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Pharmacogenetics and pharmacogenomics: a bridge to individualized cancer therapy

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Abstract

In the past decade, advances in pharmacogenetics and pharmacogenomics (PGx) have gradually unveiled the genetic basis of interindividual differences in drug responses. A large portion of these advances have been made in the field of anticancer therapy. Currently, the US FDA has updated the package inserts of approximately 30 anticancer agents to include PGx information. Given the complexity of this genetic information (e.g., tumor mutation and gene overexpression, chromosomal translocation and germline variations), as well as the variable level of scientific evidence, the FDA recommendation and potential action needed varies among drugs. In this review, we have highlighted some of these PGx discoveries for their scientific values and utility in improving therapeutic efficacy and reducing side effects. Furthermore, examples are also provided for the role of PGx in new anticancer drug development by revealing novel druggable targets.

Keywords

anticancer agents; drug label; pharmacogenetics; pharmacogenomics

The variable response to medications in the forms of lack of response and adverse reaction, and the motivation to better utilize medications, are the foundation for one of the major components of personalized medicine – personalized treatment. In light of these observations, the hypothesis suggested different genetic backgrounds among individuals as one of the major causes, even though environmental factors might also contribute to diverse drug reactions [1]. To have a better understanding of the relationship between human genetics and drug response, the discipline of pharmacogenetics has emerged as a branch of pharmacology to identify genetic variants from candidate genes related to drug metabolism, transport or molecular targets/pathways [2]. Since entering the postgenomic era in the new century, the term of pharmacogenetics has gradually evolved into pharmacogenomics as the

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genome-wide integrative analysis has been increasingly employed [3]. Today, the two terms are actually interchangeable in many scenarios. In this paper, pharmacogenetics and pharmacogenomics are uniformly referred as PGx.

So far, the US FDA has recommended PGx consideration or package-insert labeling for more than 120 drugs with relationships to greater than 50 genes [101]. These drugs are commonly indicated in the treatments of cancers, and cardiovascular, infectious and psychiatric diseases (Figure 1). It is clear that anticancer agents PGx is one of the most actively studied areas for the following reasons. First, owing to the narrow therapeutic indices, chemotherapeutics often display more severe and sometimes life-threatening toxicities than other drugs. Therefore, it is important and necessary to preidentify patients at risk for these toxicities. Second, unique to anticancer treatment, two related but different genomic systems (tumor and germline genomes) need to be studied to improve treatment efficacy and reduce toxicity. Third, the pipelines of developing anticancer agents have been really active, which results in many more drugs in the market or undergoing clinical trial evaluations [4]. Furthermore, the beneficial effects of PGx could also be extended to Phase IV postmarketing studies if the package-insert label stipulates the usage in patients with certain genotypes. Therefore, in this review, we will focus on the PGx discovery and implementation in cancer therapy.

Heritability characterization of anticancer agents

Generally speaking, the different drug responses could be attributed to either genetic factors or environmental factors. Therefore, before conducting PGx discovery research, it would be important and necessary to evaluate whether and how much genetics plays a role in variable drug responses. For this purpose, heritability analysis can be employed to qualify and quantify whether the drug response is a heritable trait. Traditional heritability analysis is conducted either in twins or in large pedigrees. Heritability measures can range from 0 to 1, with close to 0 implying that it is less likely to be a heritable trait, while close to 1 implying most phenotypic variations are due to genetics [5]. For example, heritability analysis in twins on caffeine-related traits, such as withdrawal symptoms and sleep disorder, found heritability ranging from 0.36 to 0.58 among several ethnic groups [6]; while another heritability test conducted in a pedigree study using >500 families demonstrated that platelet responsiveness to aspirin has a heritability ranging from 0.266 to 0.762 [7].

For anticancer agents, it is difficult to perform heritability tests in humans, since it is unethical to administer chemotherapeutic drugs to non-cancer relatives. Therefore, research strategy has been focused on performing heritability tests using human-derived materials. For example, lymphoblastoid cell lines derived from large pedigrees have been utilized to study cisplatin and 5-fluorouracil (5-FU)-induced cytotoxicity [8,9]. More recently, Peters *et al.* conducted heritability analysis among 29 FDA-approved anti-cancer drugs using a total of 125 lymphoblastoid cell lines from 14 large Caucasian pedigrees [10]. Cytotoxicity for each drug was estimated at various treatment doses. They observed heritability to range from 0.06 to 0.64 for these 29 agents, suggesting the variable roles of genetics in the cellular response to anticancer agents. Nineteen out of 29 drugs showed maximum heritability of more than 0.3, suggesting more than 30% of the overall cytotoxicity variation is due to genetics, which warranted further PGx research to identify genetic variants contributing to these heritable traits. Interestingly, several commonly used drugs, such as gemcitabine and fludarabine, displayed heritability lower or equal to that of control water treatment, suggesting the different cytotoxicity associated with these drugs is more likely to be caused by environmental factors instead of genetic variations [10].

Methods used in study PGx

Genetic variants

In oncology, genetic variants can be found either in the germline genome as germline variations or in the tumor genome as somatic mutations, both of which are the subjects of PGx research. A germline variation is any detectable and heritable variation in the lineage of germ cells, such as genetic polymorphisms in genes encoding drug-metabolizing enzymes; while somatic mutations are accidental changes in a genomic sequence of DNA, which may cause cancer. While germline variations could potentially predict drug efficacy and toxicities, somatic mutations are often used to optimize choice of chemotherapeutic agent to improve efficacy. The genetic variants commonly evaluated in PGx include SNPs, nucleotide insertion, deletion, tandem repeat, copy number variation and chromosomal translocation [11]. In addition, gene expression is also commonly studied in PGx for relevancy in tumorigenesis and chemotherapy response [12]. Therefore, the latest FDA definition of pharmacogenomics has officially incorporated this concept.

Currently, the most pervasively studied genetic variant is the SNP, owing to the fast improvement of technology in the speed, coverage, accuracy and reduced cost in obtaining SNP genotypes [13–16]. Furthermore, the location and the allele frequencies of genome-wide SNPs in various human populations are publicly available from many online resources, such as the NCBI dbSNP [102] and University of California at Santa Cruz (UCSC) genome browser [103]. The interest in studying SNPs also lies in their potential functional significance. These variants could subsequently influence gene transcription, gene translation and RNA splicing, as well as RNA stability in the cells. All of which could lead to variable drug responses in a population in which each individual has his/her unique genetic make up.

PGx discovery methods

Two approaches are commonly used in PGx discovery research: the candidate gene approach and genome-wide studies. The candidate gene approach focuses on one or a few genes involved in drug metabolism, transport or targeting pathways. This method has developed upon advances in pharmacology occurring since the 1950s. On the other hand, genome-wide studies take into considerations all genes and noncoding sequences of the human genome, assuming that all genetic materials have equal chances to affect drug responses. Genome-wide approaches have emerged after the completion of the Human Genome Project in 2000. To date, most of the well-established PGx biomarkers in oncology were discovered from candidate gene studies. This is probably due to the fact that the candidate gene approach has a longer history in bench or clinical work, it costs less than genomic research and it is more straightforward to explain and validate the relationship between genotypes and drugs. However, with the public availability of human genomic information and the decreasing cost of genomic sequencing, genome-wide studies have become more popular in PGx research. What is more, the factors influencing drug resistance or toxicity may not be limited to known metabolizing, transport and targeting pathways. Multigenic factors involved in protein modifications and functions, as well as epigenetic controls, might contribute to variable drug responses. These new extensions would add more weight to genome-wide studies in future PGx research, although the issue of multiple testing correction and the difficulty in interpreting genome-wide study findings remain hurdles to the broad utility of this method.

PGx discovery for optimizing anticancer agents usage

In the past decade, advances in PGx have gradually started unveiling the mystery of interindividual differences in drug responses. Currently, a large portion of the advances have

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been made in the field of anticancer therapy. Corresponding to this trend, a literature search on PGx in cancer therapy showed a steady increase of publications in the past 10 years (Figure 2). The publication number in 2011 is almost 2.5-times that of 10 years ago. These anticancer agent PGx studies have revealed many genetic variants, or pointed to some specific chromosome loci, for their potential role in tailoring individualized chemotherapy. To date, PGx information of 24 biomarkers are available in the drug labels for 30 FDA-approved anticancer agents (Table 1). These biomarkers include gene variants, functional deficiencies, expression changes, chromosomal abnormalities and others. Note some of these PGx markers are germline variants, while others are tumor specific. Based on the level of scientific evidence support, these markers have been presented differently in different sections of the FDA-approved drug labels. In this review, we have classified the level of FDA recommendation as: ‘mandatory’ – if the biomarker appears in ‘boxed warning’ or ‘contraindications’; ‘recommended’ – if the biomarker appears in ‘indications and usages’ or is clearly stipulated; or ‘proposed’ – if the biomarker is mentioned in another section of the package insert, such as ‘warning and precautions’ and ‘clinical pharmacology’ (Table 1). One should note that this classification method is not an official FDA definition. Furthermore, there is, and always will be, a lag time from the time a significant scientific discovery is made to when that finding becomes incorporated into the drug label. Therefore, all PGx markers included in the drug package inserts are of value. For those markers indicated as ‘mandatory’ or ‘recommended’, clinical action should be considered. These recommendations may change/evolve with the accumulation of additional research evidence. When incorporating these PGx markers into guiding cancer chemotherapy, improved efficacy or reduced toxicity have been observed [17–19]. Moreover, pharmacoeconomic advantages have been demonstrated by several independent reports [20,21].

PGx in cancer drug development

Every year, approximately 90% of the drugs entering clinical trials failed to reach marketing approval by the FDA [104]. This is especially true for many undertesting or failed anticancer agents, because of their intolerable side effects or undesired therapeutic efficacy in a general population. One way to circumvent this bottleneck is to stratify patients in a large population by taking advantage of the PGx information of the prospective drug. It is possible to preselect a group of people who do not have the genetic variants related to drug resistance, and reduce dosage for the individuals who carry the genetic variants with high risk of drug sensitivity in clinical trials. This genome-stratification strategy is expected to produce better therapeutic outcomes in sub-populations. It might require a smaller sample size for the trials and accelerate drug approval. With the increasing cost of clinical trials and the limited testable compounds, more and more drug companies started to consider conducting PGx research in the early stages of drug development so that the PGx data could be incorporated for new drug approval to lower the risk of rejection or delayed approval [22,23].

For economic consideration, although PGx testing is likely an added cost to the traditional chemotherapeutic prescription, and PGx research might increase drug developmental cost for industry (e.g., through costs for developing and validating biomarkers) in the long run, with the reduced adverse events and the avoided ineffective medication, PGx consideration can improve healthcare outcomes and reduce the overall healthcare costs. For clinical trials conducted by the pharmaceutical industry for new drug approval, PGx screening might engender much smaller-scale patient populations involved in trials, as well as much-reduced expenditure, which would eventually shorten the period of FDA approval and generate more cash flow for the industry [24].

Interestingly, PGx research, more often in genome-wide association PGx studies, can sometimes identify novel drug targets or pathways related to the drug or disease. As more targets or pathways are revealed by PGx studies, more comprehensive understanding of the mechanism of action of the drug could be achieved. This would in turn stimulate new rounds of drug discovery in this field [23]. A classic example is the development of imatinib, a tyrosine kinase inhibitor used to treat chronic myelogenous leukemia caused by Philadelphia chromosome. This drug development would not be possible without the knowledge of the genetic basis of this disease and the understanding of the target(s) of this agent.

Examples of PGx in anticancer agents

As shown in Table 1, more than 20 PGx markers have been included into the package inserts of 30 FDA-approved anticancer agents to date; however, the level of scientific evidence supporting these PGx marker–drug relationships vary, which leads to different FDA recommendations. In the subsequent section, we chose to highlight a few of these examples in order to:

- Showcase anticancer drug–PGx marker discoveries and their implementation in both the germline and somatic mutation aspects;
- Provide PGx marker examples in various forms (e.g., SNP/mutation, overexpression and chromosome translocation);
- Demonstrate the different levels of scientific evidence needed for different FDA recommendations.

Germline variations in anticancer agent PGx

6-mercaptopurine & TPMT—6-mercaptopurine is an antimetabolite that has been commonly used to treat leukemia and lymphoma via inhibiting new DNA synthesis. In the human body, the abundance and clearance of 6-mercaptopurine is subject to the function of TPMT, an enzyme that could transfer a methyl group to the purine and inactivate 6-mercaptopurine. Functional deficiency in TPMT would increase the level of 6-mercaptopurine *in vivo* and has been found to cause serious side effects; for example, myelosuppression [25].

Owing to the high rate of polymorphisms in its coding sequence, enzyme activity of TPMT varies greatly in a population. In previous research, the variable activity of TPMT was found to be correlated to 6-mercaptopurine efficacy and side effects, with lower activity of TPMT corresponding to better therapeutic efficacy and higher clinical toxicity [17,26]. So far, more than 20 genetic variants in *TPMT* have been identified. Most of them have shown to have reduced TPMT activity. Among them are rs1800462 (G>C), rs1142345 (A>G) and rs1800460 (G>A), which are three missense variations that were found to dramatically reduce TPMT enzyme activity, which led to relatively high levels of 6-mercaptopurine and severe toxicity in the human body [27,28]. Indeed, these three variants account for 95% of individuals with reduced TPMT activity.

Therefore, the FDA has recommended genotyping of these three *TPMT* SNPs prior to the usage of 6-mercaptopurine. If any of the three SNP sites carry the variant allele that leads to TPMT deficiency, substantial dose reduction of 6-mercaptopurine should be considered. Even though the FDA has not given the details of dose reduction, another source suggested 10% of original dose for homozygous *TPMT* deficient patient and 50% of that for heterozygous patients [29]. A group in Europe compared the hospitalization costs of patients having acute lymphoblastic leukemia treated with 6-mercaptopurine. They found the incorporation of *TPMT* genotyping in the treatment plan was more cost effective [20].

Capecitabine & DPD—Capecitabine is a prodrug of 5-FU that has been prescribed for the treatment of metastatic breast and colon cancers. *In vivo*, capecitabine is activated through a series of catalytic conversions to form 5-FU, which subsequently undergoes complex anabolic and catabolic biotransformation to achieve anticancer function. DPD is one of the enzymes that catalyzes the reduction of uracil and thymine rings and controls the rate-limiting step in 5-FU inactivation in the liver [30].

Early PGx research with candidate gene approaches suggested the association of 5-FU treatment outcomes and the germline variations in *DPD*, with reduced DPD activity corresponding to longer 5-FU half-life and increased risk of toxicity [31]. Later a heritability analysis showed that 5-FU-induced cytotoxicity phenotype is a heritable trait with heritability ranging from 0.26 to 0.65 depending on treatment dosages [9]. To date, more than 30 SNPs and insertions/deletions have been found in/near the *DPD* gene [11]. Among them, one splice-site mutation at intron 14, named IVS14+1G>A or c.1905+1G>A, causes the splicing skip of exon 14 and the subsequent loss-of-function of DPD. Its association with 5-FU-induced toxicity, such as neutropenia, has been observed in cellular models and among patients [32]. In addition, two SNPs in the coding sequence, c.1679T>G and c.2846A>T, which cause nonsynonymous mutations by changing amino acids at I560S and D949V, respectively, have been demonstrated to have low DPD enzyme activity and higher frequency of 5-FU toxicities [18]. To date, only these three variants have been consistently reported to be significantly associated with grade 3 5-FU toxicities in case-control studies. It was also reported that approximately 50–60% of patients carrying these three genetic variants in *DPD* developed severe 5-FU toxicity [33].

Recently, studies with more comprehensive sequencing further revealed the enrichment of genetic loci in the noncoding regions of *DPD* that are related to severe 5-FU toxicity in patients. One genetic variant in intron 10, c.1129-5923C>G, was found to create a cryptic splice donor site and cause the frameshift in coding sequence, which produces a premature stop codon and a truncated *DPD*. This variant was found to be significantly enriched in patients with severe 5-FU toxicity [34]. Furthermore, c.1129-5923C>G is in complete linkage with two novel haplotypes: hapB3 (comprised of four variants: c.483+18G>A; c.680+139G>A; c.959-51T>G; and c.1236G>A) and hapB6 (containing one intronic variant: c.234-123G>C). These two haplotypes were found to be associated with severe toxicity from various 5-FU-based chemotherapy regimens [35].

Although there have been many clinical studies suggesting the values of the *DPD* genetic variants in predicting 5-FU toxicities, there are conflicting reports de-emphasizing the importance of the association between them, either showing the replication only in a small proportion of the patients, or the low allele frequency of some variants in certain subpopulations [18,32,36]. Furthermore, the role of *DPD* polymorphisms in 5-FU/capecitabine treatment efficacy has not been well characterized. Therefore, in the FDA-approved package insert, only the general term of DPD deficiency (instead of specific genetic variants) is listed as contraindication for prescribing 5-FU or capecitabine.

Somatic mutations in anticancer agent PGx

Cetuximab/panitumumab & KRAS—Cetuximab and panitumumab are two monoclonal antibodies that were designed to inhibit the growth and survival of tumor cells with overexpressed *EGFR* in colon and head and neck cancers. However, these drugs were found to be inefficient in some patients, even though they did have the mutated *EGFR*. Later on, several research teams reported the association between the resistance of cetuximab/panitumumab and *KRAS* mutations [37,38]. *KRAS* is a membrane GTPase that can activate many proteins in EGFR signaling pathways, such as c-Raf and PI3K. Aberrant activation of these proteins would usually cause cancer development independent of upstream EGFR

signaling [39]. Not surprisingly, if *KRAS* is actively mutated, the inactivation of EGFR by cetuximab or panitumumab will have no beneficial effect in curing *KRAS*-induced cancers.

PGx research has found that mutations in exon 2 at G12 and G13 led to the aberrant activation of *KRAS* and subsequent cancer development [38,40]. It was shown that approximately 40% of colon cancer patients contain these mutations [37]. Therefore, a PGx test on the *KRAS* gene at these positions has been recommended by the FDA before prescribing cetuximab and panitumumab in the treatment of colon, lung, and head and neck cancers. According to the drug label, only patients with *EGFR*-expressing colon cancer and *KRAS* mutant negative (wild-type) are supposed to use these drugs.

Crizotinib & EML4-ALK—Crizotinib is an *ALK* inhibitor approved to treat non-small-cell lung cancer (NSCLC). *ALK* was found to form a fusion *EML4-ALK* gene in 3–5% of NSCLC patients. This *EML4-ALK* fusion is a constitutively activated kinase and leads to carcinogenesis [41]. Therefore, detection of fusion is required for the usage of crizotinib.

In clinical treatment of NSCLC caused by *EML4-ALK*, drug resistance to crizotinib was soon observed in certain patients and inevitably developed even in those who did respond in the first place. Later PGx research found the drug resistance is linked to several tumor-specific genetic mutations in *ALK*: L1196M, C1156Y, F1174L and G1269A [42,43]. Currently, the FDA has issued *ALK* positive as detected by an FDA-approved test as the indicator for prescribing this drug to treat patients with locally advanced or metastatic NSCLC. However, the FDA has not yet recommended PGx testing of these drug-resistant variants.

Conclusion

PGx research in anticancer drugs is an active field of research for its potential to reduce life-threatening toxicity and improve therapeutic efficacy prior to administration of chemotherapy. So far, more than 20 PGx biomarkers corresponding to approximately 30 chemotherapeutic agents have been included in drug package inserts and recommended by the FDA at different levels. Some of these biomarkers have shown to improve anticancer treatment efficacy and reduce toxicity, which could subsequently lower the overall healthcare cost.

Although promising, there are many challenges in the implementation of PGx testing in clinical practice. First, environmental factors, such as diet and comedications, affect pharmacokinetics/pharmacodynamics, therefore increasing the complexity of replicating the bio-marker functions in individual patients. These factors should be taken into consideration when conducting clinical validation experiments or prescribing the drug to patients. Second, the nature of tumor heterogeneity presents a considerable therapeutic challenge because treatment choices based on a biomarker present in a single biopsy specimen may not be relevant [44]. This highlights the need of obtaining both primary and metastatic tumors for PGx study. Third, practical genotyping is another field that needs to be further developed. It is expected that the ideal genotyping for PGx should be specific to certain genetic variants, straightforward for clinicians to interpret and affordable to payers. One accurate and reliable PGx test covering as many targets as possible would definitely be a plus for commercialization. So far, only countable numbers of Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories and companies can perform genotyping of clinical samples. With whole-genome sequencing taking the center stage, more facilities may be set up in major hospitals or medical centers in the future. Also, more extensive education should be given to researchers and clinicians, to properly disseminate and interpret the PGx findings. Last but not the least, cost-effectiveness of PGx testing needs to

be presented; this requires both lowering the expenses of performing PGx tests and providing more robust biomarkers from research.

Future perspective

It is likely that in the near future, more comprehensive PGx studies that involved epigenetic factors, such as miRNA, DNA methylation and histone modification, will be the new norm for PGx discovery. Recently, a hallmark progress made by the Cancer Genome Atlas Network demonstrated the applications of using six genomic platforms, including mRNA arrays, miRNA arrays, copy number variation arrays and DNA methylation arrays, in characterizing genomic mutations in breast cancers [45]. These mutations constitute signature spectrums of different cancer subtypes, suggesting a new way to classify cancers based on genomic mutation instead of originating organs. Similar milestones of PGx research are expected in the future to see if these tools can be employed in improving the treatment of well-characterized mutation-based cancers. In addition to the general human genome, the mitochondrial genome has attracted a lot attention in recent PGx research, because of its role in metabolism, signaling, cellular differentiation, cell cycling and so on. What is more, the higher rate of polymorphisms in mitochondrial DNA further highlights the value of studying genetic variants in mitochondria. Most importantly, considerable efforts are needed to translate scientific discovery into clinical practice and in new drug development.

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Executive summary

Heritability characterization of anticancer agents

- The importance of pharmacogenetics and pharmacogenomics (PGx) research has been acknowledged and actively pursued in recent years, especially among anticancer agents. Many cellular responses to US FDA-approved chemotherapeutics are heritable traits and deserve further study to identify specific genetic variants contributing to variable drug responses.

Methods used in PGx studies

- Candidate gene and genome-wide approaches have propelled PGx discovery. They are complimentary to each other and both have played important roles in different areas and eras.

PGx discovery for optimizing anticancer agents' usage

- Different levels of recommendation are indicated for the PGx biomarkers in the FDA-approved anticancer drug labels. With the accumulation of more PGx evidence, the recommendation may be and is likely changing.

Challenges of PGx research

- There are many hurdles affecting the translation of PGx information into personalized medicine. With the advances of PGx tools and the increased emphasis in translational efforts, we expect more PGx information to be incorporated into drug labels and real-world practice.

Future perspective of PGx research

- Incorporating epigenetics and clinical factors along with genetics will further improve our understanding of the relationship between human genomes and variable response to cancer chemotherapy.

Figure 1. US FDA-approved drugs that contain pharmacogenetics and pharmacogenomics information in their package insert labels

Number listed in each section represents the number of FDA-approved agents included in that disease category.

Figure 2. Number of publications derived from PubMed for anticancer agent pharmacogenetics and pharmacogenomics in the past decade.

US FDA-approved chemotherapeutic agents for which package inserts contain pharmacogenetics and pharmacogenomics information.

Table 1

Drug	PGx biomarker	Germline variant/tumor mutation	Variation type	FDA recommendation [†]	PGx incorporation time	Example of commercially available test [‡]
Arsenic trioxide	<i>PML/RARα</i>	T	Translocation	Mandatory	September 2000	ARUP <i>PML/RARα</i> translocation test
Busulfan	Ph Chr.	T	Translocation	Proposed	January 2003	Vysis LSI BCR/ABL ES Dual Color Translocation Probe
Capecitabine	<i>DPD</i>	G	Enzyme deficiency	Mandatory	March 2003	MYRIAD ® TheraGuide5-FU
Cetuximab	<i>EGFR</i>	T	Overexpression	Recommended	February 2004	DakoCytomation ® EGFR pharmDx ™ test [¶]
	<i>KRAS</i> [§]	T	Mutation	Recommended	July 2009	Therascreen <i>KRAS</i> RGQ PCR Kit [¶]
Cisplatin	<i>TPMT</i>	G	SNP	Recommended	December 2011	Prometheus TPMT Genetics
Crizotinib	<i>EML4-ALK</i>	T	Translocation	Recommended	August 2011	Vysis ALK Break Apart FISH Probe Kit [¶]
Dasatinib	Ph Chr.	T	Translocation	Recommended	June 2006	MolecularMD ® BCR-ABL T315I Mutation Test
Denileukin diftitox	<i>CD25</i>	T	Overexpression	Recommended	February 1999	ARUP ® CD25 by Immunohistochemistry test
Erlotinib	<i>EGFR</i>	T	Overexpression	Proposed	November 2004	See <i>EGFR</i> above
Everolimus	<i>Her2/neu</i>	T	Overexpression	Recommended	July 2012	PathVysion ® HER-2 DNA Probe Kit [¶]
Exemestane	<i>ER</i> and/or <i>PgR</i>	T	Overexpression	Recommended	October 2005	ScanScope ® XT System [ER/PR]
5-fluorouracil	<i>DPD</i>	G	Enzyme deficiency	Mandatory	October 2000	see <i>DPD</i> above
Fulvestrant	<i>ER</i>	T	Overexpression	Recommended	April 2002	See <i>ER</i> above
Gefitinib	<i>EGFR</i>	T	Overexpression	Proposed	May 2003	See <i>EGFR</i> above
Imatinib	<i>C-Kit</i>	T	Overexpression	Recommended	April 2003	DakoCytomation ® c-Kit pharmDx ^{™¶¶}

Drug	PGx biomarker	Germline variant/tumor mutation	Variation type	FDA recommendation [†]	PGx incorporation time	Example of commercially available test [‡]
	Ph Chr. §	T	Translocation	Recommended	April 2003	See Ph Chr. above
	<i>PDGFR</i>	T	Translocation	Recommended	September 2007	PAML® FISH PDGFR test
	<i>FIP1L1-PDGFR</i>	T	Translocation	Recommended	September 2007	Sonora® FISH: FIP1L1-PDGFR test
Irinotecan	<i>UGT1A1</i>	G	Insertion	Proposed	June 2005	Invader® UGT1A1 Molecular Assay [¶]
Lapatinib	<i>Her2/neu</i>	T	Overexpression	Recommended	March 2007	See <i>HER2</i> above
Lenalidomide	Chr. 5q	T	Deletion	Mandatory	December 2005	Abbott® FISH Chr. 5q probe
Letrozole	<i>ER</i> and/or <i>PgR</i>	T	Overexpression	Recommended	January 2001	See <i>ER</i> above
Mercaptopurine	<i>TPMT</i> [§]	G	SNP	Mandatory	January 2003	See <i>TPMT</i> above
Nilotinib	Ph Chr.	T	Translocation	Recommended	October 2007	See Ph Chr. above
	<i>UGT1A1</i>	G	SNP	Proposed	October 2007	See <i>UGT1A1</i> above
Panitumumab	<i>EGFR</i>	T	Overexpression	Recommended	September 2006	See <i>EGFR</i> above
	<i>KRAS</i> [§]	T	Mutation	Recommended	July 2009	See <i>KRAS</i> above
Pertuzumab	<i>Her2/neu</i>	T	Overexpression	Recommended	June 2012	See <i>HER2</i> above
Rasburicase	<i>G6PD</i> [§]	G	SNP	Mandatory	July 2002	BinaxNOW® G6PD test [¶]
Tamoxifen	<i>ER</i>	T	Overexpression	Recommended	October 1998	See <i>ER</i> above
	<i>FV</i>	G	SNP	Proposed	September 2006	Roche® Factor V Leiden Kit [¶]
	<i>F2</i>	G	SNP	Proposed	September 2006	Roche® Factor II (Prothrombin) G20210A Kit [¶]
Thioguanine	<i>TPMT</i>	G	SNP	Proposed	June 2003	See <i>TPMT</i> above
Tositumomab	<i>CD20</i>	T	Overexpression	Recommended	June 2003	ARUP® CD20 by IHC test
Trastuzumab	<i>Her2/neu</i>	T	Overexpression	Recommended	September 1998	See <i>HER2</i> above

Drug	PGx biomarker	Germline variant/tumor mutation	Variation type	FDA recommendation [†]	PGx incorporation time	Example of commercially available test [‡]
Vemurafenib	<i>BRAF</i>	T	Mutation	Recommended	August 2011	Cobas® 4800 BRAF V600 Mutation Test [¶]

Bolded drugs are discussed in more detail in the examples section of this review.

[†]US FDA recommendation was classified as: ‘mandatory’ – if the biomarker appears in ‘boxed warning’ or ‘contraindication’; ‘recommended’ – if the biomarker appears in ‘Indications and usages’, or is clearly stipulated; ‘proposed’ – if the biomarker is mentioned in another section of the package insert, such as ‘warning and precautions’ and ‘clinical pharmacology’.

[‡]For many PGx biomarkers, more than one commercially available test is available. We listed one for each biomarker as an example.

[§]Drug package labels include specific actions to be taken based on genetic information.

[¶]PGx test itself is approved by FDA.

Chr.: Chromosome; F2: Prothrombin mutations; FV: Factor V Leiden; G: Germline variant; PGx: Pharmacogenetics and pharmacogenomics; Ph Chr.: Philadelphia chromosome; T: Tumor mutation.
Data taken from [101].