

**EVALUATION OF AUTOMATIC CLASS III DESIGNATION FOR
The 23andMe Personal Genome Service (PGS) Genetic Health Risk Report for
BRCA1/BRCA2 (Selected Variants)**

DECISION SUMMARY

**This Decision Summary contains corrections to the Decision Summary originally issued in
April 2018.**

A. DEN Number:

DEN170046

B. Purpose for Submission:

De Novo request for the 23andMe Personal Genome Service (PGS) Genetic Health Risk Report for BRCA1/BRCA2 (Selected Variants)

C. Measurands:

Two specific single nucleotide polymorphisms (SNPs) in the BRCA1 gene (variants 185delAG and 5382insC) and one in the BRCA 2 gene (variant 6174delT).

D. Type of Test:

Qualitative genetic test for detection of select BRCA1 and BRCA2 SNPs.

E. Applicant:

23andMe, Inc.

F. Proprietary and Established Names:

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

G. Regulatory Information:

1. Regulation section:

21 CFR 866.6090

2. Classification:

Class II

3. Product code(s):

QAZ

4. Panel:

Pathology

H. Indications for use:

1. Indications 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 PGS Genetic Health Risk Report for BRCA1/BRCA2 (Selected Variants) is indicated for reporting of the 185delAG and 5382insC variants in the BRCA1 gene and the 6174delT variant in the BRCA2 gene. The report describes if a woman is at increased risk of developing breast and ovarian cancer, and if a man is at increased risk of developing breast cancer or may be at increased risk of developing prostate cancer. The three variants included in this report are most common in people of Ashkenazi Jewish descent and do not represent the majority of the BRCA1/BRCA2 variants in the general population. 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 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.

2. Special conditions for use statement(s):

- a. For over-the-counter (OTC) use.
- b. 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.
- c. 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.
- d. 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.
- e. The test is intended for users ≥ 18 years old.
- f. 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%.

- g. A user's race, ethnicity, age, and sex may affect how the genetic test results are interpreted.
- h. 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.
- i. Subject to meeting the limitations contained in the special controls under regulation 21 CFR 866.6090.

3. Special instrument requirements:

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

I. Device Description:

The 23andMe PGS is a non-invasive DNA testing service that combines qualitative genotyping data covering genetic ancestry, traits, and certain heritable health conditions from a single multiplex assay with descriptive information derived from peer reviewed, published genetic research studies. It is a direct-to-consumer, over-the-counter, DNA genetic test intended to provide information and tools for individual users.

A user's saliva is self-collected using the Oragene·Dx device manufactured by DNA Genotek, Inc. (previously cleared under K141410), which consists of a sealable collection tube containing a stabilizing buffer solution. Once the sample is collected, it is shipped to one of two Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories for testing.

DNA is isolated from the saliva and tested in a multiplex assay using a customized genotyping beadchip, reagents and instrumentation manufactured by Illumina. The multiplex assay simultaneously tests for more than 500,000 variants, including those for the previously authorized indications, as well as for the indication proposed herein.

The raw data is generated using Illumina GenomeStudio software, and then sent to 23andMe (the Manufacturer). The data are analyzed using the Manufacturer's proprietary Coregen software, and a genotype is determined for each tested variant. The results for certain of these variants, as noted in the indications for use, are used to generate personalized reports for users that provide information about the diseases associated with tested variants.

Personalized reports are generated for each user that provides results of the testing performed. These reports tell the user which variant(s) has/have been detected in their sample and provide information on the risk of 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 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 inform conversations with their doctor or other healthcare professional. The 23andMe PGS Genetic Health Risk Report for BRCA1/BRCA2 (Selected Variants) reports on three specific

variants including the 185delAG and 5382insC variants in the BRCA1 gene and the 6174delT variant in the BRCA2 gene. The variants included in this report are most common in people of Ashkenazi Jewish descent and do not represent the majority of BRCA1/BRCA2 variants in the general population. Therefore the absence of a variant tested does not rule out the presence of other genetic variants that may be disease-related.

J. Substantial Equivalence Information:

1. Predicate device name:

No predicate device exists.

2. Predicate 510(k) number:

Not applicable.

3. Comparison with predicate:

Not applicable.

K. Standard/Guidance Document Referenced (if applicable):

Not applicable.

L. Test Principle:

The PGS is indicated to be performed using the BeadChip v4 assay (Illumina Infinium HumanOmniExpress-24 format chip), which covers more than 500,000 genetic markers. The BeadChip consists of silicon wafers etched to form wells loaded with silica beads, on which oligonucleotide capture probes are immobilized. DNA from saliva is fragmented and captured on a bead array by hybridization to immobilized SNP-specific primers, followed by extension with hapten-labeled nucleotides. The primers hybridize adjacent to the SNPs and are extended with a single nucleotide corresponding to the variant allele. The incorporated hapten-modified nucleotides are detected by adding fluorescently labeled antibodies in several steps to amplify the signals. 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 pre-defined 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 three specific variants in the BRCA1/BRCA2 genes are integrated into the report: 185delAG and 5382insC variants in the BRCA1 gene and 6174delT variant in the BRCA2 gene.

M. Performance Characteristics:

1. Analytical performance:

The results of all the analytical performance studies met the Manufacturer’s pre-determined acceptance criteria.

a. *Precision/Reproducibility*

Reproducibility studies were conducted for the two variants reported in BRCA1 and the one variant reported in BRCA2 (as listed in Table 1). The reproducibility studies were designed to determine the imprecision due to assay run, lot, instrument, operator, day and site. DNA samples were procured and genotyped in blinded fashion. Genotypes of the DNA samples were confirmed through bidirectional Sanger sequencing. Samples included in the study are shown in Table 1 below. The study included three replicates per sample. Samples were genotyped by the PGS test at two independent laboratory sites on three days using three laboratory operator teams at each site, three lots of reagents (chosen at random from all available), three Tecan instruments, and three iScan instruments.

Table 1. Summary of Sample Genotypes in the Precision Study

Genes	Variant (Genotype)	Samples
BRCA1	185delAG wildtype (homozygous common “II”)	2
BRCA1	185delAG (heterozygous common “DI”)	1
BRCA1	5382insC wildtype (homozygous common “DD”)	2
BRCA1	5382insC (heterozygous “DI”)	1
BRCA2	6174delT wildtype (homozygous common “II”)	2
BRCA2	6174delT (heterozygous “DI”)	1

Among samples with valid calls, the precision study yielded 100% correct genotype calls with a valid call across multiple days, operator teams, instruments, and reagent lots at both laboratory sites. Information regarding samples that failed quality control (FQC) was also evaluated (as listed in Table 2). The data presented below are based on FQCs following a single run. Samples with FQC on the first run are re-tested per laboratory SOPs, therefore, it is anticipated that the observed “real-world” FQCs would be lower than what was observed in the precision study data.

Tables 2A-C. Precision Study Results Stratified by Site and Genotype

Table 2A. BRCA1 185delAG (i400377) Results

Genotype	Number of Replicates (including FQCs)	Number of Correct Calls	Number of Incorrect Calls	Number of FQCs	Percentage of FQCs
Site 1					
Homozygous Common	242	241	0	1	0.41%
Heterozygous	79	77	0	2	2.53%

Total	321	318	0	3	0.93%
Site 2					
Homozygous Common	234	225	0	9	3.85%
Heterozygous	75	69	0	6	8.00%
Total	309	294	0	15	4.85%

Table 2B. BRCA1 5382insC (i400378) Results

Genotype	Number of Replicates (including FQCs)	Number of Correct Calls	Number of Incorrect Calls	Number of FQCs	Percentage of FQCs
Site 1					
Homozygous Common	242	241	0	1	0.41%
Heterozygous	160	158	0	2	1.25%
Total	402	399	0	3	0.75%
Site 2					
Homozygous Common	234	225	0	9	3.85%
Heterozygous	157	152	0	5	3.18%
Total	391	377	0	14	3.58%

Table 2C. BRCA2 6174delT (i400379) Results

Genotype	Number of Replicates (including FQCs)	Number of Correct Calls	Number of Incorrect Calls	Number of FQCs	Percentage of FQCs
Site 1					
Homozygous Common	242	241	0	1	0.41%
Heterozygous	81	81	0	0	0%
Total	323	321	0	1	0.31%
Site 2					
Homozygous Common	234	225	0	9	3.84%
Heterozygous	79	75	0	2	2.53%
Total	313	304	0	11	3.51%

b. *Linearity/assay Reportable Range:*

Not applicable.

c. *Traceability, Stability, Expected Values (controls, calibrators, or methods):*

The PGS requires two types of controls: the sample processing control and the reproducibility control. The sample processing control material is generated from cultured cells suspended in a 50/50 mixture of (b) (4) and the Oragene-Dx saliva-kit buffer at a concentration of (b) (4). The reproducibility control material is generated from (b) (4)

DNA is extracted and genotyped on the 23andMe BeadChip according to routine laboratory SOPs. Each new lot of the reproducibility control is tested by comparison with reference BeadChip genotype results.

The sample processing control is run on every sample genotyping plate and the reproducibility control is run approximately once per week. Historical data from all such runs were analyzed for one lot of the sample processing control spanning three months and one lot of the reproducibility control spanning one year.

Stability protocols and acceptance criteria were reviewed and acceptable. 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.

d. Detection Limit:

The Limit of Detection (LoD) study was performed to determine the lowest concentration of DNA that is necessary for successful assignment of the correct 185delAG BRCA1, 5382insC BRCA1 and 6174delT BRCA2 variants using the 23andMe PGS test. Study samples were obtained from an external vendor based on their listed genotypes and included both homozygous and heterozygous common genotypes for each variant. Each sample, including four replicates per sample, was diluted to three different DNA concentrations (5, 15, and 50 ng/μl) and genotyped by the PGS test in a blinded fashion using 3 lots of reagents. To confirm the genotype call, each sample was sequenced by bidirectional Sanger sequencing. Genotype calls from the PGS test were compared with genotypes from Sanger sequencing to determine the rates of correct genotype calls at each DNA concentration.

The LoD was defined as the lowest DNA concentration at which at least 95% of samples yielded the correct call. This study yielded 100% correct calls per genotype for all samples across all reagent lots, at all sample concentrations tested. Therefore, the study passed the acceptance criteria of 95% correct calls at the lowest concentration tested (5 ng/μL). The performance requirement for the PGS Test, specified in the laboratory SOPs, is set at a minimum of 15 ng/μL DNA and maximum of 50 ng/μL DNA.

e. Interfering Substances

Endogenous and Exogenous Substances

A series of studies were conducted to assess the effects of endogenous substances, exogenous substances, microbial substances, and smoking on the 23andMe PGS Test.

The results of the Endogenous and Exogenous Interference studies can be found in the Decision Summary for DEN140044.

Interfering Mutations

Analyses were performed to identify potentially interfering variants within the 50-nucleotide probe-binding regions of the three BRCA1/BRCA2 variants detected by the test. Four potentially interfering mutations near 6174delT, two potentially interfering mutations near 185delAG, and five near 185delAG that are within the binding region for the variant being tested have been identified (see list in Table 3). The specific mutations potentially interfering with detection of each tested variant are noted below. Interference due to these mutations was not tested.

Table 3. Potentially Interfering Mutations in BRCA1 and BRCA2 genes

Select BRCA variant	Potentially Interfering Mutation
BRCA1 185delAG	rs528170710 rs540373654 rs80357134 rs528902306 rs149402012
BRCA1 5382insC	rs371203180 rs571834423
BRCA2 6174delT	rs556893517 rs148618542 rs80358833 rs554663691

f. Assay Cut-off:

Not applicable.

g. Specimen Stability at 2–8°C

Saliva samples for testing are collected with the Oragene·Dx collection device. See K141410 for sample stability information.

h. Shipping Stability

Saliva samples are shipped for testing in the Oragene·Dx collection device. See K141410 for sample shipping stability information.

2. Comparison Studies:

a. 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 Sanger bidirectional sequencing was performed at an independent laboratory site. Saliva samples were 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. Genotyping results were compared between the PGS test and bidirectional sequencing to calculate percent agreements with the sequencing results used as the reference. The comparison study results for the BRCA1/BRCA2 (Selected Variants) study report are shown in Table 4 below. 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.

Table 4. Percent Agreement for BRCA1/BRCA2 Variants by Genotypes

Genotype by Sanger	PGS Test Genotype Call				Total Sample #	%PPA	%NPA	95% CI [‡]
	Correct*	Incorrect*	No Call	FQC				
BRCA1 185delAG Homozygous Common	108	0	0	1	109	100	100	96.6 – 100
BRCA1 185delAG Heterozygous	58	0	0	0	58	100	100	93.8 – 100
BRCA1 5382insC Homozygous Common	60	0	0	0	60	100	100	94.0 – 100
BRCA1 5382insC Heterozygous	21	0	0	1	22	100	100	83.9 – 100
BRCA1 5382insC Homozygous Common	59	0	0	1	60	100	100	93.9 – 100
BRCA1 5382insC Heterozygous	45	0	0	1	46	100	100	92.1 – 100

*Relative to Sanger sequencing

[‡]Clopper-Pearson exact method

b. Matrix Comparison

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

3. Clinical Studies:

a. *Disease Description and Clinical Summary*

Clinical performance was assessed using published data and studies to support the user comprehension of the labeling and test results. Clinical data relating to pathogenic variants in BRCA1 and BRCA2 were summarized. The data include, but are not limited to, the three BRCA1/BRCA2 variants included in the PGS Genetic Health Risk Report for BRCA1/BRCA2 (Selected Variants).

The three variants in BRCA1/BRCA2 that are detected by the PGS Genetic Health Risk Test for BRCA1/BRCA2 are associated with hereditary breast and ovarian cancer (HBOC), which is characterized by an increased familial risk for female breast and ovarian cancer (including early onset breast cancer) and male breast cancer. Mutations in these variants may also be associated with and prostate cancer, pancreatic cancer and melanoma. The U.S. Preventive Services Task Force (USPSTF) currently recommends against routine genetic counseling or BRCA testing for women whose family history is not associated with an increased risk for potentially harmful mutations in the BRCA1 or BRCA2 genes.¹ Preventive measures for women with BRCA1/BRCA2 variants include earlier and more frequent breast cancer screening, along with the option of prophylactic bilateral mastectomy, salpingo-oophorectomy, or chemoprevention with tamoxifen or raloxifene. Men with BRCA1/BRCA2 variants are screened for breast cancer and may be screened for prostate cancer.

Pathogenic BRCA1 and BRCA2 variants account for 0.5%-10% of female breast cancer cases unselected for family history^{2,3,4}; 13-18% of ovarian cancer cases unselected for family history^{2,5}; and 15-20% of male breast cancers.^{6,5} Pathogenic BRCA1 and BRCA2 variants can be highly penetrant; lifetime risk estimates range from 41-90% for breast cancer and 8-62% for ovarian cancer, depending on the population studied.⁷ More than 1,000 variants have been identified in these genes that are known to increase cancer risk.

¹ U.S. Preventive Services Task Force. (2014). "Final Recommendation Statement: BRCA-Related Cancer: Risk Assessment, Genetic Counseling, and Genetic Testing." *Ann Intern Med.* 160(4): 277-281.

² Kurian AW. (2010). "BRCA1 and BRCA2 mutations across race and ethnicity: distribution and clinical implications." *Curr Opin Obstet Gynecol.* 22(1):72-8.

³ John EM *et al.* (2007). "Prevalence of pathogenic BRCA1 mutation carriers in 5 US racial/ethnic groups." *JAMA.* 298(24):2869-76.

⁴ Malone KE *et al.* (2006). "Prevalence and predictors of BRCA1 and BRCA2 mutations in a population-based study of breast cancer in white and black American women ages 35 to 64 years." *Cancer Res.* 66(16):8297-308.

⁵ Hampel H *et al.* (2015). "A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment." *Genet Med.* 17(1):70-87.

⁶ Liede A *et al.* (2004). "Cancer risks for male carriers of germline mutations in BRCA1 or BRCA2: a review of the literature." *J Clin Oncol.* 22(4):735-42.

⁷ National Comprehensive Cancer Network. (2016). "NCCN Clinical Practice Guidelines in Oncology - Genetic/Familial High-Risk Assessment: Breast and Ovarian." Version 2.2016.

Among individuals of Ashkenazi Jewish descent, the three BRCA1/BRCA2 variants included in this report 185delAG, 5382insC, and 6174delT are present at a frequency of ~1 in 40.⁷ These variants are the strongest genetic risk factors for HBOC syndrome among individuals of Ashkenazi Jewish descent, accounting for about 85% of BRCA1 and BRCA2 variants in this population.^{8,9,10}

Table 5 below summarizes the risk estimates that are provided in the 23andMe PGS BRCA1/BRCA2 (Selected Variants) test reports stratified by the cancer type. The report provides risk estimates for several cancers associated with BRCA1 and BRCA2 variants. In most cases, these estimates represent a general risk for individuals with any BRCA1 or BRCA2 variant and are not the specific risk estimates associated with the three variants reported by the test. Risk estimates for prostate cancer, pancreatic cancer and melanoma associated with BRCA1/BRCA2 variants are not provided as the information related to these cancer types are primarily based on reports from individuals with a family history of cancer.

Table 5. Health Risk Estimates and Test Interpretation^{7,11,12,13,14,15,16}

Cancer Type	General Population	For All Known BRCA1 Variants	For All Known BRCA2 Variants
Breast (female)	12.4%	45 – 85%	45 – 85%
Ovarian	1.3%	39 – 46%	10 – 27%
Breast (male)	0.12%	1 – 2%	7 – 8%
Prostate	11.6%	May have an increased risk*	Increased risk**
Pancreatic	1.6%	May have an increased risk*	May have an increased risk**
Melanoma	2.2%	Research ongoing***	May have an increased risk**

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

⁸ Hall MJ *et al.* (2009). "BRCA1 and BRCA2 mutations in women of different ethnicities undergoing testing for hereditary breast-ovarian cancer." *Cancer*. 115(10):2222-33.

⁹ Janavičius R. (2010). "Founder BRCA1/2 mutations in the Europe: implications for hereditary breast-ovarian cancer prevention and control." *EPMA J*. 1(3):397-412.

¹⁰ Rosenthal E *et al.* (2015). "Incidence of BRCA1 and BRCA2 non-founder mutations in patients of Ashkenazi Jewish ancestry." *Breast Cancer Res Treat*. 149(1):223-7.

¹¹ Howlader N *et al.* (2017). "SEER Cancer Statistics Review, 1975-2014." National Cancer Institute. Bethesda, MD. April 2017.

¹² 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.

¹³ King MC *et al.* (2003). "Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2." *Science*. 302(5645):643-6.

¹⁴ Berliner JL *et al.* (2013). "NSGC practice guideline: risk assessment and genetic counseling for hereditary breast and ovarian cancer." *J Genet Couns*. 22(2):155-63.

¹⁵ Antoniou AC *et al.* (2005). "Breast and ovarian cancer risks to carriers of the BRCA1 5382insC and 185delAG and BRCA2 6174delT mutations: a combined analysis of 22 population based studies." *J Med Genet*. 42(7):602-3.

¹⁶ U.S. Preventive Services Task Force. (2015). "Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer in Women: Recommendation Statement." *Am Fam Physician*. 91(2):Online.

prostate cancer and pancreatic cancer. **Lifetime risk estimates are not available.
***More research is needed to understand whether people with a BRCA1 variant are at increased risk for melanoma.

b. *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). See DEN160026 supportive user comprehension studies.

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.

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 users 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, and will never be shown to users unless they have specifically chosen to receive the report at any time, including after results for other reports have been received.

4. Expected values/Reference range:

Not applicable.

N. Instrument Name

Illumina iScan BeadChip scanner with GenomeStudio software (qualified by the laboratory)

O. System Descriptions:

1. Modes of Operation:

Same as referenced in DEN140044

2. Software:

FDA has reviewed applicant's Hazard Analysis and software development processes for this line of product types:

Yes or No

Level of Concern:

Moderate

Software Description:

Same as referenced in DEN140044

Revision Level History:

A software revision history record for the 23andMe software system software was acceptable.

Unresolved Anomalies:

There are no known unresolved anomalies associated with the system software.

EMC Testing:

Not applicable.

3. Specimen Identification:

Same as referenced in DEN140044.

4. Specimen Sampling and Handling:

Same as referenced in DEN140044.

5. Calibration:

Same as referenced in DEN140044.

6. Quality Control:

Same as referenced in DEN140044.

P. Other Supportive Instrument Performance Characteristics Data Not Covered In The “Performance Characteristics” Section above:

Refer to K141410 for saliva collection device details and study results.

Q. Proposed Labeling

The labeling is sufficient and it satisfies the requirements of 21 CFR Parts 801 and 809, as applicable, and the special controls for this device type.

R. Identified Risks to Health and Identified Mitigations:

The 23andMe PGS Genetic Health Risk Reports provide information derived from Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory results regarding an individual’s health risk related to inherited cancer for specific genetic variants. This device is intended for the public and does not require a prescription. The risks and risk mitigations for the 23andMe BRCA1/BRCA2 (Selected Variants) GHR report are outlined below.

Risk of False Positive Results:

False positive results could subject patients to morbidity and mortality due to earlier and more frequent radiological screening and/or unnecessary surgery or medications (i.e., tamoxifen or raloxifene) or erroneous entry into clinical investigations of cancer prevention.

False positive results could also unnecessarily cause or enhance anxiety or depression. If the false positive results are associated with diseases with significant morbidity or mortality, the users may develop severe anxiety, depression or make inappropriate lifestyle changes.

To avoid passing the variants to their children, some users could make inappropriate reproductive choices or receive unnecessary prenatal testing, which may include amniocentesis or chorionic villus sampling. Such invasive procedures carry a risk of spontaneous abortion.

Risk of False Negative Results:

False negative results could lead to inappropriate follow-up, premature death and/or severe morbidity. Users receiving a false negative result may fail to initiate known effective

preventive measures including appropriate lifestyle changes, risk reducing surgery, therapeutic options and/or targeted surveillance.

Additional Risks:

Additional risks include the risks of erroneous result interpretation by the user, Manufacturer or the healthcare professional. Given that there have been over 1,000 BRCA mutations identified that are associated with increased risk of developing cancer and the 23andMe BRCA1/BRCA2 (Selected Variants) GHR report only reports on three mutations commonly found in people of Ashkenazi Jewish descent but rarely found in other ethnicities, users may misinterpret negative results from the report to indicate that they are negative for all variants in the BRCA1/BRCA2 genes. Moreover, as the test is offered directly to consumers without the incorporation of a health care provider or genetic counselor this introduces the risk of incorrect sample collection and further increases the risk of result misinterpretation.

Special Controls:

The special controls outlined in the Order address the risks identified above:

- Special control 1 includes a detailed description of the elements to be specified in 21 CFR 809.10 compliant product labeling, pre-purchase page, or test report generated by the manufacturer for users and health care professionals. This special control mandates that over-the-counter manufacturers of these tests must provide specific warning and limiting claims for tests that are subject to this regulation to reduce inappropriate interpretation by users and health care professionals. This special control ensures that users are fully aware of what variants are included in the test report, relative to all known variants associated with the specific disease, and informs users of how the test results should and should not be used. This special control also mandates that over-the-counter manufacturers of these tests must provide information to a potential or actual test user about how to obtain access to a genetic counselor, board-certified clinical molecular geneticist, or an equivalent professional to assist in pre- and post-test counseling on the output and interpretation of the test. Moreover, this special controls ensures that users are aware that this test does not diagnose cancer or any other health conditions, should not be used to make medical decisions and that results should be confirmed in a clinical setting before taking any medical action.
- Special control 2 requires the use of a collection device that is FDA-cleared, -approved, or -classified as 510(k) exempt, with an indication for use in in vitro diagnostic use in DNA testing. The use of a FDA-compliant collection device provides assurances regarding safety, effectiveness, and quality of that component, which helps assure safety and effectiveness of the test system.
- Special control 3 includes a detailed description of information that must be provided to users in the device labeling and available on the device manufacturer's website, an

explanation of the concepts that should be explained, and a list of materials that should be provided to help the user interpret their test results. This special control also highlights the information that must be provided to allow the user to understand how the test works and how to interpret the results of the test. This special control mitigates risk by reducing inappropriate interpretation of test results by users.

- Special control 4 includes an outline of technical information that should be provided for each gene or variant and a summary of the clinical and analytical performance information that must be generated to support claims listed on the manufacturer’s website. This special control provides details about analytical testing that must be performed and provides criteria for appropriate standards that must be met for performance for many of the components of analytical testing in addition to the standards and evidence required to support clinical performance. The control also provides information on required testing for user comprehension of test reports to limit erroneous interpretation of the tests by users. This special control mitigates risk by lowering the probability of inaccurate test results and by reducing inappropriate interpretation by users.

Identified Risks to Health and Identified Mitigations:

Identified Risks to Health	Identified Mitigations
Incorrect understanding of the device and test system	General controls and special controls (1), (3) and (4).
Incorrect test results (false positives, false negatives)	General controls and special controls (1), (2), (3) and (4).
Incorrect interpretation of test results	General controls and special controls (1), (3) and (4).

S. Benefit/Risk Analysis:

SUMMARY	
Summary of Benefits	<p>(1) Direct user access to tests for genetic risk of diseases</p> <p>The PGS test provides users with easier access to their own health data compared to traditional genetic tests. This test does not require prescriptions from healthcare professionals. The sample collection kits are mailed directly to the users. Geographic location will not restrict an individual’s ability to access the tests. Although available to the general population, this test is most beneficial to users of Ashkenazi-Jewish descent.</p>

(2) Early detection of genetic risk variants

Early detection of genetic risk variants allows an individual to make informed lifestyle adjustments and to partner with healthcare professionals in early discussions regarding surveillance and management. Some positive test results may provide an opportunity for targeted screening, prevention and early intervention efforts. As a result, the adverse consequences of a disease may potentially be delayed, reduced or avoided and morbidity and mortality may be reduced in the long term. However, as this test should not be used to make medical decisions, the positive test results need to be confirmed in a clinical setting prior to any medical intervention.

(3) Promoting public awareness of genetic risks

User education materials including FAQs are included in the device labeling, some of which is accessible to the public on the Manufacturer's public website. As more users are exposed to the topic of genetic risks, such educational materials could serve as a useful resource for education.

Summary of Risks	<p>(1) Risks associated with false results</p> <p>In general, the risks associated with false results are mitigated by clinical and analytical performances of the device. False positive results may prompt unnecessary additional testing or medical intervention. Moreover, the Manufacturer has identified potential interfering mutations that could impact the performance of the test. As a measure of risk mitigation, the device label has provided recommendation for consulting healthcare professionals, genetic counselors, board-certified clinical molecular geneticist, or equivalent and has also noted the potential interfering mutations and indicated that the impact of these mutations has not been studied. Also, the device labeling specifically indicates that the healthcare professionals routinely review a patient's personal and family medical history and perform physical examinations before ordering additional diagnostic tests. The device labeling also states that the test report includes only three out of more than 1,000 mutations, emphasizing that a negative results does not mean that a user does not have a mutation in BRCA1 or BRCA2, or other cancer-related genes, which are not reported by the test. Importantly, the labeling specifically indicates that prior to making any medical decisions, confirmatory clinical testing should be performed. False positive results can also lead to unwarranted prophylactic therapy, inappropriate lifestyle choices, anxiety, or depression. False negative results can delay the identification of genetic risks and consequently lead to delayed diagnosis of certain cancers, or failure to take effective preventive measures, potentially resulting in increased morbidity and mortality. Users may not be able to initiate appropriate lifestyle changes, therapeutic options, and targeted surveillance. Taken together, the risks associated with false results are adequately mitigated by the clinical and analytical performances, appropriate labeling, and relevant special controls.</p>
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	<p>(2) Risks associated with erroneous interpretation of the results The risks of erroneous result interpretation are similar to those listed for false results. An accurate test result could be interpreted erroneously by the manufacturer or the user, or the healthcare professional. The risks of result misinterpretation by the manufacturer are mitigated by special controls for clinical performance. Therefore, the chances of result misinterpretation by the manufacturer are very low. The risks of erroneous result interpretation by the user are mitigated by a combination of properly designed user comprehension studies, adequate labeling, including an opt-in page and FAQs, and appropriate special controls. The users should discuss the results with a healthcare professional, which is emphasized throughout the labeling documents. The risks of result misinterpretation by the healthcare professionals are very low as the genetic risk test results are typically interpreted in combination with confirmatory testing, relevant clinical evaluations, which may include inquiry of medical and family history, physical examination, other laboratory tests and imaging.</p> <p>(3) Risks associated with genetic privacy violation The risks associated with genetic privacy violation are mitigated by the manufacturer providing a privacy statement on their website.</p> <p>(4) Risks associated with the use of the test in the general population There is an inherent risk with the use of this test in the general population due to the BRCA1/BRCA2 variants the test is not designed to detect. Accordingly, there is a possibility that users may have a false sense of reassurance due to true test negatives that may actually harbor other BRCA mutations not detected by the test. This risk is mitigated through device labeling to specifically note that this test detects only three specific variants in BRCA1/BRCA2 and there are more than 1,000 variants identified in these genes associated with an increased risk of developing cancer. The labeling notes that, and that the absence of a variant tested does not rule out the presence of other genetic variants that may impact cancer risk.</p>
Summary of Other Factors	The studies also included precision/reproducibility, analytical sensitivity/limit of detection, and user comprehension.
Conclusions	Given the device’s indications for use, required general controls and special controls established for this device, the probable benefits outweigh the probable risks.

Patient Perspectives:

This submission did not include specific information on patient perspectives for this device.

T. Conclusion:

The information provided in this *de novo* submission is sufficient to classify this device into class II under regulation 21 CFR 866.6090. FDA believes that the stated special controls, and applicable general controls, including design controls, provide reasonable assurance of the safety and effectiveness of the device type. The device is classified under the following:

Product Code: QAZ
Device Type: Cancer Predisposition Risk Assessment System
Class: II (special controls)
Regulation: 21 CFR 866.6090

- a) Identification. 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.
- b) Classification. Class II (special controls). A Cancer Predisposition Risk Assessment System must comply with the following special controls:
 - (1) The 21 CFR 809.10 compliant labeling and any pre-purchase page and test report generated, unless otherwise specified, must include:
 - (i) An intended use that specifies in the indications for use the genetic variants detected by the test. The specific variants must be appropriately validated as described in paragraphs (b)(4)(xii) and (b)(4)(xiii) of this section.
 - (ii) A section addressed to users with the following information:
 - (A) A warning statement accurately disclosing the genetic coverage of the test in lay terms, including information on variants not queried by the test, and the proportion of pathogenic variants in the genes that the assay detects in a specific population as identified in paragraph (b)(1)(i) of this section. The warning statement must indicate that the test [does not/ may not, as appropriate] detect all genetic variants related to the genetic disease, and that the absence of a variant tested does not rule out the presence of other genetic variants that may impact cancer risk. The warning statement must also include the relevant population for which the variants reported by the test are most relevant.
 - (B) The limiting statement explaining that some people may feel anxious about getting genetic test health results. This is normal. If the potential user feels very anxious, such user should speak to his or her doctor or other healthcare professional prior to collection of a sample for testing. This test is not a

substitute for visits to a doctor or other healthcare professional. Users should consult with their doctor or other healthcare professional if they have any questions or concerns about the results of their test or their current state of health.

- (C) The limiting statement that a user's ethnicity may affect whether the test is relevant for them and may also affect how their genetic health results are interpreted.
 - (D) A warning statement that the test is not a substitute for visits to a healthcare professional for recommended screenings, and should not be used to determine any treatments or medical interventions.
 - (E) A warning statement that the test does not diagnose cancer or any other health conditions and should not be used to make medical decisions. The warning statement must indicate that the results should be confirmed in a clinical setting before taking any medical action.
 - (F) The limiting statement explaining that other companies offering a genetic risk test may be detecting different genetic variants for the same disease, so the user may get different results using a test from a different company.
 - (G) If applicable, a limiting statement that states the test does not test for variants in other genes linked to hereditary cancer.
 - (H) The limiting statement explaining that this test does not account for non-genetic factors and that other factors such as environmental and lifestyle risk factors may affect the risk of developing a given disease.
 - (I) Information to potential purchaser or actual test report recipient about how to obtain access to a board-certified clinical molecular geneticist or equivalent to assist in pre- and post-test counseling.
 - (J) The limiting statement explaining that this test is not intended to tell you anything about your current state of health, or be used to make medical decisions, including whether or not you should take a medication or how much of a medication you should take.
 - (K) The limiting statement explaining that the laboratory may not be able to process a sample, and a description of the next steps to be taken by the manufacturer and/or the customer, as applicable.
- (iii) A section in your 21 CFR 809.10 labeling and any test report generated that is for healthcare professionals who may receive the test results from their patients with the following information:

- (A) The limiting statement explaining that 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.
 - (B) The limiting statement explaining that this test is intended to provide users with their genetic information to inform health-related lifestyle decisions and conversations with their doctor or other healthcare professional.
 - (C) The limiting statement explaining that any diagnostic or treatment decisions should be based on confirmatory prescription testing and/or other information that is determined to be appropriate for the patient (e.g., additional clinical testing and other risk factors that may affect individual risk and health care).
- (2) The genetic test must use a sample collection device that is FDA-cleared, -approved, or -classified as 510(k) exempt, with an indication for *in vitro* diagnostic use in over-the-counter DNA testing.
- (3) The device's labeling must include a hyperlink to the manufacturer's public website where the manufacturer shall make the information identified in paragraph (b)(3) of this section publicly available. The manufacturer's home page, as well as the primary part of the manufacturer's website that discusses the device, must provide a hyperlink to the Web page containing this information and must allow unrestricted viewing access. If the device can be purchased from the Web site or testing using the device can be ordered from the Web site, the same information must be found on the Web page for ordering the device or provided in a publicly accessible hyperlink on the Web page for ordering the device. Any changes to the device that could significantly affect safety or effectiveness would require new data or information in support of such changes, which would also have to be posted on the manufacturer's website. The information must include:
- (i) An index of the material being provided to meet the requirements in paragraph (b)(3) of this section and its location.
 - (ii) Technical information about the device, as specified in paragraph (b)(4) of this section.
 - (iii) A section that highlights summary information that allows the user to understand how the test works and how to interpret the results of the test. This section must, at a minimum, be written in plain language understandable to a lay user and include:
 - (A) Consistent explanations of the risk of disease associated with all variants included in the test, variants not included in the test, and specific considerations by ethnicity. If there are different categories of risk, the manufacturer must provide literature references and/or data that support the different risk categories. If there will be multiple test reports and

multiple variants, the risk categories must be defined similarly among them. For example, “increased risk” must be defined similarly between different test reports and different variant combinations.

- (B) Clear context for the user to understand the context in which the cited clinical performance data support the risk reported. This includes, but is not limited to, any risks that are influenced by ethnicity, age, gender, environment, and lifestyle choices.
- (C) Materials that explain the main concepts and terminology used in the test that include:
 - (1) Definitions: scientific terms that are used in the test reports.
 - (2) Pre-purchase page: this page must contain information that informs the user about what information the test will provide. This includes, but is not limited to, variant information, the condition(s) or disease(s) associated with the variant(s), professional guideline recommendations for general genetic risk testing, the limitations associated with the test (e.g., test does not detect all variants related to the disease), relevance of race/ethnicity, and any precautionary information about the test the user should be aware of before purchase. When the test reports the risk of a life-threatening or irreversibly debilitating disease or condition for which there are few or no options to prevent, treat, or cure the disease, a user opt-in page must be provided. This opt-in page must be provided for each disease type that falls into this category and must provide specific information relevant to each test result. The opt-in page must include:
 - (i) An option to accept or decline to receive this specific test result;
 - (ii) Specification of the risk involved if the user is found to have the specific genetic test result;
 - (iii) Summary of professional guidelines that recommend when genetic testing for the associated target condition is or is not recommended;
 - (iv) A recommendation to speak with a healthcare professional, genetic counselor, or equivalent professional before getting the results of the test;
 - (v) The implications of receiving a no variants detected result; and

(vi) The statement that the test does not diagnose cancer or any other health conditions and should not be used to make medical decision. Results should be confirmed in a clinical setting before taking any medical action. Users should consult with a healthcare professional before taking any medical action.

(3) Frequently asked questions (FAQ) page: This page must provide information that is specific for each variant/disease pair that is reported. Information provided in this section must be scientifically valid and supported by corresponding peer-reviewed publications. The FAQ page must explain the health condition/disease being tested, the purpose of the test, the information the test will and will not provide, the relevance of race and ethnicity to the test results, information about the population to which the variants in the test is most applicable, the meaning of the result(s), other risk factors that contribute to disease, appropriate follow-up procedures, how the results of the test may affect the user's family, including children, and links to resources that provide additional information.

(4) The device labeling must include a technical information section containing the following information:

- (i) Gene(s) and variant(s) the test detects using standardized nomenclature, Human Genome Organization (HUGO) nomenclature and coordinates as well as Single Nucleotide Polymorphism Database (dbSNP) reference SNP numbers (rs#).
- (ii) A statement indicating that more than 1,000 variants in the BRCA1 and BRCA2 genes are known to increase cancer risk, as applicable.
- (iii) Scientifically established disease-risk association of each variant detected and reported by the test. This risk association information must include:
 - (A) Genotype-phenotype information for the reported variants.
 - (B) When available, a table of expected frequency in the general population and different ethnicities, and risks of developing the disease in relevant ethnic populations and the general population.
 - (C) Information such as peer reviewed published literature and/or professional guidelines used to determine what types and levels of evidence will distinguish whether the selected variants are reported as "are associated with increased risk" versus "may be associated with increased risk" of developing other cancers. All selected variants must

be appropriately validated as required under paragraph (b)(1)(i) of this section. For selected variants reported as “are associated with increased risk”, the clinical evidence must be demonstrated with sufficient information (e.g., professional guidelines and consistent associations in peer-reviewed published literature). For the selected variants reported as “may be associated with increased risk”, the clinical evidence must be reported in professional guidelines but peer-reviewed published literature may not be consistent.

(D) A statement about the current professional guidelines for testing these specific gene(s) and variant(s) for the specified disease(s).

- (1) If professional guidelines are available, provide the recommendations in the professional guideline(s) for the gene, variant, and disease, for when genetic testing should or should not be performed, and cautionary information that should be communicated when a particular gene and variant is detected.
- (2) If professional guidelines are not available, provide a statement that the professional guidelines are not available for these specific gene(s) and variant(s).

(iv) The specimen type (e.g., saliva, whole blood).

(v) Assay steps and technology used.

(vi) Specification of required ancillary reagents, instrumentation, and equipment.

(vii) Specification of the specimen collection, processing, storage, and preparation methods.

(viii) Specification of risk mitigation elements and description of all additional procedures, methods, and practices incorporated into the directions for use that mitigate risks associated with testing.

(ix) Information pertaining to the probability of test failure (e.g., percentage of tests that failed quality control) based on data from clinical samples, a description of scenarios in which a test can fail (i.e., low sample volume, low DNA concentration, etc.), how users will be notified of a test failure, and the nature of follow-up actions on a failed test to be taken by the user and the manufacturer.

(x) When available, information specifying the probability of a false negative and false positive analytical result and any additional considerations by ethnicity.

(xi) Specification of the criteria for test result interpretation and reporting, including any distinctions between risk categories (i.e., increased risk and greatly increased

risk; are associated and may be associated).

(xii) Information that demonstrates the performance characteristics of the test including:

(A) Accuracy of study results for each claimed specimen type.

- (1) Accuracy of the test shall be evaluated with fresh clinical specimens collected and processed in a manner consistent with the test's instructions for use. If this is impractical, fresh clinical samples may be substituted or supplemented with archived clinical samples. Archived samples shall have been collected previously in accordance with the instructions for use, stored appropriately, and randomly selected. In some limited circumstances, use of contrived samples or human cell line samples may also be appropriate and used as an acceptable alternative. The contrived or human cell line samples shall mimic clinical specimens as much as is feasible and provide an unbiased evaluation of the test's accuracy.
- (2) Accuracy must be evaluated by comparison to bidirectional Sanger sequencing or other methods identified as appropriate by FDA. Performance criteria for both the comparator method and the test must be pre-defined and appropriate to the test's intended use. Detailed study protocols must be provided.
- (3) Information provided shall include the number and type of specimens, broken down by clinically relevant variants for each indicated report that were compared to bidirectional sequencing or other methods identified as appropriate by FDA. The accuracy as positive percent agreement (PPA) and negative percent agreement (NPA), must be measured, and accuracy point estimates must be >99% (both per reported variant and overall). Uncertainty of the point estimate must be within an acceptable range, as identified by FDA, and must be presented using the 95% confidence interval.
- (4) Sufficient specimens must be tested per genotype and must include all genotypes that will be included in the tests and reports. The number of samples tested in the accuracy study for each variant reported must be based on the variant frequency.

- (5) Any no calls (i.e., absence of a result) or invalid calls (e.g., failed quality control) in the study must be included in accuracy study results and reported separately. The percent of final ‘no calls’ or ‘invalid calls’ must be clinically acceptable. Variants that have a point estimate for PPA or NPA of <99% (incorrect test results compared to bidirectional sequencing or other methods identified as appropriate by FDA) must not be incorporated into test claims and reports. Accuracy measures generated from clinical specimens versus contrived samples or cell lines must be presented separately. Results must be summarized and presented in tabular format, by sample and by genotype.
- (6) Point estimate of PPA for each genotype must be calculated as the number of correct calls for that genotype divided by the number of samples known to contain that genotype. The point estimate of NPA for each genotype should be calculated as the number of correct calls that do not contain that genotype divided by the number of samples known to not contain that genotype. ‘No calls’ should not be included in these calculations. Point estimates should be calculated along with 95% two-sided confidence intervals.
- (B) Precision and reproducibility data must be provided using multiple instruments and multiple operators, on multiple non-consecutive days, and using multiple reagent lots. The sample panel must include specimens from the claimed sample type (e.g., saliva) representing all genotypes for each variant (e.g., wild type, heterozygous, and homozygous). Performance criteria must be predefined. A detailed study protocol must be created in advance of the study and then followed. The failed quality control (FQC) rate must be indicated (i.e., the total number of sample replicates for which a sequence variant cannot be called (no calls) or that fail sequencing quality control (QC) criteria divided by the total number of replicates tested). It must be clearly documented whether results were generated from clinical specimens, contrived samples, or cell lines. The study results shall state, in a tabular format, the variants tested in the study and the number of replicates for each variant, and what conditions were tested (i.e., number of runs, days, instruments, reagent lots, operators, specimens/type, etc.). The study must include all extraction steps from the claimed specimen type or matrix, unless a separate extraction study for the claimed sample type is performed. If the device is to be used at more than one laboratory, different laboratories must be included in the precision study (and reproducibility across sites must be

evaluated). Any no calls or invalid calls in the study must be listed as a part of the precision and reproducibility study results.

- (C) Analytical specificity data: data must be provided evaluating the test performance (e.g., specimen extraction and variant detection) effect of potential endogenous and exogenous interferents relevant to the specimen type, and assessment of cross-contamination. Alternatively, for each suspected interfering mutation for which data is not provided demonstrating the effect of the interfering variant, the manufacturer must clearly identify the suspected interfering variants in the labeling, including but not limited to user test reports, and indicate that the impact the interfering variants may have on the test's performance has not been studied by providing a statement that reads, "It is possible that the presence of [insert identifying information for the suspected interfering variant] in a sample may interfere with the performance of this test. However, its effect on the performance of this test has not been studied."
- (D) Analytical sensitivity data: data must be provided demonstrating the minimum amount of DNA that will enable the test to perform correctly in 95% of runs.
- (E) Device stability data: the manufacturer must establish upper and lower limits of input nucleic acid, sample, and reagent stability that will achieve the test's claimed accuracy and reproducibility. The manufacturer must evaluate stability using wild-type, heterozygous, and homozygous samples. Data supporting such claims must be provided.
- (F) Specimen Type and matrix comparison data: specimen type and matrix comparison data must be generated if more than one specimen type can be tested with this device, including failure rates for the different specimens.

(xiii) Clinical Performance Summary

- (A) Information to support the clinical performance of each variant in the specific condition which is labeled as "are associated with increased risk" and reported by the test must be provided, as identified in paragraph (b)(4)(iii)(C) of this section.
- (B) Manufacturers must organize information by the specific variant combination as appropriate (e.g., wild type, heterozygous, homozygous, compound heterozygous, hemizygous genotypes). For each variant combination, information must be provided in the

clinical performance section to support clinical performance for the risk category (e.g., not at risk, increased risk). For each variant combination, a summary of key results must be provided in tabular format or using another method identified as appropriate by FDA to include the appropriate information regarding variant type, data source, definition of the target condition (e.g., disease), clinical criteria for determining whether the target disease is present or absent, description of subjects with the target disease present and target disease absent (exclusion or inclusion criteria), and technical method for genotyping. When available, information on the effect of the variant on risk must be provided as the risk of a disease (lifetime risk or lifetime incidences) for an individual compared with the general population risk.

- (xiv) User comprehension study: information on a study that assesses comprehension of the test process and results by potential users of the test, must be provided, including the following, as appropriate:
 - (A) The test manufacturer must provide a genetic health risk education module to naïve user comprehension study participants prior to their participation in the user comprehension study. The module must define terms that are used in the test reports and explain the significance of genetic risk reports.
 - (B) The test manufacturer must perform pre- and post-test user comprehension studies. The comprehension test questions must directly evaluate the material being presented to the user as described in paragraph (b)(3)(ii).
 - (C) The manufacturer must provide a justification from a physician and/or genetic counselor that identifies the appropriate general and variant-specific concepts contained within the material being tested in the user comprehension study to ensure that all relevant concepts are incorporated in the study.
 - (D) The user study must meet the following criteria:
 - (1) The study participants must comprise a statistically sufficient sample size and demographically diverse population (determined using methods such as quota-based sampling) that is representative of the intended user population. Furthermore, the study participants must comprise a diverse range of age and educational levels and have no prior experience with the test or its manufacturer. These factors shall be well-defined in the inclusion and exclusion criteria.

- (2) All sources of bias (e.g., non-responders) must be predefined and accounted for in the study results with regard to both responders and non-responders.
- (3) The testing must follow a format where users have limited time to complete the studies (such as an on-site survey format and a one-time visit with a cap on the maximum amount of time that a participant has to complete the tests).
- (4) Users must be randomly assigned to study arms. Test reports in the user comprehension study given to users must define the target condition being tested and related symptoms, explain the intended use and limitations, including warnings, for the test, explain the relevant ethnicities in regard to the variant tested, explain genetic health risks and relevance to the user's ethnicity, and assess participants' ability to understand the following comprehension concepts: the test's limitations, purpose, appropriate action, test results and other factors that may have an impact on the test results.
- (5) Study participants must be untrained, be naïve to the test subject of the study, and be provided the labeling prior to the start of the user comprehension study.
- (6) The user comprehension study must meet the predefined primary endpoint criteria, including a minimum of a 90 percent or greater overall comprehension rate (i.e., selection of the correct answer) for each comprehension concept. Other acceptance criteria may be acceptable depending on the concept being tested. Meeting or exceeding this overall comprehension rate demonstrates that the materials presented to the user are adequate for over-the-counter use.
- (7) The analysis of the user comprehension results must include:
 - (i) Results regarding reports that are provided for each gene/variant/ethnicity tested;
 - (ii) Statistical methods used to analyze all data sets; and
 - (iii) Completion rate, non-responder rate, and reasons for nonresponse/data exclusion. A summary table of

comprehension rates regarding comprehension concepts (e.g., purpose of test, test results, test limitations, ethnicity relevance for the test results, appropriate actions following receipt of results, etc.) for each study report must be included.