HOTLINE: Effective November 18, 2019

New Test **3001755** ***UGT1A1* Sequencing** **UGT1A1 FGS**

Additional Technical Information

Patient History for *UGT1A1* Sequencing Testing

Supplemental Resources

Out of Pocket Estimator

Methodology: Polymerase Chain Reaction/ Sequencing
Performed: Sun-Sat
Reported: 2-3 weeks

Specimen Required: Collect: Lavender (K_2 EDTA), Pink (K_2 EDTA), or Yellow (ACD Solution A or B).
Specimen Preparation: Transport 3 mL whole blood. (Min: 1 mL)
Storage/Transport Temperature: Refrigerated
Stability (collection to initiation of testing): Ambient: 1 week; Refrigerated: 1 month; Frozen: 6 months

Interpretive Data:
Background Information for *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

CPT Code(s): 81479

New York DOH approval pending. Call for status update.

HOTLINE NOTE: Refer to the Test Mix Addendum for interface build information.