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REVIEW ARTICLE

The impact of pharmacogenetic testing in patients exposed to polypharmacy: a scoping review

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Abstract

Polypharmacy poses a significant risk for adverse reactions. While there are clinical decision support tools to assist clinicians in medication management, pharmacogenetic testing to identify potential drug–gene or drug–drug–gene interactions is not widely implemented in the clinical setting. A PRISMA-compliant scoping review was performed to determine if pharmacogenetic testing for absorption, distribution, metabolism, and excretion (ADME)-related genetic variants is associated with improved clinical outcomes in patients with polypharmacy. Six studies were reviewed. Five reported improved clinical outcomes, reduced side effects, reduction in the number of drugs used, or reduced healthcare utilization. The reviewed studies varied in methodological quality, risk of bias, and outcome measures. Age, diet, disease state, and treatment adherence also influence drug response, and may confound the relationship between genetic polymorphisms and treatment outcomes. Further studies using a randomized control design are needed. We conclude that pharmacogenetic testing represents an opportunity to improve health outcomes in patients exposed to polypharmacy, particularly in patients with psychiatric disorders and the elderly.

Introduction

Healthcare professionals have recognized polypharmacy, the concomitant use of multiple medications, as a topic of increasing concern in recent years [1, 2]. The World Health Organization anticipates increased prevalence of polypharmacy secondary to the aging population and chronic diseases requiring pharmaceutical interventions [1]. A recent analysis of polypharmacy use estimated that ~22% of adults in the US aged 40–79 consume five or more drugs concurrently [3]. The use of multiple medications is associated with an increased risk for adverse drug events (ADEs) as well as increased healthcare costs. Specifically, patients are more likely to suffer from drug–drug interactions, falls, cognitive decline, and poor nutrition, and have more emergency room visits and hospital admissions [1, 2, 4]. Issues such as decreased medication adherence, and the use of over-the-counter medications and supplements, also hinder medication management efforts. While the use of multiple medications is often necessary and effective, there is a need to identify strategies that mitigate the negative health outcomes associated with polypharmacy.

Genetic variants of drug metabolizing enzymes (DMEs) and drug transporters can have significant consequences for the pharmacokinetics of pharmaceuticals. DMEs are categorized as Phase I and Phase II enzymes, according to their roles in drug biotransformation or elimination. Phase I enzymes modify drugs into water-soluble products through the addition of reactive or polar groups, in preparation for excretion [5, 6]. Cytochrome p450 (CYP) enzymes, which represent the most significant and well-known group of Phase I enzymes, play an important role in drug metabolism. Fifty-seven CYP genes, categorized into 18 families have been identified [7]. These enzymes represent a superfamily of hemeproteins found in all tissues, with the most abundant expression in the liver and small intestine [5–7]. Approximately 70–80% of drugs are metabolized by CYP enzymes in the CYP1, CYP2, and CYP3 families [8].

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Polymorphic enzymes CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 metabolize roughly 60–70% of prescribed drugs, some of which are prodrugs that are converted to pharmacologically active metabolites [8]. Other CYP genes are important for the synthesis of steroid hormones, cholesterol biosynthesis, and vitamin metabolism [7]. The genetic variants in some of the CYP genes, such as CYP2C19 and CYP2D6, can be used to determine patient metabolizer phenotypes: poor metabolizers (PM), intermediate metabolizers, extensive (normal) metabolizers (EM), or ultrarapid metabolizers (UM) [5, 9]. For instance, CYP2D6 PMs have decreased or no enzyme activity compared to EMs. Codeine, a pro-drug that is metabolized by CYP2D6 to form morphine, is likely to be ineffective in CYP2D6 PMs, since there is less active metabolite [10]. Codeine use by patients classified as CYP2D6 UMs can lead to significant ADEs [10]. Due to increased CYP2D6 enzyme activity in UMs, these patients are at high risk for morphine toxicity. Thus, having a PM or UM phenotype can potentially lead to adverse outcomes.

Phase II metabolism modifies a drug or drug metabolites from Phase I further for elimination [5, 6]. Phase II enzymes, which are transferases, are also of clinical significance. Genetic variants of enzymes such as N-acetyltransferase, uridine 5′-diphspho-glucuronosyltransferases, and thiopurine S-methyltransferases have been associated with ADEs due to alterations in enzyme activity [5].

Drug transport proteins, such as solute carrier (SLC) transporters and ATP-binding cassette transporters act as uptake or efflux transporters to transfer molecules into or out of cells [6]. Polymorphisms in drug transporter genes, such as ATP-binding cassette subfamily B member 1 and solute carrier organic anion transporter family member 1B1, can also affect drug efficacy [5]. Many diagnostic companies use a common panel of pharmacogenetic genes for Food & Drug Administration (FDA) approved drugs with actionable pharmacogenetic drug label annotations (Table 1).

The ability to predict drug response through pharmacogenetic testing has been extremely useful for individualized drug selection and dosing. The drug label for warfarin, an anticoagulant, was the first to be updated by the US FDA to include pharmacogenomics labeling [5, 11]. There are now over 160 drug–gene pairs recognized by the FDA [12]. The FDA, the Clinical Pharmacogenetics Implementation Consortium (CPIC), and the European Medicines Agency, all monitor pharmacogenetics research and offer recommendations for clinicians to improve health outcomes and reduce ADEs [7].

An additional concern is the nongenetic factors known to affect drug metabolism. The concomitant use of DME inhibitors or inducers can impact a patient's ability to metabolize a particular drug, and will influence drug efficacy. Amiodarone, an antiarrhythmic, is an inhibitor of CYP1A2, CYP2C9, CYP2D6, and CYP3A activities [13]. Co-administration with medications, which are also substrates for these enzymes, may lead to reduced enzyme activity and ADEs. The potential for significant drug interactions with amiodarone have been documented for statins, β-receptor blocking agents, and anticoagulants [13]. Thus, genotyping for absorption, distribution, metabolism, and excretion (ADME)-related genetic variants will not necessarily predict metabolizer phenotype, which has negative implications for the clinical utility of pharmacogenetic testing. The change from the genotype-predicted metabolizer phenotype to a lower or higher metabolizer phenotype is referred to as phenoconversion [14, 15]. The issues of enzyme activity and drug–drug interactions impact the phenoconversion of an enzyme, which can be a key factor affecting the utility of a pharmacogenetic test.

Because patients are increasingly prescribed multiple medications, an evaluation of whether genetic testing could assist in medication management is warranted. Therefore, a scoping review was conducted to assess the impact of pharmacogenetic testing on health outcomes in patients with polypharmacy.

Materials and methods

Protocol

This scoping review was conducted according to the guidelines of the PRISMA Extension for Scoping Reviews [16]. Supplementary Table 1 shows the completed PRISMA-ScR checklist.

Eligibility criteria

Studies that assessed the impact of incorporating pharmacogenetic testing into a clinical decision support tool (CDST) to guide treatment were the targets of the literature search. Documentation of polypharmacy was required. There is no consensus on the number of concurrent medications that qualify as polypharmacy [1, 4]. Due to a limited number of articles that specifically focus on the intersection of polypharmacy and genetic testing, the lower limit of concomitant medications was set at two. Articles that document an average of two or more concomitant medications among study participants also satisfied the criteria for polypharmacy. There was no limitation with regard to patient condition, diagnosis, or variant/phenotype status. Outcomes could be any measure of health, healthcare usage, or ADEs.

Table 1 Important pharmacogenes and examples of medications with actionable pharmacogenetic drug label annotations.

Gene symbol[a]	Gene name[a]	Class[b]	Chromosome location[a]	# of known alleles[c]	Medications[d,e]	Therapeutic area[d]	Risk[c]
CYP2C9	Cytochrome P450 family 2 subfamily C member 9	Phase I	10q23.33	61	Siponimod	Neurology	Substantially elevated siponimod plasma levels; contraindicated in patients with CYP2C9*3/*3 genotype
					Warfarin	Hematology	Narrow therapeutic index; CYP2C9 and VKORC1 variants contribute to variability in patient response
CYP2C19	Cytochrome P450 family 2 subfamily C member 19	Phase I	10q23.33	37	Citalopram	Psychiatry	QT prolongation in CYP2C19 poor metabolizers
					Clopidogrel	Cardiology	Diminished therapeutic response in CYP2C19 poor metabolizers
CYP2D6	Cytochrome P450 family 2 subfamily D member 6	Phase I	22q13.2	145	Codeine	Anesthesiology	Life-threatening or fatal respiratory depression in CYP2D6 ultrarapid metabolizers
					Paroxetine	Psychiatry	Adverse reactions due to increased plasma levels in CYP2D6 poor metabolizers
					Tramadol	Anesthesiology	Life-threatening or fatal respiratory depression in CYP2D6 ultrarapid metabolizers
DPYD	Dihydropyrimidine dehydrogenase	Phase I	1p21.3	83	Fluorouracil	Dermatology/ oncology	Severe toxicity or fatal adverse reactions in patients with reduced or absent DPYD enzyme activity
NAT2	N-acetyltransferase 2	Phase II	8p22	95	Amifampridine	Neurology	Adverse reactions due to increased exposure in NAT2 poor metabolizers
SLCO1B1	Solute carrier organic anion transporter family member 1B1	Transporter	12p12.1	37	Simvastatin	Cardiology	Myopathy due to increased exposure in patients with intermediate or low SLCO1B1 activity
TPMT	Thiopurine S-methyltransferase	Phase II	6p22.3	43	Azathioprine	Rheumatology	Myelosuppression in intermediate and poor TPMT and/or NUDT15 metabolizers
					Mercaptopurine	Oncology	Myelosuppression in intermediate and poor TPMT and/or NUDT15 metabolizers
UGT1A1	UDP glucuronosyltransferase family 1 member A1	Phase II	2q37.1	113	Irinotecan	Oncology	Neutropenia in patients homozygous for UGT1A1*28 allele

[a]HUGO Gene Nomenclature Committee (HGNC) https://www.genenames.org/. Accessed 9 Mar 2020.

[b]PharmaADME.org http://www.pharmaadme.org/joomla/. Accessed 27 Aug 2020.

[c]The Pharmacogenomics Knowledge Base (PharmGKB) https://www.pharmgkb.org/. Accessed 17 Mar 2020.

[d]Table of Pharmacogenomic Biomarkers in Drug Labeling https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling. Accessed 17 Mar 2020.

[e]Clinical Pharmacogenetics Implementation Consortium (CPIC) https://cpicpgx.org/. Accessed 17 Mar 2020.

Search strategy

The following databases were searched for journal articles published in the English language from 2010 to February 2020: PubMed, Medline, Web of Science, Cochrane CENTRAL. Supplementary Reference 1 includes the strategy and terms used to perform database searches. The references of included articles were also reviewed for relevant studies.

Study selection

The search results were combined and duplicates were removed. Journal article titles and abstracts were reviewed by two authors (ELM and SMS) for exclusion. The full texts for the remaining articles were reviewed for eligibility (ELM). Studies could be prospective, retrospective, or randomized control trials (RCTs). Single case reports and studies that evaluated only one drug therapy were excluded. To address the research question, included studies assessed the impact of pharmacogenetic testing on health outcomes in patients with polypharmacy. Genetic screening should specify the variants tested or the phenotype status of the study participants. Outcomes could be secondary to the study focus.

Data extraction

Data extraction was conducted independently by one author (ELM) using a data extraction spreadsheet and reviewed with the authors (SMS, TKF, CLF). Data collected include: study design, funding, disease/condition, genes and variants included in pharmacogenetic testing panel, number or average number of medications used by the study population, patient population size, patient

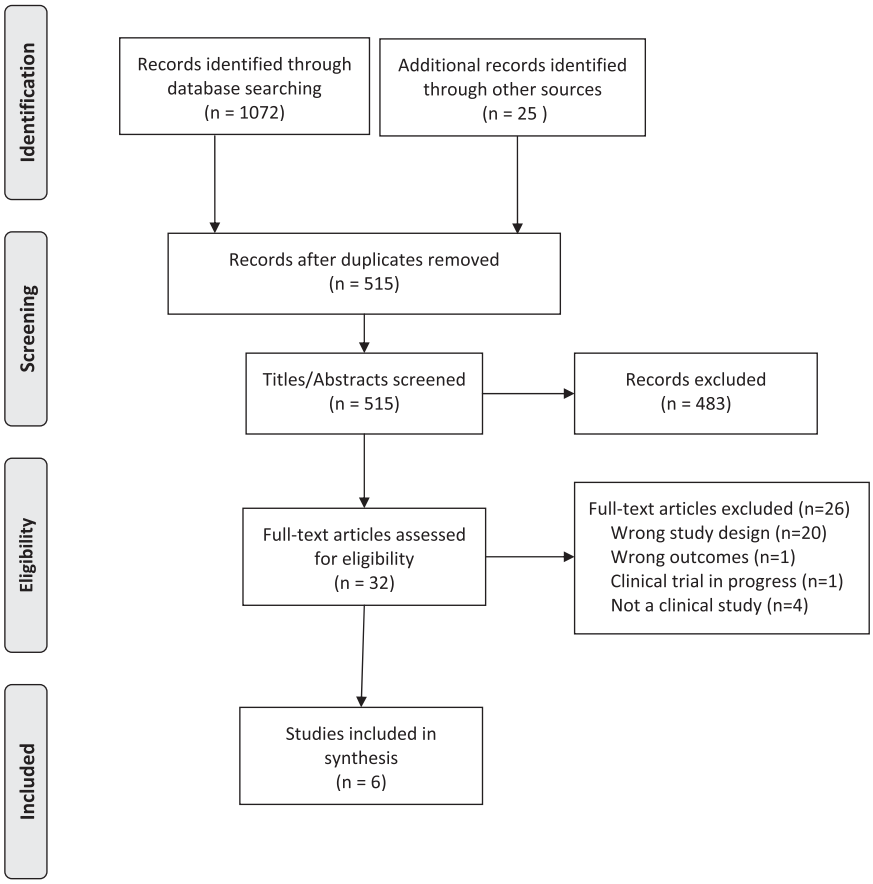


Fig. 1 Flowchart for selection of included studies.

demographics, and study outcomes. Risk of bias was assessed using guidance from Viswanathan et al. [17].

Synthesis of results

Results were summarized using a narrative format. Tables were prepared for extracted data. The criteria for the assessment of pharmacogenetic studies published by Jorgensen and Williamson and others [18–20] were used as a guide to assess study quality.

Results

Study selection

A total of 1097 journal articles were identified during the literature search. Once duplicates were removed, 515 journal titles and abstracts were reviewed to eliminate those that were irrelevant to the research question. Full-text articles were retrieved for the remaining 32 articles. Most were excluded because they did not have the appropriate study design. Additional reasons for article exclusion are listed in the PRISMA [21] flowchart in Fig. 1. Six studies were analyzed [22–27].

Study characteristics

Study characteristics and results for the articles included in this review are listed in Table 2. Five studies had a prospective study design, and one was a retrospective study. Three studies included patients with diagnoses from multiple therapeutic areas and three focused on psychiatric pharmacotherapy.

Two articles stated research goals that specifically aligned with the purpose of this review [23, 24]. Brixner et al. [23] genotyped CYP variants in study participants who were prescribed three or more medications, one of which was classified as causing ADEs if high risk variants in CYP genes were identified using the YouScript® (Genelex, Washington, USA) CDST. Hospitalizations, emergency department visits, and outpatient visits were documented 4 months after enrollment. The data were compared to an untested control group identified through an administrative claims database (Medical Outcomes Research for Effectiveness and Economics Registry). Elliot et al. [24] were also interested in the influence of pharmacogenetic testing on healthcare resource utilization. They conducted a RCT in which the number of hospitalizations and emergency department visits 30 and 60 days after enrollment was compared between the tested and untested study participants

Table 2 Study characteristics and outcomes.

Authors [ref. No.]	Research focus	Study design	Study participants	Therapeutic area	Number of medications/patient	CDST	Relevant outcomes	Funding
Brixner et al. [23]	To assess the effect of PGt on healthcare resource utilization and estimated costs in elderly patients exposed to polypharmacy	Prospective cohort study	$n = 1025$ 205 with PGt 820 without PGt	Multiple	3 or more	YouScript®/ Genelex	Significantly lower % of patients hospitalized in tested patients vs. untested patients	Genelex & Research Grant
			All participants ≥ 65 years Avg = 75 ± 6.9 with PGt Avg = 75 ± 6.5 without PGt				Significantly lower % of patients with ED visits in tested patients vs. untested patients	
			42.4% M with PGt 45.2% M without PGt				Significantly higher % of patients with outpatient visits in tested patients vs. untested patients; no significant difference in mean # of outpatient visits between groups	
			Majority Caucasian (statistic not reported)				Significantly higher % of patients with HRU overall in tested patients vs. untested patients; similar trend for mean # total HRU does not reach significance	
Elliott et al. [24]	To assess the impact of PGt on home health patients with polypharmacy	Prospective, open-label, RCT	$n = 110$ 57 with PGt 53 without PGt	Multiple	Avg = 11.6	YouScript®/ Genelex	Significantly lower # of rehospitalizations at 60 days in the tested group vs. untested group	Genelex
			All participants > 50 years Overall Avg = 75.6 ± 10.7 Avg = 76.5 ± 9.4 with PGt Avg = 74.6 ± 11.9 without PGt				Significantly lower # of ED visits at 60 days in the tested group vs. untested group	
			Overall: 42M and 68F 25M and 32F with PGt 17M and 36F without PGt				Significantly lower composite # of rehospitalizations + ED visits at 60 days in the tested group vs. untested group	
			Overall: 109 White, 1 African American PGt: 57 White, 0 African American No PGt: 52 White, 1 African American				Significantly lower composite # of rehospitalizations + ED visits + deaths at 60 days in the tested group vs. untested group	
							Similar trend for differences in outcome measures approached but did not reach significance at 30 days	
van der Wouden et al. [25]	To assess the impact of preemptive PGt on primary care patients	Prospective pilot study	$n = 200$ with PGt	Multiple	Avg = 4 ± 3.3 Avg = 3.93 ± 3.4—no DGI for the drug of enrollment Avg = 4 ± 2.9—HCP adhered to DPWG guideline Avg = 4.4 ± 3—HCP did not adhere to DPWG guideline	G-Standaard (DPWG), the Netherlands	No significant difference in healthcare utilization in patients with DGI vs. no DGI	Grants
			Overall Avg = 61.6 ± 11.2 years Avg = 62.3 ± 11—no DGI for the drug of enrollment Avg = 60.9 ± 11.5—HCP adhered to DPWG guideline Avg = 56.8 ± 13.3—HCP did not adhere to DPWG guideline				No healthcare utilization among patients whose HCPs did not adhere to CDST guidelines	

Table 2 (continued)

Authors [ref. No.]	Research focus	Study design	Study participants	Therapeutic area	Number of medications/patient	CDST	Relevant outcomes	Funding
			Overall: 103F and 97M 74F and 64M—no DGI for the drug of enrollment 25F and 24M—HCP adhered to DPWG guideline 3F and 6M—HCP did not adhere to DPWG guideline Self-reported ethnicity of father: 187 Caucasian, 13 other Self-reported ethnicity of mother: 188 Caucasian, 12 other					
Hall-Flavin et al. [27]	To assess the clinical utility of PGt to improve health outcomes in patients with major depressive disorder	Prospective, open-label	$n = 230$ 114 with PGt 113 without PGt	Psychiatry	Avg = 2.2 ± 1.48 with PGt Avg = 2.6 ± 1.56 without PGt	GeneSight®/ AssureRx Health, Inc.	Significantly greater reduction of symptoms as measured by three clinical rating instruments (HAMD-17, QIDS-C16, PHQ-9) in tested vs. untested group at study endpoint of 8 weeks	Mayo Clinic Discovery Translation Grant
			Avg = 41.0 ± 12.8 years with PGt Avg = 44.0 ± 12.1 years without PGt				Significantly greater percentage of patients in remission as measured by the QIDS-C16 clinical rating instrument in tested vs. untested group at study endpoint of 8 weeks	AssureRx Health, Inc.
			69.3% F with PGt 77.0% F without PGt				Differences in remission rates between groups as measured by HAMD-17 and PHQ-9 were not significant	
			Majority European (statistic not reported)				Significantly greater number of changed medication regimens for tested group vs. untested group	
							Significantly higher percentage of physicians satisfied with care in tested group vs. untested group	
							Significantly higher physician confidence in medication selection for tested group vs. untested group	
Winner et al. [26]	To assess the clinical impact of PGt in patients with major depressive disorder	Prospective, randomized, double-blind study	$n = 51$ 26 with PGt 25 without PGt	Psychiatry	Avg = 2.7 ± 1.2 group receiving TAU Avg = 2.9 ± 1.2 group receiving PGt	GeneSight®/ AssureRx Health, Inc.	Significantly greater % improvement in HAMD-17 scores for tested group vs. untested group 6 weeks after enrollment, but not at 4 or 10 weeks	AssureRx Health, Inc.
			Avg = 50.6 ± 14.6 years with PGt Avg = 47.8 ± 13.9 years without PGt				For patients receiving "red bin" medications (use with increase caution and with more frequent monitoring), greater % improvement in HAMD-17 scores for tested group vs. untested group at 10 weeks after enrollment approached significance	
			18F and 8M with PGt 23F and 2M without PGt PGt: 25 Non-Hispanic White, 1 African American No PGt: 25 Non-Hispanic White				For patients receiving "green bin" (use as directed) or "yellow bin" (use with caution) medications, improvement in HAMD-17 scores for tested group vs. untested group at 10 weeks after enrollment was not significant	

Table 2 (continued)

Authors [ref. No.]	Research focus	Study design	Study participants	Therapeutic area	Number of medications/patient	CDST	Relevant outcomes	Funding
Blasco-Fontecilla [22]	To determine the clinical utility of PGt in children and adolescents with severe mental disorders	Retrospective cohort study	$n = 20$ 10 in residential foster care with PGt 10 living with parents with PGt Overall Avg = 14.6 ± 1.5 years Avg = 14 ± 1.49 residential foster care Avg = 15.2 ± 1.39 living with parents Overall: 11F and 9M 8F and 2M—residential foster care 3F and 7M—living with parents Ethnicity/race not reported	Psychiatry	1–8 (Avg = 3.3 ± 1.86) Avg = 4 ± 2.26 for foster care children Avg = 2.6 ± 1.07 for non-foster care children	Neuropharmagen®/AB-Biotics SA	Significant clinical improvement for all patients as measured by CGI-S before and after PGt Significant reduction in the number of drugs after PGt overall; data did not reach significance for subgroups Reduction of adverse effects for 7/10 patients in foster care; NA reported for 3/10 Reduction of adverse effects for 4/10 patients living with parents; NA reported for 6/10	Unknown

PGt pharmacogenetic testing, *RCT* randomized control trial, *Avg* average, *DGI* drug–gene interaction, *HCP* healthcare provider, *DPWG* Dutch Pharmacogenetics Working Group, *F* female, *M* male, *CDST* clinical decision support tool, *CGI-S* Clinical Global Impression Scale-Severity, *NA* assume not applicable but not specifically defined in supplement, *ED* emergency department, *HRU* healthcare resource utilization, *HAMD-17* Hamilton Rating Scale for Depression, *QIDS-C16* Quick Inventory of Depressive Symptomatology (Clinician-Rated), *PHQ-9* Patient Health Questionnaire, *TAU* treatment as usual.

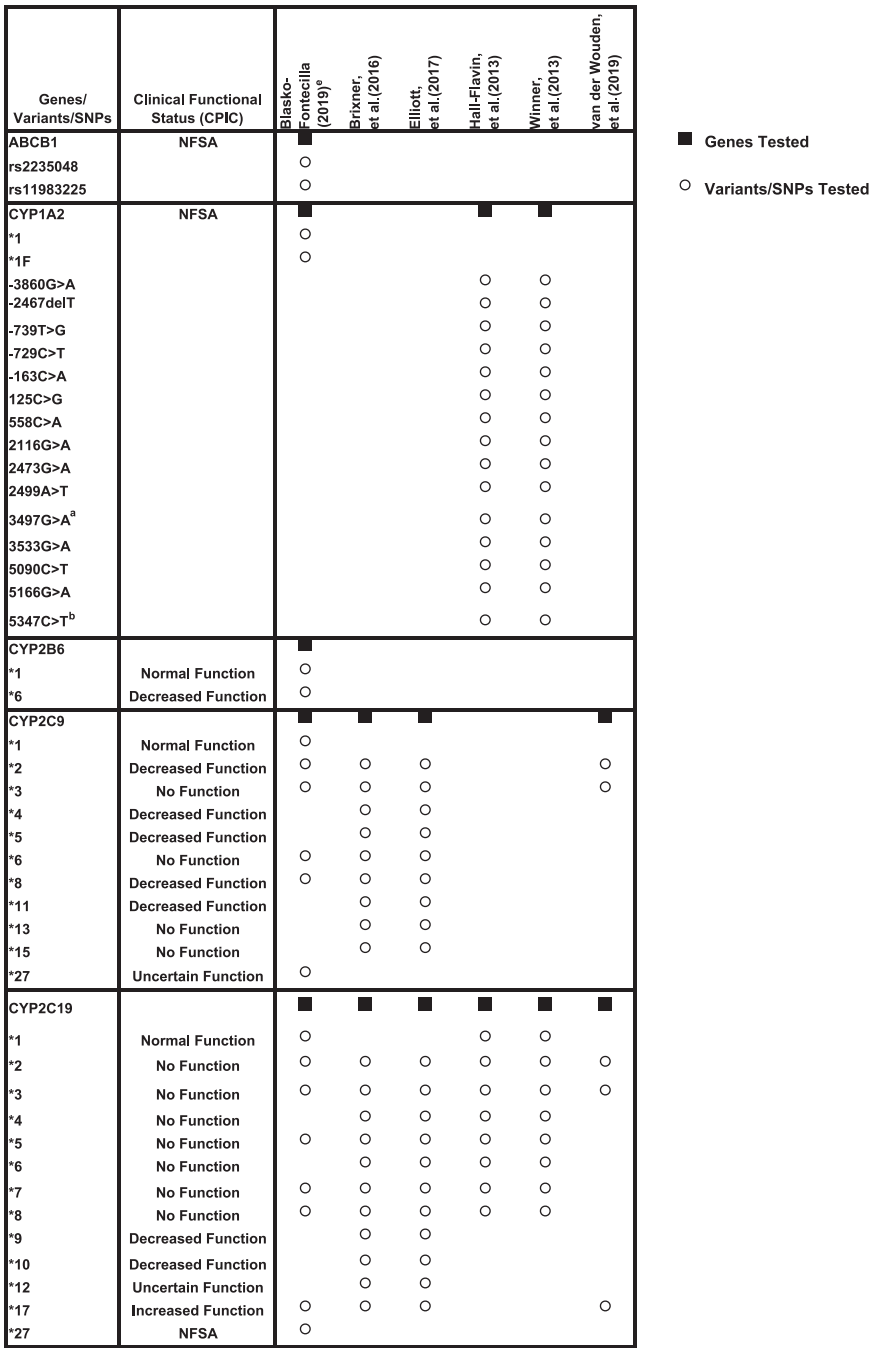
with confirmed polypharmacy. Exploratory outcomes also included number of deaths at 30 and 60 days. This study used the same CDST as Brixner et al. [23].

The remaining four articles did not specifically seek to measure health outcomes related to polypharmacy, but included relevant outcomes as secondary measures [22, 25–27]. Blasco-Fontecilla [22] assessed the impact of pharmacogenetic testing in patients diagnosed with psychiatric disorders. Outcomes included measurement of clinical improvement, reduction in number of medications used after pharmacogenetic testing, and reduction in adverse events. Both Winner et al. [26] and Hall-Flavin et al. [27] focused on study participants diagnosed with major depressive disorder. They reported clinical improvement after pharmacogenetic testing using clinical rating instruments that healthcare providers use to assess depression severity (e.g., Hamilton Rating Scale for Depression). van der Wouden et al. [25] assessed the impact of pharmacogenetic testing in a primary care setting. The primary outcomes of the study were unrelated to the purpose of this review. Relevant secondary outcomes included general practitioner consults, emergency room visits, and hospitalizations related to ADEs within 12 weeks of enrollment.

Regarding pharmacogenetic testing, genotyping for CYP2D6 and CYP2C19 variants was universal. Four out of six studies included CYP2C9. Variants and SNPs analyzed differed considerably overall. Genes unrelated to drug ADME were also tested. For example, three studies included testing for HTR2A (5-hydroxytryptamine (serotonin) receptor 2A), a gene of interest in psychiatry and neurology [22, 26, 27]. The most extensive panel was used by Blasco-Fontecilla [22] and has been described in detail by Perez et al. [28]. Brixner et al. [23] categorized study participants as having wild-type status if variant genotyping results were negative. Table 3 lists the genes, variants, and SNPs included in the pharmacogenetic testing panels as described in each study. Only ADME-related genes are listed. Inferred metabolizer phenotypes based on genotyping results were not reported or were described in referenced articles for four out of six studies. Hall-Flavin et al. [27] reported a significant difference in the frequencies of CYP2D6 metabolizer phenotypes between tested and untested patients, but not for CYP2C19 or CYP1A2. Elliott et al. [24] described the CYP metabolizer phenotypes of the study population in order to compare the distribution to another published study.

Polypharmacy among study participants was not defined in the same manner and varied across studies. The number of medications for each patient was reported or the average number of medications per patient was reported. In studies reporting averages, it is possible that a subset of the study participants could be prescribed only one medication. The mean number of medications per patient ranged from 2.2 to 11.6 for all studies analyzed.

Table 3 A comparison of genes related to drug absorption, distribution, metabolism, and excretion included in the pharmacogenetic testing panels of reviewed studies.



Quality assessment and outcomes

There were significant differences between studies regarding the study population. The number of patients ranged from 20 to 1025. Blasco-Fontecilla [22] focused on a young patient population with a mean age of 14.6. The mean age for the remaining five studies ranged from ~41 to 77. None of the studies had an ethnically diverse patient population.

Table 3 (continued)

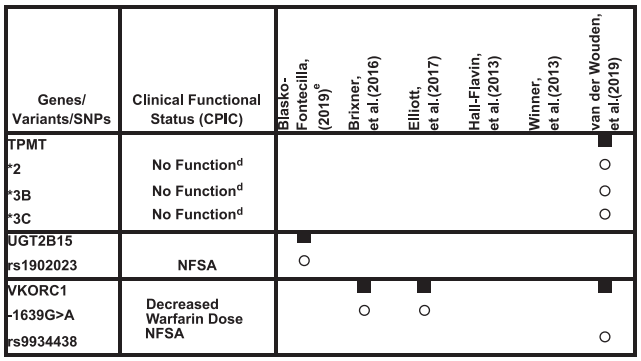
Genes/ Variants/SNPs	Clinical Functional Status (CPIC)	Blasko-Fontecilla, (2019)[e]	Brixner, et al.(2016)	Elliott, et al.(2017)	Hall-Flavin, et al.(2013)	Winner, et al.(2013)	van der Wouden, et al.(2019)
CYP2D6		■	■	■	■	■	■
*1	Normal Function	○			○	○	
*2	Normal Function	○	○	○	○	○	
*2A	NFSA		○	○	○	○	○
*3	No Function	○	○	○	○	○	○
*4	No Function	○	○	○	○	○	○
*5	No Function	○	○	○	○	○	○
*6	No Function	○	○	○	○	○	○
*7	No Function	○	○	○	○	○	○
*8	No Function	○	○	○	○	○	
*9	Decreased Function	○	○	○	○	○	○
*10	Decreased Function	○	○	○	○	○	○
*11	No Function	○	○	○	○	○	○
*12	No Function	○	○	○	○	○	○
*14	Decreased Function	○	○	○	○	○	
*15	No Function	○	○	○	○	○	
*17	Decreased Function	○	○	○	○	○	○
*18	No Function						○
*19	No Function	○	○	○			○
*20	No Function	○	○	○			○
*29	Decreased Function	○	○	○			○
*30	Uncertain Function	○					
*35	Normal Function	○	○	○			
*36	No Function		○	○			
*38	No Function						○
*40	No Function	○					○
*41	Decreased Function	○	○	○	○	○	○
*42	No Function						○
*44	No Function						○
*69	No Function	○					
*1XN	Increased Function	○					
*2XN	Increased Function	○					
*35X2	Increased Function	○					
rs1058164	NFSA						○
rs16947	NFSA						○
rs1135840	NFSA						○
deletions[c]			○	○			
duplications[c]			○	○	○	○	○
CYP3A4		■	■	■			
*1	NFSA	○					
*22	NFSA	○	○	○			
CYP3A5			■	■			■
*3	No Function		○	○			○
*6	No Function						○
DPYD							■
*2A	No Function						○
*13	No Function						○
rs56038477	Decreased Function						○
rs67376798	Decreased Function						○
SLCO1B1							■
rs4149056	NFSA						○

■ Genes Tested

○ Variants/SNPs Tested

Patients in five out of six studies were predominantly Caucasian. In general, there were minor differences in gender composition. Only Winner et al. [26] included a much higher proportion of female participants compared to the other studies. All of the studies described the inclusion and exclusion criteria for study participants and the methods used for variant and copy number determination. None of the studies discussed the degree to which the DMEs studied

Table 3 (continued)



NFSA no functional status assigned.

[a]Pharmacogene Variation Consortium (PharmVar) states 3496 G > A (CYP1A2*5): https://www.pharmvar.org/gene/CYP1A2.

[b]Pharmacogene Variation Consortium (PharmVar) states 5347 T > C: https://www.pharmvar.org/gene/CYP1A2.

[c]Not Specified.

[d]Listed as functional status not clinical functional status.

[e]Blasko-Fontecilla reports testing for 25 genes and references list from Perez et al. [28], which lists 30 genes.

ABCB1, ATP-binding cassette subfamily B member 1; CYP1A2, cytochrome P450 family 1 subfamily A member 2; CYP2B6, cytochrome P450 family 2 subfamily B member 6; CYP2C9, cytochrome P450 family 2 subfamily C member 9; CYP2C19, cytochrome P450 family 2 subfamily C member 19; CYP2D6, cytochrome P450 family 2 subfamily D member 6; CYP3A4, cytochrome P450 family 3 subfamily A member 4; CYP3A5, cytochrome P450 family 3 subfamily A member 5; DPYD, dihydropyrimidine dehydrogenase; SLCO1B1, solute carrier organic anion transporter family member 1B1; TPMT, thiopurine S-methyltransferase; UGT2B15, Uridine 5′-diphspho-glucuronosyltransferase family 2 member B15; VKORC1, vitamin K epoxide reductase complex subunit 1.

contribute to the metabolism of the drugs prescribed, screening for Hardy–Weinberg equilibrium, or confirmation of patient adherence to prescribed drug regimens. Due to the factors described above, these studies have at least a moderate risk for bias.

Overall, the studies reported the impact of pharmacogenetic testing in terms of improved clinical outcomes [22, 27], reduced side effects [22, 26], reduction in the number of drugs used [22], or reduced healthcare utilization (e.g., reduced hospitalizations and emergency room visits) [23–25]. Five out of six studies reported favorable results, meaning that use of a pharmacogenomics panel improved patient outcomes [22–24, 26, 27].

Discussion

In recent years, mounting evidence has supported the notion that pharmacogenetic testing can have a positive impact on health outcomes and advance the development of precision medicine [29, 30]. Several institutions in the USA, such as the Mayo Clinic and St. Jude Children's Research Hospital, have already established programs to incorporate pharmacogenetic testing into clinical practice [20, 31, 32]. In this review, we presented a synthesis of studies, which focus on the clinical implementation of pharmacogenetic testing in order to describe the real-world impact on patient care, as well as similarities and differences that could contribute to the growing effort to make preemptive pharmacogenetic testing mainstream. We chose to focus on patients exposed to polypharmacy, as there is a growing awareness of the impact on patient care and the growing number of patients with comorbidities [1]. Pharmacogenetic testing in patients with polypharmacy appears to have received little coverage in the literature, however, there are multiple studies reporting an association between ADEs and genotypes related to pharmacokinetics [33–36]. Recently, Licito et al. [33] showed that a genetic variant of SLCO1B1 is associated with the neuromuscular pain in type 2 diabetes mellitus patients with cardiovascular comorbidities. Mugoša et al. [34] looked at the prevalence of CYP2D6 variants associated with the PM phenotype in a hospitalized cardiac patient population taking β-blockers. They found that ADEs caused by β-blockers could be predicted by having a PM phenotype, in addition to concomitant use of other CYP2D6 substrate medications, and length of hospital stay. Five out of six studies included in this review support the use of pharmacogenetic testing as a tool to assist clinicians in medication management. van der Wouden et al. [25] did not report a benefit for tested participants whose healthcare

providers followed Dutch Pharmacogenetics Working Group (DPWG) guidelines compared to those with potential DGIs but did not receive pharmacogenetic guided therapy.

The analysis of the literature also revealed the patient populations with polypharmacy, which are likely to benefit from pharmacogenetic testing. Psychiatric patients, as well as elderly oncology and cardiology patients, are often prescribed multiple medications. In addition to improved health outcomes, patients who are provided with proper medication management and patient-centered care will also benefit from overall reductions in healthcare costs. Recent studies have reported estimated healthcare cost savings resulting from the incorporation of pharmacogenetic testing [23, 37–40]. Maciel et al. [37] estimated annual cost savings of $3962 per patient associated with pharmacogenetic testing in patients diagnosed with major depressive disorder. Saldivar et al. [38] found that 50% of patients exposed to polypharmacy in a long-term care facility could reduce or eliminate one to three medications if testing results were considered in medication management. The estimated annual savings were $621 per patient.

Genetic variants chosen for pharmacogenetic testing panels are critical to successful implementation in drug prescribing and the avoidance of ADEs. The articles reviewed show that clinicians may opt to use panels focused on a particular therapeutic area. In addition, pharmacogenetic testing panels can have several genetic markers in common, however, there may be differences in the variants included. In their study of severe mental disorders among adolescents, Blasco-Fontecella [22] used Neuropharmagen® (AB-Biotics, Barcelona, Spain), a commercial test developed to optimize drug prescribing for psychiatric conditions [28]. Testing for several genes, including HTR2A, brain-derived neurotrophic factor, and opioid receptor mu 1, is included on this panel, in addition to CYP enzymes such as CYP2C9, CYP2C19, and CYP2D6. Winner et al. [26] focused on patients with major depressive disorder, however, the investigators used the GeneSight® (Assurex Health, Ohio, USA) pharmacogenetic test. Table 3 shows that there can be significant variability in pharmacogenetic testing panels. The lack of uniformity highlights the potential need for panel standardization within specific therapeutic areas, and agreement on core genetic variants to be included on a pharmacogenetic testing panel which could be broadly applied across multiple morbidities. To address this issue, van der Wouden et al. [41] introduced a panel of pharmacogenes which they believe can be used for preemptive pharmacogenetic testing based on guidelines from the DPWG, The Pharmaogenomics Knowledgbase, CPIC, and other predefined criteria. Referred to as the pharmacogenetic testing passport, this panel includes 58 variants of 14 genes.

Studies were accepted for review if they reported outcome measures resulting from the implementation of pharmacogenetic test results. Data analyzed included event counts (e.g., ER visits, hospitalizations) [23, 24] or clinical assessment survey results [22, 26]. The timing of data collection was also important, since investigators must estimate an appropriate time point after pharmacogenetic testing which would be adequate to reveal an impact on health outcomes if an association exists. Elliott et al. [24] recorded rehospitalizations and ED visits. The data approached significance at 30 days after patients were discharged from the hospital, but significant differences were found 60 days after discharge. Winner et al. [26] assessed depression severity after changes in medications at 2, 4, 6, and 10 weeks after patient recruitment. Measured improvement was significant at 6 weeks, but not 2, 4, or 10 weeks. The retrospective study by Blasco-Fontecilla [22] did not state what period of time after pharmacogenetic testing patient records were reviewed. None of the studies measured pharmacokinetic parameters such as elimination half-life ($t_{1/2}$), clearance (Cl), area under the curve, and maximum concentration (C_{max}) [42]. These studies may shed light on another reason why healthcare institutions have been slow to adopt pharmacogenetic testing as a guide for prescribing and dosing [30]. The factors investigators use to document clinical effects or improvement are necessarily different, depending on the study focus, funding for research, and access to data. In a review article on the need for preemptive panel-based pharmacogenetic testing, Weitzel et al. [30] note that lack of awareness regarding the evidence needed to establish analytical validity, clinical validity, and clinical utility of pharmacogenetic testing represents one of many barriers to implementation.

There are several limitations that prevent generalized conclusions related to the benefits of pharmacogenetic testing among patients with polypharmacy, some of which are acknowledged by the investigators included in this review. Risk of bias was an area of concern. Five of the six studies had a small sample size and lacked racial/ethnic diversity. Data collected from medical records may be subject to reporting bias. The articles also did not report testing for Hardy–Weinberg equilibrium, which can be used as a tool to detect genotyping errors [18]. None of the studies specifically described how confirmation of treatment adherence was obtained in the study protocols. And following the advice generated from a CDST is at the discretion of the healthcare providers. Finally, not all study participants were prescribed more than one drug, although the mean number of medications per patient within treatment cohorts was greater than one. Brixner et al. [23] and Elliott et al. [24] stated a specific interest in polypharmacy. Blasco-Fontecilla [22] did not state that polypharmacy was a requirement for patient recruitment, but noted that polypharmacy is common among patients with mental illness, and included reduction in the number of drugs used after

pharmacogenetic testing as an outcome measure. The remaining articles did not include polypharmacy as a criterion for patient inclusion. Researchers and clinicians interested in the adverse effects of multiple medications should continue to work toward agreement on what number of concomitant drug therapies constitutes polypharmacy. A systematic review by Masnoon et al. [4] reported 13 different definitions of polypharmacy. Most were numerical, some were numerical and accounted for the duration of therapy, and some were descriptive. Of those studies which used numerical definitions, the range was 2 to over 21. Since polypharmacy is common in the psychiatric patients and the elderly, polypharmacy is an important confounding variable in assessing the utility of pharmacogenetic testing in these populations.

Research focused on identifying gene–drug associations is further complicated by other significant phenomena. As described previously, patients with polypharmacy are susceptible to phenoconversion. There are over ninety drugs known to inhibit CYP enzyme activity [36]. Patients who are normal metabolizers may have a drug response expected for a PM when these drugs are included in a treatment regimen. This is known to contribute to phenoconversion [14, 15, 36]. For example, quinidine, a CYP2D6 inhibitor, can reduce the efficacy of treatment with codeine, tramadol, and oxycodone [36]. The percent contribution of individual CYP genes to drug metabolism can also influence pharmacogenetic associations. Several drugs are known substrates of more than one DME. Phenobarbital, for instance, is metabolized by CYP2C9 and CYP2C19 [36]. CDSTs use algorithms to account for drug–drug–gene interactions, but we are unaware of the extent to which other influences are factored in, such as herbal medicines and diet.

Studies have shown that metabolism and bioavailability of drugs may also be affected by age, gender, ethnicity, disease state, inflammation, and pregnancy [8, 43–47]. In a review on the relationship between age, pharmacokinetics, and pharmacodynamics, Mangoni and Jackson [43] note that reduced renal clearance, liver mass and blood flow, and first-pass metabolism are associated with advanced age. In a study looking at CYP3A4 polymorphisms, Guttman et al. [44] found striking differences in allele frequencies among ethnic groups. Differences for other DMEs between ethnic groups are also described by CPIC [9]. Furthermore, a systematic review on pharmacokinetic changes during pregnancy done by Pariente et al. [42] states that renal clearance is increased during pregnancy due to increased renal blood flow and glomerular filtration rate. Many of the studies they evaluated showed decreased drug exposure in pregnant women for several classes of drugs. They also cite studies reporting changes in hepatic enzyme activity during pregnancy. The multiplicity of known physiological and genetic influences on drug efficacy have led some to investigate DME phenotyping as another approach to improve drug prescribing and dosing [48–50]. Phenotyping involves the administration of probe drugs, which are known substrates of metabolizing enzymes and drug transporters, and the measurement of pharmacokinetic parameters in order to estimate enzyme activity, and by extension, an individual's likely response to a prescribed drug. For instance, losartan can be used as a probe drug for CYP2C9, and dextromethorphan is used as a probe drug for CYP2D6 [45]. Mariappan et al. [49] note that probe drugs are used in drug development to identify potential DDIs. This is an area of research we hope will gain more attention.

This review assessed the utility of pharmacogenetic testing in patients with polypharmacy. We conclude that the use of pharmacogenomics panels can improve health outcomes, especially among the elderly and patients diagnosed with psychiatric disorders. The reviewed studies illuminate the complexities of pharmacogenomics research, and support the significance of drug–gene associations in personalized medicine. Future studies should include RCTs focusing on the impact of pharmacogenetic testing on health outcomes among patients with polypharmacy, and address, to the greatest extent possible, the multiple sources of potential confounding inherent in research which aims to establish relationships between variants of pharmacokinetic genes and ADEs.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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