23andMe® Personal Genome Service® (PGS)

Package Insert

IVD

For *in-vitro* diagnostic use

Availability of individual reports may be subject to product purchased.

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Genetic Health Risk

Intended use
The 23andMe Personal Genome Service (PGS) Test uses qualitative genotyping to detect the following clinically relevant variants in genomic DNA isolated from human saliva collected from individuals ≥18 years with the Oragene Dx model OGD-500.001 for the purpose of reporting and interpreting Genetic Health Risks (GHR).

Summary and explanation of the test
23andMe Genetic Health Risk Tests are tests you can order and use at home to learn about your DNA from a saliva sample. 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.
- Your ethnicity may affect whether these tests are relevant for you. Your ethnicity also may affect how your genetic health results are interpreted.
- Other factors, such as environmental and lifestyle risk factors, may affect the risk of developing a given disease.
- 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.
- These tests cannot determine your overall risk for developing a disease in the future.
- These tests are not intended to diagnose any disease or detect the presence of deterministic variants in autosomal dominant diseases or conditions such as Huntington's Disease.
- This device is not intended for prenatal testing.
- These tests are not for predicting predisposition for cancer for which a prophylactic screening, confirmatory procedure or treatment may incur morbidity or mortality to the patient.
- These tests are not for assessing the presence of genetic variants that may impact the metabolism, exposure, response, risk of adverse events, dosing, or mechanisms of prescription or over-the-counter medications.
- The laboratory may not be able to process your sample. If this happens, we will notify you by email and you may request one free replacement kit to provide us with a new sample.
- These tests do not diagnose any health conditions.

Other warnings, precautions, and limitations
- These tests are intended to be used to identify genetic risk for health conditions in users 18 years and above.
- These tests do not detect all genetic variants related to these health conditions. The

absence of a variant tested does not rule out the presence of other genetic variants that may be related to these health conditions.

- These tests are not a substitute for visits to a healthcare professional. You should consult with a healthcare professional if you have any questions or concerns about your results.
- These tests may not be able to determine a result for all variants analyzed.
- Different companies offering a genetic risk test may be measuring different genetic variants for the same condition, so you may get different results from a different test.
- 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.
- As with every test the possibility for an incorrect result exists. Speak to your personal healthcare professional or a genetic counselor if your results are unexpected.

For healthcare professionals

- This test is not intended to diagnose a disease, determine medical treatment, or tell the user anything about their current state of health.
- This test is intended to provide users with their genetic information, which may inform health-related lifestyle decisions and conversations with their doctor or other healthcare professional.
- Healthcare professionals should base diagnostic or treatment decisions on testing and/or other information determined to be appropriate for each patient.

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

See test-specific information for each test.

Precision/Reproducibility

See test-specific information for each test.

Minimum DNA Input
See test-specific information for each test.

Interfering Substances
Studies were performed to determine whether substances that may be present in saliva affect results of the PGS 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 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 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 Genetic Health Risk Test Reports. A diverse group of people answered questions about the 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.

Overall comprehension rates per test report concept were greater than 90% across all concepts.

Specific Genetic Health Risk test information

Age-Related Macular Degeneration
Alpha-1 Antitrypsin Deficiency
Celiac Disease
Chronic Kidney Disease (APOL1-Related)
Familial Hypercholesterolemia
G6PD Deficiency
Hereditary Amyloidosis (TTR-Related)
Hereditary Hemochromatosis (HFE-Related)
Hereditary Thrombophilia
Late-Onset Alzheimer's Disease
Parkinson's Disease

Age-Related Macular Degeneration

Indications for Use

The 23andMe PGS Genetic Health Risk Report for Age-Related Macular Degeneration (AMD) is indicated for reporting of the Y402H variant in the CFH gene and the A69S variant in the ARMS2 gene. This report describes if a person's genetic result is associated with an increased risk of developing AMD, but does not describe a person's overall risk of developing AMD. This report is most relevant for people of European descent.

Special considerations

- Genetic testing for AMD is not currently recommended by any healthcare professional organizations.

Clinical performance

The variants covered by this test are mainly found in people of European descent. Published studies estimate that 60.8% of people of European descent carry at least one copy of the Y402H variant, and 33.5% of people of European descent carry at least one copy of the A69S variant.

Frequency of variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
Y402H (CFH)	61.7%	60.2%	57.0%	10.8%	49.5%	51.3%

A69S (ARMS2)	38.6%	41.4%	36.7%	65.8%	41.6%	56.2%

The Y402H variant in the CFH gene is expected to be responsible for approximately 43% of all cases of AMD in older adults. The A69S variant in the ARMS2 gene is expected to be responsible for approximately 36% of all cases of AMD in older adults.

Accuracy
23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 71 samples with known Y402H variant status and 79 samples with known A69S 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
Precision studies were performed to test the consistency of sample measurements under different conditions. A total of 208 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 4 human cell line samples with two lots of reagents. The study yielded concordant test results for all samples at a DNA concentration of 15 ng/µL.

Interfering Mutations
The performance of this test may be affected by the presence of rare mutations, such as those listed below:

Gene	Variant	Potential Interfering Mutation(s)
CFH	Y402H	rs573331706 rs369496377
ARMS2	A69S	rs532010317

Selected References
Haines JL et al. (2005). "Complement factor H variant increases the risk of age-related macular degeneration." Science. 308(5720):419-21.

Rivera A et al. (2005). "Hypothetical LOC387715 is a second major susceptibility gene for age-related macular degeneration, contributing independently of complement factor H to disease risk." Hum Mol Genet. 14(21):3227-36.

Schaumberg DA et al. (2007). "A prospective study of 2 major age-related macular degeneration susceptibility alleles and interactions with modifiable risk factors." Arch Ophthalmol. 125(1):55-62.

Additional references included in the test report.

Alpha-1 Antitrypsin Deficiency

Indications for Use

The 23andMe PGS Genetic Health Risk Report for Alpha-1 Antitrypsin Deficiency is indicated for reporting of the PI*Z and PI*S variants in the SERPINA1 gene. This report describes if a person has variants associated with AAT deficiency and a higher risk for lung or liver disease, but it does not describe a person's overall risk of developing lung or liver disease. This report is most relevant for people of European descent.

Special considerations

- Testing for genetic variants associated with AAT deficiency is recommended under certain circumstances by several health professional organizations, including the American Thoracic Society. Refer to the American Thoracic Society guidelines for recommendations about when genetic testing for AAT deficiency is appropriate.

Clinical performance

The variants covered by this test are mainly found in people of European descent. Published studies estimate that up to 4.5% of people of European descent carry at least one copy of the PI*Z variant. Up to 18.5% of people of European descent carry at least one copy of the PI*S variant.

Frequency of SERPINA1 variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
PI*Z	3.62%	1.13%	1.82%	<0.02%	2.02%	<0.07%
PI*S	7.98%	2.84%	2.89%	<0.02%	9.19%	0.00%

Studies show that the PI*Z and PI*S variants are responsible for 95% of alpha-1 antitrypsin deficiency cases in people of European descent.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 79 samples with known PI*Z variant status and 80 samples with known PI*S variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 97.7% to 100%.

Precision/Reproducibility

Precision studies were performed to test the consistency of sample measurements under different conditions. A total of 216 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 4 human cell line samples and 1 saliva sample, with two lots of reagents. The study yielded concordant test results for all samples at a DNA concentration of 15 ng/µL.

Interfering Mutations
The performance of this test may be affected by the presence of rare mutations, such as those listed below:

Gene	Variant	Potential Interfering Mutation(s)
SERPINA1	PI*Z	rs148362959 rs533419579 rs551595739 rs201774333 rs143370956 rs1131139 rs200945035 rs373630097 rs9630
SERPINA1	PI*S	rs538675821 rs550592374 rs141095970 rs149537225 rs1049800 rs2230075

Selected References
American Thoracic Society and European Respiratory Society. (2003) "American Thoracic Society/European Respiratory Society statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency." Am J Respir Crit Care Med. 168(7): 818-900.

De Serres FJ and Blanco I. (2012) "Prevalence of α1-antitrypsin deficiency alleles PI*S and PI*Z worldwide and effective screening for each of the five phenotypic classes PI*MS, PI*MZ, PI*SS, PI*SZ, and PI*ZZ: a comprehensive review." Ther Adv Respir Dis. 6(5): 277-95.

Additional references included in the test report.

Celiac Disease

Indications for Use

The 23andMe PGS Genetic Health Risk Report for Celiac Disease is indicated for reporting of one variant associated with the HLA-DQ2.5 haplotype and one variant associated with the HLA-DQ8 haplotype. The report describes if a person has a variant linked to a haplotype that is associated with an increased risk of developing celiac disease, but it does not describe a person's overall risk for developing celiac disease. This report is most relevant for people of European descent.

Special considerations

- Genetic testing for celiac disease is recommended under certain circumstances by several health professional organizations, including the American College of Gastroenterology. Refer to the American College of Gastroenterology guidelines for recommendations about when genetic testing for celiac disease is appropriate.

Clinical performance

The variants covered by this test are common in many ethnicities, but are best studied in people of European descent. Published studies estimate that 20-30% of people of European descent have the HLA-DQ2 haplotype; the majority of these people have the HLA-DQ2.5 haplotype. Published studies estimate that 5-20% of people of European descent have the HLA-DQ8 haplotype.

Frequency of HLA-DQA1 and HLA-DQB1 variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian	Middle Eastern
rs2187668 (HLA-DQ2.5)	22.4%	15.6%	13.2%	12.2%	22.2%	14.1%	16.9%
rs7454108 (HLA-DQ8)	19.2%	9.5%	30.1%	14.1%	27.2%	17.7%	22.1%

Approximately 95% of celiac disease patients have the HLA-DQ2.5 or HLA-DQ8 haplotypes.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 75 samples with known rs2187668 variant status and 80 samples with known rs7454108 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

Precision studies were performed to test the consistency of sample measurements under different conditions. A total of 203 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 eight saliva samples, with three lots of reagents. The study yielded concordant test results for all samples at a DNA concentration of 15 ng/µL.

Interfering Mutations

The performance of this test may be affected by the presence of rare mutations, such as those listed below:

Haplotype	Potential Interfering Mutation(s)
HLA-DQ2.5	rs373744062 rs34481484 rs535725525 rs116178934 rs118073417 rs9272482
HLA-DQ8	rs575617446 rs182610396 rs564828053 rs2647088 rs3957146

Selected References

Gujral N et al. (2012). "Celiac disease: prevalence, diagnosis, pathogenesis and treatment." World J Gastroenterol. 18(42):6036-59.

Fasano A et al. (2003). "Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study." Arch Intern Med. 163(3):286-92.

Taylor AK et al. (2008). "Celiac Disease." [Updated 2015 Sep 17].

Additional references included in the test report.

Chronic Kidney Disease (APOL1-Related)

Indications for Use

The 23andMe PGS Genetic Health Risk Report for Chronic Kidney Disease (APOL1-Related) is indicated for reporting of the S342G and N388_Y389del variants in the APOL1 gene. These variants define the G1 and G2 haplotypes, respectively. This report describes if a person's genetic result is associated with an increased risk of developing chronic kidney disease, but it does not describe a person's overall risk of developing chronic kidney disease. This report is most relevant for people of African descent.

Special considerations

- This report does not include the I384M variant in the APOL1 gene, which is part of the G1 haplotype. However, the S342G variant included in this report is often used to define the G1 haplotype in clinical studies and genetic tests. S342G is sufficient to increase risk for chronic kidney disease.
- Genetic testing for APOL1 variants in the general population is not currently recommended by any healthcare professional organizations.

Clinical performance

The variants included in this test are most common and best studied in people of African descent. These variants are also found in people with African ancestry, including people of Hispanic or Latino descent. About 13% of African Americans have two APOL1 risk variants.

Frequency of APOL1 variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian	Middle Eastern
S342G (G1)	0.05%	33.44%	0.00%	<0.01%	2.47%	0.01%	0.05%
N388-Y389del (G2)	0.04%	21.56%	<0.01%	<0.01%	1.98%	0.01%	0.17%

The two variants in this report are thought to account for a large proportion of the excess risk for end-stage kidney disease among African Americans. Published studies estimate that, among African Americans, an estimated 68% of focal segmental glomerulosclerosis (FSGS) cases, 68% of HIV-associated nephropathy (HIVAN) cases, and 52% of hypertension-attributed end-stage kidney disease (HA-ESKD) cases can be attributed to having two APOL1 risk variants. The G1 and G2 haplotypes are the only APOL1 variants that have been linked to an increased risk for chronic kidney disease.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 112 samples with known S342G (G1) variant status and 111 samples with known N388_Y389del (G2) variant status. Agreement between the two methods was >99% for all samples analyzed. The overall 95% confidence interval was 98.4% to 100%.

Precision/Reproducibility

Precision studies were performed to test the consistency of sample measurements under different conditions. A total of 972 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 one human cell line sample and four saliva samples, with three lots of reagents. The study yielded concordant test results for all samples at a DNA concentration of 15 ng/µL.

Interfering Mutations

The performance of this test may be affected by the presence of rare mutations, such as those listed below:

Gene	Variant	Potential Interfering Mutation(s)
APOL1	S342G	rs139583750 rs16996616 rs373409702 rs143845266 rs151114491
APOL1	N388_Y389del	rs201657348 rs60910145 rs190804942 rs143830837 rs185040686 rs189551092

Selected References

Dummer PD et al. (2015). "APOL1 Kidney Disease Risk Variants: An Evolving Landscape." Semin Nephrol. 35(3):222-36.

Freedman BI et al. (2018). "APOL1-Associated Nephropathy: A Key Contributor to Racial Disparities in CKD." Am J Kidney Dis. 72(5 Suppl 1):S8-S16.

Reidy KJ et al. (2018). "Genetic risk of APOL1 and kidney disease in children and young adults of African ancestry." Curr Opin Pediatr. 30(2):252-259.

Additional references included in the test report.

Familial Hypercholesterolemia

Indications for Use

The 23andMe PGS Genetic Health Risk Report for Familial Hypercholesterolemia is indicated for reporting of one variant in the APOB gene and 23 variants in the LDLR gene. This report describes if a person's genetic result is associated with an increased risk of having very high LDL cholesterol, which can lead to heart disease. This test does not describe a person's overall risk of developing heart disease, and the absence of a variant tested does not rule out the presence of other variants that may be linked to familial hypercholesterolemia. The majority of the variants in this report are found in and

have been most studied in people of European and Lebanese descent, as well as in the Old Order Amish.

Special considerations

- Genetic testing for FH in the general population is not currently recommended by any healthcare professional organizations.
- However, the U.S. CDC recommends that screening using cholesterol testing with or without DNA analysis should be conducted on relatives of people with familial high cholesterol.
- Heart disease risk associated with FH variants varies from person to person. Overall risk depends on family history and other factors.

Clinical performance

The variants included in this report represent a small subset of all those linked to FH. Over 1,000 variants have been linked to FH. The 24 variants included in this test are linked to having very high LDL cholesterol, which is associated with an increased risk for heart disease. About 1 in 50 people with high LDL cholesterol have FH.

- Approximately 30-35% of people of European descent with a genetic variant linked to FH have one of the 24 variants included in this test.
- Approximately 15-20% of people of Hispanic/Latino or East Asian descent with a genetic variant linked to FH have one of the 24 variants included in this test.
- For people of Lebanese descent, the test covers about 80% of people who have a variant linked to FH.
- About 10% of the Old Order Amish have the APOB R3527Q variant linked to FH.

Frequency of the APOB and LDLR variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian	Middle Eastern
R3527Q (APOB)	0.10%	0.02%	<0.01%	<0.02%	0.04%	0.01%	0.01%
c.190+4A>T (LDLR)	0.00%	<0.01%	0.00%	<0.07%	<0.1%	0.00%	0.00%
W87G (LDLR)	<0.01%	0.00%	0.00%	0.00%	<0.01%	0.00%	0.00%
D90G (LDLR)	<0.01%	0.00%	0.00%	0.00%	<0.01%	0.00%	0.01%
E101K (LDLR)	<0.01%	<0.01%	0.00%	0.00%	<0.01%	0.01%	0.00%
S177L (LDLR)	<0.01%	<0.01%	0.00%	0.00%	<0.01%	0.01%	0.00%

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian	Middle Eastern
C184Y (LDLR)	<0.01%	<0.1%	0.00%	0.00%	<0.01%	0.00%	0.00%
G219del (LDLR)	<0.01%	0.00%	0.09%	0.00%	<0.01%	0.00%	0.01%
D221G (LDLR)	<0.01%	<0.01%	0.00%	0.00%	<0.01%	0.00%	0.00%
E228K (LDLR)	<0.01%	0.00%	0.00%	<0.01%	<0.01%	0.00%	0.01%
E228X (LDLR)	<0.01%	<0.01%	0.00%	<0.01%	<0.01%	0.00%	0.00%
D266E (LDLR)	<0.02%	<0.01%	0.00%	0.00%	<0.01%	0.00%	0.00%
S286R (LDLR)	<0.01%	0.00%	0.00%	0.00%	<0.01%	0.00%	<0.02%
G343S (LDLR)	0.01%	<0.01%	0.00%	<0.01%	0.01%	0.01%	0.01%
E408K (LDLR)	<0.01%	<0.01%	0.00%	0.00%	<0.01%	0.01%	0.00%
V429M (LDLR)	<0.01%	0.00%	0.00%	<0.01%	<0.01%	0.00%	0.00%
D482N (LDLR)	<0.01%	<0.01%	0.00%	0.00%	<0.01%	0.00%	0.00%
G549D (LDLR)	<0.01%	<0.01%	<0.01%	0.00%	<0.01%	0.00%	0.01%
W577S (LDLR)	<0.01%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
H583Y (LDLR)	<0.01%	<0.01%	0.00%	0.14%	<0.01%	<0.02%	0.00%
G592E (LDLR)	0.01%	<0.01%	0.00%	0.00%	<0.01%	0.00%	0.01%
C677R (LDLR)	<0.01%	0.00%	0.00%	0.00%	<0.01%	0.00%	0.00%
C681X (LDLR)	<0.01%	<0.01%	0.00%	0.00%	<0.01%	0.00%	0.15%
P685L	<0.01%	<0.01%	0.00%	<0.01%	<0.01%	0.01%	0.01%

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian	Middle Eastern
(LDLR)							

Accuracy
23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 3,262 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
Precision studies were performed to test the consistency of sample measurements under different conditions. A total of 20,874 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 1 human cell line sample and 41 saliva samples with three lots of reagents. The study yielded concordant test results for all samples at a DNA concentration of 15 ng/µL.

Interfering Mutations
The performance of this test may be affected by the presence of rare mutations, such as those listed below:

Gene	Variant name	Potential Interfering Mutation
APOB	R3527Q	rs200184366 rs144467873 rs142573551 rs573670976
LDLR	c.190+4A>T	rs137853960 rs138078086 rs150644181 rs376207800
	W87G	n/a
	D90G	n/a
	E101K	n/a
	S177L	n/a
	C184Y	rs146354103 rs533896621 rs555158224 rs574219590
	G219del	n/a

Gene	Variant name	Potential Interfering Mutation
LDLR	D221G	rs538030445 rs201374693 rs577934998 rs72658857 rs34093283
	E228K/E228X	n/a
	D266E	rs150673992 rs200990725 rs143992984 rs572275000 rs375163928 rs201875602 rs531199430
	S286R	rs146651743 rs148698650
	G343S	rs2738442 rs540073140 rs1270260
	E408K	n/a
	V429M	rs534782075 rs773658037
	D482N	n/a
	G549D	rs75858813
	W577S	n/a
	H583Y	n/a
	G592E	n/a
	C677R	rs529021326 rs550649956 rs369943481 rs146869252 rs551528700
	C681X	n/a
	P685L	n/a

Selected References

Defesche JC et al. (2017). "Familial hypercholesterolaemia." Nat Rev Dis Primers. 3:17093.

Khera AV et al. (2016). "Diagnostic Yield and Clinical Utility of Sequencing Familial Hypercholesterolemia Genes in Patients With Severe Hypercholesterolemia." J Am Coll Cardiol. 67(22):2578-89.

Youngblom E et al. (2014). "Familial Hypercholesterolemia." [Accessed Jun 25, 2018].

Additional references included in the test report.

G6PD Deficiency

Indications for Use

The 23andMe PGS Genetic Health Risk Report for G6PD Deficiency is indicated for reporting of the V68M and S188F variants in the G6PD gene. This report describes if a person has one or more variants linked to G6PD deficiency and a higher risk for episodes of anemia, but it does not describe a person's overall risk of developing symptoms. This report is most relevant for people of African, Southern European, Kurdish Jewish, Middle Eastern, Central Asian, and South Asian descent.

Special considerations

- This test does not include the N126D variant in the G6PD gene. In genetic testing for G6PD deficiency, the V68M variant and the N126D variant are usually tested together because they are both part of the G6PD A- haplotype. However, the N126D variant itself is not linked to G6PD deficiency.
- Genetic testing for G6PD deficiency in adults in the general population is not currently recommended by any healthcare professional organizations.

Clinical performance

The V68M variant included in this test is most common and best studied in people of African descent. This variant is also found in people with African ancestry, including people of Hispanic or Latino descent. The S188F variant included in this test is most common and best studied in people of Southern European, Kurdish Jewish, Middle Eastern, Central Asian, and South Asian descent.

Frequency of G6PD variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian	Middle Eastern
V68M	0.03%	14.93%	0.00%	<0.01%	1.23%	<0.02%	<0.20%
S188F	0.08%	0.13%	0.81%	<0.01%	0.05%	1.47%	4.01%

The V68M variant is expected to be responsible for up to 90% of cases of G6PD deficiency in people of African descent. The S188F variant is expected to be responsible for the majority of cases of G6PD deficiency in people of Southern European, Kurdish Jewish, Middle Eastern, and Central Asian descent.

Accuracy
23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 186 samples with known V68M variant status and 79 samples with known S188F variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 98.6% to 100.0%.

Precision/Reproducibility
Precision studies were performed to test the consistency of sample measurements under different conditions. A total of 590 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 3 human cell line samples and 3 saliva samples with two lots of reagents (V68M) or three lots of reagents (S188F). The study yielded concordant test results for all samples at a DNA concentration of 15 ng/µL.

Interfering Mutations
The performance of this test may be affected by the presence of rare mutations, such as those listed below:

Gene	Variant	Potential Interfering Mutation(s)
G6PD	V68M	rs138687036
G6PD	S188F	rs137852330 rs200626353 rs200111236

Selected References
Cappellini MD et al. (2008). "Glucose-6-phosphate dehydrogenase deficiency." Lancet. 371(9606):64-74.

Carter N et al. (2011). "Frequency of glucose-6-phosphate dehydrogenase deficiency in malaria patients from six African countries enrolled in two randomized anti-malarial clinical trials." Malar J. 10:241.

Frank JE. (2005). "Diagnosis and management of G6PD deficiency." Am Fam Physician. 72(7):1277-82.

Howes RE et al. (2013). "Spatial distribution of G6PD deficiency variants across malaria-endemic regions." Malar J. 12:418.

Recht J et al. (2018). "Use of primaquine and glucose-6-phosphate dehydrogenase deficiency testing: Divergent policies and practices in malaria endemic countries." PLoS Negl Trop Dis. 12(4):e0006230.

Additional references included in the test report.

Hereditary Amyloidosis (TTR-Related)

Indications for Use

The 23andMe PGS Genetic Health Risk Report for Hereditary Amyloidosis (TTR-Related) is indicated for reporting of the V122I, V30M, and T60A variants in the TTR gene. This report describes if a person has variants linked to TTR-related hereditary amyloidosis, but it does not describe a person's overall risk of developing the condition. This report is most relevant for African Americans, and for people of West African, Portuguese, Northern Swedish, Japanese, Irish, and British descent. It is also relevant for people from Brazil.

Special considerations

- Genetic testing for TTR-related hereditary amyloidosis in the general population is not currently recommended by any healthcare professional organizations.

Clinical performance

The variants included in this test are most common and best studied in African Americans; in people of West African, Portuguese, Northern Swedish, Japanese, Irish, and British descent; and in people from Brazil. In most studied populations, approximately 50-99% of TTR-related hereditary amyloidosis cases are caused by the three variants included in this test. Additionally, approximately 10% of African Americans over the age of 60 with congestive heart failure are expected to carry the V122I variant.

Frequency of TTR variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian	Middle Eastern
V122I	0.01%	2.86%	0.00%	0.01%	0.23%	<0.06%	<0.06%
V30M	0.01%	<0.02%	<0.02%	<0.02%	0.02%	<0.06%	0.00%
T60A	0.01%	0.00%	0.00%	0.00%	<0.01%	0.00%	0.00%

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 60 samples with known V122I variant status, 46 samples with known V30M variant status, and 44 samples with known T60A variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 97.6% to 100%.

Precision/Reproducibility
Precision studies were performed to test the consistency of sample measurements under different conditions. A total of 336 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 2 human cell line samples and 4 saliva samples, with three lots of reagents. The study yielded concordant test results for all samples at a DNA concentration of 15 ng/µL.

Interfering Mutations
The performance of this test may be affected by the presence of rare mutations, such as those listed below:

Gene	Variant	Potential Interfering Mutation(s)
TTR	V122I	rs28933981 rs2276382 rs557320637 rs536294863 rs3700056601 rs1269882546 rs572856125 rs12226
TTR	V30M	None identified
TTR	T60A	None identified

Selected References
Buxbaum J et al. (2006). "Transthyretin V122I in African Americans with congestive heart failure." J Am Coll Cardiol. 47(8):1724-5.

Cruz MW et al. (2019). "Baseline disease characteristics in Brazilian patients enrolled in Transthyretin Amyloidosis Outcome Survey (THAOS)." Arq Neuropsiquiatr. 77(2):96-100.

Damy T et al. (2019). "Transthyretin cardiac amyloidosis in continental Western Europe: an insight through the Transthyretin Amyloidosis Outcomes Survey (THAOS)." Eur Heart J.

Gertz MA et al. (2015). "Diagnosis, Prognosis, and Therapy of Transthyretin Amyloidosis." J Am Coll Cardiol. 66(21):2451-2466.

Rowczenio D et al. (2019). "Analysis of the TTR gene in the investigation of amyloidosis: A 25-year single UK center experience." Hum Mutat. 40(1):90-96.

Sekijima Y et al. (2019). "The current status of the Transthyretin Amyloidosis Outcomes Survey (THAOS) in Japan." Amyloid. 26(sup1):61-62.

Additional references included in the test report.

Hereditary Hemochromatosis (HFE-Related)

Indications for Use

The 23andMe PGS Genetic Health Risk Report for Hereditary Hemochromatosis is indicated for reporting of the C282Y and H63D variants in the HFE gene. This report describes if a person has variants linked to hereditary hemochromatosis and a higher risk for iron overload, but it does not describe a person's overall risk of developing iron overload. This report is most relevant for people of Northern European descent.

Special considerations

- Testing for genetic variants associated with hereditary hemochromatosis is recommended under certain circumstances by several health professional organizations, including the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Refer to the American Association for the Study of Liver Diseases or the European Association for the Study of the Liver guidelines for recommendations about when genetic testing for hereditary hemochromatosis is appropriate.

Clinical performance

The variants covered by this test are mainly found in people of Northern European descent. Published studies estimate that approximately 13% of people of European descent carry at least one copy of the C282Y variant, and 28% of people of European descent carry at least one copy of the H63D variant.

Frequency of HFE variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian	Middle Eastern
C282Y	12.2%	3.5%	2.4%	0.1%	6.5%	0.3%	0.5%
H63D	27.7%	9.5%	22.7%	6.5%	24.1%	16.6%	22.3%

About 91% of all cases of HFE-related hereditary hemochromatosis are caused by the two variants included in this test.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 75 samples with known C282Y variant status and 83 samples with known H63D 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
Precision studies were performed to test the consistency of sample measurements under different conditions. 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.

Minimum DNA Input
A minimum DNA input study was performed using 5 human cell line samples, with two lots of reagents. The study yielded concordant test results for all samples at a DNA concentration of 15 ng/µL.

Interfering Mutations
The performance of this test may be affected by the presence of rare mutations, such as those listed below:

Gene	Variant	Potential Interfering Mutation(s)
HFE	C282Y	rs140080192 rs143175221
HFE	H63D	rs28934889 rs147297176 rs147426902 rs556335391 rs62625342

Selected References
Adams PC et al. (2005) "Hemochromatosis and iron-overload screening in a racially diverse population." N Engl J Med. 352(17):1769-78.

Bacon BR et al. (2011). "Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases." Hepatology. 54(1):328-43.

Mura C et al. (1999). "HFE mutations analysis in 711 hemochromatosis probands: evidence for S65C implication in mild form of hemochromatosis." Blood. 93(8):2502-5.

Additional references included in the test report.

Hereditary Thrombophilia

Indications for Use

The 23andMe PGS Genetic Health Risk Report for Hereditary Thrombophilia is indicated for reporting of the Factor V Leiden variant in the F5 gene, and the Prothrombin G20210A variant in the F2 gene. This report describes if a person has variants associated with a higher risk of developing harmful blood clots, but it does not describe a person's overall risk of developing harmful blood clots. This report is most relevant for people of European descent.

Special considerations

- Testing for genetic variants associated with hereditary thrombophilia is recommended by ACMG and ACOG under certain circumstances. This test includes the two variants recommended for testing by ACMG and ACOG. Refer to the relevant guidelines for recommendations about when genetic testing for hereditary thrombophilia is appropriate.

Clinical performance

The variants covered by this test are mainly found in people of European descent. Published studies estimate that 3-15% of people of European descent carry at least one copy of the Factor V Leiden variant. 1-3% of people of European descent are estimated to carry at least one copy of the prothrombin G20210A variant.

Frequency of the tested variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
Factor V Leiden	5.28%	1.51%	3.75%	0.04%	3.21%	2.49%
Prothrombin G20210A	2.77%	0.91%	6.87%	<0.02%	2.77%	0.12%

The Factor V Leiden variant is estimated to be responsible for 14% of all harmful blood clots in people of European descent. The prothrombin G20210A variant is estimated to be responsible for 4% of all harmful blood clots in people of European descent.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 72 samples with known prothrombin G20210A variant status and 81 samples with known Factor V Leiden variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 97.6% to 100%.

Precision/Reproducibility

Precision studies were performed to understand the consistency of sample measurements under different conditions. A total of 205 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 4 human cell line samples and 1 saliva sample, with two lots of reagents. The study yielded concordant test results for all samples with a DNA concentration of 15 ng/µL.

Interfering Mutations

The performance of this test may be affected by the presence of rare mutations, such as those listed below:

Gene	Variant	Potential Interfering Mutation(s)
F5	Factor V Leiden	1689G>A 1692A>C
F2	Prothrombin G20210A	20207A>C

Selected References

Heit JA et al. (2011) "Genetic variation within the anticoagulant, procoagulant, fibrinolytic and innate immunity pathways as risk factors for venous thromboembolism." J Thromb Haemost. 9(6):1133-1142.

Khan S and Dickerman JD. (2006) "Hereditary thrombophilia." Thromb J. 4:15.

Kujovich JL. (2011) "Factor V Leiden thrombophilia." Genet Med. 13(1):1-16.

Additional references included in the test report.

Late-Onset Alzheimer’s Disease

Indications for Use

The 23andMe PGS Genetic Health Risk Report for Late-Onset Alzheimer's Disease is indicated for reporting of the ε4 variant in the APOE gene. This report describes if a person's genetic result is associated with an increased risk of developing late-onset Alzheimer's disease, but it does not describe a person's overall risk of developing Alzheimer's disease. The ε4 variant included in this report is found and has been studied in many ethnicities. Detailed risk estimates have been studied the most in people of European descent.

Special considerations

- This test does not identify or report on the ε2 and ε3 variants of the APOE gene. These variants are not associated with an increased risk of developing Alzheimer's disease.
- Genetic testing for late-onset Alzheimer's disease is not currently recommended by any healthcare professional organizations.

Clinical performance

The variant covered by this test is found in people of all ethnicities. Published studies of people who don't have Alzheimer's disease estimate that 13-16% of people of European descent, 18-23% of people of African American descent, 11-23% of people of Hispanic descent, and 7-14% of people of East Asian descent carry at least one copy of the ε4 variant. Among people with Alzheimer's disease, published studies estimate that 34-41% of people of European descent, 32-42% of people of African American descent, 19-32% of people of Hispanic descent, and 25-30% of people of East Asian descent carry at least one copy of the ε4 variant.

Frequency of the APOE ε4 variant in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian	Middle Eastern
ε4	26.51%	35.77%	22.07%	17.89%	22.71%	17.85%	12.78%

Approximately 65% of Alzheimer's patients have one or two copies of the ε4 variant.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 83 samples with known ε4 variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 95.7% to 100.0%.

Precision/Reproducibility

Precision studies were performed to understand the consistency of sample measurements under different conditions. A total of 209 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 4 human cell line samples and 1 saliva sample, with two lots of reagents. The study yielded concordant test results for all samples with a DNA concentration of 15 ng/µL.

Interfering Mutations

The performance of this test may be affected by the presence of rare mutations, such as those listed below:

Gene	Variant	Potential Interfering Mutation(s)
APOE	ε4	rs11542041 rs573658040 rs543363163

Selected References

Alzheimer's Association. "Alzheimer's Disease Facts and Figures." Retrieved from https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf

Farrer LA et al. (1997) “Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium.” JAMA. 278(16):1349-56.

Genin E et al. (2011). “APOE and Alzheimer disease: a major gene with semi-dominant inheritance.” Mol Psychiatry. 16(9):903-7.

Additional references included in the test report.

Parkinson’s Disease

Indications for Use

The 23andMe PGS Genetic Health Risk Report for Parkinson’s Disease is indicated for reporting of the G2019S variant in the LRRK2 gene and the N370S variant in the GBA gene. This report describes if a person's genetic result is associated with an increased risk of developing Parkinson’s disease, but it does not describe a person's overall risk of developing Parkinson’s disease. This report is most relevant for people of European, Ashkenazi Jewish, and North African Berber descent.

Special considerations

- Genetic testing for Parkinson's disease is not currently recommended by any healthcare professional organizations.

Clinical performance

The variants covered by this test are mainly found in people of European, Ashkenazi Jewish, and North African Berber descent. Published studies estimate that 1-2% of people with Parkinson's disease have the G2109S variant in the LRRK2 gene. 8-14% of people with Parkinson's disease have a variant in the GBA gene, and the N370S variant accounts for roughly half of those cases.

Frequency of the tested variants in 23andMe customers

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

G2019S	0.08%	0.06%	1.88%	<0.02%	0.18%	0.00%
N370S	0.48%	0.16%	5.96%	0.00%	0.37%	0.00%

Accuracy
23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 49 samples with known G2019S variant status and 74 samples with known N370S variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 97.0% to 100%.

Precision/Reproducibility
Precision studies were performed to understand the consistency of sample measurements under different conditions. A total of 239 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 3 human cell line samples and 2 saliva samples, with two lots of reagents. The study yielded concordant test results for all samples with a DNA concentration of 15 ng/µL.

Interfering Mutations
The performance of this test may be affected by the presence of rare mutations, such as those listed below:

Gene	Variant	Potential Interfering Mutation(s)
LRRK2	G2019S	rs150219613 rs183394865
GBA	N370S	rs187143994 rs111417507

Selected References
Cook Shukla L et al. (2004). "Parkinson Disease Overview." [Accessed Aug 25, 2020].

Healy DG et al. (2008). "Phenotype, genotype, and worldwide genetic penetrance of LRRK2-associated Parkinson's disease: a case-control study." Lancet Neurol. 7(7):583-90.

Sidransky E et al. (2009). "Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease." N Engl J Med. 361(17):1651-61.

Additional references included in the report.

Cancer Predisposition Risk Test

Intended use
23andMe Personal Genome Service (PGS) Test uses qualitative genotyping to detect the following clinically relevant variants in genomic DNA isolated from human saliva collected from individuals ≥18 years with the Oragene Dx model OGD-500.001 for the purpose of reporting and interpreting Genetic Health Risks (GHR).

Summary and explanation of the test
23andMe Genetic Health Risk Tests are tests you can order and use at home to learn about your DNA from a saliva sample (collected with Oragene Dx model OGD500.001). The tests work by detecting specific gene variants using a customized multiplex assay, reagents, and instrumentation. The probability that the laboratory cannot process a sample can be up to 7.6%. Your genetic results are returned to you in a secure online account on the 23andMe website. View Frequently Asked Questions about this report here.

Indications for use
See test-specific information for each test.

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
See test-specific information for each test.

Precision/Reproducibility
See test-specific information for each test.

Minimum DNA Input
See test-specific information for each test.

Interfering Substances
Studies were performed to determine whether substances that may be present in saliva affect results of the PGS 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 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 tests.

User studies
See test-specific information for each test.

Should you speak to a genetic counselor?
We encourage you to learn more so you can decide whether testing is right for you. A genetic counselor, a healthcare professional with special training in genetic conditions, will be able to answer your specific questions and help you make an informed decision.

Talk to your healthcare provider or, to search for a genetic counselor near you, go to the following link (this link takes you to a page managed by the National Society of Genetic Counselors: http://www.aboutgeneticcounselors.com/).

Specific Cancer Predisposition Risk Test Information

BRCA1/BRCA2 (Selected Variants)
MUTYH-Associated Polyposis
Hereditary Prostate Cancer (HOXB13-Related)

BRCA1/BRCA2 (Selected Variants)

Indications for Use
The 23andMe Personal Genome Service (PGS) Risk Report for BRCA1/BRCA2 (Selected Variants) is indicated for the reporting of the following 44 variants in the BRCA1 and BRCA2 genes.

Gene	Variant(s)
BRCA1	c.68_69del, c.213-11T>G, c.427G>T, c.815_824dup, c.1556del, c.1687C>T, c.1960A>T, c.1961del, c.2681_2682del, c.2864C>A, c.3481_3491del, c.3598C>T, c.3627dup, c.3756_3759del, c.3770_3771del, c.4035del, c.4065_4068del, c.4327C>T, c.4357+1G>A, c.4964_4982del, c.4986+6T>G, c.5123C>A, c.5177_5180del, c.5266dup
BRCA2	c.658_659del, c.771_775del, c.1929del, c.2808_2811del, c.2957_2958insG, c.3170_3174del, c.3264dup, c.3545_3546del, c.3847_3848del, c.4471_4474del, c.5542del, c.5576_5579del, c.5682C>G, c.5946del, c.6037A>T, c.6275_6276del, c.7024C>T, c.7480C>T, c.7934del, c.8904del

The report describes if a person's genetic result is associated with an increased risk of developing breast cancer and ovarian cancer and may be associated with an increased risk for prostate cancer, pancreatic cancer, and potentially other cancers. The variants included in this report do not represent the majority of the BRCA1/BRCA2 variants in people of most ethnicities. The test report does not describe a person's overall risk of developing any type of cancer, and the absence of a variant tested does not rule out the presence of other variants that may be cancer-related. This report is for over-the-counter use by adults over the age of 18, and provides genetic information to inform discussions with a healthcare professional. This test is not a substitute for visits to a healthcare provider for recommended screenings or appropriate follow-up and should not be used to determine any treatments.

Important Considerations

- This test does not diagnose cancer or any other health conditions and should not be used on its own to make medical decisions. Results should be confirmed in a clinical setting before taking any medical action.
- Please follow the instructions in the DNA Collection Kit to ensure your DNA results can be processed and connected to your online account.
- Your ethnicity may affect whether these tests are relevant for you.
- Other factors, such as environmental and lifestyle risk factors, may affect the risk of developing a given disease. This test does not account for non-genetic factors, and does not test for variants in other genes linked to hereditary cancers.
- 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.
- This test cannot determine your overall risk for developing a disease in the future.

- This device is not intended for prenatal testing.
- This test is not for assessing the presence of genetic variants that may impact the metabolism, exposure, response, risk of adverse events, dosing, or mechanisms of prescription or over-the-counter medications.
- This test is not intended to detect the presence of deterministic variants in autosomal dominant diseases or conditions.
- The laboratory may not be able to process your sample. If this happens, we will notify you by email and you may request one free replacement kit to provide us with a new sample.

Other warnings, precautions, and limitations

- This test includes 44 variants in the BRCA1 and BRCA2 genes.
- This test does not test for all possible variants in the BRCA1 and BRCA2 genes. More than 4,000 variants in the BRCA1 and BRCA2 genes are known to increase cancer risk. The absence of a variant tested does not rule out the presence of other genetic variants that may be related to these health conditions.
- If you receive a “zero variants detected” result you should not over interpret it. You could have another variant not included in this test that may impact your cancer risk.
- This test is intended to be used to identify genetic risk for health conditions in users 18 years and above.
- This test is intended to provide you with genetic information to inform conversations with your doctor or other healthcare professional.
- This test is not a substitute for visits to a healthcare professional for recommended screenings, and should not be used to determine any treatments or medical interventions. You should consult with a healthcare professional if you have any questions or concerns about your results or your current state of health.
- This test may not be able to determine a result for all variants analyzed.
- Different companies offering a genetic risk test may be measuring different genetic variants for the same condition, so you may get different results from a different test.
- Some people feel a little anxious about getting genetic health risk 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.
- As with every test the possibility for an incorrect result exists. Speak to your personal healthcare professional or a genetic counselor if your results are unexpected.

For healthcare professionals

- This test is not intended to diagnose a disease, determine medical treatment or other medical intervention, or tell the user anything about their current state of health.
- This test is intended to provide users with their genetic information, which may inform health-related lifestyle decisions and conversations with their doctor or other healthcare professional.
- Any diagnostic or treatment decisions must be based on confirmatory prescription testing and/or other information that you determine to be appropriate for your patient, such as additional clinical testing and other risk factors that may affect individual risk

and health care.

Predetermined Change Control Plan

The 23andMe Personal Genome Service (PGS) Genetic Health Risk Report for BRCA1/BRCA2 (Selected Variants) includes a predetermined change control plan (PCCP) approved by the US Food and Drug Administration (FDA). The PCCP describes a set of specific test methods for clinical and analytical validation, which include sample size determination, analysis methods, and acceptance criteria, for adding validated BRCA1 and BRCA2 variants and associated cancer risk information to the report without further regulatory review.

23andMe will perform testing of the additional BRCA1/2 variants according to the specified protocols, and if the validation data meet the specified acceptance criteria, they may add those variants to the BRCA1/2 report without additional premarket review.

The PCCP is limited to the addition of single nucleotide variants and small insertions and deletions (≤20 bp) in the BRCA1 and BRCA2 genes. The plan describes the specific clinical validation criteria that must be met to demonstrate that the new BRCA1/2 variants are high-risk, highly penetrant BRCA1/2 variants (i.e., those that are demonstrated to be linked to hereditary breast and ovarian cancer (HBOC) syndrome). Specific analytical validation protocols and acceptance criteria are also detailed in the plan to ensure that the device maintains the following performance characteristics for each new BRCA1/2 variant:

- Accuracy point estimates of ≥99% positive percent agreement (PPA) and negative percent agreement (NPA), established by comparing results of the 23andMe PGS test to bidirectional Sanger sequencing
- ≥99% correct genotype calls assigned at each of two laboratory sites
- ≥95% of samples yielding the correct genotype call at the minimum DNA input tested

Additionally, software verification and validation activities are detailed in the PCCP and all must be completed successfully to modify the report to add the new BRCA1/2 variants.

Customers who previously opted-in to receive their BRCA1/2 report will receive an email notification informing them that the report has been updated.

Test performance

The performance of the **BRCA1/BRCA2 (Selected Variants)** test was assessed only for the detection of the specific gene variants analyzed by the **BRCA1/BRCA2 (Selected Variants)** 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.

Analytical performance

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the 23andMe PGS test were compared with sequencing results; pre-defined acceptance criteria were set to a minimum of 99% Positive Percent Agreement (PPA) and 99% Negative Percent Agreement (NPA).

The method comparison study yielded >99% overall agreement for all genotypes for all samples tested, passing the predefined acceptance criteria of at least 99% PPA and 99% NPA. The widest 95% confidence interval was 47.3% to 100% for the heterozygous c.2864C>A BRCA1 genotype. See table below for sample size and percent agreements for each variant.

Genotype by Sanger	PGS Genotype Call				% PPA	% NPA	95% CI***
	Correct*	Incorrect*	No Call	FQC**			
BRCA1 c.68_69del Homozygous Common	50	0	0	4	N/A	100%	94.2% - 100%
BRCA1 c.68_69del Heterozygous	21	0	0	4	100%	N/A	86.7% - 100%
BRCA1 c.213-11T>G Homozygous Common	35	0	0	0	N/A	100%	91.8% - 100%
BRCA1 c.213-11T>G Heterozygous	15	0	0	0	100%	N/A	81.9% - 100%
BRCA1 c.427G>T Homozygous Common	21	0	0	0	N/A	100%	86.7% - 100%
BRCA1 c.427G>T Heterozygous	27	0	0	0	100%	N/A	89.5% - 100%
BRCA1 c.815_824dup Homozygous Common	22	0	0	0	N/A	100%	87.3% - 100%
BRCA1 c.815_824dup Heterozygous	26	0	0	0	100%	N/A	89.1% - 100%
BRCA1 c.1556del Homozygous Common	24	0	0	0	N/A	100%	88.3% - 100%
BRCA1 c.1556del Heterozygous	26	0	0	0	100%	N/A	89.1% - 100%
BRCA1 c.1687C>T Homozygous Common	23	0	0	0	N/A	100%	87.8% - 100%
BRCA1 c.1687C>T Heterozygous	22	0	0	0	100%	N/A	87.3% - 100%
BRCA1 c.1960A>T Homozygous Common	29	0	0	0	N/A	100%	90.2% - 100%
BRCA1	25	0	1	0	100%	N/A	88.8% - 100%

Genotype by Sanger	PGS Genotype Call				% PPA	% NPA	95% CI***
	Correct*	Incorrect*	No Call	FQC**			
c.1960A>T Heterozygous							
BRCA1 c.1961del Homozygous Common	24	0	0	0	N/A	100%	88.3% - 100%
BRCA1 c.1961del Heterozygous	13	0	0	0	100%	N/A	79.4% - 100%
BRCA1 c.2681_2682del Homozygous Common	24	0	0	0	N/A	100%	88.3% - 100%
BRCA1 c.2681_2682del Heterozygous	22	0	0	0	100%	N/A	87.3% - 100%
BRCA1 c.2864C>A Homozygous Common	24	0	0	0	N/A	100%	88.3% - 100%
BRCA1 c.2864C>A Heterozygous	4	0	0	0	100%	N/A	47.3% - 100%
BRCA1 c.3481_3491del Homozygous Common	26	0	0	0	N/A	100%	89.1% - 100%
BRCA1 c.3481_3491del Heterozygous	29	0	0	0	100%	N/A	90.2% - 100%
BRCA1 c.3598C>T Homozygous Common	21	0	0	0	N/A	100%	86.7% - 100%
BRCA1 c.3598C>T Heterozygous	24	0	0	0	100%	N/A	88.3% - 100%
BRCA1 c.3627dup Homozygous Common	22	0	0	0	N/A	100%	87.3% - 100%
BRCA1 c.3627dup Heterozygous	12	0	0	0	100%	N/A	77.9% - 100%
BRCA1 c.3756_3759del Homozygous Common	22	0	0	0	N/A	100%	87.3% - 100%
BRCA1 c.3756_3759del Heterozygous	23	0	0	0	100%	N/A	87.8% - 100%
BRCA1 c.3770_3771del Homozygous Common	22	0	0	0	N/A	100%	87.3% - 100%
BRCA1 c.3770_3771del Heterozygous	27	0	0	0	100%	N/A	89.5% - 100%
BRCA1 c.4035del Homozygous Common	24	0	0	0	N/A	100%	88.3% - 100%
BRCA1 c.4035del Heterozygous	23	0	0	0	100%	N/A	87.8% - 100%
BRCA1	24	0	0	0	N/A	100%	88.3% - 100%

Genotype by Sanger	PGS Genotype Call				% PPA	% NPA	95% CI***
	Correct*	Incorrect*	No Call	FQC**			
c.4065_4068del Homozygous Common							
BRCA1 c.4065_4068del Heterozygous	21	0	0	0	100%	N/A	86.7% - 100%
BRCA1 c.4327C>T Homozygous Common	26	0	0	0	N/A	100%	89.1% - 100%
BRCA1 c.4327C>T Heterozygous	24	0	0	0	100%	N/A	88.3% - 100%
BRCA1 c.4357+1G>A Homozygous Common	24	0	0	0	N/A	100%	88.3% - 100%
BRCA1 c.4357+1G>A Heterozygous	8	0	0	0	100%	N/A	68.8% - 100%
BRCA1 c.4964_4982del Homozygous Common	30	0	0	0	N/A	100%	90.5% - 100%
BRCA1 c.4964_4982del Heterozygous	20	0	0	0	100%	N/A	86.1% - 100%
BRCA1 c.4986+6T>G Homozygous Common	27	0	0	0	N/A	100%	89.5% - 100%
BRCA1 c.4986+6T>G Heterozygous	14	0	0	0	100%	N/A	80.7% - 100%
BRCA1 c.5123C>A Homozygous Common	24	0	0	0	N/A	100%	88.3% - 100%
BRCA1 c.5123C>A Heterozygous	29	0	0	0	100%	N/A	90.2% - 100%
BRCA1 c.5177_5180del Homozygous Common	24	0	0	0	N/A	100%	88.3% - 100%
BRCA1 c.5177_5180del Heterozygous	26	0	0	0	100%	N/A	89.1% - 100%
BRCA1 c.5266dup Homozygous Common	23	0	0	2	N/A	100%	87.8% - 100
BRCA1 c.5266dup Heterozygous	26	0	0	1	100%	N/A	89.1% - 100%
BRCA2 c.658_659del Homozygous Common	26	0	0	0	N/A	100%	89.1% - 100%
BRCA2 c.658_659del Heterozygous	20	0	0	0	100%	N/A	86.1% - 100%
BRCA2 c.771_775del Homozygous Common	23	0	0	0	N/A	100%	87.8% - 100%
BRCA2	25	0	0	0	100%	N/A	88.8% - 100%

Genotype by Sanger	PGS Genotype Call				% PPA	% NPA	95% CI***
	Correct*	Incorrect*	No Call	FQC**			
c.771_775del Heterozygous							
BRCA2 c.1929del Homozygous Common	26	0	0	0	N/A	100%	89.1% - 100%
BRCA2 c.1929del Heterozygous	25	0	0	0	100%	N/A	88.8% - 100%
BRCA2 c.2808_2811del Homozygous Common	48	0	0	0	N/A	100%	93.9% - 100%
BRCA2 c.2808_2811del Heterozygous	31	0	0	0	100%	N/A	90.8% - 100%
BRCA2 c.2957_2958insG Homozygous Common	24	0	0	0	N/A	100%	88.3% - 100%
BRCA2 c.2957_2958insG Heterozygous	6	0	0	0	100%	N/A	60.7% - 100%
BRCA2 c.3170_3174del Homozygous Common	24	0	0	0	N/A	100%	88.3% - 100%
BRCA2 c.3170_3174del Heterozygous	26	0	0	0	100%	N/A	89.1% - 100%
BRCA2 c.3264dup Homozygous Common	24	0	0	0	N/A	100%	88.3% - 100%
BRCA2 c.3264dup Heterozygous	27	0	0	0	100%	N/A	89.5% - 100%
BRCA2 c.3545_3546del Homozygous Common	27	0	0	0	N/A	100%	89.5% - 100%
BRCA2 c.3545_3546del Heterozygous	31	0	0	0	100%	N/A	90.8% - 100%
BRCA2 c.3847_3848del Homozygous Common	102	0	0	0	N/A	100%	97.1% - 100%
BRCA2 c.3847_3848del Heterozygous	108	1	0	0	99.03%	N/A	95.56% - 99.96%
BRCA2 c.4471_4474del Homozygous Common	24	0	0	0	N/A	100%	88.3% - 100%
BRCA2 c.4471_4474del Heterozygous	5	0	0	0	100%	N/A	54.9% - 100%
BRCA2 c.5542del Homozygous Common	25	0	0	0	N/A	100%	88.8% - 100%
BRCA2 c.5542del Heterozygous	6	0	0	0	100%	N/A	60.7% - 100%
BRCA2	22	0	0	0	N/A	100%	87.3% - 100%

Genotype by Sanger	PGS Genotype Call				% PPA	% NPA	95% CI***
	Correct*	Incorrect*	No Call	FQC**			
c.5576_5579del Homozygous Common							
BRCA2 c.5576_5579del Heterozygous	26	0	0	0	100%	N/A	89.1% - 100%
BRCA2 c.5682C>G Homozygous Common	26	0	0	0	N/A	100%	89.1% - 100%
BRCA2 c.5682C>G Heterozygous	27	0	0	0	100%	N/A	89.5% - 100%
BRCA2 c.5946del Homozygous Common	25	0	0	0	N/A	100%	88.8% - 100%
BRCA2 c.5946del Heterozygous	22	0	0	4	100%	N/A	87.3% - 100%
BRCA2 c.6037A>T Homozygous Common	22	0	0	0	N/A	100%	87.3% - 100%
BRCA2 c.6037A>T Heterozygous	17	0	2	0	100%	N/A	83.8% - 100%
BRCA2 c.6275_6276del Homozygous Common	25	0	0	0	N/A	100%	88.8% - 100%
BRCA2 c.6275_6276del Heterozygous	25	0	1	0	100%	N/A	88.8% - 100%
BRCA2 c.7024C>T Homozygous Common	29	0	0	0	N/A	100%	90.2% - 100%
BRCA2 c.7024C>T Heterozygous	9	0	0	0	100%	N/A	71.7% - 100%
BRCA2 c.7480C>T Homozygous Common	24	0	0	0	N/A	100%	88.3% - 100%
BRCA2 c.7480C>T Heterozygous	25	0	0	0	100%	N/A	88.8% - 100%
BRCA2 c.7934del Homozygous Common	24	0	0	0	N/A	100%	88.3% - 100%
BRCA2 c.7934del Heterozygous	15	0	0	0	100%	N/A	81.9% - 100%
BRCA2 c.8904del Homozygous Common	24	0	0	0	N/A	100%	88.3% - 100%
BRCA2 c.8904del Heterozygous	26	0	0	0	100%	N/A	89.1% - 100%

*Relative to Sanger Sequencing
** “FQC” denotes a sample or replicate which failed a quality check and was not analyzed in the study.
***calculated using the mid-p method

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. The study was performed in two laboratories, on multiple instruments, with multiple operators, on multiple non-consecutive days, and using multiple reagent lots.

See table below for total replicates and samples tested for each variant. Any sample replicates failing quality control acceptance criteria were re-tested 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.

Variant	Gene	Total Samples	Total Replicates
c.68_69del	BRCA1	2	69
c.213-11T>G	BRCA1	3	486
c.427G>T	BRCA1	3	486
c.815_824dup	BRCA1	3	486
c.1556del	BRCA1	3	486
c.1687C>T	BRCA1	3	486
c.1960A>T	BRCA1	3	486
c.1961del	BRCA1	3	486
c.2681_2682del	BRCA1	3	486
c.2864C>A	BRCA1	3	486
c.3481_3491del	BRCA1	3	486
c.3598C>T	BRCA1	3	486
c.3627dup	BRCA1	3	486
c.3756_3759del	BRCA1	3	486
c.3770_3771del	BRCA1	3	486
c.4035del	BRCA1	3	486
c.4065_4068del	BRCA1	3	486
c.4327C>T	BRCA1	3	486
c.4357+1G>A	BRCA1	3	486
c.4964_4982del	BRCA1	3	486
c.4986+6T>G	BRCA1	3	486
c.5123C>A	BRCA1	3	486

c.5177_5180del	BRCA1	3	486
c.5266dup	BRCA1	2	67
c.658_659del	BRCA2	3	486
c.771_775del	BRCA2	3	486
c.1929del	BRCA2	3	486
c.2808_2811del	BRCA2	3	486
c.2957_2958insG	BRCA2	2	324
c.3170_3174del	BRCA2	3	486
c.3264dup	BRCA2	3	486
c.3545_3546del	BRCA2	3	486
c.3847_3848del	BRCA2	3	486
c.4471_4474del	BRCA2	3	486
c.5542del	BRCA2	3	486
c.5576_5579del	BRCA2	3	486
c.5682C>G	BRCA2	3	486
c.5946del	BRCA2	2	67
c.6037A>T	BRCA2	3	486
c.6275_6276del	BRCA2	3	486
c.7024C>T	BRCA2	3	486
c.7480C>T	BRCA2	3	486
c.7934del	BRCA2	3	486
c.8904del	BRCA2	3	486

The precision study yielded greater than 99% correct genotype calls for all samples across two laboratories, on multiple instruments, with multiple operators, on multiple non-consecutive days, and using multiple reagent lots. The study passed the pre-defined acceptance criteria of at least 99% correct calls. In addition, the study had greater than 99% reproducibility and greater than 99% repeatability.

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.

This study was performed using 6 human cell line samples, and 72 saliva samples, which were diluted to 3 concentrations (5, 15, and 50ng/µL), using 3 lots of reagents. The study yielded

100% concordant test results for all samples at all DNA concentrations tested passing all pre-defined acceptance criteria. The DNA input required for testing is set at a minimum of 15ng/µL and maximum of 50ng/µL DNA.

Interfering Substances
Studies were performed to determine whether substances that may be present in saliva affect results of the PGS 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 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 tests.

Interfering Mutations
The performance of this test may be affected by the presence of rare mutations, such as those listed below. The effects of these variants on the performance of this test have not been studied.

Gene	Variant Name	Potential Interfering Mutation
BRCA1	c.68_69del	rs528170710
		rs540373654
		rs80357134
		rs528902306
		rs149402012
BRCA1	c.427G>T	rs371973519
		rs368415464

		rs200358748
		rs542687218
		rs80356888
BRCA1	c.815_824dup	rs186274774
		rs397509328
		rs8176153
		rs80357244
		rs149867679
		rs201441987
BRCA1	c.1556del	rs200616937
		rs56272539
		rs80357445
BRCA1	c.1687C>T	rs530914551
		rs552505690
		rs80357159
		rs56012641
BRCA1	c.1960A>T	rs80356895
		rs561988641
		rs28897679
BRCA1	c.1961del	rs80356895
		rs561988641
		rs28897679
BRCA1	c.2864C>A	rs559190752
		rs80356851
BRCA1	c.3481_3491del	rs56336919
		rs183119644
		rs80356918
		rs80357272
BRCA1	c.3598C>T	rs537737635
		rs56214134
		rs16942

BRCA1	c.3627dup	rs537737635
		rs56214134
BRCA1	c.3756_3759del	rs140588714
		rs200648498
		rs483353090
		rs80357099
		rs80357191
BRCA1	c.3770_3771del	rs140588714
		rs200648498
		rs483353090
		rs80357099
		rs80357191
BRCA1	c.4035del	rs80357345
		rs28897689
		rs80356828
BRCA1	c.4065_4068del	rs80357345
		rs28897689
		rs80356828
BRCA1	c.4327C>T	rs80358027
		rs80356840
		rs1060915
		rs541512953
BRCA1	c.4357+1G>A	rs80356840
		rs1060915
BRCA1	c.4964_4982del	rs549640262
		rs1799967
		rs201810810
		rs70953661
BRCA1	c.4986+6T>G	rs549640262
		rs1799967
		rs201810810

BRCA1	c.5123C>A	rs376836050
		rs397509229
		rs80356860
BRCA1	c.5177_5180del	rs8176260
		rs56195342
BRCA1	c.5266dup	rs371203180
		rs571834423
BRCA2	c.658_659del	rs81002855
		rs568027879
		rs528919073
BRCA2	c.771_775del	rs55854959
		rs549269828
		rs567889781
BRCA2	c.1929del	rs11571652
		rs28897711
		rs527579384
BRCA2	c.2808_2811del	rs2227943
		rs28897716
		rs149753706
		rs80358535
BRCA2	c.2957_2958insG	rs45525041
		rs539613324
		rs144862123
		rs11571656
		rs80358541
		rs2227944
		rs1799944
BRCA2	c.3170_3174del	rs564316199
		rs145605603
BRCA2	c.3264dup	rs145605603
		rs543748012

		rs80358575
BRCA2	c.3545_3546del	rs80358600
		rs1799952
BRCA2	c.3847_3848del	rs543304
		rs41293485
BRCA2	c.5542del	rs138489917
		rs372951842
		rs573514896
BRCA2	c.5576_5579del	rs372951842
		rs573514896
		rs80358782
BRCA2	c.5682C>G	rs55996097
		rs11571657
		rs146351301
		rs4987048
		rs149474191
		rs55875643
BRCA2	c.5946del	rs556893517
		rs148618542
		rs80358833
		rs554663691
BRCA2	c.6037A>T	rs554663691
		rs572976024
		rs540799830
		rs147961615
BRCA2	c.6275_6276del	rs541826447
		rs397507838
		rs55794205
		rs35029074
		rs79456940
BRCA2	c.7024C>T	rs186220967

		rs45574331
		rs80358932
		rs200078639
BRCA2	c.7480C>T	rs80358965
		rs11571707
		rs55716624
		rs56070345
BRCA2	c.7934del	rs529779203
BRCA2	c.8904del	rs59004709

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

The key report message concepts for the BRCA1/BRCA2 (Selected Variants) test were reviewed and determined to be the same as those previously tested in the device label comprehension study for the PGS Genetic Health Risk Test Reports (DEN160026). User comprehension studies were performed to assess how well people understand the PGS Genetic Health Risk Test Reports. This study was performed using test reports that are representative of Genetic Health Risk reports in general. The user comprehension study was performed in a sample that was demographically diverse, using quota-based sampling in a controlled laboratory-based environment. In addition to quantitative assessment of user comprehension of the test reports after viewing the educational module, the study was moderated face-to-face in order to collect observational and qualitative data on participants' overall experience with the survey. All pre-defined demographic quotas and enrollment targets were met within the expected study duration for the overall study. 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. Overall comprehension rates per test report concept were greater than 90% across all concepts. The results of the user comprehension study are presented in DEN160026.

Clinical performance

Of the variants included in this test, the majority are most commonly found in people of Ashkenazi Jewish, African American, European, and Hispanic/Latino descent. Published studies estimate that the variants covered by this test account for more than 90% of cancer-related BRCA1 and BRCA2 variants among people of Ashkenazi Jewish descent. These variants account for a much smaller proportion of cancer-related BRCA1 and BRCA2 variants found in people of other ethnicities, including about 30-40% among people of African American, European, and Hispanic/Latino descent; about 5-25% among people of East Asian descent; and up to 35% among people of South Asian descent.

Frequency of BRCA1 and BRCA2 variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian	Middle Eastern
BRCA1 variants							
c.68_69del	0.024%	0.007%	0.889%	0.000%	0.033%	0.049%	<0.014%
c.213-11T>G	0.006%	<0.004%	0.000%	0.000%	0.002%	0.000%	<0.014%
c.427G>T	0.003%	<0.004%	0.000%	0.000%	<0.001%	0.000%	0.000%
c.815_824dup	0.000%	0.022%	0.000%	0.000%	0.006%	0.000%	0.000%
c.1556del	0.001%	0.000%	0.000%	0.000%	<0.001%	0.000%	0.000%
c.1687C>T	0.003%	0.000%	0.000%	0.000%	0.002%	0.000%	0.000%
c.1960A>T	<0.001%	0.000%	0.000%	0.000%	0.003%	0.000%	0.000%
c.1961del	0.002%	0.000%	0.000%	0.000%	<0.001%	<0.012%	<0.014%
c.2681_2682del	0.005%	0.000%	0.000%	0.000%	0.001%	0.000%	0.000%
c.2864C>A	<0.001%	0.000%	0.000%	0.000%	0.002%	0.000%	0.000%
c.3481_3491del	0.003%	<0.004%	0.000%	0.000%	<0.001%	0.000%	0.000%
c.3598C>T	0.001%	0.000%	0.000%	0.000%	0.002%	<0.012%	0.000%
c.3627dup	0.001%	<0.004%	0.000%	0.004%	0.000%	0.000%	0.000%
c.3756_3759del	0.005%	<0.004%	0.000%	0.000%	0.003%	0.000%	<0.014%
c.3770_3771del	0.001%	<0.004%	0.000%	<0.003%	0.000%	<0.012%	<0.014%
c.4035del	0.003%	0.000%	0.000%	0.000%	<0.001%	0.000%	0.000%
c.4065_4068del	0.004%	<0.004%	0.000%	<0.003%	0.004%	0.014%	<0.014%
c.4327C>T	0.003%	<0.004%	0.000%	<0.003%	0.004%	0.000%	<0.014%
c.4357+1G>A	<0.001%	0.004%	0.000%	0.000%	0.000%	0.000%	<0.014%
c.4964_4982del	0.002%	0.000%	0.000%	0.000%	0.002%	0.000%	0.000%

c.4986+6T>G	<0.001%	0.000%	0.000%	0.000%	0.000%	0.000%	0.000%
c.5123C>A	0.001%	<0.004%	0.000%	<0.003%	0.008%	0.000%	<0.014%
c.5177_5180del	0.001%	0.011%	0.000%	0.000%	<0.001%	0.000%	0.000%
c.5266dup	0.026%	<0.004%	0.278%	0.000%	0.010%	0.000%	0.000%
BRCA2 variants							
c.658_659del	0.009%	0.015%	0.000%	0.005%	0.020%	0.000%	<0.014%
c.771_775del	0.001%	<0.004%	0.000%	0.003%	0.002%	0.000%	0.000%
c.1929del	0.004%	0.000%	0.000%	0.000%	0.002%	0.000%	0.000%
c.2808_2811del	0.007%	0.007%	<0.006%	0.006%	0.008%	<0.012%	<0.014%
c.2957_2958insG	<0.001%	0.004%	0.000%	0.000%	<0.001%	0.000%	0.000%
c.3170_3174del	0.003%	<0.004%	0.000%	0.000%	0.003%	0.000%	0.000%
c.3264dup	<0.001%	0.000%	0.000%	0.000%	0.021%	0.000%	0.000%
c.3545_3546del	0.007%	<0.004%	0.000%	0.000%	0.001%	0.000%	0.000%
c.3847_3848del	0.013%	0.005%	0.012%	<0.003%	0.007%	0.000%	<0.014%
c.4471_4474del	<0.001%	0.000%	0.000%	<0.003%	<0.001%	0.000%	0.000%
c.5542del	0.000%	0.000%	0.000%	0.000%	0.003%	0.000%	0.000%
c.5576_5579del	0.006%	<0.004%	0.000%	0.010%	0.003%	<0.012%	<0.014%
c.5682C>G	0.004%	0.004%	0.000%	<0.003%	0.001%	0.000%	0.000%
c.5946del	0.024%	0.007%	1.042%	0.000%	0.012%	0.000%	<0.014%
c.6037A>T	0.001%	0.000%	0.000%	0.000%	<0.001%	0.000%	0.000%
c.6275_6276del	0.009%	<0.004%	0.000%	0.000%	0.005%	0.000%	0.000%
c.7024C>T	0.000%	<0.004%	0.000%	0.000%	0.000%	0.000%	0.000%
c.7480C>T	0.001%	0.000%	0.000%	0.008%	0.001%	0.000%	<0.014%
c.7934del	0.001%	0.000%	0.000%	0.000%	0.001%	<0.012%	0.000%
c.8904del	0.002%	0.000%	0.000%	0.000%	0.001%	0.000%	0.000%

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breast-ovarian cancer prevention and control." EPMA J. 1(3):397-412.

Rebbeck TR et al. (2018). "Mutational spectrum in a worldwide study of 29,700 families with BRCA1 or BRCA2 mutations." Hum Mutat. 39(5):593-620.

Rosenthal E et al. (2015). "Incidence of BRCA1 and BRCA2 non-founder mutations in patients of Ashkenazi Jewish ancestry." Breast Cancer Res Treat. 149(1):223-7.

Data on file at 23andMe, Inc., South San Francisco, CA.

Additional references included in the test report.

MUTYH-Associated Polyposis

Indications for use

The 23andMe Personal Genome Service (PGS) uses qualitative genotyping to detect select clinically relevant variants in genomic DNA isolated from human saliva collected from individuals ≥18 years with the Oragene Dx model OGD500.001 for the purpose of reporting and interpreting genetic health risks, including the 23andMe PGS Genetic Health Risk Report for MUTYH-Associated Polyposis. The 23andMe PGS Genetic Health Risk Report for MUTYH-Associated Polyposis is indicated for reporting of the Y179C and the G396D variants in the MUTYH gene. The report describes if a person is at increased risk of developing colorectal cancer. The two variants included in this report are most common and best studied in people of Northern European descent and may not represent the majority of the MUTYH variants found in people of other ethnicities. The test report does not describe a person's overall risk of developing any type of cancer, and the absence of a variant tested does not rule out the presence of other variants that may be cancer-related. This test is not a substitute for visits to a healthcare provider for recommended screenings or appropriate follow-up and should not be used to determine any treatments.

Important considerations

- This test does not diagnose colorectal cancer or any other health conditions and should not be used on its own to make medical decisions. Results should be confirmed in a clinical setting before taking any medical action.
- Please follow the instructions in the DNA Collection Kit to ensure your DNA results can be processed and connected to your online account.
- Your ethnicity may affect whether these tests are relevant for you.
- Other factors, such as family history and lifestyle risk factors, may affect the risk of developing a given disease. This test does not account for non-genetic factors, and does not test for variants in other genes linked to hereditary colorectal cancer syndromes, such as Lynch syndrome or familial adenomatous polyposis (FAP).
- 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.
- This test cannot determine your overall risk for developing a disease in the future.
- This device is not intended for prenatal testing.

- This test is not for assessing the presence of genetic variants that may impact the metabolism, exposure, response, risk of adverse events, dosing, or mechanisms of prescription or over-the-counter medications.
- This test is not intended to detect the presence of deterministic variants in autosomal dominant diseases or conditions.
- The laboratory may not be able to process your sample. If this happens, we will notify you by email and you may request one free replacement kit to provide us with a new sample.

Other warnings, precautions, and limitations

- This test includes two variants that are most common in people of Northern European descent.
- This test does not test for all possible variants in the MUTYH gene. More than 100 variants in the MUTYH gene are known to increase cancer risk. Only two of those variants are included in this test. The absence of a variant tested does not rule out the presence of other genetic variants that may be related to these health conditions.
- If you receive a “zero variants detected” result you should not over interpret it. You could have another variant not included in this test that may impact your cancer risk.
- This test is intended to be used to identify genetic risk for health conditions in users 18 years and above.
- This test is intended to provide you with genetic information to inform conversations with your doctor or other healthcare professional.
- This test is not a substitute for visits to a healthcare professional for recommended screenings, and should not be used to determine any treatments or medical interventions. You should consult with a healthcare professional if you have any questions or concerns about your results or your current state of health.
- This test may not be able to determine a result for all variants analyzed.
- Three potentially interfering mutations near Y179C, and four potentially interfering mutations near G396D that are within the binding region for the variant being tested have been identified and are noted below. Interference due to these mutations was not tested. The effects of these variants on the performance of this test have not been studied.

MUTYH variant	Potentially Interfering Mutation
Y179C	rs190500741, rs533899702, rs201678305
G396D	rs559963863, rs529008617, rs3219490, rs531232542

- Different companies offering a genetic risk test may be measuring different genetic variants for the same condition, so you may get different results from a different test.
- Some people feel a little anxious about getting genetic health risk 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.
- As with every test the possibility for an incorrect result exists. Speak to your personal healthcare professional or a genetic counselor if your results are unexpected.

For healthcare professionals

- This test is not intended to diagnose a disease, determine medical treatment or other medical intervention, or tell the user anything about their current state of health.
- This test is intended to provide users with their genetic information, which may inform health-related lifestyle decisions and conversations with their doctor or other healthcare professional.
- Any diagnostic or treatment decisions must be based on confirmatory prescription testing and/or other information that you determine to be appropriate for your patient, such as additional clinical testing and other risk factors that may affect individual risk and healthcare.

Test performance

The performance of the MUTYH-Associated Polyposis test was assessed only for the detection of the specific gene variants analyzed by the MUTYH-Associated Polyposis 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.

Analytical performance

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 64 samples with known Y179C variant status, and 78 samples with known G396D status. Pre-defined acceptance criteria were set to a minimum of 99% Positive Percent Agreement (PPA) and 99% Negative Percent Agreement (NPA).

The method comparison study yielded >99% overall agreement for all genotypes for all samples tested, passing the predefined acceptance criteria of at least 99% PPA and 99% NPA. The comprehensive 95% confidence interval for the total number of samples tested was 97.4% to 100%. The widest confidence interval was 76.8% to 100% for 14 homozygous rare MUTYH Y179C samples.

Genotype	BeadChip Calls				% PPA	% NPA	95% CI
	Correct	Incorrect	No Call	FQC[1]			
MUTYH Y179C Homozygous common	25	0	0	0	N/A	100	86.3-100
MUTYH Y179C Heterozygous	26	0	0	0	100	N/A	86.8-100
MUTYH Y179C Homozygous rare	14	0	0	1	100	N/A	76.8-100
MUTYH G396D Homozygous common	26	0	0	0	N/A	100	86.8-100

Genotype	BeadChip Calls				% PPA	% NPA	95% CI
	Correct	Incorrect	No Call	FQC[1]			
MUTYH G396D Heterozygous	27	0	0	0	100	N/A	87.2-100
MUTYH G396D Homozygous rare	25	0	0	0	100	N/A	86.3-100

[1] "FQC" denotes a sample or replicate which failed a quality check and was not analyzed in the study.

Precision

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 2 lab sites over 3 non-consecutive days with multiple operator teams. The testing used 3 lots of reagents and 3 sets of instruments at each lab site.

A total of 360 Y179C replicates from 3 unique samples, and 486 G396D replicates from 3 unique samples were tested. Any sample replicates failing quality control acceptance criteria were re-tested 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.

The precision study yielded greater than 99% correct genotype calls for all samples across multiple days, operator teams, instruments, and reagent lots at 2 independent laboratory sites. The study passed the pre-defined acceptance criteria of at least 99% correct calls. In addition, the study had greater than 99% reproducibility and greater than 99% repeatability.

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.

This study was performed using 1 human cell line sample and 3 saliva samples, which were diluted to 3 concentrations (5, 15, and 50ng/µL), using 3 lots of reagents. The study yielded 100% concordant test results for all samples at all DNA concentrations tested passing all pre-defined acceptance criteria. The DNA input required for testing is set at a minimum of 15ng/µL and maximum of 50ng/µL DNA.

Interfering Substances

Studies were performed to determine whether substances that may be present in saliva affect results of the PGS 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 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 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

The key report message concepts for the MUTYH-Associated Polyposis (MAP) test were reviewed and determined to be the same as those previously tested in the device label comprehension study for the PGS Genetic Health Risk Test Report for BRCA1/BRCA2 (Selected Variants). User comprehension studies were performed to assess how well people understand the PGS Genetic Health Risk Test Reports. This study was performed using test reports that are representative of Genetic Health Risk reports in general. The user comprehension study was performed in a sample that was demographically diverse, using quota-based sampling in a controlled laboratory-based environment. In addition to quantitative assessment of user comprehension of the test reports after viewing the educational module, the study was moderated face-to-face in order to collect observational and qualitative data on participants' overall experience with the survey. All pre-defined demographic quotas and enrollment targets were met within the expected study duration for the overall study. 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. Overall comprehension rates per test report concept were greater than 90% across all concepts, passing the pre-defined acceptance criteria.

Clinical performance

The variants covered by this test are mainly found in people of Northern European descent. Published studies estimate that about 1-2% of the general Northern European population has one

of the two variants in this report, which means that between 1 in 10,000 and 1 in 40,000 people of Northern European descent are expected to have MAP. These two variants have also been observed in people of other ethnicities.

Frequency of MUTYH variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian	Middle Eastern
Y179C	0.41%	0.11%	<0.01%	<0.01%	0.27%	<0.01%	0.06%
G396D	1.12%	0.36%	<0.01%	0.01%	1.00%	0.04%	0.35%

References

Cleary SP et al. (2009). "Germline MutY human homologue mutations and colorectal cancer: a multisite case-control study." Gastroenterology. 136(4):1251-60.

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Win AK et al. (2014). "Risk of colorectal cancer for carriers of mutations in MUTYH, with and without a family history of cancer." Gastroenterology. 146(5):1208-11.e1-5.

Data on file at 23andMe, Inc., South San Francisco, CA.

Additional references included in the test report.

Hereditary Prostate Cancer (HOXB13-Related)

Indications for use

The 23andMe Personal Genome Service (PGS) uses qualitative genotyping to detect select clinically relevant variants in genomic DNA isolated from human saliva collected from individuals ≥18 years for the purpose of reporting and interpreting genetic health risks, including the 23andMe PGS Genetic Health Risk Report for Hereditary Prostate Cancer (HOXB13-Related). The 23andMe PGS Genetic Health Risk Report for Hereditary Prostate Cancer (HOXB13-Related) is indicated for reporting of the G84E variant in the HOXB13 gene. The report describes if a person has the G84E variant and if a male is at increased risk for prostate cancer. The variant included in this report is most common in people of European descent. The test report does not describe a person's overall risk of developing any type of cancer, and the absence of a variant tested does not rule out the presence of other variants that may be cancer-related. This test is not a substitute for visits to a healthcare provider for recommended screenings or appropriate follow-up and should not be used for diagnosis or to determine any treatments or medical interventions.

Important considerations

- This test does not diagnose prostate cancer or any other health conditions and should not be used on its own to make medical decisions. Results should be confirmed by an independent genetic test prescribed by your own healthcare provider before taking any

medical action.
- Please follow the instructions in the DNA Collection Kit to ensure your DNA results can be processed and connected to your online account.
- Your ethnicity may affect whether these tests are relevant for you.
- Other factors, such as family history, age, and lifestyle, may affect the risk of developing a given disease.
- 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.
- This test cannot determine your overall risk for developing a disease in the future.
- This device is not intended for prenatal testing.
- This test is not for assessing the presence of genetic variants that may impact the metabolism, exposure, response, risk of adverse events, dosing, or mechanisms of prescription or over-the-counter medications.
- This test is not intended to detect the presence of deterministic variants in autosomal dominant diseases or conditions.
- The laboratory may not be able to process your sample. If this happens, we will notify you by email and you may request one free replacement kit to provide us with a new sample.

Other warnings, precautions, and limitations

- This test includes one variant that is most common in people of European descent, especially in people of Northern European descent.
- This test does not test for all possible variants in the HOXB13 gene and does not test for variants in other genes linked to hereditary prostate cancer, such as variants in BRCA1, BRCA2, and genes linked to Lynch syndrome. The absence of a variant tested does not rule out the presence of other genetic variants that may be related to this health condition.
- If you receive a “zero variants detected” result you should not over interpret it. You could have another variant not included in this test that may impact your cancer risk.
- This test is intended to be used to identify genetic risk for health conditions in users 18 years and above.
- This test is intended to provide you with genetic information to inform conversations with your doctor or other healthcare professional. The section below “For healthcare professionals” should be shared with your doctor.
- This test is not a substitute for visits to a healthcare professional for recommended screenings and should not be used to determine any treatments or medical interventions. You should consult with a healthcare professional if you have any questions or concerns about your results or your current state of health.
- This test may not be able to determine a result for the variant analyzed.
- Different companies offering a genetic risk test may be measuring different genetic variants for the same condition, so you may get different results from a different test.
- Some people feel a little anxious about getting genetic health risk 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.
- As with every test the possibility for an incorrect result exists. Speak to your personal

healthcare professional or a genetic counselor if your results are unexpected.

For healthcare professionals

- This test is not intended to diagnose a disease, determine medical treatment or other medical intervention, or tell the user anything about their current state of health.
- This test is intended to provide users with their genetic information, which may inform health-related lifestyle decisions and conversations with their doctor or other healthcare professional.
- Any diagnostic or treatment decisions must be based on confirmatory prescription testing intended for diagnosis and treatment decisions, and/or other information that you determine to be appropriate for your patient, such as additional clinical testing and other risk factors that may affect individual risk and health care.

Test performance

The performance of the Hereditary Prostate Cancer (HOXB13-Related) test was assessed only for the detection of the specific gene variant analyzed by the Hereditary Prostate Cancer (HOXB13-Related) 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, GenomeStudio, and Coregen software.

Analytical performance

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay genotype calls. Results of the test were compared with sequencing results for 68 samples with known HOXB13 G84E variant status. Pre-defined acceptance criteria were set to a minimum of 99% Positive Percent Agreement (PPA) and 99% Negative Percent Agreement (NPA). The method comparison study yielded 100% PPA and NPA for all genotype calls for all samples tested, passing the predefined acceptance criteria of at least 99% PPA and 99% NPA. The 95% confidence interval was 86.1% to 100% for HOXB13 G84E CC (homozygous common), 89.1% to 100% for HOXB13 G84E CT (heterozygous), and 87.3% to 100% for HOXB13 G84E TT (homozygous rare).

Genotype	BeadChip Calls				% PPA	% NPA	95% CI†
	Correct*	Incorrect*	No Call	BeadChip FQC			
HOXB13 G84E CC	20	0	0	0	N/A	100%	86.1 – 100%
HOXB13 G84E CT	26	0	0	0	100%	N/A	89.1 – 100%
HOXB13 G84E TT	22	0	0	0	100%	N/A	87.3 – 100%

*Relative to Sanger sequencing

†mid-p method

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 2 lab sites over 3 non-consecutive days with multiple operator teams. The testing used 3 lots of reagents and 3 sets of instruments at each lab site.

A total of 486 replicates from 3 unique samples were tested. Any sample replicates failing quality control acceptance criteria were re-tested 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.

The precision study yielded greater than 99% correct genotype calls for all samples across multiple days, operator teams, instruments, and reagent lots at 2 independent laboratory sites. The study passed the pre-defined acceptance criteria of at least 99% correct calls. In addition, the study had greater than 99% reproducibility and greater than 99% repeatability.

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.

This study was performed using 3 saliva samples, which were diluted to 3 concentrations (5, 15, and 50ng/µL), using 3 lots of reagents. The study yielded 100% concordant test results for all samples at all DNA concentrations tested passing all predefined acceptance criteria. The DNA input required for testing is set at a minimum of 15ng/µL and maximum of 50ng/µL DNA.

Interfering Substances
Studies were performed to determine whether substances that may be present in saliva affect results of the PGS 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 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 tests.

Interfering Mutations
The performance of this test may be affected by the presence of rare mutations, such as those listed below:

Gene	Variant	Potential Interfering Mutation(s)
HOXB13	G84E	rs529392210 (G85S)[1]

[1] Prevalence in gnomAD: 0.0012% across all included populations, 0.0009% in non-Finnish Europeans, 0% in Finnish Europeans

The effects of this variant on the performance of this test have not been studied.

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
The key report message concepts for the Hereditary Prostate Cancer (HOXB13-Related) test were reviewed and determined to be the same as those identified and previously tested in the Genetic Health Risk device label comprehension study (DEN160026), which was determined suitable for the predicate devices (DEN170046 and K182784). The user comprehension study included participants that were demographically diverse and were selected based on quota-based sampling in a controlled laboratory-based environment. In addition to quantitative assessment of user comprehension of the test reports after viewing the educational module, the study was moderated face-to-face in order to collect observational and qualitative data on participants' overall experience with the survey. All predefined demographic quotas and enrollment targets were met within the expected study duration for the overall study. 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. Overall comprehension rates per test report concept were greater than 90% across all concepts, passing the pre-defined acceptance criteria.

Clinical performance

The variant covered by this test is most commonly found in people of European descent, especially people of Northern European descent. Up to 1 in 70 people of European descent has the HOXB13 G84E variant. This variant is expected to be less common in people of other ethnicities. The HOXB13 G84E variant accounts for up to 5% of hereditary prostate cancer in families of European descent. In some Scandinavian countries this variant accounts for about 22% (Finland) and 8% (Sweden) of hereditary prostate cancer cases.

Frequency of the HOXB13 G84E variant in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian	Middle Eastern
G84E	0.36%	0.09%	<0.01%	0.00%	0.13%	0.00%	<0.01%

References

Karlsson R et al. (2014). "A population-based assessment of germline HOXB13 G84E mutation and prostate cancer risk." Eur Urol. 65(1):169-76.

Xu J et al. (2013). "HOXB13 is a susceptibility gene for prostate cancer: results from the International Consortium for Prostate Cancer Genetics (ICPCG)." Hum Genet. 132(1):5-14.

Data on file at 23andMe, Inc., South San Francisco, CA.

Additional references included in the test report.

Pharmacogenetic Reports

Intended use

The 23andMe Personal Genome Service (PGS) is a qualitative genotyping assessment system applied to genomic DNA isolated from human saliva collected using the Oragene Dx OGD-500.001 to simultaneously detect, report, and interpret genetic variants in a broad multigene test. The assessment system is intended to enable users to access information about their genetics that could aid discussions with a healthcare professional. The 23andMe Pharmacogenetic Reports are indicated for the reporting of the following variants:

Gene	Variant(s)*
CYP2C19	*2, *3, *17
DPYD	*2A, rs67376798
SLCO1B1	c.521T>C (rs4149056)

These reports are for over-the-counter use by adults over the age of 18, and provide genetic

information to inform discussions with a healthcare professional about metabolism of therapeutics.

The 23andMe Personal Genome Service pharmacogenetic report for DPYD describes if a person has variants associated with metabolism of some therapeutics, but does not describe if a person will or will not respond to a particular therapeutic. Further, it does not describe the association between detected variants and any specific therapeutic.

The 23andMe Personal Genome Service pharmacogenetic report for CYP2C19 describes if a person has variants associated with metabolism of some therapeutics and provides interpretive drug information regarding the potential effect of the identified metabolizer phenotype on citalopram and clopidogrel therapy.

23andMe Personal Genome Service pharmacogenetics report for SLCO1B1 describes if a person has variants associated with the processing of some therapeutics and provides interpretive drug information regarding the potential effect of the identified transport function phenotype on simvastatin therapy.

The PGS Pharmacogenetic Reports are not a substitute for visits to a healthcare professional. The information provided by this report should not be used to start, stop, or change any course of treatment.

Summary and explanation of the test
23andMe Pharmacogenetic Reports are tests you can order and use at home to learn about your DNA from a saliva sample. 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 considerations

- This test is intended to detect genetic variants associated with the processing of some drugs.
- This test does not diagnose any health conditions, provide medical advice, or determine whether a drug is indicated for you.
- Other factors such as age, weight, liver and kidney function, other drugs, and behavior may affect individual drug metabolism. This test does not account for non-genetic factors that affect drug metabolism.
- Please follow the instructions in the DNA Collection Kit to ensure your DNA results can be processed and connected to your online account.
- This device is not intended for prenatal testing.
- The laboratory may not be able to process your sample. If this happens, we will notify you by email and you may request one free replacement kit to provide us with a new sample.

Other warnings, precautions, and limitations

Warnings, precautions, and limitations for DPYD

- Do not use your results to start, stop, or change any course of treatment.
- Results from this test should not be used to make medical decisions. Results should be confirmed by an independent genetic test prescribed by your own healthcare provider before taking any medical action.
- This test does not provide information on associations between specific DNA variants and any specific therapeutic.
- This test does not diagnose any health conditions, predict drug response, provide medical advice, or determine whether a medication is indicated for the user.
- This test does not determine if a person will or will not respond to a particular therapeutic.
- This test does not detect all genetic variants related to drug metabolism. The absence of a variant tested does not rule out the presence of other genetic variants that may be related to drug metabolism.
- This test is not a substitute for visits to a healthcare professional. You should consult with a healthcare professional if you have any questions or concerns about your results.
- This test may not be able to determine a result for all variants analyzed.
- Different companies offering genetic testing may be measuring different genetic variants for drug metabolism, so you may get different results from a different test.
- As with every test the possibility for an incorrect result exists. Speak to your personal healthcare professional or a genetic counselor if your results are unexpected.

Warnings, precautions, and limitations specific for CYP2C19 and SLCO1B1

- Do not use your results to start, stop, or change any course of treatment.
- This test does not diagnose any health conditions, provide medical advice, or determine whether a medication is indicated for the user.
- This test provides interpretive drug information on citalopram and clopidogrel (CYP2C19) and simvastatin (SLCO1B1).
- This test does not determine if a person will or will not respond to a particular therapeutic.
- This test does not detect all genetic variants related to drug processing. The absence of a variant tested does not rule out the presence of other genetic variants that may be related to drug processing.
- This test is not a substitute for visits to a healthcare professional. You should consult with a healthcare professional if you have any questions or concerns about your results.
- This test may not be able to determine a result for all variants analyzed.
- For CYP2C19 only: This test does not provide interpretive drug information for the CYP2C19 *3/*17 genotype or other CYP2C19 genotype combinations where the predicted metabolizer profile cannot be interpreted. In addition, results for these genotypes should be confirmed by an independent genetic test prescribed by your own healthcare provider before taking any medical action.
- Different companies offering genetic testing may be measuring different genetic variants for drug metabolism, so you may get different results from a different test.
- As with every test the possibility for an incorrect result exists. Speak to your personal healthcare professional or a genetic counselor if your results are unexpected.

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
See test-specific information for each test.

Precision/Reproducibility
See test-specific information for each test.

Minimum DNA Input
See test-specific information for each test.

Interfering Substances
Studies were performed to determine whether substances that may be present in saliva affect results of the PGS 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 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 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 Pharmacogenetics Reports. A diverse group of people answered questions about the 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.

Overall comprehension rates per test report concept were greater than 90% across all concepts.

Specific Pharmacogenetics test information

CYP2C19 Drug Metabolism
DPYD Drug Metabolism
SLCO1B1 Drug Transport

CYP2C19 Drug Metabolism

Indications for Use

The 23andMe Personal Genome Service Pharmacogenetics Report for CYP2C19 is indicated for reporting of the *2, *3, and *17, variants in the CYP2C19 gene. This report is for over-the-counter use by adults over the age of 18, and provides genetic information to inform discussions with a healthcare professional about processing of therapeutics. This report describes if a person has variants associated with metabolism of some therapeutics and provides interpretive drug information regarding the potential effect of the identified metabolizer phenotype on citalopram and clopidogrel therapy. This test is not a substitute for visits to a healthcare professional. The information provided by this report should not be used to start, stop, or change any course of treatment.

Clinical performance

The peer-reviewed literature supports the association of the variants with the predicted metabolizer phenotypes.

The *2 and *3 variants account for 95-100% of the known CYP2C19 no-function alleles found in most populations, except for the Hispanic and Latino population, where the coverage is about 86%. The *17 variant is currently the only known increased-function allele.

Allele frequency
This pharmacogenetics report tests for three (3) variants in the CYP2C19 gene: *2, *3, and *17. These variants are found in many ethnicities, at varying allele frequencies.

The allele frequencies in the following table are from the 23andMe database, and may not be representative of the actual allele frequencies in these populations.

Allele frequencies in 23andMe customers

Ancestry group	*2	*3	*17
European	14.62%	0.02%	21.76%
African American	17.34%	0.11%	21.78%
Ashkenazi Jewish	13.27%	<0.01%	21.57%
East Asian	30.65%	6.50%	0.86%
Hispanic/Latino	13.24%	0.14%	16.30%
South Asian	33.62%	0.34%	16.96%
Middle Eastern	11.19%	0.12%	21.18%
Other	18.71	1.77%	16.24%

Analytical performance

Accuracy

23andMe performed several method comparison studies using sequencing as the comparator to assess the accuracy of the assay. Results of these tests are presented in the sections below. Only sample replicates that passed quality control and produced a genotype for the 23andMe test were included in the calculations for percent agreement.

Results of the test were compared with sequencing results for 145 samples with known *2 variant status, 132 samples with known *3 variant status, and 141 samples with known *17 variant status. 17 samples did not pass initial quality control, and were not assigned a genotype. Agreement between the two methods was >99% for all samples analyzed. The overall 95% confidence intervals for the *2, *3, and *17 variants were 97.5% to 100%, 97.2% to 100%, and 97.4% to 100%, respectively.

Table 1 - Accuracy Test for DEN180028

SNP	Genotype	BeadChip Calls				% PPA	% NPA	95% CI[2]
		Correct	Incorrect	No Call	FQC[1]			
rs4244285	CYP2C19 *2 GG	47	0	0	3	N/A	100%	92.5% to 100%
	CYP2C19 *2 AG	49	0	0	0	100%	N/A	92.7% to 100%
	CYP2C19 *2 AA	49	0	0	3	100%	N/A	92.7% to 100%
rs4986893	CYP2C19 *3 GG	48	0	0	2	N/A	100%	92.6% to 100%
	CYP2C19 *3 AG	45	0	0	3	100%	N/A	92.1% to 100%
	CYP2C19 *3 AA	39	0	0	1	100%	N/A	91.0% to 100%
rs12248560	CYP2C19 *17 CC	49	0	0	1	N/A	100%	92.7% to 100%
	CYP2C19 *17 CT	45	0	0	4	100%	N/A	92.1% to 100%
	CYP2C19 *17 TT	47	0	0	0	100%	N/A	92.5% to 100%

[1] "FQC" denotes a sample or replicate which failed a quality check and was not analyzed in the study.
[2] Clopper-Pearson (Exact) Method

Supplemental Sample Collection Accuracy Test for K193492

Results of this test were compared to sequencing and reference results for 456 samples of *2 variant status, 438 samples of *3 variants status, and 444 samples of *17 status. Agreement between the comparator methods was >99% for all samples analyzed. The overall 95% confidence intervals for the *2, *3, and *17 variants were 99.2% to 100%, 99.2% to 100%, and 99.2% to 100%, respectively.

Table 2 - Supplemental Sample Collection Accuracy Test

SNP	Genotype	BeadChip Calls				% PPA	% NPA	95% CI[2]
		Correct	Incorrect	No Call	FQC[1]			
rs4244285	CYP2C19 *2 GG	304	0	0	0	N/A	100%	98.8% to 100%
	CYP2C19 *2 AG	130^	0	0	0	100%	N/A	97.2% to 100%
	CYP2C19 *2 AA	22^	0	0	0	100%	N/A	84.6% to 100%
rs4986893	CYP2C19 *3 GG	432	0	0	0	N/A	100%	99.2% to 100%
	CYP2C19 *3 AG	6^	0	0	0	100%	N/A	54.1% to 100%

SNP	Genotype	BeadChip Calls				% PPA	% NPA	95% CI[2]
		Correct	Incorrect	No Call	FQC[1]			
	CYP2C19 *3 AA	0	0	0	0	N/A	N/A	N/A
rs12248560	**CYP2C19 *17 CC**	279	0	0	0	N/A	100%	98.7% to 100%
	CYP2C19 *17 CT	140^	0	0	0	100%	N/A	97.4% to 100%
	CYP2C19 *17 TT	25^	0	0	0	100%	N/A	86.3% to 100%

[1] "FQC" denotes a sample or replicate which failed a quality check and was not analyzed in the study.
[2] Clopper-Pearson (Exact) Method
^ Reference sample included in total

Ancestry Based Sample Collection Accuracy Test for K193492

Results of this test were compared to sequencing for 229 samples of *2 variant status, 231 samples of *3 variants status, and 230 samples of *17 status. Agreement between the comparator methods was >99% for all samples analyzed. The overall 95% confidence intervals for the *2, *3, and *17 variants were 98.4% to 100%, 98.4% to 100%, and 98.4% to 100%, respectively.

Table 3 - Ancestry Based Sample Collection Accuracy Test

SNP	Genotype	BeadChip Calls				% PPA	% NPA	95% CI[2]
		Correct	Incorrect	No Call	FQC[1]			
rs4244285	**CYP2C19 *2 GG**	114	0	0	0	N/A	100%	96.8% to 100%
	CYP2C19 *2 AG	91	0	0	0	100%	N/A	96.0% to 100%
	CYP2C19 *2 AA	24	0	0	0	100%	N/A	85.8% to 100%
rs4986893	**CYP2C19 *3 GG**	197	0	0	0	N/A	100%	98.1% to 100%
	CYP2C19 *3 AG	31	0	0	0	100%	N/A	88.8% to 100%
	CYP2C19 *3 AA	3	0	0	0	100%	N/A	29.2% to 100%
rs12248560	**CYP2C19 *17 CC**	228	0	0	0	N/A	100%	98.4% to 100%
	CYP2C19 *17 CT	2	0	0	0	100%	N/A	15.8% to 100%
	CYP2C19 *17 TT	0	0	0	0	N/A	N/A	N/A

[1] "FQC" denotes a sample or replicate which failed a quality check and was not analyzed in the study.
[2] Clopper-Pearson (Exact) Method

Precision/Reproducibility - DEN180028

A precision study was performed to understand the consistency of sample measurements when tested under different conditions.

A total of 748 *2 replicates from 6 unique samples, 741 *3 replicates from 5 unique samples, and 905 *17 replicates from 5 unique samples were tested across different testing conditions. 36 replicates did not pass quality control acceptance criteria and were not assigned a genotype. Only sample replicates that passed quality control and produced a genotype for the 23andMe test were included in the calculation for percent agreement.

The precision study yielded greater than 99% correct genotype calls for all samples across all conditions tested. In addition, the study had greater than 99% reproducibility and greater than 99% repeatability.

Precision/Reproducibility - *Supplemental for K193492*
A precision study was performed with intended use samples to understand the consistency of sample measurements when tested under different conditions.

A total of 486 *2 replicates from 6 intended use samples, 243 *3 replicates from 3 intended use samples, and 405 *17 replicates from 5 intended use samples were tested across different testing conditions. A separate study was conducted for *3 AA (homozygous rare) assessment in which one sample and 98 replicates were tested. All sample replicates passed quality control and produced a genotype for the 23andMe test and were included in the calculation for percent agreement.

The precision study yielded greater than 99% correct genotype calls for all samples across all conditions tested. In addition, the study had greater than 99% reproducibility and greater than 99% repeatability.

Minimum DNA input - DEN180028
This study was performed using 8 human cell line samples, and 1 human saliva sample, using 3 lots of reagents. The study yielded 100% concordant test results for all samples at all DNA concentrations tested passing all predefined acceptance criteria. The DNA input required for testing is set at a minimum of 15ng/µL and maximum of 50ng/µL DNA.

Supplemental Intended Use Sample Study for K193492

These studies were performed using a total of seven (7) intended use samples representing each of the variants of interest, *2, *3, and *17, using 3 lots of reagents, and 3 concentrations for each. This minimum DNA input study was conducted to determine the lowest concentration of DNA that is necessary for successful assignment of the correct genotypes using intended use samples. The study yielded 100% concordant test results for all samples at all DNA concentrations tested passing all predefined acceptance criteria. The DNA input required for testing is set at a minimum of 15ng/µL and maximum of 50ng/µL DNA.

Interfering mutations
The performance of this test may be affected by the presence of rare mutations, such as those listed below:

Gene	Variant	Potential Interfering Mutation(s)
CYP2C19	*2	rs566311971 rs879130837
CYP2C19	*3	rs186489608 rs200936950 rs191690054 rs200025269
CYP2C19	*17	rs576566073 rs545523674 rs540392908 rs17880036 rs1158729 rs1262360236 rs561205449 rs185375194

Selected References

Bousman CA et al. (2023). "Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6, CYP2C19, CYP2B6, SLC6A4, and HTR2A Genotypes and Serotonin Reuptake Inhibitor Antidepressants." Clin Pharmacol Ther. online ahead of print.

Caudle KE et al. (2017). "Standardizing terms for clinical pharmacogenetic test results: consensus terms from the Clinical Pharmacogenetics Implementation Consortium (CPIC)." Genet Med. 19(2):215-223.

Lee CR et al. (2022). "Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2C19 Genotype and Clopidogrel Therapy: 2022 Update." Clin Pharmacol Ther. 112(5):959-967.

Pratt VM et al. (2018). "Recommendations for Clinical CYP2C19 Genotyping Allele Selection: A Report of the Association for Molecular Pathology." J Mol Diagn. 20(3):269-276.

Whirl-Carrillo M et al. (2012). "Pharmacogenomics knowledge for personalized medicine." Clin Pharmacol Ther. 92(4):414-7.

Additional references included in the test report.

DPYD Drug Metabolism

Indications for Use

The 23andMe Personal Genome Service Pharmacogenetics Report for DPYD is indicated for reporting of the *2A and D949V (rs67376798) variants in the DPYD gene. This report is for over-the-counter use by adults over the age of 18, and provides genetic information to inform discussions with a healthcare professional about processing of therapeutics. This report describes

if a person has DPYD variants associated with the processing of some therapeutics, but does not describe if a person will or will not respond to a particular therapeutic, and does not describe the association between detected variants and any specific therapeutic. This test is not a substitute for visits to a healthcare professional. The information provided by this report should not be used to start, stop, or change any course of treatment.

Clinical performance
The peer-reviewed literature supports the association of the variants with the predicted metabolizer phenotypes.

The *2A and D949V variants represent a subset of those in the DPYD gene that produce a nonfunctional or decreased function protein.

Allele frequency
This pharmacogenetics report tests for two (2) variants in the DPYD gene: *2A and D949V. These variants are found in many ethnicities, at varying allele frequencies.

The allele frequencies in the following table are from the 23andMe database, and may not be representative of the actual allele frequencies in these populations

Allele frequencies in 23andMe customers

Ancestry group	*2A	D949V
European	0.48%	0.55%
African American	0.13%	0.18%
Ashkenazi Jewish	0.55%	0.01%
East Asian	<0.01%	<0.01%
Hispanic/Latino	0.26%	0.43%
South Asian	0.56%	0.06%
Middle Eastern	0.42%	0.09%
Other	0.35%	0.26%

Analytical performance

Accuracy
23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 70 samples with known *2A variant status, and 114 samples with known D949V variant status. All samples passed initial quality control. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence

intervals for the *2A, and D949V variants were 83.9 % to 100%, and 88.1% to 100%, respectively.

Genotype	BeadChip Calls				PPA	NPA	95% CI
	Correct	Incorrect	No Call	FQC[1]			
***2A DPYD CC Homozygous Common**	25	0	0	0	N/A	100	86.3-100
***2A DPYD CT Heterozygous**	24	0	0	0	100	N/A	85.8-100
***2A DPYD TT Homozygous Rare**	21	0	0	0	100	N/A	83.9-100
D949V DPYD TT Homozygous Common	51	0	0	0	N/A	100	93.0-100
D949V DPYD AT Heterozygous	34	0	0	0	100	N/A	89.7-100
D949V DPYD AA Homozygous Rare	29	0	0	0	100	N/A	88.1-100

[1] "FQC" denotes a sample or replicate which failed a quality check and was not analyzed in the study.

Precision/Reproducibility

A precision study was performed to understand the consistency of sample measurements when tested under different conditions.

A total of 475 *2A DPYD replicates from 3 unique samples, and 470 D949V DPYD replicates from 3 unique samples were tested across different testing conditions. 27 replicates did not pass quality control acceptance criteria and were not assigned a genotype. Only sample replicates that passed quality control and produced a genotype for the 23andMe test were included in the calculation for percent agreement.

The precision study yielded greater than 99% correct genotype calls for all samples across all conditions tested. In addition, the study had greater than 99% reproducibility and greater than 99% repeatability.

Minimum DNA input

This study was performed using 1 human cell line sample, and 4 human saliva samples, using 3 lots of reagents. The study yielded 100% concordant test results for all samples at all DNA concentrations tested passing all predefined acceptance criteria. The DNA input required for testing is set at a minimum of 15ng/µL and maximum of 50ng/µL DNA.

Interfering mutations

The performance of this test may be affected by the presence of rare mutations, such as those listed below:

Gene	Variant	Potential Interfering Mutation(s)
DPYD	*2A	rs76551168 rs369990607 rs3918289 rs200296941 rs17376848

Selected References

Caudle KE et al. (2017). "Standardizing terms for clinical pharmacogenetic test results: consensus terms from the Clinical Pharmacogenetics Implementation Consortium (CPIC)." Genet Med. 19(2):215-223.

Whirl-Carrillo M et al. (2012). "Pharmacogenomics knowledge for personalized medicine." Clin Pharmacol Ther. 92(4):414-7.

Additional references included in the test report.

SLCO1B1 Drug Transport

Indications for Use

The 23andMe Personal Genome Service Pharmacogenetics Report for SLCO1B1 is indicated for reporting of the c.521T>C variant in the SLCO1B1 gene. This report is for over-the-counter use by adults over the age of 18, and provides genetic information about processing of therapeutics to inform discussions with a healthcare professional. This report describes if a person has a SLCO1B1 variant associated with processing of some therapeutics and provides interpretive drug information regarding the potential effect of the identified transporter protein function on simvastatin therapy. This test is not a substitute for visits to a healthcare professional. The information provided by this report should not be used to start, stop, or change any course of treatment unless directed by a healthcare professional.

Clinical performance

The peer-reviewed literature supports the association of the variants with the predicted transport function phenotypes.

This test includes the SLCO1B1 c.521T>C variant. This variant represents the most common and best studied SLCO1B1 variant that results in reduced SLCO1B1 transport function.

Allele frequency

This pharmacogenetics report tests for one (1) variant in the SLCO1B1 gene: c.521T>C. This variant is found in many ethnicities, at varying allele frequencies.

The allele frequencies in the following table are from the 23andMe database and may not be representative of the actual allele frequencies in these populations.

Allele frequencies in 23andMe customers

Ancestry group	c.521T>C (rs4149056)
European	15.99%
African American	5.21%
Ashkenazi Jewish	18.37%
East Asian	12.59%
Hispanic/Latino	13.61%
South Asian	5.00%
Middle Eastern	17.75%
Other	14.49%

Analytical performance

Accuracy

23andMe performed method comparison studies using sequencing as the comparator to assess the accuracy of the assay. Results of these tests are presented in the sections below. Only sample replicates that passed quality control and produced a genotype for the 23andMe test were included in the calculations for percent agreement.

Accuracy Test for DEN180028

Results of the test were compared with sequencing results for 101 samples with known c.521T>C variant status. Agreement between the two methods was >99% for all samples analyzed. The overall 95% confidence interval for the c.521T>C variant was 97.1% to 100% (for all c.521T>C genotype combinations).

Accuracy Test for DEN180028

Genotype	BeadChip Calls				PPA	NPA	95% CI[2]
	Correct	Incorrect	No Call	FQC[1]			
c.521T>C SLCO1B1 TT Homozygous Common	45	0	0	0	N/A	100	93.6-100
c.521T>C SLCO1B1 CT Heterozygous	30	0	0	0	100	N/A	90.5-100
c.521T>C SLCO1B1 CC Homozygous Rare	26	0	0	0	100	N/A	89.1-100

[1] "FQC" denotes a sample or replicate which failed a quality check and was not analyzed in the study.

[2] mid-p method

Blinded Sample Collection Accuracy Test
Results of this test were compared to sequencing and reference results for 256 samples of c.521T>C (rs4149056). Agreement between the comparator methods was >99% for all samples analyzed. The overall 95% confidence interval for the c.521T>C (rs4149056) variant was 98.8% to 100% (for all c.521T>C genotype combinations).

Blinded Sampling Accuracy Test

Genotype	BeadChip Calls				PPA	NPA	95% CI[2]
	Correct	Incorrect	No Call	FQC[1]			
c.521T>C SLCO1B1 TT Homozygous Common	176	0	0	0	N/A	100	98.3-100
c.521T>C SLCO1B1 CT Heterozygous	73	0	0	0	100	N/A	96.0-100
c.521T>C SLCO1B1 CC Homozygous Rare	7	0	0	0	100	N/A	65.2-100[3]

[1] "FQC" denotes a sample or replicate which failed a quality check and was not analyzed in the study.
[2] mid-p method
[3] The lower bound confidence interval for this genotype is due to the rarity of the homozygous c.521 CC diplotype frequency.

Precision/Reproducibility

A precision study was performed to understand the consistency of sample measurements when tested under different conditions.

A total of 972 c.521C>T SLCO1B1 replicates from 6 unique samples (including intended use samples for each of the c.521C>T genotype combinations) were tested across different testing conditions. One (1) replicate did not pass quality control acceptance criteria and was not assigned a genotype. Only sample replicates that passed quality control and produced a genotype for the 23andMe test were included in the calculation for percent agreement.

The precision study yielded greater than 99% correct genotype calls for all samples across all conditions tested. In addition, the study had greater than 99% reproducibility and greater than 99% repeatability.

Minimum DNA input

This study was performed using 1 human cell line sample, and 5 human saliva samples (including intended use samples for each of the c.521C>T genotype combinations), using 3 lots of reagents. The study yielded 100% concordant test results for all samples at all DNA concentrations tested passing all predefined acceptance criteria. The DNA input required for testing is set at a minimum of 15ng/µL and maximum of 50ng/µL DNA.

Interfering mutations
It is possible that the presence of rare mutations in a sample, such as those listed here, may interfere with the performance of this test. However, their effect on the performance of this test has not been studied.

Gene	Variant	Potential Interfering Mutation(s)
SLCO1B1	c521T>C (rs4149056)	rs74541382 rs141467543 rs200331427 rs4149057

Selected References
Caudle KE et al. (2017). "Standardizing terms for clinical pharmacogenetic test results: consensus terms from the Clinical Pharmacogenetics Implementation Consortium (CPIC)." Genet Med. 19(2):215-223.

Cooper-DeHoff RM et al. (2022). "The Clinical Pharmacogenetics Implementation Consortium Guideline for SLCO1B1, ABCG2, and CYP2C9 genotypes and Statin-Associated Musculoskeletal Symptoms." Clin Pharmacol Ther. 111(5):1007-1021.

Whirl-Carrillo M et al. (2012). "Pharmacogenomics knowledge for personalized medicine." Clin Pharmacol Ther. 92(4):414-7.

Additional references included in the test report.

Carrier Status Tests

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 Considerations
- 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 healthcare professional. It is recommended that you consult with a healthcare 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.

Other warnings, precautions, and 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
See test-specific information for each test.

Precision/Reproducibility
See test-specific information for each test.

Minimum DNA input
See test-specific information for each test.

Interfering Substances
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 Carrier Status 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
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
Pompe Disease
Primary Hyperoxaluria Type 2
Pyruvate Kinase Deficiency
Rhizomelic Chondrodysplasia Punctata Type 1
Salla Disease
Severe Junctional Epidermolysis Bullosa (LAMB3-related)
Sickle Cell Anemia
Sjögren-Larsson Syndrome
Tay-Sachs Disease
Tyrosinemia Type I
Usher Syndrome Type 1F
Usher Syndrome Type 3A
Zellweger Spectrum Disorder (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

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result "0 Variants Detected"
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, Maharashtrian, 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 Ashkenazi Jewish and Danish descent.

Special considerations

- Severity of symptoms can vary in people with this disorder, even when the same variants are involved.
- Individuals with two copies of the R141H variant have not been observed. This is likely because having two copies of this variant is not compatible with life [Shi et al., 2017]. Thus, if two individuals both carrying only the R141H variant have children, it is not expected that these children would be at risk for PMM2-CDG.
- 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, Danish and Dutch descent. About 1 in 61 people (1.64%) of Ashkenazi Jewish descent, 1 in 53 people (1.89%) of Danish descent and 1 in 46 people (2.17%) 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 90% of carriers of Ashkenazi Jewish descent, 89% of carriers of Danish descent and 58% 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"
Ashkenazi Jewish	90%	1 in 61	1 in 600
Danish	89%	1 in 53	1 in 470
Dutch	58%	1 in 46	1 in 110
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.

Shi L et al. (2017). "Comprehensive population screening in the Ashkenazi Jewish population for recurrent disease-causing variants." Clin Genet. 91(4):599-604.

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%
Deltal507	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%

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

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

Committee on Genetics. (2017). "Committee Opinion No. 691: Carrier Screening for Genetic Conditions." Obstet Gynecol. 129(3):e41-e55.

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 ELP1 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 ELP1 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.

Accuracy23andMe 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.
- ACOG notes that carrier 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	Middle Eastern
F1388del	<0.01%	0.00%	0.13%	0.00%	<0.01%	0.00%	0.00%
3992-9G>A	0.04%	0.01%	1.33%	0.00%	0.02%	0.00%	<0.06%
V187D	<0.01%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%

This test is expected to detect about 97% of carriers of Ashkenazi Jewish descent and 41% of carriers of Finnish 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 80	1 in 130
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.

Minimum DNA Input
A minimum DNA input study was performed using 9 saliva samples, with three lots of reagents. The study yielded concordant test results for all samples with a DNA concentration of 15 ng/µL.

Interfering Mutations
The performance of this test may be affected by the presence of rare mutations, such as those listed below:

Gene	Variant name	Potential Interfering Mutation(s)
ABCC8	F1388del	rs75218493 rs562677120 rs574684578 rs541612031
ABCC8	3992-9G>A	rs373737642 rs187475578 rs199502011 rs371185111 rs552324811
ABCC8	V187D	rs145986097 rs201051671 rs2301703 rs151211613 rs559259981

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.

Männistö JME et al. (2021). "Long-Term Outcome and Treatment in Persistent and Transient Congenital Hyperinsulinism: A Finnish Population-Based Study." J Clin Endocrinol Metab. 106(4):e1542-e1551.

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	Middle Eastern
M680I	0.01%	0.01%	0.00%	0.00%	0.01%	0.00%	1.19%
M694I	0.01%	0.01%	0.00%	0.01%	0.06%	0.00%	0.51%
M694V	0.03%	0.04%	0.01%	0.00%	0.08%	0.00%	2.31%
K695R	1.19%	0.16%	2.25%	0.00%	0.63%	0.00%	0.64%
V726A	0.26%	0.09%	7.61%	0.01%	0.25%	0.05%	4.94%
A744S	0.40%	0.24%	2.46%	0.05%	0.72%	0.05%	2.35%
R761H	0.02%	0.02%	0.00%	0.20%	0.03%	0.06%	0.39%

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 72-92% 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

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result "0 Variants Detected"
Turkish	72-92%	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 1,013 samples 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.

Minimum DNA Input

Minimum DNA input studies were performed using one human cell line sample and nine (9) saliva samples, with three lots of reagents. The study yielded concordant test results for all samples with a DNA concentration of 15 ng/µL.

Interfering Mutations

The performance of this test may be affected by the presence of rare mutations, such as those listed below:

Gene	Variant name	Potential Interfering Mutation(s)
MEFV	M680I	rs104895094 rs61752717 rs566082564 rs534682649
MEFV	M694I	rs200375017 rs2234939 rs202174893 rs104895094 rs61752717 rs566082564 rs534682649
MEFV	M694V	rs200375017 rs2234939 rs202174893

Gene	Variant name	Potential Interfering Mutation(s)
		rs104895094 rs566082564 rs534682649
MEFV	K695R	rs200375017 rs2234939 rs202174893 rs61752717 rs566082564 rs534682649
MEFV	V726A	rs11466047 rs199927442 rs139092123
MEFV	A744S	rs199927442 rs139092123 rs104895194
MEFV	R761H	rs104895194

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." [Accessed Aug 11, 2021].

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 1

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 nine 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.

Interfering Mutations
The performance of this test may be affected by the presence of rare mutations, such as those listed below:

Gene	Variant name	Potential Interfering Mutation(s)
GBA	N370S	rs111417507 rs28559737 rs187143994
GBA	84GG	rs143187997 rs150466109 rs104886460
GBA	V394L	rs149171124 rs201499639 rs187143994

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. However, ACOG notes that testing for glycogen storage disease type I 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 71 people (1.41%) 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 71	1 in 3,500
Other ethnicities*	Unknown	Unknown	Unknown

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

Accuracy23andMe 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.

Committee on Genetics. (2017). "Committee Opinion No. 690: Carrier Screening in the Age of Genomic Medicine." Obstet Gynecol. 129(3):e35-e40.

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. However, ACOG notes that testing for glycogen storage disease type I may be considered for people of Ashkenazi Jewish descent who are considering having children.

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_1043delCT	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, 39% of carriers of Serbian 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"
Japanese	42%	Unknown	Unknown
Serbian	39%	Unknown	Unknown
European	31%	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.

Skakic A et al. (2018). "Genetic characterization of GSD I in Serbian population revealed unexpectedly high incidence of GSD Ib and 3 novel SLC37A4 variants." Clin Genet. 93(2):350-355.

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.

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. However, ACOG notes that testing for maple syrup urine disease may be considered for people of Ashkenazi Jewish descent who are considering having children.

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

- ACMG recommends that people of all ethnicities who are considering having children should be offered carrier screening for MCAD deficiency.

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	Middle Eastern
c.985A>G	1.35%	0.41%	0.13%	<0.01%	0.63%	0.05%	0.11%
c.199T>C	0.17%	0.05%	0.00%	0.00%	0.05%	0.00%	0.01%
c.616C>T	0.01%	<0.01%	0.01%	<0.01%	0.01%	0.02%	0.01%
c.734C>T	0.01%	<0.01%	0.00%	0.00%	0.01%	0.00%	0.01%

This test is expected to detect 80% 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	80%	1 in 61	1 in 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 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
Arnold GL et al. (2010). "Lack of genotype-phenotype correlations and outcome in MCAD deficiency diagnosed by newborn screening in New York State." Mol Genet Metab. 99(3):263-8.

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.

Gregg AR et al. (2021). "Screening for autosomal recessive and X-linked conditions during pregnancy and preconception: a practice resource of the American College of Medical Genetics and Genomics (ACMG)." Genet Med. 23(10):1793-1806.

Jager EA et al. (2019). "A nationwide retrospective observational study of population newborn screening for medium-chain acyl-CoA dehydrogenase (MCAD) deficiency in the Netherlands." J Inherit Metab Dis. 42(5):890-897.

Rücklová K et al. (2021). "Impact of Newborn Screening and Early Dietary Management on Clinical Outcome of Patients with Long Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency and Medium Chain Acyl-CoA Dehydrogenase Deficiency-A Retrospective Nationwide Study." Nutrients. 13(9).

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	<0.01%	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." [Updated 2013 Aug 1].

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." [Updated 2013 Aug 1].

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 8 variants in the GJB2 gene. This test is intended to be used to determine carrier status for DFNB1 in adults. This report also describes if a result is associated with personal risk of having hearing loss related to DFNB1, but it does not describe a person's overall risk of having DFNB1-related hearing loss. The test is relevant for people of many ethnicities.

Special considerations

- The degree of hearing loss can vary, but there are no other symptoms associated with this condition.
- Some of the variants included in this report — including M34T and V37I — tend to be associated with milder hearing loss. In addition, some people with two GJB2 variants do not have any noticeable hearing loss.
- 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.
- ACMG recommends that people of all ethnicities who are considering having children should be offered carrier screening for DFNB1.

Clinical performance

The variants covered by this test are common in people of many ethnicities.

Frequency of GJB2 variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian	Middle Eastern
c.35delG	1.87%	0.55%	0.81%	0.01%	1.39%	0.06%	1.25%
W24X	0.01%	0.01%	0.00%	0.02%	0.01%	1.24%	0.03%
M34T	2.54%	0.79%	1.82%	<0.01%	1.65%	0.00%	0.09%
V37I	0.25%	0.31%	1.36%	13.50%	0.72%	0.03%	0.20%
c.167delT	0.08%	0.02%	3.26%	0.00%	0.08%	0.00%	0.07%
c.235delC	0.01%	0.01%	<0.02%	1.25%	0.02%	<0.02%	0.02%
S139N	0.13%	0.04%	0.07%	0.02%	0.05%	0.00%	<0.02%

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian	Middle Eastern
R143W	0.01%	0.11%	0.00%	0.04%	0.05%	0.01%	<0.02%

Carrier frequencies for DFNB1 and carrier detection rates for the 23andMe PGS Carrier Status Test for DFNB1

	Carrier frequency	Carrier detection rate for this test
Ashkenazi Jewish	1 in 20	93%
East/Southeast Asian	Up to 1 in 4	75-99%
European	1 in 20	75-98%
Ghanaian	Unknown	91%
Hispanic/Latino	Unknown	51-99%
Northern African/Middle Eastern	Unknown	74-99%
South Asian	Unknown	48-92%
Other ethnicities*	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 516 samples with known variant status. The method comparison study yielded >99% overall agreement for all genotypes for all samples tested, passing the predefined acceptance criteria of at least 99% PPA and 99% NPA. The comprehensive 95% confidence interval for the total number of samples tested was 99.4% to 100.0%. The widest confidence interval was 36.8% to 100.0% for the 3 homozygous rare GJB2 S139N samples.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 4,164 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 22 saliva samples, with three lots of reagents. The study yielded concordant test results for all samples with a DNA concentration of 15 ng/µL.

Interfering Mutations

The performance of this test may be affected by the presence of rare mutations, such as those listed below:

Gene	Variant Name	Potential Interfering Mutation(s)
GJB2	c.35delG	rs2274084 rs104894396 rs80338939 rs104894408 rs529500747 rs111033222 rs148136545 rs72561725
GJB2	W24X	rs561870637 rs72474224 rs35887622 rs564084861 rs2274084 rs80338939 rs104894408 rs529500747
GJB2	M34T	rs104894407 rs535635403 rs561870637 rs72474224 rs564084861 rs2274084 rs104894396
GJB2	V37I	rs104894407 rs535635403 rs561870637 rs35887622 rs564084861 rs2274084 rs104894396
GJB2	c.167delT	rs200023879 rs104894407 rs535635403 rs561870637
GJB2	c.235delC	rs111033299 rs139362103 rs111033218 rs199883710 rs80338943 rs80338944

Gene	Variant Name	Potential Interfering Mutation(s)
		rs200023879
GJB2	S139N	rs111033186 rs80338948 rs116769964 rs111033196 rs397516874 rs111033188
GJB2	R143W	rs111033186 rs116769964 rs76434661 rs111033196

Selected References

Chan OYM et al. (2021). "Expanded carrier screening using next-generation sequencing of 123 Hong Kong Chinese families: a pilot study." Hong Kong Med J.

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.

Green GE et al. (1999). "Carrier rates in the midwestern United States for GJB2 mutations causing inherited deafness." JAMA. 281(23):2211-6.

Gregg AR et al. (2021). "Screening for autosomal recessive and X-linked conditions during pregnancy and preconception: a practice resource of the American College of Medical Genetics and Genomics (ACMG)." Genet Med. 23(10):1793-1806.

Hall A et al. (2012). "Prevalence and audiological features in carriers of GJB2 mutations, c.35delG and c.101T>C (p.M34T), in a UK population study." BMJ Open. 2(4).

Hwa HL et al. (2003). "Mutation spectrum of the connexin 26 (GJB2) gene in Taiwanese patients with prelingual deafness." Genet Med. 5(3):161-5.

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.

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.

Wattanasirichaigoon D et al. (2004). "High prevalence of V37I genetic variant in the connexin-26 (GJB2) gene among non-syndromic hearing-impaired and control Thai individuals." Clin Genet. 66(5):452-60.

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), 35-45% of carriers of Japanese descent, and 9% of carriers of Chinese 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
Chinese	9%	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.

Zhao S et al. (2019). "Pilot study of expanded carrier screening for 11 recessive diseases in China: results from 10,476 ethnically diverse couples." Eur J Hum Genet. 27(2):254-262.

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 28 people (3.57%) of Chinese 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 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%

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
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, 29% of carriers of Chinese descent, and 20% of carriers of Korean descent for this condition. This test is also expected to detect between 63-96% of carriers of Eastern European descent, 46-87% of carriers of Western European descent, and 32-85% of carriers of Southern 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	29%	1 in 28	1 in 39
Korean	20%	1 in 50	1 in 62
Japanese	42%	1 in 200	1 in 340
Eastern European	63-96%	Unknown	Unknown
Western European	46-87%	Unknown	Unknown
Southern European	32-85%	Unknown	Unknown

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result "0 Variants Detected"
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." [Accessed Nov 1, 2018].

Zschocke J. (2003). "Phenylketonuria mutations in Europe." Hum Mutat. 21(4):345-56.
Zhao S et al. (2019). "Pilot study of expanded carrier screening for 11 recessive diseases in China: results from 10,476 ethnically diverse couples." Eur J Hum Genet. 27(2):254-262.

Additional references included in the report.

Pompe Disease

Indications for Use
The 23andMe PGS Carrier Status Test for Pompe Disease is indicated for the detection of five variants in the GAA gene. This test is intended to be used to determine carrier status for Pompe disease in adults. This report also describes if a result is associated with personal risk of developing symptoms of Pompe disease, but it does not describe a

person's overall risk of developing symptoms. This test includes variants that are most common in people of African/African American and European descent.

Special considerations

- The severity of symptoms, and when they develop, can vary greatly in people with Pompe disease. For example, certain combinations of genetic variants, including two copies of the c.-32-13T>G variant included in this report, tend to be associated with milder symptoms and later disease onset. On the other hand, some combinations of genetic variants included in this report tend to be associated with faster progression and more severe symptoms.
- ACMG recommends that people of all ethnicities who are considering having children should be offered carrier screening for Pompe disease.

Clinical performance

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

Frequency of GAA variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian	Middle Eastern
c.-32-13T>G	1.16%	0.38%	1.25%	0.02%	0.71%	0.24%	0.46%
c.307T>G	0.01%	<0.01%	0.00%	0.00%	<0.01%	0.00%	0.00%
c.525delT	0.04%	0.03%	<0.01%	<0.01%	0.02%	0.00%	0.00%
c.1548G>A	0.01%	<0.01%	0.00%	<0.01%	<0.01%	0.00%	0.00%
c.2560C>T	<0.01%	0.30%	0.00%	<0.01%	0.02%	<0.02%	<0.02%

This test is expected to detect the majority of Pompe carriers of African/African American descent and about half of Pompe carriers of European descent and in the general U.S. population. It is not expected to detect most Pompe carriers of East Asian descent.

Carrier frequencies for Pompe disease and carrier detection rates for the 23andMe PGS Carrier Status Test for Pompe Disease

	Carrier frequency	Carrier detection rate for this test
African/African American	Up to 1 in 60	70%
East Asian	1 in 56	<1%
European	1 in 59	52%

General U.S. population	1 in 51 to 1 in 80	54%
Other ethnicities*	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 213 samples with known variant status. The method comparison study yielded >99% overall agreement for all genotypes for all samples tested, passing the predefined acceptance criteria of at least 99% PPA and 99% NPA. The comprehensive 95% confidence interval for the total number of samples tested was 98.6% to 100.0%. The widest confidence interval was 60.7% to 100.0% for certain heterozygous samples.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 2,423 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 15 saliva samples, with three lots of reagents. The study yielded concordant test results for all samples with a DNA concentration of 15 ng/µL.

Interfering Mutations

The performance of this test may be affected by the presence of rare mutations, such as those listed below:

Gene	Variant Name	Potential Interfering Mutation(s)
GAA	c.-32-13T>G	rs202165487
		rs560511228
GAA	c.307T>G	rs2229222
		rs146615896
		rs534192892
		rs1800299

Gene	Variant Name	Potential Interfering Mutation(s)
		rs373307393
		rs151323405
		rs1800300
		rs574947353
GAA	c.525delT	rs564758226
		rs143523371
		rs550618589
		rs200107080
		rs529918753
		rs190153982
GAA	c.1548G>A	rs143491365
		rs566096057
		rs115427918
GAA	c.2560C>T	rs1042397
		rs17853996
		rs61736894

Selected References

Becker JA et al. (1998). "The African origin of the common mutation in African American patients with glycogen-storage disease type II." Am J Hum Genet. 62(4):991-4.

Kishnani PS et al. (2006). "Pompe disease diagnosis and management guideline." Genet

Med. 8(5):267-88.

Leslie N et al. (2007). "Pompe Disease." [Accessed Feb 1, 2022].

Park KS. (2021). "Carrier frequency and predicted genetic prevalence of Pompe disease based on a general population database." Mol Genet Metab Rep. 27:100734.

Reuser AJJ et al. (2019). "GAA variants and phenotypes among 1,079 patients with Pompe disease: Data from the Pompe Registry." Hum Mutat. 40(11):2146-2164.

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.

Pyruvate Kinase Deficiency

Indications for Use

The 23andMe PGS Carrier Status Test for Pyruvate Kinase Deficiency is indicated for the detection of the R486W variant in the PKLR gene. This test is intended to be used to determine carrier status for PK deficiency in adults. This report also describes if a result is associated with personal risk of developing symptoms of PK deficiency, but it does not describe a person's overall risk of developing symptoms.

Special considerations

- Symptoms of PK deficiency may vary widely among people with the condition.
- This test does not include the majority of PKLR variants that cause PK deficiency in any ethnicity.
- There are currently no professional guidelines in the U.S. for carrier testing for this condition.

Clinical performance

This test does not include the majority of PKLR variants that cause PK deficiency in any ethnicity.

Frequency of PKLR variants in 23andMe customers

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

R486W	0.61%	0.22%	0.55%	0.01%	0.58%	0.74%	1.81%

This test is expected to detect 26-35% of carriers of Southern European descent and 8-17% of carriers of Northern, Western, and Central European descent for this condition, depending on country or region of ancestry. This test is expected to detect less than 10% of carriers of other ethnicities.

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

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result "0 Variants Detected"
Southern European	26-35%	Unknown	Unknown
Northern, Western, and Central European	8-17%	Unknown	Unknown
Other ethnicities	<10%	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 78 samples with known variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 95.4% to 100.0%.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 648 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 4 saliva samples, with three lots of reagents. The study yielded concordant test results for all samples with a DNA concentration of 15 ng/µL.

Interfering Mutations

The performance of this test may be affected by the presence of rare mutations, such as those listed below:

Gene	Variant Name	Potential Interfering Mutation(s)
PKLR	R486W	rs551883218 rs200133000

Selected References

Bianchi P et al. (2020). "Genotype-phenotype correlation and molecular heterogeneity in pyruvate kinase deficiency." Am J Hematol. 95(5):472-482.

Lenzner C et al. (1997). "Molecular analysis of 29 pyruvate kinase-deficient patients from central Europe with hereditary hemolytic anemia." Blood. 89(5):1793-9.

Manco L et al. (1999). "PK-LR gene mutations in pyruvate kinase deficient Portuguese patients." Br J Haematol. 105(3):591-5.

Manco L et al. (2000). "A new PKLR gene mutation in the R-type promoter region affects the gene transcription causing pyruvate kinase deficiency." Br J Haematol. 110(4):993-7.

Zanella A et al. (1997). "Molecular characterization of PK-LR gene in pyruvate kinase-deficient Italian patients." Blood. 89(10):3847-52.

Zanella A et al. (2001). "Molecular characterization of the PK-LR gene in sixteen pyruvate kinase-deficient patients." Br J Haematol. 113(1):43-8.

Zarza R et al. (1998). "Molecular characterization of the PK-LR gene in pyruvate kinase deficient Spanish patients. Red Cell Pathology Group of the Spanish Society of Haematology (AEHH)." Br J Haematol. 103(2):377-82.

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.

Severe Junctional Epidermolysis Bullosa (LAMB3-related)

Indications for Use

The 23andMe PGS Carrier Status Test for Severe Junctional Epidermolysis Bullosa (LAMB3-Related) is indicated for the detection of 3 variants in the LAMB3 gene. This test is intended to be used to determine carrier status for LAMB3-related 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 LAMB3-related 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	<0.01%	<0.01%	0.00%	0.00%	0.01%	0.00%

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 LAMB3-related 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.

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. This report also describes if a result is associated with personal risk of developing symptoms of sickle cell anemia, but it does not describe a person's overall risk of developing symptoms. The test is most relevant for people of African descent. It is also relevant for people of Middle Eastern and South Asian descent, as well as people from the Caribbean, the Mediterranean, and parts of Central and South America.

Special considerations

- ACMG and ACOG recommend that people of all ethnicities who are considering having children should be offered carrier screening for hemoglobinopathies such as sickle cell anemia.

Clinical performance

Although the HbS variant covered by this test can be found worldwide, it is most common in people of African descent. This variant is also found in people of Middle Eastern and South Asian descent, as well as people from the Caribbean, the Mediterranean, and parts of Central and South America.

Frequency of the HbS variant in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian	Middle Eastern
HbS	0.03%	7.15%	0.00%	<0.01%	0.71%	0.16%	0.26%

Carrier frequencies for sickle cell anemia and carrier detection rates for the 23andMe PGS Carrier Status Test for Sickle Cell Anemia

	Carrier frequency	Carrier detection rate for this test
Worldwide	Varies by ancestry	>99%*
African American	About 1 in 13	>99%*

*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 for the total number of samples tested was 99.1% to 100.0%.

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 615 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 4 saliva samples, with three lots of reagents. The study yielded concordant test results for all samples with a DNA concentration of 15 ng/µL.

Interfering Mutations

The performance of this test may be affected by the presence of rare mutations, such as those listed below:

Gene	Variant Name	Potential Interfering Mutation(s)
HBB	HbS	rs33986703
		rs63750783
		rs33930165

Gene	Variant Name	Potential Interfering Mutation(s)
		rs33912272
		rs713040
		rs113115948

Selected References

American College of Obstetricians and Gynecologists. (2022). "Practice Advisory: Hemoglobinopathies in Pregnancy." Retrieved Oct 11, 2022, from https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2022/08/hemoglobinopathies-in-pregnancy

Bender MA et al. (2003). "Sickle Cell Disease." [Accessed Oct 11, 2022].

Gregg AR et al. (2021). "Screening for autosomal recessive and X-linked conditions during pregnancy and preconception: a practice resource of the American College of Medical Genetics and Genomics (ACMG)." Genet Med. 23(10):81793-1806.

Piel FB et al. (2013). "Global epidemiology of sickle haemoglobin in neonates: a contemporary geostatistical model-based map and population estimates." Lancet. 381(9861):142-51.

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 and ACOG for people of Ashkenazi Jewish descent considering having children. This test includes the 3 variants recommended for testing by ACMG. In addition, ACOG recommends offering carrier testing for Tay-Sachs disease to individuals of Cajun and French Canadian descent who are considering having children.
- 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

Committee on Genetics. (2017). "Committee Opinion No. 690: Carrier Screening in the Age of Genomic Medicine." Obstet Gynecol. 129(3):e35-e40.

Committee on Genetics. (2017). "Committee Opinion No. 691: Carrier Screening for Genetic Conditions." Obstet Gynecol. 129(3):e41-e55.

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. However, ACOG notes that testing for Usher syndrome 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 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. However, ACOG notes that testing for Usher syndrome 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 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 Spectrum Disorder (PEX1-Related)

Indications for Use

The 23andMe PGS Carrier Status Test for Zellweger Spectrum Disorder (PEX1-related ZSD) 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 ZSD 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 ZSD 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	Middle Eastern
G843D	0.14%	0.04%	0.01%	0.00%	0.07%	0.01%	0.02%

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 ZSD

	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). "Zellweger Spectrum Disorder." [Accessed Oct 5, 2021].

Additional references included in the report.

References

Data on file at 23andMe, South San Francisco, 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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BeadChip: v5.0
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.

PI Part Number: VV-QUAL-07687
PI Version: 18.0
PI Revision Date: January 2024

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