510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K193492

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 CYP2C19 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 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	*5
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, SLCO1B1 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 pharmacogenetic reports 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.

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

Special Conditions for Use Statements for CYP2C9, CYP3A5, UGT1A1, DPYD, TPMT, SLCO1B1, CYP2D6 reports

● 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 that is prescribed by your attending physician 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 report 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.

Special Conditions for Use Statements specific for the CYP2C19 report

● 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 certain therapeutics.
● This report 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.
● This test does not provide interpretive drug information for the CYP2C19 *3/*17 heterozygous genotype. In addition, results for this genotype should be confirmed by an independent genetic test that is prescribed by your attending physician 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 referenced 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 500,000 variants, including those for the previously authorized indications, as well as for the indication proposed herein.

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 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 metabolic function of the specific genetic variants. The genetic variants detected by the test are associated with the metabolism of some therapeutics. If no variant is detected, that information is also provided. If the association between the predicted metabolic function and the combination of detected variants has not been established, the report indicates that the results cannot be determined. 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 function that has been associated with the metabolism of some drugs, further described below. The reports are designed to help users understand the meaning of their results and inform conversations with their doctor or other healthcare professional.

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

In this 510(k), 23andMe submitted additional analytical validation for CYP450 2C9 in saliva samples. This robust analytical data demonstrating appropriate analytical accuracy and reliability was sufficient 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 CYP2C19 report.

The 23andMe PGS Pharmacogenetics Report for CYP2C19 also includes drug specific test reports for two drugs metabolized by CYP2C19, citalopram and clopidogrel. These test reports may indicate a likely typical response to medication is expected based on the users genotype inferred metabolizer phenotype. Alternatively, the reports may indicate for clopidogrel that the medication is less likely to be effective, based on the users genotype inferred metabolizer phenotype. For citalopram, the test reports may indicate that the user is at increased risk of side effects, based on the users genotype inferred metabolizer phenotype. Other possible outcomes for either test report 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 500,000 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 a single nucleotide 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 the BeadChip is used for scanning and quantification of 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
CYP2D6	*2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *15, *17, *20, *29, *35, *40, *41
CYP3A5	*3
TPMT	*2, *3C
DPYD	*2A, rs67376798
UGT1A	*6, *28
SLCO1B1	*5

V Substantial Equivalence Information:

A Predicate Device Name(s):

23andMe Personal Genome Service (PGS) Pharmacogenetic Reports

B Predicate 510(k) Number(s):
DEN180028

C Comparison with Predicate(s):
D

Device & Predicate Device(s):	K193492	DEN180028
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
Reagents	Illumina Infinium HTS Assay Reagents (Same reagents, different packaging)	Illumina Infinium HTS Extra Assay Reagents
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

Collection kit	Oragene Dx Saliva collection device (OGD-500.001)	Same
General Device Characteristic Differences		
CYP2C19 Report	Provides interpretive drug information regarding the potential effect of the identified metabolizer phenotype on citalopram and clopidogrel therapy Does not require confirmatory testing	Does not provide interpretive drug information for any drugs Confirmatory testing required for all reports

VI Standards/Guidance Documents Referenced:

None.

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:
The reproducibility information for this device that was previously described in the Decision Summary for DEN180028 was confirmed with intended use specimens (saliva) Information from a homozygous rare *3/*3 intended use sample was provided in DEN180028. Reproducibility studies were conducted for the three CYP2C19 alleles reported by the 23andMe PGS Pharmacogenetics Report for CYP2C19. The reproducibility 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 study was performed at two sites across three days using three operator teams at each site. Samples were genotyped in replicates of three using three lots of reagents and three instrument sets. 6 saliva samples were included in this study, in addition to the *3/*3 sample included in DEN180028, covering a representative set of the genotypes detected by the device. Information regarding samples that failed quality control (FQC) was also for the first run was also provided. All FQC replicates were rerun once in one confirmatory run by one operator team, using the corresponding reagent lot from the initial QC failure. All samples produced the correct genotype when rerun. No incorrect calls or no calls were observed in this study.

Results obtained are summarized below stratified by genotype and site:

CYP2C19*2

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						
Homozygous Common (GG)	2	162	147	0	15	0
Heterozygous (AG)	2	162	149	0	13	0
Homozygous Rare (AA)	2	162	149	0	13	0
Site 2						
Homozygous Common (GG)	2	162	162	0	0	0
Heterozygous (AG)	2	162	162	0	0	0
Homozygous Rare (AA)	2	162	162	0	0	0

*FQC = Failed quality controls

CYP2C19*3

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						
Homozygous Common (GG)	2	162	147	0	15	0
Heterozygous (AG)		81	74	0	7	0
Site 2						
Homozygous Common (GG)	2	162	0	0	0	0

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
Heterozygous (AG)	1	81	0	0	0	0

*(results from a saliva sample with the homozygous rare AA genotype can be found in the Decision Summary for DEN180028)

CYP2C19*17

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						
Homozygous Common (CC)	2	162	149	0	13	0
Heterozygous (CT)	1	81	75	0	6	0
Homozygous Rare (TT)	2	162	147	0	15	0
Site 2						
Homozygous Common (CC)	2	162	162	0	0	0
Heterozygous (CT)	1	81	81	0	0	0
Homozygous Rare (TT)	2	162	162	0	0	0

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

Analyses were performed to identify potentially interfering variants within the 50-nucleotide probe-binding regions of the three CYP2C19 variants detected by this test. The results of the analysis for interfering mutations can be found in the Decision Summary for DEN180028.

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. Limit of Detection:

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 the correct CYP2C19*2, *3, and *17 variants using the 23andMe PGS test. Study samples were saliva samples from the sponsor's biobank and included homozygous common, heterozygous common, and homozygous rare genotypes for each allele.

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 with Predicate Device:

Accuracy was evaluated through calculation of agreement of the genetic variant determinations between the 23andMe PGS test results and Sanger bidirectional sequencing (comparator) results. Saliva samples were randomly selected from the 23andMe customer biobank without prior reference to genotype information. Genotyping results 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 comparison study results for each allele detected for the CYP2C19 study report are shown below:

CYP2C19 *2

Genotype	Correct Calls	Incorrect Calls	No Calls	Failed Quality Controls	% PPA	%NPA
Homozygous Common (GG)	304	0	0	0	100%	100%
Heterozygous (AG)	118	0	0	0	100%	100%
Homozygous Rare (AA)	10	0	0	0	100%	100%

CYP2C19 *3

Genotype	Correct Calls	Incorrect Calls	No Calls	Failed Quality Controls	% PPA	%NPA
Homozygous Common (GG)	432	0	0	0	100	100

CYP2C19 *17

Genotype	Correct Calls	Incorrect Calls	No Calls		Failed Quality Controls	% PPA	%NPA
Homozygous Common (CC)	279	0	0		0	100	100
Heterozygous (CT)	129	0	0		0	100	100
Homozygous Rare (TT)	17	0	0		0	100	100

In a separate study, samples were selected on the basis of ethnicity to increase the proportion of rare *3 variants in the study population. Samples were not selected on the basis of genotype.

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 for each allele detected for the CYP2C19 study report are shown below:

CYP2C19 *2

Genotype	Correct Calls	Incorrect Calls	No Calls	Failed Quality Controls	% PPA	%NPA
Homozygous Common (GG)	114	0	0	0	100%	100%
Heterozygous (AG)	91	0	0	0	100%	100%
Homozygous Rare (AA)	24	0	0	0	100%	100%

CYP2C19 *3

Genotype	Correct Calls	Incorrect Calls	No Calls	Failed Quality Controls	% PPA	%NPA
Homozygous Common (GG)	197	0	0	0	100	100
Heterozygous (AG)	31	0	0	0	100	100
Homozygous Rare (AA)	3	0	0	0	100	100

*CYP2C19 *17

Genotype	Correct Calls	Incorrect Calls	No Calls	Failed Quality Controls	% PPA	%NPA
Homozygous Common (CC)	228	0	0	0	100	100
Heterozygous (CT)	2	0	0	0	100	100

Combined results:

CYP2C19 *2

Total *2 calls	Total *2 correct calls	Total *2 Incorrect calls	PPA (%)	NPA (%)	95% CI (%)
Study 1	432	0	100	100	99.2-100%
Study 2	229	0	100	100	98.4-100%
Combined	661	0	100	100	99.4-100%

CYP2C19 *3

Total *3 calls	Total *3 correct calls	Total *3 Incorrect calls	PPA (%)	NPA (%)	95% CI(%)
Study 1	432	0	100	100	99.2-100
Study 2	231	0	100	100	98.4-100
Combined	663	0	100	100	99.5-100

CYP2C19 *17

Total *17 calls	Total *17 correct calls	Total *17 Incorrect calls	PPA (%)	NPA (%)	95% CI (%)
Study 1	425	0	100	100	99.1-100
Study 2	230	0	100	100	98.4-100
Combined	655	0	100	100	99.4-100

The combined information across both studies is presented in the following table by diplotype:

Diplotype	Study 1	Study 2	Total Results (2 Studies combined)	
	n	n	n	95% Lower Confidence Interval
*1/*1	177	89	266	98.6
*1/*2	93	79	172	97.9
*1/*3	0	20	20	83.2
*1/*17	104	2	106	96.6
*2/*2	9	24	33	89.4
*2/*3	0	11	11	71.5
*2/*17	24	0	24	85.8
*3/*3	0	3	3	29.2
*17/*17	17	0	17	80.5
Total calls	424	228	652	99.4

Confirmatory testing failed to provide a result for one or more positions for 15 samples across the two studies, leading to an incomplete genotype for these samples. The calls for individual SNPs which could be confirmed for these samples are included in the tables provided for *2, *3 and *17 accuracy, however only those samples with full genotyping information are included in the 652 correct genotypes included diplotype accuracy table above.

The additional analytical information described above is sufficient to remove the residual uncertainty about the analytical results of this test. Therefore, the test reports will no longer include the statement described in DEN180028:

“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.”

Since no information for the *3/*17 genotype was included in either of the two studies described above, the sponsor will not return interpretive information for this genotype and this report will continue to include a limitation that results for this genotype should be confirmed by an independent genetic test before taking any medical action.

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 clopidogrel and citalopram therapy: The impact of protein or enzyme function for each allele and the predicted metabolizer phenotypes were previously identified from data in the literature for each allele for each gene. The potential effect of lack of effect of each of the predicted metabolizer phenotypes on clopidogrel and citalopram therapy 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 k193492. 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 reports, the user must actively agree to the following statements:

   > "I understand that my medications should always be taken as directed by my healthcare professional.
   >
   > 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 for each test report indicated that the allele frequencies provided are from the

23andMe customer database and may not be representative of the actual allele frequencies in the presented populations. The following allele frequencies will be provided in the CYP2C19 package insert and user test report:

Ethnicity	*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%

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.