Helix Tier One Population Screen

Item	Description
Test Name	Helix Tier One Population Screen
Test Type	Screening
Catalog Number	PRCD1
Procedure Code	55208-3 (LOINC)
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).
Genes Tested	*APOB, BRCA1, BRCA2, EPCAM, LDLR, LDLRAP1, PCSK9, PMS2, MLH1, MSH2, MSH6*
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.

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Conditions	Hereditary breast and ovarian cancer syndrome (BRCA1 and BRCA2) Lynch syndrome (MLH1, MSH2, MSH6, PMS2 and EPCAM) Familial hypercholesterolemia (APOB, LDLR, LDLRAP1 and PCSK9) 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 incidentally be identified: Autosomal recessive Fanconi anemia (BRCA1, BRCA2) Autosomal recessive constitutional mismatch repair deficiency syndrome (EPCAM, MLH1, MSH2, MSH6, PMS2).
Interpretation	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 or for research.
Reclassification Of Variants	Helix does not systematically review their variant database looking for classification changes. Helix will review the classification of previously reported variants upon request of the ordering physician/provider. Ordering physicians/providers may contact Helix Customer Support or their Dedicated Advisor and request a review of the variant classification to be performed. At the discretion of the laboratory director, the frequency of reclassification requests may be limited to once per year, no earlier than 12 months after initial variant interpretation has been performed.
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.
Turnaround Time	1 to 6 weeks
Available In NY State	Yes
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.
Performing Laboratory Information	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
Regulatory Information	CLIA Complexity: High Test Classification: Non-Waived/ Laboratory Developed Test
CLIA Category	Chemistry / Routine Chemistry

Methods & Limitations for Helix Tier One Population Screen

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. 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) and the Association for Molecular Pathology (AMP) or their modification by ClinGen Variant Curation Expert Panels when available. 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, 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*: 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; *PMS2*: analysis is limited to exons 1-10.

Disclaimer:
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Targeted Genes & Methodology for Helix Tier One Population Screen

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 November 2024 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
Catalog Number: PRCD1

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