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Future Medicine for Today's Cancer Patients: Therapeutic Application of Pharmacogenomics in Oncology

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Abbreviations: TPMT: Thiopurine *S*-methyltransferase; UGT1A1: Uridine diphosphate Glucuronosyltransferase 1A1; K-RAS (v-Ki-ras2 Kirsten Rat Sarcoma viral oncogene homologue), BRAF: serine/threonine-protein kinase B-Raf; ABL: Abelson; BCR: Breakpoint Cluster Region; Ph1: Philadelphia chromosome; c-KIT: v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; DPD: Dihydropyrimidine Dehydrogenase; EGFR: Epidermal Growth Factor Receptor; 5-FU: 5-Fluorouracil; G6PDH: Glucose-6-Phosphate Dehydrogenase; HER: Human Epidermal Growth Factor Receptor; 6-MP: 6-Mercaptopurine; Ph1: Philadelphia; G6PD:Glucose-6-Phosphate Dehydrogenase.

Pharmacogenomics utilizes genomic technologies to identify patient's genetic polymorphisms, making them more susceptible to developing certain diseases or impairing the pharmacologic function of, and therapeutic response to, specific drugs. The ultimate goal of pharmacogenomics is to focus therapy on specific receptors or targets in order to reduce adverse drug reactions (ADRs) and improve therapeutic outcomes by applying pharmacogenomics in selecting targeted pharmacotherapy for patients. Narrow therapeutic indices, low overall response rates, rapid and severe systemic toxicity, and unpredictable efficacy are all hallmarks of cancer therapies. Therefore, nowhere is pharmacogenomics research needed more than in cancer treatment to guide clinicians to better predict the differences in drug response, resistance, efficacy, and toxicity among chemotherapy and targeted-therapy patients, and to optimize the treatment regimens based on these differences [1]. For example, clinical evidence indicates that the steady-state levels of 6-mercaptoputine (6-MP, Purinethon) in acute lymphocytic leukemia (ALL) patients can range up to 10 fold or higher among cancer patients with the same administered drug dose because of the highly variable and polymorphic metabolic enzyme thiopurine methyltransferase (TPMT). It is critical for clinicians to identify those patients with TPMT polymorphisms and then adjust the dose of 6-MP accordingly [2]. Thus pharmacogenomics is the key to a simple question: what dose of chemotherapy is appropriate for a patient that may minimize side effects without compromising patient care? It is critical to integrate pharmacogenomics into the curriculum of nursing, pharmacy and medical education to fully prepare our future clinicians to embrace personalized medicine.

The field of Pharmacogenomics encompasses the interplay between the genome and the drug [3]. From its recent advances, we gain a deeper understanding of how the genetic variability within our population directs the pharmacokinetics and pharmacodynamics of drug therapy. To apply pharmacogenomics to cancer genetics, we need to understand how acquired (somatic) and inherited (germline) variations affect the efficacy and safety of drug therapy [4]. Acquired variations are those that apply to predicting drug efficacy and resistance (Pharmacodynamics), whereas inherited variation is the ability to identify the changes in drug metabolism (Pharmacokinetics). Pharmacogenomics is one of the key factors to take into consideration when designing and selecting a cancer therapeutic regimen. Figure 1 summarizes these factors that can potentially affect drug efficacy and toxicities of cancer treatments, including morphometric, demographic, physiologic and pathophysiologic, pharmacologic and pharmacogenomic factors [1]. In particular, there are multitudes of clinical evidence indicating that interracial and inter-individual polymorphisms in genes encoding for drug-metabolizing enzymes, drug transporters, and drug targets are linked to the toxic clinical presentation of cancer patients [1].

The application of pharmacogenomics in oncology is in the discovery of biomarkers that guide selective therapy, predict toxicities, and target the mechanisms of drug resistance. There are currently around 25 FDA approved targeted therapies that require genetic testing for biomarkers in order to determine appropriate patients who can receive them. Cutting edge pharmacogenetic research plays an essential role to identify these biomarkers that are critical for personalized patient treatments and enable clinicians to minimize the risk of one-size-fit-all or trial and failure patient care approaches. Since the FDA approved the first pharmacogenetic test (AmpliChip CYP450 Test) in 2004 to identify a patient's CYP2D6 and CYP2C19 genotype by analyzing DNA extracted from a whole blood sample, many protein and DNA based in vitro pharmacogenetic tests have been developed and approved by the FDA. Table 1 lists some examples for the FDA approved phamracogenetic tests for cancer patients [1,2-6].

Selective Biomarkers for Cancer Treatment

The study of pharmacogenomics in Oncology ushered in new therapies targeting susceptibilities in cancer cells, with the goal to spare normal cells and thereby create regimens that increase efficacy and decrease toxicities. Genetic testing of individuals for certain biomarkers allows the clinician to then tailor the treatment regimen to separate responders from non-responders, saving valuable time and limiting the toxicities associated with regimens not associated with this level of patient specificity. Examples of these biomarkers include EGFR, K-RAS, HER2, c-Kit, B-RAF, and BCR-ABL (Table 1).

The American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) guidelines recommend treatment regimens based on selective biomarkers for common

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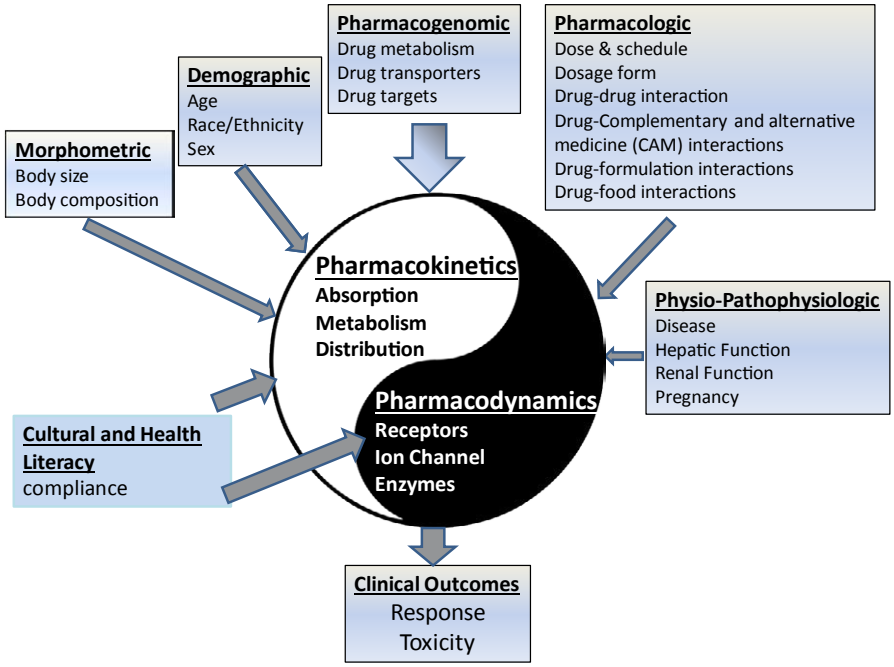

Figure 1: Factors Affect Drug Efficacy and Toxicities [1].

Types of Cancer	Related Biomarkers	Approved Tests	Related Drug Therapy	Examples of Chemotherapy Regimen
Breast Cancer	HER2/NEU	HercepTest	Trastuzumab (Herceptin) Pertuzumab (Perjeta) Ado-trastuzumab (Kadcyla) Laptinib (Tykerb)	Trastuzumab + Pertuzumab + Docetaxel AC → TH
	ESR1 PGR	ER and PGR Immunohistochemistry (IHC) Assay	Tamoxifen (Nolvadex) Fulvestrant (faslodex) Anastrozole (Arimidex)	Used as single agent
Colorectal Cancer	UGT1A1	UGT1A1 Molecular Assay	Irinotecan (Camptosar)	FOLFIRI
	EGFR and K-RAS mutation	DakoCytomation EGFr pharmDx and Nucleotide sequencing-high-resolution melting (HRM) analysis	Cetuximab (Erbitux) Panitumumab (Vectibix)	FOLFOX/FOLFIRI + Cetuximab FOLFOX/FOLFIRI + Panitumumab
Non Small Cell Lung Cancer (NSCLC)	*EGFR* and K-RAS mutation	DakoCytomation EGFr pharmDx and Nucleotide sequencing-high-resolution melting (HRM) analysis	Erlotinib (Tarceva) Gefitinib (Iressa) Afatinib (Gilotrif)	Used as single agent
	EML4-ALK fusion gene	Vysis ALK Break Apart FISH probe test	Crizotinib (Xalkori) Ceritinib (Zykadia)	Used as single agent
Chronic Myelogenous Leukemia (CML)	Ph1 chromosome	BCR/ABL test	Imatinib (Gleevec) Nilotinib (Tasigna) Dasatinib (Sprycel) Bosutinib (Bosulif) Panitinib (Iclusig)	Used as single agent
	UGT1A1	Invader UGT1A1 Molecular Assay	Nilotinib (Tasigna)	Used as single agent
Melanoma	BRAF	THxIDTM-BRAF Companion Diagnostic Test	Vemurafenib (Zelboraf) Dabrafenib (Tafinlar) Trametinib (Mekinist)	Dabrafenib + Trametinib

Table 1: Examples of Selected Clinically Valid Pharmacogenomic Tests Approved by the FDA for Cancer Patients [1,5,6].

cancers such as colorectal, lung, breast, melanoma, and certain leukemias. Common biomarkers screened for Non-Small Cell Lung Cancer (NSCLC) are EGFR and ALK mutations [1,6]. Based on amplification and/or mutation of the receptor, certain targeted agents recommended in the guidelines are cetuximab or panitumumab for EGFR amplification positive, erlotinib or afatinib for EGFR mutation positive patients, dabrafenib, vemurafenib, or tramenitinib for BRAF mutations, and crizotinib and ceritinib for ALK positive patients [6].

Another example is the Human Epidermal Growth Factor Receptor-2 (HER2) in breast cancer. Similar to EGFR, HER2 is tested for amplification by either immunohistochemistry (IHC) or the fluorescence in situ hybridization (FISH). A positive test indicates treatment with the biological agent trastuzumab, pertuzumab, ado-trastuzumab and lapatinib. Some other examples of biomarkers that are relevant to clinical practice are K-RAS in metastatic colorectal cancer, BRAF for metastatic melanoma, and the Philadelphia Chromosome

translocation causing the formation of the BCR-ABL fusion gene in Chronic Myelogenous Leukemia (CML) [1].

The Panitumumab Randomized Trial in Combination with Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy (PRIME) study established the predictive power of pharmacogenetic testing of RAS mutations (KRAS or NRAS) before utilizing Panitumumab in addition to FOLFOX regimen in patients with metastatic colorectal cancer. Progression-free survival (PFS) and overall survival (OS) were both increased in patients with non-mutated KRAS mutations with Panitumumab-FOLFOX compared with FOLFOX treatment alone, increasing the clinician's armamentarium against metastatic colorectal cancer [7-15].

Another example of how pharmacogenomics revolutionized the colon cancer field comes from the Crystal trial which evaluated the efficacy of cetuximab + FOLFIRI for 1st line treatment of metastatic colorectal cancer. The study compared FOLFIRI alone against FOLFIRI + cetuximab. The trial concluded in patients with KRAS wild type allele, the addition of cetuximab to FOLFIRI improved PFS and is an acceptable 1st line therapy for patients with KRAS wild type allele with metastatic colorectal cancer according to NCCN guidelines Table 2 [16].

Pharmacogenomic Biomarkers for Toxicities Associated with Cancer Treatments

Serious adverse drug reactions (ADRs) and dose-limiting toxicities (DLTs) are common with cytotoxic agents utilized in oncology treatment regimens. Toxicities such as severe myelosuppression, diarrhea, and nephrotoxicity can lead to treatment delays and/or dose reductions; subsequently decreasing the efficacy of treatment in a critical patient population. The genetic variability in drug-metabolizing enzymes (DMEs) between individuals is the major cause of drug

PGx Biomarker	Therapeutic Agents	Mutations to be Detected	Potential Clinical Impact	ASCO or NCCN Guidelines
EGFR (HER1) in NSCLC	Erlotinib (Tarceva), Gefitinib (Iressa) Afatinib (Gilotrif)	–Activating tumor EGFR mutations: mainly deletions in exon 19 and L858R –Resistance tumor mutation: T790M	–Presence of EGFR activating mutations predicts response to gefitinib and erlotinib –Presence of EGFR T790M mutation predicts resistance to gefitinib	Recommends testing for EGFR mutation before gefitinib, erlotinib, or afatinib treatment
ALK in NSCL	Crizotinib (Xalkori) Ceritinib (Zykadia)	EML4-ALK fusion genes	EML4-ALK fusion genes encoding chimeric oncoproteins with constitutive tyrosin kinase activities. ALK inhibitors decrease the growth and proliferation of ALK positive cancer cells.	Recommends testing for positive ALK before Crizotinib or ceritinib treatment.
HER2/neu (ErbB2) in breast cancer and gastric tumor	Trastuzumab (Herceptin), Pertuzumab (Perjeta), Ado-transtuzumab (Kadcyla) ,Lapatinib (Tykerb)	Use IHC or FISH to detect *HER2* gene overexpression	Overexpression of HER2 (+3 by IHC or FISH) predicts response to trastuzumab and lapatinib	–Recommends testing *HER2* expression for all breast cancer tumors and to use trastuzumab for patients with *HER2* overexpression –List lapatinib in combination with capecitabine as an option for trastuzumab-refractory breast cancer patients
K-RAS in metastatic colon cancer and SCCHN	Cetuximab (Erbitux), panitumumab (Vectibix)	Activating tumor K-RAS mutations: mainly exon 2 codon 12 and 13	–Presence of K-RAS mutations predicts nonresponse to cetuximab and panitumumab –Absence of K-RAS mutations predicts response to cetuximab and panitumumab	–Recommends genotyping tumor tissue for K-RAS mutation in all patients with metastatic colorectal cancer –Patients with known codon 12 and 13 K-RAS gene mutation are unlikely to respond to EGFR inhibitors and should not receive cetuximab
BCR-ABL or Philadelphia chromosome in CML	Imatinib (Gleevec), Nilotinib (Tasigna), Dasatinib (Sprycel)	–Detecting Philadelphia chromosome FISH –BCR-ABL mutations	–Presence of BCR-ABL or Philadelphia chromosome predicts response to imatinib and nilotinib –Presence of BCR-ABL mutation predicts resistance to imatinib; dasatinib overcome most BCR-ABL mutation (except T315I)	–Recommends cytogenetics and mutation analysis for patients receiving imatinib therapy and an 18-month follow-up evaluation with treatment recommendations based upon cytogenetic response [43] –Recommends dasatinib for the treatment of adults with chronic, accelerated, or myeloid or lymphoid blast phase chronic myeloid leukemia with resistance or intolerance to prior therapy, including imatinib
c-Kit in GIST	Imatinib (Gleevec)	Oncogenic c-Kit mutation in exon 9 and 11 D816V mutation of c-Kit	–Presence of a c-Kit mutation in exon 11 is associated with a more favorable prognosis and greater likelihood of response to imatinib therapy in patients with advanced GIST –Presence of D816V mutation of c-Kit predicts resistance to imatinib	–Mutational analysis of c-Kit is strongly recommended in the diagnostic work-up of GIST patients –In locally advanced, inoperable and metastatic GIST, imatinib 400 mg daily is the standard of care –In patients whose GIST harbors c-Kit exon 9 mutations, imatinib 800 mg daily is the recommended dose
BRAF	Vemurafenib (Zelboraf), Dabrafenib (Tafinlar) Trametinib (Mekinist)	BRAF V600E or V600K mutations	V600E is most common mutations in melanoma (80% of all mutations). V600K accounts for 16% BRAF mutations. Mutations lead to constitutive activation of BRAF serine/threonine-protein kinase.	FDA approved test for BRAF V600E or BRAF V600K mutations are required before the treatments of vemurafenib (V600E), dabrafenib (V600E) and trametinib (V600E/K).
PML-RAR-α translocation in APL	Arsenic trioxide (Trisenox)	t(15:17) translocation determined by FISH or PML-RAR-α gene expression	–Presence of PML-RAR-α fusion gene predicts clinical outcome following arsenic trioxide treatment	–Arsenic trioxide induces PML-RAR-α degradation –Diagnostic testing of PML-RAR-α is required for treatment with arsenic trioxide –Used for remission induction and consolidation in patients with relapsed or refractory APL characterized by PML-RAR-α expression

Table 2: Pharmacogenomic Biomarkers for Selection of Cancer Therapy [1,5,6].

toxicity [7]. Consequently, the majority of studies and standards of practice in Oncology focuses on DMEs. These enzymes can be broken into four categories of metabolizers: extensive, poor, intermediate, and ultra-rapid. Due to the nature of many chemotherapeutic agents having narrow therapeutic indices, the placing of individuals into one of these four categories through testing of pharmacogenetic biomarkers can direct selection of treatment that decreases toxicities and maintains maximal efficacy.

A prime example of this importance is in the metabolism of 6-Mercaptopurine (6-MP) by Thiopurine Methyltransferase (TPMT) in childhood patients with Acute Lymphoblastic Leukemia (ALL). The therapeutic effect of 6-MP relies on its activation by TPMT to 6-thioguanine. TPMT deficiency leads to severe myelosuppression, hepatotoxicity and increases the risk of secondary cancer formation [7]. Although partial deficiency is rare with only around 10% of Caucasians and total deficiency around 0.3%, the importance of genetic testing for TPMT deficiency is reflected in the FDA recommendation of a dosage reduction in patients with heterozygous or homozygous mutations. An example of the dose reduction for 6-MP based on TPMT phenotype variation is found on Table 3.

Other biomarkers of importance in reducing toxicity include UGT1A1 deficiency in Irinotecan and nilotinib, DPD deficiency in 5-Fluoruracil or Capecitabine, CYP3A4 variability in activation of Cyclophosphamide, and CYP2D6 variability in Tamoxifen therapies [7]. Dosing of 5-FU DPD phenotype can be found in Table 4 below.

Applying dose-finding studies directed by genotyping provide clinicians a tool for patients predicted to have DLTs an opportunity to avoid delays in therapy by tailoring individual doses. In a study by Satoh et al, patients with gastrointestinal cancer and homozygous UGT1A1×28 or UGT1A1×6 alleles –polymorphisms associated with severe myelosuppression from irinotecan administration-were given gradually increasing doses of irinotecan from 75 to 150 mg/m^2. Only 25% of patients completed two cycles of 150 mg/m^2, a dose used in FOLFIRI regimens, without treatment delays and dose reductions due to DLTs. In contrast, no DLTs occurred at doses of 100 to 125 mg/m^2, allowing the patients to receive subsequent treatment safely [17-20]. Incorporation of routine testing of DME variants in Oncology can lead to predictions in patient's response to therapy and direct treatment regimens that increase patient tolerability Table 5 [1,5-7].

Pharmacogenomic Biomarkers for Drug Resistance of Cancer Treatments

Multi-drug resistance (MDR) in Oncology can be assessed through genetic testing of biomarkers and guide the clinician in patient-specific therapies. Key contributors to MDR in cancerous cells are the drug transporters of the Adenosine Triphosphate (ATP)-Binding Cassette (ABC), most notably ABCB1 also referred to as P-glycoprotein (P-gp) and ABCG2. Commonly seen in MDR tumor cells are over-expression of P-gp or ABCG2 causing efflux of many structurally ubiquitous cytotoxic agents such as the taxane and anthracycline classes of chemotherapeutics [7-9]. Other contributors to drug resistance relate to DNA repair enzymes and enzymes responsible for detoxification. The endonuclease excision repair cross-complementing group 1 (ERCC1) is a biomarker related to oxaliplatin resistance through its important role in the mechanism of nucleotide excision repair (NER). Variants of this enzyme such as ERCC-118 T/T lead to increased production of ERCC1 that counteracts oxaliplatin's ability to induce apoptosis through crosslinking with DNA [10]. Glutathione-S-Transferase (GST) enzymes play a role in detoxification of cytotoxic agents such as cyclophosphamide and platinum-based agents. One example is with patients receiving the FOLFOX chemotherapy regimen, where the GSTP1-105×G allele lead to an increase in development of neurotoxicity, a complication of the oxaliplatin component [10-11]. Pharmacogenomics, specifically biomarker screening, is a powerful tool for the clinician to understand the basis behind drug resistance in Oncology and create patient-specific drug regimens that maximize efficacy and decrease toxicity.

Prospective Challenges

The application of Pharmacogenomics in Oncology to predict patient responsiveness is well established in both the ASCO and NCCN guidelines to serve clinicians in evidence-based treatment options. The goal of pharmacogenomics is to provide patient-specific therapy options that both increase efficacy and decrease toxicity. To meet this goal, numerous biomarkers have been discovered, leading the way to

Phenotype	Implications	Dosing recommendations
Homozygous wildtype (Normal TPMT activity)	Lower concentration of toxic metabolites of 6MP	Start 6MP with normal dose. Allow 2 weeks to reach steady state before adjusting dose
Heterozygous (Intermediate TPMT activity)	Moderate concentration of toxic metabolites of 6MP	Start with reduce dose of 6MP (30-70% of full dose) and adjust dose based on toxicities Allow 2-4 weeks to reach steady state before adjusting dose
Homozygous mutant or variant type (Low or deficient TPMT activity)	High concentration of toxic metabolites of 6MP	Start with heavily reduced dose (reduce dose by 10 fold) and adjust dose based on toxicities Allow 4-6 weeks to reach steady state before adjusting dose

Table 3: Clinical recommendation of 6MP based on TPMT phenotype.

Phenotype	Implications	Dosing recommendations
Homozygous for wild type allele (High DPD activity)	Normal DPD activity, normal risk of 5-FU toxicity	Use label-dose
Heterozygote (Intermediate DPD activity)	Decreased DPD activity, increased risk for severe or fatal 5-FU toxicities	Start with at least 50% reduction of starting dose. May titrate up the dose based on toxicities
Homozygous for variant or mutant (Deficiency of DPD activity)	No DPD activity, high risk for severe or fatal 5-FU toxicities	Use alternative drug

Adapted from Clinical Pharmacogenetics Implementation Consortium Guidelines [18]

Table 4: Clinical recommendation of 5-FU dosing based on DPD phenotype.

PGx Biomarkers	Therapeutic Agents	PK/PD impact	Frequency of variant poor-metabolism phenotype	Clinical Impact
UGT1A1 (UDP-glucuronyl-transferase) [5,6]	Irinotecan (Camptosar), Nilotinib (Tasigna)	Increased systemic exposure to SN-38 with UGT1A1*28	Deficiency of the enzyme may occur in 35% of Caucasians and African-Americans	Homozygous UGT1A1*28 genotype is a risk factor for severe diarrhea, neutropenia at doses > 200 mg/m^2
DPD (Dihudropyrimidine) [7,8]	Fluorouracil (5-FU) (Adrucil), Capecitabine (Xeloda)	Mutation causes systemic increase in 5-FU	3% of the Caucasians populations may have deficiency of this enzyme	Deficiency can lead to fatal neurological and hematological toxicities Grade 3 diarrhea and hand-foot syndrome linked with FU plasma levels more than 3 mg/L in males.
TPMT (Thiopurine methyltransferase) [2,4,9]	6-mecaptopurine (6-MP, Purinethol) Cisplatin	TPMT inactivates 6-MP, low or absent TPMT activity increases systemic drug exposure. TPMT (rs12201199) and COMT (rs9332377) have been associated with higher incidences of ototoxicity [13,14]	Approximately 10% of Caucasians are PM of this enzyme, about 0.3 of the patients have complete deficiency of the enzyme	Patients with low or absent TPMT activity are at an increased risk of developing severe, life-threatening myelotoxicity. Dose adjustment required. No current recommendation from FDA but it may be possible to identify individuals with higher risk of ototoxicity.
G6PD	Rasburicase (Elitek)	Deficiency in G6PD results in deficiency of NADPH which is involved in protecting erythrocytes from oxidative stress	G6PD deficiency is X-linked genetic trait. Higher prevalence in Mediterranean basin, Southeast Asia, Africa, and India.	FDA recommends not to administer rasburicase to patients with G6PD deficiencies, which may trigger acute hemolysis.

Table 5: Examples of Pharmacogenomic Biomarkers for Prevention of Toxicities in Cancer Therapy [1,5,6,7].

targeted drug therapies. The success of selective biomarkers in predicting response is currently not witnessed in the application of biomarkers that limit drug toxicity and resistance. An issue with wide acceptance of biomarkers in national guidelines and clinical practice is the scarcity of randomized controlled trials for every biomarker discovered [1,7]. Small sample sizes and the multitude of biomarkers make it difficult to conduct studies in pharmacogenomics at a scale the represents the population. Another area of caution is the wide acceptance of utilizing genetic tests without the proper recommendations and randomized controlled trials. This is echoed in the study by Peppercorn et al. where oncologists were evaluated in regards to genetic testing of CYP2D6 variants and tamoxifen therapy while the current understanding of the implications in pharmacotherapy were still evolving. What the authors found were 31% of oncologists used the commercially available test for CYP2D6 variants and 56% stated they would order the test outside of a clinical trial if requested by a patient [13].

One of the biggest hurdles for the widespread use of pharmacogenetic testing is the economical impact of routine commercial testing on the healthcare system. A recent review by Frank et al. [20] on the cost-effectiveness of pharmcogenomic profiling in metastatic colorectal cancer concluded that due to the increasing complexity of treatment choices, analyses of cost effectiveness and reimbursement decisions, a consensus guideline for health economic evaluations is desperately needed to create a standard approach missing from current economic studies. Nevertheless, genetic testing of biomarkers in predicting patient response is crucial to developing patient specific treatment plans in a patient population where time is of the essence. The success of applying pharmacogenomics in predicting response to treatment and its wide acceptance in national guidelines reinforces the importance of further studies in larger populations on drug toxicity and resistance. There are still many economic, ethical, legal and clinical issues needing to be addressed before pharmacogenomics is fully integrated in the care of cancer patients [1,5,7].

References

1. Feng X, Brazill B, Pearson D (2011) Therapeutic Application of Pharmacogenomics in Oncology: Selective Biomarkers for Cancer Treatment. US Pharm 36: 5-12.
2. Shah RR (2005) Pharmacogenetics in drug regulation: promise, potential and pitfalls. Philos Trans R Soc Lond B Biol Sci 360: 1617-1638.
3. Monte AA, Heard KJ, Vasiliou V (2012) Prediction of drug response and safety in clinical practice. J Med Toxicol 8: 43-51.
4. Filipski KK, Mechanic LE, Long R, Freedman AN (2014) Pharmacogenomics in oncology care. Front Genet 5: 73.
5. Ventola CL (2011) Pharmacogenomics in clinical practice: reality and expectations. P T 36: 412-450.
6. Table of Pharmacogenomic Biomarkers in Drug Labeling. Science & Research (Drugs). U.S. Food & Drug Administration.
7. Feng X, Pearson D, Listiawan M (2012) Pharmacogenomic Biomarkers for Toxicities Associated with Chemotherapy. US Pharm 37: 2-7.
8. Kao CH, Hsieh JF, Tsai SC, Ho YJ, Lee JK, et al. (2000) Quickly predicting chemotherapy response to paclitaxel-based therapy in non-small cell lung cancer by early technetium-99m methoxyisobutylisonitrile chest single-photon-emission computed tomography. Clin Cancer Res 6: 820-824.
9. Robey RW, Honjo Y, Morisaki K, Nadjem TA, Runge S, et al. (2003) Mutations at amino-acid 482 in the ABCG2 gene affect substrate and antagonist specificity. Br J Cancer 89: 1971-1978.
10. Ruzzo A, Graziano F, Loupakis F, Rulli E, Canestrari E, et al. (2007) Pharmacogenetic profiling in patients with advanced colorectal cancer treated with first-line FOLFOX-4 chemotherapy. J Clin Oncol 25: 1247-1254.
11. Ansari M, Lauzon-Joset JF, Vachon MF, Duval M, Théoret Y, et al. (2010) Influence of GST gene polymorphisms on busulfan pharmacokinetics in children. Bone Marrow Transplant 45: 261-267.
12. Peppercorn J, Hamilton E, Marcom PK, Beskow L, Lyman GH (2013) Pharmacogenetic testing in the face of unclear clinical efficacy: lessons from cytochrome P450 2D6 for tamoxifen. Cancer 119: 3703-3709.
13. Yang JJ, Lim JY, Huang J, Bass J, Wu J, et al. (2013) The role of inherited TPMT and COMT genetic variation in cisplatin-induced ototoxicity in children with cancer. Clin Pharmacol Ther 94: 252-259.
14. Ross CJ, Katzov-Eckert H, Dubé MP, Brooks B, Rassekh SR, et al. (2009) Genetic variants in TPMT and COMT are associated with hearing loss in children receiving cisplatin chemotherapy. Nat Genet 41: 1345-1349.
15. Douillard JY, Oliner KS, Siena S, Tabernero J, Burkes R, et al. (2013) Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. N Engl J Med 369: 1023-1034.
16. Van Cutsem E, Köhne CH, Hitre E, Zaluski J, Chang Chien CR, et al. (2009) Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med 360: 1408-1417.
17. Relling MV, Gardner EE, Sandborn WJ, Schmiegelow K, Pui CH, et al. (2013) Clinical pharmacogenetics implementation consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing: 2013 update. Clin Pharmacol Ther 93: 324-325.

18. Caudle KE, Thorn CF, Klein TE, Swen JJ, McLeod HL, et al. (2013) Clinical Pharmacogenetics Implementation Consortium guidelines for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing. Clin Pharmacol Ther 94: 640.

19. Satoh T, Ura T, Yamada Y, Yamazaki K, Tsujinaka T, et al. (2011) Genotype-directed, dose-finding study of irinotecan in cancer patients with UGT1A1*28 and/or UGT1A1*6 polymorphisms. Cancer Sci 102: 1868-1873.

20. Frank M, Mittendorf T (2013) Influence of pharmacogenomic profiling prior to pharmaceutical treatment in metastatic colorectal cancer on cost effectiveness : a systematic review. Pharmacoeconomics 31: 215-228.