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

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For *in-vitro* diagnostic use

Intended Use:

The 23andMe Personal Genome Service (PGS) Test detects clinically relevant variants in genomic DNA isolated from human saliva collected with the Oragene·Dx model OGD-500.001. The test uses qualitative genotyping for the purpose of reporting Genetic Health Risks (GHR). The PGS test is intended for use by adults, and is not intended for copy number variation, cytogenetic, or biochemical testing.

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.
- 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. Results should be used along with other clinical information for any medical purposes.

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 health care 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.
- The performance of these tests may be affected by the presence of rare mutations.
- 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.

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 81 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
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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
Alpha-1 Antitrypsin Deficiency
Hereditary Thrombophilia
Late-Onset Alzheimer’s Disease
Parkinson’s Disease

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.

Clinical performance

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

Frequency of SERPINA1 variants in 23andMe customers

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

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

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 207 samples with known PI*Z variant status and 202 samples with known PI*S variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 99.1% to 100%.

Precision/Reproducibility

Precision studies were performed to test the consistency of sample measurements under different conditions. A total of 2,700 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 13 human cell line samples and 3 saliva samples, with three lots of reagents. The study yielded concordant test results for all samples at a DNA concentration of 15 ng/μL.

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.

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.

Clinical performance

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

Frequency of the tested variants in 23andMe customers

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

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

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 201 samples with known prothrombin G20210A variant status and 203 samples with known Factor V Leiden variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 98.0% to 100%.

Precision/Reproducibility

Precision studies were performed to understand the consistency of sample measurements under different conditions. A total of 2,106 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 7 human cell line samples and 1 saliva sample, with three lots of reagents. The study yielded concordant test results for all samples with a DNA concentration of 15 ng/µL.

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 resultsfor 544 samples with known ε4 variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 99.0% to >99.9%.

Precision/Reproducibility

Precision studies were performed to understand the consistency of sample measurements under different conditions. A total of 957 sample replicates were run across different testing conditions. This study yielded correct results for >99% of samples across all conditions tested. The study had >99% reproducibility and >99% repeatability.

Minimum DNA Input

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

Selected References

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 80 samples with known G2019S variant status and 112 samples with known N370S variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence interval was 98.1% to 100%.

Precision/Reproducibility

Precision studies were performed to understand the consistency of sample measurements under different conditions. A total of 1,573 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 16 human cell line samples and 1 saliva sample, with three lots of reagents. The study yielded concordant test results for all samples with a DNA concentration of 15 ng/µL.

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

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