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

Physician: Doctor, Example

Patient: Patient, Example

DOB	5/4/1965
Gender:	Male
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Hereditary Cancer Panel, Sequencing and Deletion/Duplication

ARUP test code 2012032

Cancer Panel, Hereditary, Spcm	Whole Blood
Cancer Panel, Hereditary, Interp	Positive

RESULT
One pathogenic variant was detected in the ATM gene.

PATHOGENIC VARIANT
Gene: ATM (NM_000051.4)
Nucleic Acid Change: c.5763-1050A>G; Heterozygous
Inheritance: Autosomal dominant/recessive

INTERPRETATION
One pathogenic variant, c.5763-1050A>G, was detected in the ATM gene by massively parallel sequencing. Pathogenic germline variants in ATM are associated with autosomal dominant increased risk for breast cancer (MIM: 114480), ovarian cancer, pancreatic cancer, and prostate cancer. National Comprehensive Cancer Network (NCCN) guidelines are available for cancer risk management in heterozygous individuals. Other genetic/environmental factors may influence an individual's risk of developing cancer.

In addition, autosomal recessive inheritance of two ATM pathogenic variants is associated with ataxia-telangiectasia (MIM: 208900); thus, this individual is at least a carrier of this disorder.

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 ATM c.5763-1050A>G variant (rs774925473, ClinVar variation ID: 3021) also known as 5762ins137, the 4-1-8 insertion, p.Pro1922fs, is reported in the literature in numerous compound heterozygous and homozygous individuals affected with ataxia telangiectasia (A-T; selected references: Jackson 2016, McConville 1996, Schon 2019). This variant has been found in 15% of A-T families in the U.K. population, suggesting a founder variant (Stewart 2001). This variant has also been reported in breast and pancreatic cancer (Cremin 2020, Tavtigian 2009). This variant creates a cryptic donor site that results in an insertion of 137 nucleotides between exon 37 and 38 leading to a frameshift (McConville 1996). Additionally, in vitro functional analyses demonstrate a variable level of protein expression in compound heterozygous patients, suggestive of a leaky splice site (Steward 2001). This variant is found in the non-Finnish European population with an allele frequency of 0.008% (5/62558

alleles) in the Genome Aggregation Database (v2.1.1). Based on 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 ATM variant (Familial Targeted Sequencing, ARUP test code 3005867). Counseling for potential reproductive risk associated with ataxia telangiectasia is recommended (NCCN Guidelines).

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
Cremin C et al. Burden of hereditary cancer susceptibility in unselected patients with pancreatic ductal adenocarcinoma referred for germline screening. Cancer Med. 2020 Jun;9(11):4004-4013. PMID: 32255556.
Jackson TJ et al. Longitudinal analysis of the neurological features of ataxia-telangiectasia. Dev Med Child Neurol. 2016 Jul;58(7):690-7. PMID: 26896183.
McConville CM et al. Mutations associated with variant phenotypes in ataxia-telangiectasia. Am J Hum Genet. 1996 Aug;59(2):320-30. PMID: 8755918.
National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (3.2024): https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf
Schon K et al. Genotype, extrapyramidal features, and severity of variant ataxia-telangiectasia. Ann Neurol. 2019 Feb;85(2):170-180. PMID: 30549301.
Stewart GS et al. Residual ataxia telangiectasia mutated protein function in cells from ataxia telangiectasia patients, with 5762ins137 and 7271T-->G mutations, showing a less severe phenotype. J Biol Chem. 2001 Aug 10;276(32):30133-41. PMID: 11382771.
Tavtigian SV et al. Rare, evolutionarily unlikely missense substitutions in ATM confer increased risk of breast cancer. Am J Hum Genet. 2009 Oct;85(4):427-46. PMID: 19781682.

This result has been reviewed and approved by [redacted]
BACKGROUND INFORMATION: Hereditary Cancer Panel, Sequencing and Deletion/Duplication

CHARACTERISTICS: Pathogenic variants in multiple genes have been implicated in hereditary cancer, often characterized by early age of cancer onset (typically before age 50) and multiple, multifocal, and/or related cancers in an individual or in closely related family member(s). Pathogenic variants in the genes analyzed by this panel cause variable phenotypes and cancer risks.

EPIDEMIOLOGY: Approximately 5-10 percent of cancer is associated with a hereditary cause.

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

INHERITANCE: Varies depending on the gene and specific variant.

GENES TESTED: ALK; APC*; ATM; AXIN2; BAP1; BARD1; BMPR1A*; BRCA1*; BRCA2; BRIP1; CDC73; CDH1*; CDK4; CDKN1B; CDKN2A*; CHEK2*; CTNNA1*; DICER1; EGFR; EPCAM**; FH; FLCN*; HOXB13; HRAS; KIT; LZTR1; MAX; MC1R; MEN1*; MET; MITF*; MLH1; MLH3*; MSH2; MSH3; MSH6; MUTYH; NBN; NF1; NF2; NTHL1; PALB2; PDGFRA*; PMS2; POLD1; POLE; POT1; PRKAR1A; PTCH1; PTEN*; RAD51C; RAD51D; RB1*; RECQL*; RET; SDHA*; SDHAF2; SDHB; SDHC*; SDHD*; SMAD4; SMARCA4;

SMARCB1; SMARCE1*; STK11; SUFU; TERT; TMEM127; TP53; TSC1; TSC2; VHL*; WT1

* - 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 (including selected PTEN promoter variants), 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, PTEN and MSH2 was performed by bidirectional Sanger sequencing. Deletion/duplication testing of PMS2 was performed by multiplex ligation-dependent probe amplification (MLPA).

ANALYTICAL SENSITIVITY: 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 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 may have reduced sequencing sensitivity due to technical limitations of the assay:
RB1 (NM_000321) exon 22
SUFU (NM_016169, NM_001178133) exon 1

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

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

APC (NM_001354900) exon 11
BRCA1 (NM_007300) exon 13
CHEK2 (NM_001005735) exon 3
CHEK2 (NM_001349956) exon 4
FLCN (NM_001353229) exon 7
MEN1 (NM_001370251) exon 8
MITF (NM_001354607) exon 2
PDGFRA (NM_001347827) exon 17
PDGFRA (NM_001347828) exon 2
PDGFRA (NM_001347830) exon 1
RECQL (NM_002907) exons 14,15
RECQL (NM_032941) exons 15,16
SDHA (NM_004168) exon 14
SDHA (NM_001294332) exon 13
SDHA (NM_001330758) exon 12
SDHC (NM_001035511) partial exon 5 (Chr1:161332225-161332330)
SDHC (NM_001278172) partial exon 4 (Chr1:161332225-161332330)
SDHD (NM_001276506) exon 4
VHL (NM_001354723) exon 2

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; BRCA1 (NM_007294, NM_007299, NM_007300) 2; BRCA1 (NM_007298) 1; CDH1 (NM_001317185) 10; CDKN2A (NM_000077, NM_001195132, NM_001363763, NM_058195) 2; CHEK2 (NM_007194) 11-15; CHEK2 (NM_001005735) 3,12-16; CHEK2 (NM_001257387) 12-16; CHEK2 (NM_001349956) 4,10-14; CHEK2 (NM_145862) 10-14; CTNNA1 (NM_001290307) 19; CTNNA1 (NM_001324002, NM_001324004) 13; CTNNA1 (NM_001324003) 15; CTNNA1 (NM_001324005) 16; FLCN (NM_001353229) 7; MEN1 (NM_001370251) 8; MITF (NM_001354607) 2; MLH3 (NM_001040108) 7-8; MLH3 (NM_014381) 7; PDGFRA (NM_001347827) 17; PDGFRA (NM_001347828) 2; PDGFRA (NM_001347830) 1; PTEN (NM_000314, NM_001304718) 9; PTEN (NM_001304717) 1,10; RB1 (NM_000321) 22; RECQL (NM_002907) 14-15; RECQL (NM_032941) 15-16; SDHA (NM_004168) 1,10-15; SDHA (NM_001294332) 1,9-14; SDHA (NM_001330758) 1,10-13; SDHD (NM_001276506) 4; SMARCE1 (NM_003079) 7,10-11; VHL (NM_001354723) 2

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
Cancer Panel, Hereditary, Spcm	24-095-402449	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Cancer Panel, Hereditary, Interp	24-095-402449	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