August 17, 2020

23andMe, Inc.
Marianna Frendo
Program Manager, Regulatory Affairs
223 N Mathilda Ave
Sunnyvale, CA 94086

Re: K193492
Trade/Device Name: 23andMe Personal Genome Service (PGS) Pharmacogenetic Reports
Regulation Number: 21 CFR 862.3364
Regulation Name: Pharmacogenetic Assessment System
Regulatory Class: Class II
Product Code: QDJ
Dated: July 17, 2020
Received: July 17, 2020

Dear Marianna Frendo:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal

statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801 and Part 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Kellie B. Kelm, Ph.D.
Director
Division of Chemistry and
Toxicology Devices
OHT7: Office of In Vitro Diagnostics
and Radiological Health
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2020
See PRA Statement below.

510(k) Number *(if known)*
K193492

Device Name
23andMe® Personal Genome Service® (PGS) Pharmacogenetic Reports
pharmacogenetic report for CYP2C19, CYP2C9, CYP3A5, UGT1A1, DPYD, TPMT, SLCO1B1, CYP2D6

Indications for Use *(Describe)*
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: CYP2C19
Variant(s): *2, *3, *17
Gene: CYP2C9
Variant(s): *2, *3, *5, *6, rs7089580
Gene: CYP3A5
Variant(s): *3
Gene: UGT1A1
Variant(s): *6, *28
Gene: DPYD
Variant(s):*2A, rs67376798
Gene: TPMT
Variant(s): *2, *3C
Gene: SLCO1B1
Variant(s): *5
Gene: CYP2D6
Variant(s): *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.

Type of Use *(Select one or both, as applicable)*

☐ Prescription Use (Part 21 CFR 801 Subpart D) ☒ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

This section applies only to requirements of the Paperwork Reduction Act of 1995.

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SECTION 5 – 510(k) SUMMARY

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of Safe Medical Devices Act of 1990 and 21 CFR 807.92.

The assigned 510(k) number is:

Submitter / Company
Lisa Charter
Director, Regulatory Affairs
650-933-9455
LCharter@23andMe.com
Establishment Registration Number: 3007699459
Owner Operator Number: 10029404

Company Contact
Marianna Frendo
Program Manager, Regulatory Affairs
650-933-9481 ext. 7281
MFrendo@23andMe.com

Date Prepared
14Aug2020

5.1. REGULATORY INFORMATION

Table 5.1 Proposed New Device

Type of Submission:	Traditional 510(k)
Common/Usual Name:	pharmacogenetic reports for CYP2C19, CYP2C9, CYP3A5, UGT1A1, DPYD, TPMT, SLCO1B1, CYP2D6
Trade/Proprietary Name:	23andMe Personal Genome Service (PGS) Pharmacogenetic Reports

Regulation Description:	A pharmacogenetic assessment system is a qualitative in vitro molecular diagnostic system intended to detect nucleic acid variants isolated from human specimens for the purpose of assessing the presence of genetic variants that impact the metabolism, exposure, response, risk of adverse events, dosing, or mechanisms of prescription or over-the-counter medications. The intended use of the device must not include an indication for use in supporting or sustaining human life, being of substantial importance in preventing impairment of human health, or presenting a potential, unreasonable risk of illness or injury.
Regulation Number:	21 CFR 862.3364
Product Code:	QDJ
Class:	Class II
Predicate Device:	23andMe PGS Pharmacogenetic Reports authorized on October 31, 2018 under DEN180028

5.2. INDICATIONS 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.

5.3. SUBSTANTIALLY EQUIVALENT PREDICATE DEVICE

The components of the assay are unchanged from the *de novo* authorization for the predicate device. These components include the saliva collection kit, the reagents and BeadChip, the instrumentation, the software, the test processes, and procedures.

The purpose of this traditional 510(k) submission is to modify the labeling of the 23andMe Personal Genome Service (PGS) Pharmacogenetic Reports, pharmacogenetic report for CYP2C19, to add one new indication describing interpretive drug information to two specific medications (citalopram and clopidogrel), as well as to remove the limitation language requiring confirmatory testing. Interpretive drug information will be provided to users in the pharmacogenetic report for CYP2C19, and will be accessed through medication specific links in the pharmacogenetic report for CYP2C19. Pharmacogenetic reports for the other genes authorized in DEN180028 will not be modified to include interpretive drug information, or remove the confirmatory testing limitation statement.

The pharmacogenetic report for CYP2C19 results, scientific details, and FAQs were designed and developed in the same format as the predicate device, and conform to the requirements described in DEN180028.

Specifically, the pharmacogenetic report for CYP2C19 is intended for over-the-counter, direct-to-consumer use without prescription or physician order. In both the predicate device and the proposed modified device, all customers are advised to share their results with their healthcare provider regardless of their results. Customers with altered function of the CYP2C19 enzyme are strongly advised to share their results with their healthcare provider. The proposed revised labeling of the modified device includes certain healthcare provider limitations, as required. The Package Insert has been revised to incorporate information pursuant to agreements specific to this submission such modifications necessary to remove the confirmatory testing requirement for CYP2C19, and to address the inclusion of the pharmacogenetic association information for CYP2C19, consistent with the product classification under 21 CFR 862.3364. The proposed modifications are based on the additional test system performance data submitted in this 510(k).

Warnings, precautions, and limitations for CYP2C9, CYP3A5, UGT1A1, DPYD, TPMT, SLCO1B1, 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 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.

Warning, precautions, and limitations specific for only CYP2C19

- 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.

This submission proposes an intended use for the pharmacogenetics report for CYP2C19 that does not raise new questions of safety and effectiveness and is supported by performance data collected for this purpose, or similar. As such, the modified 23andMe Personal Genome Service Pharmacogenetic Reports is substantially equivalent to the predicate device authorized under DEN180028.

5.4. DEVICE DESCRIPTION

The 23andMe Personal Genome Service (PGS) is an over-the-counter (direct-to-consumer), DNA testing service that provides information and tools for consumers to learn about and explore their DNA.

The PGS is a currently marketed, non-invasive genetic information service that combines qualitative genotyping data covering genetic ancestry, traits, and certain heritable health conditions from a single multiplex assay with descriptive information derived from peer reviewed, published genetic research studies.

Customer saliva specimens are self-collected using the Oragene·Dx® Device manufactured by DNA Genotek, Inc. cleared by FDA for use with the PGS device (K141410, DEN140044, DEN160026, DEN170046, DEN180028, and K182784), which consists of a sealable collection tube containing a stabilizing buffer solution. Once the sample is collected, it is shipped to a Clinical Laboratory Improvement Amendments (CLIA) certified laboratory for testing.

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

The raw data is generated using Illumina GenomeStudio software, and then sent to 23andMe for analysis and interpretation. The raw data received is analyzed using 23andMe's proprietary Coregen software, where a genotype is determined for each tested SNP. The results for certain of these SNPs are used to generate personalized reports for the customer that provide information about the detected genotype.

Personalized reports are generated for each user that 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 metabolizer or transporter profile associated with the variant(s). If no variant was detected, that information is also provided. The personalized reports are designed to present scientific concepts to users in an easy-to-understand format. The reports provide scientifically valid information about the metabolizer or transporter phenotype associated with the presence of a particular variant, or a combination of variants. In the pharmacogenetic report for CYP2C19, information regarding interpretive drug information to certain medications will be provided to the user in a medication "mini report", which is accessed via a link in the pharmacogenetic report for CYP2C19. The reports are designed to help users understand the meaning of their results and any appropriate actions that may be taken based on their results.

The novel components in this traditional 510(k) submission are to provide interpretive drug information to two specific medications (citalopram and clopidogrel), and to remove the limitation language requiring confirmatory testing in the 23andMe pharmacogenetic report for CYP2C19. Pharmacogenetic reports for the other genes authorized in DEN180028 will not be modified to include interpretive drug information, or remove the confirmatory testing limitation.

Engineering drawings, schematics, etc. of the 23andMe Personal Genome Service (PGS) Pharmacogenetic Reports are not applicable to this device.

5.5. TECHNOLOGICAL CHARACTERISTICS

Test Type: Qualitative genetic test for single nucleotide polymorphism detection.
Sample Type: Genomic DNA obtained from a human saliva sample.
Target of detection: Single-nucleotide polymorphism.
DNA extraction: Automated and manual methods.
Gene: CYP2C19, CYP2C9, CYP3A5, UGT1A1, DPYD, TPMT, SLCO1B1, CYP2D6
Variants: *2,*3,*17 variants in the CYP2C19 gene, *2, *3, *5, *6, rs7089580 in the CYP2C9 gene, *3 in the CYP3A5 gene, *6, *28 in the UGT1A1 gene, *2A, rs67376798 in the DPYD gene, *2, *3C in the TPMT gene, *5 in the SLCO1B1 gene, *2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *15, *17, *20, *29, *35, *40, *41 in the CYP2D6 gene
SNPs: *2(rs4244285), *3(rs4986893), *17(rs12248560)
Genotyping principle: The DNA 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 SNP allele. The incorporated hapten-modified nucleotides are detected by adding fluorescently labeled antibodies in several steps to amplify the signals. Data analysis is performed using scatter plots.
Instrument: Illumina iScan and GenomeStudio system.
Assay results: The genotype content is separated, analyzed, and then integrated into pre-defined report templates specific for each condition associated with each genotype.

Table 5.2 Substantial Equivalence

	Predicate Pharmacogenetic Reports DEN180028	**Proposed modified indication for the pharmacogenetic report for CYP2C19**	**Similarities and Differences**
Indications for Use	The 23andMe Personal Genome Service (PGS) is a qualitative genotyping assessment system applied to genomic DNA isolated from human saliva to simultaneously detect, report, and interpret genetic variants in a broad multigene test. The assessment system is intended to enable users to	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	Modification of the indication to add interpretive drug information for CPY2C19 and for removal of the requirement for

	access information about their genetics that could aid discussions with a healthcare professional. Gene: CYP2C19 Variant(s): *2, *3, *17 Gene: CYP2C9 Variant(s): *2, *3, *5, *6, rs7089580 Gene: CYP3A5 Variant(s): *3 Gene: UGT1A1 Variant(s): *6, *28 Gene: DPYD Variant(s):*2A, rs67376798 Gene: TPMT Variant(s): *2, *3C Gene: SLCO1B1 Variant(s): *5 Gene: CYP2D6 Variant(s): *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. This report describes 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	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: CYP2C19 Variant(s): *2, *3, *17 Gene: CYP2C9 Variant(s): *2, *3, *5, *6, rs7089580 Gene: CYP3A5 Variant(s): *3 Gene: UGT1A1 Variant(s): *6, *28 Gene: DPYD Variant(s):*2A, rs67376798 Gene: TPMT Variant(s): *2, *3C Gene: SLCO1B1 Variant(s): *5 Gene: CYP2D6 Variant(s): *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,	confirmatory testing. New claims are limited to the CYP2C19 variant.

	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.	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.	
Collection Kit	Oragene·Dx® saliva collection device (OGD-500.001) K141410	Oragene·Dx® saliva collection device (OGD-500.001) K141410	Same
Reagents	Illumina Infinium HTS Assay Reagents	Illumina Infinium HTS Extra Assay Reagents	Same reagents. Different

			packaging.
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.	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.
Beadpool	Customized for 23andMe	Customized for 23andMe	Same
Instruments	Tecan Evo Illumina iScan	Tecan Evo Illumina iScan	Same
Software	Genome Studio Coregen	Genome Studio Coregen	Same
Sample Matrix	Saliva	Saliva	Same
Method Comparison	>99% PPA and NPA for all genotypes	>99% PPA and NPA for all genotypes	Same

5.6. PERFORMANCE TESTING SUMMARY

The purpose of this submission is to modify the 23andMe Personal Genome Service (PGS) Pharmacogenetic Reports as follows:

1. Remove confirmatory testing requirement in the pharmacogenetic report for CYP2C19
2. Provide interpretive drug information for certain therapeutics, accessible through the pharmacogenetic report for CYP2C19

In addition to the analytical data previously reviewed during DEN180028, the Company generated additional data, and performed new method comparison, precision, and minimum DNA input studies to assess the performance of the 23andMe Personal Genome Service (PGS) pharmacogenetic reports for CYP2C19, in support of the removal of the confirmatory testing requirement and clearance.

5.6.1 Method Comparison (Accuracy)

23andMe performed a method comparison study using sequencing as the comparator to assess the accuracy of the assay. Results of the test were compared with sequencing results for samples with known *2 variant status, known *3 variant status, and known *17 variant status. The method comparison study yielded 100% overall agreement for all genotypes of each of the three variants in the CYP2C19 gene (*2 (rs4244285); *3 (rs4986893); *17 (rs12248560)) for all samples compared to Sanger sequencing. Therefore, the study passed the acceptance criteria of >99% agreement, with PPA and NPA both >99%. The method comparison study showed that the assay is comparable to bi-directional Sanger sequencing for all three of the CYP2C19 gene variants: *2 (rs4244285); *3 (rs4986893); *17 (rs12248560).

To mitigate the risk for false positive / negative results potentially influenced by selecting samples with genotypes previously determined by the assay, two method comparison studies were performed utilizing a blinded sample selection method.

In the first blinded study, from a single laboratory site on a single day, incoming saliva samples were extracted, normalized, and aliquoted onto a 96 well plate, according to laboratory SOPs. Five 96-well plates from that day were sent for Sanger sequencing at an independent laboratory. Upon completion of genotyping, results were compared to sequencing results to calculate positive percent agreement (PPA) and negative percent agreement (NPA), with the bi-directional Sanger sequencing results considered as the source of truth.

Additionally, well characterized reference samples were obtained from the Coriell Institute for Medical Research, which provided genomic DNA for the three CYP2C19 variants of interest (*2, *3, *17). Genotyping results were compared to the reference results, with the reference results considered as the source of truth.

The genotyping data demonstrated 100% concordance to the comparator source of truth, achieving the pre-defined acceptance criteria of greater than 99% PPA and greater than 99% NPA.

In the second blinded study, intended use (saliva) samples were randomly selected in an unbiased manner from the 23andMe biobank based on their East Asian genetic ancestry, in order to increase the likelihood of obtaining rare *3 allele combinations. Upon completion of genotyping, results were compared to sequencing results to calculate positive percent agreement (PPA) and negative percent agreement (NPA), with the bi-directional Sanger sequencing results considered as the source of truth.

The genotyping data demonstrated 100% concordance to Sanger sequencing, achieving the pre-defined acceptance criteria of greater than 99% PPA and greater than 99% NPA.

5.6.2 Precision (Reproducibility)

23andMe performed a precision study to evaluate the following precision parameters of the assay: intra-assay, operator-to-operator, instrument-to-instrument, and reagent lot-to-lot. for the following three variants in the CYP2C19 gene *2 (rs4244285), *3 (rs41291556), *17

(rs12248560). DNA samples were obtained from Coriell based upon their listed genotypes, or obtained from the 23andMe biobank. The precision study yielded >99% correct genotype calls for all samples across multiple days, operator teams, instruments, and reagent lots, at two (2) independent laboratory sites. The study passed the acceptance criteria of at least 99% correct calls, the study had >99% reproducibility and >99% repeatability.

In order to ensure that the assay accurately reflected the reproducibility of intended use (saliva) samples, a supplemental precision study was performed utilizing saliva samples. Intended use (saliva) samples were selected from the 23andMe customer biobank based on their putative genotype. These samples were genotyped by the 23andMe BeadChip assay in a blinded fashion over 3 days, with 3 lots of reagents, by a unique operator team per day, using 3 different serial numbers of each of 2 instruments (Tecan and iScan), at each of 2 laboratory sites. To confirm the BeadChip genotype, each sample was also sequenced by bi-directional Sanger sequencing. BeadChip genotypes were compared with sequenced genotypes to determine the rates of correct BeadChip genotype calls. The acceptance criteria is a minimum of 99% correct genotype calls at each of two laboratory sites.

Results of this supplemental precision study yielded 100% correct genotype calls for all samples across multiple days, operator teams, instruments, and reagent lots at two independent laboratory sites. Therefore, the study passed the acceptance criteria of at least 99% correct calls. There was no variation between any study conditions or any replicates for a given sample. Intended use samples representing *3 CYP2C19 AA obtained in the original precision study (DEN180028) also yielded 100% correct genotype calls for all samples across multiple days, operator teams, instruments, and reagent lots at two independent laboratory sites.

The results of this Precision study demonstrate 100% reproducibility and 100% repeatability on intended use (saliva) samples for CYP2C19.

5.6.3 Minimum DNA Input (MDI)

23andMe performed a minimum DNA input study to determine the lowest concentration of DNA that is necessary for successful assignment of the correct genotypes for three variants in the CYP2C19 gene: *2 (rs4244285), *3 (rs41291556), *17 (rs12248560). DNA samples obtained from Coriell based upon their listed genotypes, or obtained from the 23andMe biobank, were diluted to 3 different DNA concentrations using 3 lots of reagents. Results of this MDI study yielded 100% concordant test results correct genotype calls for all samples and all reagent lots tested at sample DNA concentrations of 5, 15, and 50 ng/µL. Therefore, the study passed the acceptance criteria at a sample DNA concentration of 5 ng/µL.

In order to ensure that the assay accurately reflected the performance of intended use (saliva) samples at various DNA input levels, a supplemental minimum DNA input study was performed utilizing saliva samples. Intended use (saliva) samples were selected from the 23andMe customer database based on their putative genotype. The goal of the study was to determine the lowest concentration of DNA that is necessary for successful assignment of the correct

genotypes. Each sample was diluted to 3 different DNA concentrations and genotyped in a blinded fashion using 3 lots of reagents. The MDI requirement is defined as the lowest DNA concentration at which at least 95% of samples yielded the correct call.

Results of this MDI study yielded 100% correct genotype calls for all samples and all reagent lots tested at sample DNA concentrations of 5, 15, and 50 ng/µL. Therefore, the study passed the acceptance criteria at a sample DNA concentration of 5 ng/µL. Intended use samples representing *3 CYP2C19 AA obtained in the original MDI study (DEN180028) also yielded the correct genotype calls for all samples and all reagent lots tested at all DNA concentrations, and therefore met the acceptance criteria at a sample DNA concentration of 5 ng/µL.

Table 5.3 Clinical Performance
Variant frequencies from 23andMe database and other public database

This table includes data that has been updated as of 14 March 2019, subsequent to the authorization of DEN180028.

Allele frequencies from gnomAD database were obtained from https://gnomad.broadinstitute.org/ on 14Mar2019.

Variant	Percent of 23andMe customers with variant[a]	Allele frequencies among 23andMe customers[a]	Allele frequencies from gnomAD
*2 (rs4244285:A)	**n=8,004,302 customers** European: 27.09% African American: 31.61% Ashkenazi Jewish: 24.75% East Asian: 51.87% Hispanic or Latino: 24.67% South Asian: 55.54% Middle Eastern: 21.00% Other: 33.74% **Overall: 28.15%**	**n=16,008,604 alleles** European: 14.62% African American: 17.34% Ashkenazi Jewish: 13.27% East Asian: 30.65% Hispanic or Latino: 13.24% South Asian: 33.62% Middle Eastern: 11.19% Other: 18.71% **Overall: 15.33%**	**n=192,906 alleles** European (Non-Finnish): 14.68% African: 17.76% Ashkenazi Jewish: 13.20% East Asian: 30.75% Latino: 10.12% South Asian: 32.40% European (Finnish): 17.50% Other[b]: 15.95% **Overall: 17.49%**
*3 (rs4986893:A)	**n=8,004,302 customers** European: 0.04% African American: 0.22% Ashkenazi Jewish: <0.01% East Asian: 12.49% Hispanic or Latino: 0.28% South Asian: 0.67% Middle Eastern: 0.24% Other: 3.50% **Overall: 0.61%**	**n=16,008,604 alleles** European: 0.02% African American: 0.11% Ashkenazi Jewish: <0.01% East Asian: 6.50% Hispanic or Latino: 0.14% South Asian: 0.34% Middle Eastern: 0.12% Other: 1.77% **Overall: 0.32%**	**n=282,504 alleles** European (Non-Finnish): 0.02635% African: 0.03611% Ashkenazi Jewish: 0.000% East Asian: 6.261% Latino: 0.01981% South Asian: 0.3986% European (Finnish): 0.007976% Other[a]: 0.2357% **Overall: 0.5097%**
*17 (rs12248560:T)	**n=8,004,302 customers** European: 38.74% African American: 38.79% Ashkenazi Jewish: 38.41% East Asian: 1.72% Hispanic or Latino: 29.82% South Asian: 30.73% Middle Eastern: 37.72% Other: 29.77% **Overall: 36.05%**	**n=16,008,604 alleles** European: 21.76% African American: 21.78% Ashkenazi Jewish: 21.57% East Asian: 0.86% Hispanic or Latino: 16.30% South Asian: 16.96% Middle Eastern: 21.18% Other: 16.24% **Overall: 20.17%**	**n=31,250 alleles** European (Non-Finnish): 23.14% African: 20.92% Ashkenazi Jewish: 18.97% East Asian: 0.7051% Latino: 10.07% South Asian: n/a European (Finnish): 18.84% Other[a]: 22.55% **Overall: 20.52%**

[a] Small changes to observed allele and variant frequencies are expected to occur as the database grows. Frequencies are truncated at a minimum frequency if the number of carriers is fewer than 5.
[b] Individuals were classified as "Other" by gnomAD if they did not unambiguously cluster with the major populations (i.e. EUR, NFE, AFR, SAS, EAS and AMR) in a principal component analysis.

5.7. DISCUSSION

The modified 23andMe Personal Genome Service (PGS) Pharmacogenetic Reports has an anticipated intended use under DEN180028 subject to the additional analytical data, is not technologically different than the predicate, and presents no new issues of safety or effectiveness when compared to the previously authorized predicate device (DEN180028). Specifically, this submission is for the removal of the confirmatory testing requirement and the modification of the pharmacogenetic report for CYP2C19, and provides analytical and clinical data demonstrating that the assay generates accurate results specific to the CYP2C19 variants reported in the results. Additionally, it was shown through robust user comprehension testing, previously reviewed and authorized under DEN180028, that the user can adequately interpret the results for the three variants, as well as understand interpretive drug information as presented in the pharmacogenetic report for CYP2C19.

5.8. CONCLUSION

The modifications to the 23andMe Personal Genome Service (PGS) Pharmacogenetic Reports are substantially equivalent to the predicate device DEN180028. As presented, the modified pharmacogenetic report for CYP2C19, without the confirmatory testing requirement, is a safe and effective consumer product that can safely and effectively assist customers with certain CYP2C19 genotypes in understanding how their body may respond to certain medications and encourage informed conversations with their healthcare provider.