

Overview

Test Description

Helix Tier One Population Screen is a screening test that analyzes 11 genes related to hereditary breast and ovarian cancer (HBOC) syndrome, Lynch syndrome, and familial hypercholesterolemia. This test only reports clinically significant pathogenic and likely pathogenic variants but does not report variants of uncertain significance (VUS). In addition, analysis of the PMS2 gene excludes exons 11-15, which overlap with a known pseudogene (PMS2CL).

Genetics Information

This test utilizes next-generation sequencing to detect single nucleotide variants, insertions and deletions up to 20 bp, and copy number variants in genes associated with hereditary breast and ovarian cancer syndrome, Lynch syndrome, and familial hypercholesterolemia. This test only reports clinically significant pathogenic and likely pathogenic variants but does not report variants of uncertain significance (VUS).

Indications For Testing

This is a screening test and therefore is not recommended for individuals with a personal and/or family history suggestive of one of the associated conditions; in such instances, a diagnostic test is appropriate and should be discussed with a healthcare provider.

Tier 1 genomic applications are defined by the Centers for Disease Control and Prevention as those with significant potential for positive impact on public health based on available evidence-based guidelines and recommendations.

Early detection and intervention for each condition could significantly reduce morbidity and mortality. This screening test focuses on these 11 genes 1) because they are underdiagnosed 2) because of the public health burden of the diseases associated with them and 3) because there are clear steps that can be followed to improve health and prevent disease.

Clinical Descriptions

Hereditary breast and ovarian cancer (HBOC) is primarily associated with adult-onset predisposition to these cancer types. Lynch syndrome causes adult-onset colorectal cancer in addition to ovarian, uterine, stomach, small bowel, kidney, and pancreatic. Familial hypercholesterolemia is primarily an adult-onset condition associated with very high levels of LDL cholesterol, which increases the risk of coronary artery disease and heart attack. Identification of a pathogenic variant may facilitate interventions for prevention and risk-reduction. It may also help identify at-risk family members, who can pursue genetic testing and preventive or early detection measures.

The genes on this panel are associated with conditions that have autosomal dominant and/or autosomal recessive inheritance. Note that some of these genes may also be associated with other unrelated conditions. This means that when undergoing this test, there is a possibility of incidentally detecting carrier status for, or predisposition to, one of these conditions.

Test Details

Genes Tested

APOB, BRCA1, BRCA2, EPCAM, LDLR, LDLRAP1, PCSK9, PMS2, MLH1, MSH2, MSH6

Methods & Limitations

Extracted DNA is enriched for targeted regions and then sequenced using the Helix Exome+ (R) assay on an Illumina DNA sequencing system. Data is then aligned to a modified version of GRCh38 and all genes are analyzed using the MANE transcript and MANE Plus Clinical transcript, when available. Small variant calling is completed using a customized version of Sentieon's DNaseq software, augmented by a proprietary small variant caller for difficult variants. Copy number variants (CNVs) are then called using a proprietary bioinformatics pipeline based on depth analysis with a comparison to similarly sequenced samples. Analysis of the *PMS2* gene is limited to exons 1-10. Both the *MSH2* Boland inversion (exons 1-7) and the *BRCA2* Alu insertion are detected by identifying discordant read-pairs spanning the breakpoints. The interpretation and reporting of variants in *APOB*, *PCSK9*, and *LDLR* is specific to familial hypercholesterolemia; variants associated with hypobetalipoproteinemia are not included. Interpretation is based upon guidelines published by the American College of Medical Genetics and Genomics (ACMG), the Association for Molecular Pathology (AMP) or their modification by ClinGen Variant Curation Expert Panels when available and/or review of previous clinical assertions available in the ClinVar database. Interpretation is limited to the transcripts indicated on the report and +/- 10 bp into intronic regions, except as noted below. Helix variant classifications include pathogenic, likely pathogenic, variant of uncertain significance (VUS), likely benign, and benign. Only variants classified as pathogenic and likely pathogenic are included in the report. All reported variants are confirmed through secondary manual inspection of DNA sequence data or orthogonal testing. Risk estimations and management guidelines included in this report are based on analysis of primary literature and recommendations of applicable professional societies, and should be regarded as approximations.

Based on validation studies, this assay delivers > 99% sensitivity and specificity for single nucleotide variants and insertions and deletions (indels) up to 20 bp. Larger indels and complex variants are also reported but sensitivity may be reduced. Based on validation studies, this assay delivers > 99% sensitivity to multi-exon CNVs and > 90% sensitivity to single-exon CNVs. This test may not detect variants in challenging regions (such as short tandem repeats, homopolymer runs, and segment duplications), sub-exonic CNVs, chromosomal aneuploidy, or variants in the presence of mosaicism. Phasing will be attempted and reported, when possible. Structural rearrangements such as inversions, translocations, complex rearrangements, and gene conversions are not tested in this assay unless explicitly indicated. Additionally, deep intronic, promoter, and enhancer regions may not be covered. It is important to note that this is a screening test and cannot detect all disease-causing variants. A negative result does not guarantee the absence of a rare, undetectable variant in the genes analyzed; consider using a diagnostic test if there is significant personal and/or family history of one of the conditions analyzed by this test. Any potential incidental findings outside of these genes and

conditions will not be identified, nor reported. The results of a genetic test may be influenced by various factors, including bone marrow transplantation, blood transfusions, or in rare cases, hematolymphoid neoplasms.

Gene Specific Notes:

APOB: analysis is limited to c.10580G>A and c.10579C>T; *BRCA1*: sequencing analysis extends to CDS +/-20 bp; *BRCA2*: analysis includes detection of c.156_157insAlu and sequencing analysis extends to CDS +/-20 bp. *EPCAM*: analysis is limited to CNV of exons 8-9; *LDLR*: analysis includes CNV of the promoter; *MLH1*: analysis includes CNV of the promoter; *MSH2*: analysis includes detection of the Boland inversion (inversion of exons 1-7) and detection of c.942+3A>T, *PMS2*: analysis is limited to exons 1-10.

Disclaimer

This test was developed and validated by Helix, Inc. This test has not been cleared or approved by the United States Food and Drug Administration (FDA). The Helix laboratory is accredited by the College of American Pathologists (CAP) and certified under the Clinical Laboratory Improvement Amendments (CLIA #: 05D2117342) to perform high-complexity clinical tests. This test is used for clinical purposes. It should not be regarded as investigational use only or for research use only

Interpretation

All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations. Variants are classified based on known, predicted, or possible pathogenicity; however, this test only reports pathogenic and likely pathogenic variants along with interpretive comments detailing the evidence applied towards classification. Variants of uncertain significance are not reported.

Reclassification

Helix reviews variant classifications annually when they arise in routine processes and upon request from providers. The timing of re-review depends on clinical risk. Providers can request a variant re-review by contacting Helix Customer Support. If a classification by Helix is updated, Helix identifies affected past patients and issues revised reports. Updated results are communicated to providers prior to results being uploaded to the EHR, and patients are notified through the EHR patient portal.

Variant Evaluation

Variant classification is performed using the guidelines set forth by the American College of Medical Genetics and Genomics and the Association for Molecular Pathology, with modifications as suggested by domain specific Expert Panels of the Clinical Genome Resource (ClinGen) when available. Variant pathogenicity is categorized as benign, likely benign, variant of uncertain significance (VUS), likely pathogenic, or pathogenic.

Laboratory Details			
Turnaround Time - Standard	Typically 6 to 21 days	Turnaround Time - Requery (SOQO[®])	Typically ≤ 5 days
Available in NY State	Yes	Procedure Code	55208-3 (LOINC)
Test Classification	This test was developed, and its performance characteristics determined, by Helix, Inc. in a manner consistent with CLIA requirements. This test has not been cleared or approved by the US Food and Drug Administration.		
Regulatory Information	<ul style="list-style-type: none"> ● CLIA Complexity: High ● Test Classification: Non-Waived/ Laboratory Developed Test 		
CLIA Category	Chemistry / Routine Chemistry		
Performing Laboratory Information	<ul style="list-style-type: none"> ● CLIA Laboratory Number: 05D2117342 ● Laboratory Hours of Operation: Monday-Saturday (7AM-10:30PM PST) ● Address: 10170 Sorrento Valley Road, Suite 100, San Diego, CA 92121 ● Helix Customer Service: (844) 211-2070 ● Email: support@helix.com 		

- (*BRCA1, BRCA2*) Hereditary breast and ovarian cancer syndrome
- (*MLH1, MSH2, MSH6, PMS2, EPCAM*) Lynch syndrome
- (*APOB, LDLR, LDLRAP1, PCSK9*) Familial hypercholesterolemia

In addition, one or more of the genes on this panel are associated with other conditions for which a predisposition to, or carrier status of, may be identified:

- (*BRCA1, BRCA2*) Autosomal recessive Fanconi anemia
- (*EPCAM, MLH1, MSH2, MSH6, PMS2*) Autosomal recessive constitutional mismatch repair deficiency syndrome

The following applies to the Helix Tier One Population Screen. Testing is performed to evaluate for the presence of variants in coding regions and extending to +/- 10 base pairs of adjacent intronic sequences on either side of the coding exons of the genes analyzed. In addition, the analysis will cover select non-coding variants, as listed below. Next-generation sequencing is performed to test for the presence of small variants and copy number variants in the genes analyzed. Confirmation of select reportable variants may be performed by alternate methodologies based on internal laboratory criteria.

This list is current from August 2025 to the present. This document is intended to highlight additional evaluations for variants of high clinical interest as well as technical limitations. For questions regarding genes, reference transcripts, or specific regions covered, contact Helix Customer Service at (844) 211-2070.

Genomic Build: GRCh38

Gene	Transcript	Additional Evaluations	Technical Limitations
<i>APOB</i>	NM_000384.3	–	Results limited to c.10580G>A and c.10579C>T
<i>BRCA1</i>	NM_007294.4	Sequencing analysis extends to CDS +/-20 bp	–
<i>BRCA2</i>	NM_000059.4	Includes c.156_157insAlu and Sequencing analysis extends to CDS +/-20 bp	–
<i>EPCAM</i>	NM_002354.3	–	Results limited to CNV and limited to exons 8 and 9
<i>LDLR</i>	NM_000527.5	Includes CNV detection in the promoter	–
<i>LDLRAP1</i>	NM_015627.3	–	–
<i>MLH1</i>	NM_000249.4	Includes CNV detection in the promoter	–
<i>MSH2</i>	NM_000251.3	Includes detection of the exon 1-7 rearrangement known as the Boland Inversion and of c.942+3A>T	–
<i>MSH6</i>	NM_000179.3	–	–
<i>PCSK9</i>	NM_174936.4	–	–
<i>PMS2</i>	NM_000535.7	–	Analysis for exons 11 to 15 will not be performed