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

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IVD

For *in-vitro* diagnostic use

Intended use

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

Gene	Variant(s)*
CYP2C19	*2, *3, *17
DPYD	*2A, rs67376798
SLCO1B1	*5

This report is for over-the-counter use by adults over the age of 18, and provides genetic information to inform discussions with a healthcare professional about metabolism of therapeutics. This report describes if a person has variants associated with the metabolism of some therapeutics, but does not describe if a person will or will not respond to a particular therapeutic, and does not describe the association between detected variants and any specific therapeutic. The PGS Pharmacogenetic Reports are not a substitute for visits to a healthcare professional. The information provided by this report should not be used to start, stop, or change any course of treatment.

Summary and explanation of the test

23andMe Pharmacogenetic Reports are tests you can order and use at home to learn about your DNA from a saliva sample. The tests work by detecting specific gene variants. Your genetic results are returned to you in a secure online account on the 23andMe website.

Indications for use
See test-specific information for each test

Important considerations

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

Other warnings, precautions, and limitations

- Do not use your results to start, stop, or change any course of treatment.
- This test does not provide information on specific therapeutics.
- Results from this test should not be used to make medical decisions. Results should be confirmed in a clinical setting with independent genetic testing before taking any medical action.
- This test does not detect all genetic variants related to drug metabolism. The absence of a variant tested does not rule out the presence of other genetic variants that may be related to drug metabolism.
- This test is not a substitute for visits to a healthcare professional. You should consult with a healthcare professional if you have any questions or concerns about your results.
- This test may not be able to determine a result for all variants analyzed.
- Different companies offering genetic testing may be measuring different genetic variants for drug metabolism, so you may get different results from a different test.
- As with every test the possibility for an incorrect result exists. Speak to your personal healthcare professional or a genetic counselor if your results are unexpected.

Test performance

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

Clinical performance

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

See test-specific information for each test.

Analytical performance

Accuracy

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

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

Precision/Reproducibility

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

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

Minimum DNA Input

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

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

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

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

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

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

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

User studies

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

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

PGS test report user comprehension study
User comprehension studies were performed to assess how well people understand the PGS Pharmacogenetics Reports. A diverse group of people answered questions about the test reports in a controlled lab-based setting. Comprehension was tested through a two-step

process. First, participants' understanding of genetics was tested prior to viewing the educational module and test reports. Second, participants were shown the educational module and the test reports. Participants then completed the test report comprehension survey.

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

Specific test information
CYP2C19 Drug Metabolism
DPYD Drug Metabolism
SLCO1B1 Drug Transport

CYP2C19 Drug Metabolism

Indications for Use

The 23andMe Personal Genome Service Pharmacogenetics Report for CYP2C19 is indicated for reporting of the *2, *3, and *17, variants in the CYP2C19 gene. This report is for over-the-counter use by adults over the age of 18, and provides genetic information to inform discussions with a healthcare professional about processing of therapeutics. This report describes if a person has CYP2C19 variants associated with the processing of some therapeutics, but does not describe if a person will or will not respond to a particular therapeutic, and does not describe the association between detected variants and any specific therapeutic. This test is not a substitute for visits to a healthcare professional. The information provided by this report should not be used to start, stop, or change any course of treatment.

Clinical performance

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

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

Allele frequency

The Pharmacogenetics reports test for three (3) variants in the CYP2C19 gene: *2, *3, and *17. These variants are found in many ethnicities, at varying allele frequencies.

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

Allele frequencies in 23andMe customers

Ancestry group	*2	*3	*17
European	14.62%	0.02%	21.76%

African American	17.34%	0.11%	21.78%
Ashkenazi Jewish	13.27%	<0.01%	21.57%
East Asian	30.65%	6.50%	0.86%
Hispanic/Latino	13.24%	0.14%	16.30%
South Asian	33.62%	0.34%	16.96%
Middle Eastern	11.19%	0.12%	21.18%
Other	18.71	1.77%	16.24%

Analytical performance

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 145 samples with known *2 variant status, 132 samples with known *3 variant status, and 141 samples with known *17 variant status. 17 samples did not pass initial quality control, and were not assigned a genotype. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence intervals for the *2, *3, and *17 variants were 92.5 % to 100%, 91.0% to 100%, and 92.1% to 100%, respectively.

Genotype	BeadChip Calls				% PPA	% NPA	95% CI
	Correct	Incorrect	No Call	FQC[1]			
CYP2C19 *2 GG **Homozygous Common**	47	0	0	3	**100**	**100**	**92.5-100**
CYP2C19 *2 AG **Heterozygous**	49	0	0	0	**100**	**100**	**92.7-100**
CYP2C19 *2 AA **Homozygous Rare**	49	0	0	3	**100**	**100**	**92.7-100**

CYP2C19 *3 GG **Homozygous Common**	48	0	0	2	**100**	**100**	**92.6-100**
CYP2C19 *3 AG **Heterozygous**	45	0	0	3	**100**	**100**	**92.1-100**
CYP2C19 *3 AA **Homozygous Rare**	39	0	0	1	**100**	**100**	**91.0-100**
CYP2C19 *17 CC **Homozygous Common**	49	0	0	1	**100**	**100**	**92.7-100**
CYP2C19 *17 CT **Heterozygous**	45	0	0	4	**100**	**100**	**92.1-100**
CYP2C19 *17 TT **Homozygous Rare**	47	0	0	0	**100**	**100**	**92.5-100**

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

Precision/Reproducibility

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

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

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

Minimum DNA input

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

Interfering mutations

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

*2: rs566311971, rs879130837
*3: rs186489608, rs200936950, rs191690054, rs200025269
*17: rs576566073, rs545523674, rs540392908, rs17880036, rs1158729, rs1262360236, rs561205449, rs185375194

Selected References

1. Caudle KE et al. (2017). "Standardizing terms for clinical pharmacogenetic test results: consensus terms from the Clinical Pharmacogenetics Implementation Consortium (CPIC)." Genet Med. 19(2):215-223.
2. Pratt VM et al. (2018). "Recommendations for Clinical CYP2C19 Genotyping Allele Selection: A Report of the Association for Molecular Pathology." J Mol Diagn. 20(3):269-276.
3. Whirl-Carrillo M et al. (2012). "Pharmacogenomics knowledge for personalized medicine." Clin Pharmacol Ther. 92(4):414-7.

DPYD Drug Metabolism

Indications for Use

The 23andMe Personal Genome Service Pharmacogenetics Report for DPYD is indicated for reporting of the *2A and D949V (rs67376798) variants in the DPYD gene. This report is for over-the-counter use by adults over the age of 18, and provides genetic information to inform discussions with a healthcare professional about processing of therapeutics. This report describes if a person has DPYD variants associated with the processing of some therapeutics, but does not describe if a person will or will not respond to a particular therapeutic, and does not describe the association between detected variants and any specific therapeutic. This test is not a substitute for visits to a healthcare professional. The information provided by this report should not be used to start, stop, or change any course of treatment.

Clinical performance

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

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

Allele frequency

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

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

Allele frequencies in 23andMe customers

Ancestry group	*2A	D949V
European	0.48%	0.55%
African American	0.13%	0.18%

Ashkenazi Jewish	0.55%	0.01%
East Asian	<0.01%	<0.01%
Hispanic/Latino	0.26%	0.43%
South Asian	0.56%	0.06%
Middle Eastern	0.42%	0.09%
Other	0.35%	0.26%

Analytical performance

Accuracy

23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 70 samples with known *2A variant status, and 114 samples with known D949V variant status. All samples passed initial quality control. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence intervals for the *2A, and D949V variants were 83.9 % to 100%, and 88.1% to 100%, respectively.

Genotype	BeadChip Calls				PPA	NPA	95% CI
	Correct	Incorrect	No Call	FQC[1]			
***2A DPYD CC Homozygous Common**	25	0	0	0	**100**	**100**	**86.3-100**
***2A DPYD CT Heterozygous**	24	0	0	0	**100**	**100**	**85.8-100**
***2A DPYD TT Homozygous Rare**	21	0	0	0	**100**	**100**	**83.9-100**
D949V DPYD TT Homozygous Common	51	0	0	0	**100**	**100**	**93.0-1000**
D949V DPYD AT Heterozygous	34	0	0	0	**100**	**100**	**89.7-100**
D949V DPYD AA Homozygous Rare	29	0	0	0	**100**	**100**	**88.1-100**

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

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

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

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

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

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

*2A (rs3918290): rs76551168, rs369990607, rs3918289, rs200296941, rs17376848

Selected References

1. Caudle KE et al. (2017). "Standardizing terms for clinical pharmacogenetic test results: consensus terms from the Clinical Pharmacogenetics Implementation Consortium (CPIC)." Genet Med. 19(2):215-223.
2. Whirl-Carrillo M et al. (2012). "Pharmacogenomics knowledge for personalized medicine." Clin Pharmacol Ther. 92(4):414-7.

SLCO1B1 Drug Transport

Indications for Use

The 23andMe Personal Genome Service Pharmacogenetics Report for SLCO1B1 is indicated for reporting of the c.521T>C variant in the SLCO1B1 gene. This report is for over-the-counter use by adults over the age of 18, and provides genetic information to inform discussions with a healthcare professional about processing of therapeutics. This report describes if a person has a SLCO1B1 variant associated with the processing of some therapeutics, but does not describe if a person will or will not respond to a particular therapeutic, and does not describe the association between the detected variant and any specific therapeutic. This test is not a substitute for visits to a healthcare professional. The information provided by this report should not be used to start, stop, or change any course of treatment.

Clinical performance

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

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

Allele frequency

The pharmacogenetics report tests for one (1) variant in the SLCO1B1 gene: c.521T>C, *5. This variant is found in many ethnicities, at varying allele frequencies.

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

Allele frequencies in 23andMe customers

Ancestry group	c.521T>C, *5
European	15.99%
African American	5.21%

Ashkenazi Jewish	18.37%
East Asian	12.59%
Hispanic/Latino	13.61%
South Asian	5.00%
Middle Eastern	17.75%
Other	14.49%

Analytical performance

Accuracy
23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 101 samples with known c.521T>C, *5 variant status. Agreement between the two methods was >99% for all samples analyzed. The 95% confidence intervals for the c.521T>C, *5 variant was 86.8% to 100%.

Genotype	BeadChip Calls				PPA	NPA	95% CI
	Correct	Incorrect	No Call	FQC[1]			
*5 SLCO1B1 TT Homozygous Common	45	0	0	0	100	100	92.1-100
*5 SLCO1B1 CT Heterozygous	30	0	0	0	100	100	88.4-100
*5 SLCO1B1 CC Homozygous Rare	26	0	0	0	100	100	86.8-100

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

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

A total of 929 *5 SLCO1B1 replicates from 6 unique samples were tested across different testing conditions. 43 replicates did not pass quality control acceptance criteria and were not assigned a genotype. Only sample replicates that passed quality control and produced a genotype for the

23andMe test were included in the calculation for percent agreement.

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

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

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

c521T>C (*5, rs4149056): rs74541382, rs141467543, rs200331427, rs4149057

Selected References

1. Caudle KE et al. (2017). "Standardizing terms for clinical pharmacogenetic test results: consensus terms from the Clinical Pharmacogenetics Implementation Consortium (CPIC)." Genet Med. 19(2):215-223.
2. Whirl-Carrillo M et al. (2012). "Pharmacogenomics knowledge for personalized medicine." Clin Pharmacol Ther. 92(4):414-7.

References

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

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