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Patient Report

Patient Age/Gender: Female

Specimen Collected: 29-Sep-21 10:26

UGT1A1 by NGS | **Received: 29-Sep-21 13:58** **Report/Verified: 30-Sep-21 08:31**

Procedure	Result	Units	Reference Interval
UGT1A1 Specimen	Whole Blood		
UGT1A1 Interp	See Note [i1]		

Test Information

i1: UGT1A1 Interp

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 White 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.

*=Abnormal, #=Corrected, C=Critical, f=Result Footnote, H-High, i-Test Information, L-Low, t-Interpretive Text, @=Performing lab

Test Information

i1: UGT1A1 Interp

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 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 transplant. Noncoding transcripts were not analyzed. Variants of uncertain clinical significance within the UGT1A1 coding region will not be reported for pharmacogenetic testing indications.

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.