

## **Abstract**

### **Introduction**

Based on recent emerging evidence of inter-ethnic difference in drug response and toxicity, ethnic diversity in pharmacokinetics, pharmacogenomics and clinical outcomes are being investigated in order to promote improved understanding of inter-individual differences in the pharmacokinetics and tolerance of cytotoxic drugs. This article reviews potential explanations for the observed ethnic differences in treatment outcomes and provides clinical data to support this concept.

### **Area covered**

A literature search was implemented on [www.pubmed.com](http://www.pubmed.com) and [www.pharmgkb.org](http://www.pharmgkb.org) to investigate the areas of ethnic differences in pharmacogenomics, pharmacogenetics and clinical outcomes of cancer therapies.

### **Expert Opinion**

There has been a relative paucity of clinical evidence linking genetic polymorphisms of genes encoding drug-metabolizing enzymes to the pharmacokinetics, pharmacodynamics and tolerance of anti-cancer drugs. Future research should undertake such studies utilizing large sample sizes to provide adequate power to identify significant differences of clinical significance. Due to the potential for ethnic differences to impact on both toxicities and benefits of systemic cancer therapies, the development of new therapeutic agents should include patients from diverse geographical ancestries in each phase of drug development.

## Article highlight box

1. There is substantial evidence of ethnic variability in the pharmacogenetics, pharmacokinetics and clinical outcomes of patients receiving anti-cancer drugs.
2. A key reason for ethnic differences in drug response relates to variation in the distribution of allelic variants of genes that influence the pharmacokinetics and pharmacodynamics of cancer therapies.
3. Few studies have directly linked the presence of genetic polymorphisms in genes encoding drug-metabolizing enzymes to ethnic differences in the pharmacokinetics, pharmacodynamics and tolerance of anti-cancer drugs and this issue requires further investigation.
- 3.4. The development of new therapeutic agents should include patients from different ethnic groups and involve phase I studies in multiple different ethnic populations.
- 4.5. Care needs to be taken in treating patients from different ethnic backgrounds with schedules of treatment defined predominantly in people of European ancestry.

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## **Introduction**

There is wide inter-individual variation in toxicity from cancer chemotherapy as a result of variability in pharmacokinetics and pharmacodynamics of these agents in cancer patients. This means that some patients receiving a chemotherapy regimen will experience minimal toxicity while others will experience life-threatening side-effects. Similar variability in beneficial response to treatment is observed. Many factors have been suggested to contribute to this variability in response including pharmacogenomic and pharmacokinetic differences, pharmacodynamic variability, differing performance status of patients with cancer, variability in organ function, intercurrent illnesses, as well as, the use of concomitant medications (including both conventional and complementary medicines) or a combination of all of these factors. More recently there has been greater recognition that patients from different ethnic backgrounds or geographical ancestries tolerate treatments better or worse than people from other ethnic groups [1]. In this article we discuss some of the observed ethnic differences in treatment outcomes and provide potential explanations for these, with particular emphasis on ethnic differences in drug metabolising enzyme expression and variability in the pharmacokinetics of anticancer drugs.

### **1. Ethnic differences in clinical outcomes of cancer treatment.**

Ethnic differences in clinical outcomes from chemotherapy have been increasingly reported in the last decade. However, even prior to these data many physicians treating patients of Asian origin have reduced the starting doses of anti-cancer drugs for their patients because of concerns about excessive toxicity, especially where dose finding studies had been performed in predominantly Western patient populations. These concerns have been confirmed by multiple Japanese studies demonstrating efficacy and

toxicity of schedules utilising lower drug doses than are recommended in western countries. [2-4]. There is accumulating evidence of ethnic differences in the frequency of polymorphisms in genes involved in drug metabolic pathways, which result in differences in enzyme activity (see section 3). In addition, ethnic differences have been demonstrated in the presence of mutations in drug targets in tumours, especially in non-small cell lung cancer. Furthermore, as mentioned earlier, there are other factors, which might contribute to ethnic differences in drug metabolism including diet, nutritional and inflammatory status and intake of proprietary and complementary medicines that have been even less well defined. Together these issues contribute to ethnic differences in treatment outcomes, including toxicity, response and survival. Surprisingly these differences and their causes have not been widely investigated and much more research is required to fully characterise these issues. We have provided some examples below of how these differences impact on treatment outcomes in a variety of tumour types.

### **1.1 Lung cancer**

In lung cancer, Japanese and US based investigators have advocated the inclusion of a “Common Arm” of treatment in co-operative group studies undertaken in different countries to permit inter-ethnic comparisons of toxicities, response and survival. This involves the use of similar/identical inclusion/exclusion criteria, treatment schemas and drug doses. In 2 Japan-Multinational Trial Organisation (JMTO) studies and a Southwest Oncology Group (SWOG) study in advanced NSCLC involving 145, 197 and 184 patients, respectively, a common treatment arm of paclitaxel and carboplatin was employed. Japanese patients experienced more grade 3 and 4 neutropenia (70% - 88% vs. 38%), anaemia (15% vs. 7%) and febrile neutropenia (12% - 18% vs. 2%), than the American patients who were predominantly Caucasian. Japanese patients also



had longer median survivals (12 - 14 months) than the Americans (9 months). One-year survival was 51% - 57% for the Japanese compared to 37% for the Americans [5]. In this study, genotype-related associations with patient outcomes were observed for *CYP3A4\*1B* and *ERCC2 K751Q* [5]. Similarly, in a phase II study of carboplatin and docetaxel undertaken between centres in Australia and Singapore involving 68 patients (23 Asians and 43 Caucasians) there was greater haematological toxicity and febrile neutropenia in the Asian patients. This necessitated reduction in the dose of carboplatin from AUC 6 to 4.5 for Asian patients. Again, the response rate for Asians was higher than for Caucasians [6] (65% vs 31%).

Another common arm study in small cell lung cancer compared 154 Japanese and 651 eligible North American patients treated with either cisplatin/irinotecan or etoposide/cisplatin. Japanese patients had significantly higher response rates regardless of the treatment used, and higher median overall survivals in the cisplatin/irinotecan arm (12.8 vs. 9.8 months,  $P < .001$ ). However, Japanese also experienced more grade 3/4 leukopenia, neutropenia and anaemia than the North American patients, although infection was surprisingly more common in US patients [7]. In this study, 93% of North American patients were Caucasian with only 4% - 6% African Americans [8].

There have also been differences in outcomes reported with the use of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) between Asian and Caucasian patients. Initial analyses of predictive factors for benefit from gefitinib identified that people from East Asian background, women, never smokers and those with adenocarcinoma histology had a higher chance of response. It has since been shown that Asian patients exhibit a significantly higher rate of treatment sensitising

somatic mutations of EGFR than other populations (20-40% versus 6%) [1] rendering them more susceptible to treatment with the TKIs [9]. Not surprisingly, Asian patients selected for the presence of activating mutations of EGFR and treated with first line gefitinib experience tumour response in up to 71% of cases and have median survivals in excess of 18 months, which is superior to chemotherapy [10, 11]. It has also been shown that the presence of longer dinucleotide repeat segments in intron 1 of *EGFR* results in lower EGFR expression [12], which is predicted to increase the response rate to EGFR TKIs. These longer dinucleotide repeat sequences occur more commonly in Asians (63%, n = 66) than in Caucasians (21%, n = 183) while shorter sequences occur more commonly in both Caucasian and African-American populations (n=84 - 42% and 43% respectively) than Asians (17%) [1]. A trend towards higher erlotinib AUC,  $C_{max}$  and  $C_{trough}$  has been reported in patients exhibiting one of these repeat sequences (EGFR497 A/A) [13] however this finding requires confirmation in larger patient numbers [9, 14]. In addition to improved clinical outcomes there is also evidence of a higher incidence of severe interstitial lung disease and skin toxicity in Asian patients [9, 15].

## **1.2 Breast cancer**

There have also been recent suggestions of increased chemotherapy induced toxicity in Asian women with breast cancer in comparison to Caucasians. In a prospective study involving centres in Hong Kong, Singapore and Australia, 104 Asian and 68 Caucasian women with non-metastatic breast cancer were treated with identical doses and schedules of adjuvant doxorubicin and cyclophosphamide (AC) [16]. The patients were young with a median age of 50 (range 27 – 73) and 47 (range 25 – 63) years for Caucasian and Asian patients, respectively. The data have only been published in

preliminary form, but again showed worse toxicity in Asian patients. Fifty four percent of Asians experienced grade 4 neutropenia compared to 19% of Caucasians, which led to a higher incidence of febrile neutropenia. These data confirmed the findings of a previous retrospective study that compared toxicities of 85 Asian women receiving adjuvant treatment with AC in Hong Kong with published data from the National Surgical Adjuvant Breast and Bowel Project (NSABP) trials [17].

Ethnic differences in toxicity have also been reported with hormonal treatment. Retrospective analyses compared survival and toxicities between Caucasians (n = 4708) and black, Hispanic and Asian patients (n = 352) in study MA.17 that utilised letrozole as additional adjuvant treatment after 5 years of tamoxifen in post-menopausal women with early stage breast cancer. This analysis demonstrated more hot flashes, fatigue and arthritis in Caucasian patients, however there was no difference in disease free survival [18].

### **1.3 Colorectal cancer**

Ethnic differences in toxicity and response have been reported in several studies in colorectal cancer. A comparison of 344 African-Americans and 3036 Caucasians with stage II and III colorectal cancer, receiving adjuvant 5-fluorouracil (5-FU) based chemotherapy, showed similar survival between the groups, however, African-Americans had significantly lower rates of diarrhoea, nausea, vomiting, stomatitis, and overall toxicity [19]. Similarly, a subgroup analysis of a multisite National Cancer Institute-sponsored trial (N9741) in patients with metastatic cancer receiving various combinations of oxaliplatin, irinotecan and 5-FU showed that grade 3 or greater toxicities were more common in whites than blacks. However, response rates were also

significantly higher in white patients, albeit without any significant survival impact [20]. This was in spite of a higher incidence of the homozygous *UGT1A1\*28* in blacks (14 vs 9%), which has been associated with increased myelosuppression from irinotecan[21].

#### **1.4 Gynaecological cancer**

In gynaecological cancer, several studies have reported ethnic differences in toxicity between Caucasian and African-American patients. In a study comparing toxicity and survival outcomes from cisplatin-based combination chemotherapy in women with advanced/recurrent cervical cancer, similar survival times were reported, however, African-American patients experienced much less grade 3 and 4 neutropenia, leukopenia, thrombocytopenia and adverse events of any nature [22]. Reduced toxicity in African American women has also been reported in ovarian cancer patients receiving paclitaxel and cisplatin [23], and endometrial cancer patients receiving cisplatin and doxorubicin. However, the African-American patients in the endometrial study were more likely to experience grades 3-4 anaemia and genitourinary toxicity compared to Caucasian patients, however these may have been disease related [24].

#### **2.0 Ethnic differences in pharmacokinetics and pharmacogenomics relevant to systemic cancer therapies**

It is well recognised that pharmacokinetic factors that determine a patient's exposure to a drug and its metabolites influence the potential for beneficial or toxic responses to that medicine. The pharmacokinetics of a drug after any given dose are determined by an individual's pharmacological phenotype, which is a function of genetic, physiological, clinical and environmental factors [25]. Although drug disposition in the body involves the combination of absorption, distribution, metabolism and elimination,



alterations in drug metabolism are most likely to produce significant variability in patient outcomes [26]. It has been known for some time that ethnic differences in the metabolism of xenobiotics exist and may produce variable drug metabolism. This is best illustrated by ethnic variants in alcohol dehydrogenase which produce significantly lower rates of hepatic alcohol metabolism in many Asians compared to people with European ancestry [27, 28]. Similar ethnic variability in genes encoding drug metabolising enzymes has the potential to produce altered metabolic capacity, thereby altering treatment outcomes. In some cases we have clinical and pharmacokinetic evidence to support this hypothesis, however in many other circumstances confirmatory pharmacokinetic [29] and pharmacodynamic [30] studies are still required. In the next section we discuss ethnic variability in the incidence of allelic variants of common drug metabolising enzymes, in particular highlighting those that have been associated with reduced enzyme function, especially if they have been linked to altered drug pharmacokinetics or clinical outcomes.

These data are summarised in Table 1.

### **CYP1A1**

CYP1A1, an extrahepatic enzyme present in lung, placenta and lymphocytes is involved in the metabolism of many xenobiotics including the polycyclic aromatic hydrocarbons. *CYP1A1* is located on chromosome 15 q24.1 [31] and > 15 allelic variants have been reported [32]. In oncology, this enzyme is involved in the metabolism of TKIs including imatinib, gefitinib, erlotinib and sunitinib [33-35], as well as, the anti-oestrogen toremifene [25]. Although there is some evidence that *CYP1A1* polymorphisms result in altered enzyme activity, there remains little evidence that these allelic variations affect the PK/PD of anti-cancer drugs [36]. However, it has

been recently reported that several *CYP1A1* polymorphisms are associated with an increased risk of sunitinib toxicity including leukopenia and mucosal inflammation [34].

There are inter-ethnic differences in the prevalence of polymorphisms of *CYP1A1* (Table 1). While these variants in *CYP1A1* appear to contribute to differing risks of cancer development [37], there is currently no evidence to link these allelic variations to ethnic differences in drug metabolism, toxicity or response to treatment.

### **CYP2A6**

CYP2A6 metabolizes approximately 3% of all therapeutic drugs, including the anti-cancer agents tegafur, ifosfamide, cyclophosphamide and tamoxifen. *CYP2A6* has been mapped to the long arm of chromosome 19. Its expression is regulated by a number of nuclear receptors, including the constitutive androstane (CAR), pregnane X (PXR) and glucocorticoid receptors. More than 36 allelic variants (\*1B to \*37) of *CYP2A6* have been reported, which are associated with altered enzyme activity and drug clearance, as well as differing risks of lung cancer. There is evidence of ethnic variability in *CYP2A6* expression impacting on cancer drug metabolism. For example, the orally administered cytotoxic agent S-1 consists of the prodrug tegafur (FT), which is converted to 5-FU by CYP2A6 [38]. CYP2A6 activity is influenced by ethnicity with the isoenzyme CYP2A6\*4C being 4-20-fold more common in Japanese populations (n = 92) than Caucasians (n = 176) [38, 39]. In a cohort of Japanese patients, those expressing *CYP2A6\*4C* had significantly lower maximum plasma concentrations of 5-FU than those without [38]. Similarly, in a comparison of the pharmacokinetics of S-1 in Asian and Caucasian patients there was a trend towards higher tegafur concentrations in the Asian cohort associated with reduced 5-FU exposure [30]

## CYP2B6

The *CYP2B6* gene is located on chromosome 19 between 19q12 and 19q13.2, and consists of 9 exons. *CYP2B6* isoforms are expressed in liver, intestine, kidney and lung.

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It is involved in the metabolism of anti-cancer drugs including tamoxifen and cyclophosphamide [40]. Approximately 33 allelic variants of *CYP2B6* have been identified (*CYP2B6\*1* to *CYP2B6\*29*) [31, 32]. *CYP2B6* polymorphisms including *CYP2B6\*6*, *\*11*, *\*12*, *\*13*, *\*14*, *\*15*, *\*19*, *\*20*, *\*21*, *\*27*, *\*28* have been associated with reduced enzyme activity [41-44]. Patients with haematological malignancies expressing the 516G>T variant allele, which is linked to *CYP2B6\*6*, *\*7*, *\*9*, have increased cyclophosphamide clearance (almost 2-fold) compared to patients to wild-type patients [45]. In leukaemic patients undergoing transplant and receiving cyclophosphamide, *CYP2B6\*4* was associated with an increased incidence of oral mucositis, while *CYP2B6\*2A* was associated with a higher incidence of hemorrhagic cystitis, and *CYP2B6\*6* with an increased occurrence of veno-occlusive disease of the liver [46]. *CYP2B6* polymorphisms including *CYP2B6\*2* and *CYP2B6\*5* alleles have also been associated with a higher incidence of dose delay in patients receiving adjuvant therapy with doxorubicin and cyclophosphamide (AC) for breast cancer. In addition, the presence of *CYP2B6\*2*, *CYP 2B6\*4*, *CYP 2B6\*8*, *CYP 2B6\*9* alleles was associated with worse clinical outcomes [47].

Ethnic differences in *CYP2B6* polymorphisms have also been reported (Table 1) and may be associated with differences in pharmacokinetics, toxicity and clinical outcomes after treatment with cyclophosphamide, however these relationships require evaluation in prospective clinical studies.

## CYP2C family

The human *CYP2C* gene subfamily is located on chromosome 10q24 [31], and consists of at least 13 isoforms, of which 4 are principally involved in cancer drug metabolism; *CYP2C8*, *CYP2C9*, *CYP2C18* and *CYP2C19*.

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## CYP2C8

*CYP2C8* is mainly expressed in the liver, but is also found in extrahepatic sites including brain, heart, kidney, adrenal gland, breast, uterus, ovary and duodenum [48]. *CYP2C8* is involved in the metabolism of a number of commonly used cancer drugs including paclitaxel, cyclophosphamide and ifosfamide, in addition to selected non-steroidal anti-inflammatory drugs (NSAIDs) and some analgesics [48]. More than 15 allelic variants of the *CYP2C8* gene have been detected (*CYP2C8\*1* to *CYP2C8\*14*) [48]. *In vitro*, several variants including *CYP2C8\*2*, *CYP2C8\*3*, *CYP2C8\*8*, *CYP2C8\*14* have been associated with reduced *CYP2C8* metabolic activity for substrates including paclitaxel [48, 49]. However, researchers have previously failed to establish an association between *CYP2C8* polymorphisms and altered clinical outcomes [50-52]. Recently *CYP2C8\*3* was associated with reduced clearance of paclitaxel [53] and an increased risk of neurotoxicity [54]. In contrast, *CYP2C8* haplotype C has been linked to reduced risk of neurotoxicity from paclitaxel [54]. In addition, SNP rs1934951 in *CYP2C8* has been associated with an increased risk of osteonecrosis of the jaw after use of the bisphosphonates [55].

Ethnic variability in the incidence of allelic variants of *CYP2C8* has also been reported (Table 1), however, these have not been directly associated with pharmacokinetic or



toxicity differences in patients receiving cancer chemotherapy.

### **CYP2C9**

CYP2C9 is the main enzyme in the CYP2C subfamily and is principally expressed in the liver [56]. CYP2C9 is involved in the metabolism of cyclophosphamide, ifosfamide, etoposide, tamoxifen, imatinib, and other drugs used in oncology including some NSAIDs, analgesics, oral anticoagulants, antiepileptic, and psychotropic agents [25, 57]. Drug-drug interactions between tamoxifen and CYP2C9 substrates have been reported. For example, 8 of 31 patients experienced bleeding complications when concomitantly receiving tamoxifen and warfarin [58].

Approximately 34 genotypic variants in *CYP2C9* gene have been detected (*CYP2C9\*1* to *CYP2C9\*34*), along with additional SNPs where the haplotype has yet to be determined [32]. A number of these, including *CYP2C9\*2* and *CYP2C9\*3*; *CYP2C9\*5* have been associated with a significant reduction in enzymatic activity based on both *in vitro* and *in vivo* studies conducted with a variety of CYP2C9 substrates [59, 60]. However, recent studies have not demonstrated any impact of *CYP2C9* polymorphisms on the pharmacokinetics of anti-cancer drugs that are substrates of CYP2C9 or on clinical outcomes [47, 61].

Both the *CYP2C9\*2* and *CYP2C9\*3* variants have a higher prevalence in Caucasian than Asian or African populations (Table 1). Due to the association of these polymorphisms with decreased enzyme activity, studies relating *CYP2C9* genotype to cancer drug pharmacokinetics and toxicity and clinical outcomes are needed.

## CYP2C19

CYP2C19 protein is mainly present in the liver. CYP2C19 is involved in the metabolism of cyclophosphamide, ifosfamide, tamoxifen, imatinib and thalidomide. [25, 57, 62]. Approximately 30 allelic variants of *CYP2C19* have been identified, and decreased enzyme activity and poor metabolizer phenotype have been associated with polymorphisms including *CYP2C19\*2*, *CYP2C19\*3*, *CYP2C19\*4*, *CYP2C19\*8*, *CYP2C19\*9*, *CYP2C19\*10* [63-67]. However, the association between these polymorphisms and pharmacokinetics and clinical outcomes of anti-cancer drugs have not been fully explored, and in some ways, remain conflicted. While no relationship was established between *CYP2C19* polymorphisms and cyclophosphamide pharmacokinetics in a study of 124 Caucasians [61], another group found that *CYP2C19\*2* was associated with reduced elimination of cyclophosphamide, albeit in a smaller patient cohort [68]. Recently, it has been shown that breast cancer patients who were *CYP2C19\*2* carriers had significantly longer survival than wild-type patients when treated with tamoxifen [69]

Both the *CYP2C19\*2* and *CYP2C19\*3* variants have a much higher prevalence in Asians than in Caucasians or Africans (Table 1) [70, 71]. In particular, *CYP2C19\*3* is extremely uncommon in non-Asian populations. As a result, a higher prevalence of poor metabolizers for S-mephenytoin has been reported in Asian populations (13-23%) compared to Caucasians (3% - 5%) and Africans (4%) [56]. This suggests that inter-ethnic differences in adverse events and therapeutic effects of anti-cancer drugs metabolized by CYP2C19 might be anticipated, although again they remain largely unevaluated.

## CYP2D6

*CYP2D6* is located on chromosome 22q13.2 and is involved in the metabolism of a number of anticancer drugs including tamoxifen, gefitinib, and imatinib [35, 57, 62]. This enzyme is involved in the metabolism of approximately 25% of all clinically used medicines including many drugs used in supportive care such as analgesics, antiemetics and tricyclic antidepressants [72, 73].

More than 80 allelic variants of *CYP2D6* have been identified [32]. Based on their ability to metabolize *CYP2D6* substrates, individuals can be classified into 4 general categories of *CYP2D6* metabolic activity: poor metabolizers, intermediate metabolizers, extensive metabolizers and ultrarapid metabolizers. Among these, the extensive metabolizer phenotype is considered to be normal as the majority of the population falls into this category. *CYP2D6*\*3, \*4, \*5 and \*6 result in non-functional enzymes and are responsible for over 98% of poor metabolizers in Caucasian populations [56]. *CYP2D6*\*9, \*10, \*41 are associated with reduced enzyme activity [56, 74]. Genotype – phenotype correlations have been developed in attempt to translate vast genotype data into *CYP2D6* activity prediction algorithms [75].

Studies on association between *CYP2D6* and tamoxifen have shown conflicting results.

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*CYP2D6* was claimed to have an important role in the metabolism of tamoxifen and the formation of its active metabolite endoxifen. Patients with *CYP2D6* homozygous variant genotype or heterozygous variant genotype have significantly lower plasma concentrations of tamoxifen metabolites than those with the homozygous wild-type genotype [76] which is associated with reduced pharmacological effects and poor outcomes [77]. Recently, in reports of two large prospective clinical trials (ATAC and

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BIG 1-98), presented at the 33rd Annual San Antonio Breast Cancer Symposium in December 2010, which are yet to be published in the peer-reviewed literature, did not find any association between CYP2D6 phenotypes with clinical outcomes was observed. However, patients enrolled in these trials were all post menopausal and the effect on premenopausal patients remains unknown/unclear. CYP2D6 allelic distributions exhibit significant inter-ethnic differences (Table 1). Poor metabolizers are more frequent in Europeans [72, 73], which may be explained by a higher prevalence of CYP2D6\*3, \*4, \*6 in this population, while these polymorphisms are relatively rare in Asians and Africans [78, 79]. Due to the much higher prevalence of CYP2D6\*10 in Asians (38-51%), intermediate metabolizers are more prevalent in this population [73, 79], while ultrarapid metabolizers are mainly found in people from North Africa and Oceania [73]. Based on these data, drugs that are mainly metabolised by CYP2D6 need to be tested in multiple ethnic groups to produce optimal outcomes and avoid unnecessary toxicities.

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#### **CYP3A4**

CYP3A4 is located on chromosome 7. CYP3A4 is mainly expressed in the liver, and is responsible for the metabolism of more than 50% of clinically used therapeutic agents [56]. CYP3A4 is involved in the metabolism of numerous anticancer drugs including docetaxel, paclitaxel, vincristine, irinotecan, etoposide, cyclophosphamide, ifosfamide, tamoxifen, gefitinib, erlotinib, sorafenib and imatinib [56, 76, 80].

Approximately 90 polymorphisms of CYP3A4 have been reported (CYP3A4\*1 to CYP3A4\*20) [31, 32]. *In vitro* studies have shown that CYP3A4\*8, CYP3A4\*11, CYP3A4\*12, CYP3A4\*13, CYP3A4\*16A, CYP3A4\*16B, CYP3A4\*17 are associated



with reduced enzyme activity [81-83].

Several allelic variants of *CYP3A4* have been associated with variability in the pharmacokinetics of anti-cancer drugs and clinical outcomes. For example, *CYP3A4\*16B* was associated with both reduced 3'-p-hydroxylation of paclitaxel and increased levels of 6- $\alpha$ -hydroxypaclitaxel in 235 Japanese cancer patients [84]. In a pharmacogenetic - pharmacokinetic study of 58 patients receiving docetaxel, *CYP3A4\*1B* carriers (n=4), who were also *CYP3A5\*1/\*3* carriers, had a significantly higher clearance and lower dose-normalized area under the curve of docetaxel than those with the wild-type gene (*CYP3A4\*1*) [85]. However, due to the low incidence of these *CYP3A4* gene variants, the lack of subjects who are homozygous for these mutations and strong linkage disequilibrium between *CYP3A4* and *CYP3A5* haplotypes, it has been difficult to demonstrate that *CYP3A4* genotype impacts on the pharmacokinetics and pharmacodynamics of *CYP3A4* substrates [76].

Ethnic differences in the frequency of polymorphisms of *CYP3A4* have been reported however they have not been linked to differences in pharmacokinetics between ethnic groups (table 1).

### **CYP3A5**

*CYP3A5* is involved in the metabolism of a number of anti-cancer drugs including docetaxel, paclitaxel, vincristine, irinotecan, etoposide, cyclophosphamide and ifosfamide, gefitinib, imatinib and tamoxifen [57, 76, 86]. More than 25 allelic variants of *CYP3A5* have been reported including *CYP3A5\*3*, *CYP3A5\*6*, which are associated with non-functional or severely decreased enzyme activity [87]. *CYP3A5\*3* is more

common in Caucasian population, while *CYP3A5\*6* is only found in Africans (Table 1) [88]. Several pharmacokinetic studies of anti-cancer drugs including paclitaxel, imatinib and cyclophosphamide have failed to establish an association between drug pharmacokinetic parameters and polymorphisms of *CYP3A5* [52, 61, 89]. However, polymorphic expression of *CYP3A5* has been associated with significant differences in the clearance of vincristine [90].

### **CYP3A7**

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Previously it was believed that CYP3A7 was found only in foetal livers however recent studies indicate that CYP3A7 is also expressed in low levels in adult livers [91].

Further studies have also indicated that interethnic differences exist in the expression of CYP3A7 polymorphisms with the *CYP 3A7\*1B* allele observed only in Caucasians

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(1%) and the *CYP3A7\*1C* allele observed in both Caucasians and African American populations but not present in Japanese populations [87, 91, 92].

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The relevance of these findings to metabolism of chemotherapeutic agents is yet to be established.

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### **Glutathione S-Transferase (GST)**

GSTs are a family of detoxifying enzymes that catalyse the conjugation of reduced glutathione (GSH) to a wide variety of electrophilic and hydrophobic compounds. There are 2 distinct families of GSTs; the membrane bound microsomal and cytosolic families. The cytosolic GSTs are divided into 8 classes designated by members of the Greek alphabet: alpha ( $\alpha$ ), kappa ( $\kappa$ ), mu ( $\mu$ ), sigma ( $\sigma$ ), theta ( $\theta$ ), pi ( $\pi$ ), omega ( $\omega$ ), and zeta ( $\zeta$ ) [93]. They are responsible for the detoxification of many xenobiotics including many anti-cancer drugs including adriamycin, carmustine (BCNU), busulfan, carmustine, chlorambucil, cisplatin, oxaliplatin, cyclophosphamide, melphalan,

mitoxantrone, docetaxel and thiotepa [94-96].

Numerous isoforms and polymorphisms of *GST* gene have been identified and associated with alterations in enzyme activity. For example, *GSTM1\*0* results in gene deletion and absence of protein; *GSTM1\*1*×2 results in gene duplication with over-expression of M1 protein; homozygous deletion of the entire *GSTT1* (null *GSST1*) has been associated with lack of enzyme activity [94]. *GSTP1\*A* is considered to be wild-type and other polymorphisms including *GSTP1\*B*, *GSTP1\*C* and *GSTP1\*D* have been associated with decreased enzyme activity for several classes of substrates [37].

Polymorphisms of the *GST* gene have been linked to an increased risk of cancer development [97, 98], resistance to anti-cancer drugs [37], increased toxicity from chemotherapy [96, 99] and altered clinical outcomes [99-101]. In regard to associations between *GST* polymorphisms and toxicity from anti-cancer drugs; in 94 Korean patients with diffuse large B-cell lymphoma receiving R-CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab), those with *GSTT1*-null genotype experienced more frequent grade 3-4 chemotherapy-induced toxicities including leukopenia, fever and mucositis while patients with the *GSTM1/T1* double-null genotype experienced more grade 3-4 thrombocytopenia, and shorter event-free survival [99]. *GSTP1 II05V* was associated with reduced risk of neutropenia in treatment of non-small cell lung cancer [102], and neuropathy in treatment of colorectal cancer [96]. In another study of 58 patients receiving docetaxel, a significant correlation between the incidence of *GSTP1 (105)Ile/(105)Ile* genotype and  $\geq$  grade 2 peripheral neuropathy was reported [103].

However, there have been few studies that have examined the association between *GST* polymorphisms and pharmacokinetics of anti-cancer drugs. However, polymorphisms of *GST* have been linked with alterations in busulfan clearance in adults [104], but not children [105]. The *GSTP1* C341T polymorphism was reported to increase non-inducible thiotepa clearance by 52% and decrease tepla clearance by 32% in heterozygous patients [106]. However, no association between *GSTA1*, *GSTP1* and cyclophosphamide pharmacokinetics has been reported [61].

Ethnic differences in *GST* polymorphism frequency have been reported and are outlined in Table 1. The presence of significant differences in ethnic prevalence of enzyme impaired allelic variants of GSTs creates the potential for ethnic differences in toxicity and response following treatment with chemotherapy detoxified by GSTs, however confirmatory clinical studies are required.

#### **Uridine Diphosphate Glucuronotransferase (UGT)**

Glucuronidation is another important pathway in the bio-inactivation and elimination of endogenous compounds and xenobiotics. It is catalysed by UGT, which is a multi-enzyme family located in the endoplasmic reticulum of almost all tissues. In humans, the UGT enzymes have been classified into two major families including *UGT1A* and *UGT2* (subdivided in *UGT2A* and *UGT2B*) [107]. Among them, *UGT1A1* is involved in the metabolism of several anti-cancer drugs including irinotecan and etoposide [108, 109].

*UGT1A1*\*28, a *UGT1A1* polymorphism with (TA)<sub>7</sub> repeat insertion in the *UGT1A1* promoter region, has been associated with a higher risk of neutropenia after use of



irinotecan in adults [110] as well as higher SN-38 area under the plasma time-concentration curve (AUC) values and lower SN-38-glucuronide/SN-38 AUC ratios in paediatric patients [111]. The prevalence of the (TA)<sub>7</sub> repeat is lower in Asian populations and higher in Africans compared to Caucasians [76]. For example, in a study of 109 children with acute lymphoblastic leukaemia receiving etoposide, wild-type *UGT1A1* 6/6 in black children was associated with altered etoposide clearance and increased neutropenia [112]. This implies that other *UGT1A1* polymorphisms may be associated with reduced drug clearance and more severe toxicity. As the relationship between genotype and phenotype of etoposide differs by race, other ethnic associations should be explored.

*UGT1A1*\*6 is a very common polymorphism in Asians but has not been detected in Caucasians or Africans [113, 114] and has been associated with severe neutropenia from irinotecan [114, 115] and significant reduction in the SN-38G/SN-38 AUC ratio [114]. Perhaps consistent with this, Japanese researchers using lower dose of irinotecan than is conventional in combination schedules developed in Caucasians have reported efficacy comparable to studies in western patients [4].

### **Dipyrimidine dehydrogenase (DPD)**

Dipyrimidine dehydrogenase (DPD), the principal enzyme involved in the metabolism of 5-FU, also exhibits ethnic variation in expression that impacts on 5-FU clearance. For example, Ghanaian patients demonstrate significantly lower DPD activity than Caucasian, Kenyan or south-east Asian patients [116]. Partial or complete DPD deficiency has been shown to result in a reduced capacity to degrade 5-FU, increasing the risk of developing severe 5-FU associated toxicity [116]. In addition, partial

deficiency of DPD, due to heterozygosity of the IVS14 + 1G>A mutation, results in reduced clearance of 5-FU (2.5 x lower than controls with fully functional DPD) [116, 117]. Complete DPD deficiency has been associated with 10-fold longer half-life and minimal metabolism of 5-FU [118].

### **Drug transporters**

In addition to drug metabolizing enzymes, many drug transporters play a critical role in the process of drug absorption, disposition and elimination. Ethnic differences in the allelic frequency of genetic variants, particularly single nucleotide polymorphisms, of drug transporters have been reported in several studies. The incidences of polymorphic transporters are higher in Caucasians than in Africans or Asians (Table 2).

Recently, polymorphisms of drug transporters were reported to alter drug clearance and were associated with treatment outcomes. For example, *MDR1* exon 26 CC genotype was associated with higher etoposide clearance in children with acute lymphoblastic leukaemia [112]. In 117 patients receiving irinotecan-based chemotherapy, higher SN-38 AUC values were observed with *ABCB1* 2677G>T. Polymorphisms of drug transporter genes including *ABCB1*\*2, *ABCG2* (#) IIB, *SLCO1B1*\*15 x 17 were also associated with more grade 3/4 neutropenia [119]. Also, after treatment with docetaxel, grade 3 neutropenia occurred more frequently in 3435TT *MDR1* genotype carriers. However, there was no impact of *MDR1* polymorphisms on docetaxel pharmacokinetics [85]. An intronic SNP, rs2622604, in *ABCG2* was associated with severe myelosuppression after use of irinotecan [120]. Furthermore, in patients receiving single-agent sunitinib,  $\geq$  grade 2 toxicity was associated with allelic variants in the *ABCG2* (-15622C/T, 1143C/T) haplotype, while the prevalence of hand-foot

syndrome was increased with variants in the *ABCB1* (3435C/T, 1236C/T, 2677G/T) haplotype [34]. Thus it is possible that ethnic differences in the incidence of these genetic variants could contribute to variability in drug disposition and toxicity between different ethnic groups.

Clearly, the metabolism of some for some cancer drugs involves, especially paclitaxel, cyclophosphamide, irinotecan and tamoxifen, there are multiple enzymes involved in their metabolism, all of which might be subject to genetic and ethnic variability (examples of this are summarised in Table 3). This situation highlights the importance of undertaking well designed and adequately powered clinical and pharmacokinetic studies to define the relative impact of genetic variants on clinical outcomes. In addition, much of the focus of ethnic variation has centred on Caucasians, Asians and African Americans with scant attention being paid to other large ethnic groups including Indian/Pakistanis and eastern Europeans. These groups also need to be considered in future analyses.

### **3. Other factors**

A number of other factors may contribute to ethnic variability in cancer treatment outcomes including differences in nutritional status, diet, levels of plasma inflammatory markers and intake of proprietary and complementary medicines [25]. However, there have been relatively few studies that have formally addressed these issues in prospective clinical studies.

### **4. Expert Opinion**

This review has described ethnic differences in the expression of allelic variants in

genes responsible for drug metabolism of anticancer drugs. In the last few years, there has been increasing recognition of the relationship between such variants and toxicity and clinical outcomes of cancer treatment. There has also been some association identified between these allelic variants and changes in the pharmacokinetics of cytotoxic drugs. However, although there is substantial indirect evidence for the potential of ethnic differences in gene expression impacting on the pharmacokinetics and toxicities of anti-cancer drugs, these have yet to be confirmed in clinical studies. Thus, there remains a relative paucity of clinical evidence linking genetic polymorphisms of genes encoding drug-metabolizing enzymes to the pharmacokinetics, pharmacodynamics and tolerance of anti-cancer drugs, especially in regard to emphasising differences between ethnic groups. Studies similar to that reported by Innocenti, which provided comprehensive pharmacogenetic analyses of irinotecan and their relationship to neutropenia and irinotecan pharmacokinetics [121] are needed to clarify these issues. To date, very few clinical studies comparing pharmacokinetics of anti-cancer drugs between ethnicity have demonstrated differences in drug clearance [122-124] possibly due to the small sample size of these studies. Thus, future studies should incorporate larger sample sizes, although this will represent a major challenge because of the extensive time and resource commitments that are required to adequately complete such studies.

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The ultimate goal of research into inter-ethnic differences in drug metabolism and toxicity is to improve the overall safety and effectiveness of chemotherapy. Chemotherapy, even in optimal circumstances, is associated with a low therapeutic index meaning that there is only a small margin between an effective and toxic dose of treatment. Identification of the cause of inter-ethnic differences may assist in the

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elucidation of toxicity differences between individuals of the same ethnic background and lead to improvements in individualised dose selection and the safety and effectiveness of chemotherapy in general.

As mentioned, other factors including nutritional and inflammatory status and the use of concomitant medicines may also affect anti-cancer drug metabolism. Again these issues should be considered and recorded in large, prospective clinical studies involving different ethnic populations and especially in the developmental phase of new therapeutic agents.

Due to the potential for ethnic differences impacting on variability in drug metabolism and toxicity of anti-cancer drugs, the development of new therapeutic agents should include patients from different ethnic groups and involve phase I studies in multiple different populations. For existing anti-cancer drugs which were mainly developed in Caucasian patients, it may be necessary to repeat phase I in different ethnic populations if there are suggestions of increased toxicities in certain geographic regions.

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## References

1. O'Donnell PH and Dolan ME. Cancer pharmacogenetics: ethnic differences in susceptibility to the effects of chemotherapy. *Clin Cancer Res.* 2009 Aug 1;15(15):4806-14.
2. Watanabe A, Taniguchi M and Sasaki S. Induction chemotherapy with docetaxel, cisplatin, fluorouracil and l-leucovorin for locally advanced head and neck cancers: a modified regimen for Japanese patients. *Anticancer Drugs.* 2003 Nov;14(10):801-7.
3. Fuse N, Doi T, Ohtsu A, *et al.* Safety of irinotecan and infusional fluorouracil/leucovorin (FOLFIRI) in Japan: a retrospective review of 48 patients with metastatic colorectal cancer. *Int J Clin Oncol.* 2008 Apr;13(2):144-9.
4. Yukawa N, Yamamoto Y, Akaike M, *et al.* [Modified FOLFIRI (I-LV, 5-fluorouracil and irinotecan) therapy for Japanese patients with metastatic colorectal cancer]. *Gan To Kagaku Ryoho.* 2010 Jul;37(7):1291-5.
5. Gandara DR, Kawaguchi T, Crowley J, *et al.* Japanese-US common-arm analysis of paclitaxel plus carboplatin in advanced non-small-cell lung cancer: a model

- for assessing population-related pharmacogenomics. *J Clin Oncol*. 2009 Jul 20;27(21):3540-6.
6. Millward MJ, Boyer MJ, Lehnert M, *et al*. Docetaxel and carboplatin is an active regimen in advanced non-small-cell lung cancer: a phase II study in Caucasian and Asian patients. *Ann Oncol*. 2003 Mar;14(3):449-54.
  7. Lara PN, Jr., Chansky K, Shibata T, *et al*. Common arm comparative outcomes analysis of phase 3 trials of cisplatin + irinotecan versus cisplatin + etoposide in extensive stage small cell lung cancer1: Final patient-level results from Japan Clinical Oncology Group 9511 and Southwest Oncology Group 0124. *Cancer*. 2010 Dec 15;116(24):5710-5.
  8. Lara PN, Natale R, Crowley J, *et al*. Phase III trial of irinotecan/cisplatin compared with etoposide/cisplatin in extensive-stage small-cell lung cancer: clinical and pharmacogenomic results from SWOG S0124. *J Clin Oncol*. 2009 May 20;27(15):2530-5.
  9. Sekine I, Yamamoto N, Nishio K, *et al*. Emerging ethnic differences in lung cancer therapy. *Br J Cancer*. 2008 Dec 2;99(11):1757-62.
  10. Gridelli C, De Marinis F, Di Maio M, *et al*. Gefitinib as first-line treatment for patients with advanced non-small-cell lung cancer with activating epidermal growth factor receptor mutation: Review of the evidence. *Lung Cancer*. 2011 Mar;71(3):249-57.
  11. Thatcher N, Chang A, Parikh P, *et al*. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). *Lancet*. 2005 Oct 29-Nov 4;366(9496):1527-37.
  12. Liu W, Innocenti F, Chen P, *et al*. Interethnic difference in the allelic distribution of human epidermal growth factor receptor intron 1 polymorphism. *Clin Cancer Res*. 2003 Mar;9(3):1009-12.
  13. Rudin CM, Liu W, Desai A, *et al*. Pharmacogenomic and pharmacokinetic determinants of erlotinib toxicity. *J Clin Oncol*. 2008 Mar 1;26(7):1119-27.
  14. Ganjoo KN and Wakelee H. Review of erlotinib in the treatment of advanced non-small cell lung cancer. *Biologics*. 2007 Dec;1(4):335-46.
  15. Kubota K, Nishiwaki Y, Tamura T, *et al*. Efficacy and safety of erlotinib monotherapy for Japanese patients with advanced non-small cell lung cancer: a phase II study. *J Thorac Oncol*. 2008 Dec;3(12):1439-45.
  16. Beith JM GB, Yeo W *et al*. Inter-ethnic differences in the myelotoxicity of adriamycin/cyclophosphamide (AC) for adjuvant breast cancer. *Proceedings of the American Society of Clinical Oncology*. 2002;21:252.
  17. Ma B, Yeo W, Hui P, *et al*. Acute toxicity of adjuvant doxorubicin and cyclophosphamide for early breast cancer -- a retrospective review of Chinese patients and comparison with an historic Western series. *Radiother Oncol*. 2002 Feb;62(2):185-9.
  18. Moy B, Tu D, Pater JL, *et al*. Clinical outcomes of ethnic minority women in MA.17: a trial of letrozole after 5 years of tamoxifen in postmenopausal women with early stage breast cancer. *Ann Oncol*. 2006 Nov;17(11):1637-43.
  19. McCollum AD, Catalano PJ, Haller DG, *et al*. Outcomes and toxicity in african-american and caucasian patients in a randomized adjuvant chemotherapy trial for colon cancer. *J Natl Cancer Inst*. 2002 Aug 7;94(15):1160-7.
  20. Sanoff HK, Sargent DJ, Green EM, *et al*. Racial differences in advanced colorectal cancer outcomes and pharmacogenetics: a subgroup analysis of a large randomized clinical trial. *J Clin Oncol*. 2009 Sep 1;27(25):4109-15.



21. Goldberg RM, Sargent DJ, McLeod H. Leveraging learning from a phase III colorectal cancer clinical trial: outcomes, methodology, meta-analysis and pharmacogenetics. *Trans Am Clin Climatol Assoc.* 2010;121:21-32; discussion 32-3.
22. Plaxe SC, Brooks SE, Tian C, *et al.* Influence of race on tolerance of platinum-based chemotherapy and clinical outcomes in women with advanced and recurrent cervical cancer: a pooled analysis of 3 Gynecologic Oncology Group studies. *Am J Obstet Gynecol.* 2008 Nov;199(5):539 e1-6.
23. Farley JH, Tian C, Rose GS, *et al.* Race does not impact outcome for advanced ovarian cancer patients treated with cisplatin/paclitaxel: an analysis of Gynecologic Oncology Group trials. *Cancer.* 2009 Sep 15;115(18):4210-7.
24. Farley JH, Tian C, Rose GS, *et al.* Chemotherapy intensity and toxicity among black and white women with advanced and recurrent endometrial cancer: a Gynecologic Oncology Group Study. *Cancer.* 2010 Jan 15;116(2):355-61.
25. Phan VH, Moore MM, McLachlan AJ, *et al.* Ethnic differences in drug metabolism and toxicity from chemotherapy. *Expert Opin Drug Metab Toxicol.* 2009 Mar;5(3):243-57.
26. Wilkinson GR. Drug metabolism and variability among patients in drug response. *N Engl J Med.* 2005;352(21):2211-21.
27. Chen C, Lu, RB, Chen, YC, *et al.* . Interaction between the functional polymorphisms of the alcohol-metabolism genes in protection against alcoholism. *Am J Hum Genet.* 1999;65(3):795-807.
28. Duranceaux N, Shuckit, MA, Luczak, ME *et al.* Ethnic differences in level of response to alcohol between Chinese Americans and Korean Americans. *J Stud Alcohol Drugs.* 2008;69:227-34.
29. Ball SE, Scatina J, Kao J, *et al.* Population distribution and effects on drug metabolism of a genetic variant in the 5' promoter region of CYP3A4. *Clin Pharmacol Ther.* 1999 Sep;66(3):288-94.
30. Goh B, Soo, RA, Zhang, LJ, Furule, T, Urrea, PD, Rosen, LS. Inter-ethnic variability of S-1 pharmacokinetics (PK) and correlation with CYP2A6 phenotyping. ASCO General Meeting; 2008; Chicago: American Society of Clinical Oncology; 2008.
31. Available from: <http://www.pharmgkb.org>.
32. Available from: [www.imm.ki.se/CYPalleles](http://www.imm.ki.se/CYPalleles).
33. van Erp NP, Gelderblom HandGuchelaar HJ. Clinical pharmacokinetics of tyrosine kinase inhibitors. *Cancer Treat Rev.* 2009 Dec;35(8):692-706.
34. van Erp NP, Eechoute K, van der Veldt AA, *et al.* Pharmacogenetic pathway analysis for determination of sunitinib-induced toxicity. *J Clin Oncol.* 2009 Sep 10;27(26):4406-12.
35. Li J, Zhao M, He P, *et al.* Differential metabolism of gefitinib and erlotinib by human cytochrome P450 enzymes. *Clin Cancer Res.* 2007 Jun 15;13(12):3731-7.
36. Chowbay B, Zhou SandLee EJ. An interethnic comparison of polymorphisms of the genes encoding drug-metabolizing enzymes and drug transporters: experience in Singapore. *Drug Metab Rev.* 2005;37(2):327-78.
37. Robert J, Morvan VL, Smith D, *et al.* Predicting drug response and toxicity based on gene polymorphisms. *Crit Rev Oncol Hematol.* 2005 Jun;54(3):171-96.
38. Kaida Y, Inui N, Suda T, *et al.* The CYP2A6\*4 allele is determinant of S-1 pharmacokinetics in Japanese patients with non-small-cell lung cancer. *Clin Pharmacol Ther.* 2008 Apr;83(4):589-94.
39. Nakajima M, Fukami T, Yamanaka H, *et al.* Comprehensive evaluation of variability in nicotine metabolism and CYP2A6 polymorphic alleles in four ethnic populations. *Clin Pharmacol Ther.* 2006 Sep;80(3):282-97.

40. Jinno H, Tanaka-Kagawa T, Ohno A, *et al.* Functional characterization of cytochrome P450 2B6 allelic variants. *Drug Metab Dispos.* 2003 Apr;31(4):398-403.
41. Hofmann MH, Bliedernicht JK, Klein K, *et al.* Aberrant splicing caused by single nucleotide polymorphism c.516G>T [Q172H], a marker of CYP2B6\*6, is responsible for decreased expression and activity of CYP2B6 in liver. *J Pharmacol Exp Ther.* 2008 Apr;325(1):284-92.
42. Klein K, Lang T, Saussele T, *et al.* Genetic variability of CYP2B6 in populations of African and Asian origin: allele frequencies, novel functional variants, and possible implications for anti-HIV therapy with efavirenz. *Pharmacogenet Genomics.* 2005 Dec;15(12):861-73.
43. Lang T, Klein K, Richter T, *et al.* Multiple novel nonsynonymous CYP2B6 gene polymorphisms in Caucasians: demonstration of phenotypic null alleles. *J Pharmacol Exp Ther.* 2004 Oct;311(1):34-43.
44. Rotger M, Tegude H, Colombo S, *et al.* Predictive value of known and novel alleles of CYP2B6 for efavirenz plasma concentrations in HIV-infected individuals. *Clin Pharmacol Ther.* 2007 Apr;81(4):557-66.
45. Xie H, Griskevicius L, Stahle L, *et al.* Pharmacogenetics of cyclophosphamide in patients with hematological malignancies. *Eur J Pharm Sci.* 2006 Jan;27(1):54-61.
46. Rocha V, Porcher R, Fernandes JF, *et al.* Association of drug metabolism gene polymorphisms with toxicities, graft-versus-host disease and survival after HLA-identical sibling hematopoietic stem cell transplantation for patients with leukemia. *Leukemia.* 2009 Mar;23(3):545-56.
47. Bray J, Sludden J, Griffin MJ, *et al.* Influence of pharmacogenetics on response and toxicity in breast cancer patients treated with doxorubicin and cyclophosphamide. *Br J Cancer.* 2010 Mar 16;102(6):1003-9.
48. Daily EB and Aquilante CL. Cytochrome P450 2C8 pharmacogenetics: a review of clinical studies. *Pharmacogenomics.* 2009 Sep;10(9):1489-510.
49. Hanioka N, Matsumoto K, Saito Y, *et al.* Functional characterization of CYP2C8.13 and CYP2C8.14: catalytic activities toward paclitaxel. *Basic Clin Pharmacol Toxicol.* 2010 Jul;107(1):565-9.
50. Marsh S, Paul J, King CR, *et al.* Pharmacogenetic assessment of toxicity and outcome after platinum plus taxane chemotherapy in ovarian cancer: the Scottish Randomised Trial in Ovarian Cancer. *J Clin Oncol.* 2007 Oct 10;25(29):4528-35.
51. Marsh S, Somlo G, Li X, *et al.* Pharmacogenetic analysis of paclitaxel transport and metabolism genes in breast cancer. *Pharmacogenomics J.* 2007 Oct;7(5):362-5.
52. Henningson A, Marsh S, Loos WJ, *et al.* Association of CYP2C8, CYP3A4, CYP3A5, and ABCB1 polymorphisms with the pharmacokinetics of paclitaxel. *Clin Cancer Res.* 2005 Nov 15;11(22):8097-104.
53. Bergmann TK, Brasch-Andersen C, Green H, *et al.* Impact of CYP2C8\*3 on paclitaxel clearance: a population pharmacokinetic and pharmacogenomic study in 93 patients with ovarian cancer. *Pharmacogenomics J.* 2010 Apr 6;6:6.
54. Leskela S, Jara C, Leandro-Garcia LJ, *et al.* Polymorphisms in cytochromes P450 2C8 and 3A5 are associated with paclitaxel neurotoxicity. *Pharmacogenomics J.* 2010 Mar 9;9:9.
55. Sarasquete ME, Garcia-Sanz R, Marin L, *et al.* Bisphosphonate-related osteonecrosis of the jaw is associated with polymorphisms of the cytochrome P450 CYP2C8 in multiple myeloma: a genome-wide single nucleotide polymorphism analysis. *Blood.* 2008 Oct 1;112(7):2709-12.
56. van Schaik RH. CYP450 pharmacogenetics for personalizing cancer therapy. *Drug Resist Updat.* 2008 Jun;11(3):77-98.



57. Peng B, Lloyd P, Schran H. Clinical pharmacokinetics of imatinib. *Clin Pharmacokinet.* 2005;44(9):879-94.
58. Givens CB, Bullock LN, Franks AS. Safety of concomitant tamoxifen and warfarin. *Ann Pharmacother.* 2009 Nov;43(11):1867-71.
59. Van Booven D, Marsh S, McLeod H, *et al.* Cytochrome P450 2C9-CYP2C9. *Pharmacogenet Genomics.* 2010 Apr;20(4):277-81.
60. Garcia-Martin E, Martinez C, Ladero JM, *et al.* Interethnic and intraethnic variability of CYP2C8 and CYP2C9 polymorphisms in healthy individuals. *Mol Diagn Ther.* 2006;10(1):29-40.
61. Ekhardt C, Doodeman VD, Rodenhuis S, *et al.* Influence of polymorphisms of drug metabolizing enzymes (CYP2B6, CYP2C9, CYP2C19, CYP3A4, CYP3A5, GSTA1, GSTP1, ALDH1A1 and ALDH3A1) on the pharmacokinetics of cyclophosphamide and 4-hydroxycyclophosphamide. *Pharmacogenet Genomics.* 2008 Jun;18(6):515-23.
62. Schroth W, Antoniadou L, Fritz P, *et al.* Breast cancer treatment outcome with adjuvant tamoxifen relative to patient CYP2D6 and CYP2C19 genotypes. *J Clin Oncol.* 2007 Nov 20;25(33):5187-93.
63. Roh HK, Dahl ML, Tybring G, *et al.* CYP2C19 genotype and phenotype determined by omeprazole in a Korean population. *Pharmacogenetics.* 1996 Dec;6(6):547-51.
64. Kaneko A, Lum JK, Yaviong L, *et al.* High and variable frequencies of CYP2C19 mutations: medical consequences of poor drug metabolism in Vanuatu and other Pacific islands. *Pharmacogenetics.* 1999 Oct;9(5):581-90.
65. Ferguson RJ, De Morais SM, Benhamou S, *et al.* A new genetic defect in human CYP2C19: mutation of the initiation codon is responsible for poor metabolism of S-mephenytoin. *J Pharmacol Exp Ther.* 1998 Jan;284(1):356-61.
66. Ibeanu GC, Blaisdell J, Ferguson RJ, *et al.* A novel transversion in the intron 5 donor splice junction of CYP2C19 and a sequence polymorphism in exon 3 contribute to the poor metabolizer phenotype for the anticonvulsant drug S-mephenytoin. *J Pharmacol Exp Ther.* 1999 Aug;290(2):635-40.
67. Blaisdell J, Mohrenweiser H, Jackson J, *et al.* Identification and functional characterization of new potentially defective alleles of human CYP2C19. *Pharmacogenetics.* 2002 Dec;12(9):703-11.
68. Timm R, Kaiser R, Lotsch J, *et al.* Association of cyclophosphamide pharmacokinetics to polymorphic cytochrome P450 2C19. *Pharmacogenomics J.* 2005;5(6):365-73.
69. Ruiters R, Bijl MJ, van Schaik RH, *et al.* CYP2C19\*2 polymorphism is associated with increased survival in breast cancer patients using tamoxifen. *Pharmacogenomics.* 2010 Oct;11(10):1367-75.
70. Luo HR, Poland RE, Lin KM, *et al.* Genetic polymorphism of cytochrome P450 2C19 in Mexican Americans: a cross-ethnic comparative study. *Clin Pharmacol Ther.* 2006 Jul;80(1):33-40.
71. Xiao ZS, Goldstein JA, Xie HG, *et al.* Differences in the incidence of the CYP2C19 polymorphism affecting the S-mephenytoin phenotype in Chinese Han and Bai populations and identification of a new rare CYP2C19 mutant allele. *J Pharmacol Exp Ther.* 1997 Apr;281(1):604-9.
72. Bernard S, Neville KA, Nguyen AT, *et al.* Interethnic differences in genetic polymorphisms of CYP2D6 in the U.S. population: clinical implications. *Oncologist.* 2006 Feb;11(2):126-35.
73. Ingelman-Sundberg M, Sim SC, Gomez A, *et al.* Influence of cytochrome P450

polymorphisms on drug therapies: pharmacogenetic, pharmacoepigenetic and clinical aspects. *Pharmacol Ther.* 2007 Dec;116(3):496-526.

74. Schroth W, Goetz MP, Hamann U, *et al.* Association between CYP2D6 polymorphisms and outcomes among women with early stage breast cancer treated with tamoxifen. *Jama.* 2009 Oct 7;302(13):1429-36.

75. Gaedigk A, Simon SD, Pearce RE, *et al.* The CYP2D6 activity score: translating genotype information into a qualitative measure of phenotype. *Clin Pharmacol Ther.* 2008 Feb;83(2):234-42.

76. Bosch TM, Meijerman I, Beijnen JH, *et al.* Genetic polymorphisms of drug-metabolising enzymes and drug transporters in the chemotherapeutic treatment of cancer. *Clin Pharmacokinet.* 2006;45(3):253-85.

77. Higgins MJ and Stearns V. CYP2D6 polymorphisms and tamoxifen metabolism: clinical relevance. *Curr Oncol Rep.* 2010 Jan;12(1):7-15.

78. Ingelman-Sundberg M. Genetic polymorphisms of cytochrome P450 2D6 (CYP2D6): clinical consequences, evolutionary aspects and functional diversity. *Pharmacogenomics J.* 2005;5(1):6-13.

79. Man M, Farmen M, Dumaul C, *et al.* Genetic variation in metabolizing enzyme and transporter genes: comprehensive assessment in 3 major East Asian subpopulations with comparison to Caucasians and Africans. *J Clin Pharmacol.* 2010 Aug;50(8):929-40.

80. Keating GM and Santoro A. Sorafenib: a review of its use in advanced hepatocellular carcinoma. *Drugs.* 2009;69(2):223-40.

81. Dai D, Tang J, Rose R, *et al.* Identification of variants of CYP3A4 and characterization of their abilities to metabolize testosterone and chlorpyrifos. *J Pharmacol Exp Ther.* 2001 Dec;299(3):825-31.

82. Murayama N, Nakamura T, Sacki M, *et al.* CYP3A4 gene polymorphisms influence testosterone 6beta-hydroxylation. *Drug Metab Pharmacokinet.* 2002;17(2):150-6.

83. Eiselt R, Domanski TL, Zibat A, *et al.* Identification and functional characterization of eight CYP3A4 protein variants. *Pharmacogenetics.* 2001 Jul;11(5):447-58.

84. Nakajima Y, Yoshitani T, Fukushima-Uesaka H, *et al.* Impact of the haplotype CYP3A4\*16B harboring the Thr185Ser substitution on paclitaxel metabolism in Japanese patients with cancer. *Clin Pharmacol Ther.* 2006 Aug;80(2):179-91.

85. Tran A, Jullien V, Alexandre J, *et al.* Pharmacokinetics and toxicity of docetaxel: role of CYP3A, MDR1, and GST polymorphisms. *Clin Pharmacol Ther.* 2006 Jun;79(6):570-80.

86. Wegman P, Elingarami S, Carstensen J, *et al.* Genetic variants of CYP3A5, CYP2D6, SULT1A1, UGT2B15 and tamoxifen response in postmenopausal patients with breast cancer. *Breast Cancer Res.* 2007;9(1):R7.

87. Kuehl P, Zhang J, Lin Y, *et al.* Sequence diversity in CYP3A promoters and characterization of the genetic basis of polymorphic CYP3A5 expression. *Nat Genet.* 2001 Apr;27(4):383-91.

88. Daly AK. Significance of the minor cytochrome P450 3A isoforms. *Clin Pharmacokinet.* 2006;45(1):13-31.

89. Takahashi N, Miura M, Scott SA, *et al.* Influence of CYP3A5 and drug transporter polymorphisms on imatinib trough concentration and clinical response among patients with chronic phase chronic myeloid leukemia. *J Hum Genet.* 2010 Nov;55(11):731-7.

90. Dennison JB, Jones DR, Renbarger JL, *et al.* Effect of CYP3A5 expression on



- vincristine metabolism with human liver microsomes. *J Pharmacol Exp Ther.* 2007 May;321(2):553-63.
91. Yamaori S, Yamazaki H, Iwano S, *et al.* Ethnic differences between Japanese and Caucasians in the expression levels of mRNAs for CYP3A4, CYP3A5 and CYP3A7: lack of co-regulation of the expression of CYP3A in Japanese livers. *Xenobiotica.* 2005 Jan;35(1):69-83.
  92. Fukushima-Uesaka H, Saito Y, Watanabe H, *et al.* Haplotypes of CYP3A4 and their close linkages with CYP3A5 haplotypes in a Japanese population. *Hum Mutat.* 2004;23:100.
  93. Yang P, Ebbert JO, Sun Z, *et al.* Role of the glutathione metabolic pathway in lung cancer treatment and prognosis: a review. *J Clin Oncol.* 2006 Apr 10;24(11):1761-9.
  94. Hayes JD, Flanagan JU and Jowsey IR. Glutathione transferases. *Annu Rev Pharmacol Toxicol.* 2005;45:51-88.
  95. Edvardsen H, Brunsvig PF, Solvang H, *et al.* SNPs in genes coding for ROS metabolism and signalling in association with docetaxel clearance. *Pharmacogenomics J.* 2010 Dec;10(6):513-23.
  96. Lecomte T, Landi B, Beaune P, *et al.* Glutathione S-transferase P1 polymorphism (Ile105Val) predicts cumulative neuropathy in patients receiving oxaliplatin-based chemotherapy. *Clin Cancer Res.* 2006 May 15;12(10):3050-6.
  97. Wang B, Huang G, Wang D, *et al.* Null genotypes of GSTM1 and GSTT1 contribute to hepatocellular carcinoma risk: evidence from an updated meta-analysis. *J Hepatol.* 2010 Sep;53(3):508-18.
  98. Li D, Dandara C and Parker MI. The 341C/T polymorphism in the GSTP1 gene is associated with increased risk of oesophageal cancer. *BMC Genet.* 2010;11(47):47.
  99. Cho HJ, Eom HS, Kim HJ, *et al.* Glutathione-S-transferase genotypes influence the risk of chemotherapy-related toxicities and prognosis in Korean patients with diffuse large B-cell lymphoma. *Cancer Genet Cytogenet.* 2010 Apr 1;198(1):40-6.
  100. Stoehlmacher J, Park DJ, Zhang W, *et al.* A multivariate analysis of genomic polymorphisms: prediction of clinical outcome to 5-FU/oxaliplatin combination chemotherapy in refractory colorectal cancer. *Br J Cancer.* 2004 Jul 19;91(2):344-54.
  101. Oliveira AL, Rodrigues FF, Santos RE, *et al.* GSTT1, GSTM1, and GSTP1 polymorphisms and chemotherapy response in locally advanced breast cancer. *Genet Mol Res.* 2010;9(2):1045-53.
  102. Booton R, Ward T, Heighway J, *et al.* Glutathione-S-transferase P1 isoenzyme polymorphisms, platinum-based chemotherapy, and non-small cell lung cancer. *J Thorac Oncol.* 2006 Sep;1(7):679-83.
  103. Mir O, Alexandre J, Tran A, *et al.* Relationship between GSTP1 Ile(105)Val polymorphism and docetaxel-induced peripheral neuropathy: clinical evidence of a role of oxidative stress in taxane toxicity. *Ann Oncol.* 2009 Apr;20(4):736-40.
  104. Kim SD, Lee JH, Hur EH, *et al.* Influence of GST gene polymorphisms on the clearance of intravenous busulfan in adult patients undergoing hematopoietic cell transplantation. *Biol Blood Marrow Transplant.* 2011 Jan 5;5:5.
  105. Zwaveling J, Press RR, Bredius RG, *et al.* Glutathione S-transferase polymorphisms are not associated with population pharmacokinetic parameters of busulfan in pediatric patients. *Ther Drug Monit.* 2008 Aug;30(4):504-10.
  106. Ekhart C, Doodeman VD, Rodenhuis S, *et al.* Polymorphisms of drug-metabolizing enzymes (GST, CYP2B6 and CYP3A) affect the pharmacokinetics of thiotepa and tepa. *Br J Clin Pharmacol.* 2009 Jan;67(1):50-60.
  107. Guillemette C, Levesque E, Harvey M, *et al.* UGT genomic diversity: beyond

- gene duplication. *Drug Metab Rev.* 2010 Feb;42(1):24-44.
108. Watanabe Y, Nakajima M, Ohashi N, *et al.* Glucuronidation of etoposide in human liver microsomes is specifically catalyzed by UDP-glucuronosyltransferase 1A1. *Drug Metab Dispos.* 2003 May;31(5):589-95.
109. Ando Y, Fujita K, Sasaki Y, *et al.* UGT1A1\*6 and UGT1A1\*27 for individualized irinotecan chemotherapy. *Curr Opin Mol Ther.* 2007 Jun;9(3):258-62.
110. Glimelius B, Garmo H, Berglund A, *et al.* Prediction of irinotecan and 5-fluorouracil toxicity and response in patients with advanced colorectal cancer. *Pharmacogenomics J.* 2010 Feb 23;23:23.
111. Stewart CF, Panetta JC, O'Shaughnessy MA, *et al.* UGT1A1 promoter genotype correlates with SN-38 pharmacokinetics, but not severe toxicity in patients receiving low-dose irinotecan. *J Clin Oncol.* 2007 Jun 20;25(18):2594-600.
112. Kishi S, Yang W, Boureau B, *et al.* Effects of prednisone and genetic polymorphisms on etoposide disposition in children with acute lymphoblastic leukemia. *Blood.* 2004 Jan 1;103(1):67-72.
113. Akaba K, Kimura T, Sasaki A, *et al.* Neonatal hyperbilirubinemia and mutation of the bilirubin uridine diphosphate-glucuronosyltransferase gene: a common missense mutation among Japanese, Koreans and Chinese. *Biochem Mol Biol Int.* 1998 Sep;46(1):21-6.
114. 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 Jul;17(7):497-504.
115. Nakamura Y, Soda H, Oka M, *et al.* Randomized phase II trial of irinotecan with paclitaxel or gemcitabine for non-small cell lung cancer: association of UGT1A1\*6 and UGT1A1\*27 with severe neutropenia. *J Thorac Oncol.* 2011 Jan;6(1):121-7.
116. Morsman JM, Sludden J, Ameyaw MM, *et al.* Evaluation of dihydropyrimidine dehydrogenase activity in South-west Asian, Kenyan and Ghanaian populations. *Br J Clin Pharmacol.* 2000 Sep;50(3):269-72.
117. Maring JG, Groen HJ, Wachtters FM, *et al.* Genetic factors influencing pyrimidine-antagonist chemotherapy. *Pharmacogenomics J.* 2005;5(4):226-43.
118. Diasio RB and Johnson MR. The role of pharmacogenetics and pharmacogenomics in cancer chemotherapy with 5-fluorouracil. *Pharmacology.* 2000 Sep;61(3):199-203.
119. 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.* 2010 May;66(1):95-105.
120. Cha PC, Mushiroda T, Zembutsu H, *et al.* Single nucleotide polymorphism in ABCG2 is associated with irinotecan-induced severe myelosuppression. *J Hum Genet.* 2009 Oct;54(10):572-80.
121. Innocenti F, Kroetz DL, Schuetz E, *et al.* Comprehensive pharmacogenetic analysis of irinotecan neutropenia and pharmacokinetics. *J Clin Oncol.* 2009 Jun 1;27(16):2604-14.
122. Reigner B, Watanabe T, Schuller J, *et al.* Pharmacokinetics of capecitabine (Xeloda) in Japanese and Caucasian patients with breast cancer. *Cancer Chemother Pharmacol.* 2003 Sep;52(3):193-201.
123. Lewis LD, Miller AA, Rosner GL, *et al.* A comparison of the pharmacokinetics and pharmacodynamics of docetaxel between African-American and Caucasian cancer patients: CALGB 9871. *Clin Cancer Res.* 2007 Jun 1;13(11):3302-11.
124. Ranson M, Wilson RH, O'Sullivan JM, *et al.* Pharmacokinetic and tolerability



- profile of once-daily zibotentan (ZD4054) in Japanese and Caucasian patients with hormone-resistant prostate cancer. *Int J Clin Pharmacol Ther.* 2010 Nov;48(11):708-17.
125. Garte S, Gaspari L, Alexandrie AK, *et al.* Metabolic gene polymorphism frequencies in control populations. *Cancer Epidemiol Biomarkers Prev.* 2001 Dec;10(12):1239-48.
126. Inoue K, Asao T, Shimada T. Ethnic-related differences in the frequency distribution of genetic polymorphisms in the CYP1A1 and CYP1B1 genes in Japanese and Caucasian populations. *Xenobiotica.* 2000 Mar;30(3):285-95.
127. Cascorbi I, Brockmoller J, Roots I. A C4887A polymorphism in exon 7 of human CYP1A1: population frequency, mutation linkages, and impact on lung cancer susceptibility. *Cancer Res.* 1996 Nov 1;56(21):4965-9.
128. Davaalkham J, Hayashida T, Tsuchiya K, *et al.* Allele and genotype frequencies of cytochrome P450 2B6 gene in a Mongolian population. *Drug Metab Dispos.* 2009 Oct;37(10):1991-3.
129. Guan S, Huang M, Li X, *et al.* Intra- and inter-ethnic differences in the allele frequencies of cytochrome P450 2B6 gene in Chinese. *Pharm Res.* 2006 Sep;23(9):1983-90.
130. Kim KA, Song WK, Park JY. Association of CYP2B6, CYP3A5, and CYP2C19 genetic polymorphisms with sibutramine pharmacokinetics in healthy Korean subjects. *Clin Pharmacol Ther.* 2009 Nov;86(5):511-8.
131. Totah RA, Rettie AE. Cytochrome P450 2C8: substrates, inhibitors, pharmacogenetics, and clinical relevance. *Clin Pharmacol Ther.* 2005 May;77(5):341-52.
132. Rodriguez-Antona C, Gomez A, Karlgren M, *et al.* Molecular genetics and epigenetics of the cytochrome P450 gene family and its relevance for cancer risk and treatment. *Hum Genet.* 2010 Jan;127(1):1-17.
133. Scordo MG, Caputi AP, D'Arrigo C, *et al.* Allele and genotype frequencies of CYP2C9, CYP2C19 and CYP2D6 in an Italian population. *Pharmacol Res.* 2004 Aug;50(2):195-200.
134. Sata F, Sapone A, Elizondo G, *et al.* CYP3A4 allelic variants with amino acid substitutions in exons 7 and 12: evidence for an allelic variant with altered catalytic activity. *Clin Pharmacol Ther.* 2000 Jan;67(1):48-56.
135. Zeigler-Johnson CM, Walker AH, Mancke B, *et al.* Ethnic differences in the frequency of prostate cancer susceptibility alleles at SRD5A2 and CYP3A4. *Hum Hered.* 2002;54(1):13-21.
136. Rebbeck TR. Molecular epidemiology of the human glutathione S-transferase genotypes GSTM1 and GSTT1 in cancer susceptibility. *Cancer Epidemiol Biomarkers Prev.* 1997 Sep;6(9):733-43.
137. Nelson HH, Wiencke JK, Christiani DC, *et al.* Ethnic differences in the prevalence of the homozygous deleted genotype of glutathione S-transferase theta. *Carcinogenesis.* 1995 May;16(5):1243-5.
138. Zhong SL, Zhou SF, Chen X, *et al.* Relationship between genotype and enzyme activity of glutathione S-transferases M1 and P1 in Chinese. *Eur J Pharm Sci.* 2006 May;28(1-2):77-85.
139. Lampe JW, Bigler J, Horner NK, *et al.* UDP-glucuronosyltransferase (UGT1A1\*28 and UGT1A6\*2) polymorphisms in Caucasians and Asians: relationships to serum bilirubin concentrations. *Pharmacogenetics.* 1999 Jun;9(3):341-9.
140. Cropp CD, Yee SW, Giacomini KM. Genetic variation in drug transporters in ethnic populations. *Clin Pharmacol Ther.* 2008 Sep;84(3):412-6.



**Table 1. Prevalence of polymorphisms in enzymes responsible for the metabolism of chemotherapeutic agents/drug-metabolising enzymes**

**Comment [A3]:** Changed title

Enzymes	Drugs	Allelic variants	Caucasians % (N)	Asians % (N)	Africans % (N)	Effects	Reference
<b>CYP1A1</b>	Imatinib	<i>CYP1A1*1</i>	89% (3814)	63% (626)	66% (445)		[33, 125-127]
	Gefitinib	<i>CYP1A1*2A</i>	5.8% (3814)	14.9% (626)	21.8% (445)		
	Erlotinib	<i>CYP1A1*2B</i>	3.2% (3814)	21.2% (626)	1.8% (445)		
	Sunitinib	<i>CYP1A1*2C</i>	1.8% (3814)	1.5% (626)	0.7% (445)		
		<i>CYP1A1*3</i>	0% (735)	0% (39)	9.3% (464)		
<b>CYP2B6</b>	Cyclophosphamide	<i>CYP2B6*1</i>	50.7% - 53.7% (270 - 430)	58.8% - 78.3% (46 - 386)	39.1% - 44.3% (64 - 70)		[42, 128-130]
	Tamoxifen	<i>CYP2B6*2</i>	3.7% - 5.3% (270 - 430)	2.7% - 13.2% (46 - 386)	3.1% - 4.3% (64 - 70)		
		<i>CYP2B6*3</i>	0% - 1.1% (270 - 430)	0% - 1.1% (46 - 386)	0% (64 - 70)		

<b>CYP2C8</b>	Paclitaxel Cyclophosphamide Ifosfamide	<i>CYP2B6</i> *4	2.2% - 3.9% (270 - 430)	3.3% - 12% (46 - 386)	0%		
		<i>CYP2B6</i> *5	10.9% - 12.2% (270 - 430)	0% - 4.9% (46 - 386)	1.6% - 8.6% (64 - 70)		
		<i>CYP2B6</i> *6	25.6% - 28.2% (270 - 430)	9.8% - 21.4% (46 - 386)	32.8% - 46.9% (64 - 70)	Decreased activity	
<b>CYP2C9</b>	Cyclophosphamide Ifosfamide Tamoxifen Etoposide Imatinib	<i>CYP2C8</i> *2	0% (30 - 1468)	0% (20 - 200)	4% - 18% (26 - 82)	Decreased activity	[60, 131]
		<i>CYP2C8</i> *3	10% - 23% (28 - 1468)	0% - 0.7% (73 - 200)	0% - 2% (26 - 82)	Decreased activity	
		<i>CYP2C8</i> *4	5.5% - 11% (28 - 107)	0% (20 - 200)	0% (26)		
		<i>CYP2C9</i> *2	11% - 17% (115 - 430)	0% - 0.1% (64 - 574)	0% - 4% (66 - 150)	Decreased activity	[59]
<b>CYP2C19</b>	Cyclophosphamide Ifosfamide	<i>CYP2C9</i> *3	5% - 11% (115 - 430)	1% - 5% (64 - 574)	1% - 2% (66 - 150)	Decreased activity	
		<i>CYP2C19</i> *2	9.1% - 15% (273 - 454)	28.6% - 30.7% (200 - 500)	18.2% - 19.2% (236 - 250)	Decreased activity	[57, 62, 70, 71, 79, 132, 133]



		<i>CYP2C19</i> *3	0% - 0.9% (273 - 454)	4.5 % - 13.1% (200 - 500)	0% - 0.8% (236 - 250)	Decreased activity	
<b>CYP2D6</b>	Tamoxifen						
	Thalidomide						
	Imatinib					No activity	[57, 62, 73, 78, 79]
	Tamoxifen	<i>CYP2D6</i> *3	2.2% (454)	0% (200 - 500)	0% (250)	No activity	
	Gefitinib						
	Imatinib	<i>CYP2D6</i> *4	18.8% (454)	0.1% - 1.1% (200 - 500)	6.1% (250)	No activity	
<b>CYP3A4</b>	Docetaxel	<i>CYP2D6</i> *6	1.7% (454)	0% (200 - 500)	0% (250)	No activity	
	Paclitaxel	<i>CYP2D6</i> *10	2.8% (454)	37.8% - 49.9% (200 - 500)	5.7% (250)	Decreased activity	
	Vincristine	<i>CYP2D6</i> *4I	11.7% (454)	1.6% - 3.8% (200 - 500)	3.1% (250)	Decreased activity	
	Irinotecan	<i>CYP3A4</i> *1B	4% - 10% (97 - 410)	0% (32 - 73)	59% - 81% (129 - 178)		[5, 29, 56, 76, 80, 81, 134, 135]
	Etoposide	<i>CYP3A4</i> *2	3% (55)	0% (54)	0% (53)		
	Cyclophosphamide	<i>CYP3A4</i> *18	0% (24)	2% (24)	0% (24)		
Ifosfamide	<i>CYP3A4</i> *19	0% (24)	2% (24)	0% (24)			

<b>CYP3A5</b>	Tamoxifen								
	Gefitinib								
	Erlotinib								
	Sorafenib								
	Imatinib								
	Docetaxel	<i>CYP3A5</i> *3	85% - 98% (24 - 500)	60% - 77% (24 - 265)	35% - 48% (20 - 24)	Decreased activity	[88]		
	Paclitaxel								
Vincristine	<i>CYP3A5</i> *6	0% (24 - 500)	0% (24 - 265)	17%- 22% (20 - 24)	Decreased activity				
Irinotecan									
Etoposide	<i>CYP3A5</i> *7	0% (24 - 500)	0% (24 - 265)	8% - 10% (20 - 24)					
Cyclophosphamide									
Ifosfamide									
Gefitinib									
Imatinib									
Tamoxifen									
<b>GST</b>	Doxorubicin	<i>GSTM1</i> *0	38% - 67% (104 - 1473)	35% - 63% (196)	22% - 35% (203)	Gene deletion	[136-138]		
	BCNU								
	Busulfan	<i>GSTT1</i> *0	20.4% (442)	60.2% - 64.4% (45 - 103)	21.8% (119)	Decreased activity			
	Carmustine								
Chlorambucil	<i>GSTP1</i> *B	30% - 33%	14% - 22%	42%	Decreased				

	Cisplatin Oxaliplatin Cyclophosphamide Melphalan Mitoxantrone Docetaxel Thiotepa		(287)	(116 - 196)	(137)	activity	
<b>UGT1A1</b>	Irinotecan Etoposide	UGT1A1*6	0% (50 - 147)	13%– 23% (42)	0% (148)	Decreased activity	[76, 112, 113, 139]
		UGT1A1*28	29.5 - 39% (71 - 202)	13.3%– 33% (30)	40% - 43% (54)	Decreased activity	

**Table 2: Polymorphisms in drug transporters [140]**

Transporters Protein	Gene symbol	Amino acid variants	African Americans	European Americans	Asians
OCT1	<i>SLC22A1</i>	Val408Met	26.5%	40.2%	23.8%
OCT2	<i>SLC22A2</i>	Ala270Ser	11%	15.8%	8.6%
OATP1A2	<i>SLCO1A2</i>	Ile13Thr	2.5%	16.3%	0%
OATP1B1	<i>SLCO1B1</i>	Asp130Asn	27.2%	44.1%	20%
BSEP	<i>ABCB11</i>	Ala444Val	47%	42.9%	33.3%
MRP4	<i>ABCC4</i>	Lys304Asn	18.1%	8.7%	22.5%
MRP6	<i>ABCC6</i>	Val614Ala	41.2%	41.9%	14.2%
BCRP	<i>ABCG2</i>	Gln141Lys		8.1%	40.8%

**Comment [A4]:** Table 3 – really just a rehash of some of the info in table 1 but might placate reviewer 1?

**Table 3: Chemotherapeutic drugs metabolised by multiple enzyme pathways**

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<b>Drug</b>	<b>Enzymes Involved in Metabolism</b>
<u>Tamoxifen</u>	<u>CYP2D6</u> <u>CYP3A4</u> <u>CYP3A5</u> <u>CYP2B6</u> <u>CYP2C9</u> <u>CYP2C19</u> <u>CYP2C8</u>
<u>Cyclophosphamide</u>	<u>CYP2B6</u> <u>CYP2C8</u> <u>CYP2C9</u> <u>CYP2C19</u> <u>CYP3A4</u> <u>CYP3A5</u>
<u>Imatinib</u>	<u>CYP1A1</u> <u>CYP2C9</u> <u>CYP2C19</u> <u>CYP2D6</u> <u>CYP3A4</u> <u>CYP3A5</u>
<u>Gefitinib</u>	<u>CYP1A1</u> <u>CYP2D6</u>



	<u>CYP3A4</u> <u>CYP3A5</u>
<u>Etoposide</u>	<u>CYP3A4</u> <u>CYP2C9</u> <u>CYP3A5</u> <u>UGT1A1</u>
<u>Ifosfamide</u>	<u>CYP2C8</u> <u>CYP2C19</u> <u>CYP3A4</u> <u>CYP3A5</u>
<u>Paclitaxel</u>	<u>CYP3A4</u> <u>CYP2C8</u> <u>CYP3A5</u>
<u>Irinotecan</u>	<u>CYP3A4</u> <u>CYP3A5</u> <u>UGT1A1</u>
<u>Erlotinib</u>	<u>CYP3A4</u> <u>CYP1A1</u>
<u>Docetaxel</u>	<u>GST</u> <u>CYP3A5</u>
<u>Vincristine</u>	<u>CYP3A5</u> <u>CYP3A4</u>

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