PRECISION MEDICINE

Clinical Opportunities for Germline Pharmacogenetics and Management of Drug-Drug Interactions in Patients With Advanced Solid Cancers

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abstract

PURPOSE Precision medicine approaches, including germline pharmacogenetics (PGx) and management of drug-drug interactions (DDIs), are likely to benefit patients with advanced cancer who are frequently prescribed multiple concomitant medications to treat cancer and associated conditions. Our objective was to assess the potential opportunities for PGx and DDI management within a cohort of adults with advanced cancer.

METHODS Medication data were collected from the electronic health records for 481 subjects since their first cancer diagnosis. All subjects were genotyped for variants with clinically actionable recommendations in Clinical Pharmacogenetics Implementation Consortium guidelines for 13 pharmacogenes. DDIs were defined as concomitant prescription of strong inhibitors or inducers with sensitive substrates of the same drug-metabolizing enzyme and were assessed for six major cytochrome P450 (CYP) enzymes.

RESULTS Approximately 60% of subjects were prescribed at least one medication with Clinical Pharmacogenetics Implementation Consortium recommendations, and approximately 14% of subjects had an instance for actionable PGx, defined as a prescription for a drug in a subject with an actionable genotype. The overall subject-level prevalence of DDIs and serious DDIs were 50.3% and 34.8%, respectively. Serious DDIs were most common for CYP3A, CYP2D6, and CYP2C19, occurring in 24.9%, 16.8%, and 11.7% of subjects, respectively. When assessing PGx and DDIs together, approximately 40% of subjects had at least one opportunity for a precision medicine–based intervention and approximately 98% of subjects had an actionable phenotype for at least one CYP enzyme.

CONCLUSION Our findings demonstrate numerous clinical opportunities for germline PGx and DDI management in adults with advanced cancer.

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INTRODUCTION

Pharmacogenetics (PGx) and management of drug-drug interactions (DDIs) are two aspects of precision medicine that have the potential to optimize medication therapy in oncology and other therapeutic disciplines. PGx-guided approaches have been shown to enhance drug efficacy and safety, including within results from prospective clinical trials.[1-5] Accordingly, the US Food and Drug Administration (FDA) currently includes PGx information within the labels for nearly 300 medications.[6] Moreover, clinical practice guidelines that include PGx-guided recommendations have been published by the Clinical Pharmacogenetics Implementation Consortium (CPIC) and prominent discipline-specific professional organizations (eg, the National Comprehensive Cancer Network) for over 100 medications.[7,8] Similarly, DDIs are known to contribute to adverse drug events,[9,10] and strategies to manage DDIs have been shown to improve patient outcomes.[11] Given their important clinical implications, recommendations to manage DDIs are included both in FDA drug development guidance to industry[12] and in numerous clinical practice guidelines.[13,14]

The clinical utility of precision medicine is expected to be especially high for patients with advanced cancer given that drug therapy is commonly used not only to treat cancer but also to manage both cancer treatment–related adverse events (eg, nausea and vomiting) and comorbid conditions associated with cancer (eg, psychiatric conditions and pain syndromes). As a result, polypharmacy, typically defined as the concomitant use of five or more drugs, is exceedingly common in patients with advanced cancer.[15] Polypharmacy carries an increased risk for DDIs,[16] and, predictably, multiple investigations have identified serious DDIs in advanced cancer that affect

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT SUMMARY

Key Objective

How prevalent are opportunities for precision medicine–based clinical interventions, including germline pharmacogenetics and management of drug-drug interactions (DDIs), in patients with advanced cancer seen at our institutional molecular tumor board?

Knowledge Generated

Our findings indicate that approximately one in seven patients with advanced cancer had an opportunity for actionable pharmacogenetics during the study period (median follow-up: 2.9 years). In addition, approximately one in three patients had a potentially serious DDI affecting a major cytochrome P450 enzyme, and one in 14 patients had a potentially serious DDI involving a tyrosine kinase inhibitor and acid-reducing medication.

Relevance

Our findings suggest that patients with advanced cancer are a high-value population for clinical implementation of precision medicine.

patient outcomes.[17] PGx-guided approaches also offer the ability to optimize therapy for numerous anticancer medications on the basis of somatic and germline genetic biomarkers. While molecular tumor boards have effectively harnessed somatic genome-guided treatment approaches to improve patient outcomes,[18] germline PGx biomarkers can enhance medication safety with agents such as fluoropyrimidine and thiopurine chemotherapies.[19,20] Additionally, PGx-guided approaches have been shown to enhance both efficacy and safety of selective serotonin reuptake inhibitors, tricyclic antidepressants, and opioid analgesics that are often prescribed for comorbid conditions prevalent in cancer.[21-23] Given these abundant PGx opportunities in patients with cancer, it has been suggested that preemptive testing for PGx variants at first cancer diagnosis may be an effective clinical strategy to optimize patient outcomes.[24] Furthermore, recent advancements in bioinformatics technology have enhanced the feasibility of PGx approaches in cancer through the creation of methods to extract PGx information from existing germline sequencing data generated during the clinical workflow of molecular tumor boards.[25,26]

Although past studies have characterized opportunities for DDI management and PGx-guided approaches in patients with advanced cancer, we are not aware of any work that has simultaneously investigated both approaches to provide a comprehensive assessment of the potential for precision medicine. Therefore, the objective of this study was to determine composite opportunities for precision medicine, incorporating both PGx-guided and DDI management strategies, within a cohort of adults with advanced solid cancers. By analyzing the potential for PGx-guided interventions since each subject's respective date of first cancer diagnosis, we also directly investigate the potential clinical utility of pre-emptively obtaining PGx information when patients are first diagnosed with cancer.

METHODS

Subject Enrollment and Eligibility

This study involved prospective genotyping and retrospective electronic health record (EHR) review of patients with solid cancers at Indiana University Health in Indianapolis, IN. Subjects were eligible to participate in the study if they had been seen in the Indiana University Health Precision Genomics clinic and enrolled in the accompanying Indiana University Total Cancer Care Protocol (part of the Oncology Research Information Exchange Network-wide Total Cancer Care initiative)[27] and agreed to submit a blood sample for genotyping. Subjects were enrolled at clinic visits from February 2015 to February 2018. This research protocol and the parent Total Cancer Care Protocol were approved by Indiana University's Institutional Review Board. All subjects provided written informed consent.

Study Design and Data Collection

The purpose of this study was to investigate potential opportunities for precision medicine interventions, including PGx and management of DDIs, within a cohort of 481 adults seen at our institutional precision oncology clinic and associated solid tumor board. Demographic and clinical data, including medication prescriptions, were collected from the EHRs of all institutions participating in the Indiana Health Information Exchange, a statewide EHR data repository that includes 38 health care systems. Demographic data included age, sex, and race. Clinical data included first oncologic diagnosis and all inpatient and outpatient prescriptions. Genotyping of clinically actionable variants within major pharmacogenes was performed at the College of American Pathologists–accredited Indiana University Pharmacogenomics Laboratory using a laboratory-developed assay on the basis of the OpenArray Platform (ThermoFisher; Waltham, MA). The genes included on the genotyping platform, along with the number of variants tested for each gene, were as follows: *CYP2B6* (two), *CYP2C19* (six), *CYP2C9* (six), *CYP2D6* (11, including copy number targeting exon 9),

CYP3A4 (two), *CYP3A5* (three), *CYP4F2* (one), *DPYD* (two), *G6PD* (two), *IFNL3* (one), *SLCO1B1* (two), *TPMT* (two), and *VKORC1* (one). Detailed genotyping methods are provided in the Data Supplement, and a complete list of tested variants is available in the Data Supplement.

Precision Medicine Analyses

Detailed information about the specific methods used in the PGx, DDI, and composite precision medicine analyses, including the medication inclusion criteria and assumptions made, is available in the Data Supplement. Briefly, the PGx analyses assessed the prevalence of (1) prescriptions for medications with CPIC recommendations and (2) instances for actionable PGx, defined as prescription of a medication with a CPIC recommendation for a subject with a CPIC-defined actionable genotype-predicted phenotype. The DDI analyses assessed the prevalence of concomitant administration of perpetrator drugs with sensitive substrates of CYP2B6, CYP2C19, CYP2C8, CYP2C9, CYP2D6, and CYP3A and of coadministration of acid reducers and tyrosine kinase inhibitors. The composite precision medicine analyses compiled results from our PGx and DDI analyses and assessed the prevalence of CYP inhibitor–mediated phenoconversion for CYP2B6, CYP2C19, CYP2C9, CYP2D6, and CYP3A4.

Statistical Analyses

Data were analyzed using descriptive statistics (counts and percentages) using JMP Pro v.15.0.0.

RESULTS

Subject Demographic, Clinical, and Medication Data

Demographic and clinical characteristics of the 481 study subjects with advanced cancer included are summarized in Table 1. The median age of our cohort was 57 ± 16.6 (median ± interquartile range) years, and most subjects were White (87.9%) and female (53.2%). The most common types of cancers at first diagnosis included breast (12.7%), pancreatic (10.8%), and colorectal (9.6%). The median duration of follow-up, defined as the time between the date of first cancer diagnosis and the date of last prescription, was 2.9 ± 4.9 (median ± interquartile range) years.

Extracted medication data contained ≥ 1 prescription for 469 of 481 (97.5%) subjects. Filtering to include only prescriptions since each subject's respective date of first cancer diagnosis yielded 158,188 unique prescriptions that were assessed within our precision medicine analyses (schematic of filtering results shown in the Data Supplement). Since first cancer diagnosis, our cohort had a total of 7,074 unique prescriptions for medications contained within a CPIC guideline (herein called PGx medications) and a total of 22,642 unique prescriptions for medications that were defined as inducers, inhibitors, or sensitive substrates of CYP2B6, CYP2C19, CYP2C8, CYP2C9, CYP2D6, and/or CYP3A; acid reducers; or tyrosine kinase inihibitors (TKIs; herein called DDI medications).

PGx Analyses

Distributions of genotype-predicted phenotypes within our cohort for all pharmacogenes are displayed in Table 2. When defining actionable phenotypes as those with clinically actionable recommendations within CPIC guidelines for at least one medication, the rates of actionable phenotypes were highest for CYP2C19 (59.5%) and VKORC1 (52.4%) and lowest for TPMT (7.3%), G6PD (1.5%), and DPYD (1.0%).

Of 469 analyzed subjects, 282 (60.1%) were prescribed at least one PGx medication. These included a total of 1,045 unique PGx medications (ie, prescription of a unique PGx medication for a unique subject), with an average of 2.2 ± 2.4 (mean ± standard deviation) PGx medications/subject and a maximum of 12 PGx medications in one subject. When considering both prescribed medications and genotype-predicted phenotypes, we identified a total of 81 unique opportunities for actionable PGx. Instances of actionable PGx occurred for 67 subjects (14.3%), with 56 subjects having instances of actionable PGx involving one medication, eight subjects having actionable PGx involving two medications, and three subjects having actionable PGx involving three medications.

The prevalence of instances of actionable PGx, when stratified by the drug-gene pairs involved, are summarized in Table 3. For PGx medications prescribed in at least five subjects, the rates of actionable PGx were highest for warfarin (87.5%), amitriptyline (58.3%), and clopidogrel (42.9%). Conversely, capecitabine, fluorouracil, sertraline, and celecoxib had no instances for actionable PGx. For warfarin, subjects were considered to have actionable PGx recommendations on the basis of *CYP2C9*, *CYP4F2*, and *VKORC1* genotype-based phenotypes in 20.8%, 58.3%, and 50.0% of cases, respectively. For amitriptyline, subjects were considered to have actionable PGx recommendations on the basis of *CYP2C19* and *CYP2D6* genotype-based phenotypes in 16.7% and 50.0% of cases, respectively.

DDI Analyses

Of 469 analyzed subjects, the prevalence of ≥ 1 prescription for an inducer, inhibitor, or substrate of any CYP enzyme was 49.0%, 58.0%, and 64.0%, respectively. The Data Supplement displays the prevalence of subjects with prescriptions for inducers, inhibitors, and substrates across the six enzyme systems that were assessed. Prescriptions for CYP inducers were most common for CYP2C19, CYP2C9, and CYP3A, occurring in 49.0% of subjects. Prescriptions for inhibitors were most common for CYP2D6 (occurring in 53.3% of subjects), CYP2C9 (35.0%), CYP3A (33.9%), and CYP2C19 (31.8%) while prescriptions for sensitive substrates were most common for CYP3A, CYP2D6, and CYP2C19 (prescribed in 60.3%, 59.9%, and 48.2% of subjects, respectively).

TABLE 1. Demographic and Clinical Characteristics of Study Cohort With Advanced Cancer

Variable	Value in Full Cohort (N = 481)
Age in years at first cancer diagnosis, median (IQR)	57.4 (16.6)
Sex, count (%)	
Female	256 (53.2)
Male	225 (46.8)
Race, count (%)	
White	423 (87.9)
Black	38 (7.9)
Asian	8 (1.7)
Other[a]	3 (0.4)
Unknown	9 (1.9)
Cancer type at first diagnosis, count (%)	
Breast	61 (12.7)
Pancreatic	52 (10.8)
Colorectal	46 (9.6)
Prostate	40 (8.3)
Soft-tissue sarcoma	36 (7.5)
Ovarian	26 (5.4)
Non–small-cell lung	23 (4.8)
Renal	18 (3.7)
Thymic	13 (2.7)
Cholangiocarcinoma	12 (2.5)
Head and neck	11 (2.3)
Bladder	10 (2.1)
Unknown primary	13 (2.7)
Duration of follow-up in years,[b] median (IQR)	2.9 (4.9)

Abbreviation: IQR, interquartile range.

[a]One individual who reported a race of other reported Hispanic ethnicity.

[b]Defined as the time elapsed between date of first cancer diagnosis and date of most recent prescription

When assessing concomitant prescription of both a relevant perpetrator (inducer or inhibitor) and victim (sensitive substrate) drug, 236 subjects (50.3%) had a DDI affecting at least one CYP enzyme system. Given the frequent use of corticosteroids to treat and manage treatment-related complications for many types of cancer,[29] we also performed DDI analyses excluding corticosteroids, which are potent inducers of CYP2C19, CYP2C9, and CYP3A; 225 subjects (48.0%) had a DDI affecting at least one major CYP enzyme when excluding corticosteroids. As summarized in Table 4, the prevalence of DDIs in our cohort was highest for CYP2D6 (affecting 45.2% of subjects; average of 1.5 DDIs/subject), followed by CYP3A (29.9%; 0.8 DDIs/subject), CYP2C19 (23.9%; 0.5 DDIs/subject), CYP2C9 (11.7%; 0.2 DDIs/subject), CYP2B6 (0.2%), and CYP2C8 (0%). When excluding corticosteroids, the prevalence of DDIs for CYP2C19, CYP2C9, and CYP3A was reduced to 10.2%, 7.0%, and 20.3%, respectively (Table 4). The most common drug-drug pairs contained within observed DDIs, stratified by enzyme, are available in the Data Supplement. The subject-level prevalence for serious DDIs, which were classified by the substrates involved, was 34.8% for any CYP enzyme when including corticosteroids and 29.4% when excluding corticosteroids (Table 4). Serious DDIs were most common for CYP3A, occurring in 24.9% of subjects and including sensitive substrates such as fentanyl, midazolam, and tramadol. In contrast, serious DDIs were less common for CYP2C19 (11.7% of subjects; sensitive substrates included escitalopram, sertraline, and citalopram), CYP2C9 (4.7% of subjects; substrates included warfarin, dronabinol, and phenytoin), and CYP2D6 (16.8% of subjects; substrates included tramadol, sertraline, and mirtazapine). When adjusting the prevalence of CYP enzyme-mediated DDIs on the basis of subject genotype (ie, excluding DDIs involving inducer or inhibitor drugs in subjects who are genotype-predicted poor metabolizers), the subject-level prevalence is as follows: CYP2B6: 0.2%; CYP2C19: 23.9%; CYP2C8: 0%; CYP2C9: 11.7%; CYP2D6: 44.1%; and CYP3A: 29.6% (adjusted on the basis of *CYP3A4* genotype).

TKIs have emerged as first-line treatments for many cancers, but recent investigations have described clinically significant DDIs with orally administered TKIs and acid-reducing agents, including antacids, histamine-2 receptor antagonists (H2RAs), and proton pump inhibitors (PPIs), that reduce TKI bioavailability and affect treatment outcomes.[30-32] Accordingly, we characterized the prevalence of DDIs involving TKIs and acid reducers in our study population. Within our cohort, 68 subjects (14.5%) were prescribed at least one TKI, with pazopanib (prescribed in 17 subjects), sunitinib (10), and crizotinib (nine) being the most commonly prescribed. Of the 68 subjects prescribed a TKI, 33 (48.5%) had a concomitant prescription of at least one acid reducer. The most common acid reducer classes involved in DDIs were PPIs (perpetrator drug in 34 DDIs), followed by H2RAs (10) and antacids (six).

Composite Precision Medicine Analyses

To assess the prevalence of composite opportunities for precision medicine interventions, we aggregated findings from our actionable PGx, serious CYP-mediated DDI, and acid reducer TKI DDI analyses at the subject level. As shown in Figure 1, 186 subjects (39.7%) had at least one opportunity for a precision medicine intervention. Sixty-eight subjects (14.5%) had opportunities for more than one type of precision medicine intervention, with nine of these subjects (1.9%) having opportunities for PGx and management of both CYP-mediated and acid reducer TKI DDIs.

Finally, we assessed the prevalence of CYP inhibitor–mediated phenoconversion, the process by which coadministration of a strong inhibitor functionally converts those with any genotype to a poor metabolizer phenotype, for CYP2B6, CYP2C19, CYP2C9, CYP2D6, and CYP3A4. As shown in Figure 2, CYP

TABLE 2. Distribution of Genotype-Predicted Phenotypes Within Study Cohort for Major Pharmacogenes

Gene	Ultrarapid Metabolizer, No. (%)	Normal Metabolizer, No. (%)	Intermediate Metabolizer, No. (%)	Poor Metabolizer, No. (%)	Indeterminate, No. (%)	Actionable, No. (%)
CYP2B6		248 (51.6)	199 (41.4)	34 (7.1)		233 (48.4)
CYP2C19	153 (31.8)[a]	189 (39.3)	124 (25.8)	9 (1.9)	6 (1.2)	286 (59.5)
CYP2C9		321 (66.7)	146 (30.4)	14 (2.9)		160 (33.3)
CYP2D6	9 (1.9)	254 (52.8)	182 (37.8)	24 (5.0)	12 (2.5)	215 (44.7)
CYP3A4		437 (90.9)	41 (8.5)	2 (0.4)	1 (0.2)	43 (8.9)[b]
CYP3A5		17 (3.5)	71 (14.8)	391 (81.3)	2 (0.4)	88 (18.3)
CYP4F2		265 (55.1)	175 (36.4)	41 (8.5)		216 (44.9)
DPYD		476 (99.0)	5 (1.0)	0 (0)		5 (1.0)
G6PD[c]		474 (98.5)	4 (0.8)	3 (0.6)		7 (1.5)
IFNL3 (IL28B)[c]		204 (42.4)	220 (45.7)	57 (11.9)		0 (0)
SLCO1B1[c]		333 (69.2)	107 (22.2)	11 (2.3)	30 (6.2)	118 (24.5)
TPMT		440 (91.5)	35 (7.3)	0 (0)	6 (1.2)	35 (7.3)
VKORC1[c]		229 (47.6)	199 (41.4)	53 (11.0)		252 (52.4)

Abbreviation: CPIC, Clinical Pharmacogenetics Implementation Consortium.

[a]For CYP2C19, count in ultrarapid metabolizer column includes counts of both ultrarapid metabolizers (n = 20) and rapid metabolizers (n = 133).

[b]While CPIC does not make *CYP3A4* genetic-guided recommendations for any drugs, we classify subjects with one or two copies of the *CYP3A4*22* loss-of-function allele as intermediate and poor metabolizers, respectively, and consider these phenotypes to be actionable since they are used at our institution to guide tacrolimus dosing in CYP3A5 nonexpressers.

[c]For designated genes, normal metabolizer, intermediate metabolizer, and poor metabolizer designations refer to subjects who are noncarriers, heterozygous, and homozygous for CPIC-defined actionable variants, respectively.

inhibitor–mediated phenoconversion enhanced the number of subjects with actionable phenotypes for CYP2C19, CYP2C9, CYP2D6, and CYP3A4, increasing the prevalence from 59.5% to 72.8%, 33.3% to 55.9%, 44.7% to 76.3%, and 8.9% to 38.9%, respectively. In contrast, CYP inhibitor–mediated phenoconversion only slightly changed the number of actionable phenotypes for CYP2B6 (prevalence increased from 48.4% to 49.1%) because of the low prevalence of prescription of CYP2B6 inhibitors within our cohort. When considering all five investigated CYPs together, nearly every subject in our cohort (98.3%) had an actionable phenotype (either genotype-predicted or from CYP inhibitor–mediated phenoconversion) for at least one CYP since their date of first cancer diagnosis. In addition, 47 subjects (9.8%) had genotype-predicted or phenoconverted actionable phenotypes for all five CYP enzymes.

DISCUSSION

We provide quantitative evidence to support the immense clinical opportunities for precision medicine approaches, including germline PGx and management of DDIs, in a cohort of patients with advanced cancer. Our findings indicate that approximately 14% of subjects had opportunities for actionable PGx and that approximately 35% and approximately 7% of subjects had potentially serious DDIs involving major CYP enzymes and acid reducers coprescribed with TKIs, respectively. When incorporating both PGx and DDIs, we found that approximately 40% of subjects had at least one opportunity for a precision medicine–based intervention, and nearly all subjects (approximately 98%) had an actionable phenotype for ≥ 1 CYP enzyme. On the basis of our findings, implementation of precision medicine approaches at first cancer diagnosis is likely to provide clinical benefit to a significant proportion of patients. Although a limited number of other studies have addressed similar topics, our investigation has significant methodological advantages, including a larger cohort (N = 481), a broader PGx analysis consisting of 13 CPIC-actionable pharmacogenes, and utilization of a statewide data repository to enable more comprehensive collection of medication data.

Previous investigations have demonstrated the potential clinical impact of PGx approaches in patients with advanced cancer. Nichols et al found that 65% of patients were taking at least one PGx medication (ie, those with a CPIC guideline) and, on the basis of allele frequencies, estimated that 7.1% of patients could benefit from at least one PGx intervention.[33] A study by Hertz et al[34] found that 2.6% of 115 adult and pediatric patients with cancer could have benefited from PGx interventions involving CYP2C19, DPYD, and TPMT. Kasi et al[35] also predicted abundant opportunities for PGx within patients with advanced cancer on the basis of genotypes for major CYP450 enzymes, although they did not analyze medication data. Many of our findings are similar to those reported in past investigations. For instance, the prevalence of prescription of PGx medications in our study was remarkably similar to that of Nichols et al when considering both prescriptions for any PGx medication and for specific PGx drugs such as ondansetron, capecitabine, and simvastatin.[33] Our

TABLE 3. Prevalence of PGx Medications Prescribed in Subjects With Clinically Actionable Genotype-Predicted Phenotypes on the Basis of CPIC Recommendations

Drug-Gene Pair	No. Prescribed Drug	% With Actionable PGx
Ondansetron-*CYP2D6*	256	0.8
Pantoprazole-*CYP2C19*	171	4.7
Omeprazole-*CYP2C19*	99	2.0
Ibuprofen-*CYP2C9*	93	5.4
Tramadol-*CYP2D6*	81	6.2
Capecitabine-*DPYD*	62	0
Fluorouracil-*DPYD*	40	0
Sertraline-*CYP2C19*	28	0
Escitalopram-*CYP2C19*	25	12.0
Lansoprazole-*CYP2C19*	24	4.2
Warfarin-*CYP2C9/CYP4F2/VKORC1*	24	87.5[a]
Citalopram-*CYP2C19*	21	23.8
Simvastatin-*SLCO1B1*	21	23.8
Meloxicam-*CYP2C9*	16	12.5
Celecoxib-*CYP2C9*	15	0
Amitriptyline-*CYP2C19/CYP2D6*	12	58.3
Nortriptyline-*CYP2D6*	9	11.1
Dexlansoprazole-*CYP2C19*	8	12.5
Clopidogrel-*CYP2C19*	7	42.9
Codeine-*CYP2D6*	7	14.3
Paroxetine-*CYP2D6*	6	16.7
Tamoxifen-*CYP2D6*	6	33.3
Doxepin-*CYP2C19/CYP2D6*	3	100
Voriconazole-*CYP2C19*	3	66.7
Rasburicase-*G6PD*	2	0
Atomoxetine-*CYP2D6*	1	0
Azathioprine-*TPMT*	1	0
Imipramine-*CYP2C19/CYP2D6*	1	100
Phenytoin-*CYP2C9*	1	0
Ribavirin-*IFNL3*	1	0
Tacrolimus-*CYP3A5*	1	0
Total	1,045	

NOTE. No. of prescribed drug indicates the number of subjects within our cohort who were prescribed the corresponding drug. % with actionable PGx, which was calculated at the subject level, indicates the percent of subjects prescribed the corresponding drug that had genotypes for which current CPIC guidelines recommend actionable clinical management strategies.

Abbreviations: CPIC, Clinical Pharmacogenetics Implementation Consortium; PGx, pharmacogenetics.

[a]For warfarin, the percent with actionable PGx was calculated as having an actionable phenotype for any of the three genes (*CYP2C9*, *CYP4F2*, and *VKORC1*) that influence warfarin dosing requirements in current CPIC guidelines.[28]

findings related to the distribution of actionable phenotypes are also consistent with those from past investigations[33,35] and from large analyses of population allele frequencies.[36] In contrast, our finding for the prevalence of subjects with potential PGx interventions (14.3%) is higher than those reported by Nichols et al (7.1%) or Hertz et al (2.6%).[33,34] These differences are likely attributable to the facts (1) that we investigated the potential for PGx interventions across a wider array of pharmacogenes and (2) that we used a statewide repository to enhance the richness of our collected medication data.

Multiple investigations have also characterized the opportunities for DDI management strategies in adults with

TABLE 4. Number and Prevalence of Unique DDIs (ie, unique coprescription of a relevant drug-drug pair in a unique subject) by the Enzyme Involved in n = 469 Subjects Prescribed ≥ 1 Medication, Including (left) and Excluding (right) DDIs Involving Corticosteroids

	DDIs Including Corticosteroids				DDIs Excluding Corticosteroids			
Enzyme	Total DDIs	DDIs/Subject (mean)	DDI Prevalence (%)	Serious DDI Prevalence (%)	Total DDIs	DDIs/Subject (mean)	DDI Prevalence (%)	Serious DDI Prevalence (%)
CYP2B6	1	0.00	0.2	0.2	1	0.00	0.2	0.2
CYP2C19	237	0.51	23.9	11.7	89	0.19	10.2	5.8
CYP2C8	0	0	0	0	0	0	0	0
CYP2C9	76	0.16	11.7	4.7	39	0.08	7.0	2.3
CYP2D6	695	1.48	45.2	16.8	695	1.48	45.2	16.8
CYP3A	392	0.84	29.9	24.9	217	0.46	20.3	18.6
Any DDI	1,401	2.99	50.3	34.8	1,041	2.22	48.0	29.4

NOTE. All DDI prevalence calculations are at the subject level.
Abbreviation: DDI, drug-drug interaction.

advanced cancer, estimating DDIs to occur in 27%-78% of patients.[37-42] The large differences in these estimates are likely due to methodological differences among studies. For instance, studies that included both pharmacokinetic- and pharmacodynamic-based DDIs and studies that used medication lists from the EHR (rather than those verified by patients during medication reconciliation) had higher rates of potential DDIs.[38,39] Our DDI prevalence of approximately 52% falls in the middle of those reported by past investigations. In terms of methodology, extracting medication data from the EHR and not being able to resolve medication days supply or whether medications were prescribed on an as-needed basis likely resulted in a higher DDI prevalence in our study. However, our DDI prevalence was likely conservative relative to other studies on the basis of other elements in our methodology, including that we excluded DDIs with pharmacodynamic mechanisms and those involving drugs commonly coadministered as cancer treatment regimens (eg, corticosteroids with docetaxel).

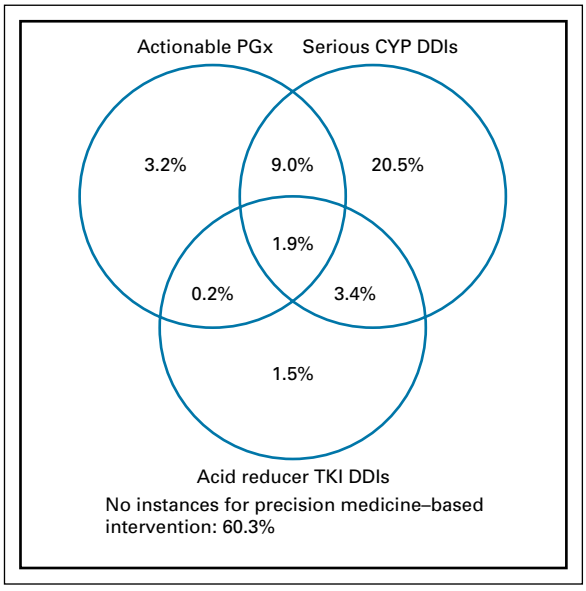

FIG 1. Subject-level prevalence for composite precision medicine opportunities, including actionable PGx, management of serious CYP-mediated DDIs, and management of DDIs including acid reducers and TKIs. CYP, cytochrome P450; DDI, drug-drug interaction; PGx, pharmacogenetics; TKI, tyrosine kinase inihibitors.

Our findings are impactful since they demonstrate abundant clinical opportunities for PGx in patients with advanced cancer and support preemptive genotyping at first cancer diagnosis. Our results corroborate those from other studies that identified significant opportunities for PGx in patients with cancer, including via optimization of selective serotonin reuptake inhibitor, tricyclic antidepressants, opioid, and antiemetic therapies.[33,35] Relative to past investigations quantifying PGx opportunities within general medical populations, our findings suggest that patients with advanced cancer may be more likely to be prescribed drugs with CPIC recommendations and, relatedly, more likely to have opportunities for PGx interventions, although differences in study methodologies limit direct comparisons.[43,44] Advances in technology have improved PGx feasibility by reducing the cost of obtaining genetic information and enabling repurposing of genetic information obtained from molecular tumor boards.[26] Economic analyses have demonstrated cost savings because of toxicity sparing for both *DPYD* and *TPMT* testing,[45,46] and there is currently clinical momentum to standardize PGx markers for fluoropyrimidine and thiopurine chemotherapies.[47,48]

We found that over half of study subjects had a DDI affecting at least one major CYP enzyme. This finding is important given that DDIs have been associated with reduced efficacy and increased adverse drug events in patients with cancer. CYP-mediated DDIs have been shown to increase adverse events attributable to both cancer therapies and concomitant medications in patients with cancer.[49,50] Additionally, several studies have demonstrated clinically significant DDIs between acid-reducing agents and TKIs, evidenced by reduced progression-free and overall survival.[30-32] Our findings demonstrate that these DDIs are common in patients with advanced cancer, occurring in nearly half of subjects in our

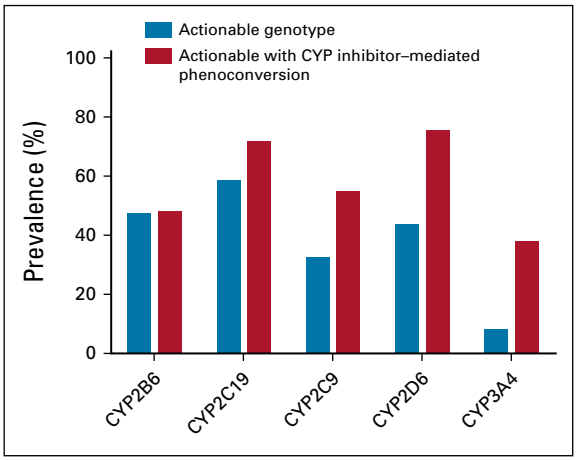

FIG 2. Subject-level prevalence of clinically actionable phenotypes for major CYP enzymes on the basis of genotype and because of CYP inhibitor–mediated phenoconversion. CYP, cytochrome P450.

study prescribed a TKI. However, it is possible that the providers told the patient to discontinue the acid reducers while taking the TKIs. Finally, to our knowledge, our work is one of the first to assess the prevalence of potential drug-drug-gene interactions (DDGIs; ie, CYP inhibitor–mediated phenoconversion) within a clinical cohort. While the strategies to manage DDGIs borrow from both PGx and DDI management approaches, consideration of DDGIs may provide critical information that modifies the risk of adverse drug events predicted from consideration of either approach in isolation.[51] As demonstrated by our composite study findings that approximately 40% of subjects had at least one opportunity for precision medicine intervention and approximately 98% of subjects had an actionable phenotype for $\geq$ 1 CYP enzymes, PGx information and concomitant drug lists should be used in tandem to most accurately inform approaches to optimize medication therapy.

We acknowledge several limitations of our study. First, we did not mine the EHR to identify prescribing decisions or health outcomes related to the instances for precision medicine identified within our analyses. Next, our extracted medication data did not include ways to conclusively determine whether medications were prescribed on an as-needed basis or ascertain days supply to assess temporal overlap between perpetrator and victim drugs within our DDI analyses. To compensate for these limitations, we used conservative methods in our DDI analyses to estimate days supply for each prescription. Our medication data also did not consistently contain information about the medication dose. As a result, our analysis may have overestimated the prevalence of instances for actionable PGx with amitriptyline since current CPIC guidelines do not recommend clinical action at daily doses under 50 mg.[21] In addition, our panel-based genotyping method only tested for relatively common functional variants in the assessed genes within our primary ethnic and racial populations. Additionally, advances in knowledge since study initiation limited our ability to assess variants with newly established relevance to pharmacotherapy (eg, HapB3 in *DPYD*). Finally, our genotyping panel also did not assess every pharmacogene included in CPIC guidelines but did cover genes serving as the basis for over 80% of CPIC recommendations.[7]

In conclusion, our work provides quantitative evidence of the vast clinical opportunities for precision medicine approaches in patients with advanced cancer, demonstrating the clinical utility of both germline PGx and DDI management strategies. Given their established clinical benefits and the abundant opportunities for their use demonstrated by our results, precision medicine approaches are likely to improve medication outcomes in patients with cancer and may provide clinical benefit if incorporated into the workflow of molecular tumor boards.

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