UGT1A1 Mutation Analysis for Irinotecan Response

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan’s procedure code list for management requirements.

<table>
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<tr>
<th>Procedure addressed by this guideline</th>
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<td>UGT1A1 Targeted Mutation Analysis</td>
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What are UGT1A1 and irinotecan

Definition

Irinotecan is a chemotherapy drug often prescribed together with other standard agents for treating patients with metastatic and recurrent colorectal cancer. Irinotecan is metabolized by a gene called UGT1A1 in the liver.¹

- A common change, or variant, in the UGT1A1 gene called UGT1A1*28 can lead to reduced enzyme activity. This can cause a buildup of drug metabolites, resulting in toxicity.¹,²
- Several studies have confirmed an increased risk of having reduced white blood cell count, or neutropenia, in people with UGT1A1 genetic variants. Some studies, but not all, have shown an increased risk of severe diarrhea.³
- About 10% of North Americans have two copies of the UGT1A1*28 mutation (homozygous, also referred to as UGT1A1 7/7) and 40% have just one copy (heterozygous).²
- Not all people with UGT1A1*28 mutations will experience increased toxicity.³ People homozygous for the *28 mutation are 3.5 times more likely to develop severe neutropenia than those with the wild genotype.¹

Test information

- Targeted mutation analysis of the UGT1A1 gene sequence by polymerase chain reaction (PCR) identifies any mutation in the region. The results are reported as negative, heterozygous or homozygous.¹,²,⁴
- **Negative** = UGT1A1 6/6 (*1/*1) genotype; Wild-type genotype; No UGT1A1*28 mutation is identified. Low risk of severe toxicity from standard initial dosages of irinotecan.

- **Heterozygous** = UGT1A1 6/7 (*1/*28) genotype; One wild-type allele and one UGT1A1*28 mutation allele identified. Increased risk for irinotecan toxicity, but initial standard doses may be still be tolerated.

- **Homozygous** = UGT1A1 7/7 (*28/*28) genotype. Increased risk for severe toxicity from standard initial doses of irinotecan, thus irinotecan product labeling recommends considering a reduced initial dose.

### Guidelines and evidence

- In May 2010, the FDA announced a safety change to the prescribing information for Camptosar® (irinotecan) Injection:
  - “When administered in combination with other agents, or as a single-agent, a reduction in the starting dose by at least one level of Camptosar® should be considered for patients known to be homozygous for the UGT1A1*28 allele. However, the precise dose reduction in this patient population is not known and subsequent dose modifications should be considered based on individual patient tolerance to treatment.”
  - “A laboratory test is available to determine the UGT1A1 status of patients. Testing can detect UGT1A1 6/6, 6/7, 7/7 genotypes.”

- UGT1A1 *28 testing for irinotecan is included on the FDA’s table for therapeutic products with pharmacogenomic data on the drug label.

- Guidelines for genetic testing have not been established by organizations such as the National Comprehensive Cancer Network (NCCN) and the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. However, both organizations recognize the availability and utility of testing UGT1A1 *28 prior to treatment with irinotecan.

- The NCCN states the following:
  - “Also, a warning was added to the label for irinotecan indicating that a reduced starting dose of the drug should be used in patients known to be homozygous for UGT1A1*28.”
  - “A practical approach to the use of UGT1A1*28 allele testing with respect to patients receiving irinotecan has been presented, although guidelines for the use of this test in clinical practice have not been established.”
  - “UGT1A1 testing on patients who experience irinotecan toxicity is not recommended, because they will require a dose reduction regardless of the UGT1A1 test result.”
Criteria
UGT1A1 testing is indicated in individuals with metastatic and/or recurrent colorectal cancer prior to the initiation of irinotecan therapy.

References