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

For *in-vitro* diagnostic use

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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.
- Your genetic results were analyzed on a previous version of our genotyping platform. Click here for more information.

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.

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

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.

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.

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.

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.

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.
- Depending on your genotyping platform, your report may not include all variants.

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.

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 Hemochromatosis (HFE-Related)

Indications for Use

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

Special considerations

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

Clinical performance

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

Frequency of HFE variants in 23andMe customers

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

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

Selected References

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

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

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

Additional references included in the test report.

Hereditary Thrombophilia

Indications for Use

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

Special considerations

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

Clinical performance

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

Frequency of the tested variants in 23andMe customers

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

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

Selected References

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

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

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

Additional references included in the test report.

Late-Onset Alzheimer’s Disease

Indications for Use

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

European descent.

Special considerations

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

Clinical performance

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

Frequency of the APOE ε4 variant in 23andMe customers

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

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

Selected References

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

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

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

Additional references included in the test report.

Parkinson’s Disease

Indications for Use

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

Special considerations

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

Clinical performance

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

Frequency of the tested variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
G2019S	0.08%	0.06%	1.88%	<0.02%	0.18%	0.00%

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)

Intended 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).

Indications for Use

The 23andMe PGS Genetic Health Risk Report for BRCA1/BRCA2 (Selected Variants) is indicated for reporting of the c.68_69del and c.5266dup variants in the BRCA1 gene and the c.5946del variant in the BRCA2 gene. The report describes if a person's genetic result is associated with an increased risk of developing breast cancer and ovarian cancer and may be associated with an increased risk for prostate cancer, pancreatic cancer, and potentially other cancers. The 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 people of most ethnicities. The test report does not describe a person's overall risk of developing any type of cancer, and the absence of a variant tested does not rule out the presence of other variants that may be cancer-related. This report is for over-the-counter use by adults over the age of 18, and provides genetic information to inform discussions with a healthcare professional. This test is not a substitute for visits to a healthcare provider for recommended screenings or appropriate follow-up and should not be used to determine any treatments.

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.

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

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.

You can search for a genetic counselor near you on the following website, which is managed by the National Society of Genetic Counselors: https://www.aboutgeneticcounselors.org/.

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.

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 c.68_69del variant, 0.11% carry one copy of the c.5266dup variant, and 1.36% carry one copy of the c.5946del variant. The variants covered by this test are expected to account for more than 90% of cancer-related BRCA1 and BRCA2 variants among people of Ashkenazi Jewish descent and a much smaller proportion of cancer-related BRCA1/2 variants found in people of other ethnicities.

Frequency of BRCA1 and BRCA2 variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian	Middle Eastern
c.68_69del	0.024%	0.007%	0.889%	0.000%	0.033%	0.049%	<0.014%
c.5266dup	0.026%	<0.004%	0.278%	0.000%	0.010%	0.000%	0.000%
c.5946del	0.024%	0.007%	1.042%	0.000%	0.012%	0.000%	<0.014%

References

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

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 Genomics LLC, Palo Alto, CA

Additional references included in the test report.

Carrier Status

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.
- Your genetic results were analyzed on a previous version of our genotyping platform. Click here for more information.

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.

User studies

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

The overall comprehension rate on the collection kit instructions was 92.1% and greater than

97% of samples met all laboratory quality criteria, demonstrating that users from diverse backgrounds can understand the collection kit instructions and provide adequate saliva samples.

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

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

Specific test information
Agenesis of the Corpus Callosum with Peripheral Neuropathy
ARSACS
Autosomal Recessive Polycystic Kidney Disease
Beta Thalassemia and Related Hemoglobinopathies
Bloom Syndrome
Canavan Disease
Congenital Disorder of Glycosylation Type 1a (PMM2-CDG)
Cystic Fibrosis
D-Bifunctional Protein Deficiency
Dihydrolipoamide Dehydrogenase Deficiency
Familial Dysautonomia
Familial Hyperinsulinism (ABCC8-Related)
Fanconi Anemia Group C
Gaucher Disease Type 1
Glycogen Storage Disease Type Ia
Glycogen Storage Disease Type Ib
GRACILE Syndrome
Hereditary Fructose Intolerance
Leigh Syndrome, French Canadian Type
Limb-Girdle Muscular Dystrophy Type 2D
Limb-Girdle Muscular Dystrophy Type 2E
Limb-Girdle Muscular Dystrophy Type 2I
Maple Syrup Urine Disease Type 1B
MCAD Deficiency
Mucolipidosis Type IV
Neuronal Ceroid Lipofuscinosis (CLN5-Related)
Neuronal Ceroid Lipofuscinosis (PPT1-Related)

Agenesis of the Corpus Callosum with Peripheral Neuropathy (ACCPN)

Indications for Use

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

Special considerations

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

Clinical performance

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

Frequency of SLC12A6 variants in 23andMe customers

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

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

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

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

*This condition is not well studied in other ethnicities.

Selected References

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

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

Additional references included in the test report.

ARSACS

Indications for Use

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

Special considerations

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

Clinical performance

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

Frequency of SACS variants in 23andMe customers

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

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

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

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

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

Selected References

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

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

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

Additional references included in the test report.

Autosomal Recessive Polycystic Kidney Disease

Indications for Use

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

Special considerations

- The test does not include the majority of PKHD1 variants that cause ARPKD in most ethnicities. However, it includes one variant that is relatively common in people of Finnish descent.
- Most people with ARPKD have two variants in the PKHD1 gene. However, some people with the condition have variants in the DZIP1L gene.
- ACMG recommends that everyone who is considering having children should be offered carrier screening for ARPKD. This recommendation applies to people of all ethnicities and genetic ancestries. Please note that 23andMe does not test for all variants linked to this condition.

Clinical performance

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%

One of the variants included in this test is relatively common among people of Finnish descent. However, the test does not cover variants causing the majority of ARPKD in people of most ethnicities.

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"
Worldwide	Varies by ancestry (higher in European than other populations)	1 in 70	Unknown

Selected References

Bergmann C et al. (2003). "Spectrum of mutations in the gene for autosomal recessive polycystic kidney disease (ARPKD/PKHD1)." J Am Soc Nephrol. 14(1):76-89.

Burgmaier K et al. (2001). "Autosomal Recessive Polycystic Kidney Disease – *PKHD1*."

[Accessed Nov 21, 2023].

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.
- ACMG and ACOG recommend that everyone who is considering having children should be offered carrier screening for beta thalassemia and related hemoglobinopathies. This recommendation applies to people of all ethnicities and genetic ancestries. Please note that 23andMe does not test for all variants linked to these conditions.

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%

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

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

Selected References

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

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

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

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

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

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

Theodoridou S et al. (2008). "Carrier screening and prenatal diagnosis of hemoglobinopathies. A study of indigenous and immigrant couples in northern Greece,

over the last 5 years." Hemoglobin. 32(5):434-9.

Additional references included in the report.

Bloom Syndrome

Indications for Use

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

Special considerations

- Symptoms of Bloom syndrome may vary between people with the condition even if they have the same genetic variants.
- ACMG recommends that everyone who is considering having children should be offered carrier screening for Bloom syndrome. This recommendation applies to people of all ethnicities and genetic ancestries. Please note that 23andMe does not test for all variants linked to 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 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.

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

- ACMG recommends that everyone who is considering having children should be offered carrier screening for Canavan disease. This recommendation applies to people of all ethnicities and genetic ancestries. Please note that 23andMe does not test for all variants linked to this condition.

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.

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.

- ACMG recommends that everyone who is considering having children should be offered carrier screening for PMM2-CDG. This recommendation applies to people of all ethnicities and genetic ancestries. Please note that 23andMe does not test for all variants linked to this condition.

Clinical performance

The variants covered by this test are most common in people of Ashkenazi Jewish, Danish, and Dutch descent. About 1 in 61 people (1.64%) of Ashkenazi Jewish descent, 1 in 53 people (1.89%) of Danish descent, and 1 in 46 people (2.17%) of Dutch descent are carriers for PMM2-CDG. This test does not include a large fraction of PMM2 variants that cause PMM2-CDG in people of Dutch descent.

Frequency of PMM2 variants in 23andMe customers

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

This test is expected to detect 90% of carriers of Ashkenazi Jewish descent, 89% of carriers of Danish descent and 58% of carriers of Dutch descent for this condition.

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

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result “0 Variants Detected”
Ashkenazi Jewish	90%	1 in 61	1 in 600
Danish	89%	1 in 53	1 in 470
Dutch	58%	1 in 46	1 in 110
Other ethnicities*	Unknown	Unknown	Unknown

*This condition is not well studied in other ethnicities.

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. 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 that everyone who is considering having children should be offered carrier screening for cystic fibrosis. This recommendation applies to people of all ethnicities and genetic ancestries. Please note that 23andMe does not test for all variants linked to this condition.
- Depending on your genotyping platform, your report may not include all variants.

Clinical performance

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

Frequency of CFTR variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
DeltaF508	2.67%	0.88%	1.04%	0.00%	1.51%	0.52%
Deltal507	0.01%	<0.01%	0.00%	0.00%	0.02%	0.00%
G85E	0.01%	<0.01%	0.00 %	0.00%	0.01%	0.00%

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

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

Selected References

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

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

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

Additional references included in the report.

D-Bifunctional Protein Deficiency

Indications for Use

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

Special considerations

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

Clinical performance

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

Frequency of HSD17B4 variants in 23andMe customers

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

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

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

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

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

- ACMG recommends that everyone who is considering having children should be offered carrier screening for DLD deficiency. This recommendation applies to people of all ethnicities and genetic ancestries. Please note that 23andMe does not test for all variants linked to 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.

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

- ACMG recommends that everyone who is considering having children should be offered carrier screening for familial dysautonomia. This recommendation applies to people of all ethnicities and genetic ancestries. Please note that 23andMe does not test for all variants linked to this condition.

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.

Selected References

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

Additional references included in the report.

Familial Hyperinsulinism (ABCC8-Related)

Indications for Use

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

Special considerations

- Symptoms of familial hyperinsulinism may vary between people with the condition even if they have the same genetic variants.
- ACOG notes that carrier testing for familial hyperinsulinism may be considered for people of Ashkenazi Jewish descent who are considering having children. Please note that 23andMe does not test for all variants linked to this condition.

Clinical performance

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

Frequency of ABCC8 variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian	Middle Eastern
F1388del	<0.01%	0.00%	0.13%	0.00%	<0.01%	0.00%	0.00%
3992-9G>A	0.04%	0.01%	1.33%	0.00%	0.02%	0.00%	<0.06%
V187D	<0.01%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%

This test is expected to detect about 97% of carriers of Ashkenazi Jewish descent and 41% of carriers of Finnish descent for this condition.

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

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result "0 Variants Detected"
Ashkenazi Jewish	97%	1 in 52	1 in 1,700
Finnish	41%	1 in 80	1 in 130
Other ethnicities*	Unknown	Unknown	Unknown

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

Selected References

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

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

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

Additional references included in the report.

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

- ACMG recommends that everyone who is considering having children should be offered carrier screening for Fanconi anemia group C. This recommendation applies to people of all ethnicities and genetic ancestries. Please note that 23andMe does not test for all variants linked to this condition.

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.

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.
- ACMG recommends that everyone who is considering having children should be offered carrier screening for Gaucher disease type 1. This recommendation applies to people of all ethnicities and genetic ancestries. Please note that 23andMe does not test for all variants linked to this condition.

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.

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

- ACMG recommends that everyone who is considering having children should be offered carrier screening for GSDIa. This recommendation applies to people of all ethnicities and genetic ancestries. Please note that 23andMe does not test for all variants linked to this condition.

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.

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.
- ACMG recommends that everyone who is considering having children should be offered carrier screening for GSDIb. This recommendation applies to people of all ethnicities and genetic ancestries. Please note that 23andMe does not test for all variants linked to 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_1043delCT	0.06%	0.03%	0.02%	0.03%	0.06%	0.00%
W118R	<0.01%	0.00%	0.00%	<0.02%	0.00%	0.00%

This test is expected to detect 42% of carriers of Japanese descent, 39% of carriers of Serbian descent, and 31% of carriers of European descent for this condition.

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

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result "0 Variants Detected"
Japanese	42%	Unknown	Unknown
Serbian	39%	Unknown	Unknown
European	31%	Unknown	Unknown
Other ethnicities*	Unknown	Unknown	Unknown

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

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.

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

- ACMG recommends that everyone who is considering having children should be offered carrier screening for hereditary fructose intolerance. This recommendation applies to people of all ethnicities and genetic ancestries. Please note that 23andMe does not test for all variants linked to 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.

Selected References

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

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

Additional references included in the report.

Leigh Syndrome, French-Canadian Type (LSFC)

Indications for Use

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

Special considerations

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

Clinical performance

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

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

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

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

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

*This condition is not well studied in other ethnicities.

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.

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.

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. The test is most relevant for people of European 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 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 75% 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	75%	1 in 200	1 in 810
Other ethnicities*	Unknown	Unknown	Unknown

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

Selected References

Bourteel H et al. (2009). "Clinical and mutational spectrum of limb-girdle muscular dystrophy type 2I in 11 French patients." J Neurol Neurosurg Psychiatry. 80(12):1405-8.

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.

Fichna JP et al. (2018). "Whole-exome sequencing identifies novel pathogenic mutations and putative phenotype-influencing variants in Polish limb-girdle muscular dystrophy patients." Hum Genomics. 12(1):34.

Ten Dam L et al. (2019). "Autosomal recessive limb-girdle and Miyoshi muscular dystrophies in the Netherlands: The clinical and molecular spectrum of 244 patients." Clin Genet. 96(2):126-133.

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

Zídková J et al. (2023). "Genetic findings in Czech patients with limb girdle muscular dystrophy." Clin Genet. 104(5):542-553.

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

- ACMG recommends that everyone who is considering having children should be offered carrier screening for MSUD 1B. This recommendation applies to people of all ethnicities and genetic ancestries. Please note that 23andMe does not test for all variants linked to this condition.

Clinical performance

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

Frequency of BCKDHB variants in 23andMe customers

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

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

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

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

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

Selected References

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

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

Additional references included in the report.

MCAD Deficiency

Indications for Use

The 23andMe PGS Carrier Status Test for Medium-Chain Acyl-CoA Dehydrogenase (MCAD) Deficiency is indicated for the detection of 4 variants in the ACADM gene. This test is intended to be used to determine carrier status for MCAD deficiency in adults, but

cannot determine if a person has two copies of a tested variant. The test is most relevant for people of European descent.

Special considerations

- ACMG recommends that everyone who is considering having children should be offered carrier screening for MCAD deficiency. This recommendation applies to people of all ethnicities and genetic ancestries. Please note that 23andMe does not test for all variants linked to 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	Middle Eastern
c.985A>G	1.35%	0.41%	0.13%	<0.01%	0.63%	0.05%	0.11%
c.199T>C	0.17%	0.05%	0.00%	0.00%	0.05%	0.00%	0.01%
c.616C>T	0.01%	<0.01%	0.01%	<0.01%	0.01%	0.02%	0.01%
c.734C>T	0.01%	<0.01%	0.00%	0.00%	0.01%	0.00%	0.01%

This test is expected to detect 80% of carriers of European descent for this condition.

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

	Carrier detection rate for this test	Pre-test (average) carrier risk	Post-test carrier risk for result "0 Variants Detected"
European	80%	1 in 61	1 in 300
Other ethnicities*	Unknown	Unknown	Unknown

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

Selected References

Arnold GL et al. (2010). "Lack of genotype-phenotype correlations and outcome in MCAD deficiency diagnosed by newborn screening in New York State." Mol Genet Metab. 99(3):263-8.

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

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

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

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

Additional references included in the report.

Mucolipidosis Type IV

Indications for Use

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

Special considerations

- ACMG recommends that everyone who is considering having children should be offered carrier screening for mucolipidosis IV. This recommendation applies to people of all ethnicities and genetic ancestries. Please note that 23andMe does not test for all variants linked to this condition.

Clinical performance

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

About 1 in 127 people (0.79%) of Ashkenazi Jewish descent is a carrier for mucolipidosis IV.

Frequency of MCOLN1 variants in 23andMe customers

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

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

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

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

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

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.

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.

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

- ACMG recommends that everyone who is considering having children should be offered carrier screening for Niemann-Pick disease type A. This recommendation applies to people of all ethnicities and genetic ancestries. Please note that 23andMe does not test for all variants linked to this condition.

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.

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.

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. This report also describes if a result is associated with personal risk of having hearing loss related to

DFNB1, but it does not describe a person's overall risk of having DFNB1-related hearing loss. The test is most relevant for people of Ashkenazi Jewish and European descent.

Special considerations

- The degree of hearing loss can vary, but there are no other symptoms associated with this condition.
- Some people with two GJB2 variants do not have any noticeable hearing loss.
- Most people with DFNB1 have two variants in the GJB2 gene. However, some people with the condition have one variant in the GJB2 gene and a second variant not tested (a deletion) in the GJB6 gene.
- ACMG recommends that everyone who is considering having children should be offered carrier screening for DFNB1. This recommendation applies to people of all ethnicities and genetic ancestries. Please note that 23andMe does not test for all variants linked to this condition.

Clinical performance

The variants covered by this test are most common in people of Ashkenazi Jewish and European descent. This test does not include the majority of GJB2 variants that cause DFNB1 in people of East/Southeast Asian descent. It also 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	Middle Eastern
c.35delG	1.87%	0.55%	0.81%	0.01%	1.39%	0.06%	1.25%
c.167delT	0.08%	0.02%	3.26%	0.00%	0.08%	0.00%	0.07%

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

	Carrier frequency	Carrier detection rate for this test
Ashkenazi Jewish	1 in 20	93%
East/Southeast Asian	Up to 1 in 4	<1%
European	1 in 20	71-96%
South Asian	Unknown	0-73%

Other ethnicities*	Unknown	Unknown

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

Selected References

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

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

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

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

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

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

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

Mishra S et al. (2018). "Connexin 26 (GJB2) Mutations Associated with Non-Syndromic Hearing Loss (NSHL)." Indian J Pediatr. 85(12):1061-1066.

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

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

Additional references included in the report.

Pendred Syndrome and DFNB4 Hearing Loss (SLC26A4-Related)

Indications for Use

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

Special considerations

- Symptoms of Pendred syndrome and DFNB4 vary in severity depending on which variants are causing the condition.
- This test does not include a large fraction of SLC26A4 variants that cause Pendred syndrome or DFNB4 in any ethnicity.
- ACMG recommends that everyone who is considering having children should be offered carrier screening for Pendred syndrome and DFNB4. This recommendation applies to people of all ethnicities and genetic ancestries. Please note that 23andMe does not test for all variants linked to these conditions.

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.

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.
- ACMG recommends that everyone who is considering having children should be

offered carrier screening for PKU and related disorders. This recommendation applies to people of all ethnicities and genetic ancestries. Please note that 23andMe does not test for all variants linked to 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%

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

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.

Regier DS et al. (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.

Selected References

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

Additional references included in the report.

Rhizomelic Chondrodysplasia Punctata Type 1 (RCDP1)

Indications for Use

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

Special considerations

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

Clinical performance

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

Frequency of PEX7 variants in 23andMe customers

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

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

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

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

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

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 84 people (1.2%) 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 84	1 in 920
Swedish	85%	Unknown	Unknown
Other ethnicities*	Unknown	Unknown	Unknown

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

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.

Huizing M et al. (2021). "Free sialic acid storage disorder: Progress and promise." Neurosci Lett. 755:135896.

Additional references included in the report.

Severe Junctional Epidermolysis Bullosa (LAMB3-Related)

Indications for Use

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

Special considerations

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

Clinical performance

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

Frequency of LAMB3 variants in 23andMe customers

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

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

Pre-test and post-test carrier risks for the 23andMe PGS Carrier Status Test for LAMB3-related JEB

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

Selected References

Varki R et al. (2006). "Epidermolysis bullosa. I. Molecular genetics of the junctional and

hemidesmosomal variants." J Med Genet. 43(8):641-52.

Additional references included in the report.

Sickle Cell Anemia

Indications for Use

The 23andMe PGS Carrier Status Test for Sickle Cell Anemia is indicated for the detection of the HbS variant in the HBB gene. This test is intended to be used to determine carrier status for sickle cell anemia in adults. This report also describes if a result is associated with personal risk of developing symptoms of sickle cell anemia, but it does not describe a person's overall risk of developing symptoms. The test is most relevant for people of African descent. It is also relevant for people of Middle Eastern and South Asian descent, as well as people from the Caribbean, the Mediterranean, and parts of Central and South America.

Special considerations

- ACMG and ACOG recommend that everyone who is considering having children should be offered carrier screening for hemoglobinopathies such as sickle cell anemia. This recommendation applies to people of all ethnicities and genetic ancestries.
- For customers who purchased their 23andMe kit before November 2013, the test does not report if someone has two copies of the HbS variant.

Clinical performance

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

Frequency of the HbS variant in 23andMe customers

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

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

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

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

Selected References

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

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

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

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

Additional references included in the report.

Sjögren-Larsson Syndrome

Indications for Use

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

Special considerations

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

Clinical performance

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

Frequency of ALDH3A2 variants in 23andMe customers

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

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

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

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

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

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.
- ACMG recommends that everyone who is considering having children should be offered carrier screening for Tay-Sachs disease. This recommendation applies to people of all ethnicities and genetic ancestries. Please note that 23andMe does not test for all variants linked to this condition.

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. This test does not cover variants causing Tay-Sachs disease that are more common in people of French Canadian descent.

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.

Selected References

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

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

- ACMG recommends that everyone who is considering having children should be offered carrier screening for tyrosinemia type I. This recommendation applies to people of all ethnicities and genetic ancestries. Please note that 23andMe does not test for all variants linked to 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.

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

- ACMG recommends that everyone who is considering having children should be offered carrier screening for Usher 1F. This recommendation applies to people of all ethnicities and genetic ancestries. Please note that 23andMe does not test for all variants linked to this condition.

Clinical performance

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

Frequency of PCDH15 variants in 23andMe customers

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

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

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

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

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

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

- ACMG recommends that everyone who is considering having children should be offered carrier screening for Usher 3A. This recommendation applies to people of all ethnicities and genetic ancestries. Please note that 23andMe does not test for all variants linked to this condition.

Clinical performance

The variant covered by this test is most common in people of Ashkenazi Jewish descent. About 1 in 120 people (0.83%) of Ashkenazi Jewish descent is a carrier for Usher 3A. The test does not include the majority of CLRN1 variants that cause Usher 3A in people of Finnish descent.

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.

Selected References

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

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

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

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

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

Additional references included in the report.

Zellweger Spectrum Disorder (PEX1-Related)

Indications for Use

The 23andMe PGS Carrier Status Test for Zellweger Spectrum Disorder (PEX1-related ZSD) is indicated for the detection of the G843D variant in the PEX1 gene. This test is intended to be used to determine carrier status for PEX1-related ZSD in adults, but cannot

determine if a person has two copies of a tested variant.

Special considerations

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

Clinical performance

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

Frequency of PEX1 variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian	Middle Eastern
G843D	0.14%	0.04%	0.01%	0.00%	0.07%	0.01%	0.02%

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

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

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

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

Selected References

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

Steinberg SJ et al. (2003). "Zellweger Spectrum Disorder." [Accessed Oct 5, 2021].

Additional references included in the report.

References

Data on file at 23andMe Genomics LLC, Palo Alto, CA

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