23andMe® Personal Genome Service® (PGS)
Genetic Health Risk Reports V5 Package Insert

Table of contents

IVD

For *in-vitro* diagnostic use

Intended Use:

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

Summary and explanation of the test:
23andMe Genetic Health Risk Tests are tests you can order and use at home to learn about your DNA from a saliva sample. The tests work by detecting specific gene variants. Your genetic results are returned to you in a secure online account on the 23andMe website.

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

Important:

- Please follow the instructions in the DNA Collection Kit to ensure your DNA results can be processed and connected to your online account.
- Your ethnicity may affect whether these tests are relevant for you. Your ethnicity also may affect how your genetic health results are interpreted.
- Other factors, such as environmental and lifestyle risk factors, may affect the risk of developing a given disease.
- If you have a family history of a condition, or think you have symptoms of a condition, consult with your healthcare provider about appropriate testing.
- These tests cannot determine your overall risk for developing a disease in the future.
- These tests are not intended to diagnose any disease or detect the presence of

deterministic variants in autosomal dominant diseases or conditions such as Huntington's Disease.
- This device is not intended for prenatal testing.
- These tests are not for predicting predisposition for cancer for which a prophylactic screening, confirmatory procedure or treatment may incur morbidity or mortality to the patient.
- These tests are not for assessing the presence of genetic variants that may impact the metabolism, exposure, response, risk of adverse events, dosing, or mechanisms of prescription or over-the-counter medications.
- The laboratory may not be able to process your sample. If this happens, we will notify you by email and you may request one free replacement kit to provide us with a new sample.
- These tests do not diagnose any health conditions.

Warnings:

- These tests are intended to be used to identify genetic risk for health conditions in users 18 years and above.
- These tests do not detect all genetic variants related to these health conditions. The absence of a variant tested does not rule out the presence of other genetic variants that may be related to these health conditions.
- These tests are not a substitute for visits to a healthcare professional. You should consult with a health care professional if you have any questions or concerns about your results.
- These tests may not be able to determine a result for all variants analyzed.
- Different companies offering a genetic risk test may be measuring different genetic variants for the same condition, so you may get different results from a different test.
- Some people feel a little anxious about getting genetic health results. This is normal. If you feel very anxious, you should speak to your doctor or a genetic counselor prior to collecting your sample for testing. You may also consider getting your test done by your doctor.
- As with every test the possibility for an incorrect result exists. Speak to your personal healthcare professional or a genetic counselor if your results are unexpected.

For healthcare professionals

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

Test performance

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

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

See test-specific information for each test.

Analytical performance

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

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

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

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

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

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

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

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

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

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

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

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

User studies

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

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

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

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

Specific test information
Age-Related Macular Degeneration
Alpha-1 Antitrypsin Deficiency
Celiac Disease
Familial Hypercholesterolemia
G6PD Deficiency
Hereditary Amyloidosis (TTR-Related)
Hereditary Hemochromatosis (HFE-Related)
Hereditary Thrombophilia
Late-Onset Alzheimer’s Disease
Parkinson’s Disease

Age-Related Macular Degeneration

Indications for Use

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

Special considerations

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

Clinical performance

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

Frequency of variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
Y402H (CFH)	61.7%	60.2%	57.0%	10.8%	49.5%	51.3%
A69S (ARMS2)	38.6%	41.4%	36.7%	65.8%	41.6%	56.2%

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

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 71 samples with known Y402H variant status and 79 samples with known A69S variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 97.6% to 100.0%.

Precision/Reproducibility

Precision studies were performed to test the consistency of sample measurements under different conditions. A total of 208 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Minimum DNA Input

A minimum DNA input study was performed using 6 human cell line samples with two lots of reagents. The study yielded concordant test results for all samples at a DNA concentration of 15 ng/µL.

Interfering Mutations

The performance of this test may be affected by the presence of rare mutations, such as rs573331706 and rs369496377 for Y402H, or rs532010317for A69S.

Selected References

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

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

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

Additional references included in the test report.

Alpha-1 Antitrypsin Deficiency

Indications for Use

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

Special considerations

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

Clinical performance

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

Frequency of SERPINA1 variants in 23andMe customers

Variant name	European	African	Ashkenaz	East	Hispanic	Sout

		American	i Jewish	Asian	or Latino	h 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 alpha1 antitrypsin deficiency cases in people of European descent.

Accuracy

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

Precision/Reproducibility

Precision studies were performed to test the consistency of sample measurements under different conditions. A total of 216 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Minimum DNA Input

A minimum DNA input study was performed using 5 human cell line samples and 1 saliva sample, with two lots of reagents. The study yielded concordant test results for all samples at a DNA concentration of 15 ng/µL.

Interfering Mutations

The performance of this test may be affected by the presence of rare mutations, such as rs148362959, rs533419579, rs551595739, rs201774333, rs143370956, rs1131139, rs200945035, rs373630097, and rs9630 for PI*Z, or rs538675821, rs550592374, rs141095970, rs149537225, rs1049800, and rs2230075 for PI*S.

Selected References

American Thoracic Society and European Respiratory Society. (2003) "American Thoracic Society/European Respiratory Society statement: standards for the diagnosis and management of individuals with alpha1 antitrypsin deficiency." Am J Respir Crit Care Med. 168(7): 818900.

De Serres FJ and Blanco I. (2012) "Prevalence of α1antitrypsin 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): 27795.

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
rs2187668 (HLA-DQ2.5)	22.4%	15.6%	13.2%	12.2%	22.2%	14.1%
rs7454108 (HLA-DQ8)	19.2%	9.5%	30.1%	14.1%	27.2%	17.7%

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

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 75 samples with known rs2187668 variant status and 80 samples with known rs7454108 variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 97.6% to 100.0%.

Precision/Reproducibility

Precision studies were performed to test the consistency of sample measurements under different conditions. A total of 203 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Interfering Mutations

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

Selected References

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

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

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

Additional references included in the test report.

Familial Hypercholesterolemia

Indications for Use

The 23andMe PGS Genetic Health Risk Report for Familial Hypercholesterolemia is indicated for reporting of one variant in the APOB gene and 23 variants in the LDLR

gene. This report describes if a person's genetic result is associated with an increased risk of having very high LDL cholesterol, which can lead to heart disease. This test does not describe a person's overall risk of developing heart disease, and the absence of a variant tested does not rule out the presence of other variants that may be linked to familial hypercholesterolemia. The majority of the variants in this report are found in and have been most studied in people of European and Lebanese descent, as well as in the Old Order Amish.

Special considerations

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

Clinical performance

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

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

Frequency of the APOB and LDLR variants in 23andMe customers

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

D90G (LDLR)	<0.01%	0.00%	0.00%	0.00%	<0.01%	0.00%
E101K (LDLR)	<0.01%	<0.01%	0.00%	0.00%	<0.01%	0.01%
S177L (LDLR)	<0.01%	<0.01%	0.00%	0.00%	<0.01%	0.01%
C184Y (LDLR)	<0.01%	<0.1%	0.00%	0.00%	<0.01%	0.00%
G219del (LDLR)	<0.01%	0.00%	0.09%	0.00%	<0.01%	0.00%
D221G (LDLR)	<0.01%	<0.01%	0.00%	0.00%	<0.01%	0.00%
E228K (LDLR)	<0.01%	0.00%	0.00%	<0.01%	<0.01%	0.00%
E228X (LDLR)	<0.01%	<0.01%	0.00%	<0.01%	<0.01%	0.00%
D266E (LDLR)	<0.02%	<0.01%	0.00%	0.00%	<0.01%	0.00%
S286R (LDLR)	<0.01%	0.00%	0.00%	0.00%	<0.01%	0.00%
G343S (LDLR)	0.01%	<0.01%	0.00%	<0.01%	0.01%	0.01%
E408K (LDLR)	<0.01%	<0.01%	0.00%	0.00%	<0.01%	0.01%
V429M (LDLR)	<0.01%	0.00%	0.00%	<0.01%	<0.01%	0.00%
D482N (LDLR)	<0.01%	<0.01%	0.00%	0.00%	<0.01%	0.00%
G549D (LDLR)	<0.01%	<0.01%	<0.01%	0.00%	<0.01%	0.00%
W577S (LDLR)	<0.01%	0.00%	0.00%	0.00%	0.00%	0.00%
H583Y (LDLR)	<0.01%	<0.01%	0.00%	0.14%	<0.01%	<0.02%
G592E (LDLR)	0.01%	<0.01%	0.00%	0.00%	<0.01%	0.00%
C677R (LDLR)	<0.01%	0.00%	0.00%	0.00%	<0.01%	0.00%
C681X (LDLR)	<0.01%	<0.01%	0.00%	0.00%	<0.01%	0.00%
P685L (LDLR)	<0.01%	<0.01%	0.00%	<0.01%	<0.01%	0.01%

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 3,262 samples with known variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 99.9% to 100.0%.

Precision/Reproducibility

Precision studies were performed to test the consistency of sample measurements under different conditions. A total of 20,874 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Minimum DNA Input

A minimum DNA input study was performed using 1 human cell line sample and 41 saliva samples with three lots of reagents. The study yielded concordant test results for all samples at a DNA concentration of 15 ng/µL.

Interfering Mutations

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

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

		rs574219590
	G219del	n/a
	D221G	rs538030445 rs201374693 rs577934998 rs72658857 rs34093283
	E228K/E228X	n/a
	D266E	rs150673992 rs200990725 rs143992984 rs572275000 rs375163928 rs201875602 rs531199430
	S286R	rs146651743 rs148698650
	G343S	rs2738442 rs540073140 rs1270260
	E408K	n/a
	V429M	rs534782075 rs773658037
	D482N	n/a
	G549D	rs75858813
	W577S	n/a
	H583Y	n/a
	G592E	n/a
	C677R	rs529021326 rs550649956 rs369943481 rs146869252 rs551528700
	C681X	n/a
	P685L	n/a

Selected References

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

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

Youngblom E et al. (2014). "Familial Hypercholesterolemia." [Updated 2016 Dec 8].

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 Val68Met variant in the G6PD gene. This report describes if a person has a variant associated with 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 descent.

Special considerations

- This test does not include the Asn126Asp variant in the G6PD gene. The Asn126Asp variant is not linked to G6PD deficiency but is commonly included in genetic tests for this condition.
- Genetic testing for G6PD deficiency in adults in the general population is not currently recommended by any healthcare professional organizations.

Clinical performance

The variant included in this test is most common and best studied in people of African descent. It is also found in populations with African ancestry, such as Hispanics or Latinos. Published studies estimate that approximately 11% of African Americans carry this variant.

Frequency of the G6PD Val68Met variant in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
Val68Met	0.02%	14.50%	0.00%	0.00%	1.20%	<0.07%

The Val68Met variant is expected to be responsible for up to 90% of cases of G6PD deficiency in people of African descent.

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 186 samples with known Val68Met variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 98.0% to 100.0%.

Precision/Reproducibility

Precision studies were performed to test the consistency of sample measurements under different conditions. A total of 104 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Minimum DNA Input

A minimum DNA input study was performed using 2 human cell line samples and 1 saliva sample with three lots of reagents. The study yielded concordant test results for all samples at a DNA concentration of 15 ng/µL.

Interfering Mutations

The performance of this test may be affected by the presence of rare mutations, such as rs138687036.

Selected References

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.

Additional references included in the test report.

Hereditary Amyloidosis (TTR-Related)

Indications for Use

The 23andMe PGS Genetic Health Risk Report for Hereditary Amyloidosis (TTR-Related) is indicated for reporting of the V122I, V30M, and T60A variants in the TTR gene. This

report describes if a person has variants linked to TTR-related hereditary amyloidosis, but it does not describe a person's overall risk of developing the condition. This report is most relevant for African Americans, and for people of West African, Portuguese, Northern Swedish, Japanese, Irish, and British descent.

Special considerations

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

Clinical performance

The variants included in this test are most common and best studied in African Americans, and in people of West African, Portuguese, Northern Swedish, Japanese, Irish, and British descent. Published studies estimate that approximately 50-80% of TTR-related hereditary amyloidosis cases are caused by the three variants included in this test. Additionally, approximately 10% of African Americans over the age of 60 with congestive heart failure are expected to carry the V122I variant.

Frequency of TTR variants in 23andMe customers

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

Accuracy

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

Precision/Reproducibility

Precision studies were performed to test the consistency of sample measurements under different conditions. A total of 336 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Minimum DNA Input

A minimum DNA input study was performed using 2 human cell line samples and 4 saliva samples, with three lots of reagents. The study yielded concordant test results for all samples at a DNA concentration of 15 ng/µL.

Interfering Mutations

The performance of this test may be affected by the presence of rare mutations, such as rs28933981, rs2276382, rs557320637, rs536294863, rs3700056601, rs1269882546, rs572856125, and rs12226 for V122I. No interfering mutations were identified for either V30M or T60A.

Selected References

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

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

Additional references included in the test report

Hereditary Hemochromatosis (HFE-Related)

Indications for Use

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

Special considerations

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

Clinical performance

The variants covered by this test are mainly found in people of Northern European descent. Published studies estimate that approximately 13% of people of European descent carry at least one copy of the C282Y variant, and 28.3% of people of European descent carry at least one copy of the H63D variant.

Frequency of HFE variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
C282Y	12.1%	3.9%	2.4%	0.0%	6.9%	0.3%
H63D	27.7%	9.8%	22.4%	6.2%	24.5%	17.5%

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

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 75 samples with known C282Y variant status and 83 samples with known H63D variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 97.7% to 100.0%.

Precision/Reproducibility

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

Minimum DNA Input

A minimum DNA input study was performed using 6 human cell line samples, with two lots of reagents. The study yielded concordant test results for all samples at a DNA concentration of 15 ng/µL.

Interfering Mutations

The performance of this test may be affected by the presence of rare mutations, such as rs140080192 and rs143175221 for C282Y, or rs28934889, rs147297176, rs147426902, rs556335391, and rs62625342 for H63D.

Selected References

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

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

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

Additional references included in the test report.

Hereditary Thrombophilia

Indications for Use

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

Special considerations

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

Clinical performance

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

Frequency of the tested variants in 23andMe customers

Variant name	European	African	Ashkenaz	East	Hispanic	South

		American	i Jewish	Asian	or Latino	Asian
Factor V Leiden	5.28%	1.51%	3.75%	0.04%	3.21%	2.49%
Prothrombin G20210A	2.77%	0.91%	6.87%	<0.02%	2.77%	0.12%

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

Accuracy

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

Precision/Reproducibility

Precision studies were performed to understand the consistency of sample measurements under different conditions. A total of 205 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Minimum DNA Input

A minimum DNA input study was performed using 5 human cell line samples and 1 saliva sample, with two lots of reagents. The study yielded concordant test results for all samples with a DNA concentration of 15 ng/µL.

Interfering Mutations

The performance of this test may be affected by the presence of rare mutations, such as 1689G>A and 1692A>C for Factor V Leiden, or 20207A>C for Prothrombin G20210A>C.

Selected References

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

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

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

Additional references included in the test report.

Late-Onset Alzheimer's Disease

Indications for Use

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

Special considerations

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

Clinical performance

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

Frequency of the APOE ε4 variant in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
ε4	26.02%	34.10%	21.84%	17.39%	22.44%	17.16%

Approximately 40-65% of Alzheimer's patients have one or two copies of the ε4 variant.

Accuracy

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

Precision/Reproducibility

Precision studies were performed to understand the consistency of sample measurements under different conditions. A total of 209 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Minimum DNA Input

A minimum DNA input study was performed using 4 human cell line samples and 1 saliva sample, with two lots of reagents. The study yielded concordant test results for all samples with a DNA concentration of 15 ng/µL.

Interfering Mutations

The performance of this test may be affected by the presence of rare mutations, such as rs11542041, rs573658040, or rs543363163.

Selected References

Alzheimer’s Association. (2016) “2016 Alzheimer's disease facts and figures.” Alzheimers Dement. 12(4):459-509.

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

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

Additional references included in the test report.

Parkinson’s Disease

Indications for Use

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

Special considerations

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

Clinical performance

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

Frequency of the tested variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
G2019S	0.08%	0.06%	1.88%	<0.02%	0.18%	0.00%
N370S	0.48%	0.16%	5.96%	0.00%	0.37%	0.00%

Accuracy

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

Precision/Reproducibility

Precision studies were performed to understand the consistency of sample measurements under different conditions. A total of 239 sample replicates were run across different testing

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

Minimum DNA Input

A minimum DNA input study was performed using 4 human cell line samples and 2 saliva samples, with two lots of reagents. The study yielded concordant test results for all samples with a DNA concentration of 15 ng/µL.

Interfering Mutations

The performance of this test may be affected by the presence of rare mutations, such as rs150219613 and rs183394865 for G2019S, or rs187143994 and rs111417507 for N370S.

Selected References

Farlow J et al. (1993). "Parkinson Disease Overview" In: Pagon RA et al., editors. GeneReviews. [updated 2014 Feb 27]

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.

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

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

Manufactured by:

23andMe, Inc.
899 West Evelyn
Mountain View, CA 94041-1225

Contact us:
Customer Care: 1-800-239-5230
customercare.23andme.com

PI Part Number VV-QUAL-03049
PI Version 3.0
PI Revision Date March 2019