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

Physician: Doctor, Example

Patient: Patient, Example

DOB	6/25/2006
Gender:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Hereditary Myeloid Neoplasms Panel, Sequencing

ARUP test code 3001842

Hereditary Myeloid Neoplasms Specimen: Whole Blood

Hereditary Myeloid Neoplasms Interp: Positive

RESULT
One likely pathogenic variant was detected in the PTPN11 gene. Please note, this test cannot differentiate between germline (inherited) and somatic (acquired) variants when performed on whole blood from individuals with active hematological disease or abnormal complete blood count. Further testing may be warranted, if clinically indicated; see the recommendations section below.

LIKELY PATHOGENIC VARIANT
Gene: PTPN11 (NM_002834.5)
Nucleic Acid Change: c.1282G>A; Heterozygous
Amino Acid Alteration: p.Val428Met
Inheritance: Autosomal dominant

INTERPRETATION
One likely pathogenic variant, c.1282G>A; p.Val428Met, was detected in the PTPN11 gene by massively parallel sequencing in this whole blood sample. Pathogenic germline PTPN11 variants are inherited in an autosomal dominant manner, and are associated with LEOPARD syndrome 1 (MIM: 151100), Noonan syndrome 1 (MIM: 163950), and metachondromatosis (MIM: 156250, OMIM(R)). Therefore, this result is consistent with a diagnosis of a PTPN11-related disorder if this variant is determined to be germline in origin. If determined to be germline, this individual's offspring have a 50 percent chance of inheriting the likely 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 PTPN11 c.1282G>A; p.Val428Met variant (rs397507536) is reported in the literature as de novo variant in an individual with PTPN11-associated syndrome affected with multiple abnormalities of the vertebrae and dysmorphic features (Imafidon 2021). This variant is also reported in ClinVar (Variation ID: 40545). This variant is only observed on two alleles in the Genome Aggregation Database (v2.1.1), indicating it is not a common polymorphism. Computational analyses predict that this variant is deleterious (REVEL: 0.906). Based on available information, this variant is considered to be likely pathogenic.

RECOMMENDATIONS

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

Genetic and hematologic consultations are indicated, including a discussion of medical screening and management. Close correlation with clinical findings, family history, and laboratory data including hematologic parameters is recommended. If this variant was detected in a whole blood sample from an individual with active hematological disease or abnormal complete blood count, confirmation of this variant in an unaffected sample type (i.e. cultured skin fibroblasts) is necessary to establish germline variant status. Additionally, interpretation of this test result may be impacted if the patient had an allogeneic stem cell transplant. If the intended testing was to assess for somatic variants that may have prognostic or therapeutic significance in an individual with certain active hematologic malignancies, consider ordering the Myeloid Malignancies Mutation Panel by Next Generation Sequencing (test code 2011117) on a blood or bone marrow sample. If determined to be germline, at-risk family members, especially potential stem cell donors, may consider testing for the identified likely pathogenic PTPN11 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
Imafidon ME et al. Strategies in Rapid Genetic Diagnostics of Critically Ill Children: Experiences From a Dutch University Hospital. Front Pediatr. 2021 PMID: 34136434

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Hereditary Myeloid Neoplasms Panel, Sequencing
CHARACTERISTICS: While the majority of myeloid neoplasms and malignancies occur sporadically due to somatic mutations, a portion are due to inherited or hereditary predispositions. Individuals with an inherited predisposition to myeloid neoplasms may present at a younger age, with more than one first-degree relative with myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML), solid tumors, and/or a family history of physical findings associated with a known cancer predisposition syndrome.

EPIDEMIOLOGY: MDS occurs in approximately 4.5 per 100,000 individuals in the general population. MDS is rare in children and young adults; approximately 50 percent of childhood MDS is associated with an inherited cause. AML occurs in approximately 3.7 per 100,000 individuals in the general population.

CAUSE: Pathogenic germline variants in genes associated with predisposition to MDS and/or AML.

INHERITANCE: Variable, dependent on gene/condition.

GENES TESTED: ANKRD26*, ATM, BLM, CBL, CEBPA, DDX41, ELANE, ETV6, GATA1, GATA2, KRAS, NBN, PTPN11*, RUNX1, SAMD9, SAMD9L, SRP72*, TERC, TERT, TP53
*One or more exons are not covered by sequencing for the indicated gene; see limitations section below.

METHODOLOGY: Targeted capture of all coding exons and exon-intron junctions of the targeted genes (unless otherwise specified in the limitations section below), 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. Human genome build 19 (Hg 19) was used for data analysis.

ANALYTICAL SENSITIVITY/SPECIFICITY: The analytical sensitivity of this test is approximately 99 percent for single nucleotide variants (SNVs) and greater than 93 percent for insertions/duplications/deletions from 1-10 base pairs in size. Variants greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced.

LIMITATIONS: A negative result does not exclude a diagnosis of cancer nor a heritable form of myeloid neoplasm. This test only detects variants within the coding regions and intron-exon boundaries of the targeted genes. Regulatory region variants and deep intronic variants will not be identified unless specifically targeted for their clinical relevance. Deletions/duplications/insertions of any size may not be detected by massive parallel sequencing. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions. This assay is not intended to detect somatic variants associated with hematologic malignancy, though such variants may be detected incidentally. Though this test is designed to identify germline variants associated with predisposition to myeloid neoplasms, it cannot definitively determine the germline or somatic origin of detected variants when the patient has a hematologic malignancy and the assay is performed on blood or other tissue that may be contaminated by malignant cells. In addition, this assay may not detect low-level mosaic or somatic variants associated with disease, including variants that have undergone somatic reversion. 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:
ANKRD26 (NM_014915) exon 19
PTPN11 (NM_002834) exon 9
SRP72 (NM_006947) exon 19

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the US 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.

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VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Hereditary Myeloid Neoplasms Specimen	24-296-401763	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Hereditary Myeloid Neoplasms Interp	24-296-401763	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