clinical reviews

All You Need to Know About *UGT1A1* Genetic Testing for Patients Treated With Irinotecan: A Practitioner-Friendly Guide

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abstract

Irinotecan is an anticancer agent widely used for the treatment of solid tumors, including colorectal and pancreatic cancers. Severe neutropenia and diarrhea are common dose-limiting toxicities of irinotecan-based therapy, and *UGT1A1* polymorphisms are one of the major risk factors of these toxicities. In 2005, the US Food and Drug Administration revised the drug label to indicate that patients with *UGT1A1*28* homozygous genotype should receive a decreased dose of irinotecan. However, *UGT1A1*28* testing is not routinely used in the clinic, and specific reasons include lack of access to concise information on this wide issue as well as mixed recommendations by regulatory and professional entities. To assist oncologists in assessing whether and when to use *UGT1A1* genetic testing in patients receiving irinotecan-based therapies, this article provided (1) essential knowledge of *UGT1A1* polymorphisms; (2) an update on the impact of *UGT1A1* polymorphisms on efficacy and toxicity of contemporary irinotecan-based regimens; (3) dosing adjustments based upon the *UGT1A1* genotypes, and (4) recommendations from currently available guidelines from the US and international scientific consortia and major oncology societies.

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INTRODUCTION

Irinotecan is an anticancer agent widely used to treat solid tumors, including colorectal and pancreatic cancers.[1] The most common dose-limiting toxicities are severe neutropenia and late-onset diarrhea that may require treatment interruption or dose reduction.[1,2] The irinotecan-induced toxicities are mainly because of the active metabolite, SN-38, with the potential contribution of irinotecan.[2] The *UGT1A1*28* polymorphism reduces the metabolism of SN-38, thereby affecting the risk of irinotecan-induced toxicities.[3] In 2005, the US Food and Drug Administration (FDA) revised the irinotecan label to indicate that a reduced initial dose should be considered for the *UGT1A1*28* homozygous patients,[4] but this is not routinely implemented in the clinic.[5] Over almost two decades, the clinical impact of *UGT1A1* polymorphisms on toxicity and efficacy of irinotecan-based therapy has been extensively studied, yet the clinical context in which this test can be used remains to be established.

This review is focused on the clinical utility of the *UGT1A1* genetic testing in irinotecan-based therapy. This document is not intended to proclaim the benefit of using *UGT1A1* genetic information in irinotecan therapy but rather to provide oncologists concise, up-to-date information that will assist clinical decision making as to whether and when to use *UGT1A1* genetic testing in patients receiving irinotecan therapy.

Drug Information

Irinotecan is a prodrug with topoisomerase I inhibitory activity.[2] Irinotecan HCl (Camptosar, Pfizer, New York, NY) is a conventional form of irinotecan that is FDA-approved for advanced metastatic colorectal cancer in combination with fluorouracil (5-FU) and leucovorin (FOLFIRI).[1] Irinotecan liposome (Onivyde, Merrimack Pharmaceuticals, Cambridge, MA) is irinotecan encapsulated in liposomes approved for the treatment of metastatic pancreatic cancer in combination with 5-FU and leucovorin.[6] Sacituzumab govitecan-hziy (Trodelvy, Immunomedics, Morris Plains, NJ) is an antibody-SN-38 conjugate approved for metastatic triple-negative breast cancer.[7]

Prevalence of Irinotecan Toxicity and Patient Characteristics Increasing Risk

The most common irinotecan toxicities are severe neutropenia and diarrhea.[1,8] Approximately 20%-54% of patients treated with irinotecan experience severe (Common Terminology Criteria for Adverse Events grade 3-4) neutropenia, and 11%-23% experience severe diarrhea.[1,6,9] In addition, 8%-23% of patients are hospitalized because of these toxicities.[1,10] Irinotecan toxicities are highly unpredictable and increase morbidity

ASSOCIATED CONTENT

See accompanying commentaries on pages 278 and 281

Author affiliations and support information (if applicable) appear at the end of this article.

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and mortality.[11,12] Risk factors include age > 65 years,[13,14] female sex,[15] poor performance status (≥ 2),[16,17] impaired liver function,[16] coadministration of CYP3A4[18] and/or UGT1A1 inhibitors, and reduced UGT1A1 enzyme activity.[1,19]

The Prevalence of Toxicity-Related Mortality from Irinotecan in the United States

In 2021, 149,500 individuals in the United States are predicted to be diagnosed with colorectal cancer, and 32,890 (22%) of them are candidates for irinotecan therapy because they are predicted to present with advanced and/or metastatic disease.[20] The prevalence of irinotecan toxicity-related mortality is < 1% across different irinotecan-based treatment regimens: 0.3% for FOLFIRI,[21] 0.44% for FOLFIRINOX (5-FU, leucovorin, irinotecan, and oxaliplatin),[22] 0.6% for XELIRI (capecitabine and irinotecan).[21]

Disposition of Irinotecan and SN-38 and Relationship with Toxicity

The most clinically relevant metabolic steps for irinotecan are as follows. Irinotecan is hydrolyzed to SN-38 in the liver.[23] SN-38 is then subsequently metabolized to SN-38 glucuronide (SN-38G) in the liver via glucuronidation mainly by UGT1A1.[24] SN-38G excreted into the bile can be deconjugated back into SN-38 via bacterial β-glucuronidases.[2,25,26]

Increasing concentrations of SN-38 in plasma are the main determinants of neutropenia, although the contribution of increased exposure to irinotecan cannot be entirely ruled out.[27] Late-onset diarrhea is primarily because of excessive SN-38 accumulation in the intestine.[26-28]

UGT1A1 Deficiency: Symptoms, Laboratory Alterations, and Prevalence in the General Population

UGT1A1 deficiency is related to decreased UGT1A1 expression or enzymatic activity leading to reduced conversion of lipophilic molecules (eg, bilirubin, SN-38, etc) into water-soluble metabolites that can be eliminated through the bile and urine.[29] Gilbert's syndrome is an inherited UGT1A1 deficiency (approximately 30% reduction in UGT1A1 function) caused by polymorphisms in the *UGT1A1* gene (eg, *UGT1A1*28/*28*) and characterized by increased unconjugated bilirubin in the blood. Gilbert's syndrome is usually asymptomatic and occurs in 5%-10% of the US population.[30]

UGT1A1 Polymorphisms Conferring Increased Risk of Irinotecan Toxicity: Nomenclature and Population Frequency

The list of *UGT1A1* polymorphisms is available at PharmGKB.[31] The most studied and clinically relevant *UGT1A1* polymorphisms are *UGT1A1*28*, *UGT1A1*93*, and *UGT1A1*6* (Table 1). Patients with these polymorphisms have an increased risk of severe irinotecan toxicity partially because of impaired clearance of SN-38 by UGT1A1-mediated metabolism.[3,15,32,33] Using the star nomenclature, *UGT1A1*1* contains six thymine-adenine (TA) repeats in the gene promoter and is associated with normal UGT1A1 enzyme activity and expression.[34]

*UGT1A1*28* contains seven TA repeats in the promoter, and this extra TA repeat results in decreased *UGT1A1* transcription efficiency,[35] leading to reduced *UGT1A1* expression.[34] It is commonly found in African (43%) and European ancestries (39%), but is less common in East Asian ancestry (16%).[35]

*UGT1A1*93* is a polymorphism (G>A) about 3 Kbs upstream of the *UGT1A1* exon 1[36] and is in linkage disequilibrium with *UGT1A1*28* (r^2 = 0.68).[37] Although its functional significance is unknown, *UGT1A1*93* is significantly associated with increased exposure to SN-38 and irinotecan toxicity, especially severe neutropenia.[15] It is commonly found in African (34%) and European ancestries (27%), but is less common in East Asian ancestry (13%).[38]

*UGT1A1*6* is a polymorphism (G>A) in the exon 1 region[39] that is significantly associated with irinotecan toxicity.[32,40] This polymorphism reduces UGT1A1 enzyme activity by substituting glycine into arginine (Gly71Arg). It is more commonly found in East Asian ancestry (15%) than African (0.1%) or European (1%) ancestry (Table 1).[39]

Association Between Alleles and Irinotecan Toxicity and Their Severity

The *UGT1A1*28* and/or **6* polymorphisms were significantly associated with severe irinotecan toxicity. In a prospective study (N = 66) of single-agent irinotecan, patients (mainly White) carrying *UGT1A1*28/*28* had a higher risk of grade 4 neutropenia than those carrying *UGT1A1*1/*1* or **1/*28* (relative risk = 9.3; 95% CI, 2.4 to 36.4).[3] In a retrospective study (N = 118) of irinotecan-based therapy, Japanese patients carrying *UGT1A1*28/*28* or **1/*28* had a 5.2-fold risk of grade 4 leukopenia and/or grade 3 or 4 diarrhea (odds ratio = 5.21; 95% CI, 1.98 to 13.96; P < .001).[33] In a prospective study (N = 107) of irinotecan and cisplatin, Korean patients carrying *UGT1A1*6/*6* had a higher risk of grade 4 neutropenia than those carrying *UGT1A1*1/*1* or **1/*6* (relative risk = 7.4; 95% CI, 1.2 to 44.2; P = .028).[41]

Interpretation of the Results of *UGT1A1* Genetic Testing

The Clinical Pharmacogenetics Implementation Consortium (CPIC) assigned level A to the *UGT1A1*-irinotecan pair, indicating that genetic information should be used to change prescribing of the affected drug. However, a CPIC guideline for *UGT1A1* and irinotecan is currently not available.[42] The Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP) and the French National Network of Pharmacogenetics (RNPGx) provide specific dose recommendations on the basis of the *UGT1A1* genotype.[43,44] For patients carrying *UGT1A1*28/*28*, KNMP-DPWG recommends starting with a 30% reduced irinotecan dose; RNPGx recommends starting with a 30%

TABLE 1. Common *UGT1A1* Variants and Their Impact on UGT1A1 Function

Allele	Nucleotide Change	Amino Acid Change	UGT1A1 Activity or Expression
*UGT1A1*1*	$(TA)_6$	—	Reference
*UGT1A1*28*	$(TA)_7$	—	Reduced expression
*UGT1A1*93*	-3156 G>A	—	Reduced expression
*UGT1A1*6*	c.211 G>A	p.Gly71Arg	Reduced activity

Abbreviation: TA, thymine-adenine.

reduced dose for an irinotecan dose of 180-240 mg/m^2 every three weeks as a single agent, whereas contraindication for an irinotecan dose of 240 mg/m^2 or higher.

Based upon the information reported so far in this article, we provide the interpretation of the results of *UGT1A1* genetic testing, its clinical implication, and clinical interventions in Table 2. Patients carrying two *UGT1A1* alleles conferring decreased expression or function (ie, **28/*28*, **6/*6*, **28/*6*) are at the highest risk for severe neutropenia and diarrhea, followed by those carrying one allele (ie, **1/*28, *1/*6*) and no allele (ie, *UGT1A1*1/*1*).[49,50] To manage the risk of toxicity, patients carrying **28/*28*, **6/*6*, or **28/*6* are recommended to receive a reduced dose of irinotecan.

Economic Impact of Irinotecan-Related Toxicity in Carriers of *UGT1A1*28*

There are no recent data available on financial costs of toxicity management in patients with *UGT1A1*28/*28* in the US health care system. However, decision-tree modeling studies on the basis of treatment costs reported in 2006[51] and 2007[52] suggest that preemptive *UGT1A1* genetic testing to guide irinotecan dosing (20%-25% dose reduction in patients with *UGT1A1*28/*28*) can reduce the cost of treatment with single-agent irinotecan[51] or FOLFIRI[52] in US patients with metastatic colorectal cancer compared with no *UGT1A1* genetic testing. Consistent results were found in a more recent study using data from treated patients. A retrospective analysis of patients with colorectal cancer (N = 243) receiving FOLFIRI in Italy showed that the toxicity management cost was about six times higher in patients with *UGT1A1*28/*28* (€4,886) than those with *UGT1A1*1/*1* (€812; $P < .001$).[53] The primary source of the cost was hospitalization because of irinotecan toxicity, which was much greater than the cost of *UGT1A1* genetic testing.

Prevalence of Irinotecan-Related Toxic Deaths in Carriers of *UGT1A1*28*

According to a study of Israeli patients with colorectal cancer treated with irinotecan-based regimen,[10] patients carrying *UGT1A1*28/*28* showed higher short-term death within 2 months of treatment onset compared with those carrying *UGT1A1*1/*1* or **1/*28* (13% *v* 3% and 5%, $P = .027$). However, since potential confounding factors (eg, coadministration of 5-FU) might have influenced this death, further studies are required to elucidate the effect of *UGT1A1*28* polymorphism.

The Predictive Value of *UGT1A1*28* Genetic Testing

*UGT1A1*28* genetic testing for severe neutropenia had sensitivity of 11%, specificity of 94%, positive predictive value of 30%, and negative predictive value of 82%, considering **28/*28* as a positive test result.[54] Similar test performance was observed for severe diarrhea: sensitivity of 13%, specificity of 92%, positive predictive value of 22%, and negative predictive value of 85%. Similar to other tests like *DPYD* testing for 5-FU toxicity,[55] *UGT1A1*28* genetic testing has low predictive power in patients who are not carriers of homozygous deficient alleles.

The number needed to genotype and the number needed to treat are[54] 79 and 9 for severe neutropenia, and 127 and 14 for severe diarrhea, respectively. For every 100 patients, 11 patients will have positive test results and may benefit from an intervention to reduce the risk of severe toxicity.

Effect of *UGT1A1* Genetic Testing on Reduction of the Risk of Severe Irinotecan Toxicity

A model-based clinical simulation study[45,56-59] demonstrated that the risk of severe irinotecan toxicity in patients carrying *UGT1A1*28* could be reduced through *UGT1A1* genetic testing. According to this study, if *UGT1A1* genetic

TABLE 2. Clinical Recommendations for Patients Receiving Irinotecan on the basis of the Interpretation of the Results of the *UGT1A1* Genetic Test

UGT1A1 Genotype	Effect on UGT1A1 Activity or Expression	Clinical Implication	Clinical Intervention
**1/*1*	Normal	Average risk of irinotecan toxicity	Use standard starting dose[1,6,7] These patients may be able to tolerate irinotecan doses higher than the standard dose without compromising safety[5,45-48]
**1/*28*	Reduced expression	Higher risk of irinotecan toxicity	Use standard starting dose[1,6,7]
**1/*6*	Reduced activity		These patients may be able to tolerate irinotecan doses higher than the standard dose without compromising safety[5,45-48]
**28/*28*	Further reduction in expression	Highest risk of irinotecan toxicity	Reduce the starting dose to at least one level lower than the standard dose.[1] For specific dosing recommendations, see Table 3 After cycle 1 at a reduced dose, upward titration at subsequent cycles can be considered, on the basis of individual tolerance[1,6,7]
**6/*6*	Further reduction in activity		
**6/*28*	Further reduction in activity and expression		

testing is performed and 25% reduced irinotecan dose is administered to patients carrying *UGT1A1*28/*28*, the prevalence of severe neutropenia and severe diarrhea will be reduced from 45% to 18% and from 19% to 9%, respectively. If, instead of a 25% dose reduction, prophylactic granulocyte colony-stimulating factors (eg, pegfilgrastim) with the standard dose of irinotecan is administered to these patients, the prevalence of severe neutropenia will be reduced to a similar extent (from 45% to 17%), but the prevalence of severe diarrhea will not be reduced. Prospective data on treated patients are not available yet. Whether a dose reduction based upon genotype can preserve antitumor efficacy is still an unanswered question.

Tolerability of Irinotecan Dosing on the basis of *UGT1A1*28* and **6*

Several phase I studies showed that patients with *UGT1A1*1/*1*, **1/*28*, or **1/*6* genotypes could tolerate irinotecan doses substantially higher than standard doses. Some of these studies have also established the levels of dose reductions in patients with *UGT1A1*28/*28*, **6/*28*, or **6/*6*. For single-agent irinotecan (350 mg/m^2 every 3 weeks), patients carrying *UGT1A1*1/*1* and **1/*28* could tolerate irinotecan up to 850 mg and 700 mg (500 mg/m^2 and 412 mg/m^2, assuming average body surface area is 1.7 mg/m^2), respectively, whereas those with **28/*28* could tolerate irinotecan up to 400 mg (235 mg/m^2).[46] The plasma exposure to SN-38 was simlar between these three genotype groups.

For FOLFIRI (irinotecan dose, 180 mg/m^2 every 2 weeks), patients with European ancestry carrying *UGT1A1*1/*1* and **1/*28* could tolerate irinotecan up to 370-390 mg/m^2 and 310-340 mg/m^2, respectively,[45,47] whereas those with **28/*28* could tolerate irinotecan up to 130 mg/m^2.[47] Similarly, patients with Asian ancestry carrying *UGT1A1*1/*1* and **1/*28* or **1/*6* could tolerate irinotecan up to 330 mg/m^2 and 300 mg/m^2, respectively, whereas those carrying **28/*28*, **6/*28*, or **6/*6* could tolerate irinotecan up to 150 mg/m^2.[48]

For FOLFIRI plus bevacizumab, patients with European ancestry carrying **1/*1* and **1/*28* could tolerate irinotecan up to 310 mg/m^2 and 260 mg/m^2, respectively.[5]

For FOLFIRINOX, further dose reduction of irinotecan may be required for patients carrying *UGT1A1*28*. A study of modified FOLFIRINOX (N = 79)[60] showed that, while patients carrying *UGT1A1*1/*1* could tolerate a standard dose of irinotecan (180 mg/m^2), those carrying **28* could not tolerate the regimen even with reduced doses of irinotecan (135 mg/m^2 for **1/*28*; 90 mg/m^2 for **28/*28*). Currently, the maximum tolerated dose of irinotecan on the basis of the *UGT1A1* genotype has not been established yet for FOLFIRINOX.

Efficacy and Toxicity of Increased Irinotecan Dose on the basis of *UGT1A1* Genotype

The study examined whether the administration of increased irinotecan dose is as safe and more effective than the standard dose in patients with metastatic colorectal cancer with *UGT1A1*1/*1* or **1/*28*. In a randomized phase II study (N = 79) of *UGT1A1* genotype-guided increased dose (300 mg/m^2 for **1/*1*; 260 mg/m^2 for **1/*28*) or standard dose (180 mg/m^2) of irinotecan of FOLFIRI in Spanish patients with metastatic colorectal cancer, the overall response rate was 67.5% in patients receiving increased dose of irinotecan versus 43.6% in patients receiving a standard dose (P = .001).[61] Rates of severe toxicities were similar between the two groups, and no differences in survival were observed.

Combined Effect of *UGT1A1* Polymorphism and Demographic or Clinical Risk Factors on Irinotecan Toxicity

A pharmacokinetic study[62] suggests that potential demographic or clinical risk factors that interacted with *UGT1A1* polymorphism may also need to be considered for *UGT1A1* genotype-guided dosing. *UGT1A1* polymorphism showed an additive effect with high pretreatment total bilirubin, but not with demographic risk factors (age > 65 years or female sex), on SN-38 clearance. Compared with *UGT1A1* polymorphism alone, a combination with high (> 0.8 mg/dL) pretreatment total bilirubin further reduced SN-38 clearance, which may lead to increased irinotecan toxicity.

Oncology Guidelines on the *UGT1A1*28* Polymorphism

The National Comprehensive Cancer Network Guidelines[63] state that irinotecan should be used with caution in patients with Gilbert syndrome or elevated serum bilirubin. There is a commercially available test for *UGT1A1*. The guideline for its use in clinical practice has not been established. It also includes a caution that *UGT1A1* testing on patients who experience irinotecan toxicity is not recommended because they will require a dose reduction regardless of *UGT1A1* test result.

ASCO does not provide any guidelines on this matter.

The European Society for Medical Oncology consensus guidelines[64] acknowledge the *UGT1A1* polymorphism as a predictive biomarker of irinotecan toxicity. It states that UGT1A1 phenotyping remains an option and should be carried out in patients with a suspicion of UGT1A1 deficiency as reflected by low conjugated bilirubin (< 20% of total bilirubin) and in patients where an irinotecan dose of > 180 mg/m^2 per administration is planned (recommendation grade C [insufficient evidence]).

The Japanese Society for Cancer of the Colon and Rectum guidelines[65] state that because irinotecan toxicity cannot be predicted with certainty on the basis of the presence of a *UGT1A1* genetic polymorphism alone, it is essential to monitor patients' general condition during treatment and to manage adverse drug reactions carefully, irrespective of whether a genetic polymorphism is detected.

Drug Label Information in the United States and Other Countries

According to the Table of Pharmacogenetic Associations from the FDA,[66] *UGT1A1 *28/*28* results in higher

TABLE 3. Information on Dose Reductions to be Applied in Patients With the Highest Risk of Toxicity From Irinotecan HCl, Irinotecan Liposome, and Sacituzumab Govitecan-hziy

Formulation	Regimen	Standard Dose[1,6,7]	Reduced Dose	IV Infusion Duration[1,6,7]	Frequency[1,6,7]
Irinotecan HCl (Camptosar)	Single agent	350 mg/m^2	300 mg/m^2 [1]	90 minutes	Every 3 weeks
	FOLFIRI with or without bevacizumab	180 mg/m^2	150 mg/m^2 [1]	90 minutes	Every 2 weeks
	FOLFIRINOX with or without cetuximab	180 mg/m^2	150 mg/m^2 [67,68]	90 minutes	Every 2 weeks
	FOLFOXIRI with cetuximab or bevacizumab	165 mg/m^2	125 mg/m^2 [69,70]	60 minutes	Every 2 weeks
Irinotecan liposome (Onivyde)	With 5-FU, leucovorin	70 mg/m^2	50 mg/m^2 [6,71]	90 minutes	Every 2 weeks
Sacituzumab Govitecan-hziy (Trodelvy)	Single agent	10 mg/kg	7.5 mg/kg[72]	3 hours for the first infusion. 1-2 hours if prior infusions were tolerated	Days 1 and 8 of each 21-day cycle

NOTE. Doublet and triplet regimens listed here are irinotecan-based combination therapies for advanced and metastatic colorectal cancer or pancreatic cancer recommended by the National Comprehensive Cancer Network (NCCN) guidelines. The reduced dose for irinotecan HCl or irinotecan liposome in combination with 5-FU and leucovorin (eg, FOLFIRI) is based on the dose reduction recommended by the FDA-approved labels.[1,6] The reduced dose for FOLFIRINOX is based on the studies demonstrating tolerability.[67,68] The reduced dose for FOLFOXIRI is based on the trial protocol dose reduction and the study demonstrating tolerability.[69,70] The reduced dose for sacituzumab govitecan-hziy is based on the trial protocol dose reduction.[72]

Abbreviations: FDA, US Food and Drug Administration; FOLFIRI, fluorouracil, leucovorin, and irinotecan; FOLFIRINOX, fluorouracil, leucovorin, irinotecan, and oxaliplatin; FOLFOXIRI, fluorouracil, folinic acid, oxaliplatin, and irinotecan; FU, fluorouracil.

systemic active metabolite concentrations and higher adverse reaction risk (severe neutropenia). Consider reducing the starting dosage by one level and modify the dosage on the basis of individual patient tolerance. Consistent with this, the FDA-approved drug labels for irinotecan and SN-38 (Camptosar, Onivyde, and Trodelvy) state that patients carrying *UGT1A1*28/*28* are at increased risk of neutropenia.[1,6,7] For these patients, the drug label for Camptosar (irinotecan HCl) recommends at least one level lower starting dose of irinotecan when administered in combination with other agents, or as a single agent[1] (Table 3).[1] However, the precise dose reduction in this patient population is not known, and subsequent dose modifications should be considered on the basis of individual patient tolerance to treatment. The FDA-approved drug label for Onivyde (irinotecan liposome) recommends a starting dose of 50 mg/m^2 (approximately 30% reduction of the standard dose), with an increased dose to 70 mg/m^2 as tolerated in subsequent cycles.[2] The FDA-approved drug label for Trodelvy (sacituzumab govitecan-hziy) indicates that the dose should be adjusted on the basis of individual patient tolerance because the appropriate dose for these patients is unknown.[6]

The Health Canada (Santé Canada)-approved drug label for irinotecan HCl recommends a reduction in the starting dose when administered in combination with other agents, or as a single agent but does not provide a specific dosing guideline.[73] The Pharmaceuticals and Medical Devices Agency–approved drug labels for irinotecan HCl and irinotecan liposome in Japan indicate caution for increased risk of irinotecan toxicity in patients carrying *UGT1A1*28/*28*, **6/*6*, or **28/*6*.[74,75] Although the drug label for irinotecan HCl does not provide a specific dosing guideline, the label for irinotecan liposome recommends a starting dose of 50 mg/m^2 (70 mg/m^2 in the subsequent cycle if tolerated) in these patients.[75]

Laboratories Providing *UGT1A1* Genetic Testing

The NIH's Genetic Testing Registry[76] lists 34 Clinical Laboratory Improvement Amendments–certified laboratories (29 in the United States and five in Europe) that provide *UGT1A1* genetic testing.

DISCUSSION

This review presents a concise, albeit comprehensive, overview of clinical perspectives on using *UGT1A1* genetic testing to obtain an evidence-based informed decision on irinotecan dosing. *UGT1A1* genetic testing was initially proposed to reduce the risk of irinotecan toxicity in patients with high-risk *UGT1A1* genotypes (*UGT1A1*28/*28*, **28/*6*, and **6/*6*).[4] However, recent studies[5,45,48,60,61] demonstrate a potential value of this testing as a means of maximizing treatment efficacy by increasing the dose in patients with low-risk *UGT1A1* genotypes (*UGT1A1*1/*1*, **1/*28*, and **1/*6*). However, there are still barriers to implement this test in clinical practice. Although *UGT1A1* genotype-based dosing has been extensively studied, neither the specific target exposure nor well-defined dosing recommendations have been established yet. Consequently, drug labels, oncology and pharmacology societies, and regulatory agencies in different countries vary significantly in their recommendations or lack thereof. The dose modification strategies using the *UGT1A1* genotype are

currently being actively investigated in patients treated with irinotecan-containing regimens. Once standardized dosing management strategies are established, we envision this approach as a strong framework for accelerating the implementation of precision dosing in patients with cancer receiving irinotecan-based chemotherapy.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

All You Need to Know About *UGT1A1* Genetic Testing for Patients Treated With Irinotecan: A Practitioner-Friendly Guide

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Patents, Royalties, Other Intellectual Property: United States Patent: Flavopiridol drug combinations and methods with reduced side effects, Ratain MJ, Innocenti F, Iyer L. Filed on April 12, 2001, serial number 09/835,082. United States Patent: Optimization of cancer treatment with irinotecan, Ratain MJ, Innocenti F, Karabatsos P, Grimsley C, Di Rienzo A. Filed on February 12, 2003, serial number 60/446,942. United States Patent: Methods of identifying risk of bevacizumab-induced proteinuria and hypertension, Innocenti F, Quintanilha J, Lin D, Owzar K, Wang J. Filed on July 17, 2020, serial number 16/932,002. United States Provisional Patent Application: Plasma Levels of Angiopoietin-2, VEGF-A, And VCAM-1 as Markers of Bevacizumab Induced Hypertension, Innocenti F, Quintanilha J. Filed on April 1, 2021, serial number 63/169,301

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