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

Physician: Doctor, Example

Patient: Patient, Example

DOB	12/3/1989
Gender:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

von Willebrand Disease (VWF) Sequencing

ARUP test code 3004379

von Willebrand Disease Specimen	Whole Blood
von Willebrand Disease Interp	Positive

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

RESULT
One pathogenic variant was detected in the VWF gene.

PATHOGENIC VARIANT
Gene: VWF (NM_000552.5)
Nucleic Acid Change: c.1239dup; Heterozygous
Amino Acid Alteration: p.Leu414AlafsTer15
Inheritance: Autosomal dominant

INTERPRETATION
One pathogenic variant, c.1239dup; p.Leu414AlafsTer15, was detected in the VWF gene by massively parallel sequencing. This result is consistent with a diagnosis of von Willebrand disease (VWD) type 1 (MIM: 193400). VWD type 1 usually presents with mild mucocutaneous bleeding, epistaxis, bruising, and menorrhagia. VWD type 1 is usually inherited in an autosomal dominant pattern; therefore, this individual's offspring have a 50 percent chance of inheriting the pathogenic variant.

Please refer to the background information included in this report for the methodology and limitations of this test.

Evidence for variant classification:
The VWF c.1239dup; p.Leu414AlafsTer15 variant (rs770203987) is reported in the heterozygous state in individuals with VWD type 1 and in the compound heterozygous state in individuals with VWD type 3 (Veyradier 2016). This variant is also reported in ClinVar (Variation ID: 1065243) and is only observed on two alleles in the Genome Aggregation Database, indicating it is not a common polymorphism. This variant causes a frameshift by inserting a single nucleotide, 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 pathogenic.

RECOMMENDATIONS
Referral to a comprehensive bleeding disorders program is recommended. Genetic consultation is indicated, including a discussion of medical screening and management. At-risk family members should be offered testing for the identified pathogenic VWF variant (Familial Targeted Sequencing, ARUP test code 3005867).

COMMENTS
Unless otherwise specified, confirmation by Sanger sequencing was not performed for variants with acceptable quality metrics. Likely benign and benign variants, other than the benign c.4414G>C; p.Asp1472His variant, 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
Veyradier A et al. A Laboratory Phenotype/Genotype Correlation of 1167 French Patients From 670 Families With von Willebrand Disease: A New Epidemiologic Picture. Medicine (Baltimore). 2016 Mar;95(11):e3038. PMID: 26986123.

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: von Willebrand Disease (VWF) Sequencing

CHARACTERISTICS: Von Willebrand disease (VWD) is the most common inherited bleeding disorder and is classified into three major types: type 1, type 2, and type 3. VWF is a large multimeric glycoprotein that plays a critical role in hemostasis. VWF binds factor VIII to protect it from premature degradation, which causes platelet recruitment via the GP1BA receptor and facilitates clot formation. VWD type 1 results from a partial quantitative deficiency of normal plasma von Willebrand factor

(VWF), type 2 results from a qualitative defect of VWF, and type 3 results from severe quantitative VWF deficiency. Type 2 VWD is divided into 4 subtypes: type 2A is characterized by reduced or absent high-molecular weight VWF, type 2B results from gain of function in VWF that increases affinity for platelets or collagen, type 2M is caused by reduced VWF interactions with platelets or collagen, and type 2N results from reduced binding of VWF to FVIII. Individuals with VWD may experience excessive mucocutaneous bleeding including, bruising without trauma, bleeding from gums, prolonged recurrent nosebleeds, menorrhagia, gastrointestinal bleeding, and prolonged bleeding following childbirth, trauma, or surgery.

EPIDEMIOLOGY: Prevalence of symptomatic VWD is estimated at 1 in 10,000. Of individuals with VWD, approximately 30 percent have type 1, 60 percent have type 2, and less than 10 percent have type 3.

CAUSE: Pathogenic germline variants in the VWF gene.

INHERITANCE: Autosomal dominant: types 1, 2B, 2M, and most cases of type 2A. Autosomal recessive: types 2N, 3, and 20 percent of type 2A cases.

PENETRANCE: For autosomal dominant types 1, 2A, 2B, and 2M, penetrance is incomplete when VWF:Ag and VWF:RCo levels are between 30 and 50 IU/dL. Full penetrance is expected when VWF:Ag and VWF:RCo levels are less than 30 IU/dL. Heterozygous carriers of type 3 or type 2N are often asymptomatic; however, some individuals may show mild bleeding symptoms.

CLINICAL SENSITIVITY: 80 percent for VWD type 1 and 90 percent for VWD types 2 and 3.

GENE TESTED: VWF (NM_000552)
Exons 26 and 34 are not covered by sequencing, and deletion/duplication analysis is not available for this gene.

METHODOLOGY: Capture of all coding exons and exon-intron junctions of the VWF gene, followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage and confirm reported variants. 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 von Willebrand disease. This test only detects variants within the coding regions and intron-exon boundaries of the VWF gene. Regulatory region variants and deep intronic variants will not be identified. Deletions/duplications/insertions of any size may not be detected by massively 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 may not detect low-level mosaic or somatic variants associated with disease. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Noncoding transcripts were not analyzed. Variants interpreted as pathogenic, likely pathogenic, and of uncertain significance will be reported, as will the benign variant VWF c.4414G>C; p.Asp1472His; other likely benign or benign variants are not reported.

The following regions are not sequenced due to technical limitations of the assay: VWF (NM_000552) exon(s) 26, 34

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.

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
von Willebrand Disease Specimen	23-110-401117	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
von Willebrand Disease Interp	23-110-401117	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