Published in final edited form as:

Clin Pharmacol Ther. 2011 September ; 90(3): 461–466. doi:10.1038/clpt.2011.126.

CANCER PHARMACOGENOMICS

SW Paugh^{1,2}, G Stocco^{1,2}, JR McCorkle^{1,2}, B Diouf^{1,2}, KR Crews^{1,2}, and WE Evans^{1,2,*}

¹Department of Pharmaceutical Sciences, St Jude Children's Research Hospital, Memphis, TN 38105, USA

²Hematological Malignancies Program, St Jude Children's Research Hospital, Memphis, TN 38105, USA

Abstract

Pharmacogenomics research is yielding molecular diagnostic tools that can be used to optimize the selection of medications and their doses for individual patients. Given the narrow therapeutic index of most anticancer agents and the serious consequences of undertreatment, cancer chemotherapy is a compelling therapeutic area for translation of pharmacogenomics to the clinic. This review addresses how inherited (germline) and acquired (somatic) sources of genome variability can alter the toxicity or efficacy of cancer chemotherapy.

Cancer, a leading cause of morbidity and mortality in industrialized countries, is responsible for more than 500,000 deaths each year in the United States alone. Moreover, despite the remarkable progress that has been made in improving cure rates in childhood malignancies, cancer remains the leading cause of death by disease in US children >1 year of age. The current treatment for most cancers involves the use of cytotoxic chemotherapy that is not precisely targeted against the primary genetic abnormalities responsible for human cancers, in part because the genetic drivers of malignant transformation are not fully understood. There are some notable exceptions, such as the use of tyrosine kinase inhibitors in human malignancies in which cancer cell proliferation is driven by dysregulation of tyrosine kinases as a consequence of chromosomal translocations (e.g., BCR/ABL from the t(9;22) chromosomal translocation in chronic myeloid leukemia (CML) and acute lymphocytic leukemia (ALL)) or of somatic mutations in genes encoding tyrosine kinases (e.g., FLT3 mutations in acute myeloid leukemia). There are also anticancer medications that are targeted against aberrant expression of cell-surface antigens. An example of such a medication is trastuzumab, a monoclonal antibody used against early-stage breast cancer cells that express the human epidermal growth factor receptor 2 (HER2⁺). Unfortunately, however, these “targeted” agents constitute a relatively small fraction of cancer chemotherapy currently in use to treat malignancies in humans.

Although many ongoing cancer genome sequencing efforts are beginning to provide new insights into the genetic origins of many human cancers, it will be decades before the drivers of most cancers are fully understood, and even longer before targeted treatments can be developed to exploit this knowledge. In the meantime, hundreds of thousands of patients with cancers will be cured and additional lives will be prolonged by the use of classical nontargeted cancer chemotherapy with drugs that unfortunately often produce serious toxicities at doses in the range required for maximum anticancer effects. This review focuses on the potential of pharmacogenomics to yield insights and molecular diagnostic tools that can be used to individualize the selection of anticancer agents and determine their optimal

*Corresponding Author: William E. Evans, PharmD, Director and CEO, St. Jude Children's Research Hospital, 262 Danny Thomas Place, Memphis, TN 38105, William.Evans@stjude.org.

dosage for individual patients—perhaps a more immediately available form of “personalized medicine” for cancer patients. A unique challenge of cancer pharmacogenomics is that the combination of inherited (germline) genome variation and acquired (somatic) genome variation will influence the toxicity and efficacy of cancer chemotherapy; this review touches on both of these aspects (Figure 1).

INHERITED GENOME VARIATION AND CANCER CHEMOTHERAPY RESPONSE

Here we offer two of the more extensively studied examples of inherited genome variation that influence the clinical effects of cancer chemotherapy. Because of space limitations we could not include all such examples, but others (e.g., irinotecan and *UGT1A1*;¹ methotrexate and *SLCO1B1* (ref. 2) are included in the Supplementary Data online. It should also be noted that strong associations have recently been reported between the efficacy of treatment for ALL in children and inherited genome variation, with ongoing research focused on elucidating the precise causative genes.³

Thiopurines and TPMT

Mercaptopurine (6MP) is a thiopurine antimetabolite used in the treatment of lymphoid malignancies and as an immunosuppressant in some nonmalignant diseases;⁴ mercaptopurine treatment is a major component of continuation therapy for pediatric ALL.⁵ Mercaptopurine is converted by enzymes in the purine salvage pathway to 6-thioguanine nucleotides (TGNs) that are incorporated into the DNA and then exert cytotoxic effects by interfering with the activity of nucleic acid-processing enzymes. Methylated thiopurine nucleotides inhibit *de novo* purine synthesis, which probably contribute to the observed cytotoxic effects.⁶ In lymphoid tissues, mercaptopurine is inactivated primarily by thiopurine-*S*-methyltransferase (TPMT) because xanthine oxidase activity is low in these tissues; TPMT converts 6MP to methylmercaptopurine, which cannot be converted to TGNs. TPMT is encoded by a gene that has allelic variants containing nonsynonymous single-nucleotide polymorphisms, leading to reduced TPMT activity and important clinical consequences.⁷ In the majority of world populations studied to date, approximately 1 in 180 to 1 in 3,700 individuals (depending on the ethnic population) inherit two nonfunctional variants of the *TPMT* gene, 3–14% are heterozygous, and the rest are homozygous wild-type.^{8,9} With chronic conventional doses of 6MP, patients who inherit two inactive TPMT alleles are at very high risk of life-threatening toxicity (~100% penetrance) because of accumulation of high levels of cellular TGNs; 30–60% of patients heterozygous for a TPMT variant allele do not tolerate full doses of 6MP, again because of excessive TGNs.^{10,11} Identification of TPMT deficiency by genotyping for the most common inactivating single-nucleotide polymorphisms can prospectively identify patients at higher risk of mercaptopurine hematopoietic toxicity;^{9,12} such genotyping is recommended in US Food and Drug Administration–approved labeling. The diagnosis of TPMT deficiency allows the rational reduction of mercaptopurine dosages while other concurrent cytotoxic agents remain at their usual unadjusted doses,⁹ thereby avoiding toxicity without compromising efficacy. This is most useful in a clinical setting in which mercaptopurine is prescribed at higher doses (e.g., protocols for the treatment of leukemia involving doses of 50 mg/m²/day or more).¹³ Indeed, it has been shown that, in an ALL protocol using mercaptopurine at 75 mg/m²/day, prospective adjustment of mercaptopurine based on TPMT status^{11,14} allowed successful treatment of patients with variant TPMT at a reduced dose, with toxicity and efficacy comparable to those in patients with wild-type TPMT.^{6,15} In addition to TPMT, other genetic factors may influence the effects of mercaptopurine, although their clinical importance has not been as well characterized. As illustrated in Figure 2, a recent study

showed that once mercaptopurine treatment was individualized for TPMT, the effect of genetic polymorphisms in inosine triphosphate pyrophosphatase (ITPA) emerged.⁶

Tamoxifen and CYP2D6

It is well established that many breast cancers are driven by estrogen (i.e., estrogen receptor-positive), motivating the development of anti-estrogen therapies including aromatase inhibitors, estrogen receptor downregulators, and selective estrogen receptor modulators. One such selective estrogen receptor modulator, tamoxifen, is the most prominently prescribed agent for treating metastatic breast cancer, for adjuvant therapy of the primary disease, and for chemoprevention in women at high risk of developing breast carcinoma.¹⁶ Although tamoxifen is used widely, failure occurs in 30–50% of patients treated with it.¹⁷ Tamoxifen is a prodrug, and its metabolism is mediated by cytochrome P450 enzymes, leading to the production of 4-hydroxytamoxifen and *N*-desmethyl-tamoxifen, as well as secondary metabolism to 4-hydroxy-*N*-desmethyl-tamoxifen, also known as endoxifen.¹⁸ Current evidence suggests that endoxifen is the primary metabolite exerting the antiestrogen effects of tamoxifen. The production of endoxifen is dependent on the cytochrome P450 2D6 (CYP2D6), and there are clinical trial results indicating that polymorphisms in CYP2D6 are associated with a significantly higher risk of recurrent breast cancer.¹⁹ Patients are typically categorized into four distinct CYP2D6 phenotypes: extensive metabolizers, intermediate metabolizers, poor metabolizers, and ultra-rapid metabolizers. About 100 polymorphic variants have been identified for *CYP2D6*, including the common alleles **3*, **4*, **5*, and **6*, which fail to produce a functional enzyme (poor metabolizers), and **9*, **10*, **17*, **29*, and **41*, which encode CYP2D6 with impaired catalytic activity.²⁰ The most common poor metabolizer allele, **4*, accounts for 75% of such traits in individuals of European descent: the **4*/**4* genotype was associated with poorer rates of disease-free survival in women with breast cancer as compared to rates in women with at least one extensive-metabolizer allele.²¹ Another retrospective study of 1,325 German and US patients receiving adjuvant tamoxifen therapy indicated that women whose CYP2D6 genotype makes them an intermediate metabolizer or poor metabolizer indeed have a greater risk of recurrence than patients who are homozygous for the extensive metabolizer alleles (hazard ratio, 1.4); however, the analysis failed to establish significant differences in overall survival rates (hazard ratio, 1.15).²² Although these clinical and mechanistic data support the existence of an association between CYP2D6 and the outcome of tamoxifen treatment in breast cancer, not all studies have documented this association.^{23,24} Recent studies deploying a more comprehensive strategy of genotyping for CYP2D6 and other polymorphic P450s (eg, CYP2C9), suggest that prior studies that failed to find an association between tamoxifen effects and CYP2D6 genotype may have been limited by the number of genetic polymorphisms interrogated.²⁵

SOMATIC GENOME VARIATION AND CHEMOTHERAPEUTIC RESPONSE

Here we offer a few examples of acquired genome variation that influence the effects of cancer chemotherapy. Because of space limitations, we could not include all such examples, but have discussed others in the Supplementary Data online (e.g., trastuzumab and HER2,²⁶ EGFR mutations and kinase inhibitors in lung cancer,²⁷ and KRAS and kinase inhibitors in colorectal cancer²⁸).

Imatinib and BCR/ABL

Imatinib was the first member of a new class of “targeted” anticancer agents that inhibit particular tyrosine kinase enzymes instead of nonspecifically inhibiting rapidly dividing cells.²⁹ Imatinib inhibits tyrosine kinase activity caused by the most common chromosomal translocation in CML, BCR/ABL. Imatinib is also indicated for unresectable and/or

metastatic malignant gastrointestinal stromal tumors²⁹ that exhibit elevated tyrosine kinase activity caused by a gain-of-function mutation of c-kit. Resistance to imatinib has been linked to more than a dozen mutations in the BCR/ABL fusion gene that lead to resistance through a variety of mechanisms, including P-loop or activation loop conformational change and steric clashing in the binding site. This is particularly troubling because targeted inhibition of imatinib may lead to clonal selection of BCR/ABL-resistant mutants. However, if a significant number of mutations leading to resistance are due to the inability of BCR/ABL to achieve the closed conformation required for imatinib binding, molecules targeting the open conformation may be an effective alternative or concomitant therapeutic strategy. Inhibition of signaling pathways downstream of BCR/ABL could also overcome BCR/ABL kinase domain mutation resistance to imatinib. Prospective testing for imatinib-resistant BCR/ABL mutations in CML provides valuable clinical information because a small number of mutations account for the majority of resistant cases.³⁰ Second-generation BCR/ABL inhibitors such as dasatinib and nilotinib are able to overcome resistance caused by some BCR/ABL mutations; however, the T351I BCR/ABL mutation remains refractory to both therapies. Dasatinib also has activity against additional downstream kinases, making it a particularly attractive therapeutic option. The decision as to whether to treat patients with imatinib is based on the presence of genetic biomarkers, including BCR/ABL, as well as *c-KIT* and *PDGFR* gene rearrangements.

Jak2 mutations and JAK2 inhibitors

Activating mutations of Janus kinase 2 (Jak2), including the substitution of phenylalanine for valine 617, make hematopoietic cells more responsive to growth factors; a high proportion of patients with myeloproliferative disorders harbor this type of mutation. In addition to their role in myeloproliferative disorders, at least 10 distinct mutations in JAK2 have been linked with hematological malignancies, including ALL, CML, and AML.³¹ Translocations of JAK2 with ETV6 (an ETS family transcription factor) and PCM1 (pericentriolar material 1) have been reported, and it is likely that these translocations engender constitutive tyrosine kinase activity. Although no Jak2 inhibitors are currently approved by the Food and Drug Administration for any indication, more than half a dozen companies are currently developing Jak2 inhibitors. As with many tyrosine kinase inhibitors, a potential problem facing Jak2 inhibition as a therapeutic mechanism is lack of specificity for mutated Jak2. The function of Jak2 is critical for hematopoiesis; therefore, blocking wild-type Jak2 function may have undesired effects. In this context, inhibitors that are specific for mutant Jak2 would be an attractive alternative. JAK inhibition may be of particular importance as a therapeutic strategy in the treatment of a subgroup of patients with ALL who are known to have a poor prognosis, as recently identified by different studies.^{32,33} These patients have no evidence of chromosomal rearrangement and a gene expression signature related to activated tyrosine kinase signaling, in particular, similar to patients with the t(9;22)(q34;q11) translocation,⁵ that encodes the constitutively active BCR/ABL tyrosine kinase and is a major unfavorable marker in ALL. In these patients, activating mutations of JAKs have been reported to be present; these mutations have been shown to result in increased sensitivity to the cytotoxic activity of JAK inhibitors *in vitro*.³⁴

Somatic changes altering cellular pharmacokinetics/pharmacodynamics and drug sensitivity

Genomic changes in cancer cells can alter *de novo* sensitivity or acquired resistance to cancer chemotherapy by modulating the cellular disposition of anticancer agents. Examples include the acquisition of additional copies of chromosomes that carry genes encoding drug transporters or drug metabolizing enzymes, leading to changes in the accumulation of the active drug in cancer cells. This phenomenon has been shown for methotrexate and either the reduced folate carrier³⁵ or γ -glutamyl hydrolase.³⁶ The levels of expression of certain

genes in cancer cells have also been linked to drug resistance and treatment response in some cancers.³⁷ The association of amplification of dihydrofolate reductase (DHFR) with methotrexate (MTX) resistance and the association of overexpression of MDR1 (*ABCB1*) with doxorubicin resistance are classic examples of somatic changes leading to acquired drug resistance. More recently, somatic deletions of genes regulating MSH2 stability have been shown to cause DNA mismatch repair deficiency and increase resistance of ALL cells to thiopurines.³⁸

TRANSLATING PHARMACOGENOMICS INTO CLINICAL PRACTICE

The science of pharmacogenomics has always been “translational,” in part because many of the initial discoveries of inherited differences in drug response were made in humans (e.g., ethnic differences in isoniazid-induced peripheral neuropathy,³⁹ exacerbated hypotensive effects of debrisoquine and the subsequent discovery of its association with CYP2D6,⁴⁰ and family studies of TPMT activity in normal blood donors and the subsequent discovery of its link with thiopurine toxicity⁴¹). Some argue that these early discoveries represent some of the most penetrant pharmacogenetic traits (“low-hanging fruit”), and that many future pharmacogenomic associations will be more subtle and perhaps represent only one of several genomic determinants of drug response (i.e., polygenetic traits). Given that pharmacogenomic associations such as the ones between CYP2D6 and codeine, between TPMT and thiopurines, between CYP2C19 and clopidogrel, and between CYP2C9/VKORC1 and warfarin are considered to be among the “strongest” drug-response phenotype–genotype associations, it is difficult to explain why these have been slow to migrate to the clinic. In such a situation, what is the likelihood that less penetrant pharmacogenetic tests will ever become a routine part of medical care? In each of the prior examples, the role of pharmacogenetic testing is to alter the risk of toxicity but not efficacy (thiopurine and TPMT); to avoid prescribing a drug that cannot be activated, albeit in a non-life-threatening situation (codeine and CYP2D6); or to prescribe a drug for which there are other tests (e.g., international normalized ratio) to guide dosing (warfarin and CYP2C9/VKORC1). Some argue that, in these situations, it is just not worth the time, effort, or expense of carrying out pharmacogenomic testing. These arguments fall short, however, if one has an inexpensive, easy, and reliable way to diagnose these inherited determinants of drug response such as a high-throughput genotyping array that can yield robust genotypes for pennies per test (and one need have the test done only once in a lifetime). This begins to change the equation, even when the illness for which prescribing is being optimized is something as “benign” as a toothache. And the rationale for testing grows stronger if one is avoiding potentially life-threatening toxicity such as thiopurine hematopoietic toxicity or improving anticoagulation for serious cardiovascular diseases by optimizing warfarin or clopidogrel therapy.

One of the challenges facing the medical and pharmaceutical fields is determining what constitutes a sufficient body of evidence to migrate a given pharmacogenomic test into routine clinical practice. This issue has recently been reviewed and is the subject of ongoing efforts to establish a mechanism through which available data can be vetted and consensus reached on the appropriate health-care situations (i.e., genes, drugs, and illnesses) for translating pharmacogenomic tests to the clinic (e.g., the Clinical Pharmacogenomics Implementation Consortium⁴²). Waiting for results from prospective, randomized clinical trials will probably mean that many important tests will never reach the patient’s bedside because there are too few resources to conduct such trials within the academic community and too few incentives to do so outside academia. In the absence of aggressive marketing efforts to push forward the utilization of these tests (unlike many medical innovations that have been actively promoted, such as proton beam radiation therapy), or landmark liability cases, or Food and Drug Administration requirements for pharmacogenetic testing before a

drug can be marketed or prescribed (e.g., Herceptin), or financial gains for health-care providers/insurers, it will probably be left to science and healthcare providers to drive prospective (preemptive) pharmacogenetic testing into routine clinical practice. Usage of pharmacogenomic testing may also be accelerated by well-informed and proactive patients who insist on knowing their *CYP2D6* genotypes before leaving the dental office with a codeine prescription or before initiating therapy with warfarin or clopidogrel.

One would think that, in cancer chemotherapy at least, where the risk of potentially life-threatening drug toxicity and the risk of subtherapeutic treatment (i.e., potential progression of the cancer) would make the consequences of suboptimal drug selection or dosing too compelling to ignore, pharmacogenetic data would come into use in individualizing treatment regimens. Yet, in the area of cancer therapy there are still relatively few centers where pharmacogenetic testing is a routine part of drug selection and dosing for most patients. It is not uncommon to hear: “We have done it this way for 50 years; why do we need to do genetic testing now?” Certainly, we did without computers for thousands of years, but remove the computer today and out go magnetic resonance imaging, the computed tomography scan, the electronic medical record, the controlled intravenous infusion of fluids and medications, and so on. We can certainly survive without computers, but why would we want to? Technology is making the determination of genotypes simple, robust, and cheap; the big challenge now is doing the science and clinical trials that are needed to establish when and how to use pharmacogenetic tests to improve drug therapy and health-care outcomes. Such science, coupled with technology to yield user-friendly decision support systems, will make pharmacogenomic tests more readily interpretable and actionable for clinicians. As this is accomplished, the deployment of pharmacogenomic testing will augment, although never replace, the clinical acumen of physicians, pharmacists, and others making treatment decisions for individual patients. Pharmacogenomics can help to make those decisions more science and less art and, in the ultimate analysis, better for patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported, in part, by National Institutes of Health grants R37CA36401 (W.E.E.) National Institutes of Health/National Institute of General Medical Sciences Pharmacogenomics Research Network grant U01 GM92666 (W.E.E.) and F32 CA141762 (S.W.P.), and American Lebanese Syrian Associated Charities (ALSAC).

Literature Cited

1. Innocenti F, et al. Comprehensive pharmacogenetic analysis of irinotecan neutropenia and pharmacokinetics. *J Clin Oncol.* 2009; 27:2604–2614. [PubMed: 19349540]
2. Treviño LR, et al. Germline genetic variation in an organic anion transporter polypeptide associated with methotrexate pharmacokinetics and clinical effects. *J Clin Oncol.* 2009; 27:5972–5978. [PubMed: 19901119]
3. Yang JJ, et al. Ancestry and pharmacogenomics of relapse in acute lymphoblastic leukemia. *Nat Genet.* 2011; 43:237–241. [PubMed: 21297632]
4. Elion GB. The purine path to chemotherapy. *Science.* 1989; 244:41–47. [PubMed: 2649979]
5. Pui CH, Evans WE. Treatment of acute lymphoblastic leukemia. *N Engl J Med.* 2006; 354:166–178. [PubMed: 16407512]
6. Stocco G, et al. Genetic polymorphism of inosine triphosphate pyrophosphatase is a determinant of mercaptopurine metabolism and toxicity during treatment for acute lymphoblastic leukemia. *Clin Pharmacol Ther.* 2009; 85:164–172. [PubMed: 18685564]

7. Krynetski E, Evans WE. Drug methylation in cancer therapy: lessons from the TPMT polymorphism. *Oncogene*. 2003; 22:7403–7413. [PubMed: 14576848]
8. Paugh SW, Stocco G, Evans WE. Pharmacogenomics in pediatric leukemia. *Curr Opin Pediatr*. 2010; 22:703–710. [PubMed: 20861736]
9. Relling MV, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing. *Clin Pharmacol Ther*. 2011; 89:387–391. [PubMed: 21270794]
10. Relling MV, et al. Mercaptopurine therapy intolerance and heterozygosity at the thiopurine S-methyltransferase gene locus. *J Natl Cancer Inst*. 1999; 91:2001–2008. [PubMed: 10580024]
11. Stocco G, Crews KR, Evans WE. Genetic polymorphism of inosine-triphosphate-pyrophosphatase influences mercaptopurine metabolism and toxicity during treatment of acute lymphoblastic leukemia individualized for thiopurine-S-methyl-transferase status. *Expert Opin Drug Saf*. 2010; 9:23–37. [PubMed: 20021291]
12. Evans WE, et al. Preponderance of thiopurine S-methyltransferase deficiency and heterozygosity among patients intolerant to mercaptopurine or azathioprine. *J Clin Oncol*. 2001; 19:2293–2301. [PubMed: 11304783]
13. Pui CH, Robison LL, Look AT. Acute lymphoblastic leukaemia. *Lancet*. 2008; 371:1030–1043. [PubMed: 18358930]
14. Pui CH, et al. Improved outcome for children with acute lymphoblastic leukemia: results of Total Therapy Study XIIIIB at St Jude Children's Research Hospital. *Blood*. 2004; 104:2690–2696. [PubMed: 15251979]
15. Relling MV, Pui CH, Cheng C, Evans WE. Thiopurine methyltransferase in acute lymphoblastic leukemia. *Blood*. 2006; 107:843–844. [PubMed: 16401827]
16. Hoskins JM, Carey LA, McLeod HL. CYP2D6 and tamoxifen: DNA matters in breastcancer. *Nat Rev Cancer*. 2009; 9:576–586. [PubMed: 19629072]
17. Schroth W, et al. CYP2D6 polymorphisms as predictors of outcome in breast cancer patients treated with tamoxifen: expanded polymorphism coverage improves risk stratification. *Clin Cancer Res*. 2010; 16:4468–4477. [PubMed: 20515869]
18. Wu X, Hawse JR, Subramaniam M, Goetz MP, Ingle JN, Spelsberg TC. The tamoxifen metabolite, endoxifen, is a potent antiestrogen that targets estrogen receptor alpha for degradation in breast cancer cells. *Cancer Res*. 2009; 69:1722–1727. [PubMed: 19244106]
19. Goetz MP, et al. The impact of cytochrome P450-2D6 metabolism in women receiving adjuvant tamoxifen. *Breast Cancer Res Treat*. 2007; 101:113–121. [PubMed: 17115111]
20. Jin Y, et al. CYP2D6 genotype, antidepressant use, and tamoxifen metabolism during adjuvant breast cancer treatment. *J Natl Cancer Inst*. 2005; 97:30–39. [PubMed: 15632378]
21. Goetz MP, et al. Pharmacogenetics of tamoxifen biotransformation is associated with clinical outcomes of efficacy and hot flashes. *J Clin Oncol*. 2005; 23:9312–9318. [PubMed: 16361630]
22. Schroth W, et al. Association between CYP2D6 polymorphisms and outcomes among women with early stage breast cancer treated with tamoxifen. *JAMA*. 2009; 302:1429–1436. [PubMed: 19809024]
23. Park IH, et al. Lack of any association between functionally significant CYP2D6 polymorphisms and clinical outcomes in early breast cancer patients receiving adjuvant tamoxifen treatment. *Breast Cancer Res Treat*. 2011 e-pub ahead of print 25 March 2011.
24. Madlensky L, et al. Tamoxifen Metabolite Concentrations, CYP2D6 Genotype, and Breast Cancer Outcomes. *Clin Pharmacol Ther*. 2011; 89:718–725. [PubMed: 21430657]
25. Mürdter TE, et al. Activity levels of tamoxifen metabolites at the estrogen receptor and the impact of genetic polymorphisms of phase I and II enzymes on their concentration levels in Plasma. *Clin Pharmacol Ther*. 2011; 89:708–717.
26. Slamon DJ, et al. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. *Science*. 1989; 244:707–712. [PubMed: 2470152]
27. Lynch TJ, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med*. 2004; 350:2129–2139. [PubMed: 15118073]

28. Allegra CJ, et al. American Society of Clinical Oncology provisional clinical opinion: testing for KRAS gene mutations in patients with metastatic colorectal carcinoma to predict response to anti-epidermal growth factor receptor monoclonal antibody therapy. *J Clin Oncol*. 2009; 27:2091–2096. [PubMed: 19188670]
29. Klein TE, et al. Integrating genotype and phenotype information: an overview of the PharmGKB project. *Pharmacogenetics Research Network and Knowledge Base. Pharmacogenomics J*. 2001; 1:167–170. [PubMed: 11908751]
30. Shah NP, et al. Multiple BCR-ABL kinase domain mutations confer polyclonal resistance to the tyrosine kinase inhibitor imatinib (STI571) in chronic phase and blast crisis chronic myeloid leukemia. *Cancer Cell*. 2002; 2:117–125. [PubMed: 12204532]
31. Sayyah J, Sayeski PP. Jak2 inhibitors: rationale and role as therapeutic agents in hematologic malignancies. *Curr Oncol Rep*. 2009; 11:117–124. [PubMed: 19216843]
32. Mullighan CG, et al. Deletion of IKZF1 and prognosis in acute lymphoblastic leukemia. *N Engl J Med*. 2009; 360:470–480. [PubMed: 19129520]
33. Den Boer ML, et al. A subtype of childhood acute lymphoblastic leukaemia with poor treatment outcome: a genome-wide classification study. *Lancet Oncol*. 2009; 10:125–134. [PubMed: 19138562]
34. Mullighan CG, et al. JAK mutations in high-risk childhood acute lymphoblastic leukemia. *Proc Natl Acad Sci USA*. 2009; 106:9414–9418. [PubMed: 19470474]
35. Belkov VM, et al. Reduced folate carrier expression in acute lymphoblastic leukemia: a mechanism for ploidy but not lineage differences in methotrexate accumulation. *Blood*. 1999; 93:1643–1650. [PubMed: 10029593]
36. Cheng Q, Yang W, Raimondi SC, Pui CH, Relling MV, Evans WE. Karyotypic abnormalities create discordance of germline genotype and cancer cell phenotypes. *Nat Genet*. 2005; 37:878–882. [PubMed: 16041371]
37. Holleman A, et al. Gene-expression patterns in drug-resistant acute lymphoblastic leukemia cells and response to treatment. *N Engl J Med*. 2004; 351:533–542. [PubMed: 15295046]
38. Diouf B, et al. Somatic deletions of genes regulating MSH2 protein stability cause DNA mismatch repair deficiency and drug resistance in human leukemia cells. *Nature Med*. 2011 in press.
39. Evans DA, Manley KA, McKusick VA. Genetic control of isoniazid metabolism in man. *Br Med J*. 1960; 2:485–491. [PubMed: 13820968]
40. Gonzalez FJ, et al. Characterization of the common genetic defect in humans deficient in debrisoquine metabolism. *Nature*. 1988; 331:442–446. [PubMed: 3123997]
41. Weinshilboum RM, Sladek SL. Mercaptopurine pharmacogenetics: monogenic inheritance of erythrocyte thiopurine methyltransferase activity. *Am J Hum Genet*. 1980; 32:651–662. [PubMed: 7191632]
42. Relling MV, Klein TE. CPIC: Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network. *Clin Pharmacol Ther*. 2011; 89:464–467. [PubMed: 21270786]

CANCER PHARMACOGENOMICS

Figure 1.

In cancer pharmacogenomics, there are at least two genomes of importance: the patient's germline genome (inherited genome variation) and the tumor genome (inherited genome variation plus acquired genome variation). Moreover, there may be additional acquired genome variations in metastatic or recurrent tumor cells that influence drug response and treatment outcome. A comprehensive pharmacogenomic strategy interrogates multiple mechanisms of genome variation in both germline and tumor genetic material (blue box), assessing their influence on multiple drug-response phenotypes (green box). GWAS, genome-wide association studies.

Figure 2.

For drug-response phenotypes, it is not uncommon for an inherited variation in one gene to have a dominant effect on drug disposition or response phenotype (left panel). However, once the treatment is adjusted for the predominant inherited determinant of drug disposition or response (right panel), additional, less penetrant genetic polymorphisms may emerge as being significant (a recent example involves the use of mercaptopurine and polymorphisms of TPMT (thiopurine-*S*-methyltransferase) and ITPA (inosine triphosphate pyrophosphatase).⁶