Helix Hereditary Breast and Gynecologic Cancers Panel

Item	Description
Test Name	Helix Hereditary Breast and Gynecologic Cancers Panel
Test Type	Hereditary Cancer
Catalog Number	BRGY1
Procedure Code	97655-5 (LOINC)
Test Description	This panel evaluates 21 genes that have an established, primary association with hereditary breast and/or gynecologic cancers (ovarian and uterine).
Genes Tested	*ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, DICER1, EPCAM, MLH1, MSH2, MSH6, NF1, PALB2, PMS2, PTEN, RAD51C, RAD51D, SMARCA4, STK11, TP53*
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 forms of breast and gynecological cancer.
Indications For Testing	A personal and/or family history suggestive of a hereditary form of breast and gynecologic cancers (ovarian and uterine).
Clinical Descriptions	Hereditary predisposition to breast and gynecologic cancer refers to the increased likelihood of developing adult-onset uterine and ovarian cancer in addition to breast cancer. The most well-known genes are *BRCA1* and *BRCA2* and those associated with Lynch syndrome, although there are others, including the genes on this panel. Individuals with a pathogenic variant may also have an increased risk of other cancers such as colorectal and prostate, depending on the affected gene. The genes on this panel were specifically selected for their established association with breast and gynecologic cancers. Identification of a pathogenic variant may facilitate increased cancer screening and preventive surgery for early-detection and prevention. Identification of a pathogenic variant also helps identify at-risk family members, who can pursue genetic testing and preventive 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.
Conditions	Hereditary breast and ovarian cancer syndrome (BRCA1 and BRCA2) Hereditary diffuse gastric cancer (CDH1) PALB2-related cancer susceptibility (PALB2) PTEN hamartoma tumor syndrome (PTEN) Peutz-Jeghers syndrome (STK11) Li-Fraumeni syndrome (TP53) ATM-related cancer susceptibility (ATM) BARD1-related cancer susceptibility (BARD1) BRIP1-related cancer susceptibility (BRIP1) CHEK2-related cancer susceptibility (CHEK2) Neurofibromatosis (NF1)

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Item	Description
Conditions (conditions)	RAD51C-related cancer susceptibility (RAD51C) RAD51D-related cancer susceptibility (RAD51D) Lynch syndrome (MLH1, MSH2, MSH6, PMS2 and EPCAM) Constitutional mismatch repair deficiency (MLH1, MSH2, MSH6, PMS2 and EPCAM) DICER1 pleuropulmonary blastoma tumor predisposition syndrome (DICER1) SMARCA4 rhabdoid tumor predisposition syndrome, type 2 (SMARCA4) 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 dominant Coffin-Siris syndrome (SMARCA4) Autosomal recessive ataxia-telangiectasia (ATM) Autosomal recessive Fanconi anemia (BRCA1, BRCA2, PALB2, BRIP1 and RAD51C)
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 and reported with interpretive comments detailing their potential or known significance.
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	7 to 24 days
Available In NY State	No
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 Hereditary Breast and Gynecologic Cancel Panel

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. Reportable variants in *PMS2* exons 12-15 are confirmed by PacBio long reads. The *MSH2* Boland inversion (exons 1-7) is detected by identifying discordant read-pairs spanning the presumed breakpoint. 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, +/- 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. Variants classified as pathogenic, likely pathogenic, or VUS are included in the report. All reported variants (except for VUSs with limited evidence of pathogenicity) are confirmed through secondary manual inspection of DNA sequence data or orthogonal testing. Benign and likely benign variants are not reported but are available upon request. 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 assay cannot detect all variants known to increase disease risk, and that a negative result does not guarantee that the tested individual does not carry a rare, undetectable variant in genes analyzed. 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:
APC: analysis includes CNV of promoters 1A and 1B and sequencing of promoter 1B; *BMPR1A*: analysis includes CNV of promoter; *BRCA1*: sequencing analysis extends to CDS +/-20 bp; *BRCA2*: sequencing analysis extends to CDS +/-20 bp. *CDKN2A*: analysis includes sequencing of the p16 (p16INK4a) and p14 (p14ARF) transcripts; *EGFR*: analysis is limited to the NM_005228(EGFR):c.2369C>T (p.Thr790Met) variant; *EPCAM*: analysis is limited to CNV of exons 8-9; *GREM1*: analysis is limited to CNV of the promoter; *HOXB13*: analysis is limited to the NM_006361.6(HOXB13):c.251G>A (p.Gly84Glu) variant; *MITF*: analysis is limited to the NM_000248.4(MITF):c.952G>A (p.Glu318Lys) variant; *MLH1*: analysis includes CNV of the promoter; *MSH2*: analysis includes detection of the Boland inversion (inversion of exons 1-7) and detection of NM_000251.3(MSH2):c.942+3A>T; *MSH3*: analysis excludes sequencing of exon 1 repeat region (chr5:80654878-80654946); *POLD1*: CNV analysis is not performed and sequencing is limited to the 3'-5' exonuclease domain (chr19:50402681-50407039); *POLE*: CNV analysis is not performed and sequencing is limited to the 3'-5' exonuclease domain (chr12:132676653-132672296); *PTCH1*: sensitivity of exon 1 analysis may be reduced; *PTEN*: analysis includes CNV of the promoter; *SDHA*: analysis excludes CNV; *STK11*: sensitivity of exon 3 analysis may be reduced; *TP53*: analysis includes CNV of the promoter; *TSC1*: sensitivity of exon 21 analysis may be reduced; *VHL*: analysis excludes coverage of the cryptic E1' exon (chr3:10142758-10143009)

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 or for research.

Targeted Genes & Methodology for Helix Hereditary Breast and Gynecologic Cancers Panel

The following applies to the Helix Hereditary Breast and Gynecologic Cancers Panel. 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 January 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: BRGY1

Gene	Transcript	Additional Evaluations	Technical Limitations
ATM	NM_000051.4	–	–
BARD1	NM_000465.4	–	–
BRCA1	NM_007294.4	Sequencing analysis extends to CDS +/-20 bp	–
BRCA2	NM_000059.4	Sequencing analysis extends to CDS +/-20 bp	–
BRIP1	NM_032043.3	–	–
CDH1	NM_004360.5	–	–
CHEK2	NM_007194.4	–	–
DICER1	NM_177438.3	–	–
EPCAM	NM_002354.3	–	Results limited to CNV and limited to exons 8 and 9
MLH1	NM_000249.4	Includes CNV detection in the promoter	–
MSH2	NM_000251.3	Includes detection of the exon 1-7 rearrangement known as the Boland Inversion and of c.942+3A>T	–
MSH6	NM_000179.3	–	–
NF1	NM_001042492.3	–	–
PALB2	NM_024675.4	–	–
PMS2	NM_000535.7	–	–
PTEN	NM_000314.8	Includes CNV detection in the promoter	–
RAD51C	NM_058216.3	–	–
RAD51D	NM_002878.4	–	–
SMARCA4	NM_003072.5, NM_001387283.1	–	–

Gene	Transcript	Additional Evaluations	Technical Limitations
STK11	NM_000455.5	–	Sensitivity in STK11 exon 3 may be reduced
TP53	NM_000546.6	Includes CNV detection in the promoter	–