23andMe, Inc.
Marianna Frendo
Manager Regulatory Affairs
349 Oyster Point Blvd
South San Francisco, California 94080

August 31, 2023

Re: K223597
Trade/Device Name: 23andMe® Personal Genome Service® (PGS®) Cancer Predisposition Genetic Health Risk Report for BRCA1/BRCA2 (Selected Variants)
Regulation Number: 21 CFR 866.6090
Regulation Name: Cancer Predisposition Risk Assessment System
Regulatory Class: Class II
Product Code: QAZ
Dated: November 29, 2022
Received: December 2, 2022

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.

FDA's substantial equivalence determination also included the review and clearance of your Predetermined Change Control Plan (PCCP). Under section 515C(b)(1) of the Act, a new premarket notification is not

required for a change to a device cleared under section 510(k) of the Act, if such change is consistent with an established PCCP granted pursuant to section 515C(b)(2) of the Act. Under 21 CFR 807.81(a)(3), a new premarket notification is required if there is a major change or modification in the intended use of a device, or if there is a change or modification in a device that could significantly affect the safety or effectiveness of the device, e.g., a significant change or modification in design, material, chemical composition, energy source, or manufacturing process. Accordingly, if deviations from the established PCCP result in a major change or modification in the intended use of the device, or result in a change or modification in the device that could significantly affect the safety or effectiveness of the device, then a new premarket notification would be required consistent with section 515C(b)(1) of the Act and 21 CFR 807.81(a)(3). Failure to submit such a premarket submission would constitute adulteration and misbranding under sections 501(f)(1)(B) and 502(o) of the Act, respectively. Additional information about changes that may require a new premarket notification are provided in the FDA guidance documents entitled "Deciding When to Submit a 510(k) for a Change to an Existing Device" (https://www.fda.gov/media/99812/download) and "Deciding When to Submit a 510(k) for a Software Change to an Existing Device" (https://www.fda.gov/media/99785/download).

Your device is also subject to, among other requirements, the Quality System (QS) regulation (21 CFR Part 820), which includes, but is not limited to, 21 CFR 820.30, Design controls; 21 CFR 820.90, Nonconforming product; and 21 CFR 820.100, Corrective and preventive action. Please note that regardless of whether a change requires premarket review, the QS regulation requires device manufacturers to review and approve changes to device design and production (21 CFR 820.30 and 21 CFR 820.70) and document changes and approvals in the device master record (21 CFR 820.181).

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 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,

Shyam Kalavar -S

Shyam Kalavar
Deputy Branch Chief
Molecular Pathology and Cytology Branch
Division of Molecular Genetics
and Pathology
OHT7: Office of In Vitro Diagnostics
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: 06/30/2023
See PRA Statement below.

510(k) Number *(if known)*
K223597

Device Name
23andMe Personal Genome Service (PGS) Genetic Health Risk Report for BRCA1/BRCA2 (Selected Variants)

Indications for Use *(Describe)*
The 23andMe Personal Genome Service (PGS) uses qualitative genotyping to detect select clinically relevant variants in genomic DNA isolated from human saliva collected from individuals ≥18 years with the Oragene Dx model OGD500.001 for the purpose of reporting and interpreting genetic health risks, including the 23andMe PGS Genetic Health Risk Report for BRCA1/BRCA2 (Selected Variants).

The 23andMe Personal Genome Service (PGS) Risk Report for BRCA1/BRCA2 (Selected Variants) is indicated for the reporting of the following 44 variants in the BRCA1 and BRCA2 genes.

BRCA1: c.68_69del, c.213-11T>G, c.427G>T, c.815_824dup, c.1556del, c.1687C>T, c.1960A>T, c.1961del, c.2681_2682del, c.2864C>A, c.3481_3491del, c.3598C>T, c.3627dup, c.3756_3759del, c.3770_3771del, c.4035del, c.4065_4068del, c.4327C>T, c.4357+1G>A, c.4964_4982del, c.4986+6T>G, c.5123C>A, c.5177_5180del, c.5266dup

BRCA2: c.658_659del, c.771_775del, c.1929del, c.2808_2811del, c.2957_2958insG, c.3170_3174del, c.3264dup, c.3545_3546del, c.3847_3848del, c.4471_4474del, c.5542del, c.5576_5579del, c.5682C>G, c.5946del, c.6037A>T, c.6275_6276del, c.7024C>T, c.7480C>T, c.7934del, c.8904del

The report describes if a person's genetic result is associated with an increased risk of developing breast cancer and ovarian cancer and may be associated with an increased risk for prostate cancer, pancreatic cancer, and potentially other cancers. The variants included in this report do not represent the majority of the BRCA1/BRCA2 variants in people of most ethnicities. The test report does not describe a person's overall risk of developing any type of cancer, and the absence of a variant tested does not rule out the presence of other variants that may be cancer-related. 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. This test is not a substitute for visits to a healthcare provider for recommended screenings or appropriate follow-up and should not be used to determine any treatments.

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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Traditional 510(k) Summary

This summary of Traditional 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 Traditional 510(k) number is: K223597

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Date Prepared
29 August 2023

5.0 PURPOSE OF SUBMISSION

In this Traditional 510(k) submission 23andMe seeks the following:

1. Clearance for an additional 41 BRCA1 and BRCA2 variants to be added to the existing authorized BRCA1/BRCA2 (Selected Variants) report, (DEN170046);
2. Establish a Pre-Determined Change Control Plan (PCCP) for reporting additional BRCA1 and BRCA2 variants and associated cancer risk information to the report.

This 510(k) summary describes the submission content supporting pre-market review for the proposed 41 additional variants to be added to the existing BRCA1/BRCA2 (Selected Variants) report, (DEN170046). This submission included a predetermined change control plan (PCCP) that was reviewed and authorized by FDA for adding additional

validated BRCA1 and BRCA2 variants and associated cancer risk information to the 23andMe PGS® Cancer Predisposition Genetic Health Risk Report for BRCA1/BRCA2 (Selected Variants) without additional pre-market review. The PCCP outlined the specific protocols and acceptance criteria that 23andMe intends to use to clinically and analytically validate eligible BRCA1/BRCA2 variants.

5.1. REGULATORY INFORMATION

Table 1. Proposed New Device

Type of Submission:	Traditional 510(k)
Common/Usual Name:	BRCA1/BRCA2 (Selected Variants)
Trade/proprietary Name:	23andMe Personal Genome Service (PGS) Genetic Health Risk Report for BRCA1/BRCA2 (Selected Variants)
Regulation Description:	A Cancer Predisposition Risk Assessment System is a qualitative in vitro molecular diagnostic system used for determining predisposition for cancer where the result of the test may lead to prophylactic screening, confirmatory procedures, or treatments that may incur morbidity or mortality to the patient. The test could help to inform conversations with a healthcare professional. This assessment system is for over-the-counter use. This device does not determine the person's overall risk of developing any types of cancer. This test is not a substitute for visits to a healthcare provider for recommended screenings or appropriate follow-up and should not be used to determine any treatments.
Regulation Number:	21 CFR §866.6090
Product Code:	QAZ
Class	Class II
Predicate Device:	23andMe PGS Risk Report for BRCA1/BRCA2 (Selected Variants), DEN170046, authorized on March 6, 2018

5.2. INTENDED USE

The 23andMe Personal Genome Service (PGS) uses qualitative genotyping to detect select clinically relevant variants in genomic DNA isolated from human saliva collected from individuals ≥18 years with the Oragene Dx model OGD500.001 for the purpose of reporting and interpreting genetic health risks, including the 23andMe PGS Genetic Health Risk Report for BRCA1/BRCA2 (Selected Variants).

5.3. INDICATIONS FOR USE

The 23andMe Personal Genome Service (PGS) Risk Report for BRCA1/BRCA2 (Selected Variants) is indicated for the reporting of the following 44 variants in the BRCA1 and BRCA2 genes.

Gene	Variant(s)
BRCA1	c.68_69del, c.213-11T>G, c.427G>T, c.815_824dup, c.1556del, c.1687C>T, c.1960A>T, c.1961del, c.2681_2682del, c.2864C>A, c.3481_3491del, c.3598C>T, c.3627dup, c.3756_3759del, c.3770_3771del, c.4035del, c.4065_4068del, c.4327C>T, c.4357+1G>A, c.4964_4982del, c.4986+6T>G, c.5123C>A, c.5177_5180del, c.5266dup
BRCA2	c.658_659del, c.771_775del, c.1929del, c.2808_2811del, c.2957_2958insG, c.3170_3174del, c.3264dup, c.3545_3546del, c.3847_3848del, c.4471_4474del, c.5542del, c.5576_5579del, c.5682C>G, c.5946del, c.6037A>T, c.6275_6276del, c.7024C>T, c.7480C>T, c.7934del, c.8904del

The report describes if a person's genetic result is associated with an increased risk of developing breast cancer and ovarian cancer and may be associated with an increased risk for prostate cancer, pancreatic cancer, and potentially other cancers. The variants included in this report do not represent the majority of the BRCA1/BRCA2 variants in people of most ethnicities. The test report does not describe a person's overall risk of developing any type of cancer, and the absence of a variant tested does not rule out the presence of other variants that may be cancer-related. 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. This test is not a substitute for visits to a healthcare provider for recommended screenings or appropriate follow-up and should not be used to determine any treatments.

5.4. SUBSTANTIALLY EQUIVALENT PREDICATE DEVICE

The components of the PGS are unchanged from the *De Novo* authorization for the predicate device, the PGS Genetic Health Risk Report for BRCA1/BRCA2 (Selected Variants) (DEN170046). These components include the saliva collection kit, reagents, beadchip, instrumentation, software, test processes and procedures.

The purpose of this Traditional 510(k) submission is to modify the 23andMe Personal Genome Service (PGS) Genetic Health Risk Report for BRCA1/BRCA2 (Selected Variants) to include 41 additional BRCA1 and BRCA2 variants to the existing authorized BRCA1/BRCA2 (Selected Variants) report (DEN170046) and to establish a Pre-Determined Change Control Plan (PCCP) for adding additional BRCA1 and BRCA2 variants and associated cancer risk information to the report.
The 23andMe Personal Genome Service (PGS) Risk Report for BRCA1/BRCA2 (Selected Variants) is similar to the predicate, having similar indications for use, the same intended use, and the same technological characteristics as its predicate device, with the exception of the implementation of a Predetermined Change Control Plan (PCCP) that specifies the protocols and acceptance criteria for making modifications to the reportable BRCA1/BRCA2 variants in a controlled manner such that the device is as safe and effective as the predicate.

Specific test methods for clinical and analytical validation are specified in the PCCP to establish substantial equivalence relative to DEN170046, and include sample size determination, analysis methods, and acceptance criteria. The Sponsor will perform testing of the additional BRCA1/2 variants according to the specified protocols, and if the validation data meet the specified acceptance criteria, they may add those variants to the BRCA1/2 report without additional premarket review.

The PCCP is limited to the addition of single nucleotide variants and small insertions and deletions (≤20 bp) in the BRCA1 and BRCA2 genes. The plan describes the specific clinical validation criteria that must be met to demonstrate that the new BRCA1/2 variants are high-risk, highly penetrant BRCA1/2 variants (i.e., those that are demonstrated to be linked to hereditary breast and ovarian cancer (HBOC) syndrome). Specific analytical validation protocols and acceptance criteria are also detailed in the plan to ensure that the device maintains the following performance characteristics for each new BRCA1/2 variant:

- Accuracy point estimates of ≥99% positive percent agreement (PPA) and negative percent agreement (NPA), established by comparing the results of the 23andMe to bidirectional Sanger sequencing
- ≥99% correct genotype calls assigned at each of two laboratory sites
- ≥95% of samples yielding the correct genotype call at the minimum DNA input tested

Additionally, software verification and validation activities are detailed in the PCCP and all must be completed successfully to modify the report to add the new BRCA1/2 variants. The plan specifies change control for genotype calling definitions and labeling updates to ensure the device remains as safe and effective as the predicate device.

Customers who previously opted-in to receive their BRCA1/2 report will receive an email notification informing them that the report has been updated. Customers will have access to their updated report unless they exercise their option to opt-out.

The PGS Genetic Health Risk Report for BRCA1/BRCA2 (Selected Variants) report is intended for over-the-counter, direct-to consumer use without prescription or physician order. As with the predicate device, the proposed modifications to the labeling of the BRCA1/BRCA2 (Selected Variants) report conform to submission requirements, and special controls of the original authorization (DEN170046). Before viewing the proposed modified labeling, customers must view an updated version of the BRCA1/BRCA2 (Selected Variants) education module that reflects the additional 41 variants, and customers with positive results are strongly advised to share their results with their healthcare provider. As instructed in the predicate device authorization DEN170046, the same healthcare provider limitations are included in the package insert:

- This test is not intended to diagnose a disease, determine medical treatment or other medical intervention, or tell the user anything about their current state of health.
- This test is intended to provide users with their genetic information, which may inform health-related lifestyle decisions and conversations with their doctor or other healthcare professional.
- Any diagnostic or treatment decisions must be based on confirmatory prescription testing and/or other information that you determine to be appropriate for your patient, such as additional clinical testing and other risk factors that may affect individual risk and health care.

The Package Insert has been revised to incorporate information pursuant to the special controls agreed upon during DEN170046 — in particular, the addition of clinical and analytical validation information in support of the proposed additional 41 BRCA1/BRCA2 variants introduced in the modified BRCA1/BRCA2 (Selected Variants) report. Additionally, the Package Insert has been revised to provide a link to consumers to find a genetic counselor in the area in which they live. These revisions are consistent with the product classification under 21 CFR §866.6090. The proposed modifications are based on the additional test system performance data, developed according to the well-

established study protocols and acceptance criteria for 23andMe PGS cancer predisposition risk reports and submitted in this Traditional 510(k).

This submission proposes the same intended use for the Genetic Health Risk Report for BRCA1/BRCA2 (Selected Variants), does not introduce new risks to safety and effectiveness, and is supported by performance data collected for this purpose. As such, the proposed modifications to the labeling of the 23andMe Personal Genome Service Genetic Health Risk Report for BRCA1/BRCA2 (Selected Variants) are substantially equivalent to the predicate device authorized under DEN170046.

5.5. DEVICE DESCRIPTION

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 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 manufactured by Illumina.

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 genetic health risk variant(s) have been detected in their sample and provide information about the disease 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 and clinically valid information about the risks associated with the presence of a particular variant. 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.

Engineering drawings, schematics, etc. of the 23andMe Personal Genome Service (PGS) BRCA1/BRCA2 (Selected Variants) report are not applicable to this device.

5.6. 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(s): BRCA1, BRCA2
Variants:
BRCA1 gene variants: c.68_69del, c.213-11T>G, c.427G>T, c.815_824dup, c.1556del, c.1687C>T, c.1960A>T, c.1961del, c.2681_2682del, c.2864C>A, c.3481_3491del, c.3598C>T, c.3627dup, c.3756_3759del, c.3770_3771del, c.4035del, c.4065_4068del, c.4327C>T, c.4357+1G>A, c.4964_4982del, c.4986+6T>G, c.5123C>A, c.5177_5180del, c.5266dup

BRCA2 gene variants: c.658_659del, c.771_775del, c.1929del, c.2808_2811del, c.2957_2958insG, c.3170_3174del, c.3264dup, c.3545_3546del, c.3847_3848del, c.4471_4474del, c.5542del, c.5576_5579del, c.5682C>G, c.5946del, c.6037A>T, c.6275_6276del, c.7024C>T, c.7480C>T, c.7934del, c.8904del

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 2. Substantial Equivalence

	Predicate BRCA1/BRCA2 (Selected Variants) Report DEN170046	**Proposed modified BRCA1/BRCA2 (Selected Variants) Report K223597**
General Device Characterisitic Similarities		
Intended Use	The 23andMe Personal Genome Service (PGS)	Same

	Predicate BRCA1/BRCA2 (Selected Variants) Report DEN170046	**Proposed modified BRCA1/BRCA2 (Selected Variants) Report K223597**
	uses qualitative genotyping to detect select clinically relevant variants in genomic DNA isolated from human saliva collected from individuals ≥18 years with the Oragene Dx model OGD500.001 for the purpose of reporting and interpreting genetic health risks, including the 23andMe PGS Genetic Health Risk Report for BRCA1/BRCA2 (Selected Variants).	
Collection Kit	Oragene·Dx® saliva collection device (OGD-500.001) K141410	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)	Same

	Predicate BRCA1/BRCA2 (Selected Variants) Report DEN170046	Proposed modified BRCA1/BRCA2 (Selected Variants) Report K223597
	reference human genome.	
Beadpool	Customized for 23andMe	Same
Instruments	Tecan Evo Illumina iScan	Same
Software	Genome Studio Coregen	Same
Specimen Type	Saliva	Same
Differences		
Measurand	3 variants	44 variants
Reagents	Illumina Infinium HTS Assay Reagents	Illumina Infinium HTS Extra Assay Reagents

5.7. PERFORMANCE TESTING SUMMARY

5.7.1 Method Comparison (Accuracy)

23andMe performed a method comparison study to assess the accuracy of the 23andMe Personal Genome Service (PGS) test for the additional 41 variants to be added to the existing BRCA1/BRCA2 (Selected Variants) report. All 41 variants were included in this study.

The purpose of the study was to show equivalent genotype assignment between the 23andMe PGS assay and bidirectional Sanger sequencing. Samples were randomly selected from the 23andMe customer database based on their putative genotype. Genotyping of these samples was performed at a CLIA certified contract laboratory. All chosen samples were then tested using bidirectional Sanger sequencing. Genotyping results were compared between the 23andMe PGS assay and sequencing to calculate

positive percent agreement (PPA) and negative percent agreement (NPA), with the sequencing results considered to be “truth”. The passing criteria were greater than 99% PPA and greater than 99% NPA for each SNP.

This method comparison study yielded greater than 99% agreement. Therefore, the study passed the acceptance criteria of greater than 99% PPA and greater than 99% NPA. The method comparison study showed that the 23andMe assay is comparable to bidirectional Sanger sequencing.

5.7.2 Precision (Reproducibility)

23andMe performed a precision study to assess the repeatability and reproducibility of the 23andMe Personal Genome Service (PGS) test for the additional 41 variants to be added to the existing BRCA1/BRCA2 (Selected Variants) report. All 41 variants were included in this study.

This study evaluated intra-assay, inter-lot, inter-instrument, inter-operator, inter-day, and inter-lab precision. Samples were identified from the 23andMe customer database based on their putative genotype and genotyped by the assay in a blinded fashion, with 3 lots of reagents, by multiple operator teams per day, using 3 different serial numbers of each of 2 instruments, over 3 days, at each of 2 laboratory sites. Genotype results were confirmed using bidirectional Sanger sequencing. The passing criteria were a minimum of 99% correct genotype calls at each of two laboratory sites.

This precision study yielded 100% correct genotype calls for all samples across multiple days, operator teams, instruments, and reagent lots at 2 independent laboratory sites. Therefore, the study passed the acceptance criteria of at least 99% correct calls. In addition, the study had greater than 99% reproducibility and greater than 99% repeatability.

5.7.3 Minimum DNA Input (MDI)

23andMe performed a minimum DNA input study to assess the sensitivity of the 23andMe Personal Genome Service (PGS) test for the additional 41 variants to be added to the existing BRCA1/BRCA2 (Selected Variants) report. All 41 variants were included in this study.

Samples were identified from the 23andMe customer database based on their putative genotype. Each sample was diluted to 3 different concentrations and genotyped by the assay in a blinded fashion using 3 lots of reagents. Genotype results were confirmed using bidirectional Sanger sequencing. The minimum DNA requirement was defined as the lowest concentration at which at least 95% of samples yield the correct call.

This minimum DNA input study yielded 100% correct genotype calls for all samples and 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. The performance requirement, specified by contract laboratory SOPs, is conservatively set at a minimum of 15 ng/µL and a maximum of 50 ng/µL. This minimum DNA input study demonstrated that the 23andMe assay is valid for samples with a DNA concentration range of 5 ng/µL to 50 ng/µL.

5.7.4 Shelf life

The PGS requires the use of the same FDA-cleared collection device and reagents that have been previously reviewed and authorized in K141410 and DEN140044.

5.8. CLINICAL PERFORMANCE

The variants included in the modified BRCA1/BRCA2 (Selected Variants) report account for more than 90% of cancer-related BRCA1 and BRCA2 variants among people of Ashkenazi Jewish descent; about 30-40% among African Americans, people of European descent, and people of Hispanic or Latino descent; about 5-25% among people of East Asian Descent; and up to 35% among people of South Asian descent[1]. The pathogenicity of each variant is supported by multiple peer-reviewed studies and, in many cases, by the classification determination of an expert panel (ENIGMA[2]). In addition, most pathogenic BRCA1/2 variants are truncating; for those that are not, we rely on strong functional evidence demonstrating an impact on protein function.

Table 3. Allele frequencies from 23andMe database and Genome Aggregation Database (gnomAD)

Variant #	Gene	Variant name	rsID	Population	Allele frequencies from 23andMe (%)*	Allele frequencies from gnomAD (%)**
1	BRCA1	c.68_69del	rs386833395	European	0.012%	0.009%
				African American	0.004%	0.000%
				Ashkenazi Jewish	0.445%	0.405%
				East Asian	0.000%	0.000%
				Hispanic or Latino	0.017%	0.003%
				South Asian	0.025%	0.013%
				Middle Eastern	0.007%	not available
2	BRCA1	c.213-11T>G	rs80358061	European	0.003%	0.003%
				African American	<0.002%	0.000%
				Ashkenazi Jewish	0.000%	0.000%

[1] Rebbeck TR et al. (2018). "Mutational spectrum in a worldwide study of 29,700 families with BRCA1 or BRCA2 mutations." Hum Mutat. 39(5):593-620; Bhaskaran SP et al. (2021). "Ethnic-specific BRCA1/2 variation within Asia population: evidence from over 78 000 cancer and 40 000 non-cancer cases of Indian, Chinese, Korean and Japanese populations." J Med Genet. 58(11):752-759.

[2] Evidence-based Network for the Interpretation of Germline Mutant Alleles (ENIGMA) classification criteria: https://enigmaconsortium.org/library/general-documents/enigma-classification-criteria/

Variant #	Gene	Variant name	rsID	Population	Allele frequencies from 23andMe (%)*	Allele frequencies from gnomAD (%)**
				East Asian	0.000%	0.000%
				Hispanic or Latino	0.001%	0.000%
				South Asian	0.000%	0.000%
				Middle Eastern	<0.007%	not available
3	BRCA1	c.427G>T	rs80356991	European	0.001%	not observed in gnomAD
				African American	<0.002%	
				Ashkenazi Jewish	0.000%	
				East Asian	0.000%	
				Hispanic or Latino	<0.001%	
				South Asian	0.000%	
				Middle Eastern	0.000%	
4	BRCA1	c.815_824dup	rs387906563	European	0.000%	0.000%
				African American	0.011%	0.004%
				Ashkenazi Jewish	0.000%	0.000%
				East Asian	0.000%	0.000%
				Hispanic or Latino	0.003%	0.003%
				South Asian	0.000%	0.000%
				Middle Eastern	0.000%	not available
5	BRCA1	c.1556del	rs80357662	European	0.001%	not observed in gnomAD
				African American	0.000%	

Variant #	Gene	Variant name	rsID	Population	Allele frequencies from 23andMe (%)*	Allele frequencies from gnomAD (%)**
				Ashkenazi Jewish	0.000%	
				East Asian	0.000%	
				Hispanic or Latino	<0.001%	
				South Asian	0.000%	
				Middle Eastern	0.000%	
6	BRCA1	c.1687C>T	rs80356898	European	0.002%	0.006%
				African American	0.000%	0.000%
				Ashkenazi Jewish	0.000%	0.000%
				East Asian	0.000%	0.000%
				Hispanic or Latino	0.001%	0.000%
				South Asian	0.000%	0.000%
				Middle Eastern	0.000%	not available
7	BRCA1	c.1960A>T	rs80357355	European	<0.001%	0.006%
				African American	0.000%	0.000%
				Ashkenazi Jewish	0.000%	0.000%
				East Asian	0.000%	0.000%
				Hispanic or Latino	0.001%	0.000%
				South Asian	0.000%	0.000%
				Middle Eastern	0.000%	not available
8	BRCA1	c.1961del	rs80357522	European	0.001%	0.002%

Variant #	Gene	Variant name	rsID	Population	Allele frequencies from 23andMe (%)*	Allele frequencies from gnomAD (%)**
				African American	0.000%	0.000%
				Ashkenazi Jewish	0.000%	0.000%
				East Asian	0.000%	0.000%
				Hispanic or Latino	<0.001%	0.000%
				South Asian	<0.006%	0.000%
				Middle Eastern	<0.007%	not available
9	BRCA1	c.2681_2682del	rs80357971	European	0.002%	not observed in gnomAD
				African American	0.000%	
				Ashkenazi Jewish	0.000%	
				East Asian	0.000%	
				Hispanic or Latino	0.001%	
				South Asian	0.000%	
				Middle Eastern	0.000%	
10	BRCA1	c.2864C>A	rs80357295	European	<0.001%	not observed in gnomAD
				African American	0.000%	
				Ashkenazi Jewish	0.000%	
				East Asian	0.000%	
				Hispanic or Latino	0.001%	
				South Asian	0.000%	
				Middle Eastern	0.000%	

Variant #	Gene	Variant name	rsID	Population	Allele frequencies from 23andMe (%)*	Allele frequencies from gnomAD (%)**
11	BRCA1	c.3481_3491del	rs80357877	European	0.001%	not observed in gnomAD
				African American	<0.002%	
				Ashkenazi Jewish	0.000%	
				East Asian	0.000%	
				Hispanic or Latino	<0.001%	
				South Asian	0.000%	
				Middle Eastern	0.000%	
12	BRCA1	c.3598C>T	rs62625307	European	<0.001%	0.000%
				African American	0.000%	0.000%
				Ashkenazi Jewish	0.000%	0.000%
				East Asian	0.000%	0.000%
				Hispanic or Latino	0.001%	0.000%
				South Asian	<0.006%	0.003%
				Middle Eastern	0.000%	not available
13	BRCA1	c.3627dup	rs80357729	European	0.000%	0.000%
				African American	<0.002%	0.000%
				Ashkenazi Jewish	0.000%	0.000%
				East Asian	0.002%	0.011%
				Hispanic or Latino	0.000%	0.000%
				South Asian	0.000%	0.000%

Variant #	Gene	Variant name	rsID	Population	Allele frequencies from 23andMe (%)*	Allele frequencies from gnomAD (%)**
				Middle Eastern	0.000%	not available
14	BRCA1	c.3756_3759del	rs80357868	European	0.003%	0.004%
				African American	<0.002%	0.000%
				Ashkenazi Jewish	0.000%	0.000%
				East Asian	0.000%	0.000%
				Hispanic or Latino	0.001%	0.000%
				South Asian	0.000%	0.000%
				Middle Eastern	<0.007%	not available
15	BRCA1	c.3770_3771del	rs80357579	European	<0.001%	0.001%
				African American	<0.002%	0.000%
				Ashkenazi Jewish	0.000%	0.000%
				East Asian	<0.002%	0.000%
				Hispanic or Latino	0.000%	0.000%
				South Asian	<0.006%	0.003%
				Middle Eastern	<0.007%	not available
16	BRCA1	c.4035del	rs80357711	European	0.002%	0.009%
				African American	0.000%	0.000%
				Ashkenazi Jewish	0.000%	0.000%
				East Asian	0.000%	0.000%
				Hispanic or Latino	<0.001%	0.000%

Variant #	Gene	Variant name	rsID	Population	Allele frequencies from 23andMe (%)*	Allele frequencies from gnomAD (%)**
				South Asian	0.000%	0.000%
				Middle Eastern	0.000%	not available
17	BRCA1	c.4065_4068del	rs80357508	European	0.002%	0.002%
				African American	<0.002%	0.000%
				Ashkenazi Jewish	0.000%	0.000%
				East Asian	<0.002%	0.000%
				Hispanic or Latino	0.002%	0.000%
				South Asian	0.007%	0.003%
				Middle Eastern	<0.007%	not available
18	BRCA1	c.4327C>T	rs41293455	European	0.002%	0.004%
				African American	<0.002%	0.004%
				Ashkenazi Jewish	0.000%	0.000%
				East Asian	<0.002%	0.000%
				Hispanic or Latino	0.002%	0.008%
				South Asian	0.000%	0.000%
				Middle Eastern	<0.007%	not available
19	BRCA1	c.4357+1G>A	rs80358027	European	<0.001%	0.000%
				African American	0.002%	0.000%
				Ashkenazi Jewish	0.000%	0.000%
				East Asian	0.000%	0.000%

Variant #	Gene	Variant name	rsID	Population	Allele frequencies from 23andMe (%)*	Allele frequencies from gnomAD (%)**
				Hispanic or Latino	0.000%	0.000%
				South Asian	0.000%	0.000%
				Middle Eastern	<0.007%	not available
20	BRCA1	c.4964_4982del	rs80359876	European	0.001%	0.000%
				African American	0.000%	0.000%
				Ashkenazi Jewish	0.000%	0.000%
				East Asian	0.000%	0.000%
				Hispanic or Latino	0.001%	0.000%
				South Asian	0.000%	0.000%
				Middle Eastern	0.000%	not available
21	BRCA1	c.4986+6T>G	rs80358086	European	<0.001%	0.001%
				African American	0.000%	0.000%
				Ashkenazi Jewish	0.000%	0.000%
				East Asian	0.000%	0.000%
				Hispanic or Latino	0.000%	0.000%
				South Asian	0.000%	0.000%
				Middle Eastern	0.000%	not available
22	BRCA1	c.5123C>A	rs28897696	European	0.000%	0.003%
				African American	<0.002%	0.000%
				Ashkenazi Jewish	0.000%	0.000%

Variant #	Gene	Variant name	rsID	Population	Allele frequencies from 23andMe (%)*	Allele frequencies from gnomAD (%)**
				East Asian	<0.002%	0.000%
				Hispanic or Latino	0.004%	0.006%
				South Asian	0.000%	0.000%
				Middle Eastern	<0.007%	not available
23	BRCA1	c.5177_5180del	rs80357867	European	<0.001%	0.000%
				African American	0.005%	0.012%
				Ashkenazi Jewish	0.000%	0.000%
				East Asian	0.000%	0.000%
				Hispanic or Latino	<0.001%	0.000%
				South Asian	0.000%	0.000%
				Middle Eastern	0.000%	not available
24	BRCA1	c.5266dup	rs80357906	European	0.013%	0.019%
				African American	<0.002%	0.000%
				Ashkenazi Jewish	0.139%	0.231%
				East Asian	0.000%	0.000%
				Hispanic or Latino	0.005%	0.003%
				South Asian	0.000%	0.000%
				Middle Eastern	0.000%	not available
25	BRCA2	c.658_659del	rs80359604	European	0.004%	0.006%
				African American	0.007%	0.013%

Variant #	Gene	Variant name	rsID	Population	Allele frequencies from 23andMe (%)*	Allele frequencies from gnomAD (%)**
				Ashkenazi Jewish	0.000%	0.000%
				East Asian	0.003%	0.000%
				Hispanic or Latino	0.010%	0.006%
				South Asian	0.000%	0.003%
				Middle Eastern	<0.007%	not available
26	BRCA2	c.771_775del	rs80359671	European	<0.001%	0.000%
				African American	<0.002%	0.000%
				Ashkenazi Jewish	0.000%	0.000%
				East Asian	0.002%	0.000%
				Hispanic or Latino	0.001%	0.000%
				South Asian	0.000%	0.000%
				Middle Eastern	0.000%	not available
27	BRCA2	c.1929del	rs80359316	European	0.002%	not observed in gnomAD
				African American	0.000%	
				Ashkenazi Jewish	0.000%	
				East Asian	0.000%	
				Hispanic or Latino	0.001%	
				South Asian	0.000%	
				Middle Eastern	0.000%	
28	BRCA2	c.2808_2811del	rs80359351	European	0.004%	0.002%

Variant #	Gene	Variant name	rsID	Population	Allele frequencies from 23andMe (%)*	Allele frequencies from gnomAD (%)**
				African American	0.003%	0.000%
				Ashkenazi Jewish	<0.003%	0.000%
				East Asian	0.003%	0.000%
				Hispanic or Latino	0.004%	0.000%
				South Asian	<0.006%	0.000%
				Middle Eastern	<0.007%	not available
29	BRCA2	c.2957_2958insG	rs1555282969	European	<0.001%	0.000%
				African American	0.002%	0.006%
				Ashkenazi Jewish	0.000%	0.000%
				East Asian	0.000%	0.000%
				Hispanic or Latino	<0.001%	0.000%
				South Asian	0.000%	0.000%
				Middle Eastern	0.000%	not available
30	BRCA2	c.3170_3174del	rs80359373	European	0.001%	0.003%
				African American	<0.002%	0.000%
				Ashkenazi Jewish	0.000%	0.000%
				East Asian	0.000%	0.000%
				Hispanic or Latino	0.001%	0.000%
				South Asian	0.000%	0.000%
				Middle Eastern	0.000%	not available

Variant #	Gene	Variant name	rsID	Population	Allele frequencies from 23andMe (%)*	Allele frequencies from gnomAD (%)**
31	BRCA2	c.3264dup	rs80359380	European	<0.001%	0.000%
				African American	0.000%	0.000%
				Ashkenazi Jewish	0.000%	0.000%
				East Asian	0.000%	0.000%
				Hispanic or Latino	0.010%	0.020%
				South Asian	0.000%	0.000%
				Middle Eastern	0.000%	not available
32	BRCA2	c.3545_3546del	rs80359388	European	0.004%	0.004%
				African American	<0.002%	0.000%
				Ashkenazi Jewish	0.000%	0.000%
				East Asian	0.000%	0.000%
				Hispanic or Latino	0.001%	0.000%
				South Asian	0.000%	0.000%
				Middle Eastern	0.000%	not available
33	BRCA2	c.3847_3848del	rs80359405	European	0.006%	0.010%
				African American	0.003%	0.004%
				Ashkenazi Jewish	0.006%	0.000%
				East Asian	<0.002%	0.000%
				Hispanic or Latino	0.003%	0.000%
				South Asian	0.000%	0.000%

Variant #	Gene	Variant name	rsID	Population	Allele frequencies from 23andMe (%)*	Allele frequencies from gnomAD (%)**
				Middle Eastern	<0.007%	not available
34	BRCA2	c.4471_4474del	rs80359451	European	<0.001%	0.000%
				African American	0.000%	0.006%
				Ashkenazi Jewish	0.000%	0.000%
				East Asian	<0.002%	0.000%
				Hispanic or Latino	<0.001%	0.000%
				South Asian	0.000%	0.000%
				Middle Eastern	0.000%	not available
35	BRCA2	c.5542del	rs80359519	European	0.000%	0.000%
				African American	0.000%	0.000%
				Ashkenazi Jewish	0.000%	0.000%
				East Asian	0.000%	0.000%
				Hispanic or Latino	0.002%	0.003%
				South Asian	0.000%	0.000%
				Middle Eastern	0.000%	not available
36	BRCA2	c.5576_5579del	rs80359520	European	0.003%	0.002%
				African American	<0.002%	0.006%
				Ashkenazi Jewish	0.000%	0.000%
				East Asian	0.005%	0.006%
				Hispanic or Latino	0.001%	0.000%

Variant #	Gene	Variant name	rsID	Population	Allele frequencies from 23andMe (%)*	Allele frequencies from gnomAD (%)**
				South Asian	<0.006%	0.000%
				Middle Eastern	<0.007%	not available
37	BRCA2	c.5682C>G	rs41293497	European	0.002%	0.001%
				African American	0.002%	0.000%
				Ashkenazi Jewish	0.000%	0.000%
				East Asian	<0.002%	0.000%
				Hispanic or Latino	0.001%	0.000%
				South Asian	0.000%	0.000%
				Middle Eastern	0.000%	not available
38	BRCA2	c.5946del	rs80359550	European	0.012%	0.011%
				African American	0.003%	0.000%
				Ashkenazi Jewish	0.521%	0.589%
				East Asian	0.000%	0.000%
				Hispanic or Latino	0.006%	0.000%
				South Asian	0.000%	0.000%
				Middle Eastern	<0.007%	not available
39	BRCA2	c.6037A>T	rs80358840	European	0.001%	not observed in gnomAD
				African American	0.000%	
				Ashkenazi Jewish	0.000%	
				East Asian	0.000%	

Variant #	Gene	Variant name	rsID	Population	Allele frequencies from 23andMe (%)*	Allele frequencies from gnomAD (%)**
				Hispanic or Latino	<0.001%	
				South Asian	0.000%	
				Middle Eastern	0.000%	
40	BRCA2	c.6275_6276del	rs11571658	European	0.004%	0.005%
				African American	<0.002%	0.000%
				Ashkenazi Jewish	0.000%	0.000%
				East Asian	0.000%	0.000%
				Hispanic or Latino	0.003%	0.006%
				South Asian	0.000%	0.000%
				Middle Eastern	0.000%	not available
41	BRCA2	c.7024C>T	rs80358928	European	0.000%	0.000%
				African American	<0.002%	0.006%
				Ashkenazi Jewish	0.000%	0.000%
				East Asian	0.000%	0.000%
				Hispanic or Latino	0.000%	0.000%
				South Asian	0.000%	0.000%
				Middle Eastern	0.000%	not available
42	BRCA2	c.7480C>T	rs80358972	European	<0.001%	0.000%
				African American	0.000%	0.000%
				Ashkenazi Jewish	0.000%	0.000%

Variant #	Gene	Variant name	rsID	Population	Allele frequencies from 23andMe (%)*	Allele frequencies from gnomAD (%)**
				East Asian	0.004%	0.016%
				Hispanic or Latino	0.001%	0.000%
				South Asian	0.000%	0.003%
				Middle Eastern	<0.007%	not available
43	BRCA2	c.7934del	rs80359688	European	<0.001%	not observed in gnomAD
				African American	0.000%	
				Ashkenazi Jewish	0.000%	
				East Asian	0.000%	
				Hispanic or Latino	0.001%	
				South Asian	<0.006%	
				Middle Eastern	0.000%	
44	BRCA2	c.8904del	rs80359730	European	0.001%	not observed in gnomAD
				African American	0.000%	
				Ashkenazi Jewish	0.000%	
				East Asian	0.000%	
				Hispanic or Latino	<0.001%	
				South Asian	0.000%	
				Middle Eastern	0.000%	

* Based on approximately 2,944,000 individuals with European ancestry, 138,000 individuals with African American ancestry, 83,000 individuals with Ashkenazi Jewish ancestry, 157,000 individuals with East Asian ancestry, 535,000 individuals with Hispanic/Latino ancestry, 42,000 individuals with South Asian ancestry, and 37,000 individuals with Middle Eastern ancestry. Small changes to observed allele frequencies are expected to occur as the database grows. Because of the privacy considerations surrounding the use of

customer data (namely, the risk of exposing the identity of individuals in the database), the frequencies provided are rounded to a thousandth of a percent and truncated at a minimum frequency if the number of individuals with a variant is fewer than 5.

** Allele frequencies from gnomAD database were obtained from https://gnomad.broadinstitute.org/ on 08Feb2022.

5.9. DISCUSSION

This Traditional 510(k) submission for the addition of 41 variants to the existing BRCA1/BRCA2 (Selected Variants) report provides analytical and clinical data demonstrating that the PGS Test generates an accurate result, and uses the same report concepts that have been previously validated by comprehensive user comprehension testing.

This submission included a predetermined change control plan (PCCP) that was reviewed and authorized by FDA for adding additional validated BRCA1 and BRCA2 variants and associated cancer risk information to the 23andMe PGS® Cancer Predisposition Genetic Health Risk Report for BRCA1/BRCA2 (Selected Variants) without additional pre-market review. The PCCP outlined the specific protocols and acceptance criteria that 23andMe intends to use to clinically and analytically validate eligible BRCA1/2 variants.

The 23andMe Personal Genome Service (PGS) Genetic Health Risk report for BRCA1/BRCA2 (Selected Variants) is not technologically different, with the exception of the implementation of a PCCP, nor does it introduce any new concerns of safety or effectiveness when compared to the previously authorized predicate device (DEN170046).

5.10. CONCLUSION

The 23andMe Personal Genome Service (PGS) Genetic Health Risk Report for BRCA1/BRCA2 (Selected Variants), has similar indications for use, the same intended use, and the same principles of operation as its predicate device, DEN170046. The technological characteristics are identical with the exception of the implementation of a PCCP, and this difference does not raise new questions of safety and effectiveness. Thus, the subject device is substantially equivalent.