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

Physician: Doctor, Example

Patient: Patient, Example

DOB	1/7/1979
Gender:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Hereditary Bone Marrow Failure Panel, Sequencing and Deletion/Duplication

ARUP test code 3001615

BMF Specimen: Whole Blood

BMF Interp: Positive

RESULT
One copy of a likely pathogenic variant was detected in the TERT gene.

NOTE: It is uncertain whether this variant is of constitutional (germline) or somatic origin given that this test was performed on whole blood from an individual with possible hematologic malignancy; please see comments and recommendations below.

LIKELY PATHOGENIC VARIANT
Gene: TERT (NM_198253.3)
Nucleic Acid Change: c.521_522insACGGGCCGCC; Likely heterozygous
Amino Acid Alteration: p.Leu175ArgfsTer20
Inheritance: Autosomal Dominant, Autosomal Recessive

INTERPRETATION
One copy of a likely pathogenic variant, c.521_522insACGGGCCGCC; p.Leu175ArgfsTer20, was detected in the TERT gene by massively parallel sequencing in this whole blood specimen. Pathogenic germline TERT variants can be inherited in both autosomal dominant and autosomal recessive patterns and are associated with autosomal dominant/autosomal recessive dyskeratosis congenita (MIM: 613989) and autosomal dominant telomere-related pulmonary fibrosis and/or bone marrow failure (PFBMFT1) (MIM: 614742), as well as susceptibility to acute myelogenous leukemia (MIM: 601626) and melanoma (MIM: 615134). It is uncertain whether this is a constitutional or somatic variant given that this test was performed on whole blood from an individual with a possible hematologic malignancy. If this variant is confirmed to be germline in origin by sequencing of non-hematologic tissue, then, depending on the patient's clinical findings, this result would be consistent with a diagnosis of autosomal dominant dyskeratosis congenita or PFBMFT1; as well, this patient would at least be a carrier of autosomal recessive dyskeratosis congenita. However, our analysis cannot detect variants in deep intronic or regulatory regions; therefore, the presence of additional pathogenic variants in these regions has not been excluded. If confirmed to be germline, this individual s offspring would have a 50 percent chance of inheriting the likely pathogenic TERT variant.

No additional pathogenic variants or variants of uncertain significance were identified in the targeted genes by massively parallel sequencing or deletion/duplication analysis. Please refer to the background information included in this report for

a list of the genes analyzed and limitations of this test.

Evidence for variant classification:
The TERT c.521_522insACGGGCCGCC; p.Leu175ArgfsTer20 variant, to our knowledge, is not reported in the medical literature or gene specific databases. This variant is also absent from the Genome Aggregation Database (v2.1.1), indicating it is not a common polymorphism. This variant causes a frameshift by inserting 10 nucleotides, so it is predicted to result in a truncated protein or mRNA subject to nonsense-mediated decay. Based on available information, this variant is considered to be likely 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. The TERT variant was detected in a whole blood sample from an individual with possible hematological malignancy; therefore, confirmation of this variant in an unaffected sample type (i.e. cultured skin fibroblasts) would be necessary to establish germline variant status. If confirmed to be germline, at-risk family members should be offered testing for the identified likely pathogenic TERT 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:
CEBPA(NM_004364.4) exon 1

This result has been reviewed and approved by [redacted]

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
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	24-100-401423	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
BMF Interp	24-100-401423	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