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Client: Example Client ABC123
123 Test Drive
Salt Lake City, UT 84108
UNITED STATES

Physician: Doctor, Example

Patient: Patient, Example

DOB	Unknown
Gender:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Hereditary Gastric Cancer Panel, Sequencing and Deletion/Duplication

ARUP test code 3005963

Spcm GASCAN	Whole Blood
GASCAN Interp	Positive

H=High, L=Low, *=Abnormal, C=Critical

RESULT
One pathogenic variant was detected in the CDH1 gene.

PATHOGENIC VARIANT
Gene: CDH1 (NM_004360.4)
Nucleic Acid Change: c.1565+2dupT; Heterozygous
Inheritance: Autosomal dominant

INTERPRETATION
One pathogenic variant, c.1565+2dupT, was detected in the CDH1 gene by massively parallel sequencing. Pathogenic germline variants in CDH1 are associated with autosomal dominant increased risk of lobular breast cancer (MIM: 114480) and hereditary diffuse gastric cancer (MIM: 137215). This individual's offspring have a 50 percent chance of inheriting the pathogenic variant.

Please refer to the background information included in this report for a list of the genes analyzed, methodology, and limitations of this test.

Evidence for variant classification:
The CDH1 c.1565+2dupT variant (rs1555516200) is reported in the literature in at least five probands and multiple family members who were affected with diffuse gastric cancer (Benusiglio, 2013; Kluijt, 2012; Nadauld, 2014; Rogers, 2008; van der Post, 2015). This variant is also reported in ClinVar (Variation ID: 406624). It is absent from the Genome Aggregation Database, indicating it is not a common polymorphism. This is an intronic variant in a highly conserved nucleotide, and computational analyses (Alamut v.2.11) predict that this variant abolishes the canonical splice donor site. Based on the available information, this variant is considered to be pathogenic.

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of medical screening and management. At-risk family members should be offered testing for the identified pathogenic CDH1 variant (Familial Targeted Sequencing, ARUP test code 3005867).

COMMENTS
Likely benign and benign variants are not reported.
Variants in the following region(s) may not be detected by NGS with sufficient confidence in this sample due to technical limitations:
NONE

REFERENCES
Benusiglio PR, et al. CDH1 germline mutations and the hereditary diffuse gastric and lobular breast cancer syndrome: a multicentre study. J Med Genet. 2013;50(7):486-9. PMID: 23709761.

Kluijt I, et al. CDH1-related hereditary diffuse gastric cancer syndrome: clinical variations and implications for counseling. Int J Cancer. 2012;131(2):367-76. PMID: 22020549.

Nadauld, LD et al. Metastatic tumor evolution and organoid modeling implicate TGFBR2 as a cancer driver in diffuse gastric cancer. Genome Biol. 2014;15(8):428. PMID: 25315765.

Rogers WM, et al. Risk-reducing total gastrectomy for germline mutations in E-cadherin (CDH1): pathologic findings with clinical implications. Am J Surg Pathol. 2008;32(6):799-809. PMID: 18391748.

van der Post RS, et al. Accuracy of hereditary diffuse gastric cancer testing criteria and outcomes in patients with a germline mutation in CDH1. Gastroenterology. 2015;149(4):897-906.e19. PMID: 26072394.

BACKGROUND INFORMATION: Hereditary Gastric Cancer Panel,

Sequencing and Deletion/Duplication

CHARACTERISTICS: Pathogenic germline variants in multiple genes have been implicated in hereditary gastric cancer. Hereditary gastric cancer syndromes are often characterized by early age of disease onset (typically before 50 years of age) and multiple, multifocal, and/or similar cancers in a single individual or in a closely related family member(s).

EPIDEMIOLOGY: Approximately 5-10 percent of gastric cancers are associated with a hereditary cause.

CAUSE: Pathogenic germline variants in genes associated with hereditary gastric cancer

INHERITANCE: Autosomal dominant. Additionally, some genes are also associated with autosomal recessive childhood cancer predisposition or other syndromes.

GENES TESTED: APC*; BMPR1A*; CDH1*; CTNNA1*; EPCAM**; MLH1; MSH2; MSH6; PMS2; SMAD4; STK11; TP53

*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.

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 gastric cancer or other 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 2 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
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; BMPR1A (NM_004329) 12-13; CDH1 (NM_001317185) 10; CTNNA1 (NM_001290307) 19; CTNNA1 (NM_001324002, NM_001324004) 13; CTNNA1 (NM_001324003) 15; CTNNA1 (NM_001324005) 16

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.

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Spcm GASCAN	23-052-100917	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
GASCAN Interp	23-052-100917	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

H=High, L=Low, *=Abnormal, C=Critical