MEDICAL POLICY

MEDICAL POLICY DETAILS	
Medical Policy Title	**GENOTYPING URIDINE DIPHOSPHATE GLYCURONOSYLTRANSFERASE (UGT1A1) FOR PATIENTS TREATED WITH IRINOTECAN**
Policy Number	**2.02.34**
Category	**Laboratory Tests**
Effective Date	**12/20/07**
Revised Date	**12/18/08, 12/17/09, 12/16/10, 12/15/11, 12/20/12, 12/19/13, 12/18/14, 12/17/15, 12/15/16**
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Edited Date	**12/20/18**
Product Disclaimer	• *If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.* • *If a commercial product (including an Essential Plan product) or a Medicaid product covers a specific service, medical policy criteria apply to the benefit.* • *If a Medicare product covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.*

POLICY STATEMENT

Based upon our criteria and review of peer-reviewed literature, genotyping to determine UGT1A1 genetic polymorphisms for the purpose of avoiding irinotecan-related toxicity is considered **investigational**.

Refer to Corporate Medical Policy #2.02.41 regarding Genotyping – RAS Mutation Analysis in Metastatic Colorectal Cancer.

Refer to Corporate Medical Policy #11.01.03 regarding Experimental and Investigational Services.

POLICY GUIDELINES

The Federal Employee Health Benefit Program (FEHBP/FEP) requires that procedures, devices or laboratory tests approved by the U.S. Food and Drug Administration (FDA) may not be considered investigational and thus these procedures, devices or laboratory tests may be assessed only on the basis of their medical necessity.

DESCRIPTION

Colorectal cancer (CRC) is one of the most common malignancies in the US, and has been associated with genetic as well as lifestyle factors. Irinotecan (Camptosar) is a chemotherapeutic agent approved as a combination therapy with 5-fluorouracil/leucovorin for the treatment of advanced CRC. However, the response to irinotecan is variable, possibly because of individuals' variation in the expression of the enzymes that metabolize irinotecan. Although multiple genes may play a role in irinotecan activity, the uridine diphosphate glycuronosyltransferase 1 family, polypeptide A1 (UGT1A1) enzyme has been strongly associated with irinotecan-related toxicity. The UGT1A1 gene is responsible for glucuronidation of the active metabolite of irinotecan. A common di-nucleotide repeat polymorphism in the UGT1A1 promoter region (UGT1A1*28) has been correlated with toxicity in cancer patients receiving irinotecan-containing therapy. Other polymorphism of UGT1A1, such as, UGT1A1*6, UGT1A1*7 and UGT1A1*9 are being investigated for use in predicting toxicities for patients receiving irinotecan therapy.

RATIONALE

The Invader UGT1A1 molecular assay was cleared by the FDA on August 22, 2005. The test can be performed before starting irinotecan therapy and is designed to identify patients who may be at risk for adverse reactions to the

chemotherapeutic agent by detecting a genetic variation in the UGT1A1 gene which produces an enzyme that is "active in the metabolism" of the colon cancer drug irinotecan. Variations in the UGT1A1 gene can influence a patient's ability to break down irinotecan, which can lead to increased blood levels of the drug and a higher risk of side effects. The Invader assay was studied in 66 patients who were receiving irinotecan therapy. The study showed that persons with one type of genetic variation have a five times greater risk of experiencing irinotecan toxicity. The Invader UGT1A1 Molecular Assay should not be used: 1) as the only test to determine specific drug dose. Other clinical information and patient history should primarily be considered; 2) to aid in predicting a patient's drug response for drugs that are not metabolized by the enzyme encoded by UGT1A1; and 3) to aid in predicting a patient's response to drugs for which the mutant UGT1A1 phenotype has not been clearly established (FDA, 2005).

While initial reports suggested that UGT1A1*28 homozygotes were at high risk for worse irinotecan-related hematologic and gastrointestinal toxicity, more recent reports suggest that the magnitude of the problem (particularly the association with worse diarrhea) is not as great as was initially suspected. In a prospective study of 250 patients with metastatic colorectal cancer starting irinotecan, fluorouracil and leukovorin, the relative risk for grade 3 or 4 hematologic toxicity was significantly higher among UGT1A1*28 homozygotes (odds ratio 8.63, 95% confidence interval 1.31 to 56.55) (Toffoli et al., 2006). However, the absolute magnitude of risk was relatively low (13.6 percent versus 1.7 percent for those with the wild-type alleles), and relevant for the first cycle only. Furthermore, there was no significant association between the presence of a UGT1A1*28 polymorphism and severity of diarrhea, or the need for irinotecan dose reduction.

One study found higher rates of neutropenia in persons homozygous for the UGT1A1*28 allele, regardless of whether the combination chemotherapy regimen included irinotecan (McLeod, et al., 2006). In a preliminary analysis of data from 520 patients with colorectal cancer enrolled in the United States Intergroup (INT) 9741 trial, which compared a variety of first-line oxaliplatin and irinotecan-containing chemotherapy regimens, the risk of grade 3 or 4 neutropenia was significantly higher for homozygotes (but not heterozygotes) regardless of whether they received irinotecan or oxaliplatin-based chemotherapy (36.2 percent versus 18.2 percent and 14.8 percent for homozygotes, heterozygotes, and wild-type alleles, respectively). Similar to the study by Toffoli, et al. (2006) described above, the investigators found no association between inheritance of UGT1A1*28 alleles and treatment-related diarrhea. UGT1A1*28 was also not a predictor of tumor response, time to progression, or overall survival.

A meta-analysis by Hoskins et al. (2007) assessed the association of irinotecan dose with the risk of irinotecan-related hematologic toxicities for patients with a UGT1A1*28/*28 genotype. Nine studies were included in the review (821 patients). According to the authors, those patients with the UGT1A1*28/*28 genotype had a higher risk of toxicity than those patients with the UGT1A1*1/*1 or UGT1A1*1/*28 genotypes at both high doses (200-350 mg/m² every 21 days) ($p = .005$) and medium doses (180 mg/m² every two weeks) ($p = .008$). At low doses (80-125 mg/m² weekly), the risk was similar for all genotypes. Although initial studies found UGT1A1*28 genotype to be associated with the risk of toxicity, subsequent studies have been inconsistent. They also indicated that analysis of the studies was limited by the many sources of heterogeneity among the studies. This data suggest that there may be an association between the UGT1A1*28 genotype and irinotecan-induced toxicity at higher irinotecan doses however, further well-designed studies are warranted to address many unanswered questions including those regarding dosing strategies based on the UGT1A1*28 genotype.

Liu et al. (2008) conducted a retrospective review of 128 patients with metastatic colorectal cancer who had received treatment with irinotecan plus 5-fluorouracil/leukovorin to analyze the influence of the UGT1A1*28 polymorphism on toxicity and treatment outcome. Approximately 20% of the patients were found to have the UGT1A1*28 polymorphism. This included 15.6% (n = 20 patients) with (TA)6/TA7 genotype and 4.7% (n = 6 patients) with the TA7/TA7 genotype. The remaining 79.7% of patients (n =102) had wild type TA6/TA6. A significant increase in grade 3 or 4 neutropenia (53.8% vs. 4.9%; p less than.01), neutropenic fever (38.5% vs. 3.9%; p less than.01), diarrhea (26.9% vs. 5.9%; p less than.01), and pretreatment bilirubin level (23.1% vs. 8.8%; p less than.04) was noted in patients with the TA6/TA7 or

TA7/TA7 genotypes. Patients with the UGT1A1*28 genetic variant required greater dose reductions than those patients without the variant (p less than.01). The authors indicated that this did not affect the response rate to irinotecan (p =.80), the progression-free survival (p =.94) or the overall survival (p =.84). The authors concluded that although the data suggest that the polymorphism UGT1A1*28 may play a role in predicting irinotecan-induced severe toxicities, further prospective studies are needed to confirm this.

The 2017 National Comprehensive Cancer Network (NCCN) guidelines for both colon and rectal cancer mention that Irinotecan should not be used in the adjuvant setting for patients with stage II or III colon cancer outside the setting of a clinical trial. Toxicities associated with irinotecan include both early and late forms of diarrhea, dehydration, and severe neutropenia. Irinotecan is inactivated by the enzyme uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), which is also involved in converting substrates such as bilirubin into more soluble forms through conjugation with certain glycosyl groups. Deficiencies in UGTA1A1 can be caused by certain genetic polymorphisms and can result in conditions associated with accumulation of unconjugated hyperbilirubinemias, such as types I and II of the Crigler-Najjar and Gilbert syndromes. Thus, irinotecan should be used with caution and with decreased doses in patients with Gilbert's disease or elevated serum bilirubin. Similarly, certain genetic polymorphisms in the gene encoding for UGT1A1 can result in a decreased level of glucuronidation of the active metabolite of irinotecan, resulting in an accumulation of the drug and increased risk of toxicity, although severe irinotecan-related toxicity is not experienced by all patients with these polymorphisms. Commercial tests are available to detect the UGT1A1*28 allele, which is associated with decreased gene expression and, hence, reduced levels of UGT1A1 expression. Also a warning was added to the label for irinotecan indicating that a reduced starting dose of the drug should be used inpatients 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 use in clinical practice have not been established. Furthermore, UGT1A1 testing on patients who experience irinotecan toxicity is not recommended because they will require a dose reduction regardless of the UGT1A1 test result.

While several investigators have reported that testing of patients carrying the UGT1A1*28 polymorphism may detect their susceptibility to irinotecan-related toxicity, others have questioned its clinical value. The product labeling for irinotecan (Camptosar) was updated to recommend that a reduced initial dose should be considered for patients homozygous for UGT1A1*28 allele, although the precise dose reduction in this group of patients is unknown. The product labeling, however, does not include a recommendation for assessment of UGT1A1 status prior to initiation of irinotecan therapy. Although it has been advocated that pharmacogenetic testing of patients with colorectal cancer before chemotherapy with irinotecan may reduce the frequency of severe toxicities by allowing alternate therapy selections for patients carrying the UGT1A1*28 polymorphism, the clinical value of this testing has yet to be established by prospective, randomized, controlled trials. There is a lack of consensus on whether initial dose reduction is needed for UGT1A1*28 homozygotes, and the precise dose reduction that is warranted in this patient population has not been determined. Further studies are needed to determine how drug metabolizing enzyme genotyping systems such as the Invader® UGT1A1 Molecular Assay might be utilized to improve health outcomes

CODES

- *Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.*
- *CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.*
- *Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.*

CPT Codes

Code	Description
81350 **(E/I)**	UGT1A1 (UDP glycuronosyltransferase 1 family, polypeptide A1) (e.g., Irinotecan metabolism), gene analysis, common variants (e.g., *28, *36, *37)

Code	Description
81479	Unlisted molecular pathology procedure

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HCPCS Codes

Code	Description
No Code(s)	

ICD10 Codes

Code	Description
	Investigational for all codes

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KEY WORDS

Invader UGT1A, Irinotecan (Camptosar)

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently a Local Coverage Determination (LCD) for Molecular Pathology Procedures. Please refer to the following LCD website for Medicare Members: https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=35000&ver=59&CntrctrSelected=298*1&Cntrctr=298&s=41&DocType=All&bc=AggAAAIAIAAAAA%3d%3d&