December 23, 2020

Helix OpCo, LLC
Gloria Lee
Senior Director Regulatory Affairs
96 Colbeck Street
Toronto, M6S1 V2 Ontario Canada

Re: K192073
Trade/Device Name: The Helix Genetic Health Risk app for late-onset Alzheimer's disease
Regulation Number: 21 CFR 866.5950
Regulation Name: Genetic health risk assessment system
Regulatory Class: Class II
Product Code: PTA
Dated: July 31, 2019
Received: August 2, 2019

Dear Gloria Lee:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part

801 and Part 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Ying (Katelin) Mao
Branch Chief
Division of Immunology and Hematology Devices
OHT7: Office of In Vitro Diagnostics
and Radiological Health
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2020
See PRA Statement below.

510(k) Number *(if known)*
k192073

Device Name
Helix Genetic Health Risk App for late-onset Alzheimer*s disease

Indications for Use *(Describe)*

The Helix Genetic Health Risk App (HRA) uses qualitative genotyping to detect clinically relevant variants in genomic DNA isolated from human saliva collected from individuals ≥18 years with Oragene®•Dx OGD-610 for the purpose of reporting and interpreting Genetic Health Risks (GHR):

The Helix Genetic Health Risk App (HRA) for late-onset Alzheimer's disease is indicated for reporting of the e2/e2, e2/e3, e3/e3, e2/e4, e3/e4 and e4/e4 genotypes in the APOE gene. The report describes if a person*s genetic result is associated with an increased or decreased risk of developing late-onset Alzheimer's disease. The e2 and e4 variants included in this report are found and have been studied in many ethnicities. Detailed risk estimates have been studied the most in people of European descent.

The Helix Genetic Health Risk App (HRA) is to be used with the Helix Laboratory Platform.

Type of Use *(Select one or both, as applicable)*

☐ Prescription Use (Part 21 CFR 801 Subpart D) ☒ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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510(k) SUMMARY

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of Safe Medical Devices Act of 1990 and 21 CFR 807.92

The assigned 510(k) number is: K192073

Submitter / Company

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Date Prepared

December 1, 2020

5.1 Regulatory Information

Table 5.1 Proposed new device

Type of Submission:	Traditional 510k
Common/ Usual Name:	Helix Genetic Health Risk App
Regulation Name:	Genetic Health Risk Assessment System
Regulation Description:	Genetic health risk assessment system is a qualitative in vitro molecular test that detects variants in genomic DNA isolated from human specimens. This assessment system provides users with a genetic health risk assessment of developing a disease and is intended to inform users of lifestyle choices and/or encourage 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 a disease.
Regulation Number:	21 CFR 866.5950
Product Code:	PTA
Class:	2

Predicate Device:	23andMe PGS Genetic Health Risk Report for Late-onset Alzheimer's Disease

5.2 Intended Use / Indications for Use

The Helix Genetic Health Risk App (HRA) uses qualitative genotyping to detect clinically relevant variants in genomic DNA isolated from human saliva collected from individuals ≥18 years with Oragene®•Dx OGD-610 for the purpose of reporting and interpreting Genetic Health Risks (GHR):

The Helix Genetic Health Risk App (HRA) for late-onset Alzheimer's disease is indicated for reporting of the e2/e2, e2/e3, e3/e3, e2/e4, e3/e4 and e4/e4 genotypes in the APOE gene. The report describes if a person's genetic result is associated with an increased or decreased risk of developing late-onset Alzheimer's disease. The e2 and e4 variants included in this report are found and have been studied in many ethnicities. Detailed risk estimates have been studied the most in people of European descent.

The Helix Genetic Health Risk App (HRA) is to be used with the Helix Laboratory Platform.

5.4. Substantially Equivalent Predicate Device

See Table 5.2 for list of similarities and differences with the predicate device.

Table 5.2 Substantial Equivalence

	Helix Genetic Health Risk App for late-onset Alzheimer's disease	23andMe PGS Genetic Health Risk Report for Late-onset Alzheimer's Disease (DEN160026)	Similarities and Differences
Intended Use / Indications for use	The Helix Genetic Health Risk App (HRA) uses qualitative genotyping to detect clinically relevant variants in genomic DNA isolated from human saliva collected from individuals ≥18 years with Oragene®•Dx OGD-610 for the purpose of reporting and	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	Similar

	interpreting Genetic Health Risks (GHR): The Helix Genetic Health Risk App (HRA) for late-onset Alzheimer's disease is indicated for reporting of the e2/e2, e2/e3, e3/e3, e2/e4, e3/e4 and e4/e4 genotypes in the APOE gene. The report describes if a person's genetic result is associated with an increased or decreased risk of developing late-onset Alzheimer's disease. The e2 and e4 variants included in this report are found and have been studied in many ethnicities. Detailed risk estimates have been studied the most in people of European descent. The Helix Genetic Health Risk App (HRA) is to be used with the Helix Laboratory Platform.	for the purpose of reporting and interpreting Genetic Health Risks (GHR) The 23andMe PGS Genetic Health Risk Report for Late-onset Alzheimer's Disease is indicated for reporting of the e4 variant in the APOE gene. The report describes if a person's genetic result is associated with an increased risk of developing Late-onset Alzheimer's Disease, but it does not describe a person's overall risk of developing Alzheimer's Disease. The e4 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.	
Target Population	≥ 18 years old	≥ 18 years old	Similar
Interpretation of Results	For over-the-counter use (OTC). Specialized interpretation by a physician not required	For over-the-counter use (OTC). Specialized interpretation by a physician not required	Similar
Human Factors	User comprehension testing	User comprehension testing	Similar
Compatibility with the environment and other devices	NA - it is a software application to be viewed on a mobile phone or desktop	NA - it is a software application to be viewed on a mobile phone or desktop	Similar

	computer	computer	
Design	Software application that includes product information page, e-commerce (registration and order DNA kit), secure login, download genetic report.	Software application that includes product information page, ecommerce (registration and order DNA kit), secure login, download genetic report.	Similar
Specimen Collection Kit	DNA Genotek Inc., Oragene®·Dx (OGD-610)	DNA Genotek Inc., Oragene®·Dx (OGD500.001)	Similar
Sample matrix	Saliva	Saliva	Similar
Variants detected	The APOE e2, e3, and e4 alleles at rs429358 and rs7412 SNPs. rs429358 is a SNP at position chr19::44908684 (GRCh38). rs7412 is a SNP at position chr19:44908822 (GRCh38).	Only reports at APOE e4, and looks at rs429358 SNPs that define APOE e4. The 23andMe PGS Genetic Health Risk Report for Late-onset Alzheimer's Disease only looks at: rs429358 is a SNP at position chr19: NC_000019.10:g.44908684 (GRCh38)	Different
Sequencing Platform	Helix Laboratory Platform, sequencing and pipeline analysis (authorized under DEN190035)	Tecan Evo Illumina iScan Illumina Infinium BeadChip genotyping chip customized for the PGS. The chip is designed to detect specific single nucleotide polymorphisms (SNPs) as well as other genetic variants; all markers refer to specific positions in the National Center for Biotechnology Information (NCBI)	Different

		reference human genome.	
Software	Helix Bioinformatics Pipeline (authorized under DEN190035)	Genome Studio Coregen	Different
Technology	Next Generation Sequencing	Microarray genotyping	Different

The Helix Genetic Health Risk App for late-onset Alzheimer's disease is intended for over-the-counter, direct-to-consumer use without prescription or physician order. When a customer purchases the Helix Genetic Health Risk App for late-onset Alzheimer's disease, the customer must first opt-in to receive the late-onset Alzheimer's disease risk report. As instructed in predicate device authorization DEN160026, similar healthcare provider limitations applicable to results for late-onset Alzheimer's disease are included in the package insert:

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

Thus, the Helix Genetic Health Risk App for late-onset Alzheimer's Disease is substantially equivalent to the predicate 23andMe Personal Genome Service (PGS) Genetic Health Risk Test for Alzheimer's disease authorized under DEN160026.

5.5 Device Description

The Helix Genetic Health Risk App is an over-the-counter (direct-to-consumer), DNA testing service that provides information and tools for consumers to learn about and explore their DNA.

The Helix Genetic Health Risk App is a currently marketed, non-invasive genetic information service that combines qualitative genotyping data indicate for late-onset Alzheimer's disease for reporting of the e2/e2, e2/e3, e2/e4, e3/e3, e3/e4 and e4/e4 genotypes in the *APOE* gene with descriptive information derived from peer reviewed, published genetic research studies. It is a home use, over-the-counter (direct-to-consumer) DNA testing service intended to provide information and tools for consumers to learn about and explore their DNA. Customer saliva is self-collected using the FDA cleared Oragene®·Dx OGD-610 saliva collection kit manufactured by DNA Genotek, Inc. (k192920), which consists of a sealable collection tube containing a stabilizing

buffer solution. Once the sample is collected, it is shipped to the CLIA-certified and College of American Pathologists (CAP) -accredited Helix laboratory for testing.

DNA is isolated from the saliva and tested using Helix's proprietary whole exome sequencing assay authorized under DEN190035 in the Helix laboratory. The genomic DNA is processed and sequenced using next generation sequencing (NGS) reagents and instrumentation manufactured by Illumina. The sequencing data is analyzed using Helix's proprietary software, where the genetic variants of interest are determined. All samples must pass Helix's stringent quality control metrics prior to analysis. Samples that do not pass quality thresholds will undergo re-sequencing and/or sample re-collection.

The genetic variant results are used to generate personalized reports that provide information about the detected genotype for the customer. These reports tell the user which genotype has/have been detected in their sample and provide information on the risk of disease associated with the genotype. If no genotype was determined, 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 genetic variant. The reports are designed to help users understand the meaning of their results and any appropriate actions that may be taken based on their results.

5.6 Technological Characteristics

Test Type: Qualitative genetic test for single nucleotide polymorphism detection in the *APOE* gene.
Sample Type: Genomic DNA obtained from a human saliva sample.
Target of detection: Single-nucleotide polymorphism.
DNA extraction: Automated method.
Gene: APOE
Alleles: e2, e3 and e4 alleles in the *APOE* gene
SNPs: rs429358 and rs7412.
Testing principle: DNA is isolated from saliva and tested on the Helix Laboratory Platform. The genomic DNA is processed and sequenced using next generation sequencing (NGS) reagents and instrumentation. The sequencing data is analyzed using Helix's proprietary software, where the genetic variants of interest are determined.
Instrument: Illumina HiSeq system.
Assay results: The raw sequencing data is analyzed, and the genotypes are determined and integrated into a report.

5.7 Performance Testing Summary

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 2.5%. The device performance was evaluated in the analytical and clinical studies as follows.

All results presented below met the pre-defined acceptance criteria outlined in the Special Controls of 21 CFR 866.5950. Information regarding samples that failed quality control (FQC) was also evaluated and presented in each study below.

5.7.1 Method Comparison (Accuracy)

For evaluation of accuracy, three studies were conducted: the first study was conducted with human saliva samples with known genotypes and a second study was conducted with human cell line samples with known genotypes to determine the rates of correct APOE genotype calls. A third study was conducted with human saliva and/or human cell line samples with known variants in genes other than the APOE gene to determine the agreement of the genotype calls.

a) Accuracy study with human saliva samples:
Accuracy of the HRA for late-onset Alzheimer's disease was evaluated by testing human saliva samples with known APOE genotypes. Presence of the two variants in the APOE gene was analyzed on the HLP and the genotyping results were compared to the known genotypes confirmed by Sanger sequencing (comparator). The accuracy for detecting the two variants in the APOE gene on the HLP (genotype call) using DNA isolated from human saliva samples (n=99) was 100% with a lower bound of 96.3% using a 95% CI for all samples tested. The test results are shown in the table below.

APOE Genotype	N	No. of Correct Genotype Calls	No. of Incorrect Genotype Calls	No. of FQC	Percent of FQC (%)	Percent Correct Genotype Calls (%)
e2/e2	12	12	0	0	0	100
e2/e3	17	17	0	0	0	100
e2/e4	10	10	0	0	0	100
e3/e3	20	20	0	0	0	100
e3/e4	20	20	0	0	0	100
e4/e4	20	20	0	0	0	100
All	99	99	0	0	0	100

b) Accuracy study with human cell line samples:
Accuracy for detecting two variants, rs7412 and rs429358, in the APOE gene on the HLP was evaluated by using six cell lines with known APOE genotypes

(e2/e3, e2/e4, e3/e3, e3/e4, e3/e4, and e4/e4). The accuracy of detecting the two variants in the APOE gene was 100% for all samples tested.

Cell Line	N	APOE Genotype	No. of replicates	No. of Correct Genotype Calls	No. of Incorrect Genotype Calls	No. of FQC	Percent of FQC (%)	Percent Correct Genotype Calls (%)
NA24385	1	e2/e3	1	1	0	0	0	100
NA24149	1	e2/e4	1	1	0	0	0	100
NA12878	1	e3/e3	1	1	0	0	0	100
NA12877	1	e3/e4	1	1	0	0	0	100
NA24143	1	e3/e4	1	1	0	0	0	100
NA24631	1	e4/e4	1	1	0	0	0	100

c) Accuracy study with 3,295 human saliva and cell line samples with known variants in genes other than APOE:

In addition to the two variants in the APOE gene, accuracy of the HLP for detecting variants in the genes associated with other clinical conditions included in DEN160026 was evaluated on the HLP using specimens carrying unique genetic variants linked to the specific clinical conditions as listed in the table below:

Clinical condition	Gene	SNP
Hereditary Thrombophilia	FS	rs6025
Hereditary Thrombophilia	F2	rs1799963
Alpha-1 Antitrypsin Deficiency	SERPINA1	rs28929474
Alpha-1 Antitrypsin Deficiency	SERPINA1	rs17580
Late-Onset Alzheimer’s Disease	APOE	rs429358
Parkinson’s Disease	LRRK2	rs34637584

Parkinson's Disease; Gaucher Disease Type 1	GBA	rs76763715
Gaucher Disease Type 1	GBA	rs387906315
Gaucher Disease Type 1	GBA	rs80356769
Factor XI Deficiency	FXI	rs121965064
Factor XI Deficiency	FXI	rs121965063
Factor XI Deficiency	FXI	rs373297713
Celiac Disease	HLA-DQA1	rs2187668
Glucose-6-Phosphate-Dehydrogenase Deficiency	G6PD	rs1050828
Hereditary Hemochromatosis	HFE	rs1800562
Hereditary Hemochromatosis	HFE	rs1799945
Early-Onset Primary Dystonia	DYT1	rs724159981

The overall number of true positive, false positives, true negative and false negatives were analyzed for seventeen (17) variants in eleven (11) genes. A total of 4,282 true positive and 51,731 true negative calls were reported. There were no false positive and no false negative results reported for the known variants tested. One no call was reported each for rs76763715 and rs429358.

5.7.2 Precision/Reproducibility

Reproducibility of the APOE genotype calls made by the HRA for late-onset Alzheimer's disease was assessed by testing 24 samples that include 6 human B-lymphocyte cell lines (6 cell lines hereafter) and 18 unique saliva-derived DNA samples) in two independent studies (Study 1 and Study 2). The calls for the APOE genotypes in the well-characterized cell line samples were compared to known APOE genotypes.

Study 1 tested 24 samples (6 cell lines and 18 unique saliva-derived DNA samples) with up to 72 replicates (3 replicates / sample / library prep plate x 3 plates x 2 enrichments x 4 independent runs of cBot and HiSeq instruments) for the APOE genotype calls. The test results are summarized below:

Cell Line	N	APOE Genotype	No. of replicates	No. of Correct Genotype Calls	No. of Incorrect Genotype Calls	No. of FQC	Percent of FQC (%)	Percent Correct Genotype Calls (%)

Study 1: Cell lines								
NA24385	1	e2/e3	72	72	0	0	0	100
NA24149	1	e2/e4	72	72	0	0	0	100
NA12878	1	e3/e3	72	72	0	0	0	100
NA12877	1	e3/e4	72	72	0	0	0	100
NA24143	1	e3/e4	72	72	0	0	0	100
NA24631	1	e4/e4	72	72	0	0	0	100
Study 1: Clinical Samples								
	4	e2/e3	288	276	0	12	4.2	100
	2	e2/e4	144	141	0	3	2.1	100
	7	e3/e3	504	484	0	20	4.0	100
	2	e3/e4	144	136	0	8	5.6	100
	2	e4/e4	144	141	0	3	2.1	100
	1	Unknown	72	N/A	N/A	72	100	N/A

Study 2 tested 24 samples (6 cell lines and 18 unique saliva-derived DNA samples) with up to 54 replicates (3 replicates / sample / library prep plate x 3 plates x 2 enrichments x 3 reagent lots) for the APOE genotype calls. The test results are summarized below:

Cell Line	N	APOE Genotype	No. of replicates	No. of Correct Genotype Calls	No. of Incorrect Genotype Calls	No. of FQC	Percent of FQC (%)	Percent Correct Genotype Calls (%)

Study 2: Cell lines								
NA24385	1	e2/e3	54	54	0	0	0	100
NA24149	1	e2/e4	54	54	0	0	0	100
NA12878	1	e3/e3	54	54	0	0	0	100
NA12877	1	e3/e4	54	54	0	0	0	100
NA24143	1	e3/e4	54	54	0	0	0	100
NA24631	1	e4/e4	54	48	0	6	11.1	100
Stud 2: Clinical Samples								
	2	e2/e3	108	108	0	0	0	100
	7	e3/e3	378	377	0	1	0.3	100
	7	e3/e4	378	376	0	2	0.5	100
	2	e4/e4	108	108	0	0	0	100

The calls for concordance on the APOE genotypes were analyzed in the clinical samples. Genotyping results produced 100% replicates that were called correctly for all APOE genotypes.

5.7.3 DNA Input

This study evaluated the impact of different levels of DNA input on the performance of the HRA for late-onset Alzheimer's disease. The study yielded concordant test results for all 19 saliva samples with known APOE genotypes when tested at sample DNA concentrations between 3.5 to 10 ng/µL, an input corresponding to a range of 35 to 100 ng of DNA in the library preparation.

APOE Genotype	No. of replicates	No. of Correct Genotype Calls	No. of Incorrect Genotype Calls	No. of FQC	Percent of FQC (%)	Percent Correct Genotype Calls (%)
e2/e3	12	12	0	0	0	100

e3/e3	84	79	0	5	6	100
e3/e4	18	18	0	0	0	100

5.7.4 Interfering Substances

Four studies were performed to determine the effects of substances found in saliva that may interfere with the performance of the HRA for late-onset Alzheimer's disease. Per study protocol, for sequenced samples to be included in the data analyses (e.g., evaluable samples), the sample(s) must pass pre-defined QC thresholds.

a. In study 1, four endogenous proteins commonly found in saliva, including alpha-amylase (395 U/mL), hemoglobin (20 mg/mL), immunoglobulin A (IgA) (0.43 mg/mL), and albumin (2.67mg/mL) were each added to saliva samples. These proteins did not affect test performance for saliva samples (n=29-30 evaluable samples across four endogenous proteins). The test results are shown below.

APOE Genotype	No. of replicates	No. of Correct Genotype Calls	No. of Incorrect Genotype Calls	No. of FQC	Percent of FQC (%)	Percent Correct Genotype (%)
e2/e3	18	18	0	0	0	100
e2/e4	4	4	0	0	0	100
e3/e3	76	75	0	1	1.3	100
e3/e4	18	18	0	0	0	100
e4/e4	4	4	0	0	0	100

b. In study 2, saliva samples were tested before and after (either immediately or 30 minutes after) exposure to one of four exogenous substances: eating food, drinking liquids, using mouthwash, or chewing gum. This study showed that exogenous substances did not interfere with test performance for saliva samples (n=12-15 evaluable samples across testing time for four exogenous substances). The test results are shown below.

APOE Genotype	No. of replicates	No. of Correct Genotype Calls	No. of Incorrect Genotype Calls	No. of FQC	Percent of FQC (%)	Percent Correct Genotype Calls (%)
e2/e4	12	12	0	0	0	100
e3/e3	90	83	0	7	7.8	100
e3/e4	24	21	0	3	12.5	100
Unknown	6	N/A	N/A	6	100	N/A

c. In study 3, saliva samples were tested at 60 minutes before smoking, immediately after smoking, and 30 minutes after smoking and showed that smoking did not interfere with test performance (n=15 evaluable samples across three smoking conditions). The test results are shown below.

APOE Genotype	No. of replicates	No. of Correct Genotype Calls	No. of Incorrect Genotype Calls	No. of FQC	Percent of FQC (%)	Percent Correct Genotype Calls (%)
e3/e3	18	18	0	0	0	100
e3/e4	12	12	0	0	0	100

d. In study 4, bacterial DNA from a commercial source (American Type Culture Collection) was added in various amounts into six cell line DNA samples (NA24385, NA24149, NA12878, NA12877, NA24143, and NA24631) to evaluate the effects of bacterial contamination in the test performance. This bacterial sample (ATCC MSA-1003) is comprised of twenty (20) fully sequenced cultures that encompass a variety of characteristics including bacterial species found in mouse and oral cavity. The six cell lines were tested across five levels of bacterial content (0%, 10%, 20%, 30%, and 50%). This study showed that microbial DNA did not interfere with test performance (n=11-18 evaluable samples across five levels of bacterial content). In addition, study 4 tested various amounts of microbial and yeast DNA added to the saliva samples from 3 volunteers (0%, 10% Candida albicans, and 30% of ATCC MSA-1003). This study showed that yeast DNA did not interfere with test performance in clinical samples. The test results are shown below.

APOE Genotype	No. of replicates	No. of Correct Genotype Calls	No. of Incorrect Genotype Calls	No. of FQC	Percent of FQC (%)	Percent Correct Genotype Calls (%)
Cell lines						
e2/e3	15	15	0	0	0	100
e2/e4	15	13	0	2	13.3	100
e3/e3	15	11	0	4	26.7	100
e3/e4	30	28	0	2	6.7	100
e4/e4	15	14	0	1	6.7	100
Clinical samples						
e3/e3	12	12	0	0	0	100
e3/e4	6	6	0	0	0	100

5.7.5 Potentially Interfering Mutations

Not conducted

5.7.6 Matrix Comparison

Human saliva is the only suitable sample matrix, therefore Matrix Comparison studies are not applicable.

5.7.7 Shelf Life

The Helix Genetic Health Risk App requires the use of the same FDA-cleared saliva collection device that was reviewed and cleared in submission K192920. Shelf life data, summarized below, was previously reviewed and authorized in the clearance of the predicate device DEN160026.

5.7.8 Clinical Performance

Three common versions of the *APOE* gene are: e2, e3, and e4 alleles. Genetic studies on late-onset Alzheimer's disease have associated this disease with the *APOE* gene and more specifically the *APOE* e2 and *APOE* e4 allele, as the main link for late-onset Alzheimer's disease in all ethnicities. The *APOE* e2 allele is associated with a decreased risk to develop late-onset Alzheimer's disease after the age of 65 years, whereas the *APOE* e4 allele is associated with an increased risk to develop late-onset Alzheimer's disease after the age of 65 years. This test looks at the 2 SNPs, rs429358 and rs7412, that define the *APOE* e2, e3, and e4 versions of the gene.

The different combinations of the *APOE* gene's versions (e2, e3 and e4) were grouped based on their association with developing late-onset Alzheimer's disease:

- Individuals with the *APOE* e3/e3 genotype are considered to have an average risk of developing late-onset Alzheimer's disease based on this genetic result.
- Individuals with the *APOE* e2/e2 or e2/e3 genotype are considered to have a decreased risk of developing late-onset Alzheimer's disease compared to individuals with the *APOE* e3/e3 genotype.
- Individuals with the *APOE* e2/e4, e3/e4, or e4/e4 genotypes are considered to have an increased risk of developing late-onset Alzheimer's disease compared to individuals with the *APOE* e3/e3 genotype.
- Individuals who have none of these *APOE* combinations will not receive information on their relative risk to develop late-onset Alzheimer's disease due to the lack of studies in the scientific literature.

The variants covered by this test are found in people of all ethnicities. The percentage of the population carrying each combination will vary from study to study based on the enrollment criteria to the genetic study. A summary of the frequency of each combination in different ethnicities gathered from multiple references is represented in the table below:

Table 5.3a. Frequency of *APOE e2, e3 and e4* combinations in different ethnicities

		e2/e2	e2/e3	e3/e3	e2/e4	e3/e4	e4/e4	Ref
		Decreased risk		**Average risk**	**Increased risk**			
European descent	AD	0.2%	4.8%	36.4%	2.6%	41.1%	14.8%	Farrer et al., 1997
European descent	controls	0.8%	12.7%	60.9%	2.6%	21.3%	1.8%	
African descent	AD	0.6%	7.4%	37.7%	3.7%	37.7%	13.0%	Murrell et al., 2006
African descent	controls	1.9%	15.1%	51.3%	4.1%	24.2%	3.5%	
South Asian descent	AD	0.2%	6.2%	44.8%	6.2%	37.2%	5.3%	Agarwal et al., 2014
South Asian descent	controls	2.0%	11.8%	72.0%	1.5%	11.7%	0.9%	
East Asian descent	AD	0.9%	7.9%	51.0%	3.3%	29.3%	7.6%	Liu et al., 2014
East Asian descent	controls	0.8%	11.8%	73.1%	1.7%	12.4%	0.3%	

AD = Alzheimer's disease.

Using the same references, it is possible to calculate likelihood ratios (LR), which represent an estimate of how the test result affects the chances of a condition.

Table 5.3b: Alzheimer's disease likelihood ratios (LR) for *APOE e2*, *e3* and *e4* combinations in different ethnicities. The table was adapted from table on p.35 of DEN160026 decision summary.

Ethnicity	Test result	Genotype	LR	95% CI for LR	References	Study summary
European descent	Decreased risk	e2/e2	0.3	0.1-0.5	Farrer et al., 1997	A meta-analysis of 5,930 patients who met criteria for probable or definite Alzheimer's disease and 8,607 controls. Among study participants, there were 5,107 Alzheimer's disease patients from European descent, and 6,262 controls from European descent.
		e2/e3	0.4	0.3-0.4		
	Average risk	e3/e3	0.6	0.57-0.62		
	Increased risk	e2/e4	1	0.8-1.3		
		e3/e4	1.9	1.8-2.1		
		e4/e4	8.2	6.8-10.0		
African descent	Decreased risk	e2/e2	0.3	0.04-2.7	Murrell et al., 2006	This study included 162 individuals from African American descent with Alzheimer's disease and 318 controls from African American descent
		e2/e3	0.5	0.3-0.9		
	Average risk	e3/e3	0.7	0.6-0.9		
	Increased risk	e2/e4	0.9	0.4-2.3		
		e3/e4	1.6	1.2-2.1		
		e4/e4	3.8	1.9-7.6		

South Asian descent	Decreased risk	e2/e2	0.1	0.02-0.9	Agarwal et al., 2014	A meta-analysis of 417 individuals from South Asian descent with Alzheimer's disease and 651 controls from South Asian descent.
		e2/e3	0.5	0.3-0.8		
	Average risk	e3/e3	0.6	0.6-0.7		
	Increased risk	e2/e4	4.1	2.0-8.3		
		e3/e4	3.2	2.5-4.1		
		e4/e4	5.7	2.3-14.0		
East Asian descent	Average risk	e2/e2*	1.1	0.5-2.3	Liu et al., 2014	A meta-analysis of 1,576 individuals from East Asian descent with Alzheimer's disease and 1,741 controls from East Asian descent. (*limited number of e2/e2 samples used for analysis)
		e2/e3	0.7	0.5-0.8		
		e3/e3	0.7	0.6-0.7		
	Increased risk	e2/e4	1.9	1.2-3.0		
		e3/e4	2.5	2.2-2.9		
		e4/e4	25.6	10.5-62.6		

5.7.9 Labeling Comprehension

All predefined demographic quotas and enrollment targets were met. Primary comprehension assessment addressed the following five core concepts: purpose of the test, limitations, relevant ethnicities, meaning of results, and appropriate follow-up. The average comprehension rate per comprehension category ranged from 85.2% to 100%, and the overall comprehension rate for all core concepts across each of the four study arms was greater than 90%. The representative Helix Genetic Health Risk report and supporting information provided in the pre-purchase page were effective in communicating relevant concepts to users unfamiliar with genetic testing sufficient for the safe use of the Helix Genetic Health Risk App for late-onset Alzheimer's disease.

5.8. Discussion

The Helix Genetic Health Risk App (HRA) for late-onset Alzheimer's disease has a similar intended use as the predicate and therefore presents no new issues of safety or effectiveness when compared to the previously authorized predicate device (DEN160026).

5.9. Conclusion

The Helix Genetic Health Risk App (HRA) for late-onset Alzheimer's disease is substantially equivalent to the predicate device DEN160026 (23andMe PGS Genetic Health Risk Report for Late-onset Alzheimer's Disease). As presented, the Helix Genetic Health Risk App for late-onset Alzheimer's disease is a safe and effective consumer product that can safely and effectively assist and encourage users to discuss the report with their healthcare provider.