

# UGT1A1 (TA)<sub>n</sub> Polymorphisms and Expression of Uridine Diphosphate-Glucuronosyltransferase

*TO IDENTIFY PATIENTS AT RISK FOR TOXICITY ASSOCIATED WITH IRINOTECAN AND RELATED DRUGS*

## Disease Overview

- Irinotecan (CPT-11; Camptosar®) is a camptothecin analogue approved for treatment of advanced stage colorectal cancer and may also be used for lung, brain, and breast tumors.
- Irinotecan therapy is associated with severe (grade 3/4) diarrhea and neutropenia in 20–35 percent of patients treated. Related fatalities have been reported.
- UDP-glucuronosyltransferase (*UGT1A1*) is responsible for the clearance, by glucuronidation, of drugs (e.g., irinotecan) and endogenous substances (e.g., bilirubin).
- The primary active and toxic metabolite of irinotecan, SN-38, is inactivated by *UGT1A1* to form SN-38G, which is eliminated via the bile.
- Variations of the TA repeat length in the *UGT1A1* promoter TATA element may lead to decreased gene expression, accumulation of SN-38, and irinotecan-related toxicities.
- In 2005, the FDA approved the inclusion of *UGT1A1* genotype-associated risk of toxicity on the irinotecan package insert and cites that a clinical test to detect common *UGT1A1* alleles is available.
- *UGT1A1* variants may also be associated with Gilbert syndrome (a benign familial hyperbilirubinemia) and Crigler-Najjar syndrome (a rare form of non-hemolytic jaundice which may lead to brain damage).

## Epidemiology

The frequency of the (TA)<sub>6</sub> and (TA)<sub>7</sub> repeats varies across ethnic groups.

(TA)	Caucasian	Asian	African
6	61%	84%	47%
7	39%	16%	43%

## Genetics

- The *UGT1A1* gene is located on chromosome 2q37.
- The polymorphic TA repeat in the TATA element of the 5'-promoter region of *UGT1A1* may consist of five, six, seven, or eight repeats.
- The common number of repeats is six; (TA)<sub>6</sub> is also known as the *UGT1A1\*1* allele.

- An increased number of TA repeats may reduce transcription efficiency, lower enzyme concentrations, and lead to the accumulation of SN-38 and the risk for toxicities.
- Seven TA repeats is known to cause reduced transcriptional activity; (TA)<sub>7</sub> is also known as the *UGT1A1\*28* allele.
- The (TA)<sub>5</sub> and (TA)<sub>8</sub> alleles are rare.

## Indications for Ordering

- Plans to administer irinotecan or related compounds.
- Patients with a personal or family history of irinotecan sensitivity.
- Confirm a diagnosis of Gilbert syndrome.

## Interpretation

- The risk of irinotecan toxicity and dosing recommendations by genotype are shown below.<sup>1</sup>

TA genotype	Diarrhea risk	Neutropenia risk	Irinotecan dosing
6/6 (*1/*1)	17%	15%	Standard
6/7 (*1/*28)	33%	27%	Dose based on clinical findings
7/7 (*28/*28)	70%	40%	Dose reduction is recommended

- The *UGT1A1* genotype does not significantly influence the risk of irinotecan toxicity when low-dose therapy with irinotecan (e.g., 15 to 75 mg/m<sup>2</sup> daily for five days for two consecutive weeks) is employed (J Clin Oncol 2007;25:2594-600).
- Homozygosity for the (TA)<sub>7</sub> allele is also associated with Gilbert syndrome (a benign familial hyperbilirubinemia).
- The rare (TA)<sub>5</sub> and (TA)<sub>8</sub> alleles are detected by this assay; however, their clinical significance is not well-established.

## Limitations

- Other variations in the *UGT1A1* gene, such as those associated with Crigler-Najjar syndrome, will not be detected by this assay.
- Other factors that may contribute to irinotecan toxicity and efficacy cannot be predicted by this test.

## Methodology

- Polymerase chain reaction followed by size analysis using capillary electrophoresis.
- Analytical sensitivity is greater than 99 percent.
- Clinical sensitivity varies by ethnicity.

## References

1. Marcuello E, et al. UGT1A1 gene variations and irinotecan treatment in patients with metastatic colorectal cancer. *Br J Cancer* 2004;91:678–82.
2. Stewart CF, et al. UGT1A1 promoter genotype correlates with SN-38 pharmacokinetics, but not severe toxicity in patients receiving low-dose irinotecan. *J Clin Oncol* 2007;25(18):2594–600.
3. Innocenti F, et al. Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan. *J Clin Oncol* 2004;22:1382–8.
4. Rouits E, et al. Relevance of different UGT1A1 polymorphisms in irinotecan-induced toxicity: a molecular and clinical study of 75 patients. *Clin Cancer Res* 2004;10:5151–9.
5. Mackenzie PI, et al. Nomenclature update for the mammalian UDP glycosyltransferase (UGT) gene superfamily. *Pharmacogenet Genomics* 2005;15:677–85.
6. Hahn KK, Wolff JJ, Kolesar JM. Pharmacogenetics and irinotecan therapy. *Am J Health-Syst Pharm* 2006; 63:2211–17.

## Test Information

0051332

UDP glucuronosyltransferase 1A1 (UGT1A1)

For specific collection, transport, and testing information, refer to the ARUP website at [www.aruplab.com](http://www.aruplab.com).

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at [www.arupconsult.com](http://www.arupconsult.com).