%	0.00%	0.00%	<0.01%	<0.05%
D3230fs	0.01%	<0.01%	0.00%	0.00%	0.08%	0.00%

This test is expected to detect about 66% of carriers of Finnish descent. The test does not cover variants causing the majority of ARPKD in people of general European, Hispanic, Middle Eastern, or Turkish descent.

Pre-test and post-test carrier risks for the 23andMe PGS Carrier Status Test for ARPKD

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result "0 Variants Detected"
Finnish	66%	1 in 70	1 in 200
European	25%	1 in 70	1 in 93
Hispanic	22%	1 in 70	1 in 89
Middle Eastern	<1%	1 in 70	1 in 70
Turkish	<1%	1 in 70	1 in 70
Other ethnicities*	Unknown	Unknown	Unknown

*This condition is not well studied in other ethnicities.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 154 samples with known variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 97.6% to 100.0%.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 197 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Selected References

ARPKD Mutation Database. URL: http://www.humgen.rwth-aachen.de/

Sweeney WE et al. (2001). "Polycystic Kidney Disease, Autosomal Recessive." [Updated 2016 Sep 15].

Additional references included in the report.

Beta Thalassemia and Related Hemoglobinopathies

Indications for Use

The 23andMe PGS Carrier Status Test for Beta Thalassemia and Related Hemoglobinopathies is indicated for the detection of 10 variants in the HBB gene. This test is intended to be used to determine carrier status for beta thalassemia and related hemoglobinopathies in adults, but cannot determine if a person has two copies of a tested variant. The test is most relevant for people of Cypriot, Greek, Italian (particularly Sicilian), and Sardinian descent.

Special considerations

- Symptoms of beta thalassemia may vary between people with the condition depending on the variants involved.
- Carrier screening for beta thalassemia and related hemoglobinopathies is recommended by ACOG via complete blood count and hemoglobin electrophoresis for people of African, Southeast Asian, Mediterranean, Middle Eastern, and West Indian descent considering having children.

Clinical performance

The variants covered by this test are most common in people of Cypriot, Greek, Italian/Sicilian, Sardinian, Albanian, Macedonian, Bangladeshi, and Indonesian descent. This test does not cover a large fraction of HBB variants that cause beta thalassemia in people of Turkish, Croatian, Maharashtran, Azerbaijani, Pakistani, Pathan, Punjabi, Taiwanese, Malaysian, Singaporean, Thai, North African, Middle Eastern, and Chinese descent. About 1 in 8 people (12.5%) of Cypriot descent, 1 in 10 people (10%) of Greek descent, up to 1 in 12 people (8.33%) of Italian (particularly from Sicily) descent, 1 in 9 people (11.11%) of Sardinian descent, and 1 in 23 people (4.35%) of Turkish descent are carriers for beta thalassemia.

Frequency of HBB variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
-29A>G	0.00%	0.37%	0.00%	<0.02%	0.01%	0.00%
IVS1−(−1)G>C	<0.01%	0.00%	0.00%	0.00%	0.00%	<0.05%
IVS1−5G>C	0.01%	0.00%	0.00%	<0.02%	0.00%	0.82%
IVS1−6T>C	0.02%	<0.01%	0.00%	0.00%	0.02%	0.00%
IVS1−110G>A	0.05%	0.01%	0.00%	0.00%	0.05%	0.00%
IVS2−654C>T	0.01%	0.01%	0.00%	0.26%	<0.01%	0.00%
IVS2−745C>G	0.01%	0.00%	0.00%	0.00%	<0.01%	0.00%
W15X	0.00%	0.00%	0.00%	0.00%	<0.01%	0.12%

Q39X	0.07%	0.01%	0.00%	0.00%	0.07%	0.00%
HbC	<0.01%	1.75%	0.00%	0.00%	0.14%	<0.05%

This test is expected to detect 97% of carriers of Sardinian descent, 90% of carriers of Cypriot descent, 82% of carriers of Italian (particularly from Sicily) descent, 75% of carriers of Greek descent, and 66% of carriers of Turkish descent for this condition. This test is also expected to detect between 41-80% of carriers of Balkan descent, 20-70% of carriers of South Asian descent, 11-73% of carriers of Southeast Asian descent, 50-61% of carriers of North African descent, 29-64% of carriers of Middle Eastern descent, and 5-30% of carriers of Southern Chinese descent, all depending on the region of origin.

Pre-test and post-test carrier risks for the 23andMe PGS Carrier Status Test for Beta Thalassemia and Related Hemoglobinopathies

	Carrier detection rate for this test	**Pre-test (average) carrier risk**	**Post-test carrier risk for result "0 Variants Detected"**
Greek and Turkish Cypriot	90%	1 in 8	1 in 71
Greek	75%	1 in 10	1 in 37
Italian (particularly from Sicily)	82%	1 in 12	1 in 61
Sardinian	97%	1 in 9	1 in 250
Turkish	66%	1 in 23	1 in 65
Balkan	41-80%	1 in 12	Unknown
South Asian	20-70%	1 in 16	Unknown
Southeast Asian	11-73%	1 in 12	Unknown
North African	50-61%	1 in 22	Unknown
Middle Eastern	29-64%	1 in 22	Unknown
Chinese (particularly from Southern China)	5-30%	1 in 14	Unknown
Other ethnicities*	Unknown	Unknown	Unknown

*This condition is not as well studied in other ethnicities.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 2,989 samples with known variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 99.9% to 100.0%.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 3,312 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Selected References

Amato A et al. (2014). "Carrier screening for inherited haemoglobin disorders among secondary school students and young adults in Latium, Italy." J Community Genet. 5(3):265-8.

Canatan D et al. (2006). "Hemoglobinopathy control program in Turkey." Community Genet. 9(2):124-6.

Giambona A et al. (2015). "Incidence of haemoglobinopathies in Sicily: the impact of screening and prenatal diagnosis." Int J Clin Pract.

HbVar Database. http://globin.bx.psu.edu/hbvar/menu.html.

Kyrri AR et al. (2013). "The changing epidemiology of beta-thalassemia in the Greek-Cypriot population." Hemoglobin. 37(5):435-43.

Longinotti M et al. (1994). "A 12-year preventive program for beta-thalassemia in Northern Sardinia." Clin Genet. 46(3):238-43.

Theodoridou S et al. (2008). "Carrier screening and prenatal diagnosis of hemoglobinopathies. A study of indigenous and immigrant couples in northern Greece, over the last 5 years." Hemoglobin. 32(5):434-9.

Additional references included in the report.

Bloom Syndrome

Indications for Use

The 23andMe PGS Carrier Status Test for Bloom Syndrome is indicated for the detection of the BLM^{Ash} variant in the BLM gene. This test is intended to be used to determine carrier status for Bloom syndrome in adults, but cannot determine if a person has two copies of a tested variant. The test is most relevant for people of Ashkenazi Jewish descent.

Special considerations

- Symptoms of Bloom syndrome may vary between people with the condition even if they have the same genetic variants.
- Carrier testing for Bloom syndrome is recommended by ACMG for people of Ashkenazi Jewish descent considering having children. This test includes the variant recommended for testing by ACMG.

Clinical performance

The variant covered by this test is most common in people of Ashkenazi Jewish descent. About 1 in 107 people (0.93%) of Ashkenazi Jewish descent carries this variant.

Frequency of BLM variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
BLM^{Ash}	0.02%	< 0.01%	1.04%	0.00%	0.05%	0.00%

This test is expected to detect more than 99% of carriers of Ashkenazi Jewish descent for this condition.

Pre-test and post-test carrier risks for the 23andMe PGS Carrier Status Test for Bloom Syndrome

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result "0 Variants Detected"
Ashkenazi Jewish	> 99%	1 in 107	1 in 11,000
Other ethnicities*	Unknown	Unknown	Unknown

*This condition is rare and not well studied in other ethnicities.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 52 samples with known variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 93.2% to 100.0%.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 100 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and 99% repeatability.

Selected References

Gross, S.J., Pletcher, B.A., Monaghan, K.G. (2008). "ACMG Practice Guidelines: Carrier screening in individuals of Ashkenazi Jewish descent." Genet Med. 10(1):54–56.

Additional references included in the report.

Canavan Disease

Indications for Use

The 23andMe PGS Carrier Status Test for Canavan Disease is indicated for the detection of 3 variants in the ASPA gene. This test is intended to be used to determine carrier status for Canavan disease in adults, but cannot determine if a person has two copies of a tested variant. The test is most relevant for people of Ashkenazi Jewish descent.

Special considerations

- Carrier testing for Canavan disease is recommended by ACMG for people of Ashkenazi Jewish descent considering having children. This test includes the 2 variants recommended for testing by ACMG.

Clinical performance

The variants covered by this test are most common in people of Ashkenazi Jewish descent. About 1 in 41 people (2.44%) of Ashkenazi Jewish descent is a carrier for Canavan disease.

Frequency of ASPA variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
Y231X	0.01%	<0.01%	0.22%	<0.02%	<0.01%	0.00%
E285A	0.05%	0.01%	2.00%	0.00%	0.02%	0.00%
A305E	0.08%	0.03%	<0.01%	0.00%	0.03%	0.00%

This test is expected to detect 98% of carriers of Ashkenazi Jewish descent for this condition.

Pre-test and post-test carrier risks for the 23andMe PGS Carrier Status Test for Canavan Disease

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result "0 Variants Detected"
Ashkenazi Jewish	98%	1 in 41	1 in 2,000
European	53%	Unknown	Unknown
Other ethnicities*	Unknown	Unknown	Unknown

*This condition is not as well studied in other ethnicities.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 242 samples with known variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 98.5% to 100.0%.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 273 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Selected References

Gross SJ et al. (2008). "Carrier screening in individuals of Ashkenazi Jewish descent." Genet Med. 10(1):54-6.

Kaul R et al. (1994). "Canavan disease: mutations among Jewish and non-Jewish patients." Am J Hum Genet. 55(1):34-41.

Monaghan KG et al. (2008). "Technical standards and guidelines for reproductive screening in the Ashkenazi Jewish population." Genet Med. 10(1):57-72.

Additional references included in the report.

Congenital Disorder of Glycosylation Type 1a (PMM2-CDG)

Indications for Use

The 23andMe PGS Carrier Status Test for Congenital Disorder of Glycosylation Type 1a (PMM2-CDG) is indicated for the detection of 2 variants in the PMM2 gene. This test is intended to be used to determine carrier status for PMM2-CDG in adults, but cannot determine if a person has two copies of a tested variant. The test is most relevant for people of Danish descent.

Special considerations

- Severity of symptoms can vary in people with this disorder, even when the same variants are involved.
- There are currently no professional guidelines in the U.S. for carrier testing for this condition.

Clinical performance

The variants covered by this test are most common in people of Danish and Dutch descent. About 1 in 52 people (1.92%) of Danish descent and 1 in 62 people (1.61%) of Dutch descent are carriers for PMM2-CDG. This test does not include a large fraction of PMM2 variants that cause PMM2-CDG in people of Dutch descent.

Frequency of PMM2 variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
R141H	1.02%	0.33%	1.52%	<0.02%	0.72%	0.05%

F119L	0.01%	0.00%	0.00%	0.00%	<0.01%	0.00%

This test is expected to detect 89% of carriers of Danish descent and 55% of carriers of Dutch descent for this condition.

Pre-test and post-test carrier risks for the 23andMe PGS Carrier Status Test for PMM2-CDG

	Carrier detection rate for this test	**Pre-test (average) carrier risk**	**Post-test carrier risk for result "0 Variants Detected"**
Danish	89%	1 in 52	1 in 450
Dutch	55%	1 in 62	1 in 137
Other ethnicities*	Unknown	Unknown	Unknown

*This condition is not well studied in other ethnicities.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 110 samples with known variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 96.7% to 100.0%.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 210 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Selected References

Schollen E et al. (2000). "Lack of Hardy-Weinberg equilibrium for the most prevalent PMM2 mutation in CDG-Ia (congenital disorders of glycosylation type Ia)." Eur J Hum Genet. 8(5):367-71.

Additional references included in the report.

Cystic Fibrosis

Indications for Use

The 23andMe PGS Carrier Status Test for Cystic Fibrosis is indicated for the detection of 29 variants in the CFTR gene, including 22 of 23 variants recommended for testing by ACMG. This test is intended to be used to determine carrier status for cystic fibrosis in adults, but cannot determine if a person has two copies of a tested variant. The test is most relevant for people of Ashkenazi Jewish, European, and Hispanic/Latino descent.

Special considerations

- Symptoms of cystic fibrosis may vary depending on the variants involved.
- ACMG recommends carrier testing for cystic fibrosis for people of all ethnicities considering having children. This test includes 22 of 23 variants recommended for testing by ACMG.

Clinical performance

The variants covered by this test are found in people of all ethnicities. About 1 in 24 people (4.17%) of Ashkenazi Jewish descent, 1 in 25 people (4.00%) of European descent, 1 in 58 people (1.72%) of Hispanic or Latino descent, 1 in 61 people (1.64%) of African American descent, and 1 in 94 people (1.06%) of Asian descent are carriers for cystic fibrosis.

Frequency of CFTR variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
DeltaF508	2.67%	0.88%	1.04%	0.00%	1.51%	0.52%
DeltaI507	0.01%	<0.01%	0.00%	0.00%	0.02%	0.00%
G85E	0.01%	<0.01%	0.00 %	0.00%	0.01%	0.00%
R334W	0.01%	<0.01%	0.00%	<0.02%	0.03%	0.00%
R347H	0.01%	<0.01%	0.00%	<0.02%	0.01%	0.00%
R347P	0.01%	0.00%	0.00%	0.00%	<0.01%	0.00%
A455E	0.01%	0.00%	0.07%	<0.02%	0.01%	0.00%
V520F	0.01%	<0.01%	0.00%	0.00%	<0.01%	0.00%
G542X	0.09%	0.04%	0.20%	0.00%	0.10%	0.00%
S549N	<0.01%	0.02%	0.00%	0.00%	<0.01%	<0.05%
G551D	0.08%	0.02%	0.00%	0.00%	0.03%	0.00%
R553X	0.04%	0.03%	0.00%	<0.02%	0.02%	0.00%
R560T	0.01%	0.00%	0.00%	0.00%	<0.01%	0.00%
R1162X	0.01%	<0.01%	0.00%	0.00%	0.02%	<0.05%
W1282X	0.06%	0.02%	1.93%	0.00%	0.03%	0.00%
N1303K	0.05%	0.01%	0.16%	0.00%	0.05%	0.00%
394delTT	0.01%	0.00%	0.00%	0.00%	<0.01%	0.00%
621+1G>T	0.04%	<0.01%	0.00%	0.00%	0.02%	0.00%
711+1G>T	0.01%	0.00%	0.00%	<0.02%	0.01%	0.00%
1078delT	<0.01%	0.00%	0.00%	0.00%	0.01%	0.00%
1717-1G>A	0.04%	<0.01%	0.05%	<0.02%	0.02%	0.00%
1898+1G>A	0.01%	<0.01%	0.00%	0.00%	<0.01%	<0.05%
2789+5G>A	0.03%	0.01%	0.00%	0.00%	0.02%	0.00%
3120+1G>A	<0.01%	0.19%	0.00%	0.00%	0.02%	0.00%
3659delC	0.03%	<0.01%	<0.01%	<0.02%	0.02%	<0.05%
3905insT	0.01%	<0.01%	0.00%	0.00%	<0.01%	0.00%
3849+10kbC>T	0.03%	<0.01%	0.21%	0.00%	0.04%	0.05%

2184delA	0.01%	0.00%	0.00%	0.02%	0.01%	0.00%
3876delA	0.00%	<0.01%	0.00%	0.00%	0.01%	0.00%

This test is expected to detect 94% of carriers of Ashkenazi Jewish descent, 89% of carriers of European descent, 73% of carriers of Hispanic descent, 65% of carriers of African American descent, and 55% of carriers of Asian descent for this condition.

Pre-test and post-test carrier risks for the 23andMe PGS Carrier Status Test for Cystic Fibrosis

	Carrier detection rate for this test	**Pre-test (average) carrier risk**	**Post-test carrier risk for result "0 Variants Detected"**
Ashkenazi Jewish	94%	1 in 24	1 in 390
European	89%	1 in 25	1 in 230
Hispanic	73%	1 in 58	1 in 210
African American	65%	1 in 61	1 in 170
Asian	55%	1 in 94	1 in 210
Other ethnicities*	Unknown	Unknown	Unknown

*This condition is not as well studied in other ethnicities.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 2,333 samples with known variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 99.8% to 100.0%.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 3,786 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Selected References

American College of Obstetricians and Gynecologists Committee on Genetics. (2011). "ACOG Committee Opinion No. 486: Update on carrier screening for cystic fibrosis." Obstet Gynecol. 117(4):1028-31.

Bobadilla JL et al. (2002). "Cystic fibrosis: a worldwide analysis of CFTR mutations--correlation with incidence data and application to screening." Hum Mutat. 19(6):575-606.

Watson MS et al. (2004). "Cystic fibrosis population carrier screening: 2004 revision of American College of Medical Genetics mutation panel." Genet Med. 6(5):387-91.

Additional references included in the report.

D-Bifunctional Protein Deficiency

Indications for Use

The 23andMe PGS Carrier Status Test for D-Bifunctional Protein Deficiency (DBPD) is indicated for the detection of 2 variants in the HSD17B4 gene. This test is intended to be used to determine carrier status for DBPD in adults, but cannot determine if a person has two copies of a tested variant.

Special considerations

- This test does not include the majority of HSD17B4 variants that cause DBPD in any ethnicity.
- There are currently no professional guidelines in the U.S. for carrier testing for this condition.

Clinical performance

The variants covered by this test are rare in all ethnicities.

Frequency of HSD17B4 variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
G16S	0.09%	0.01%	0.00%	0.00%	0.03%	0.00%
N457Y	<0.01%	0.00%	0.00%	0.00%	0.04%	0.00%

This test is expected to detect 35% of carriers for this condition.

Pre-test and post-test carrier risks for the 23andMe PGS Carrier Status Test for DBPD

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result "0 Variants Detected"
All ethnicities	35%	Unknown	Unknown

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 99 samples with known variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 96.3% to 100.0%.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 135 sample replicates were run across different testing conditions. This study yielded correct results

for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Selected References

Ferdinandusse S et al. (2006). "Mutational spectrum of D-bifunctional protein deficiency and structure-based genotype-phenotype analysis." Am J Hum Genet. 78(1):112-24.

Additional references included in the report.

Dihydrolipoamide Dehydrogenase Deficiency

Indications for Use

The 23andMe PGS Carrier Status Test for Dihydrolipoamide Dehydrogenase (DLD) Deficiency is indicated for the detection of the G229C variant in the DLD gene. This test is intended to be used to determine carrier status for DLD deficiency in adults, but cannot determine if a person has two copies of a tested variant. The test is most relevant for people of Ashkenazi Jewish descent.

Special considerations

- There are currently no professional guidelines in the U.S. for carrier testing for this condition.

Clinical performance

The variant covered by this test is most common in people of Ashkenazi Jewish descent. About 1 in 107 people (0.93%) of Ashkenazi Jewish descent is a carrier for DLD deficiency.

Frequency of DLD variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
G229C	0.03%	<0.01%	1.15%	0.00%	0.01%	<0.05%

This test is expected to detect 86% of carriers of Ashkenazi Jewish descent for this condition.

Pre-test and post-test carrier risks for the 23andMe PGS Carrier Status Test for DLD Deficiency

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result "0 Variants Detected"
Ashkenazi Jewish	86%	1 in 107	1 in 740
Other ethnicities*	Unknown	Unknown	Unknown

*This condition is not well studied in other ethnicities.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 51 samples with known variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 93.0% to 100.0%.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 62 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Selected References

Scott SA et al. (2010). "Experience with carrier screening and prenatal diagnosis for 16 Ashkenazi Jewish genetic diseases." Hum Mutat. 31(11):1240-50.

Shaag A et al. (1999). "Molecular basis of lipoamide dehydrogenase deficiency in Ashkenazi Jews." Am J Med Genet. 82(2):177-82.

Additional references included in the report.

Familial Dysautonomia

Indications for Use

The 23andMe PGS Carrier Status Test for Familial Dysautonomia is indicated for the detection of the 2507+6T>C variant in the IKBKAP gene. This test is intended to be used to determine carrier status for familial dysautonomia in adults, but cannot determine if a person has two copies of a tested variant. The test is most relevant for people of Ashkenazi Jewish descent.

Special considerations

- Carrier testing for familial dysautonomia is recommended by ACMG for people of Ashkenazi Jewish descent considering having children. This test includes 1 of 2 variants recommended for testing by ACMG.

Clinical performance

The variant covered by this test is most common in people of Ashkenazi Jewish descent. About 1 in 31 people (3.23%) of Ashkenazi Jewish descent is a carrier for familial

dysautonomia.

Frequency of IKBKAP variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
2507+6T>C	0.07%	0.03%	3.22%	0.00%	0.05%	0.00%

This test is expected to detect about 99% of carriers of Ashkenazi Jewish descent for this condition.

Pre-test and post-test carrier risks for the 23andMe PGS Carrier Status Test for Familial Dysautonomia

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result "0 Variants Detected"
Ashkenazi Jewish	99%	1 in 31	1 in 2,300
Other ethnicities*	Unknown	Unknown	Unknown

*This condition is not as well studied in other ethnicities.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 52 samples with known variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 93.2% to 100.0%.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 69 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Selected References

Gross SJ et al. (2008). "Carrier screening in individuals of Ashkenazi Jewish descent." Genet Med. 10(1):54-6.

Additional references included in the report.

Familial Hyperinsulinism (ABCC8-Related)

Indications for Use

The 23andMe PGS Carrier Status Report for Familial Hyperinsulinism (ABCC8-Related) is indicated for the detection of three variants in the ABCC8 gene. This test is intended to

be used to determine carrier status for ABCC8-related familial hyperinsulinism in adults, but cannot determine if a person has two copies of a tested variant. This report also describes if a result is associated with personal risk for developing symptoms of ABCC8-related familial hyperinsulinism, but it does not describe a person's overall risk of developing symptoms. This test is most relevant for people of Ashkenazi Jewish descent.

Special considerations

- Symptoms of familial hyperinsulinism may vary between people with the condition even if they have the same genetic variants.
- There are currently no professional guidelines in the U.S. for carrier testing for this condition. However, ACOG notes that testing for familial hyperinsulinism may be considered for people of Ashkenazi Jewish descent who are considering having children.

Clinical performance

The variant covered by this test is most common in people of Ashkenazi Jewish descent. About 1 in 52 people (1.92%) of Ashkenazi Jewish descent is a carrier for ABCC8-related familial hyperinsulinism.

Frequency of ABCC8 variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
F1388del	<0.01%	0.00%	0.13%	0.00%	<0.05%	0.00%
3992-9G>A	0.04%	0.01%	1.33%	0.00%	0.02%	0.00%
V187D	<0.01%	0.00%	0.00%	0.00%	0.00%	0.00%

This test is expected to detect about 97% of carriers of Ashkenazi Jewish descent for this condition.

Pre-test and post-test carrier risks for the 23andMe PGS Carrier Status Test for Familial Hyperinsulinism (ABCC8-Related)

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result "0 Variants Detected"
Ashkenazi Jewish	97%	1 in 52	1 in 1,700
Finnish	41%	1 in 100	1 in 170
Other ethnicities*	Unknown	Unknown	Unknown

*This condition is not as well studied in other ethnicities.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 130 samples with known variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 97.2% to 100%.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 196 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Selected References

Glaser B et al. (2011). "ABCC8 mutation allele frequency in the Ashkenazi Jewish population and risk of focal hyperinsulinemic hypoglycemia." Genet Med. 13(10):891-4.

Otonkoski T et al. (1999). "A point mutation inactivating the sulfonylurea receptor causes the severe form of persistent hyperinsulinemic hypoglycemia of infancy in Finland." Diabetes. 48(2):408-15.

Additional references included in the report.

Familial Mediterranean Fever

Indications for Use

The 23andMe PGS Carrier Status Report for Familial Mediterranean Fever (FMF) is indicated for the detection of seven variants in the MEFV gene. This test is intended to be used to determine carrier status for FMF in adults. This report also describes if a result is associated with personal risk for developing symptoms of FMF, but it does not describe a person's overall risk of developing symptoms. This test is most relevant for people of Arab, Armenian, Sephardic Jewish, and Turkish descent.

Special considerations

- There are currently no professional guidelines in the U.S. for carrier testing for this condition.
- The E148Q variant is one of five founder variants commonly observed in ethnic groups originating from the Mediterranean basin, such as Arabs, Armenians, Sephardic Jews, and Turks. This variant is not included in this test because it is currently considered a variant of uncertain significance.
- Symptoms of FMF may vary between people with the condition even if they have the same genetic variants.
- In some cases, people with only a single MEFV variant can experience symptoms of FMF. In addition, some studies have identified individuals who meet clinical criteria for FMF but do not have any MEFV variants.

Clinical performance

The variants covered by this test are most common in people of Arab, Armenian, Sephardic Jewish, and Turkish descent.

Frequency of MEFV variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
M680I	0.01%	0.01%	0.00%	0.00%	0.01%	0.00%
M694I	0.01%	0.01%	0.00%	0.01%	0.06%	0.00%
M694V	0.03%	0.04%	0.01%	0.00%	0.08%	0.00%
K695R	1.19%	0.16%	2.25%	0.00%	0.63%	0.00%
V726A	0.26%	0.09%	7.61%	0.01%	0.25%	0.05%
A744S	0.40%	0.24%	2.46%	0.05%	0.72%	0.05%
R761H	0.02%	0.02%	0.00%	0.20%	0.03%	0.06%

This test is expected to detect 71-96% of carriers of Arab descent, 92% of carriers of Armenian descent, 75-89% of carriers of Sephardic Jewish descent, and 73-92% of carriers of Turkish descent for this condition.

Pre-test and post-test carrier risks for the 23andMe PGS Carrier Status Test for Familial Mediterranean Fever

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result “0 Variants Detected”
Arab	71-96%	Unknown	Unknown
Armenian	92%	Unknown	Unknown
Sephardic Jewish	75-89%	Unknown	Unknown
Turkish	73-92%	Unknown	Unknown
Other ethnicities*	Unknown	Unknown	Unknown

*This condition is not as well studied in other ethnicities.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 1,013samples with known variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 99.7% to 100%.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 1,464 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Selected References

Touitou I. (2001). "The spectrum of Familial Mediterranean Fever (FMF) mutations." Eur J

Hum Genet. 9(7):473-83.

Shohat M et al. (2000). "Familial Mediterranean Fever." [Updated 2016 Dec 15].

Additional references included in the report.

Fanconi Anemia Group C

Indications for Use

The 23andMe PGS Carrier Status Test for Fanconi Anemia Group C is indicated for the detection of 3 variants in the FANCC gene. This test is intended to be used to determine carrier status for Fanconi anemia group C in adults, but cannot determine if a person has two copies of a tested variant. The test is most relevant for people of Ashkenazi Jewish descent.

Special considerations

- Carrier testing for Fanconi anemia group C is recommended by ACMG for people of Ashkenazi Jewish descent considering having children. This test includes the 1 variant recommended for testing by ACMG.

Clinical performance

The variants covered by this test are most common in people of Ashkenazi Jewish descent. About 1 in 89 people (1.12%) of Ashkenazi Jewish descent is a carrier for Fanconi anemia group C.

Frequency of FANCC variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
IVS4+4A>T	0.03%	0.02%	1.18%	0.00%	0.02%	0.00%
R548X	0.03%	<0.01%	0.00%	0.00%	0.02%	0.00%
322delG	0.04%	0.01%	0.00%	0.00%	0.01%	0.00%

This test is expected to detect more than 99% of carriers of Ashkenazi Jewish descent for this condition.

Pre-test and post-test carrier risks for the 23andMe PGS Carrier Status Test for Fanconi Anemia Group C

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result "0 Variants Detected"
Ashkenazi Jewish	>99%	1 in 89	1 in 88,000
Other ethnicities*	Unknown	Unknown	Unknown

*This condition is not as well studied in other ethnicities.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 159 samples with known variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 97.7% to 100.0%.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 206 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Selected References

Gross SJ et al. (2008). "Carrier screening in individuals of Ashkenazi Jewish descent." Genet Med. 10(1):54-6.

Additional references included in the report.

Gaucher Disease Type I

Indications for Use

The 23andMe PGS Carrier Status Report for Gaucher Disease Type 1 is indicated for reporting of the N370S, 84GG, and V394L variants in the GBA gene. This report describes carrier status for Gaucher disease type 1 in adults. This report also describes if a result is associated with personal risk for developing symptoms of Gaucher disease type 1, but it does not describe a person's overall risk of developing symptoms. This test is most relevant for people of Ashkenazi Jewish descent.

Special considerations

- The severity of symptoms, and when they develop, can vary greatly in people with Gaucher disease type 1. Some people may never develop symptoms.
- The 84GG and V394L variants can occasionally be found in people with the more severe, type 2 or type 3 forms of Gaucher disease. People with two copies of the N370S variant, or one copy of N370S and one copy of another variant, typically have the less severe, type 1 form of the disease.
- Carrier testing for Gaucher disease type 1 is recommended by ACMG for people of Ashkenazi Jewish descent considering having children. This test includes 2 of 4 variants recommended for testing by ACMG.

Clinical performance

The variants covered by this test are most common in people of Ashkenazi Jewish descent, although they also appear in people of other ethnicities. About 1 in 18 people (5.56%) of Ashkenazi Jewish descent is a carrier for Gaucher disease.

Frequency of GBA variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
N370S	0.48%	0.16%	6.52%	0%	0.37%	0%
84GG	0.01%	<0.02%	0.15%	0%	0.05%	0%
V394L	<0.01%	0%	0.08%	0%	0.01%	0%

This test is expected to detect 92% of carriers of Ashkenazi Jewish descent for this condition.

Pre-test and post-test carrier risks for the 23andMe PGS Carrier Status Test for Gaucher Disease Type 1

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result "0 Variants Detected"
Ashkenazi Jewish	92%	1 in 18	1 in 200
Other ethnicities*	Unknown	Unknown	Unknown

*This condition is not as well studied in other ethnicities.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 282 samples with known variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 98.7% to 100.0%.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 341 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Minimum DNA Input

A minimum DNA input study was performed using 8 human cell line samples with three lots of reagents. The study yielded concordant test results for all samples with a DNA concentration of 15 ng/µL.

Selected References

Beutler E et al. (1992). "Mutations in Jewish patients with Gaucher disease." Blood. 79(7):1662-6.

Gross SJ et al. (2008). "Carrier screening in individuals of Ashkenazi Jewish descent." Genet Med. 10(1):54-6.

Torralba MA et al. (2002). "High prevalence of the 55-bp deletion (c.1263del55) in exon 9 of the glucocerebrosidase gene causing misdiagnosis (for homozygous N370S (c.1226A > G) mutation) in Spanish Gaucher disease patients." Blood Cells Mol Dis. 29(1):35-40.

Additional references included in the report.

Glycogen Storage Disease Type Ia

Indications for Use

The 23andMe PGS Carrier Status Test for Glycogen Storage Disease Type Ia (GSDIa) is indicated for the detection of the R83C variant in the G6PC gene. This test is intended to be used to determine carrier status for GSDIa in adults, but cannot determine if a person has two copies of a tested variant. The test is most relevant for people of Ashkenazi Jewish descent.

Special considerations

- There are currently no professional guidelines in the U.S. for carrier testing for this condition.

Clinical performance

The variant covered by this test is most common in people of Ashkenazi Jewish descent. About 1 in 70 people (1.43%) of Ashkenazi Jewish descent is a carrier for GSDIa.

Frequency of G6PC variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
R83C	0.11%	0.03%	1.40%	<0.02%	0.12%	<0.05%

This test is expected to detect 98% of carriers of Ashkenazi Jewish descent for this condition.

Pre-test and post-test carrier risks for the 23andMe PGS Carrier Status Test for GSDIa

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result "0 Variants Detected"
Ashkenazi Jewish	98%	1 in 70	1 in 3,200
Other ethnicities*	Unknown	Unknown	Unknown

*This condition is not as well studied in other ethnicities.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 53 samples with known variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 93.3% to 100.0%.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 61 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Selected References

Chou JY et al. (2008). "Mutations in the glucose-6-phosphatase-alpha (G6PC) gene that cause type Ia glycogen storage disease." Hum Mutat. 29(7):921-30.

Ekstein J et al. (2004). "Mutation frequencies for glycogen storage disease Ia in the Ashkenazi Jewish population." Am J Med Genet A. 129A(2):162-4.

Additional references included in the report.

Glycogen Storage Disease Type Ib

Indications for Use

The 23andMe PGS Carrier Status Test for Glycogen Storage Disease Type Ib (GSDIb) is indicated for the detection of 2 variants in the SLC37A4 gene. This test is intended to be used to determine carrier status for GSDIb in adults, but cannot determine if a person has two copies of a tested variant.

Special considerations

- This test does not include the majority of SLC37A4 variants that cause GSDIb in any ethnicity.
- There are currently no professional guidelines in the U.S. for carrier testing for this condition.

Clinical performance

The variants covered by this test are rare in all ethnicities.

Frequency of SLC37A4 variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
1042_1043del	0.06%	0.03%	0.02%	0.03%	0.06%	0.00%
W118R	<0.01%	0.00%	0.00%	<0.02%	0.00%	0.00%

This test is expected to detect 42% of carriers of Japanese descent and 31% of carriers of European descent for this condition.

Pre-test and post-test carrier risks for the 23andMe PGS Carrier Status Test for GSDIb

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result "0 Variants Detected"
European	31%	Unknown	Unknown
Japanese	42%	Unknown	Unknown
Other ethnicities*	Unknown	Unknown	Unknown

*This condition is not as well studied in other ethnicities.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 97 samples with known variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 96.3% to 100.0%.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 162 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Selected References

Chou JY et al. (2002). "Type I glycogen storage diseases: disorders of the glucose-6-phosphatase complex." Curr Mol Med. 2(2):121-43.

Additional references included in the report.

GRACILE Syndrome

Indications for Use

The 23andMe PGS Carrier Status Test for GRACILE Syndrome is indicated for the

detection of the S78G variant in the BCS1L gene. This test is intended to be used to determine carrier status for GRACILE Syndrome in adults, but cannot determine if a person has two copies of a tested variant. The test is most relevant for people of Finnish descent.

Special considerations

- There are currently no professional guidelines in the U.S. for carrier testing for this condition.

Clinical performance

The variant covered by this test is most common in people of Finnish descent. About 1 in 110 people (0.91%) of Finnish descent is a carrier for GRACILE syndrome.

Frequency of BCS1L variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
S78G	0.03%	<0.01%	0.00%	0.00%	0.02%	0.00%

This test is expected to detect more than 99% of carriers of Finnish descent for this condition.

Pre-test and post-test carrier risks for the 23andMe PGS Carrier Status Test for GRACILE Syndrome

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result "0 Variants Detected"
Finnish	>99%	1 in 110	1 in 1,100,000
Other ethnicities*	Unknown	Unknown	Unknown

*This condition is not as well studied in other ethnicities.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 47 samples with known variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 92.5% to 100.0%.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 66 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Selected References

Fellman V. (2002). "The GRACILE syndrome, a neonatal lethal metabolic disorder with iron overload." Blood Cells Mol Dis. 29(3):444-50.

Fellman V et al. (2008). "Screening of BCS1L mutations in severe neonatal disorders suspicious for mitochondrial cause." J Hum Genet. 53(6):554-8.

Visapää I et al. (2002). "GRACILE syndrome, a lethal metabolic disorder with iron overload, is caused by a point mutation in BCS1L." Am J Hum Genet. 71(4):863-76.

Additional references included in the report.

Hereditary Fructose Intolerance

Indications for Use

The 23andMe PGS Carrier Status Test for Hereditary Fructose Intolerance is indicated for the detection of 4 variants in the ALDOB gene. This test is intended to be used to determine carrier status for hereditary fructose intolerance in adults, but cannot determine if a person has two copies of a tested variant. The test is most relevant for people of European descent.

Special considerations

- There are currently no professional guidelines in the U.S. for carrier testing for this condition.

Clinical performance

The variants covered by this test are most common in people of European descent. About 1 in 71 people (1.41%) of European descent is a carrier for hereditary fructose intolerance.

Frequency of ALDOB variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
A149P	0.90%	0.30%	0.44%	0.00%	0.70%	<0.05%
A174D	0.08%	0.03%	0.40%	0.00%	0.07%	0.00%
N334K	0.04%	<0.01%	0.00%	<0.02%	0.03%	0.00%
Delta4E4	0.01%	<0.01%	0.00%	0.03%	0.04%	<0.05%

This test is expected to detect 85% of carriers of European descent (averaged across multiple countries) for this condition.

Pre-test and post-test carrier risks for the 23andMe PGS Carrier Status Test for Hereditary Fructose Intolerance

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result "0 Variants Detected"
European	85%	1 in 71	1 in 460
Other ethnicities*	Unknown	Unknown	Unknown

*This condition is not as well studied in other ethnicities.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 275 samples with known variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 98.7% to 100.0%.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 370 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Selected References

Coffee EM et al. (2010). "Increased prevalence of mutant null alleles that cause hereditary fructose intolerance in the American population." J Inherit Metab Dis. 33(1):33-42.

Coffee EM et al. (2010). "Mutations in the promoter region of the aldolase B gene that cause hereditary fructose intolerance." J Inherit Metab Dis. 33(6):715-25.

Additional references included in the report.

Herlitz Junctional Epidermolysis Bullosa (LAMB3-related)

Indications for Use

The 23andMe PGS Carrier Status Test for Herlitz Junctional Epidermolysis Bullosa (LAMB3-Related) (Herlitz JEB) is indicated for the detection of 3 variants in the LAMB3 gene. This test is intended to be used to determine carrier status for Herlitz JEB in adults, but cannot determine if a person has two copies of a tested variant.

Special considerations

- This test does not include the majority of LAMB3 variants that cause Herlitz JEB in any ethnicity.
- There are currently no professional guidelines in the U.S. for carrier testing for this

condition.

Clinical performance

The variants covered by this test are rare in all ethnicities.

Frequency of LAMB3 variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
R635X	0.16%	0.02%	0.00%	0.00%	0.04%	0.00%
R42X	0.02%	<0.01%	<0.01%	0.00%	0.01%	0.00%
Q243X	0.00%	<0.01%	0.00%	0.00%	0.00%	0.01%

This test is expected to detect 48% of carriers for this condition.

Pre-test and post-test carrier risks for the 23andMe PGS Carrier Status Test for Herlitz JEB

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result "0 Variants Detected"
All ethnicities	48%	Unknown	Unknown

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 157 samples with known variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 97.7% to 100.0%.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 204 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Selected References

Varki R et al. (2006). "Epidermolysis bullosa. I. Molecular genetics of the junctional and hemidesmosomal variants." J Med Genet. 43(8):641-52.

Additional references included in the report.

Leigh Syndrome, French-Canadian Type (LSFC)

Indications for Use

The 23andMe PGS Carrier Status Test for Leigh Syndrome, French Canadian Type (LSFC) is indicated for the detection of the A354V variant in the LRPPRC gene. This test is intended to be used to determine carrier status for LSFC in adults, but cannot determine if a person has two copies of a tested variant. The test is most relevant for people of French Canadian descent.

Special considerations

- There are currently no professional guidelines in the U.S. for carrier testing for this condition.

Clinical performance

The variant covered by this test is most common in people of French Canadian descent. About 1 in 23 people (4.35%) of French Canadian descent from the Saguenay-Lac-St. Jean region of Quebec is a carrier for LSFC.

Frequency of LRPPRC variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
A354V	<0.01%	0.00%	0.00%	0.00%	0.01%	0.00%

This test is expected to detect more than 99% of carriers of French Canadian descent for this condition.

Pre-test and post-test carrier risks for the 23andMe PGS Carrier Status Test for LSFC

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result "0 Variants Detected"
French Canadian	>99%	1 in 23	1 in 2,500
Other ethnicities*	Unknown	Unknown	Unknown

*This condition is not well studied in other ethnicities.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 40 samples with known variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 91.2% to 100.0%.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 67 sample replicates were run across different testing conditions. This study yielded correct results for >99% of

samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Selected References

Debray FG et al. (2011). "LRPPRC mutations cause a phenotypically distinct form of Leigh syndrome with cytochrome c oxidase deficiency." J Med Genet. 48(3):183-9.

Morin C et al. (1993). "Clinical, metabolic, and genetic aspects of cytochrome C oxidase deficiency in Saguenay-Lac-Saint-Jean." Am J Hum Genet. 53(2):488-96.

Additional references included in the report.

Limb-Girdle Muscular Dystrophy Type 2D

Indications for Use

The 23andMe PGS Carrier Status Test for Limb-Girdle Muscular Dystrophy Type 2D (LGMD2D) is indicated for the detection of the R77C variant in the SGCA gene. This test is intended to be used to determine carrier status for LGMD2D in adults, but cannot determine if a person has two copies of a tested variant. The test is most relevant for people of Finnish descent.

Special considerations

- Symptoms can vary greatly in people with this condition, and can be mild in some cases.
- There are currently no professional guidelines in the U.S. for carrier testing for this condition.

Clinical performance

The variant covered by this test is most common in people of Finnish descent. About 1 in 250 people (0.4%) of Finnish descent is a carrier for LGMD2D.

Frequency of SGCA variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
R77C	0.10%	0.03%	0.00%	<0.02%	0.05%	0.00%

This test is expected to detect 95% of carriers of Finnish descent for this condition.

Pre-test and post-test carrier risks for the 23andMe PGS Carrier Status Test for LGMD2D

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result "0 Variants Detected"

Finnish	95%	1 in 250	1 in 5,500
Other ethnicities*	Unknown	Unknown	Unknown

*This condition is not as well studied in other ethnicities.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 50 samples with known variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 92.9% to 100.0%.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 68 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Selected References

Hackman P et al. (2005). “Enrichment of the R77C alpha-sarcoglycan gene mutation in Finnish LGMD2D patients.” Muscle Nerve. 31(2):199-204.

Additional references included in the report.

Limb-Girdle Muscular Dystrophy 2E

Indications for Use

The 23andMe PGS Carrier Status Test for Limb-Girdle Muscular Dystrophy Type 2E (LGMD2E) is indicated for the detection of the T151R variant in the SGCB gene. This test is intended to be used to determine carrier status for LGMD2E in adults, but cannot determine if a person has two copies of a tested variant. The test is most relevant for people of Southern Indiana Amish descent.

Special considerations

- Symptoms can vary greatly in people with this condition, and can be mild in some cases.
- There are currently no professional guidelines in the U.S. for carrier testing for this condition.

Clinical performance

The variant covered by this test is most common in people of Southern Indiana Amish descent, though carrier frequency in this population is not known.

Frequency of SGCB variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
T151R	<0.01%	0.00%	0.00%	0.00%	0.00%	0.00%

This test is expected to detect more than 99% of carriers of Southern Indiana Amish descent for this condition.

Pre-test and post-test carrier risks for the 23andMe PGS Carrier Status Test for LGMD2E

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result "0 Variants Detected"
Amish from southern Indiana	> 99%	Unknown	Unknown
Other ethnicities*	Unknown	Unknown	Unknown

*This condition is not as well studied in other ethnicities.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 40 samples with known variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 91.9% to 100.0%.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 68 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Selected References

Lim LE et al. (1995). "Beta-sarcoglycan: characterization and role in limb-girdle muscular dystrophy linked to 4q12." Nat Genet. 11(3):257-65.

Additional references included in the report.

Limb-Girdle Muscular Dystrophy 2I

Indications for Use

The 23andMe PGS Carrier Status Test for Limb-Girdle Muscular Dystrophy Type 2I

(LGMD2I) is indicated for the detection of the L276I variant in the FKRP gene. This test is intended to be used to determine carrier status for LGMD2I in adults, but cannot determine if a person has two copies of a tested variant.

Special considerations

- Symptoms can vary greatly in people with this condition, and can be mild in some cases.
- There are currently no professional guidelines in the U.S. for carrier testing for this condition.

Clinical performance

The variant covered by this test is most common in people of European descent. About 1 in 200 people (0.5%) of European descent is a carrier for LGMD2I.

Frequency of FKRP variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
L276I	0.39%	0.08%	0.00%	0.00%	0.15%	0.00%

This test is expected to detect 62% of carriers of European descent for this condition.

Pre-test and post-test carrier risks for the 23andMe PGS Carrier Status Test for LGMD2I

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result "0 Variants Detected"
European	62%	1 in 200	1 in 520
Other ethnicities*	Unknown	Unknown	Unknown

*This condition is not as well studied in other ethnicities.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 228 samples with known variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 98.4% to 100.0%.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 139 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Selected References

Brockington M et al. (2001). “Mutations in the fukutin-related protein gene (FKRP) identify limb girdle muscular dystrophy 2I as a milder allelic variant of congenital muscular dystrophy MDC1C.” Hum Mol Genet. 10(25):2851-9.

Walter MC et al. (2004). “FKRP (826C>A) frequently causes limb-girdle muscular dystrophy in German patients.” J Med Genet. 41(4):e50.

Additional references included in the report.

Maple Syrup Urine Disease (MSUD) Type 1B

Indications for Use

The 23andMe PGS Carrier Status Test for Maple Syrup Urine Disease Type 1B (MSUD 1B) is indicated for the detection of 2 variants in the BCKDHB gene. This test is intended to be used to determine carrier status for MSUD 1B in adults, but cannot determine if a person has two copies of a tested variant. The test is most relevant for people of Ashkenazi Jewish descent.

Special considerations

- There are currently no professional guidelines in the U.S. for carrier testing for this condition.

Clinical performance

The variants covered by this test are most common in people of Ashkenazi Jewish descent. About 1 in 97 people (1.03%) of Ashkenazi Jewish descent is a carrier for MSUD 1B.

Frequency of BCKDHB variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
R183P	0.01%	<0.01%	0.66%	<0.02%	<0.01%	0.00%
G278S	0.08%	<0.01%	0.26%	0.00%	0.03%	0.00%

This test is expected to detect 92% of carriers of Ashkenazi Jewish descent for this condition.

Pre-test and post-test carrier risks for the 23andMe PGS Carrier Status Test for MSUD 1B

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result “0 Variants Detected”
Ashkenazi Jewish	92%	1 in 97	1 in 1,200
Other ethnicities*	Unknown	Unknown	Unknown

*This condition is not as well studied in other ethnicities.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 109 samples with known variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 96.7% to 100.0%.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 137 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Selected References

Edelmann L et al. (2001). "Maple syrup urine disease: identification and carrier-frequency determination of a novel founder mutation in the Ashkenazi Jewish population." Am J Hum Genet. 69(4):863-8.

Scott SA et al. (2010). "Experience with carrier screening and prenatal diagnosis for 16 Ashkenazi Jewish genetic diseases." Hum Mutat. 31(11):1240-50.

Additional references included in the report.

MCAD Deficiency

Indications for Use

The 23andMe PGS Carrier Status Test for Medium-Chain Acyl-CoA Dehydrogenase (MCAD) Deficiency is indicated for the detection of 4 variants in the ACADM gene. This test is intended to be used to determine carrier status for MCAD deficiency in adults, but cannot determine if a person has two copies of a tested variant. The test is most relevant for people of European descent.

Special considerations

- There are currently no professional guidelines in the U.S. for carrier testing for this condition.

Clinical performance

The variants covered by this test are most common in people of European descent. About 1 in 61 people (1.64%) of European descent is a carrier for MCAD deficiency.

Frequency of ACADM variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
K304E	1.25%	0.44%	0.09%	<0.02%	0.63%	<0.05%
Y42H	0.17%	0.06%	0.00%	0.00%	0.05%	0.00%
R181C	0.01%	0.00%	0.00%	<0.02%	0.02%	0.00%
S220L	0.01%	<0.01%	0.00%	0.00%	0.00%	0.00%

This test is expected to detect 75% of carriers of European descent for this condition.

Pre-test and post-test carrier risks for the 23andMe PGS Carrier Status Test for MCAD Deficiency

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result "0 Variants Detected"
European	75%	1 in 61	1 in 240
Other ethnicities*	Unknown	Unknown	Unknown

*This condition is not as well studied in other ethnicities.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 289 samples with known variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 98.7% to 100.0%.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 307 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Selected References

Gregersen N et al. (1993). "Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency: the prevalent mutation G985 (K304E) is subject to a strong founder effect from northwestern Europe." Hum Hered. 43(6):342-50.

Tanaka K et al. (1997). "A survey of the newborn populations in Belgium, Germany, Poland, Czech Republic, Hungary, Bulgaria, Spain, Turkey, and Japan for the G985 variant allele with haplotype analysis at the medium chain Acyl-CoA dehydrogenase gene locus: clinical and evolutionary consideration." Pediatr Res. 41(2):201-9.

Yokota I et al. (1992). "The molecular basis of medium chain acyl-CoA dehydrogenase deficiency: survey and evolution of 985A----G transition, and identification of five rare types of mutation within the medium chain acyl-CoA dehydrogenase gene." Prog Clin Biol

Res. 375:425-40.

Additional references included in the report.

Mucolipidosis Type IV

Indications for Use

The 23andMe PGS Carrier Status Test for Mucolipidosis Type IV is indicated for the detection of the IVS3-2A>G variant in the MCOLN1 gene. This test is intended to be used to determine carrier status for mucolipidosis IV in adults, but cannot determine if a person has two copies of a tested variant. The test is most relevant for people of Ashkenazi Jewish descent.

Special considerations

- Carrier testing for mucolipidosis IV is recommended by ACMG for people of Ashkenazi Jewish descent considering having children. This test includes 1 of 2 variants recommended for testing by ACMG and does not include the second most common variant among people of Ashkenazi Jewish descent.

Clinical performance

The variant covered by this test is most common in people of Ashkenazi Jewish descent. About 1 in 127 people (0.79%) of Ashkenazi Jewish descent is a carrier for mucolipidosis IV.

Frequency of MCOLN1 variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
IVS3-2A>G	0.02%	<0.01%	0.77%	0.00%	0.02%	0.00%

This test is expected to detect 77% of carriers of Ashkenazi Jewish descent for this condition.

Pre-test and post-test carrier risks for the 23andMe PGS Carrier Status Test for Mucolipidosis Type IV

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result "0 Variants Detected"
Ashkenazi Jewish	77%	1 in 127	1 in 550
Other ethnicities*	Unknown	Unknown	Unknown

*This condition is not as well studied in other ethnicities.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 51 samples with known variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 93.0% to 100.0%.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 69 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Selected References

Gross SJ et al. (2008). "Carrier screening in individuals of Ashkenazi Jewish descent." Genet Med. 10(1):54-6.

Additional references included in the report.

Neuronal Ceroid Lipofuscinosis (CLN5-Related)

Indications for Use

The 23andMe PGS Carrier Status Test for Neuronal Ceroid Lipofuscinosis (CLN5-related NCL) is indicated for the detection of the Y392X variant in the CLN5 gene. This test is intended to be used to determine carrier status for CLN5-related NCL in adults, but cannot determine if a person has two copies of a tested variant. The test is most relevant for people of Finnish descent.

Special considerations

- There are currently no professional guidelines in the U.S. for carrier testing for this condition.

Clinical performance

The variant covered by this test is most common in people of Finnish descent. About 1 in 108 people (0.93%) of Finnish descent is a carrier for CLN5-related NCL.

Frequency of CLN5 variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
Y392X	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%

This test is expected to detect 94% of carriers of Finnish descent for this condition.

Pre-test and post-test carrier risks for the 23andMe PGS Carrier Status Test for CLN5-related NCL

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result "0 Variants Detected"
Finnish	94%	1 in 108	1 in 1,800
Other ethnicities*	Unknown	Unknown	Unknown

*This condition is not as well studied in other ethnicities.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 45 samples with known variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 92.1% to 100.0%.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 66 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Selected References

Mole SE et al. (1993). "Neuronal Ceroid-Lipofuscinoses"

Savukoski M et al. (1998). "CLN5, a novel gene encoding a putative transmembrane protein mutated in Finnish variant late infantile neuronal ceroid lipofuscinosis." Nat Genet. 19(3):286-8.

Additional references included in the report.

Neuronal Ceroid Lipofuscinosis (PPT1-Related)

Indications for Use

The 23andMe PGS Carrier Status Test for Neuronal Ceroid Lipofuscinosis (PPT1-related NCL) is indicated for the detection of 3 variants in the PPT1 gene. This test is intended to be used to determine carrier status for PPT1-related NCL in adults, but cannot determine if a person has two copies of a tested variant. The test is most relevant for people of Finnish descent.

Special considerations

- There are currently no professional guidelines in the U.S. for carrier testing for this condition.

Clinical performance

The variants covered by this test are most common in people of Finnish descent. About 1 in 75 people (1.33%) of Finnish descent, 1 in 319 people (0.31%) of Northern European descent, and 1 in 319 people (0.31%) of Western European descent is a carrier for PPT1-related NCL.

Frequency of PPT1 variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
R151X	0.09%	0.04%	0.00%	0.00%	0.05%	0.00%
T75P	0.02%	<0.01%	0.00%	0.00%	0.01%	0.00%
R122W	0.02%	0.00%	0.00%	0.00%	<0.01%	0.00%

This test is expected to detect 98% of carriers of Finnish descent, 59% of carriers of Northern European descent, and 59% of carriers of Western European descent for this condition.

Pre-test and post-test carrier risks for the 23andMe PGS Carrier Status Test for PPT1-related NCL

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result "0 Variants Detected"
Finnish	98%	1 in 75	1 in 3,700
Northern European	59%	1 in 319	1 in 780
Western European	59%	1 in 319	1 in 780
Other ethnicities*	Unknown	Unknown	Unknown

*This condition is not as well studied in other ethnicities.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 159 samples with known variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 97.7% to 100.0%.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 206 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Selected References

Das AK et al. (1998). "Molecular genetics of palmitoyl-protein thioesterase deficiency in the U.S." J Clin Invest. 102(2):361-70.

Mole SE et al. (1993). "Neuronal Ceroid-Lipofuscinoses"

Vesa J et al. (1995). "Mutations in the palmitoyl protein thioesterase gene causing infantile neuronal ceroid lipofuscinosis." Nature. 376(6541):584-7.

Additional references included in the report.

Niemann-Pick Disease Type A

Indications for Use

The 23andMe PGS Carrier Status Test for Niemann-Pick Disease Type A is indicated for the detection of 3 variants in the SMPD1 gene. This test is intended to be used to determine carrier status for Niemann-Pick disease type A in adults, but cannot determine if a person has two copies of a tested variant. The test is most relevant for people of Ashkenazi Jewish descent.

Special considerations

- Carrier testing for Niemann-Pick disease type A is recommended by ACMG for people of Ashkenazi Jewish descent considering having children. This test includes the 3 variants recommended for testing by ACMG.

Clinical performance

The variants covered by this test are most common in people of Ashkenazi Jewish descent. About 1 in 90 people (1.11%) of Ashkenazi Jewish descent is a carrier for Niemann-Pick disease type A.

Frequency of SMPD1 variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
L302P	0.01%	0.00%	0.12%	0.00%	<0.01%	0.00%
fsP330	0.01%	0.00%	0.35%	0.00%	<0.01%	0.00%
R496L	0.01%	<0.01%	0.47%	0.00%	<0.01%	0.00%

This test is expected to detect 97% of carriers of Ashkenazi Jewish descent for this condition.

Pre-test and post-test carrier risks for the 23andMe PGS Carrier Status Test for Niemann-

Pick Disease Type A

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result "0 Variants Detected"
Ashkenazi Jewish	97%	1 in 90	1 in 3,000
Other ethnicities*	Unknown	Unknown	Unknown

*This condition is not as well studied in other ethnicities.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 151 samples with known variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 97.6% to 100.0%.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 273 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Selected References

Gross SJ et al. (2008). "Carrier screening in individuals of Ashkenazi Jewish descent." Genet Med. 10(1):54-6.

Additional references included in the report.

Nijmegen Breakage Syndrome

Indications for Use

The 23andMe PGS Carrier Status Test for Nijmegen Breakage Syndrome is indicated for the detection of the 657del5 variant in the NBN gene. This test is intended to be used to determine carrier status for Nijmegen breakage syndrome in adults, but cannot determine if a person has two copies of a tested variant. The test is most relevant for people of Eastern European (particularly Slavic) descent.

Special considerations

- There are currently no professional guidelines in the U.S. for carrier testing for this condition.

Clinical performance

The variant covered by this test is most common in people of Eastern European descent. About 1 in 154 people (0.65%) of Eastern European (particularly Slavic) descent is a carrier for Nijmegen breakage syndrome.

Frequency of NBN variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
657del5	0.09%	0.01%	0.00%	0.00%	0.04%	0.00%

This test is expected to detect more than 99% of carriers of Eastern European descent for this condition.

Pre-test and post-test carrier risks for the 23andMe PGS Carrier Status Test for Nijmegen Breakage Syndrome

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result "0 Variants Detected"
Eastern European (particularly Slavic)	> 99%	1 in 154	1 in 15,000
Other ethnicities*	Unknown	Unknown	Unknown

*This condition is not as well studied in other ethnicities.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 53 samples with known variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 93.3% to 100.0%.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 64 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Selected References

Chrzanowska KH et al. (2012). "Nijmegen breakage syndrome (NBS)." Orphanet J Rare Dis. 7:13.

Maurer MH et al. (2010). "High prevalence of the NBN gene mutation c.657-661del5 in Southeast Germany." J Appl Genet. 51(2):211-4.

Resnick IB et al. (2002). "Nijmegen breakage syndrome: clinical characteristics and mutation analysis in eight unrelated Russian families." J Pediatr. 140(3):355-61.

Varon R et al. (2000). "Clinical ascertainment of Nijmegen breakage syndrome (NBS) and prevalence of the major mutation, 657del5, in three Slav populations." Eur J Hum Genet. 8(11):900-2.

Additional references included in the report.

Nonsyndromic Hearing Loss and Deafness, DFNB1 (GJB2-Related)

Indications for Use

The 23andMe PGS Carrier Status Test for Nonsyndromic Hearing Loss and Deafness, DFNB1 (GJB2-Related) is indicated for the detection of 2 variants in the GJB2 gene. This test is intended to be used to determine carrier status for DFNB1 in adults, but cannot determine if a person has two copies of a tested variant. The test is most relevant for people of European and Ashkenazi Jewish descent.

Special considerations

- The severity of hearing loss can vary, but there are no other symptoms associated with this condition.
- Most people with DFNB1 have two variants in the GJB2 gene. However, some people with the condition have one variant in the GJB2 gene and a second variant not tested (a deletion) in the GJB6 gene.
- There are currently no professional guidelines in the U.S. for carrier testing for this condition.

Clinical performance

The variants covered by this test are most common in people of European and Ashkenazi Jewish descent. About 1 in 33 people (3.03%) of European descent and 1 in 20 people (5%) of Ashkenazi Jewish descent are carriers for DFNB1. This test does not include the majority of GJB2 variants that cause DFNB1 in people of East Asian descent.

Frequency of GJB2 variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
35delG	1.87%	0.55%	0.72%	<0.02%	1.50%	<0.05%
167delT	0.09%	0.02%	3.19%	0.00%	0.07%	0.00%

This test is expected to detect 93% of carriers of Ashkenazi Jewish descent and 85% of carriers of European descent (averaged across multiple countries) for this condition.

Pre-test and post-test carrier risks for the 23andMe PGS Carrier Status Test for DFNB1

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result "0 Variants Detected"
Ashkenazi Jewish	93%	1 in 20	1 in 280
European	85%	1 in 33	1 in 220
East Asian	<1%	1 in 30	1 in 30
Other ethnicities*	Unknown	Unknown	Unknown

*This condition is not as well studied in other ethnicities.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 164 samples with known variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 97.8% to 100.0%.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 280 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Selected References

Cohn ES et al. (1999). Clinical phenotype and mutations in connexin 26 (DFNB1/GJB2), the most common cause of childhood hearing loss. Am J Med Genet. 89(3):130-6.

Dong J et al. (2001). Nonradioactive detection of the common Connexin 26 167delT and 35delG mutations and frequencies among Ashkenazi Jews. Mol Genet Metab. 73(2):160-3.

Han SH et al. (2008). Carrier frequency of GJB2 (connexin-26) mutations causing inherited deafness in the Korean population. J Hum Genet. 53(11-12):1022-8.

Lerer I et al. (2000). Contribution of connexin 26 mutations to nonsyndromic deafness in Ashkenazi patients and the variable phenotypic effect of the mutation 167delT. Am J Med Genet. 95(1):53-6.

Taniguchi M et al. (2015). Carrier frequency of the GJB2 mutations that cause hereditary hearing loss in the Japanese population. J Hum Genet.

Tsukada K et al. (2015). "Ethnic-specific spectrum of GJB2 and SLC26A4 mutations: their origin and a literature review." Ann Otol Rhinol Laryngol. 124 Suppl 1:61S-76S.

Additional references included in the report.

Pendred Syndrome and DFNB4 Hearing Loss (SLC26A4-Related)

Indications for Use

The 23andMe PGS Carrier Status Test for Pendred Syndrome and DFNB4 Hearing Loss is indicated for the detection of 6 variants in the SLC26A4 gene. This test is intended to be used to determine carrier status for Pendred syndrome and DFNB4 in adults, but cannot determine if a person has two copies of a tested variant.

Special considerations

- Symptoms of Pendred syndrome and DFNB4 vary in severity depending on which variants are causing the condition.
- This test does not include a large fraction of SLC26A4 variants that cause Pendred syndrome or DFNB4 in any ethnicity.
- There are currently no professional guidelines in the U.S. for carrier testing for this condition.

Clinical performance

The variants covered by this test are most common in people of European and Japanese descent.

Frequency of SLC26A4 variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
L236P	0.10%	0.01%	0.00%	0.00%	0.03%	0.00%
E384G	0.06%	0.02%	0.00%	0.00%	0.02%	0.00%
T416P	0.06%	0.02%	0.00%	0.00%	0.03%	0.00%
V138F	0.05%	0.03%	0.02%	0.00%	0.02%	0.00%
H723R	<0.01%	<0.01%	0.00%	0.30%	0.01%	0.00%
L445W	0.03%	<0.01%	0.00%	<0.02%	0.03%	0.00%

This test is expected to detect 13-61% of carriers of European descent (depending on country of ancestry) and 35-45% of carriers of Japanese descent for this condition.

Pre-test and post-test carrier risks for the 23andMe PGS Carrier Status Test for Pendred Syndrome and DFNB4 (SLC26A4-Related)

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result "0 Variants Detected"
European	13-61%	Unknown	Unknown
Japanese	35-45%	Unknown	Unknown
Other ethnicities*	Unknown	Unknown	Unknown

*This condition is not as well studied in other ethnicities.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 347 samples with known variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 98.9% to 100.0%.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 466 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Selected References

Miyagawa M et al. (2014). "Mutation spectrum and genotype-phenotype correlation of hearing loss patients caused by SLC26A4 mutations in the Japanese: a large cohort study." J Hum Genet. 59(5):262-8.

Tsukada K et al. (2015). "Ethnic-specific spectrum of GJB2 and SLC26A4 mutations: their origin and a literature review." Ann Otol Rhinol Laryngol. 124 Suppl 1:61S-76S.
Additional references included in the report.

Phenylketonuria and Related Disorders

Indications for Use

The 23andMe PGS Carrier Status Test for Phenylketonuria (PKU) and Related Disorders is indicated for the detection of 23 variants in the PAH gene. This test is intended to be used to determine carrier status for PKU and related disorders in adults, but cannot determine if a person has two copies of a tested variant. The test is most relevant for people of Northern European descent, particularly those of Irish ancestry.

Special considerations

- PKU and related disorders can be managed with appropriate treatment.
- Symptoms of these disorders vary in severity depending on which variants are causing the condition.
- There are currently no professional guidelines in the U.S. for carrier testing for these conditions.

Clinical performance

The variants covered by this test are most common in people of Northern European descent, particularly those of Irish ancestry. This test does not include a large fraction of

PAH variants that cause PKU and related disorders in people of other ethnicities. About 1 in 26 people (3.85%) of Turkish descent, 1 in 33 people (3.03%) of Irish descent, 1 in 50 people (2.00%) of Northern European descent, 1 in 50 people (2.00%) of Chinese descent, 1 in 50 people (2.00%) of Korean descent, and 1 in 200 people (0.5%) of Japanese descent are carriers for PKU or a related disorder.

Frequency of PAH variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
F39L	0.05%	<0.01%	0.00%	0.00%	0.02%	0.00%
L48S	0.01%	<0.01%	0.00%	<0.02%	0.01%	0.00%
I65T	0.10%	0.03%	0.00%	<0.02%	0.08%	0.00%
R111X	0.01%	0.00%	0.00%	0.03%	0.01%	0.00%
R158Q	0.03%	<0.01%	0.00%	<0.02%	0.02%	0.00%
R243Q	<0.01%	0.00%	0.00%	0.04%	0.02%	0.00%
R243X	0.03%	<0.01%	0.00%	<0.02%	0.02%	0.00%
R252W	0.01%	<0.01%	0.00%	<0.02%	0.02%	<0.05%
R261Q	<0.01%	<0.01%	0.00%	0.00%	<0.01%	0.00%
R261X	0.01%	0.00%	0.00%	0.00%	0.01%	0.00%
G272X	0.02%	0.00%	0.00%	0.00%	<0.01%	0.00%
E280K	0.03%	0.01%	0.00%	<0.02%	0.05%	0.00%
P281L	0.05%	0.01%	0.00%	<0.02%	0.04%	0.00%
A300S	0.04%	<0.01%	0.64%	0.00%	0.03%	<0.05%
L348V	0.05%	<0.01%	0.00%	0.00%	0.02%	0.00%
E390G	0.04%	<0.01%	0.00%	0.00%	0.03%	0.00%
A403V	0.08%	<0.01%	0.44%	0.00%	0.07%	0.00%
R408W	0.19%	0.04%	0.03%	0.02%	0.05%	0.00%
R408Q	0.02%	0.02%	0.00%	0.05%	0.01%	0.00%
R413P	<0.01%	0.00%	<0.01%	0.04%	0.00%	0.00%
Y414C	0.10%	0.01%	0.00%	0.00%	0.05%	0.00%
IVS10-11G>A	0.04%	0.01%	0.00%	0.00%	0.03%	0.00%
IVS12+1G>A	0.08%	0.02%	0.00%	0.00%	0.04%	0.00%

This test is expected to detect 82% of carriers of Irish descent, 75% of carriers of Northern European descent (averaged across multiple countries), 63% of carriers of Turkish descent, 42% of carriers of Japanese descent, 33% of carriers of Chinese descent, and 20% of carriers of Korean descent for this condition. This test is also expected to detect between 46-87% of carriers of Western European descent, 32-85% of carriers of Southern European descent, and 63-96% of carriers of Eastern European descent, depending on the country of origin.

Pre-test and post-test carrier risks for the 23andMe PGS Carrier Status Test for Phenylketonuria and Related Disorders

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result “0 Variants Detected”

Irish	82%	1 in 33	1 in 179
Northern European	75%	1 in 50	1 in 197
Turkish	63%	1 in 26	1 in 68
Chinese	33%	1 in 50	1 in 74
Korean	20%	1 in 50	1 in 62
Japanese	42%	1 in 200	1 in 340
Western European	46-87%	Unknown	Unknown
Southern European	32-85%	Unknown	Unknown
Eastern European	63-96%	Unknown	Unknown
Other ethnicities*	Unknown	Unknown	Unknown

*This condition is not as well studied in other ethnicities.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 2,894 samples with known variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 99.9% to 100.0%.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 4,488 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Selected References

Dobrowolski SF et al. (2011). “Molecular genetics and impact of residual in vitro phenylalanine hydroxylase activity on tetrahydrobiopterin responsiveness in Turkish PKU population.” Mol Genet Metab. 102(2):116-21.

Lee DH et al. (2004). “The molecular basis of phenylketonuria in Koreans.” J Hum Genet. 49(11):617-21.

Li N et al. (2015). “Molecular characterisation of phenylketonuria in a Chinese mainland population using next-generation sequencing.” Sci Rep. 5:15769.

Mitchell JJ. (2000). “Phenylalanine Hydroxylase Deficiency.” [Updated 2017 Jan 5].

Zschocke J. (2003). “Phenylketonuria mutations in Europe.” Hum Mutat. 21(4):345-56.

Additional references included in the report.

Primary Hyperoxaluria Type 2

Indications for Use

The 23andMe PGS Carrier Status Test for Primary Hyperoxaluria Type 2 (PH2) is indicated for the detection of the 103delG variant in the GRHPR gene. This test is intended to be used to determine carrier status for PH2 in adults, but cannot determine if a person has two copies of a tested variant.

Special considerations

- This test does not include a large fraction of GRHPR variants that cause PH2.
- There are currently no professional guidelines in the U.S. for carrier testing for this condition.

Clinical performance

The variant covered by this test is most common in people of European descent. About 1 in 282 people (0.35%) of European descent is a carrier for PH2.

Frequency of GRHPR variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
103delG	0.10%	0.04%	0.00%	0.00%	0.03%	0.00%

This test is expected to detect 68% of carriers of European descent for this condition.

Pre-test and post-test carrier risks for the 23andMe PGS Carrier Status Test for PH2

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result "0 Variants Detected"
European	68%	1 in 282	1 in 880
Other ethnicities*	Unknown	Unknown	Unknown

*This condition is not as well studied in other ethnicities.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 51 samples with known variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 93.0% to 100.0%.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 69 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Selected References

Takayama T et al. (2014). "Ethnic differences in GRHPR mutations in patients with primary hyperoxaluria type 2." Clin Genet. 86(4):342-8.

Additional references included in the report.

Rhizomelic Chondrodysplasia Punctata Type 1 (RCDP1)

Indications for Use

The 23andMe PGS Carrier Status Test for Rhizomelic Chondrodysplasia Punctata Type 1 (RCDP1) is indicated for the detection of the L292X variant in the PEX7 gene. This test is intended to be used to determine carrier status for RCDP1 in adults, but cannot determine if a person has two copies of a tested variant.

Special considerations

- This test does not include a large fraction of PEX7 variants that cause RCDP1 in any ethnicity.
- There are currently no professional guidelines in the U.S. for carrier testing for this condition.

Clinical performance

The variant covered by this test is most common in people of European descent.

Frequency of PEX7 variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
L292X	0.15%	0.05%	0.00%	0.00%	0.07%	<0.05%

This test is expected to detect about 50% of carriers of European descent for this condition.

Pre-test and post-test carrier risks for the 23andMe PGS Carrier Status Test for RCDP1

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result "0 Variants Detected"
European	About 50%	Unknown	Unknown
Other ethnicities*	Unknown	Unknown	Unknown

*This condition is not as well studied in other ethnicities.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 51 samples with known variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 93.0% to 100.0%.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 68 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Selected References

Braverman NE et al. (2001). "Rhizomelic Chondrodysplasia Punctata Type 1." [Updated 2012 Sep 13].

Braverman N et al. (2002). "Mutation analysis of PEX7 in 60 probands with rhizomelic chondrodysplasia punctata and functional correlations of genotype with phenotype." Hum Mutat. 20(4):284-97.

Additional references included in the report.

Salla Disease

Indications for Use

The 23andMe PGS Carrier Status Test for Salla Disease is indicated for the detection of the R39C variant in the SLC17A5 gene. This test is intended to be used to determine carrier status for Salla disease in adults, but cannot determine if a person has two copies of a tested variant. The test is most relevant for people of Finnish and Swedish descent.

Special considerations

- There are currently no professional guidelines in the U.S. for carrier testing for this condition.

Clinical performance

The variant covered by this test is most common in people of Finnish and Swedish descent. About 1 in 200 people (0.5%) of Finnish descent is a carrier for Salla disease.

Frequency of SLC17A5 variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian

R39C	0.06%	<0.01%	<0.01%	0.00%	0.02%	0.00%

This test is expected to detect 91% of carriers of Finnish descent and 85% of carriers of Swedish descent for this condition.

Pre-test and post-test carrier risks for the 23andMe PGS Carrier Status Test for Salla disease

	Carrier detection rate for this test	**Pre-test (average) carrier risk**	**Post-test carrier risk for result "0 Variants Detected"**
Finnish	91%	1 in 200	1 in 2,200
Swedish	85%	Unknown	Unknown
Other ethnicities*	Unknown	Unknown	Unknown

*This condition is not as well studied in other ethnicities.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 54 samples with known variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 93.4% to 100.0%.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 66 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Selected References

Aula N et al. (2000). "The spectrum of SLC17A5-gene mutations resulting in free sialic acid-storage diseases indicates some genotype-phenotype correlation." Am J Hum Genet. 67(4):832-40.

Erikson A et al. (2002). "Free sialic acid storage (Salla) disease in Sweden." Acta Paediatr. 91(12):1324-7.

Additional references included in the report.

Sickle Cell Anemia

Indications for Use

The 23andMe PGS Carrier Status Test for Sickle Cell Anemia is indicated for the detection of the HbS variant in the HBB gene. This test is intended to be used to

determine carrier status for sickle cell anemia in adults, but cannot determine if a person has two copies of the tested variant. The test is most relevant for people of African descent.

Special considerations

- Carrier screening for hemoglobinopathies such as sickle cell anemia is recommended by ACOG via complete blood count and hemoglobin electrophoresis for people of African, Southeast Asian, Mediterranean, Middle Eastern, and West Indian descent considering having children.

Clinical performance

The variant covered by this test is most common in people of African descent. About 1 in 12 people (8.33%) of African American descent is a carrier for sickle cell anemia.

Frequency of the HbS variant in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
HbS	0.03%	6.73%	0.00%	0.00%	0.71%	0.15%

This test is expected to detect more than 99% of carriers for this condition. This report covers the only variant that causes sickle cell anemia.

Pre-test and post-test carrier risks for the 23andMe PGS Carrier Status Test for Sickle Cell Anemia

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result "0 Variants Detected"
African American*	>99%	1 in 12	-
African	>99%	Varies by country	-

*This test covers the only variant that causes sickle cell anemia.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 350 samples with known variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 99.0% to 100.0%.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 453 sample replicates were run across different testing conditions. This study yielded correct results

for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Selected References

Bender MA et al. (2003). "Sickle Cell Disease." [Updated 2017 Aug 17].

Additional references included in the report.

Sjögren-Larsson Syndrome

Indications for Use

The 23andMe PGS Carrier Status Test for Sjögren-Larsson Syndrome is indicated for the detection of the P315S variant in the ALDH3A2 gene. This test is intended to be used to determine carrier status for Sjögren-Larsson syndrome in adults, but cannot determine if a person has two copies of a tested variant. The test is most relevant for people of Swedish descent.

Special considerations

- There are currently no professional guidelines in the U.S. for carrier testing for this condition.

Clinical performance

The variant covered by this test is most common in people of Swedish descent. About 1 in 200 people (0.50%) of Swedish descent is a carrier for Sjögren-Larsson syndrome.

Frequency of ALDH3A2 variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
P315S	0.01%	0.00%	0.00%	0.00%	<0.01%	0.00%

This test is expected to detect 81% of carriers of Swedish descent for this condition.

Pre-test and post-test carrier risks for the 23andMe PGS Carrier Status Test for Sjögren-Larsson Syndrome

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result "0 Variants Detected"
Swedish	81%	1 in 200	1 in 1,100
Other ethnicities*	Unknown	Unknown	Unknown

*This condition is not as well studied in other ethnicities.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 48 samples with known variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 92.6% to 100.0%.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 69 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Selected References

Gånemo A et al. (2009). "Sjögren-larsson syndrome: a study of clinical symptoms and dermatological treatment in 34 Swedish patients." Acta Derm Venereol. 89(1):68-73.

Jagell S et al. (1981). "Sjögren-Larsson syndrome in Sweden. A clinical, genetic and epidemiological study." Clin Genet. 19(4):233-56.

Additional references included in the report.

Tay-Sachs Disease

Indications for Use

The 23andMe PGS Carrier Status Test for Tay-Sachs Disease is indicated for the detection of 4 variants in the HEXA gene. This test is intended to be used to determine carrier status for Tay-Sachs disease in adults, but cannot determine if a person has two copies of a tested variant. The test is most relevant for people of Ashkenazi Jewish and Cajun descent.

Special considerations

- Symptoms of this disease vary in severity depending on which variants are causing the condition.
- Carrier testing for Tay-Sachs disease is recommended by ACMG for people of Ashkenazi Jewish descent considering having children. This test includes the 3 variants recommended for testing by ACMG.
- When carrier testing for Tay-Sachs disease is indicated in people who are not of Ashkenazi Jewish descent, ACMG recommends biochemical carrier screening as a first step. Genetic testing can then be used to confirm carrier status in people with a positive result.
- This test does not cover variants causing Tay-Sachs disease that are more

common in people of French Canadian descent.

Clinical performance

The variants covered by this test are most common in people of Ashkenazi Jewish and Cajun descent. About 1 in 31 people (3.23%) of Ashkenazi Jewish descent, 1 in 30 people (3.33%) of Cajun descent, and 1 in 30 people (3.33%) of French Canadian descent are carriers for Tay-Sachs disease.

Frequency of HEXA variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
G269S	0.07%	<0.01%	0.21%	0.00%	0.03%	0.00%
1278insTATC	0.13%	0.02%	2.85%	<0.02%	0.05%	<0.05%
IVS12+1G>C	0.02%	<0.01%	0.65%	0.00%	0.01%	0.00%
IVS9+1G>A	0.10%	0.02%	0.00%	<0.02%	0.04%	0.00%

This test is expected to detect 99% of carriers of Ashkenazi Jewish descent and more than 99% of carriers of Cajun descent for this condition.

Pre-test and post-test carrier risks for the 23andMe PGS Carrier Status Test for Tay-Sachs Disease

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result "0 Variants Detected"
Ashkenazi Jewish	99%	1 in 31	1 in 2,700
Cajun	>99%	1 in 30	1 in 29,000,000
French Canadian	<10%	1 in 30	Unknown
Other ethnicities*	Unknown	Unknown	Unknown

*This condition is not as well studied in other ethnicities.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 205 samples with known variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 98.2% to 100.0%.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 308 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and

>99% repeatability.

Selected References

ACOG Committee on Genetics. (2009). "ACOG Committee Opinion No. 442: Preconception and prenatal carrier screening for genetic diseases in individuals of Eastern European Jewish descent." Obstet Gynecol. 114(4):950-3.

Gross SJ et al. (2008). "Carrier screening in individuals of Ashkenazi Jewish descent." Genet Med. 10(1):54-6.

McDowell GA et al. (1992). "The presence of two different infantile Tay-Sachs disease mutations in a Cajun population." Am J Hum Genet. 51(5):1071-7.

Additional references included in the report.

Tyrosinemia Type I

Indications for Use

The 23andMe PGS Carrier Status Test for Tyrosinemia Type I is indicated for the detection of 4 variants in the FAH gene. This test is intended to be used to determine carrier status for tyrosinemia type I in adults, but cannot determine if a person has two copies of a tested variant. The test is most relevant for people of French Canadian and Finnish descent.

Special considerations

- There are currently no professional guidelines in the U.S. for carrier testing for this condition.

Clinical performance

The variants covered by this test are most common in people of French Canadian, Ashkenazi Jewish, and Finnish descent. About 1 in 21 people (4.76%) of French Canadian descent, 1 in 150 people (0.67%) of Ashkenazi Jewish descent, and 1 in 123 people (0.81%) of Finnish descent are carriers for tyrosinemia type I.

Frequency of FAH variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
W262X	<0.01%	<0.01%	0.00%	0.00%	<0.01%	0.00%
P261L	0.02%	<0.01%	0.74%	<0.02%	0.01%	0.00%
IVS12+5G>A	0.09%	0.04%	0.00%	0.00%	0.02%	0.05%
IVS6-1G>T	0.04%	<0.01%	0.00%	0.00%	0.04%	0.00%

This test is expected to detect 90% of carriers of French Canadian descent, more than 99% of carriers of Ashkenazi Jewish descent, and 86% of carriers of Finnish descent for this condition.

Pre-test and post-test carrier risks for the 23andMe PGS Carrier Status Test for Tyrosinemia Type I

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result "0 Variants Detected"
French Canadian	90%	1 in 21	1 in 200
Ashkenazi Jewish	>99%	1 in 150	1 in 149,000,000
Finnish	86%	1 in 123	1 in 870
European	60%	1 in 150	1 in 370
Norwegian	42%	1 in 137	1 in 240
Turkish	30%	1 in 150	1 in 210
Other ethnicities*	Unknown	Unknown	Unknown

*This condition is not as well studied in other ethnicities.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 249 samples with known variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 98.5% to 100.0%.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 340 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Selected References

De Braekeleer M et al. (1990). "Genetic epidemiology of hereditary tyrosinemia in Quebec and in Saguenay-Lac-St-Jean." Am J Hum Genet. 47(2):302-7.

Grompe M et al. (1994). "A single mutation of the fumarylacetoacetate hydrolase gene in French Canadians with hereditary tyrosinemia type I." N Engl J Med. 331(6):353-7.

Rootwelt H et al. (1994). "Novel splice, missense, and nonsense mutations in the fumarylacetoacetase gene causing tyrosinemia type 1." Am J Hum Genet. 55(4):653-8.

Rootwelt H et al. (1996). "Fumarylacetoacetase mutations in tyrosinaemia type I." Hum Mutat. 7(3):239-43.

Sniderman King L et al. (2006). "Tyrosinemia Type I." [Updated 2017 May 25].

St-Louis M et al. (1994). "Identification of a stop mutation in five Finnish patients suffering from hereditary tyrosinemia type I." Hum Mol Genet. 3(1):69-72.

Additional references included in the report.

Usher Syndrome Type 1F

Indications for Use

The 23andMe PGS Carrier Status Test for Usher Syndrome Type 1F (Usher 1F) is indicated for the detection of the R245X variant in the PCDH15 gene. This test is intended to be used to determine carrier status for Usher 1F in adults, but cannot determine if a person has two copies of a tested variant. The test is most relevant for people of Ashkenazi Jewish descent.

Special considerations

- There are currently no professional guidelines in the U.S. for carrier testing for this condition.

Clinical performance

The variant covered by this test is most common in people of Ashkenazi Jewish descent. About 1 in 147 people (0.68%) of Ashkenazi Jewish descent is a carrier for Usher 1F.

Frequency of PCDH15 variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
R245X	0.02%	<0.01%	0.87%	0.00%	0.03%	0.00%

This test is expected to detect 91% of carriers of Ashkenazi Jewish descent for this condition.

Pre-test and post-test carrier risks for the 23andMe PGS Carrier Status Test for Usher 1F

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result "0 Variants Detected"
Ashkenazi Jewish	91%	1 in 147	1 in 1,600
Other ethnicities*	Unknown	Unknown	Unknown

*This condition is not as well studied in other ethnicities.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 56 samples with known

variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 93.6% to 100.0%.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 66 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Selected References

Ben-Yosef T et al. (2003). "A mutation of PCDH15 among Ashkenazi Jews with the type 1 Usher syndrome." N Engl J Med. 348(17):1664-70.

Brownstein Z et al. (2004). "The R245X mutation of PCDH15 in Ashkenazi Jewish children diagnosed with nonsyndromic hearing loss foreshadows retinitis pigmentosa." Pediatr Res. 55(6):995-1000.

Scott SA et al. (2010). "Experience with carrier screening and prenatal diagnosis for 16 Ashkenazi Jewish genetic diseases." Hum Mutat. 31(11):1240-50.

Additional references included in the report.

Usher Syndrome Type 3A

Indications for Use

The 23andMe PGS Carrier Status Test for Usher Syndrome Type 3A (Usher 3A) is indicated for the detection of the N48K variant in the CLRN1 gene. This test is intended to be used to determine carrier status for Usher 3A in adults, but cannot determine if a person has two copies of a tested variant. The test is most relevant for people of Ashkenazi Jewish descent.

Special considerations

- The test does not include the majority of CLRN1 variants that cause Usher 3A in people of Finnish descent.
- There are currently no professional guidelines in the U.S. for carrier testing for this condition.

Clinical performance

The variant covered by this test is most common in people of Ashkenazi Jewish descent. About 1 in 120 people (0.83%) of Ashkenazi Jewish descent is a carrier for Usher 3A.

Frequency of CLRN1 variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
N48K	0.02%	<0.01%	1.06%	0.00%	0.01%	0.00%

This test is expected to detect 93% of carriers of Ashkenazi Jewish descent for this condition.

Pre-test and post-test carrier risks for the 23andMe PGS Carrier Status Test for Usher 3A

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result "0 Variants Detected"
Ashkenazi Jewish	93%	1 in 120	1 in 1,700
Finnish	<10%	Unknown	Unknown
Other ethnicities*	Unknown	Unknown	Unknown

*This condition is not as well studied in other ethnicities.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 50 samples with known variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 92.9% to 100.0%.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 67 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Selected References

Adato A et al. (2002). "USH3A transcripts encode clarin-1, a four-transmembrane-domain protein with a possible role in sensory synapses." Eur J Hum Genet. 10(6):339-50.

Fields RR et al. (2002). "Usher syndrome type III: revised genomic structure of the USH3 gene and identification of novel mutations." Am J Hum Genet. 71(3):607-17.

Herrera W et al. (2008). "Retinal disease in Usher syndrome III caused by mutations in the clarin-1 gene." Invest Ophthalmol Vis Sci. 49(6):2651-60.

Ness SL et al. (2003). "Genetic homogeneity and phenotypic variability among Ashkenazi Jews with Usher syndrome type III." J Med Genet. 40(10):767-72.

Scott SA et al. (2010). "Experience with carrier screening and prenatal diagnosis for 16 Ashkenazi Jewish genetic diseases." Hum Mutat. 31(11):1240-50.

Additional references included in the report.

Zellweger Syndrome Spectrum (PEX1-Related)

Indications for Use

The 23andMe PGS Carrier Status Test for Zellweger Syndrome Spectrum (PEX1-related ZSS) is indicated for the detection of the G843D variant in the PEX1 gene. This test is intended to be used to determine carrier status for PEX1-related ZSS in adults, but cannot determine if a person has two copies of a tested variant.

Special considerations

- This test does not include the majority of PEX1 variants that cause ZSS in any ethnicity.
- There are currently no professional guidelines in the U.S. for carrier testing for this condition.

Clinical performance

The variant covered by this test is rare in all ethnicities.

Frequency of PEX1 variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
G843D	0.13%	0.06%	0.00%	0.00%	0.05%	0.00%

This test is expected to detect 41% of carriers for this condition.

Pre-test and post-test carrier risks for the 23andMe PGS Carrier Status Test for PEX1-related ZSS

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result "0 Variants Detected"
European	41%	Unknown	Unknown
All ethnicities*	Unknown	Unknown	Unknown

* This condition is not as well studied in other ethnicities.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 54 samples with known variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 93.4% to 100.0%.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 66 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Selected References

Steinberg S et al. (2004). "The PEX Gene Screen: molecular diagnosis of peroxisome biogenesis disorders in the Zellweger syndrome spectrum." Mol Genet Metab. 83(3):252-63.

Steinberg SJ et al. (2003). "Peroxisome Biogenesis Disorders, Zellweger Syndrome Spectrum." [Updated 2012 May 10].

Additional references included in the report.

References
Data on file at 23andMe, Mountain View, CA

This package insert describes the analytical performance of the 5th version (v5) of the genotyping chip used to test a sample for the 23andMe Personal Genome Service.

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