ARUP LABORATORIES
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Tracy I. George, MD, Chief Medical Officer

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

Physician: Doctor, Example

Patient: Patient, Example

DOB	10/27/2019
Gender:	Male
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	01/01/2017 12:34

UGT1A1 Sequencing (Temporary Referral as of 12/07/20)

ARUP test code 3001755

Specimen UGT1A1 FGS	Whole Blood
UGT1A1 FGS Interpretation	Negative

TEST PERFORMED - 3001755
TEST DESCRIPTION - Gilbert and Crigler-Najjar Syndromes (UGT1A1) Sequencing
INDICATION FOR TEST - Confirm a diagnosis of Crigler-Najjar/Gilbert Syndrome

RESULT
No pathogenic variants were detected in the UGT1A1 gene.

INTERPRETATION
No pathogenic variants were detected in the UGT1A1 gene by bidirectional sequencing of the coding region, exon/intron boundaries, and the polymorphic (TA)nTAA promoter region.

Two copies of the *1 (TA)6 allele were detected. The *1 allele is associated with normal UGT1A1 enzyme level.
This result decreases the likelihood of, but does not exclude a diagnosis of Gilbert or Crigler-Najjar syndromes.

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

RECOMMENDATIONS
Medical management should rely on clinical findings and family history.

COMMENTS
Reference Sequences: GenBank # NM_000463.2, NC_000002.11 (promoter)
Nucleotide numbering begins at the "A" of the ATG initiation codon.
Likely benign and benign variants other than the (TA)nTAA promoter polymorphism are not included in this report.

This result has been reviewed and approved by [redacted]

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

BACKGROUND INFORMATION: UGT1A1 Sequencing

CHARACTERISTICS: UGT1A1 encodes the bilirubin uridine diphosphate glucuronosyl transferase 1A1 enzyme, which is responsible for the clearance of drugs (eg, irinotecan) and endogenous compounds (eg, 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.
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.
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.
INHERITANCE: Autosomal recessive for Crigler-Najjar and Gilbert syndromes.
CLINICAL SENSITIVITY/SPECIFICITY: Unknown for Crigler-Najjar and Gilbert syndromes. 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.
METHODOLOGY: Bidirectional sequencing of the UGT1A1 coding regions, intron/exon boundaries, and polymorphic (TA)nTAA repeat within the promoter region.
ANALYTICAL SENSITIVITY: Greater than 99 percent.
LIMITATIONS: Diagnostic errors can occur due to rare sequence variations. UGT1A1 regulatory region variants other than the (TA)nTAA promoter variant will not be analyzed. Deep intronic variants, large deletions/duplications/insertions, and gene conversion events will not be detected. Variants of uncertain clinical significance within the UGT1A1 coding region will not be reported for pharmacogenetic indications. Genetic and non-genetic factors other than UGT1A1, may contribute to irinotecan toxicity and efficacy.

See Compliance Statement C: www.aruplab.com/CS

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Specimen UGT1A1 FGS	19-344-118772	12/10/2019 6:47 00 AM	12/11/2019 10:37:00 AM	12/24/2019 5:36:00 PM
UGT1A1 FGS Interpretation	19-344-118772	12/10/2019 6:47 00 AM	12/11/2019 10:37:00 AM	12/24/2019 5:36:00 PM

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