ARUP Laboratories
500 Chipeta Way – Salt Lake City, UT 84108
(800)522-2787 - www.aruplab.com
Julio C. Delgado, M.D. M.S., Director of Laboratories

*****Example Report*****

Patient Age/Gender: Unknown Female
Printed: 24-Sep-19 12:11:10

Procedure	Result	Units	Ref Interval	Accession	Collected	Received	Reported/ Verified
Specimen UGT1A1 FGS	Whole Blood			19-255-900242	12-Sep-19 15:23:00	12-Sep-19 15:25:00	12-Sep-19 15:45:09
UGT1A1 FGS Interpretation	Positive f			19-255-900242	12-Sep-19 15:23:00	12-Sep-19 15:25:00	12-Sep-19 15:45:09

***** Abnormal, **#** = Corrected, **C** = Critical, **f** = Footnote, **H** = High, **L** = Low, **t** = Interpretive Text, **@** = Reference Lab

12-Sep-19 15:23:00 UGT1A1 FGS Interpretation:
TEST PERFORMED - 3001755
TEST DESCRIPTION - Gilbert and Crigler-Najjar Syndromes (UGT1A1) Sequencing
INDICATION FOR TEST - Not Provided

RESULT
Two mildly pathogenic variants were detected in the UGT1A1 gene.

DNA VARIANTS
Classification: Pathogenic Mild
Gene: UGT1A1
Nucleic Acid Change: g.234668881_234668882TA[8]; Heterozygous/Homozygous
Commonly Known As: (TA)7 or *28 allele

INTERPRETATION
Two copies of a mildly pathogenic variant, (TA)7, were detected in the UGT1A1 gene by bidirectional sequencing of the coding region, exon/intron boundaries, and the polymorphic (TA)nTAA promoter region.

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 clinical sensitivity 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 allele 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
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.

REFERENCES
Barbarino JM et al. PharmGKB summary: very important pharmacogene information for UGT1A1. Pharmacogenet Genomics. 2014 24:177-183.

Beutler E et al. Racial variability in the UDP-glucuronosyltransferase 1 (UGT1A1) promoter: a balanced polymorphism for regulation of bilirubin metabolism? Proc Natl Acad Sci U S A. 1998 95:8170-8174.

Bosma PJ et al. The genetic basis of the reduced expression of bilirubin UDP-glucuronosyltransferase 1 in Gilbert's syndrome. N Engl J Med. 1995 333:1171-1175.

Gammal RS et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for UGT1A1 and Atazanavir Prescribing. Clin Pharmacol Ther. 2016 99:363-369.

Iolascon A et al. UGT1 promoter polymorphism accounts for increased neonatal appearance of hereditary spherocytosis. Blood. 1998 91:1093.

Marcuello E et al. UGT1A1 gene variations and irinotecan treatment in patients with metastatic colorectal cancer. Br J Cancer. 2004 91:678-682.

Nikolac N et al. Rare TA repeats in promoter TATA box of the UDP glucuronosyltranferase (UGT1A1) gene in Croatian subjects. Clin Chem Lab Med. 2008 46:174-178.

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.

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.

This result has been reviewed and approved by Rong Mao, M.D.

12-Sep-19 15:23:00 UGT1A1 FGS Interpretation:
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