Using Pharmacogene Polymorphism Panels to Detect Germline Pharmacodynamic Markers in Oncology
Daniel L. Hertz1 and Howard L. McLeod2,3

Abstract
The patient (germline) genome can influence the pharmacokinetics and pharmacodynamics of cancer therapy. The field of pharmacogenetics (PGx) has primarily focused on genetic predictors of pharmacokinetics, largely ignoring pharmacodynamics, using a candidate approach to assess single-nucleotide polymorphisms (SNP) with known relevance to drug pharmacokinetics such as enzymes and transporters. A more comprehensive approach, the genome-wide association study, circumvents candidate selection but suffers because of the necessity for substantial statistical correction. Pharmacogene panels, which interrogate hundreds to thousands of SNPs in genes with known relevance to drug pharmacokinetics or pharmacodynamics, represent an attractive compromise between these approaches. Panels with defined or customizable SNP lists have been used to discover SNPs that predict pharmacokinetics or pharmacodynamics of cancer drugs, most of which awaited successful replication. PGx discovery, particularly for SNPs that influence drug pharmacodynamics, is limited by weaknesses in both genetic and phenotypic data. Selection of candidate SNPs for inclusion on pharmacogene panels is difficult because of limited understanding of biology and pharmacology. Phenotypes used in analyses have primarily been complex toxicities that are known to be multifactorial. A more measured approach, in which sensitive phenotypes are used in place of complex clinical outcomes, will improve the success rate of pharmacodynamics SNP discovery and ultimately enable identification of pharmacodynamics SNPs with meaningful effects on treatment outcomes.

See all articles in this CCR Focus section, "Progress in Pharmacodynamic Endpoints."

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Introduction
The promise of pharmacogenetics (PGx) is to select the right dose of the right drug for the right tumor in the right patient. In this paradigm of individualized cancer therapy, drug and dose selection are guided by knowledge of somatic (tumor) and patient (germline) genetics (1, 2). These two genomes contain different information that is relevant to the patient, his or her disease, and the optimal course of therapy.

Immense progress has been made in identifying somatic genetic aberrations responsible for oncogenic conversion, describing their utility as markers of disease prognosis, and using them to inform decisions on treatment aggressiveness (3). Selection of the right drug for the right tumor is being realized through development of targeted agents that are highly effective in tumors harboring specific somatic variants. Clinical implementation of tumor genomic analysis to guide therapeutic selection is under way (4). In terms of choosing the correct drug for the correct tumor to maximize efficacy, the somatic genome is a critical source of genetic information.

The germline (patient) genome is less relevant to treatment efficacy, but still informative for drug and dose selection. The germline genome influences treatment outcomes through two systems, pharmacokinetics (PK) and pharmacodynamics (PD; ref. 5). Most germline PGx work has focused on PK relevant genes, including drug metabolizing enzymes and transporters. Activity of these proteins dictates the patient’s drug exposure, which is critical for determining efficacy and toxicity for many drugs, especially chemotherapeutic agents (Fig. 1). Variation in PK genes can be used to individualize dosing, such as decreasing 6-mercaptopurine or 6-thioguanine doses in patients with low-activity germ-line TPMT variants (6).

In oncology, the term pharmacodynamics typically refers to the biochemical response to modulation of an oncogenic pathway in cancer cells, but pharmacodynamics applies equally to the response in noncancer cells (Fig. 2). Whether this response occurs in a cancer or noncancer cell dictates whether PD leads to efficacy or toxicity, respectively. Germline genetic variation in drug targets
or effectors can modulate the magnitude of the downstream response, either enhancing or limiting the efficacy/toxicity of therapy. At this time, it seems that the role of germline genetics in efficacy determination is pretty limited, aside from the influence of BRCA variation on PARP inhibitor response (7). Alternatively, the extraordinary variability in patient sensitivity to treatment-related adverse effects is likely explained by variation in off-target drug receptors or effectors of toxicity development or resolution. As an illustrative example of a possible pharmacodynamic PGx interaction, germline variability in \( TUBB2A \) seems to affect expression of \( \beta \)-tubulin (8), the known target of paclitaxel, and patients carrying \( TUBB2A \) polymorphisms may be at increased risk of paclitaxel-induced neuropathy (9). A comprehensive understanding of germline PD markers would enable toxicity sensitivity prediction and inform therapeutic decision making to select the correct drug for the correct patient.

The progress toward realizing the goal of genetically informed cancer treatment individualization has been impeded by an inability to discover and validate germline PD markers that predict toxicity sensitivity. This can be partially attributed to the reliance on candidate single-nucleotide polymorphism (SNP) studies and genome-wide association studies (GWAS), neither of which is optimized for discovery of germline genetic PD markers. This article highlights the challenges, progress, and future of discovering germline genetic PD markers. The first section introduces the limitations of candidate-SNP and GWAS discovery. The second section summarizes the use of SNP panels, both for PK and PD marker discovery, as an attractive compromise between these two more established methods. The final section makes specific recommendations for improving PGx analyses to facilitate discovery of germline PD markers that have clinically meaningful effects on cancer treatment outcomes.

Limitations of PGx Discovery Approaches

Candidate-SNP and GWAS represent two ends of a continuum of depth and breadth. Candidate PCx studies, which interrogate a single or small group of SNPs with known putative mechanistic importance, are ideal for marker validation. On the other end of the spectrum is the genome-wide approach in which SNPs distributed throughout the genome are simultaneously assessed, enabling discovery of markers in genes without regard for existing evidence of importance. Most PGx analyses have used either of these approaches; however, neither has been a panacea for PGx discovery in part because of their unique statistical limitations. Candidate-SNP studies have been criticized for a high rate of false-positive findings and overestimation of effect sizes, whereas the multiple comparisons correction necessary in a GWAS leads to false negatives (10). In addition to general statistical challenges, candidate-SNP and GWAS studies have specific PD-relevant limitations in the genotype and phenotype data being analyzed.

Genotyping in candidate-SNP studies

The candidate-SNP approach relies on the investigator’s knowledge of which genes are relevant to the phenotype. For a variety of reasons, the understanding of drug
movement throughout the body is more advanced than the understanding of drug action within the body, hence the focus on PK markers in candidate-SNP studies. PK is limited to a small number of processes—absorption, distribution, metabolism, and excretion—which are consistent across drugs and carried out by a tractable number of proteins. Understanding of the genes, proteins, and processes in the PK system, as naive as it may currently be, far outpaces that of the PD system. Mechanisms of action of many drugs, particularly in oncology, are not definitively determined. Beyond that, there is little understanding of the interactions of drugs with targets, downstream consequences of those interactions, and mechanisms underlying toxicity development and resolution. PD processes are not broadly shared across chemical or mechanistic classes of drugs; PD is drug, organ, and outcome specific, exponentially increasing the scope and complexity of the system while dispersing the research efforts. For these reasons, effective selection of PD markers for candidate-SNP studies remains a major challenge.

**Genotyping in genome-wide association studies**

Simultaneous interrogation of SNPs distributed across the genome was expected to overcome the major limitation of the candidate-SNP approach by eliminating the necessity for effective candidate selection. However, GWAS has other limitations, some of which are highlighted by Low and colleagues elsewhere in this CCR Focus section (11). GWAS chips have pretty good coverage of PK genes but lower coverage of known PD genes (12). In addition, GWAS chips were designed to focus on tag SNPs that give representation to as many linkage blocks or regions as possible; to cover
most areas of the genome, making it difficult to identify the putative functional variant in a region of association.

**Phenotyping in PD PGx discovery**

For PK studies, drug exposure represents a relatively easily collected phenotype; however, in vivo PD phenotypes are less well established, as described in this CCR Focus section by Gainor and colleagues (13). The current NCI clinical trials measures of toxicity are ordinal in nature and do not allow for accurate quantitation of phenotype severity or complexity. More importantly, toxicity is not a clean phenotype analogous to drug exposure. Most toxicities, like complex diseases, are highly multifactorial and are influenced by PK, PD, and other factors that are difficult to quantify such as environment, diet, and comorbidities (14). Because many factors contribute to the phenotype, the importance of any single factor, such as a SNP, is marginal, making direct detection of true associations with clinically important outcomes very difficult (15).

**Germline SNP Panels**

An ideal compromise between the narrow (candidate-SNP) and broad (GWAS) genotyping methods would maintain the efficiency of simultaneous parallel genotyping while limiting the required statistical correction by including only candidate SNPs with putative importance. This compromise is realized in SNP panels that interrogate hundreds to thousands of SNPs in relevant pharmacogenes. Investigators have the option to use pharmacogene panels with a defined list of candidate SNPs or custom panels that allow the investigator to choose their candidate genes and SNPs.

**SNP panels for PD discovery**

Somatic PD panels have been successfully utilized to identify oncogenic mutations, translocations, and amplifications within specific tumor types (16), but germline PD panels have been less successful at discovering germline predictors of treatment toxicity. This imbalance is partially because of the imbalance in the mechanistic understanding of oncogenesis versus toxicity. Enhanced understanding of toxicity PD mechanisms will improve SNP candidate selection for PD panels, to test for associations with clean PD phenotypes. Similarly, PK SNP panels should be used to identify genetic predictors of drug PK in cohorts with drug exposure data. When panel content and phenotype are not strongly aligned skepticism of initial findings is warranted.

**Panels with defined SNP lists**

Currently available germline pharmacogene SNP panels, including the DMET Plus (Affymetrix, Inc.), VeraCode ADME Core Panel (Illumina, Inc.), and the iPLEX ADME PGx panel (Sequenom, Inc.), are heavily enriched for PK-relevant pharmacogenes (Table 1). However, these panels do include some markers in known PD genes and could be used, in carefully planned analyses, to discover germline PD genetic associations (Fig. 3). These panels return accurate genotype calls (17) with only slightly diminished performance when using whole-genome–amplified DNA (18) or DNA from nonblood sources such as saliva or buccal swab (19). Open source or commercially available software for basic data storage and analysis are available, facilitating the use of these tools by investigators (20, 21).

DMET Plus was the first pharmacogene panel with a defined SNP list to become available and the only one with published results in oncology PGx to our knowledge. This chip has been used in several tumor types and treatment regimens to find genetic predictors of a variety of clinical phenotypes (Table 2). Three published studies have used DMET for discovering predictors of oncology drug PK, the ideal use of a PK-centric SNP panel. ten Brink and colleagues identified 7 SNPs and haplotypes that were associated with busulfan PK in a discovery cohort, but the clearance algorithm performed poorly in the validation set ($r^2 = 0.028$; ref. 22). The one haplotype (GSTAS: rs4715354 and rs7746993) associated with clearance in the validation cohort is in linkage disequilibrium with a GSTA1 SNP (rs3957357) that was previously known to influence busulfan clearance (23, 24). A study from de Graan and colleagues used a similar two-stage method to develop a 14-SNP model that accurately predicted which patients in the validation set would have low paclitaxel clearance [adjusted $OR = 10.9$ (95% CI, 1.4–86.3) $P = 0.024$; ref. 25]. The model, which had impressive sensitivity (20/21 = 95%) but poor positive predictive value (20/93 = 22%), was built from SNPs with no known influence on paclitaxel PK whereas genes with

<table>
<thead>
<tr>
<th>Panel</th>
<th>DMET plus</th>
<th>VeraCode ADME core panel</th>
<th>iPLEX ADME PGx panel</th>
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<tr>
<td>Company</td>
<td>Affymetrix, Inc.</td>
<td>Illumina, Inc.</td>
<td>Sequenom, Inc.</td>
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<td>Genes (total)</td>
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<td>34</td>
<td>36</td>
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<td>PK genes</td>
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<tr>
<td>PD genes</td>
<td>46</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total SNPs</td>
<td>1,931</td>
<td>180</td>
<td>192</td>
</tr>
<tr>
<td>Gene copy number variants</td>
<td>GSTM1, GSTT1, UGT2B17</td>
<td>4: GSTM1, GSTT1, SULT1A1, UGT2B17</td>
<td>7: CYP2A6, CYP2B6, CYP2D6, GSTT2B, GSTT1, SULT1A1, UGT2B17</td>
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assumed relevance such as CYP2C8/3A4, SLCO1B1/1B3, and ABCB1 (26–30) did not make it into the model. The third study, from Uchiyama and colleagues, used a hybrid two-stage design that identified 28 SNPs associated with docetaxel PK that were then tested for an association with grade 4 neutropenia (31). The hits from the discovery set included genes implicated in docetaxel transport such as ABCB1 (32) and SLCO1B1 (33), but the SNP in CYP39A1 (rs7761731) that was nominally replicated (OR = 9; P = 0.049) lacks known mechanistic relevance. Notably, the two studies assessing taxane PK had no overlap in identified SNP hits.

The remaining studies used the DMET Plus panel to discover predictors of a clinical outcome (Table 2). Given the multifactorial nature of the outcomes, use of composite phenotypes, and inclusion of patients on combination therapy, these associations deserve additional scrutiny and require independent replication and/or mechanistic validation. Deeken and colleagues identified 10 SNPs from 3 genes that predicted tumor response and 11 SNPs from 8 genes that predicted severe toxicity in 47 patients with castrate-resistant prostate cancer treated with docetaxel with or without thalidomide (34). None of the SNPs reported in this analysis overlap with those reported by Uchiyama and colleagues, suggesting that if they are true associations they must be working through a PD mechanism. Iacobucci and colleagues reported associations of ALDH1A with treatment response, CYP2E1 and SLCO1B1 with toxicity, and...
<table>
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<tr>
<th>Phenotype Drug</th>
<th>Discovery</th>
<th>Replication</th>
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<tbody>
<tr>
<td><strong>PK</strong>&lt;br&gt;Ten Brink et al. (22)&lt;br&gt;Busulfan Clearance</td>
<td>65</td>
<td>1 haplotype GSTA5 rs4715354 rs7746993</td>
</tr>
<tr>
<td><strong>PK</strong>&lt;br&gt;De Graan et al. (25)&lt;br&gt;Paclitaxel Clearance</td>
<td>140</td>
<td>130 Used 14-SNP model developed in discovery cohort</td>
</tr>
<tr>
<td><strong>PK</strong>&lt;br&gt;Uchiyama et al. (31)&lt;br&gt;Docetaxel Area under the curve</td>
<td>10</td>
<td>Not attempted</td>
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<tr>
<td><strong>Treatment outcome</strong>&lt;br&gt;Deeken et al. (34)&lt;br&gt;Docetaxel + thalidomide Clinical response</td>
<td>47</td>
<td>Not attempted</td>
</tr>
<tr>
<td><strong>Treatment outcome</strong>&lt;br&gt;Deeken et al. (34)&lt;br&gt;Docetaxel + thalidomide Grade 3+ toxicity</td>
<td>47</td>
<td>Not attempted</td>
</tr>
<tr>
<td><strong>Iacobucci et al. (35)&lt;br&gt;Gemtuzumab-ozogamicin, fludarabine, cytarabine, and idarubicin Clinical response</strong></td>
<td>91</td>
<td>Not attempted</td>
</tr>
<tr>
<td><strong>Iacobucci et al. (35)&lt;br&gt;Gemtuzumab-ozogamicin, fludarabine, cytarabine, and idarubicin Liver toxicity</strong></td>
<td>91</td>
<td>Not attempted</td>
</tr>
<tr>
<td><strong>Rumiato et al. (36)&lt;br&gt;5-Fluorouracil-based chemotherapy Infusion reaction</strong></td>
<td>91</td>
<td>Not attempted</td>
</tr>
<tr>
<td><strong>Di Martino et al. (37)&lt;br&gt;Zoledronic acid Osteonecrosis of the jaw</strong></td>
<td>91</td>
<td>Not attempted</td>
</tr>
<tr>
<td><strong>Di Martino et al. (37)&lt;br&gt;Irinotecan GI toxicity</strong></td>
<td>91</td>
<td>Not attempted</td>
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</table>

**Abbreviation:** GI, gastrointestinal.
SULT2B1 and SLC22A12 with infusion reactions in 91 patients with acute myeloid leukemia (AML) receiving combination therapy (35). Rumiato and colleagues identified a variant in CHST1 (rs978901) that was associated with grade 3+ toxicity in 104 patients with colorectal cancer treated with 5-fluorouracil–based adjuvant chemotherapy (36). Di Martino and colleagues reported variants in ABCC5 (rs562), ABCG1 (rs425215), and SLC01B1 (rs2306283) that were associated with grade 3+ gastrointestinal toxicity in irinotecan-treated patients (37). Interestingly, this SLC01B1 SNP has been identified in other candidate association studies to be a predictor of irinotecan toxicity risk (38, 39). This same group published a case–control analysis of zoledronic acid–induced osteonecrosis of the jaw, which identified SNPs in PPARC, ABP1, CHST11, and CROT (40); however, none of these genes were associated with this phenotype in a large GWAS (41). Finally, we have reported preliminary findings that a SNP in ABCG1 (rs492338) may be a marker for paclitaxel-induced sensory neuropathy (42). Each of these studies has reported SNPs that are worth following up with PGx replication or mechanistic validation, but it is very likely that most are false-positive findings attributable to insufficient statistical rigor.

Panels with customizable SNP lists

The alternative to using PK-centric, defined SNP list panels, for investigators interested specifically in discovering PD SNPs, is to design a custom panel. This approach enables creation of a panel that includes all genes relevant to the drug and phenotype of interest while excluding all other genes to limit the statistical penalty. It can be time and labor intensive to select candidate SNPs, and these selections will be based on extremely limited understanding of PD. Unsurprisingly, the vast majority of attempts at custom panel creation have focused on PK genes. Another important consideration for interpreting initial findings from custom panels is that every association will, by definition, have a putative mechanistic explanation, making it even more difficult to differentiate false positives from true positives.

The Illumina Goldengate platform is commonly used for creating custom chips (43). Ross and colleagues designed a panel that interrogates 1,949 SNPs in 220 drug metabolism, transport, and elimination genes, similar to the DMET chip. They reported the discovery of SNPs in TPMT and COMT that predict cisplatin-induced ototoxicity in 54 pediatric oncology patients, and then replicated the associations in an independent cohort of 112 patients, although limited methodologic information makes it difficult to assess the adequacy of statistical correction (44). Further sequencing revealed putative causative variants, including a loss of function TPMT3A haplotype (rs1142345 and rs1800460) and a low-activity synonymous COMT SNP (rs4818). Somewhat surprisingly, given the custom chip design, neither gene has a strong mechanistic basis for influencing cisplatin-induced ototoxicity. The same group published a second independent replication of TPMT, but not COMT, in 155 patients with cisplatin-treated pediatric cancer with adjustment for relevant covariates (45). However, an independent group of investigators was unable to replicate this association in 213 patients with cisplatin-treated pediatric cancer and performed preclinical studies that failed to support any of the proposed mechanisms underlying this interaction (46). This led to several editorials contrasting the studies in an attempt to explain the discrepant results (47, 48). It is possible that this association is limited to only a subset of patients and that retrospective analyses, which cannot adequately control confounding, will continue to have difficulty verifying the association, similar to previous highly debated pharmacogenetic associations in oncology (49–51). This group has also utilized their custom platform to discover SNPs predictive of anthracycline-induced cardiotoxicity (52), including a protective SNP in SLC28A3 (rs7853758) that displayed a concordant effect in an independent patient cohort (53).

Another custom Goldengate panel was used to assess 139 SNPs in 10 genes relevant to cytosine arabinosine (Ara-C) transport and metabolism (54). After multiple comparisons, correction, and adjustment for relevant prognostic factors one SNP in DCK (rs4694362) was associated with overall survival [HR = 33.20 (4.94–223.27)]. Bonferroni-adjusted P = 0.017, and an interaction between SNPs in SLC29A1 and TYMS was associated with relapse-free survival [HR = 17.63 (4.83–63.47)]. Bonferroni-adjusted P = 0.021 in 97 patients with AML. There has been independent replication that DCK is a PD marker of Ara-C efficacy (55), and additional validation in independent cohorts is of high interest. Caronia and colleagues created a custom panel to search for predictors of treatment effectiveness in 91 patients with osteosarcoma treated with combination therapy (56). Their custom panel included 346 SNPs and two copy-number variants in 24 genes relevant to the transport or metabolism of five drugs used in this treatment setting (cisplatin, doxorubicin, methotrexate, vincristine, and cyclophosphamide). Four synonymous or intronic SNPs were significantly associated with overall survival after correcting for multiple comparisons by permutation testing, one in ABCG3 (rs4148416) and three in ABCB1 (rs418737, rs1128503, and rs10273036). Interpretation of these findings is complicated by the use of combination therapy and the lack of a putative causal variant.

The Bank-On-A-Cure (BOAC) project created a custom panel using the Affymetrix GeneChip Scanner 3000 Targeted Genotyping System that interrogates 3,404 SNPs from 983 genes relevant to multiple myeloma and the drugs used in its treatment. Their first analysis reported a multi-SNP model that differentiated patients with short (<1 year) and long (>3 year) progression-free survival [OR = 3.9 (95% CI, 2.0–7.8), P = 7.7 × 10−4]; however, no single SNP had a strong and reproducible effect (57). This panel has also been utilized to detect predictors of treatment-related toxicity. An analysis of 544 thalidomide-treated Caucasian patients identified 18 SNPs that may predict thalidomide-induced venous thromboembolism (58). Pathway analysis suggests that these SNPs were enriched for response to DNA damage, cytokine response, and apoptosis, although it is difficult to assess how much of this enrichment is because of the initial
selection of SNPs for inclusion on the chip. This group also created a 7-SNP model from recursive partitioning, but these SNPs did not overlap with the 18 SNPs previously identified and this partitioning model was unable to predict thalidomide-induced venous thromboembolism risk in an independent cohort of 111 patients with myeloma (\(P = 0.40\); ref. 59). Finally, their panel was used to discover SNPs that predict neuropathy risk in 471 bortezomib-treated patients (60). A total of 56 SNPs with nominal association (\(P < 0.05\)) in the discovery cohort, which were enriched for cardiovascular disease, genetic disorder, and neurologic disease pathways, could not be reproduced in the validation cohort, although one SNP in \(CYP17A1\) (rs619824) showed a concordant trend.

**Improving PD Germline PGx Marker Discovery**

Discovery of germline PD markers in oncology using pharmacogene panels would benefit from improved phenotype and genotype data. Development of sensitive PD endpoints to be used as endophenotypes, discussed elsewhere in this CCR Focus section, is critical for this field. Until then, another possible approach in datasets with clinical outcome and PK data would be to deconvolute the influence of PK and PD on treatment outcomes and discover PGx predictors of each independently (61). First, the PK data could be used as a clean phenotype to screen PK SNPs using a PK-centric panel. Then, the treatment outcome data could be adjusted for drug exposure, removing this source of variability, leaving a cleaner phenotype for screening PD associations. Figure 4 depicts hypothetical drug exposure, toxicity, and genetic data for 2 SNPs. Before deconvolution, the PD \(^*/C3\) allele is not predictive of drug toxicity. After accounting for variability in drug exposure, the PD \(^*/C3\) SNP is highly predictive of sensitivity to toxicity; at any given exposure level, wild-type patients have low toxicity, heterozygous patients have moderate toxicity, and homozygous variant patients have high toxicity. This illustrates the potential for deconvolution to be a valuable tool for improving discovery of both PK and PD germline SNPs.

The other area for focused effort is in identifying appropriate candidates for PD-centric SNP panels. For a given drug-induced phenotype (i.e., toxicity), the candidate list should begin with the current understanding of drug pharmacology, such as including \(\beta\)-tubulin polymorphisms in assessments of taxane-related toxicity (8), and toxicity
pathophysiology. There is evidence that genes responsible for hereditary neuropathy may be genetic predictors of drug-induced neuropathy, suggesting that causative variants from hereditary diseases, some of which have preconceived genotyping panels for diagnosis, would be reasonable candidates. Another potential source of candidates is previously reported GWAS of the toxicity and perhaps GWAS of similar phenotypes in untreated healthy patients (i.e., healthy patient neutrophil count GWAS for candidates of drug-induced neutropenia). Preclinical lines of evidence should also be mined. GWAS in animal models, such as genetically diverse mouse populations, have been used to investigate drug toxicities (62), and GWAS in immortalized noncancer cells have been used to discover PD factors influencing sensitivity to chemotherapeutic drugs (14, 63).

Conclusions

The germline genome is likely to explain the substantial variability in treatment toxicity among patients. Identification of germline PD markers of toxicity sensitivity could inform drug selection; however, discovery of the germline genetic markers dictating drug PD is an extremely difficult task. SNP panels that include PD markers have the potential to be a useful tool for approaching this challenge. Currently there are serious limitations in our understanding and measurement of drug PD, in addition to the general limitations in PCx methodologies. Continued work in understanding PD, identifying the appropriate SNPs to include on PD-centric panels, and measuring PD phenotypes will enable discovery of germline PD SNPs that can eventually be used to help clinicians select the right dose of the right drug for the right patient.

Disclosure of Potential Conflicts of Interest

H.L. McLeod is a consultant/advisory board member for Genentrix Corp.

No potential conflicts of interest were disclosed by the other author.

Authors’ Contributions

Conception and design: D.L. Hertz, H.L. McLeod

Development of methodology: D.L. Hertz

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): H.L. McLeod

Writing, review, and or revision of the manuscript: D.L. Hertz, H.L. McLeod

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