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Review

Germline pharmacogenomics in oncology: Decoding the patient for targeting therapy

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ABSTRACT

Pharmacogenomics is the study of genetic factors determining drug response or toxicity. The use of pharmacogenomics is especially desirable in oncology because the therapeutic index of oncology drugs is often narrow, the need for favorable drug response is often acute, and the consequences of drug toxicity can be life-threatening. In this review, we examine the state of pharmacogenomics in oncology, focusing only on germline pharmacogenomic variants. We consider several critical points when assessing the quality of pharmacogenomic findings and their relevance to clinical use, and discuss potential confounding factors limiting interpretation and implementation. Several of the most extensively studied drug–gene pairs (irinotecan and UGT1A1; tamoxifen and CYP2D6; 5-fluorouracil and DPYD) are inspected in depth as illustrations of both the state of advancement—and the current limitations of—present knowledge. We argue that there will likely soon be a critical mass of important germline pharmacogenomic biomarkers in oncology which deserve clinical implementation to provide optimal, personalized oncologic care. We conclude with a vision of how routine clinical testing of such germline markers could one day change the paradigm for cancer care.

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1. Introduction

Pharmacogenomics is the study of genetic factors determining response to, or toxicity from, drugs. While the field originally centered on the relationship between drugs and single

genes (pharmacogenetics), pharmacogenomics now encompasses information from the entire genome including germline variation (single nucleotide polymorphisms [SNPs], gene copy number alterations) and acquired changes (tumor mutations) as they relate to drug response or toxicity (Wang et al.,

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2011; Watson and McLeod, 2011). In contrast to disease genetics, pharmacogenomics focuses specifically on predictive genetic markers of outcome from pharmacologic interventions.

The use of pharmacogenomic markers is perhaps especially desirable in the field of oncology, where the therapeutic index of drugs is often narrow, and the consequences of drug toxicity can be life-threatening. However, since adverse drug reactions are reported to be the fifth leading cause of death in the United States, the risks are not specific to oncology drugs (Davies et al., 2007). At the same time, it is likely that we have failed to capitalize on the increased benefit that could be achieved with some therapies if we knew which patients were most likely to respond, or which patients required alternative dosing. If we could better predict which individuals are at the greatest risk of suffering chemotherapy-related toxicities while simultaneously identifying those most likely to benefit, then the overall care of cancer patients could be greatly improved.

In this review, we will examine the state of pharmacogenomics in the field of oncology. We will specifically restrict our considerations to germline genetic discoveries related to oncologic therapeutics; a discussion of the growing number of “molecularly-targeted” drugs based upon tumor pharmacogenomics is beyond the scope of this current manuscript. To date, most germline oncology pharmacogenomic information has simply been cataloged, or, in a few instances, has led to FDA drug label changes. Therefore, we will also consider the barriers and means by which oncology pharmacogenomic information—which is increasing every day—can become more commonly integrated into the routine care of cancer patients. We will posit that use of such patient-specific information should soon become the standard of care, rather than the exception.

2. Major current pharmacogenomic findings in oncology

The number of germline oncology drug–gene pharmacogenomic pairs having high levels of evidentiary support is relatively small compared to other drugs. Perhaps the strongest examples are those for which the strength and scope of the data has resulted in FDA-mandated label changes so that prescribing clinicians are aware of well-characterized, pertinent germline pharmacogenomic information when prescribing (United States Food and Drug Administration, 2011). These highest level drug-variant pairs, along with several other of the most extensively studied oncology drug-variant pairs, are summarized in Table 1.

As can be seen from Table 1, most of the existing described relationships have focused on genetic predictors of oncology drug-related toxicity phenotypes, rather than disease outcome phenotypes, although accumulating data suggest that germline polymorphisms might also affect treatment outcomes (see references in Table 1; and selected others (Huang et al., 2011; Wu et al., 2010; Ziliak et al., 2011; Yang et al., 2009)). Of the drug–gene pairs in Table 1, the pharmacogenomic relationships between irinotecan and *UGT1A1* (for neutropenia risk) (Innocenti and Ratain, 2006), and 6-mercaptopurine/thioguanine and *TPMT* (for severe

myelosuppression) (Relling et al., 2011) have the most consistent, strong supporting evidence in favor of their routine use. For *UGT1A1* as an example, several prospective studies have demonstrated that patients with the high-risk genotypes (*UGT1A1**28 and *UGT1A1**6) are significantly more likely to experience neutropenia, with two of these studies corroborating the relationship with pharmacokinetic supportive data (Innocenti et al., 2004; Minami et al., 2007). In the largest such study of 250 metastatic colorectal cancer patients, the odds ratio of risk of cycle 1 grade 3 or 4 neutropenia was ~9, although the relationship did not persist for subsequent cycles (Toffoli et al., 2006). A meta-analysis of published studies on *UGT1A1*-irinotecan (including 821 patients) also confirmed the association for patients homozygous for the *UGT1A1**28 allele who are receiving higher doses of irinotecan (≥ 150 mg/m²) (Hoskins et al., 2007). Including other risk alleles within *UGT1A* in a haplotype-based analysis may increase the predictive value of pharmacogenomic testing, since several other variants in these genes have now also been shown to alter enzymatic activity and impact irinotecan-related outcomes (Cecchin et al., 2009).

There has also been significant interest in the relationship between tamoxifen and *CYP2D6* (discussed further below). While the preponderance of the published data support the utility of *CYP2D6* testing for tamoxifen use, there has not been a recommended pharmacogenomic FDA label change for this drug, and recent data presented in abstract form have been contradictory (Goetz et al., 2009; Rae et al., 2010; Leyland-Jones et al., 2010). There is also a large body of growing evidence for many more oncology drug polymorphisms and various phenotypes. The best-performed studies of emerging pharmacogenomic associations now routinely include replication testing upfront, and these drug-variant pairs deserve further examination for how they might be considered in clinical utility investigations.

Despite the existence of well-performed studies and validation in many cases, some have still questioned whether any present germline oncology findings are currently clinically actionable without further prospective follow-up trials being performed (Coate et al., 2010). Certainly even the best-studied drug–gene relationships have recognized limitations in applicability which must be considered (Lee and McLeod, 2011). We believe that the clinical utility of each finding must be interpreted not only in light of the composite evidence describing a given relationship but also in the context of the clinical scenario in which the relative benefit versus risk must be considered. If a pharmacogenomic test could potentially mitigate risk without compromising efficacy, then we believe its practical value is high. We will discuss this topic further below. It is important to first consider interpretation of published pharmacogenomic findings as a starting point.

3. Limitations to pharmacogenomic data interpretability

As evidenced by the examples shown above, the most convincing drug-variant relationships are those identified through well-performed studies in which prospective phenotype collection is performed and in which the potential for

Table 1 – Summary of the most extensively studied germline pharmacogenomic relationships for oncology drugs.

Drug	Phenotype(s) evaluated	Genes	Variants	FDA label includes pharmacogenomic prescribing considerations?	Important considerations	Key references
Irinotecan	Neutropenia	UGT1A1	*28; plus others likely important	YES	1) Variants may only be predictive for patients receiving higher drug doses; 2) Unclear if other irinotecan toxicities (like diarrhea) are similarly governed; 3) Optimal strategy for treating *28/*28 patients is not defined	Innocenti et al., 2004; Minami et al., 2007; Toffoli et al., 2006; Hoskins et al., 2007; Cecchin et al., 2009; Innocenti and Ratain, 2006
6-mercaptopurine /thioguanine	Myelosuppression	TPMT	*1, *2, *3A, *3B, *3C, *4, plus others	YES	1) Complementary clinical laboratory tests are available to functionally assess TPMT activity	Relling et al., 2011
Tamoxifen	Disease recurrence	CYP2D6	Loss-of-function alleles: *3 (rs35742686); *4 (rs3892097); *5 (gene deletion); *6 (rs5030655); *7 (rs5030867) Decreased function alleles: *10 (rs1065852); *41 (rs28371725); *9 (rs5030656) Plus potentially others	NO	1) Some studies have been unable to reproduce the relationships; 2) Many studies have not included all of the known, main alleles; 3) Genotyping (consideration of gene duplication) may be technically difficult which could confound results	Schroth et al., 2007, 2009; Nowell et al., 2005; Kiyotani et al., 2010; Jin et al., 2005; Ferraldeschi and Newman, 2010; Rae, 2011
5-fluorouracil /capecitabine	Neutropenia, stomatitis, diarrhea	DPYD	DPYD*2A (IVS14 + 1 G > A), plus others	YES, but genetic variants are not mentioned; only functional DPD deficiency is included as a consideration	1) Sensitivity of best-studied DPYD variant is only ~30% and has not been consistently reproducible; 2) Results with other DPYD variants, or with variants in other genes (TYMS, MTHFR), have been inconsistent	Yen and McLeod, 2007; van Kuilenburg, 2004
Rituximab/cetuximab /trastuzumab	Disease progression, response	FcγRIIIa, FcγRIIIb	FcγRIIIa-131H/R; FcγRIIIa-158 V/F	NO	1) Some conflicting data; positive data mostly from small studies	Bibeau et al., 2009; Musolino et al., 2008; Kim et al., 2006; Weng and Levy, 2003; Carlotti et al., 2007

false discovery is minimized either (optimally) by inclusion of a replication set, or by conservative adjustment for multiple comparisons (Chanock et al., 2007; van den Oord, 2008). Studies which are underpowered to adequately test less common variants—variants which in reality may be potentially important pharmacogenomic markers—can have (falsely) negative results and can confuse the ability to understand conflicting data from several studies on a given drug–gene pair. Inadequate consideration of the potentially numerous different alleles which may contribute to a given phenotype may also cause false negative results. This latter scenario may, in fact, be one of the causes of the recent conflicting data surrounding tamoxifen pharmacogenomics and CYP2D6 (Higgins and Stearns, 2011; Ferraldeschi and Newman, 2010; Rae, 2011).

For that drug–gene pair, multiple studies have demonstrated that patients with poor metabolizer genotypes are more likely to have worse outcomes. This is due to suboptimal conversion (primarily via CYP2D6) of tamoxifen into the more potent, active antiestrogenic metabolites, endoxifen and 4-hydroxytamoxifen (Higgins and Stearns, 2010), a relationship which is supported by pharmacokinetic data showing that patients with these genotypes have lower levels of endoxifen (Borges et al., 2006). In one study, 206 tamoxifen-treated patients receiving the drug in the adjuvant setting were compared based upon genotype groups (Schroth et al., 2007) for disease-related outcomes. Patients with poor metabolizer CYP2D6 genotypes were significantly more likely to experience recurrence of breast cancer, had shorter times to relapse, and worse event-free survival compared with patients having functional alleles (Schroth et al., 2007). Importantly, this study also examined genotypes for an identical control group of women not treated with adjuvant tamoxifen, and genotype had no bearing on disease-related outcomes. A 1325-patient international consortium study confirmed these findings (Schroth et al., 2009). A smaller prior study (also including a control group) had failed to demonstrate the association of three loss-of-function CYP2D6 genotypes (CYP2D6*3, *4, and *6) with reduced tamoxifen-related survival benefit, but importantly, this study did not test for any of the other now known loss-of-function and reduced-function alleles (Nowell et al., 2005). The recent data presented only in abstract form (Goetz et al., 2009) from the International Tamoxifen Pharmacogenomics Consortium study on >2800 patients receiving adjuvant tamoxifen did not show an association with survival outcomes, however, a number of patients was excluded from the analysis because of incomplete genotypic or clinical data, including lack of information about concomitant medication use (Ferraldeschi and Newman, 2010). Two other, recent large prospective trials (both also only presented in abstract form thus far) which examined CYP2D6 genotypes with outcomes in patients receiving tamoxifen also failed to show associations (Rae et al., 2010; Leyland-Jones et al., 2010). The apparent importance of considering co-administered drugs—including simply whether the antineoplastic drug being studied is being given as monotherapy or as part of a larger combination regimen—has been elegantly illustrated by Kiyotani et al. (2010). These authors showed that, for multiple studies (including theirs) where tamoxifen was given as part of a combination chemotherapy regimen, analyses were unable to demonstrate a positive relationship

between CYP2D6 genotype and disease outcomes. However, in their study and in seven of eight other prior published studies of patients receiving tamoxifen as monotherapy, the relationship between CYP2D6 genotype and tamoxifen response was positive (Kiyotani et al., 2010).

This drug–gene example is instructive for three reasons. First, for genes where genotyping may be difficult or complex, inaccurate or incomplete genotyping can be a significant barrier to pharmacogenomic interpretation. CYP2D6 is known to be frequently duplicated, which can confound interpretation of genotyping results if duplication is not well-characterized. Moreover, over 100 different alleles of CYP2D6 have been reported (Higgins and Stearns, 2010; Bradford, 2002), with at least five of these variants well-characterized as loss-of-function alleles, and another three well-described as associated with decreased enzymatic function (Becquemont et al., 2011). None of the above studies comprehensively included all of the common functional variants. The lack of standardized inclusion of all of the various known functional variants in clinical studies may therefore be a source of inconsistency in reported response outcomes. Secondly, the presence of concomitant medications may be important when interrogating pharmacogenomic relationships. For tamoxifen, co-administered inhibitors of CYP2D6 can functionally “cause” the poor metabolizer phenotype (Jin et al., 2005) and confound genetic influences. Or, as just mentioned, even the presence of drugs not known to be directly acting via the same pathway as the antineoplastic of interest (including other concomitant antineoplastics) may mask the “penetrance” of pharmacogenomic risk alleles. The reduced penetrance could be due to direct effects of the other drugs, plus potentially the reduced effect on the drug of interest, especially if there was dose reduction. This issue has now been suggested to be important for both the tamoxifen (Kiyotani et al., 2010) and irinotecan examples (Hoskins et al., 2007). Third, one of the common problems confounding oncology pharmacogenomics is that evaluated studies often lack a control group (the relatively well-performed study referenced above on tamoxifen—which did—is an exception). Especially when the phenotype of interest is progression-free survival or overall survival, without such a group, or without an intermediate phenotype which relates the ultimate outcome to drug response, it can be difficult to determine whether an associated variant is actually predictive of treatment effect (truly pharmacogenomic) rather than simply prognostic (i.e., a marker for disease severity). This consideration can be especially relevant when the gene(s) being studied could theoretically be related to not only drug response, but also disease propensity or severity (like, for example, genes in DNA repair pathways). All three of these are important points to consider when assessing the quality of pharmacogenomic findings and their relevance to clinical use, and their confounding nature has tempered clinical implementation of some results.

Separately, racial/ethnic differences in genetic variation must be considered. The example of dihydropyrimidine dehydrogenase (DPD) deficiency and 5-fluorouracil (5-FU) toxicity exemplifies this point. DPD catabolizes >80% of 5-FU into fluorinated β -alanine (Heggie et al., 1987). A causative link between DPD deficiency and severe toxicity in response to 5-FU treatment has been repeatedly shown (Milano et al.,

1999; van Kuilenburg et al., 2000; Johnson et al., 1999). While clinical assays of enzymatic DPD activity are available, they are not always easy to obtain, and there has been a substantial effort to characterize causative genetic variants within the *DPYD* gene relating to the DPD deficient phenotype (Yen and McLeod, 2007; Van Kuilenburg et al., 1999). In fact, over 40 SNPs and deletion mutations have been identified within *DPYD*, but most have been shown to have no functional consequences on enzymatic activity (Yen and McLeod, 2007). The best-studied of these SNPs, the IVS14+1 G>A variant (*DPYD**2A), has been found in up to 40–50% of people with partial or complete DPD deficiency (van Kuilenburg, 2004). Yet a recent summary of the data on *DPYD**2A, including multiple studies of this variant alone or in combination with other common variants, showed a performance sensitivity (the percentage of actual patients with severe toxicity who were correctly identified by the allele) ranging between 6.3 and 83%, with a median sensitivity of 30% (Yen and McLeod, 2007). Even more importantly, despite the fact that the prevalence of functional enzymatic DPD deficiency is higher in African Americans (Mattison et al., 2006), the *DPYD**2A variant is not even present in African Americans (van Kuilenburg, 2004), making such testing of limited generalizability and utility. Direct to consumer genetic testing services like 23andMe fail to convey these nuances: 23andMe Inc (2011) advertises genetic testing for 5-FU sensitivity, but their testing consists only of genotyping of the *DPYD**2A variant, and it is not mentioned directly on their website that there is likely to be no relevant information about 5-FU susceptibility for certain ethnic groups like African Americans. This notwithstanding, the data on *DPYD* testing overall is insufficient to support routine pharmacogenomic testing for 5-FU, in our opinion.

Finally, even the results of well-performed studies which include replication may be of limited utility because of the opposite problem: it might be unclear how to assimilate a larger number of different variants—each of which might have a small (but real) impact on the phenotype of interest—into one coherent pharmacogenomic model, let alone a model which might also include clinical factors. The very novel finding of 102 different variants associated with treatment outcome in pediatric acute lymphoblastic leukemia—identified through a very well-conducted analysis of two independent cohorts—might beg that question (Yang et al., 2009). Even if a clinician could test for all these variants, how would he or she assimilate information about all the variants in composite when determining treatment options? These types of questions are becoming more relevant as pharmacogenomic discoveries increase and as the field moves into tackling the issues not of discovery, but of clinical implementation.

4. Clinical implementation of pharmacogenomics into oncology practice

In 2001, when the first draft sequence of the human genome was released (Lander et al., 2001; Venter et al., 2001), there was significant public expectation that this information would be quickly utilized to individualize medical care (Ratain and Relling, 2001). However, work during the past decade has, within oncology, focused mostly on tumor-specific changes

rather than germline variation as the keys to advancement in clinical care. The two disciplines—tumor versus germline variation—are of course very different. The former explains variability in disease, which can usually be associated with differences in natural history and/or etiology, and occasionally in treatment response. On the other hand, germline variation explains variability in the patient, which does affect both pharmacokinetics and pharmacodynamics, as well as potentially disease risk (even risk for specific mutations (Liu et al., 2011)). Some might argue that especially for the latter group of drug-related germline variants, the list of the most extensively studied within oncology (summarized in Table 1) and especially the list of those that has become routinely clinically tested remains relatively small.

Implementation into routine practice has been hindered by lack of knowledge about such information (on the part of both patients and physicians), uncertainty about how to order such tests, and reimbursement, and timeliness of results. We believe that we are now at a point where SNP genotyping has become so widely available and inexpensive that this should no longer be the barrier. Indeed, whole genome sequencing is itself likely to quickly surmount these same barriers in the very near future. And it is also likely that in the very near future, we will have a critical mass of information regarding germline pharmacogenomic biomarkers in oncology which deserve clinical implementation to provide optimal (personalized) oncologic care. Before discussing the ways to bring this goal to fruition, it is worthwhile to examine the question of whether prospective, randomized data need to be demonstrated for a drug-variant pair before clinical implementation can be considered.

5. Necessity of prospective validation?

Pharmacogenomic findings even from a well-performed single study require validation in a separate patient population to confirm that such results are reproducible (Chanock et al., 2007). Successful reproducibility in a separate cohort provides considerable confidence that the original findings were not false positives and were not misleading due to some unique phenotypic or measurement characteristics of the original population. Outside of the oncology realm, however, even two of the most prominent drugs with repeatedly reproducible pharmacogenomic information—warfarin and clopidogrel—have not yet seen widespread clinical implementation of genomic prescribing. It has been felt that prospective, randomized studies for each of these drugs (the ongoing Clarification of Optimal Anticoagulation through Genetics [COAG] trial for warfarin (French et al., 2010); and the proposed and funded Pharmacogenomics of Anti-Platelet Intervention [PAPI-2] study for clopidogrel (United States Department of Health and Human Services, 2011)) are needed to demonstrate the clear utility of the pharmacogenomic information. Skeptics of pharmacogenomics will argue that this type of prospective randomized validation (ideally double-blind) might be necessary for any pharmacogenomic discovery before it is clinically implemented, including those for oncology drugs. In contrast, we, like others (Altman, 2011; Frueh, 2009), argue that this will not only be practically infeasible given the burgeoning

number of pharmacogenomic discoveries that continue to be reported, but also potentially unnecessary given the diminishing costs of genotyping, the idea that in many cases a pharmacogenomically-informed prescribing decision will at least be non-inferior to the alternatives (Altman, 2011) (and potentially highly advantageous to the individual patient being considered), and the idea that comparative effectiveness research will likely continue to validate pharmacogenomically-informed prescribing in real practice without needing to wait for the randomized controlled trial (Epstein et al., 2010). We propose instead that using a broad pre-emptive genotyping model, described further below, which eliminates marginal costs, that the plausible benefit of using pharmacogenomics for any given patient should only be weighed against the plausible risk.

6. Pre-emptive genotyping

It is our vision that the implementation of pharmacogenomics in the clinic will require a transformation from the current paradigm of genotyping as a laboratory test, to a future paradigm of genotyping conducted at a single time, and perpetually available as part of the “genetic examination”. Whether this will involve whole genome sequencing or multiplexed genotyping is irrelevant, as the key concept is that the genetic examination will be performed in anticipation of future medical needs, as opposed to the current paradigm where genotyping is performed when clinically indicated (like all other current laboratory tests). Thus, we envision that future physicians will utilize a “genomic prescribing system” at every prescribing encounter (Ratain, 2007), including if and when a patient might be diagnosed with cancer. Others have argued for a similar approach (Relling et al., 2010). In this model, patients could be examined with a single blood sample, used for genotyping all polymorphisms of potential pharmacogenomic significance. If the same panel is used for all patients, and if patients are genotyped in large batches, this would also reduce the costs of genotyping, creating feasibility for the approach.

This approach would address one of the key barriers to pharmacogenomic implementation—that physicians are reluctant to wait for pharmacogenomic results before prescribing. This might be especially true for oncologists and for their patients diagnosed with cancer, since there is often (much warranted) urgency on the part of oncologists, and patients, to begin treatment quickly.

Successful implementation of this type of model (Ratain, 2007) will require the training of physicians (and related health care providers) with expertise in pharmacogenomics, genetic testing, and informatics. It will also require the development of medical records systems which can accommodate large-scale, patient-specific genotypic information and deliver such information in a usable, succinct format to busy clinicians.

We at the University of Chicago (www.clinicaltrials.gov study identifier NCT01280825) and others (e.g. Ohio State-Coriell Personalized Medicine Study (Coriell, 2011); Vanderbilt's VESPA project (Snyder, 2009; St. Jude Children's Research Hospital, 2011)) currently have pharmacogenomic

implementation efforts underway which are beginning to study—and realize—the goal of routine incorporation of pharmacogenomics in patient care, including oncology care. Implementation of the best-evidence variants should be the starting point for such studies. Equally important will be simultaneous pharmacogenomic discovery research and ongoing confirmatory studies of contradictory drug–gene pairs, in order to properly define the scope of which variants to include and to increase the number of drug–gene pairs having adequate clinical evidence to warrant implementation.

7. Special considerations in implementing oncology pharmacogenomics

Knowledge about pharmacogenomic susceptibility (either response or toxicity prediction) may be most obviously usable to inform treatment choices in disease settings where several equivalent therapies exist. This would allow the physician to potentially choose one therapy over another if specific toxicity risks were high for one of the given drugs, or, alternatively, to select a therapy if the expected likelihood of response was higher. In settings where more than one treatment choice may not exist, information about a drug may allow the physician to weigh toxicity risks of that treatment versus potential benefits, and such questions are of course even more relevant when treatments are being used in palliative settings. The third, different, scenario where implementation questions can arise is that of potential patient-specific dose modifications based upon pharmacogenomic knowledge of toxicity risk. In other words, if a patient is known to be at high (genetic) risk of toxicity from a drug at standard treatment doses, could the clinician still use that drug, but at a lower dose? Specific dose-reduction pharmacogenomic prescribing recommendations are, to our knowledge, not available for any oncology drugs except for the above-mentioned TPMT substrates (Relling et al., 2011). For irinotecan, a genotype-driven dose-finding study using pharmacogenomics showed that the recommended 180 mg/m² dose for irinotecan in the FOLFIRI regimen is considerably lower than what can be actually tolerated if patients with high-risk UGT1A1 genotypes are excluded (Toffoli et al., 2010).

A final potential concern surrounding implementation is that, especially when considering toxicity pharmacogenomics, one must consider the additional question of whether the same variants governing toxicity susceptibility might also govern antitumor response. If that were known to be true, the question arises whether dose reduction (to avoid toxicity) would still be appropriate. In the absence of prospective, randomized dose-ranging phase II trials examining each possible drug–gene pair, such answers may only be gathered in the future from large, retrospective analyses once genotyping becomes more common. Alternatively, in cases of identified potential pharmacogenomic toxicity risk, prophylactic interventions (e.g. growth factor support for neutropenia risk) might allow full dose-maintenance while minimizing toxicity risk. While we are currently unaware of any data in oncology pharmacogenomics that has demonstrated the existence of this theoretical toxicity-response link for a given variant or gene, the consideration will be important for clinical

implementation. Clinicians may, in some cases, be forced to carefully consider the risk-benefit ratio and pharmacogenomic probability for a given drug to ensure that pharmacogenomically-guided dose reduction or drug avoidance to prevent toxicity would not compromise the treatment goals, especially if the therapy is being used for curative intent. In effect, this is simply an extension of the same risk-benefit calculation that must be made when using any biomarker to guide therapeutics, in oncology or elsewhere.

8. Conclusions

Achieving personalized care is increasingly important among cancer patients since many oncologic diseases now have several, often apparently equivalent, treatment options available to oncologists, and many cancers can now often be successfully treated into forms of chronic disease (e.g. chronic myelogenous leukemia, androgen-sensitive prostate cancer, node-positive breast cancer, surgically-resectable colon cancer, and others). Such patients, like patients with diabetes or cardiac disease, often require complex and coordinated ongoing medical attention and require multiple long-term medications to prevent disease recurrence, manage disease-related symptoms, or treat long-term therapy-induced toxicities. Cancer patients therefore represent a population that could stand to particularly benefit from the incorporation of pharmacogenomically-informed prescribing decisions. The relevant pharmacogenomic information extends beyond improved knowledge of the molecular aspects of the patient's tumor and must include knowledge of the patient's germline genetics as well. Implementing a pre-emptive medical system which incorporates knowledge of the patient's germline variation along with the ability to offer informed pharmacogenomic prescribing consultation services therefore should be the new paradigm for which we strive. We believe that such a clinical care system has great potential for improving the care of cancer patients someday—and maybe, that 'someday' should be now.

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