510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K223597

B Applicant

23andMe, Inc.

C Proprietary and Established Names

23andMe® Personal Genome Service® (PGS®) Cancer Predisposition Genetic Health Risk Report for BRCA1/BRCA2 (Selected Variants)

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
QAZ	Class II	21 CFR 866.6090 - Cancer Predisposition Risk Assessment System	Pathology

II Submission/Device Overview:

A Purpose for 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 adding additional validated BRCA1 and BRCA2 variants and associated cancer risk information to the report.

B Measurand:

44 variants (single-nucleotide polymorphism) in the BRCA1 and BRCA2 genes. Refer to the intended use statement for complete list.

C Type of Test:

Qualitative genetic test for single nucleotide polymorphism detection.

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) 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.

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.

C Special Conditions for Use Statement(s):

1. For over-the-counter (OTC) use.
2. The test does not diagnose cancer or any other health condition and should not be used to make medical decisions. Results should be confirmed in a clinical setting before taking any medical action.

3. This test is not a substitute for visits to a healthcare provider for recommended screening or appropriate follow-up. It is recommended that users consult with a healthcare provider if there are any questions or concerns about the test results or their current state of health.
4. The 23andMe PGS Genetic Health Risk Report for BRCA1/BRCA2 (Selected Variants) detects only three variants and does not detect all genetic variants in these genes associated with increased risk of developing breast, ovarian or prostate cancer. There are more than 1,000 different BRCA1/BRCA2 variants known to be associated with increased risk of developing cancer. The absence of a variant tested does not rule out the presence of other genetic variants that may be disease-related.
5. The test is intended for users ≥ 18 years old.
6. The laboratory may not be able to process a user's sample. The probability that the laboratory cannot process a sample can be up to 7.6%.
7. A user's race, ethnicity, age, and sex may affect how the genetic test results are interpreted.
8. It is important for the user to discuss their personal or family history of cancer with a healthcare professional. If the user has a personal or family history of cancer or think they may have symptoms of cancer, the user should consult with their healthcare provider about appropriate testing.
9. Subject to meeting the limitations contained in the special controls under regulation 866.6090.

D Special Instrument Requirements:

Tecan Evo, Illumina iScan and GenomeStudio system (qualified by the laboratory).

IV Device/System Characteristics:

A Device Description:

Customer saliva specimens are 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. Specimens are shipped to either one of two 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.

B Principle of Operation:

The assay uses multiplex microarray technology for the simultaneous detection of variants in human DNA. The BeadChip v5 assay (Illumina Infinium HumanOmniExpress-24 format chip)

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. The Tecan Evo and Illumina iScan instruments are used for extraction and processing of the DNA, and the BeadChip for scanning and quantification of the results. The genotype content is separated, analyzed, and then integrated into predefined report templates specific for each condition associated with each genotype. Genotypes are determined using the GenomeStudio and Coregen software packages. For the 23andMe PGS Genetic Health Risk Report for BRCA1/BRCA2 (Selected Variants) information on 44 specific variants in the BRCA1/BRCA2 genes are integrated into the report.

V Substantial Equivalence Information:

A Predicate Device Name(s):

23andMe PGS Genetic Health Risk Report for BRCA1/BRCA2 (Selected Variants)

B Predicate 510(k) Number(s):

DEN170046

C Comparison with Predicate(s):

The subject device 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 as effective as the predicate.

Specific test methods for clinical and analytical validation are specified in the a 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 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 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.

Device & Predicate Device(s):	**K223597**	**DEN170046**
Device Trade Name	23andMe Personal Genome Service (PGS) Genetic Health Risk Report for BRCA1/BRCA2 (Selected Variants)	23andMe PGS Genetic Health Risk Report for BRCA1/BRCA2 (Selected Variants)
General Device Characteristics: Similarities		
Intended Use	Same	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).
Specimen Type	Same	Saliva
Collection Kit	Same	Oragene·Dx® saliva collection device (OGD-500.001) K141410
BeadChip	Same	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.
Beadpool	Same	Customized for 23andMe
Instruments	Same	Tecan Evo

Device & Predicate Device(s):	K223597	DEN170046
		Illumina iScan
Software	Same	Genome Studio Coregen
Differences		
Measurand	44 variants	3 variants
Reagents	Illumina Infinium HTS Extra Assay Reagents	Illumina Infinium HTS Assay Reagents

VI Standards/Guidance Documents Referenced:

Special controls 21 CFR 866.6090, established in DEN170046

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

Precision studies were performed to assess the repeatability and reproducibility of the 23andMe Personal Genome Service (PGS) test for the 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.

There were 2 homozygous common (WT) and 1 heterozygous sample per variant used to evaluate the precision of the assay, with the exception of c.2957_2958insG BRCA2 variant, which included 1 WT and 1 heterozygous sample. Replicates failing quality control acceptance criteria were re-tested per lab procedures. Only sample replicates that passed quality control and produced a genotype for the 23andMe test were included in the calculation for percent agreement.

The precision study yielded greater than 99% correct genotype calls for all samples across two laboratories, on multiple instruments, with multiple operators, on multiple non-consecutive days, and using multiple reagent lots. In addition, the study had greater than 99% reproducibility and greater than 99% repeatability. Results for heterozygous and homozygous common (wild-type) are shown in Table 1. Results with no calls are in bold and shaded in Table 1. FQC refers to Failed Quality Control.

Table 1. Precision Study Results Stratified by Site and Genotype

Variant	Genotype	Site	Replicates Pass QC	Correct Calls	Incorrect Calls	No Calls	FQCs	% Correct Calls
c.213-11T>G BRCA1	**AA (Homozygous Common)**	**1**	162	162	0	0	0	100%
	AC (Heterozygous)	**1**	81	81	0	0	0	100%
	AA (Homozygous Common)	**2**	162	162	0	0	0	100%
	AC (Heterozygous)	**2**	81	81	0	0	0	100%
c.427G>T BRCA1	**CC (Homozygous Common)**	**1**	162	162	0	0	0	100%
	AC (Heterozygous)	**1**	81	79	0	**2**	0	100%
	CC (Homozygous Common)	**2**	162	162	0	0	0	100%
	AC (Heterozygous)	**2**	81	81	0	0	0	100%
c.815_824dup BRCA1	**DD (Homozygous Common)**	**1**	162	162	0	0	0	100%
	DI (Heterozygous)	**1**	81	81	0	0	0	100%
	DD (Homozygous Common)	**2**	162	162	0	0	0	100%
	DI (Heterozygous)	**2**	81	81	0	0	0	100%
c.1556del BRCA1	**II (Homozygous Common)**	**1**	162	162	0	0	0	100%
	DI (Heterozygous)	**1**	81	81	0	0	0	100%
	II (Homozygous Common)	**2**	162	162	0	0	0	100%
	DI (Heterozygous)	**2**	81	81	0	0	0	100%
c.1687C>T BRCA1	**GG (Homozygous Common)**	**1**	162	162	0	0	0	100%
	AG (Heterozygous)	**1**	81	81	0	0	0	100%
	GG (Homozygous Common)	**2**	162	162	0	0	0	100%
	AG (Heterozygous)	**2**	81	81	0	0	0	100%
c.1960A>T BRCA1	**TT (Homozygous Common)**	**1**	162	162	0	0	0	100%
	AT (Heterozygous)	**1**	81	79	0	**2**	0	100%

Variant	Genotype	Site	Replicates Pass QC	Correct Calls	Incorrect Calls	No Calls	FQCs	% Correct Calls
	TT (Homozygous Common)	**2**	162	162	0	0	0	100%
	AT (Heterozygous)	**2**	81	80	0	**1**	0	100%
c.1961del BRCA1	**II (Homozygous Common)**	**1**	162	162	0	0	0	100%
	DI (Heterozygous)	**1**	81	79	0	**2**	0	100%
	II (Homozygous Common)	**2**	162	162	0	0	0	100%
	DI (Heterozygous)	**2**	81	81	0	0	0	100%
c.2681_2682del BRCA1	**II (Homozygous Common)**	**1**	162	162	0	0	0	100%
	DI (Heterozygous)	**1**	81	81	0	0	0	100%
	II (Homozygous Common)	**2**	162	162	0	0	0	100%
	DI (Heterozygous)	**2**	81	81	0	0	0	100%
c.2864C>A BRCA1	**GG (Homozygous Common)**	**1**	162	162	0	0	0	100%
	GT (Heterozygous)	**1**	81	81	0	0	0	100%
	GG (Homozygous Common)	**2**	162	162	0	0	0	100%
	GT (Heterozygous)	**2**	81	81	0	0	0	100%
c.3481_3491del BRCA1	**II (Homozygous Common)**	**1**	162	162	0	0	0	100%
	DI (Heterozygous)	**1**	81	81	0	0	0	100%
	II (Homozygous Common)	**2**	162	162	0	0	0	100%
	DI (Heterozygous)	**2**	81	79	0	**2**	0	100%
c.3598C>T BRCA1	**GG (Homozygous Common)**	**1**	162	162	0	0	0	100%
	AG (Heterozygous)	**1**	81	81	0	0	0	100%
	GG (Homozygous Common)	**2**	162	162	0	0	0	100%
	AG (Heterozygous)	**2**	81	81	0	0	0	100%
c.3627dup BRCA1	**DD (Homozygous Common)**	**1**	162	162	0	0	0	100%
	DI (Heterozygous)	**1**	81	81	0	0	0	100%

Variant	Genotype	Site	Replicates Pass QC	Correct Calls	Incorrect Calls	No Calls	FQCs	% Correct Calls
	DD (Homozygous Common)	**2**	162	162	0	0	0	100%
	DI (Heterozygous)	**2**	81	81	0	0	0	100%
c.3756_3759del BRCA1	**II (Homozygous Common)**	**1**	162	162	0	0	0	100%
	DI (Heterozygous)	**1**	81	81	0	0	0	100%
	II (Homozygous Common)	**2**	162	162	0	0	0	100%
	DI (Heterozygous)	**2**	81	81	0	0	0	100%
c.3770_3771del BRCA1	**II (Homozygous Common)**	**1**	162	162	0	0	0	100%
	DI (Heterozygous)	**1**	81	81	0	0	0	100%
	II (Homozygous Common)	**2**	162	162	0	0	0	100%
	DI (Heterozygous)	**2**	81	81	0	0	0	100%
c.4035del BRCA1	**II (Homozygous Common)**	**1**	162	162	0	0	0	100%
	DI (Heterozygous)	**1**	81	81	0	0	0	100%
	II (Homozygous Common)	**2**	162	162	0	0	0	100%
	DI (Heterozygous)	**2**	81	81	0	0	0	100%
c.4065_4068del BRCA1	**II (Homozygous Common)**	**1**	162	162	0	0	0	100%
	DI (Heterozygous)	**1**	81	81	0	0	0	100%
	II (Homozygous Common)	**2**	162	162	0	0	0	100%
	DI (Heterozygous)	**2**	81	81	0	0	0	100%
c.4327C>T BRCA1	**GG (Homozygous Common)**	**1**	162	162	0	0	0	100%
	AG (Heterozygous)	**1**	81	81	0	0	0	100%
	GG (Homozygous Common)	**2**	162	162	0	0	0	100%
	AG (Heterozygous)	**2**	81	81	0	0	0	100%
c.4357+1G>A BRCA1	**CC (Homozygous Common)**	**1**	162	162	0	0	0	100%
	CT (Heterozygous)	**1**	81	81	0	0	0	100%
	CC (Homozygous Common)	**2**	162	162	0	0	0	100%

Variant	Genotype	Site	Replicates Pass QC	Correct Calls	Incorrect Calls	No Calls	FQCs	% Correct Calls
	CT (Heterozygous)	**2**	81	80	0	**1**	0	100%
c.4964_4982del BRCA1	**II (Homozygous Common)**	**1**	162	162	0	0	0	100%
	DI (Heterozygous)	**1**	81	81	0	0	0	100%
	II (Homozygous Common)	**2**	162	162	0	0	0	100%
	DI (Heterozygous)	**2**	81	81	0	0	0	100%
c.4986+6T>G BRCA1	**AA (Homozygous Common)**	**1**	162	162	0	0	0	100%
	AC (Heterozygous)	**1**	81	81	0	0	0	100%
	AA (Homozygous Common)	**2**	162	162	0	0	0	100%
	AC (Heterozygous)	**2**	81	81	0	0	0	100%
c.5123C>A BRCA1	**GG (Homozygous Common)**	**1**	162	162	0	0	0	100%
	GT (Heterozygous)	**1**	81	81	0	0	0	100%
	GG (Homozygous Common)	**2**	162	162	0	0	0	100%
	GT (Heterozygous)	**2**	81	81	0	0	0	100%
c.5177_5180del BRCA1	**II (Homozygous Common)**	**1**	162	162	0	0	0	100%
	DI (Heterozygous)	**1**	81	81	0	0	0	100%
	II (Homozygous Common)	**2**	162	162	0	0	0	100%
	DI (Heterozygous)	**2**	81	81	0	0	0	100%
c.658_659del BRCA2	**II (Homozygous Common)**	**1**	162	162	0	0	0	100%
	DI (Heterozygous)	**1**	81	81	0	0	0	100%
	II (Homozygous Common)	**2**	162	162	0	0	0	100%
	DI (Heterozygous)	**2**	81	81	0	0	0	100%
c.771_775del BRCA2	**II (Homozygous Common)**	**1**	162	162	0	0	0	100%
	DI (Heterozygous)	**1**	81	81	0	0	0	100%
	II (Homozygous Common)	**2**	162	162	0	0	0	100%
	DI (Heterozygous)	**2**	81	81	0	0	0	100%

Variant	Genotype	Site	Replicates Pass QC	Correct Calls	Incorrect Calls	No Calls	FQCs	% Correct Calls
c.1929del BRCA2	**II (Homozygous Common)**	**1**	162	162	0	0	0	100%
	DI (Heterozygous)	**1**	81	81	0	0	0	100%
	II (Homozygous Common)	**2**	162	162	0	0	0	100%
	DI (Heterozygous)	**2**	81	81	0	0	0	100%
c.2808_2811del BRCA2	**II (Homozygous Common)**	**1**	162	162	0	0	0	100%
	DI (Heterozygous)	**1**	81	81	0	0	0	100%
	II (Homozygous Common)	**2**	162	162	0	0	0	100%
	DI (Heterozygous)	**2**	81	81	0	0	0	100%
c.2957_2958insG BRCA2	**DD (Homozygous Common)**	**1**	81	81	0	0	0	100%
	DI (Heterozygous)	**1**	81	81	0	0	0	100%
	DD (Homozygous Common)	**2**	81	81	0	0	0	100%
	DI (Heterozygous)	**2**	81	79	0	**2**	0	100%
c.3170_3174del BRCA2	**II (Homozygous Common)**	**1**	162	162	0	0	0	100%
	DI (Heterozygous)	**1**	81	80	0	**1**	0	100%
	II (Homozygous Common)	**2**	162	162	0	0	0	100%
	DI (Heterozygous)	**2**	81	81	0	0	0	100%
c.3264dup BRCA2	**DD (Homozygous Common)**	**1**	162	162	0	0	0	100%
	DI (Heterozygous)	**1**	81	81	0	0	0	100%
	DD (Homozygous Common)	**2**	162	162	0	0	0	100%
	DI (Heterozygous)	**2**	81	81	0	0	0	100%
c.3545_3546del BRCA2	**II (Homozygous Common)**	**1**	162	162	0	0	0	100%
	DI (Heterozygous)	**1**	81	81	0	0	0	100%
	II (Homozygous Common)	**2**	162	162	0	0	0	100%
	DI (Heterozygous)	**2**	81	81	0	0	0	100%
c.3847_3848del BRCA2	**II (Homozygous Common)**	**1**	162	162	0	0	0	100%

Variant	Genotype	Site	Replicates Pass QC	Correct Calls	Incorrect Calls	No Calls	FQCs	% Correct Calls
	DI (Heterozygous)	**1**	81	81	0	0	0	100%
	II (Homozygous Common)	**2**	162	162	0	0	0	100%
	DI (Heterozygous)	**2**	81	81	0	0	0	100%
c.4471_4474del BRCA2	**II (Homozygous Common)**	**1**	162	162	0	0	0	100%
	DI (Heterozygous)	**1**	81	81	0	0	0	100%
	II (Homozygous Common)	**2**	162	162	0	0	0	100%
	DI (Heterozygous)	**2**	81	81	0	0	0	100%
c.5542del BRCA2	**II (Homozygous Common)**	**1**	162	162	0	0	0	100%
	DI (Heterozygous)	**1**	81	81	0	0	0	100%
	II (Homozygous Common)	**2**	162	162	0	0	0	100%
	DI (Heterozygous)	**2**	81	81	0	0	0	100%
c.5576_5579del BRCA2	**II (Homozygous Common)**	**1**	162	162	0	0	0	100%
	DI (Heterozygous)	**1**	81	79	0	**2**	0	100%
	II (Homozygous Common)	**2**	162	162	0	0	0	100%
	DI (Heterozygous)	**2**	81	79	0	**2**	0	100%
c.5682C>G BRCA2	**CC (Homozygous Common)**	**1**	162	162	0	0	0	100%
	CG (Heterozygous)	**1**	81	81	0	0	0	100%
	CC (Homozygous Common)	**2**	162	162	0	0	0	100%
	CG (Heterozygous)	**2**	81	81	0	0	0	100%
c.6037A>T BRCA2	**AA (Homozygous Common)**	**1**	162	162	0	0	0	100%
	AT (Heterozygous)	**1**	81	81	0	0	0	100%
	AA (Homozygous Common)	**2**	162	162	0	0	0	100%
	AT (Heterozygous)	**2**	81	81	0	0	0	100%
c.6275_6276del BRCA2	**II (Homozygous Common)**	**1**	162	162	0	0	0	100%
	DI (Heterozygous)	**1**	81	81	0	0	0	100%

Variant	Genotype	Site	Replicates Pass QC	Correct Calls	Incorrect Calls	No Calls	FQCs	% Correct Calls
	II (Homozygous Common)	**2**	162	162	0	0	0	100%
	DI (Heterozygous)	**2**	81	81	0	0	0	100%
c.7024C>T BRCA2	**CC (Homozygous Common)**	**1**	162	162	0	0	0	100%
	CT (Heterozygous)	**1**	81	77	0	**4**	0	100%
	CC (Homozygous Common)	**2**	162	162	0	0	0	100%
	CT (Heterozygous)	**2**	81	78	0	**3**	0	100%
c.7480C>T BRCA2	**CC (Homozygous Common)**	**1**	162	162	0	0	0	100%
	CT (Heterozygous)	**1**	81	81	0	0	0	100%
	CC (Homozygous Common)	**2**	162	162	0	0	0	100%
	CT (Heterozygous)	**2**	81	81	0	0	0	100%
c.7934del BRCA2	**II (Homozygous Common)**	**1**	162	162	0	0	0	100%
	DI (Heterozygous)	**1**	81	81	0	0	0	100%
	II (Homozygous Common)	**2**	162	162	0	0	0	100%
	DI (Heterozygous)	**2**	81	81	0	0	0	100%
c.8904del BRCA2	**II (Homozygous Common)**	**1**	162	162	0	0	0	100%
	DI (Heterozygous)	**1**	81	81	0	0	0	100%
	II (Homozygous Common)	**2**	162	162	0	0	0	100%
	DI (Heterozygous)	**2**	81	81	0	0	0	100%

2. Linearity:

   Not applicable

3. Analytical Specificity/Interference:

   a. Interfering Substances

   A series of studies were previously performed to determine whether endogenous substances, exogenous substances, microbial substances, and smoking, affect results of the 23andMe PGS tests. The results of interference studies can be found in the Decision Summary for DEN140044.

b. Interfering Mutations

The Sponsor identified in the labeling the following rare mutations that may interfere with the performance of the test (Table 2). Interference due to these mutations was not tested. The package insert captures this with a statement indicating that:

"The performance of this test may be affected by the presence of rare mutations, such as those listed below. The effects of these variants on the performance of this test have not been studied."

Table 2. Potentially Interfering Mutations in the BRCA1 and BRCA2 genes

Gene	Variant Name	Potential Interfering Mutation
BRCA1	c.68_69del	rs528170710
		rs540373654
		rs80357134
		rs528902306
		rs149402012
BRCA1	c.427G>T	rs371973519
		rs368415464
		rs200358748
		rs542687218
		rs80356888
BRCA1	c.815_824dup	rs186274774
		rs397509328
		rs8176153
		rs80357244
		rs149867679
		rs201441987
BRCA1	c.1556del	rs200616937
		rs56272539
		rs80357445
BRCA1	c.1687C>T	rs530914551
		rs552505690
		rs80357159
		rs56012641
BRCA1	c.1960A>T	rs80356895
		rs561988641
		rs28897679
BRCA1	c.1961del	rs80356895
		rs561988641
		rs28897679
BRCA1	c.2864C>A	rs559190752
		rs80356851

Gene	Variant Name	Potential Interfering Mutation
BRCA1	c.3481_3491del	rs56336919
		rs183119644
		rs80356918
		rs80357272
BRCA1	c.3598C>T	rs537737635
		rs56214134
		rs16942
BRCA1	c.3627dup	rs537737635
		rs56214134
BRCA1	c.3756_3759del	rs140588714
		rs200648498
		rs483353090
		rs80357099
		rs80357191
BRCA1	c.3770_3771del	rs140588714
		rs200648498
		rs483353090
		rs80357099
		rs80357191
BRCA1	c.4035del	rs80357345
		rs28897689
		rs80356828
BRCA1	c.4065_4068del	rs80357345
		rs28897689
		rs80356828
BRCA1	c.4327C>T	rs80358027
		rs80356840
		rs1060915
		rs541512953
BRCA1	c.4357+1G>A	rs80356840
		rs1060915
BRCA1	c.4964_4982del	rs549640262
		rs1799967
		rs201810810
		rs70953661
BRCA1	c.4986+6T>G	rs549640262
		rs1799967
		rs201810810
BRCA1	c.5123C>A	rs376836050
		rs397509229
		rs80356860
BRCA1	c.5177_5180del	rs8176260

Gene	Variant Name	Potential Interfering Mutation
		rs56195342
BRCA1	c.5266dup	rs371203180
		rs571834423
BRCA2	c.658_659del	rs81002855
		rs568027879
		rs528919073
BRCA2	c.771_775del	rs55854959
		rs549269828
		rs567889781
BRCA2	c.1929del	rs11571652
		rs28897711
		rs527579384
BRCA2	c.2808_2811del	rs2227943
		rs28897716
		rs149753706
		rs80358535
BRCA2	c.2957_2958insG	rs45525041
		rs539613324
		rs144862123
		rs11571656
		rs80358541
		rs2227944
		rs1799944
BRCA2	c.3170_3174del	rs564316199
		rs145605603
BRCA2	c.3264dup	rs145605603
		rs543748012
		rs80358575
BRCA2	c.3545_3546del	rs80358600
		rs1799952
BRCA2	c.3847_3848del	rs543304
		rs41293485
BRCA2	c.5542del	rs138489917
		rs372951842
		rs573514896
BRCA2	c.5576_5579del	rs372951842
		rs573514896
		rs80358782
BRCA2	c.5682C>G	rs55996097
		rs11571657
		rs146351301
		rs4987048

Gene	Variant Name	Potential Interfering Mutation
		rs149474191
		rs55875643
BRCA2	c.5946del	rs556893517
		rs148618542
		rs80358833
		rs554663691
BRCA2	c.6037A>T	rs554663691
		rs572976024
		rs540799830
		rs147961615
BRCA2	c.6275_6276del	rs541826447
		rs397507838
		rs55794205
		rs35029074
		rs79456940
BRCA2	c.7024C>T	rs186220967
		rs45574331
		rs80358932
		rs200078639
BRCA2	c.7480C>T	rs80358965
		rs11571707
		rs55716624
		rs56070345
BRCA2	c.7934del	rs529779203
BRCA2	c.8904del	rs59004709

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. The assay requires two types of controls: the sample processing control and the reproducibility control. The information provided demonstrates that the sample processing control is stable for up to three months and the reproducibility control is stable for up to 12 months. See DEN140044 for detailed information.

6. Detection Limit:

   A minimum DNA input study was performed to determine the lowest concentration of DNA that is necessary for successful assignment of correct genotypes 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 for this study were selected from the 23andMe customer database based on their putative genotype and included homozygous common (1 or more sample(s) per variant) and heterozygous common (1 sample per variant) genotypes for each variant. The sample input for the assay is 15 ng/ µL. Therefore, samples were diluted to 3 different concentrations (5, 15, and 50 ng/µL) and genotyped by the assay in a blinded fashion in triplicates 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 all sample DNA concentrations. Therefore, the study passed the acceptance criteria of 95% correct calls at the lowest concentration tested (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.

7. Assay Cut-Off:

   Not applicable

B Comparison Studies:

1. Comparison with Sanger bidirectional Sequencing:

Accuracy was evaluated through calculation of agreement of the genetic variant determinations between the 23andMe PGS test results and Sanger bidirectional sequencing (comparator) results. All additional 41 variants to be added to the existing BRCA1/BRCA2 (Selected Variants) report were included in the study.

Saliva samples were randomly selected from the 23andMe customer biobank based on predetermined genotypes and the minimum volume required for testing. All chosen samples were then genotyped using Sanger bidirectional sequencing. All Sanger bidirectional sequencing was performed at an independent laboratory site. Genotyping results were compared between the PGS test and bidirectional sequencing to calculate percent agreements with the sequencing results used as the reference. The accuracy data generated for each test report met the Manufacturer's pre-defined acceptance criteria: a minimum of 99% positive percent agreement (PPA) and negative percent agreement (NPA) for each genotype. All results were correct except for BRCA2c.3847_3848del Heterozygous which had one incorrect false negative call. There were 4 no calls. The widest 95% confidence interval was 47.3% to 100% for the heterozygous c.2864C>A BRCA1 genotype. The data is shown in Table 3.

Table 3. Percent Agreement for BRCA1/BRCA2 Variants by Genotypes

Genotype by Sanger	PGS Genotype Call				% PPA	% NPA	95% CI**
	Correct*	Incorrect*	No Call	FQC			
BRCA1 c.213-11T>G Homozygous Common	35	0	0	0	N/A	100%	91.8% - 100%

Genotype by Sanger	PGS Genotype Call				% PPA	% NPA	95% CI**
	Correct*	Incorrect*	No Call	FQC			
BRCA1 c.213-11T>G Heterozygous	15	0	0	0	100%	N/A	81.9% - 100%
BRCA1 c.427G>T Homozygous Common	21	0	0	0	N/A	100%	86.7% - 100%
BRCA1 c.427G>T Heterozygous	27	0	0	0	100%	N/A	89.5% - 100%
BRCA1c.815_824dup Homozygous Common	22	0	0	0	N/A	100%	87.3% - 100%
BRCA1c.815_824dup Heterozygous	26	0	0	0	100%	N/A	89.1% - 100%
BRCA1c.1556del Homozygous Common	24	0	0	0	N/A	100%	88.3% - 100%
BRCA1c.1556del Heterozygous	26	0	0	0	100%	N/A	89.1% - 100%
BRCA1 c.1687C>T Homozygous Common	23	0	0	0	N/A	100%	87.8% - 100%
BRCA1 c.1687C>T Heterozygous	22	0	0	0	100%	N/A	87.3% - 100%
BRCA1 c.1960A>T Homozygous Common	29	0	0	0	N/A	100%	90.2% - 100%
BRCA1 c.1960A>T Heterozygous	25	0	**1**	0	100%	N/A	88.7% - 100%
BRCA1c.1961del Homozygous Common	24	0	0	0	N/A	100%	88.3% - 100%
BRCA1c.1961del Heterozygous	13	0	0	0	100%	N/A	79.4% - 100%
BRCA1c.2681_2682del Homozygous Common	24	0	0	0	N/A	100%	88.3% - 100%
BRCA1c.2681_2682del Heterozygous	22	0	0	0	100%	N/A	87.3% - 100%
BRCA1 c.2864C>A Homozygous Common	24	0	0	0	N/A	100%	88.3% - 100%
BRCA1 c.2864C>A Heterozygous	4	0	0	0	100%	N/A	47.3% - 100%
BRCA1c.3481_3491del Homozygous Common	26	0	0	0	N/A	100%	89.1% - 100%
BRCA1c.3481_3491del Heterozygous	29	0	0	0	100%	N/A	90.2% - 100%
BRCA1 c.3598C>T Homozygous Common	21	0	0	0	N/A	100%	86.7% - 100%
BRCA1 c.3598C>T Heterozygous	24	0	0	0	100%	N/A	88.3% - 100%
BRCA1c.3627dup Homozygous Common	22	0	0	0	N/A	100%	87.3% - 100%

Genotype by Sanger	PGS Genotype Call				% PPA	% NPA	95% CI**
	Correct*	Incorrect*	No Call	FQC			
BRCA1c.3627dup Heterozygous	12	0	0	0	100%	N/A	77.9% - 100%
BRCA1c.3756_3759del Homozygous Common	22	0	0	0	N/A	100%	87.3% - 100%
BRCA1c.3756_3759del Heterozygous	23	0	0	0	100%	N/A	87.8% - 100%
BRCA1c.3770_3771del Homozygous Common	22	0	0	0	N/A	100%	87.3% - 100%
BRCA1c.3770_3771del Heterozygous	27	0	0	0	100%	N/A	89.5% - 100%
BRCA1c.4035del Homozygous Common	24	0	0	0	N/A	100%	88.3% - 100%
BRCA1c.4035del Heterozygous	23	0	0	0	100%	N/A	87.8% - 100%
BRCA1c.4065_4068del Homozygous Common	24	0	0	0	N/A	100%	88.3% - 100%
BRCA1c.4065_4068del Heterozygous	21	0	0	0	100%	N/A	86.7% - 100%
BRCA1 c.4327C>T Homozygous Common	26	0	0	0	N/A	100%	89.1% - 100%
BRCA1 c.4327C>T Heterozygous	24	0	0	0	100%	N/A	88.3% - 100%
BRCA1 c.4357+1G>A Homozygous Common	24	0	0	0	N/A	100%	88.3% - 100%
BRCA1 c.4357+1G>A Heterozygous	8	0	0	0	100%	N/A	68.8% - 100%
BRCA1c.4964_4982del Homozygous Common	30	0	0	0	N/A	100%	90.5% - 100%
BRCA1c.4964_4982del Heterozygous	20	0	0	0	100%	N/A	86.1% - 100%
BRCA1 c.4986+6T>G Homozygous Common	27	0	0	0	N/A	100%	89.5% - 100%
BRCA1 c.4986+6T>G Heterozygous	14	0	0	0	100%	N/A	80.7% - 100%
BRCA1 c.5123C>A Homozygous Common	24	0	0	0	N/A	100%	88.3% - 100%
BRCA1 c.5123C>A Heterozygous	29	0	0	0	100%	N/A	90.2% - 100%
BRCA1c.5177_5180del Homozygous Common	24	0	0	0	N/A	100%	88.3% - 100%
BRCA1c.5177_5180del Heterozygous	26	0	0	0	100%	N/A	89.1% - 100%
BRCA2c.658_659del Homozygous Common	26	0	0	0	N/A	100%	89.1% - 100%

Genotype by Sanger	PGS Genotype Call				% PPA	% NPA	95% CI**
	Correct*	Incorrect*	No Call	FQC			
BRCA2c.658_659del Heterozygous	20	0	0	0	100%	N/A	86.1% - 100%
BRCA2c.771_775del Homozygous Common	23	0	0	0	N/A	100%	87.8% - 100%
BRCA2c.771_775del Heterozygous	25	0	0	0	100%	N/A	88.7% - 100%
BRCA2c.1929del Homozygous Common	26	0	0	0	N/A	100%	89.1% - 100%
BRCA2c.1929del Heterozygous	25	0	0	0	100%	N/A	88.7% - 100%
BRCA2c.2808_2811del Homozygous Common	48	0	0	0	N/A	100%	93.9% - 100%
BRCA2c.2808_2811del Heterozygous	31	0	0	0	100%	N/A	90.8% - 100%
BRCA2c.2957_2958insG Homozygous Common	24	0	0	0	N/A	100%	88.3% - 100%
BRCA2c.2957_2958insG Heterozygous	6	0	0	0	100%	N/A	60.7% - 100%
BRCA2c.3170_3174del Homozygous Common	24	0	0	0	N/A	100%	88.3% - 100%
BRCA2c.3170_3174del Heterozygous	26	0	0	0	100%	N/A	89.1% - 100%
BRCA2c.3264dup Homozygous Common	24	0	0	0	N/A	100%	88.3% - 100%
BRCA2c.3264dup Heterozygous	27	0	0	0	100%	N/A	89.5% - 100%
BRCA2c.3545_3546del Homozygous Common	27	0	0	0	N/A	100%	89.5% - 100%
BRCA2c.3545_3546del Heterozygous	31	0	0	0	100%	N/A	90.8% - 100%
BRCA2c.3847_3848del Homozygous Common	102	0	0	0	N/A	100%	97.1% - 100%
BRCA2c.3847_3848del Heterozygous	108	**1**	0	0	99.03%	N/A	95.56% - 99.96%
BRCA2c.4471_4474del Homozygous Common	24	0	0	0	N/A	100%	88.3% - 100%
BRCA2c.4471_4474del Heterozygous	5	0	0	0	100%	N/A	54.9% - 100%
BRCA2c.5542del Homozygous Common	25	0	0	0	N/A	100%	88.7% - 100%
BRCA2c.5542del Heterozygous	6	0	0	0	100%	N/A	60.7% - 100%
BRCA2c.5576_5579del Homozygous Common	22	0	0	0	N/A	100%	87.3% - 100%

Genotype by Sanger	PGS Genotype Call				% PPA	% NPA	95% CI**
	Correct*	Incorrect*	No Call	FQC			
BRCA2c.5576_5579del Heterozygous	26	0	0	0	100%	N/A	89.1% - 100%
BRCA2 c.5682C>G Homozygous Common	26	0	0	0	N/A	100%	89.1% - 100%
BRCA2 c.5682C>G Heterozygous	27	0	0	0	100%	N/A	89.5% - 100%
BRCA2 c.6037A>T Homozygous Common	22	0	0	0	N/A	100%	87.3% - 100%
BRCA2 c.6037A>T Heterozygous	17	0	**2**	0	100%	N/A	83.8% - 100%
BRCA2c.6275_6276del Homozygous Common	25	0	0	0	N/A	100%	88.7% - 100%
BRCA2c.6275_6276del Heterozygous	25	0	**1**	0	100%	N/A	88.7% - 100%
BRCA2 c.7024C>T Homozygous Common	29	0	0	0	N/A	100%	90.2% - 100%
BRCA2 c.7024C>T Heterozygous	9	0	0	0	100%	N/A	71.7% - 100%
BRCA2 c.7480C>T Homozygous Common	24	0	0	0	N/A	100%	88.3% - 100%
BRCA2 c.7480C>T Heterozygous	25	0	0	0	100%	N/A	88.7% - 100%
BRCA2c.7934del Homozygous Common	24	0	0	0	N/A	100%	88.3% - 100%
BRCA2c.7934del Heterozygous	15	0	0	0	100%	N/A	81.9% - 100%
BRCA2c.8904del Homozygous Common	24	0	0	0	N/A	100%	88.3% - 100%
BRCA2c.8904del Heterozygous	26	0	0	0	100%	N/A	89.1% - 100%

*****Relative to Sanger Sequencing
******calculated using the mid-p method

2. Matrix Comparison:

Not applicable. This test is for use with human saliva samples only.

C Clinical Studies:

1. Disease Description and Clinical Summary

The 23andMe PGS® Genetic Health Risk Test for BRCA1/BRCA2 (Selected Variants) is indicated for the detection of 44 variants in the BRCA1 and BRCA2 genes. These variants are associated with an increased risk for female breast and ovarian cancer (including early-onset breast cancer) and male breast cancer and may be associated with an increased risk for prostate cancer, pancreatic cancer, and potentially other cancers (NCCN 2023). The clinical validity of

the BRCA1/2 variants is supported by clinical guidelines, public and proprietary databases, published data, and frequency data from the 23andMe customer database.

Pathogenic BRCA1 and BRCA2 variants are highly penetrant: for example, females with a variant have a 45-85% chance of developing breast cancer and up to a 46% chance of developing ovarian cancer by age 70 (ACOG 2017, *Obstet Gynecol.* 2017 Sept, 130 (3): e110-e126.PMID: 28832484).

The overall prevalence of pathogenic variants in BRCA1 and BRCA2 is estimated to be between 1 in 300 and 1 in 800 in the general population (ACOG 2017, *Obstet Gynecol.* 2017 Sept, 130 (3): e110-e126.PMID: 28832484), and thousands of unique variants have been identified (BRCA Exchange; ACOG 2017, *Obstet Gynecol.* 2017 Sept, 130 (3): e110-e126.PMID: 28832484; Petrucelli et al, *Genet Med* 2010,12(5):245-59. PMID: 20216074).

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 (Bhaskaran et al, *J. Med Genet* 2021 Nov, 58 (11):752-759. PMID 32963034).

The table below summarizes the population risk for certain cancers provided in the 23andMe PGS BRCA1/BRCA2 (Selected variants) test reports. The report provides risk estimates for several cancers in individuals with any pathogenic variant in the BRCA1 or BRCA2 gene rather than estimates specific to the variant detected.

Table 4. Numerical and qualitative risk estimates provided in the 23andMe PGS BRCA1/BRCA2 (Selected Variants) test reports

Cancer Type	General population	BRCA1 variant	BRCA2 variant
Breast (female)	12.9%	45-85%	45-85%
Ovarian	1.1%	39-46%	10-27%
Breast (male)	0.1%	1-2%	7-8%
Prostate	12.6%	May have an increased risk*	Increased risk
Pancreatic	1.7%	May have an increased risk	Increased risk
Melanoma	2.1%	Research ongoing	Research ongoing

* For males with a BRCA1 variant, some studies did not observe an increased risk for prostate cancer

Risk estimates in the table above are based on the following references:

- Committee on Practice Bulletins–Gynecology, Committee on Genetics, Society of Gynecologic Oncology. (2017). “Practice Bulletin No 182: Hereditary Breast and Ovarian Cancer Syndrome.” Obstet Gynecol. 130(3):e110-e126.
- Evans DG et al. (2010). “Risk of breast cancer in male BRCA2 carriers.” J Med Genet. 47(10): 10-1.
- Surveillance Research Program, National Cancer Institute. "SEER*Explorer: An interactive website for SEER cancer statistics." 2017-2019. Retrieved Dec 6, 2022, from https://seer.cancer.gov/statistics-network/explorer/

- Tai YC et al. (2007). “Breast cancer risk among male BRCA1 and BRCA2 mutation carriers.” J Natl Cancer Inst. 99(23):1811-4.

2. Clinical Sensitivity:

   Not applicable

3. Clinical Specificity:

   Not applicable

4. Other Clinical Supportive Data:

   i. User Comprehension Study

   Specific user comprehension studies were not performed to specifically assess the comprehension of the Genetic Health Risk report for BRCA1/BRCA2 (Selected Variants). To fulfill special control 21CFR 866.6090 (b) (4) (xiv), 23andMe provided real world data that included customer service records, adverse event reports, Corrective and Preventive Actions (CAPA) documentation, user feedback, and ethnicity information, collected since the marketing authorization date of each of the cancer predisposition risk reports (DEN170046, K182784, K211499) up to July 13, 2023. The study population consisted of users who had opted in to receive their Cancer Predisposition Risk reports. Less than 0.1% (one-tenth of one percent) of the total number of customers who viewed each Cancer Predisposition Risk report had customer contacts or complaints related to the comprehension concepts for each type of report. There were no adverse events (zero) related to the Cancer Predisposition Risk reports, and there had been only 2 (two) complaints related to user comprehension for which corrective actions resolved. Overall, it was determined that the data was not conclusive of the user comprehension because it excludes customers who may have contacted a health care professional to resolve their questions, or customers who don’t realize they misunderstood the report. However, it was determined that the test has appropriate mitigations in place to address potential false interpretation of the results. These mitigations include warnings in the customer report that indicate that the results should be shared with a healthcare professional, the results should be confirmed by an independent genetic test prescribed by your own healthcare provider before taking any medical action, and that the test only includes 44 out of more than 4000 variants in the BRCA1 and BRCA2 genes that are known to increase cancer risk and customer could still have a variant not included in this test. These warnings and limitations are present in several areas of the report (report overview page, scientific details page, FAQ section, and package insert) and provide users with information to adequately understand the purpose, limitations and meaning of the results of the test.

   ii. Frequently Asked Questions Material

   The Manufacturer has developed a Frequently Asked Questions (FAQ) section for the BRCA1/BRCA2 (Selected Variants) Genetic Health Risk (GHR) report, which is included in the test report and accessible to the user on the Manufacturer’s public website. The FAQs are specific to the variants and disease risk associations being reported, where applicable. The FAQ section was created to provide users with information to adequately understand the purpose, limitations and meaning of the results of the test. The FAQ section was developed using methodology consistent with the

Manufacturer's labeling design, identification of primary communication messages, and label comprehension. The concepts covered in the FAQ section include: the test results, purpose of the test, limitations of the test, relevance of race and ethnicity on test results, meaning of the result, other risk factors that contribute to disease, appropriate follow-up procedures, how the results of the test may affect the user's family and children, and links to resources that provide additional information. Additionally, the FAQ section provides definitions for terminology found in Genetic Health Risk Reports that is used to describe risks associated with detected variants. The specific questions and answers provided are customized based on the customer's result.

iii. User Opt-In Page

Prior to receiving the test results, a pre-purchase page informs users that there is a choice of whether or not to receive the BRCA1/BRCA2 (Selected Variants) test report. Users have an opportunity to opt into receiving these results after reviewing important information included in an opt-in page. The opt-in page is provided for the BRCA1/BRCA2 (Selected Variants) GHR report users due to the nature of the diseases and associated risks for this report, the availability of risk-reducing surgery or medication available for individuals who carry BRCA1 or BRCA2 variants, and the fact that this test is not designed to inform clinical decision-making. Users will be directed to a page entitled, "Choose your health reports" which provides the option to exclude this report from the user's account. The report selection page includes important information to allow the users to make an informed decision. Results of the BRCA1/BRCA2 (Selected Variants) report are locked by default. Customers must elect to opt-in to receive cancer predisposition risk reports and are able to update their report opt-in selections at any time within their account settings. Existing customers who have already opted in to the BRCA1/BRCA2 (Selected Variants) report will not be prompted to opt in again after the report labeling has been modified. New customers, or customers who have not previously opted in, will be required to opt in to the BRCA1/BRCA2 (Selected Variants) report prior to viewing their results, as authorized in DEN170046. All customers must complete the revised education module in order to view the report. Until this is completed, report results will not be viewable within a customer's account.

D Clinical Cut-Off:

Not applicable

E Expected Values/Reference Range:

The variants included in the report cover more than 90% of pathogenic BRCA variants in individuals of Ashkenazi Jewish descent (Janavicius et al, *EPMA J*, (2010), (3):397-412. PMID: 23199084; Rosenthal et al, *Breast Cancer Res Treat*. (2015), 149 (1): 223-7. PMID: 25476495); about 30-40% in people of African American, European, and Hispanic/Latino descent (Rebbeck et al, *Hum Mutat*. (2018), 39 (5): 593-620. PMID 29446198); about 5-25% among people of East Asian descent; and up to 35% among people of South Asian descent (Bhaskaran et al, J Med Genet. (2021), Nov; 58 (11): 752-759. PMID 32963034).

The user test reports include allele frequencies from 23andMe customers in the Scientific Details Page. These allele frequencies are from the 23andMe database and may not be representative for the actual allele frequencies.

VIII Proposed Labeling:

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

IX Conclusion:

The subject device, 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.

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