



Irinotecan Therapy and *UGT1A1* Genotype

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Introduction

Irinotecan (brand name Camptosar) is a topoisomerase I inhibitor widely used in the treatment of cancer. It is most frequently used in combination with other drugs to treat advanced or metastatic colorectal cancer. However, irinotecan therapy is associated with a high incidence of toxicity, including severe neutropenia and diarrhea (1).

Irinotecan is converted in the body to an active metabolite known as SN-38, which is then inactivated and detoxified by a UDP-glucuronosyltransferase (UGT) enzyme encoded by the *UGT1A1* gene. The UGT enzymes are responsible for glucuronidation, a process that transforms lipophilic metabolites into water-soluble metabolites that can be excreted from the body.

The risk of irinotecan toxicity increases with genetic variants associated with reduced UGT enzyme activity, such as *UGT1A1**28. The presence of this variant results in reduced excretion of irinotecan metabolites, which leads to increased active irinotecan metabolites in the blood. Approximately 10% of North Americans carry 2 copies of the *UGT1A1**28 allele (homozygous, *UGT1A1* *28/*28), and are more likely to develop neutropenia following irinotecan therapy (1-3).

The FDA-approved drug label for irinotecan states that “when administered as a single-agent, a reduction in the starting dose by at least one level of irinotecan hydrochloride injection 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” (Table 1) (1).

The Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP) recommends starting with 70% of the standard dose for homozygous carriers of the *UGT1A1**28 allele. If the patient tolerates this initial dose, the dose can be increased guided by the neutrophil count. They state that no action is needed for heterozygous carriers of the *UGT1A1**28 allele (e.g., *UGT1A1* *1/*28) (Table 2) (4). In addition, the French National Network of Pharmacogenetics (RNPGx) has proposed a decision tree for guiding irinotecan prescribing based on the *UGT1A1* genotype and irinotecan dose (Table 3) (5).

Table 1. FDA (2017) Drug Label for Irinotecan. Therapeutic Recommendations based on *UGT1A1* Genotype. Dosage and Administration.

Genotype	Recommendations
<i>UGT1A1</i> *28/*28	When administered as a single-agent, a reduction in the starting dose by at least one level of irinotecan hydrochloride injection, USP ¹ should be considered for patients known to be homozygous for the <i>UGT1A1</i> *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.

Please see Therapeutic Recommendations based on Genotype for more information from the FDA. Table adapted from (1).

Table 2. DPWG (2014) Recommendations for Irinotecan and *UGT1A1* Genotype.

Phenotype / genotype	Recommendations
<i>UGT1A1</i> intermediate metabolizer (IM)	NO action is needed for this gene-drug interaction.
<i>UGT1A1</i> poor metabolizer (PM)	Start with 70% of the standard dose If the patient tolerates this initial dose, the dose can be increased, guided by the neutrophil count.
<i>UGT1A1</i> *1/*28	NO action is needed for this gene-drug interaction.
<i>UGT1A1</i> *28/*28	Start with 70% of the standard dose If the patient tolerates this initial dose, the dose can be increased, guided by the neutrophil count.

Please see Therapeutic Recommendations based on Genotype for more information from the DPWG. Table is adapted from (4).

Table 3. RNPGx (2017) Recommendations for Irinotecan and *UGT1A1* Genotype.

Dose of irinotecan	Recommendation
low doses (<180 mg/m ² /week)	Presence of the <i>UGT1A1</i> *28 allele is not a major risk factor (little difference in risk of hematological or digestive toxicity irrespective of the genotype)
180–230 mg/m ² spaced by 2–3-week intervals	Patients who are homozygous for the <i>UGT1A1</i> *28 allele have a higher risk of hematological and/or digestive toxicity than patients who are heterozygous or non-carriers. For these *28/*28 patients, a 25-30% dose reduction is recommended, especially if the patient presents other risk factors for toxicity. Dose can be adjusted for subsequent cycles depending on the tolerance.
240 mg/m ² or higher spaced by 2–3-week intervals	Homozygous <i>UGT1A1</i> *28 patients have a greatly increased risk of hematological toxicity (neutropenia) compared with other genotypes, contraindicating administration at this higher dose and leading to discussion of a standard dose depending on the associated risk factors. Administration of an intensive dose (240 mg/m ²) is recommended only for *1/*1 patients, or for *1/*28 patients who have no other risk factors and who benefit from intensive surveillance.

Please see Therapeutic Recommendations based on Genotype for more information from the RNPGx. Table is adapted from (5).

Drug: Irinotecan

Irinotecan is used to treat colorectal cancer, which is the third most common cancer worldwide (6). It is often used in combination with other drugs to treat patients with advanced or metastatic colorectal cancer, when the cancer has recurred, or has progressed following initial treatment. A common irinotecan-based combination therapy is referred to as FOLFIRI (FOLinic acid [also known as leucovorin], Fluorouracil, IRInotecan).

Irinotecan is a semisynthetic derivative of the antineoplastic agent camptothecin, which derives its name from the Camptotheca tree where it was first isolated. Like camptothecin, irinotecan is an inhibitor of the nuclear

¹ USP stands for the United States Pharmacopeia. The USP establishes standards that promote safe medication use (e.g., procurement, prescribing, transcribing, order entry, preparation, dispensing, administration, and monitoring of medications).

enzyme, topoisomerase I. This enzyme catalyzes a number of nuclear processes; regulation of DNA supercoiling, replication, recombination, and repair.

Topoisomerase I decreases the torsional strain in the helical strands of DNA by making single strand breaks in the DNA. Single strands of DNA pass through the breaks and bind to the topoisomerase to form a cleavable complex. Once the DNA is sufficiently relaxed and the passage of strands has been completed, topoisomerase re-ligates the broken DNA strands and allows for transcription to proceed (7, 8).

Irinotecan is a pro-drug, and is converted by carboxylesterase enzymes to the active metabolite SN-38, which is 100–1000 times more potent than its parent drug, after administration by intravenous injection (9). The SN-38 metabolite exerts its cytotoxic effects by binding to the cleavable complex to form a ternary drug-topoisomerase-DNA complex. This complex is thought to prevent the re-ligation of the single strand breaks, which interrupts the moving DNA replication fork. The arrest of replication and the interaction between replication enzymes and the ternary complex introduces lethal double-stranded breaks in DNA causing irreparable DNA damage and subsequent cell apoptosis. (10, 11).

SN-38 is lipophilic, and it needs to be inactivated by undergoing phase II metabolism (glucuronidation). The resulting conjugated SN-38 glucuronide is water-soluble, and is mainly excreted through the bile, with about 30% excreted by the kidneys (12).

Irinotecan-based combination therapy has been found to be superior in overall response and survival when compared with the use of 5-fluorouracil/leucovorin therapy alone for patients with metastatic colorectal cancer (3). However, the use of irinotecan is limited by a high incidence of unpredictable and severe dose-limiting toxicity, including severe neutropenia, fever, and diarrhea (13). The rate of grade 3 or 4 adverse events is around 20-25% (14). Approximately 7% of patients who present with severe neutropenia and fever following treatment with irinotecan will die from these complications (3, 15-18).

Gene: *UGT1A1*

The UGT enzymes (uridine diphosphate-glucuronosyltransferase, or UDP-glucuronosyltransferase) are a superfamily of enzymes that metabolize a wide range of lipophilic molecules such as bilirubin, steroids, toxins, and drugs—including irinotecan's active metabolite, SN-38. These enzymes mediate the process of glucuronidation, which is a phase II metabolic pathway during which glucuronic acid is conjugated to specific targets to convert them to water-soluble metabolites that can then be eliminated from the body.

The UGT genes are polymorphic, and genomic processes, such as copy-number variations, variant splicing, and epigenetic factors, likely contribute to their diversity. As a result, the substrates that the UGT enzymes catalyze are particularly variable (19).

The UGT superfamily contains at least 117 enzymes divided into 4 families, of which UGT1A is a member (20). The *UGT1A* gene locus, located on chromosome 2q37, is complex—it encodes multiple genes and pseudogenes, and alternatively spliced isoforms also exist (21).

The *UGT1A* locus contains multiple alternative first coding exons, each of which has its own promoter site, enabling the transcription of 9 unique UGT1A enzymes (22). One of these transcripts is *UGT1A1*, which encodes UGT1A1, the bilirubin-UGT enzyme. Whereas many UGT enzymes overlap in the substrates they glucuronidate, UGT1A1 is the only enzyme that glucuronidates bilirubin (23).

Bilirubin is a yellow waste product produced during the catabolism of heme, a constituent of hemoglobin. When old or damaged red blood cells are broken down in the spleen, their hemoglobin is broken down to heme, which is then converted into bilirubin. The UGT1A1 enzyme converts this toxic, insoluble form of bilirubin (unconjugated bilirubin) to its nontoxic form (conjugated bilirubin). Because conjugated bilirubin is water-soluble, it can be dissolved in bile and eliminated with solid waste. If bilirubin is not eliminated and instead

accumulates to high levels (hyperbilirubinemia), it can cause a yellowish discoloration of the skin and eyes, a condition known as jaundice.

Variants of the *UGT1A1* gene that decrease UGT1A1 enzyme activity can lead to jaundice. The data suggests that one copy of *28 allele results in about a 35% decrease in transcriptional activity, and 2 copies (*28/*28, homozygous) results in about a 70% decrease (24, 25).

The jaundice may be mild, as seen in Gilbert syndrome, or severe, as seen in Crigler-Najjar syndrome. Crigler-Najjar syndrome presents in 2 forms called type 1 and type 2. Type 1 is the extremely severe form where affected individuals can die in childhood due to kernicterus (bilirubin-induced brain injury), although they may survive for longer with treatment. Type 2 is less severe; the affected individuals are less likely to develop kernicterus and most survive into adulthood.

Currently, over 135 genetic variants of *UGT1A1* have been reported (23, 26). *UGT1A1*1* is the wild-type allele associated with normal enzyme activity. The most common variant allele is *UGT1A1*28*, which is commonly found in African-Americans (0.42–0.45 allele frequency) and Caucasians (0.26–0.31), and is less common in Asian populations (0.09–0.16) (27, 28). Within Caucasian and African American populations, the *UGT1A1*28* variant is a common cause of Gilbert syndrome and is also a cause of Crigler-Najjar syndrome types 1 and 2 (19, 27).

The *UGT1A1*28* [(TA)₇TAA] variant contains an extra thymine-adenine (TA) repeat within the TATA box promoter region (7 TA repeats compared with 6 in the wild-type allele) (29). This extra (TA) repeat decreases the rate of transcription initiation of the *UGT1A1* gene, leading to decreased enzyme activity and decreased glucuronidation of bilirubin to about 30% of wild-type levels (30).

Another variant allele, *UGT1A1*37* [(TA)₈TAA], has 8 TA repeats at this site, and results in reduced promoter activity of the gene to levels lower than the *UGT1A1*28* allele. In contrast, the *UGT1A1*36* [(TA)₅TAA] allele only has 5 repeats and is associated with increased promoter activity and a reduced risk of neonatal hyperbilirubinemia (a common, and typically benign condition). Both *UGT1A1*36* and *UGT1A1*37* occur almost exclusively in populations of African origin, with estimated allele frequencies of 0.03–0.10 and 0.02–0.07, respectively.

The *UGT1A1*28* variant is also associated with drug toxicity. Approximately 10% of the North American population is homozygous for the *28 allele (*28/*28 genotype, also known as *UGT1A1 7/7* genotype) and are at an increased risk of neutropenia following intravenous irinotecan therapy (28). The rate of severe neutropenia in *28/*28 homozygous patients is as high as 36%, and is strongly associated with a higher hospitalization rate (7, 31, 32).

There is less evidence to support a link between *UGT1A1* genotype and irinotecan treatment-related diarrhea, and there is conflicting data on whether an individual's *UGT1A1* genotype influences their response to irinotecan therapy (8, 33).

Another variant allele, *UGT1A1*6*, is more prevalent in Asian populations, with an allele frequency of around 15–30% in Chinese, Korean, and Japanese populations (24, 34, 35). In this variant, there is a switch of amino acids, from a glycine to an arginine at position 71 within a coding region (p.Arg71Gly). Individuals who are homozygous for this allele have reduced UGT1A1 enzyme activity, which can cause Gilbert syndrome and prolonged neonatal jaundice (36–39). This variant also appears to be an important predictor of severe toxicity to irinotecan therapy in Asian populations (35, 40–47).

In addition to genetic variations in the *UGT1A1* gene, several other genetic markers may influence the risk of irinotecan toxicity. These include genetic variation in the adenosine triphosphate (ATP)-binding cassette (ABC) transporter genes, *ABCC1* and *ABCB2* (43, 48, 49), the solute carrier (*SLC*) transporter genes (48, 50, 51), the transforming growth factor (*TGFB*) gene (52), and the xenobiotic-sensing receptor, *NR1I2* (53).

The emerging data suggests that other variant alleles may have a protective effect. The newly discovered marker rs11563250 (NM_001287395.1:c.-1068A>G), located in the 3′-flanking region of *UGT1A1*, has a major A allele (rs11563250A) and a relatively common variant G allele (rs11563250G, found in 12% of the population). Carriers of the G allele have a lower risk of irinotecan-induced neutropenia. They also tend to have lower total plasma bilirubin levels, suggesting that this variant is associated with an enhanced capacity for glucuronidation. Evidence suggests that carriers of rs11563250G could tolerate a higher dose of irinotecan, especially if they also have the *UGT1A1**1/*1 genotype (54).

Genetic Testing

The NIH's Genetic Testing Registry provides examples of the genetic tests currently available for [irinotecan response](#) and for the [UGT1A1 gene](#).

Genetic testing can be used to optimize irinotecan dosing. For example, the use of genotyping in selective cases may make the following patient choices possible:

- If the patient prefers aggressive treatment: genotyping might allow higher dosing for *1/*1 and *1/*28 genotypes (55-59).
- If the patient prefers maximizing quality of life: genotyping might allow lower dosing for *28/*28 genotype (7, 31, 32).

Genotyping may also enable irinotecan to be added to the treatment of other gastrointestinal tumors without the risk of hematologic toxicity (60). Genotyping may also be used as part of the management of Gilbert syndrome (15).

In the USA, the common *1 and *28 *UGT1A1* alleles comprise 98–99% of genotypes (61). Routine genotyping typically tests for *UGT1A1* *1/*1, *1/*28, and *28/*28 genotypes (also known as 6/6, 6/7, and 7/7, respectively).

Routine screening does not rule out other *UGT1A1* polymorphisms that are more common in specific populations (7). For example, the *UGT1A1**6 allele is common in Asian populations, and in Japan, a reduced dose of irinotecan is recommended for individuals with *UGT1A1* *6/*6, *6/*28, and *28/*28 genotypes (62). In addition, routine screening does not identify patients who are being under-dosed and could potentially tolerate a much higher dose of irinotecan.

The adoption of preemptive *UGT1A1**28 genotyping to increase irinotecan safety and efficacy in clinical practice is still limited and often not covered by health insurance, despite the significant costs of treating irinotecan-related toxicities (63, 64).

Part of the reason that healthcare providers forgo testing may be because the standard dose of irinotecan used in FOLFIRI is low (180 mg/m²). A phase II trial is currently determining whether dosing irinotecan based on genotype, as part of a FOLFIRI treatment regime, is effective and safe. The standard irinotecan dose of 180 mg/m² is being used for patients with the 28/*28 genotype, a dose of 260 mg/m² is being used for patients with the *1/*28 genotype, and a dose of 310 mg/m² is being used for patients with the *1/*1 genotype (65).

Therapeutic Recommendations based on Genotype

This section contains excerpted² information on gene-based dosing recommendations. Neither this section nor other parts of this review contain the complete recommendations from the sources.

² The FDA labels specific drug formulations. We have substituted the generic names for any drug labels in this excerpt. The FDA may not have labeled all formulations containing the generic drug.

2017 Statement from the US Food and Drug Administration (FDA)

Individuals who are homozygous for the *UGT1A1**28 allele (*UGT1A1* 7/7 genotype) are at increased risk for neutropenia following initiation of Irinotecan Hydrochloride Injection, USP treatment.

In a study of 66 patients who received single-agent Irinotecan Hydrochloride Injection, USP (350 mg/m² once-every-3-weeks), the incidence of grade 4 neutropenia in patients homozygous for the *UGT1A1**28 allele was 50%, and in patients heterozygous for this allele (*UGT1A1* 6/7 genotype) the incidence was 12.5%. No grade 4 neutropenia was observed in patients homozygous for the wild-type allele (*UGT1A1* 6/6 genotype).

When administered as a single-agent, a reduction in the starting dose by at least one level of Irinotecan Hydrochloride Injection, USP 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.

UGT1A1 Testing

A laboratory test is available to determine the *UGT1A1* status of patients. Testing can detect the *UGT1A1* 6/6, 6/7 and 7/7 genotypes.

Please review the complete therapeutic recommendations that are located here: (1).

2017 Recommendations from the French National Network of Pharmacogenetics (RNPGx)

Interpreting Results

The RNPGx has proposed a decision tree for guiding irinotecan prescription based on the *UGT1A1* genotype and the protocol's theoretical dose:

- for low doses (< 180 mg/m² /week), presence of the *UGT1A1**28 allele is not a major risk factor (little difference in risk of hematological or digestive toxicity irrespective of the genotype);
- for doses in the 180—230mg/m² spaced by 2—3-week intervals, patients who are homozygous for the *UGT1A1**28 allele have a higher risk of hematological and/or digestive toxicity than patients who are heterozygous or non-carriers. For these *28/*28 patients, a 25% to 30% dose reduction is recommended, especially if the patient presents other risk factors for toxicity. Dose can be adjusted for subsequent cycles depending on the tolerance;
- for doses of 240mg/m² or higher spaced by 2—3 weeks intervals, homozygous *UGT1A1**28 patients have a greatly increased risk of hematological toxicity (neutropenia) compared with other genotypes, contraindicating administration at this higher dose and leading to discussion of a standard dose depending on the associated risk factors. Administration of an intensive dose (240 mg/m²) is recommended only for *1/*1 patients, or for *1/*28 patients who have no other risk factors and who benefit from intensive surveillance.

[...]

The first-intention of this strategy for analysis of *UGT1A1* status is to detect the *28 variant, the most common deficiency variant observed in the Caucasian population, to be performed before initiating treatment. Referring to the level of evidence classification for RNPGx recommendations detailed in the article by Picard et al. in this issue, *UGT1A1* genotyping is advisable for a standard dose (180—230mg/m²) and essential for intensified dose (> 240 mg/m²).

Thus, individualized treatment can be proposed based on the *UGT1A1* genotype, with either a dose reduction for *28/*28 homozygous patients, or possibly dose intensification for non-carriers of the *28 allele.

For the other *UGT1A1* alleles, genotyping is performed by a limited number of laboratories and is considered a second- intention test.

Moreover, the RNPGx suggests that this analysis could be performed concomitantly with other genetic explorations for colorectal cancer patients (search for *KRAS*, *BRAF* mutations. . .) and constitutional (search for *DYPD* variants) in order to guarantee optimal irinotecan therapy within adequate delay for optimal hospital practices.

Please review the complete therapeutic recommendations that are located here: (5).

2014 Recommendations from the Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP)

UGT1A1 Intermediate Metabolizers (IM)

NO action is needed for this gene-drug interaction.

This genetic variation (IM) is more common in Western populations than the wild-type (*1/*1). This means that treatment is largely geared to patients with this genetic variation. Adjustment of the treatment is therefore not useful.

UGT1A1 Poor Metabolizers (PM)

Genetic variation reduces conversion of irinotecan to inactive metabolites. This increases the risk of serious, life-threatening adverse events.

Recommendation:

1. Start with 70% of the standard dose

If the patient tolerates this initial dose, the dose can be increased, guided by the neutrophil count.

UGT1A1 *1/*28

NO action is needed for this gene-drug interaction.

This genetic variation (*1/*28) is more common in Western populations than the wild-type (*1/*1). This means that treatment is largely geared to patients with this genetic variation. Adjustment of the treatment is therefore not useful.

UGT1A1 *28/*28

Genetic variation reduces conversion of irinotecan to inactive metabolites. This increases the risk of serious, life-threatening adverse events.

Recommendation:

1. Start with 70% of the standard dose

If the patient tolerates this initial dose, the dose can be increased, guided by the neutrophil count.

Please review the complete therapeutic recommendations that are located here: (4).

Nomenclature of selected *UGT1A1* variants

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
<i>UGT1A1</i> *1	(TA) ₆ TAA	NM_000463.2:c.-53_-52TA[7]	Not applicable—variant occurs in a non-coding (TATA box promoter) region	rs8175347
<i>UGT1A1</i> *6	211G>A Gly71Arg	NM_000463.2:c.211G>A	NP_000454.1:p.Gly71Arg	rs4148323

Table continued from previous page.

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
<i>UGT1A1</i> *36	(TA) ₅ TAA	NM_000463.2:c.-53_-52TA[6]	Not applicable—variant occurs in a non-coding (TATA box promoter) region	rs8175347
<i>UGT1A1</i> *28	(TA) ₇ TAA	NM_000463.2:c.-53_-52[8]	Not applicable—variant occurs in a non-coding (TATA box promoter) region	rs8175347
<i>UGT1A1</i> *37	(TA) ₈ TAA	NM_000463.2:c.-53_-52TA[9]	Not applicable—variant occurs in a non-coding (TATA box promoter) region	rs8175347

*UGT1A1**1 is the wild-type allele and is associated with normal enzyme activity.

Note: The *UGT1A1**28 variant has 8 TA repeats, as shown by the “[8]” in the official HGVS term, “NM_000463.2:c.-53_-52[8]”. In the medical literature, the term “(TA)₇TAA” is commonly used. Here, 7 of the TA repeats are shown in parentheses “(TA)₇”, followed by the 8th repeat “(TAA)”.

For an overview of the haplotypes for *UGT1A1*, please see the PharmGKB’s [Haplotype Translation Table](#).

Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS).

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References

1. IRINOTECAN HYDROCHLORIDE- irinotecan hydrochloride injection [package insert]. Orlando, FL, USA; June 5, 2017. Available from: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=d04f2471-3085-4fc8-a657-bb3918d48e6e>

2. Fujita K., Sparreboom A. Pharmacogenetics of irinotecan disposition and toxicity: a review. *Curr Clin Pharmacol*. 2010 Aug;5(3):209–17. PubMed PMID: 20406168.
3. Liu X., Cheng D., Kuang Q., Liu G., et al. Association of UGT1A1*28 polymorphisms with irinotecan-induced toxicities in colorectal cancer: a meta-analysis in Caucasians. *Pharmacogenomics J*. 2014 Apr;14(2):120–9. PubMed PMID: 23529007.
4. Royal Dutch Pharmacists Association (KNMP). Dutch Pharmacogenetics Working Group (DPWG). Pharmacogenetic Guidelines [Internet]. Netherlands. Irinotecan – UGT1A1 [Cited May 2017]. Available from: <http://kennisbank.knmp.nl> [Access is restricted to KNMP membership.]
5. Quaranta S., Thomas F. Pharmacogenetics of anti-cancer drugs: State of the art and implementation - recommendations of the French National Network of Pharmacogenetics. *Therapie*. 2017 Apr;72(2):205–215. PubMed PMID: 28262261.
6. Shike M., Winawer S.J., Greenwald P.H., Bloch A., et al. Primary prevention of colorectal cancer. The WHO Collaborating Centre for the Prevention of Colorectal Cancer. *Bull World Health Organ*. 1990;68(3):377–85. PubMed PMID: 2203551.
7. *Should UGT1A1 Genotyping Be Used to Predict Response to Irinotecan Chemotherapy? EGAPP™ Recommendation Statement*. *Public Health Genomics* 2009 [cited May 5, 2015]; Available from: <http://www.cdc.gov/genomics/gtesting/EGAPP/recommend/UGT1A1.htm>.
8. Dias M.M., McKinnon R.A., Sorich M.J. Impact of the UGT1A1*28 allele on response to irinotecan: a systematic review and meta-analysis. *Pharmacogenomics*. 2012 Jun;13(8):889–99. PubMed PMID: 22676194.
9. Chabot G.G. Clinical pharmacokinetics of irinotecan. *Clin Pharmacokinet*. 1997 Oct;33(4):245–59. PubMed PMID: 9342501.
10. Pommier Y., Pourquier P., Fan Y., Strumberg D. Mechanism of action of eukaryotic DNA topoisomerase I and drugs targeted to the enzyme. *Biochim Biophys Acta*. 1998 Oct 1;1400(1-3):83–105. PubMed PMID: 9748515.
11. Di Paolo A., Bocci G., Polillo M., Del Re M., et al. Pharmacokinetic and pharmacogenetic predictive markers of irinotecan activity and toxicity. *Curr Drug Metab*. 2011 Dec;12(10):932–43. PubMed PMID: 21787264.
12. Slatter J.G., Schaaf L.J., Sams J.P., Feenstra K.L., et al. Pharmacokinetics, metabolism, and excretion of irinotecan (CPT-11) following I.V. infusion of [(14)C]CPT-11 in cancer patients. *Drug Metab Dispos*. 2000 Apr;28(4):423–33. PubMed PMID: 10725311.
13. Hoskins J.M., Goldberg R.M., Qu P., Ibrahim J.G., et al. UGT1A1*28 genotype and irinotecan-induced neutropenia: dose matters. *J Natl Cancer Inst*. 2007 Sep 5;99(17):1290–5. PubMed PMID: 17728214.
14. Tam V.C., Rask S., Koru-Sengul T., Dhesy-Thind S. Generalizability of toxicity data from oncology clinical trials to clinical practice: toxicity of irinotecan-based regimens in patients with metastatic colorectal cancer. *Curr Oncol*. 2009 Dec;16(6):13–20. PubMed PMID: 20016742.
15. Douillard J.Y., Cunningham D., Roth A.D., Navarro M., et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet*. 2000 Mar 25;355(9209):1041–7. PubMed PMID: 10744089.
16. Obradovic M., Mrhar A., Kos M. Cost-effectiveness of UGT1A1 genotyping in second-line, high-dose, once every 3 weeks irinotecan monotherapy treatment of colorectal cancer. *Pharmacogenomics*. 2008 May;9(5):539–49. PubMed PMID: 18466101.
17. Lankisch T.O., Schulz C., Zwingers T., Erichsen T.J., et al. Gilbert's Syndrome and irinotecan toxicity: combination with UDP-glucuronosyltransferase 1A7 variants increases risk. *Cancer Epidemiol Biomarkers Prev*. 2008 Mar;17(3):695–701. PubMed PMID: 18349289.
18. Ratain M.J. Irinotecan dosing: does the CPT in CPT-11 stand for "Can't Predict Toxicity"? *J Clin Oncol*. 2002 Jan 1;20(1):7–8. PubMed PMID: 11773147.
19. Guillemette C. Pharmacogenomics of human UDP-glucuronosyltransferase enzymes. *Pharmacogenomics J*. 2003;3(3):136–58. PubMed PMID: 12815363.

20. Mackenzie P.I., Bock K.W., Burchell B., Guillemette C., et al. Nomenclature update for the mammalian UDP glycosyltransferase (UGT) gene superfamily. *Pharmacogenet Genomics*. 2005 Oct;15(10):677–85. PubMed PMID: 16141793.
21. van Es H.H., Bout A., Liu J., Anderson L., et al. Assignment of the human UDP glucuronosyltransferase gene (UGT1A1) to chromosome region 2q37. *Cytogenet Cell Genet*. 1993;63(2):114–6. PubMed PMID: 8467709.
22. Girard H., Levesque E., Bellemare J., Journault K., et al. Genetic diversity at the UGT1 locus is amplified by a novel 3' alternative splicing mechanism leading to nine additional UGT1A proteins that act as regulators of glucuronidation activity. *Pharmacogenet Genomics*. 2007 Dec;17(12):1077–89. PubMed PMID: 18004212.
23. Strassburg C.P. Pharmacogenetics of Gilbert's syndrome. *Pharmacogenomics*. 2008 Jun;9(6):703–15. PubMed PMID: 18518849.
24. Pharmacogenomics: Challenges and Opportunities in Therapeutic Implementation. Chapter 1 - Principles of Pharmacogenomics: Pharmacokinetic, Pharmacodynamic, and Clinical Implications. [Cited March 2018]. Available from: <https://www.sciencedirect.com/science/book/9780123919182>
25. Barbarino J.M., Haidar C.E., Klein T.E., Altman R.B. PharmGKB summary: very important pharmacogene information for UGT1A1. *Pharmacogenet Genomics*. 2014 Mar;24(3):177–83. PubMed PMID: 24492252.
26. Pharmacogenomics Laboratory, Canada Research Chair in Pharmacogenomics [Internet]. UGT Official Nomenclature: UGT1A and UGT2B haplotypes and SNPs tables. [Cited March 2018]. Available from: <https://www.pharmacogenomics.pha.ulaval.ca/ugt-alleles-nomenclature/>
27. Beutler E., Gelbart T., Demina A. Racial variability in the UDP-glucuronosyltransferase 1 (UGT1A1) promoter: a balanced polymorphism for regulation of bilirubin metabolism? *Proc Natl Acad Sci U S A*. 1998 Jul 7;95(14):8170–4. PubMed PMID: 9653159.
28. Hall D., Ybazeta G., Destro-Bisol G., Petzl-Erler M.L., et al. Variability at the uridine diphosphate glucuronosyltransferase 1A1 promoter in human populations and primates. *Pharmacogenetics*. 1999 Oct;9(5):591–9. PubMed PMID: 10591539.
29. NCBI ClinVar [Internet]. ClinVar: UGT1A1*28 [Cited March 20, 2018]. Available from: <https://www.ncbi.nlm.nih.gov/clinvar/variation/12275/>
30. Bosma P.J., Chowdhury J.R., Bakker C., Gantla S., et al. The genetic basis of the reduced expression of bilirubin UDP-glucuronosyltransferase 1 in Gilbert's syndrome. *N Engl J Med*. 1995 Nov 2;333(18):1171–5. PubMed PMID: 7565971.
31. Shulman K., Cohen I., Barnett-Griness O., Kuten A., et al. Clinical implications of UGT1A1*28 genotype testing in colorectal cancer patients. *Cancer*. 2011 Jul 15;117(14):3156–62. PubMed PMID: 21287524.
32. Etienne-Grimaldi M.C., Boyer J.C., Thomas F., Quaranta S., et al. UGT1A1 genotype and irinotecan therapy: General review and implementation in routine practice. *Fundam Clin Pharmacol*. 2015 Mar 27;29(3):219–37. PubMed PMID: 25817555.
33. EGAPP; Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. Recommendations from the EGAPP Working Group: can UGT1A1 genotyping reduce morbidity and mortality in patients with metastatic colorectal cancer treated with irinotecan? *Genet Med*. 2009 Jan;11(1):15–20. PubMed PMID: 19125128.
34. Akaba K., Kimura T., Sasaki A., Tanabe S., et al. Neonatal hyperbilirubinemia and a common mutation of the bilirubin uridine diphosphate-glucuronosyltransferase gene in Japanese. *J Hum Genet*. 1999;44(1):22–5. PubMed PMID: 9929972.
35. Zhang X., Yin J.F., Zhang J., Kong S.J., et al. UGT1A1*6 polymorphisms are correlated with irinotecan-induced neutropenia: a systematic review and meta-analysis. *Cancer Chemother Pharmacol*. 2017 Jul;80(1):135–149. PubMed PMID: 28585035.
36. Akaba K., Kimura T., Sasaki A., Tanabe S., et al. Neonatal hyperbilirubinemia and mutation of the bilirubin uridine diphosphate-glucuronosyltransferase gene: a common missense mutation among Japanese, Koreans and Chinese. *Biochem Mol Biol Int*. 1998 Sep;46(1):21–6. PubMed PMID: 9784835.

37. Yamamoto K., Sato H., Fujiyama Y., Doida Y., et al. Contribution of two missense mutations (G71R and Y486D) of the bilirubin UDP glycosyltransferase (*UGT1A1*) gene to phenotypes of Gilbert's syndrome and Crigler-Najjar syndrome type II. *Biochim Biophys Acta*. 1998 Apr 28;1406(3):267–73. PubMed PMID: 9630669.
38. Maruo Y., Nishizawa K., Sato H., Doida Y., et al. Association of neonatal hyperbilirubinemia with bilirubin UDP-glucuronosyltransferase polymorphism. *Pediatrics*. 1999 Jun;103(6 Pt 1):1224–7. PubMed PMID: 10353933.
39. Boyd M.A., Srasuebkul P., Ruxrungtham K., Mackenzie P.I., et al. Relationship between hyperbilirubinaemia and UDP-glucuronosyltransferase 1A1 (*UGT1A1*) polymorphism in adult HIV-infected Thai patients treated with indinavir. *Pharmacogenet Genomics*. 2006 May;16(5):321–9. PubMed PMID: 16609363.
40. Hazama S., Mishima H., Tsunedomi R., Okuyama Y., et al. *UGT1A1**6, *1A7**3, and *1A9**22 genotypes predict severe neutropenia in FOLFIRI-treated metastatic colorectal cancer in two prospective studies in Japan. *Cancer Sci*. 2013 Dec;104(12):1662–9. PubMed PMID: 24033692.
41. Atasilp C., Chansriwong P., Sirachainan E., Reungwetwattana T., et al. Correlation of *UGT1A1*(*)28 and (*)6 polymorphisms with irinotecan-induced neutropenia in Thai colorectal cancer patients. *Drug Metab Pharmacokinet*. 2016 Feb;31(1):90–4. PubMed PMID: 26830078.
42. Takano M., Yamamoto K., Tabata T., Minegishi Y., et al. Impact of *UGT1A1* genotype upon toxicities of combination with low-dose irinotecan plus platinum. *Asia Pac J Clin Oncol*. 2016 Jun;12(2):115–24. PubMed PMID: 26862009.
43. Yan L., Wang X.F., Wei L.M., Nie Y.L., et al. Effects of *UGT1A1**6, *UGT1A1**28, and *ABCB1*-3435C>T polymorphisms on irinotecan induced toxicity in Chinese cancer patients. *Int J Clin Pharmacol Ther*. 2016 Mar;54(3):193–9. PubMed PMID: 26857783.
44. Liu X.H., Lu J., Duan W., Dai Z.M., et al. Predictive Value of *UGT1A1**28 Polymorphism In Irinotecan-based Chemotherapy. *J Cancer*. 2017;8(4):691–703. PubMed PMID: 28367249.
45. Liu D., Li J., Gao J., Li Y., et al. Examination of multiple *UGT1A* and *DPYD* polymorphisms has limited ability to predict the toxicity and efficacy of metastatic colorectal cancer treated with irinotecan-based chemotherapy: a retrospective analysis. *BMC Cancer*. 2017 Jun 20;17(1):437. PubMed PMID: 28637434.
46. Xu C., Tang X., Qu Y., Keyoumu S., et al. *UGT1A1* gene polymorphism is associated with toxicity and clinical efficacy of irinotecan-based chemotherapy in patients with advanced colorectal cancer. *Cancer Chemother Pharmacol*. 2016 Jul;78(1):119–30. PubMed PMID: 27220761.
47. Cui C., Shu C., Cao D., Yang Y., et al. *UGT1A1**6, *UGT1A7**3 and *UGT1A9**1b polymorphisms are predictive markers for severe toxicity in patients with metastatic gastrointestinal cancer treated with irinotecan-based regimens. *Oncol Lett*. 2016 Nov;12(5):4231–4237. PubMed PMID: 27895797.
48. Chen S., Villeneuve L., Jonker D., Couture F., et al. *ABCC5* and *ABCG1* polymorphisms predict irinotecan-induced severe toxicity in metastatic colorectal cancer patients. *Pharmacogenet Genomics*. 2015 Dec;25(12):573–83. PubMed PMID: 26352872.
49. Li M., Seiser E.L., Baldwin R.M., Ramirez J., et al. ABC transporter polymorphisms are associated with irinotecan pharmacokinetics and neutropenia. *Pharmacogenomics J*. 2018 Nov 15;18(1):35–42. PubMed PMID: 27845419.
50. Crona D.J., Ramirez J., Qiao W., de Graan A.J., et al. Clinical validity of new genetic biomarkers of irinotecan neutropenia: an independent replication study. *Pharmacogenomics J*. 2016 Feb;16(1):54–9. PubMed PMID: 25869015.
51. Toshimoto K., Tomaru A., Hosokawa M., Sugiyama Y. Virtual Clinical Studies to Examine the Probability Distribution of the AUC at Target Tissues Using Physiologically-Based Pharmacokinetic Modeling: Application to Analyses of the Effect of Genetic Polymorphism of Enzymes and Transporters on Irinotecan Induced Side Effects. *Pharm Res*. 2017 Aug;34(8):1584–1600. PubMed PMID: 28397089.
52. Li J., Yu Q., Fu S., Xu M., et al. A novel genetic score model of *UGT1A1* and *TGFB* pathway as predictor of severe irinotecan-related diarrhea in metastatic colorectal cancer patients. *J Cancer Res Clin Oncol*. 2016 Jul;142(7):1621–8. PubMed PMID: 27160286.

53. Mbatchi L.C., Robert J., Ychou M., Boyer J.C., et al. Effect of Single Nucleotide Polymorphisms in the Xenobiotic-sensing Receptors NR1I2 and NR1I3 on the Pharmacokinetics and Toxicity of Irinotecan in Colorectal Cancer Patients. *Clin Pharmacokinet.* 2016 Sep;55(9):1145–57. PubMed PMID: 27116457.
54. Chen S., Laverdiere I., Tourancheau A., Jonker D., et al. A novel UGT1 marker associated with better tolerance against irinotecan-induced severe neutropenia in metastatic colorectal cancer patients. *Pharmacogenomics J.* 2015 Mar 17;15(6):513–20. PubMed PMID: 25778466.
55. Toffoli G., Sharma M.R., Marangon E., Posocco B., et al. Genotype-Guided Dosing Study of FOLFIRI plus Bevacizumab in Patients with Metastatic Colorectal Cancer. *Clin Cancer Res.* 2017 Feb 15;23(4):918–924. PubMed PMID: 27507617.
56. Phelip J.M., Mineur L., De la Fouchardiere C., Chatelut E., et al. High Resectability Rate of Initially Unresectable Colorectal Liver Metastases After UGT1A1-Adapted High-Dose Irinotecan Combined with LV5FU2 and Cetuximab: A Multicenter Phase II Study (ERBIFORT). *Ann Surg Oncol.* 2016 Jul;23(7):2161–6. PubMed PMID: 26739304.
57. Toffoli G., Cecchin E., Gasparini G., D'Andrea M., et al. Genotype-driven phase I study of irinotecan administered in combination with fluorouracil/leucovorin in patients with metastatic colorectal cancer. *J Clin Oncol.* 2010 Feb 10;28(5):866–71. PubMed PMID: 20038727.
58. Marcuello E., Paez D., Pare L., Salazar J., et al. A genotype-directed phase I-IV dose-finding study of irinotecan in combination with fluorouracil/leucovorin as first-line treatment in advanced colorectal cancer. *Br J Cancer.* 2011 Jun 28;105(1):53–7. PubMed PMID: 21654688.
59. Innocenti F., Schilsky R.L., Ramirez J., Janisch L., et al. Dose-finding and pharmacokinetic study to optimize the dosing of irinotecan according to the UGT1A1 genotype of patients with cancer. *J Clin Oncol.* 2014 Aug 1;32(22):2328–34. PubMed PMID: 24958824.
60. McWilliams R.R., Foster N.R., Mahoney M.R., Smyrk T.C., et al. North Central Cancer Treatment Group N0543 (Alliance): A phase 2 trial of pharmacogenetic-based dosing of irinotecan, oxaliplatin, and capecitabine as first-line therapy for patients with advanced small bowel adenocarcinoma. *Cancer.* 2017 May 10;123(18):3494–3501. PubMed PMID: 28493308.
61. Evaluation of Genomic Applications in P. and Prevention Working, G., *Recommendations from the EGAPP Working Group: can UGT1A1 genotyping reduce morbidity and mortality in patients with metastatic colorectal cancer treated with irinotecan?* *Genet Med.* 2009 Jan;11(1):15–20. PubMed PMID: 19125128.
62. Fujita K., Kubota Y., Ishida H., Sasaki Y. Irinotecan, a key chemotherapeutic drug for metastatic colorectal cancer. *World J Gastroenterol.* 2015 Nov 21;21(43):12234–48. PubMed PMID: 26604633.
63. Roncato R., Cecchin E., Montico M., De Mattia E., et al. Cost Evaluation of Irinotecan-Related Toxicities Associated With the UGT1A1*28 Patient Genotype. *Clin Pharmacol Ther.* 2017;(Jan):11. PubMed PMID: 28074472.
64. Butzke B., Oduncu F.S., Severin F., Pfeufer A., et al. The cost-effectiveness of UGT1A1 genotyping before colorectal cancer treatment with irinotecan from the perspective of the German statutory health insurance. *Acta Oncol.* 2016;55(3):318–28. PubMed PMID: 26098842.
65. ClinicalTrials.gov. Genotype-Directed Study Of Irinotecan Dosing In FOLFIRI + Bevacizumab Treated Metastatic Colorectal Cancer [Cited March 2018]. Available from: <https://clinicaltrials.gov/show/NCT02138617>

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