Published in final edited form as:
Future Oncol. 2010 April ; 6(4): 563–585. doi:10.2217/fon.10.17.

Uridine 5′-diphosphoglucuronosyltransferase genetic polymorphisms and response to cancer chemotherapy

Jacqueline Ramírez, MS,
Department of Medicine, The University of Chicago, 5841 S. Maryland Avenue, MC2115, Chicago, IL, USA 60637, Tel.: +1 773 834 2451, Fax: +1 773 702 9268, jramirez@medicine.bsd.uchicago.edu

Mark J Ratain, MD, and
Department of Medicine, Committee on Clinical Pharmacology & Pharmacogenomics, Cancer Research Center, The University of Chicago, 5841 S. Maryland Avenue, MC2115, Chicago, IL, USA 60637, Tel.: +1 773 702 4400, Fax: +1 773 702 3969, mratain@medicine.bsd.uchicago.edu

Federico Innocenti, MD, PhD[†]
Department of Medicine, Committee on Clinical Pharmacology & Pharmacogenomics, Cancer Research Center, The University of Chicago, 5841 S. Maryland Avenue, MC2115, Chicago, IL, USA 60637, Tel.: +1 773 834 2452, Fax: +1 773 702 9268, finnocen@medicine.bsd.uchicago.edu

Abstract

Pharmacogenetics aims to elucidate how genetic variation affects the efficacy and side effects of drugs, with the ultimate goal of personalizing medicine. Clinical studies of the genetic variation in the uridine 5′-diphosphoglucuronosyltransferase gene have demonstrated how reduced-function allele variants can predict the risk of severe toxicity and help identify cancer patients who could benefit from reduced-dose schedules or alternative chemotherapy. Candidate polymorphisms have also been identified *in vitro*, although the functional consequences of these variants still need to be tested in the clinical setting. Future approaches in uridine 5′-diphosphoglucuronosyltransferase pharmacogenetics include genetic testing prior to drug treatment, genotype-directed dose-escalation studies, study of genetic variation at the haplotype level and genome-wide studies.

Keywords

epirubicin; flavopiridol; glucuronidation; irinotecan; neutropenia; raloxifene; tamoxifen; TAS-103; uridine 5′-diphosphoglucuronosyltransferase; vorinostat

Cancer constitutes one of the main leading causes of death worldwide. One of the principal modalities of cancer treatment is chemotherapy. There is high interindividual variability in response to anticancer agents, some of which is caused by inherited variation in drug

[†]Author for correspondence: Department of Medicine, Committee on Clinical Pharmacology & Pharmacogenomics, Cancer Research Center, The University of Chicago, 5841 S. Maryland Avenue, MC2115, Chicago, IL, USA 60637 ■ Tel.: +1 773 834 2452 ■ Fax: +1 773 702 9268, finnocen@medicine.bsd.uchicago.edu.

Financial & competing interests disclosure
Drs Federico Innocenti and Mark Ratain receive royalties related to UGT1A1 genotyping. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.
No writing assistance was utilized in the production of this manuscript.

metabolizing enzymes. Pharmacogenetics investigates how genetic variation affects drug efficacy and side effects, with the goal of individualizing medical treatment to improve patient care.

Many anticancer agents are metabolized by glucuronidation, a metabolic reaction that increases drug solubility in water and facilitates their biliary or urinary excretion from the human body [1-3]. The glucuronidation reaction involves conjugation of uridine 5′-diphosphoglucuronic acid to aglycones that contain oxygen, carboxyl, nitrogen or sulfur functional groups via uridine 5′-diphosphoglucuronosyltransferase (UGT) enzymes. UGTs are differentially expressed throughout the human body. Most human UGTs are found in the liver (e.g., UGT1A1, UGT1A3, UGT1A4, UGT1A5, UGT1A6, UGT1A9, UGT2B4, UGT2B7, UGT2B10, UGT2B15 and UGT2B17), the main organ responsible for drug metabolism. However, other UGTs (e.g., UGT1A7, UGT1A8, UGT1A10, UGT2B11 and UGT2B28) are expressed exclusively in extrahepatic tissues [4-7]. The *UGT* genes are classified into families, *UGT1* and *UGT2*, and, based on their sequence similarity, are further organized into subfamilies, *UGT1A, UGT2A* and *UGT2B*. Extensive genetic variation exists in the *UGT1A* and *UGT2B* genes [8,9]. Table 1 provides an overview of the many anticancer drugs that are glucuronidated in humans. Specific allele frequencies and a description of the *in vitro* effects of the *UGT* variants investigated in pharmacogenetic studies of anticancer agents are listed in Table 2.

This article will focus on how genetic variation in the *UGT* genes affects anticancer drug response, including both toxicity and efficacy. We report on anticancer drugs for which there is considerable glucuronidation and for which the UGTs responsible for the reaction have been identified. We will discuss pharmacogenetic studies of irinotecan, tamoxifen, raloxifene, epirubicin, vorinostat, flavopiridol and TAS-103 in detail. In this article, we use the nomenclature described in the *UGT* nomenclature webpage [301].

Irinotecan

The best example of how *UGT* genetic variation alters drug response is provided by irinotecan. This anticancer drug is used in many different schedules and disease settings, including colorectal cancer, small-cell lung cancer, breast cancer and gastric cancer [10-12]. It has also been approved by the US FDA for use in combination with 5-fluorouracil and leucovorin (folinic acid, fluorouracil and irinotecan [FOLFIRI]) for first-line treatment of patients with metastatic colorectal cancer and as second-line therapy for metastatic colorectal cancer refractory to 5-fluorouracil and leucovorin treatment [302].

Irinotecan is a prodrug of SN-38, a topoisomerase I inhibitor [13]. The cytotoxic activity of SN-38 is 100- to 1000-times greater than that of irinotecan [14]. SN-38 is further metabolized and deactivated in the liver to SN-38G [15], primarily by UGT1A1 [16-18] and to a lower extent also by UGT1A3, UGT1A6 and UGT1A9 [17-21]. UGT1A7 metabolizes SN-38 *in vitro* to a very high extent [18-20,22], but, since it is exclusively found in extrahepatic tissues [23] (reviewed in [4,24,25]), it does not contribute to SN-38 glucuronidation in the liver, where most SN-38G is formed.

Patients receiving irinotecan commonly experience severe myelosuppression (resulting in neutropenia) and delayed-onset diarrhea. Severe neutropenia and diarrhea seem to be caused by SN-38-induced damage to the bone marrow and gastrointestinal mucosa, respectively. Both myelosuppression and diarrhea need to be closely monitored. When experienced as grade 3 or 4 toxicities, they require treatment delay to allow for recovery and a decrease in dosing before the next irinotecan treatment.

More than 35 pharmacogenetic studies have evaluated whether there is a genetic predisposition to the risk of severe toxicity from irinotecan. Most studies have focused on investigating how genetic variation in the *UGT1A1* gene affects the drug pharmacodynamics owing to its primary role in the elimination of SN-38. An association between irinotecan toxicity and impaired UGT1A1 activity was initially observed in cancer patients suffering from Gilbert's syndrome [26,27], a common and mild inherited liver disorder that causes mild hyperbilirubinemia owing to a deficiency in UGT1A1 activity [28]. Case reports indicated that these patients developed severe diarrhea, neutropenia and transient increases in unconjugated bilirubin following irinotecan treatment [26,27]. The patients had high biliary SN-38 concentrations, suggesting reduced glucuronidation. Around the same time, *in vitro* studies showed that SN-38 is metabolized by UGT1A1, and there is an inverse correlation between the number of thymineadenine (TA) repeats in the promoter region of *UGT1A1* and glucuronidation of SN-38 and bilirubin [16,29]. Since then, many clinical studies have investigated whether genetic polymorphisms in the *UGT1A* genes involved in SN-38 disposition, particularly *UGT1A1*, predispose patients to severe irinotecan toxicity. These studies have been summarized in Table 3.

UGT1A variation & irinotecan toxicity

Many irinotecan pharmacogenetic studies have investigated whether the *UGT1A1*28* allele is associated with the risk of developing severe drug-related toxicity. *UGT1A1*28* has an additional TA repeat [A(TA)$_7$TAA] in the TATA box of the promoter region, which in most individuals contains the A(TA)$_6$TAA allele known as *UGT1A1*1*. Transcriptional activity is inversely related to the number of TA repeats, and as the number of TA repeat increases, UGT1A1 glucuronidation activity is significantly reduced [28-32]. *UGT1A1*28* is also associated with reduced *UGT1A1* mRNA expression [33]. The first prospective irinotecan pharmacogenetic study investigated whether the incidence of toxicity correlated with variability in the *UGT1A1* promoter. The trial enrolled predominantly Caucasian patients with refractory disease to be treated with 300–350 mg/m^2 irinotecan once every 3 weeks. At 300 mg/m^2, patients with one or two *UGT1A1*28* alleles had a trend toward lower absolute neutrophil counts (n = 20) [30]. In 65 patients enrolled in the same trial and treated with 350 mg/m^2 irinotecan (the current dosage of irinotecan, after a change in FDA recommendations), 50% of *UGT1A1*28* homozygotes experienced grade 4 neutropenia as the most common toxicity compared with 13% of heterozygotes and 0% of the *UGT1A1*1/*1* patients [32]. Having a *UGT1A1*28/*28* genotype conferred a 9.3-fold risk (95% CI: 2.4–36.4) of suffering neutropenia when compared with *UGT1A1*28/*1* and *UGT1A1*1/*1*. Multiple subsequent irinotecan studies have also reported increased risk in carriers of *UGT1A1*28/*28* for developing neutropenia [34-38]. The largest study group was trial N9741, comprised of 520 advanced colorectal cancer patients treated with combination therapy (irinotecan/5-fluorouracil/leucovorin: n = 114; oxaliplatin/5-fluorouracil/leucovorin: n = 299; and irinotecan/oxaliplatin: n = 107) [35]. Preliminary reports found a statistically significant association between *UGT1A1*28/*28* and higher incidence of severe neutropenia in all patients combined and in patients on the irinotecan/oxaliplatin arm. Irinotecan/oxaliplatin patients homozygous for *UGT1A1*28* had a 15.3-fold (95% CI: 3.0–77.9) and 35.0-fold (95% CI: 3.6–40.9) increased risk of developing grade 4 neutropenia and grade 3 febrile neutropenia, respectively. Japanese carriers of *UGT1A1*28* are also at higher risk for developing severe leukopenia and neutropenia [39-42]. For example, in a Japanese cohort of 118 patients in different regimens containing irinotecan, the *UGT1A1*28* allele distribution in patients who experienced grade 4 leukopenia was significantly different from that of patients without toxicity [39]. Multivariate analysis also showed that patients with one or two *UGT1A1*28* alleles had a significant risk for severe toxicity.

An association between the incidence of diarrhea and *UGT1A1*28* has also been observed by some investigators. In a study of Caucasians receiving irinotecan-containing regimes, 70% of the carriers of *UGT1A1*28/*28* developed diarrhea versus 33% of *UGT1A1*28/*1* versus 17% of *UGT1A1*1/*1* [43]. Metastatic colorectal patients on FOLFIRI who were homozygous for *UGT1A1*28* were also at higher risk of severe diarrhea [38]. The presence of the *UGT1A1*28* allele also correlated with severe diarrhea and was a significant risk factor for toxicity in additional studies in Caucasian and Japanese populations [39-40,44-46]. However, other studies have not provided evidence of an association between severe irinotecan-induced diarrhea and *UGT1A1*28*, possibly owing to insufficient sample size, low allele frequency in Asian studies, lower irinotecan doses and heterogeneity in treatment schedules [42,47-54].

To investigate the reason for the inconsistencies observed in the relationship between *UGT1A1*28* and severe irinotecan-induced toxicity, a meta-analysis was conducted integrating the results of nine clinical trials including 821 patients in total and encompassing different dose schedules (weekly, biweekly and every 3 weeks) [55]. The study found that the risk for severe hematologic toxicity in patients with *UGT1A1*28/*28* was dose dependent. The risk of developing grade 3–4 neutropenia in patients with *UGT1A1*28/*28* genotype is significantly higher than for carriers of *UGT1A1*1/*28* or *UGT1A1*1/*1* at high (dose: >250 mg/m^2; odds ratio [OR]: 3.22; 95% CI: 1.52–6.81; p = 0.008) and medium doses (dose: 150–250 mg/m^2; OR: 27.8; 95% CI: 4.00–195; p = 0.005) but not at lower doses (dose: <150 mg/m^2; OR: 1.80; 95% CI: 0.37–8.84; p = 0.41) [55]. The authors concluded that the *UGT1A1*28/*28* genotype may be useful as a predictive marker of toxicity only at intermediate or high irinotecan doses (150–250 mg/m^2) administered every 2 or 3 weeks, but treatment decisions at lower doses do not need to be made based on genotype. No associations were found between *UGT1A1*28* and diarrhea, and for incidence of diarrhea in *UGT1A1*28/*28* patients and dose (p = 0.8).

*UGT1A1*6* (211G>A, G71R), a missense mutation found in Asians [9,56], is associated with reduced enzyme activity [18,57,58]. It has been shown to predict for toxicity in Asian patients receiving irinotecan for the treatment of non-small-cell lung cancer. A clinical trial of 81 Koreans given irinotecan and cisplatin found an association between homozygosity for *UGT1A1*6* and the incidence of grade 4 neutropenia (OR: 6.11) [48,49]. Additional studies conducted in Japanese and Chinese have confirmed the association between *UGT1A1*6* and incidence of severe leukopenia and neutropenia [41,42,59,60]. Coexistence of *UGT1A1*28* and *UGT1A1*6* has been shown to decrease glucuronidation activity in an additive manner [39,41,61-64] and genotyping both alleles would be important to predict toxicity in Asians (reviewed in [65,66]) Genotyping *UGT1A1*6* in Caucasians, however, has no practical value due to its rarity [32,34].

Irinotecan pharmacogenetic studies have also investigated the impact of *UGT1A1*27, UGT1A1*93* and *UGT1A1*60* on toxicity. The effect of the *UGT1A1*27* (686C>A, P229Q) allele, which reduces glucuronidation activity, has not been evaluated in Caucasians due to its rarity [32,34]. It has been found to be associated with severe neutropenia and diarrhea in Japanese but as it co-occurs with *UGT1A1*28*, it is hard to assess its effect [39,62,67]. *UGT1A1*93* (−3156G>A) and *UGT1A1*60 (*−3279T>G*)* occur in Caucasians, Asians and Africans [30,56,68]. *UGT1A1*93* was strongly correlated with severe neutropenia in irinotecan patients with advanced disease refractory to other agents and seemed to distinguish between different phenotypes of total bilirubin (an established marker of *UGT1A1* status) better than *UGT1A1*28* [32]. Consistent with this hypothesis, a study of colorectal cancer patients treated with FOLFIRI demonstrated a significant trend of increased incidence of severe neutropenia among −3156 genotypes [37]. Severe hematologic toxicity was more frequent in individuals with −3156A regardless of whether

they carried the *UGT1A1*1* or *UGT1A1*28* alleles. A hazard ratio for severe hematological toxicity of 8.4 was found for patients with −3156A/A genotype compared with −3156G/G. Homozygosity for −3156G>A was also related to the risk of neutropenia in irinotecan patients with extensive-stage small-cell lung cancer [69]. However, as no functional studies have been performed for *UGT1A1*93*, and since this allele is highly linked to *UGT1A1*28* and *UGT1A1*60* in Caucasians and Asians [32,62,67,70], further studies are needed. *UGT1A1*60* has decreased transcriptional activity [71]. In Caucasian metastatic patients treated with FOLFIRI, *UGT1A1*60/*60* was associated with severe hematologic toxicity in the first treatment cycle when compared with −3279T/T carriers, although it was not a significant predictor after multivariate analysis [70]. In Japanese patients, *UGT1A1*60* has been associated with severe leukopenia and/or diarrhea [40]. Homozygosity for *UGT1A1*60* also increased the risk of severe toxicity. However, in multivariate analyses including *UGT1A1*28*, this association did not hold, although the association with *UGT1A1*28* did, suggesting that *UGT1A1*28* is a stronger predictive factor for toxicity than *UGT1A1*60*. Another study investigating the role of *UGT1A1*60* in the severe side effects experienced by Korean patients could not demonstrate an association with toxicity [48]. Owing to the high linkage between *UGT1A1*28*, *UGT1A1*60* and *UGT1A1*93*, more evidence is needed to assess whether genotyping *UGT1A1*60* and *UGT1A1*93* would add predictive power to that provided by *UGT1A1*28*, especially in Caucasian populations where *UGT1A1*28* is common.

UGT1A9 and UGT1A7 also metabolize SN-38. UGT1A9 is expressed in the liver but UGT1A7 is only expressed in extrahepatic sites. Common polymorphisms in *UGT1A9* include *UGT1A9*1b* (−118(dT)$_{9>10}$), generated by insertion of an extra thymidine in the promoter region [72], and I399C>T [73]. The functional significance of both polymorphisms is unclear. Although *UGT1A9*1b* has been associated with increased luciferase activity [72], further studies have not shown a significant increase in reporter gene expression or alterations in hepatic protein expression or activity when compared with the reference allele *UGT1A9*1a* [73-75]. I399C>T was originally correlated with increased UGT1A9 protein levels and activities and in low linkage disequilibrium with *UGT1A9*1b* in Caucasian livers [73]. However, a second study did not find an association between I399C>T and *UGT1A9* mRNA expression and activity, and found I399C>T and *UGT1A9*1b* to be in complete linkage disequilibrium [75]. An *in vivo* study also could not find an association between I399C>T and glucuronidation of mycophenolic acid, a probe UGT1A9 substrate [76]. *UGT1A7* is also polymorphic; *UGT1A7*2* (387T>G/391C>A/392G>A, N129K/R131K) and *UGT1A7*3* (387T>G/391C>A/392G>A/622T>C, N129K/R131K/W208R) are common while *UGT1A7*4* (622T>C, W208R) is very rare (reviewed in [9,77]). *UGT1A7*2* has similar glucuronidation activity to *UGT1A7*1*. Both *UGT1A7*3* and *UGT1A7*4* have reduced activity [18,23].

Most studies of the effect of genetic variation in *UGT1A9* and *UGT1A7* on irinotecan toxicity have shown an association between low-activity alleles and increased toxicity. In Koreans, increased incidence of grade 3 diarrhea has correlated with both *UGT1A9*1a/*1a* and *UGT1A7*3/*3* [48]. In this study, increased incidence of severe toxicity was also found in the presence of combined mutations with low activity (*UGT1A1*28* and *UGT1A7*4*). However, studies in Japanese and Caucasians found that severe hematologic toxicity was more frequent in individuals with *UGT1A9*1b* [60,70], although the results did not hold in multivariate analyses [70]. Two Caucasian clinical trials showed that carriers of the low-activity allele *UGT1A7*3* had increased severe hematologic toxicity and/or diarrhea [46,70]. *UGT1A7* −57T>G, in linkage disequilibrium with *UGT1A7*4*, was associated with anemia, and both leukopenia and thrombocytopenia were more prevalent in patients with the high-risk alleles *UGT1A1*28*, *UGT1A7*2* and *UGT1A7* −57T>G [78]. Overall, these results do not allow any firm conclusion to be drawn owing to the high linkage existing between

*UGT1A7*3* and *UGT1A9*1a* with both *UGT1A1*28* and *UGT1A1*6* [47,48,70,79-82]. Regarding *UGT1A9* I399C>T, no association was found between this allele and severe neutropenia in Japanese patients [83]. In this same study, this variant was in linkage with *UGT1A9*1b, UGT1A7*2* and *UGT1A7*3,* and 85% of the *T* alleles were linked with the *UGT1A1* wild-type haplotype.

The most common *UGT1A1* haplotype in Caucasians (frequency of 34.2%) harbors all reference sequence alleles except for *UGT1A9*1a*: *UGT1A1* −3279T, *UGT1A1* −3156G, *UGT1A1* $-53(TA)_6$, *UGT1A7* +387T, *UGT1A7* +622T and *UGT1A9* $-118(T)_{10}$. In a clinical study, this haplotype together with sex had a protective effect on irinotecan-induced severe hematologic toxicity during the entire course of therapy [70]. In Japanese patients, haplotypes containing *UGT1A1*28, UGT1A7*1* and *UGT1A9*1b* or *UGT1A1*6, UGT1A7*3* and *UGT1A9*1a* had a greater incidence of severe neutropenia when compared with the reference sequence haplotype containing *UGT1A1*1, UGT1A7*1* and *UGT1A9*1a*, demonstrating the clinical impact of *UGT1A1*28* and *UGT1A1*6* [42].

UGT1A1 variation & irinotecan pharmacokinetics

Many studies have used the relative extent of SN-38 glucuronidation (area under curve $[AUC]_{SN\text{-}38G}/AUC_{SN\text{-}38}$) as a marker for UGT1A1 activity. The majority of the studies investigating the role of *UGT1A1*28* on irinotecan pharmacokinetics have found a significant reduction in the relative extent of glucuronidation in Caucasian [31,32,36,52,54,62,84,85] and Japanese subjects [40-42] carrying this allele. A similar relationship has been found between *UGT1A1*6* and the extent of glucuronidation in Japanese patients [41-42,62,63], Koreans [48,49], Chinese patients, Malays and Indians [59]. An additive effect of *UGT1A1*28* and *UGT1A1*6* on the relative extent of SN-38 glucuronidation has been reported in Japanese [42]. Caucasian and Japanese carriers of *UGT1A1*60* have also shown decreased $AUC_{SN\text{-}38G}$:$AUC_{SN\text{-}38}$ ratios [40,42,70].

*UGT1A7*3* and homozygosity for *UGT1A9*1a/*1a* have been reported to be associated with reduced glucuronidation ratios in Koreans [48,49]. The same association with *UGT1A7*3* was observed in Caucasians [70]. As both *UGT1A7*3* and *UGT1A9*1a* are linked with *UGT1A1*28* and *UGT1A1*6* [42,47,81,82,86], and UGT1A7 is not expressed in the liver, the effect of these variants on SN-38 glucuronidation requires further investigation. *UGT1A9* I399T carriers have shown increased glucuronidation ratios in Japanese populations, but this is very likely to be due to the close association of I399C with *UGT1A1*28, UGT1A1*6* or *UGT1A1*60*, as after stratifying patients by *UGT1A1*28, UGT1A1*6* or *UGT1A1*60* haplotypes associated with reduced glucuronidation activity, the significant effect was no longer observed [83]. In another study, I399T alleles were associated with higher glucuronidation activity and lower systemic exposure to SN-38 when analysis was restricted to patients with *UGT1A1*1/*1* genotype [87]. However, when analyzing only *UGT1A1*6/*6* patients, the effect was not observed. In this population, there was very low degree of linkage between I399C>T and the rest of the *UGT1A1* functional variants (i.e., *UGT1A1*28, UGT1A1*6, UGT1A1*93* and *UGT1A1*60*) and only a weak linkage with *UGT1A9*1b*.

*UGT1A1*28* has also been associated with increased SN-38 AUC in some studies [31,32], but it does not have an effect on irinotecan AUC, as expected. In a trial of Asian cancer patients (Chinese, Malays and Indians), *UGT1A1*6* was associated with higher SN-38 exposure, but the same effect was not observed in *UGT1A1*28* carriers [59]. In Koreans, patients with *UGT1A1*6/*6, UGT1A7*3/*3* and *UGT1A9*1a/*1a* genotypes had increased SN-38 AUC [48]. Overall, these results suggest that the relative extent of glucuronidation of SN-38 is a good marker of *UGT1A1* status.

A few studies in Japanese populations have analyzed the correlation between haplotypes and glucuronidation activity. Japanese patients bearing haplotypes harboring either *UGT1A1*6* or *UGT1A1*28* exhibited lower glucuronidation ratios than those without these alleles [42,62]. An additive effect of haplotypes containing *UGT1A1*28* and *UGT1A1*6* on reduced AUC ratio was also observed [42]. Haplotypes with *UGT1A1*60* had reduced glucuronidation although the trend did not reach statistical significance. In another trial, reduced glucuronidation was observed in patients homozygous for the haplotype *UGT1A1*6 UGT1A7* −57G *UGT1A7*3 UGT1A9*1a* (present in 15% of the patients) due mainly to the presence of *UGT1A1*6* [82].

UGT1A variation & antitumor efficacy

Studies evaluating the role of *UGT1A1*28* in antitumor response of Caucasian patients treated with irinotecan have given contradictory results. *UGT1A1*28/*28* was associated with complete and partial response [70] and higher response rate [36] in FOLFIRI trials. However, other studies have found homozygosity for *UGT1A1*28* to be associated instead with lower response [38] or to have no relationship with it [35,47,88]. Studies have reported an association between homozygosity for *UGT1A1*28* and both stable disease [70] and decreased risk of tumor progression [36]. By contrast, another study found no significant improvement in time to progression in carriers of *UGT1A1*28* [35,51].

Most studies have found no correlation between *UGT1A1*28* and median survival [51], overall survival [35,70] or disease-free survival [88]. A marginally significant association has been found between poorer overall survival and *UGT1A1*28* [43], and between lower median survival and *UGT1A1*28/*28* [51]. However, another study observed a marginally significant tendency for better disease-free survival for *UGT1A1*28/*28* carriers [37].

*UGT1A1*6/*6* has been correlated with lower tumor response, progression-free survival and overall survival in non-small-cell lung cancer Asian patients [48,49] *UGT1A1*93/*93*, which also reduces glucuronidating activity, has been associated with partial and complete response in Caucasians, in agreement with the observations previously described with *UGT1A1*28/*28* carriers [70]. However, a similar association was not observed in *UGT1A1*60/*60* patients [70].

In metastatic Caucasian cancer patients, patients with *UGT1A1*93/*93* genotype showed significantly better responses than those with *UGT1A1*1/*1* [70]. In the same study, no associations with tumor response were observed with *UGT1A1*60*, *UGT1A7*2*, *UGT1A7*3*, *UGT1A7*4* and *UGT1A9*1b* variants. In other studies, *UGT1A9*1b/*1b* was predictive of worse progression-free survival in Koreans [49], and *UGT1A9*1a/*1a* was associated with increased response in Caucasians [47].

Given the contradictory nature of some of these results, prospective and randomized studies are needed to evaluate whether *UGT1A* variation can predict antitumor efficacy, also considering additional factors, such as patient characteristics, the biological state of the tumors and environmental factors.

Genetic testing for irinotecan treatment

The irinotecan label was amended in 2005, prompted by findings from clinical trials linking *UGT1A1*28* homozygosity to increased risk for neutropenia. The revised package insert recommends that patients with *UGT1A1*28/*28* genotype should receive a lower irinotecan dose [302]. To facilitate the clinical integration of the genetic test, the FDA approved the Invader® UGT1A1 Molecular Assay from Third Wave Technologies, Inc. (WI, USA) [303]. This genetic test helps identify cancer patients who might be at increased risk of severe

toxicity and could benefit from either an irinotecan dose reduction or alternative chemotherapy regimens [65].

Further evaluation of the relationship between genotype and severe toxicity has shown that *UGT1A1*28/*28* may be useful as a predictive marker of toxicity at only intermediate or high irinotecan doses (150–250 mg/m^2) administered every 2 or 3 weeks [55]. Patients with *UGT1A*28/*28* genotype do not tolerate standard doses of irinotecan owing to excessive toxicity and should undergo dose reductions [32,34,43,89], the extent of which is still not established. Patients of Asian origin would benefit from genetic testing for *UGT1A1*6* because of its predictive value for toxicity [90,91].

Genotype-directed dose-escalation studies

It can be postulated that the dose of irinotecan is suboptimal in patients with both *UGT1A1*1/*28* and *UGT1A1*1/*1* genotypes. These individuals may benefit from higher doses.

A recent study performed in FOLFIRI patients of Caucasian origin demonstrated the feasibility of optimization of irinotecan dosing according to *UGT1A1*28* genotype [92]. By performing dose-escalation studies in patients with *UGT1A1*1/*1* and *UGT1A1*1/*28* genotypes, the clinical trial demonstrated that *UGT1A1*1/*1* and *UGT1A1*1/*28* patients could be safely treated every 2 weeks with irinotecan doses of 370 and 310 mg/m^2, respectively. These doses are considerably higher that the recommended irinotecan dose of 180 mg/m^2 in FOLFIRI, and demonstrates that patients who are not homozygous for *UGT1A1*28* can tolerate higher doses of irinotecan. Additionally, a genotype-directed dose-escalation study of a population consisting mainly of Caucasian patients is ongoing and aims to determine the optimal doses of irinotecan administered as single agent and stratified by *UGT1A1* genotype [93]. So far, the study shows that *UGT1A1*1/*1* patients can be treated safely at higher doses and that dose escalation beyond the standard irinotecan dose is not tolerated by *UGT1A1*1/*28* patients. Genotype-directed dosing, including *UGT1A1*6* in addition to *UGT1A*28*, has also been studied. Korean patients treated with irinotecan and a fixed dose of capecitabine every 3 weeks can tolerate 350 mg/m^2 irinotecan if they have *UGT1A1*1/*1*, *UGT1A1*28/*1* or *UGT1A1*1/*6* genotypes, and 200 mg/m^2 if their genotypes are *UGT1A1*28/*28*, *UGT1A1*28/*6* or *UGT1A1*6/*6* [94]. Japanese patients harboring *UGT1A1*28/*28*, *UGT1A1*28/*6* or *UGT1A1*6/*6* genotypes tolerate lower irinotecan doses administered every 2 weeks (maximum tolerated dose: 150 mg/m^2) than patients with one or two copies of the *UGT1A1*1* allele [95].

Tamoxifen

Tamoxifen is an oral, nonsteroidal anti-estrogen for the prevention and treatment of steroid hormone receptor-positive breast cancer and for lowering breast cancer incidence in high-risk women [96-98]. The drug binds to the estrogen receptor and competitively inhibits the binding of estrogen in breast tissue. Tamoxifen undergoes extensive hepatic metabolism by cytochrome P (CYP) 450 [99-109], UGT [110-120] and sulfotransferase enzymes [116,121].

The most abundant tamoxifen metabolite is *N*-desmethyltamoxifen, produced by CYP3A4 and CYP3A5 [101-103,108,122]. Tamoxifen has two clinically active metabolites: *trans*-4-hydroxytamoxifen [123,124] and *trans*-4-hydroxy-*N*-desmethyl-tamoxifen [96,109,110,123-126], also known as endoxifen [127]. *Trans*-4-hydroxytamoxifen is a primary metabolite formed mainly by CYP2D6 [99,101,103-107,109], while endoxifen is formed by 4-hydroxylation of *N*-desmethyltamoxifen by CYP2D6 and by demethylation of *trans*-4-hydroxytamoxifen by CYP3A4 and CYP3A5 [101,102]. Endoxifen has equivalent potency to 4-hydroxytamoxifen [109,126], but as the patient plasma levels of endoxifen are

higher than those of 4-hydroxytamoxifen [109,127], endoxifen may contribute more significantly to the anti-estrogenic action of tamoxifen, especially in CYP2D6-extensive metabolizers [109,123,126].

Tamoxifen and its two clinically active metabolites, *trans*-4-hydroxytamoxifen and *trans*-endoxifen, undergo extensive glucuronidation in humans [110-117,119,120]. Both tamoxifen and *trans*-4-hydroxytamoxifen undergo *N*-glucuronidation by UGT1A4 to form *trans*-tamoxifen-N^+-glucuronide, *trans*-4-hydroxytamoxifen-N^+-glucuronide and the geometrical isomer *cis*-4-hydroxytamoxifen-N^+-glucuronide [113,115,116,120]. The isomerization reaction favors *trans*-4-hydroxytamoxifen over the *cis*-isomer [117,128]. *Trans*-4-hydroxytamoxifen and *trans*-endoxifen are conjugated by *O*-glucuronidation to form *trans*-4-hydroxytamoxifen-*O*-glucuronide by UGT2B7 [113,115], *cis*-4-hydroxytamoxifen-*O*-glucuronide by UGT1A10, UGT1A1, UGT2B7 and UGT2B15 [113,115,116], *trans*-endoxifen-*O*-glucuronide by UGT1A10, UGT1A8 and UGT2B7 [113], and *cis*-endoxifen-*O*-glucuronide by UGT1A10, UGT1A9 and UGT1A1 [113].

In vitro studies have investigated the effect of genetic variants in *UGT1A1 (UGT1A1*28)*, *UGT1A4 (UGT1A4*2* and *UGT1A4*3b), UGT1A8 (UGT1A8*2* and *UGT1A8*3), UGT1A10* (*UGT1A10*2a*) and *UGT2B7 (UGT2B7*2a)* on the glucuronidation of tamoxifen and its active metabolites (Table 4). *UGT2B7*2a* exhibited a decrease in glucuronidation activity against *trans*-4-hydroxytamoxifen and *trans*-endoxifen in human liver microsomes and cell homogenates [119]. Similar results were obtained for homozygotes compared with wild-type in human liver microsomes. *UGT1A8*3* completely abolished the glucuronidation activity of both compounds, while *UGT1A8*2* had a very minor effect (reduction) on endoxifen glucuronidation. *UGT1A4*3b*, a low-activity allele, showed increased activity against *N*-glucuronidation of tamoxifen and 4-hydroxytamoxifen in one study [129], and no effect in another [119]. The other variants had no effect compared with the reference alleles. Future studies should explore whether these polymorphisms can predict clinical response to treatment with tamoxifen.

Raloxifene

Raloxifene is an oral selective estrogen receptor modulator (reviewed in [130]). It has been approved by the FDA as adjuvant therapy for reducing the risk for invasive breast cancer in postmenopausal women with either osteoporosis or at increased risk for invasive breast cancer [131]. Raloxifene appears to be as effective as tamoxifen in reducing invasive breast cancer risk and has a lower risk of adverse events [132]. The drug is also used for the prevention and treatment of osteoporosis in postmenopausal women (reviewed in [133]).

Raloxifene undergoes extensive presystemic glucuronidation and enterohepatic circulation [130,133,134]. The metabolites produced are raloxifene-4′-β-glucuronide and raloxifene-6-β-glucuronide, both of which have low affinity for the estrogen receptor and are less potent at inhibiting cell proliferation than raloxifene [135]. The main metabolite found in human plasma and in jejunal and ileal microsomes is raloxifene-4′-β-glucuronide [134,136,137], which is formed mainly by UGT1A10 followed by UGT1A8. Hepatic UGT1A9, UGT1A1, UGT1A3 and UGT2B7 also contribute to the reaction to a lower extent [136,138]. Human liver microsomes, on the other hand, favor glucuronidation at the 6-position [136]. The main enzyme producing raloxifene-6-β-glucuronide is UGT1A1, but there is also some contribution by extrahepatic UGT1A8 and hepatic UGT1A9 and UGT1A3 [136,138].

Only one study has evaluated the influence of polymorphic variation in *UGT*, in particular *UGT1A1*28*, on raloxifene glucuronidation. This *in vivo* study of 57 postmenopausal women treated for osteoporosis measured the concentrations of raloxifene and its two glucuronides in serum samples, and the change in bone mineral density after 1 year of

raloxifene therapy [139]. Patients with *UGT1A1*28/*28* genotype had increased exposure to raloxifene and its glucuronides, and a significant increase in hip bone mineral density compared with *UGT1A1*1/*28* and *UGT1A1*1/*1* patients. A significant increase in glucuronides in *UGT1A1*28/*28* carriers was unexpected, and the authors hypothesized that it may be due to impaired excretion. Additional studies are needed to clarify the relationship between glucuronidation and *UGT1A1*28*, and to examine whether the variants have an effect on breast cancer reduction in women undergoing raloxifene treatment.

Epirubicin

Epirubicin, the 4′-epi-isomer of doxorubicin [140], is used for the treatment of advanced breast cancer (reviewed in [141,142]) and gynecological cancers [143,144]. Its primary cellular target is topoisomerase II [140], and one of its main toxic effects is myelosuppresssion [145]. Epirubicin is metabolized quickly in the human body to form epirubicin-glucuronide, epirubicinol and epirubicinol-glucuronide [146,147]. Studies with human liver microsomes expressing specific human UGTs and recombinant enzymes have demonstrated that epirubicin glucuronide is formed by UGT2B7 [148]. No differences in glucuronidation were observed in HEK-293 cells expressing *UGT2B7*1a* (reference sequence) and the common *UGT2B7*2a* variant [148]. Subsequent studies in Caucasian human liver microsomes showed that samples containing *UGT2B7* haplotype 4 (−45597G; −6682_−6683A; 372A; IVS1+9_IVS1+10A; IVS1+829T; IVS1+985G; IVS1+999C; IVS1+1250G; 801T; IVS4+185C) had a statistically significant 27% average increase in epirubicin glucuronidation compared with the diplotypes without haplotype 4 [149]. The putative functional variants of haplotype 4 are *IVS1* +985A>G, +735A>G and +1062C>T. One of these variants, 735A>G (*UGT2B7*1c*), has recently been associated with higher *in vivo* and *in vitro* zidovudine clearance and hepatic *UGT2B7* expression [150]. The effect of this allele and the other two putative functional variants in the *in vivo* glucuronidation of epirubicin need to be tested in clinical studies.

The *UGT2B7* promoter variant −161C/T has been associated with differences in morphine glucuronidation in acute pain patients. In this study, −161C/T was in complete linkage disequilibrium with *UGT2B7*2a*, and individuals with −161C/C and 802C/C genotypes had reduced morphine glucuronidation [151]. However, other clinical studies have not found an association between these two variants and either morphine glucuronidation to morphine serum ratios or morphine analgesic effect [152-154]. A recent pharmacogenetic study of epirubicin in breast cancer patients studied the impact of −161C/T on pharmacokinetics and toxicity [155]. Patients with the CC genotype had a significant decrease in epirubicin clearance (88.9 l/h) compared with CT and TT patients (129 l/h). Incidence rates of grade 3–4 leukopenia during cycle 1 were also higher in CC carriers (78%) versus CT and TT (48%) [155]. As the functional significance of −161C/T has not been proven, future studies are needed to validate these findings and assess the impact of haplotype 4 on epirubicin pharmacokinetics and pharmacodynamics.

Vorinostat

Vorinostat, also known as suberoylanilide hydroxamic acid, is an oral inhibitor of histone deacetylases. It was approved in 2006 by the FDA for the treatment of cutaneous T cell lymphoma [156]. It is also being tested for the treatment of a number of solid malignancies [157-159]. Toxicity includes thrombocytopenia, diarrhea, nausea and anorexia [158-160].

Vorinostat undergoes extensive metabolism to two inactive metabolites: an *O*-glucuronide and 4-anilino-4-oxobutanoic acid [161-163]. *In vitro* experiments with UGT overexpressing cell homogenates showed high levels of vorinostat glucuronidation metabolism by hepatic UGT2B17 and UGT1A9, and extrahepatic UGT1A8 and UGT1A10 [164]. UGT1A3 and

UGT1A7 also glucuronidated vorinostat but to a lower extent. Another study of recombinant UGTs confirmed the major contribution of UGT2B17 to vorinostat glucuronidation and also identified UGT1A1 and UGT2B7 as important hepatic isoforms [165]. *In vitro* experiments investigated the effect of the copy-number variation in *UGT2B17 (UGT2B17*2)* and missense polymorphisms in *UGT1A7, UGT1A8* and *UGT1A10* on vorinostat glucuronidation (Table 4) [164]. Human liver microsomes with *UGT2B17*2/*2* genotype had significantly lower vorinostat glucuronidation activity and *UGT2B17* mRNA levels compared with livers with at least one *UGT2B17*1* allele. Similar levels of glucuronidation and gene expression were observed for individuals with one or two *UGT2B17*1* alleles. Homozygotes for *UGT2B17*2* also had lower affinity (higher Michaelis constant value) for vorinostat compared with homozygotes for *UGT2B17*1*. Regarding the polymorphisms in extra hepatic tissues, *UGT1A7*2, *3* and **4* did not have an impact on vorinostat glucuronidation, while *UGT1A8*2* had decreased glucuronidation capacity, and both *UGT1A8*3* and *UGT1A10*2a* exhibited no glucuronidation activity. Clinical studies are needed to further explore the association of *UGT* polymorphic variation and response to vorinostat.

Flavopiridol

Flavopiridol is a cyclin-dependent kinase inhibitor in clinical development for the treatment of chronic lymphocytic leukemia [166]. It has a dose-limiting toxicity of secretory diarrhea when administered as a 72-h continuous infusion [167-169] attributable to luminal exposure to flavopiridol [167].

Studies in human liver microsomes have shown that flavopiridol forms two glucuronides. The major metabolite is 7-*O*-β-glucopyranuronosyl-flavopiridol, formed mainly by UGT1A9 and to a minor extent by UGT1A1, UGT1A4, UGT1A8 and UGT1A10 [170,171]. 5-*O*-β-glucopyranuronosyl-flavopiridol, the minor glucuronide, is formed by UGT1A1, UGT1A4 and to a lower extent by UGT1A9 [170,171]. In a study with Caucasian human livers, no association was observed between flavopiridol glucuronidation, *UGT1A9* mRNA levels and *UGT1A9*1b* and I399C>T polymorphisms [171]. *In vitro* hepatic flavopiridol glucuronidation also does not appear to be affected by the rare coding variants, *UGT1A9*2* (C3Y) and *UGT1A9*3* (M33T) [80].

Flavopiridol glucuronidation has correlated with toxicity. A clinical trial of 22 metastatic renal cancer patients used the ratio of flavopiridol glucuronide to parent drug in plasma (metabolic ratios) at the end of the infusion during cycle 1 as a marker for UGT activity [167]. The metabolic ratios showed a bimodal distribution. Patients who experienced diarrhea had significantly lower glucuronidation activity than those without toxicity. Correlation between glucuronidation and response rates could not be examined, as the drug was inactive in this patient cohort.

A pharmacogenetic study administered flavopiridol as an intravenous infusion for 1 h to 55 patients with refractory neoplasms [172]. The dose-limiting toxicities observed were neutropenia, fatigue and diarrhea. The study investigated the effect of *UGT1A1*28* and found no association between the variant allele and either pharmacokinetics or the occurrence and severity of diarrhea and neutropenia. This is consistent with *in vitro* evidence showing that UGT1A1 plays a minor role in flavopiridol glucuronidation.

TAS-103

TAS-103 inhibits topoisomerases I and II and the function of the signal-recognition particle in directing the delivery of secretory proteins [173]. Correlation studies with human liver microsomes showed that TAS-103 is glucuronidated mainly by UGT1A1 [174]. A clinical

trial of TAS-103 administered weekly at various doses investigated the influence of *UGT1A1*28* on pharmacokinetics and severe toxicity [175]. Drug-related toxicities included neutropenia and mild thrombocytopenia. There was no relationship between TAS-103 and TAS-103G concentrations and *UGT1A1*28*. At 130- and 160-mg/m^2 doses, the majority of the *UGT1A1*28/*28* carriers experienced dose limiting toxicities (67%) compared with 40% of the individuals with *UGT1A1*28/*1* and 11% of those with *UGT1A1*1/*1*. The number of patients in each dose group was small, however, and further studies are needed to evaluate the effect of *UGT1A1* genetic variation on response to TAS-103.

Additional genetic variation to be investigated in future studies

This article focused on polymorphisms associated with response to anticancer agents. Genetic variation also exists in other *UGT* genes and could be investigated in future studies of drugs metabolized by these specific *UGT* isoforms. Among these additional candidate polymorphisms is *UGT2B15*2* (235G>T, D85Y) [176], a common allele (reviewed in [9]) that is associated with reduced *in vitro* and *in vivo* glucuronidation of oxazepam [177-179] and diminished *in vivo* clearance of lorazepam [180]. Another important and common polymorphism is *UGT1A6*2* (S7A/T181A/R184S) [181], which appears to play an important role in the glucuronidation of UGT1A6 substrates, although these effects are substrate dependent *in vitro* [181-183]. *In vivo*, *UGT1A6*2* has been associated with reduced exposure to acetaminophen and salicylic acid [184,185]. Other *UGT1A6* variants, present at a lower frequency (1–2%), include *UGT1A6*3* (R184S) and *UGT1A6*4* (T181A), but their functionality has not been studied (reviewed in [9]). Additional *UGT1A9* polymorphisms to those discussed include *UGT1A9*3* (M33T), which also shows a substrate-dependent effect *in vitro* and is present at an allele frequency of 4% in Caucasians [80,186].

Discussion

Many anticancer agents are metabolized by glucuronidation. Polymorphisms in the *UGT* genes may affect how patients respond to these drugs. Irinotecan, a drug used for treating metatastic colorectal cancer and other tumor types, has been studied in multiple pharmacogenetic studies aiming to determine how genetic variation in *UGT1A* influences drug-treatment response. Many studies have demonstrated how *UGT1A1*28* and *UGT1A1*6* increase the risk for experiencing severe neutropenia [32,34-38,41,42,46,48,49,59,60,64,88], the most frequent dose-limiting toxicity of irinotecan treatment. Although some studies suggest genetic variation in *UGT1A9* and *UGT1A7* may also influence response to irinotecan treatment [46,47,48,49,60,70], no firm conclusion can be drawn as there is high linkage between allelic variation in these genes and both *UGT1A1*28* and *UGT1A1*6* [42,47,48,70,79-82,86]. The latest studies are using haplotype approaches to study the combined effects of *UGT* polymorphisms on irinotecan pharmacodynamics and pharmacokinetics [42,62,70,82]. Genotype-directed studies are also being conducted to individualize treatment and find optimal irinotecan doses in patients, depending on their *UGT1A1* genotypes [92-95]. Tamoxifen, used in the treatment of estrogen-receptor-positive breast cancer, is metabolized extensively in the human body. *In vitro* studies have investigated the effect of several *UGT* variants on glucuronidation of the drug and its active metabolites. Candidate polymorphisms to be studied *in vivo* for their capacity to predict clinical response include *UGT2B7*2a*, *UGT1A8*3* and *UGT1A4*3b* [119,129]. Epirubicin, used to treat advanced breast and gynecological cancers, causes leukopenia. Incidence of severe toxicity in breast cancer patients taking epirubicin has been associated with the *UGT2B7* −161C/T variant [155]. Future studies are needed to validate these findings and study the effect of *UGT2B7* haplotype 4 on drug response [149]. *In vitro* studies of vorinostat, used in the treatment of cutaneous T cell lymphoma and solid

malignancies, suggest that *UGT2B17*2* and *UGT1A8*2* may influence how individuals react to the drug [164]. In conclusion, candidate polymorphisms in the *UGT* genes have been identified for a number of anticancer drugs. Future studies are needed to validate findings and clinically test whether genotyping will help predict response to these drugs.

Conclusion

Genetic variation in the *UGT* gene is associated with response to anticancer agents. The best example to demonstrate the clinical impact of *UGT* polymorphisms on anticancer treatment is irinotecan, used in colorectal cancer therapy. The reduced-function alleles *UGT1A1*28* and *UGT1A1*6* predict for the risk of severe irinotecan toxicity and help identify cancer patients who could benefit from reduced doses of irinotecan or alternative chemotherapy. Functional variants in the *UGT1A4*, *UGT1A8*, *UGT2B7* and *UGT2B17* genes also predict the *in vitro* or *in vivo* glucuronidation of tamoxifen, epirubicin and vorinostat, although the functional consequences of these variants still need to be tested in the clinical setting.

Future perspective

The results from studies that have been conducted thus far are promising, and future studies will continue to identify and investigate the functional consequences of individual polymorphic variants and haplotypes to predict drug pharmacokinetics and pharmacodynamics.

Prospective studies of the effect of genetic variation in candidate genes should be conducted, ensuring that the study design has adequate statistical power and controls to account for the effects of covariates. Genetic testing will be more widely used prior to treatment in order to optimize dosage, predict risk for adverse effects and help identify patients who could benefit from either reduced doses or other chemotherapy agents.

Although selecting genes associated with drug disposition has shown promising results for irinotecan patients, new technological advances will allow researchers to adopt genome-wide approaches involving single nucleotide polymorphisms arrays, microarrays and proteomics to select new candidate genes and analyze extended haplotypes.

Bibliography

Papers of special note have been highlighted as:

■ of interest

■■ of considerable interest

1. King CD, Rios GR, Green MD, Tephly TR. UDP-glucuronosyltransferases. Curr. Drug Metab. 2000; 1(2):143–161. [PubMed: 11465080]
2. Ritter JK. Roles of glucuronidation and UDP-glucuronosyltransferases in xenobiotic bioactivation reactions. Chem. Biol. Interact. 2000; 129(1–2):171–193. [PubMed: 11154740]
3. Fisher MB, Paine MF, Strelevitz TJ, Wrighton SA. The role of hepatic and extrahepatic UDP-glucuronosyltransferases in human drug metabolism. Drug Metab. Rev. 2001; 33(3–4):273–297. [PubMed: 11768770]
4. Tukey RH, Strassburg CP. Human UDP-glucuronosyltransferases: metabolism, expression, and disease. Annu. Rev. Pharmacol. Toxicol. 2000; 40:581–616. [PubMed: 10836148]
5. Turgeon D, Carrier JS, Lévesque E, Hum DW, Bélanger A. Relative enzymatic activity, protein stability and tissue distribution of human steroid metabolizing UGT2B subfamily members. Endocrinology. 2001; 142(2):778–787. [PubMed: 11159850]

6. Finel M, Li X, Gardner-Stephen D, Bratton S, Mackenzie PI, Radominska-Pandya A. Human UDP-glucuronosyltransferase 1A5: identification, expression, and activity. J. Pharmacol. Exp. Ther. 2005; 315(3):1143–1149. [PubMed: 16120810]
7. Izukawa T, Nakajima M, Fujiwara R, et al. Quantitative analysis of UDP-glucuronosyltransferase (UGT) 1A and UGT2B expression levels in human livers. Drug Metab. Dispos. 2009; 37(8):1759–1768. [PubMed: 19439486]
8. Strassburg CP, Kalthoff S, Ehmer U. Variability and function of family 1 uridine-5′-diphosphate glucuronosyltransferases (UGT1A). Crit. Rev. Clin. Lab. Sci. 2008; 45(6):485–530. [PubMed: 19003600]
9. Guillemette C. Pharmacogenomics of human UDP-glucuronosyltransferase enzymes. Pharmacogenomics J. 2003; 3(3):136–158. [PubMed: 12815363]
10. Meyerhardt JA, Mayer RJ. Systemic therapy for colorectal cancer. N. Engl. J. Med. 2005; 352(5): 476–487. [PubMed: 15689586]
11. Catalano V, Labianca R, Beretta GD, Gatta G, de Braud F, Van Cutsem E. Gastric cancer. Crit. Rev. Oncol. Hematol. 2009; 71(2):127–164. [PubMed: 19230702]
12. Murphy CG, Seidman AD. Evolving approaches to metastatic breast cancer previously treated with anthracyclines and taxanes. Clin. Breast Cancer. 2009; 9(Suppl. 2):S58–S65. [PubMed: 19596644]
13. Burris HA, Rothenberg ML, Kuhn JG, Von Hoff DD. Clinical trials with the topoisomerase I inhibitors. Semin. Oncol. 1992; 19(6):663–669. [PubMed: 1334279]
14. Kawato Y, Aonuma M, Hirota Y, Kuga H, Sato K. Intracellular roles of SN-38, a metabolite of the camptothecin derivative CPT-11, in the antitumor effect of CPT-11. Cancer Res. 1991; 51(16): 4187–4191. [PubMed: 1651156]
15. Rivory LP, Robert J. Identification and kinetics of a β-glucuronide metabolite of SN-38 in human plasma after administration of the camptothecin derivative irinotecan. Cancer Chemother. Pharmacol. 1995; 36(2):176–179. [PubMed: 7767955]
16. Iyer L, King CD, Whitington PF, et al. Genetic predisposition to the metabolism of irinotecan (CPT-11). Role of uridine diphosphate glucuronosyltransferase isoform 1A1 in the glucuronidation of its active metabolite (SN-38) in human liver microsomes. J. Clin. Invest. 1998; 101(4):847–854. [PubMed: 9466980]
17. Hanioka N, Ozawa S, Jinno H, Ando M, Saito Y, Sawada J. Human liver UDP-glucuronosyltransferase isoforms involved in the glucuronidation of 7-ethyl-10-hydroxycamptothecin. Xenobiotica. 2001; 31(10):687–699. [PubMed: 11695848]
18. Gagne JF, Montminy V, Belanger P, et al. Common human *UGT1A* polymorphisms and the altered metabolism of irinotecan active metabolite 7-ethyl-10-hydroxycamptothecin (SN-38). Mol. Pharmacol. 2002; 62(3):608–617. [PubMed: 12181437]
19. Ciotti M, Basu N, Brangi M, Owens IS. Glucuronidation of 7-ethyl-10-hydroxycamptothecin (SN-38) by the human UDP-glucuronosyltransferases encoded at the UGT1 locus. Biochem. Biophys. Res. Commun. 1999; 260(1):199–202. [PubMed: 10381366]
20. Tallman MN, Ritter JK, Smith PC. Differential rates of glucuronidation for 7-ethyl-10-hydroxy-camptothecin (SN-38) lactone and carboxylate in human and rat microsomes and recombinant UDP-glucuronosyltransferase isoforms. Drug Metab. Dispos. 2005; 33(7):977–983. [PubMed: 15833930]
21. Yong WP, Ramirez J, Innocenti F, Ratain MJ. Effects of ketoconazole on glucuronidation by UDP-glucuronosyltransferase enzymes. Clin. Cancer Res. 2005; 11(18):6699–6704. [PubMed: 16166450]
22. Lankisch TO, Vogel A, Eilermann S, et al. Identification and characterization of a functional TATA box polymorphism of the UDP glucuronosyltransferase 1A7 gene. Mol. Pharmacol. 2005; 67(5):1732–1739. [PubMed: 15716465]
23. Guillemette C, Ritter JK, Auyeung DJ, Kessler FK, Housman DE. Structural heterogeneity at the UDP-glucuronosyltransferase 1 locus: functional consequences of three novel missense mutations in the human *UGT1A7* gene. Pharmacogenetics. 2000; 10(7):629–644. [PubMed: 11037804]
24. Tukey RH, Strassburg CP. Genetic multiplicity of the human UDP-glucuronosyltransferases and regulation in the gastrointestinal tract. Mol. Pharmacol. 2001; 59(3):405–414. [PubMed: 11179432]

25. Zheng Z, Fang JL, Lazarus P. Glucuronidation: an important mechanism for detoxification of benzo[A]pyrene metabolites in aerodigestive tract tissues. Drug Metab. Dispos. 2002; 30(4):397–403. [PubMed: 11901093]
26. Wasserman E, Myara A, Lokiec F, et al. Severe CPT-11 toxicity in patients with Gilbert's syndrome: two case reports. Ann. Oncol. 1997; 8(10):1049–1051. [PubMed: 9402181]
27. Wasserman E, Cuvier C, Lokiec F, et al. Combination of oxaliplatin plus irinotecan in patients with gastrointestinal tumors: results of two independent Phase I studies with pharmacokinetics. J. Clin. Oncol. 1999; 17(6):1751–1759. [PubMed: 10561212]
28. Bosma PJ, Chowdhury RJ, Bakker C, et al. The genetic basis of the reduced expression of bilirubin UDP-glucuronosyltransferase 1 in Gilbert's syndrome. N. Engl. J. Med. 1995; 333(18):1171–1175. [PubMed: 7565971] ■■ First report of the genetic basis of Gilbert's syndrome.
29. Iyer L, Hall D, Das S, et al. Phenotype-genotype correlation of *in vitro* SN-38 (active metabolite of irinotecan) and bilirubin glucuronidation in human liver tissue with *UGT1A1* promoter polymorphism. Clin. Pharmacol. Ther. 1999; 65(5):576–582. [PubMed: 10340924]
30. Innocenti F, Grimsley C, Das S, et al. Haplotype structure of the UDP-glucuronosyltransferase 1A1 promoter in different ethnic groups. Pharmacogenetics. 2002; 12(9):725–733. [PubMed: 12464801]
31. Iyer L, Das S, Janisch L, et al. *UGT1A1*28* polymorphism as a determinant of irinotecan disposition and toxicity. Pharmacogenomics J. 2002; 2(1):43–47. [PubMed: 11990381]
32. Innocenti F, Undevia SD, Iyer L, et al. Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan. J. Clin. Oncol. 2004; 22(8):1382–1388. [PubMed: 15007088] ■■ **First irinotecan prospective trial.**
33. Ramírez J, Mirkov S, Zhang W, et al. Hepatocyte nuclear factor-1 α is associated with *UGT1A1*, *UGT1A9* and *UGT2B7* mRNA expression in human liver. Pharmacogenomics J. 2008; 8(2):152–161. [PubMed: 17440429]
34. Rouits E, Boisdron-Celle M, Dumont A, Guerin O, Morel A, Gamelin E. Relevance of different *UGT1A1* polymorphisms in irinotecan-induced toxicity: a molecular and clinical study of 75 patients. Clin. Cancer Res. 2004; 10(15):5151–5159. [PubMed: 15297419]
35. McLeod, HL.; Parodi, L.; Sargent, DJ., et al. *UGT1A1*28*, toxicity and outcome in advanced colorectal cancer: results from trial N9741; Presented at: American Society of Clinical Oncology (ASCO) 2006 Annual Meeting; Atlanta, GA, USA. 2–6 June (2006);
36. Toffoli G, Cecchin E, Corona G, et al. The role of *UGT1A1*28* polymorphism in the pharmacodynamics and pharmacokinetics of irinotecan in patients with metastatic colorectal cancer. J. Clin. Oncol. 2006; 24(19):3061–3068. [PubMed: 16809730]
37. Côté JF, Kirzin S, Kramar A, et al. *UGT1A1* polymorphism can predict hematologic toxicity in patients treated with irinotecan. Clin. Cancer Res. 2007; 13(11):3269–3275. [PubMed: 17510208]
38. Capitain, O.; Asevoaia, A.; Boisdron-Celle, M., et al. Influence of pharmacogenetic polymorphisms on 5-fluorouracil and irinotecan efficacy and tolerance in patients treated for advanced colorectal cancer; Presented at: 2008 Gastrointestinal Cancers Symposium; Orlando, FL, USA. 25–28 January (2008);
39. Ando Y, Saka H, Ando M, et al. Polymorphisms of UDP-glucuronosyltransferase gene and irinotecan toxicity: a pharmacogenetic analysis. Cancer Res. 2000; 60(24):6921–6926. [PubMed: 11156391]
40. Kitagawa C, Ando M, Ando Y, et al. Genetic polymorphism in the phenobarbital-responsive enhancer module of the UDP-glucuronosyltransferase 1A1 gene and irinotecan toxicity. Pharmacogenet. Genomics. 2005; 15(1):35–41. [PubMed: 15864124]
41. Yamamoto N, Takahashi T, Kunihane H, et al. Phase I/II pharmacokinetic and pharmacogenomic study of *UGT1A1* polymorphism in elderly patients with advanced non-small cell lung cancer treated with irinotecan. Clin. Pharmacol. Ther. 2009; 85(2):149–154. [PubMed: 18685565]
42. Minami H, Sai K, Saeki M, et al. Irinotecan pharmacokinetics/pharmacodynamics and *UGT1A* genetic polymorphisms in Japanese: roles of *UGT1A1*6* and **28*. Pharmacogenet. Genomics. 2007; 17(7):497–504. [PubMed: 17558305]

43. Marcuello E, Altes A, Menoyo A, Del Rio E, Gomez-Pardo M, Baiget M. *UGT1A1* gene variations and irinotecan treatment in patients with metastatic colorectal cancer. Br. J. Cancer. 2004; 91(4): 678–682. [PubMed: 15280927]
44. De Jong FA, Kehrer DF, Mathijssen RH, et al. Prophylaxis of irinotecan-induced diarrhea with neomycin and potential role for *UGT1A1*28* genotype screening: a double-blind, randomized, placebo-controlled study. Oncologist. 2006; 11(8):944–954. [PubMed: 16951398]
45. Massacesi C, Terrazzino S, Marcucci F, et al. Uridine diphosphate glucuronosyl transferase 1A1 promoter polymorphism predicts the risk of gastrointestinal toxicity and fatigue induced by irinotecan-based chemotherapy. Cancer. 2006; 106(5):1007–1016. [PubMed: 16456808]
46. Chiara, S.; Lastraioli, P.; Marroni, L., et al. Polymorphisms in *UGT1A* gene family and irinotecan toxicity in patients with advanced colorectal cancer; Presented at: American Society of Clinical Oncology (ASCO) 2006 Annual Meeting; Atlanta, GA, USA. 2–6 June (2006);
47. Carlini LE, Meropol NJ, Bever J, et al. *UGT1A7* and *UGT1A9* polymorphisms predict response and toxicity in colorectal cancer patients treated with capecitabine/irinotecan. Clin. Cancer Res. 2005; 11(3):1226–1236. [PubMed: 15709193]
48. Han JY, Lim HS, Shin ES, et al. Comprehensive analysis of *UGT1A* polymorphisms predictive for pharmacokinetics and treatment outcome in patients with non-small-cell lung cancer treated with irinotecan and cisplatin. J. Clin. Oncol. 2006; 24(15):2237–2244. [PubMed: 16636344] ■■ First report of an association between *UGT1A1*6* and severe neutropenia.
49. Han, J.; Lee, S.; Lee, D.; Kim, H.; Lee, J. Pharmacogenetic prediction for tumor response, toxicity, and survival of NSCLC patients treated with irinotecan and cisplatin chemotherapy; Presented at: American Society of Clinical Oncology (ASCO) 2007 Annual Meeting; Chicago, IL, USA. 1–5 June (2007);
50. Soepenberg O, Dumez H, Verweij J, et al. Phase I pharmacokinetic, food effect, and pharmacogenetic study of oral irinotecan given as semisolid matrix capsules in patients with solid tumors. Clin. Cancer Res. 2005; 11(4):1504–1511. [PubMed: 15746053]
51. Font A, Sanchez JM, Taron M, et al. Weekly regimen of irinotecan/docetaxel in previously treated non-small cell lung cancer patients and correlation with uridine diphosphate glucuronosyltransferase 1A1 (*UGT1A1*) polymorphism. Invest. New Drugs. 2003; 21(4):435–443. [PubMed: 14586211]
52. Singh L, Singh AS, Price DK, et al. Influence of genetic variants in *UGT1A1* and *UGT1A9* on the *in vivo* glucuronidation of SN-38. J. Clin. Pharmacol. 2004; 44(8):854–860. [PubMed: 15286088]
53. Singh, A.; Paoluzzi, L.; Price, D., et al. Influence of genetic variants in *UGT1A1* and *UGT1A9* on the *in vivo* glucuronidation of SN-38; Presented at: American Society of Clinical Oncology (ASCO) 2004 Annual Meeting; New Orleans, LA, USA. 5–8 June (2004);
54. De Jong FA, Scott-Horton TJ, Kroetz DL, et al. Irinotecan-induced diarrhea: functional significance of the polymorphic ABCC2 transporter protein. Clin. Pharmacol. Ther. 2007; 81(1): 42–49. [PubMed: 17185998]
55. Hoskins JM, Goldberg RM, Qu P, Ibrahim JG, McLeod HL. *UGT1A1*28* genotype and irinotecan-induced neutropenia: dose matters. J. Natl Cancer Inst. 2007; 99(17):1290–1295. [PubMed: 17728214] ■■ Report of the role of irinotecan dose and schedule on risk of severe neutropenia for *UGT1A1*28/*28* patients.
56. Saito Y, Maekawa K, Ozawa S, Sawada J. Genetic polymorphisms and haplotypes of major drug metabolizing enzymes in East Asians and their comparison with other ethnic populations. Curr. Pharmacogenomics. 2007; 5(1):49–78.
57. Yamamoto K, Sato H, Fujiyama Y, Doida Y, Bamba T. 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; 1406(3): 267–273. [PubMed: 9630669]
58. Jinno H, Saeki M, Saito Y, et al. Functional characterization of human UDP-glucuronosyltransferase 1A9 variant, D256N, found in Japanese cancer patients. J. Pharmacol. Exp. Ther. 2003; 306(2):688–693. [PubMed: 12730278]

59. Jada SR, Lim R, Wong CI, et al. Role of *UGT1A1**6, *UGT1A1*28* and *ABCG2* c.421C>A polymorphisms in irinotecan-induced neutropenia in Asian cancer patients. Cancer Sci. 2007; 98(9):1461–1467. [PubMed: 17627617]
60. Hazama, S.; Okuyama, Y.; Kato, T., et al. Use of genotype subset selections of multi-UGT1As polymorphisms to predict severe neutropenia and tumor responses of metastatic CRC patients received FOLFIRI regimen; Presented at: American Society of Clinical Oncology (ASCO) 2009 Annual Meeting; Orlando, FL, USA. 29 May–2 June (2009);
61. Hsieh SY, Wu YH, Lin DY, Chu CM, Wu M, Liaw YF. Correlation of mutational analysis to clinical features in Taiwanese patients with Gilbert's syndrome. Am. J. Gastroenterol. 2001; 96(4): 1188–1193. [PubMed: 11316168]
62. Sai K, Saeki M, Saito Y, et al. *UGT1A1* haplotypes associated with reduced glucuronidation and increased serum bilirubin in irinotecan-administered Japanese patients with cancer. Clin. Pharmacol. Ther. 2004; 75(6):501–515. [PubMed: 15179405]
63. Araki K, Fujita K, Ando Y, et al. Pharmacogenetic impact of polymorphisms in the coding region of the *UGT1A1* gene on SN-38 glucuronidation in Japanese patients with cancer. Cancer Sci. 2006; 97(11):1255–1259. [PubMed: 16965601]
64. Sai K, Saito Y, Sakamoto H, et al. Importance of UDP-glucuronosyltransferase 1A1*6 for irinotecan toxicities in Japanese cancer patients. Cancer Lett. 2008; 261(2):165–171. [PubMed: 18082937]
65. Innocenti F, Ratain MJ. Pharmacogenetics of irinotecan: clinical perspectives on the utility of genotyping. Pharmacogenomics. 2006; 7(8):1211–1221. [PubMed: 17184208]
66. Sai K, Saito Y, Maekawa K, et al. Additive effects of drug transporter genetic polymorphisms on irinotecan pharmacokinetics/pharmacodynamics in Japanese cancer patients. Cancer Chemother. Pharmacol. 2009 DOI: 10.1007/s00280-009-1138-y. Epub ahead of print.
67. Kaniwa N, Kurose K, Jinno H, et al. Racial variability in haplotype frequencies of *UGT1A1* and glucuronidation activity of a novel single nucleotide polymorphism 686C>T (P229L) found in an African-American. Drug Metab. Dispos. 2005; 33(3):458–465. [PubMed: 15572581]
68. Innocenti F, Liu W, Chen P, Desai AA, Das S, Ratain MJ. Haplotypes of variants in the UDP-glucuronosyltransferase 1A9 and 1A1 genes. Pharmacogenet. Genomics. 2005; 15(5):295–301. [PubMed: 15864130]
69. Lara, P., Jr; Redman, M.; Lenz, H., et al. Cisplatin (Cis)/etoposide (VP16) compared with cis/irinotecan (CPT-11) in extensive-stage small cell lung cancer (E-SCLC): pharmacogenomic (PG) and comparative toxicity analysis of JCOG 9511 and SWOG 0124; Presented at: American Society of Clinical Oncology (ASCO) 2007 Annual Meeting; Chicago, IL, USA. 1–5 June (2007);
70. Cecchin E, Innocenti F, D'Andrea M, et al. Predictive role of the *UGT1A1*, *UGT1A7*, and *UGT1A9* genetic variants and their haplotypes on the outcome of metastatic colorectal cancer patients treated with fluorouracil, leucovorin, and irinotecan. J. Clin. Oncol. 2009; 27(15):2457–2465. [PubMed: 19364970] ■ Largest study conducted so far investigating the role of *UGT1A* haplotypes on the outcomes of folinic acid, fluorouracil and irinotecan cancer patients.
71. Sugatani J, Yamakawa K, Yoshinari K, et al. Identification of a defect in the *UGT1A1* gene promoter and its association with hyperbilirubinemia. Biochem. Biophys. Res. Commun. 2002; 292(2):492–497. [PubMed: 11906189]
72. Yamanaka H, Nakajima M, Katoh M, et al. A novel polymorphism in the promoter region of human *UGT1A9* gene (*UGT1A9**22) and its effects on the transcriptional activity. Pharmacogenetics. 2004; 14(5):329–332. [PubMed: 15115919]
73. Girard H, Villeneuve L, Court MH, et al. The novel *UGT1A9* intronic I399 polymorphism appears as a predictor of 7-ethyl-10-hydroxycamptothecin glucuronidation levels in the liver. Drug Metab. Dispos. 2006; 34(7):1220–1228. [PubMed: 16595709]
74. Girard H, Court MH, Bernard O, et al. Identification of common polymorphisms in the promoter of the *UGT1A9* gene: evidence that *UGT1A9* protein and activity levels are strongly genetically controlled in the liver. Pharmacogenetics. 2004; 14(8):501–515. [PubMed: 15284532]
75. Ramírez J, Liu W, Mirkov S, et al. Lack of association between common polymorphisms in *UGT1A9* and gene expression and activity. Drug Metab. Dispos. 2007; 35(12):2149–2153. [PubMed: 17761781]

76. Inoue K, Miura M, Satoh S, et al. Influence of *UGT1A7* and *UGT1A9* intronic I399 genetic polymorphisms on mycophenolic acid pharmacokinetics in Japanese renal transplant recipients. Ther. Drug Monit. 2007; 29(3):299–304. [PubMed: 17529886]
77. Huang MJ, Yang SS, Lin MS, Huang CS. Polymorphisms of uridine-diphosphoglucuronosyltransferase 1A7 gene in Taiwan Chinese. World J. Gastroenterol. 2005; 11(6):797–802. [PubMed: 15682470]
78. Lankisch TO, Schulz C, Zwingers T, et al. Gilbert's Syndrome and irinotecan toxicity: combination with UDP-glucuronosyltransferase 1A7 variants increases risk. Cancer Epidemiol. Biomarkers Prev. 2008; 17(3):695–701. [PubMed: 18349289]
79. Kohle C, Mohrle B, Munzel PA, et al. Frequent co-occurrence of the TATA box mutation associated with Gilbert's syndrome (*UGT1A1*28*) with other polymorphisms of the UDP-glucuronosyltransferase-1 locus (*UGT1A*6*2 and *UGT1A7**3) in Caucasians and Egyptians. Biochem. Pharmacol. 2003; 65(9):1521–1527. [PubMed: 12732365]
80. Villeneuve L, Girard H, Fortier LC, Gagné JF, Guillemette C. Novel functional polymorphisms in the *UGT1A7* and *UGT1A9* glucuronidating enzymes in Caucasian and African-American subjects and their impact on the metabolism of 7-ethyl-10-hydroxycamptothecin and flavopiridol anticancer drugs. J. Pharmacol. Exp. Ther. 2003; 307(1):117–128. [PubMed: 12944498]
81. Saeki M, Saito Y, Jinno H, et al. Haplotype structures of the *UGT1A* gene complex in a Japanese population. Pharmacogenomics J. 2006; 6(1):63–75. [PubMed: 16314888]
82. Fujita KI, Ando Y, Nagashima F, et al. Genetic linkage of *UGT1A7* and *UGT1A9* polymorphisms to *UGT1A1**6 is associated with reduced activity for SN-38 in Japanese patients with cancer. Cancer Chemother. Pharmacol. 2007; 60(4):515–522. [PubMed: 17406868]
83. Saito Y, Sai K, Maekawa K, et al. Close association of *UGT1A9* IVS1+399C>T with *UGT1A1*28, *6*, or *60* haplotype and its apparent influence on 7-ethyl-10-hydroxycamptothecin (SN-38) glucuronidation in Japanese. Drug Metab. Dispos. 2009; 37(2):272–276. [PubMed: 18981166]
84. Mathijssen RH, de Jong FA, van Schaik RH, et al. Prediction of irinotecan pharmacokinetics by use of cytochrome P450 3A4 phenotyping probes. J. Natl. Cancer Inst. 2004; 96(21):1582–1592.
85. Paoluzzi L, Singh AS, Price DK, et al. Influence of genetic variants in *UGT1A1* and *UGT1A9* on the *in vivo* glucuronidation of SN-38. J. Clin. Pharmacol. 2004; 44(8):854–860. [PubMed: 15286088]
86. Kohle C, Mohrle B, Munzel PA, et al. Frequent co-occurrence of the TATA box mutation associated with Gilbert's syndrome (*UGT1A1*28*) with other polymorphisms of the UDP-glucuronosyltransferase-1 locus (*UGT1A6*2* and *UGT1A7**3) in Caucasians and Egyptians. Biochem. Pharmacol. 2003; 65(9):1521–1527. [PubMed: 12732365]
87. Sandanaraj E, Jada SR, Shu X, et al. Influence of *UGT1A9* intronic I399C>T polymorphism on SN-38 glucuronidation in Asian cancer patients. Pharmacogenomics J. 2008; 8(3):174–185. [PubMed: 17700594]
88. Rouits E, Charasson V, Pétain A, et al. Pharmacokinetic and pharmacogenetic determinants of the activity and toxicity of irinotecan in metastatic colorectal cancer patients. Br. J. Cancer. 2008; 99(8):1239–1245. [PubMed: 18797458]
89. Slatter JG, Schaaf LJ, Sams JP, 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; 28:423–433. [PubMed: 10725311]
90. Innocenti F, Vokes EE, Ratain MJ. Irinogenetics: what is the right star? J. Clin. Oncol. 2006; 24(15):2221–2224. [PubMed: 16636339]
91. Kim TW, Innocenti F. Insights, challenges and future directions in irinogenetics. Ther. Drug. Monit. 2007; 29(3):265–270. [PubMed: 17529881]
92. Toffoli G, Cecchin E, Gasparini G, et al. Genotype driven Phase-1 study of irinotecan administered in combination with 5-fluorouracil/leucovorin (FOLFIRI) in metastatic colorectal cancer patients. J. Clin. Oncol. 2010; 28(5):866–871. [PubMed: 20038727] ■■ First dose-escalation study based on *UGT1A1* genotype.
93. Innocenti, F.; Janisch, L.; Das, S., et al. A genotype-directed Phase I study of irinotecan in advanced cancer patients; Presented at: American Society of Clinical Oncology (ASCO) 2007 Annual Meeting; Chicago, IL, USA. 1–5 June (2007);

94. Kim, T.; Sym, S.; Lee, S., et al. A *UGT1A1* genotype-directed Phase I study of irinotecan (CPT-11) combined with fixed dose of capecitabine in patients with metastatic colorectal cancer (mCRC); Presented at: American Society of Clinical Oncology (ASCO) 2009 Annual Meeting; Orlando, FL, USA. 29 May–2 June (2009);
95. Esaki, T.; Satoh, T.; Ura, T., et al. A prospective PGx and PK/PD dose-finding study of irinotecan based on *UGT1A1*6* and *28* genotyping (UGT0601); Presented at: American Society of Clinical Oncology (ASCO) 2009 Annual Meeting; Orlando, FL, USA. 29 May–2 June (2009);
96. Jordan VC. Tamoxifen: the herald of a new era of preventive therapeutics. J. Natl Cancer Inst. 1997; 89(11):747–749. [PubMed: 9182965]
97. Osborne CK. Tamoxifen in the treatment of breast cancer. N. Engl. J. Med. 1998; 339(22):1609–1618. [PubMed: 9828250]
98. Cuzick J, Powles T, Veronesi U, et al. Overview of the main outcomes in breast-cancer prevention trials. Lancet. 2003; 361(9354):296–300. [PubMed: 12559863]
99. Boocock DJ, Brown K, Gibbs AH, Sanchez E, Turteltaub KW, White IN. Identification of human CYP forms involved in the activation of tamoxifen and irreversible binding to DNA. Carcinogenesis. 2002; 23(11):1897–1901. [PubMed: 12419838]
100. Kim SY, Suzuki N, Santosh Laxmi YR, Rieger R, Shibutani S. α-hydroxylation of tamoxifen and toremifene by human and rat cytochrome P450 3A subfamily enzymes. Chem. Res. Toxicol. 2003; 16(9):1138–1144. [PubMed: 12971802]
101. Desta Z, Ward BA, Soukhova NV, Flockhart DA. Comprehensive evaluation of tamoxifen sequential biotransformation by the human cytochrome P450 system *in vitro*: prominent roles for CYP3A and CYP2D6. J. Pharmacol. Exp. Ther. 2004; 310(3):1062–1075. [PubMed: 15159443] Comprehensive investigation of tamoxifen metabolism by cytochrome P450 enzymes.
102. Jacolot F, Simon I, Dreano Y, Beaune P, Riche C, Berthou F. Identification of the cytochrome P450 IIIA family as the enzymes involved in the *N*-demethylation oftamoxifen in human liver microsomes. Biochem. Pharmacol. 1991; 41(12):1911–1919. [PubMed: 2039544]
103. Crewe HK, Ellis SW, Lennard MS, Tucker GT. Variable contribution of cytochromes P450 2D6, 2C9 and 3A4 to the 4-hydroxylation of tamoxifen by human liver microsomes. Biochem. Pharmacol. 1997; 53(2):171–178. [PubMed: 9037249]
104. Crewe HK, Notley LM, Wunsch RM, Lennard MS, Gillam EM. Metabolism of tamoxifen by recombinant human cytochrome P450 enzymes: formation of the 4-hydroxy, 4′-hydroxy and *N*-desmethyl metabolites and isomerization of *trans*-4-hydroxytamoxifen. Drug Metab. Dispos. 2002; 30(8):869–874. [PubMed: 12124303]
105. Hu Y, Dehal SS, Hynd G, Jones GB, Kupfer D. CYP2D6-mediated catalysis of tamoxifen aromatic hydroxylation with an NIH shift: similar hydroxylation mechanism in chicken, rat and human liver microsomes. Xenobiotica. 2003; 33(2):141–151. [PubMed: 12623757]
106. Dehal SS, Kupfer D. CYP2D6 catalyzes tamoxifen 4-hydroxylation in human liver. Cancer Res. 1997; 57(16):3402–3406. [PubMed: 9270005]
107. Coller JK. Oxidative metabolism of tamoxifen to *Z*-4-hydroxy-tamoxifen by cytochrome P450 isoforms: an appraisal of *in vitro* studies. Clin. Exp. Pharmacol. Physiol. 2003; 30(11):845–848. [PubMed: 14678248]
108. Coller JK, Krebsfaenger N, Klein K, et al. Large interindividual variability in the *in vitro* formation of tamoxifen metabolites related to the development of genotoxicity. Br. J. Clin Pharmacol. 2004; 57(1):105–111. [PubMed: 14678348]
109. Stearns V, Johnson MD, Rae JM, et al. Active tamoxifen metabolite plasma concentrations after coadministration of tamoxifen and the selective serotonin reuptake inhibitor paroxetine. J. Natl Cancer Inst. 2003; 95(23):1758–1764. [PubMed: 14652237]
110. Lien EA, Solheim E, Kvinnsland S, Ueland PM. Identification of 4-hydroxy-*N*-desmethyltamoxifen as a metabolite of tamoxifen in human bile. Cancer Res. 1988; 48(8):2304–2308. [PubMed: 3349495]
111. Lien EA, Solheim E, Lea OA, Lundgren S, Kvinnsland S, Ueland PM. Distribution of 4hydroxy-*N*-desmethyltamoxifen and other tamoxifen metabolites in human biological fluids during tamoxifen treatment. Cancer Res. 1989; 49(8):2175–2183. [PubMed: 2702659]

112. Poon GK, Chui YC, McCague R, et al. Analysis of Phase I and Phase II metabolites of tamoxifen in breast cancer patients. Drug Metab. Dispos. 1993; 21(6):1119–1124. [PubMed: 7905393]
113. Sun D, Sharma AK, Dellinger RW, et al. Glucuronidation of active tamoxifen metabolites by the human UDP glucuronosyltransferases. Drug Metab. Dispos. 2007; 35(11):2006–2014. [PubMed: 17664247]
114. Zhao L, Krishnan S, Zhang Y, Schenkman JB, Rusling JF. Differences in metabolite-mediated toxicity of tamoxifen in rodents versus humans elucidated with DNA/microsome electro-optical arrays and nanoreactors. Chem. Res. Toxicol. 2009; 22(2):341–347. [PubMed: 19166339]
115. Ogura K, Ishikawa Y, Kaku T, et al. Quaternary ammonium-linked glucuronidation of *trans*-4-hydroxytamoxifen, an active metabolite of tamoxifen, by human liver microsomes and UDP-glucuronosyltransferase 1A4. Biochem. Pharmacol. 2006; 71(9):1358–1369. [PubMed: 16480962]
116. Nishiyama T, Ogura K, Nakano H, et al. Reverse geometrical selectivity in glucuronidation and sulfation of *cis*- and *trans*-4-hydroxytamoxifens by human liver UDP-glucuronosyltransferases and sulfotransferases. Biochem. Pharmacol. 2002; 63(10):1817–1830. [PubMed: 12034366]
117. Zheng Y, Sun D, Sharma AK, Chen G, Amin S, Lazarus P. Elimination of antiestrogenic effects of active tamoxifen metabolites by glucuronidation. Drug Metab. Dispos. 2007; 35(10):1942–1948. [PubMed: 17620345]
118. Lazarus P, Blevins-Primeau AS, Zheng Y, Sun D. Potential role of UGT pharmacogenetics in cancer treatment and prevention: focus on tamoxifen. Ann. NY Acad. Sci. 2009; 1155:99–111. [PubMed: 19250197]
119. Blevins-Primeau AS, Sun D, Chen G, et al. Functional significance of UDP-glucuronosyltransferase variants in the metabolism of active tamoxifen metabolites. Cancer Res. 2009; 69(5):1892–1900. [PubMed: 19244109] ■ Investigates how uridine 5′-diphosphoglucuronosyltransferase (UGT) genetic variation affects glucuronidation of active tamoxifen metabolites.
120. Kaku T, Ogura K, Nishiyama T, Ohnuma T, Muro K, Hiratsuka A. Quaternary ammonium-linked glucuronidation of tamoxifen by human liver microsomes and UDP-glucuronosyltransferase 1A4. Biochem. Pharmacol. 2004; 67(11):2093–2102. [PubMed: 15135306]
121. Apak TI, Duffel MW. Interactions of the stereoisomers of α-hydroxytamoxifen with human hydroxysteroid sulfotransferase SULT2A1 and rat hydroxysteroid sulfotransferase STa. Drug Metab. Dispos. 2004; 32(12):1501–1508. [PubMed: 15371299]
122. Coller JK, Krebsfaenger N, Klein K, et al. The influence of *CYP2B6, CYP2C9* and *CYP2D6* genotypes on the formation of the potent antioestrogen *Z*-4-hydroxy-tamoxifen in human liver. Br. J. Clin. Pharmacol. 2002; 54(2):157–167. [PubMed: 12207635]
123. Lim YC, Desta Z, Flockhart DA, Skaar TC. Endoxifen (4-hydroxy-*N*-desmethyl-tamoxifen) has anti-estrogenic effects in breast cancer cells with potency similar to 4-hydroxy-tamoxifen. Cancer Chemother. Pharmacol. 2005; 55(5):471–478. [PubMed: 15685451]
124. Katzenellenbogen BS, Norman MJ, Eckert RL, Peltz SW, Mangel WF. Bioactivities, estrogen receptor interactions, and plasminogen activator-inducing activities of tamoxifen and hydroxy-tamoxifen isomers in MCF-7 human breast cancer cells. Cancer Res. 1984; 44(1):112–119. [PubMed: 6537799]
125. Furr BJ, Jordan VC. The pharmacology and clinical uses of tamoxifen. Pharmacol. Ther. 1984; 25(2):127–205. [PubMed: 6438654]
126. Johnson MD, Zuo H, Lee KH, et al. Pharmacological characterization of 4-hydroxy-*N*-desmethyl tamoxifen, a novel active metabolite of tamoxifen. Breast Cancer Res. Treat. 2004; 85(2):151–159. [PubMed: 15111773]
127. Jin Y, Desta Z, Stearns V, et al. *CYP2D6* genotype, antidepressant use, and tamoxifen metabolism during adjuvant breast cancer treatment. J. Natl Cancer Inst. 2005; 97(1):30–39. [PubMed: 15632378]
128. Malet C, Spritzer P, Cumins C, Guillaumin D, Mauvais-Jarvis P, Kuttenn F. Effect of 4-hydroxytamoxifen isomers on growth and ultrastructural aspects of normal human breast epithelial (HBE) cells in culture. J. Steroid Biochem. Mol. Biol. 2002; 82(4–5):289–296. [PubMed: 12589935]

129. Sun D, Chen G, Dellinger RW, Duncan K, Fang JL, Lazarus P. Characterization of tamoxifen and 4-hydroxytamoxifen glucuronidation by human *UGT1A*4 variants. Breast Cancer Res. 2006; 8(4):R50. [PubMed: 16884532]
130. Heringa M. Review on raloxifene: profile of a selective estrogen receptor modulator. Int. J. Clin. Pharmacol. Ther. 2003; 41(8):331–345. [PubMed: 12940590]
131. Visvanathan K, Chlebowski RT, Hurley P, et al. American society of clinical oncology clinical practice guideline update on the use of pharmacologic interventions including tamoxifen, raloxifene, and aromatase inhibition for breast cancer risk reduction. J. Clin. Oncol. 2009; 27(19):3235–3258. [PubMed: 19470930]
132. Vogel VG. The NSABP Study of Tamoxifen and Raloxifene (STAR) trial. Expert Rev. Anticancer Ther. 2009; 9(1):51–60. [PubMed: 19105706]
133. Snyder KR, Sparano N, Malinowski JM. Raloxifene hydrochloride. Am J. Health Syst. Pharm. 2000; 57(18):1669–1675. [PubMed: 11006795]
134. Hochner-Celnikier D. Pharmacokinetics of raloxifene and its clinical application. Eur. J. Obstet. Gynecol. Reprod. Biol. 1999; 85(1):23–29. [PubMed: 10428318]
135. Dodge JA, Lugar CW, Cho S, et al. Evaluation of the major metabolites of raloxifene as modulators of tissue selectivity. J. Steroid Biochem. Mol. Biol. 1997; 61(1–2):97–106. [PubMed: 9328215]
136. Kemp DC, Fan PW, Stevens JC. Characterization of raloxifene glucuronidation *in vitro*: contribution of intestinal metabolism to presystemic clearance. Drug Metab. Dispos. 2002; 30(6): 694–700. [PubMed: 12019197]
137. Jeong EJ, Liu Y, Lin H, Hu M. Species- and disposition model-dependent metabolism of raloxifene in gut and liver: role of *UGT1A10*. Drug Metab. Dispos. 2005; 33(6):785–794. [PubMed: 15769887]
138. Chang JH, Yoo P, Lee T, Klopf W, Takao D. The role of pH in the glucuronidation of raloxifene, mycophenolic acid and ezetimibe. Mol. Pharm. 2009; 6(4):1216–1227. [PubMed: 19449843]
139. Trontelj J, Marc J, Zavratnik A, Bogataj M, Mrhar A. Effects of *UGT1A1*28* polymorphism on raloxifene pharmacokinetics and pharmacodynamics. Br. J. Clin. Pharmacol. 2009; 67(4):437–444. [PubMed: 19371317]
140. Ganzina F. 4′-epi-doxorubicin, a new analogue of doxorubicin: a preliminary overview of preclinical and clinical data. Cancer Treat Rev. 1983; 10(1):1–22. [PubMed: 6342772]
141. Brunello A, Roma A, Falci C, Basso U. Chemotherapy and targeted agents for elderly women with advanced breast cancer. Recent Pat. Anticancer Drug Discov. 2008; 3(3):187–201. [PubMed: 18991787]
142. Levine M. Epirubicin in breast cancer: present and future. Clin. Breast Cancer. 2000; 1(Suppl. 1):S62–S67. [PubMed: 11970752]
143. Li YF, Fu S, Hu W, et al. Systemic anticancer therapy in gynecological cancer patients with renal dysfunction. Int. J. Gynecol. Cancer. 2007; 17(4):739–763. [PubMed: 17309673]
144. Ormrod D, Holm K, Goa K, Spencer C. Epirubicin: a review of its efficacy as adjuvant therapy and in the treatment of metastatic disease in breast cancer. Drugs Aging. 1999; 15(5):389–416. [PubMed: 10600046]
145. Sassi G, Striano B, Merlo UA. A reporting system for the assessment of chemotherapy toxicity. J. Oncol. Pharm. Pract. 2005; 11(2):63–67. [PubMed: 16460607]
146. Morris RG, Kotasek D, Paltridge G. Disposition of epirubicin and metabolites with repeated courses to cancer patients. Eur. J. Clin. Pharmacol. 1991; 40(5):481–487. [PubMed: 1884722]
147. Lunardi G, Venturini M, Vannozzi MO, et al. Influence of alternate sequences of epirubicin and docetaxel on the pharmacokinetic behaviour of both drugs in advanced breast cancer. Ann. Oncol. 2002; 13(2):280–285. [PubMed: 11886006]
148. Innocenti F, Iyer L, Ramírez J, Green MD, Ratain MJ. Epirubicin glucuronidation is catalyzed by human UDP-glucuronosyltransferase 2B7. Drug Metab. Dispos. 2001; 29(5):686–692. [PubMed: 11302935]
149. Innocenti F, Liu W, Fackenthal D, et al. Single nucleotide polymorphism discovery and functional assessment of variation in the UDP-glucuronosyltransferase 2B7 gene.

Pharmacogenet. Genomics. 2008; 18(8):683–697. [PubMed: 18622261] ■ Investigates *UGT2B7* genetic variation and its effect on epirubicin and morphine metabolism.

150. Kwara A, Lartey M, Boamah I, et al. Interindividual variability in pharmacokinetics of generic nucleoside reverse transcriptase inhibitors in TB/HIV-coinfected Ghanaian patients: *UGT2B7*1c* is associated with faster zidovudine clearance and glucuronidation. J. Clin. Pharmacol. 2009; 49(9):1079–1090. [PubMed: 19628728]
151. Sawyer MB, Innocenti F, Das S, et al. A pharmacogenetic study of uridine diphosphate-glucuronosyltransferase 2B7 in patients receiving morphine. Clin. Pharmacol. Ther. 2003; 73(6): 566–574. [PubMed: 12811366]
152. Holthe M, Rakvåg TN, Klepstad P, et al. Sequence variations in the UDP-glucuronosyltransferase 2B7 (*UGT2B7*) gene: identification of 10 novel single nucleotide polymorphisms (SNPs) and analysis of their relevance to morphine glucuronidation in cancer patients. Pharmacogenomics J. 2003; 3(1):17–26. [PubMed: 12629580]
153. Coulbault L, Beaussier M, Verstuyft C, et al. Environmental and genetic factors associated with morphine response in the postoperative period. Clin. Pharmacol. Ther. 2006; 79(4):316–324. [PubMed: 16580900]
154. Ross JR, Rutter D, Welsh K, et al. Clinical response to morphine in cancer patients and genetic variation in candidate genes. Pharmacogenomics J. 2005; 5(5):324–336. [PubMed: 16103897]
155. Sawyer, MB.; Damaraju, S.; Pituskin, E., et al. Uridine glucuronosyltransferase 2B7 pharmacogenetics predicts epirubicin clearance and myelosuppression; Presented at: American Society of Clinical Oncology (ASCO) 2009 Annual Meeting; Orlando, FL, USA. 29 May–2 June (2009);
156. Lane AA, Chabner BA. Histone deacetylase inhibitors in cancer therapy. J. Clin. Oncol. 2009; 27(32):5459–5468. [PubMed: 19826124]
157. Rasheed W, Bishton M, Johnstone RW, Prince HM. Histone deacetylase inhibitors in lymphoma and solid malignancies. Expert Rev. Anticancer Ther. 2008; 8(3):413–432. [PubMed: 18366289]
158. Fakih MG, Pendyala L, Fetterly G, et al. A Phase I, pharmacokinetic and pharmacodynamic study on vorinostat in combination with 5-fluorouracil, leucovorin, and oxaliplatin in patients with refractory colorectal cancer. Clin. Cancer Res. 2009; 15(9):3189–3195. [PubMed: 19383814]
159. Fujiwara Y, Yamamoto N, Yamada Y, et al. Phase I and pharmacokinetic study of vorinostat (suberoylanilide hydroxamic acid) in Japanese patients with solid tumors. Cancer Sci. 2009; 100(9):1728–1734. [PubMed: 19575752]
160. Munster PH, Marchion D, Thomas S, et al. Phase I trial of vorinostat and doxorubicin in solid tumours: histone deacetylase 2 expression as a predictive marker. Br. J. Cancer. 2009; 101(7): 1044–1050. [PubMed: 19738609]
161. Du L, Musson DG, Wang AQ. High turbulence liquid chromatography online extraction and tandem mass spectrometry for the simultaneous determination of suberoylanilide hydroxamic acid and its two metabolites in human serum. Rapid Commun. Mass Spectrom. 2005; 19(13): 1779–1787. [PubMed: 15945019]
162. Du L, Musson DG, Wang AQ. Stability studies of vorinostat and its two metabolites in human plasma, serum and urine. J. Pharm. Biomed. Anal. 2006; 42(5):556–564. [PubMed: 16824724]
163. Parise RA, Holleran JL, Beumer JH, Ramalingam S, Egorin MJ. A liquid chromatography-electrospray ionization tandem mass spectrometric assay for quantitation of the histone deacetylase inhibitor, vorinostat (suberoylanilide hydroxamicacid, SAHA), and its metabolites in human serum. J. Chromatogr. B Analyt. Technol. Biomed. Life Sci. 2006; 840(2):108–115.
164. Balliet RM, Chen G, Gallagher CJ, Dellinger RW, Sun D, Lazarus P. Characterization of UGTs active against SAHA and association between SAHA glucuronidation activity phenotype with UGT genotype. Cancer Res. 2009; 69(7):2981–2989. [PubMed: 19318555] ■ Reports how *UGT* genetic variation affects vorinostat metabolism.
165. Kang, S.; Ramirez, J.; House, L.; Ratain, MJ. *In vitro* glucuronidation of vorinostat; Presented at: American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2009 Annual Meeting; National Harbor, MD, USA. 18–21 March (2009);
166. Christian BA, Grever MR, Byrd JC, Lin TS. Flavopiridol in chronic lymphocytic leukemia: a concise review. Clin. Lymphoma Myeloma. 2009; 9(Suppl. 3):S179–S185. [PubMed: 19778838]

167. Innocenti F, Stadler WM, Iyer L, Ramírez J, Vokes EE, Ratain MJ. Flavopiridol metabolism in cancer patients is associated with the occurrence of diarrhea. Clin. Cancer Res. 2000; 6(9):3400–3405. [PubMed: 10999721]

168. Thomas, J.; Tutsch, K.; Arzoomanian, R., et al. Phase I clinical and pharmacokinetic trial of the cyclin-dependent kinase (CDK) inhibitor flavopiridol; Presented at: American Society of Clinical Oncology (ASCO) 1998 Annual Meeting; Los Angeles, CA, USA. 16–19 May (1998);

169. Senderowicz AM, Headlee D, Stinson SF, et al. Phase I trial of continuous infusion flavopiridol, a novel cyclin-dependent kinase inhibitor, in patients with refractory neoplasms. J. Clin. Oncol. 1998; 16(9):2986–2999. [PubMed: 9738567]

170. Hagenauer B, Salamon A, Thalhammer T, et al. *In vitro* glucuronidation of the cyclin-dependent kinase inhibitor flavopiridol by rat and human liver microsomes: involvement of UDP-glucuronosyltransferases 1A1 and 1A9. Drug Metab. Dispos. 2001; 29(4 Pt 1):407–414. [PubMed: 11259324]

171. Ramírez J, Iyer L, Journault K, et al. *In vitro* characterization of hepatic flavopiridol metabolism using human liver microsomes and recombinant UGT enzymes. Pharm. Res. 2002; 19(5):588–594. [PubMed: 12069159]

172. Zhai S, Sausville EA, Senderowicz AM, et al. Clinical pharmacology and pharmacogenetics of flavopiridol 1-h i.v. infusion in patients with refractory neoplasms. Anticancer Drugs. 2003; 14(2):125–135. [PubMed: 12569299]

173. Yoshida M, Kabe Y, Wada T, Asai A, Handa H. A new mechanism of 6-((2-(dimethylamino) ethyl)amino)-3-hydroxy-7*H*-indeno(2,1-c) quinolin-7-one dihydrochloride (TAS-103) action discovered by target screening with drug-immobilized affinity beads. Mol. Pharmacol. 2008; 73(3):987–994. [PubMed: 18089836]

174. Iyer, L.; Mortell, MA.; Azuma, R., et al. Glucuronidation of TAS-103: a novel anticancer agent; Presented at: American Society of Clinical Oncology (ASCO) 1998 Annual Meeting; Los Angeles, CA, USA. 16–19 May (1998);

175. Ewesuedo RB, Iyer L, Das S, et al. Phase I clinical and pharmacogenetic study of weekly TAS-103 in patients with advanced cancer. J. Clin. Oncol. 2001; 19(7):2084–2090. [PubMed: 11283142]

176. Lévesque E, Beaulieu M, Green MD, et al. Isolation and characterization of UGT2B15(Y85): a UDP-glucuronosyltransferase encoded by a polymorphic gene. Pharmacogenetics. 1997; 7(4): 317–325. [PubMed: 9295060]

177. Court MH, Duan SX, Guillemette C, et al. Stereoselective conjugation of oxazepam by human UDP-glucuronosyltransferases (UGTs): *S*-oxazepam is glucuronidated by UGT2B15, while *R*-oxazepam is glucuronidated by UGT2B7 and UGT1A9. Drug Metab. Dispos. 2002; 30(11): 1257–1265. [PubMed: 12386133]

178. Court MH, Hao Q, Krishnaswamy S, et al. UDP-glucuronosyltransferase (UGT) 2B15 pharmacogenetics: *UGT2B15* D85Y genotype and gender are major determinants of oxazepam glucuronidation by human liver. J. Pharmacol. Exp. Ther. 2004; 310(2):656–665. [PubMed: 15044558]

179. He X, Hesse LM, Hazarika S, et al. Evidence for oxazepam as an *in vivo* probe of *UGT2B15*: oxazepam clearance is reduced by *UGT2B15* D85Y polymorphism but unaffected by *UGT2B17* deletion. Br. J. Clin. Pharmacol. 2009; 68(5):721–730. [PubMed: 19916996]

180. Chung JY, Cho JY, Yu KS, et al. Effect of the *UGT2B15* genotype on the pharmacokinetics, pharmacodynamics, and drug interactions of intravenous lorazepam in healthy volunteers. Clin. Pharmacol. Ther. 2005; 77(6):486–494. [PubMed: 15961980]

181. Ciotti M, Marrone A, Potter C, et al. Genetic polymorphism in the human *UGT1A*6 (planar phenol) UDP-glucuronosyltransferase: pharmacological implications. Pharmacogenetics. 1997; 7(6):485–495. [PubMed: 9429234]

182. Nagar S, Zalatoris JJ, Blanchard RL. Human *UGT1A*6 pharmacogenetics: identification of a novel SNP, characterization of allele frequencies and functional analysis of recombinant allozymes in human liver tissue and in cultured cells. Pharmacogenetics. 2004; 14(8):487–499. [PubMed: 15284531]

183. Krishnaswamy S, Hao Q, Al-Rohaimi A, et al. UDP glucuronosyltransferase (UGT) 1A6 pharmacogenetics: II. Functional impact of the three most common nonsynonymous *UGT1A*6 polymorphisms (S7A, T181A, and R184S). J. Pharmacol. Exp. Ther. 2005; 313(3):1340–1346. [PubMed: 15761113]

184. van Oijen MG, Barthélémy C, Janssen MJ, et al. Effect of genetic polymorphisms in UDP-glucuronosyltransferase 1A6 (*UGT1A6*) on acetylsalicylic acid metabolism in healthy female volunteers. Pharmacology. 2009; 83(4):237–242. [PubMed: 19262071]

185. Tankanitlert J, Morales NP, Howard TA, et al. Effects of combined UDP-glucuronosyltransferase (UGT) *1A1*28* and *1A6*2* on paracetamol pharmacokinetics in β-thalassemia/HbE. Pharmacology. 2007; 79(2):97–103. [PubMed: 17164591]

186. Ehmer U, Vogel A, Schütte JK, et al. Variation of hepatic glucuronidation: novel functional polymorphisms of the UDP-glucuronosyltransferase *UGT1A4*. Hepatology. 2004; 39(4):970–977. [PubMed: 15057901]

187. Innocenti, F.; Mirkov, S.; Ramírez, J., et al. *In vitro* glucuronidation of ABT-751, a novel anticancer agent; Presented at: American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2004 Annual Meeting; Miami Beach, FL, USA. 24–27 March (2004);

188. Hande KR, Hagey A, Berlin J, et al. The pharmacokinetics and safety of ABT-751, a novel, orally bioavailable sulfonamide antimitotic agent: results of a Phase 1 study. Clin. Cancer Res. 2006; 12(9):2834–2840. [PubMed: 16675578]

189. Rudek MA, Zhao M, He P, Messersmith WA, Baker SD. Validation and implementation of a liquid chromatography/tandem mass spectrometry assay to quantitate ABT-751, ABT-751 glucuronide, and ABT-751 sulfate in human plasma for clinical pharmacology studies. J. Pharm. Biomed. Anal. 2006; 42(2):253–260. [PubMed: 16765012]

190. Lazarus P, Sun D. Potential role of UGT pharmacogenetics in cancer treatment and prevention: focus on tamoxifen and aromatase inhibitors. Drug Metab. Rev. 2010; 42(1):176–188.

191. Mareck U, Geyer H, Guddat S, et al. Identification of the aromatase inhibitors anastrozole and exemestane in human urine using liquid chromatography/tandem mass spectrometry. Rapid Commun. Mass Spectrom. 2006; 20(12):1954–1962. [PubMed: 16715475]

192. Kamath AV, Wang J, Lee FY, et al. Preclinical pharmacokinetics and *in vitro* metabolism of dasatinib (BMS-354825): a potent oral multi-targeted kinase inhibitor against SRC and BCR-ABL. Cancer Chemother. Pharmacol. 2007; 61(3):365–376. [PubMed: 17429625]

193. Liu H, Bolton JL, Thatcher GR. Chemical modification modulates estrogenic activity, oxidative reactivity, and metabolic stability in 4′F-DMA, a new benzothiophene selective estrogen receptor modulator. Chem. Res. Toxicol. 2006; 19(6):779–787. [PubMed: 16780356]

194. Miners JO, Valente L, Lillywhite KJ, et al. Preclinical prediction of factors influencing the elimination of 5,6-dimethylxanthenone-4-acetic acid, a new anticancer drug. Cancer Res. 1997; 57(2):284–289. [PubMed: 9000569]

195. Jameson MB, Baguley BC, Kestell P, et al. Cancer Research (UK) Phase I/II Trials Committee: Pharmacokinetics of 5,6-dimethylxanthenone-4-acetic acid (AS1404), a novel vascular disrupting agent, in Phase I clinical trial. Cancer Chemother. Pharmacol. 2007; 59(5):681–687. [PubMed: 17021822]

196. Zhou SF, Paxton JW, Tingle MD, et al. Identification and reactivity of the major metabolite (β-1-glucuronide) of the anti-tumour agent 5,6-dimethylxanthenone-4-acetic acid (DMXAA) in humans. Xenobiotica. 2001; 31(5):277–293. [PubMed: 11491389]

197. Zhou S, Kestell P, Baguley BC, Paxton JW. Preclinical factors influencing the relative contributions of Phase I and II enzymes to the metabolism of the experimental anti-cancer drug 5,6-dimethylxanthenone-4-acetic acid. Biochem. Pharmacol. 2003; 65(1):109–120. [PubMed: 12473385]

198. Takanashi S, Bachur NR. Adriamycin metabolism in man. Evidence from urinary metabolites. Drug Metab. Dispos. 1976; 4(1):79–87. [PubMed: 3405]

199. Weenen H, Lankelma J, Penders PG, et al. Pharmacokinetics of 4′-epi-doxorubicin in man. Invest New Drugs. 1983; 1(1):59–64. [PubMed: 6590528]

200. Weenen H, van Maanen JM, de Planque MM, McVie JG, Pinedo HM. Metabolism of 4′-modified analogs of doxorubicin. Unique glucuronidation pathway for 4′-epidoxorubicin. Eur. J. Cancer Clin. Oncol. 1984; 20(7):919–926. [PubMed: 6589165]

201. Cassinelli G, Configliacchi E, Penco S, et al. Separation, characterization, and analysis of epirubicin (4′-epidoxorubicin) and its metabolites from human urine. Drug Metab. Dispos. 1984; 12(4):506–510. [PubMed: 6148220]

202. Robert J, David M, Granger C. Metabolism of epirubicin to glucuronides: relationship to the pharmacodynamics of the drug. Cancer Chemother. Pharmacol. 1990; 27(2):147–150. [PubMed: 2249331]

203. Robert J, Vrignaud P, Nguyen-Ngoc T, Iliadis A, Mauriac L, Hurteloup P. Comparative pharmacokinetics and metabolism of doxorubicin and epirubicin in patients with metastatic breast cancer. Cancer Treat. Rep. 1985; 69(6):633–640. [PubMed: 3893693]

204. Zaya MJ, Hines RN, Stevens JC. Epirubicin glucuronidation and UGT2B7 developmental expression. Drug Metab. Dispos. 2006; 34(12):2097–2101. [PubMed: 16985101]

205. Ling J, Johnson KA, Miao Z, et al. Metabolism and excretion of erlotinib, a small molecule inhibitor of epidermal growth factor receptor tyrosine kinase, in healthy male volunteers. Drug Metab. Dispos. 2006; 34(3):420–426. [PubMed: 16381666]

206. Watanabe Y, Nakajima M, Ohashi N, Kume T, Yokoi T. Glucuronidation of etoposide in human liver microsomes is specifically catalyzed by UDP-glucuronosyltransferase 1A1. Drug Metab. Dispos. 2003; 31(5):589–595. [PubMed: 12695347]

207. Wen Z, Tallman MN, Ali SY, Smith PC. UDP-glucuronosyltransferase 1A1 is the principal enzyme responsible for etoposide glucuronidation in human liver and intestinal microsomes: structural characterization of phenolic and alcoholic glucuronides of etoposide and estimation of enzyme kinetics. Drug Metab. Dispos. 2007; 35(3):371–380. [PubMed: 17151191]

208. Ito M, Yamamoto K, Maruo Y, Sato H, Fujiyama Y, Bamba T. Effect of a conserved mutation in uridine diphosphate glucuronosyltransferase 1A1 and 1A6 on glucuronidation of a metabolite of flutamide. Eur. J. Clin. Pharmacol. 2002; 58(1):11–14. [PubMed: 11956667]

209. Helsby NA, Goldthorpe MA, Tang MH, et al. Influence of mustard group structure on pathways of *in vitro* metabolism of anticancer *N*-(2-hydroxyethyl)-3,5-dinitrobenzamide 2-mustard prodrugs. Drug Metab. Dispos. 2008; 36(2):353–360. [PubMed: 17998296]

210. Van sen Bongard HJ, Pluim D, et al. An excretion balance and pharmacokinetic study of the novel anticancer agent E7070 in cancer patients. Anticancer Drugs. 2002; 13(8):807–814. [PubMed: 12394264]

211. Beumer JH, Hillebrand MJ, Pluim D, et al. Human metabolism of [(C14)]indisulam following i.v. infusion in cancer patients. Invest. New Drugs. 2005; 23(4):317–330. [PubMed: 16012791]

212. Prakash C, Johnson KA, Gardner MJ. Disposition of lasofoxifene, a next-generation selective estrogen receptor modulator, in healthy male subjects. Drug Metab. Dispos. 2008; 36(7):1218–1226. [PubMed: 18372400]

213. Lakhani NJ, Sparreboom A, Xu X, et al. Characterization of *in vitro* and *in vivo* metabolic pathways of the investigational anticancer agent, 2-methoxyestradiol. J. Pharm. Sci. 2007; 96(7): 1821–1831. [PubMed: 17252610]

214. Cummings J, Ethell BT, Jardine L, et al. Glucuronidation as a mechanism of intrinsic drug resistance in human colon cancer: reversal of resistance by food additives. Cancer Res. 2003; 63(23):8443–8450. [PubMed: 14679008]

215. Cummings J, Ethell BT, Jardine L, Burchell B. Glucuronidation of SN-38 and NU/ICRF in human colon cancer and adjacent normal colon. Anticancer Res. 2006; 26(3B):2189–2196. [PubMed: 16821585]

216. Cummings J, Boyd G, Ethell BT, et al. Enhanced clearance of topoisomerase I inhibitors from human colon cancer cells by glucuronidation. Biochem. Pharmacol. 2002; 63(4):607–613. [PubMed: 11992628]

217. Dalvie D, Kang P, Zientek M, Xiang C, Zhou S, Obach RS. Effect of intestinal glucuronidation in limiting hepatic exposure and bioactivation of raloxifene in humans and rats. Chem. Res. Toxicol. 2008; 21(12):2260–2271. [PubMed: 19548350]

218. Kim AR, Lim SJ, Lee BJ. Metabolic inhibition and kinetics of raloxifene by pharmaceutical excipients in human liver microsomes. Int. J. Pharm. 2009; 368(1–2):37–44. [PubMed: 18977285]

219. Azuma R, Saeki M, Yamamoto Y, Hagiwara Y, Grochow LB, Donehower RC. Metabolism and urinary excretion of a new quinoline anticancer drug, TAS-103, in humans. Xenobiotica. 2002; 32(1):63–72. [PubMed: 11820510]

220. Garner RC, Goris I, Laenen AA, et al. Evaluation of accelerator mass spectrometry in a human mass balance and pharmacokinetic study-experience with 14C-labeled (R)-6-[amino(4-chlorophenyl) (1-methyl-1H-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1- methyl-2(1H)-quinolinone (R115777), a farnesyl transferase inhibitor. Drug Metab. Dispos. 2002; 30(7):823–830. [PubMed: 12065441]

221. Zhang S, Zannikos P, Awada A, et al. Pharmacokinetics of tipifamib after oral and intravenous administration in subjects with advanced cancer. J. Clin. Pharmacol. 2006; 46(10):1116–1127. [PubMed: 16988200]

222. Rosing H, van Zomeren DM, Doyle E, Bult A, Beijnen JH. *O*-glucuronidation, a newly identified metabolic pathway for topotecan and *N*-desmethyl topotecan. Anticancer Drugs. 1998; 9(7):587–592. [PubMed: 9773801]

223. Aono S, Adachi Y, Uyama E, et al. Analysis of genes for bilirubin UDP-glucuronosyltransferase in Gilbert's syndrome. Lancet. 1995; 345(8955):958–959. [PubMed: 7715297]

224. 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. USA. 1998; 95(14):8170–8174. [PubMed: 9653159]

225. Sugatani J, Kojima H, Ueda A, et al. The phenobarbital response enhancer module in the human bilirubin UDP-glucuronosyltransferase *UGT1A1* gene and regulation by the nuclear receptor CAR. Hepatology. 2001; 33(5):1232–1238. [PubMed: 11343253]

226. Wiener D, Doerge DR, Fang JL, Upadhyaya P, Lazarus P. Characterization of *N*-glucuronidation of the lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) in human liver: importance of UDP-glucuronosyltransferase 1A4. Drug Metab. Dispos. 2004; 32(1):72–79. [PubMed: 14709623]

227. Saeki M, Saito Y, Jinno H, et al. Genetic variations and haplotypes of *UGT1A*4 in a Japanese population. Drug Metab. Pharmacokinet. 2005; 20(2):144–151. [PubMed: 15855727]

228. Huang YH, Galijatovic A, Nguyen N, et al. Identification and functional characterization of UDP glucuronosyltransferases *UGT1A8*1*, *UGT1A8*2* and *UGT1A8*3*. Pharmacogenetics. 2002; 12(4):287–297. [PubMed: 12042666]

229. Bernard O, Guillemette C. The main role of *UGT1A9* in the hepatic metabolism of mycophenolic acid and the effects of naturally occurring variants. Drug Metab. Dispos. 2004; 32(8):775–778. [PubMed: 15258099]

230. Thomas SS, Li SS, Lampe JW, Potter JD, Bigler J. Genetic variability, haplotypes, and htSNPs for exons 1 at the human *UGT1A* locus. Hum. Mutat. 2006; 27(7):717. [PubMed: 16786511]

231. Elahi A, Bendaly J, Zheng Z, et al. Detection of *UGT1A10* polymorphisms and their association with orolaryngeal carcinoma risk. Cancer. 2003; 98(4):872–880. [PubMed: 12910533]

232. Jin C, Miners JO, Lillywhite KJ, Mackenzie PI. Complementary deoxyribonucleic acid cloning and expression of a human liver uridine diphosphate-glucuronosyltransferase glucuronidating carboxylic acid-containing drugs. J. Pharmacol. Exp. Ther. 1993; 264(1):475–479. [PubMed: 8423545]

233. Coffman BL, King CD, Rios GR, Tephly TR. The glucuronidation of opioids, other xenobiotics, and androgens by human UGT2B7Y(268) and UGT2B7H(268). Drug Metab. Dispos. 1998; 26(1):73–77. [PubMed: 9443856]

234. Bhasker CR, McKinnon W, Stone A, et al. Genetic polymorphism of UDP-glucuronosyltransferase 2B7 (*UGT2B7*) at amino acid 268: ethnic diversity of alleles and potential clinical significance. Pharmacogenetics. 2000; 10(8):679–685. [PubMed: 11186130]

235. Wilson W 3rd, Pardo-Manuel de Villena F, Lyn-Cook BD, et al. Characterization of a common deletion polymorphism of the *UGT2B17* gene linked to *UGT2B15*. Genomics. 2004; 84(4):707–714. [PubMed: 15475248]

236. Murata M, Warren EH, Riddell SR. A human minor histocompatibility antigen resulting from differential expression due to a gene deletion. J. Exp. Med. 2003; 197(10):1279–1289. [PubMed: 12743171]

237. Lazarus P, Zheng Y, Aaron Runkle E, Muscat JE, Wiener D. Genotype–phenotype correlation between the polymorphic *UGT2B17* gene deletion and NNAL glucuronidation activities in human liver microsomes. Pharmacogenet. Genomics. 2005; 15(11):769–778. [PubMed: 16220109]

238. Jakobsson J, Ekström L, Inotsume N, et al. Large differences in testosterone excretion in Korean and Swedish men are strongly associated with a UDP-glucuronosyl transferase 2B17 polymorphism. J. Clin. Endocrinol. Metab. 2006; 91(2):687–693. [PubMed: 16332934]

239. Gallagher CJ, Muscat JE, Hicks AN, et al. The UDP-glucuronosyltransferase *2B17* gene deletion polymorphism: sex-specific association with urinary 4-(methylnitrosamino)-1-(3pyridyl)-1-butanol glucuronidation phenotype and risk for lung cancer. Cancer Epidemiol. Biomarkers Prev. 2007; 16(4):823–828. [PubMed: 17416778]

240. Swanson C, Mellström D, Lorentzon M, et al. The uridine diphosphate glucuronosyltransferase 2B15 D85Y and 2B17 deletion polymorphisms predict the glucuronidation pattern of androgens and fat mass in men. J. Clin. Endocrinol. Metab. 2007; 92(12):4878–4882. [PubMed: 17698910]

241. Yang TL, Chen XD, Guo Y, et al. Genome-wide copy-number-variation study identified a susceptibility gene, *UGT2B17*, for osteoporosis. Am J. Hum Genet. 2008; 83(6):663–674. [PubMed: 18992858]

242. Karypidis AH, Olsson M, Andersson SO, Rane A, Ekström L. Deletion polymorphism of the *UGT2B17* gene is associated with increased risk for prostate cancer and correlated to gene expression in the prostate. Pharmacogenomics J. 2008; 8(2):147–151. [PubMed: 17387331]

243. Ménard V, Eap O, Harvey M, Guillemette C, Lévesque E. Copy-number variations (CNVs) of the human sex steroid metabolizing genes *UGT2B17* and *UGT2B28* and their associations with a *UGT2B15* functional polymorphism. Hum. Mutat. 2009; 30(9):1310–1319. [PubMed: 19572376]

Websites

301. *UGT1A* and *UGT2B* haplotypes and SNPs tables. www.pharmacogenomics.pha.ulaval.ca/sgc/ugt_alleles

302. MedWatch Safety Alerts for Human Medical Products. www.fda.gov/medwatch/SAFETY/2005/Jun_PI/Camptosar_PI.pdf

303. US FDA Press Release: FDA clears genetic test that advances personalized medicine. August 22. 2005 www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2005/ucm108475.htm

304. EMEA. Nexavar. www.emea.europa.eu/humandocs/PDFs/EPAR/nexavar/H-690-en6.pdf

Table 1

List of anticancer drugs metabolized by glucuronidation.

Drug	Class	UGT enzyme	Ref.
ABT-751	Antimitotic agent	UGT1A1, UGT1A4, UGT1A8 (major) and UGT2B7 [187]	[187-189]
Anastrozole	Aromatase inhibitor	UGT1A4 [190]	[190,191]
Dasatinib	Tyrosine kinase inhibitor	Unknown	[192]
Desmethyl arzoxifene and 4′F-desmethyl arzoxifene	Benzothiophene selective estrogen receptor modulators	Unknown	[193]
5,6-dimethylxanthenone-4-acetic acid	Vascular-disrupting agent	UGT1A9 and UGT2B7 (major) [194]	[194-197]
Doxorubicin	Anthracycline	Unknown	[198]
Epirubicin	Anthracycline	UGT2B7 [148]	[146-149,199-204]
Erlotinib	Tyrosine kinase inhibitor	Unknown	[205]
Etoposide	Topoisomerase II inhibitor	UGT1A1 [206,207]	[206,207]
Flavopiridol	Cyclin-dependent kinase inhibitor	UGT1A1, UGT1A4, UGT1A9 (major) and UGT1A10 [170,171]	[75,167,170,171]
Flutamide	Nonsteroidal anti-androgen drug	UGT1A1 and UGT1A6 (major) [208]	[208]
N-(2-hydroxyethyl)-3,5-dinitrobenzamide 2-mustard prodrugs: SN 27858 (PR-140A), SN 29546, SN 27686 and SN 29893	Dinitrobenzamide mustards	Unknown	[209]
Indisulam	Multitargeted cell-cycle inhibitor	Unknown	[210,211]
Lasofoxifene	Selective estrogen receptor modulator	UGT1A1, UGT1A3, UGT1A6, UGT1A8, UGT1A9 and UGT1A10 [212]	[212]
2-methoxyestradiol	Angiogenesis inhibitor	Unknown	[213]
NU/ICRF 505	Topoisomerase I inhibitor	UGT1A1, UGT1A8, UGT1A9 (main enzyme for tyrosine glucuronide formation), UGT1A10 and UGT2B7 (main enzyme for *O*-glucuronide formation) [214,215]	[214-216]
Raloxifene	Selective estrogen receptor modulator	UGT1A1 (main enzyme for 6-glucuronide formation), UGT1A3, UGT1A8, UGT1A9 (major enzyme for 4′-glucuronide formation), UGT1A10 and UGT2B7 [136-138]	[134, 136-139, 217,218]
SN-38 (active metabolite of irinotecan)	Topoisomerase I inhibitor	UGT1A1 (major), UGT1A3, UGT1A6, UGT1A7 and UGT1A9 [16-22,215]	[16-22,215]

Drug	Class	UGT enzyme	Ref.
Sorafenib	Tyrosine protein kinase inhibitor	UGT1A9 [304]	[304]
Tamoxifen	Anti-estrogen	UGT1A4 for *N*-glucuronidation of tamoxifen and 4-hydroxytamoxifen [112,114,115,119]; UGT1A1, UGT1A8 UGT1A9, UGT1A10, UGT2B7, UGT2B15 for *O*-glucuronidation of 4-hydroxytamoxifen and endoxifen [113,115,116]	[110-117,119,120]
TAS-103	Topoisomerase I and II inhibitor	UGT1A1 [174]	[174,175,219]
Tipifarnib	Farnesyltransferase inhibitor	Unknown	[220,221]
Topotecan	Topoisomerase I inhibitor	Unknown	[222]
Vorinostat	Histone deacetylase inhibitor	UGT1A1, UGT1A3, UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2B7 and UGT2B17 (major) [164,165]	[164,165]

UGT: Uridine 5′-diphosphoglucuronosyltransferase.

Table 2

Allele frequencies and *in vitro* effects of *UGT1A* variants examined in pharmacogenetic studies of anticancer drugs.

UGT	Expression	*UGT* alleles	Nucleotide change (amino acid change)	*In vitro* effect	Frequency
UGT1A1	Hepatic	*UGT1A1*1*		Normal activity	61–72% in Caucasians, 45–52% in black populations, 90–98% in Japanese populations, 87–93% in Koreans and 84% in Chinese populations [9,56]
		*UGT1A1*6*	211G>A(G71R) [223;	Reduced activity [18,57]	0–1% in Caucasians, 0% in black populations, 13–18% in Japanese populations, 21–24% in Koreans and 23% in Chinese populations [9,56,67]
		*UGT1A1*27*	686C>A (P229Q) [223	Reduced activity [18]	0% in Caucasians and black populations and 1–4% in Asians [23,71]
		*UGT1A1*28*	A(TA)6TAA>A(TA)7TAA [28]	Reduced activity [16,28,224]	29–39% in Caucasians, 35–45% in black populations, 9–13% in Japanese populations, 7–13% in Koreans and 16% in Chinese populations [9,56]
		*UGT1A1*60*	−3279T>G [225]	Reduced activity [30,71]	44–55% in Caucasians, 85% in African–Americans, 17–26% in Japanese populations, 24–33% in Koreans and 30% in Chinese populations [30,56]
		*UGT1A1*93*	−3156G>A [225]	Reduced activity [30]	30–31% in Caucasians, 29% in African–Americans and 10% in Asians [30,68]
UGT1A4	Hepatic	*UGT1A4*1a*		Normal activity	
		*UGT1A4*2*	70C>A (P24T) [186]	Substrate-dependent effect [186,226]	8% in Caucasians [186]
		*UGT1A4*3b*	142T>G (L48V) [186]	Decreased or no activity [186]	9% in Caucasians and 13% in Japanese populations [186,227]
UGT1A7	Extrahepatic	*UGT1A7*1a*		High activity	34–42% in Caucasians, 38% in African–Americans and 59% in Japanese populations [9]
		*UGT1A7*2*	387T>G/391C>A/392G>A (N129K/R131K) [23]	High activity [18,23]	24–34% in Caucasians, 39% in African–Americans, 15% in Japanese populations and 27% in Taiwanese Chinese populations [9,77]
		*UGT1A7*3*	387T>G/391C>A/392G>A/622T>C (N129K/R131K/W208R) [23]	Low activity [18,23]	23–36% in Caucasians, 23% in African–Americans, 26% in Japanese populations and 15% in Taiwanese Chinese populations [9,77]
		*UGT1A7*4*	622T>C (W208R) [23]	Low activity [18,23]	1–2% in Caucasians, 1% in black populations, 0% in Japanese populations and 0% in Taiwanese Chinese populations [9,77]
UGT1A8	Extrahepatic	*UGT1A8*1a*		Normal activity	55% in unknown population [228]
		*UGT1A8*2*	UGT1A8*2 (518G>C, A173G) [228]	Similar activity to *UGT1A8*1a* [228]	15% in unknown population [228]
		*UGT1A8*3*	UGT1A8*3 (830G>A, C277Y) [228,229]	Severely reduced activity [228,229]	2% in unknown population [228]

UGT	Expression	*UGT* alleles	Nucleotide change (amino acid change)	*In vitro* effect	Frequency
UGT1A9	Hepatic	*UGT1A9*1a*			
		*UGT1A9*1b*	−118(dT)$_{9>10}$ [72]	Luciferase activity increased in one study [72], but another study [74] did not find a significant change in luciferase activity or an association with hepatic UGT1A9 protein content	36–41% in Caucasians, 44% in black populations and 51–60% in Asians [68,72,75,230]
		I399C>T	*I399C>T* [73]	Increased protein expression and activity in one study [73]. No association with gene expression and activity in another study [75]	38–49% in Caucasians, 42% in Africans and 64% in Japanese populations [73,75,83]
UGT1A10	Extrahepatic	*UGT1A10*1a*		Normal activity	
		*UGT1A10*2a*	415G>A (E139K) [231]		0% in Caucasians, 3–5% in black populations and 0% in Asians [231]
UGT2B7	Hepatic	*UGT2B7*1a*			46–51% in Caucasians and 73% in Asian–Americans and Japanese populations [9]
		*UGT2B7*2a*	802C>T (H268Y) [232]	No change in substrate activity for most substrates [148,232-234], increased activity for very few substrates [233]	49–54% in Caucasians and 27% in Asian–Americans and Japanese populations [9]
		−161T>C	−161T>C (relative to the ATG) [151]	Decreased activity [151]	49% in Caucasians and 69% in African–Americans [151]
UGT2B17	Hepatic	*UGT2B17*1*			68–69% in Caucasians and 79% in African–Americans [235,240]
		*UGT2B17*2*	Deletion of a 150-kbp region spanning the *UGT2B17* gene [235,236]	Reduced activity in the homozygous state [237-241]	19–33% in Caucasians, 21% in African–Americans, 22% in Yorubans and 84% in Japanese populations and Chinese populations [235,239,240,242,243]

UGT: Uridine 5′-diphosphoglucuronosyltransferase.

Table 3
Polymorphic variation in *UGT* associated with irinotecan toxicity ($p < 0.05$).

UGT allele	Clinical effect
*UGT1A1*28*	Increased severe neutropenia in Caucasians [32,34-38,46,88] and Japanese populations [41,42] Increased leukopenia in Japanese populations [39-41] Decreased ANC nadir in Caucasians [31,32] Increased severe diarrhea in Caucasians [38,43-46] and Japanese populations [39,40]
*UGT1A1*60*	G/G genotype was associated with severe hematologic toxicity when compared with T/T at frst cycle in Caucasians [70] but was not confirmed in multivariate analysis
*UGT1A1*93*	Increased severe neutropenia in Caucasians [32,37,69] Decreased ANC nadir in Caucasians [32]
*UGT1A1*6*	Increased severe neutropenia in Japanese populations [41,42,48,49,60,64], Koreans [48,49] and Chinese populations [59] Increased leukopenia in Japanese populations [41]
*UGT1A7*2*	Lack of severe neutropenia or diarrhea in Caucasians [47]
*UGT1A7*3*	Lack of severe neutropenia or diarrhea in Caucasians [47] Increased severe hematologic toxicity in Caucasians [70] Increased severe diarrhea in Koreans [48,49]
*UGT1A7*4*	Increased severe neutropenia and/or diarrhea in Caucasians [46]
*UGT1A9*1b*	Increased severe neutropenia or diarrhea in Caucasians [47] Increased severe neutropenia in Japanese populations [60] Severe hematologic toxicity in Caucasians [70] Decreased severe diarrhea in Koreans [48,49]

ANC: Absolute neutrophil count; UGT: Uridine 5′-diphosphoglucuronosyltransferase.

Future Oncol. Author manuscript; available in PMC 2011 May 26.

Table 4

Pharmacogenetic studies of anticancer drugs that undergo glucuronidation.

Anticancer agent	Type of study	*UGT* allele or genotype	Effect
Tamoxifen	*In vitro* studies using UGT1A4-, UGT1A8-, UGT1A10- and UGT2B7-overexpressing HK293 cells [118,129] and human liver microsomes [118]	*UGT1A1*28/*28*	Nonsignificant decreases in *O*-glucuronidation activity against the *trans* isomers of 4-hydroxytamoxifen and endoxifen in human liver microsomes with genotypes *UGT1A1*28/*28* compared with *UGT1A1*1/*1*, or *UGT1A1*28/*28* and *UGT1A1*28/*1* compared with *UGT1A1*1/*1* [118]
		*UGT1A4*2*	No differences in *N*-glucuronidation activity against tamoxifen, *trans*-4-hydroxytamoxifen and *cis*-4-hydroxytamoxifen compared with *UGT1A4*1a* [129]. No significant association with *N*-glucuronidation activity of *trans*-4-hydroxytamoxifen in human liver microsomes [118]
		*UGT1A4*3b*	Increased activity against *N*-glucuronidation activity of tamoxifen, *trans*-4-hydroxytamoxifen and *cis*-4-hydroxytamoxifen [129]. No significant association with *N*-glucuronidation activity of *trans*-4-hydroxytamoxifen in human liver microsomes [118]
		*UGT1A8*2*	No difference in *O*-glucuronidation activity against *trans*-4-hydroxytamoxifen. Small but significant decrease against *trans*-endoxifen compared with wild-type *UGT1A8*1a* using cell homogenates [118]
		*UGT1A8*3*	No *O*-glucuronidation activity activity against *trans*-4-hydroxytamoxifen and *trans*-endoxifen using cell homogenates [118]
		*UGT1A10*2a*	No difference in *O*-glucuronidation activity activity against *trans*-4-hydroxytamoxifen and *trans*-endoxifen nusing cell homogenates [118]
		*UGT2B7*2a*	Decreased *O*-glucuronidation activity against *trans*-4-hydroxytamoxifen and *trans*-endoxifen in human liver microsomes and cell homogenates [118]
		*UGT2B7*1a/*2a*	Nonsignificant decrease of *O*-glucuronidation against *trans*-4-hydroxytamoxifen and *trans*-endoxifen compared with *UGT2B7*1a/*1a* in human liver microsomes [118]
		*UGT2B7*2a/*2a*	Significant decrease in of *O*-glucuronidation against *trans*-4-hydroxytamoxifen and *trans*-endoxifen glucuronidation activity compared with *UGT2B7*1a/*1a* in human liver microsomes [118]
Raloxifene	Study of postmenopausal females treated for osteoporosis [139]	*UGT1A1*28*	Increased glucuronide levels in *UGT1A1*28/*28* carriers compared with *UGT1A1*28/*1* or *UGT1A1*1/*1*. The parent drug concentrations were also increased in individuals with *UGT1A1*28/*28* but not significantly [139]
Epirubicin	*In vitro* study in HEK-293 cell membranes expressing UGT2B7 encoded by *UGT2B7*1a* and *UGT2B7*2a* alleles [148]	*UGT2B7*2a*	No detectable differences in activity compared with *UGT2B7*1a* [148]
	In vitro study with human livers [149]	*UGT2B7* haplotype 4†	Increased enzyme activity and gene expression. Diplotypes containing haplotype 4 had a significant 27% average increase in glucuronidation and more than a fivefold increase in mRNA expression compared with diplotypes without haplotype 4 [149]
	Clinical trial in breast cancer patients receiving adjuvant or neoadjuvant FEC100 every 3 weeks [155]	−161T>C	Reduced clearance and increased severe leukopenia [155]
Flavopiridol	Phase 1 clinical trial of patients with refractory neoplasms taking flavopiridol	*UGT1A1*28*	No association with pharmacokinetics or the occurrence and severity of diarrhea and

Anticancer agent	Type of study	*UGT* allele or genotype	Effect
	1-h intravenous infusion daily [172]		neutropenia [172]
Vorinostat	*In vitro* study with UGT-overexpressing HEK-293 cell homogenates, human liver microsomes and human colon homogenates [164]	*UGT1A7*2*	No detectable differences in activity compared with *UGT1A7*1a* [164]
		*UGT1A7*3*	No detectable differences in activity compared with *UGT1A7*1a* [164]
		*UGT1A7*4*	No detectable differences in activity compared with *UGT1A7*1a* [164]
		*UGT1A8*2*	Threefold decrease in activity compared with *UGT1A8*1a* [164]
		*UGT1A8*3*	No detectable activity [164]
		*UGT1A10*2a*	No detectable activity [164]
		*UGT2B17*2*	Reduced activity, gene expression and enzyme affinity [164]
TAS-103	Phase I clinical trial of weekly TAS-103 in patients with advanced cancer [175]	*UGT1A1*28*	No correlation with TAS-103, TAS-103 glucuronide or clearance although it may correlate with severe neutropenia at high dose levels [175]

†UGT2B7 haplotype 4 is defined by −45597G; −6682_−6683A; 372A; IVS1+9_IVS1+10A; IVS1+829T; IVS1+985G; IVS1+999C; IVS1+1250G; 801T; IVS4+185C. FEC100: 5-fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2 and cyclophosphamide 500 mg/m^2; UGT: Uridine 5′-diphosphoglucuronosyltransferase.