Kathy Hibbs
Chief Legal & Regulatory Affairs Officer
23andMe, Inc.
223 N. Mathilda Avenue
Sunnyvale, CA 94086
www.23andme.com

November 21, 2019

Therapeutic Goods Administration
PO Box 100
WODEN ACT 2606

Attn: IVD Reforms Team, Medical Devices Branch

Re: Consultation: Review of the regulation of certain self-testing IVDs in Australia

Dear Therapeutic Goods Administration,

Attached are 23andMe's comments as to whether the Therapeutic Goods (Excluded Purposes) Specification 2010 continues to serve a useful and necessary purpose in prohibiting supply of certain self-testing IVDs for serious diseases.

If you need any further information or have any questions or comments, please do not hesitate to contact me.

Very truly yours,

[redacted]

Chief Legal & Regulatory Affairs Officer

Regulatory Considerations for Offering a Safe Path for Direct to Consumer Genetic Testing in Australia

23andMe, as the only company in the world to have received premarket clearance for Direct-to-Consumer (DTC) / Over-the-Counter (OTC) genetic testing from any regulatory agency, appreciates the opportunity to provide comments to the Therapeutic Goods Administration (TGA) on the current self-testing IVD prohibitions and a regulatory framework to offer safe and effective self-testing products. As the first and only company to have obtained US Food and Drug Administration (FDA) authorization to market DTC / OTC genetic testing[1], the Company strongly believes that with appropriate regulatory oversight and quality assurance safeguards in place, self-testing, or Direct-to-Consumer, Genetic Tests (DTC GT) can be safely permitted in Australia.

The Company is aware of and follows the current Australian prohibition of certain self-testing IVDs, including genetic tests to determine the presence of, or susceptibility to, diseases in humans and does not offer its Genetic Health Risk tests in Australia.

23andMe is pleased to provide the following response to TGA's questions on DTC GT's, specifically:

- the risks and benefits of 23andMe's DTC genetic health testing product
- examples of the parallel regulatory frameworks from the UK and the USA that have demonstrated that such tests can be offered safely when overseen by regulatory agencies
- the urgent need for TGA to provide a regulatory framework in order to enable legally marketed products directly to Australian consumers to effectively reduce the risks presented by the current state of Australian consumers purchasing unvalidated overseas products of specious safety and quality

BACKGROUND ON 23ANDME

The 23andMe Personal Genome Service (PGS) is a currently-marketed, non-invasive genetic information service that combines qualitative genotyping data covering genetic ancestry, traits, and certain heritable health conditions from a single multiplex assay. The PGS provides descriptive information which reports on scientifically validated gene disease risk associations which have been derived from peer reviewed, published genetic research studies and can identify unknown genetic risks factors, but does not diagnose whether an individual has a disease or condition. It is a direct-to-consumer (over-the-counter) DNA testing service intended to provide information and tools for consumers to learn about and explore their DNA.

Some benefits of DTC genetic testing include: enabling individuals who would not be eligible for clinical screening to learn about their risk for passing variants onto offspring or their own risk of certain conditions, and engaging people to be proactive about their health and modify certain behaviors such as smoking and diet to better prevent or mitigate certain diseases and conditions. Currently, 23andMe sells it's DTC Health product with the full knowledge of and in compliance with local regulations, in the United States, Canada, the United Kingdom and certain European Union countries.

[1] https://www.fda.gov/medical-devices/vitro-diagnostics/direct-consumer-tests

With a database of over 10 million genotyped consumers, 23andMe has developed a novel method for DTC GT that has proven to be safe and effective for consumer use. The 23andMe Personal Genome Service (PGS) has undergone a vigorous validation that included an extensive regulatory review to ensure our service is safe and effective for consumer use, without the immediate need of a healthcare professional such as a physician or genetic counselor. Significant care has been taken by the Company to ensure analytical, clinical and scientific validity, and user comprehension. As a result, 23andMe is uniquely positioned to comment on this initiative and best practices for review and oversight by the TGA to ensure Australian consumer desires for DTC GT are met, enabling an appropriate consumer pathway for individuals to learn about their personal genetic information and actively participate with their physicians in making healthcare decisions.

RELEVANT REGULATORY BACKGROUND IN UNITED KINGDOM AND EUROPEAN UNION

In 2014, the Company began working with the authorities in the UK to legally market the PGS in the UK and Ireland. Prior to launching its Health Reports in the UK, the Company met and reviewed its product with representatives of several UK governmental bodies including the Medicines and Healthcare products Regulatory Agency (MHRA). MHRA confirmed that premarket review was not required by the UK or IVD regulations in place, but that it appreciated the opportunity to discuss the product with the Company. The Company incorporated certain labeling and promotional changes recommended by MHRA into the UK Health product prior to launch. The Company also agreed to voluntarily collaborate with the MHRA to perform a one-year post market surveillance study. The post market surveillance program was conducted from December of 2014 to the end of November of 2015 during which time more than 25,000 UK customers purchased the 23andMe PGS with Health reports. Data presented to the MHRA demonstrated the PGS performed as expected; there were no vigilance reports, no field safety corrective actions, and no reported cases of harm due to test results during this one-year reporting period, nor was there evidence the test created any undue burden on the National Health Service (NHS) through inappropriate utilization of healthcare services by 23andMe customers. The Company continues to work with MHRA and apprise it of updates to its product and performance in the UK.

In addition to its engagement with regulatory agencies in the UK, the Company also engaged an Authorized Representative in the EU to advise best practices for preparation of all the Technical Documentation required to create Technical Files that conform to the requirements of the Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices.

Further, in order to maintain our continued market presence in the UK and EU, the Company is actively working with a Notified Body to ensure all In Vitro Diagnostic Regulation (IVDR 2017/746) (IVDR) requirements will be met prior to the May 2022 implementation deadline.

RELEVANT REGULATORY BACKGROUND IN UNITED STATES

23andMe has worked extensively with the US FDA which has resulted in the authorization of four De Novo submissions and one 510(k) clearance for our genetic health models and reports. Through the 23andMe premarket submissions and related authorization regulations, the US FDA has established a regulatory standard for safe and effective DTC GT. FDA's own website contains information for consumers on genetic tests which makes clear that 23andMe is the only legally marketed DTC genetic health test and highlights key considerations for consumers. See **Attachment 1 - Lists of Direct-To-Consumer Tests with FDA Marketing Authorization** and **Attachment 2(a through d) - FDA Decision Summaries.**

Through their 23andMe health reports, numerous individuals who would not have met clinical testing criteria have been found to have genetic mutations associated with conditions such as hemochromatosis and thrombophilia, both of which can be much more effectively managed, from both a cost and an outcome standpoint, if identified prior to a health crisis. In addition, 23andMe reports on selected BRCA1/BRCA2 variants associated with as much as an 85% risk of certain cancers in some individuals. As many as half of the BRCA+ individuals found through their 23andMe results report no personal or family history of cancer or ethnicity which would have identified them as in need of clinical testing.

However, 23andMe recognizes the importance of mitigating potential risks of DTC GT. The Benefit-Risk considerations of the 23andMe DTC GT are summarized in Table 1 below:

Table 1 - Benefit-Risk Considerations

Benefit-Risk Considerations	
Summary of Benefits	When used as intended/indicated, the benefits to the consumer in the general healthy population include: 1. Establishment of PGS Test performance for the detection of variants in a manner that demonstrates consistent, accurate test results and information about those results. 2. Ability to use an analytically well-validated testing system for detection of variants 3. Ability to use a DTC GT with labeling that has been clinically well-validated, and designed and validated for consumer comprehension in the general population 4. Greater genetic literacy and understanding of risk, both by the general public and medical professionals, through labeling for each indication that has been well-validated for clinical content and user comprehension 5. Universal access to a well-validated testing system reporting genetic variants, consistent with increasing acceptance of direct access to reliable genetic information for consumers

	6. Increased consumer involvement in his/her own health care, which supports national public health objectives 7. Informed reproductive health care decision making 8. Opportunity to improve quality of life by enabling early identification of individuals at increased risk for various heritable conditions, thereby allowing targeted surveillance and conversations with healthcare professionals.
Summary of Risks	The risks associated with the PGS Test and the PGS Health Reports, when used as intended/indicated, are those related to: 1. The risk of a false positive result 2. False negative result and the potential for delayed identification of a variant 3. Transient anxiety caused by a false positive or unclear result 4. Failure to correctly understand the genetic health risk test report results, including inappropriate consumer action based on consumer misunderstanding of results 5. Failure to correctly use the PGS saliva collection device

As set forth more fully in Table 2 below, 23andMe has demonstrated that the risks identified can be mitigated. The risk mitigations include: robust analytical validity, established clinical validity, and user comprehension of key report concepts. These risk mitigations have been shown to be effective and could be adopted by TGA so that Australian consumers can have the opportunity to benefit from a safe and well-validated product and will not be tempted to purchase unsafe products currently flooding the market.

Table 2 - Identified Risks and Required Mitigations

RISK MITIGATIONS for DTC GT	IDENTIFIED RISKS			
	Incorrect understanding of the device and test system	**Incorrect test results (false positives or false negatives)**	**Incorrect interpretation of test results**	**Incorrect action based on test results**
Provider must provide purchaser information about how to obtain access to a board-certified clinical molecular geneticists or equivalent for pre- or post-test counseling.	✓		✓	
Pre-purchase labeling with unrestricted, public access that must contain a clear description of the test comprising: ● Technology ● What the test reports ● Relevant clinical claims ● Clear description of what information the test will provide ● Limitations, warnings, and precautionary information ● Summary of clinical and analytical performance ● Summary of user comprehension performance ● FAQ's	✓	✓	✓	✓
Post-test labeling must include detailed information comprising: ● Intended use that specifies the indications for use and genetic variants detected by the test ● Technical and scientific information for each gene or variant ● Warnings, precautions, and limitations of the test(s) ● Information to help the user and healthcare professionals interpret test results ● Summary of clinical and analytical performance information and criteria ● Summary of user comprehension testing ● Information such as peer reviewed published literature and/or professional guidelines related to the variants ● Statement about current professional guidelines for specific gene(s) and variant(s), if applicable and available	✓	✓	✓	✓

Analytical validation should include data appropriate to demonstrate the reliability of the device, such as: ● Accuracy ● Reproducibility and Repeatability ● Analytical Specificity ● Analytical Sensitivity ● Stability ● Matrix comparison Detailed study protocols with predetermined acceptance criteria should be created in advance of all studies.		✓		
Test reports appropriate for consumers must include an appropriate description of how the test results should be used by healthcare providers who may receive the test results from their patients.		✓	✓	✓
User comprehension testing of the report information must be tested. Acceptance criteria should meet the primary endpoint criteria of a minimum of >90% overall comprehension. Participants should include a statistically sufficient sample size and demographically diverse population representative of the intended use population that are naïve to use of the device.		✓	✓	✓
The intended use of the device must not include an indication for use in supporting or sustaining human life, being of substantial importance in preventing impairment of human health, or present a potential, unreasonable risk of illness or injury.	✓		✓	✓
The genetic test must use a sample collection device with an indication for in vitro diagnostic use in DNA testing that has been validated for use with the test, and if appropriate, authorized for use by the TGA.		✓	✓	
The distribution of the device should be limited to: ● The manufacturer ● Manufacturer's subsidiaries ● Manufacturer's contracted regulated laboratories		✓		

Further, 23andMe has developed specialized risk mitigations for certain sensitive health report results, including cancer risk and the risk of Parkinson's Disease and Late-Onset Alzheimer's Disease. All of the above risk mitigations were applied to these health reports, and the reports also caution users about the potential for emotional distress related to learning about such sensitive results. This section of the PGS specifically requires users to opt-in and review an educational report tutorial prior to viewing their results. The opt-in page provides specific warnings relevant to each test result, information indicating whether professional guidelines advise against genetic testing for the condition, and information encouraging the user to seek advice from their healthcare provider if they are at all uncertain about receiving their results. The opt-in section requires the consumer to choose to accept or decline to receive these sensitive test results prior to viewing their results.

CURRENT STATE OF AUSTRALIAN DTC GT MARKET

Despite the self-testing prohibition of the Therapeutic Goods (Excluded Purposes) Specification 2010, as TGA has noted, though there are no DTC GT legally marketed in Australia, due to the ease of online ordering, several overseas providers sell DTC GT to Australian consumers:

"However, DTC GT that are advertised and supplied from overseas are currently outside the reach of Australia's legislation. Some of these tests may have limited clinical evidence to support their use. . . The number of services supplied via the internet cannot be determined but it would appear that consumers are increasingly accessing these services from overseas in response to their promotion" [2]

In 23andMe's cursory review, we discovered that at least 20 companies currently sell DTC GT to Australian consumers, none of which have undergone any formal review or approval process by any regulatory body. These tests include reports for genetic cancer and other serious risk diseases, aptitude and personality prediction tests for pediatric uses, and purported response to medications and illegal drugs.

Nearly all of the US-based test manufacturers selling in Australia are selling prescription tests, intended for use by physicians and for which in the US, these same providers bundle a physician's prescription with the purchase price of their product. None of these tests have been reviewed by the FDA, or any other regulatory authority. Their test results are of unknown validity and they do not conform to FDA or IVD quality systems requirements. It is clear that these tests are prohibited by the Excluded Purposes Specification as the test is sold directly to a lay person who self collects the sample, and to whom results are returned directly to the consumer without the direct supervision of a health professional.

All companies that report test results should demonstrate their tests meet scientific and analytical performance criteria and that users can comprehend the genetic concepts reported. That

[2] Australian Government Department of Health. "Consultation: Review of the Regulation of Certain Self-Testing IVDs in Australia." *Therapeutic Goods Administration (TGA)*, Australian Government Department of Health, 27 Sep. 2019, https://www.tga.gov.au/sites/default/files/consultation-review-regulation-certain-self-testing-ivds-australia.pdf (Page 9).

demonstration should take the form of a TGA review which should include report labeling and a demonstration of marketing materials. Current guidance/regulation by TGA prohibits these devices from the market, which creates a vacuum for TGA-reviewed products, and consumers are turning to unapproved product to meet their testing needs or desires. If the TGA was to regulate these products and then allow marketing of these products, consumers would have a viable, safe option for testing.

PRIVACY CONCERNS

23andMe recognizes the concern from the TGA and consumers about data privacy and secondary uses of genetic data, and has developed a comprehensive privacy policy to protect the consumer. In accordance with our privacy policy, data from an individual will never be provided to a third party without prior consent. Prior consent is also required for participation in 23andMe Research studies, in which de-identified aggregate data may be published in peer-reviewed scientific journals. Our full Privacy Statement can be found on our website: https://www.23andme.com/about/privacy/

CONCLUSION

As the first of its kind DTC GT, 23andMe has provided over 10 million customers in the US, Europe, and Canada with invaluable access to their genetic information and the education needed to understand genetics at a consumer level. Through the development and launch of over fifty carrier status and genetic health risk reports, our team has collaborated with industry experts and global regulatory agencies to develop thorough validation testing and mitigations to the potential risks associated with DTC GTs, including genetic educational modules and resources for consumers, risk mitigations, surveillance monitoring, and a comprehensive privacy policy.

To summarize, 23andMe's responses to TGA's specific questions towards DTC GT are as follows:

Should Direct to Consumer Genetic Tests be permitted in Australia (following evaluation by the TGA) to provide consumers with an alternative to overseas testing which has not been evaluated by the TGA for its quality and performance?

Currently, the only DTC GT products being sold into Australia are ones that have not met any regulatory requirements. Furthermore, they are being sold by unscrupulous companies willing to violate Australian law. Importing such untested products for personal use presents unmitigated risks.

We believe that with appropriate oversight by TGA, DTC GT can be safely offered to Australian consumers. 23andMe, through its robust standards and post market history, has demonstrated that DTC GTs can be safe and beneficial to interested consumers who would undoubtedly prefer a safe and legal alternative to their current option of buying specious products from unscrupulous providers. Pursuant to IVD and FDA quality system requirements, 23andMe continues to monitor post market surveillance in all countries where our health product is sold (United States, UK, certain European Countries, and Canada) and there have been no reported cases of harm due to test results to date, since such monitoring began in 2014.

Are there any particular genetic tests that should not be available as a self-test? Please provide reasons why not.

As detailed above 23andMe has demonstrated that a number of important genetic health results can be safely provided via DTC, including certain sensitive results such as those for cancer risk and for conditions such as Late On-set Alzheimer's Disease and Parkinson's Disease when appropriate validation and labeling is present to mitigate potential risks.

However, 23andMe does not offer any DTC GT results for highly penetrant autosomal dominant variants where the mere detection of the variant is known to be deterministic for the disease. In particular, this limitation would prevent the offering of a DTC GT for Huntington's Disease.

Additionally, tests which lack scientifically established disease-risk association of each variant detected and reported by each test as demonstrated by peer reviewed published studies and or clinical guidelines should not be offered to consumers.

Do you have any suggestions on how potential risks to consumers could be mitigated if genetic self-tests were allowed to be supplied in Australia?

The Company believes that the currently utilized risk mitigations have been shown to be effective and could be adopted by TGA so that Australian consumers can have the opportunity to benefit from a safe and well-validated DTC GT product, provided manufacturers fully comply with TGA pre- and post-market requirements so that consumers will not be tempted to purchase unsafe products currently flooding the market.

List of Attachments

Attachment 1: Lists of Direct-To-Consumer Tests with FDA Marketing Authorization

Attachment 2: US FDA Decision Summaries

- Attachment 2a: DEN180028 Decision Summary
- Attachment 2b: DEN170046 Decision Summary
- Attachment 2c: DEN160026 Decision Summary
- Attachment 2d: DEN140044 Decision Summary

Attachment 1

Lists of Direct-To-Consumer Tests with FDA Marketing Authorization

https://www.fda.gov/medical-devices/vitro-diagnostics/direct-consumer-tests#list

Lists of Direct-To-Consumer Tests with Marketing Authorization

The following is a list of direct-to-consumer tests have received marketing authorization by the FDA. The direct-to-consumer tests listed below have undergone an evaluation by the FDA for accuracy, reliability, and consumer comprehension.

Test Trade Name (FDA Submission Number)	Sponsor	Intended Use / Indications for Use
23andMe PGS Carrier Screening Test for Bloom Syndrome (DEN140044)	23andMe, Inc.	The 23andMe PGS Carrier Screening Test for Bloom Syndrome is indicated for the detection of the BLMAsh variant in the BLM gene from saliva collected using an FDA cleared collection device (Oragene DX model OGD-500.001). This test can be used to determine carrier status for Bloom syndrome in adults of reproductive age, but cannot determine if a person has two copies of the BLMAsh variant. The test is most relevant for people of Ashkenazi Jewish descent.
23andMe PGS Genetic Health Risk Test (DEN160026)	23andMe, Inc.	The 23andMe Personal Genome Service (PGS) Test uses qualitative genotyping to detect the following clinically relevant variants in genomic DNA isolated from human saliva collected from individuals ≥18 years with the Oragene Dx model OGD-500.001 for the purpose of reporting and interpreting Genetic Health Risks (GHR): The 23andMe PGS Genetic Health Risk Report for Hereditary Thrombophilia is indicated for reporting of the Factor V Leiden variant in the F5 gene, and the Prothrombin G20210A variant in the F2 gene. This report describes if a person has variants associated with a higher risk of developing harmful blood clots, but it does not describe a person's overall risk of developing harmful blood clots. This test is most relevant for people of European descent. The 23andMe PGS Genetic Health Risk Report for Alpha-1 Antitrypsin Deficiency is indicated for reporting of the PI*Z and PI*S variants in the SERPINA1 gene. This report describes if a person has variants associated with AAT deficiency and a higher risk for lung or liver disease, but it does not describe a person's overall risk of developing lung or liver disease. This test is most relevant for people of European descent. The 23andMe PGS Genetic Health Risk Report for Late-onset Alzheimer's Disease is indicated for reporting of the ε4 variant in the APOE gene. The report describes if a person's genetic result is associated with an increased

Test Trade Name (FDA Submission Number)	Sponsor	Intended Use / Indications for Use
		risk of developing Late-onset Alzheimer's Disease, but it does not describe a person's overall risk of developing Alzheimer's Disease. The ε4 variant included in this report is found and has been studied in many ethnicities. Detailed risk estimates have been studied the most in people of European descent. The 23andMe PGS Genetic Health Risk Report for Parkinson's Disease is indicated for reporting of the G2019S variant in the LRRK2 gene and the N370S variant in the GBA gene. The report describes if a person's genetic result is associated with an increased risk of developing Parkinson's disease, but it does not describe a person's overall risk of developing Parkinson's disease. The test is most relevant for people of European, Ashkenazi Jewish, and North African Berber descent. The 23andMe PGS Genetic Health Risk Report for Gaucher Disease Type 1 is indicated for reporting of the N370S, 84GG, and V394L variants in the GBA gene. This report describes if a person has variants associated with an increased risk for developing symptoms of Gaucher Disease Type 1, but it does not describe a person's overall risk of developing Gaucher Disease Type 1. This test is most relevant for people of Ashkenazi Jewish descent. The 23andMe PGS Genetic Health Risk Report for Factor XI Deficiency is indicated for reporting of the variants F283L, E117X, IVS14+1G>A in the F11 gene. This report describes if a person has a variant associated with Factor XI deficiency and the potential for a higher risk of excessive bleeding following trauma or surgery, but it does not describe a person's overall risk for excessive bleeding. This test is most relevant for people of Ashkenazi Jewish descent. The 23andMe PGS Genetic Health Risk Report for Celiac Disease is indicated for reporting of a variant associated with the HLA-DQ2.5 haplotype. The report describes if a person has a haplotype associated with an increased risk of developing celiac disease, but it does not describe a person's overall risk for developing celiac disease. This report is most relevant for people of European descent. The 23andMe PGS Genetic Health Risk Report for Glucose-6-Phosphate-Dehydrogenase Deficiency is indicated for reporting of the Val68Met variant in the G6PD gene. This report describes if a person has a variant associated with G6PD deficiency and a higher risk for episodes of anemia, but it does not describe a person's overall risk of developing anemia. This test is most relevant for people of African descent.

Test Trade Name (FDA Submission Number)	Sponsor	Intended Use / Indications for Use
		The 23andMe PGS Genetic Health Risk Report for Hereditary Hemochromatosis is indicated for reporting of the C282Y and H63D variants in the HFE gene. This report describes if a person has variants associated with hereditary hemochromatosis and a higher risk for iron overload, but it does not describe a person's overall risk of developing iron overload. This report is most relevant for people of European descent. The 23andMe PGS Genetic Health Risk Report for Early-Onset Primary Dystonia (DYT1/TOR1A-Related) is indicated for reporting of the deltaE302/303 variant in the DYT1 gene. This report describes if a person has variants associated with a higher risk for early-onset primary dystonia, but it does not describe a person's overall risk of developing dystonia. This report is most relevant for people of Ashkenazi Jewish descent.
23andMe PGS Genetic Health Risk Report for BRCA1/BRCA2 (Selected Variants) (DEN170046)	23andMe, Inc.	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 health care provider for recommended screenings or appropriate follow-up and should not be used to determine any treatments.

Attachment 2
US FDA Decision Summaries

Attachment 2a
DEN180028 Decision Summary

EVALUATION OF AUTOMATIC CLASS III DESIGNATION FOR
The 23andMe Personal Genome Service (PGS) Pharmacogenetic Reports

DECISION SUMMARY
This Decision Summary contains corrections to the [December 2018] Decision Summary.

A. DEN Number:

DEN180028

B. Purpose for Submission:

De Novo request for evaluation of automatic class III designation for the 23andMe Personal Genome Service (PGS) Pharmacogenetic Reports

C. Measurand:

Genotype of select alleles in Cytochrome P450 2C19 (CYP2C19), 2C9 (CYP2C9), 2D6 (CYP2D6), 3A5 (CYP3A5), thiopurine methyltransferase (TPMT), dihydropyrimidine dehydrogenase (DPYD), UDP glucoronosyltransferase family 1 member A1 (UGT1A1), and solute carrier organic anion transporter family member 1B1 (SLCO1B1)

D. Type of Test:

Qualitative genotyping microarray

E. Applicant:

23andMe, Inc.

F. Proprietary and Established Names:

23andMe Personal Genome Service (PGS) Pharmacogenetic Reports

G. Regulatory Information:

Regulation	Name	Product Code	Panel
21 CFR 862.3364	Pharmacogenetic assessment system	QDJ	Chemistry (75)

H. Indications for Use:

1. Indications for Use:

The 23andMe Personal Genome Service (PGS) is a qualitative genotyping assessment

system applied to genomic DNA isolated from human saliva collected using the Oragene Dx OGD-500.001 to simultaneously detect, report, and interpret genetic variants in a broad multigene test. The assessment system is intended to enable users to access information about their genetics that could aid discussions with a healthcare professional. The 23andMe Personal Genome Service Pharmacogenetic Reports are indicated for reporting of the following variants:

Gene	Variant(s)
CYP2C19	*2, *3, *17
CYP2C9	*2, *3, *5, *6, rs7089580
CYP3A5	*3
UGT1A1	*6, *28
DPYD	*2A, rs67376798
TPMT	*2, *3C
SLCO1B1	*5
CYP2D6	*2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *15, *17, *20, *29, *35, *40, *41

This report is for over-the-counter use by adults over the age of 18 and provides genetic information to inform discussions with a healthcare professional about metabolism of therapeutics. This report describes if a person has variants associated with metabolism of some therapeutics, but does not describe if a person will or will not respond to a particular therapeutic, and does not describe the association between detected variants and any specific therapeutic. The PGS Pharmacogenetic Reports are not a substitute for visits to a healthcare professional. The information provided by this report should not be used to start, stop, or change any course of treatment.

2. Special conditions for use statement(s)

- For over-the-counter (OTC) use.
- Results from this test should not be used to make medical decisions. Results should be confirmed in a clinical setting with independent genetic testing before taking any medical action.
- The user should not use results to start, stop, or change any course of treatment. Medications should always be taken as directed. Making changes can lead to harmful side effects or reduce intended benefits of the medication.
- This test does not diagnose any health conditions, predict drug response, provide medical advice, or determine whether a medication is indicated for the user.
- This test does not provide information on associations between specific DNA variants and any specific therapeutic.
- This test does not account for lifestyle or other health factors that may affect individual metabolism of medications.
- This test does not test for DNA variants in other genes that may affect other enzymes involved in the metabolism of medications.
- This test does not test for all possible DNA variants that may affect enzyme or protein function.

- This test is not a substitute for visits to a healthcare professional. The user should consult with a healthcare professional if the user has any questions or concerns about the results.

3. Special instrument requirements:

   Same as referenced in DEN140044.

I. Device Description:

The 23andMe PGS is a non-invasive DNA testing service that uses qualitative genotyping. It is a direct-to-consumer, over-the-counter, DNA genetic test. A user's saliva is self-collected using the Oragene·Dx device manufactured by DNA Genotek, Inc. (previously cleared under K141410), which consists of a sealable collection tube containing a stabilizing buffer solution. Once the sample is collected, it is shipped to one of two Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories for testing.

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

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

Personalized reports are generated for each user to provide results of the testing performed. These reports tell the user which variant(s) has/have been detected in their sample and provide information on the predicted metabolic function of the specific genetic variants. The genetic variants detected by the test are associated with the metabolism of some therapeutics. If no variant is detected, that information is also provided. If the association between the predicted metabolic function and the combination of detected variants has not been established, the report indicates that the results cannot be determined. The personalized reports are intended to present scientific concepts to users in an easy-to-understand format. The reports provide information about the association between the detected variant and the predicted metabolic function that has been associated with the metabolism of some drugs, further described below. The reports are designed to help users understand the meaning of their results and inform conversations with their doctor or other healthcare professional. The test reports do not provide any information on associations between the detected variants and any specific therapeutic and therefore, the test does not describe if a person will or will not respond to any specific therapeutic.

The 23andMe PGS Pharmacogenetic Reports detect 33 variants in 8 genes: CYP2C19, CYP2C9, CYP2D6, CYP3A5, CYP2D6, DPYD, TPMT, and UGT1A1. The 23andMe PGS

Pharmacogenetic Reports provide information on the associated enzyme or protein function and the predicted metabolizer phenotype for variants in drug metabolizing enzymes: CYP2C19, CYP2C9, CYP2D6, CYP3A5, CYP2D6, DPYD, TPMT, and UGT1A1. The predicted metabolizer phenotype is identified according to the number and consequence of each allele where two no-function alleles are associated with being poor metabolizers, one no-function allele is associated with being an intermediate metabolizer, two functional alleles are associated with being normal metabolizers, one gain-of-function allele is associated with being a rapid metabolizer, and two gain-of-function alleles are associated with being an ultrarapid metabolizer. The predicted metabolizer phenotype or protein function is then used to provide information on the potential consequence on metabolism of some medications. For example, poor metabolizers may process some medications slower, intermediate metabolizers may process some medications slightly slower than normal, normal metabolizers may process some medication at a normal rate, rapid metabolizers may process some medications slightly faster than normal, and ultrarapid metabolizers may process some medications faster than normal.

The 23andMe PGS Pharmacogenetic Report for SLCO1B1 will indicate that the detected variant is associated with a loss-of-function and slightly decreased transport of some medications.

J. Standard/Guidance Documents Referenced:

None.

K. Test Principle:

The PGS is indicated to be performed using a genotyping BeadChip assay, which covers more than 500,000 genetic markers. The BeadChip consists of silicon wafers etched to form wells loaded with silica beads, on which oligonucleotide capture probes are immobilized. DNA from saliva is fragmented and captured on a bead array by hybridization to immobilized SNP-specific primers, followed by extension with hapten-labeled nucleotides. The primers hybridize adjacent to the SNPs and are extended with a single nucleotide corresponding to the variant allele. The incorporated hapten-modified nucleotides are detected by adding fluorescently labeled antibodies in several steps to amplify the signals. Instrumentation is used for extraction and processing of the DNA, and the BeadChip is used for scanning and quantification of the results. The genotype content is separated, analyzed, and then integrated into pre-defined report templates specific for each condition associated with each genotype. Genotypes are determined using[(b) (4)] software packages. For the 23andMe PGS Pharmacogenetic Reports, the variants detected are:

Gene	Variants
CYP2C19	*2, *3, *17
CYP2C9	*2, *3, *5, *6, rs7089580
CYP2D6	*2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *15, *17, *20, *29, *35, *40, and *41
CYP3A5	*3
TPMT	*2, *3C

Gene	Variants
DPYD	*2A, rs67376798
UGT1A1	*6, *28
SLCO1B1	*5

L. Performance Characteristics:

1. Analytical performance:

Data to demonstrate analytical performance for the three detected alleles for CYP2C19 were provided and are described herein. Protocols and acceptance criteria to establish the analytical performance of each detected allele for CYP2C9, CYP2D6, CYP3A5, DPYD, TPMT, UGT1A1, and SLCO1B1 were reviewed and found to be acceptable. The sponsor will perform testing of the additional genes/variants according to the specified protocols, and if the validation data meet the specified acceptance criteria, they may add those genes/variants to the Pharmacogenetic Reports.

a. Reproducibility/Precision:

Reproducibility studies were conducted for the three CYP2C19 alleles reported by the PGS Pharmacogenetic report. The reproducibility studies were designed to determine the imprecision due to assay run, lot, instrument, operator, day, and site. DNA samples were obtained from an external vendor and genotyped in blinded fashion. Genotypes of the DNA samples were confirmed using bidirectional Sanger sequencing.

The study was performed at two sites across three days using three operator teams. Samples were genotyped in replicates of three using three lots of reagents, and three instrument sets.

Results obtained are summarized below stratified by genotype and site:

CYP2C19*2

Genotype	Number of samples (81 replicates per sample)	Number of total replicates (including FQCs* and no calls)	Number of Correct Calls	Number of Incorrect Calls	Number of FQCs (first run)	Number of No Calls
	Site 1					
Homozygous Common (GG)	1	81	81	0	0	0
Heterozygous (AG)	2	162	162	0	0	0

Genotype	Number of samples (81 replicates per sample)	Number of total replicates (including FQCs* and no calls)	Number of Correct Calls	Number of Incorrect Calls	Number of FQCs (first run)	Number of No Calls
Homozygous Rare (AA)	1	81	81	0	0	0
	Site 2					
Homozygous Common (GG)	1	81	81	0	0	0
Heterozygous (AG)	2	162	157	0	5	0
Homozygous Rare (AA)	1	81	81	0	0	0

*FQC = Failed quality controls

CYP2C19*3

Genotype	Number of samples (81 replicates per sample)	Number of total replicates (including FQCs and no calls)	Number of Correct Calls	Number of Incorrect Calls	Number of FQCs (first run)	Number of No Calls
	Site 1					
Homozygous Common (GG)	2	162	162	0	0	0
Heterozygous (AG)	1	81	81	0	0	0
Homozygous Rare (AA)	1	81	81	0	0	0
	Site 2					
Homozygous Common (GG)	2	162	157	0	5	0
Heterozygous (AG)	1	81	79	0	2	0
Homozygous Rare (AA)	1	81	81	0	0	0

*FQC = Failed quality controls

CYP2C19*17

Genotype	Number of samples (81 replicates per sample)	Number of total replicates (including FQCs and no calls)	Number of Correct Calls	Number of Incorrect Calls	Number of FQCs (first run)	Number of No Calls
	Site 1					
Homozygous Common (CC)	2	162	162	0	0	0
Heterozygous (CT)	1	81	81	0	0	0
Homozygous Rare (TT)	2	162	162	0	0	0
	Site 2					
Homozygous Common (CC)	2	162	158	0	4	0
Heterozygous (CT)	1	81	80	0	1	0
Homozygous Rare (TT)	2	162	160	0	2	0

*FQC = Failed quality controls

A second precision study was conducted at two sites on one day. At each site, one sample of each genotype for each allele was genotyped in replicates of three using two lots of reagents and three operator teams. 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. There were zero 'no calls' in this study. The percentage of failed quality controls (FQCs) ranged from zero to 22.2% per sample.

b. *Linearity/assay reportable range:*

Not applicable.

c. *Traceability, Stability, Expected values:*

The PGS requires (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 CYP2C19*2, *3, and *17 variants using the 23andMe PGS test. Study samples were obtained from an external vendor based on their listed genotypes and included homozygous common, heterozygous common, and homozygous rare genotypes for each allele.

Three replicates of each sample were diluted to three different DNA concentrations (5, 15, and 50 ng/µl) and genotyped by the PGS test in a blinded fashion using 3 lots of reagents. To confirm the genotype call, each sample was sequenced by bidirectional Sanger sequencing. Genotype calls from the PGS test were compared with genotypes from Sanger sequencing to determine the rates of correct genotype calls at each DNA concentration.

This study yielded 100% correct calls per genotype for all samples across all reagent lots, at all sample concentrations tested. Therefore, the LoD is set 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. Analytical specificity:

Endogenous and Exogenous Substances
A series of studies were conducted to assess the effects of endogenous substances, exogenous substances, microbial substances, and smoking on the 23andMe PGS Test. The results of the Endogenous and Exogenous Interference studies can be found in the Decision Summary for DEN140044.

Interfering Mutations
Analyses were performed to identify potentially interfering variants within the 50-nucleotide probe-binding regions of the three CYP2C19 variants detected by this test. Two potentially interfering mutations near *2, four potentially interfering mutations

near *3, and eight near *17 that are within the binding region for the variant being tested have been identified (see list below). The labeling specifies that the following mutations may potentially interfere with the CYP2C19 test.

CYP2C19 Variant	Potentially Interfering Mutation
(b) (4)	(b) (4)
(b) (4)	
(b) (4)	

f. Assay Cut-off:

Not applicable.

g. Specimen Stability at 2–8°C

Saliva samples for testing are collected with the Oragene·Dx OGD-500.001 collection device. See K141410 for sample stability information.

h. Shipping Stability

Saliva samples are shipped for testing in the Oragene·Dx OGD-500.001 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. 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 each allele detected for the CYP2C19 study report are shown below.

CYP2C19*2

Genotype	Correct Calls	Incorrect Calls	No Calls	Failed Quality Controls (FQCs)	%PPA	%NPA	95% CI
Homozygous Common (GG)	47	0	0	3	100	100	92.5-100
Heterozygous (AG)	49	0	0	0	100	100	92.7-100
Homozygous Rare (AA)	48	0	0	3	100	100	92.6-100

*FQC = Failed quality controls

CYP2C19*3

Genotype	Correct Calls	Incorrect Calls	No Calls	Failed Quality Controls (FQCs)	%PPA	%NPA	95% CI
Homozygous Common (GG)	48	0	0	2	100	100	92.6-100
Heterozygous (AG)	45	0	0	3	100	100	92.1-100
Homozygous Rare (AA)	39	0	0	1	100	100	91.0-100

*FQC = Failed quality controls

Genotype	Correct Calls	Incorrect Calls	No Calls	Failed Quality Controls (FQCs)	%PPA	%NPA	95% CI
Homozygous Common (CC)	49	0	0	1	100	100	92.7-100
Heterozygous (CT)	45	0	0	4	100	100	92.1-100
Homozygous Rare (TT)	47	0	0	0	100	100	92.5-100

*FQC = Failed quality controls

Due to the large margin of error (i.e., wide confidence intervals), and selection bias

(i.e., samples were chosen from a biobank based on the variants already detected by the candidate assay), there is residual uncertainty about the analytical results of this test. This uncertainty is mitigated because this device is indicated as providing only a preliminary test result that must be confirmed using an independent pharmacogenetic test. Results from this device should not be used for clinical decision making.

The labeling for the device indicates the following: "Results from this test should not be used to make medical decisions. Results should be confirmed in a clinical setting with independent genetic testing before taking any medical action."

b. Matrix Comparison

Not applicable.

3. Clinical studies:

a. Clinical Sensitivity

Not applicable.

b. Clinical Specificity

Not applicable.

c. Other clinical supportive data (when a. and b. are not applicable)

i. Predicted Pharmacogenetic Associations: The impact of protein or enzyme function for each allele and the predicted metabolizer phenotypes were identified from data in the literature for each allele for each gene.

ii. User Comprehension Study: A user comprehension study was conducted to assess comprehension of the proposed labeling of the pharmacogenetic test reports in a demographically diverse (e.g., age, education) set of users naïve to the study subject. A total of 602 participants completed the study; the completion rate was 100%. Participants were assigned to one of five different types of pharmacogenetic reports (e.g., variant(s) detected, results cannot be determined, cannot interpret results). Eight participants (1.3%) were excluded from the analysis because they were determined to be a careless responder who got a pre-defined "red-herring" question wrong (6), determined to have previously received a 23andMe report (1), or a technical issue occurred during testing (1). Therefore, 594 subjects were included in the primary endpoint analysis. A second analysis was performed excluding participants that did not scroll/read through the test reports as identified by the moderators of the test (63 participants). It may not be appropriate to exclude participants that did not scroll/read the test reports, since users may not read or scroll through the test report when receiving and interpreting results from this device.

The results of the overall comprehension rate for each identified comprehension concept are summarized below for each analysis provided by the sponsor:

Comprehension Concept	All participants (n=594)	Participants that scrolled/read the test reports (n=531)
Purpose of the test	89.9%	90.8%
Result and meaning	89.9%	90.2%
Limitations and variant coverage	93.1%	94.2%
Limitations of medication coverage	94.8%	95.1%
Appropriate actions	92.3%	92.8%
Treatment adherence	97.0%	97.2%
Other risk factors	95.0%	95.5%

iii. Frequently Asked Questions: The labeling for each pharmacogenetic report includes a Frequently Asked Questions (FAQ) section. The FAQ section was created to provide users information to adequately understand the purpose, limitations, and the meaning of the results of the test. The concepts covered in the FAQ section include: the test results, the purpose of the test, limitations of the test, the meaning of the result, other risks factors that contribute to drug metabolism, and appropriate follow-up actions (e.g., user should not stop or change any medication they may be taking, results should be confirmed in a clinical setting with additional testing prior before taking any medication action).

4. Expected Values

The package insert and user test reports include allele frequencies from 23andMe customers. The package insert for each test report indicates that the allele frequencies provided are from the 23andMe customer database and may not be representative of the actual allele frequencies in the presented populations. The following allele frequencies will be provided in the CYP2C19 package insert and user test report:

Ethnicity	*2	*3	*17
European	(b) (4)		
African American			
Ashkenazi Jewish			
East Asian			
Hispanic/Latino			
South Asian			

c. Instrument Name:

Same as referenced in DEN140044.

d. System Description:

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___X___or No _____

   Level of Concern

   Moderate

   Software Description:

   Same as referenced in DEN140044.

   Revision Level History:

   Changes since DEN140044 and DEN170046 were reviewed and found acceptable.

   Unresolved Anomalies:

   Sponsor states that 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.

M. Other Supportive Instrument Performance Characteristics Data Not Covered In the "Performance Characteristics" Section above:

Not applicable.

N. Proposed Labeling:

The labeling supports the decision to grant the De Novo request for this device.

O. Patient Perspectives:

This submission did not include specific information on patient perspectives for this device. However, in making our decision, we considered that patients want easy access to information about their genetics, and they want this information in a manner they can easily understand and appropriately apply.

P. Identified Risks to Health and Identified Mitigations:

Identified Risks to Health	Identified Mitigations
Incorrect test results (false positive or false negative results)	Special controls (1), (2), (3), (4), and (5)
Incorrect interpretation of test results	Special controls (1)(ii), (2), (3), (4), (5) and (6)
Incorrect action based on test results	Special controls (1)(ii), (2), (3), (4), and (6)

Q. Benefit/Risk Analysis

Summary of the Assessment of Benefit
For the Proposed Indications for Use

The PGS test pharmacogenetic reports provide users with easier access to their own health data compared to traditional genetic tests. This test does not require a prescription from a healthcare professional and the sample collection kits are mailed directly to the users. Adults may potentially benefit from the use of this test to inform conversations with their healthcare professionals regarding DNA variants that may impact metabolism of some therapeutics. These conversations may then prompt clinicians to perform confirmatory pharmacogenetic tests which may have an impact on personalizing medical management.

Summary of the Assessment of Risk
For the Proposed Indications for Use

Risks associated with this device include erroneous test results (false positive or false negative results), incorrect interpretation of the test report by the user or healthcare provider, incorrect user action based on the test result (e.g., self-directing a change in drug dosage or stopping of a medication that has been prescribed by a healthcare provider), and incorrect action by the healthcare provider (e.g., use of the results by the healthcare provider prior to confirming the test result). Incorrect interpretation and action by the user may lead to user harm. Incorrect interpretation and action by the healthcare provider may lead to inappropriate clinical decision making and user harm.

Summary of the Assessment of Benefit-Risk
For the Proposed Indications for Use

Given that there are possible risks associated with an incorrect test result, incorrect interpretation of test results, and incorrect action based on the test result, the benefit-risk balance of this device is undetermined and requires additional mitigations in the form of limitations and special controls, beyond general controls.

Summary of the Assessment of Benefit-Risk, considering risk mitigation strategies
For the Proposed Indications for Use

The risks of incorrect user interpretation and self-directing a change in drug dosage or stopping of a medication (i.e., an incorrect action based on test results) is mitigated by results from a user comprehension study that demonstrated overall comprehension of the critical concepts for the device including medication adherence. This risk is further mitigated by labeling which includes user reports that specify that users should not use the results to stop or change any medication. The user test report also indicates that the test does not provide any information on any specific medication.

The risk of erroneous interpretation and incorrect action by the healthcare provider is mitigated by adequate labeling including user test reports that specify that results should not be used for clinical decision making and that results should be confirmed in a clinical setting with additional testing before making any medical decisions.

Risks associated with erroneous test results are mitigated by limited analytical performance studies, supportive clinical information for each allele, and adequate labeling. The user test report indicates that results should not be used for clinical decision making and that results should be confirmed by an independent pharmacogenetic test before making any medical decisions since there is residual uncertainty associated with the analytical validation data.

Overall, the likelihood of benefit of the pharmacogenetic reports to describe variants associated with the metabolism of some drugs in user reports and inform conversations with healthcare providers that may prompt confirmatory pharmacogenetic testing outweighs the likelihood of erroneous interpretation and incorrect action by the user or healthcare provider,

when considering the mitigations provided by the limitations and special controls, beyond general controls.

R. Conclusion:

The information provided in this de novo submission is sufficient to classify this device into class II under regulation 21 CFR 862.3364. FDA believes that the special controls, in combination with the general controls, provide a reasonable assurance of the safety and effectiveness of the device type. The device is classified under the following:

Product Code: QDJ
Device Type: Pharmacogenetic assessment system
Class: II (special controls)
Regulation: 21 CFR 862.3364

a.) Identification: A pharmacogenetic assessment system is a qualitative in vitro molecular diagnostic system intended to detect nucleic acid variants isolated from human specimens for the purpose of assessing the presence of genetic variants that impact the metabolism, exposure, response, risk of adverse events, dosing, or mechanisms of prescription or over-the-counter medications. The intended use of the device must not include an indication for use in supporting or sustaining human life, being of substantial importance in preventing impairment of human health, or presenting a potential, unreasonable risk of illness or injury.

b.) Classification: Class II (special controls). A pharmacogenetic assessment system must comply with the following special controls:

(1) Design verification and validation must include:
(i) Data appropriate, as determined by FDA, to demonstrate the analytical accuracy and reliability of the device in intended use specimens, including but not limited to precision, reproducibility, accuracy, limits of detection, and interferences. This information must include:
(A) Data demonstrating appropriate, as determined by FDA, reproducibility for each genotype using each claimed sample type. Reproducibility data shall be evaluated using specimens collected and processed in a manner consistent with the device's instructions for use, or, as determined by FDA, an appropriate alternative sample panel.
(B) Analytical data demonstrating the limits of detection, including the minimum amount of input DNA that will consistently produce accurate results.
(C) Data demonstrating no clinically significant effects from endogenous and exogenous interferents relevant to each intended use specimen type. Interference data must also include an

assessment of potentially interfering genetic sequences (e.g., variants proximal to the variant of interest, pseudogenes).

(D) Validation data appropriate, as determined by FDA, to support specimen collection and handling claims.

(E) Clinical data generated in intended use patient populations demonstrating the pharmacogenetic association between the genetic variant tested and any clinical claims or therapy-related recommendations associated with that genotype.

(ii) Results from an appropriate, as determined by FDA, user comprehension study that demonstrate the intended user can use the device safely. The user comprehension study must be designed to include the following:

(A) Study participants from a statistically sufficient sample size and a demographically diverse (e.g., age, education level) population that is representative of the intended use population and naïve to use of the device, and

(B) An evaluation of all result comprehension concepts that are critical for safe use of the device.

(2) The 21 CFR 809.10 labeling must include:

(i) Clear information, written in language appropriate for the intended user, that describes instructions for how test results should be interpreted. These instructions must be supported by valid scientific evidence and include:

(A) Appropriate explanation of the claimed pharmacogenetic associations for all variants included in the test, any relevant variants not included in the test (e.g., that may contribute to false negative results), and specific considerations by ethnicity, and

(B) Appropriate explanation of non-genetic and non-tested genetic factors that may impact interpretation of the test results;

(ii) Detailed descriptions of analytical performance including, as applicable, precision, reproducibility, accuracy, limits of detection, and interferences as specified in paragraph (b)(1)(i) of this section, in language appropriate for the intended user;

(iii) A warning statement that the patient should not use the test results to stop or change any medication, and that medications should always be taken as prescribed by a healthcare professional;

(iv) A limiting statement explaining that this test is not intended to inform the patient about their current state of health, including whether or not the patient should or should not take a medication, or how much of a medication the patient should take, as appropriate;

(v) A warning statement that the test does not diagnose any health conditions and is not a substitute for visits to a doctor or other healthcare professional; and

(vi) A prominent and conspicuous limiting statement that the test provides only a preliminary test result that needs to be confirmed using an independent pharmacogenetic test without such a limitation prior to making any medical decisions. Alternatively, appropriate design

verification and validation activities, including the generation of robust analytical data demonstrating appropriate analytical accuracy and reliability of test results for each genetic variant included in the test report, must be performed that demonstrate that the test can be used to make well-informed clinical decisions.

(3) The test report must include an appropriate description of how the test results should be used by healthcare providers who may receive the test results from their patients, as applicable.

(4) Publicly available pre-purchase labeling with unrestricted access that contains the following information must be provided:
   (i) A clear description of the test and its technology, the genotypes detected, and relevant clinical claims associated with each genotype;
   (ii) A clear description of what information the test will provide. This includes, but is not limited to, variant information, the limitations associated with the test, and any precautionary information about the test the user should be aware of before purchase; and
   (iii) A discussion of answers to frequently asked questions that is sufficient to provide intended users with an appropriate understanding of information specific to each pharmacogenetic association that is claimed.

(5) 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 DNA testing.

(6) The intended use of the device must not include an indication for use in supporting or sustaining human life, being of substantial importance in preventing impairment of human health, or presenting a potential, unreasonable risk of illness or injury.

Attachment 2b
DEN170046 Decision Summary

EVALUATION OF AUTOMATIC CLASS III DESINGATION 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*

<u>Endogenous and Exogenous Substances</u>

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					%PPA	%NPA	95% CI‡
	Correct*	Incorrect*	No Call	FQC	Total Sample #			
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.

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[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 22population 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 __X__ 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	(1) Direct user access to tests for genetic risk of diseases 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.

	(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	(1) Risks associated with false results 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.

	(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. (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. (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.
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.

Attachment 2c
DEN160026 Decision Summary

Due to the large size, the DEN160026 Decision Summary can be viewed at:
http://www.accessdata.fda.gov/cdrh_docs/reviews/DEN160026.pdf

Attachment 2d
DEN140044 Decision Summary

Due to the large size, the DEN140044 Decision Summary can be viewed at:
http://www.accessdata.fda.gov/cdrh_docs/reviews/DEN140044.pdf