23andMe® Personal Genome Service® (PGS)
Genetic Health Risk Report Package Insert
MUTYH-Associated Polyposis

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For *in-vitro* diagnostic use

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 MUTYH-Associated Polyposis. The 23andMe PGS Genetic Health Risk Report for MUTYH-Associated Polyposis is indicated for reporting of the Y179C and the G396D variants in the MUTYH gene. The report describes if a person is at increased risk of developing colorectal cancer. The two variants included in this report are most common and best studied in people of Northern European descent and may not represent the majority of the MUTYH variants found in people of other ethnicities. The test report does not describe a person's overall risk of developing any type of cancer, and the absence of a variant tested does not rule out the presence of other variants that may be cancer-related. This 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.

Summary and explanation of the test:
23andMe Genetic Health Risk Tests are tests you can order and use at home to learn about your DNA from a saliva sample (collected with Oragene Dx model OGD500.001). The tests work by detecting specific gene variants using a customized multiplex assay, reagents, and instrumentation. The probability that the laboratory cannot process a sample can be 7-33%. Your genetic results are returned to you in a secure online account on the 23andMe website.

Important considerations:

- This test does not diagnose colorectal cancer or any other health conditions and should not be used on its own to make medical decisions. Results should be confirmed in a clinical setting before taking any medical action.
- Please follow the instructions in the DNA Collection Kit to ensure your DNA results can be processed and connected to your online account.
- Your ethnicity may affect whether these tests are relevant for you.
- Other factors, such as family history and lifestyle risk factors, may affect the risk of developing a given disease. This test does not account for non-genetic factors, and does not test for variants in other genes linked to hereditary colorectal cancer syndromes, such as Lynch syndrome or familial adenomatous polyposis (FAP).
- If you have a family history of a condition, or think you have symptoms of a condition, consult with your healthcare provider about appropriate testing.
- This test cannot determine your overall risk for developing a disease in the future.
- This device is not intended for prenatal testing.
- This test is not for assessing the presence of genetic variants that may impact the metabolism, exposure, response, risk of adverse events, dosing, or mechanisms of prescription or over-the-counter medications.
- This test is not intended to detect the presence of deterministic variants in autosomal dominant diseases or conditions.
- The laboratory may not be able to process your sample. If this happens, we will notify you by email and you may request one free replacement kit to provide us with a new sample.

Other warnings, precautions, and limitations:

- This test includes two variants that are most common in people of Northern European descent.
- This test does not test for all possible variants in the MUTYH gene. More than 100 variants in the MUTYH gene are known to increase cancer risk. Only two of those variants are included in this test. The absence of a variant tested does not rule out the presence of other genetic variants that may be related to these health conditions.
- If you receive a “zero variants detected” result you should not over interpret it. You could have another variant not included in this test that may impact your cancer risk.
- This test is intended to be used to identify genetic risk for health conditions in users 18 years and above.
- This test is intended to provide you with genetic information to inform conversations with your doctor or other healthcare professional.
- This 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. You should consult with a healthcare professional if you have any questions or concerns about your results or your current state of health.
- This test may not be able to determine a result for all variants analyzed.
- Three potentially interfering mutations near Y179C, and four potentially interfering mutations near G396D that are within the binding region for the variant being tested have been identified and are noted below. Interference due to these mutations was

not tested. The effects of these variants on the performance of this test have not been studied.

MUTYH variant	Potentially Interfering Mutation
Y179C	rs190500741, rs533899702, rs201678305
G396D	rs559963863, rs529008617, rs3219490, rs531232542

- Different companies offering a genetic risk test may be measuring different genetic variants for the same condition, so you may get different results from a different test.
- Some people feel a little anxious about getting genetic health risk results. This is normal. If you feel very anxious, you should speak to your doctor or a genetic counselor prior to collecting your sample for testing. You may also consider getting your test done by your doctor.
- As with every test the possibility for an incorrect result exists. Speak to your personal healthcare professional or a genetic counselor if your results are unexpected.

For healthcare professionals:

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

Should you speak to a genetic counselor?

We encourage you to learn more so you can decide whether testing is right for you. A genetic counselor, a healthcare professional with special training in genetic conditions, will be able to answer your specific questions and help you make an informed decision.

Talk to your healthcare provider or, to search for a genetic counselor near you, go to the following link (this link takes you to a page managed by the National Society of Genetic Counselors: http://www.aboutgeneticcounselors.com/)

Test performance:

The performance of the **MUTYH-Associated Polyposis** test was assessed only for the detection of the specific gene variants analyzed by the **MUTYH-Associated Polyposis** test in adults. Samples were collected using the Oragene·Dx® saliva collection device (OGD-

500.001). The samples were tested on the Illumina® Infinium BeadChip. Results were analyzed using the Illumina iScan System and GenomeStudio and Coregen software.

Analytical performance:

Accuracy
23andMe performed a method comparison study to assess the accuracy of the assay. Results of the test were compared with sequencing results for 64 samples with known Y179C variant status, and 78 samples with known G396D status. Pre-defined acceptance criteria were set to a minimum of 99% Positive Percent Agreement (PPA) and 99% Negative Percent Agreement (NPA).

The method comparison study yielded >99% overall agreement for all genotypes for all samples tested, passing the predefined acceptance criteria of at least 99% PPA and 99% NPA. The comprehensive 95% confidence interval for the total number of samples tested was 97.4% to 100%. The widest confidence interval was 76.8% to 100% for 14 homozygous rare MUTYH Y179C samples.

Genotype	BeadChip Calls				% PPA	% NPA	95% CI
	Correct	Incorrect	No Call	FQC[1]			
MUTYH Y179C Homozygous common	25	0	0	0	100	100	86.3-100
MUTYH Y179C Heterozygous	26	0	0	0	100	100	86.8-100
MUTYH Y179C Homozygous rare	14	0	0	1	100	100	76.8-100
MUTYH G396D Homozygous common	26	0	0	0	100	100	86.8-100
MUTYH G396D Heterozygous	27	0	0	0	100	100	87.2-100
MUTYH G396D Homozygous rare	25	0	0	0	100	100	86.3-100

[1] "FQC" denotes a sample or replicate which failed a quality check and was not analyzed in the study.

Precision/Reproducibility
Precision studies were performed to understand the consistency of sample measurements when tested under different conditions. Human samples of known variant status were tested for precision. Testing was performed at 2 lab sites over 3 non-consecutive days with multiple operator teams. The testing used 3 lots of reagents and 3 sets of instruments at each lab site.

A total of 360 Y179C replicates from 3 unique samples, and 486 G396D replicates from 3 unique samples were tested. Any sample replicates failing quality control acceptance criteria were re-tested per lab procedures. Only sample replicates that passed quality control and produced a genotype for the 23andMe test were included in the calculation for percent agreement.

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

Minimum DNA Input
A minimum DNA input study was performed to understand the lowest concentration of DNA needed for at least 95% concordant test results.

This study was performed using 2 human cell line samples and 3 saliva samples, which were diluted to 3 concentrations (5, 15, and 50ng/µL), using 3 lots of reagents. The study yielded 100% concordant test results for all samples at all DNA concentrations tested passing all pre-defined acceptance criteria. The DNA input required for testing is set at a minimum of 15ng/µL and maximum of 50ng/µL DNA.

Interfering Substances
Studies were performed to determine whether substances that may be present in saliva affect results of the PGS tests. Four proteins that may be found in human saliva were added to saliva samples. These proteins did not affect test performance.

Studies were also performed to determine whether foreign substances found in saliva affect results of the PGS tests. Saliva samples were collected from five people at three time points. First, a sample was collected before consuming a substance. Then, a sample was collected immediately after consumption. Finally, a sample was collected thirty minutes after consumption.

The following conditions were tested:
- Eating food containing beef
- Eating food other than beef
- Drinking
- Chewing gum
- Using mouthwash
- Smoking

The studies indicated that saliva samples should be collected at least thirty (30) minutes after eating, drinking, chewing gum, using mouthwash, or smoking.

Another study was performed to assess the effects of five microbes that may be found in human saliva. The microbial DNA had no effect on the accuracy of the PGS tests.

User studies:

Saliva collection kit user study
User studies were performed to assess how well people understand the saliva collection kit instructions and to assess the ability of lay users to provide samples adequate for testing. Study participants represented a wide range of demographic characteristics. Participants were asked to collect and mail a saliva sample and answer an online survey about the collection kit instructions from home. Saliva samples were processed according to standard laboratory procedures.

The overall comprehension rate on the collection kit instructions was 92.1% and greater than 97% of samples met all laboratory quality criteria, demonstrating that users from diverse backgrounds can understand the collection kit instructions and provide adequate saliva samples.

PGS test report user comprehension study
The key report message concepts for the MUTYH-Associated Polyposis (MAP) test were reviewed and determined to be the same as those previously tested in the device label comprehension study for the PGS Genetic Health Risk Test Report for BRCA1/BRCA2 (Selected Variants). User comprehension studies were performed to assess how well people understand the PGS Genetic Health Risk Test Reports. This study was performed using test reports that are representative of Genetic Health Risk reports in general. The user comprehension study was performed in a sample that was demographically diverse, using quota-based sampling in a controlled laboratory-based environment. In addition to quantitative assessment of user comprehension of the test reports after viewing the educational module, the study was moderated face-to-face in order to collect observational and qualitative data on participants' overall experience with the survey. All pre-defined demographic quotas and enrollment targets were met within the expected study duration for the overall study. Comprehension was tested through a two-step process. First, participants' understanding of genetics was tested prior to viewing the educational module and test reports. Second, participants were shown the educational module and the test reports. Participants then completed the test report comprehension survey. Overall comprehension rates per test report concept were greater than 90% across all concepts, passing the pre-defined acceptance criteria.

Clinical performance:
The variants covered by this test are mainly found in people of Northern European

descent. Published studies estimate that about 1-2% of the general Northern European population has one of the two variants in this report, which means that between 1 in 10,000 and 1 in 40,000 people of Northern European descent are expected to have MAP. These two variants have also been observed in people of other ethnicities.

Frequency of MUTYH variants in 23andMe customers

Variant name	European	African American	Ashkenazi Jewish	East Asian	Hispanic or Latino	South Asian
Y179C	0.41%	0.11%	<0.01%	<0.01%	0.27%	<0.01%
G396D	1.12%	0.36%	<0.01%	0.01%	1.00%	0.04%

References

1. Cleary SP et al. (2009). "Germline MutY human homologue mutations and colorectal cancer: a multisite case-control study." Gastroenterology. 136(4):1251-60.
2. Nielsen M et al. (2012). "*MUTYH*-Associated Polyposis." [Updated 2017 Sep 24].
3. Win AK et al. (2014). "Risk of colorectal cancer for carriers of mutations in MUTYH, with and without a family history of cancer." Gastroenterology. 146(5):1208-11.e1-5.
4. Data on file at 23andMe, Inc., Mountain View, CA

This package insert describes the analytical performance of the 5th version (v5) of the genotyping chip used to test a sample for the 23andMe Personal Genome Service.

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PI Part Number VV-QUAL-06761
PI Revision 2.0
PI Revision Date June 2019