



Review Article

Pharmacogenomics Driving Precision Cancer Medicine

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Abstract

Genetically-driven variations in the proteins associated with drug action and adverse effects can lead to a significant influence on cancer therapy. Cancer cells can accumulate a plethora of somatic mutations, beyond any existing germline variants, during their progression from normalcy to malignancy. The narrow therapeutic index that characterizes cancer drugs and the life-threatening failure of therapy all point to the importance of considering the inclusion of pharmacogenomics when treating cancers. This narrative review discusses the application, merits and challenges of pharmacogenomics knowledge using a few representative examples. The adoption of a properly considered pharmacogenomic program during cancer treatments can be life-saving and rewarding.

Keywords: Cancer Pharmacogenomics, Cancer pharmacogenetics, Precision medicine, Cancer precision medicine.

علم الصيدلة الجيني يقود الطب الدقيق للسرطان

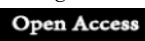
الخلاصة

يمكن ان تؤدي الاختلافات الوراثية في البروتينات المرتبطة بعمل الدواء وآثاره الضارة الى تأثير كبير على علاج السرطان. تتراكم في الخلايا السرطانية عدداً كبيراً من الطفرات الجسدية اثناء تقدمها من الحالة الطبيعية الى الحالة الخبيثة، بالإضافة الى ما يكون موجداً من متغيرات موروثية، يشير المؤشر العلاجي الضيق الذي تتميز به أدوية السرطان وكذلك تهديد الحياة عند فشل العلاج إلى أهمية مراعاة ادراج واستخدام علم الصيدلة الجيني عند علاج السرطان. تناقش هذه المراجعة السردية امكانية تطبيق ومزايا وتحديات علم الصيدلة الجيني باستخدام بعض الأمثلة الشائعة. يمكن ان يكون اعتماد برنامج علم الصيدلة الجيني المدروس بشكل صحيح اثناء علاج السرطان مفيداً لانقاذ ارواح بعض المرضى.

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INTRODUCTION

Cancer is a common complex disease that claims up to 10 million lives a year across the world and is a leading frontier in precision medicine [1-7]. It is characterized by the accumulation of genetic and epigenetic alterations in the genome of dividing cells. The role of epigenetic modifications in the initiation and progression of cancer and the impact of that on the therapy cannot be overlooked but will not be the focus of this review. Meanwhile, genetic alterations often result in variants in the gene they

occur in and consequently the protein it encodes can either be inherited in the germline DNA or acquired during the lifetime of the individual as somatic DNA changes [8-10]. Unlike other diseases, cancer genetics must take into account both of these sources of variability which could influence the efficacy and safety of therapy [11]. The current phase of the 1000 genome project, an international effort to sequence the genomes of at least 1000 individuals from different populations to improve our understanding of the genetic contribution to human health and

disease, has sequenced the genomes of 3202 persons and yielded 111 million single nucleotide variants (SNVs), 14 million insertions and deletions (INDELs) and 170,000 structural variants (SVs) [12] (<http://www.internationalgenome.org>). This translates to an average variability per genome of 4 million SNVs, 187,000 INDELs and 9000 SVs. The term single nucleotide polymorphism (SNP) also refers to a single base variation but is limited to inherited mutations that are present in at least 1% of the population thus making the term SNV more comprehensive. The genes carrying variants with anticipated influence on drug response and adverse effects are sometimes referred to as “pharmacogenes”. It is estimated that 99% of the human population carry at least one actionable variant within 13 of the documented pharmacogenes [13,14]. In addition to variants, the term “allele” is more than often mentioned in the literature. As human cells are usually diploid, having two copies of the DNA sequence, an allele represents a single copy of any sequence. The fundamental aspects of linking the ingestion of foreign material with the development of adverse effects can be traced back to over 2500 years ago when it was noted that certain individuals who consume fava beans can become ill [14]. We now know that this illness, favism, is due to the deficiency in the enzyme glucose-6-phosphate dehydrogenase (G6PD), caused by variants in the gene encoding this enzyme, in people consuming fava beans. It was not until 1959 that the term pharmacogenetic was coined to describe the field of how genetic variations in drug-metabolizing enzymes, receptors, transporters and targets interact to produce phenotypes such as drug response and toxicity [15-17]. The correlation between genetic variations and drug effects provided the clinical opportunity to stratify patients according to their

response to the medicine or the extent to they experience its toxicity. More recently, the word pharmacogenomics started to be more commonly employed in the literature as it is a broader-based term that encompasses all the genes in the genome with relevant effects on drug response and toxicity [18-20]. Pharmacogenomics also comprises the development of new drugs targeting specific disease-causing genes [21]. Although the terms pharmacogenetics and pharmacogenomics are often interchangeable, pharmacogenomics will be a term used in the remainder of this review. Knowledge of genetic variants is particularly relevant in the field of oncology as the therapeutic index of cancer drugs is often narrow, the consequence of toxicity might be severe and failed treatment is often life-threatening [19,22,23]. This review will look at the current state of pharmacogenomics in connection with the treatment of cancer and how this field is increasingly being employed in “personalizing” therapy and departing from a “one-size-fits-all” approach. The effect of individual variations in the rate of metabolizing anti-cancer drugs is illustrated in Figure 1 reflecting the need to personalize cancer therapy. The term “personalized medicine” is slowly being replaced by “precision medicine” as the former terminology has concerns about it being misinterpreted as medicine designed around a particular person [24]. Precision medicine is defined as the use of therapeutics that are expected to confer benefit to a subset of patients whose cancer displays specific molecular biomarkers as a result of the genetic variation [25,26]. The increasing and growing interest in characterizing new biomarkers for cancer have led to a paradigm shift away from nonspecific chemotherapies and toward precision treatment strategies based on the genomic profile of cancer [27,28].

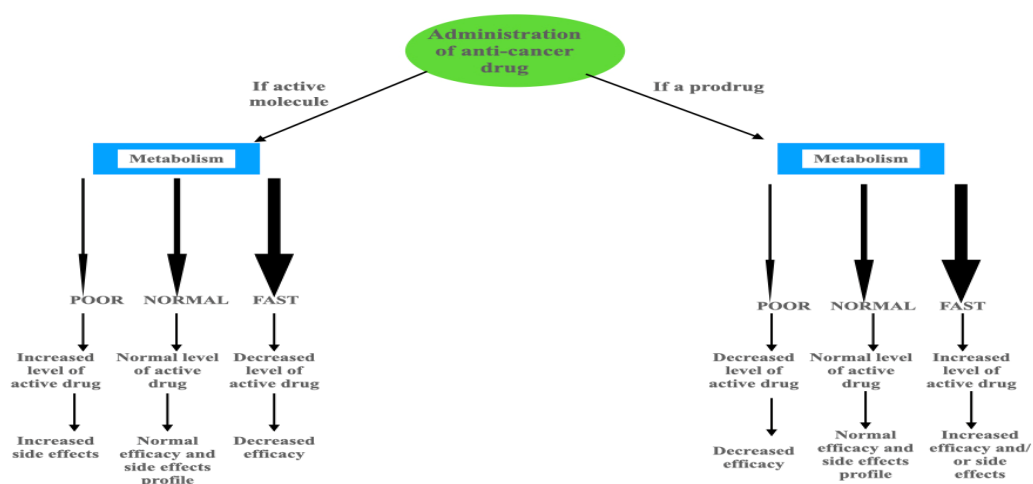


Figure 1

Figure 1: A schematic representation of the effect of metabolism on the administration of anti-cancer drugs.

This paradigm shift was largely helped with the advancement of new technologies enabling high volume testing and genome sequencing. A technological breakthrough in molecular testing also promoted the re-classification, diagnosis and prognosis of cancers as in the case of employing molecular biomarkers to assign a status to breast cancer independent of its tissue origin or morphology [29]. The classical morphology-based World Health Organization classification will have to be supplemented by genomic data for an optimal therapeutic strategy. Of all the United States 499 Food and Drug Administration (FDA) drug label warnings related to pharmacogenomic biomarkers, 213 (43%) are on drugs for the treatment of cancer [30].

METHODS

For this narrative review published peer-reviewed articles between the years 1995 and 2022 in PubMed and Google Scholar databases were examined. The keywords, given earlier, were used for selecting the appropriate references for inclusion. Studies of particular historic significance were also selected despite them falling below the lower date limit of the inclusion criteria. The chosen articles were then further refined by selecting those that are of a review nature or clinically dealing with the illustrative examples chosen in this manuscript.

DISCUSSION

Combination of germline and somatic alterations characterizes cancers

Cancer is different from other diseases when considering the application of pharmacogenomics knowledge to its treatment. Tumors develop due to the acquisition of various genetic and epigenetic modifications to the DNA of the cells during the lifetime of the individual and are collectively termed somatic mutations [31,32]. However, that individual was also born with inherited mutations, collectively termed germline mutations, that are present in all cells [33,34]. Accordingly, when cancer develops the tumor tissue will have a combination of somatic and germline mutations. Pharmacogenomics allows us to analyze the genomic data of cancer patients and select those subjects that might benefit from a particular treatment. The germline mutations are readily discernible from analyzing blood or buccal samples. Somatic mutations are however a little more difficult to establish and usually involve a more invasive tumor biopsy and subtraction of the background germline noise [17]. Clinically relevant germline variations may be valuable in determining the pharmacokinetic profile of cancer drugs and their response in addition to the identification of disease-susceptibility variants. On the other hand, somatic mutations within the tumor are useful in assessing the pharmacodynamic effects of the cancer drug and ultimately the tumor response to that drug [17,35]. Genomic variations in cancer, whether germline or somatic, may ultimately lead to a useful biomarker with a significant diagnostic and prognostic utility as well as being a predictive tool for the estimation of an individual's response to therapy [17] (Figure 2).

Chromosome number	2	6	7	9	12	17	19		
Biomarker	ALK	UGT1A1	TPMT	EGFR	BRAF	ABL	KRAS	HER2	CYP2D6
Type of alteration	Translocation	Repeats in promoter	Single nucleotide polymorphism (SNP)	Single and multiple nucleotide change	Single nucleotide change	Fusion	Single nucleotide change	Amplification	Single nucleotide polymorphism (SNP)
Detection	IHC ISH Seq.	Genot.	Genot. Phenot.	Seq.	Seq.	IHC ISH Seq. PCR	Seq.	IHC ISH	Genot.

Figure 2: Selected examples of cancer biomarkers and their common detection methods.

ALK=anaplastic lymphoma kinase; UGT1A1= (uridine diphosphate glucose pyrophosphorylase)-glucuronosyltransferase 1A1; TPMT=thiopurine methyltransferase; EGFR=epidermal growth factor receptor, BRAF=homolog B1 of v-raf murine sarcoma virus gene; ABL=homolog of Abelson murine leukemia virus gene; KRAS=Kirsten rat sarcoma virus; HER2=human epidermal growth factor receptor 2; CYP2D6=cytochrome p450 2D6; IHC=immunohistochemistry; ISH=in-situ hybridization; Seq=sequencing; Genot.=genotyping; Phenot.=phenotyping; PCR=polymerase chain reaction.

Germline Mutations

The current treatment for most cancers continues to include the use of cytotoxic chemotherapies which are imprecise in targeting the mutations that drive malignant transformation [22]. Studies on cell lines exposed to various chemotherapeutic drugs revealed that some cytotoxic effects are probably heritable [36-38]. This, together with observed variations in the toxicities and responses experienced by cancer patients following chemotherapy has led to a deeper search for chemotherapy-induced phenotypes. The following are selected examples of three pairs of cancer drugs and germline biomarkers that have a high level of supporting evidence pointing to their useful adoption in pharmacogenomics monitoring programs. These three pairs are: 1) 6-methylmercaptopurine (6-MP) and thiopurine

methyltransferase (TPMT), 2) Irinotecan and (uridine diphosphate glucose pyrophosphorylase)-glucuronosyltransferase 1A1 (UGT1A1) and 3) Tamoxifen and cytochrome P450 2D6 enzyme (CYP2D6).

6-methylmercaptopurine and TPMT enzyme

The chemotherapeutic agent 6-methylmercaptopurine (6-MP) belongs to a group of drugs known as Thiopurines. It is used for the treatment of acute lymphoblastic leukemia (ALL) after conversion into Thioguanine nucleotides and the incorporation of the latter into a newly-synthesized DNA in competition with the natural purine bases thus terminating the cell cycle and resulting in cancer cell death [39] (Figure 3).

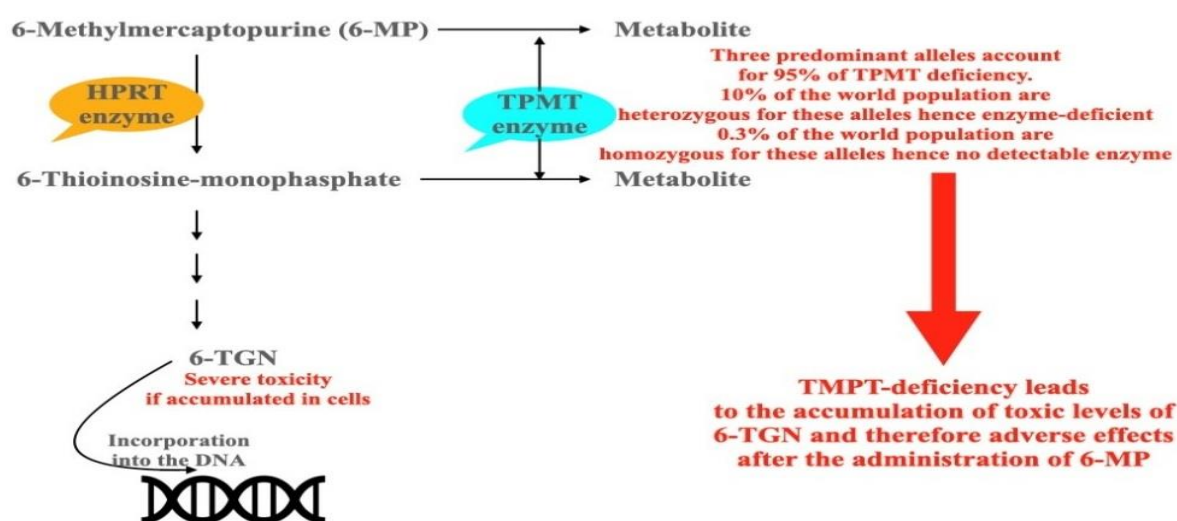


Figure 3: A simplified 6-methylmercaptopurine metabolism.

HPRT=hypoxanthine phosphoribosyl transferase; TPMT=thiopurine methyltransferase; 6-TGN=6-thioguanine nucleotide.

The Thiopurines, in general, have demonstrated wide inter-subject variations in response. Between 15% and 28% of patients experience adverse effects [40-43]. Moreover, about 9% of patients with inflammatory bowel disease (IBD) are classified as resistant to Thiopurines [44]. This inter-subject variability results mainly from Thiopurine metabolism and understanding that at the molecular level is a cornerstone for optimizing Thiopurine therapy. The drug, 6-MP, is metabolized to Thioguanine nucleotide by the enzyme hypoxanthine phosphoribosyl transferase (HPRT). However, another enzyme called thiopurine methyltransferase (TPMT) also metabolizes 6-MP, as well as an intermediate product of its conversion by HPRT, into Thioguanine [24,43,45]. Certain patients receiving 6-MP can experience severe myelosuppression and other adverse effects as a result of low metabolism of 6-MP by TPMT and the consequent accumulation of toxic levels of Thioguanine in the cells [24,43]. Three germline polymorphisms in TPMT account for over 90% of

the clinical variations [11,15]. Ten per cent of the population is heterozygous for these polymorphisms and require dosage reductions. It has been recommended that intermediate and poor metabolizers should start with 50% and 10% of the conventional dose of 6-MP respectively [46-48]. Chouchana *et al.* produced an algorithm for integrating pharmacogenomics into the initiation of 6-MP treatment of IBD [43]. The authors suggested a standard dose of 6-MP for patients exhibiting normal/high TPMT phenotype (homozygous wild-type genotype) and 30-70% of the standard dose for those showing intermediate TPMT phenotype (heterozygous genotype). For those patients with low/absent TPMT phenotype (homozygous mutant genotype), the authors advised considering alternative therapy. The algorithm of Chouchana *et al.* also involves carrying out regular blood and liver tests following the initiation of therapy to monitor response and toxicity and to fine-tune the dose [43]. Another metabolizing enzyme called nudix hydrolase 15 (NUDT15) also plays a role in the

conversion of 6-MP into Thioguanine. Reduced activity of NUDT15 in patients receiving normal doses of 6-MP can lead to the accumulation of excessive concentrations of Thioguanine and a higher risk of myelosuppression [49,50]. There are two ways to determine whether a subject is at risk of developing adverse reactions from 6-MP. The first method is by assessing the activity level of the TPMT enzyme (phenotype testing) and the second approach is through a genetic test (genotype testing) to identify genetic variations in the gene [51].

Irinotecan and UGT1A1 enzyme

Irinotecan is a prodrug licensed for the treatment of several malignancies including colorectal cancer and lung cancer. The promoter region of the

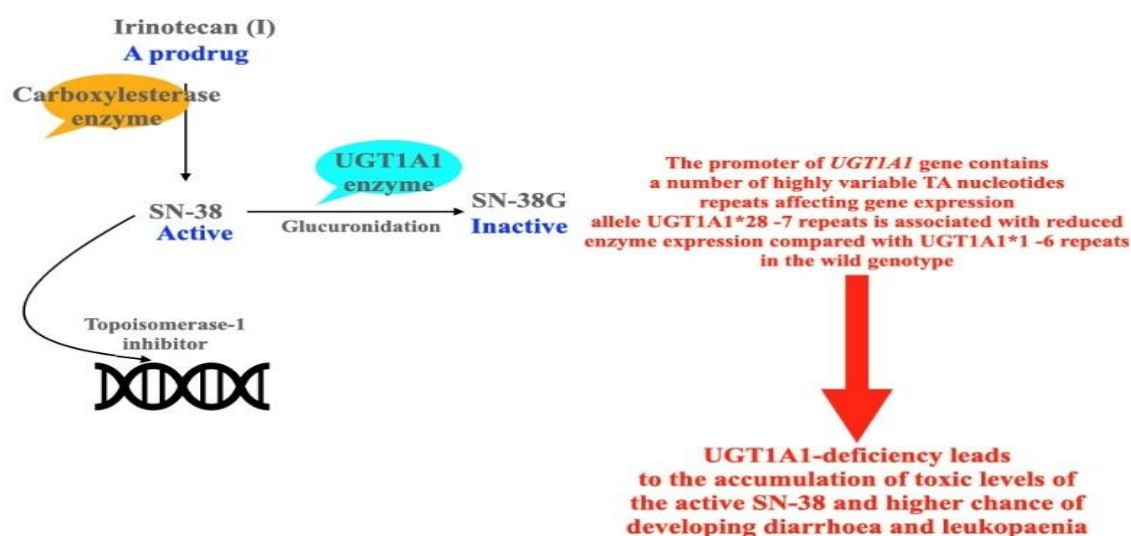


Figure 4: A simplified Irinotecan metabolism.

UGT1A1= (uridine diphosphate glucose pyrophosphorylase)-glucuronosyltransferase 1A1; SN-38=active form of Irinotecan; SN-38G=inactive form of irinotecan.

Degradation of SN-38 inversely correlates with the number of repeats in the *UGT1A1* gene and the expression of this gene is significantly reduced in individuals who are homozygous for the *UGT1A1**28 allele [54]. Several groups have found that a polymorphism with the *UGT1A1* gene correlated with those patients who had severe toxicity from Irinotecan [55]. Irinotecan toxicity tends to increase as degradation of SN-38 declines, because of the increased bioavailability of SN-38 and the resulting greater tissue exposure to this active metabolite [54,56]. This prompted the recommendation to reduce the initial dose of Irinotecan by 30%, in patients treated with higher than 250mg/m², then increase the dose progressively in response to neutrophil count [24]. The FDA also advocates testing for the *UGT1A1**28 allele before initiating therapy with Irinotecan and appropriate dose reduction in the homozygous carriers of this variant to minimize the likelihood of neutropenia [57]. There are no recommendations, however, on the extent of dose reduction. Importantly, both

UGT1A1 gene contains several highly variable germline TA dinucleotide repeats affecting gene expression [20]. The wild-type allele, referred to as *UGT1A1**1, contains six of these repeats. A commonly encountered mutated allele is *UGT1A1**28 which contains seven repeats and is associated with low expression levels compared to the wild-type [52]. Individuals homozygous for the *UGT1A1**28 allele are predisposed to serious adverse drug reactions including leukopenia (neutropenia) and diarrhea [53]. A low expression level of *UGT1A1* reduces the glucuronidation of SN-38, the active metabolite of Irinotecan, leading to its accumulation and a higher chance of developing adverse reactions from Irinotecan therapy (Figure 4).

neutropenia and diarrhea (the other common adverse event of Irinotecan therapy) is dependent on many other factors such as the duration of therapy, cycle of treatment and other operating key enzymes and transporters [58].

Tamoxifen and CYP2D6

Tamoxifen is a selective estrogen receptor modulator prodrug that is widely prescribed for the treatment and prevention of estrogen-positive (ER⁺) breast cancer [59,60]. The CYP2D6 is a key metabolic enzyme that is thought to take part in the metabolism of around 25% of all licensed drugs including Tamoxifen [61,62]. This enzyme is highly polymorphic with up to 10% of the world population carrying two non-functional alleles showing a pronounced decrease in the steady-state plasma concentration of the active metabolite [63-68]. On the other hand, 1-30% of the population (the wide range is dependent on ethnicity) carry duplications of functional alleles [14]. The CYP2D6 enzyme,

together with other cytochrome P450 enzymes, participates in the conversion of the prodrug,

Tamoxifen, into an active form known as Endoxifen [14,24,69,70] (Figure 5).

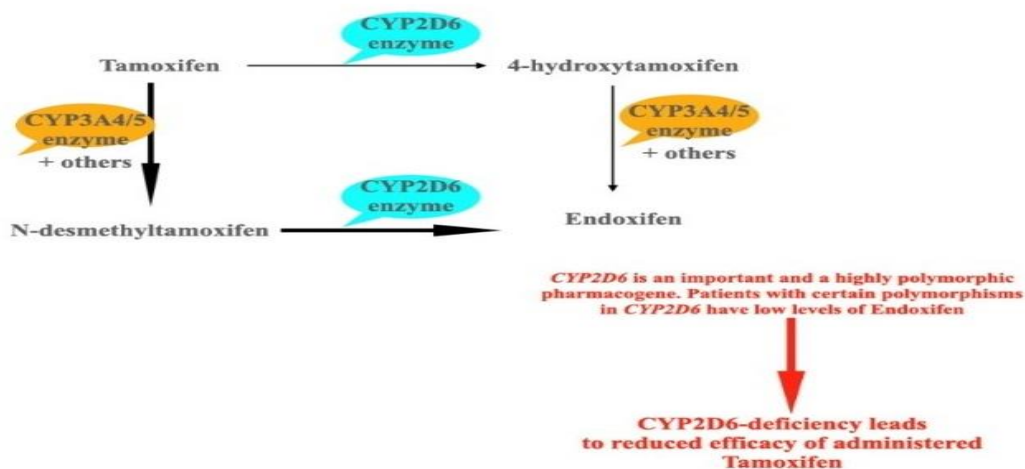


Figure 5: A simplified Tamoxifen metabolism. CYP3A4/5=cytochrome p450 3A4/5; CYP2D6=cytochrome p450 2D6.

Current evidence suggests that Endoxifen is the primary metabolite exerting the anti-estrogen effects of Tamoxifen [71]. Clinical trial results indicate that polymorphisms in CYP2D6 are associated with a significantly higher risk of recurrent breast cancer [72]. The standard of care dose of Tamoxifen is 20mg/day and avoiding concomitant administration of other drugs known to inhibit CYP2D6 activity. Poor metabolisers (PMs) of Tamoxifen typically have lower circulating levels of Endoxifen [73]. Various guidelines recommend that PMs receive alternative therapies such as aromatase inhibitors or if the latter is contraindicated an increase in Tamoxifen dose to 40mg/day should be considered [71]. About 100 polymorphic variants have been identified with the CYP2D6 enzyme and patients are typically categorized into four distinct CYP2D6 phenotypes: extensive metabolisers (EM), intermediate metabolisers (IM), poor metabolisers (PM) and ultra-rapid metabolisers (UM) [74]. The most common poor metabolizer allele is CYP2D6*4 which accounts for 75% of the poor metabolism of Tamoxifen in Europeans. The CYP2D6 *4/*4 homozygous genotype is associated with poor rates of breast cancer-free survival [75]. Genotype testing is normally carried out to assess the polymorphic status of the CYP2D6 gene [76].

Somatic Mutations

The application of pharmacogenomics in the management of cancer presents additional challenges because both germline and somatic mutations must be considered when selecting a biomarker [16]. Cancer cells carry the same germline mutations unless they somatically acquire deletions of these polymorphisms. However, the high level of genomic instability often acquired by malignant cells can give rise to additional tumor-

specific genomic alterations [77]. Of the 291 cancer genes reported by Futreal *et al.*, 90% of them were found to have acquired somatic mutations during the development of various tumors [33]. The field of cancer pharmacogenomics has gained a large amount of knowledge regarding these tumor-specific somatic alterations that are involved in driving cancer development and progression. Based on this knowledge, several targeted cancer drugs were developed such as the targeting of BCR-ABL protein in the Philadelphia chromosome-positive chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL). These precision drugs are aimed at targeting a particular genetic alteration in the cancer cells that are found to drive the progression of the malignancy (see Figure 6). The followings are six selected examples of precision drugs and their target genetic alteration (biomarkers) that were successfully developed and employed in the treatment of various malignancies: 1) Ceritinib/ALK (anaplastic lymphoma kinase), 2) Imatinib/BCR-ABL (breakpoint cluster region-homolog of Abelson murine leukemia virus gene), 3) Cetuximab/EGFR (epidermal growth factor receptor), 4) Dabrafenib/BRAF (homolog B1 of v-raf murine sarcoma virus gene), 5) Trastuzumab/HER2 (human epidermal growth factor receptor 2 sometimes referred to as ERBB2 or HER2/neu) and 6) Lapatinib/HER2.

Ceritinib and ALK

A somatic genomic alteration in the ALK gene in the form of rearrangement is an oncogenic driver in up to 5% of lung cancers [78-80]. This rearrangement is commonly encountered in young non-smoker or light smoker patients [78,80]. The most common gene rearrangement in lung cancers is the inversion of chromosome 2 where the ALK gene resides. This

inversion results in the fusion of the *ALK* gene with another gene called *EML4* (echinoderm microtubule-associated protein-like 4). There are 27 reported *ALK* fusion variants in non-small cell lung cancers (NSCLC) including 21 *EML4-ALK*

isoforms resulting in proteins with different signaling, tumorigenic potential and susceptibilities to *ALK* inhibitors [78,81]. The *EML4-ALK* fusion was found to occur in a subset (6.7%) of Japanese patients with NSCLC [82].

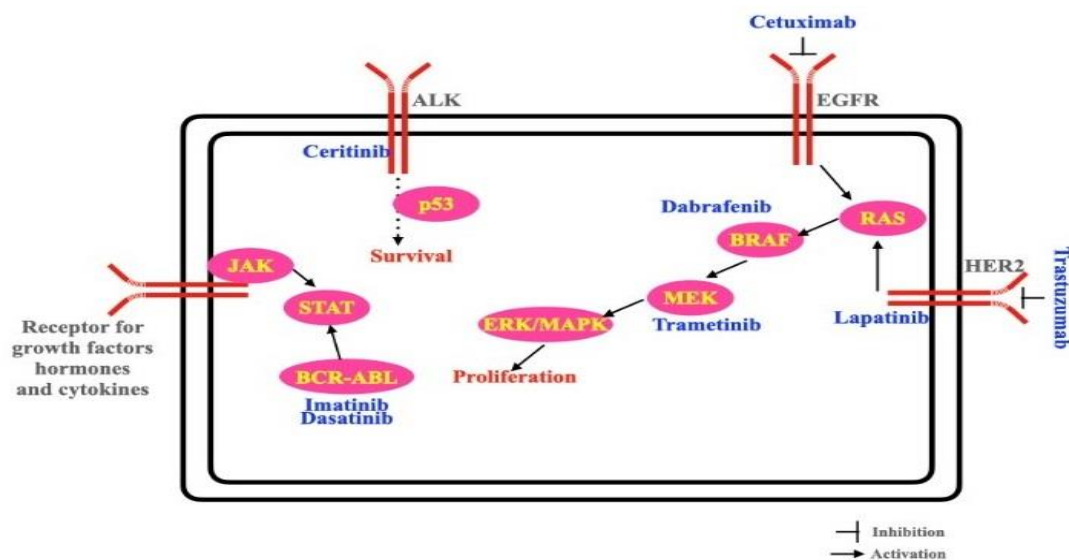


Figure 6: Selected cancer precision drugs and their targets.

ALK=anaplastic lymphoma kinase; *JAK*=Janus kinase; *STAT*=signal transducer and activator of transcription; *BCR-ABL*= breakpoint cluster region-homolog of Abelson murine leukaemia virus gene; *p53*=protein 53 (tumor suppressor); *EGFR*=epidermal growth factor receptor; *RAS*=rat sarcoma virus; *BRAF*=homolog B1 of v-raf murine sarcoma virus gene; *MEK*=mitogen-activated kinase; *ERK/MAPK*=extracellular signal-regulated kinase/mitogen-activated protein kinase; *HER2*=human epidermal growth factor receptor 2.

This group of patients did not have *EGFR* or *KRAS* (Kirsten rat sarcoma viral oncogene homolog) mutations, which could also be drivers of NSCLC indicating that lung cancers, with *ALK*-positive results only, are novel and unique subclass within NSCLC. The *EML4-ALK* fusion constitutively activates the *ALK* kinase which leads to the continuous activation of downstream signaling culminating in increased cell proliferation [83]. This situation can result in oncogenic addiction and dependency on *ALK* signaling for the survival of cancer cells. The addiction can be broken using *ALK* inhibitors thus providing a valuable tool for treating this subset of NSCLC [84]. Ceritinib is an oral *ALK*-inhibitor currently FDA-approved for the treatment of *ALK*-positive metastatic NSCLC. Fluorescent in-situ hybridization (FISH) assay is recommended to test for the presence of *EML4-ALK* fusion although an immunohistochemistry assay may be considered for rapid pre-screening [85]. Broad molecular profiling using next-generation sequencing (NGS) may also be used.

Imatinib and BCR-ABL

In 1960 a minute chromosome was consistently detected in the bone marrow cells of patients suffering from chronic myeloid leukemia (CML)

[86]. This chromosome was later named the Philadelphia chromosome (Ph chromosome) after the American city where it was first discovered. Further work revealed that the Philadelphia chromosome was the result of a reciprocal translocation between chromosome 9 and chromosome 22 [87]. This translocation resulted in the juxtaposition of the *ABL1* gene from chromosome 9 and another gene of unknown function which was called the *BCR* gene (breakpoint cluster region) from chromosome 22 to the Philadelphia chromosome [88,89]. This created a new fusion gene called *BCR-ABL1* which was found to be highly linked with CML. An association of the Philadelphia chromosome and acute lymphoblastic leukemia (ALL) was also discovered later on [90]. The Philadelphia chromosome is now known to be present in about 95% of CML and in about 30% of ALL cases [91,92]. The native function of the *ABL1* protein is a key to understanding how *BCR-ABL1* can promote malignancy. It appears that the *ABL1* protein serves as an important hub to integrate various extracellular and intracellular signals that control cell cycle progression and apoptosis [93,94]. Losing the function of *ABL1* leads to malignant transformation mainly through altering cell adhesion, constitutively activating mitogenic signaling and reducing apoptosis [95]. Targeting *BCR-ABL1* was considered a paradigm shift in

precision medicine as this fusion molecule was a single deregulated protein exhibiting gain of function in a subset of leukemia patients and not found in normal cells [94]. One of the common diagnostic tests employed for the detection of BCR-ABL1 uses reverse-transcriptase quantitative polymerase chain reaction (RQ-PCR) on whole blood or bone marrow sample [30].

Cetuximab and EGFR

The epidermal growth factor receptor (EGFR), also known as HER1 or ERBB1, is a member of the HER family of receptors which includes three others: HER2, HER3 and HER4 [96,97]. Each of these four receptors is structured in three parts: an extracellular part, a region that goes through the cell membrane anchoring the receptor to the cell and an intracellular domain harboring the tyrosine kinase activity. The external domain of EGFR can bind six EGF-like ligands which cause dimerization with other receptors of the HER family [98]. This dimerization leads to the activation of the tyrosine kinase through autophosphorylation and the subsequent activation of downstream signaling including that of the RAS protein. This activated cascade eventually leads to the alteration of cell functions such as proliferation, angiogenesis, apoptosis and motility [99,100]. Overexpression of EGFR can increase the possibility of dimerization and the subsequent activation of the downstream signaling pathway. Cetuximab is a monoclonal antibody that selectively binds to the extracellular domain of EGFR preventing it from binding to its normal ligands [101]. This blocks signal transduction and eventually exerts antitumor effects including cell-cycle arrest, induction of apoptosis, inhibition of angiogenesis and inhibition of metastasis [102]. Several studies highlighted that KRAS mutation status can negatively affect the antitumor activity of Cetuximab [102-104]. Therefore, only patients with wild-type KRAS will benefit from anti-EGFR therapies and that is reflected in Cetuximab labelling [30]. A qualitative immunohistochemical test is commonly employed to identify EGFR expression status in normal and malignant tissues.

Dabrafenib and BRAF

The BRAF protein is an intracellular kinase and part of the mitogen-activated protein kinase (MAPK) pathway. This pathway regulates important cell functions such as growth, division, differentiation and apoptosis [105]. Variation in BRAF is detectable in over 50% of malignant melanoma [106,107]. When the *BRAF* gene is mutated, the MAPK pathway is activated leading to uncontrolled cell growth and division [106,107]. The most common BRAF variant is V600E which results in the substitution of Valine for Glutamate at amino acid position 600 of the protein. This variant is

caused by a single nucleotide polymorphism (SNP) substituting Adenine for Thymine in the DNA sequence of the gene. The V600E variant is constitutively active with an increase in the kinase activity by as much as 500-fold compared to the wild-type and accounts for about 90% of BRAF mutations in Melanoma [106-109]. The second most common variant of BRAF is V600K where the amino acid Valine is replaced by the amino acid Lysine at the same position 600 of the protein. Other less common variants of BRAF also exist. Dabrafenib is a BRAF kinase inhibitor approved for patients with unresectable or metastatic melanoma [30,105,110]. The drug acts by inhibiting the signaling through the MAPK pathway leading to its antitumor effects. Dabrafenib is indicated as a single agent for the treatment of melanoma with BRAF V600E. It is also indicated in combination with Trametinib (an inhibitor of MEK kinase, which is located downstream of BRAF) for the treatment of melanoma with BRAF V600E or BRAF V600K [105]. Therefore, it becomes necessary to establish not only the mutation status of BRAF but also the type of variant before initiating treatment to effectively target the root cause of the malignancy. Another interesting point to make here is that Dabrafenib has a potential risk to cause hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency [105]. Patients with this deficiency need to be monitored for signs of hemolytic anemia and screening for this genetic abnormality is also recommended. The FDA label states that BRAF mutation status should be confirmed using an approved test before starting treatment with Dabrafenib [30]. A real-time PCR is used for the detection of BRAF V600E and BRAF V600K as an aid in selecting melanoma patients with tumours carrying these mutations to be assigned to the appropriate treatment.

Trastuzumab and HER2

As indicated earlier HER2 is a member of the HER family of receptors which include three other proteins namely: HER1, HER3 and HER4. A commonly encountered mechanism for the upregulation of HER2 signaling is through the formation of homodimers or heterodimers with other members of the HER family of receptors which activates downstream pathways influencing proliferation, differentiation, migration and apoptosis [111,112]. Amplification of the *HER2* gene and/or overexpression of its protein has been demonstrated in 15-20% of breast cancers [113]. This upregulation is associated with poor prognosis, increased risk of cancer recurrence and lower survival thus it is essential to establish HER2 protein overexpression or *HER2* gene amplification for initial therapy with Trastuzumab [114]. Clinical studies have shown that cancer patients with tumours exhibiting high HER2 protein overexpression and/or

amplification of the *HER2* gene benefit most from Trastuzumab therapy [115]. In addition to breast cancers, *HER2* was also found to be upregulated in gastric cancers [114]. Gastric cancers are a collection of heterogeneous diseases characterized by various genomic alterations and one such alteration is the upregulation of *HER2* which was established as a valid therapeutic target for esophagogastric cancers. Trastuzumab was the first humanized monoclonal antibody that binds specifically to the *HER2* receptor and suppresses cell proliferation that is driven by the overexpression of *HER2* protein [116-118]. Trastuzumab efficacy is thought to be largely due to the engagement of Fc gamma receptors on immune effector cells leading to the destruction of the tumor by a process known as antibody-dependent cell-mediated cytotoxicity [119]. Studies on the pharmacogenomics of Trastuzumab have mostly focused on polymorphisms of the Fc gamma receptors. The results of these investigations have not been conclusive which precludes the use of pharmacogenomic tests on the variants of the Fc receptors to predict Trastuzumab response [120,121]. The combination of Trastuzumab with chemotherapy has led to an even better reduction in breast cancer recurrence and mortality in *HER2* amplified tumours particularly in an adjuvant setting [122-124]. Resistance to Trastuzumab is not uncommon and occurs predominantly through *HER2* signaling pathways [125,126]. Truncated forms of *HER2* lacking targets for Trastuzumab constitute an active form of signaling due to the formation of stable *HER2* homodimers [127,128]. Establishing the presence of amplification of the *HER2* gene and/or overexpression of its protein is usually carried out using one or more of the following methods: a) *HER2* immunochemistry test to semi-quantitatively determine the *HER2* status in cancer tissue in comparison with control slides demonstrating *HER2* expression at 0, +1, +2 and +3 intensities., b) next-generation sequencing test for the detection of substitutions, insertions, deletions and copy number changes and c) fluorescent in-situ hybridization (FISH) or a variation of it called chromogenic in-situ hybridization (CISH) for the quantitative determination of *HER2* in a cancer tissue specimen [30].

Lapatinib and *HER2*

Lapatinib is a small molecule inhibitor of the tyrosine kinase domain not only *HER2* but also *HER1* [129]. Lapatinib binds to the ATP-binding site of the tyrosine kinase thus blocking phosphorylation and activation of that particular receptor. This drug was found active against Trastuzumab-resistant breast cancer [130]. Lapatinib is currently FDA-recommended to be used with either Capecitabine for the treatment of patients with advanced or metastatic breast cancer

whose tumours overexpress *HER2* or in combination with Letrozole (an aromatase inhibitor that works by lowering the amount of estrogen produced in the body) for the treatment of postmenopausal women with *HER2*-positive metastatic breast cancer that overexpresses *HER2* [30]. No specific testing is given by the FDA although the upregulation status of *HER2* can be established by similar tests as mentioned earlier. Women with *HER2*-positive breast cancer, judged by 3+ results through an immunohistochemistry (IHC) test alone or 2+ by an IHC test and gene amplification by FISH, showed an improved response in prolonging the time to tumor progression when Lapatinib was combined with Capecitabine (a chemotherapy drug). A randomized CT on women with *HER2*- and HR-positive metastatic breast cancers showed a significantly lower risk of disease progression when Lapatinib is used in combination with Letrozole in comparison with Letrozole alone [131,132].

Detection of Cancer Biomarkers

A cancer biomarker is a biological molecule usually found in body fluids or tissues reflecting the presence of cancer and can be employed for diagnostic, prognostic or predictive purposes [133]. Our main focus in this review is the predictive biomarkers allowing insight into the likely therapeutic response to targeted therapy and determining which cancer therapy has the potential to be most effective [133,134]. The use of biomarkers to guide patient treatment has been in use for over 30 years. Just to mention two examples: a) patients with ALL exhibiting the BCR-ABL biomarker would be offered Imatinib or other ABL tyrosine kinase inhibitors and b) breast cancer patients with *HER2* amplification might be treated with Trastuzumab or Lapatinib [135]. Currently, several cancer biomarkers are employed to guide treatment strategies. These include: a) *HER2*/*HR* in breast cancer, b) BCR-ABL in CML, c) *KRAS* in CRC and NSCLC, d) *PD1* in metastatic melanoma, NSCLC, renal cell carcinoma (RCC) and Hodgkin lymphoma, e) *PDL1* in urothelial carcinoma, NSCLC, f) *CTLA4* in advanced melanoma, g) *EGFR* in NSCLC, head and neck squamous cell carcinoma (HNSCC) and *KRAS* wild-type CRC, h) *BRAF* in melanoma and i) *ALK* in NSCLC [134] (refer to Table 1). Pharmacogenomic testing began with testing hereditary germline alterations to the genome analyzing variants of the same gene and targeting the most common and effective variants [136]. However, developments in genotyping techniques and sequencing methods made it possible and easy to sequence the whole genome of cancer tissue [17,118]. Multiplex methods are quickly replacing single gene testing given the comparative cost of performing several single-gene tests with the price of conducting modern sequencing. New

generation sequencing (NGS), also called second-generation sequencing or massive parallel sequencing or massively parallel sequencing, with its lower costs and reduced turnaround time has the advantage to screen thousands of germline and somatic mutations in the DNA [17,137]. The adoption of new technologies has expanded our knowledge of cancer genomics and resulted in a transition from characterizing cancers solely by anatomical location and histology to molecular profiling as seen in several tumor-agnostic biomarker-driven clinical trials [138]. In these trials, the presence or absence of a particular biomarker dictated the interpretation of the results. Pharmacogenomic tests employed to test the correlation between biomarkers and drugs generally

fall into two broad categories: a) nucleic acid-based tests in which mostly the DNA and sometimes the RNA is analyzed and b) protein-based tests. The nucleic acid-based tests can be: a) single gene tests, b) tests based on panels of genes and c) genomic sequencing [136]. The panels usually include the best studied and most relevant genes and may contain SNP combinations based on a literature review or investigative studies. Panels containing many genes may not necessarily provide additional value to the patient as some of these genes might not be clinically relevant. Moreover, variants of a certain gene might not be relevant for a particular population but can be quite common within other groups [139].

Table 1: Selected cancer drug/biomarker pairs and their main FDA's pharmacogenomic considerations

Drug	Biomarker (germline/somatic)	Main FDA recommendations
Mercaptopurine	TPMT (germline)	Test for TPMT deficiency in patients with myelosuppression. Reduce dose depending on TPMT status. No specific test given.
Irinotecan	UGT1A1 (germline)	The active metabolite of Irinotecan is SN-38 which is metabolized and deactivated by UGT1A1. Genetic variants of the <i>UGT1A1</i> gene such as <i>UGT1A1</i> such as *28 and *6 lead to reduced enzyme expression and function. Consider dose reduction. No specific test given
Tamoxifen	CYP2D6 (germline)	Patients carrying two non-functional alleles exhibit significantly lower Endoxifen levels. However, the impact on the efficacy of Tamoxifen remains not well established. No specific test given
Ceritinib	ALK (somatic)	Indicated for the treatment of NSCLC patients who are positive for ALK rearrangements. The tests recommended are NGS to detect <i>ALK</i> gene rearrangements and IHC test to follow protein expression.
Imatinib	BCR-ABL1 (somatic)	Indicated for Ph+ CML and ALL patients. A BCR-ABL1 test using reverse transcriptase quantitative polymerase chain reaction (RQ-PCR) to detect the presence of Philadelphia chromosome.
Cetuximab	EGFR (somatic)	Indicated for the treatment of RAS-wild type metastatic colorectal cancer expressing EGFR. A qualitative IHC test is used to identify EGFR expression in normal and cancer tissues.
Dabrafenib	BRAF (somatic)	Indicated for the treatment of unresectable or metastatic melanoma with BRAF V600E mutation. A qualitative real-time polymerase chain reaction (RT-PCR) is used to identify BRAF V600E and BRAF V600K mutations.
Trastuzumab	HER2 (somatic)	Indicated for the treatment of breast cancer, gastric cancer and gastroesophageal junction adenocarcinoma when these cancers are over expressing HER2. Various tests are recommended. For protein overexpression, a semi-quantitative IHC test is employed. For <i>HER2</i> gene amplification a range of tests can be used based on NGS, quantitative chromogenic in situ hybridization (CISH) or quantitative fluorescent in situ hybridization (FISH).
Lapatinib	HER2 (somatic)	Indicated in combination with either Capecitabine or Letrozole for advanced or metastatic breast cancers that overexpress HER2. The status of HER2 is assessed in a similar way as above.

TPMT=Thiopurine methyltransferase; UGT1A1=Uridine diphosphate glucuronosyl transferase 1A1; CYP2D6=Cytochrome P450 family 2 subfamily D member 6; ALK=Anaplastic lymphoma kinase; NSCLC=Non-small cell lung cancer; NGS=Next generation sequencing; IHC=Immunohistochemistry; BCR=Breakpoint cluster region; ABL1=Name originally derived from a homolog in Abelson murine leukaemia virus; Ph+=Philadelphia chromosome positive; CML=Chronic myeloid leukaemia; ALL=Acute lymphoblastic leukaemia; EGFR=Epidermal growth factor receptor; RAS=Name originally derived from rat sarcoma virus; BRAF=v-raf murine sarcoma viral oncogene homolog B1; V600E=A mutation in BRAF protein that changes the amino acid in position 600 from valine to glutamic acid; HER2=Human epidermal growth factor receptor 2.

A panel can be more beneficial to the patient if it analyses variants matching their ethnic origin. For instance, the *CYP2D6* gene can exist in multiple copies in 10% of subjects, particularly those of black or Asian origins. Such gene duplication can cause

elevated *CYP2D6* enzymatic activity and clinical manifestations. Furthermore, it must be borne in mind that not all panels can reveal the presence or the extent of gene duplications [140]. Genomic sequencing, most often accomplished nowadays

using NGS, can reveal rare variations and allow for a better understanding of the genetic function. According to PharmGKB resource website, 68 very important genes are relevant, from the pharmacogenomic point of view to the action and/or adverse effects of drugs [141]. The United States FDA imposes mandatory diagnostic tests before prescribing several anticancer drugs most of these are tyrosine kinase inhibitors as can be seen by the selected examples shown in Table 1 [30,142]. These recommended pharmacogenomic tests for the biomarker/drug pairs chosen for illustration in this review include immunochemical assays, polymerase chain reaction tests, quantitative in-situ hybridization and next-generation sequencing.

Conclusions

The main objective of pharmacogenomics is to locate the source(s) of variability in drug response and/or adverse reactions across populations [24]. However, translating pharmacogenomic knowledge into clinical applications has been slow with a handful of institutions implementing single gene testing as in the case of the routine genotyping of the *DPYD* gene which was demonstrated to be acceptable and feasible in reducing adverse events of Fluoropyrimidine [143-145]. Even though not all pharmacogenomic variants are actionable (capable to be translated into a clinical application), it was estimated that 99% of the human population carry at least one actionable variant within the most common 13 pharmacogenes [146].

This has accelerated the implementation of panel testing by some groups such as the European Ubiquitous Pharmacogenomics Consortium which implemented genotyping of 44 variants in 12 genes including genes connected with cancer therapy such as *CYP2D*, *DPYD*, *TPMT* and *UGT1A1* in a single test for patients starting on one of 42 drugs [147]. Implementation of PG testing in other areas of therapeutics, other than oncology, can also be highly relevant in the treatment of cancer as patients with cancer can have/or developed other indications for gene/drug pairs [14].

To give just a few examples where knowledge of gene/drug pairs investigated for other conditions can help the treatment of similar symptoms encountered in cancer: *CYP2D6*/Ondansetron and nausea, *CYP2D6*/Codeine or Tramadol and pain, *SLOC1B1*/Simvastatin and cardiovascular risks and *CYP2D6* or *CYP2C19*/selective Serotonin reuptake inhibitors and anxiety or depression [14]. New technologies that assist in rapid and high-volume testing together with the continuous discoveries of actionable variants have contributed to the growing interest from clinicians and patients alike in the field of precision medicine. Advanced molecular testing enabled the classification and diagnosis of cancer

with greater precision thus potentially assisting clinical decision-making, and prognosis and sparing patients from ineffective treatments [28]. The implementation of precision medicine in clinical practice can be challenging for reasons such as the complexity of molecular information generated, the clinical utility of the information and the economic costs of the tests involved [26]. Regarding costs, the good news is once an individual's genome is defined it can be used to guide drug therapy for a lifetime [16]. Single-gene testing is likely to be gradually replaced by multiple genomic characterizations using next-generation sequencing particularly as the cost of these technologies continues to decline [148]. In the future, precision medicine is likely to integrate multi-omic cancer characterisations with automated systems of analysing and interpreting the results possibly based on artificial intelligence [149].

Conflict of interests

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