Client: ARUP Example Report Only
500 Chipeta Way
Salt Lake City, UT 84108
UNITED STATES

Physician: TEST,

Patient: BMF NGS, POS EXAMPLE

DOB	
Sex:	Male
Patient Identifiers:	44257
Visit Number (FIN):	44584
Collection Date:	11/15/2022 08:55

Hereditary Bone Marrow Failure Panel, Sequencing and Deletion/Duplication

ARUP test code 3001615

BMF Specimen	Whole Blood
BMF Interp	Positive

RESULT
One pathogenic variant was detected in the SAMD9 gene.

PATHOGENIC VARIANT
Gene: SAMD9 (NM_017654.4)
Nucleic Acid Change: c.2471G>A; Heterozygous
Amino Acid Alteration: p.Arg824Gln
Inheritance: Autosomal Dominant

INTERPRETATION
One copy of a pathogenic variant, c.2471G>A; p.Arg824Gln, was detected in the SAMD9 gene by massively parallel sequencing in this whole blood specimen. Pathogenic variants in SAMD9 are inherited in an autosomal dominant manner and are associated with monosomy 7-related myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) (MIM: 619041) and MIRAGE syndrome (MIM: 617053). Therefore, this result is consistent with a diagnosis of MIRAGE syndrome. This individuals 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 SAMD9 c.2471G>A; p.Arg824Gln variant (rs1435946172), is reported in the literature in at least three individuals affected with MIRAGE syndrome (Formankova 2019, Jeffries 2018, Zheng 2021). In vitro functional analyses demonstrate restricted cell development, proliferation, and premature apoptosis (Formankova 2019, Jeffries 2018). This variant is also absent from the Genome Aggregation Database, indicating it is not a common polymorphism. The arginine at codon 824 is highly conserved, but computational analyses predict that this variant is neutral (REVEL: 0.035). Based on available information, this variant is considered to be pathogenic.

RECOMMENDATIONS
Genetic consultation is 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. At-risk family members should be offered targeted testing for the identified pathogenic SAMD9 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
Formankova R et al. Novel SAMD9 Mutation in a Patient with Immunodeficiency, Neutropenia, Impaired Anti-CMV Response, and Severe Gastrointestinal Involvement. Front Immunol. 2019 PMID: 31620126

Jeffries L et al. A novel SAMD9 mutation causing MIRAGE syndrome: An expansion and review of phenotype, dysmorphology, and natural history. Am J Med Genet A. 2018 Feb. PMID: 29266745

Zheng RF et al. [MIRAGE syndrome caused by variation of sterile alpha motif domain-containing protein 9 gene]. Zhonghua Er Ke Za Zhi. 2021 May 2. PMID: 33902229

BACKGROUND INFORMATION: Hereditary Bone Marrow Failure Panel Sequencing and Deletion/Duplication

CHARACTERISTICS: Bone marrow failure (BMF) encompasses a heterogeneous array of acquired and germline conditions characterized by qualitative or quantitative defects in one or more hematopoietic lineages resulting in cytopenias and hypocellular bone marrow. Hereditary BMF syndromes are caused by germline pathogenic variants that disrupt DNA repair, telomere maintenance, ribosome biogenesis, and structural protein pathways. These syndromes include Fanconi anemia (FA), telomere biology disorders (TBD) such as dyskeratosis congenita, Schwachman-Diamond syndrome (SDS), Diamond-Blackfan anemia (DBA), congenital amegakaryocytic thrombocytopenia (CAMT), severe congenital neutropenia (SCN), aplastic anemia, and others. In addition to BMF, these conditions may also be accompanied by syndromic physical findings and predisposition to hematologic and other malignancies. While most patients with hereditary BMF present in childhood, these conditions may manifest at any age. This multigene panel includes genes causative for hereditary BMF syndromes as well genes associated with hereditary predisposition to myeloid neoplasms, as there is often clinical overlap between these two entities.

CAUSE: Pathogenic germline variants in genes associated with bone marrow failure or predisposition to myeloid neoplasms.

INHERITANCE: May be autosomal dominant, autosomal recessive, or X-linked, depending on the gene.

GENES TESTED: ACD; ALAS2; ANKRD26; ATM; BLM; BRCA1* (NM_007294); BRCA2 (NM_000059); BRIP1; CBL; CEBPA**; CSF3R; CTC1; CXCR4*; DDX41; DKC1; DNAJC21*; ELANE; ERCC4; ERCC6L2*; ETV6; FANCA*; FANCB; FANCC; FANCD2*; FANCE; FANCF; FANCG; FANCI; FANCL*; G6PC3; GATA1; GATA2; GFI1; HAX1; HOXA11; IKZF1; KRAS; MBD4; MPL; MYH9; NBN; NHP2; NOP10**; NRAS; PALB2; PARN; PTPN11; RAD51C; RMRP**; RPL11; RPL15**; RPL26; RPL35A; RPL5; RPS10; RPS19; RPS24; RPS26; RPS7; RTEL1; RUNX1; SAMD9; SAMD9L; SLX4; SRP72; TERC***; TERT; TET2; TINF2; TP53; UBE2T; USB1; VPS45; WAS; WRAP53

*One or more exons are not covered by sequencing for the indicated gene; see limitations section below.
**Deletion/duplication detection is not available for this gene.
***Duplication detection 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 were confirmed using an orthogonal exon-level microarray. Human genome build 19 (Hg 19) was used for data analysis.

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.

LIMITATIONS: A negative result does not exclude a diagnosis of bone marrow failure. This test only detects variants within the coding regions and intron-exon boundaries of the targeted genes. Please note, the SBDS gene associated with Schwachman-Diamond syndrome is not included in this panel due to technical limitations caused by a pseudogene.
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, or repetitive, or homologous regions. This test is not intended to detect low-level mosaic variants, gene conversion events, complex inversions, translocations, mitochondrial DNA (mtDNA) mutations, or repeat expansions. This assay is also 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 BMF and 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 clonal or malignant cells. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Non-coding transcripts were not analyzed.

SNVs and indels will not be called in the following regions due to technical limitations of the assay:
CXCR4 (NM_001348056) exon(s) 2
CXCR4 (NM_001348059) exon(s) 2
DNAJC21 (NM_001348420) partial exon 9 (Chr5:34945827-34945845)
ERCC6L2 (NM_001375291) exon(s) 19
ERCC6L2 (NM_001375292) exon(s) 19
ERCC6L2 (NM_001375293) exon(s) 18
ERCC6L2 (NM_001375294) exon(s) 18
FANCA (NM_001018112) exon(s) 11

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

FANCA (NM_001351830) exon(s) 10
FANCD2 (NM_033084) exon(s) 14,17,21,22
FANCD2 (NM_001018115) exon(s) 14,17,21,22
FANCD2 (NM_001319984) exon(s) 14,17,21,22
FANCD2 (NM_001374253) exon(s) 14,17,20,21
FANCD2 (NM_001374254) exon(s) 14,17,21,22
FANCD2 (NM_001374255) exon(s) 10
FANCL (NM_001374615) exon(s) 8

Deletions/duplications in CEBPA, NOP10, RMRP, and RPL15 and duplications in TERC will not be evaluated.

Single exon deletions/duplications may not be called in the following exons:
ANKRD26 (NM_014915, NM_001256053): 19
BRCA1 (NM_007294): 2
CXCR4 (NM_001348056, NM_001348059): 2
ERCC6L2 (NM_001375291, NM_001375292):19; (NM_001375293, NM_001375294): 18
FANCA (NM_001018112): 11; (NM_001351830): 10
FANCD2 (NM_033084, NM_001018115, NM_001319984, NM_001374254): 12-14, 17, 22; (NM_001374253): 12-14, 17, 21; (NM_001374255): 10
FANCL (NM_001374615): 8
G6PC3 (NM_001319945): 5
IKZF1 (NM_001291846, NM_001291847): 4
PARN (NM_002582, NM_001134477): 24; (NM_001242992): 23
PTPN11 (NM_002834, NM_001330437, NM_001374625, NM_080601): 8
SRP72 (NM_006947): 17, 19; (NM_001267722): 15, 17

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
BMF Specimen	22-319-101733	11/15/2022 8:55:00 AM	11/15/2022 8:55:14 AM	11/15/2022 11:32:00 AM
BMF Interp	22-319-101733	11/15/2022 8:55:00 AM	11/15/2022 8:55:14 AM	11/15/2022 11:32:00 AM

END OF CHART

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