

23andMe® Personal Genome Service® (PGS)
Package Insert



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.

Warnings

- 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

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

All test results demonstrated at least 99% agreement with sequencing and passed all pre-defined acceptance criteria.

Precision/Reproducibility

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

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

All test results demonstrated at least 99% agreement between replicates and passed all pre-defined acceptance criteria.

Minimum DNA Input

A minimum DNA input study was performed to understand the lowest concentration of DNA needed for at least 95% concordant test results. The study yielded concordant test results for samples with a DNA concentration of 15 ng/ μ L and passed all acceptance criteria.

See test-specific information for Accuracy, Precision/Reproducibility, and Minimum DNA Input study details for each test.

Interferences

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 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 6 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 rs573331706 and rs369496377 for Y402H, or rs532010317 for A69S.

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 5 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 rs148362959, rs533419579, rs551595739, rs201774333, rs143370956, rs1131139, rs200945035, rs373630097, and rs9630 for PI*Z, or rs538675821, rs550592374, rs141095970, rs149537225, rs1049800, and rs2230075 for PI*S.

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.

Interfering Mutations

The performance of this test may be affected by the presence of rare mutations, such as rs373744062, rs34481484, rs535725525, rs116178934, rs118073417, and rs9272482 for HLA-DQ2.5 (rs2187668), or rs575617446, rs182610396, rs564828053, rs2647088, and rs3957146 for HLA-DQ8 (rs7454108).

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 two human cell line samples 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/ μ L.

Interfering Mutations

The performance of this test may be affected by the presence of rare mutations, such as rs139583750, rs16996616, rs373409702, rs143845266, and rs151114491 for S342G (G1), and rs201657348, rs60910145, rs190804942, rs143830837, rs185040686, and rs189551092 for N388_Y389del (G2).

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% |
| 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 | 0.01% | <0.01% | 0.00% | 0.00% | <0.01% | 0.00% | 0.01% |

| | | | | | | | |
|--------------|--------|--------|-------|--------|--------|-------|-------|
| (LDLR) | | | | | | | |
| 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 (LDLR) | <0.01% | <0.01% | 0.00% | <0.01% | <0.01% | 0.01% | 0.01% |

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 |
| | 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 rs138687036 for V68M, or rs137852330, rs200626353, and rs200111236 for S188F.

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.

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, and in people of West African, Portuguese, Northern Swedish, Japanese, Irish, and British descent. Published studies estimate that approximately 50-80% 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 rs28933981, rs2276382, rs557320637, rs536294863, rs3700056601, rs1269882546, rs572856125, and rs12226 for V122I. No interfering mutations were identified for either V30M or T60A.

Selected References

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

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

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 |
|--------------|----------|------------------|------------------|------------|--------------------|-------------|
| C282Y | 12.1% | 3.9% | 2.4% | 0.0% | 6.9% | 0.3% |
| H63D | 27.7% | 9.8% | 22.4% | 6.2% | 24.5% | 17.5% |

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 6 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 rs140080192 and rs143175221 for C282Y, or rs28934889, rs147297176, rs147426902, rs556335391, and rs62625342 for H63D.

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 under certain circumstances. This test includes the two variants recommended for testing by ACMG. Refer to the ACMG 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 5 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 1689G>A and 1692A>C for Factor V Leiden, or 20207A>C for Prothrombin G20210A>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 |
|--------------|----------|------------------|------------------|------------|--------------------|-------------|
| ε4 | 26.02% | 34.10% | 21.84% | 17.39% | 22.44% | 17.16% |

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 rs11542041, rs573658040, or rs543363163.

Selected References

Alzheimer's Association. (2020). "2020 Alzheimer's Disease Facts and Figures." *Alzheimers Dement.* 16(3):391+.

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 4 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 rs150219613 and rs183394865 for G2019S, or rs187143994 and rs111417507 for N370S.

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.

BRCA1/BRCA2 (Selected Variants)

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 BRCA1/BRCA2 (Selected Variants). The 23andMe PGS Genetic Health Risk Report for BRCA1/BRCA2

(Selected Variants) is indicated for reporting of the 185delAG and 5382insC variants in the BRCA1 gene and the 6174delT variant in the BRCA2 gene. The report describes if a woman is at increased risk of developing breast and ovarian cancer, and if a man is at increased risk of developing breast cancer or may be at increased risk of developing prostate cancer. The three variants included in this report are most common in people of Ashkenazi Jewish descent and do not represent the majority of the BRCA1/BRCA2 variants in the general population. 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.

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.](#)

Important

- 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 three variants that are most common in people of Ashkenazi Jewish descent.
- This test does not test for all possible variants in the BRCA1 and BRCA2 genes. More

than 1,000 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.

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/>)

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 test were compared with sequencing results for 71 samples with known 185delAG variant status, 49 samples with known 5382insC status, and 47 samples with known 6174delT 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 >99% overall agreement for all genotypes for all samples tested, passing the predefined acceptance criteria of at least 99% PPA and 99% NPA. The 95% confidence interval was 83.9% to 100%.

| Genotype | BeadChip Calls | | | | % PPA | % NPA | 95% CI |
|--|----------------|-----------|---------|------------------|-------|-------|----------|
| | Correct | Incorrect | No Call | FQC ¹ | | | |
| BRCA1 185delAG Homozygous common | 50 | 0 | 0 | 4 | 100 | 100 | 92.9-100 |
| BRCA1 185delAG Heterozygous | 21 | 0 | 0 | 4 | 100 | 100 | 83.9-100 |
| BRCA1 5382insC Homozygous common | 23 | 0 | 0 | 2 | 100 | 100 | 85.2-100 |
| BRCA1 5382insC Heterozygous | 26 | 0 | 0 | 1 | 100 | 100 | 86.8-100 |
| BRCA2 6174delT Homozygous common | 25 | 0 | 0 | 0 | 100 | 100 | 86.3-100 |
| BRCA2 6174delT Heterozygous | 22 | 0 | 0 | 4 | 100 | 100 | 84.6-100 |

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

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 69 185delAG replicates from 2 unique samples, 67 5382insC replicates from 2 unique samples, and 67 6174delT replicates from 2 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 6 human cell line 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

It is possible that the presence of the following variants in a sample may interfere with the performance of this test.

185delAG: rs528170710, rs540373654, rs80357134, rs528902306, rs149402012

5382insC: rs371203180, rs571834423

6174delT: rs556893517, rs148618542, rs80358833, rs554663691

The effects of these variants 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 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

The variants covered by this test are mainly found in people of Ashkenazi Jewish descent. Published studies estimate that 1.05% of people of Ashkenazi Jewish descent carry one copy of the 185delAG variant, 0.11% carry one copy of the 5382insC variant, and 1.36% of people carry one copy of the 6174delT variant.

Frequency of BRCA1 and BRCA2 variants in 23andMe customers

| Variant name | European | African American | Ashkenazi Jewish | East Asian | Hispanic or Latino | South Asian |
|--------------|----------|------------------|------------------|------------|--------------------|-------------|
| 185delAG | 0.03% | <0.02% | 0.89% | 0.00% | 0.04% | 0.10% |
| 5382insC | 0.03% | <0.02% | 0.20% | 0.00% | 0.01% | 0.00% |
| 6174delT | 0.03% | <0.02% | 1.03% | 0.00% | 0.01% | 0.00% |

References

Tonin P et al. (1996). "Frequency of recurrent BRCA1 and BRCA2 mutations in Ashkenazi Jewish breast cancer families." *Nat Med.* 2(11):1179-83.

Data on file at 23andMe, Inc., Sunnyvale, CA

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.

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 7-33%. Your genetic results are returned to you in a secure online account on the 23andMe website.

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.

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/>)

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 ² | | | |
| MUTYH Y179C Homozygous common | 25 | 0 | 0 | 0 | 100 | 100 | 86.3-100 |
| MUTYH Y179C Heterozygous | 26 | 0 | 0 | 0 | 100 | 100 | 86.8-100 |
| MUTYH Y179C Homozygous rare | 14 | 0 | 0 | 1 | 100 | 100 | 76.8-100 |
| MUTYH G396D Homozygous common | 26 | 0 | 0 | 0 | 100 | 100 | 86.8-100 |
| MUTYH G396D | 27 | 0 | 0 | 0 | 100 | 100 | 87.2-100 |

² "FQC" denotes a sample or replicate which failed a quality check and was not analyzed in the study.

| | | | | | | | |
|---|----|---|---|---|-----|-----|----------|
| Heterozygous | | | | | | | |
| MUTYH G396D Homozygous rare | 25 | 0 | 0 | 0 | 100 | 100 | 86.3-100 |

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 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 2 human cell line samples 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.

Nielsen M et al. (2012). "*MUTYH*-Associated Polyposis." [Updated 2017 Sep 24].

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., Sunnyvale, CA

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 | *5 |

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 reports for DPYD and SLCO1B1 describe if a person has variants associated with metabolism of some therapeutics, but do not describe if a person will or will not respond to a particular therapeutic, and do 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.

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 metabolism 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 and SLCO1B1

- 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 only CYP2C19

- 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.
- 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.
- 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

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

All test results demonstrated at least 99% agreement with sequencing and passed all pre-defined acceptance criteria.

Precision/Reproducibility

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

All test results demonstrated at least 99% agreement between replicates and passed all pre-defined acceptance criteria.

Minimum DNA Input

A minimum DNA input study was performed to understand the lowest concentration of DNA needed for at least 95% concordant test results. The study yielded concordant test results for samples with a DNA concentration of 15 ng/μL and passed all acceptance criteria.

See test-specific information for Accuracy, Precision/Reproducibility, and Minimum DNA Input study details 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 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 | 100% | 100% | 92.5% to 100% |

| | | | | | | | | |
|-------------------|-----------------------|----|---|---|---|------|------|---------------|
| | CYP2C19 *2 AG | 49 | 0 | 0 | 0 | 100% | 100% | 92.7% to 100% |
| | CYP2C19 *2 AA | 49 | 0 | 0 | 3 | 100% | 100% | 92.7% to 100% |
| rs4986893 | CYP2C19 *3 GG | 48 | 0 | 0 | 2 | 100% | 100% | 92.6% to 100% |
| | CYP2C19 *3 AG | 45 | 0 | 0 | 3 | 100% | 100% | 92.1% to 100% |
| | CYP2C19 *3 AA | 39 | 0 | 0 | 1 | 100% | 100% | 91.0% to 100% |
| rs12248560 | CYP2C19 *17 CC | 49 | 0 | 0 | 1 | 100% | 100% | 92.7% to 100% |
| | CYP2C19 *17 CT | 45 | 0 | 0 | 4 | 100% | 100% | 92.1% to 100% |
| | CYP2C19 *17 TT | 47 | 0 | 0 | 0 | 100% | 100% | 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 | 100% | 100% | 98.8% to 100% |
| | CYP2C19 *2 AG | 130 [^] | 0 | 0 | 0 | 100% | 100% | 97.2% to 100% |
| | CYP2C19 *2 AA | 22 [^] | 0 | 0 | 0 | 100% | 100% | 84.6% to 100% |
| rs4986893 | CYP2C19 *3 GG | 432 | 0 | 0 | 0 | 100% | 100% | 99.2% to 100% |

| | | | | | | | | |
|-------------------|-----------------------|------------------|---|---|---|------|------|---------------|
| | CYP2C19 *3 AG | 6 [^] | 0 | 0 | 0 | 100% | 100% | 54.1% to 100% |
| | CYP2C19 *3 AA | 0 | 0 | 0 | 0 | N/A | N/A | N/A |
| rs12248560 | CYP2C19 *17 CC | 279 | 0 | 0 | 0 | 100% | 100% | 98.7% to 100% |
| | CYP2C19 *17 CT | 140 [^] | 0 | 0 | 0 | 100% | 100% | 97.4% to 100% |
| | CYP2C19 *17 TT | 25 [^] | 0 | 0 | 0 | 100% | 100% | 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 | 100% | 100% | 96.8% to 100% |
| | CYP2C19 *2 AG | 91 | 0 | 0 | 0 | 100% | 100% | 96.0% to 100% |
| | CYP2C19 *2 AA | 24 | 0 | 0 | 0 | 100% | 100% | 85.8% to 100% |
| rs4986893 | CYP2C19 *3 GG | 197 | 0 | 0 | 0 | 100% | 100% | 98.1% to 100% |
| | CYP2C19 *3 AG | 31 | 0 | 0 | 0 | 100% | 100% | 88.8% to 100% |
| | CYP2C19 *3 AA | 3 | 0 | 0 | 0 | 100% | 100% | 29.2% to 100% |
| rs12248560 | CYP2C19 *17 CC | 228 | 0 | 0 | 0 | 100% | 100% | 94.8% to 100% |
| | CYP2C19 *17 CT | 2 | 0 | 0 | 0 | 100% | 100% | 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 here.

*2: rs566311971, rs879130837

*3: rs186489608, rs200936950, rs191690054, rs200025269

*17: rs576566073, rs545523674, rs540392908, rs17880036, rs1158729, rs1262360236, rs561205449, rs185375194

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.
- 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.

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 | 100 | 100 | 86.3-100 |
| *2A DPYD CT Heterozygous | 24 | 0 | 0 | 0 | 100 | 100 | 85.8-100 |
| *2A DPYD TT Homozygous Rare | 21 | 0 | 0 | 0 | 100 | 100 | 83.9-100 |
| D949V DPYD TT Homozygous Common | 51 | 0 | 0 | 0 | 100 | 100 | 93.0-1000 |
| D949V DPYD AT Heterozygous | 34 | 0 | 0 | 0 | 100 | 100 | 89.7-100 |
| D949V DPYD AA Homozygous Rare | 29 | 0 | 0 | 0 | 100 | 100 | 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 here.

*2A (rs3918290): 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.

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 to inform discussions with a healthcare professional about processing of therapeutics. This report describes if a person has a SLCO1B1 variant 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 the detected variant 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.

This test includes the SLCO1B1 c.521T>C variant, which is present in *5, *15, and *17 haplotypes. This variant represents the most common and best studied SLCO1B1 variation that results in reduced SLCO1B1 transport function.

Allele frequency

This pharmacogenetics report tests for one (1) variant in the SLCO1B1 gene: c.521T>C, *5. 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, *5 |
|------------------|--------------|
| 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 a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 101 samples with known c.521T>C, *5 variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence intervals for the c.521T>C, *5 variant was 86.8% to 100%.

| Genotype | BeadChip Calls | | | | PPA | NPA | 95% CI |
|---|----------------|-----------|---------|------------------|-----|-----|----------|
| | Correct | Incorrect | No Call | FQC ¹ | | | |
| *5 SLCO1B1 TT Homozygous Common | 45 | 0 | 0 | 0 | 100 | 100 | 92.1-100 |
| *5 SLCO1B1 CT Heterozygous | 30 | 0 | 0 | 0 | 100 | 100 | 88.4-100 |

| | | | | | | | |
|---|----|---|---|---|-----|-----|----------|
| *5 SLCO1B1 CC Homozygous Rare | 26 | 0 | 0 | 0 | 100 | 100 | 86.8-100 |
|---|----|---|---|---|-----|-----|----------|

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 929 *5 SLCO1B1 replicates from 6 unique samples were tested across different testing conditions. 43 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 5 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 here.

c521T>C (*5, 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.

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

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

- 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.

Limitations

- These tests do not detect all genetic variants related to these diseases.
- The American College of Medical Genetics (ACMG) and American Congress of Obstetricians and Gynecologists (ACOG) have issued recommendations for carrier testing of certain health conditions. Some of our tests may not cover all of the variants

recommended for testing.

- These tests do not always identify if a person has two copies of any variants.
- These tests may not be able to determine a result for all variants analyzed.
- The performance of these tests may be affected by the presence of rare mutations. The impact of potentially interfering mutations has not been evaluated.
- The laboratory may not be able to process your sample. The probability that the laboratory cannot process your saliva sample can be up to 3%. If this happens, we will notify you by email and you may request one free replacement kit to provide us with a new sample.

Test performance

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

Clinical performance

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

See test-specific information for each test.

Analytical performance

Accuracy

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

Precision/Reproducibility

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

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

All test results demonstrated at least 99% agreement between replicates.

Minimum DNA input

A minimum DNA input study was performed to understand the lowest concentration of DNA

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

Interferences

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

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

The following conditions were tested:

- Eating food containing beef
- Eating food other than beef
- Drinking
- Chewing gum
- Using mouthwash
- Smoking

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

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

User studies

Saliva collection kit user study

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

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

PGS test report user comprehension study

User comprehension studies were performed to assess how well people understand the PGS

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

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

Specific test information

[Agnesis of the Corpus Callosum with Peripheral Neuropathy](#)

[ARSACS](#)

[Autosomal Recessive Polycystic Kidney Disease](#)

[Beta Thalassemia and Related Hemoglobinopathies](#)

[Bloom Syndrome](#)

[Canavan Disease](#)

[Congenital Disorder of Glycosylation Type 1a \(PMM2-CDG\)](#)

[Cystic Fibrosis](#)

[D-Bifunctional Protein Deficiency](#)

[Dihydrolipoamide Dehydrogenase Deficiency](#)

[Familial Dysautonomia](#)

[Familial Hyperinsulinism \(ABCC8-Related\)](#)

[Familial Mediterranean Fever](#)

[Fanconi Anemia Group C](#)

[Gaucher Disease Type 1](#)

[Glycogen Storage Disease Type Ia](#)

[Glycogen Storage Disease Type Ib](#)

[GRACILE Syndrome](#)

[Hereditary Fructose Intolerance](#)

[Herlitz Junctional Epidermolysis Bullosa \(LAMB3-related\)](#)

[Leigh Syndrome, French Canadian Type](#)

[Limb-Girdle Muscular Dystrophy Type 2D](#)

[Limb-Girdle Muscular Dystrophy Type 2E](#)

[Limb-Girdle Muscular Dystrophy Type 2I](#)

[Maple Syrup Urine Disease Type 1B](#)

[MCAD Deficiency](#)

[Mucopolidosis Type IV](#)

[Neuronal Ceroid Lipofuscinosis \(CLN5-Related\)](#)

[Neuronal Ceroid Lipofuscinosis \(PPT1-Related\)](#)

[Niemann-Pick Disease Type A](#)

[Nijmegen Breakage Syndrome](#)

[Nonsyndromic Hearing Loss and Deafness, DFNB1 \(GJB2-Related\)](#)

[Pendred Syndrome and DFNB4 Hearing Loss \(SLC26A4-Related\)](#)

[Phenylketonuria and Related Disorders](#)

- [Primary Hyperoxaluria Type 2](#)
- [Pyruvate Kinase Deficiency](#)
- [Rhizomelic Chondrodysplasia Punctata Type 1](#)
- [Salla Disease](#)
- [Sickle Cell Anemia](#)
- [Sjögren-Larsson Syndrome](#)
- [Tay-Sachs Disease](#)
- [Tyrosinemia Type I](#)
- [Usher Syndrome Type 1F](#)
- [Usher Syndrome Type 3A](#)
- [Zellweger Syndrome Spectrum \(PEX1-Related\)](#)

Agnesis of the Corpus Callosum with Peripheral Neuropathy (ACCPN)

Indications for Use

The 23andMe PGS Carrier Status Test for Agnesis 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-CI 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 saccin mutations causing autosomal recessive spastic ataxia of Charlevoix-Saguenay." Genet Test. 5(3):255-9.

Additional references included in the test report.

Autosomal Recessive Polycystic Kidney Disease

Indications for Use

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

Special considerations

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

Clinical performance

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

Frequency of PKHD1 variants in 23andMe customers

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

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

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

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

*This condition is not well studied in other ethnicities.

Accuracy

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

Precision/Reproducibility

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

Selected References

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

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

Additional references included in the report.

Beta Thalassemia and Related Hemoglobinopathies

Indications for Use

The 23andMe PGS Carrier Status Test for Beta Thalassemia and Related Hemoglobinopathies is indicated for the detection of 10 variants in the HBB gene. This

test is intended to be used to determine carrier status for beta thalassemia and related hemoglobinopathies in adults, but cannot determine if a person has two copies of a tested variant. The test is most relevant for people of Cypriot, Greek, Italian (particularly Sicilian), and Sardinian descent.

Special considerations

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

Clinical performance

The variants covered by this test are most common in people of Cypriot, Greek, Italian/Sicilian, Sardinian, Albanian, Macedonian, Bangladeshi, and Indonesian descent. This test does not cover a large fraction of HBB variants that cause beta thalassemia in people of Turkish, Croatian, 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>.

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

Frequency of PMM2 variants in 23andMe customers

| Variant name | European | African American | Ashkenazi Jewish | East Asian | Hispanic or Latino | South Asian |
|--------------|----------|------------------|------------------|------------|--------------------|-------------|
| R141H | 1.02% | 0.33% | 1.52% | <0.02% | 0.72% | 0.05% |
| F119L | 0.01% | 0.00% | 0.00% | 0.00% | <0.01% | 0.00% |

This test is expected to detect 90% of carriers of Ashkenazi Jewish descent, 89% of carriers of Danish descent and 55% of carriers of Dutch descent for this condition.

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

| | Carrier detection rate for this test | Pre-test (average) carrier risk | Post-test carrier risk for result “0 Variants Detected” |
|-------------------------|--------------------------------------|---------------------------------|---|
| Ashkenazi Jewish | 90% | 1 in 61 | 1 in 600 |
| Danish | 89% | 1 in 52 | 1 in 450 |

| | | | |
|---------------------------|---------|---------|----------|
| Dutch | 55% | 1 in 62 | 1 in 137 |
| Other ethnicities* | Unknown | Unknown | Unknown |

*This condition is not well studied in other ethnicities.

Accuracy

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

Precision/Reproducibility

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

Selected References

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

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% |
| DeltaI507 | 0.01% | <0.01% | 0.00% | 0.00% | 0.02% | 0.00% |
| G85E | 0.01% | <0.01% | 0.00 % | 0.00% | 0.01% | 0.00% |
| R334W | 0.01% | <0.01% | 0.00% | <0.02% | 0.03% | 0.00% |
| R347H | 0.01% | <0.01% | 0.00% | <0.02% | 0.01% | 0.00% |
| R347P | 0.01% | 0.00% | 0.00% | 0.00% | <0.01% | 0.00% |
| A455E | 0.01% | 0.00% | 0.07% | <0.02% | 0.01% | 0.00% |
| V520F | 0.01% | <0.01% | 0.00% | 0.00% | <0.01% | 0.00% |
| G542X | 0.09% | 0.04% | 0.20% | 0.00% | 0.10% | 0.00% |
| S549N | <0.01% | 0.02% | 0.00% | 0.00% | <0.01% | <0.05% |
| G551D | 0.08% | 0.02% | 0.00% | 0.00% | 0.03% | 0.00% |
| R553X | 0.04% | 0.03% | 0.00% | <0.02% | 0.02% | 0.00% |
| R560T | 0.01% | 0.00% | 0.00% | 0.00% | <0.01% | 0.00% |
| R1162X | 0.01% | <0.01% | 0.00% | 0.00% | 0.02% | <0.05% |
| W1282X | 0.06% | 0.02% | 1.93% | 0.00% | 0.03% | 0.00% |
| N1303K | 0.05% | 0.01% | 0.16% | 0.00% | 0.05% | 0.00% |
| 394delTT | 0.01% | 0.00% | 0.00% | 0.00% | <0.01% | 0.00% |
| 621+1G>T | 0.04% | <0.01% | 0.00% | 0.00% | 0.02% | 0.00% |
| 711+1G>T | 0.01% | 0.00% | 0.00% | <0.02% | 0.01% | 0.00% |

| | | | | | | |
|------------------------|--------|--------|--------|--------|--------|--------|
| 1078delT | <0.01% | 0.00% | 0.00% | 0.00% | 0.01% | 0.00% |
| 1717-1G>A | 0.04% | <0.01% | 0.05% | <0.02% | 0.02% | 0.00% |
| 1898+1G>A | 0.01% | <0.01% | 0.00% | 0.00% | <0.01% | <0.05% |
| 2789+5G>A | 0.03% | 0.01% | 0.00% | 0.00% | 0.02% | 0.00% |
| 3120+1G>A | <0.01% | 0.19% | 0.00% | 0.00% | 0.02% | 0.00% |
| 3659delC | 0.03% | <0.01% | <0.01% | <0.02% | 0.02% | <0.05% |
| 3905insT | 0.01% | <0.01% | 0.00% | 0.00% | <0.01% | 0.00% |
| 3849+10kbC>T | 0.03% | <0.01% | 0.21% | 0.00% | 0.04% | 0.05% |
| 2184delA | 0.01% | 0.00% | 0.00% | 0.02% | 0.01% | 0.00% |
| 3876delA | 0.00% | <0.01% | 0.00% | 0.00% | 0.01% | 0.00% |

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

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

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

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

Accuracy

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

Precision/Reproducibility

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

Selected References

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

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

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

Additional references included in the report.

D-Bifunctional Protein Deficiency

Indications for Use

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

Special considerations

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

Clinical performance

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

Frequency of HSD17B4 variants in 23andMe customers

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

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

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

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

Accuracy

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

Precision/Reproducibility

A study was performed to assess the precision of the test. A total of 135 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Selected References

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

Additional references included in the report.

Dihydrolipoamide Dehydrogenase Deficiency

Indications for Use

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

people of Ashkenazi Jewish descent.

Special considerations

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

Clinical performance

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

Frequency of DLD variants in 23andMe customers

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

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

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

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

*This condition is not well studied in other ethnicities.

Accuracy

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

Precision/Reproducibility

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

Selected References

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

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

Additional references included in the report.

Familial Dysautonomia

Indications for Use

The 23andMe PGS Carrier Status Test for Familial Dysautonomia is indicated for the detection of the 2507+6T>C variant in the 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.

Accuracy

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

Precision/Reproducibility

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

Selected References

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

Additional references included in the report.

Familial Hyperinsulinism (ABCC8-Related)

Indications for Use

The 23andMe PGS Carrier Status Report for Familial Hyperinsulinism (ABCC8-Related) is indicated for the detection of three variants in the ABCC8 gene. This test is intended to be used to determine carrier status for ABCC8-related familial hyperinsulinism in adults, but cannot determine if a person has two copies of a tested variant. This report also describes if a result is associated with personal risk for developing symptoms of ABCC8-related familial hyperinsulinism, but it does not describe a person's overall risk of developing symptoms. This test is most relevant for people of Ashkenazi Jewish descent.

Special considerations

- Symptoms of familial hyperinsulinism may vary between people with the condition

even if they have the same genetic variants.

- There are currently no professional guidelines in the U.S. for carrier testing for this condition. However, ACOG notes that testing for familial hyperinsulinism may be considered for people of Ashkenazi Jewish descent who are considering having children.

Clinical performance

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

Frequency of ABCC8 variants in 23andMe customers

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

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

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

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

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

Accuracy

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

Precision/Reproducibility

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

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.

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 73-92% of carriers of Turkish descent for this condition.

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

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

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

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 1,013 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

A minimum DNA input study was performed using 1 human cell line samples and 12 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 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." [Updated 2016 Dec 15].

Additional references included in the report.

Fanconi Anemia Group C

Indications for Use

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

Special considerations

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

Clinical performance

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

Frequency of FANCC variants in 23andMe customers

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

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

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

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

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

Accuracy

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

Precision/Reproducibility

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

Selected References

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

Additional references included in the report.

Gaucher Disease Type 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 8 human cell line samples with three lots of reagents. The study yielded concordant test results for all samples with a DNA concentration of 15 ng/μL.

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.

Accuracy

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

Precision/Reproducibility

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

Selected References

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

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.

Clinical performance

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

Frequency of SLC37A4 variants in 23andMe customers

| Variant name | European | African American | Ashkenazi Jewish | East Asian | Hispanic or Latino | South Asian |
|------------------------|----------|------------------|------------------|------------|--------------------|-------------|
| 1042_1043del CT | 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.

Herlitz Junctional Epidermolysis Bullosa (LAMB3-related)

Indications for Use

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

Special considerations

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

Clinical performance

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

Frequency of LAMB3 variants in 23andMe customers

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

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

Accuracy

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

Precision/Reproducibility

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

Selected References

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

Additional references included in the report.

Leigh Syndrome, French-Canadian Type (LSFC)

Indications for Use

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

Special considerations

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

Clinical performance

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

Frequency of LRPPRC variants in 23andMe customers

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

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

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

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

*This condition is not well studied in other ethnicities.

Accuracy

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

Precision/Reproducibility

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

Selected References

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

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

Additional references included in the report.

Limb-Girdle Muscular Dystrophy Type 2D

Indications for Use

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

Special considerations

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

Clinical performance

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

Frequency of SGCA variants in 23andMe customers

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

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

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

| | Carrier detection rate for this test | Pre-test (average) carrier risk | Post-test carrier risk for result “0 Variants Detected” |
|---------------------------|---|--|--|
| Finnish | 95% | 1 in 250 | 1 in 5,500 |
| Other ethnicities* | Unknown | Unknown | Unknown |

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

Accuracy

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

Precision/Reproducibility

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

Selected References

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

Additional references included in the report.

Limb-Girdle Muscular Dystrophy 2E

Indications for Use

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

Special considerations

- Symptoms can vary greatly in people with this condition, and can be mild in some

cases.

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

Clinical performance

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

Frequency of SGCB variants in 23andMe customers

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

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

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

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

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

Accuracy

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

Precision/Reproducibility

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

Selected References

Lim LE et al. (1995). “Beta-sarcoglycan: characterization and role in limb-girdle muscular

dystrophy linked to 4q12.” Nat Genet. 11(3):257-65.

Additional references included in the report.

Limb-Girdle Muscular Dystrophy 2I

Indications for Use

The 23andMe PGS Carrier Status Test for Limb-Girdle Muscular Dystrophy Type 2I (LGMD2I) is indicated for the detection of the L276I variant in the FKRP gene. This test is intended to be used to determine carrier status for LGMD2I in adults, but cannot determine if a person has two copies of a tested variant.

Special considerations

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

Clinical performance

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

Frequency of FKRP variants in 23andMe customers

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

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

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

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

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

Accuracy

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

Precision/Reproducibility

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

Selected References

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

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

Additional references included in the report.

Maple Syrup Urine Disease (MSUD) Type 1B

Indications for Use

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

Special considerations

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

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

Clinical performance

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

Frequency of ACADM variants in 23andMe customers

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

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

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

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

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

Accuracy

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

Precision/Reproducibility

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

Selected References

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

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

Yokota I et al. (1992). "The molecular basis of medium chain acyl-CoA dehydrogenase deficiency: survey and evolution of 985A----G transition, and identification of five rare types of mutation within the medium chain acyl-CoA dehydrogenase gene." *Prog Clin Biol Res.* 375:425-40.

Additional references included in the report.

Mucopolipidosis Type IV

Indications for Use

The 23andMe PGS Carrier Status Test for Mucopolipidosis 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 mucopolipidosis 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 mucopolipidosis 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 mucopolipidosis 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 Mucopolipidosis 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 2 variants in the GJB2 gene. This test is intended to be used to determine carrier status for DFNB1 in adults, but cannot determine if a person has two copies of a tested variant. The test is most relevant for people of European and Ashkenazi Jewish descent.

Special considerations

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

Clinical performance

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

Frequency of GJB2 variants in 23andMe customers

| Variant name | European | African American | Ashkenazi Jewish | East Asian | Hispanic or Latino | South Asian |
|----------------|----------|------------------|------------------|------------|--------------------|-------------|
| 35delG | 1.88% | 0.55% | 0.72% | <0.02% | 1.51% | <0.05% |
| 167delT | 0.09% | 0.02% | 3.19% | 0.00% | 0.07% | 0.00% |

This test is expected to detect 93% of carriers of Ashkenazi Jewish descent and 85% of carriers of European descent (averaged across multiple countries), <1% of carriers of East Asian descent, and 0-73% of carriers of South Asian descent for this condition.

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

| | Carrier detection rate for this test | Pre-test (average) carrier risk | Post-test carrier risk for result “0 Variants Detected” |
|---------------------------|--------------------------------------|---------------------------------|---|
| Ashkenazi Jewish | 93% | 1 in 20 | 1 in 280 |
| European | 85% | 1 in 33 | 1 in 220 |
| East Asian | <1% | 1 in 30 | 1 in 30 |
| South Asian | 0-73%, depending on the region | 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 164 samples with known variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 97.8% to 100.0%.

Precision/Reproducibility

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

Selected References

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

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

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

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

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

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

Additional references included in the report.

Pendred Syndrome and DFNB4 Hearing Loss (SLC26A4-Related)

Indications for Use

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

Special considerations

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

Clinical performance

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

Frequency of SLC26A4 variants in 23andMe customers

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

This test is expected to detect 13-61% of carriers of European descent (depending on country of ancestry), 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% |
| 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 |
| 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.

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 rs551883218 and 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.

Sickle Cell Anemia

Indications for Use

The 23andMe PGS Carrier Status Test for Sickle Cell Anemia is indicated for the detection of the HbS variant in the HBB gene. This test is intended to be used to determine carrier status for sickle cell anemia in adults, but cannot determine if a person has two copies of the tested variant. The test is most relevant for people of African descent. It is also relevant for other ethnicities in which the HbS variant is found, including 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

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

Clinical performance

The variant covered by this test is most common in people of African descent. About 1 in 13 people (7.69%) of African American descent is a carrier for sickle cell anemia. 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% | 7.10% | 0.00% | <0.01% | 0.74% | 0.16% | 0.25% |

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

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

| | Carrier detection rate for this test | Pre-test (average) carrier risk | Post-test carrier risk for result "0 Variants Detected" |
|------------------|--------------------------------------|---------------------------------|---|
| Worldwide | >99%* | Varies by ethnicity | - |

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

Accuracy

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

Precision/Reproducibility

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

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

Selected References

Bender MA et al. (2003). "Sickle Cell Disease." [Accessed Nov 1, 2018].

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 Syndrome Spectrum (PEX1-Related)

Indications for Use

The 23andMe PGS Carrier Status Test for Zellweger Syndrome Spectrum (PEX1-related

ZSS) is indicated for the detection of the G843D variant in the PEX1 gene. This test is intended to be used to determine carrier status for PEX1-related ZSS in adults, but cannot determine if a person has two copies of a tested variant.

Special considerations

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

Clinical performance

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

Frequency of PEX1 variants in 23andMe customers

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

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

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

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

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

Accuracy

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

Precision/Reproducibility

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

>99% repeatability.

Selected References

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

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

Additional references included in the report.

References

Data on file at 23andMe, Sunnyvale, 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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