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ARTICLE

Identifying the prevalence of clinically actionable drug-gene interactions in a health system biorepository to guide pharmacogenetics implementation services

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Abstract

Understanding patterns of drug-gene interactions (DGIs) is important for advancing the clinical implementation of pharmacogenetics (PGx) into routine practice. Prior studies have estimated the prevalence of DGIs, but few have confirmed DGIs in patients with known genotypes and prescriptions, nor have they evaluated clinician characteristics associated with DGI-prescribing. This retrospective chart review assessed prevalence of DGI, defined as a medication prescription in a patient with a PGx phenotype that has a clinical practice guideline recommendation to adjust therapy or monitor drug response, for patients enrolled in a research genetic biorepository linked to electronic health records (EHRs). The prevalence of prescriptions for medications with pharmacogenetic (PGx) guidelines, proportion of prescriptions with DGI, location of DGI prescription, and clinical service of the prescriber were evaluated descriptively. Seventy-five percent (57,058/75,337) of patients had a prescription for a medication with a PGx guideline. Up to 60% (n = 26,067/43,647) of patients had at least one DGI when considering recommendations to adjust or monitor therapy based on genotype. The majority (61%) of DGIs occurred in outpatient prescriptions. Proton pump inhibitors were the most common DGI medication for 11 of 12 clinical services. Almost 25% of patients (n = 10,706/43,647) had more than one unique DGI, and, among this group of patients, 61% had a DGI with more than one gene. These findings can inform future clinical implementation by identifying key stakeholders for initial DGI prescriptions, helping to inform workflows. The high prevalence of multigene interactions identified also support the use of panel PGx testing as an implementation strategy.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Most patients have a pharmacogenetic (PGx) variant and medications with PGx guidance are commonly prescribed, however, the number of patients who experience drug-gene interactions (DGIs), where a medication change is recommended based on genotype, is less well-defined. Key factors of successful implementation include identification of stakeholders and understanding institutional workflows.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study evaluated the prevalence of DGIs, according to the Clinical Pharmacogenetics Implementation Consortium guidelines, in a research biorepository linked to an electronic health record and assessed the location and clinical services most likely to prescribe different DGIs to determine how frequently and where DGIs are occurring in routine clinical practice.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This study has demonstrated most patients who receive a PGx medication experience a DGI and approximately one-quarter of patients experience more than one DGI. In patients who experience greater than one DGI, over 60% had DGIs attributed to more than one gene. The majority of prescriptions were in outpatient settings and varied across provider groups.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

This study provides additional evidence for the potential impact of clinical PGx testing and supports the use of panel-based tests. The findings can be used to identify clinician stakeholders for specific DGIs and inform workflows for future implementation projects. Future studies could assess clinical outcomes of the observed DGIs.

INTRODUCTION

Pharmacogenetics (PGx) can help identify patients who may be at higher risk of experiencing side effects or suboptimal response to standard treatment. Experiencing adverse side effects is an established risk factor for decreased patient adherence to their treatment regimen. With over 99% of individuals predicted to carry a pharmacogenetic variant,[1,2] the integration of PGx into clinical prescribing decisions could help to improve medication-related outcomes. Clinical practice guidelines are available from multiple organizations, such as the Clinical Pharmacogenetics Implementation Consortium (CPIC) or Dutch Pharmacogenetics Working Group (DPWG), to assist with the interpretation and application of pharmacogenetic results into prescribing decisions.

Despite these resources and increasing test availability, PGx is not routinely applied for all impacted medications. A variety of authors have discussed existing barriers to routine uptake, such as lack of education and knowledge of PGx among clinicians, difficulty identifying patients who would most benefit from PGx testing, prolonged turn-around time for test results, and integration of results into the electronic medical records.[3,4] Prior groups have also shared best practices for establishing new PGx services, which include identification of clinical stakeholders, identification of target patient populations, and identification of target genes.[5,6] The ideal stakeholder, population, and gene(s) may vary among different institutions, which has been highlighted in the available literature of PGx implementation programs, based on their clinical specialties, structures, and workflows.[7–9]

Increasingly, genetic biorepositories are being developed which offer unique opportunities for genetic discovery and translation of clinically relevant findings. Some institutions have developed research biorepositories, where genetic data from enrolled participants are linked to medical record data for research of genetic associations.[10–13] Others have established biorepositories where the biorepository data is generated in a Clinical Laboratory Improvement Amendment (CLIA)-certified laboratory or variants of interest are confirmed in a CLIA-certified laboratory and the results of the biorepository genetic testing can be returned to patients and/or their providers for use in clinical decisions.[14,15] PGx implementation initiatives

can be enhanced by leveraging available biorepository data by increasing PGx discovery to improve clinical guidance and demonstrate the clinical utility of the PGx findings. Additionally, for biorepositories with clinical genetic testing, the results can be used to guide clinical interventions for individual patients.

Over 10 years ago, our institution established the Michigan Genomics Initiative (MGI) biorepository that links research genetic testing results to the patient's electronic medical record (EMR) for genomic discovery. To date, the MGI has consented over 85,000 patients using an opportunistic recruitment of participants at the time of a surgical visit.[16] Participants may complete additional symptoms surveys which are available for use by researchers and agree to re-contact for future research opportunities. For this study, we utilized MGI data to determine the prevalence of prescriptions for medications with PGx recommendations, the proportion of prescription with clinically actionable drug-gene interactions (DGIs). Additionally, we evaluated the clinical services prescribing the medications with DGIs at our institution to gain an enhanced understanding of the appropriate stakeholders, populations, and genetic testing options for our patient population. We hypothesized that these findings could be used to develop new clinical PGx testing services that would have the most potential impact to improve patient care.

METHODS

Data collection

Patients were included in this study if they were enrolled in the internal research biorepository, the MGI, were greater than or equal to 18 years old at the time of biorepository enrollment and had either an inpatient or outpatient medication order placed for a medication with a CPIC guideline between July 1, 2014, and December 21, 2020, in the University of Michigan Health system. All CPIC guidelines published before December 31, 2020, were used to compile the medication list for inclusion (Table S1), excluding the guidelines for cystic fibrosis transmembrane conductance regulator (*CFTR*)-ivacaftor, interferon lambda 3 (*IFNL3*)-peginterferon-alpha, and ryanodine receptor 1/calcium voltage-gated channel subunit alpha1 S (*RYR1/CACNA1S*)-inhaled anesthetics for either limited clinical use in our population (*CFTR*, *INFL3*) or inability to extract the medication administration from the available system (inhaled anesthetics). For guidelines addressing medication classes, such as proton pump inhibitors (PPIs), only medications with recommendations for PGx-guided modifications within the CPIC guideline were included in the medication queries (e.g., esomeprazole was not included). Topical formulations of medications, such as fluorouracil, were also excluded. Medication queries were performed within the University of Michigan Precision Health Analytics platform,[17] a de-identified internal search engine that allows for extraction of discrete medical record data from our Epic based EMR (Epic Systems Corporation, 2022). Data extracted in the query included: subject study ID, sex, race, ethnicity, medication name, date of medication administration or prescription (equally shifted for de-identification), order type (medication administration record for inpatient and prescription order for outpatient), and provider login location of order entry. Dates of either medication administration or medication prescription were used to identify the initial medication exposure for each patient and only the initial medication exposure was included in analyses, meaning patients were only included in the analysis once for each unique DGI.

The location of medication order entry for the initial medication exposure was used to determine (1) whether the medication order was for inpatient or outpatient use and (2) the clinical service of the ordering provider. Inpatient orders included those documented in the electronic medication administration record, whereas outpatient orders were those placed during an admission for outpatient use or during an ambulatory encounter. Clinical services were identified by the outpatient clinic name or, for inpatient services, were categorized as the primary admitting service to that location in the hospital.

Each CPIC medication order was evaluated for a DGI, defined as a medication order in a patient whose genomic data contained within the MGI indicated carriage of a PGx phenotype that would result in a recommendation to modify therapy based on the respective CPIC guideline. DGIs were grouped into two categories for analysis: (1) those with strong, moderate, and optional recommendations for initial treatment adjustments for all patients and (2) all strong, moderate, and optional recommendations for treatment adjustments including initial dosing, special populations (e.g., omeprazole and CYP2C19 rapid metabolizers with *Helicobacter pylori*), or medication considerations for efficacy monitoring (e.g., tramadol and CYP2D6 intermediate metabolizer). For medications with CPIC guidelines that contain separate pediatric and adult recommendations, only the adult recommendations were applied to DGI determinations as all patients were greater than or equal to 18 years old for inclusion into MGI.

Genotyping

Patients enrolled in MGI provided a blood sample and were genotyped on a custom Illumina CoreExome array, which has been previously described.[16,18] The single-nucleotide polymorphism (SNP) data were provided for variants that were imputed with an estimated R^2 greater than 0.3 from the Trans-Omics for Precision Medicine panel (version r2). Results for *CYP2B6*, *CYP2C19*, *CYP2C9*, *CYP2D6*, *CYP3A5*, *NUDT15*, *SLCO1B1*, and *TPMT* were translated into inferred PGx star-allele diplotypes using the Stargazer version 1.15 algorithm and PGx phenotypes using the PyPGx version 0.1.34 algorithm.[19,20] Phenotype assignments were compared between the PyPGx algorithm and the CPIC diplotype-phenotype translation tables, in instances of disagreement, custom modifications were made to the MGI bioinformatics pipeline to ensure all phenotypes matched the CPIC designations. CYP2D6 copy number variations could not be detected on the MGI platform and were not included in the analysis. Although *UGT1A1* was included in the Stargazer algorithm, the algorithm includes *UGT1A1**28 which was not imputed from the TOPMed panel. However, the MGI platform imputed *UGT1A1**80 (rs887829), which was used as a surrogate for *UGT1A1**28, and was manually combined with the Stargazer *UGT1A1* star allele output to determine final UGT1A1 phenotype. HLA genotypes were inferred as either present or absent by MGI using the SNP2HLA imputation software and a reference panel from the 1000 Genomes Project.[21] For the remaining CPIC genes, *DPYD*, *CYP4F2*, *VKORC1*, and *G6PD*, we identified the functionally consequential SNPs that were imputed in MGI from the TOPMed reference panel. Individual SNPs results were requested for *DPYD*, *CYP4F2*, *CYP2C*, *VKORC1*, and *G6PD*; genotype results (Table S2) were then manually translated into star-alleles and PGx phenotypes for that gene according to CPIC definitions. A full list of included rsIDs for phenotype assignments are listed in Table S3.

Analysis

For the prespecified time frame, the number of prescriptions for each medication, the location of the medication order, and the clinical service that placed the medication order with a CPIC guideline were summarized using descriptive statistics. The number of DGIs were calculated for each medication and each patient, respectively, for both initial CPIC dosing recommendations and any CPIC dosing recommendation. Overall DGI prevalence was summarized descriptively for the location of DGI medication order and the clinical service. DGI for the different CPIC medication classes and CPIC genes were summarized within each of the clinical services; clinical services accounting for less than 1% of all overall DGIs were grouped into a single "other" category for this analysis. In patients who experienced at least two unique DGIs when considering all CPIC prescribing recommendations, the DGIs were evaluated to determine: (1) the proportion of DGI where a single medication was accounting for greater than one DGI (e.g., warfarin/CYP2C9 and warfarin/VKORC1), (2) the proportion of DGIs where a single gene was accounting for greater than one DGI (e.g., citalopram/CYP2C19 and omeprazole/CYP2C19), and (3) the proportion of DGI where different genes accounted for greater than one DGI (e.g., citalopram/CYP2C19 and warfarin/CYP2C9). All data analysis was completed in Microsoft Excel.

TABLE 1 Demographics of Michigan Genomics Initiative participants with at least one prescription for a CPIC medication

	N (%)
Total	57,058
Male	25,283 (44.3)
Race	
White	49,983 (87.6)
African American	3548 (6.2)
Asian	1305 (2.3)
Other/unknown	2222 (3.9)

Abbreviations: CPIC, Clinical Pharmacogenetics Implementation Consortium; DGI, drug-gene interaction.

RESULTS

A total of 75,337 patients were enrolled in MGI and had a clinical encounter at Michigan Medicine between July 1, 2014, and December 31, 2020; 57,058 (75.8%) of these patients received an inpatient or outpatient prescription for at least one CPIC medication for a total of 151,325 initial medication prescribing events. Patient demographics are shown in Table 1 and Figure 1 describes patient inclusion and use of medications with CPIC guidelines. The majority (87.6%) of patients identified as White, consistent with expected institutional demographics.

Prescriptions for CPIC medications

The number of prescriptions by medication are shown in Table 2 and the overall frequency of prescriptions by drug class are shown in Figure 2. The majority (52.2%) of prescriptions for CPIC medications were initiated for outpatient use. The five most commonly prescribed medications or classes of medications included the anti-emetic ondansetron (22%), followed by nonsteroidal anti-inflammatory

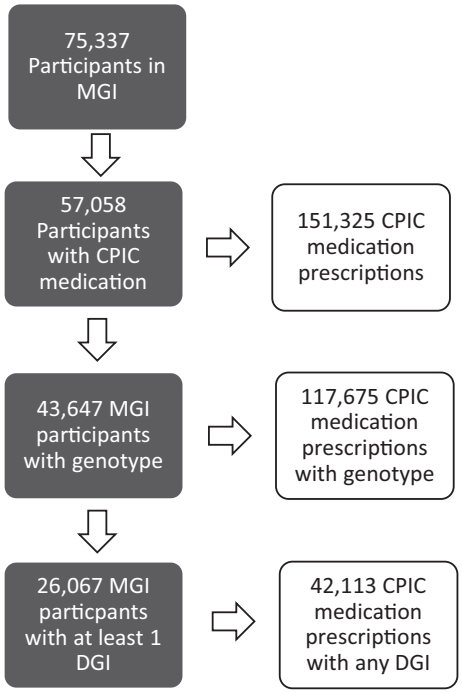

FIGURE 1 Participant inclusion with prescription data. The number of participants and corresponding prescriptions to determine number of prescriptions for medications with pharmacogenetic recommendations and the number of DGIs in the population over the 6.5 year study period. CPIC, Clinical Pharmacogenetics Implementation Consortium; DGI, drug-gene interaction; MGI, Michigan Genomics Initiative.

drugs (NSAIDs; 21.4%), PPIs (19.6%), opioids (9.9%), and selective serotonin reuptake inhibitors (SSRIs; 9.7%). The number of prescriptions among the different clinical services are shown in Table 3. Surgery accounted for over a quarter (27.8%) of all CPIC prescriptions in MGI, with internal medicine, cardiology, oncology, and emergency medicine each accounting for over 5% of prescriptions. The proportion of prescriptions by medication class for each clinical service are shown in Figure 3.

Drug-gene interactions for CPIC medications

Genotypes were available in MGI for 43,647 (76.4%) of the patients who received a CPIC medication, representing 117,675 unique prescriptions. The number of patients with each phenotype for the pharmacogenes of interest in the cohort are provided in Table S2. A total of 14,433 (12.2%) prescriptions had at least one DGI for initial prescribing adjustments, whereas 42,113 (35.8%) prescriptions had at least one DGI when considering all CPIC recommendations. Sixty-one percent of all identified DGIs occurred as outpatient prescriptions. When considering the location of the DGI by clinical service, surgery, cardiology, and emergency medicine were the only services with a majority of DGI prescriptions in the inpatient setting with 60.5%, 50.4%, and 56.3% of DGI, respectively (Figure S1). Almost 27% of patients (n = 11,699) experienced at least one DGI when considering initial prescribing recommendations for dose adjustment or treatment modification, which increased to almost 60% of patients (n = 26,067) experiencing at least one DGI when considering all CPIC recommendations. The number of DGIs by medication are shown in Table 2. When considering initial DGI recommendations, warfarin accounted for over a quarter of identified DGI (28% of all DGI; 4671/16,529), followed by NSAIDs (20.4% of all DGIs; 3385/16,529), then tricyclic antidepressants (TCAs; 14% of all DGIs; 2334/16,529), SSRIs (13.1%; 2177/16,529), and PPIs (6.6%; 1097/16,529). PPIs became the most common DGI when considering all CPIC recommendations, accounting for 52% of DGI (23,236/42,113), followed by warfarin (10.6%; 4671/42,113), opioids (10.6%; 4682/42,113), and SSRIs (7.8%; 3486/42,113).

The prevalence of DGIs by clinical service are shown in Table 3. Surgery was the clinical service with the highest overall number of DGIs (n = 8347), followed by internal medicine (n = 6101), cardiology (n = 4696), oncology (n = 3446), and family medicine (n = 2257). Of the clinical services accounting for greater than 1% of initial DGI, psychiatry was the clinical service most likely to prescribe a medication with an initial DGI (21% of prescriptions; 266/1245), followed by pain management (20.2% of prescriptions; 133/659), urology (19.6% of prescriptions; 261/1329), and cardiology (19.4% of prescriptions; 1933/9988). When considering recommendations for services accounting for greater than 1% of all DGI recommendations, gastroenterology had the highest proportion of prescriptions with any DGI (61.8% of prescriptions; 1620/2620), followed by pulmonology (58.2%; 432/1220), otolaryngology (50.8%; 1065/2097), cardiology (47%; 4969/9988), and internal medicine (45.6%; 6101/13,366).

The breakdown of all identified DGIs by each drug class among the different clinical services are shown in Figure 4. PPIs accounted for the highest proportion of DGIs for all services except psychiatry, where SSRIs accounted for the greatest proportion of DGI (63%). Opioids had the second highest proportion of DGI for eight of the 12 clinical service groupings. *CYP2C19* interactions accounted for the majority (55%–85%) of all identified DGIs for all clinical services except orthopedics, although it was still the most common gene with DGIs in orthopedics, accounting for 38% of observed DGIs. *CYP2D6* interactions had the second highest proportion of all identified DGIs for all clinical services except surgery, pediatrics, obstetrics, and gynecology, which all saw more interactions for *CYP2C9*, and cardiology which saw more interactions for *VKORC1* (Figure S2).

TABLE 2 Number of prescriptions and DGI by medication for the 6.5-year study period

Medication	Number of unique prescriptions	Number of unique prescriptions with at least one DGI for initial dosing adjustments[a]	Number of unique DGI with CPIC recommendations for initial dosing adjustments[a]	Number of unique DGI for all CPIC recommendations
Total	117,675	14,433 (12%)	16,529	44,113
Abacavir	54	1 (1.8%)	1	1
Allopurinol	2527	39 (0.3%)	39	39
Amitriptyline[b]	1990	918 (46%)	1107	1107
Atazanavir	18	1 (5.6%)	1	1
Atomoxetine[b]	230	20 (32%)	20	20
Azathioprine	766	33 (4.3%)	34	34
Capecitabine	472	18 (3.8%)	18	18
Carbamazepine	422	11 (2.6%)	11	11
Celecoxib	4997	506 (10%)	506	506
Citalopram	3812	1012 (26.5%)	1012	1012
Clomipramine[b]	41	17 (41%)	23	23
Clopidogrel	3515	767 (22%)	767	767
Codeine[b]	3473	129 (3.7%)	129	1124
Desipramine[b]	21	9 (43%)	9	9
Dexlansoprazole	170	3 (1.8%)	3	132
Doxepin[b]	380	167 (44%)	212	212
Efavirenz	30	10 (33%)	10	10
Escitalopram	3861	922 (24%)	922	922
Fluorouracil	446	23 (4.9%)	23	23
Flurbiprofen	11	2 (18%)	2	2
Fluvoxamine[b]	59	1 (1.7%)	1	1
Fosphenytoin	36	7 (19%)	7	7
Ibuprofen	24,114	2552 (11%)	2552	2552
Imipramine[b]	279	127 (46%)	149	149
Lansoprazole	967	48 (5%)	48	966
Meloxicam	3038	310 (10%)	310	310
Mercaptopurine	71	6 (8.4%)	6	6
Nortriptyline	2490	826 (33%)	826	826
Omeprazole	22,147	809 (3.7%)	809	17,285
Ondansetron[b]	33,230	0	0	0
Oxcarbazepine	439	0	0	0
Pantoprazole	6179	237 (3.8%)	237	4853
Paroxetine[b]	1206	44 (3.6%)	44	44
Phenytoin	197	25 (13%)	25	25
Piroxicam	165	15 (9.1%)	15	15
Rasburicase	19	0	0	0
Sertraline	5747	103 (1.8%)	103	1507
Simvastatin	5489	927 (17%)	927	927
Tacrolimus	1512	221 (15%)	221	221
Tamoxifen	870	267 (31%)	267	267
Thioguanine	4	1 (25%)	1	1

(Continues)

TABLE 2 (Continued)

Medication	Number of unique prescriptions	Number of unique prescriptions with at least one DGI for initial dosing adjustments[a]	Number of unique DGI with CPIC recommendations for initial dosing adjustments[a]	Number of unique DGI for all CPIC recommendations
Tramadol[b]	11,451	416 (3.6%)	416	3558
Voriconazole	187	45 (24%)	45	45
Warfarin	3932	2824 (72%)	4671	4671

Abbreviations: CPIC, Clinical Pharmacogenetics Implementation Consortium; DGI, drug-gene interaction.

[a]Some medications have more than one interacting gene and potential DGI (amitriptyline, azathioprine, carbamazepine, clomipramine, doxepin, fosphenytoin, imipramine, mercaptopurine, phenytoin, thioguanine, and warfarin).

[b]CYP2D6 ultra-rapid metabolizer recommendations not included in DGI analysis.

Almost 25% of patients ($n = 10{,}706$) experienced two or more DGIs when considering all CPIC recommendations. Sixteen percent of these patients (1723) experienced more than one DGI for the same medication. When considering the percent of DGIs for a single gene or multiple genes, the highest proportion of patients, 61% (6535/10,706), experienced DGIs for multiple genes, with 33.9% having all DGIs from different genes and 27.1% experiencing multiple DGIs for the same and different genes (Figure 5).

DISCUSSION

In this study of our internal research biorepository, three-fourths of patients received a prescription for at least one CPIC medication, approximately one-third had a DGI impacting initial prescribing decisions, and almost two-thirds had at least one clinically significant DGI when considering all CPIC recommendations impacting any prescribing decision. Additionally, up to a quarter of patients experienced more than one DGI during the 6.5-year study period. A majority of DGI prescriptions were initiated in the outpatient setting. Surgery and internal medicine were the clinical services with the highest overall number of prescriptions with DGIs, whereas gastroenterology, urology, and cardiology were the services with the highest proportion of prescriptions with DGIs. When considering initial prescribing recommendations, warfarin and NSAIDs had the highest proportion of DGIs, whereas PPIs accounted for the highest proportion of DGIs when considering all recommendations. As a research biorepository, the genetic results in our study cannot be directly translated into practice to inform prescribing decisions as they have not met appropriate regulatory standards for clinical practice. However, these results are informative for identifying populations and/or medications that could benefit from future clinical PGx testing initiatives.

These findings are consistent with, or higher than, prior estimations of the prescribing prevalence for medications with PGx guidelines. A study of prescriptions with PGx guidance in the US Veterans Affairs Health System identified that 55% of patients received at least one prescription for a CPIC medication with level A evidence over the 6-year study period.[22] Similarly, an evaluation of prescribing incidence among US payers identified 50% of patients received at least one prescription with a PGx guideline over a 4-year period, whereas an assessment of the Estonia Biobank found 37% of patients had a PGx prescription as of March 2019.[23,24] In a clinical proof-of-concept PGx testing project, 56% of participants who were genotyped on a nine-gene panel received at least one of up to 35 medications with clinical guidance.[25] These studies all had more limited medication lists than was included in our analysis, notably not including PPIs or NSAIDs, which did not have a CPIC guideline when these studies were completed.

An analysis of prescribing data from 11 different hospitals estimated the prevalence of an adult patient receiving at least one prescription for a CPIC medication per year to be 15,000–17,000 per 100,000,[26] when considering CPIC level A medications between 2011 and 2016, with ~7000 per 100,000 receiving more than one CPIC medication per year. Notably, this study also included substantially fewer medications, as the CPIC has published additional guidelines since 2016. An assessment of medication prescribing in the Netherlands that did include PPIs identified an average of 5.3 exposures to a medication with a PGx recommendation from the DPWG per patient over the 7-year study period.[27] This is higher than our average of 2.7 medications with a PGx recommendation per patient, however, we only included the initial medication exposure in the analysis which may explain this difference.

The proportion of prescriptions with clinically significant DGIs in prior studies are more variable, likely due to varying methods. Not all studies estimating DGIs have had confirmatory genotype information available for the study

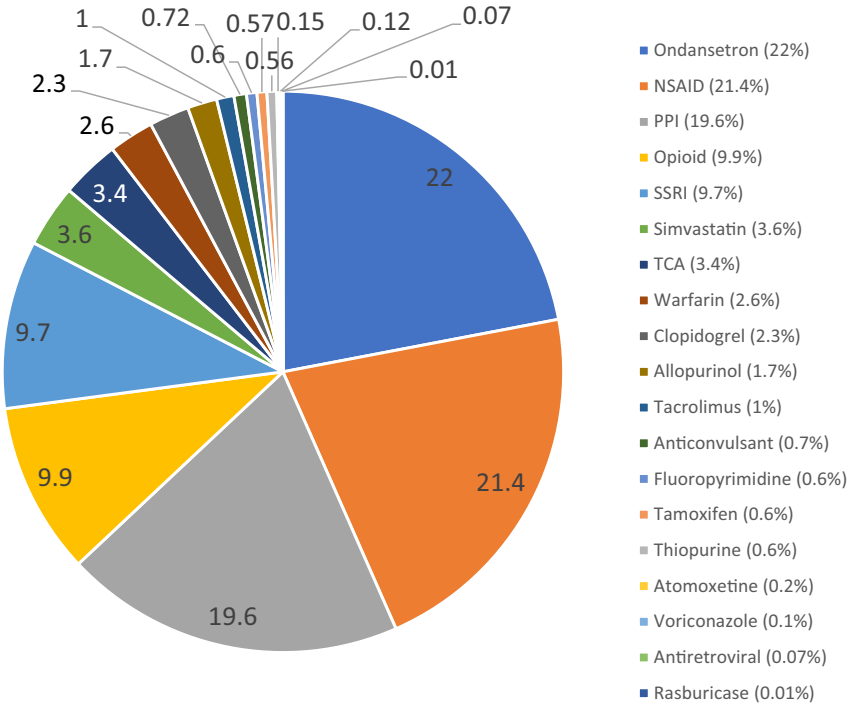

FIGURE 2 Prevalence of CPIC medication prescriptions by drug class. The percent of prescriptions by medication class out of the 151,325 prescriptions observed within the Michigan Genomics Initiative cohort over a 6.5-year time period. CPIC, Clinical Pharmacogenetics Implementation Consortium; NSAID, nonsteroidal anti-inflammatory drug: celecoxib, flurbiprofen, ibuprofen, meloxicam, piroxicam; PPI, proton pump inhibitor: dexlansoprazole, lansoprazole, omeprazole, and pantoprazole; SSRI, selective serotonin reuptake inhibitor: citalopram, escitalopram, fluvoxamine, paroxetine, and sertraline; TCA, tricyclic antidepressant: amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline; Anticonvulsant: carbamazepine, oxcarbazepine, phenytoin; Antiretroviral: efavirenz, atazanavir; Opioid: codeine, tramadol; Thiopurine: azathioprine, mercaptopurine, thioguanine

population. Rather, investigators estimated the anticipated allele frequencies based on their cohort demographics to estimate DGIs for available prescription data. Two studies in the Netherlands, which each evaluated prescription data for 45 medications with DPWG recommendations, estimated approximately one in four prescriptions would result in a clinically significant DGI.[27,28] Bank et al.[28] further differentiated prescription DGIs as those with initial medications adjustments (5.4%) and those with monitoring recommendations (18.2%). An assessment of prescription data at 11 US-based healthcare systems estimated ~4750 per 100,000 prescribing events would include a clinically significant DGI when considering 47 CPIC level A medications through 2016.[26] In our study, ~12% of prescriptions had at least one DGI with an initial recommendation to modify therapy and ~36% (42,113/117,675) of prescriptions had at least one DGI when considering all possible DGIs in the population. Notably, none of the prior studies included PPIs or NSAIDs as medications of interest, which could contribute to the higher proportion of DGIs observed in our study.

Similar to our investigation, other investigators evaluated DGIs using linked prescription and genetic data and have reported between 1% and 73% of patients experienced a clinically significant DGI.[10,24,25,29–33] The wide variability in reported clinically significant DGIs can likely be attributed to differences in the evaluated genes and medications, as well as the population demographics of the cohorts. For example, Van Dreist et al. reported 42%–48% of study participants had a DGI; the higher exposure was observed in a cohort of patients who were recruited to the PREDCIT study and therefore had a higher likelihood for being prescribed a cardiovascular medication with PGx recommendations.[31] Others evaluated the number of DGIs for a select number of single drug-gene pairs where the linked genetic and prescription data were available.[10,32] Shah et al.[10] evaluated DGIs for four drug-gene pairs (*HLA-B*15:02*, *HLA-A*31:01*, *TPMT*, and *VKORC1*) and identified a DGI prevalence of 0.8%–8.9% among these genes. Conversely, Verbeurgt et al.[32] evaluated DGIs for *CYP2C19*, *CYP2D6*, and *CYP2C9* and identified DGIs in ~15% of prescriptions that were seen over 2 months, although the exact medications under consideration for DGIs were not included. Assessment of DGIs for genes with lower variant allele frequencies in the patient population, such as HLA-B*15:02 in a predominantly White population, or medications with lower prescription frequencies, such

TABLE 3 Overall prescriptions and DGI by clinical service

Clinical service	Total prescriptions	Prescriptions with genotypes	Rx with any initial DGI recommendation (%)	Rx with any DGI recommendation (%)
Surgery	42,092	33,046	2769 (8.4%)	8347 (25%)
Internal medicine	16,964	13,366	1834 (14%)	6101 (36%)
Cardiology	12,259	9988	1933 (19%)	4696 (47%)
Unknown	12,061	9017	865 (10%)	3203 (36%)
Oncology	11,296	9013	1285 (14%)	3446 (38%)
Emergency medicine	9824	7515	594 (8%)	2045 (27%)
Family medicine	7038	5273	862 (16%)	2257 (43%)
Neurology	6434	5064	651 (13%)	1713 (34%)
Orthopedics	4554	3614	477 (13%)	1067 (30%)
Gastroenterology	3517	2620	285 (11%)	1620 (62%)
Obstetrics/gynecology	3293	2371	289 (12%)	622 (26%)
Pediatrics	2915	2209	308 (14%)	785 (36%)
Otolaryngology	2617	2097	303 (14%)	1065 (51%)
Psychiatry	2059	1245	266 (21%)	432 (35%)
Endocrinology	1900	1555	236 (15%)	621 (40%)
Urology	1704	1329	261 (20%)	602 (45%)
Pulmonology	1518	1220	139 (11%)	432 (35%)
Rheumatology	1406	1056	128 (12%)	401 (38%)
Transplant	1200	946	140 (15%)	402 (42%)
Physical medicine	1185	929	158 (17%)	334 (36%)
Ophthalmology	982	715	123 (17%)	344 (48%)
Pain management	850	659	133 (20%)	203 (31%)
Geriatrics	722	570	81 (14%)	251 (44%)
Nephrology	413	317	43 (14%)	104 (33%)
Interventional radiology	368	282	28 (10%)	52 (18%)
Dermatology	314	238	38 (16%)	85 (36%)
Infectious diseases	277	227	38 (17%)	84 (37%)
Trauma/burn	270	203	19 (9%)	79 (39%)
Hepatology	256	175	22 (13%)	87 (50%)
Allergy	235	180	30 (17%)	108 (60%)
Pharmacy	227	182	34 (19%)	74 (41%)
Sleep medicine	175	132	17 (13%)	66 (50%)
Podiatry	154	126	16 (13%)	36 (29%)
Dentistry	140	115	15 (13%)	31 (27%)
Wound care	59	48	4 (8%)	18 (38%)
Genetics	42	28	6 (21%)	16 (57%)
Hematology	5	5	1 (20%)	2 (40%)
Total	151,325	117,675	14,433 (12%)	42,113 (36%)

Abbreviations: DGI, drug-gene interaction; Rx, prescription.

as thiopurines, may underestimate the impact of routine PGx testing in patient care.

The definition of a clinically significant DGI is also constantly evolving, making time of the assessment and the medications and genes included a key consideration for comparisons. In a clinical PGx testing study using a panel of up to 14 genes, 78% of patients had an exposure to a PGx medication and 39% of prescriptions

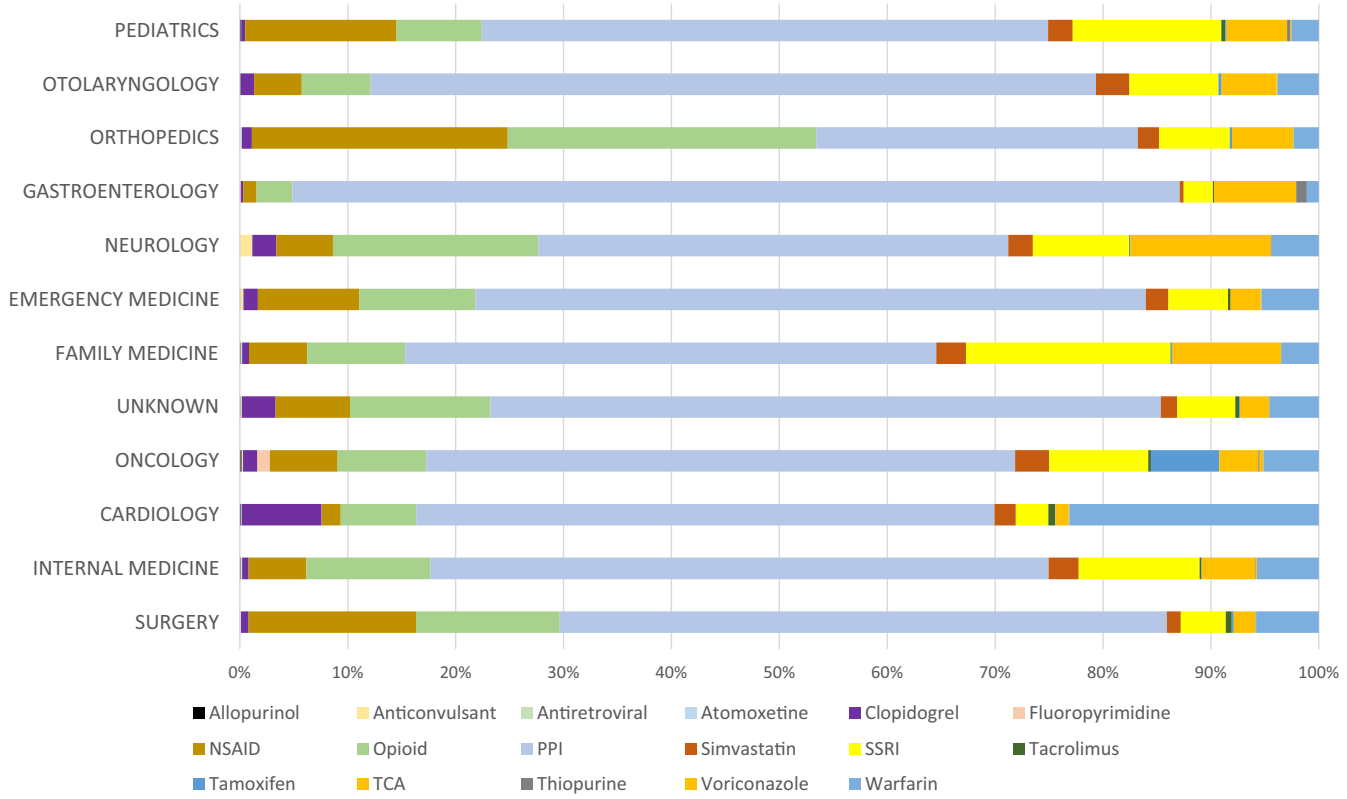

FIGURE 3 Prevalence of CPIC medication prescriptions among different clinical services. For each medication class, the proportion of the overall number of prescriptions are displayed for each prescribing clinical service over a 6.5-year time period. CPIC, Clinical Pharmacogenetics Implementation Consortium; NSAID, nonsteroidal anti-inflammatory drug: celecoxib, flurbiprofen, ibuprofen, meloxicam, and piroxicam; PPI, proton pump inhibitor: dexlansoprazole, lansoprazole, omeprazole, and pantoprazole; SSRI, selective serotonin reuptake inhibitor: citalopram, escitalopram, fluvoxamine, paroxetine, and sertraline; TCA, tricyclic antidepressant: amitriptyline, clomipramine, desipramine, doxepin, imipramine, and nortriptyline; Anticonvulsant: carbamazepine, oxcarbazepine, and phenytoin; Antiretroviral: efavirenz and atazanavir; Opioid: codeine and tramadol; Thiopurine: azathioprine, mercaptopurine, and thioguanine

had a clinically significant (e.g., contraindicated, severe, and moderate) DGI where a therapeutic modification was recommended at the time of pharmacist review of the results.[33] The overall exposure to a PGx medication was similar to what we observed and the prevalence of DGIs is similar to our observed rate for initial dosing adjustments. Krebs et al.[24] determined 66% of observed prescriptions in a biorepository as of March 2019 had a DGI when considering 46 medications and 11 genes with CPIC guidelines. These findings are similar to our overall estimated prevalence of DGIs when considering all PGx recommendations.

Unique to our study is the assessment of where the patients experienced the first DGI and what clinical specialties were prescribing the DGI medication. This information can enhance future implementation efforts by (1) ensuring all appropriate clinical stakeholders are involved, (2) developing tailored PGx education to the DGIs most likely to be impactful in their population, (3) enhancing decision making for testing selection by ensuring that options meet the needs and demographics of the institution, and (4) informing development of clinical decision support (CDS) that can be tailored to the specific workflows of the prescribing location. Engagement of appropriate stakeholders as well as clinician education have consistently been identified as key components of successful pharmacogenetic programs.[4,6,34] Additionally, CDS tools frequently need to be tailored to the specific needs and existing workflows of the institution to develop effective interventions.[7,9,35] An understanding of the overall demographics associated with DGIs at an institutional level can also help to identify needed PGx test offerings and prioritize DGIs for implementation based on anticipated impact.

We also identified that almost a quarter of patients experienced more than one DGI over the study period and approximately two-thirds of those patients experienced a DGI for more than one gene. In our study, DGIs for CYP2C19 and CYP2D6 were the most commonly observed for the same patient, followed by CYP2C19 and CYP2C9. The number of patients with more than one DGI is consistent with a prior evaluation from a pilot PGx

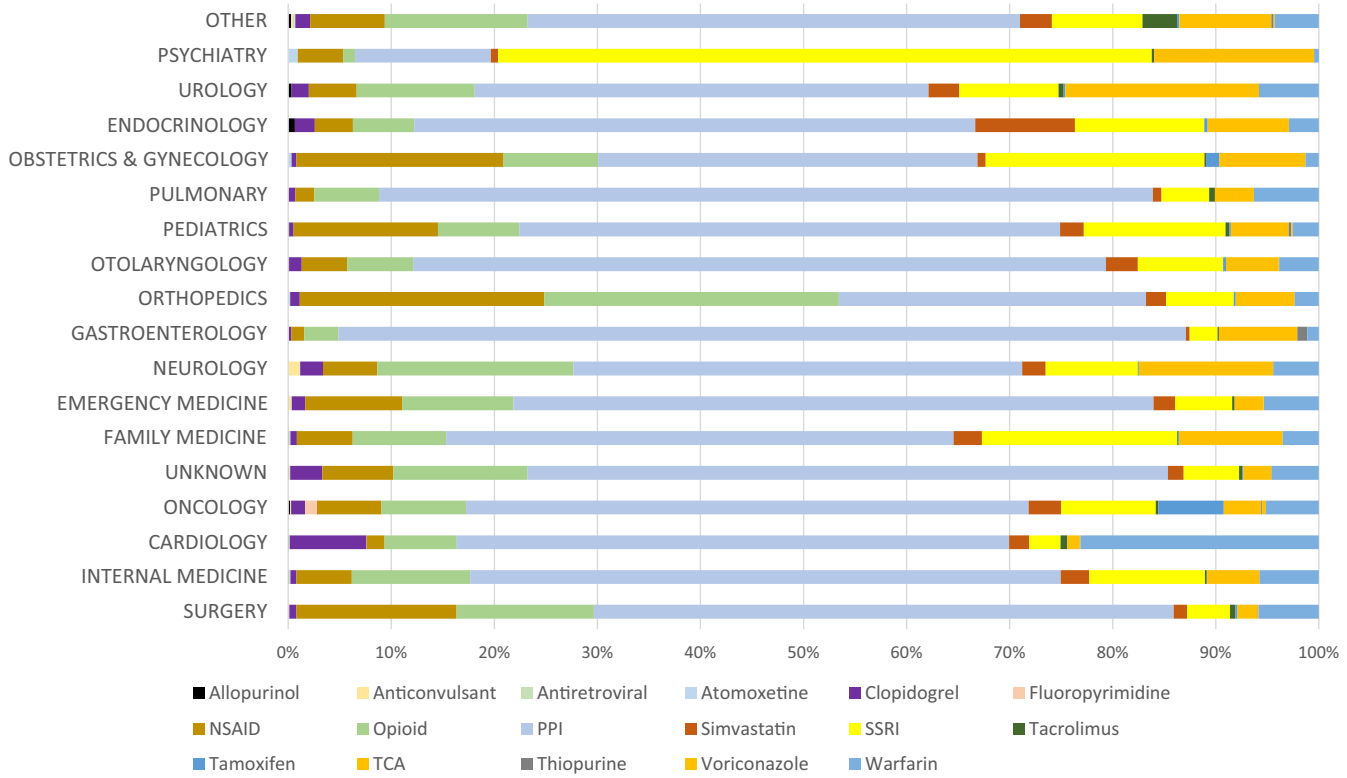

FIGURE 4 Proportion of DGI observed for CPIC drug classes among different clinical services. For each clinical service, the proportion of the overall number of prescriptions with a DGI are displayed for each drug class. CPIC, Clinical Pharmacogenetics Implementation Consortium; DGI, drug-gene interaction; NSAID, nonsteroidal anti-inflammatory drug: celecoxib, flurbiprofen, ibuprofen, meloxicam, and piroxicam; PPI, proton pump inhibitor: dexlansoprazole, lansoprazole, omeprazole, and pantoprazole; SSRI, selective serotonin reuptake inhibitor: citalopram, escitalopram, fluvoxamine, paroxetine, and sertraline; TCA, tricyclic antidepressant: amitriptyline, clomipramine, desipramine, doxepin, imipramine, and nortriptyline; Anticonvulsant: carbamazepine, oxcarbazepine, and phenytoin; Antiretroviral: efavirenz and atazanavir; Opioid: codeine and tramadol; Thiopurine: azathioprine, mercaptopurine, and thioguanine

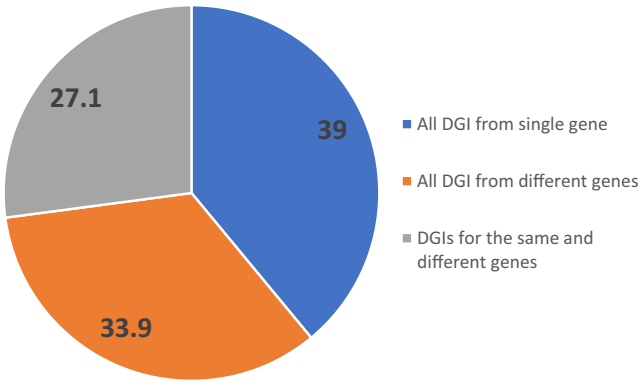

FIGURE 5 Proportion of single or multi-gene DGI among patients experiencing more than one DGI. In patients with more than one DGI ($N = 10{,}706$), the additional DGIs were categorized as impacting the same gene as the initial DGI (e.g., citalopram/CYP2C19 and omeprazole/CYP2C19), a different gene than the initial DGI (e.g., warfarin/CYP2C9 and warfarin/VKORC1), or both (e.g., citalopram/CYP2C19 and omeprazole/CYP2C19 and warfarin/CYP2C9). DGI, drug-gene interaction

study, where ~25% of patients experienced a DGI with each subsequent PGx prescription within 2.5 years of clinical PGx panel testing.[29] However in the prior study, the second DGI generally represented similar medication classes and the same gene, with PPIs and statin therapies being the most commonly reported.[29] As these studies had relatively brief follow-up, the proportion of prescriptions with DGIs could be considered conservative estimates for the potential lifetime utility of the PGx result. This finding supports the potential clinical benefit for implementing panel-based PGx testing where results can be available for future prescribing decisions.

The findings of this study do need to be interpreted in the context of its limitations. MGI most frequently recruits patients to participate in the biorepository when they arrive for a surgery or procedure, so although patients are not preselected for recruitment based on a predicted medication need, they may have a higher likelihood for receiving certain types of medications, such as anesthesia, analgesics, or anti-emetics due to the biorepository

recruitment strategy. This could explain why surgical services had the highest overall prescriptions in this study and may contribute to the higher proportion of CPIC medication prescriptions within our population compared with others. *CYP2D6* copy number variant was not captured in this analysis, so no CYP2D6 ultrarapid metabolizers were identified, and *CYP2D6**5 carriers could have been misclassified. Although a limitation to determining true prevalence of DGIs across the population, this likely results in a slight underestimation of the overall number of DGIs. Because MGI only recruits adult patients, it also remains unclear whether these prescribing patterns would be similar within the pediatric population within our institution. Secondary to the de-identified data extraction process, the clinical specialty of the ordering provider could not be extracted and had to be inferred based on the provider log-in location at the time of medication order entry, which has the potential for misclassification. We did not evaluate medication dose, nor frequency of use, only presence or absence of a prescription; this could cause an overestimation of clinically actionable DGIs as in some scenarios, such as TCAs, for which the PGx recommendation is dose dependent. We did attempt to control for this by assessing all initial dose adjustment recommendations and all recommendations to provide a range of DGI estimates. Additionally, we were only able to capture administration of prescriptions within our EHR, so it is possible the first documented medication use was not the patient's initial medication exposure.

In conclusion, through review of a linked EHR and genetic biorepository, we identified that up to 60% of patients in our institution experienced a clinically actionable DGI per current CPIC guidelines over a 6.5-year period. We also established that the majority of DGIs occurred for outpatient medication use and determined the clinical services mostly likely to interact with unique DGIs, both of which can inform future clinical implementation projects. The prevalence of DGIs across the institution also support the use of panel test results to inform future prescribing needs.

AUTHOR CONTRIBUTIONS

A.L.P., K.W., M.I., C.O., D.H., L.F., S.Z., J.V., H.M.C., and V.E. wrote the manuscript. A.L.P., K.W., J.V., H.M.C., and V.E. designed the research. A.L.P., M.I., C.O., D.H., and J.V. performed the research. A.L.P., M.I., C.O., D.H., L.F., and S.Z. analyzed the data.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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