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PATIENT REPORT

Patient Age/Sex: Female

Specimen Collected: 21-Jul-22 13:24

HR Hereditary GI Cancer by NGS, DelDup	**Received: 21-Jul-22 13:24**		**Report/Verified: 03-Aug-22 14:07**
Procedure	**Result**	**Units**	**Reference Interval**
GIHR Interp	See Note [i1]		

HR Hereditary GI Cancer by NGS, DelDup	**Received: 21-Jul-22 13:24**		**Report/Verified: 03-Aug-22 14:08**
Procedure	**Result**	**Units**	**Reference Interval**
GIHR Specimen	See Note		

Test Information

i1: GIHR Interp

BACKGROUND INFORMATION: Hereditary Gastrointestinal Cancer High-Risk Panel, Sequencing and Deletion/Duplication

CHARACTERISTICS: Pathogenic germline variants in multiple genes have been implicated in hereditary gastrointestinal (GI) cancer. Hereditary cancer predisposition is often characterized by early age of onset (typically before age 50) and multiple, multifocal, and/or similar cancers in a single individual or in closely related family member(s). Lynch syndrome (LS), the most common hereditary predisposition to colorectal cancer, is caused by pathogenic germline variants in the MLH1, MSH2, MSH6, PMS2, and EPCAM genes. Pathogenic germline variants in the APC gene are causative for familial adenomatous polyposis (FAP) and other APC-associated polyposis conditions. Biallelic pathogenic germline variants in MUTYH are causative for MUTYH-associated polyposis (MAP).

EPIDEMIOLOGY: Greater than 2-4 percent of colorectal cancers are associated with a hereditary cause. Prevalence of LS in the general population has been estimated at 1 in 279 individuals. The prevalence of FAP has been estimated to be between 1 in 6,850 to 1 in 31,250 live births. The prevalence of MAP is estimated to be between 1 in 20,000 to 1 in 60,000 individuals.

CAUSE: Pathogenic germline variants in genes associated with a high lifetime risk of colorectal cancer.

INHERITANCE: LS and FAP/APC-associated conditions are autosomal dominant. MAP is autosomal recessive.

GENES TESTED: APC*; EPCAM**; MLH1; MSH2; MSH6; MUTYH; PMS2

*One or more exons are not covered by sequencing and/or deletion/duplication analysis for the indicated gene; see limitations section below.
**Deletion/duplication analysis of EPCAM (NM_002354) exon 9 only; sequencing is not available for this gene.

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METHODOLOGY: Probe hybridization-based capture of all coding exons and exon-intron junctions of the targeted genes, followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage and to confirm reported variants that do not meet acceptable quality metrics. A proprietary bioinformatic algorithm was used to detect large (single exon-level or larger) deletions or duplications in the indicated genes. Large deletions/duplications confirmed using an orthogonal exon-level microarray. Human genome build 19 (Hg 19) was used for data analysis. Testing of selected exons (and exon/intron boundaries) of PMS2 and MSH2 was performed by bidirectional Sanger sequencing. Deletion/duplication testing of PMS2 was performed by multiplex ligation-dependent probe amplification (MLPA).

ANALYTICAL SENSITIVITY/SPECIFICITY: The analytical sensitivity is approximately 99 percent for single nucleotide variants (SNVs) and greater than 93 percent for insertions/duplications/deletions (indels) from 1-10 base pairs in size. Indels greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced. Deletions of 2 exons or larger are detected with sensitivity greater than 97 percent; single exon deletions are detected with 62 percent sensitivity. Duplications of 3 exons or larger are detected at greater than 83 percent sensitivity. Specificity is greater than 99.9 percent for all variant classes. The analytical sensitivity for MLPA is greater than 99 percent.

LIMITATIONS: A negative result does not exclude a heritable form of cancer. This test only detects variants within the coding regions and intron-exon boundaries of the targeted genes. Deletions/duplications/insertions of any size may not be detected by massively parallel sequencing. Regulatory region variants and deep intronic variants will not be identified. Precise breakpoints for large deletions or duplications are not determined in this assay and single exon deletions/duplications may not be detected based on the breakpoints of the rearrangement. The actual breakpoints for the deletion or duplication may extend beyond or be within the exon(s) reported. This test is not intended to detect duplications of two or fewer exons in size, though these may be identified. Single exon deletions are reported but called at a lower sensitivity. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations caused by the presence of pseudogenes, repetitive, or homologous regions. This test is not intended to detect low-level mosaic or somatic variants, gene conversion events, complex inversions, translocations, mitochondrial DNA (mtDNA) variants, or repeat expansions. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Noncoding transcripts were not analyzed.

The following regions are not sequenced due to technical limitations of the assay:
APC (NM_001354896) exon 12

Test Information

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APC (NM_001354898, NM_001354904) exon 2
APC (NM_001354900) exon 11

Deletions/duplications will not be called for the following exons:
APC (NM_001354896) 12; APC (NM_001354898, NM_001354904) 2; APC (NM_001354900) 11

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the U.S. Food and Drug Administration. This test was performed in a CLIA-certified laboratory and is intended for clinical purposes.

Counseling and informed consent are recommended for genetic testing. Consent forms are available online.