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Real-World Utilization of Medications With Pharmacogenetic Recommendations in Older Adults: A Scoping Review

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ABSTRACT

Pharmacogenetic testing provides patient genotype information which could influence medication selection and dosing for optimal patient care. Insurance coverage for pharmacogenetic testing varies widely. A better understanding of the commonly used medications with clinically important pharmacogenetic recommendations can inform which medications and/or genes should be prioritized for coverage and reimbursement in the context of finite healthcare resources. The aim of this scoping review was to collate previous studies that investigated the utilization rate of medications that could be guided by pharmacogenetic testing. Included studies utilized electronic medical records or claims data to assess pharmacogenetic medication prescription rates for older adults (≥65 years old). Identified pharmacogenetic medications were classified according to therapeutic class and assessed for actionability based on the Clinical Pharmacogenetics Implementation Consortium guidelines. Across the 31 included studies, analgesic ($n=29$), psychotropic ($n=29$), and cardiovascular ($n=27$) therapeutic classes were most commonly investigated. Study populations were primarily generalized (48%); however, some studies focused on specific populations, such as, cancer ($n=6$), mental health ($n=1$), and nursing home ($n=2$) cohorts. A total of 215 unique pharmacogenetic medications were reported, of which, 82 were associated with actionable pharmacogenetic recommendations. The most frequent genes implicated in potential drug–gene interactions with these actionable pharmacogenetic drugs were *CYP2D6* (25.6%), *CYP2C19* (18.3%), and *CYP2C9* (11%). Medications most frequently prescribed included pantoprazole (range 0%–49.6%), simvastatin (range 0%–54.9%), and ondansetron (range 0.1%–62.6%). Overall, the frequently prescribed medications and associated genes identified in this review could guide pharmacogenetic testing implementation into clinical practice, including insurer subsidization.

1 | Introduction

Pharmacogenetic (PGx) testing is a key component of precision medicine that provides information about a patient's genotype. Information about interindividual genetic variants involved in drug metabolism, drug transport, and target binding can support safer and more effective use of medicines compared to traditional prescribing approaches. For example, in older adults, prescribing choices often combine a cautious "start low, go slow" approach with clinical trial data conducted in younger populations [1]. PGx testing can guide a more appropriate choice of drugs and/or drug dosage by assessing the likelihood of

Summary

- What is the current knowledge on the topic?
  - International consensus groups such as the Clinical Pharmacogenetics Implementation Consortium provide access to a range of actionable pharmacogenetic guidelines and resources for specific drug–gene pairs. However, pharmacogenetic testing implementation and utilization of these resources can be limited by government and patient-level financial inaccessibility. Thus, there is a need to determine the most prevalent medications to facilitate prioritization of pharmacogenetic testing implementation. This need is especially prevalent in older adults who are at higher risk of polypharmacy.
- What question did this study address?
  - Whilst multiple international studies have been conducted to determine population-specific utilization rates of drugs potentially influenced by pharmacogenetics, there has not been a review conducted to synthesize these findings. The aim of this review was to fill this gap in older adult populations.
- What does this study add to our knowledge?
  - The findings of this review indicate that drugs metabolized by *CYP2C19*, *CYP2D6*, and *CYP2C9* are most frequently used by older adults. Pantoprazole (range 0%–49.6%), simvastatin (range 0%–54.9%), and ondansetron (range 0.1%–62.6%) were the medications with the highest potential prescribing rates in older adults across health systems.
- How might this change clinical pharmacology or translational science?
  - This review may help guide the prioritization of specific drug–gene interactions for pharmacogenetic testing implementation. It also supports the implementation of pre-emptive panel-gene testing over single-gene testing to cater for the broad range of genes implicated in common drug–gene interactions identified within this review.

therapeutic benefit versus toxicity from PGx-associated medications, and reduce potential for adverse drug reactions (ADRs) or therapeutic failure [2–4].

There are a multitude of international peer-reviewed resources which provide prescribing recommendations for specific drug–gene pairs. Of these, the Clinical Pharmacogenetics Implementation Consortium (CPIC) and Pharmacogenomics Knowledgebase (PharmGKB) are most notable [5, 6]. CPIC translates pharmacogenetic test results into actionable clinical guidelines for prescribers whilst PharmGKB clinically annotates these CPIC drug dosing guidelines to improve prescriber understanding and implementation of PGx recommendations into clinical practice. Other well-known PGx resources include the Dutch Pharmacogenetics Working Group (DPWG), and United States (US) Food and Drug Administration (FDA) labels [7, 8]. Associated drug–gene pairs or interactions are classified according to levels of evidence, for example, CPIC level A, A/B, or B interactions indicate sufficient evidence is available to inform prescribing decisions, whereas CPIC level B/C, C, C/D, or D interactions require more robust evidence and thus have no associated prescribing recommendations [5, 6]. It is worth noting that categories differ slightly between PGx resources; however, recommendations are often the same and can be directly compared in PharmGKB [5].

Studies have shown through pre-emptive pharmacogenetic testing that greater than 95% of the population is at risk of experiencing at least one clinically actionable drug–gene interaction, as defined by CPIC and PharmGKB PGx resources [9–12]. Older adults (those greater than 65 years old) are particularly vulnerable to the potential consequences of these drug–gene interactions including ADRs as compared to individuals less than 65 years old. Reasons for this include, higher rates of polypharmacy in older adults and increased risk of exposure to medications with PGx recommendations, changes in pharmacokinetics, and multimorbidity [13, 14]. Hence, it is well established that PGx testing has the potential to play a crucial role in healthcare, especially in the older population.

Despite this, widespread implementation of PGx testing in clinical practice has yet to occur. Several barriers to effective PGx testing implementation have been outlined in the literature, including, results turnaround time, portability of results and inadequate prescriber education [15, 16]. Additionally, affordability and accessibility of tests are influenced by health insurance coverage and reimbursement, and public health schemes. For instance, in Australia, only two PGx tests are currently covered under the national Medicare Benefit Schedule: tests for thiopurine methyltransferase (*TPMT*) and *HLA-B*5701* prior to treatment with thiopurine drugs and abacavir, respectively; with DPYD genotyping and HLA testing for treatment with fluoropyrimidines and carbamazepine, respectively, under review for Medicare coverage [17, 18]. Better understanding of the commonly used medications with clinically important PGx recommendations can inform which medications and/or genes should be prioritized for coverage and reimbursement in the context of finite healthcare resources.

The aim of this scoping review is to ascertain, in older adults, the commonly used medications with potentially actionable PGx recommendations. Findings of this review can inform which of these medications and associated genes could be prioritized when implementing PGx testing.

2 | Materials and Methods

This scoping review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist [19].

2.1 | Search Strategy

Five electronic databases were searched including Medline (via Ovid), Embase, Scopus, CINAHL, and PubMed from database inception to 28th March 2024. There were no limits (e.g., publication period) placed on the search. Key search themes included: prescription rate, pharmacogenetic dosing recommendations,

and real-world data. The full search strategy is available in Table S1.

2.2 | Eligibility Criteria

This scoping review included original studies which used real-world data to assess the prescribing rates of medications which could be guided by PGx testing. To minimize recall bias, only studies utilizing administrative health care data (i.e., electronic medical records [EMR], health insurance claims, or drug dispensing data) were included in the review, and studies investigating patient-reported data were excluded. We defined older adults as those aged 65 years and above [20, 21]. In order to assess PGx drug use in older adults, studies reporting data among older individuals (≥ 65 years old) were included. Studies were excluded if data for children and adolescents (< 18 years old) could not be separated from adult and older adult data (≥ 18 years old including ≥ 65 years old). Studies with cohorts ≥ 18 years old were included only if the cohort included individuals aged ≥ 65 years old. There were no limits on included patient populations with particular medical conditions. Non-English studies and nonoriginal investigations, such as literature reviews, editorials, letters to the editor, or news articles, were also excluded from the review.

2.3 | Screening and Data Extraction

After removing duplicates, studies were merged into Covidence, an online software platform (Veritas Health Innovation, Melbourne, Australia) [22]. Two independent authors (B.D.I. and C.H.Y.) screened titles and abstracts to identify potentially eligible studies. These studies were then assessed in full text to confirm eligibility. Discrepancies were resolved via consensus or discussions with a third author (C.Y.L.). For included articles, data extraction was completed by two authors (B.D.I. and C.H.Y.). Extracted data included: authors, publication year and country, study period, population characteristics (eligibility criteria, age, sex, sample size), PGx guideline or resource used to identify PGx drugs, database used to extract rates (EMR or claims), PGx drugs investigated, and number of prescriptions and rates of use of PGx drugs.

2.4 | Data Synthesis

Prescribing rates of drugs which could be guided by PGx testing were not reported homogenously across all studies. Where it was required, rates of prescribing at drug level were converted to the same units using a simple percentage calculation: total number of prescriptions reported for a drug over total population sample size, multiplied by 100. These conversion calculations were performed and cross-checked by two independent authors (B.D.I. and C.H.Y.).

In order to synthesize and analyze results, medications were categorized into nine key therapeutic classes including: "analgesic," "anti-infective," "antineoplastic," "cardiovascular," "gastrointestinal," "immunomodulator," "neurological," "psychotropic," and "other" for medications which could not be classified under the first eight therapeutic classes (Table S2). To mitigate international variability in therapeutic class classification for medications with multiple potential indications, medications were classified, where possible, according to the Australian Medicines Handbook—an Australian drug information source for healthcare professionals [23]. For each study, in order to create rates of prescribing at the therapeutic level the following formula was applied: total number of prescriptions for drugs within the designated therapeutic class divided by the total number of prescriptions for all drugs in the corresponding study, multiplied by 100.

The number of actionable PGx medications was quantified by assigning CPIC levels to each of the medications examined across the studies. Actionable drug–gene interactions were those classified as CPIC level A ("Genetic information should be used to change prescribing of affected drug"), A/B ("Preliminary review indicates it is likely that the definitive CPIC level will be either A or B"), or B ("Genetic information could be used to change prescribing of the affected drug because alternative therapies/dosing are extremely likely to be as effective and as safe as non-genetically based dosing") [6].

3 | Results

3.1 | Study Selection

The search generated 6516 articles with 5203 articles to screen after duplicate removal. Title and abstract screening identified 115 articles eligible for full-text screening, after which, a total of 31 studies [12, 24–53] were included in the review (Figure 1).

3.2 | Study Characteristics

Individual study characteristics are described in Table 1 including, country of origin, population criteria (age, sex, sample size), study period, database, and PGx resources used. The 31 included articles examined data from seven different countries with 77% of studies originating from the US [12, 25–32, 34–36, 39, 41–51] ($n = 24$), two studies from Denmark [52, 53], and one study each from Saudi Arabia [24], the Netherlands [40], Taiwan [38], Canada [33], and the United Kingdom [37]. Of the 31 included studies, five studies [24, 33, 44, 46, 52] (16%) reported on a population with individuals exclusively 65 years or older; the remaining 26 studies combined adults and older adults. Study sample sizes ranged from 90 nursing home residents to 7,769,359 veterans. Patient and drug utilization data were primarily derived from EMRs (84%) as compared to insurance claims databases (13%). However, one study [40] published in 2007, used "prescription data" to determine drug usage and was included in this review as it was written prior to EMR implementation and used physical medical records thereby minimizing recall bias. Thirteen studies [24, 27, 29, 32, 33, 38, 44–46, 49, 50, 52, 53] (42%) used multiple PGx resources to identify medications which could be guided by PGx testing—CPIC guidelines were the single most commonly used resource (81%) followed by FDA labels (26%), PharmGKB (23%), and DPWG (13%). Four studies [12, 28, 40, 47] did not report which PGx resources, if any, were used to identify drugs with potential for drug–gene interactions. Study periods

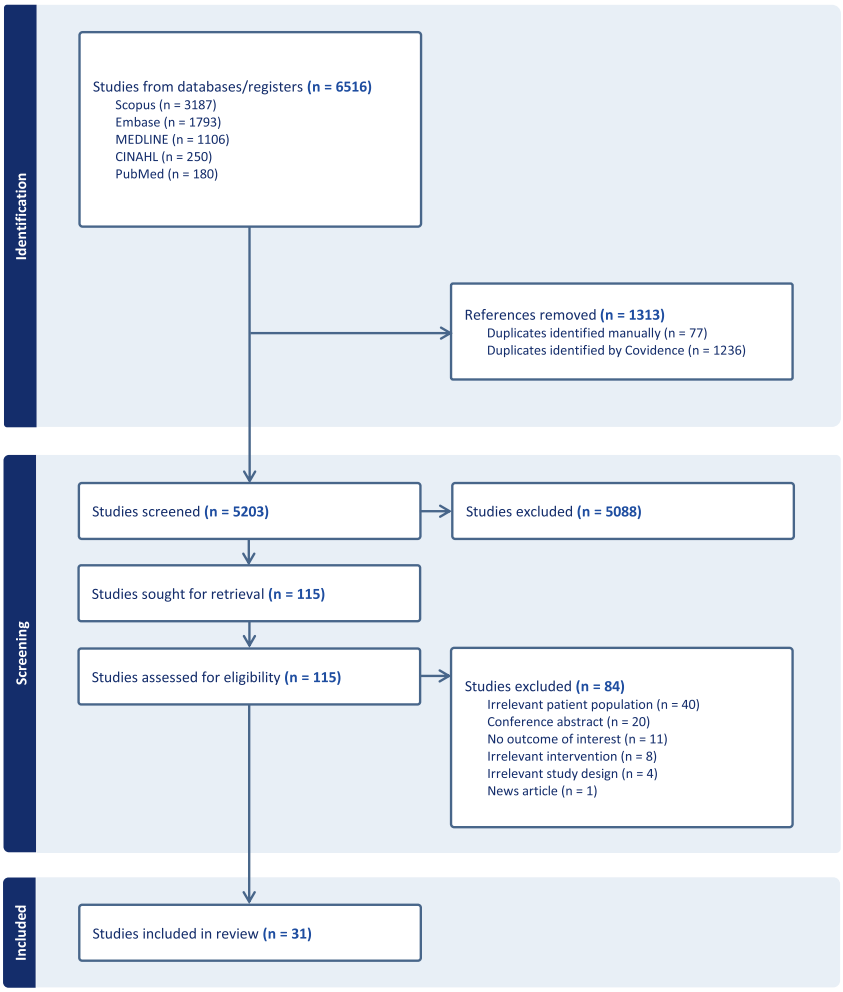

FIGURE 1 | PRISMA-ScR flow diagram [19, 22].

varied in duration including, less than 1 year ($n = 3$, 10%), exactly 1 year ($n = 6$, 19%), between 1 and 5 years ($n = 6$, 19%) or greater than 5 years ($n = 11$, 35%); however, two cancer-cohort studies [45, 48] uniquely used individualized time periods depending on patient data availability, and four studies [33, 35, 38, 41] did not report on the period in which they were conducted. Most studies (48%) gathered data on generalized populations [12, 24, 26, 29, 35–40, 46, 47, 49, 51, 53] ($n = 15$) whilst other studies looked at specific patient populations including cancer [41–45, 48] ($n = 6$), cardiac [27, 32, 43] ($n = 3$), nursing home [33, 52] ($n = 2$), veteran [30, 31] ($n = 2$), COVID-19 [50] ($n = 1$), mental health [25] ($n = 1$), emergency [28] ($n = 1$), chronic kidney disease [53] ($n = 1$), chronic pain [34] ($n = 1$), and gastroesophageal reflux disease [34] ($n = 1$) patients. Interestingly, 13 studies [29, 30, 33, 34, 37, 42–44, 46, 47, 50, 51, 53] (42%) included data on poly PGx drug use (≥ 2 concurrent PGx drugs, range 15.3%–94%). Of these 13 studies, three studies [33, 44, 46] comprising populations with only older adults (≥ 65 years old) reported that 25%–94% of older adults were exposed to poly PGx drugs. There were nine studies [24, 26, 29–31, 43–45, 47] (29%) which reported on sex differences in prescribed PGx drugs, and 10 studies [12, 29–31, 42–45, 47, 50] (32%) which reported on racial/ethnic differences of PGx drug use. Of these, two studies [24, 44] discussed racial/ethnic differences and one study [44] reported sex differences in PGx drug use among exclusively older adult populations.

3.3 | Overview of Reported Medications

Table S3 comprises a complete list of medications with PGx biomarkers investigated in each study. The three most frequent therapeutic classes across the included studies were "analgesic" ($n = 29$), "psychotropic" ($n = 29$), and "cardiovascular" ($n = 27$) (Figure 2). Note, medications categorized as "other" made up the fourth most prevalent therapeutic class across studies.

There was a total of 215 unique medications reported across the 31 included studies. Of these medications, 82 different medications (40%) were associated with an actionable CPIC guideline, including level A ($n = 61$), level A/B ($n = 7$), and level B ($n = 18$) medications. Note that valproic acid, phenytoin, sertraline, and carbamazepine were associated with at least two different genes wherein the interaction belonged to two different CPIC levels. The psychotropic therapeutic class contained the most medications with actionable PGx guidelines ($n = 18$ drugs) (Table 2). Table 3 lists these 82 medications with their corresponding CPIC level (levels A, A/B, and B) and their corresponding genes. A total of 33 unique genes were associated with the 82 medications with actionable (level A or B) or provisional/potentially actionable (level A/B or B) CPIC guidelines. Among these drugs, the top three most frequent genes included *CYP2D6* (25.6%), *CYP2C19* (18.3%), and *CYP2C9* (11%).

TABLE 1 | Characteristics of included studies ($n = 31$).

First author, year	Country	Database used	Resources used (level of evidence)	Population criteria	Study period	Age as reported[a]	Female (%)	Sample size (*n*)
Alshabeeb et al., 2022 [24]	Saudi Arabia	EMR	CPIC (A, A/B, B) PharmGKB (1, 2)	Ministry of National Guard Health Affairs patients	2015 to 2021	≥65	48.4	328,417
Anderson et al., 2022 [25]	USA	Claims data	CPIC	Adult patients with depression taking antidepressant metabolized by *CYP2D6*	Jan 1, 2013 to Jun 30, 2018	43.2 ± 15.8	66.5	921
				Adult patients with depression taking antidepressant metabolized by *CYP2C19*				1026
Bianchini et al., 2023 [26]	USA	Claims data	CPIC (A, A/B, B)	Adult patients with ≥1 incident fill of a pharmacogenetic drug	Jan 1, 2012 to Sep 30, 2018	45.1 ± 15.2 (18–83)	59.7	605,355
Black et al., 2020 [27]	USA	EMR	CPIC (A, B) FDA	Adult patients with percutaneous coronary intervention at an academic medical center	Jan 1, 2015 to Dec 31, 2015	63.3 ± 11.9	29.9	646
Cai et al., 2024 [28]	USA	EMR	—	Emergency physicians with opioid claims to Medicare beneficiaries	2013 to 2019	67.35 ± 4.28 (beneficiaries)	26.5	63,586
Carpenter et al., 2016 [29]	USA	EMR	CPIC CPNDS DPWG FDA	Patients with incident prescription for ≥1 of 30 target medications at an Eskenazi hospital	Jan 1, 2013 to Jun 20, 2014	51 ± 14.4	56	7039
Chanfreau-Coffinier et al., 2019 [30]	USA	EMR	CPIC (A)	Veterans using national Veterans Health Administration pharmacy service	Oct 1, 2011 to Sep 30, 2017	58.1 ± 17.8	9.6	7,769,359
Chanfreau-Coffinier et al., 2022 [31]	USA	EMR	CPIC	Veterans Health Administration pharmacy patients dispensed ≥1 opioid metabolized by *CYP2D6*	Dec 1, 2011 to Sep 30, 2017	56.2 ± 15.9	9.6	2,436,654
Dong et al., 2018 [32]	USA	EMR	CPIC FDA	University of California biorepository patients referred to cardiac catheterization lab for coronary angiography to detect coronary artery disease	Sep, 2012 to Feb, 2014	18–80	62.8	122

(Continues)

TABLE 1 | (Continued)

First author, year	Country	Database used	Resources used (level of evidence)	Population criteria	Study period	Age as reported[a]	Female (%)	Sample size (*n*)
Dorfman et al., 2020 [33]	Canada	EMR	CPIC FDA	Nursing home residents taking ≥ 2 drugs which could be guided by pharmacogenetic testing	—	80.1 ± 10.2	—	90
Elchynski et al., 2021 [34]	USA	EMR	CPIC (A, B)	University of Florida patients enrolled in trial of genotype-guided management of chronic pain	Aug, 2019 to Aug, 2020	58 ± 13	68	337
				University of Florida patients enrolled in trial of genotype-guided management of GERD		52 ± 16	68	111
Hellwig et al., 2024 [35]	USA	EMR	CPIC	Patients of a National Military Medical Centre primary care clinic	—	18–89	41.8	165
Hicks et al., 2021 [36]	USA	EMR	CPIC (A)	Adults with ≥ 1 medical encounter eligible for drug prescribing in a calendar year	Jan 1, 2011 to Dec 31, 2016	54.3 (36.5–66.8)	56.8	7,204,434
Kimpton et al., 2019 [37]	United Kingdom	EMR	PharmGKB	English primary care patients	2011 to 2012	50–99	—	648,141
					2003 to 2012			538,602
					1993 to 2012			289,186
Lu et al., 2022 [38]	Taiwan	EMR	CPIC PharmGKB	Taiwanese Han patients enrolled in Taiwan Biobank	—	49.46 ± 20.96	54	172,854
Mathias et al., 2017 [39]	USA	EMR	PharmGKB (1, 2, 3, 4)	Patients enrolled in multisite repository who visited involved hospitals or clinics	Jan, 2011 to Dec, 2013	38–65	54	132,340
Mulder et al., 2007 [40]	Netherlands	Prescribed drug data	—	Adults taking ≥ 1 medication	—	32–98	—	150
Nichols et al., 2019 [41]	USA	EMR	CPIC	Patients with advanced cancer enrolled in institutional Molecular Tumor Board and clinical trial prior to Jan 16, 2018	May 10, 2017 to Jan 10, 2018	60 ± 12	53	193

(Continues)

TABLE 1 | (Continued)

First author, year	Country	Database used	Resources used (level of evidence)	Population criteria	Study period	Age as reported[a]	Female (%)	Sample size (*n*)
Patel et al., 2021 [42]	USA	EMR	CPIC (A, B)	Adult ambulatory cancer patients at Levine Cancer Institute with first outpatient visit within study period	Jan 1, 2017 to Dec 31, 2017	60 (18–97)	65	6985
Ratner et al., 2022 [43]	USA	EMR	CPIC (A, A/B, B)	Adult patients with percutaneous coronary intervention	Jan, 2016 to Dec, 2016	63.2 ± 11.2	31.6	215
				Adult patients with allogeneic hematopoietic cell transplant	Jan, 2014 to Apr, 2016	52.4 ± 12.0	42	131
Rivers et al., 2022 [44]	USA	Claims data	CPIC FDA	Metastatic colorectal cancer patients receiving chemotherapy	2004 to 2015	66–85+	47.6	6957
				Metastatic colorectal cancer patients not receiving chemotherapy			51.1	2223
Ronquillo et al., 2023 [45]	USA	EMR	CPIC FDA	Adults enrolled in the "*All of Us*" cancer cohort	Individualized	≥ 18	59	22,223
Samwald et al., 2016 [46]	USA	Claims data	CPIC DPWG Pharma ADME PharmGKB	Medicare patients with incident claims	Jan 1, 2009 to Dec 31, 2012	72	55.2	5,429,266
Schildcrout et al., 2012 [47]	USA	EMR	—	Vanderbilt University Medical Centre primary care "medical home" patients with three outpatient visits within 2 years	Jan, 2005 to Jun, 2010	54 (31–75)	57.7	52,942
Shugg et al., 2022 [48]	USA	EMR	CPIC	Patients with advanced solid cancer with available EMR data since first cancer diagnosis	Individualized	57.4	53.2	481
Smith et al., 2020 [49]	USA	EMR	CPIC FDA	Adults who received clinical pharmacogenetic testing in a multisite pilot	Dec, 2017 to Apr, 2018	70 (61–76)	51	667
Stevenson et al., 2021 [50]	USA	EMR	CPIC (A, B) DPWG FDA	Adult patients hospitalized with COVID-19 infection	Mar 12, 2020 to Jun 26, 2020	60.1 ± 18.8	46.7	1852

(Continues)

TABLE 1 | (Continued)

First author, year	Country	Database used	Resources used (level of evidence)	Population criteria	Study period	Age as reported[a]	Female (%)	Sample size (*n*)
Van Driest et al., 2014 [12]	USA	EMR	—	Adults with "PREDICT" genetic testing before Sep 30, 2012	Sep, 2010 to Sep, 2012	63 (55–71)	41	9589
Verma et al., 2022 [51]	USA	EMR	CPIC (A, B)	Adult patients enrolled in Penn Medicine Biobank	Jan 1, 2012 to Dec 13, 2020	56	56.1	1,896,012
Vermehren et al., 2020 [52]	Denmark	EMR	CPIC DPWG PharmGKB	Nursing home residents taking ≥ 5 drugs	2017 to 2018	65–98	56.7	141
Westergaard et al., 2024 [53]	Denmark	EMR	CPIC DPWG PharmGKB (LA)	Chronic kidney disease patients on dialysis	Jan 1, 2021 to Dec 31, 2021	63 (53–73)	34.3	316
				Chronic kidney disease patients not on dialysis		72 (58–79)	35.8	925
				General population		≥ 65	—	1,176,272

Abbreviations: CPIC, Clinical Pharmacogenetics Implementation Consortium; CPNDS, Canadian Pharmacogenomics Network for Drug Safety; DPWG, Dutch Pharmacogenetics Working Group; EMR, electronic medical record; FDA, Food and Drug Administration; PharmGKB, Pharmacogenomics Knowledgebase.

[a]Median (range), median, range, mean ± SD (range) or mean ± SD.

3.4 | Frequently Prescribed Medications

Table 4 depicts the most frequently prescribed medications that were investigated by more than half of the included studies. Three genes were associated with these frequently reported and prescribed medications: *CYP2D6* ($n = 6$), *CYP2C19* ($n = 6$), and *CYP2B6* ($n = 1$). Codeine, tramadol, and citalopram ($n = 26$) were the most commonly investigated drugs across studies. The medications with the highest reported prescribing rates were ondansetron (range 0.1%–62.6%), codeine (range 0%–48.3%), and pantoprazole (range 0%–49.26%).

Table 5 includes, among all medications with individual prescribing rates extracted, those with the highest potential utilization rate. The highest reported utilization rate was for pantoprazole (range 0%–49.6%), simvastatin (range 0%–54.9%), and ondansetron (range 0.1%–62.6%). The most frequently associated genes with these frequently prescribed medications were *CYP2D6* ($n = 4$) and *CYP2C19* ($n = 5$). Overall potential prescribing rates at the therapeutic level have also been calculated: anti-infective (range 0%–11.6%), antineoplastic (range 0%–80.3%), immunomodulator (range 0.2%–3.2%), neurological (range 0%–2.6%), and other, unclassified medications (range 0%–15.3%).

3.5 | Older Adults

Five of the 31 included studies [24, 33, 44, 46, 52] (16%) reported on a population with individuals exclusively 65 years or older. Aligning with overall findings, the therapeutic classes most frequently reported on (by all five studies) included "analgesic," "psychotropic," "cardiovascular," and "gastrointestinal." Four studies [24, 33, 46, 52] reported on drugs classified as "other," three on "neurological" [24, 33, 46] and "antineoplastic," [24, 44, 46] and two [24, 46] on "anti-infective" and "immunomodulator." There was a total of 108 different medications included amongst the five studies which constituted half of the total drugs included in the 31 studies. Of these 108 medications, there were 10 (9%) potentially actionable drugs reported in either four ($n = 7$) or five ($n = 3$) studies. Of these frequently reported medications, simvastatin (range 2.1%–21.3%), clopidogrel (range 4.5%–29.8%), and pantoprazole (range 3.9%–34.4%) had the highest potential prescribing rates (Table 4). The genes primarily associated with these actionable medications included *CYP2C19* ($n = 7$) and *CYP2D6* ($n = 3$). Only citalopram, warfarin, and clopidogrel (all CPIC level A drugs) were reported in all five studies. There were 59 (55%) unique medications classified as potentially actionable PGx drugs including CPIC level A ($n = 45$, 76%), A/B ($n = 2$, 3%), and B ($n = 12$, 20%) medications. These 59 medications comprised 72% of the total actionable drugs found amongst the 31 included studies. Most potentially actionable medications were within the "psychotropic" therapeutic class ($n = 16$, 27%) which aligned with overall results. This exclusively older adult population also had the highest potential prescribing rate for "psychotropic" class drugs (range 5.5%–86.5%). Amongst all the drugs included in the five studies, clopidogrel (range 4.5%–29.8%), atorvastatin (range 8.5%–32.2%), and pantoprazole (range 3.9%–34.4%) had the highest potential utilization rate, and *CYP2C19* ($n = 5$) was the most predominant gene involved in metabolizing the top 10 medications

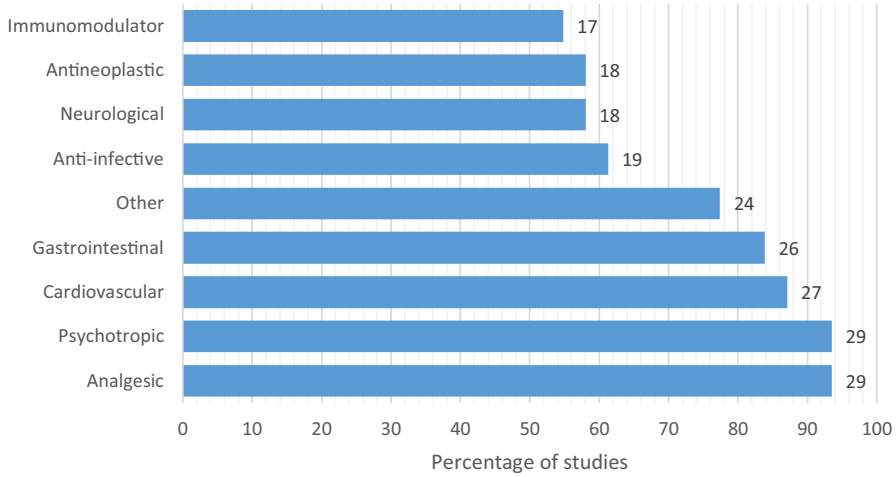

FIGURE 2 | Frequency of therapeutic classes across studies.

TABLE 2 | Actionability of identified drugs with pharmacogenetic guidelines within therapeutic classes.

Therapeutic class	No. of drugs (%)	No. of CPIC level A drugs (%)	No. of CPIC level A/B drugs (%)	No. of CPIC level B drugs (%)	No. of drugs with no or low level[b] CPIC evidence (%)
Total	215 (100)	61 (28.4)	7 (3.3)	18 (8.4)	133 (61.9)
Analgesic	15 (7.0)	7 (46.7)	0 (0)	2 (13.3)	6 (40)
Anti-infective	34 (15.8)	13 (38.2)	0 (0)	0 (0)	21 (61.8)
Antineoplastic	36 (16.7)	6 (16.7)	0 (0)	0 (0)	30 (83.3)
Cardiovascular	26 (12.1)	9 (34.6)	1 (3.8)	0 (0)	16 (61.5)
Gastrointestinal	9 (4.2)	4 (44.4)	0 (0)	1 (11.1)	4 (44.4)
Immunomodulator	5 (2.3)	4 (80)	0 (0)	1 (20)	0 (0)
Neurological	10 (4.7)	4[a] (40)	3[a] (30)	3[a] (30)	3 (30)
Psychotropic	41 (19.1)	8[a] (19.5)	1 (2.4)	10[a] (24.4)	23 (56.1)
Other	39 (18.1)	6 (15.4)	2 (5.1)	1 (2.6)	30 (76.9)

Abbreviation: CPIC, Clinical Pharmacogenetics Implementation Consortium.
[a]Valproic acid has CPIC level A/B and B level drug–gene interactions, carbamazepine and phenytoin both have CPIC level A and B drug–gene interactions, and sertraline has CPIC level A and B drug–gene interactions [6].
[b]CPIC level B/C, C, C/D, and/or D drugs [6].

with the highest potential prescribing rate (Table 5). Overall, these results aligned similarly with the analysis conducted using all 31 studies.

4 | Discussion

This scoping review included 31 studies [12, 24–53] predominantly from North America and Europe that investigated the commonly used medications with potentially actionable PGx recommendations in older adults. Within the included studies, a total of 82 unique prescription medications with potentially actionable PGx guidelines (CPIC level A, A/B, or B) were identified. This review established highly prescribed medications and their commonly associated genes that could be prioritized for PGx testing. Drugs with the highest reported prescribing rate were ondansetron, simvastatin, pantoprazole, codeine, and omeprazole. The most commonly implicated drug–gene interactions frequently involved *CYP2D6* and *CYP2C19* which, together, accounted for 44% of the 82 identified medications with actionable CPIC guidelines. The findings of this review suggest that there is substantial opportunity for pharmacogenetic-guided prescribing for older adults in clinical practice.

Currently, many health systems subsidize single-gene testing [15]. For example, as mentioned prior, the Australian government currently only reimburses a couple of single-gene PGx tests (e.g., thiopurines and *TPMT*) [17]. However, there is increasing evidence supporting multi-gene panel testing. First, the costs of multi-gene and single-gene tests are now similar. For example, in Australia, a "Cytochrome P450 Comprehensive Gene Panel" which tests for *CYP2D6*, *CYP2C19*, *CYP2C9*, *CYP3A4*, *CYP3A5*, *CYP1A2*, *SLCO1B1*, and *VKORC1* is commercially available at

TABLE 3 | CPIC level A, A/B, and B medications and their corresponding biomarkers included across studies.

Drug	Gene	CPIC Level
Abacavir	*HLA-B*	A
Allopurinol	*HLA-B*	A
Amikacin	*MT-RNR1*	A
Amitriptyline	*CYP2C19*, *CYP2D6*	A
Atazanavir	*UGT1A1*	A
Atomoxetine	*CYP2D6*	A
Atorvastatin	*SLCO1B1*	A
Azathioprine	*NUDT15*, *TPMT*	A
Capecitabine	*DPYD*	A
Carbamazepine[b]	*HLA-A*, *HLA-B*	A
Celecoxib	*CYP2C9*	A
Citalopram	*CYP2C19*	A
Clopidogrel	*CYP2C19*	A
Codeine	*CYP2D6*	A
Dapsone	*G6PD*	A
Efavirenz	*CYP2B6*	A
Escitalopram	*CYP2C19*	A
Fluorouracil	*DPYD*	A
Flurbiprofen	*CYP2C9*	A
Fluvastatin	*CYP2C9*, *SLCO1B1*	A
Fosphenytoin	*CYP2C9*, *HLA-B*	A
Gentamicin	*MT-RNR1*	A
Ibuprofen	*CYP2C9*	A
Irinotecan	*UGT1A1*	A
Ivacaftor	*CFTR*	A
Lansoprazole	*CYP2C19*	A
Lovastatin	*SLCO1B1*	A
Meloxicam	*CYP2C9*	A
Mercaptopurine	*NUDT15 TPMT*	A
Methylene	*G6PD*	A
Neomycin	*MT-RNR1*	A
Nitrofurantoin	*G6PD*	A
Nortriptyline	*CYP2D6*	A
Omeprazole	*CYP2C19*	A
Ondansetron	*CYP2D6*	A
Oxcarbazepine	*HLA-B*	A
Pantoprazole	*CYP2C19*	A
Paromomycin	*MT-RNR1*	A
Paroxetine	*CYP2D6*	A
Peginterferon alfa-2a	*IFNL3*, IFNL4	A
Peginterferon alfa-2b	*IFNL3, IFNL4*	A
Pegloticase	*G6PD*	A
Phenytoin[b]	*CYP2C9, HLA-B*	A
Piroxicam	*CYP2C9*	A
Pitavastatin	*SLCO1B1*	A
Pravastatin	*SLCO1B1*	A
Primaquine	*G6PD*	A
Rasburicase	*G6PD*	A
Rosuvastatin	*ABCG2*, *SLCO1B1*	A
Sertraline[b]	*CYP2C19*	A
Simvastatin	*SLCO1B1*	A
Streptomycin	*MT-RNR1*	A
Succinylcholine	*CACNA1S*, *RYR1*	A
Tacrolimus	*CYP3A5*	A
Tamoxifen	*CYP2D6*	A
Thioguanine	*NUDT15*, *TPMT*	A
Tobramycin	*MT-RNR1*	A
Tramadol	*CYP2D6*	A
Voriconazole	*CYP2C19*	A
Vortioxetine	*CYP2D6*	A
Warfarin	*CYP2C9*, *CYP4F2*, *VKORC1*	A
Divalproex sodium[a]	*POLG*	A/B
Eliglustat[a]	*CYP2D6*	A/B
Hydralazine	*NAT2*	A/B
Pimozide[a]	*CYP2D6*	A/B
Tetrabenazine[a]	*CYP2D6*	A/B
Valproic acid[a,b]	*POLG*	A/B
Velaglucerase[a]	*GBA*	A/B
Aripiprazole[a]	*CYP2D6*	B
Carbamazepine[a,b]	*SCN1A*	B
Carglumic Acid[a]	*NAGS*	B
Clomipramine	*CYP2C19*, *CYP2D6*	B

(Continues)

TABLE 3 | (Continued)

Drug	Gene	CPIC Level
Desipramine	*CYP2D6*	B
Dexlansoprazole	*CYP2C19*	B
Doxepin	*CYP2C19*, *CYP2D6*	B
Fluvoxamine	*CYP2C19*	B
Hydrocodone	*CYP2D6*	B
Imipramine	*CYP2C19*, *CYP2D6*	B
Methadone	*CYP2B6*	B
Mycophenolic acid[a]	*HPRT1*	B
Phenytoin[a,b]	*SCN1A*	B
Risperidone[a]	*CYP2D6*	B
Sertraline[b]	*CYP2B6*	B
Trimipramine	*CYP2C19*, *CYP2D6*	B
Valproic acid[a,b]	*ABL2*, *ASL*, *ASS1*, *CPS1*, *NAGS*, *OTC*	B
Venlafaxine	*CYP2D6*	B

Abbreviation: CPIC, Clinical Pharmacogenetics Implementation Consortium.
[a]Provisional CPIC level with no currently available guideline for the corresponding drug–gene pair.
[b]Carbamazepine, phenytoin, sertraline, and valproic acid have at least two different gene interactions classified under different CPIC levels.

an out-of-pocket cost of AUD$190 (~US$126) per test [54]. In contrast, a typical single-gene test is commercially priced at AUD$140 (~US$93) per test, which is not substantially cheaper than multigene PGx tests that cover eight genes with potential relevance to over 50 actionable PGx drugs [54]. Second, multigene tests provide potentially clinically relevant information for later use. Chambal et al. [55] found that targeting PGx testing by specialty (e.g., psychiatry) leads to up to 95% of total PGx drug–gene interactions being missed or not reported which may be implicated in future therapeutic failure or ADRs. The case for panel-based testing over single-gene testing is well established by Haidar et al. [15]. Supporting factors include the broad use of actionable PGx medications in inpatient and outpatient settings, high prevalence of at least one actionable variant in all individuals, and the pre-emptive nature of panel-based testing which mitigates concerns around test turnaround time often associated with single-gene testing which is generally reactive [15]. Finally, there is evidence on their cost-effectiveness. A recent systematic review suggested that, compared to other strategies such as single-gene testing, multigene PGx testing may exhibit favorable cost-effectiveness [56].

It is also important to consider the impact, if any, PGx testing implementation will have on prescribing choices and patient-related outcomes including ADRs. A study analyzing allele and phenotype frequencies in 5408 individuals found that only 53.2% were predicted to be normal metabolizers (recommended to take standard dosing) for *CYP2D6*, 39.7% for *CYP2C19*, and 64.8% for *CYP2C9* [57]. These findings indicate that a significant proportion of the population may require drug dosing or choice changes to receive the most appropriate care and thus could benefit from PGx testing. Likewise, several studies have demonstrated that drug–gene interactions are often implicated in treatment failure and ADRs in both inpatient and outpatient healthcare settings [2, 3]. If drug–gene interactions can be predicted and addressed a priori, up to an approximate 30% of clinically relevant ADRs could be prevented, highlighting the benefit of PGx testing to maximize therapeutic efficacy and patient-related outcomes [58]. Additionally, with the Australian government spending AUD$1.4 billion (~US$925 million) on medication-related admissions annually, this reduction in ADRs could also reduce medication-related hospitalization rates and in turn reduce their financial burden on the healthcare system [59].

As the older population is at an increased risk of polypharmacy, they are also at an increased risk of being prescribed medications with clinically important PGx recommendations [13]. In fact, as high as 94% of individuals within the included studies of this review were prescribed two or more medications with potential for PGx recommendations—a compelling argument for multigene PGx testing implementation in this population. Unsurprisingly, nursing home residents made up the highest proportion (94%) of patients taking two or more of these medications [33]. Further, Swen et al. [58] implemented a 12-gene PGx panel and found that 93.5% of the population carried at least one actionable phenotype and were recommended an alternative to standard drug treatment per DPWG guidelines. Hence, it can be deduced that a significant proportion of older patients could benefit from PGx testing as they are not only at high risk of being prescribed impacted medications but also of genotype-predicted phenotypic variation.

5 | Limitations

There were some limitations of the included studies in this review. It is well known that sex, race, and/or ethnicity can play a role in genetic expression and potentially prescribing choices [60, 61]. Despite this, only 29% and 32% of studies specifically reported sex and racial/ethnic data, respectively. Future studies should take these factors into consideration, noting, however, that race and/or ethnicity have lower correlation to PGx testing than genetic (or biogeographical) ancestry [62]. On another note, whilst multiple studies acknowledged polypharmacy-associated overestimation of some rates of medication use, they did not specify which medications were used concurrently. This would be an interesting avenue to investigate in future research.

There were a few limitations of this scoping review. Firstly, the included studies were heterogenous, particularly with regard to study population and investigated medications. There was a focus on medications with PGx recommendations which were investigated across more than 40% of the included studies. Hence, prescribing rates were not extracted for medications reported in 40% or less of the included studies. Additionally, this review included studies comprising general patient populations as well as studies investigating patients with specific medical conditions. This meant that total drug use within specific populations

TABLE 4 | Drugs with their associated actionable pharmacogenetic biomarker investigated and reported in majority[b] of included studies.

Therapeutic class	Drug	No. of studies (%)	Prescription rate (% range across studies, % median)	Predominant gene(s) affected[a]
Studies ($n = 31$) reporting combined adult (≥18) and older adult (≥65) cohorts				
Analgesic	Codeine	26 (83.9)	0–48.3 (4.6)	*CYP2D6*
	Tramadol	26 (83.9)	0–26.5 (8.5)	*CYP2D6*
Gastrointestinal	Omeprazole	16 (50)	0–34.8 (19.5)	*CYP2C19*
	Ondansetron	16 (50)	0.1–62.6 (12.1)	*CYP2D6*
	Pantoprazole	16 (50)	0–49.6 (11.8)	*CYP2C19*
Psychotropic	Amitriptyline	23 (74.2)	0–20.1 (2.4)	*CYP2C19, CYP2D6*
	Citalopram	26 (83.9)	0–17.8 (4.9)	*CYP2C19*
	Escitalopram	22 (71)	0–10.6 (2.5)	*CYP2C19*
	Nortriptyline	19 (61.3)	0–4.2 (0.9)	*CYP2D6*
	Paroxetine	21 (67.7)	0.3–6.3 (1.6)	*CYP2D6*
	Sertraline	20 (64.5)	0.9–17.6 (4.6)	*CYP2C19, CYP2B6*
Studies ($n = 5$) reporting older adults (≥65) as a separate cohort				
Analgesic	Codeine	4 (80)	4.1–8.2 (4.9)	*CYP2D6*
	Tramadol	4 (80)	5.1–8.5 (7.4)	*CYP2D6*
Cardiovascular	Clopidogrel	5 (100)	4.5–29.8 (6.3)	*CYP2C19*
	Simvastatin	4 (80)	2.1–21.3 (14.8)	*SLCO1B1*
	Warfarin	5 (100)	1.1–11.1 (5.6)	*CYP2C9, CYP4F2, VKORC1*
Gastrointestinal	Omeprazole	4 (80)	2.1–10.2 (9.7)	*CYP2C19*
	Pantoprazole	4 (80)	3.9–34.4 (7.5)	*CYP2C19*
Psychotropic	Amitriptyline	4 (80)	1.3–5 (1.3)	*CYP2C19, CYP2D6*
	Citalopram	5 (100)	1.4–17.8 (5.4)	*CYP2C19*
	Sertraline	4 (80)	2.9–15.6 (6.5)	*CYP2C19, CYP2B6*

[a]Genes with CPIC level A, A/B, or B evidence for the given drug [6].
[b]50% or more of total 31 studies or 80%–100% of five studies reporting older adults as a separate cohort.

was likely not captured, as demonstrated by Cai, Knudsen and Weant [28] which exclusively assessed opioid prescribing by emergency physicians. Conducting reviews of prescribed drugs with PGx recommendations in patients with specific medical conditions may provide a more accurate representation of drug use in these populations. Ultimately, prescribing rates for drugs with PGx recommendations were potentially underestimated in this review.

Additionally, whilst this review provides valuable insight into the most frequently prescribed actionable PGx medications internationally, it does not consider the severity of potential ADRs or therapeutic failure. Of note, the Royal College of Pathologists of Australasia (RCPA) recently categorized drugs by ADR severity and implications of therapeutic failure. The drugs flagged in this review were not listed among the 12 drugs the RCPA recommended for testing, that is, those drugs where ADRs or therapeutic failure are known to be severe and potentially life-threatening including, for example, abacavir, thiopurines, capecitabine, carbamazepine, and voriconazole [18]. Further research is required to determine patient-reported and cost-related benefits of providing PGx testing for the PGx medications highlighted in this review.

6 | Conclusion

This scoping review provides insight into the prevalence and utilization rates of medications with PGx recommendations in older adults. By identifying commonly used medications and genes involved in potentially actionable drug–gene interactions across study populations, this review is able to potentially guide prioritization of future PGx testing implementation. Across studies, *CYP2D6*, *CYP2C19*, and *CYP2C9* were the most frequently implicated biomarkers in actionable drug–gene interactions, whilst pantoprazole, simvastatin, and ondansetron were

TABLE 5 | Top 10 medications with the highest potential prescribing rates investigated by included studies with their associated actionable pharmacogenetic biomarker.

Therapeutic class	Drug	Prescription rate (%, range across studies)	Predominant gene(s) affected[a]
Studies ($n = 31$) reporting combined adult (≥18) and older adult (≥65) cohorts			
Analgesic		1.7–100[b]	
	Codeine	0–48.3	*CYP2D6*
	Tramadol	0.6–26.5	*CYP2D6*
Cardiovascular		1.5–97[b]	
	Clopidogrel	0–48.9	*CYP2C19*
	Simvastatin	0–54.9	*SLCO1B1*
	Warfarin	0–21.6	*CYP2C9, CYP4F2, VKORC1*
Gastrointestinal		5.6–68.6[b]	
	Omeprazole	0–34.8	*CYP2C19*
	Ondansetron	0.1–62.6	*CYP2D6*
	Pantoprazole	0–49.6	*CYP2C19*
Psychotropic		1.7–100[b]	
	Amitriptyline	0–20.1	*CYP2C19, CYP2D6*
Anti-infective		0–11.6[b]	
	Voriconazole	0–19.9	*CYP2C19*
Studies ($n = 5$) reporting older adults (≥65) as a separate cohort			
Analgesic		4.2–26.7[b]	
	Tramadol	5.1–8.5	*CYP2D6*
Cardiovascular		3.4–47.2[b]	
	Atorvastatin	8.5–32.2	*SLCO1B1*
	Clopidogrel	4.5–29.8	*CYP2C19*
	Simvastatin	2.1–21.2	*SLCO1B1*
	Metoprolol	5.8–17.7	*CYP2D6*
	Warfarin	1.1–11.1	*CYP2C9, CYP4F2, VKORC1*
Gastrointestinal		10.1–17.7[b]	
	Pantoprazole	3.9–34.4	*CYP2C19*
	Omeprazole	2.1–10.2	*CYP2C19*
Psychotropic		1.7–39.4[b]	
	Citalopram	1.4–17.8	*CYP2C19*
	Sertraline	2.9–15.6	*CYP2C19, CYP2B6*

[a]CPIC level A, A/B, or B evidence [6].
[b]Prescription rate by therapeutic class for each paper was calculated by dividing the total number of prescriptions for drugs within the corresponding therapeutic class by the total number of prescriptions for all drugs within the paper.

the medications with the highest potential prescribing rates in older adults across health systems. A multigene PGx testing panel covering these drugs and/or genes seems clinically relevant to this specific patient population which is most at risk of polypharmacy. Future research is needed to investigate the rate of PGx testing in clinical practice and related health outcomes.

Author Contributions

B.D.I., C.H.Y., E.C.K.T., and C.Y.L. wrote the manuscript; C.Y.L. and B.D.I designed the research; B.D.I. and C.H.Y. performed the research; B.D.I. and C.Y.L. analyzed the data.

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Conflicts of Interest

The authors declare no conflicts of interest.

References

1. S. R. Maxwell, "Rational Prescribing: The Principles of Drug Selection," *Clinical Medicine* 16 (2016): 459–464.

2. A. Bollinger, C. K. Stäuble, C. Jeiziner, et al., "Genotyping of Patients With Adverse Drug Reaction or Therapy Failure: Database Analysis of a Pharmacogenetics Case Series Study," *Pharmacogenomics and Personalized Medicine* 16 (2023): 693–706.

3. S. L. Chan, X. Ang, L. L. Sani, et al., "Prevalence and Characteristics of Adverse Drug Reactions at Admission to Hospital: A Prospective Observational Study," *British Journal of Clinical Pharmacology* 82 (2016): 1636–1646.

4. K. Kim, J. W. Magness, R. Nelson, V. Baron, and D. I. Brixner, "Clinical Utility of Pharmacogenetic Testing and a Clinical Decision Support Tool to Enhance the Identification of Drug Therapy Problems Through Medication Therapy Management in Polypharmacy Patients," *Journal of Managed Care & Specialty Pharmacy* 24 (2018): 1250–1259.

5. Pharmacogenomics Knowledgebase (PharmGKB), "Clinical Guideline Annotations," 2024, accessed March 27, 2024, https://www.pharmgkb.org/guidelineAnnotations.

6. Clinical Pharmacogenetics Implementation Consortium (CPIC). 2024, accessed March 27, 2024, https://cpicpgx.org/.

7. Dutch Pharmacogenetics Working Group (DPWG), "Farmacogenetica," 2024, accessed May 11, 2024, https://www.knmp.nl/dossiers/farmacogenetica.

8. Food and Drug Administration (FDA), "Table of Pharmacogenetic Associations," 2022, accessed May 11, 2024, https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations.

9. Q. Huang, Y. Liao, T. Yu, et al., "A Retrospective Analysis of Preemptive Pharmacogenomic Testing in 22,918 Individuals From China," *Journal of Clinical Laboratory Analysis* 37 (2023): e24855.

10. C. Lunenburg, J. P. Thirstrup, J. Bybjerg-Grauholm, et al., "Pharmacogenetic Genotype and Phenotype Frequencies in a Large Danish Population-Based Case-Cohort Sample," *Translational Psychiatry* 11 (2021): 294.

11. T. A. Roberts, J. A. Wagner, T. Sandritter, B. T. Black, A. Gaedigk, and S. L. Stancil, "Retrospective Review of Pharmacogenetic Testing at an Academic Children's Hospital," *Clinical and Translational Science* 14 (2021): 412–421.

12. S. L. Van Driest, Y. Shi, E. A. Bowton, et al., "Clinically Actionable Genotypes Among 10,000 Patients With Preemptive Pharmacogenomic Testing," *Clinical Pharmacology and Therapeutics* 95 (2014): 423–431.

13. X. Wang, K. Liu, K. Shirai, et al., "Prevalence and Trends of Polypharmacy in U.S. Adults, 1999–2018," *Global Health Research and Policy* 8 (2023): 25.

14. M. B. Zazzara, K. Palmer, D. L. Vetrano, A. Carfì, and G. Onder, "Adverse Drug Reactions in Older Adults: A Narrative Review of the Literature," *European Geriatric Medicine* 12 (2021): 463–473.

15. C. E. Haidar, K. R. Crews, J. M. Hoffman, M. V. Relling, and K. E. Caudle, "Advancing Pharmacogenomics From Single-Gene to Preemptive Testing," *Annual Review of Genomics and Human Genetics* 23 (2022): 449–473.

16. A. C. Wu, K. M. Mazor, R. Ceccarelli, S. Loomer, and C. Y. Lu, "Access to Guideline-Recommended Pharmacogenomic Tests for Cancer Treatments: Experience of Providers and Patients," *Journal of Personalized Medicine* 7 (2017): 17.

17. The Royal Australian College of General Practitioners (RACGP), "Pharmacogenomics," 2024, accessed March 27, 2024, https://www.racgp.org.au/.

18. The Royal College of Pathologists of Australasia (RCPA), "RCPA Develops Guidance for Pharmacogenomic Testing," 2024, accessed May 26, 2024, https://www.rcpa.edu.au/Home.

19. A. C. Tricco, E. Lillie, W. Zarin, et al., "PRISMA Extension for Scoping Reviews (PRISMA-ScR); Checklist and Explanation," *Annals of Internal Medicine* 169 (2018): 467–473.

20. M. Delara, L. Murray, B. Jafari, et al., "Prevalence and Factors Associated With Polypharmacy: A Systematic Review and Meta-Analysis," *BMC Geriatrics* 22 (2022): 601.

21. K. Fujita, N. Masnoon, J. Mach, L. K. O'Donnell, and S. N. Hilmer, "Polypharmacy and Precision Medicine," *Cambridge Prisms: Precision Medicine* 1 (2023): e22.

22. *Covidence Systematic Review Software* (Melbourne, Victoria, Australia: Veritas Health Innovation, 2024), www.covidence.org.

23. *Australian Medicines Handbook (Online)* (Adelaide, South Australia, Australia: Australian Medicines Handbook Pty Ltd, 2024), https://amhonline.amh.net.au/.

24. M. A. Alshabeeb, M. Alyabsi, and B. Paras, "Prevalence of Exposure to Pharmacogenetic Drugs by the Saudis Treated at the Health Care Centers of the Ministry of National Guard," *Saudi Pharmaceutical Journal* 30 (2022): 1181–1192.

25. H. D. Anderson, T. M. Thant, D. P. Kao, K. R. Crooks, N. D. Mendola, and C. L. Aquilante, "Pharmacogenetic Testing Among Patients With Depression in a US Managed Care Population," *Clinical and Translational Science* 15 (2022): 1644–1653.

26. M. L. Bianchini, C. L. Aquilante, D. P. Kao, J. L. Martin, and H. D. Anderson, "Patient-Level Exposure to Actionable Pharmacogenomic Medications in a Nationally Representative Insurance Claims Database," *Journal of Personalized Medicine* 13 (2023): 1574.

27. R. M. Black, A. K. Williams, L. Ratner, et al., "Projected Impact of Pharmacogenomic Testing on Medications Beyond Antiplatelet Therapy in Percutaneous Coronary Intervention Patients," *Pharmacogenomics* 21 (2020): 431–441.

28. C. Cai, S. Knudsen, and K. Weant, "Opioid Prescribing by Emergency Physicians: Trends Study of Medicare Part D Prescriber Data 2013-2019," *Journal of Emergency Medicine* 66 (2024): e313–e322.

29. J. S. Carpenter, M. B. Rosenman, M. R. Knisely, B. S. Decker, K. D. Levy, and D. A. Flockhart, "Pharmacogenomically Actionable Medications in a Safety Net Health Care System," *SAGE Open Medicine* 4 (2016): 2050312115624333.

30. C. Chanfreau-Coffinier, L. E. Hull, J. A. Lynch, et al., "Projected Prevalence of Actionable Pharmacogenetic Variants and Level A Drugs Prescribed Among US Veterans Health Administration Pharmacy Users," *JAMA Network Open* 2 (2019): e195345.

31. C. Chanfreau-Coffinier, S. Tuteja, L. E. Hull, et al., "Drug-Drug-Gene Interaction Risk Among Opioid Users in the U.S. Department of Veterans Affairs," *Pain* 163 (2022): 2390–2397.

32. O. M. Dong, A. Li, O. Suzuki, et al., "Projected Impact of a Multigene Pharmacogenetic Test to Optimize Medication Prescribing in Cardiovascular Patients," *Pharmacogenomics* 19 (2018): 771–782.

33. R. Dorfman, Z. London, M. Metias, B. Kabakchiev, G. Mukerjee, and A. Moser, "Individualized Medication Management in Ontario Long-Term Care Clinical Impact on Management of Depression, Pain, and Dementia," *Journal of the American Medical Directors Association* 21 (2020): 823–829.e5.

34. A. L. Elchynski, E. J. Cicali, M. C. Ferrer del Busto, et al., "Determining the Potential Clinical Value of Panel-Based Pharmacogenetic Testing in Patients With Chronic Pain or Gastroesophageal Reflux Disease," *Pharmacogenomics Journal* 21 (2021): 657–663.

35. L. D. Hellwig, C. Turner, C. Olsen, et al., "Assessing Clinical Utility of Pharmacogenetic Testing in the Military Health System," *Military Medicine* 189 (2024): e198–e204.

36. J. K. Hicks, N. el Rouby, H. H. Ong, et al., "Opportunity for Genotype-Guided Prescribing Among Adult Patients in 11 US Health Systems," *Clinical Pharmacology and Therapeutics* 110 (2021): 179–188.

37. J. E. Kimpton, I. M. Carey, C. J. D. Threapleton, et al., "Longitudinal Exposure of English Primary Care Patients to Pharmacogenomic Drugs: An Analysis to Inform Design of Pre-Emptive Pharmacogenomic Testing," *British Journal of Clinical Pharmacology* 85 (2019): 2734–2746.

38. H. F. Lu, T. Y. Liu, Y. P. Chou, et al., "Comprehensive Characterization of Pharmacogenes in a Taiwanese Han Population," *Frontiers in Genetics* 13 (2022): 948616.

39. P. C. Mathias, N. Hendrix, W. J. Wang, et al., "Characterizing Pharmacogenomic-Guided Medication Use With a Clinical Data Repository," *Clinical Pharmacology and Therapeutics* 102 (2017): 340–348.

40. H. Mulder, E. R. Heerdink, E. E. van Iersel, F. W. Wilmink, and A. C. Egberts, "Prevalence of Patients Using Drugs Metabolized by Cytochrome P450 2D6 in Different Populations: A Cross-Sectional Study," *Annals of Pharmacotherapy* 41 (2007): 408–413.

41. D. Nichols, S. Arnold, H. L. Weiss, et al., "Pharmacogenomic Potential in Advanced Cancer Patients," *American Journal of Health-System Pharmacy* 76 (2019): 415–423.

42. J. N. Patel, D. Boselli, E. J. Jandrisevits, et al., "Potentially Actionable Pharmacogenetic Variants and Symptom Control Medications in Oncology," *Supportive Care in Cancer* 29 (2021): 5927–5934.

43. L. Ratner, J. D. Zhu, M. N. Gower, et al., "Pharmacogenomic Prescribing Opportunities in Percutaneous Coronary Intervention and Bone Marrow Transplant Patients," *Pharmacogenomics* 23 (2022): 183–194.

44. Z. T. Rivers, H. M. Parsons, P. A. Jacobson, K. M. Kuntz, J. F. Farley, and D. J. Stenehjem, "Opportunities for Personalizing Colorectal Cancer Care: An Analysis of SEER-Medicare Data," *Pharmacogenomics Journal* 22 (2022): 198–209.

45. J. G. Ronquillo and W. T. Lester, "Pharmacogenomic Testing and Prescribing Patterns for Patients With Cancer in a Large National Precision Medicine Cohort," *Journal of Medical Genetics* 60 (2023): 81–83.

46. M. Samwald, H. Xu, K. Blagec, et al., "Incidence of Exposure of Patients in the United States to Multiple Drugs for Which Pharmacogenomic Guidelines Are Available," *PLoS One* 11 (2016): e0164972.

47. J. S. Schildcrout, J. C. Denny, E. Bowton, et al., "Optimizing Drug Outcomes Through Pharmacogenetics: A Case for Preemptive Genotyping," *Clinical Pharmacology and Therapeutics* 92 (2012): 235–242.

48. T. Shugg, R. C. Ly, E. J. Rowe, et al., "Clinical Opportunities for Germline Pharmacogenetics and Management of Drug-Drug Interactions in Patients With Advanced Solid Cancers," *JCO Precision Oncology* 6 (2022): e2100312.

49. D. M. Smith, B. N. Peshkin, T. B. Springfield, et al., "Pharmacogenetics in Practice: Estimating the Clinical Actionability of Pharmacogenetic Testing in Perioperative and Ambulatory Settings," *Clinical and Translational Science* 13 (2020): 618–627.

50. J. M. Stevenson, G. C. Alexander, N. Palamuttam, and H. B. Mehta, "Projected Utility of Pharmacogenomic Testing Among Individuals Hospitalized With COVID-19: A Retrospective Multicenter Study in the United States," *Clinical and Translational Science* 14 (2021): 153–162.

51. S. S. Verma, K. Keat, B. Li, et al., "Evaluating the Frequency and the Impact of Pharmacogenetic Alleles in an Ancestrally Diverse Biobank Population," *Journal of Translational Medicine* 20 (2022): 550.

52. C. Vermehren, R. Søgaard Nielsen, S. Jørgensen, A. M. Drastrup, and N. Westergaard, "Drug Use Among Nursing Home Residents in Denmark for Drugs Having Pharmacogenomics Based (PGx) Dosing Guidelines: Potential for Preemptive PGx Testing," *Journal of Personalized Medicine* 10 (2020): 78.

53. N. Westergaard, M. Baltzer Houlind, L. L. Christrup, H. G. Juul-Larsen, C. Strandhave, and A. E. Olesen, "Use of Drugs With Pharmacogenomics (PGx)-Based Dosing Guidelines in a Danish Cohort of Persons With Chronic Kidney Disease, Both on Dialysis and Not on Dialysis: Perspectives for Prescribing Optimization," *Basic & Clinical Pharmacology & Toxicology* 134 (2024): 531–542.

54. Australian Clinical Labs, "Pharmacogenetic Testing," 2023, accessed May 20, 2024, https://www.clinicallabs.com.au/doctor/specialists-services/pharmacogenetic-testing/.

55. M. Chambal, C. Forsthoffer, A. Egnaczyk, et al., "Comparison of Targeted vs. Expanded Pharmacogenomic Testing: What Are We Missing?," *Journal of the American Pharmacists Association* 63 (2023): 939–945.

56. S. A. Morris, A. T. Alsaidi, A. Verbyla, et al., "Cost Effectiveness of Pharmacogenetic Testing for Drugs With Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines: A Systematic Review," *Clinical Pharmacology and Therapeutics* 112 (2022): 1318–1328.

57. S. Mostafa, C. M. J. Kirkpatrick, K. Byron, and L. Sheffield, "An Analysis of Allele, Genotype and Phenotype Frequencies, Actionable Pharmacogenomic (PGx) Variants and Phenoconversion in 5408 Australian Patients Genotyped for CYP2D6, CYP2C19, CYP2C9 and VKORC1 Genes," *Journal of Neural Transmission (Vienna)* 126 (2019): 5–18.

58. J. J. Swen, C. H. van der Wouden, L. E. N. Manson, et al., "A 12-Gene Pharmacogenetic Panel to Prevent Adverse Drug Reactions: An Open-Label, Multicentre, Controlled, Cluster-Randomised Crossover Implementation Study," *Lancet* 401 (2023): 347–356.

59. R. Lim, L. M. K. Ellett, S. Semple, and E. E. Roughead, "The Extent of Medication-Related Hospital Admissions in Australia: A Review From 1988 to 2021," *Drug Safety* 45 (2022): 249–257.

60. E. Cecchin, B. Posocco, S. Mezzalira, M. Appetecchia, and G. Toffoli, "The Role of Gender Pharmacogenetics in the Personalization of Drug Treatment," *Journal of Pharmacology and Experimental Therapeutics* 386 (2023): 190–197.

61. V. E. Ortega and D. A. Meyers, "Pharmacogenetics: Implications of Race and Ethnicity on Defining Genetic Profiles for Personalized Medicine," *Journal of Allergy and Clinical Immunology* 133 (2014): 16–26.

62. C. W. Goodman and A. S. Brett, "Race and Pharmacogenomics—Personalized Medicine or Misguided Practice?," *Journal of the American Medical Association* 325 (2021): 625–626.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.