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

Physician: Doctor, Example

Patient: Patient, Example

DOB	4/23/2023
Gender:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Hereditary Central Nervous System Cancer Panel, Sequencing and Deletion/Duplication

ARUP test code 3001633

CNSCAN Specimen: Whole Blood

CNSCAN Interp: Positive

RESULT
One pathogenic variant was detected in the SMARCB1 gene. One variant of uncertain significance was detected in the NF1 gene.

PATHOGENIC VARIANT
Gene: SMARCB1 (NM_003073.5)
Nucleic Acid Change: Deletion of exons 4-5; Heterozygous
Inheritance: Autosomal dominant

VARIANT OF UNCERTAIN SIGNIFICANCE
Gene: NF1 (NM_001042492.3)
Nucleic Acid Change: c.2803A>C; Heterozygous
Amino Acid Alteration: p.Asn935His
Inheritance: Autosomal dominant

INTERPRETATION
According to information provided to ARUP, this patient had a posterior fossa mass suspicious for an atypical teratoid rhabdoid tumor (ATRT). One pathogenic variant, deletion of exons 4-5, was detected in the SMARCB1 gene by massively parallel sequencing-based deletion/duplication analysis and confirmed by exon-level microarray. Pathogenic germline variants in SMARCB1 are associated with autosomal dominant Coffin-Siris syndrome 3 (MIM: 614608), as well as susceptibility to rhabdoid tumors (MIM: 609322) and schwannomatosis (MIM: 162091). This result is consistent with a diagnosis of a SMARCB1-related disorder.

In addition, one variant of uncertain clinical significance, c.2803A>C; p.Asn935His, was detected in the NF1 gene by massively parallel sequencing. Pathogenic germline variants in NF1 are associated with neurofibromatosis type 1 (NF1; MIM: 162200). However, it is uncertain whether this variant is disease-associated or benign.

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 SMARCB1 deletion of exons 4-5 is reported in the literature in an individual affected with rhabdoid tumors (Eaton 2011). This variant is also reported in ClinVar (Variation ID: 1455673), but is absent from the Genome Aggregation Database, indicating it is not a common polymorphism. This variant deletes two exons, and is predicted to result in an out-of-frame

deletion and thus result in a truncated protein or mRNA subject to nonsense-mediated decay. Based on available information, this variant is considered to be pathogenic.

The NF1 c.2803A>C; p.Asn935His variant (rs786201823), to our knowledge, is not reported in the medical literature but is reported in ClinVar (Variation ID: 184962). This variant is also absent from the Genome Aggregation Database, indicating it is not a common polymorphism. Computational analyses are uncertain whether this variant is neutral or deleterious (REVEL: 0.374). Due to limited information, the clinical significance of this variant is uncertain at this time.

RECOMMENDATIONS
Genetic consultation is indicated for the family, including a discussion of medical screening and management. At-risk family members should be offered testing for the identified pathogenic variant. Surveillance of the literature for new information concerning the uncertain variant is recommended.

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
Eaton KW et al. Spectrum of SMARCB1/INI1 mutations in familial and sporadic rhabdoid tumors. Pediatr Blood Cancer. 2011 Jan;56(1):7-15. PMID: 21108436.

This result has been reviewed and approved by

BACKGROUND INFORMATION: Hereditary Central Nervous System Cancer Panel, Sequencing and Deletion/Duplication
CHARACTERISTICS: Pathogenic germline variants in multiple genes have been implicated in hereditary central nervous system (CNS) tumors and cancer. Hereditary cancer predisposition is often characterized by early age of onset (typically before age 50), the presence of any number of CNS tumors in a single individual or closely related family member(s), and variable systemic manifestations.

EPIDEMIOLOGY: Approximately 5% of central nervous system tumors are associated with a hereditary cause.
CAUSE: Pathogenic germline variants in genes associated with a high lifetime risk of central nervous system tumors or cancer.

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

GENES TESTED: ALK; APC*; DICER1; EPCAM**; HRAS; LZTR1; MEN1*; MLH1; MSH2; MSH6; NF1; NF2; PMS2; POT1; PRKAR1A; PTCH1; PTEN*; RB1*; SMARCA4; SMARCB1; SMARCE1*; SUFU; TP53; TSC1; TSC2; VHL*
*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/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 central nervous system 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 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
APC (NM_001354900) exon 11
MEN1 (NM_001370251) exon 8
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; MEN1 (NM_001370251) 8; PTEN (NM_000314, NM_001304718) 9; PTEN (NM_001304717) 1,10; RB1 (NM_000321) 22; 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
CNSCAN Specimen	23-132-401741	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
CNSCAN Interp	23-132-401741	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