UGT1A1 Genotype Predicts Irinotecan Toxicity or Confirms Gilbert's Syndrome

The UNC Molecular Genetics Laboratory performs a molecular test to detect heritable variants in *UGT1A1* that are associated with altered drug metabolism and risk of toxicity with the antineoplastic agent, irinotecan (CPT-11, Camptostar). The same assay is used to evaluate patients for Gilbert's syndrome.

Biology of genotype/phenotype correlations:

Toxicities associated with high dose irinotecan include diarrhea and neutropenia. The active metabolite of irinotecan, SN-38, is eliminated in bile after glucuronidation to SN-38G by UDP glucuronosyltransferase 1 polypeptide A1 (*UGT1A1*). Heritable variants in the number of TA repeats in the *UGT1A1* promoter sequence affect transcriptional efficiency and enzymatic clearance of SN-38. The normal allele has six TA repeats (also called *1) while the most common variant has seven TA repeats (*28). Homozygosity for the 7/7 genotype confers higher risk of irinotecan toxicity compared with those with two normal alleles (6/6), while heterozygosity (6/7) confers an intermediate risk of toxicity. The 5 and 8 TA repeat alleles are of uncertain significance with regard to toxicity.

Gilbert's syndrome, resulting from homozygosity for the *UGT1A1* 7/7 genotype, is a benign condition affecting 3 to 10% of the US population in which the liver insufficiently processes bilirubin from lysed red cells resulting in high serum bilirubin. UGT1A1 is the enzyme necessary for bilirubin conjugation. Gilbert syndrome is characterized by mild, chronic elevation of unconjugated serum bilirubin with normal liver function. *UGT1A1* 7/7 genotype diminishes the likelihood that occult, chronic, or progressive liver disease is the underlying cause of hyperbilirubinemia.

Clinical Indications for *UGT1A1* genotyping:

1. To predict toxicity and adjust drug dose accordingly in a patient being considered for high dose irinotecan (>250mg/m^2).
2. To investigate Gilbert's syndrome as a potential cause of unconjugated hyperbilirubinemia in a patient with mildly elevated serum bilirubin.

Laboratory Testing for *UGT1A1* gene variants: The preferred sample is 3ml of EDTA anticoagulated blood (lavender-top), which may be refrigerated up to 48 hours before analysis by PCR using primers flanking the *UGT1A1* promoter sequence followed by capillary electrophoresis to detect length polymorphisms reflecting the number of TA-repeats within the TATA box. Results are reported as heterozygous or homozygous for 5, 6, 7, or 8 TA repeats.

References:

Hoskins JM, Goldberg RM, Qu P, Ibrahim JG, McLeod HL: UGT1A1*28 genotype and irinotecan-induced neutropenia: dose matters. *J Natl Cancer Inst* 2007, 99:1290-1295

Liu CY et al: UGT1A1*28 polymorphism predicts irinotecan-induced severe toxicities without affecting treatment outcome and survival in patients with metastatic colorectal carcinoma. *Cancer* 2008, 112:1932

Huang CK, Dulau A, Su-Rick CJ, Pan Q: Validation of rapid polymerase chain reaction-based detection of all length polymorphisms in the UGT1A1 gene promoter. *Diagn Mol Pathol* 2007, 16:50-53

Questions? Call the **Molecular Genetics Lab** at **(919) 966-4408**
or Dr. Gulley at 843-4595. E-mail margaret_gulley@ med.unc.edu
Website=http://labs.unchealthcare.org/directory/molecular_pathology/index_html