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

Physician: Doctor, Example

Patient: Patient, Example

DOB	5/27/1948
Gender:	Male
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

UGT1A1 Sequencing

ARUP test code 3004386

UGT1A1 Specimen	Whole Blood
UGT1A1 Interp	Positive

RESULT
Two copies of a mildly pathogenic variant were detected in the UGT1A1 gene.

PATHOGENIC MILD VARIANT
Gene: UGT1A1 (NC_000002.11)
Nucleic Acid Change: g.234668881TA[8]; Homozygous
Commonly Known As: (TA)7 or *28 allele
Inheritance: Autosomal recessive

INTERPRETATION
Two copies of a mildly pathogenic variant, *28 (TA)7, were detected in the UGT1A1 gene by massively parallel sequencing. UGT1A1 full gene deletions are rare and the (TA)7 variant is common in the general population; thus, this individual most likely has two copies of the mildly pathogenic variant. This combination of variants is associated with Gilbert syndrome, characterized by mild, fluctuating hyperbilirubinemia. This result decreases the likelihood of, but does not exclude a diagnosis of Crigler-Najjar syndrome. Clinical presentation may be influenced by other genetic modifiers or co-existing conditions. This genotype may impact the metabolism of certain drugs and dosing should be based on clinical findings. Guidelines for genotype-based dosing recommendations published by the Clinical Pharmacogenetic Implementation Consortium (CPIC) are located at: https://cpicpgx.org/guidelines/.

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

Evidence for variant classification:
The UGT1A1 TATA box commonly has 6 TA repeats; however, there can be 5 TA repeats, 7 TA repeats, or less commonly, 8 and 9 TA repeats (Barbarino 2014). In vitro studies have shown that UGT1A1 promoter expression decreases as the number of TA repeats increases (Beutler 1998). Genotypes that are homozygous for (TA)7, homozygous for (TA)8, or compound heterozygotes for (TA)7, (TA)8, or (TA)9 cause reduced expression of UGT1A1 and are associated with Gilbert syndrome, which is characterized by increased bilirubin levels, and may have a neonatal appearance of hereditary spherocytosis (Bosma 1995, Iolascon 1998, Nikolac 2008, Ostanek 2007). Individuals who are heterozygous for the (TA)7 *28 promoter variant may have an increased risk for drug toxicity when treated with irinotecan (Marcuello 2004, Riera 2018). Individuals who are homozygous for (TA)7 or compound heterozygous for more than 6 TA

repeats may experience an increased incidence of atazanavir-associated hyperbilirubinemia (Gammal 2016).

RECOMMENDATIONS
Medical management should rely on clinical findings and family history. Genetic consultation is recommended.

COMMENTS
Likely benign and benign variants other than the (TA)nTAA promoter polymorphism 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
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Gammal RS et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for UGT1A1 and Atazanavir Prescribing. Clin Pharmacol Ther. 2016 99:363-369. PMID: 26417955
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Ostanek B et al. UGT1A1(TA)n promoter polymorphism--a new case of a (TA)8 allele in Caucasians. Blood Cells Mol Dis. 2007 38:78-82. PMID: 17196409
Riera P et al. Relevance of CYP3A4*20, UGT1A1*37 and UGT1A1*28 variants in irinotecan-induced severe toxicity. Br J Clin Pharmacol. 2018 84:1389-1392. PMID: 29504153

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: UGT1A1 Sequencing

CHARACTERISTICS: UGT1A1 encodes the bilirubin uridine diphosphate glucuronosyl transferase 1A1 enzyme, which is responsible for the metabolism of drugs (e.g., irinotecan) and endogenous compounds (e.g., bilirubin). UGT1A1 deficiency is associated with inherited nonhemolytic unconjugated hyperbilirubinemia and a spectrum of phenotypes dependent on the level of residual enzyme activity. Crigler-Najjar syndrome type I results from absent enzyme activity and severe unconjugated hyperbilirubinemia causing jaundice and risk for kernicterus. Crigler-Najjar syndrome type II is associated with reduced hepatic enzyme activity, intermediate levels of hyperbilirubinemia, and low risk for kernicterus. Gilbert syndrome is clinically benign and associated with mild, fluctuating hyperbilirubinemia, which can be caused by impaired bilirubin glucuronidation. Pathogenic UGT1A1 variants are also associated with an increased risk for irinotecan toxicity (neutropenia and diarrhea) and bilirubin-related discontinuation of atazanavir.

EPIDEMIOLOGY: Incidence of Crigler-Najjar syndrome is estimated at 1 in 1 million newborns worldwide. Approximately 3-7 percent of individuals in the U.S. have Gilbert syndrome.
Estimated risk of irinotecan toxicity by genotype in Caucasian patients with colorectal cancer (PMID: 23529007).

(TA)6/6 (*1/*1): diarrhea 15 percent; neutropenia 11 percent.
(TA)6/7 (*1/*28): diarrhea OR=1.20; neutropenia OR=1.90.
(TA)7/7 (*28/*28): diarrhea OR=1.84; neutropenia OR=4.79.
Risks for bilirubin-related atazanavir discontinuation by predicted UGT1A1 phenotype (PMID: 26417955):
Poor metabolizer (*28/*28, *28/*37, *37/*37): 20-60 percent.
Intermediate metabolizer (*1/*28, *1/*37, *36/*28, *36/*37): less than 5 percent.
Extensive or normal metabolizer (*1/*1, *1/*36, *36/*36): less than 5 percent.

CAUSE: Two pathogenic UGT1A1 variants on opposite chromosomes. A variable number of TA repeats in the (TA)nTAA element of the UGT1A1 promoter affects transcription efficiency. The common number of repeats is six (TA)6, *1 allele, while seven repeats (TA)7, *28 allele is associated with reduced transcription activity.

INHERITANCE: Autosomal recessive for Crigler-Najjar and Gilbert syndromes.

CLINICAL SENSITIVITY: Unknown for Crigler-Najjar and Gilbert syndromes.

GENE TESTED: UGT1A1 (NM_000463), promoter (NC_000002)
Deletion/duplication analysis is not available for this gene.

METHODOLOGY: Capture of all coding exons and exon-intron junctions of the UGT1A1 gene, including the (TA)nTAA promoter region, followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage and confirm reported variants.

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 Crigler-Najjar or Gilbert syndromes. Other genetic factors and nongenetic factors may contribute to irinotecan toxicity and efficacy. This test only detects variants within the coding regions, intron-exon boundaries, and promoter region of the UGT1A1 gene. Regulatory region variants other than the (TA)nTAA promoter region, 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 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 transplant. Noncoding transcripts were not analyzed.

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
UGT1A1 Specimen	24-267-401734	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
UGT1A1 Interp	24-267-401734	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