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PHARMACOGENOMICS OF CYTOCHROME P450 FAMILY ENZYMES: IMPLICATIONS FOR DRUG-DRUG INTERACTION IN ANTICANCER THERAPY

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ABSTRACT: *In the oncology field, predictive markers allow physicians to improve the efficacy of cancer therapy, and prognostic markers allow for selection of patients with high risk of cancer recurrence for treatment, and those with low risk of recurrence for less intensive treatment or observation only.*

This review provides an overview on the commonly occurring, functionally and/or clinically relevant genetic polymorphisms within the genes encoding Cytochrome P450 (CYP) super-family. In particular, the genetic variations in the CYP2D6 gene and the pharmacokinetics and/or response of Tamoxifen-based chemotherapy have been highlighted. Further, effective re-evaluation of drug design based on CYP enzymes may eventually be personalized and individualized to the patient for maximum efficacy of the therapies.

KEY WORDS: *Pharmacogenetics, Tamoxifen, Genotyping methods, Cost-effectiveness, Genotyping cost.*

INTRODUCTION

The new era of pharmacogenomics, which integrates the exclusivity of an individual genetic profile with respect to the pharmacokinetics and pharmacodynamics of a drug, provides greater safety and efficacy in drug therapy[1]. Personalized medicine is particularly important in oncology whereby most clinically used anticancer drugs have a narrow therapeutic window, exhibit a large inter-individual pharmacokinetic and pharmacodynamic variability. This variability can lead to therapeutic failure or severe toxicity. Understanding how genetic variations influence drug disposition and action could help in tailoring cancer therapy based on individual's genetic makeup. Pharmacogenomics is the study of how variations in the human genome affect the response to medications. Each drug, after it distribution in the body, interacts with numerous proteins, such as

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carrier proteins, transporters, metabolizing enzymes, and multiple types of receptors. These protein interactions determine drug pharmacokinetics (i.e., drug absorption, distribution, metabolism, and excretion) and pharmacodynamics (i.e., target site of action, pharmacological and toxicological effects)[2]. Moreover, drugs trigger downstream secondary events which may impact additional gene or protein expression responses and can also vary among patients. As a result, the overall response to a drug is determined by the interplay of multiple genes that are involved in the pharmacokinetic and pharmacodynamic pathways of a drug. In general, important genetic variation in drug effect can be envisioned at the level of drug metabolizing enzymes, drug transporters, and drug targets. This review provides an overview on the commonly occurring, functionally and/or clinically relevant genetic polymorphisms within the genes encoding Cytochrome P450 (CYP) super-family, with emphasis whereby genetic variations in these genes influence the pharmacokinetics and/or response of Tamoxifen-based chemotherapy[3].

CYP450 FAMILY

The most important Phase I enzymes that exhibit clinical relevant genetic polymorphisms are the cytochrome P450 (CYP) superfamily. The human CYP superfamily represents the most important system responsible for catalyzing the oxidation of a large number of endogenous and exogenous compounds including drugs, toxins, and carcinogens. In this superfamily, 57 genes and 58 pseudogenes have been identified, which are divided into 18 families and 43 subfamilies (http://drnelson.utmem.edu/cytochromeP450.html). Among them, three subfamilies of CYPs, including CYP1, CYP2, and CYP3, contribute to the oxidative metabolism of more than 90% of clinically used drugs and other xenobiotics[4].

The single nucleotide polymorphisms (SNP) within the CYP genes, which include gene deletions, missense mutations, deleterious mutations creating splicing defects or premature stop codon, and gene duplications, could produce abolished, reduced, normal, or enhanced enzyme activity. As a result, patients can be classified into four phenotypes based on the level of a CYP enzyme activity: poor metabolizer (abolished activity), intermediate metabolizer (reduced activity), extensive metabolizer (normal activity), and ultrarapid metabolizer (enhanced activity). It is expected that poor metabolizers would have higher concentrations of a drug that is inactivated by that enzyme pathway and therefore require a lower dose to avoid adverse reactions, whereas ultrarapid metabolizers would require a higher dose to achieve therapeutic effective drug concentrations. The opposite pattern of reactions is expected for a prodrug that undergoes metabolic activation. A prodrug may have little therapeutic effect in poor metabolizers, while producing a toxic level of active form in ultrarapid metabolizers. Substantial evidence suggests that genetic polymorphisms within the CYP genes have significant impact on drug disposition and/or response. The common functional SNPs in the major human CYP genes and their clinical relevance are summarized in table 1. Notably, the most pharmacologically and clinically relevant CYP polymorphisms are found in *CYP2D6*, *CYP2C9*, and *CYP2C19*. Among the Food and Drug Administration (FDA)-approved drug labels referring human genomic biomarkers, 62% are pertained to polymorphisms in the CYP enzymes, with *CYP2D6* (35%), *CYP2C19* (17%), and *CYP2C9* (7%) being the most common[4].

CYP2D6 is not inducible and therefore the variations in the enzyme expression and activity are largely attributable to genetic polymorphisms. The *CYP2D6* gene is highly polymorphic with more than 63 functional variants identified to date (http://www.cypalleles.ki.se). These alleles result in abolished, decreased, normal, or ultrarapid *CYP2D6* enzyme activity. The most important null alleles are *CYP2D6*4* (splicing defect) and *CYP2D6*5* (gene deletion); the common alleles with severely reduced enzyme activity are represented by *CYP2D6*10*, **17*, and **41*; duplication or multiduplications of active *CYP2D6* genes (e.g., *CYP2D6*1* × N (N ≥ 2)) result in ultrarapid enzyme activity[5]. The distributions of *CYP2D6* alleles exhibit notable interethnic differences. The nonfunctional allele *CYP2D6*4* is prevalent in Caucasians (allelic frequency, ~25%), while the reduced function alleles *CYP2D6*10* and *CYP2D6*17* are common in Asians (allelic frequency, ~40%) and Africans (allelic frequency, ~34%). As a result, poor metabolizers of CYP2D6, mainly resulted from null allele *CYP2D6*4*, have a higher frequency in Caucasians (5%-14%) compared with Africans (0%-5%) and Asians (0%-1%). Ultrarapid metabolizers of CYP2D6, resulted from gene duplication or multiple duplications, have a higher frequency in Saudi Arabians (20%) and black Ethiopians (29%) compared with Caucasians (1%-10%)[5]. The inter-ethnic difference in the *CYP2D6* genotypes may contribute to the inter-ethnic variations in the disposition and response of substrate drugs. *CYP2D6* is involved in the metabolism of ~25% of all drugs in clinical use, although it accounts for ~2% of total hepatic CYP content. *CYP2D6* genotype is of

TABLE 1. MOST COMMON POLYMORPHISMS IN THE MAJOR HUMAN CYP GENES: ALLELE FREQUENCY, FUNCTIONAL EFFECT, AND HIGHLIGHTS OF CLINICAL RELEVANCE

Common *allelic variants	Polymorphism/ substitution	Allele frequency (%)[a]			Functional effect[b]	Highlights of clinical relevancec
		Caucasian	Asian	African		
CYP1A1 group						Mainly expressed in extra hepatic tissues.
CYP1A1*2A	3698T>C	6.6–19.0	33–54	22–28	↑ Inducibility	CYP1A1, 1A2, and 1B1 play important role in the bioactivation of a variety of carcinogens.
CYP1A1*2B	I462V; 3698T>C	–	–	–	↑ Inducibility	↑Lung cancer risk generally associated with highly inducible or active CYP1A1 polymorphisms such as CYP1A1*2C.
CYP1A1*2C	I462V	2.2–8.9	28–31	0.0–2.7	↑ Activity	CYP1A1 genotypes also associated with risk to breast, prostate, and ovarian cancers, which are possibly related to estrogen activation.
CYP1A1*3	3204T>C	0	0	7.6–14.0	Normal	
CYP1A1*4	T461N	2.0–5.7	–	–	Normal	
CYP1A2						CYP1A2 accounts for ~13% of total hepatic CYP content.
CYP1A2*1C	–3860G>A				↓ Inducibility	High inducible *1F genotype associated with ↑clearance of CYP1A2 substrates (e.g., caffeine) after smoking or omeprazole treatment.
CYP1A2*1F	–163C>A	33	68		↑ Inducibility	*1K associated with ↓ in vivo caffeine metabolism.
CYP1A2*1K	Haplotype (–63C>A, –739T>G, –729C>T)	0.5			↓ Inducibility ↓ Activity	
CYP2A6 group						CYP2A6 accounts for 1%-10% of total hepatic CYPs.
CYP2A6*1 ×2	Gene duplication	1.7		0.4	↑ Activity	The frequency of CYP2A6 alleles has marked ethnic difference.
CYP2A6*2	L160H	1-3		<1	↓ Activity	CYP2A6*4 accounts for the majority of PMs in Asians.
CYP2A6*4	Gene deletion	0.5-1.0	7-22	15-20	Abolished activity	Because nicotine is converted to cotinine by CYP2A6, a high expression/activity of CYP2A6 is proposed to increase the susceptibility to nicotine addiction and the risk of tobacco-related cancers. Therefore, CYP2A6 genetic variation could play a role in nicotine addition and tobacco-related cancer risks.
CYP2B6						CYP2B6 is mainly expressed in the liver, accounting for 6% of total CYPs.
CYP2B6*4	K262R	5			↑ Activity	The anticancer drug CPA is bioactivated by CYP2B6. CYP2B6 polymorphisms would likely affect the PK and/or PD of CPA.
CYP2B6*5	R487C	11-14	1		↓ Expression	For example, CYP2B6*6 carriers exhibited ↑ CPA clearance and CPA 4-hydroxylation activity.
CYP2B6*6	Q172H; K262R	16-26	16		↑ Activity	CYP2B6 polymorphisms may affect the PK and therapeutic outcome of anti-HIV agents such as efavirenz and nevirapine. For example, CYP2B6 Q172H variant is associated with ↑ plasma concentrations of efavirenz and nevirapine.
CYP2B6*7	Q172H; K262R; R487C13	0			↑ Activity	

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Common *allelic variants	Polymorphism/ substitution	Allele frequency (%)[a]			Functional effect[b]	Highlights of clinical relevancec
		Caucasian	Asian	African		
CYP2C8						CYP2C8 accounts for ~7% of total hepatic CYP contents. CYP2C8*3 is associated with ↓ clearance of both R- and S-ibuprofen.
CYP2C8*2	I269F	0.4		18	↓ Activity	
CYP2C8*3	R139K; K399R	13	0	2	↓ Activity	
CYP2C8*4	I264M	7.5			↓ Activity	
CYP2C9						CYP2C9 accounts for ~20% of total hepatic CYP contents. CYP2C9*2 and *3 have been shown to affect the oral clearance of at least 17 different CYP2C9 substrate drugs, e.g., S-warfarin, celecoxib, ibuprofen, and phenytoin.
CYP2C9*2	R144C	13-22	0	3	↓ Activity	
CYP2C9*3	I359L	3-16	3	1.3	↓ Activity	
CYP2C9*5	D360E	0	2	0	↓ Activity	
CYP2C19						The PM phenotype of CYP2C19 occurs in 12%-23% of Asian population, while in 1%-6% of Caucasians and 1.0%-7.5% of black Africans. Polymorphisms in the CYP2C19 gene are known to affect the PK and/or response of several classes of drugs, including proton pump inhibitors (e.g., omeprazole) and barbiturates.
CYP2C19*2	Splicing defect; I331V	15	30	17	Abolished activity	
CYP2C19*3	W212X; I331V	0.04	5	0.4	Abolished activity	
CYP2C19*17	I331V	18	4		↑ Transcription	
CYP2D6						CYP2D6 accounts for ~2% of total hepatic CYP contents. However, it is involved in the metabolism of ~25% of all drugs in clinical use. Unlike other CYPs, CYP2D6 is not inducible, and thus genetic polymorphisms are largely responsible for the variation in enzyme expression and activity. CYP2D6 genotypes exhibit large interethnic differences: low frequency of PM in Asian (~1%) and African (0%-5%) population, compared with Caucasian (5%-14%). CYP2D6 genotype is of great importance for the PK and response of many drugs, including tricyclic antidepressants, antiarrhytmics, neuroleptics, analgesics, antiemetics, and anticancer drugs.
CYP2D6*3	Frameshift	1-2	<1		Abolished activity (PM)	
CYP2D6*4	Splicing defect	20-25	1	6-7	Abolished activity (PM)	
CYP2D6*5	Gene deletion	4-6	4-6	4-6	Abolished activity (PM)	
CYP2D6*10	P34S; S486T	<2	50	3-9	↓ Activity (IM)	
CYP2D6*17	T107I; R296C; S486T	<1		20-34	↓ Activity (IM)	
CYP2D6*41	R296C; splicing defect; S486T	1.3	2	5.8	↓ Activity (IM)	
CYP2D6*1 ×N, N ≥ 2	Gene duplication				↑ Activity (UM)	
CYP2D6*2 ×N, N ≥ 2	Gene duplication				↑ Activity (UM)	

Continued

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Common *allelic variants	Polymorphism/ substitution	Allele frequency (%)[a]			Functional effect[b]	Highlights of clinical relevancec
		Caucasian	Asian	African		
CYP3A4						CYP3A4 has the highest abundance in the human liver (~40%) and metabolizes over 50% of all currently used drugs. Genetic polymorphisms in CYP3A4 appear to be more prevalent in Caucasians than in Asians. There is no consensus on a direct functional or clinical association of CYP3A4 polymorphism. CYP3A4 polymorphism may have minor or moderate clinical relevance.
CYP3A4						
CYP3A4*1B	5′ flanking region	2-9	0	35-67	Altered expression	
CYP3A4*2	S222P	2.7-4.5	0	0	Substrate-dependent altered activity	
CYP3A4*3	M445T	1.1			↓ Activity	
CYP3A4*17	F189S	2.1			↓ Activity	
CYP3A4*18	L293P	0		1	↑ Activity	
CYP3A5						The clinical relevance of the CYP3A5 polymorphism is demonstrated by the fact that the PK of the immunosuppressive drug tacrolimus is associated with CYP3A5 genotype.
CYP3A5*3	Splicing defect	90	75	50	Abolished activity	
CYP3A5*6	Splicing defect	0	0	7.5	Severely ↓ activity	
CYP3A5*7	346Frameshift	0	0	8	Severely ↓ activity	
CYP3A7						CYP3A7 is a predominantly fetal enzyme. The *in vivo* functional effect of CYP3A7 SNP is demonstrated by the fact that carriers of CYP3A7*1C allele had significantly decreased endogenous level of DHEAS, (substrate of CYP3A7).
CYP3A7*1C	Promoter	3		6	↑ Expression	
CYP3A7*2	T409R	8	28	62	↑ Activity	

Notes: [a,b]Functional effect and Allele frequency data are obtained from the Human Cytochrome P450 (CYP) Allele Nomenclature Committee website (http://www.cypalleles.ki.se/); CPA, cyclophosphamide; CYP, cytochrome P450; DHEAS, dehydroepiandrosterone sulfate; IM, intermediate metabolizer; PD, pharmacodynamics; PK, pharmacokinetics; PM, poor metabolizer; UM, ultra rapid metabolizer.

great importance for the pharmacokinetics and response of many drugs, including tricyclic antidepressants, antiarrhythmics, neuroleptics, analgesics, antiemetics, and anticancer drugs[6].

The human *CYP2C9* and *CYP2C19* genes are highly homologous at the nucleotide level. The most common nonsynonymous *CYP2C9* polymorphisms, *CYP2C9*2* and *CYP2C9*3*, produce enzyme with differing affinity or intrinsic clearance for different substrates. While *CYP2C9*2* effects appear to be more substrate specific, *CYP2C9*3* variant exhibits reduced catalytic activity towards the majority of CYP2C9 substrates. The clinical importance of *CYP2C9* polymorphisms is exemplified by the dose adjustment of an oral anticoagulant warfarin based on CYP2C9 genotype. The patients carrying either*CYP2C9*2* or *CYP2C9*3* require a significantly smaller daily dose of warfarin to maintain desired therapeutic effects while avoiding severe toxicity, compared with patients carrying the wild-type *CYP2C9*[6]. With regard to *CYP2C19*, a splice site mutation in exon 4 (*CYP2C19*2*) and a premature stop codon in exon 4 (*CYP2C19*3*) represent the two most predominant null alleles. The allele frequence of of poor CYP2C19 metabolizers for *CYP2C19*2* and **3*, is about ~6%, ~1%, and 10% in Caucasians, Asians, and Africans, respectively. Including also *CYP2C19*4* and **6* alleles, ~8% of poor metabolizers in Caucasians can be detected. Generally, the poor metabolizer phenotype of *CYP2C19* occurs in 12%-23% of the Asian population, in 1%-6% of Caucasians, and in 1%-7.5% of black Africans. Polymorphisms in *CYP2C19* are known to affect the pharmacokinetics and/or response of several classes of drugs, including proton pump inhibitors (e.g., omeprazole), barbiturates, and anticancer drugs[6]. The clinical utility of germline markers predicting for treatment responses is less well established[7]. One of the most extensively studied examples is the relation between CYP2D6 activity and outcome[8].

EXAMPLE OF TAMOXIFEN

Tamoxifen is a selective estrogen receptor (ER) modulator. It represents a standard therapy for the treatment and prevention of ER-positive breast cancer. ER-positive breast cancers are often dependent on estrogen for growth. Selective drugs bind to ER ligand-binding domain and block the binding of estrogen. This prevents conformational changes of the ER and subsequently reduces or eliminates estrogen-driven proliferation of ER-positive tumors.

The CYP2D6 is responsible for the biotransformation of tamoxifen into its active metabolite, endoxifen. Decreased CYP2D6 activity, due to CYP2D6*10 polymorphism, has been previously thought to be associated with poorer clinical outcome in breast cancer patients treated with tamoxifen in adjuvant setting[9]. Whether variation in the dose of tamoxifen would affect the outcome remains not known. To complicate matters, the rates of adherence to hormonal therapy may affect tamoxifen efficacy. In a prospective observational trial, CYP2D6 extensive metabolizers had higher discontinuation rates at 4 months[10]. The extensive metabolizers who potentially may benefit from tamoxifen are also puzzlingly more likely to stop therapy early[10]. Currently, it is still recommended that patients taking tamoxifen avoid potent CYP2D6 inhibitors (i.e. fluoxetine, clopidrogel. Etc.). Although the specific CYP2D6 test has been approved by the Food and Drug Administration (FDA) for detection individual metabolizer status, the predictive value of CYP2D6 genotyping on tamoxifen outcome remains low, and more validation studies are needed.

Tamoxifen can be considered as a prodrug, which requires metabolic activation to exert its pharmacological activity. The metabolism of tamoxifen is complex and involves hepatic Phase I enzymes (including CYP3A4, CYP3A5, CYP2C9, CYP2C19, CYP1A2, CYP2B6, and CYP2D6, as well as flavin-containing monooxygenase 1 and 3) and Phase II enzymes (including SULT1A1 and UGTs). Specifically, tamoxifen is metabolized by hepatic CYP enzymes (mainly by CYP2D6 and CYP3A4/5) to form two main primary metabolites, 4-hydroxytamoxifen and N-desmethyltamoxifen. The formation of these metabolites accounts for ~92% and ~7% of primary tamoxifen oxidation, respectively[11]. Both of these metabolites are further converted to abundant and pharmacologically active 4-hydroxy-N-desmethyltamoxifen (endoxifen). Endoxifen formation from N-desmethyltamoxifen is almost exclusively catalyzed by CYP2D6, and formation from 4-hydroxytamoxifen by CYP3A4/5. In addition, tamoxifen and its metabolites undergo Phase II metabolism including sulphation and glucuronidation. Endoxifen and 4-hydroxytamoxifen show much greater affinity for the estrogen receptor than tamoxifen. While 4-hydroxytamoxifen and endoxifen have a similar anti-estrogen activity, endoxifen plasma concentrations are 6- to 12-fold higher than those of 4-hydroxytamoxifen, suggesting endoxifen is the predominant and crucial active metabolite responsible for the *in vivo* pharmacological activity of tamoxifen[12].

There is evidence that women with nonfunctional and reduced-function *CYP2D6* alleles appear to have significantly lower circulating

endoxifen concentrations than those with wild-type *CYP2D6*[13]. Similarly, concomitant CYP2D6 inhibitors, such as certain selective serotonin reuptake inhibitors (fluoretine and paroxetine), have been shown to reduce the plasma concentrations of endoxifen. Collectively, these data support the notion that low CYP2D6 activity, caused by genetic polymorphisms or drug interactions, leads to low levels of the active tamoxifen metabolite[14].

The effect of CYP2D6 activity on tamoxifen pharmacokinetics also translates into an effect on clinical outcome. Despite some conflicting data, the majority of retrospective studies suggest that the presence of nonfunctional or reduced-function alleles of CYP2D6 is associated with worse outcome of patients receiving tamoxifen[15].

Besides *CYP2D6*, genetic variations in genes encoding for other enzymes involved in tamoxifen metabolism as well as genes encoding for the drug target (i.e., estrogen receptor) may influence the efficacy and toxicity of tamoxifen. This may explain, at least in part, the discrepancies of results from different studies with respect to the role of CYP2D6 genotype in the clinical outcome of tamoxifen. Tamoxifen and its metabolites undergo Phase II metabolism by SULT1A1 and UGTs. Interindividual variation in the activity of Phase II enzymes may contribute to variability in circulating endoxifen levels and patient response to tamoxifen. It has been reported that women with highly active *UGT2B15* genotype (*UGT2B15*2/*2*) had a worse recurrence-free survival than those with wild-type alleles. Interestingly, a retrospective analysis of 337 tamoxifen-treated women with breast cancer has found that those with low-active *SULT1A1* genotype (*SULT1A1*2/*2*) have had approximately three times the risk of death than controls. One possible explanation for this observation could be that sulfation of tamoxifen metabolites (4-hydroxytamoxifen and endoxifen) by SULT1A1 forms highly reactive products leading to DNA adducts, and therefore, individuals with low-activity *SULT1A1* genotype have poor clinical outcomes[16].

In conclusion, tamoxifen metabolism is complex and involves multiple Phase I and II enzymes. Genetic variations in these metabolizing enzymes likely contribute to the variability in tamoxifen active metabolite concentrations and patient outcome. It is generally agreed that women with reduced CYP2D6 activity genotype appear to have lower circulating endoxifen concentration and are less likely to obtain therapeutic benefit from tamoxifen compared with those with normal CYP2D6 activity. However, because of the lack of concordant data, mandatory *CYP2D6* genotyping test to guide the selection and dose of tamoxifen is premature. Ideally, large, prospective clinical studies should be conducted to systematically assess the impact of multiple genetic polymorphisms within multiple genes involved in the disposition and action of tamoxifen on the clinical outcome of patients receiving tamoxifen.

EVALUATION COSTS OF PHARMACOGENOMICS

The finite nature of healthcare budget requires treatments and biomarkers to be cost effective. Pharmacogenomics fields can potentially reduce healthcare cost by allowing the clinician to identify patients who are most likely to benefit from treatment, thus reducing unnecessary treatments and minimize costs incurred during management of treatment related toxicities and hospitalizations.[17]

The prevalence of a marker is an important factor that needs to be considered when validation trials are designed to determine clinical cost-effectiveness. Many pharmacogenetic markers have a low frequency in the population, making difficult their validation and clinical implementation. E relevant example is the allelic frequency of DPYD*2A is only about 1.8% in European Caucasians and less than 1% in Asian populations[18]. The majority, up to two-thirds, of patients who experienced severe treatment toxicity after 5-fluorouracil do not have a molecular basis for DPYD deficiency[19].

The integration of PGs into the clinic is often delayed by the cost of testing or lack of reimbursement from public or private insurances. Many countries, especially developing ones, do not even have access to pharmacogenetic testing.

Several methods to assess the quality of cost-effectiveness, cost-utility and cost-benefit of PGs tests have become available. A relevant example is the National Institute for Health and Clinical Excellence (NICE). NICE forms a Diagnostic Advisory committee, which stimulates Pharma and Academic communities to produce a robust set of data, including the design and data source, for economic models of healthcare. In addition, NICE serve to better quantify the potential benefits of PGs testing in oncology[20]. However, limitations of individual economic evaluation models include the inability to capture important factors, such as, willingness of the patient to pay, psychological impact and patient preference.

Study focusing on the cost of genotyping are few. It has been demonstrated that the mean calculated cost per life-year gained by TPMT genotyping in acute lymphoblastic leukemia patients treated with 6-MP is € 2100, based on genotyping costs of € 150 per patient[21]. A more efficient PGs test is often not necessarily the cheapest test, but

one that predicts with more reliably the intended outcome, and allows for selection of the optimal treatment. With advances in technology, the cost and time of genotyping have dramatically decreased, with eventual realization of the "€20,00" per single polymorphisms[22]. In consideration of the dropping cost of genotyping, the incorporation of genomic scans in the patient evaluation becomes a dynamic and ongoing process, that should be constantly checked and updated by policy makers in accordance to the depreciating costs, to allow for more accessibility for genotyping and its benefits as more evidence becomes available[23].

CONCLUSIONS

Pharmacogenomics provides a unique approach toward investigating, appreciating, and therapeutically serving the cancer patient. This approach could allow the use of new natural remedies either to prevent or minimize toxicity[24]. Further, effective re-evaluation of drug design toward the generation of novel and specific therapies focused on enzyme pertaining to malignancy may eventually be personalized and individualized to the patient for maximum efficacy.

Author Disclosure:
The authors report no conflicts of interest in this work.

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