510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K221885

B Applicant

23andMe, Inc.

C Proprietary and Established Names

23andMe Personal Genome Service (PGS) Pharmacogenetic Reports

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
QDJ	Class II	21 CFR 862.3364 - Pharmacogenetic Assessment System	CH - Clinical Chemistry

II Submission/Device Overview:

A Purpose for Submission:

Modification of the SLCO1B1 report

B Measurand:

Genotype of select alleles in Cytochrome P450 2C19 (CYP2C19), 2C9 (CYP2C9), 2D6 (CYP2D6), 3A5 (CYP3A5), UDP glucoronosyltransferase family member A1 (UGT1A1), dihydropyrimidine dehydrogenase (DPYD), thiopurine methyltransferase (TPMT), solute carrier organic anion transporter family member 1B1 (SLCO1B1)

C Type of Test:

Qualitative genotyping microarray

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for 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 reporting of the following variants:

Gene	Variant(s)
CYP2C19	*2, *3, *17
CYP2C9	*2, *3, *5, *6, rs7089580
CYP3A5	*3
UGT1A1	*6, *28
DPYD	*2A, rs67376798
TPMT	*2, *3C
SLCO1B1	c.521T>C (rs4149056)
CYP2D6	*2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *15, *17, *20, *29, *35, *40, *41

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.

The 23andMe Personal Genome Service pharmacogenetic reports for CYP2C9, CYP3A5, UGT1A1, DPYD, TPMT and CYP2D6 describe if a person has variants associated with 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.

23andMe Personal Genome Service pharmacogenetics report for CYP2C19 describes if a person has variants associated with metabolism of some therapeutics and provides interpretive drug information regarding the potential effect of the identified metabolizer phenotype on citalopram and clopidogrel therapy.

23andMe Personal Genome Service pharmacogenetics report for SLCO1B1 describes if a person has variants associated with the processing of some therapeutics and provides interpretive drug

information regarding the potential effect of the identified transport function phenotype on simvastatin therapy.

The PGS Pharmacogenetic Reports are not a substitute for visits to a healthcare professional. The information provided by this report should not be used to start, stop, or change any course of treatment.

C Special Conditions for Use Statement(s):

OTC - Over The Counter

Warnings, precautions, and limitations for CYP2C9, CYP3A5, UGT1A1, DPYD, TPMT, CYP2D6:

● Do not use your results to start, stop or change any course of treatment.
● Results from this test should not be used to make medical decisions. Results should be confirmed by an independent genetic test prescribed by your own healthcare provider before taking any medical action.
● This test does not provide information on associations between specific DNA variants and any specific therapeutic.
● This test does not diagnose any health conditions, predict drug response, provide medical advice, or determine whether a medication is indicated for the user.
● This test does not determine if a person will or will not respond to a particular therapeutic.
● This test does not detect all genetic variants related to drug metabolism. The absence of a variant tested does not rule out the presence of other genetic variants that may be related to drug metabolism.
● This test is not a substitute for visits to a healthcare professional. You should consult with a healthcare professional if you have any questions or concerns about your results.
● This test may not be able to determine a result for all variants analyzed.
● Different companies offering genetic testing may be measuring different genetic variants for drug metabolism, so you may get different results from a different test.
● As with every test the possibility for an incorrect result exists. Speak to your personal healthcare professional or a genetic counselor if your results are unexpected.

Warning, precautions, and limitations specific for CYP2C19 and SLCO1B1:

● Do not use your results to start, stop or change any course of treatment.
● This test does not diagnose any health conditions, provide medical advice, or determine whether a medication is indicated for the user.
● This test provides interpretive drug information on citalopram and clopidogrel (CYP2C19) and simvastatin (SLCO1B1).
● This test does not determine if a person will or will not respond to a particular therapeutic.
● This test does not detect all genetic variants related to drug metabolism. The absence of a variant tested does not rule out the presence of other genetic variants that may be related to drug metabolism.
● This test is not a substitute for visits to a healthcare professional. You should consult with a healthcare professional if you have any questions or concerns about your results.
● This test may not be able to determine a result for all variants analyzed.
● For CYP2C19 only: This test does not provide interpretive drug information for the CYP2C19 *3/*17 genotype or other CYP2C19 genotype combinations where the predicted metabolizer profile cannot be interpreted. In addition, results for these genotypes should be confirmed by an

independent genetic test that is prescribed by your own healthcare provider before taking any medical action.
● Different companies offering genetic testing may be measuring different genetic variants for drug metabolism, so you may get different results from a different test.
● As with every test the possibility for an incorrect result exists. Speak to your personal healthcare professional or a genetic counselor if your results are unexpected.

D Special Instrument Requirements:

Same as described in DEN140044.

IV Device/System Characteristics:

A Device Description:

The 23andMe PGS is a non-invasive DNA testing service that uses qualitative genotyping. It is a direct-to-consumer, over-the-counter, DNA genetic test. A user's saliva is self-collected using the Oragene·Dx device manufactured by DNA Genotek, Inc. (previously cleared under K141410), which consists of a sealable collection tube containing a stabilizing buffer solution. Once the sample is collected, it is shipped to one of two Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories for testing.

DNA is isolated from the saliva and tested in a multiplex assay using a customized genotyping beadchip, reagents, and instrumentation. The multiplex assay simultaneously tests for more than 600,000 variants, including those for the previously authorized PGS test indications.

The raw data is generated by the scanning instrument's software, and then sent to 23andMe (the Manufacturer). The data are analyzed using the Manufacturer's proprietary software, and a genotype is determined for each tested variant. The results for certain of these variants, as noted in the indications for use, are used to generate personalized reports for users that provide information about the predicted metabolic or transporter function of the tested variants. Personalized reports are generated for each user to provide results of the testing performed. These reports tell the user which variant(s) has/have been detected in their sample and provide information on the predicted metabolizer or transporter profile associated with the variant(s). If no variant is detected, that information is also provided. The personalized reports are intended to present scientific concepts to users in an easy-to-understand format. The reports provide information about the association between the detected variant and the predicted metabolic or transport function that has been associated with the metabolism or transport of some drugs, further described below.

The 23andMe PGS Pharmacogenetic Reports detect 33 variants in 8 genes: CYP2C19, CYP2C9, CYP3A5, UGT1A1, DPYD, TPMT, SLCO1B1, and CYP2D6. The 23andMe PGS Pharmacogenetic Reports provide information on the associated enzyme or protein function and the predicted metabolizer or transporter phenotype for variants in drug metabolizing enzymes: CYP2C19, CYP2C9, CYP3A5, UGT1A1, DPYD, TPMT, SLCO1B1, and CYP2D6. The metabolizer or transporter phenotypes and corresponding identification is described in DEN180028.

In this 510(k) submission, the sponsor submitted additional analytical validation data demonstrating sufficient analytical accuracy and reliability such that the limitation statement regarding independent confirmation of the result required per the Special Control (2)(iv) of 21 CFR 862.3364 was no longer required in the labeling for the SLCO1B1 report.

The 23andMe PGS Pharmacogenetic Report for SLCO1B1 includes a drug specific test report for simvastatin. The test report may describe the predicted SLCO1B1 transporter protein function (i.e., normal, decreased, poor) based on the user's genotype inferred transporter phenotype and the predicted response to simvastatin (i.e., likely typical or increased chance of experiencing side effects). Other possible reported outcomes are that the result cannot be determined or the result cannot be interpreted.

B Principle of Operation:

The PGS is indicated to be performed using a genotyping BeadChip assay, which covers more than 600,000 genetic markers. The BeadChip consists of silicon wafers etched to form wells loaded with silica beads, on which oligonucleotide capture probes are immobilized. DNA from saliva is fragmented and captured on a bead array by hybridization to immobilized SNP-specific primers, followed by extension with hapten-labeled nucleotides. The primers hybridize adjacent to the SNPs and are extended with single nucleotide(s) corresponding to the variant allele. The incorporated hapten-modified nucleotides are detected by adding fluorescently labeled antibodies in several steps to amplify the signals. Instrumentation is used for extraction and processing of the DNA, and for scanning the BeadChip to quantify the results. The genotype content is separated, analyzed, and then integrated into pre-defined report templates specific for each condition associated with each genotype. Genotypes are determined using two software packages. For 23andMe PGS Pharmacogenetics Report, the variants detected are:

Gene	Variants
CYP2C19	*2, *3, *17
CYP2C9	*2,*3,*5,*6, rs7089580
CYP3A5	*3
UGT1A	*6, *28
DPYD	*2A, rs67376798
TPMT	*2, *3C
SLCO1B1	c.521T>C (rs4149056)
CYP2D6	*2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *15, *17, *20, *29, *35, *40, *41

V Substantial Equivalence Information:

A Predicate Device Name(s):

23andMe Personal Genome Service (PGS) Pharmacogenetic Reports

B Predicate 510(k) Number(s):

K193492

C Comparison with Predicate(s):

Device & Predicate Device(s):	K221885	K193492
Device Trade Name	23andMe Personal Genome Service (PGS) Pharmacogenetic Reports	23andMe Personal Genome Service (PGS) Pharmacogenetic Reports
General Device Characteristic Similarities		
Intended Use	Provides genetic information to inform discussion with a healthcare professional about metabolism of therapeutics	Same
Collection Kit	Oragene·Dx® saliva collection device (OGD-500.001)	Same
Reagents	Illumina Infinium HTS Extra Assay Reagents	Same
BeadChip	Illumina Global Screening Array customized for the PGS. The chip is designed to detect specific single nucleotide polymorphisms (SNPs) as well as other genetic variants; all markers refer to specific positions in the National Center for Biotechnology Information (NCBI) reference human genome.	Same
Sample Matrix	Saliva	Same
General Device Characteristic Differences		
SLCO1B1 Report	Provides interpretive drug information regarding the potential effect of the identified transport function	Does not provide interpretive drug information regarding the potential effect of the identified transport

	phenotype on simvastatin therapy. Does not require confirmatory testing.	function phenotype on simvastatin therapy. Requires confirmatory testing.

VI Standards/Guidance Documents Referenced:

- Special Controls 21 CFR 862.3364, established in DEN180028

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

Precision studies were performed to assess the repeatability and reproducibility of the 23andMe Personal Genome Service (PGS) test for the variant included in the Pharmacogenetics (PGt) report for SLCO1B1 Drug Transport. The studies were designed to determine the imprecision due to assay run, lot, instrument, operator, day, and site. Genotypes of the DNA samples were confirmed using bidirectional Sanger sequencing.

The studies were performed at two sites across three days using three operator teams at each site. Six saliva samples were used in this study. Samples were genotyped in a blinded fashion using three lots of reagents and three instrument sets. All replicates that failed quality control (FQC) were rerun once. If the sample failed the rerun, it was given a result of FQC (failed QC). If a sample replicate passed overall laboratory QC, but did not produce a result for a specific variant, the result for that variant is designated as a "no call".

Results obtained are summarized below stratified by genotype and site.

Genotype	Number of samples (81 replicates per sample)	Number of total replicates (including FQCs* and no calls)	Number of Correct Calls	Number of Incorrect Calls	Number of FQCs* (First run)	Number of No Calls
Site 1						
TT (Homozygous Common)	2	162	161	0	1	0
CT (Heterozygous)	3	243	236	0	7	0
CC (Homozygous Rare)	1	81	81	0	0	0
Site 2						
TT (Homozygous Common)	2	162	160	0	2	0
CT (Heterozygous)	3	243	227	0	16	0
CC (Homozygous Rare)	1	81	55	0	25	0

*FQC=Failed quality controls

After rerun of the first-run FQCs, there were 162 correct calls for the TT genotype and 243 correct calls for CT at Site 1. At Site 2, after rerun there were 162 correct calls for the TT genotype, 243 correct calls for CT, and 80 correct calls for CC. One CC sample at Site 2 received an FQC result after rerunning. No incorrect calls were observed in this study.

2. Linearity:

Not applicable.

3. Analytical Specificity/Interference:

Endogenous and Exogenous Substances
A series of studies were conducted to assess the effects of endogenous substances, exogenous substances, microbial substances, and smoking on the 23andMe PGS Test. The results of the endogenous and exogenous interference studies can be found in the Decision Summary for DEN140044.

Interfering Mutations
In the labeling, the sponsor identified the following rare mutations that may interfere with the performance of the test: rs74541382, rs141467543, rs200331427, and rs4149057.

4. Assay Reportable Range:

   Not applicable.

5. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):

   The traceability, stability and expected values for the device were previously reviewed in DEN140044.

6. Detection Limit:

   The Limit of Detection (LoD) study was performed to confirm the lowest concentration of DNA, starting from intended use samples, that is necessary for successful assignment of correct genotypes. Study samples were saliva samples and included homozygous common (2 samples), heterozygous common (3 samples), and homozygous rare genotypes (1 sample).

   DNA was extracted from the samples according to laboratory SOPs. Three replicates of each sample were diluted to three different DNA concentrations (5, 15, and 50 ng/µl) and genotyped by the PGS test in a blinded fashion using 3 lots of reagents. To confirm the genotype call, each sample was sequenced by bidirectional Sanger sequencing. Genotype calls from the PGS test were compared with genotypes from Sanger sequencing to determine the rates of correct genotype calls at each DNA concentration.

   This study yielded 100% correct calls per genotype for all samples across all reagent lots, at all sample concentrations tested. Therefore, the LoD is confirmed at the lowest concentration tested (5 ng/µL). The performance requirement for the PGS test, specified in the laboratory standard operating procedures (SOPs), is set at a minimum of 15 ng/µL DNA and maximum of 50 ng/µL DNA.

7. Assay Cut-Off:

   Not applicable.

B Comparison Studies:

1. Method Comparison:

   Accuracy was evaluated through calculation of agreement of the genetic variant determinations between the 23andMe PGS test results and Sanger bidirectional sequencing (comparator) results. Genotyping results of saliva samples were compared between the PGS test and bidirectional sequencing to calculate positive and negative percent agreement (PPA and NPA) with the sequencing results used as the reference. The overall 95% confidence interval for the correct calls for the c.521T>C variant was 97.1% to 100% (for all c.521T>C genotype combinations). The comparison study results are shown below per sample genotype.

Genotype	Correct Calls[1]	Incorrect Calls	No Calls	Failed Quality Controls	% PPA	% NPA	95% Confidence Interval[2]
TT (Homozygous Common)	45	0	0	0	100	100	93.6-100%
CT (Heterozygous)	30	0	0	0	100	100	90.5-100%
CC (Homozygous Rare)	26	0	0	0	100	100	89.1-100%

[1] Relative to bidirectional Sanger sequencing
[2] mid-p method

In a separate study, saliva samples were selected blindly from a biobank to mitigate the risk of false-negative and false-positive results potentially influenced by selecting samples with previously-determined genotypes. Genotyping results were compared between the PGS test and bidirectional sequencing to calculate percent agreement with the sequencing results used as the reference. The comparison study results are shown below per sample genotype. The overall 95% confidence interval for the correct calls for the c.521T>C (rs4149056) variant was 98.8% to 100% (for all genotype combinations).

Genotype	Correct Calls[1]	Incorrect Calls	No Calls	Failed Quality Controls	% PPA	% NPA	95% Confidence Interval[2]
TT (Homozygous Common)	176	0	0	0	100	100	98.3-100%
CT (Heterozygous)	73	0	0	0	100	100	96.0-100%
CC (Homozygous Rare)	7	0	0	0	100	100	65.2-100%

[1] Relative to bidirectional Sanger sequencing
[2] mid-p method

2. Matrix Comparison:

   Not applicable.

C Clinical Studies:

1. Clinical Sensitivity:

   Not applicable.

2. Clinical Specificity:

   Not applicable.

3. Other Clinical Supportive Data (When 1. and 2. Are Not Applicable):

   i. Potential effect of genetic result on simvastatin therapy: The predicted SLCO1B1 transporter phenotypes and the resulting likelihood of side effects from simvastatin were

identified from data in the literature.

ii. User Comprehension Study: The user comprehension study previously described for DEN180028 was leveraged to support the test reports in K221885. Information regarding the user comprehension testing can be found in the Decision Summary for DEN180028.

In addition to supportive user comprehension testing, prior to opening a drug specific test report, the user must actively agree to the following statements:

> "I understand that I should always take my medications as directed by my healthcare provider.
>
> I will NOT use my results to start, stop, or change any medication on my own."

D Clinical Cut-Off:

Not applicable.

E Expected Values/Reference Range:

The package insert and user test reports include allele frequencies from 23andMe customers. The package insert indicated that this pharmacogenetics report tests for one (1) variant in the SLCO1B1 gene: c.521T>C (rs4149056:C). 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.

Ancestry Group	c.521T>C (rs4149056:C)
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%

VIII Proposed Labeling:

The labeling supports the finding of substantial equivalence for this device.

IX Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.