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Analyzing the Clinical Actionability of Germline Pharmacogenomic Findings in Oncology

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Abstract

Background—Germline and tumor pharmacogenomics impact drug responses, but germline markers less commonly guide oncology prescribing. We hypothesized that a critical number of

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-K.D., M.J.R., and P.H.O. are co-inventors on a pending patent application for the Genomic Prescribing System. M.J.R. is a co-inventor holding patents related to pharmacogenetic diagnostics and receives royalties related to *UGT1A1* genotyping. No royalties were received from this work.

Conflicts of Interest

Related to this work, Keith Danahey, Peter H. O'Donnell, and Mark J. Ratain report a pending patent for the Genomic Prescribing System. Peter H. O'Donnell reports grants received from the National Institutes of Health and Mark J. Ratain from the The Conquer Cancer Foundation of the American Society for Clinical Oncology for work performed as part of the current study. Mark J. Ratain is a co-inventor holding patents related to pharmacogenetic diagnostics and receives royalties related to *UGT1A1* genotyping, though no royalties were received from this work. Dr. Ratain also reports receiving personal fees from AbbVie, Amgen, Ascentage, Circle Pharma, Cyclacel, Drais Pharmaceuticals, Elion Oncology, Genentech, Shionogi, and multiple generic pharmaceutical companies, in addition to grant funding from Abbvie and Dicerna, for work unrelated to the current study. Dr. Ratain is the Director and Treasurer of the Value in Cancer Care Consortium.

Author Contributions:

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B.A.B.: Methodology/investigation/analysis/writing–original draft&preparation/writing–review&editing
K.D.: Software/investigation/writing–review&editing
R.N.: Investigation/writing–review&editing
B.P.: Investigation/writing–review&editing
W.M.S.: Investigation/writing–review&editing
M.J.R.: Conceptualization/methodology/software/investigation/writing–review&editing/funding
P.H.O.: Conceptualization/methodology/software/investigation/analysis/writing–original draft&preparation/writing–review&editing/funding

clinically actionable germline pharmacogenomic associations exist, representing clinical implementation opportunities.

Methods—We analyzed 125 oncology drugs for positive germline pharmacogenomic associations in journals with impact factors ≥5. Studies were assessed for design and genotyping quality, clinically-relevant outcomes, statistical rigor, and evidence of drug-gene effects. Associations from studies of high methodologic quality were deemed potentially clinically actionable, and translational summaries were written as point-of-care clinical decision support (CDS) tools and formally evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument.

Results—We identified germline pharmacogenomic results for 56/125 (45%) oncology drugs across 173 publications. Actionable associations were detected for 12 drugs, including six with germline pharmacogenomic information within Food and Drug Administration labels or published guidelines (capecitabine/fluorouracil/*DPYD*, irinotecan/*UGT1A1*, mercaptopurine/thioguanine/*TPMT*, tamoxifen/*CYP2D6*), while six others were novel (asparaginase/*NFACT2/HLA-DRB1*, cisplatin/*ACYP2*, doxorubicin/*ABCC2/RAC2*, lapatinib/*HLA-DQA1*, sunitinib/*CYP3A5*, vincristine/*CEP72*). Using AGREE II, developed CDS summaries had high scores (mean ± standard deviation [SD]; maximum score=100) for Scope and Purpose (92.7 ± 5.1) and Rigour of Development (87.6 ± 7.4) and moderate, yet robust scores for Clarity of Presentation (58.6 ± 25.1) and Applicability (55.9 ± 24.6). Overall mean guideline quality score was 5.2 ± 1.0 (maximum score=7). Germline pharmacogenomic CDS summaries for these 12 drugs were recommended for implementation.

Conclusion—A number of oncology drugs have actionable germline pharmacogenomic information, justifying delivery through institutional pharmacogenomic implementations, to determine clinical utility.

Keywords

clinical decision support; germline mutation; pharmacogenetics; pharmacogenomic variants; precision medicine

Introduction

The discipline of pharmacogenomics aims to identify genetic variants that contribute to individual drug response in order to reduce adverse drug reactions and increase drug efficacy. Pharmacogenomic information plays a unique role in cancer therapy because both the tumor (somatic) genome and the patient's germline genome can impact drug response[1]. Further, as the consequences of drug toxicity can sometimes be particularly life-threatening in oncology, using pharmacogenomics to prevent such events is desirable[2]. There is, indeed, a rich history in oncology of germline pharmacogenomic variants playing a role in serious and life-threatening toxicities. Traditionally, germline variants of interest include those of drug-metabolizing enzymes, transporters, and other proteins involved in a drug's mechanism of action[3], as such proteins are critical in determining the efficacy and toxicity of many chemotherapeutic agents[4]. Such germline pharmacogenomic information has been incorporated into Food and Drug Administration (FDA) labels for capecitabine[5], fluorouracil[6], irinotecan[7], 6-mercaptopurine[8], and thioguanine[9], and Clinical

Pharmacogenetics Implementation Consortium (CPIC) guidelines have been written for capecitabine/fluorouracil[10], mercaptopurine/thioguanine[11], and tamoxifen[12]. While these well-recognized examples already have established clinical implementation guidelines, other potential germline pharmacogenomic associations with strong supporting evidence have yet to be translated into clinical practice.

Increasingly, tumor pharmacogenomic information is incorporated into oncologic clinical decision-making[13], and in some cases the use of oncology drugs is restricted to patients carrying explicit tumor mutations[14,15]. Germline pharmacogenomic variants, in the more traditional sense (those involved in drug metabolism or mechanisms of action), less commonly guide oncology prescribing. Despite fervent, ongoing discovery research in the field, the current number of high-level, actionable germline pharmacogenomic markers in oncology is less clear than that for tumor genomics[16], and has either been outpaced by or overshadowed by the routine clinical utilization of somatic markers. Regardless, incorporating actionable information about both tumor and germline genomics into cancer treatment plans has the potential to improve patient outcomes, yet clear recommendations or standardized guidance is rarely available.

We aimed to critically appraise the current germline pharmacogenomic discoveries in oncology using a prospective methodology to discover whether additional germline pharmacogenomic markers have sufficient evidence for clinical implementation. We sought to identify replicated, high-level evidence associations for which translation into clinical decision support (CDS) guidelines is warranted. Simultaneously, we aimed to identify associations for which intriguing germline pharmacogenomic data exist, yet evidence in support of implementation may be limited due to methodological limitations of current studies. We hypothesized that the findings will enable clinical consideration of germline variants and facilitate future examinations of clinical utility in practice.

Methods

Data Collection

A total of 125 commonly prescribed cancer drugs were included[17] (Supplementary Table 1). An automated search algorithm of “[drug name] polymorphism” in PubMed was used to identify pharmacogenomic publications for each drug. Articles examining the association between a germline genetic variant and a pharmacogenomic outcome were included. Specific exclusion criteria have been previously published[18] and are described in the Supplementary Methods. Drug-genetic associations reported as being nominally statistically significant by the authors were recorded at first-pass as “positive” in the database, while non-significant associations were labeled “negative.”

All positive associations in a journal with a five-year impact factor (IF)≥5 were taken forward for critical analysis (described below). To ensure that no important publications were missed by the automated PubMed algorithm, in February 2017 each drug was also manually searched in PubMed using our updated search string[18] (see Supplementary Methods). The same process of manual inclusion/exclusion was performed for any additionally identified studies from journals with IF ≥8.5 since the purpose of this second

search was to identify any additional major findings (emphasizing specificity, whereas the first search emphasized sensitivity).

Data Analysis

Each positive drug-genetic association from the included articles was assessed using our previously described methodology[19] to determine whether the association was potentially clinically actionable (see also Supplementary Methods). Studies employing multi-drug regimens were generally excluded from critical analysis, since direct attribution of a genetic association with a single drug could not be made. Exceptions were made for publications with specific drug-genetic pairs for which the variant or gene was implicated in a particular drug's activity or if a toxicity outcome studied was known to be associated with one particular drug. Similarly, studies reporting only associations with multi-variant genetic haplotypes were excluded from our analysis, as we were interested in identifying single polymorphisms that could be clinically assessed. However, gene-level associations employed for *CYP2D6* or other similar genes with known enzymatic phenotypes (e.g., "poor metabolizer"/"rapid metabolizer") were included.

The presence of large cohort sizes, control populations, high quality phenotype measurements, treatment homogeneity amongst study subjects, and appropriate statistical measures all increased support for clinical actionability. Drug-genetic pairs that were not statistically significant after multiple testing corrections were not deemed clinically actionable unless another well-performed study supported the same genotype-phenotype association. Generally, drug-genetic pairs were also deemed not actionable if associated with only prognostic outcomes. Publications that studied response but included stable disease in the definition of clinical response were deemed not actionable. Associations from genome-wide association studies that did not meet genome-wide significance were not deemed actionable unless convincing replication or functional data existed.

Two independent reviewers considered the resulting drug-genetic pairs from the above analysis. Dedicated, manual "[drug name] [variant rs number]" PubMed searches were separately conducted for each as part of this final step to ensure that no studies were missed. Complementary to this comprehensive analysis, consideration of FDA label information, CPIC guidelines, and other published guidance (e.g., PharmGKB, Dutch Pharmacogenomics Working Group) was given. Capecitabine[5], fluorouracil[6], irinotecan[7], mercaptopurine[8], and thioguanine[9] have germline pharmacogenomic information containing a recommended clinical action already incorporated into FDA labels. Capecitabine, fluorouracil, mercaptopurine, tamoxifen, and thioguanine have published CPIC guidelines[10–12]. Clinically actionable information for these six drugs, along with potentially actionable information for any other drugs that emerged from our comprehensive analysis, was taken forward for development into draft CDS summaries.

Finally, we considered germline genetic findings that represent gene-disease associations but which may also directly guide the prescribing of certain oncology drugs. The FDA Table of Pharmacogenomic Biomarkers in Drug Labeling[14] was analyzed for oncology drugs with germline gene-disease information included in the package labeling. We reviewed each drug label for actionable prescribing recommendations based on germline disease variants.

CDS Summary Development

CDS summaries that translated genetic information into point-of-care guidance were independently written by a member or members of the CDS development team using methods previously described[18] (see also Supplementary Methods). Resulting draft CDS were independently reviewed by two members of the evidence evaluation team (R.W. and P.H.O.) and were then subjected to formal Appraisal of Guidelines for Research and Evaluation (AGREE) II scoring.

AGREE II Scoring

We used a modified AGREE II[20] scoring instrument to determine whether each draft CDS summary warranted clinical implementation (see Supplementary Methods for full details). Our modified AGREE II instrument included the specific items from the domains of Scope and Purpose, Rigour of Development, Clarity of Presentation, and Applicability. Four independent appraisers (R.N., B.P., W.M.S., M.J.R.) rated each draft summary on all four domains, gave each an overall score, and voted (independently) whether the summary deserved deployment as a clinical guideline. The AGREE appraisal of whether to recommend or not was used as the final determination for inclusion into our institutional pharmacogenomic program[21]. Unless a summary received unanimous agreement in favor of clinical deployment, it was not clinically implemented.

Results

Study Demographics

Of the 125 drugs evaluated, 67 (53.6%) had ≥1 published pharmacogenomic study, regardless of journal IF. We first examined the number of pharmacogenomic publications/drug according to drug approval year (Figure 1). We did not detect any trends suggesting that time since FDA approval was correlated with number of pharmacogenomic publications. Instead, there are a relatively small number of oncology drugs for which a large amount of pharmacogenomic research has been performed. In total, 19/67 drugs (28.4%) have >20 published pharmacogenomic studies. Publications describing ≥1 positive genetic association vastly outweighed the number of publications reporting only negative associations (Supplementary Figure 1).

Of the drugs evaluated, 56 (44.8%) were reported to have positive oncologic pharmacogenomic associations in journals with IF ≥5 (Supplementary Table 2). These 56 drugs were supported by an average of 8 publications/drug (range: 1–72), representing 173 unique high-impact publications initially critically appraised. In total, 154 were brought forward for further analyses (see Supplementary Results). Overall, 246 genes were reported as positive pharmacogenomic findings in the included publications, comprising 436 unique gene-publication pairs. Many genes were studied in multiple publications. In fact, we found that 35.1% of these unique gene-publication pairs were comprised of a relatively small list of key pharmacogenes (Figure 2). These included the *ABC, CYP, GST, FCGR, SLC, ERCC,* and *VEGF* gene families[22], as well as the *MTHFR* gene.

Supplementary Figure 2 displays the 6 most common clinical outcomes analyzed for pharmacogenomic association. Progression-free survival (including disease-free, event-free, recurrence-free, and relapse-free survival) was the most common clinical outcome studied across the critically analyzed studies [in 56/154 publications (36.4%)]. Overall survival and response rate were analyzed in 29.2% and 27.3% of studies, respectively (see Supplementary Results for additional details).

The sample size distribution of the publications analyzed is displayed in Figure 3. Sizes ranged from 6–4925 (median=179 patients). The highest percentage of studies (29.9%) had sample sizes between 101–200; interestingly, only 4.3% of studies in this range resulted in a draft CDS summary (see below). In contrast, only 6.5% of analyzed studies had sample sizes >1000 patients, and 20.0% of these resulted in a draft CDS summary.

Out of the publications critically assessed, 11/154 (7.1%) ultimately described drug-genetic pairs that resulted in draft CDS summaries. Detailed reasons explaining why the remaining 143 publications were deemed not actionable (and did not result in a summary) are available in the Supplementary Results.

Potentially Clinically Actionable Associations

Our critical analysis resulted in 12 drugs with genetic information deemed potentially clinically actionable. These highest level pharmacogenomic results are shown in Table 1. Six unique drugs–asparaginase, cisplatin, doxorubicin, lapatinib, sunitinib, and vincristine–were identified as having novel, potentially clinically actionable pharmacogenomic information through our analysis. An additional 13 drugs not currently clinically actionable were deemed to be deserving of future follow-up (see Supplementary Table 3 and Supplementary Results). Consideration of germline gene-disease (as distinct from the above gene-drug) associations that also directly impact oncology prescribing revealed three additional drugs with actionable prescribing information included in their FDA labeling: olaparib/*BRCA*, rucaparib/*BRCA*, and dabrafenib/*G6PD* (Supplementary Table 4).

AGREE II Analysis Results

Draft CDS summaries for the potentially clinical actionable drug-genetic pairs were developed and then subjected to final, formal AGREE appraisal. The AGREE scores for each CDS summary, the overall mean ± SD scores for each domain, and the ultimate determination surrounding clinical actionability are displayed in Table 2. Of the CDS guidelines that were written for the six drug-genetic pairs that were *a priori* denoted as deserving CDS based on FDA/CPIC designations, the mean ± SD scores were: Domain 1 (Scope and Purpose): 97.6 ± 1.9 (range, 95.8–100.0); Domain 3 (Rigour of Development): 93.2 ± 9.1 (range, 79.6–98.6); Domain 4 (Clarity of Presentation): 90.9 ± 8.0 (range, 81.5–98.6); and Domain 5 (Applicability): 86.5 ± 4.0 (range, 80.6–88.9). Additionally, the mean ± SD overall quality score for these CDS guidelines was 6.5 ± 0.6 (range 5.7–7.0). Notably, the summaries for capecitabine/fluorouracil (*DPD*) and mercaptopurine/thioguanine (*TPMT*) received the maximum possible mean overall quality score of 7.

Scores for our six novel drugs were similarly high for Domain 1 (Scope and Purpose) and Domain 3 (Rigour of Development), while scores for Domain 4 (Clarity of Presentation) and

Domain 5 (Applicability) were lower. The mean ± SD scores were: Domain 1: 90.6 ± 4.5 (range, 86.1–100.0); Domain 3: 85.2 ± 5.4 (range, 80.6–97.2); Domain 4: 44.3 ± 13.0 (range, 29.2–76.4); and Domain 5: 42.4 ± 15.1 (range, 27.1–68.8). The mean overall quality score for these six drugs was 4.6 ± 0.4 (range, 4.3–5.8). Of these drugs, the summary for vincristine/rs924607 scored the highest, with an overall mean quality score (± SD) of 5.8 ± 1.3.

We chose a standard of requiring 100% consensus among AGREE scorers on the "recommend/do not recommend" assessment before affirming a summary as ultimately actionable for clinical implementation. The CDS summaries for all but one of the draft drug-genetic pairs (sunitinib/rs307826) attained 100% agreement among scorers.

As an illustrative example, Figure 4 displays the CDS summary for vincristine that was recommended for implementation. This CDS guideline is currently delivered to institutional oncologists through our Genomic Prescribing System (GPS)[18,21]. Details regarding the evidence supporting this specific summary, and the development of its CDS language, are available in the Supplementary Results. CDS summaries exist in GPS for all 12 drugs that were deemed clinically actionable through this study.

Discussion

Clinical use of genomic information in oncology has become commonplace, with the vast amount of actionable information consisting of somatic alterations from tumor sequencing. However, for the comprehensive clinical care of oncology patients in the precision medicine era, somatic information might also be integrated with patient-specific germline information. To our knowledge, ours is the first study to comprehensively and critically appraise the available evidence for utilizing germline information during the prescribing of oncology drugs, and to propose actionable CDS summaries based on published evidence. We found that there is now a critical mass of clinically actionable germline pharmacogenomic associations, with half of these well-known for decades and the other half previously unrecognized but recently identified based on discovery research. In total, we identified 12 drugs for which consistent germline pharmacogenomic information has sufficient evidence to deserve point-of-care clinical consideration. Deployment of CDS tools for these germline variants within ongoing institutional implementation efforts (coupled with appropriate genotyping) will permit future studies of clinical utility for these germline pharmacogenomic biomarkers.

Oncologists are uniquely primed for the idea of assimilating pharmacogenomic information into treatment decision-making. A survey of over 10,000 United States physicians found that oncologists were >5 times more likely to have ordered a pharmacogenomic test in the past six months when compared to general or family practitioners[23]. Perhaps this should not be surprising, given that oncologists are well-versed in making decisions about oncologic therapies based on tumor genomics[24,25]. Indeed, oncology practices have had to already solve many of the barriers of genomic clinical implementation. These include finding trusted laboratories to perform the testing, managing cost hurdles and insurance coverage questions, pursuing results in a timely fashion, storing results within the electronic health record, and

communicating results with patients[25–27]. Changes in FDA labeling only comprise a small part of the key step of learning about important genomic information, and most oncologists probably depend on other sources to develop and hone this proficiency (e.g., national meetings, American Society of Clinical Oncology guidelines, local/institutional genomic 'tumor boards')[28–30]. Further, oncologists may find pharmacogenomics to be useful in multiple facets of oncologic care. Utility of certain results may, in fact, change based on the disease setting. For example, if the treatment goal is to cure the patient, guidelines for gene-drug interactions that predict a greater response to a drug for those carrying a certain genotype may be more desirable than guidelines that warn of a modest toxicity risk. Conversely, in the palliative treatment setting, avoiding toxicity may be considered more important; therefore, guidelines indicating that patients carry increased risk of side effects may allow providers to successfully avoid a harmful drug altogether, or adopt upfront dose-reduction.

In order to translate germline genomic findings into clinical practice, one has to first define and characterize what information is potentially ready for consideration of implementation. Several gene/drug examples have been described for decades[1], with various degrees of implementation across oncology institutions and practices[31–33]. We utilized a previously-published methodology[19] to critically assess the vast number of germline pharmacogenomic studies about oncology drugs. Interestingly, the majority of drugs have had positive pharmacogenomics associations described about them (67 of the 125 drugs), with published associations for 12 drugs withstanding rigorous evidence standards required for clinical actionability. Our data, perhaps not surprisingly, also suggest that the more pharmacogenomic publications a drug-genetic pair has, the higher the likelihood that the reported association is truly clinically actionable, illustrating the importance of replication[34]. We interestingly found that very few of the genomic polymorphisms supporting the associations for these 12 drugs are currently reported alongside somatic markers on our institutional Clinical Laboratory Improvement Amendments-accredited laboratory OncoPanel (J. Segal, personal communication), highlighting the need for more comprehensive or additional genotyping in order to make implementation of such germline markers a reality.

In determining which pharmacogenomic information should be implemented, we posit that a number of factors should be carefully considered. We were unable to detect clinically actionable associations for 11 of the top 20 drugs with the highest number of pharmacogenomic publications, despite there being many more studies reporting positive associations than negative associations for these drugs. It seems obvious that this may be due to publication bias, and one must therefore remember that the quality of published studies (and quality of replication), not the total number of studies, should drive actionability determinations. Additionally, progression-free survival and overall survival necessarily encapsulate prognostic information about the disease, and therefore published 'pharmacogenomic studies' examining these phenotypes may in fact be describing disease-related genetic associations not pharmacogenomic associations. If more oncologic pharmacogenomic studies in the future were to include control groups and/or would analyze non-prognostic outcomes (like response), an increased number of truly pharmacogenomic

associations could potentially be identified. Increasing the power of future studies, through analysis of larger samples sizes, will also be essential.

In conjunction with a rigorous assessment of what to implement, it is of great importance to also critically appraise proposed clinical guidelines prior to implementation. Scores from a modified version of a well-established, validated tool—the AGREE II instrument—were, in general, high for our proposed germline pharmacogenomic CDS summaries. Importantly, we adopted a stringent requirement of unanimous recommendation for clinical deployment among our four independent AGREE scorers for guideline implementation. Although certain CDS summaries scored lower on the domains of Clarity of Presentation and Applicability, a number of previous studies have placed a particular emphasis on the Rigour of Development domain, suggesting that this domain is indicative of high quality guidelines[35–38]. Notably, all of our guidelines scored well above the common “high quality” threshold of 60% on this domain. Further, many past studies have classified guidelines as “recommended” for implementation if the overall quality score exceeded 50%[39,40]. All of our proposed guidelines exceeded this threshold. Finally, both the domain and overall quality scores of our CDS recommendations were very similar to, and in many cases higher than, AGREE II scores for guidelines currently implemented in clinical practice[40–43].

Our study had limitations. Because we used the criterion of only evaluating studies published in journals with IF≥5, it is possible that we missed other potentially actionable germline associations, although this would seem unlikely. Additionally, our analyses were limited to unique drug-genetic associations where the genetic association could confidently be attributed to a clinical outcome from a specific oncology drug. We therefore did not include genetic signals associated with outcomes from multi-drug regimens where the phenotype of interest may have represented a composite drug outcome (‘regimen effect’). Finally, our comprehensive critical appraisal process of the published literature specifically excluded publications for which the studied germline genomic associations represented gene-disease, as opposed to gene-drug, interactions. Nevertheless, given the recent impact of several germline gene-disease relationships to directly impact the prescribing of certain oncology drugs, we comprehensively analyzed FDA labels for gene-disease interactions with actionable prescribing recommendations and included the findings in our results. We acknowledge that some other potentially relevant or emerging germline associations may have been missed. For example, the *EGFR* T790M germline mutation is a predisposing factor for lung cancer and frequently confers resistance to tyrosine kinase inhibitors when present in the tumor genome[44,45]. As a non-oncologic example, some diseases that are caused by germline mutations may be exacerbated by cancer medications, as is the case with Charcot-Marie-Tooth neuropathy and vincristine[46,47]. These examples represent additional important considerations during oncologic prescribing.

The direct application of this study’s findings will be actualized through clinical implementations that are now ongoing at many institutions, including ours. We have designed a pharmacogenomic CDS system that allows for the availability of preemptive germline results at the point-of-care[18]. The goal of these efforts is to permit eventual realization of a clinical care model that allows consideration of both germline and somatic genomic information at the time of prescribing. Clinicians will then be able to test the

hypothesis that doing so ultimately improves clinical decision-making, aids in prescribing, reduces toxicities, improves response rates, and benefits patients. This of course represents both the challenge and the promise of precision medicine in the genomic era.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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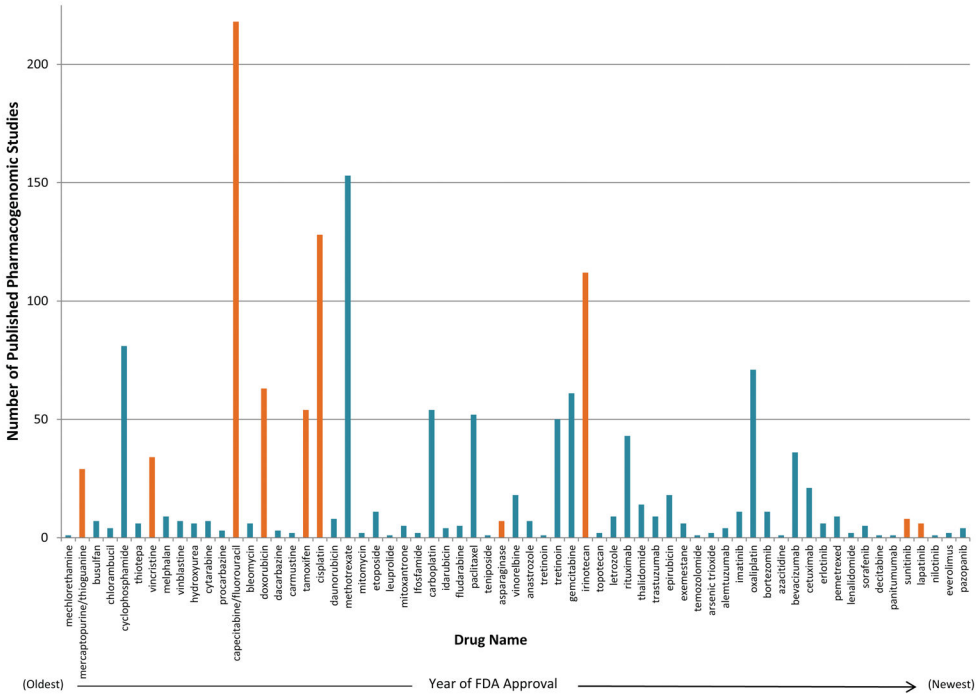

Figure 1. Number of Published Pharmacogenomic Studies per Drug in Order of FDA Approval Year

Of the 125 oncology drugs evaluated, 67 (53.6%) had at least 1 published pharmacogenomic study, regardless of journal impact factor. In total, 19 of the 67 drugs (28.4%) have more than 20 published pharmacogenomic studies. We did not detect any trends suggesting that time since FDA approval is correlated with the amount of pharmacogenomic data published. Instead, the data suggest that there are a relatively small number of oncology drugs for which a large amount of pharmacogenomic research has been performed. Drugs deemed as being potentially clinically actionable (with a clinical decision support summary sent for AGREE scoring) are shown in orange.

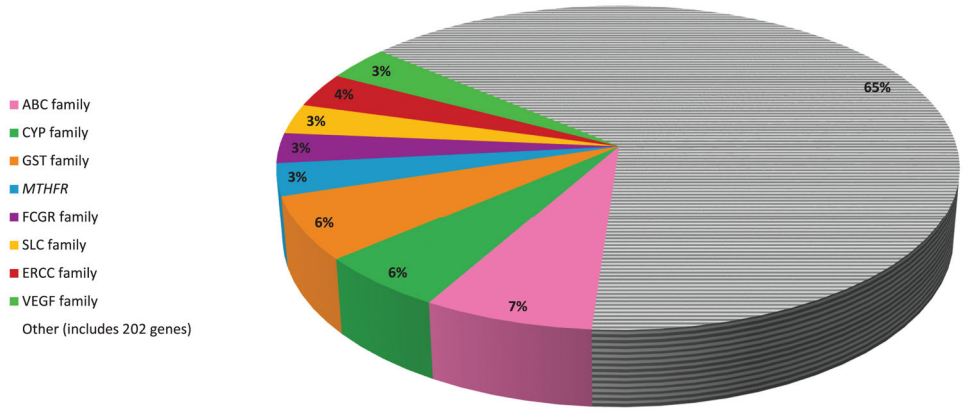

Figure 2. Genes/Gene Families Represented in Positive Pharmacogenomic Associations

Overall, 246 genes were found to have positive pharmacogenomic associations in our 154 critically analyzed publications, comprising 436 unique gene-publication pairs. Many genes were studied in multiple publications. In fact, we found that over a third (35.1%) of the unique gene-publication pairs were comprised of a relatively small list of key pharmacogenes. These included the *ABC, CYP, GST, FCGR, SLC, ERCC*, and *VEGF* gene families, as well as the *MTHFR* gene. Each gene/gene family on the figure is represented as a percentage of the 436 total gene-publication pairs.

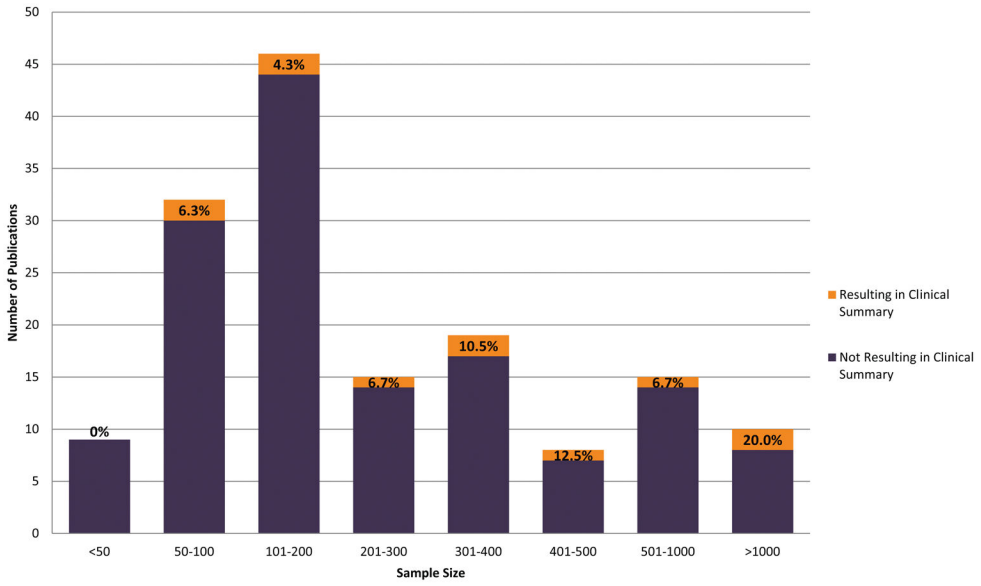

Figure 3. Sample Size Distribution of 154 Publications Analyzed

Sample sizes ranged from 6 to 4925, and the median sample size was 179. The highest percentage of studies (29.9%) had sample sizes in the range between 101 and 200; only 4.3% of studies in this range resulted in an ultimate draft clinical decision support summary. On the contrary, only 6.5% of analyzed studies had sample sizes greater than 1000 patients, and 20.0% of these resulted in a draft clinical decision support summary. Orange shading highlights the percentage of studies for each sample size group (i.e. 101–200, 201–300, etc.) that resulted in a clinical decision support summary.

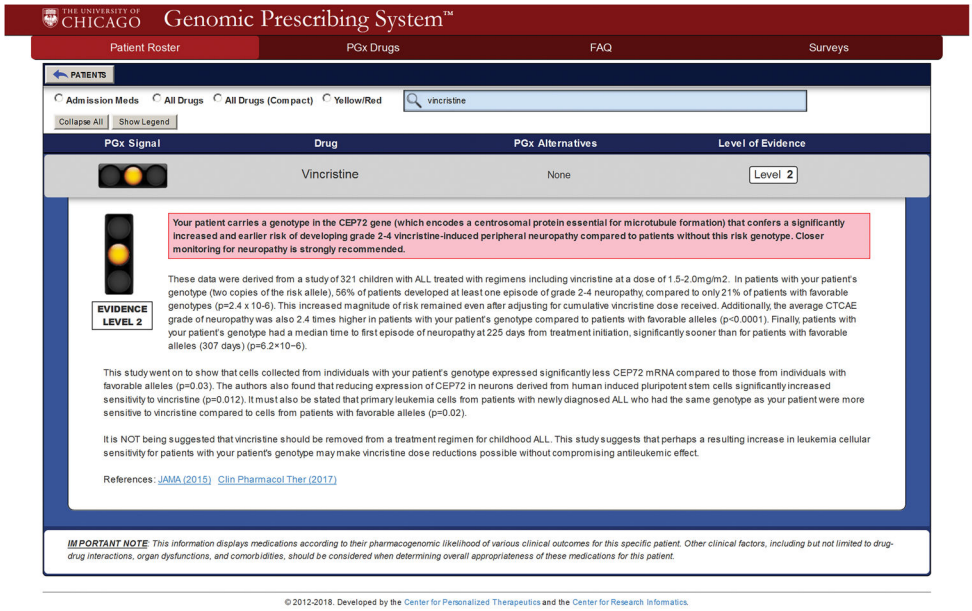

Figure 4. Example of Clinical Decision Support Summary Written for Vincristine/rs924607 TT and Deployed in the Genomic Prescribing System

This summary received scores of 100.0 for Domain 1 (Scope and Purpose), 97.2 for Domain 3 (Rigour of Development), 76.4 for Domain 4 (Clarity of Presentation), and 68.8 for Domain 5 (Applicability) on our modified AGREE II scoring instrument. Further, the overall mean quality score for this summary was 5.8. The unanimous recommendation was in support of clinical deployment of this association. It is therefore now being delivered to clinicians (for genotyped patients) using our institutional Genomic Prescribing System.

Table 1

Clinically Actionable Associations Detected in Critical Analysis

Drug(s)	No. of PGx Publications	No. of Positive Publications in High IF Journals	Clinically Actionable Gene(s)/Variant(s)	Gene(s)	Phenotype	Supporting Publication(s)	Sample Size	Effect Size	Recommended Clinical Action
asparaginase	7	5	rs6021191, rs17885382	*NFATC2, HLA-DRB1*	hypersensitivity	Fernandez et al. *Blood.* 2015;126(1): 69–75	589	OR=3.1	• Closer monitoring for hypersensitivity is strongly recommended for those carrying any risk alleles at either of the specified loci.
capecitabine/fluorouracil	218	72	DPD deficient	*DPYD*	systemic toxicity	FDA label[5,6]/CPIC guideline[10]			• For those with decreased DPD activity, decrease dose by 25–50%. • For those with complete DPD deficiency, avoid use of fluoropyrimidine drugs.
cisplatin	128	28	rs1872328	*ACYP2*	ototoxicity	Xu et al. *Nat Genet.* 2015;47(3):263–266, Vos et al. *Pharmacogenet Genomics.* 2016;26(5):243–247	306, 156	HR=4.5	• Closer monitoring for ototoxicity is strongly recommended for patients carrying the risk allele (heterozygotes and homozygotes).
doxorubicin	63	19	rs1883112	*NCF4*	cardiotoxicity	Wojnowski et al. *Circulation.* 2005;112(24):3754–3762, Rossi et al. *Leukemia.* 2009;23(6):1118–1126	450, 106	OR=2.5	• For carriers of one risk allele, no modifications are warranted. • For carriers of two risks alleles, closer monitoring for cardiotoxicity is strongly recommended.
			rs8187710	*ABCC2*	cardiotoxicity	Wojnowski et al. *Circulation.* 2005;112(24):3754–3762, Armenian et al. *Br J Haematol.* 2013;163(2): 205–213	450, 255	OR=4.3	• Closer monitoring for cardiotoxicity is strongly recommended for patients carrying the risk allele (heterozygotes and homozygotes).
			rs13058338	*RAC2*				OR=2.8	• Closer monitoring for cardiotoxicity is strongly recommended for patients carrying the risk allele (heterozygotes and homozygotes).
irinotecan	112	38	*UGT1A1**28	*UGT1A1*	toxicity (primarily diarrhea and neutropenia)	FDA label[7]			• For those carrying one risk allele, monitor closely for toxicities. • For those homozygous for the risk allele, reduce starting dose.
lapatinib	6	4	*HLA-DQA1**02:01	*HLA*	ALT elevation	Spraggs et al. *J Clin Oncol.* 2011;29(6):667–673, Schaid et al. *J Clin Oncol.* 2014;32(22):2296–2303; see also FDA label[†]	1275, 1194	OR=14.1	• Closer monitoring for hepatotoxicity is strongly recommended for patients carrying the risk allele (heterozygotes and homozygotes).
mercaptopurine/thioguanine	29	6	IM/PM	*TPMT*	myelosuppression	FDA label[8,9]/CPIC guideline[11]			• For intermediate metabolizers, decrease starting dose by 30–70% and adjust doses based on degree of myelosuppression. • For poor metabolizers, drastically decrease starting dose and dosing frequency and adjust doses based on degree of myelosuppression.
sunitinib	8	4	rs307826	*VEGFR3*	PFS, RR	Garcia-Donas et al. *Lancet Oncol.* 2011;12(12):1143–1150	95	HR=8.8	• Not recommended for clinical implementation at this time.

Drug(s)	No. of PGx Publications	No. of Positive Publications in High IF Journals	Clinically Actionable Gene(s)/Variant(s)	Gene(s)	Phenotype	Supporting Publication(s)	Sample Size	Effect Size	Recommended Clinical Action
			rs776746	*CYP3A5*	toxicity-induced dose reduction			HR=3.8	• For those carrying the risk allele, closer monitoring for toxicities is strongly recommended. Earlier dose reduction may be required.
tamoxifen	54	22	UM/NM/IM/PM	*CYP2D6*	recurrence, DFS, RFS, DRFS, BCSS, OS	CPIC guideline[12]			• For intermediate metabolizers, consider an alternative drug (e.g., an aromatase inhibitor), or an increased tamoxifen dose if aromatase inhibitors are contraindicated. • For poor metabolizers, an alternative drug is recommended (e.g., an aromatase inhibitor). An increased tamoxifen dose could be considered if aromatase inhibitors are contraindicated.
vincristine	34	13	rs924607	*CEP72*	peripheral neuropathy	Diouf et al. *JAMA.* 2015;313(8):815–823, Stock et al. *Clin Pharmacol Ther.* 2017;101(3):391–395	321, 96	OR=4.3	• For carriers of one risk allele, no modifications are warranted. • For carriers of two risk alleles, closer monitoring for neuropathy is strongly recommended.

PGx=pharmacogenomics/IF=impact factor/OR=odds ratio/HR=hazard ratio/PFS=progression-free survival/RR=response rate/DFS=disease-free survival/RFS=recurrence-free survival/DRFS=distant relapse-free survival/BCSS=breast cancer-specific survival/OS=overall survival/UM=ultrarapid metabolizer/NM=normal metabolizer/IM=intermediate metabolizer/PM=poor metabolizer

[†]The Food and Drug Administration label for lapatinib indicates that *HLA-DQA1**02:01 has been associated with hepatotoxicity, but a specific clinical recommendation/action is not provided in the FDA label.

Table 2

AGREE Scores for Draft Clinical Decision Support Summaries

Drug/genetic pair	Identified *a priori* or novel finding?	Domain 1 (Scope and Purpose)	Domain 3 (Rigour of Development)	Domain 4 (Clarity of Presentation)	Domain 5 (Applicability)	Overall mean ± SD quality score (averaged across reviewers)	Guideline recommended for clinical deployment?
asparaginase/rs6021191/rs17885382	novel	93.1	86.1	29.2	29.2	4.5±0.6	Yes
capectabine/fluorouracil/*DPYD*	*a priori*	98.1	96.3	96.3	88.9	7±0.0	Yes
cisplatin/rs1872328	novel	88.9	81.9	37.5	41.7	4.5±0.6	Yes
doxorubicin/rs1883112	novel	86.1	83.3	44.4	27.1	4.5±1.3	Yes
doxorubicin/rs8187710	novel	86.1	83.3	44.4	33.3	4.5±1.3	Yes
doxorubicin/rs13058338	novel	86.1	83.3	44.4	33.3	4.5±1.3	Yes
irinotecan/*UGT1A1*28*	*a priori*	96.3	79.6	81.5	80.6	5.7±0.6	Yes
lapatanib/*HLA-DQA1*02:01*	novel	91.7	90.3	38.9	33.3	4.3±1.0	Yes
mercaptopurine/thioguanine/*TPMT*	*a priori*	95.8	98.6	98.6	87.5	7±0.0	Yes
sunitinib/rs307826	novel	93.1	80.6	41.7	60.4	4.5±1.3	No
sunitinib/rs776746	novel	90.3	80.6	41.7	54.2	4.8±1.3	Yes
tamoxifen/*CYP2D6*	*a priori*	100.0	98.1	87.0	88.9	6.3±0.6	Yes
vincristine/rs924607	novel	100.0	97.2	76.4	68.8	5.8±1.3	Yes
Overall mean ± SD scores		92.7±5.1	87.6±7.4	58.6±25.1	55.9±24.6	5.2±1.0	

SD=standard deviation