BMJ Open

A Scoping Review of Enablers and Challenges of Implementing Pharmacogenomics Testing in the Primary Care Settings

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-087064
Article Type:	Original research
Date Submitted by the Author:	30-Mar-2024
Complete List of Authors:	Mai, Chun-Wai; UCSI University, Faculty of Pharmaceutical Sciences Sridhar, Sathvik B; RAK Medical & Health Sciences University Karattuthodi, Mohammed Salim; Manipal College of Pharmaceutical Sciences Department of Pharmaceutical Biotechnology Ganesan, Perishithaa M; IMU University, Department of Pharmacy Practice shareef, javedh; RAK Medical & Health Sciences University Lee, E Lyn; IMU University Armani, Keivan; Imperial College London, Department of Primary Care and Public Health; UCSI University
Keywords:	Primary Health Care, Health Services, Health Workforce, Review, THERAPEUTICS

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

A Scoping Review of Enablers and Challenges of Implementing Pharmacogenomics Testing in the Primary Care Settings

Abstract

Introduction: Pharmacogenomic testing (PGx) plays a crucial role in improving patient medication safety, yet ethical concerns and limitations impede its clinical implementation in the primary care settings.

Aims: To systematically review the current state of PGx in the primary care settings and determine the enablers and challenges of its implementation.

Design: A scoping review was carried out by adhering to Arksey and O'Malley's 6-stage methodological framework and the 2020 Joanna Briggs Institute and Levac *et al*.

Data sources: Cochrane Library, EMBASE, Global Health, MEDLINE, and PubMed were searched up to 17th July 2023.

Eligibility criteria: All peer-reviewed studies in English, reporting the enablers and the challenges of implementing PGx in the primary care settings were included.

Date extraction and synthesis: Two independent reviewers extracted the data. Information was synthesised based on the reported enablers and the challenges of implementing PGx testing in the primary care settings. Information was then presented to stakeholders for their inputs.

Results: 78 studies discussing the implementation of PGx testing are included, in which 57% were published between 2019-2023. 68% of the studies discussed PGx testing in the primary care setting as disease-specific themes. Healthcare professionals were the major stakeholders, with primary care physicians (55%) being the most represented. Enablers encompassed various advantages such as diagnostic and therapeutic benefits, cost reduction, and the empowerment of healthcare professionals. Challenges included the absence of sufficient scientific evidence, insufficient training for healthcare professionals, ethical and legal aspects of PGx data, low patient awareness and acceptance, and the high costs linked to PGx testing.

Conclusion: Pharmacogenomic testing integration in primary care necessitates increased consumer awareness, comprehensive healthcare provider training on legal and ethical aspects, and global feasibility studies to better understand implementation challenges. Managing high costs entails streamlining processes, advocating for reimbursement policies, and investing in innovation and affordability research.

Background

Pharmacogenomics (PGx) broadly defines how genomic variation affects a patient's response to a drug [1]. Distinct polymorphisms in drug-metabolizing enzymes and drug transporters were a foundation for PGx[2]. The 2000 collaborative effort to draft the human genome marked a turning point, followed by the International Single Nucleotide Polymorphisms (SNP) Map Working Group's efforts to map variations in the human genome sequence [2,3]. PGx is recognised as a key component in the field of personalised medicine. The application of mutation-specific therapies, personalising early detection of disease strategies, personalised disease prevention, and personalised medicines have been increasingly utilised [4]. This approach tailors medical treatment to an individual's unique genomic makeup to improve treatment outcomes and minimise adverse effects [5].

Individual genetic variations play a significant role in influencing the effectiveness and safety of medications. Genetic differences in drug-metabolising enzymes, transporters, receptors, and other therapeutic targets have been related to interindividual variances in the efficacy and safety of several frequently prescribed medications (20-30% of medication response variability) [6]. Inter-individual genetic differences within and between ethnic groups contribute significantly to medication response variability and are linked to variants affecting the pharmacokinetics (PK) and pharmacodynamics (PD) of drugs [7,8]. The British Pharmacological Society and the Royal College of Physicians have urged patients to be examined for genetic variations that can impact respond to commonly utilised drugs [9]. The U.S. Food and Drug Administration (FDA) recommends genetic screening before using certain medications [10].

Developing countries are the strongest users of PGx-guided therapy [11–14]. However, the utilisation of PGx across Europe varies [15–17]. The public seemed to prefer and opt for PGx testing, especially those with chronic diseases [18]. Gene-drug interaction variability within the European population has been established and has thus increased the scope for PGx [19].

The adoption of PGx testing services in different healthcare settings has varied owing to a multitude of factors, including rational medicine utilisation, ethical considerations, legal implications, healthcare provider and patient education, support for electronic health records, clinical utility and validity of test outcomes, accessibility, regulatory frameworks, as well as availability and affordability. [14,20–23]. The cost implications of PGx testing would depend on the insurance coverage companies offer. Not all insurance firms offer coverage for PGx testing, and those offering are subjected to their policies and test reasons [24]. This can affect the preference for pre-emptive PGx and active PGx testing [25]. Pre-emptive PGx, a cost-effective method, is performed before the drug administration and greatly impacts the patient's clinical outcome [26].

The US FDA has emphasised the importance of PGx testing for drug discovery, development, and treatment of patients. Five hundred different biomarkers concerning drugs have been stated in their public domain [27]. Similarly, the European Medicines Agency has guidelines regarding the use of PGx testing during drug approval processes [28]. Despite the regulatory authorities' new recommendation to incorporate PGx testing in the drug approval process, testing regarding marketed products is also not a routine practice. Moreover, patients were also disrupted from subscribing to the PGx testing due to the availability of resources and many hindrances factors that may vary across the nation [29].

While PGx testing offers several benefits, it is important to acknowledge the presence of ethical concerns surrounding it, especially in a primary care setting. References in the literature provide evidence for pharmacogenomics testing in primary care. Through prospective trials, it has been demonstrated that when paired with comprehensive medication management services and point-of-care clinical decision support systems, improvised drug prescribing lessened the burden of mental illness, thereby enhancing clinical outcomes [30]. Barriers such as a perceived lack of knowledge on acceptance, scalability, and implementation and insufficient evidence of therapeutic outcomes improvement have been reported [31]. Financial constraints and the knowledge and abilities of healthcare professionals hinder implementation [32]. Ethical challenges emerge due to considerations regarding the role of informed consent in genomic testing, encompassing several elements such as potential dangers, benefits, and consequences associated with genomic information [33,34]. In addition, genomic information may give rise to questions on ownership, access rights, affordability, fiduciary responsibility, respect, and the possibility of discrimination [33–35].

Moreover, the interpretation of genomic information is still evolving, and errors or misunderstandings in the analysis could lead to incorrect treatment choices, further complicating the ethical landscape [36]. While PGx testing offers positive benefits, it is important to acknowledge the presence of ethical concerns related to this practice, especially in a primary care setting. Thus, this scoping review was conducted to systematically review the current state of PGx in the primary care setting and determine the enablers and challenges of implementing PGx testing in primary care settings.

Methods

A scoping review was carried out by adhering to Arksey and O'Malley's 6-stage methodological framework and the 2020 Joanna Briggs Institute (JBI) [37,38]. Covidence™, a web-based collaboration software platform designed to facilitate carrying out reviews such as systematic reviews and scoping reviews, was utilised for the review [39]. Further, Levac and colleagues' recommendations were applied

to maximise the methodological rigor and, thus, reported the details of the six stages under the following subheading [40]. The Preferred Reporting Items for Systematic Review and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) checklist was used to guide the reporting of this review [41].

Identifying the review question

CWM, an expert in the field of PGx, and KA, a primary care research expert had the initial discussion about the potential review questions that could address some of the gaps in the current literature on PGx testing and its applications in primary care settings. SBS, JS, MSKT, and ELE are academics who joined the subsequent discussions, clarified the aims and objectives of the scoping review, and collectively agreed on the following review question: "What are the enablers and the challenges of implementing PGx testing in primary care settings?"

Identifying the relevant studies

The authors agreed on the search strategy with no limits on publication dates. The search was concluded on 17th July 2023. We consolidated the search resources following advice from a subject librarian to ensure a wide range of relevant databases such as Cochrane Library, EMBASE, Global Health, MEDLINE, and PubMed. The International Prospective Registry of Systematic Reviews (PROSPERO) was also reviewed for any similar studies, both ongoing or completed, to avoid any potential duplication. Articles in English were only considered due to a lack of resources for translating studies. The inclusion and exclusion criteria were finalised through an iterative process to allow necessary refinements following initial searches (see Table 1).

Table 1 Inclusion and Exclusion Criteria

Criterion	Inclusion	Exclusion
Period	Any	-
Literature	Peer-reviewed articles	Review articles of any type, non-peer-reviewed academic articles
Geographical location	Any	-
Setting	Primary care settings	Secondary and tertiary care settings
Study Focus	Information on the pharmacogenomics testing implementation in primary care settings	No information is directly related to the implementation of pharmacogenomics testing in primary care settings.

Study Design	All types of qualitative and quantitative studies, clinical audits	All types of reviews, including systematic reviews, meta-analysis
Language	English	Other languages than English

Selecting the studies

A total of 1251 articles were initially identified across five databases, i.e., PubMed (n = 690), MEDLINE (n = 288), Embase (n = 239), Cochrane Library (n = 26), and Global Health (n=8). Articles were exported into Covidence™. Covidence™ removed 290 duplicate articles, while one duplicate article was removed manually, leaving 960 articles for title and abstract screening. A total of 378 articles met the inclusion and exclusion criteria for full-text screening. Two reviewers independently screened each article, and a third reviewer resolved any discrepancies. The full-text screening eliminated 290 articles because of wrong context/setting (n = 148), no full-text availability, e.g., for poster/conference papers (n = 59), wrong study design or application or outcomes (n = 51) and non-peer reviewed commentary (n = 32) and thus, 78 studies were included in the final review upon which results are reported (Figure 1).

Charting the data

Data charting facilitates the transfer of the relevant information from the selected articles into a data extraction table (5). The authors created a data extraction template using the Covidence™ extraction template. The data extraction template was contextualized to meet the study objectives and the research questions proposed at the beginning of the review, which contained standard information such as title, lead author, type of study, aims, objectives, key stakeholders, findings in relation to the enablers and the challenges of implementing PGx in the primary care settings and recommendations. All authors were involved in charting the data, and PMG carried out most data extraction. Although data extraction needed one reviewer per article, KA checked each article's extraction data for final approval.

Collating, summarising, and reporting the results

KA and PMG synthesized the results by collating and summarising the findings following data charting. Results were then presented to the rest of the authors for their comments and interpretations. The authors were registered pharmacists who had the experience of practicing in primary care settings. They discussed the results from the practice and policy's point of view. The authors did not carry out a quality assessment exercise as scoping reviews do not normally need an appraisal for quality and bias due to their descriptive nature (6).

Consulting stakeholders

Although stakeholders' involvement and consultation are not mandatory stages for conducting scoping reviews, we involved the stakeholders in two stages. First, we conducted a brainstorming session with a subgroup of stakeholders, which were primary care physicians and community pharmacists. The ten stakeholders were from independent or chain medical clinics (n = 5) or community pharmacies (n = 5). Second, we presented the findings to them for their comments and feedback.

Patient and public involvement

There were no patient or public involvement in addition to the above-mentioned stakeholders.

Results

We present the findings from 78 studies on different aspects of PGx testing implementation in primary care settings, such as stakeholders' views and involvement, enablers, and challenges of implementing PGx testing (Table 2). The PGx testing in the primary care setting in these studies was discussed either as disease-specific themes (n = 53), such as mental health conditions, cardiovascular conditions, diabetes, etc., or population-specific themes (n= 11), such as general patient population, paediatric and geriatric patient population, or public health themes (n=3) and others not specified (n=11).

Insert Figure 1 here.

Publication date

The earliest publication was in the Year 2007, and the latest publication was in 2023 when data collection ended. More than half of the studies (57%) were published in the period between 2019 to date. Nearly one-third (n=22) of studies were published between the years 2016 and 2018. The number of publications has increased significantly in the last six years, i.e., between 2018 and 2023.

Types of studies, location

A wide array of study designs was pulled together in this review, ranging from commentaries (n =2) to qualitative studies (n = 7) to quantitative studies (n=16), including randomised controlled trials (n=5) to mixed methods studies (n =54). An overwhelming majority of the studies were from the global north (n = 77), e.g., 51 studies from the US and its territory, 12 studies from Canada, 14 studies from the EU, while there was only one study from Singapore. (Figure 2)

Stakeholders

The stakeholders were the service users/patients, members of the public, healthcare professionals including general practitioners, physicians, pharmacists, nurses, physician assistants, public health consultants/professionals, geneticists, phlebotomists, genetic counsellors, mental health providers, obstetricians, gynaecologist, psychiatrists, cardiologist. Most of the healthcare professionals were primary care physicians (n = 43), followed by pharmacists (n=32), allied healthcare professionals (n=27), and primary care providers who were not specified (n=15). Moreover, upon the presentation of the findings to a panel of stakeholders (n = 10) that we had consulted individually at the beginning of the study, there was an overall agreement with the findings.

Current status of pharmacogenomics testing in the primary care settings

More than half (52%) of the studies had favourable views toward the status of PGx testing in primary care settings, whereas 43% of the studies had unfavourable views, and 5% of the studies offered neither favourable nor unfavourable views. Most of the favourable views stemmed from the perceived benefits of PGx testing to the patient's clinical outcomes, selection of the most precise treatment modality, decrease in the incidences of adverse drug reactions due to polypharmacy, and improved medication adherence.[42,43] Other favourable opinions were the health systems level benefits of PGx testing, such as lowering the healthcare costs and broader applicability of PGx in the areas of preventive care, population health, and community health interventions [44].

The main reasons for unfavourable opinions were the perceived lack of information or findings on the acceptability, scalability, and implementation aspects of pharmacogenomics testing in primary care settings. Furthermore, the perceived limited evidence of the effectiveness of PGx testing on impacting clinical outcomes, limited knowledge and skills of the healthcare professionals to operationalize PGx testing in the routine delivery of care as well and financial concerns, data security were some of the unfavourable concerns to implementing PGx testing in the primary care settings [45,46].

Enablers of PGx testing implementation in the primary care setting

The benefits of using PGx testing in primary care settings were discussed in almost all studies (n=77). PGx testing implementation was facilitated by three main factors, broadly: a) diagnostic and therapeutic benefits in collaborative practice; b) reduction in healthcare costs; and c) empowering healthcare professionals to deliver their clinical services, especially for the physicians and community pharmacists. A total of 23 studies reported other possible enablers, including programmes that support clinical decision-making, precision medicine, personalised medicine, individualized care, drug-drug interactions, patient safety, and optimal medication use.

Diagnostic and therapeutic benefits in collaborative practice:

Around 10% (n =12) of the studies reported the findings that pharmacogenomics supports collaborative clinical practice by allowing a precise choice of therapeutic agents in treating patients. For example, findings from a primary care precision medicine clinic offering PGx services at the University of Pittsburgh Medical Center Health System showed that genotype-guided clinical decisions successfully supported the primary care providers' adoption of genetic information to guide statin therapy in routine clinical practice [47]. A UK study described the benefits of PGx testing to support personalised medicine and the management of calcium channel blocker side effects through genomic-guided information on pharmacogenetic variations [48].

Reduction in healthcare costs:

The possible cost-saving features of PGx testing implementation were mentioned in 20 % of the studies (n = 15). According to a prospective and randomised study, using PGx testing to guide drug selection and dosage decisions may help reduce medical bills associated with adverse drug events in patients with psychiatric disorders [49]. PGx, when combined with the use of a pharmacogenetics-based medical decision support system to direct subsequent drug dosing, has been shown to positively influence healthcare quality and cost-effectiveness, according to a prospective cohort study conducted in Singapore [50].

Empowering healthcare professionals to deliver their clinical services

28% of the studies (n = 6) viewed the use of PGx testing in primary care settings as a potential means of enabling medical professionals, including community pharmacists, to assist in giving patients the best possible care. An open-label, non-randomised observational study brought to light the benefits of community pharmacists implementing PGx screening in their practices [51]. The effectiveness of PGx testing performed by community pharmacists is improved by integration within a clinical decision support system [52]. Due to the ease of accessing genomic services in the primacy care settings, physicians' preference for pharmacogenomics and cancer risk assessment has increased recently [53].

Challenges of pharmacogenomics testing implementation in the primary care setting

The challenges of implementing PGx testing in primary care settings were discussed in all studies (n=78). There were four main areas of challenge: a) dearth of data on the scientific evidence such as clinical-genomic databases; b) lack of bespoke PGx training modules/courses for the healthcare

professionals to apply the PGx testing principles; c) dearth of data on patient awareness and acceptability of the use of PGx testing in patient care; and d) high costs associated with PGx testing.

The dearth of data on scientific evidence, such as clinical-genomic databases:

Forty-five percent of the studies (n = 35) reported the lack of solid scientific evidence to produce reliable clinical-genomic databases and clinical practice guidelines (n = 35), followed by perceived publication bias (n = 23) in the studies in the field of PGx. For example, a 2017 study highlighted that a constraint of the study was the limited sample size, which might have introduced bias as the findings might not accurately reflect the viewpoints of all primary care physicians or those within the chosen primary practice sites [54]. Recruitment bias, too, could limit the generalisability of the findings, which was mentioned in almost a quarter (n = 18) of the studies.

Lack of bespoke PGx training modules/courses for the healthcare professionals:

Another main challenge was the lack of suitable training for the healthcare professionals in the primary care settings to offer PGx testing (n = 17). PGx testing was viewed as a technically advanced field that needed bespoke training courses to ensure the healthcare professionals were able to fully utilise the benefits of this technology during their day-to-day clinical duties. However, there are currently not many training packages available [5,55].

The dearth of data on patient awareness and acceptability of the use of PGx testing

Around 10% of the studies reported the dearth of data on patient awareness and patient acceptability of the PGx testing as a barrier to the implementation of pharmacogenomics testing in primary care settings. For instance, a 2017 study showed the importance of patients' willingness to consent to be involved in clinical-genomic treatment modalities, which would need patients to be fully aware of the technical aspects of PGx testing, including ethical aspects [56]. A qualitative study revealed that patient anxiety and fear of disclosing genetic information to a third party was the main barrier to the implementation of PGx testing in primary care settings [55].

High costs associated with PGx testing:

Almost 20% (n = 14) of the studies mentioned high costs associated with pharmacogenomics testing in primary care settings. Insurance coverage, out-of-pocket expenditure, and institutional return of investment – investment in setting up PGx testing – were among the points raised in regards to the costs and who should bear the cost based on the healthcare systems in the global north, Western Europe, and Australasia [5,57,58].

Insert Figure 2 here.

Discussion

Primary care physicians play a key role in incorporating PGx into standard clinical practice. Primary healthcare professionals need to educate patients on the importance of genetic data and how it affects individualised treatment plans. Collaboration with genetic counsellors and other medical professionals can also help maximise the use of PGx in patient care. Genetic counselors assist individuals and healthcare providers in better understanding intricate genetic details (63).

Collaboration among academia, healthcare, industry, and regulatory agencies is essential for integrating PGx into clinical practice [59,60]. PGx has been effectively integrated into healthcare systems in both the US and the UK. There is significant variation in the implementation of PGx across Europe [15] and Gulf Cooperation Council (GCC) countries like Saudi Arabia, UAE, and Qatar [11,12].PGx has made significant progress in the UK, with the NHS supporting genetic screening to enhance medication therapy [16]. Similarly, it is also utilised in Australia and Canada to enhance the optimal clinical decision [61,62]. On the other hand, there is a rise in the PGx utility in Singapore, Japan, South Korea, and China, particularly for chronic diseases [13,50,63]. Some regions still face complex regulatory structures and ethical issues, and this is a big challenge [64]. Regulatory agencies' well-defined guidelines give healthcare providers confidence and create an environment in which PGx practices are not only acceptable but actively promoted [65]. The regulatory environment is greatly influenced by policymakers, who make sure that it permits a smooth integration of PGx into standard primary care practice and keeps pace with the field's rapid evolution.

Several studies emphasise the importance of PGx testing in cardiovascular diseases and neuropsychiatry disorders [17,49,66–68] due to its ability to choose more precise treatment modalities, a reduction in adverse drug reactions caused by polypharmacy, and a significantly improved medication adherence [67,69,70]. However, the dearth of data on scientific evidence, particularly in areas such as clinical genomic databases, poses a significant challenge for pharmacogenomic testing. One of the obstacles is the limited availability of high-quality genomic data linked to clinical outcomes [71]. Clinical genomic databases that integrate genetic information with patient health records are crucial for understanding how genetic variations influence drug response and adverse reactions. Moreover, the heterogeneity of genetic backgrounds among populations further complicates the issue [72].

Additionally, there are challenges related to data privacy, consent, and ethical considerations when it comes to sharing genomic and clinical information [73]. Striking the right balance between data accessibility and protection of patient privacy is essential but complex. Investments in data infrastructure, standardisation of data formats and protocols, and initiatives to promote data sharing and collaboration are critical.

Another challenge is the rapid pace of advancements in PGx, which can make it difficult for healthcare professionals to stay updated with the latest developments [74]. Without clear guidelines or accreditation standards, healthcare professionals may struggle to identify reputable training opportunities or gauge the quality of the education they receive. Addressing these challenges requires concerted efforts from various stakeholders. Healthcare institutions and professional regulatory bodies can play a crucial role in advocating for the integration of PGx education into medical school curricula, residency training programs, and continuing education courses [12].

Additionally, there may be barriers to patient acceptability related to trust and confidence in the healthcare system and genetic testing technologies. Patients may have concerns about the privacy and security of their genetic information, as well as apprehensions about potential discrimination or stigmatisation based on genetic predispositions to certain health conditions. Building trust and addressing these concerns is essential for promoting patient acceptability of PGx testing. Tailoring educational materials and communication strategies to meet the needs of diverse patient populations is crucial for promoting awareness and acceptability of PGx testing.

PGx testing's extensive utilisation can reduce healthcare costs and enhance preventive care, population health, and community initiatives [75,76]. Moreover, PGx testing costs have decreased over time, but access for patients may still be restricted by financial issues, especially in primary care settings where resources may be scarce.

Strength & Limitations

The main strengths of this review were the consultation sessions with the stakeholders at two stages. At the onset of the study, we involved the stakeholders in co-developing the research questions, ensuring their relevance and the need for this review. In the second stage, we presented them with the preliminary findings for their input. This extra layer of peer reviewing helped us to sense-check the findings and consolidate the discussion points pertinent to the findings.

We did not search for grey literature as the main aim of this review was to analyse peer-reviewed literature. However, we would suggest the inclusion of grey literature in future reviews to gain a deeper, more detailed understanding of the field. The other plausible limitation was the lack of critical appraisal of the included studies for their quality in this review. Although critical appraisal is not needed for scoping reviews, such quality control techniques would add value.

Conclusion

Successful integration of pharmacogenomic testing into primary care demands a multi-faceted approach. This entails enhancing consumer awareness, providing comprehensive training for healthcare providers, and furthering scientific research to elucidate both the clinical benefits and cost-effectiveness of such testing. Additionally, it is imperative to conduct feasibility studies encompassing various countries and healthcare systems to fully understand the potential enablers and challenges of implementing pharmacogenomic testing in primary care. Currently, the available data predominantly stems from the global north, leading to a gap in knowledge regarding its applicability in diverse cultural and resource-constrained settings.

Addressing the high costs associated with PGx testing requires a multi-faceted approach. Efforts are needed to streamline testing processes, improve efficiency, and reduce the overall cost of testing. This may involve the development of standardised testing protocols, the use of automation and high-throughput technologies, and the optimisation of bioinformatics pipelines.

Contributors

CWM and KA contributed to the conception and design of the review. All authors contributed to the screening, data extraction. CWM analysed the data and led on stakeholders' consultation sessions. KA drafted the methodology and the results sections. All authors contributed to the subsequent drafts, revisions; and gave approval to the final version of the for publication.

Funding

The UCSI University Research Excellence & Innovation Grant (REIG-FPS-2023/038) and the Fundamental Research Grant Scheme (FRGS/1/2023/SKK10/UCSI/02/1) from the Malaysia's Ministry of Health."

KA is in part supported by the National Institute for Health and Care Research (NIHR) Applied Research Collaboration (ARC) Northwest London. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

"Funding to pay the Open Access publication charges for this article was provided by the Imperial Open Access Fund".

Competing interests

None declared.

Provenance and peer review

None commissioned, externally peer reviewed.

Data sharing statement

Data obtained from 78 included studies are listed in Table 2.

ORCID iD

Keivan Armani: https://orcid.org/0000-0001-5674-2765

References

1. Pirmohamed M. Pharmacogenetics and pharmacogenomics. *Br J Clin Pharmacol*. 2001;52(4):345-347. doi:10.1046/j.0306-5251.2001.01498.x

2. Nebert DW. Pharmacogenetics and pharmacogenomics: why is this relevant to the clinical geneticist? *Clin Genet*. 1999;56(4):247-258. doi:10.1034/j.1399-0004.1999.560401.x

3. Sachidanandam R, Weissman D, Schmidt SC, et al. A map of human genome sequence variation containing 1.42 million single nucleotide polymorphisms. *Nature*. 2001;409(6822):928-933. doi:10.1038/35057149

4. Goetz LH, Schork NJ. Personalised medicine: motivation, challenges, and progress. *Fertil Steril*. 2018;109(6):952-963. doi:10.1016/j.fertnstert.2018.05.006

5. Brown-Johnson CG, Safaeinili N, Baratta J, et al. Implementation outcomes of Humanwide: integrated precision health in team-based family practice primary care. *BMC Fam Pract*. 2021;22(1):28. doi:10.1186/s12875-021-01373-4

6. Heller F. Genetics/genomics and drug effects. *Acta Clin Belg*. 2013;68(2):77-80. doi:10.2143/ACB.3210

7. McGraw J, Waller D. Cytochrome P450 variations in different ethnic populations. *Expert Opin Drug Metab Toxicol*. 2012;8(3):371-382. doi:10.1517/17425255.2012.657626

8. Pirmohamed M. Personalised pharmacogenomics: predicting efficacy and adverse drug reactions. *Annu Rev Genomics Hum Genet*. 2014;15:349-370. doi:10.1146/annurev-genom-090413-025419

9. Mahase E. Offer patients genetic tests to see if medicines are safe and effective, says Royal College of Physicians. *BMJ*. 2022;376:o821. doi:10.1136/bmj.o821

10. Chang CJ, Chen CB, Hung SI, Ji C, Chung WH. Pharmacogenetic Testing for Prevention of Severe Cutaneous Adverse Drug Reactions. *Front Pharmacol*. 2020;11:969. doi:10.3389/fphar.2020.00969

11. Algahtani M. Knowledge, Perception, and Application of Pharmacogenomics Among Hospital Pharmacists in Saudi Arabia. *Risk Manag Healthc Policy*. 2020;13:1279-1291. doi:10.2147/RMHP.S267492

12. Rahma AT, Elbarazi I, Ali BR, Patrinos GP, Ahmed LA, Al Maskari F. Genomics and Pharmacogenomics Knowledge, Attitude and Practice of Pharmacists Working in United Arab Emirates: Findings from Focus Group Discussions—A Qualitative Study. *J Pers Med*. 2020;10(3):134. doi:10.3390/jpm10030134

13. Zhang J, Qi G, Han C, et al. The Landscape of Clinical Implementation of Pharmacogenetic Testing in Central China: A Single-Center Study. *Pharmacogenomics Pers Med*. 2021;14:1619-1628. doi:10.2147/PGPM.S338198

14. Ayati N, Afzali M, Hasanzad M, Kebriaeezadeh A, Rajabzadeh A, Nikfar S. Pharmacogenomics Implementation and Hurdles to Overcome; In the Context of a Developing Country. *Iran J Pharm Res IJPR*. 2021;20(4):92. doi:10.22037/ijpr.2021.114899.15091

15. Bank PCD, Swen JJ, Schaap RD, Klootwijk DB, Baak-Pablo R, Guchelaar HJ. A pilot study of the implementation of pharmacogenomic pharmacist initiated pre-emptive testing in primary care. *Eur J Hum Genet EJHG*. 2019;27(10):1532-1541. doi:10.1038/s41431-019-0454-x

16. Turner RM, Newman WG, Bramon E, et al. Pharmacogenomics in the UK National Health Service: opportunities and challenges. *Pharmacogenomics*. 2020;21(17):1237-1246. doi:10.2217/pgs-2020-0091

17. Bose-Brill S, Xing J, Barnette DJ, Hanks C. Pharmacogenomic testing: aiding in the management of psychotropic therapy for adolescents with autism spectrum disorders. *Pharmacogenomics Pers Med*. 2017;10(101514107):247-252. doi:10.2147/PGPM.S130247

18. O'Shea J, Ryan C, Gallagher J, et al. Public perceptions of pharmacogenomic services in Ireland - Are people with chronic disease more likely to want service availability than those without? A questionnaire study. *Explor Res Clin Soc Pharm*. 2022;8(9918266300706676):100182. doi:10.1016/j.rcsop.2022.100182

19. Mizzi C, Dalabira E, Kumuthini J, et al. A European Spectrum of Pharmacogenomic Biomarkers: Implications for Clinical Pharmacogenomics. *PloS One*. 2016;11(9):e0162866. doi:10.1371/journal.pone.0162866

20. Stanek EJ, Sanders CL, Taber KAJ, et al. Adoption of pharmacogenomic testing by US physicians: results of a nationwide survey. *Clin Pharmacol Ther*. 2012;91(3):450-458. doi:10.1038/clpt.2011.306

21. Liko I, Lee YM, Stutzman DL, et al. Providers' perspectives on the clinical utility of pharmacogenomic testing in pediatric patients. *Pharmacogenomics*. 22(5):263-274. doi:10.2217/pgs-2020-0112

22. Saunders H, Harris D, Chirilă RM. Pharmacogenomics: introduction and use in clinical practice. *Romanian J Intern Med Rev Roum Med Interne*. 2020;1;58(2):69–74.

23. Kabbani D, Akika R, Wahid A, Daly AK, Cascorbi I, Zgheib NK. Pharmacogenomics in practice: a review and implementation guide. *Front Pharmacol*. 2023;14(1189976).

24. Pharmacogenomic cost, Mankato. Mayo Clinic Health System. Accessed March 6, 2024. https://www.mayoclinichealthsystem.org/locations/mankato/services-and-treatments/pharmacogenomics/cost-and-insurance

25. Zhu Y, Moriarty JP, Swanson KM, et al. A model-based cost-effectiveness analysis of pharmacogenomic panel testing in cardiovascular disease management: preemptive, reactive, or none? *Genet Med Off J Am Coll Med Genet*. 2021;23(3):461-470. doi:10.1038/s41436-020-00995-w

26. Roden DM, Van Driest SL, Mosley JD, et al. Benefit of pre-emptive pharmacogenetic information on clinical outcome. *Clin Pharmacol Ther*. 2018;103(5):787-794. doi:10.1002/cpt.1035

27. Research C for DE and. Table of Pharmacogenomic Biomarkers in Drug Labeling. *FDA*. Published online February 2, 2024. Accessed March 6, 2024. https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling

28. Use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products - Scientific guideline | European Medicines Agency. Accessed March 6, 2024.

https://www.ema.europa.eu/en/use-pharmacogenetic-methodologies-pharmacokinetic-evaluation-medicinal-products-scientific-guideline

29. Young J, Bhattacharya K, Ramachandran S, Lee A, Bentley JP. Rates of genetic testing in patients prescribed drugs with pharmacogenomic information in FDA-approved labeling. *Pharmacogenomics J*. 2021;21(3):318-325. doi:10.1038/s41397-021-00211-1

30. O'Donnell PH, Wadhwa N, Danahey K, et al. Pharmacogenomics-Based Point-of-Care Clinical Decision Support Significantly Alters Drug Prescribing. *Clin Pharmacol Ther*. 2017;102(5):859-869. doi:10.1002/cpt.709

31. Kehr AM, Ayers G, Saxena S, et al. Integration of a pharmacist-led pharmacogenomic service in a geriatric clinic: Barriers and outcomes. *J Am Pharm Assoc*. 2023;63(3):778-784. doi:10.1016/j.japh.2023.01.001

32. Rafi I, Crinson I, Dawes M, Rafi D, Pirmohamed M, Walter FM. The implementation of pharmacogenomics into UK general practice: a qualitative study exploring barriers, challenges and opportunities. *J Community Genet*. 2020;11(3):269-277. doi:10.1007/s12687-020-00468-2

33. Gershon ES, Alliey-Rodriguez N, Grennan K. Ethical and public policy challenges for pharmacogenomics. *Dialogues Clin Neurosci*. 2014;16(4):567-574.

34. Peterson-Iyer K. Pharmacogenomics, ethics, and public policy. *Kennedy Inst Ethics J*. 2008;18(1):35-56. doi:10.1353/ken.0.0004

35. Stratton TP, Olson AW. Personalizing Personalised Medicine: The Confluence of Pharmacogenomics, a Person's Medication Experience and Ethics. *Pharmacy*. 2023;11(3):101. doi:10.3390/pharmacy11030101

36. Donohue KE, Gooch C, Katz A, Wakelee J, Slavotinek A, Korf BR. Pitfalls and challenges in genetic test interpretation: An exploration of genetic professionals experience with interpretation of results. *Clin Genet*. 2021;99(5):638-649. doi:10.1111/cge.13917

37. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. *Int J Soc Res Methodol*. 2005;8(1):19-32. doi:10.1080/1364557032000119616

38. Peters MDJ, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. *Int J Evid Based Healthc*. 2015;13(3):141-146. doi:10.1097/XEB.0000000000000050

39. Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org.

40. Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. *Implement Sci*. 2010;5(1):69. doi:10.1186/1748-5908-5-69

41. Tricco AC, Lillie E, Zarin W, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Ann Intern Med*. 2018;169(7):467-473. doi:10.7326/M18-0850

42. van der Wouden CH, Paasman E, Teichert M, Crone MR, Guchelaar HJ, Swen JJ. Assessing the Implementation of Pharmacogenomic Panel-Testing in Primary Care in the Netherlands Utilizing a Theoretical Framework. *J Clin Med*. 2020;9(3). doi:10.3390/jcm9030814

43. Gammal RS, Berenbrok LA, Empey PE, Massart MB. Documenting Pharmacogenomic Test Results in Electronic Health Records: Practical Considerations for Primary Care Teams. *J Pers Med*. 2021;11(12). doi:10.3390/jpm11121296

44. Brunette CA, Miller SJ, Majahalme N, et al. Pragmatic Trials in Genomic Medicine: The Integrating Pharmacogenetics In Clinical Care (I-PICC) Study. *Clin Transl Sci*. 2020;13(2):381-390. doi:10.1111/cts.12723

45. Virelli CR, Ebrahimi M, Mohiuddin AG, et al. User Experiences of Pharmacogenomic Testing and Opinions among Psychiatry Patients. *J Pers Med*. 2024;14(1). doi:10.3390/jpm14010022

46. Melendez K, Gutierrez-Meza D, Gavin KL, et al. Patient Perspectives of Barriers and Facilitators for the Uptake of Pharmacogenomic Testing in Veterans Affairs' Pharmacogenomic Testing for the Veterans (PHASER) Program. *J Pers Med*. 2023;13(9). doi:10.3390/jpm13091367

47. Obeng AO, Scott SA, Kaszemacher T, et al. Prescriber Adoption of SLCO1B1 Genotype-Guided Simvastatin Clinical Decision Support in a Clinical Pharmacogenetics Program. *Clin Pharmacol Ther*. 2023;113(2):321-327. doi:10.1002/cpt.2773

48. Turkmen D, Masoli JAH, Delgado J, et al. Calcium-channel blockers: Clinical outcome associations with reported pharmacogenetics variants in 32 000 patients. *Br J Clin Pharmacol*. 2023;89(2):853-864. doi:10.1111/bcp.15541

49. Jablonski MR, Lorenz R, Li J, Dechairo BM. Economic Outcomes Following Combinatorial Pharmacogenomic Testing for Elderly Psychiatric Patients. *J Geriatr Psychiatry Neurol*. 2020;33(6):324-332. doi:10.1177/0891988719892341

50. Smith H, Dawes M, Katzov-Eckert H, Burrell S, Xin Hui S, Winther MD. Improving prescribing: a feasibility study of pharmacogenetic testing with clinical decision support in primary healthcare in Singapore. *Fam Pr*. Published online 2022. doi:10.1093/fampra/cmac124

51. Papastergiou J, Tolios P, Li W, Li J. The Innovative Canadian Pharmacogenomic Screening Initiative in Community Pharmacy (ICANPIC) study. *J Am Pharm Assoc JAPhA*. 2017;57(5):624-629. doi:10.1016/j.japh.2017.05.006

52. Carroll J.C., Allanson J., Morrison S., et al. Informing Integration of Genomic Medicine Into Primary Care: An Assessment of Current Practice, Attitudes, and Desired Resources. *Front Genet*. 2019;10((Carroll) Sinai Health System, Department of Family and Community Medicine, University of Toronto, Toronto, ON, Canada(Allanson, Morrison) Department of Genetics, Children's Hospital of Eastern Ontario, Ottawa, ON, Canada(Miller) Institute of Health Polic):1189. doi:10.3389/fgene.2019.01189

53. Massart M, Berenbrok LA, Munro C, Berman NR, Empey PE. A Multidisciplinary Precision Medicine Service in Primary Care. *Ann Fam Med*. 2022;20(1):88. doi:10.1370/afm.2764

54. Sharma M, Lee C, Kantorovich S, Tedtaotao M, Smith GA, Brenton A. Validation Study of a Predictive Algorithm to Evaluate Opioid Use Disorder in a Primary Care Setting. *Health Serv Res Manag Epidemiol*. 2017;4:2333392817717411. doi:10.1177/2333392817717411

55. Frigon MP, Blackburn ME, Dubois-Bouchard C, Gagnon AL, Tardif S, Tremblay K. Pharmacogenetic testing in primary care practice: opinions of physicians, pharmacists and patients. *Pharmacogenomics*. 2019;20(8):589-598. doi:10.2217/pgs-2019-0004

56. Schwartz EJ, Turgeon J, Patel J, et al. Implementation of a Standardized Medication Therapy Management Plus Approach within Primary Care. *J Am Board Fam Med JABFM*. 2017;30(6):701-714. doi:10.3122/jabfm.2017.06.170145

57. Natasha Petry, Baye J, Aifaoui A, et al. Implementation of wide-scale pharmacogenetic testing in primary care. *Pharmacogenomics*. 2019;20(12):903-913. doi:10.2217/pgs-2019-0043

58. Haga S.B. Delivering pharmacogenetic testing to the masses: An achievable goal? *Pharmacogenomics*. 2014;15(1):1-4. doi:10.2217/pgs.13.211

59. Bienfait K, Chhibber A, Marshall JC, et al. Current challenges and opportunities for pharmacogenomics: perspective of the Industry Pharmacogenomics Working Group (I-PWG). *Hum Genet*. 2022;141(6):1165-1173. doi:10.1007/s00439-021-02282-3

60. Caraballo PJ, Hodge LS, Bielinski SJ, et al. Multidisciplinary model to implement pharmacogenomics at the point of care. *Genet Med*. 2017;19(4):421-429. doi:10.1038/gim.2016.120

61. Tiwari AK, Zai CC, Altar CA, et al. Clinical utility of combinatorial pharmacogenomic testing in depression: A Canadian patient- and rater-blinded, randomized, controlled trial. *Transl Psychiatry*. 2022;12(1):101. doi:10.1038/s41398-022-01847-8

62. Bose-Brill S, Xing J, Barnette DJ, Hanks C. Pharmacogenomic testing: aiding in the management of psychotropic therapy for adolescents with autism spectrum disorders. *Pharmacogenomics Med*. 2017;10(101514107):247-252.

63. Lee M, Gwak HS, Choi KH. Comparison of pharmacogenomic information for drug approvals provided by the national regulatory agencies in Korea, Europe, Japan, and the United States. *Front Pharmacol*. 2023;14. doi:10.3389/fphar.2023.1205624

64. Ishiguro A, Toyoshima S, Uyama Y. Current Japanese regulatory situations of pharmacogenomics in drug administration. *Expert Rev Clin Pharmacol*. Published online July 1, 2008. Accessed March 8, 2024. https://www.tandfonline.com/doi/full/10.1586/17512433.1.4.505

65. Mwale S, Farsides B. Imagining genomic medicine futures in primary care: General practitioners' views on mainstreaming genomics in the National Health Service. *Sociol Health Illn*. 2021;43(9):2121-2140. doi:10.1111/1467-9566.13384

66. Dong OM, Wheeler SB, Cruden G, et al. Cost-Effectiveness of Multigene Pharmacogenetic Testing in Patients With Acute Coronary Syndrome After Percutaneous Coronary Intervention. *Value Health*. 2020;23(1):61-73. doi:10.1016/j.jval.2019.08.002

67. Herman L, Froelich J, Kanelos D, et al. Utility of a genomic-based, personalised medicine test in patients presenting with symptoms suggesting coronary artery disease. *J Am Board Fam Med JABFM*. 2014;27(2):258-267. doi:10.3122/jabfm.2014.02.130155

68. Bishop J.R. Pharmacists as facilitators of pharmacogenomic guidance for antidepressant drug selection and dosing. *Clin Transl Sci*. 2021;14(4):1206-1209. doi:10.1111/cts.13057

69. Cavallari L.H., Johnson J.A. Use of a multi-gene pharmacogenetic panel reduces adverse drug effects. *Cell Rep Med*. 2023;4(5):101021. doi:10.1016/j.xcrm.2023.101021

70. Elliott LS, Henderson JC, Neradilek MB, Moyer NA, Ashcraft KC, Thirumaran RK. Clinical impact of pharmacogenetic profiling with a clinical decision support tool in polypharmacy home health patients: A prospective pilot randomized controlled trial. *PLoS One*. 2017;12(2):e0170905. doi:10.1371/journal.pone.0170905

71. Ingelman-Sundberg M, Nebert DW, Lauschke VM. Emerging trends in pharmacogenomics: from common variant associations toward comprehensive genomic profiling. *Hum Genomics*. 2023;17(1):105. doi:10.1186/s40246-023-00554-9

72. Ahsan T, Urmi NJ, Sajib AA. Heterogeneity in the distribution of 159 drug-response related SNPs in world populations and their genetic relatedness. *PLOS ONE*. 2020;15(1):e0228000. doi:10.1371/journal.pone.0228000

73. Moore C, Lazarakis S, Stenta T, et al. A systematic review of knowledge, attitude and practice of pharmacogenomics in pediatric oncology patients. *Pharmacol Res Perspect*. 2023;11(6):e01150. doi:10.1002/prp2.1150

74. Rollinson V, French N, Turner R, Pirmohamed M. A Survey of the UK Pharmacy Profession's Educational Needs on Pharmacogenomics. *J Clin Pharm Ther*. 2023;2023:e2388845. doi:10.1155/2023/2388845

75. Natarajan P, Young R, Stitziel NO, et al. Polygenic Risk Score Identifies Subgroup With Higher Burden of Atherosclerosis and Greater Relative Benefit From Statin Therapy in the Primary Prevention Setting. *Circulation*. 2017;135(22):2091-2101. doi:10.1161/CIRCULATIONAHA.116.024436

76. Hutchcraft ML, Zhang S, Lin N, et al. Real-World Evaluation of a Population Germline Genetic Screening Initiative for Family Medicine Patients. *J Pers Med*. 2022;12(8). doi:10.3390/jpm12081297

Table 2 Stakeholders' views and involvement, enablers, and challenges of implementing PGx testing

Study ID	Title	Study type, year	Disease/Condition under study	Aims/Objectives	Key stakeholders	Country
Ahmed 2022	Psychotropic prescribing rates and pharmacogenomic testing implications for autism in the Canadian primary care sentinel surveillance network.	Retrospective study, 2021	Autism	Assess the prescription pattern of 92 psychotropic drugs in autistic patients and measure its pharmacogenomic testing implication.	Physician	Canada
Arwood 2020	Design and Early Implementation Successes and Challenges of a Pharmacogenetics Consult Clinic.	2020	Patients in the general internal medicine	A pharmacist-initiated pharmacogenomics clinic and state its success and challenges that came across within two years of its implementation	Pharmacist	United States
Bank 2019	A pilot study of the implementation of pharmacogenomic pharmacist-initiated pre-emptive testing in primary care.	Prospective multicenter observational study, 2019	Adult patients with an incident prescription for at least 28 days for amitriptyline, atomoxetine, atorvastatin, (es)citalopram, clomipramine, doxepin, nortriptyline, simvastatin or venlafaxine	Assess the feasibility of pharmacist-initiated pharmacogenomic analysis in primary care and investigate the actionable phenotypes for improving patient clinical outcomes.	Community Pharmacist	Netherlands
Bank 2019	Estimated nationwide impact of implementing a preemptive pharmacogenetic panel approach to guide drug prescribing in primary care in The Netherlands.	2016	All prescriptions for the selected 45 drugs	To estimate the potential impact of the implementation of pharmacogenetic screening for eight genes related to drugs used in primary care.	Pharmacists	Netherlands
Behr 2023	Healthcare professionals' knowledge, confidence and perceptions of pharmacogenomics in primary care and pain management.	25-question survey, 2023	Pain management	To assess clinician knowledge with clinical pharmacogenomic (PGx) scenarios involving commonly used drugs that have both CPIC guidelines and FDA PGx dosing recommendations.	Physicians, physician assistants, and nurse practitioners	United States

Bishop 2021	Pharmacists as facilitators of pharmacogenomic guidance for antidepressant drug selection and dosing	Commentary, 2021	Mental health	To comment on the role of pharmacists in pharmacogenomics practice	Clinician, Pharmacist	United States
Biswas 2020	A Centralized Approach for Practicing Genomic Medicine.	Case study, 2020	Paediatric Condition	To propose a practical and centralized approach to providing genomic services through an independent, enterprise-wide clinical service model.	Clinician	United States
Brown 2017	Economic Utility: Combinatorial Pharmacogenomics and Medication Cost Savings for Mental Health Care in a Primary Care Setting.	A Subanalysis of a prospective trail - 2017	Mental illness	To determine potential cost savings of combinatorial pharmacogenomics testing over one year in patients with mental illness treated by primary care providers and psychiatrists who had switched or added a new psychiatric medication after patients failed to respond to monotherapy.	Primary care providers treat psychiatric patients through general practice, internal medicine, family medicine, and obstetrician/gynecology. Psychiatrist (not included as PCPs)	United States
Brown 2021	Characterizing Pharmacogenetic Testing Among Children's Hospitals.	Cross-sectional study, 2021	Pediatric patients	Determining availability, concerns, and barriers of pharmacogenomic testing in pediatric hospitals	Pharmacist, Physician	United States
Brown-Johnson 2021	Implementation outcomes of Humanwide: integrated precision health in team-based family practice primary care.	Mixed methods research in Quality Improvement, 2021	Patients with cardiovascular risk factors	To assess the implementation outcomes, specifically penetration/reach, acceptability, feasibility, and sustainability of Humanwide, a pilot embedding multi-faceted precision health into a team-based primacy care setting To inform future implementation initiatives and facilitate the scale/spread of precision health in primary care. To assess its early potential clinical benefit to patients.	MDs, Advance Practice Provider (NP or PA) health professionals, diabetes pharmacists, dieticians, mental health providers, triage nurse	United States
Brunette 2019	Pragmatic Trials in Genomic Medicine: The	Pragmatic Clinical Trial, 2019	Cardiovascular disease (needing statin therapy without previous	To apply Pragmatic Clinical Trial (PCT) principles to The Integrating Pharmacogenetics In Clinical	Primary care provider	United States

	Integrating Pharmacogenetics in Clinical Care (I-PICC) Study		history of statin use).	Care (I-PICC) Study. To generate evidence for the clinical utility of pre-emptive pharmacogenetic testing in the initiation of statin therapy.		
Carroll 2016	Primary care providers' experiences with and perceptions of personalised genomic medicine.	A qualitative study involving focus groups	Cancer	To assess primary care providers' (PCPs) experiences with, perceptions of, and desired role in personalised medicine, with a focus on cancer.	primary care providers	Canada
Carroll 2019	Informing Integration of Genomic Medicine Into Primary Care: An Assessment of Current Practice, Attitudes, and Desired Resources	Questionnaire Design and Administration	NA	to determine family physicians' (FP) current involvement in GM (general medicine), confidence in GM primary care competencies, attitudes regarding the clinical importance of GM, awareness of genetic services, resources required, and suggestions for changes that would enable the integration of GM into practice.	Physicians	Canada
Cavallari 2023	Use of a multi-gene pharmacogenetic panel reduces adverse drug effects	Review of a Muti-centric cohort, 2023	Adult patients with newly initiated drugs stated in the Dutch Pharmacogenomics Working Group guideline	The effect of twelve gene panel pharmacogenomic testing to prevent adverse drug reactions in patients across seven countries	Pharmacist, Physician	United States
Chapdelaine 2021	Sociodemographic factors and beliefs about medicines in the uptake of pharmacogenomic testing in older adults.	Secondary data analysis, 2021	Geriatric patients without moderate to severe cognitive impairment	Assess the factors of older adults that affect pharmacogenomic testing in primary care	Primary care providers	Canada
Crown 2020	A Continuing Professional Development Program for Pharmacists Implementing Pharmacogenomics into Practice.	prospective cohort study	Not Mentioned/Not Applicable	Examining the impact of the CPD program on practicing pharmacists' knowledge, readiness and comfort, and ability to implement pharmacogenomics services in their practices	Pharmacists	Canada
Dressler 2019	Implementing pharmacogenetic testing in rural primary care practices: a pilot feasibility study.	This prospective, observational feasibility study was conducted		Assess feasibility and perspectives of pharmacogenetic testing/PGx in rural primary care physician (PCP) practices, when PCPs are trained to	Physicians	United States

		between September 2016 and December 2017		interpret/apply results and testing costs are covered		
Elliott 2017	Clinical impact of pharmacogenetic profiling with a clinical decision support tool in polypharmacy home health patients: A prospective pilot randomised controlled trial.	prospective, open-label, randomised controlled trial	50 years and older taking or initiating treatment with at least one of fifty-five single-ingredient or six medication combinations (Polypharmacy)	Assessment of clinical impact of pharmacogenetic profiling integrating binary and cumulative drug and gene inter-action warnings on home health polypharmacy patients	Physicians	United States
Forester 2020	Combinatorial Pharmacogenomic Testing Improves Outcomes for Older Adults With Depression	Post hoc analysis of data from a blinded, randomised controlled trial comparing two active treatment arms.	major depressive disorder (MDD)	valuate the clinical utility of combinatorial pharmacogenomic testing for informing medication selection among older adults who have experienced antidepressant medication failure for major depressive disorder (MDD)	Physicians	United States
Frigon 2019	Pharmacogenetic testing in primary care practice: opinions of physicians, pharmacists and patients.	Focus Group interviews / 2019	NA	To better understand the perceptions of PCPs, pharmacists, and patients regarding the implementation of PGx testing in clinical practice,	Primary care physicians (PCPs), pharmacists and patients	Canada
Gammal 2021	Documenting Pharmacogenomic Test Results in Electronic Health Records: Practical Considerations for Primary Care Teams.	2021	General population	The problems and solutions concerning the integration of pharmacogenomics to the clinical decision support system in a clinical setting	Physician, Pharmacist	United States
Grant 2009	The clinical application of genetic testing for type 2 diabetes: A patient and physician survey	Cross-sectional, 2009	Type 2 diabetes mellitus	Assess the physicians and patient's views on pharmacogenomic testing for the prediction and management of diabetes.	Physicians	United States
Haga 2012	Primary care physicians' knowledge of and experience with	Cross-sectional Survey & 2012	NA	To seek PCPs views on their willingness and readiness to utilise PGx testing, desirable test properties, and factors relevant to the use of PGx tests	Primary Care Physicians (PCPs)	United States

	pharmacogenetic testing.					
Haga 2012	Professional perspectives about pharmacogenetic testing and managing ancillary findings.	Pilot Study, 2012	NA	Pharmacogenetic (PGx) tests are intended to inform therapeutic decision-making through prediction of patient likelihood to respond to or experience an adverse effect from a specific treatment may also generate ancillary, or incidental, disease information unrelated to the purpose for which the test was ordered. To assess attitudes toward PGx testing, ancillary disease risk information, and related clinical issues, we conducted a series of focus groups among health professionals.	Primary care Professionals and Genetic Professionals	United States
Haga 2014	Delivering pharmacogenetic testing to the masses: An achievable goal?	2014	General	Displays delivery models of pharmacogenomic screening for healthcare settings	Pharmacist	United States
Haga 2017	Primary care providers' use of pharmacist support for delivery of pharmacogenetic testing.	Pilot study, 2017		To investigate provider utilization of pharmacist support in the delivery of pharmacogenetic testing in a primary care setting.	Primary care providers' and Pharmacists.	United States
Hajek 2022	Improved provider preparedness through an 8-part genetics and genomic education program.	2022	NA	To offer guidance to health systems developing genetic education programs that are appropriate to the needs of providers who are not genetic specialists.	Health Care Providers'	United States
Herman 2014	Utility of a genomic-based, personalised medicine test in patients presenting with symptoms suggesting coronary artery disease.	Clinical trial, 2014	Non-diabetes patient under evaluation for obstructive coronary artery disease (CAD)	Assessing the benefits of gene expression score in the diagnosis of obstructive CAD	Physicians, nurses, and physician assistants	United States
Hundertmark 2020	Pharmacist's attitudes and knowledge of pharmacogenomics and the factors that may predict future engagement.	The thirteen-question survey, 2020	Pharmacist Knowledge from postgraduate education and training.	The primary objective of this survey was to determine how postgraduate education and training influence pharmacists' knowledge and attitudes toward pharmacogenomic testing.	Pharmacist	United States

Hutchcraft 2022	Real-World Evaluation of a Population Germline Genetic Screening Initiative for Family Medicine Patients.	Single institution prospective cohort study, 2022.	Hereditary Disease	To assess the clinical utility of germline medical exome sequencing in patients recruited from a family medicine clinic and comparing the mutation frequency of hereditary predisposition genes to established general population frequencies.	Physicians	United States
Jablonski 2020	Economic Outcomes Following Combinatorial Pharmacogenomic Testing for Elderly Psychiatric Patients.	Sub analysis of a 1-year prospective Assessment of medication cost, 2019.	Psychiatric (Mental Illness).	Comparison of economic outcomes when elderly patients with neuropsychiatric disorders received psychotropic medications guided by a combinatorial pharmacogenomic (PGx) test.	Primary Care Providers'	United States
Jarvis 2022	Real-World Impact of a Pharmacogenomics-Enriched Comprehensive Medication Management Program.	Retrospective study, 20233	Older adult population	Evaluating a large real-world pharmacogenomic implementation to the comprehensive medication management system in the US	Pharmacist	United States
Kehr 2023	Integration of a pharmacist-led pharmacogenomic service in a geriatric clinic: Barriers and outcomes.	Single center, non-interventional, retrospective cohort study.	Older adults within an outpatient geriatric clinic.	The primary objective was to identify the proportion of patients who completed PGx testing. Secondary objectives included determining the proportion of patients with actionable PGx results, determining the proportion of patients with a baseline medication intervention within six months of completing PGx testing, and identifying barriers to not completing testing.	Pharmacist	United States
Kennedy 2013	Incorporating psychiatric pharmacogenetics into family practice	2013	Psychiatric patients	Feasibility of pharmacogenomic testing in primary care	Physician	Canada
Kimpton 2019	Longitudinal exposure of English primary care patients to pharmacogenomic drugs: An analysis to inform the design of pre-emptive pharmacogenomic testing.	Retrospective study, 2019.	Exposure of patients to pharmacogenomic drugs retrospectively.	To investigate the longitudinal exposure of English primary care patients to pharmacogenomic drugs to inform the design of pre-emptive testing.	Practitioners	United Kingdom
Ladapo 2015	Enhanced assessment of chest pain and	Prospective Muti-centric	Coronary artery disease (CAD)	Assess the usage of blood gene expression diagnostic tests and their clinical	Physician, nurse, phlebotom	United States

	related symptoms in the primary care setting through the use of a novel personalised medicine genomic test: results from a prospective registry study.	Observational Study, 2015		benefit in confirming obstructive CAD in primary care.	ist, office manager	
Leger 2016	Pharmacogenetics of efavirenz discontinuation for reported central nervous system symptoms appears to differ by race.	Retrospective study, 2016	HIV infection	Examination of genetic data with the efavirenz discontinuation from central nervous system adverse events in HIV primary care patients of Southeastern United States	Physician	United States
Lemke 2017	Primary care physician experiences with integrated pharmacogenomic testing in a community health system.	Descriptive Study	NA	To explore primary care physicians, views of the utility and delivery of direct access to pharmacogenomics (PGx) testing in a community health system.	Primary Care Physicians	United States
Li 2014	Genetically guided statin therapy on statin perceptions, adherence, and cholesterol-lowering: A pilot implementation study in primary care patients	Pilot Study, 2014.	Hyperlipidemia (Statin Therapy).	To improve statin adherence, it is tailored to an individuals' SLCO1B1*5 genotype and addresses a major driver of statin adherence in the primary care population.	Physicians	United States
Luke 2021	Pharmacists as Personalised Medicine Experts (PRIME): Experiences Implementing Pharmacist-Led Pharmacogenomic Testing in Primary Care Practices.	Qualitative Descriptive Approach, 2021.	In this study, additional internal factors related to the capabilities, opportunities, and motivations of pharmacists that influence their ability to implement PGx testing were analyzed.	To further elucidate the factors influencing the integration of PGx testing by pharmacists in their practices, the BCW approach should be used to inform future intervention options to support pharmacists with this integration.	Pharmacists	Canada
Marzullo 2014	Are public health professionals prepared for public health genomics? A cross-sectional survey in Italy.	A cross-sectional survey, 2014.	A self-administered questionnaire was used to carry out a cross-sectional survey of a random sample of Italian public	To assess the knowledge, attitudes, and training needs of public health professionals in the field of predictive genetic testing for chronic diseases.	Public health practitioners	Italy

			health professionals.			
Massart 2022	A Multidisciplinary Precision Medicine Service in Primary Care.	2022	Public	Display a precision medicine center in primary care settings	Physicians and pharmacists trained in genetics and genetic counselors	United States
Mills 2013	Delivering pharmacogenetic testing in a primary care setting	2013	Public	Key elements to communicate with patients before and when reporting pharmacogenomic data	Physician, pharmacist, and genetic counselor	United States
Mwale 2021	Imagining genomic medicine futures in primary care: General practitioners' views on mainstreaming genomics in the National Health Service.	Qualitative interview/ Semi-structured interviews with GPs as well as documentary analysis of policy/ 2021	N/A Genomic medicine in the NHS and practice implementation	To explore GPs, views on mainstreaming genomic medicine in the NHS and implications for their practice. To examine how visions of genomic futures in the NHS are conceived and received by GPs by engaging the concept of "sociotechnical imaginaries." To undertake documentary analysis of publicly available policy documents relating to the mainstreaming of genomics, such as the Human Genomics Strategy Group (2012), the Chief Medical Officer of England's (2016) report, the Life Sciences Industrial Strategy (2020), and editorial material on NHSE and Genomics England websites provided an alternative official account of how genomic futures are imagined, presented, and enacted.	General practitioners (GPs)	United Kingdom
NatashaPetry 2019	Implementation of wide-scale pharmacogenetic testing in primary care.	The five Iâ€™sâ€™ as a template for other institutions seeking to start a "de novo" pharmacogenomics program.	Manuscript, 2019.	Describes our efforts to place pharmacogenomics in the hands of the primary care provider, integrating this information into a patient's healthcare over their lifetime.	Pharmacists, Nurses, Genetic Counselors, and other healthcare workers	United States
O'Donnell 2017	Pharmacogenomics-Based Point-of-Care Clinical	Prospective	NA	To examine prospectively the impact of available pharmacogenomic	Physicians	United States

	Decision Support Significantly Alters Drug Prescribing.			information on physician prescribing behaviors.		
Olander 2018	Primary Care Clinicians Attitudes and Knowledge of Pharmacogenetics in a Large, Multi-state Healthcare System.	Survey, 2018.	NA	The primary objective of this survey was to ascertain primary care clinicians' perceptions of pharmacogenetic use and implementation in an integrated health system of metropolitan and rural settings across several states.	Primary Care Clinicians	United States
Olson 2017	Clinical Impact of Pharmacogenetic-Guided Treatment for Patients Exhibiting Neuropsychiatric Disorders: a Randomised Controlled Trial	A prospective, randomised study	Neuropsychiatric Disorders	Pharmacogenetic testing holds promise as a personalised medicine tool by permitting individualization of pharmacotherapy in accordance with genes influencing therapeutic response, side effects, and adverse events. The authors evaluated the effect of outcomes for the patients diagnosed with neuropsychiatric disorders of pharmacogenetics-guided treatment compared to the usual standard of care.	Clinicians	United States
O'Shea 2022	Public perceptions of pharmacogenomic services in Ireland - Are people with chronic disease more likely to want service availability than those without? A questionnaire study.	A questionnaire study, 2022.	An anonymous, online questionnaire generated using Qualtrics® and circulated via social media and posters placed in eight participating community pharmacies was conducted with Irish adults.	To establish perceptions of pharmacogenomics (awareness, understanding, openness to availability, perceived benefits and concerns, willingness to pay, and service setting) and investigate if they differ between those with and without chronic disease(s).	Community Pharmacists, Primary Healthcare Providers	Ireland
Overkleeft 2020	Using Personal Genomic Data within Primary Care: A Bioinformatics Approach to Pharmacogenomics.	A Bioinformatics Approach, 2020.	The illustration of the 4MedBOX system.	To provide a description of the Personal Genetic Locker project and show its utility through a use case based on open standards, which is illustrated by the 4MedBox system.	Primary care professionals	Netherlands
Papastergiou 2017	The Innovative Canadian Pharmacogenomic Screening Initiative in Community Pharmacy (ICANPIC) study.	Open-label, non-randomised, Observational.	NA	To evaluate the feasibility of implementing personalised medication services into community pharmacy practice To assess the number of drug therapy problems identified as a result of	Pharmacists	Canada

				pharmacogenomic screening		
Papastergiou 2021	Pharmacogenomics guided versus standard antidepressant treatment in a community pharmacy setting: A randomised controlled trial.	Prospective, single-blind, randomised controlled design	Major depressive disorder and/or generalized anxiety disorder,	Impact of pharmacogenomics guided versus standard antidepressant treatment of depression and anxiety, implemented in three large community pharmacies.	Pharmacists	Canada
Park 2007	Anticipating clinical integration of genetically tailored tobacco dependence treatment: Perspectives of primary care physicians	Focus group Interviews	Smoking Cessation /Tobacco dependence	(a) to explore physicians' attitudes toward treatment strategies that include matching patients to smoking cessation treatment by genotype, and (b) to identify concerns that would need to be addressed prior to the clinical integration of a genetic test to tailor smoking cessation treatment.	Physicians	United States
Prather 2022	Idiopathic Symptoms Resolved by Pharmacogenomics-Enriched Comprehensive Medication Management: A Case Report.	Case Report/2022	Post CVA (Cerebro Vascular Accident)	Assessing the positive impact of personalised medicine in post-CVA patients with idiopathic symptoms	Pharmacist	United States
Rafi 2020	The implementation of pharmacogenomics into UK general practice: a qualitative study exploring barriers, challenges and opportunities.	A Qualitative Study, 2020.	Semi-structured interviews were undertaken with 18 clinical participants (16 GPs and two other clinicians). All interviews were recorded and transcribed verbatim.	To explore the potential barriers, opportunities, and challenges facing the implementation of pharmacogenomics into primary care.	General practitioners	United Kingdom
Rigter 2020	Implementation of Pharmacogenetics in Primary Care: A Multi-Stakeholder Perspective	Focus group Interviews, Meetings, and Delphi Technique		To define actions, roles, and responsibilities for the implementation of pharmacogenetics by conducting a multi-phased stakeholder study.	pharmacists and primary care physicians	Netherlands
RodrÃ-guez-Escudero 2020	Assessment of the clinical utility of pharmacogenetic guidance in a comprehensive medication	Pilot study, following a pre- and post-interventional experimen	Psychiatry	aimed at demonstrating the benefit of incorporating PGx information into Comprehensive Medication Management (CMM) services.	Pharmacist	Puerto Rico

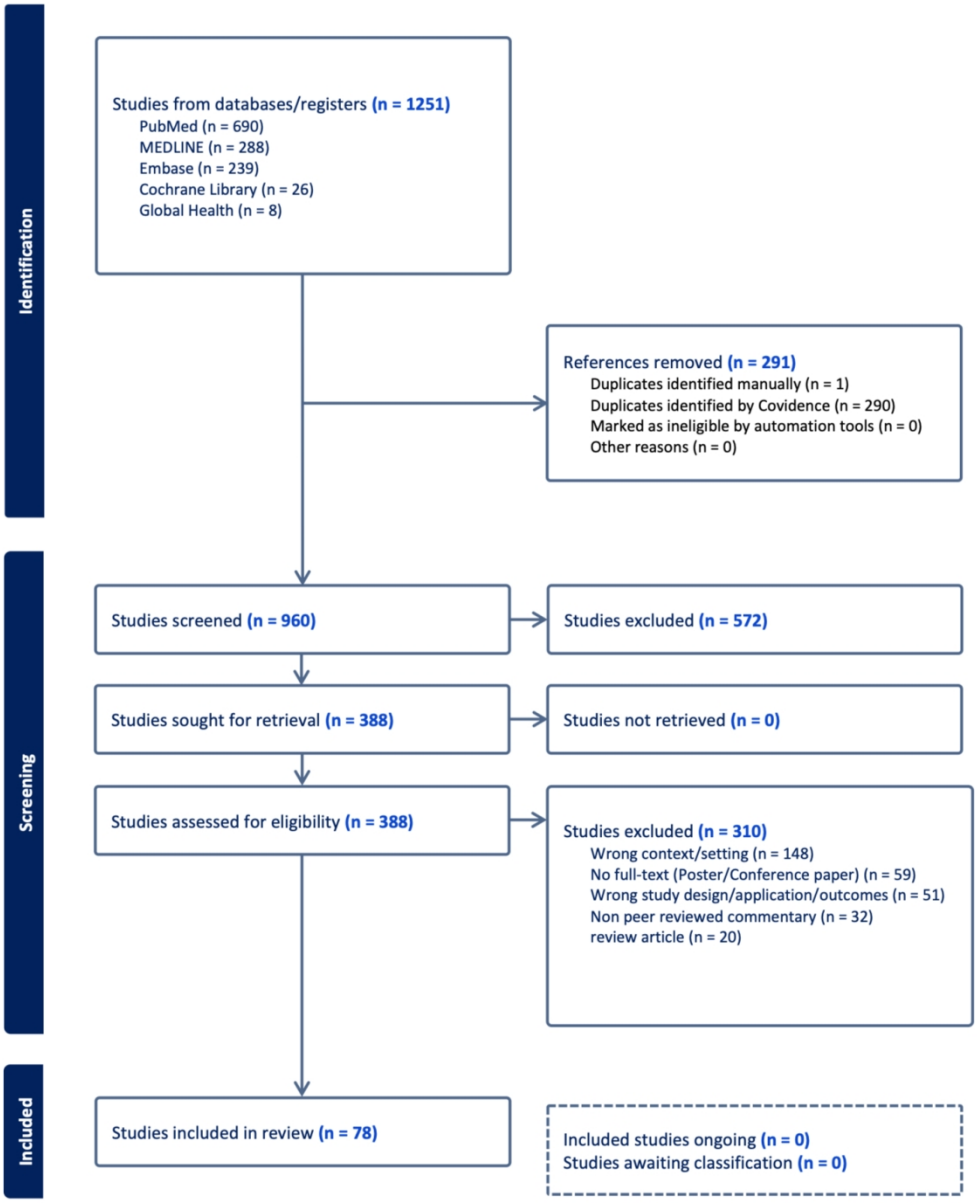
	management service.	tal design, 2020				
Schwartz 2017	Implementation of a Standardized Medication Therapy Management Plus Approach within Primary Care.	2017	Hyperlipidemia Hypertension Type 2 diabetes mellitus Hypothyroidism Vitamin D deficiency Allergic rhinitis Anxiety Gastroesophageal reflux disorder Major depressive disorder Insomnia	The purpose of this study was to implement a clinical pharmacist-led MTM service within a primary care setting that is enhanced by 1) a clinical decision support system (CDSS) that includes a unique combination of medication risk mitigation factors, which aids the pharmacist in interpreting the medication profile, and 2) pharmacogenomics (PGx) testing	Pharmacist	United States
Sharma 2017	Validation Study of a Predictive Algorithm to Evaluate Opioid Use Disorder in a Primary Care Setting.	Validation Study, 2017.	Opioid Use Disorder.	To determine the predictability of aberrant behavior to opioids using a comprehensive scoring algorithm incorporating phenotypic and, more uniquely, genotypic risk factors.	Primary care Physicians	United States
Shields 2008	Anticipating clinical integration of pharmacogenetic treatment strategies for addiction: are primary care physicians ready?.	2008	Drugs and Alcohol Addiction	To review challenges related to provider readiness. To address physicians' knowledge of genetics and the barriers posed by complex genetic traits in particular. To document PCPs' actual experience in ordering and referring patients for genetic testing. Finally, To make recommendations for addressing these concerns and for facilitating the integration of pharmacogenetic treatment strategies for addiction into primary care practice.	Physicians	United States
Shields 2008	Primary care physicians' willingness to offer a new genetic test to tailor smoking treatment according to test characteristics	Survey, 2008	Smoking Cessation	To assess physicians' willingness to offer a new genetic test to tailor smoking treatment individually	Physicians	United States
Silva 2021	Implementation of Pharmacogenomics and Artificial Intelligence Tools for Chronic Disease Management in	Informatic and Bioanalytic method, 2021.	Chronic diseases such as antiepileptic, antiemetics, and antihypertensives.	To provide facile clinical decision support to inform and augment medication management in the primary care setting.	Pharmacists	United States

	Primary Care Setting.					
Smith 2022	Improving prescribing: a feasibility study of pharmacogenetic testing with clinical decision support in primary healthcare in Singapore.	Prospective Cohort Study Design, 2022.	The general practitioners recruited 189 patients between October 2020 and March 2021. The sample size was calculated on the basis of allele frequencies from a similar primary care study in Canada.	To assess the feasibility of collecting buccal samples by general practitioners (GPs) at private practices in Singapore within a usual consultation, incorporating the use of a pharmacogenetics-based medical decision support system to guide subsequent drug dosing.	General practitioners	Singapore
Srinivasan 2021	Integrating Genomic Screening into Primary Care: Provider Experiences Caring for Latino Patients at a Community-Based Health Center.	Open-ended, semi-structured interviews, 2021.	Patients who received positive genomic screening results.	To examine primary care providers (PCP) experiences in reporting genomic screening results and integrating those results into patient care.	Primary Care Providers	United States
StSauver 2016	Integrating Pharmacogenomics into Clinical Practice: Promise vs Reality.	Survey, 2016.	A total of 159 clinicians within the Mayo Clinic primary care practice received email surveys with the aim of gaining insights into their views regarding the integration and application of pharmacogenomic testing within their clinical practice. These surveys were designed to evaluate the clinicians' sentiments regarding pharmacogenomics and to gauge their opinions on the usefulness of electronic pharmacogenomics clinical decision support (PGx-CDS) alerts.	To describe early clinician experience with pharmacogenomics in the clinical setting.	Primacy Care Physicians	United States
Swen 2012	Feasibility of pharmacy-initiated pharmacogenetic screening for CYP2D6 and CYP2C19.	Elderly patients over the age of 60, who were on multiple	Patients were selected from the pharmacy records if they used at least one drug that CYP2D6 metabolizes or	To investigate the feasibility of pharmacy-initiated pharmacogenetic screening in primary care with respect to patient willingness to participate, quality of DNA collection with saliva kits,	Pharmacists	Netherlands

		medications and had used at least one drug falling under specific Anatomical Therapeutic Chemical (ATC) codes, including within the previous two years, were chosen randomly for the study, 2012.	CYP2C19 and at least four additional drugs in the preceding two years.	genotyping, and dispensing data retrieved from the pharmacy.		
Tanner 2018	Combinatorial pharmacogenomics and improved patient outcomes in depression: Treatment by primary care physicians or psychiatrists.	A naturalistic, open-label, prospective study, 2018.	Major Depressive Disorder, Depression.	To evaluate the utility of combinatorial pharmacogenomics in patients with major depressive disorder in primary care and psychiatric care settings.\ To evaluate symptom improvement, response, and remission rates following treatment guided by combinatorial pharmacogenomic testing among patients with major depressive disorder enrolled in a large, prospective study.	Primary care physicians, psychiatrists	Canada
Tiwari 2022	Clinical utility of combinatorial pharmacogenomic testing in depression: A Canadian patient- and rater-blinded, randomised, controlled trial.	Rater-blinded, randomised, controlled trial, 2022	Depression	To evaluate the utility of the combinatorial pharmacogenomic test in a Canadian population, this trial was assessed in conjunction with a trial conducted in a U.S. population (GUIDED trial).	physicians	Canada
Turkmen 2023	Calcium-channel blockers: Clinical outcome associations with reported pharmacogenetics variants in 32,000 patients.	The study analyzed up to 32 360 UK Biobank participants prescribed dCCB in primary care (from	Incident diagnosis of coronary heart disease, heart failure (HF), chronic kidney disease, edema, and switching antihypertensive medication.	To estimate associations between reported pharmacogenetic variants and incident adverse events in a community-based cohort prescribed dihydropyridine calcium channel blockers.	General Practitioners	United Kingdom

		UK general practices, 1990â€"2017), 2022.				
vander Woude n 2016	Consumer Perceptions of Interactions With Primary Care Providers After Direct-to-Consumer Personal Genomic Testing.	Longitudinal, prospective cohort study, 2016.	TC PGT consumers.	To describe the characteristics and perceptions of DTC PGT consumers who discuss their results with their PCP.	Primary Care Providers	United States
vander Woude n 2019	Pharmacist-Initiated Pre-Emptive Pharmacogenetic Panel Testing with Clinical Decision Support in Primary Care: Record of PGx Results and Real-World Impact.	The prospective pilot study, 2019.	In this study, Community pharmacists were provided the opportunity to request a panel of eight pharmacogenetics to guide drug dispensing within a clinical decision support system (CDSS) for 200 primary care patients.	To quantify both the feasibility and the real-world impact of this approach in primary care.	Community pharmacists	Netherlands
vander Woude n 2020	Assessing the Implementation of Pharmacogenomic Panel-Testing in Primary Care in the Netherlands Utilizing a Theoretical Framework.	PREPARE study, 2020.	Enrollment of patients under their pharmacists who plan to initiate one of 39 drugs with a Dutch Pharmacogenetics Working Group (DPWG) recommendations.	To study pharmacists' perceived enablers and barriers for PGx panel-testing among pharmacists participating in a PGx implementation study.	Pharmacists	Netherlands
Vassy 2018	How Primary Care Providers Talk to Patients about Genome Sequencing Results: Risk, Rationale, and Recommendation	Qualitative Analysis, 2018.	Primary Care Physicians and their generally healthy patients undergoing genome sequencing	To illuminate how PCPs communicate different types of genome sequencing results and their management recommendations for those results of uncertain clinical utility.	primary care physicians	United States
Vassy 2020	Effect of Pharmacogenetic Testing for Statin Myopathy Risk vs Usual Care on Blood Cholesterol: A Randomised Clinical Trial.	Randomised trial, 2020.	Stating myopathy risk.	To determine the impact of delivering SLCO1B1 pharmacogenetic results to physicians on the effectiveness of atherosclerotic cardiovascular disease (ASCVD) prevention (measured by low-density lipoprotein cholesterol [LDL-C] levels) and concordance	Physicians	United States

				with prescribing guidelines for statin safety and effectiveness.		
Weinstein 2020	Perspectives of a pharmacist-run pharmacogenomic service for depression in interdisciplinary family medicine practices	A qualitative study, 2019.	Depression	To explore pharmacist and physician perspectives on the utility and critical considerations for designing a pharmacist-run pharmacogenomic service for depression in primary care.	Pharmacists	United States
Wildin 2022	Primary care implementation of genomic population health screening using a large gene sequencing panel.	Consolidated Framework for Implementation Research (CFIR), 2022.	Genetic Disease.	To review the barriers, solutions, and perceived gaps in the context of an implementation research framework.	Primary Care Provider	United States
Williams 2016	Primary Care Providers' Interest in Using a Genetic Test to Guide Alcohol Use Disorder Treatment.	Qualitative study, A top-down sampling method, 2016.	Alcohol use disorders	Qualitative interviews with primary care providers from 5 clinics in the Veterans Health Administration (VA) to assess their interest in using a genetic test to inform the treatment of alcohol use disorders with pharmacotherapy.	Primary Care Providers, physicians	United States



Flow diagram of the scoping review.

258x312mm (144 x 144 DPI)

Country of origin of the articles included in this review.

490x172mm (144 x 144 DPI)

Supplementary files

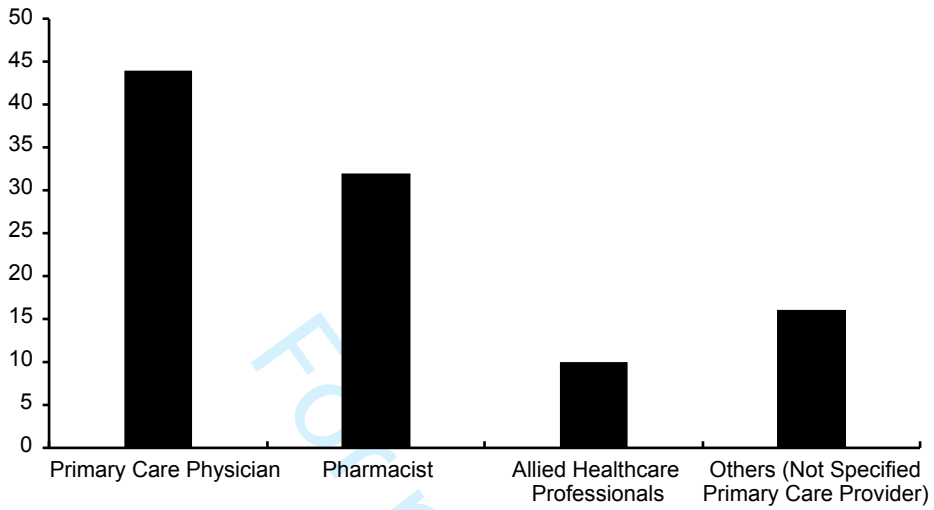


Figure 1 Key stakeholders for the implementation of pharmacogenomics testing in the primary care settings.

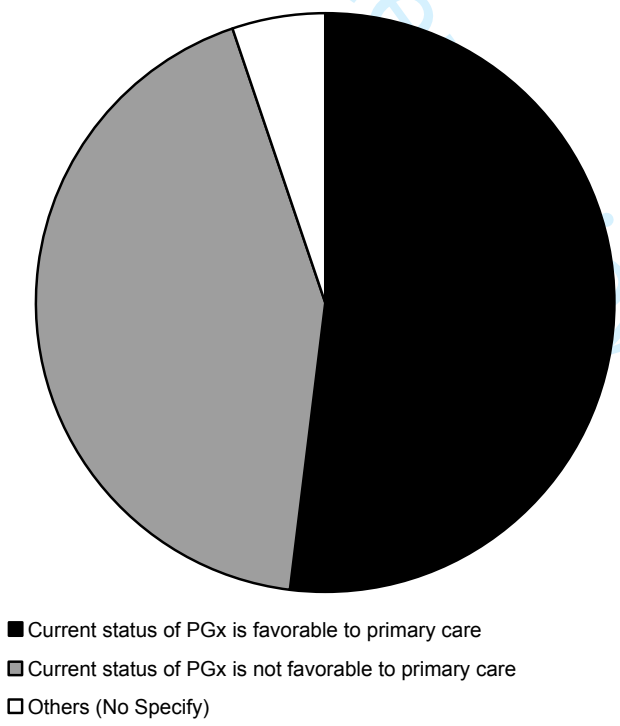


Figure 2 Opinion towards implementation of pharmacogenomics testing in the primary care settings

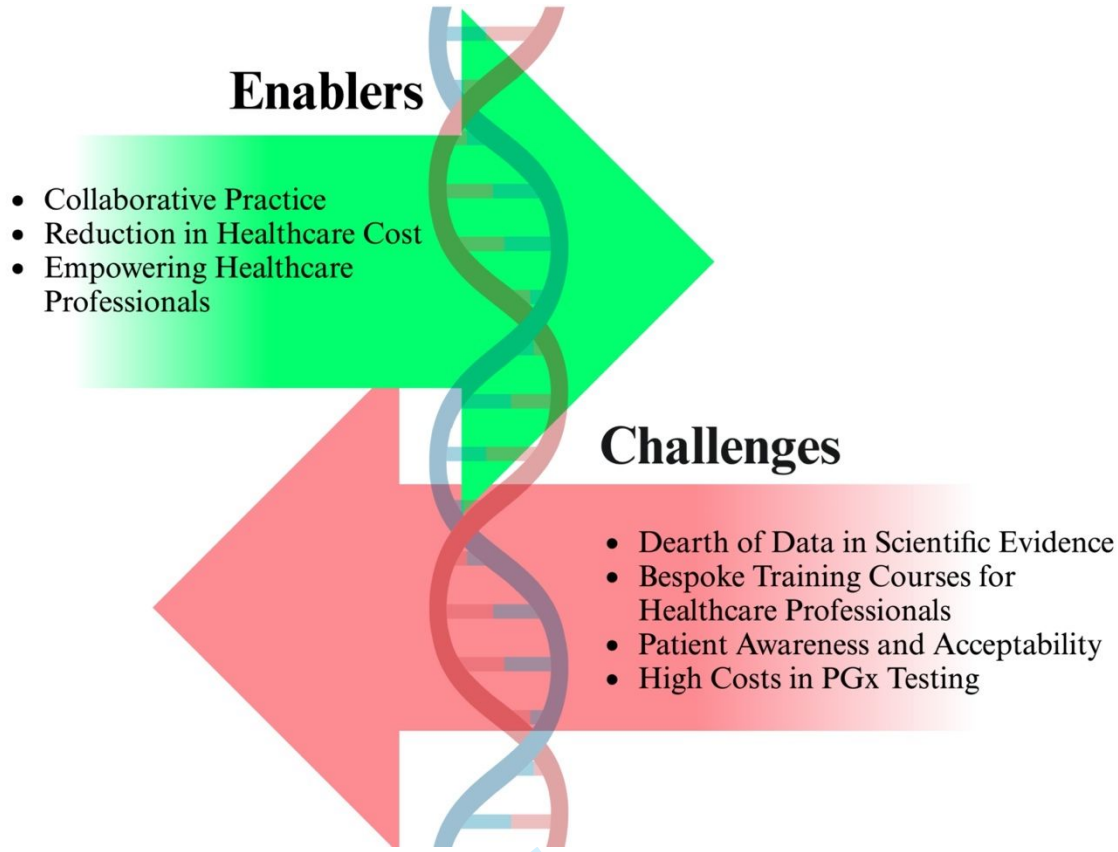


Figure 3 Enablers and challenges of implementation of pharmacogenomics testing in primary care settings.

BMJ Open

A Scoping Review of Enablers and Challenges of Implementing Pharmacogenomics Testing in the Primary Care Settings

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-087064.R1
Article Type:	Original research
Date Submitted by the Author:	02-Sep-2024
Complete List of Authors:	Mai, Chun-Wai; UCSI University, Faculty of Pharmaceutical Sciences Sridhar, Sathvik B; RAK Medical & Health Sciences University Karattuthodi, Mohammed Salim; Manipal College of Pharmaceutical Sciences Department of Pharmaceutical Biotechnology Ganesan, Perishithaa M; IMU University, Department of Pharmacy Practice shareef, javedh; RAK Medical and Health Sciences University Lee, E Lyn; IMU University Armani, Keivan; Imperial College London Faculty of Medicine, Department of Primary Care and Public Health, School of Public Health; UCSI University Faculty of Pharmaceutical Sciences
Primary Subject Heading:	Genetics and genomics
Secondary Subject Heading:	Evidence based practice, Patient-centred medicine, Pharmacology and therapeutics, Public health
Keywords:	Primary Health Care, Health Services, Health Workforce, Review, THERAPEUTICS

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

A Scoping Review of Enablers and Challenges of Implementing Pharmacogenomics Testing in the Primary Care Settings

Abstract

Introduction: Pharmacogenomic testing (PGx) plays a crucial role in improving patient medication safety, yet ethical concerns and limitations impede its clinical implementation in the primary care settings.

Aims: To systematically review the current state of PGx in the primary care settings and determine the enablers and challenges of its implementation.

Design: A scoping review was carried out by adhering to Arksey and O'Malley's 6-stage methodological framework and the 2020 Joanna Briggs Institute and Levac *et al*.

Data sources: Cochrane Library, EMBASE, Global Health, MEDLINE, and PubMed were searched up to 17th July 2023.

Eligibility criteria: All peer-reviewed studies in English, reporting the enablers and the challenges of implementing PGx in the primary care settings were included.

Date extraction and synthesis: Two independent reviewers extracted the data. Information was synthesised based on the reported enablers and the challenges of implementing PGx testing in the primary care settings. Information was then presented to stakeholders for their inputs.

Results: 78 studies discussing the implementation of PGx testing are included, in which 57% were published between 2019-2023. 68% of the studies discussed PGx testing in the primary care setting as disease-specific themes. Healthcare professionals were the major stakeholders, with primary care physicians (55%) being the most represented. Enablers encompassed various advantages such as diagnostic and therapeutic benefits, cost reduction, and the empowerment of healthcare professionals. Challenges included the absence of sufficient scientific evidence, insufficient training for healthcare professionals, ethical and legal aspects of PGx data, low patient awareness and acceptance, and the high costs linked to PGx testing.

Conclusion: Pharmacogenomic testing integration in primary care requires increased consumer awareness, comprehensive healthcare provider training on legal and ethical aspects, and global feasibility studies to better understand its implementation challenges. Managing high costs entails streamlining processes, advocating for reimbursement policies, and investing in research on innovation and affordability research to improve life expectancy.

Strengths and limitations of this study

- The consultation sessions with the stakeholders were conducted to co-develop the research questions, to sense-check the findings and to consolidate the discussion points pertinent to the findings.

- Grey literature that was not peer-reviewed, was not included in the study .
- A plausible limitation was the lack of critical appraisal of the included studies for their quality in this review, despite the fact that critical appraisal is not required for scoping reviews.

Background

Pharmacogenomics (PGx) broadly defines how genomic variation affects a patient's response to a drug [1]. Distinct polymorphisms in drug-metabolising enzymes and drug transporters were a foundation for PGx[2]. With the advance in health technology, the 2000 collaborative effort to draft the human genome marked a turning point, followed by the International Single Nucleotide Polymorphisms (SNP) Map Working Group's efforts to map variations in the human genome sequence [2,3]. More importantly, the advancement of health technology has positioned PGx as a key component in the field of personalised medicine. The application of health technology has ranged from rationalising mutation-specific therapies to personalising early detection strategies, disease prevention, and treatments, have been increasingly utilised in both clinical settings and research contexts based on individual patient profiles [4]. This approach tailors medical treatment to an individual's unique genomic makeup to improve treatment outcomes and minimise adverse effects [5]. While PGx testing provides useful information by detecting genetic variants that impact medication metabolism and response, it is not ideal for all patients [6]. PGx testing can help guide the selection of drugs that are more likely to be beneficial and have fewer adverse effects depending on an individual's genetic makeup [7]. However, it does not consider other important aspects, such as the influence of environment, comorbid diseases, and patient adherence, which can substantially impact treatment results. As a result, while PGx testing is an effective tool for customizing therapy, it should be used with extensive clinical judgment rather than as a sole predictor of optimal treatment [8]. This approach tailors medical treatment to an individual's unique genomic makeup to improve treatment outcomes and minimise adverse effects [5].

Individual genetic variations play a significant role in influencing the effectiveness and safety of medications. Genetic differences in drug-metabolising enzymes, transporters, receptors, and other therapeutic targets have been related to interindividual variances in the efficacy and safety of several frequently prescribed medications such as antidepressants (e.g., selective serotonin uptake inhibitors, SSRI) and anticoagulants (e.g., warfarin), which account for approximately 20-30% of medication response variability [9]. Genetic differences do not follow a consistent pattern among populations. Instead, they show significant variation within and between different geographical ancestries [10]. For example, specific PGx variants that impact drug metabolism are more commonly found in certain populations, leading to variations in drug response and the occurrence of adverse effects.

Acknowledging and understanding these genetic variations specific to different populations is essential for the successful application of personalised medicine. This knowledge enables clinicians to customize treatments that are safe and effective for a wide range of patients [11,12]. Inter-individual genetic differences within and between geographical ancestry contribute significantly to medication response variability and are linked to variants affecting the pharmacokinetics (PK) and pharmacodynamics (PD) of drugs [13,14]. The British Pharmacological Society and the Royal College of Physicians have urged patients to be examined for genetic variations that can impact respond to commonly utilised drugs [15]. The U.S. Food and Drug Administration (FDA) recommends genetic screening before using certain medications [16].

Developing countries are the strongest users of PGx-guided therapy [17–20]. However, the utilisation of PGx across Europe varies [21–23]. The public seemed to prefer and opt for PGx testing, especially those with chronic diseases [24]. Gene-drug interaction variability within the European population has been established and has thus increased the scope for PGx [25].

An observational study from the United Kingdom discussed the implementation of PGx testing in secondary care for high-risk medications. The authors emphasised the need for broader application in primary care owing to the high prescribing tendency in the community [26] . The adoption of PGx testing services in different healthcare settings has varied owing to a multitude of factors, including the promotion of appropriate and evidence-based medication usage, ethical considerations, legal implications, healthcare provider and patient education, support for electronic health records, clinical utility and validity of test outcomes, accessibility, regulatory frameworks, as well as availability and affordability. [20,27–30]. The cost implications of PGx testing depend on the insurance coverage offered by companies. Few insurance firms offer coverage for PGx testing, and those that do must follow strict guidance and policies to justify and approve requested PGx tests [31]. This can affect the preference for pre-emptive PGx and reactive PGx testing [32]. Both pre-emptive and reactive testing have been found to be cost-effective in different disease states or clinical care contexts and positively impact patient outcomes [33].

The US FDA has emphasised the importance of PGx testing for drug discovery, development, and treatment of patients. Five hundred different biomarkers concerning drugs have been stated in their public domain [34]. Similarly, the European Medicines Agency has guidelines regarding the use of PGx testing during drug approval processes [35]. Despite the regulatory authorities' new recommendation to incorporate PGx testing in the drug approval process, testing regarding marketed products is also not a routine practice. Moreover, patients were also disrupted from subscribing to the PGx testing due to the availability of resources and many hindrances factors that may vary across the nation [36].

While PGx testing offers several benefits, it is important to acknowledge the ethical concerns surrounding it, especially in a primary care setting. Ethical dilemmas may emerge due to the potential misuse of informed consent in genomic testing, including the potential dangers, risk, harms, and consequences associated with genomic information [37,38]. Additionally, genomic information may raise questions about ownership, access rights, affordability, fiduciary responsibility, respect, and the possibility of discrimination [37,38]. Furthermore, there are concerns about the administering PGx testing among vulnerable communities. Assessing the potential long-term implication of identifying genomic variability in different categories of vulnerable population may raise ethical concerns. [37–39].

References in the literature provide evidence for pharmacogenomics testing in primary care. Through prospective trials, it has been demonstrated that when paired with comprehensive medication management services and point-of-care clinical decision support systems, improvised drug prescribing lessened the burden of mental illness, thereby enhancing clinical outcomes [40]. Barriers such as a perceived lack of knowledge on acceptance, scalability, and implementation and insufficient evidence of therapeutic outcomes improvement have been reported [41]. Financial constraints and the knowledge and abilities of healthcare professionals hinder implementation [42].

Moreover, since the interpretation of genomic information is still evolving, inadequate inferences or confounding factors may cause healthcare providers to opt for incorrect treatment, complicating the ethical landscape and raising public concern about their health [43]. While PGx testing offers positive benefits, it is important to acknowledge the concerns related to this practice, especially in a primary care setting. Thus, this scoping review was conducted to systematically review the current state of PGx in the primary care and determine the enablers as well as challenges of implementing PGx testing in primary care settings.

Methods

A scoping review was carried out by adhering to Arksey and O'Malley's 6-stage (step 1 to step 6) methodological framework and the 2020 Joanna Briggs Institute (JBI) [44,45]. Covidence™, a web-based collaboration software platform designed to facilitate carrying out reviews such as systematic reviews and scoping reviews, was utilised for the review [46]. Further, Levac and colleagues' recommendations were applied to maximise the methodological rigor and, thus, reported the details of the six stages under the following subheading [47]. The Preferred Reporting Items for Systematic Review and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) checklist was used to guide the reporting of this review [48].

1- Identifying the review question

CWM, an expert in the field of PGx, and KA, a primary care research expert had the initial discussion about the potential review questions that could address some of the gaps in the current literature on PGx testing and its applications in primary care settings. All authors are academics who joined the subsequent discussions, clarified the aims and objectives of the scoping review, and collectively agreed on the following review question: "What are the enablers and the challenges of implementing PGx testing in primary care settings?"

2- Identifying the relevant studies

The authors agreed on the search strategy with no limits on publication dates. The search was concluded on 17th July 2023 based on the predetermined search strategy (Supplementary File 1). We consolidated the search resources following advice from a subject librarian to ensure a wide range of relevant databases such as Cochrane Library, EMBASE, Global Health, MEDLINE, and PubMed. The International Prospective Registry of Systematic Reviews (PROSPERO) was also reviewed for any similar studies, both ongoing or completed, to avoid any potential duplication. Articles in English were only considered due to a lack of resources for translating studies. The inclusion and exclusion criteria were finalised through an iterative process to allow necessary refinements following initial searches (see Table 1).

Table 1 Inclusion and Exclusion Criteria

Criterion	Inclusion	Exclusion
Period	Any	-
Literature	Peer-reviewed articles	Review articles of any type, non-peer-reviewed academic articles
Geographical location	Any	-
Setting	Primary care settings	Secondary and tertiary care settings
Study Focus	Information on the pharmacogenomics testing implementation in primary care settings	No information is directly related to the implementation of pharmacogenomics testing in primary care settings.
Study Design	All types of qualitative and quantitative studies, clinical audits	All types of reviews, including systematic reviews, meta-analysis
Language	English	Other languages than English

3- Selecting the studies

Articles were identified across five databases, which were exported into Covidence™ for further processing. Two reviewers independently screened each article, and a third reviewer resolved any discrepancies.

4- Charting the data

Data charting facilitates the transfer of the relevant information from the selected articles into a data extraction table (5). The authors created a data extraction template using the Covidence™ extraction template. The data extraction template was contextualized to meet the study objectives and the research questions proposed at the beginning of the review, which contained standard information such as title, lead author, type of study, aims, objectives, key stakeholders, findings in relation to the enablers and the challenges of implementing PGx in the primary care settings and recommendations. All authors were involved in charting the data, and PMG carried out most data extraction. Although data extraction needed one reviewer per article, KA checked each article's extraction data for final approval.

5- Collating, summarising, and reporting the results

KA and PMG synthesized the results by collating and summarising the findings following data charting. Results were then presented to the rest of the authors for their comments and interpretations. The authors were registered pharmacists who had the experience of practicing in primary care settings. They discussed the results from the practice and policy's point of view. The authors did not carry out a quality assessment exercise as scoping reviews do not normally need an appraisal for quality and bias due to their descriptive nature (6).

6- Consulting stakeholders

Although stakeholders' involvement and consultation are not mandatory stages for conducting scoping reviews, we involved a subset of stakeholders who were available to us in two stages. These stakeholders were the primary care physicians or community pharmacists who were elected leaders in their respective professional societies and had at least 10 years primary care clinical experience. Invitations were sent by the research team to all eligible stakeholders. All stakeholders who declared no conflict of interests with any PGx service provider were to participate. We conducted a brainstorming session with these stakeholders. The ten stakeholders were from independent or chain medical clinics (n = 5) or community pharmacies (n = 5). We then presented the findings to them for their comments and feedback.

Patient and public involvement

There were no patient or public involvement in addition to the above-mentioned stakeholders.

Results

A total of 1251 articles were initially identified across five databases, i.e., PubMed (n = 690), MEDLINE (n = 288), Embase (n = 239), Cochrane Library (n = 26), and Global Health (n=8). 291 duplicates were removed, leaving 960 articles for title and abstract screening. A total of 378 articles met the inclusion and exclusion criteria for full-text screening. We present the findings from 78 studies on different aspects of PGx testing implementation in primary care settings, such as stakeholders' views and involvement, enablers, and challenges of implementing PGx testing (Supplementary File 2). The PGx testing in the primary care setting in these studies was discussed either as disease-specific themes (n = 53), such as mental health conditions, cardiovascular conditions, diabetes, etc., or population-specific themes (n= 11), such as general patient population, paediatric and geriatric patient population, or public health themes (n=3) and others not specified (n=11). The full-text screening eliminated 290 articles because of wrong context/setting (n = 148), no full-text availability, e.g., for poster/conference papers (n = 59), wrong study design or application or outcomes (n = 51) and non-peer reviewed commentary (n = 32) and thus, 78 studies were included in the final review upon which results are reported (Figure 1).

Insert Figure 1 here.

Publication date

The earliest publication was in the Year 2007, and the latest publication was in 2023 when data collection ended. More than half of the studies (57%) were published in the period between 2019 to date. Nearly one-third (n=22) of studies were published between the years 2016 and 2018. The number of publications has increased significantly in the last six years, i.e., between 2018 and 2023.

Types of studies and location

A wide array of study designs was pulled together in this review, ranging from commentaries (n =2) to qualitative studies (n = 7) to quantitative studies (n=16), including randomised controlled trials (n=5) to mixed methods studies (n =54). An overwhelming majority of the studies were from the global north (n = 77), e.g., 51 studies from the US and its territory, 12 studies from Canada, 14 studies from the EU, while there was only one study from Singapore. (Figure 2) The study types can be categorised into Quantitative Studies (n = 16) and Mixed Method Studies (n = 54). Quantitative studies can be further divided into (i) Randomized Controlled Trials (n = 5), wher the controlled experimental settings were

used to assess the efficacy of PGx testing; (ii) Cohort Studies (n = 4), where these groups were monitored over time to evaluate the outcomes of PGx testing; (iii) Cross-Sectional Surveys (n = 3), where one-time data collection methods were used to evaluate respondents' beliefs, expertise, and PGx-related behaviour; (iv) Case-Control Studies (n = 2) where the effects of PGx testing were examined by comparing individuals with particular results to those without; and (v) Pre-Post Intervention Studies (n = 2), where the outcomes were examined both before and after PGx testing was used.

In addition, Mixed Methods Studies (n = 54) can be further categorised into (i) Explanatory Sequential Designs (n = 15), where quantitative data were gathered first, followed by qualitative data to explain the quantitative results; (ii) Exploratory Sequential Designs (n = 20), where quantitative data were collected after conducting qualitative research to create or refine hypotheses; and (iii) Convergent Parallel Designs (n = 19),where qualitative and quantitative data were gathered concurrently, the finding were compared and comprehensive conclusions were drawn. This thorough analysis addresses the variability within the broader categories of quantitative and mixed methods research, providing a deeper understanding of the studies covered in the study.

Stakeholders

From the selected literature, the stakeholders included the service users/patients, members of the public, healthcare professionals including general practitioners, physicians, pharmacists, nurses, physician assistants, public health consultants/professionals, geneticists, phlebotomists, genetic counsellors, mental health providers, obstetricians, gynaecologist, psychiatrists, and cardiologist. Most of the stakeholders were primary care physicians (n = 43), followed by pharmacists (n = 32), allied healthcare professionals (n = 27), and primary care providers who were not specified (n = 15) (Supplementary File 3). Additionally, there was general agreement with the results when they were presented to a panel of stakeholders (n = 10) whom we had individually consulted for this study.

Current status of pharmacogenomics testing in the primary care settings

To understand the current status of PGx testing in primary care, we classified the key conclusion of these studies into 3 categories, namely the (i) favourable view in which the key conclusion supports PGx implementation in primary care; (ii) not favourable, in which the key conclusion does not support PGx implementation in primary care; and (iii) neutral views in which the study did not provide a clear stance on supporting or not supporting PGx implementation in primary care. More than half (52%) of the studies had favourable views toward the status of PGx testing in primary care settings, whereas

43% of the studies had unfavourable views, and 5% of the studies offered neither favourable nor unfavourable views (Supplementary File 4). Most of the favourable views stemmed from the perceived benefits of PGx testing to the patient's clinical outcomes, selection of the most precise treatment modality, decrease in the incidences of adverse drug reactions due to polypharmacy, and improved medication adherence.[49,50] Other favourable opinions were the health systems level benefits of PGx testing, such as lowering the healthcare costs and broader applicability of PGx in the areas of preventive care, population health, and community health interventions [51].

The main reasons for unfavourable opinions were the perceived lack of information or findings on the acceptability, scalability, and implementation aspects of pharmacogenomics testing in primary care settings. Furthermore, the perceived limited evidence of the effectiveness of PGx testing on impacting clinical outcomes, limited knowledge and skills of the healthcare professionals to operationalize PGx testing in the routine delivery of care as well and financial concerns, data security were some of the unfavourable concerns to implementing PGx testing in the primary care settings [49,52,53]. Specifically, Türkmen D et al highlighted PGx results could be guided by databases such as PharmGKB, which contains studies with low or moderate level of evidence. They also noted that the study design, with qualitative studies not being meantfor generalisability of the findings, along with factors such as diverse ethnicity, heterogeneity, poor compliance to medication, statistical bias and publication bias, may further limit the implementation of PGx in primary care[49].

Enablers of PGx testing implementation in the primary care setting

The benefits of using PGx testing in primary care settings were discussed in almost all studies (n=77). PGx testing implementation was facilitated by three main factors, broadly: a) diagnostic and therapeutic benefits in collaborative practice; b) reduction in healthcare costs; and c) empowering healthcare professionals to deliver their clinical services, especially for the physicians and community pharmacists. A total of 23 studies reported other possible enablers, including programmes that support clinical decision-making, precision medicine, personalised medicine, individualized care, drug-drug interactions, patient safety, and optimal medication use.

Diagnostic and therapeutic benefits in collaborative practice:

Around 10% (n = 12) of the studies reported the findings that pharmacogenomics supports collaborative clinical practice by allowing a precise choice of therapeutic agents in treating patients. For example, findings from a primary care precision medicine clinic offering PGx services at the University of Pittsburgh Medical Centre Health System showed that genotype-guided clinical decisions

successfully supported the primary care providers' adoption of genetic information to guide statin therapy in routine clinical practice [54]. A UK study described the benefits of PGx testing to support personalised medicine and the management of calcium channel blocker side effects through genomic-guided information on pharmacogenetic variations [55].

Reduction in healthcare costs:

The potential for cost-saving associated with the implementation of PGx testing was mentioned in 20% of the studies (n = 15). Various cost-saving approaches were proposed, namely (i) economic evaluations; (ii) stakeholders perceptions; and (ii) indirect evidence. Formal economic evaluations were used in several studies to determine whether PGx testing was cost-effective. Cost-utility, cost-benefit, and cost-effectiveness studies were frequently performed as part of these assessments. For example, when PGx testing guided drug selection and dose decisions, a randomized controlled trial found lower healthcare expenditures due to fewer adverse drug events (ADEs) occurred. This study measured the financial gains connected with fewer ADEs and hospitalizations using a cost-effectiveness methodology [56]. An economic evaluation approach was employed in prospective cohort research conducted in Singapore to evaluate the effects of a PGx-based medical decision support system on healthcare expenditures and quality. The study showed that by enhancing medication dosage and improving treatment results, PGx testing led to cost savings [57].

In term of stakeholder perceptions, some research examined cost-savings from the viewpoint of stakeholders, such as legislators and healthcare professionals, in addition to economic evaluations. Stakeholders believed that PGx testing could be an effective way to reduce overall healthcare costs by minimizing trial-and-error prescribing and the adverse drug experiences that come with it. Qualitative interviews with primary care physicians, for instance, revealed that PGx testing could save long-term expenses by enabling more accurate medication administration. Alternative approaches would be through indirect evidence. A few studies highlighted improvements in patient outcomes that were associated with lower healthcare utilization, which served as an indirect source of cost-saving data. These studies suggested that more targeted treatments resulting from PGx testing could reduce total healthcare costs by avoiding the need for extra interventions, even though they did not conduct direct economic evaluations.

Empowering healthcare professionals to deliver their clinical services

Over 28% studies emphasized the importance of incorporating healthcare professionals such as community pharmacists, to improve patient care through implementing PGx in a primary care setting.

The advantages of involving community pharmacists in administering PGx testing include (i) enhanced medical management, (ii) increased accessibility and patient engagement, (iii) better integration with clinical decision support systems, and (iv) increased physician adoption of PGx. By using PGx testing, community pharmacists can customize more drug regimens based on each patient's unique genetic profile, leading to fewer adverse drug reactions (ADRs) and increased efficacy. An open-label, non-randomized observational trial reported better patient outcomes from community pharmacists based PGx screening, since pharmacists could efficiently provide more input on the regimens [58].

In addition, patients' accessibility to PGx testing is increased when it is incorporated into community pharmacy practices, especially in underprivileged areas. Research indicated that patients whom experienced easier access to genomic services via their neighbourhood pharmacies, were likely to have thoughtful and educated conversations regarding their treatment options [59] . Community pharmacists play a crucial role in helping patients understand the meaning of PGx test results. Patients would then adhere to the individualized treatment programs when they are more educated about how genetic information can guide their pharmaceutical choices.

Interesting, including PGx testing in a clinical decision support system (CDSS), greately enhanced its efficacy. Research indicated that community pharmacists who used CDSSs in combination with PGx testing were more capable of making well-informed choices regarding medication dosage and therapy modifications. This integration reduces the possibility of drug errors and helps provide more accurate recommendations [59] . Moreover, physician preference for PGx in patient care has increased due to the convenience of receiving PGx services through community pharmacists. By collaborating with pharmacists, who perform PGx testing, physician can focus on better decision-making, and ultimately improves patient outcomes [60].

Challenges of pharmacogenomics testing implementation in the primary care setting

The challenges of implementing PGx testing in primary care settings were discussed in all studies (n = 78). There were four main areas of challenge: a) dearth of data on the scientific evidence such as clinical-genomic databases; b) lack of bespoke PGx training modules/courses for the healthcare professionals to apply the PGx testing principles; c) dearth of data on patient awareness and acceptability of the use of PGx testing in patient care; and d) high costs associated with PGx testing.

The dearth of data on scientific evidence, such as clinical-genomic databases:

Forty-five percent of the studies (n = 35) reported the lack of solid scientific evidence to produce reliable clinical-genomic databases and clinical practice guidelines (n = 35), followed by perceived publication bias (n = 23) in the studies in the field of PGx. For example, a 2017 study highlighted that

a constraint of the study was the limited sample size, which might have introduced bias as the findings might not accurately reflect the viewpoints of all primary care physicians or those within the chosen primary practice sites [61]. Almost a quarter (n = 18) of the studies also acknowledged that their studies may had the inevitable recruitment bias, which could limit the potential to immediately implement PGx findings across all populations in primary care settings.

Lack of bespoke PGx training modules/courses for the healthcare professionals:

The insufficiency of appropriate training for primary care providers to administer PGx testing was a notable obstacle identified in 17 studies. Each healthcare practitioner have distinct PGx training. Due to their limited exposure to genetic concepts and how they are applied in daily practice, many primary care physicians (PCPs) report feeling unprepared to use PGx testing. PCPs need comprehensive primary care training to evaluate PGx test results and incorporate them into clinical decision-making. Training courses must concentrate on managing drug-gene interactions, using genetic information to inform medication selection and dosage, and clearly communicating findings to patients. Nurse practitioners' capacity to offer effective patient education and individualized medication management is hampered by their lack of PGx testing-specific training such as data analysis, and the incorporation of PGx data into patient care plans. In addition, the limited availability of specialised training programs for pharmacists also hinders their ability to apply PGx testing in their practice [62]. Specific trainings for pharmacists should include interpreting of genetic data, applying PGx in drug therapy management, and integrating into pharmacy practice. The inadequacy of customized training programs for these diverse healthcare worker groups limits their ability to apply PGx testing in primary care environments. Addressing this gap with focused educational initiatives is essential to optimizing the benefits of PGx technology.

The dearth of data on patient awareness and acceptability of the use of PGx testing

Around 10% of the studies reported the dearth of data on patient awareness and patient acceptability of the PGx testing as a barrier to the implementation of pharmacogenomics testing in primary care settings. For instance, a 2017 study showed the importance of patients' willingness to consent to be involved in clinical-genomic treatment modalities, which would need patients to be fully aware of the technical aspects of PGx testing, including ethical aspects [63]. A qualitative study revealed that patient anxiety and fear of disclosing genetic information to a third party was the main barrier to the implementation of PGx testing in primary care settings [62].

High costs associated with PGx testing:

Almost 20% (n = 14) of the studies mentioned high costs associated with pharmacogenomics testing in primary care settings. Insurance coverage, out-of-pocket expenditure, and institutional return of

investment – investment in setting up PGx testing – were among the points raised in regards to the costs and who should bear the cost based on the healthcare systems in the global north, Western Europe, and Australasia [5,64,65].

Insert Figure 2 here.

Discussion

Primary care physicians play a key role in incorporating PGx into standard clinical practice. Primary healthcare professionals need to educate patients on the importance of genetic data and how it affects individualised treatment plans. Collaboration with genetic counsellors and other medical professionals can also help maximise the use of PGx in patient care. Genetic counselors assist individuals and healthcare providers in better understanding intricate genetic details (63).

Collaboration among academia, healthcare, industry, and regulatory agencies is essential for integrating PGx into clinical practice [66,67]. PGx has been effectively integrated into healthcare systems in both the US and the UK. There is significant variation in the implementation of PGx across Europe [21] and Gulf Cooperation Council (GCC) countries like Saudi Arabia, UAE, and Qatar [17,18].PGx has made significant progress in the UK, with the NHS supporting genetic screening to enhance medication therapy [22]. Similarly, it is also utilised in Australia and Canada to enhance the optimal clinical decision [68,69]. On the other hand, there is a rise in the PGx utility in Singapore, Japan, South Korea, and China, particularly for chronic diseases [19,57,70]. Some regions still face complex regulatory structures and ethical issues, and this is a big challenge [71]. Regulatory agencies' well-defined guidelines give healthcare providers confidence and create an environment in which PGx practices are not only acceptable but actively promoted [72]. The regulatory environment is greatly influenced by policymakers, who make sure that it permits a smooth integration of PGx into standard primary care practice and keeps pace with the field's rapid evolution.

Several studies emphasise the importance of PGx testing in cardiovascular diseases and neuropsychiatry disorders [23,56,73–75] due to its ability to choose more precise treatment modalities, a reduction in adverse drug reactions caused by polypharmacy, and a significantly improved medication adherence [74,76,77]. However, the dearth of data on scientific evidence, particularly in areas such as clinical genomic databases, poses a significant challenge for pharmacogenomic testing. One of the obstacles is the limited availability of high-quality genomic data linked to clinical outcomes [78]. Clinical genomic databases that integrate genetic information with patient health records are crucial for understanding how genetic variations influence drug response and adverse reactions. Moreover, the heterogeneity of genetic backgrounds among populations further complicates the issue [79].

Additionally, there are challenges related to data privacy, consent, and ethical considerations when it comes to sharing genomic and clinical information [80]. Striking the right balance between data accessibility and protection of patient privacy is essential but complex. Investments in data infrastructure, standardisation of data formats and protocols, and initiatives to promote data sharing and collaboration are critical.

Another challenge is the rapid pace of advancements in PGx, which can make it difficult for healthcare professionals to stay updated with the latest developments [81]. Without clear guidelines or accreditation standards, healthcare professionals may struggle to identify reputable training opportunities or gauge the quality of the education they receive. Addressing these challenges requires concerted efforts from various stakeholders. Healthcare institutions and professional regulatory bodies can play a crucial role in advocating for the integration of PGx education into medical school curricula, residency training programs, and continuing education courses [18].

Additionally, there may be barriers to patient acceptability related to trust and confidence in the healthcare system and genetic testing technologies. Patients may have concerns about the privacy and security of their genetic information, as well as apprehensions about potential discrimination or stigmatisation based on genetic predispositions to certain health conditions [82–84]. Commercial companies' access to patients' genetic data is also a concern, hence the need for reviewing and updating the existing data privacy act and rules to improve the public preferences towards PGx testing [66]. Building trust using enhanced medical technologies and addressing these concerns is essential for promoting patient acceptability of PGx testing [85]. Tailoring educational materials and communication strategies to meet the needs of diverse patient populations is crucial for promoting awareness and acceptability of PGx testing.

PGx testing's extensive utilisation can reduce healthcare costs and enhance preventive care, population health, and community initiatives [86,87]. Moreover, PGx testing costs have decreased over time, but access for patients may still be restricted by financial issues, especially in primary care settings where resources may be scarce.

Conclusion

Successful integration of pharmacogenomic testing into primary care demands a multi-faceted approach that strengthens enablers and addresses challenges (Supplementary File 5) . This entails enhancing consumer awareness, providing comprehensive training for healthcare providers, and

furthering scientific research to elucidate both the clinical benefits and cost-effectiveness of such testing. Additionally, it is imperative to conduct feasibility studies encompassing various countries and healthcare systems to fully understand the potential enablers and challenges of implementing pharmacogenomic testing in primary care. Currently, the available data predominantly stems from the global north, leading to a gap in knowledge regarding its applicability in diverse cultural and resource-constrained settings.

Addressing the high costs associated with PGx testing requires a multi-faceted approach. Efforts are needed to streamline testing processes, improve efficiency, and reduce the overall cost of testing. This may involve the development of standardised testing protocols, the use of automation and high-throughput technologies, and the optimisation of bioinformatics pipelines.

Contributors

CWM and KA contributed to the planning and finalizing of the conception as well as design of the review. All authors (CWM, SBS, MSK, PMG, JS, ELL, and KA) contributed in the screening, and data extraction. CWM and KA analysed the data. CWM led on stakeholder consultation sessions. KA drafted the methodology and results sections. All authors (CWM, SBS, MSK, PMG, JS, ELL, and KA) contributed to the data interpretation and subsequently to the drafting, and revisions of the manuscript. All authors (CWM, SBS, MSK, PMG, JS, ELL, and KA) gave their approval to the final version of the for publication. KA is responsible for the overall content as the guarantor.

Funding

CWM is a recipient for the Fundamental Research Grant Scheme (Grant Number: FRGS/1/2023/SKK10/UCSI/02/1) from the Malaysia's Ministry of Higher Education and UCSI University Research Excellence & Innovation Grant (Grant Number: REIG-FPS-2023/038) .

KA is in part supported by the National Institute for Health and Care Research (NIHR) Applied Research Collaboration (ARC) Northwest London (Grant Number: N/A). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

Funding to pay the Open Access publication charges for this article was provided by the Imperial Open Access Fund (Grant Number: N/A).

Competing interests

None declared.

Provenance and peer review

None commissioned, externally peer reviewed.

Data sharing statement

Data are available upon reasonable request.

Ethics approval statement

This study does not involve human participants.

References

1. Pirmohamed M. Pharmacogenetics and pharmacogenomics. *Br J Clin Pharmacol*. 2001;52(4):345-347. doi:10.1046/j.0306-5251.2001.01498.x

2. Nebert DW. Pharmacogenetics and pharmacogenomics: why is this relevant to the clinical geneticist? *Clin Genet*. 1999;56(4):247-258. doi:10.1034/j.1399-0004.1999.560401.x

3. Sachidanandam R, Weissman D, Schmidt SC, et al. A map of human genome sequence variation containing 1.42 million single nucleotide polymorphisms. *Nature*. 2001;409(6822):928-933. doi:10.1038/35057149

4. Goetz LH, Schork NJ. Personalized medicine: motivation, challenges, and progress. *Fertil Steril*. 2018;109(6):952-963. doi:10.1016/j.fertnstert.2018.05.006

5. Brown-Johnson CG, Safaeinili N, Baratta J, et al. Implementation outcomes of Humanwide: integrated precision health in team-based family practice primary care. *BMC Fam Pract*. 2021;22(1):28. doi:10.1186/s12875-021-01373-4

6. Hull LE, Vassy JL, Stone A, et al. Identifying End Users' Preferences about Structuring Pharmacogenetic Test Orders in an Electronic Health Record System. *J Mol Diagn JMD*. 2020;22(10):1264-1271. doi:10.1016/j.jmoldx.2020.06.015

7. Chenchula S, Atal S, Uppugunduri CRS. A review of real-world evidence on preemptive pharmacogenomic testing for preventing adverse drug reactions: a reality for future health care. *Pharmacogenomics J*. 2024;24(2):9. doi:10.1038/s41397-024-00326-1

8. Polasek TM, Mina K, Suthers G. Pharmacogenomics in general practice: The time has come. *Aust J Gen Pract*. 2019;48(3):100-105. doi:10.31128/AJGP-10-18-4733

9. Heller F. Genetics/genomics and drug effects. *Acta Clin Belg*. 2013;68(2):77-80. doi:10.2143/ACB.3210

10. Dattani S, Howard DM, Lewis CM, Sham PC. Clarifying the causes of consistent and inconsistent findings in genetics. *Genet Epidemiol*. 2022;46(7):372-389. doi:10.1002/gepi.22459

11. Nagar SD, Conley AB, Jordan IK. Population structure and pharmacogenomic risk stratification in the United States. *BMC Biol*. 2020;18(1):140. doi:10.1186/s12915-020-00875-4

12. Magavern EF, Gurdasani D, Ng FL, Lee SSJ. Health equality, race and pharmacogenomics. *Br J Clin Pharmacol*. 2022;88(1):27-33. doi:10.1111/bcp.14983

13. McGraw J, Waller D. Cytochrome P450 variations in different ethnic populations. *Expert Opin Drug Metab Toxicol*. 2012;8(3):371-382. doi:10.1517/17425255.2012.657626

14. Pirmohamed M. Personalized pharmacogenomics: predicting efficacy and adverse drug reactions. *Annu Rev Genomics Hum Genet*. 2014;15:349-370. doi:10.1146/annurev-genom-090413-025419

15. Mahase E. Offer patients genetic tests to see if medicines are safe and effective, says Royal College of Physicians. *BMJ*. 2022;376:o821. doi:10.1136/bmj.o821

16. Chang CJ, Chen CB, Hung SI, Ji C, Chung WH. Pharmacogenetic Testing for Prevention of Severe Cutaneous Adverse Drug Reactions. *Front Pharmacol*. 2020;11:969. doi:10.3389/fphar.2020.00969

17. Algahtani M. Knowledge, Perception, and Application of Pharmacogenomics Among Hospital Pharmacists in Saudi Arabia. *Risk Manag Healthc Policy*. 2020;13:1279-1291. doi:10.2147/RMHP.S267492

18. Rahma AT, Elbarazi I, Ali BR, Patrinos GP, Ahmed LA, Al Maskari F. Genomics and Pharmacogenomics Knowledge, Attitude and Practice of Pharmacists Working in United Arab Emirates: Findings from Focus Group Discussions—A Qualitative Study. *J Pers Med*. 2020;10(3):134. doi:10.3390/jpm10030134

19. Zhang J, Qi G, Han C, et al. The Landscape of Clinical Implementation of Pharmacogenetic Testing in Central China: A Single-Center Study. *Pharmacogenomics Pers Med*. 2021;14:1619-1628. doi:10.2147/PGPM.S338198

20. Ayati N, Afzali M, Hasanzad M, Kebriaeezadeh A, Rajabzadeh A, Nikfar S. Pharmacogenomics Implementation and Hurdles to Overcome; In the Context of a Developing Country. *Iran J Pharm Res IJPR*. 2021;20(4):92. doi:10.22037/ijpr.2021.114899.15091

21. Bank PCD, Swen JJ, Schaap RD, Klootwijk DB, Baak-Pablo R, Guchelaar HJ. A pilot study of the implementation of pharmacogenomic pharmacist initiated pre-emptive testing in primary care. *Eur J Hum Genet EJHG*. 2019;27(10):1532-1541. doi:10.1038/s41431-019-0454-x

22. Turner RM, Newman WG, Bramon E, et al. Pharmacogenomics in the UK National Health Service: opportunities and challenges. *Pharmacogenomics*. 2020;21(17):1237-1246. doi:10.2217/pgs-2020-0091

23. Bose-Brill S, Xing J, Barnette DJ, Hanks C. Pharmacogenomic testing: aiding in the management of psychotropic therapy for adolescents with autism spectrum disorders. *Pharmacogenomics Pers Med*. 2017;10(101514107):247-252. doi:10.2147/PGPM.S130247

24. O'Shea J, Ryan C, Gallagher J, et al. Public perceptions of pharmacogenomic services in Ireland - Are people with chronic disease more likely to want service availability than those without? A questionnaire study. *Explor Res Clin Soc Pharm*. 2022;8(9918266300706676):100182. doi:10.1016/j.rcsop.2022.100182

25. Mizzi C, Dalabira E, Kumuthini J, et al. A European Spectrum of Pharmacogenomic Biomarkers: Implications for Clinical Pharmacogenomics. *PloS One*. 2016;11(9):e0162866. doi:10.1371/journal.pone.0162866

26. Youssef E, Kirkdale CL, Wright DJ, Guchelaar HJ, Thornley T. Estimating the potential impact of implementing pre-emptive pharmacogenetic testing in primary care across the UK. *Br J Clin Pharmacol*. 2021;87(7):2907-2925. doi:10.1111/bcp.14704

27. Stanek EJ, Sanders CL, Taber KAJ, et al. Adoption of pharmacogenomic testing by US physicians: results of a nationwide survey. *Clin Pharmacol Ther*. 2012;91(3):450-458. doi:10.1038/clpt.2011.306

28. Liko I, Lee YM, Stutzman DL, et al. Providers' perspectives on the clinical utility of pharmacogenomic testing in pediatric patients. *Pharmacogenomics*. 22(5):263-274. doi:10.2217/pgs-2020-0112

29. Saunders H, Harris D, Chirilă RM. Pharmacogenomics: introduction and use in clinical practice. *Romanian J Intern Med Rev Roum Med Interne*. 2020;1;58(2):69–74.

30. Kabbani D, Akika R, Wahid A, Daly AK, Cascorbi I, Zgheib NK. Pharmacogenomics in practice: a review and implementation guide. *Front Pharmacol*. 2023;14(1189976).

31. Pharmacogenomic cost, Mankato. Mayo Clinic Health System. Accessed March 6, 2024. https://www.mayoclinichealthsystem.org/locations/mankato/services-and-treatments/pharmacogenomics/cost-and-insurance

32. Zhu Y, Moriarty JP, Swanson KM, et al. A model-based cost-effectiveness analysis of pharmacogenomic panel testing in cardiovascular disease management: preemptive, reactive, or none? *Genet Med Off J Am Coll Med Genet*. 2021;23(3):461-470. doi:10.1038/s41436-020-00995-w

33. Roden DM, Van Driest SL, Mosley JD, et al. Benefit of pre-emptive pharmacogenetic information on clinical outcome. *Clin Pharmacol Ther*. 2018;103(5):787-794. doi:10.1002/cpt.1035

34. Research C for DE and. Table of Pharmacogenomic Biomarkers in Drug Labeling. *FDA*. Published online February 2, 2024. Accessed March 6, 2024. https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling

35. Use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products - Scientific guideline | European Medicines Agency. Accessed March 6, 2024. https://www.ema.europa.eu/en/use-pharmacogenetic-methodologies-pharmacokinetic-evaluation-medicinal-products-scientific-guideline

36. Young J, Bhattacharya K, Ramachandran S, Lee A, Bentley JP. Rates of genetic testing in patients prescribed drugs with pharmacogenomic information in FDA-approved labeling. *Pharmacogenomics J*. 2021;21(3):318-325. doi:10.1038/s41397-021-00211-1

37. Gershon ES, Alliey-Rodriguez N, Grennan K. Ethical and public policy challenges for pharmacogenomics. *Dialogues Clin Neurosci*. 2014;16(4):567-574.

38. Peterson-Iyer K. Pharmacogenomics, ethics, and public policy. *Kennedy Inst Ethics J*. 2008;18(1):35-56. doi:10.1353/ken.0.0004

39. Stratton TP, Olson AW. Personalizing Personalized Medicine: The Confluence of Pharmacogenomics, a Person's Medication Experience and Ethics. *Pharmacy*. 2023;11(3):101. doi:10.3390/pharmacy11030101

40. O'Donnell PH, Wadhwa N, Danahey K, et al. Pharmacogenomics-Based Point-of-Care Clinical Decision Support Significantly Alters Drug Prescribing. *Clin Pharmacol Ther*. 2017;102(5):859-869. doi:10.1002/cpt.709

41. Kehr AM, Ayers G, Saxena S, et al. Integration of a pharmacist-led pharmacogenomic service in a geriatric clinic: Barriers and outcomes. *J Am Pharm Assoc*. 2023;63(3):778-784. doi:10.1016/j.japh.2023.01.001

42. Rafi I, Crinson I, Dawes M, Rafi D, Pirmohamed M, Walter FM. The implementation of pharmacogenomics into UK general practice: a qualitative study exploring barriers, challenges and opportunities. *J Community Genet*. 2020;11(3):269-277. doi:10.1007/s12687-020-00468-2

43. Donohue KE, Gooch C, Katz A, Wakelee J, Slavotinek A, Korf BR. Pitfalls and challenges in genetic test interpretation: An exploration of genetic professionals experience with interpretation of results. *Clin Genet*. 2021;99(5):638-649. doi:10.1111/cge.13917

44. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. *Int J Soc Res Methodol*. 2005;8(1):19-32. doi:10.1080/1364557032000119616

45. Peters MDJ, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. *Int J Evid Based Healthc*. 2015;13(3):141-146. doi:10.1097/XEB.0000000000000050

46. Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org.

47. Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. *Implement Sci*. 2010;5(1):69. doi:10.1186/1748-5908-5-69

48. Tricco AC, Lillie E, Zarin W, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Ann Intern Med*. 2018;169(7):467-473. doi:10.7326/M18-0850

49. van der Wouden CH, Paasman E, Teichert M, Crone MR, Guchelaar HJ, Swen JJ. Assessing the Implementation of Pharmacogenomic Panel-Testing in Primary Care in the Netherlands Utilizing a Theoretical Framework. *J Clin Med*. 2020;9(3). doi:10.3390/jcm9030814

50. Gammal RS, Berenbrok LA, Empey PE, Massart MB. Documenting Pharmacogenomic Test Results in Electronic Health Records: Practical Considerations for Primary Care Teams. *J Pers Med*. 2021;11(12). doi:10.3390/jpm11121296

51. Brunette CA, Miller SJ, Majahalme N, et al. Pragmatic Trials in Genomic Medicine: The Integrating Pharmacogenetics In Clinical Care (I-PICC) Study. *Clin Transl Sci*. 2020;13(2):381-390. doi:10.1111/cts.12723

52. Virelli CR, Ebrahimi M, Mohiuddin AG, et al. User Experiences of Pharmacogenomic Testing and Opinions among Psychiatry Patients. *J Pers Med*. 2024;14(1). doi:10.3390/jpm14010022

53. Melendez K, Gutierrez-Meza D, Gavin KL, et al. Patient Perspectives of Barriers and Facilitators for the Uptake of Pharmacogenomic Testing in Veterans Affairs' Pharmacogenomic Testing for the Veterans (PHASER) Program. *J Pers Med*. 2023;13(9). doi:10.3390/jpm13091367

54. Obeng AO, Scott SA, Kaszemacher T, et al. Prescriber Adoption of SLCO1B1 Genotype-Guided Simvastatin Clinical Decision Support in a Clinical Pharmacogenetics Program. *Clin Pharmacol Ther*. 2023;113(2):321-327. doi:10.1002/cpt.2773

55. Turkmen D, Masoli JAH, Delgado J, et al. Calcium-channel blockers: Clinical outcome associations with reported pharmacogenetics variants in 32 000 patients. *Br J Clin Pharmacol*. 2023;89(2):853-864. doi:10.1111/bcp.15541

56. Jablonski MR, Lorenz R, Li J, Dechairo BM. Economic Outcomes Following Combinatorial Pharmacogenomic Testing for Elderly Psychiatric Patients. *J Geriatr Psychiatry Neurol*. 2020;33(6):324-332. doi:10.1177/0891988719892341

57. Smith H, Dawes M, Katzov-Eckert H, Burrell S, Xin Hui S, Winther MD. Improving prescribing: a feasibility study of pharmacogenetic testing with clinical decision support in primary healthcare in Singapore. *Fam Pr*. Published online 2022. doi:10.1093/fampra/cmac124

58. Papastergiou J, Tolios P, Li W, Li J. The Innovative Canadian Pharmacogenomic Screening Initiative in Community Pharmacy (ICANPIC) study. *J Am Pharm Assoc JAPhA*. 2017;57(5):624-629.

59. J.C. C, J. A, S. M, F.A. M, B.J. W, J.A. P. Informing Integration of Genomic Medicine Into Primary Care: An Assessment of Current Practice, Attitudes, and Desired Resources. *Front Genet*. 2019;10((Carroll).

60. Massart M, Berenbrok LA, Munro C, Berman NR, Empey PE. A Multidisciplinary Precision Medicine Service in Primary Care. *Ann Fam Med*. 2022;20(1).

61. Sharma M, Lee C, Kantorovich S, Tedtaotao M, Smith GA, Brenton A. Validation Study of a Predictive Algorithm to Evaluate Opioid Use Disorder in a Primary Care Setting. *Health Serv Res Manag Epidemiol*. 2017;4:2333392817717411. doi:10.1177/2333392817717411

62. Frigon MP, Blackburn ME, Dubois-Bouchard C, Gagnon AL, Tardif S, Tremblay K. Pharmacogenetic testing in primary care practice: opinions of physicians, pharmacists and patients. *Pharmacogenomics*. 2019;20(8):589-598. doi:10.2217/pgs-2019-0004

63. Schwartz EJ, Turgeon J, Patel J, et al. Implementation of a Standardized Medication Therapy Management Plus Approach within Primary Care. *J Am Board Fam Med JABFM*. 2017;30(6):701-714. doi:10.3122/jabfm.2017.06.170145

64. Natasha Petry, Baye J, Aifaoui A, et al. Implementation of wide-scale pharmacogenetic testing in primary care. *Pharmacogenomics*. 2019;20(12):903-913. doi:10.2217/pgs-2019-0043

65. Haga S.B. Delivering pharmacogenetic testing to the masses: An achievable goal? *Pharmacogenomics*. 2014;15(1):1-4. doi:10.2217/pgs.13.211

66. Bienfait K, Chhibber A, Marshall JC, et al. Current challenges and opportunities for pharmacogenomics: perspective of the Industry Pharmacogenomics Working Group (I-PWG). *Hum Genet*. 2022;141(6):1165-1173. doi:10.1007/s00439-021-02282-3

67. Caraballo PJ, Hodge LS, Bielinski SJ, et al. Multidisciplinary model to implement pharmacogenomics at the point of care. *Genet Med*. 2017;19(4):421-429. doi:10.1038/gim.2016.120

68. Tiwari AK, Zai CC, Altar CA, et al. Clinical utility of combinatorial pharmacogenomic testing in depression: A Canadian patient- and rater-blinded, randomized, controlled trial. *Transl Psychiatry*. 2022;12(1):101. doi:10.1038/s41398-022-01847-8

69. Bose-Brill S, Xing J, Barnette DJ, Hanks C. Pharmacogenomic testing: aiding in the management of psychotropic therapy for adolescents with autism spectrum disorders. *Pharmacogenomics Med*. 2017;10(101514107):247-252.

70. Lee M, Gwak HS, Choi KH. Comparison of pharmacogenomic information for drug approvals provided by the national regulatory agencies in Korea, Europe, Japan, and the United States. *Front Pharmacol*. 2023;14. doi:10.3389/fphar.2023.1205624

71. Ishiguro A, Toyoshima S, Uyama Y. Current Japanese regulatory situations of pharmacogenomics in drug administration. *Expert Rev Clin Pharmacol*. Published online July 1, 2008. Accessed March 8, 2024. https://www.tandfonline.com/doi/full/10.1586/17512433.1.4.505

72. Mwale S, Farsides B. Imagining genomic medicine futures in primary care: General practitioners' views on mainstreaming genomics in the National Health Service. *Sociol Health Illn*. 2021;43(9):2121-2140. doi:10.1111/1467-9566.13384

73. Dong OM, Wheeler SB, Cruden G, et al. Cost-Effectiveness of Multigene Pharmacogenetic Testing in Patients With Acute Coronary Syndrome After Percutaneous Coronary Intervention. *Value Health*. 2020;23(1):61-73. doi:10.1016/j.jval.2019.08.002

74. Herman L, Froelich J, Kanelos D, et al. Utility of a genomic-based, personalized medicine test in patients presenting with symptoms suggesting coronary artery disease. *J Am Board Fam Med JABFM*. 2014;27(2):258-267. doi:10.3122/jabfm.2014.02.130155

75. Bishop J.R. Pharmacists as facilitators of pharmacogenomic guidance for antidepressant drug selection and dosing. *Clin Transl Sci*. 2021;14(4):1206-1209. doi:10.1111/cts.13057

76. Cavallari L.H., Johnson J.A. Use of a multi-gene pharmacogenetic panel reduces adverse drug effects. *Cell Rep Med*. 2023;4(5):101021. doi:10.1016/j.xcrm.2023.101021

77. Elliott LS, Henderson JC, Neradilek MB, Moyer NA, Ashcraft KC, Thirumaran RK. Clinical impact of pharmacogenetic profiling with a clinical decision support tool in polypharmacy home health patients: A prospective pilot randomized controlled trial. *PLoS One*. 2017;12(2):e0170905. doi:10.1371/journal.pone.0170905

78. Ingelman-Sundberg M, Nebert DW, Lauschke VM. Emerging trends in pharmacogenomics: from common variant associations toward comprehensive genomic profiling. *Hum Genomics*. 2023;17(1):105. doi:10.1186/s40246-023-00554-9

79. Ahsan T, Urmi NJ, Sajib AA. Heterogeneity in the distribution of 159 drug-response related SNPs in world populations and their genetic relatedness. *PLOS ONE*. 2020;15(1):e0228000. doi:10.1371/journal.pone.0228000

80. Moore C, Lazarakis S, Stenta T, et al. A systematic review of knowledge, attitude and practice of pharmacogenomics in pediatric oncology patients. *Pharmacol Res Perspect*. 2023;11(6):e01150. doi:10.1002/prp2.1150

81. Rollinson V, French N, Turner R, Pirmohamed M. A Survey of the UK Pharmacy Profession's Educational Needs on Pharmacogenomics. *J Clin Pharm Ther*. 2023;2023:e2388845. doi:10.1155/2023/2388845

82. Stiles D, Appelbaum PS. Cases in Precision Medicine: Concerns About Privacy and Discrimination After Genomic Sequencing. *Ann Intern Med*. 2019;170(10):717-721. doi:10.7326/M18-2666

83. Clayton EW, Halverson CM, Sathe NA, Malin BA. A systematic literature review of individuals' perspectives on privacy and genetic information in the United States. *PloS One*. 2018;13(10):e0204417. doi:10.1371/journal.pone.0204417

84. Clayton EW, Evans BJ, Hazel JW, Rothstein MA. The law of genetic privacy: applications, implications, and limitations. *J Law Biosci*. 2019;6(1):1-36. doi:10.1093/jlb/lsz007

85. Dhasaratha C, Hasan MK, Islam S, et al. Data privacy model using blockchain reinforcement federated learning approach for scalable internet of medical things. *CAAI Trans Intell Technol*. n/a(n/a). doi:10.1049/cit2.12287

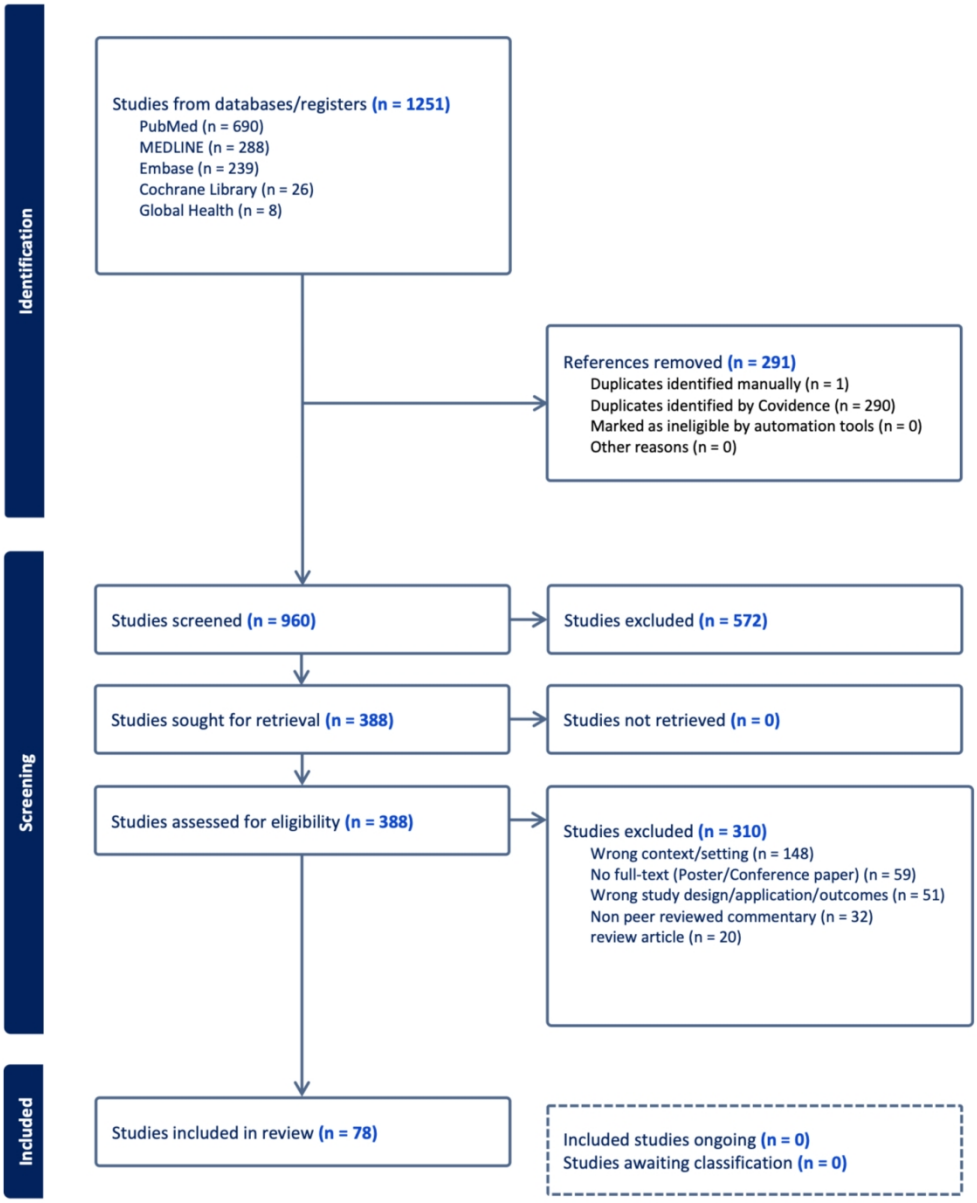
86. Natarajan P, Young R, Stitziel NO, et al. Polygenic Risk Score Identifies Subgroup With Higher Burden of Atherosclerosis and Greater Relative Benefit From Statin Therapy in the Primary Prevention Setting. *Circulation*. 2017;135(22):2091-2101. doi:10.1161/CIRCULATIONAHA.116.024436

87. Hutchcraft ML, Zhang S, Lin N, et al. Real-World Evaluation of a Population Germline Genetic Screening Initiative for Family Medicine Patients. *J Pers Med*. 2022;12(8). doi:10.3390/jpm12081297

Figure caption

Figure 1: Flow diagram of the scoping review

Figure 2: Country of origin of the articles included in this review.



Flow diagram of the scoping review

258x312mm (144 x 144 DPI)

Country of origin of the articles included in this review.

490x172mm (144 x 144 DPI)

Supplementary File 1:

Search strategy for all database:

1. primary care.mp. or exp Primary Health Care
2. exp Pharmacogenomic Variants/ or exp Pharmacogenomic Testing/ or pharmacogenomic*.mp. or genomics/ or exp pharmacogenetics/ or exp pharmaco-omics/ or exp pharmacogenetics/ or *Genome, Human/ or Genomic medicine.mp. or exp Genomic Medicine/ or exp Precision Medicine/ or exp Pharmacogenetics/ or *Genomics/
3. 1 AND 2

Supplementary File 2:

Stakeholders' views and involvement, enablers, and challenges of implementing PGx testing

Study ID	Study type, year	Disease/ Condition under study	Aims/Objectives	Key stakeholders	Country	Key Findings
Ahmed 2022	Retrospective study, 2021	Autism	Assess the prescription pattern of 92 psychotropic drugs in autistic patients and measure its pharmacogenomic testing implication.	Physician	Canada	• One third of psychotropic drugs has a PGx based treatment guideline. Sertraline, citalopram, risperidone and amitriptyline were mostly benefited from PGx testing. • PGx interpretations varied by ethnicity
Arwood 2020	2020	Patients in the general internal medicine	A pharmacist-initiated pharmacogenomics clinic and state its success and challenges that came across within two years of its implementation	Pharmacist	United States	• In two years, 72 patients were seen in clinic. Of patients who received PGx, 77% had at least one CYP2C19 and/or CYP2D6 phenotype that would make conventional prescribing unfavorable. Recommendations to physicians was made for 59% of patients; 87% were accepted. • Challenges included PGx reimbursement and referral maintenance.
Bank 2019	Prospective multicenter observational study, 2019	Adult patients with an incident prescription for at least 28 days for amitriptyline, atomoxetine, atorvastatin, (es)citalopram, clomipramine, doxepin, nortriptyline, simvastatin or venlafaxine	Assess the feasibility of pharmacist-initiated pharmacogenomic analysis in primary care and investigate the actionable phenotypes for improving patient clinical outcomes.	Community Pharmacist	Netherlands	• Included 200 patients: 90% carried at least one actionable PGx test result. In 31.0% of the incident prescriptions a combination between a drug with a known gene-drug interaction and an actionable genotype was present and a therapeutic recommendation was provided. Recommendations were accepted by clinicians in 88.7% of the patients. • Limited patient accessibility to PGx services. No financial benefit for the involved healthcare professional. Evidence constraints with the implementation of preemptive PGx panel approach in primary care of the European medical sector.

Bank 2019	2016	All prescriptions for the selected 45 drugs	To estimate the potential impact of the implementation of pharmacogenetic screening for eight genes related to drugs used in primary care.	Pharmacists	Netherlands	• In 23.6% of all new prescriptions of 45 drugs (n = 856,002 new prescriptions/year), an actionable gene-drug interaction was present. • These GDIs would result in a dose adjustment or switch to another drug in 5.4% of all new prescriptions. • Dispensing Database: Lack of complete clinical data (such as comorbidities, reduced clearance of drugs, and information on indications) in the available dataset. • Lack of data supply to the database by the outpatient pharmacy, who often dispense more specialized pharmacotherapy.
Behr 2023	25-question survey, 2023	Pain management	To assess clinician knowledge with clinical pharmacogenomic (PGx) scenarios involving commonly used drugs that have both CPIC guidelines and FDA PGx dosing recommendations.	Physicians, physician assistants, and nurse practitioners	United States	• Thirty-four clinicians completed the survey. • Respondents had minimal experience with PGx and limited awareness of PGx resources. Although respondents expressed belief that PGx has utility to improve medication-related patient outcomes, many lack confidence to apply PGx results • to their practice. For clinical drug–gene questions relevant to primary care and/or pain management, respondents scored poorly.
Bishop 2021	Commentary, 2021	Mental health	To comment on the role of pharmacists in pharmacogenomics practice	Clinician, Pharmacist	United States	• PGx testing has the potential to optimise antidepressant treatment by tailoring drug choice and reducing treatment failures/occurrence of adverse drug reactions. • Involving pharmacists in the PGx process can leverage their expertise in medication management and patient communication, enhancing the overall effectiveness of PGx implementation. • PGx test results can be complex and difficult to interpret, requiring specialized knowledge and training for clinicians. • Other challenges include variability in PGx tests, lack of clear guidelines on how PGx results should be used in clinical practice, limited evidence base for PGx use in

						mental health, expensive cost of PGx testing, time constraint in primary care
Biswas 2020	Case study, 2020	Paediatric Condition	To propose a practical and centralized approach to providing genomic services through an independent, enterprise-wide clinical service model.	Clinician	United States	• Challenges in PGx testing: Lack of knowledge and access to genetics specialists, difficulty interpreting complex test results, insurance reimbursement limitations, integrating genomic findings into patient care. • The Robert Individualized Medical Genetics Center (RIMGC) Model offers a centralized resource for all clinical divisions, provides services like test selection, insurance pre-authorization, genetic counseling, and result interpretation, collaborates with the diagnostic laboratory for clinical correlation of findings, utilizes "genetic champions" from various specialties for expert input.
Brown 2017	A Subanalysis of a prospective trail - 2017	Mental illness	To determine potential cost savings of combinatorial pharmacogenomics testing over one year in patients with mental illness treated by primary care providers and psychiatrists who had switched or added a new psychiatric medication after patients failed to respond to monotherapy.	Primary care providers treat psychiatric patients through general practice, internal medicine, family medicine, and obstetrician/gynecology. Psychiatrist (not included as PCPs)	United States	• Primary care providers (PCPs) congruent with combinatorial PGx testing provided the most medication cost savings for payers and patients at $3988 per member per year (P < 0.001). • PCPs congruent with the combinatorial PGx test recommendations saved patients $2690 in medication costs compared with psychiatrists.
Brown 2021	Cross-sectional study, 2021	Pediatric patients	Determining availability, concerns, and barriers of pharmacogenomic	Pharmacist, Physician	United States	• Healthcare sector can link the drug gene interaction reports to the clinical decision support of the electronic prescribing system. The most common drug gene interaction test identified in pediatric setting were

			testing in pediatric hospitals			thiopurine TMPT followed by Voriconazole/ CYP2C19 and Codeine/CYP2D6 • Barriers: Cost & reimbursement for the PGx test, potential for genetic discrimination, sharing results with family members, and availability of tests in certified laboratories.
Brown-Johnson 2021	Mixed methods research in Quality Improvement, 2021	Patients with cardiovascular risk factors	To assess the implementation outcomes, specifically penetration/reach, acceptability, feasibility, and sustainability of Humanwide, a pilot embedding multi-faceted precision health into a team-based primacy care setting To inform future implementation initiatives and facilitate the scale/spread of precision health in primary care. To assess its early potential clinical benefit to patients.	MDs, Advance Practice Provider (NP or PA) health professionals, diabetes pharmacists, dieticians, mental health providers, triage nurse	United States	• Patients and providers reported Humanwide was acceptable, engaged patients holistically, supported faster medication titration, and strengthened patient-provider relationships. All patients benefited clinically from at least one Humanwide component. • Feasibility challenges included: low provider self-efficacy for interpreting genetics and pharmacogenomics; difficulties with data integration; patient technology challenges; and additional staffing needs. Patient financial burden concerns surfaced with respect to sustainability.
Brunette 2019	Pragmatic Clinical Trial, 2019	Cardiovascular disease (needing statin therapy without previous history of statin use).	To apply Pragmatic Clinical Trial (PCT) principles to The Integrating Pharmacogenetics In Clinical Care (I-PICC) Study.	Primary care provider	United States	• The trial achieved high engagement with providers (85% enrolled of those approached) and enrolled a representative sample of participants for which statin therapy would be recommended. • PCT is a valuable tool for generating high quality and generalizable evidence about the effectiveness of genomic interventions.

			To generate evidence for the clinical utility of pre-emptive pharmacogenetic testing in the initiation of statin therapy.			• PCTs allow for the post-trial implementation of their interventions, increasing the likelihood that beneficial interventions will be taken up into clinical care. • Barriers: Time and resource constraints: Implementing a new testing and intervention process requires additional time and resources from healthcare providers; Patient engagement: Ensuring patient understanding and consent for genetic testing can be time-consuming; Insurance authorization: Obtaining insurance approval for genetic tests can be complex and time-consuming.
Carroll 2016	A qualitative study involving focus groups	Cancer	To assess primary care providers' (PCPs) experiences with, perceptions of, and desired role in personalised medicine, with a focus on cancer.	primary care providers	Canada	• Primary care providers have limited experience in personalised medicine; main areas of involvement are breast cancer and prenatal care. PCPs expect growing involvement in personalised medicine due to patient demand and trust • PCPs were concerned over their lack of knowledge, with some who based their practices on personal experience rather than evidence. They are also concerned about information overload due to the rapid pace of discoveries in geneomics (particularly in direct-to-consumer personal genomic testing). • Need for support: Increased knowledge, collaboration with genetics specialists, and accessible resources are crucial for successful implementation.
Carroll 2019	Questionnaire Design and Administration	NA	to determine family physicians' (FP) current involvement in GM (general medicine), confidence in GM primary care competencies, attitudes regarding the clinical importance of GM, awareness of genetic	Physicians	Canada	• FPs see their role as making appropriate referrals, are somewhat optimistic • about the contribution GM may make to patient care, but express caution about its current clinical benefits. • There is a need for evidence-based educational resources integrated into primary care and improved communication with genetic specialists.

			services, resources required, and suggestions for changes that would enable the integration of GM into practice.			
Cavallari 2023	Review of a Muti-centric cohort, 2023	Adult patients with newly initiated drugs stated in the Dutch Pharmacogenomics Working Group guideline	The effect of twelve gene panel pharmacogenomic testing to prevent adverse drug reactions in patients across seven countries	Pharmacist, Physician	United States	• Effective educational strategy and mechanism for returning pharmacogenetic results led to high recommendation acceptance rate by providers. • Adverse drug reactions significantly declined among the actionable genotype patients where treatment recommendations were considered.
Chapdelaine 2021	Secondary data analysis, 2021	Geriatric patients without moderate to severe cognitive impairment	Assess the factors of older adults that affect pharmacogenomic testing in primary care	Primary care providers	Canada	• Majority were willing to provide their samples and pay from their pockets for carrying out PGx analysis for an effective treatment. • Age was inversely proportional to the their willingness to provide samples for PGx analysis. Lower level of education affected their willingness to pay for PGx testing
Crown 2020	prospective cohort study	Not Mentioned/Not Applicable	Examining the impact of the CPD program on practicing pharmacists' knowledge, readiness and comfort, and ability to implement pharmacogenomics services in their practices	Pharmacists	Canada	• This multi-component CPD program successfully increased pharmacists' knowledge, readiness, and comfort in applying PGx to patient care in the short-term, yet some pharmacists struggled to integrate this new service into their practices.
Dressler 2019	This prospective, observational feasibility study was		Assess feasibility and perspectives of pharmacogenetic testing/PGx in rural primary care physician	Physicians	United States	• Prestudy, no PCP had ever ordered a PGx test. Test results demonstrated gene variations in 30% of patients, related to current medications, with PCPs reporting changes to drug management. • PCPs and patients had favorable responses to testing.

	conducted between September 2016 and December 2017		(PCP) practices, when PCPs are trained to interpret/apply results and testing costs are covered			• PCPs were concerned about their lack of expertise, lack of comfort applying results and out-of-pocket expense for their patients/lack of reimbursement • for the test
Elliott 2017	prospective, open-label, randomised controlled trial	50 years and older taking or initiating treatment with at least one of fifty-five single-ingredient or six medication combinations (Polypharmacy)	Assessment of clinical impact of pharmacogenetic profiling integrating binary and cumulative drug and gene inter-action warnings on home health polypharmacy patients	Physicians	United States	• Subjects (n = 110) were randomized to pharmacogenetic profiling (n = 57) • PGx reduced hospitalisations and emergency department visits at 60 days. • Of the total 1,296 drug therapy recommendations passed on to clinicians, 996 (77%) were followed.
Forester 2020	Post hoc analysis of data from a blinded, randomised controlled trial comparing two active treatment arms.	major depressive disorder (MDD)	Evaluate the clinical utility of combinatorial pharmacogenomic testing for informing medication selection among older adults who have experienced antidepressant medication failure for major depressive disorder (MDD)	Physicians	United States	• Remission and response rates improved significantly with the use of combinatorial pharmacogenomic testing to identify medications with potential gene-drug interactions and guide medication selection. • At week 8, symptom improvement was not significantly different for guided-care than for treatment as usual (TAU); however, guided-care showed significantly improved response and remission relative to TAU.
Frigon 2019	Focus Group interviews/ 2019	NA	To better understand the perceptions of PCPs, pharmacists, and patients regarding the implementation of PGx testing in clinical practice,	Primary care physicians (PCPs), pharmacists and patients	Canada	• Majority of the participants showed enthusiasm toward the implementation of PGx in clinics. The reduction of adverse events is seen as a main benefit of PGx testing. • Challenges: High cost, need for accessible PGx guidelines, ethical (revealing genetic information, confidentiality) and insurance issues, need for training for health professionals, need for computerised systems for successful implementation.

Gammal 2021	2021	General population	The problems and solutions concerning the integration of pharmacogenomics to the clinical decision support system in a clinical setting	Physician, Pharmacist	United States	• Integrating pharmacogenomics into electronic health records with customized clinical decision support system requires significant resources and specifically trained personnel to implement and maintain. • Problems: A single pharmacogenomic result can affect various medications; no standard location for pharmacogenomic results in EHR; results should be accessible to clinicians, like drug allergies; pharmacogenomic results need permanent access, not archiving; test variability: Multiple tests for the same gene can produce different results; evolving evidence: pharmacogenomic interpretations may change over time. • Solutions: problem list entries: use standardised phenotype terms for actionable pharmacogenomic results; utilize existing drug allergy alerts for high-risk pharmacogenomic findings; train clinicians on the importance of these entries and how to use them; improve data sharing between healthcare institutions; educate patients about their pharmacogenomic results and encourage sharing; promote broader pharmacogenomics knowledge among clinicians; incorporate pharmacogenomic inquiries into standard patient care.
Grant 2009	Cross-sectional, 2009	Type 2 diabetes mellitus	Assess the physicians and patient's views on pharmacogenomic testing for the prediction and management of diabetes.	Physicians	United States	• More specialized physicians were more enthusiastic in FDA approved genetic testing for guiding the treatment for diabetes and also predicting the disease. Patients were in more eager for a genetic test that would gain them the best treatment. • Patients were concerned about their privacy, high cost of PGx testing
Haga 2012	Cross-sectional Survey & 2012	NA	To seek PCPs views on their willingness and readiness to utilise PGx testing, desirable test properties, and factors	Primary Care Physicians (PCPs)	United States	• Most respondents were aware of PGx testing and recognised its potential to predict drug response. However, few felt confident ordering these tests, and many lacked PGx education.

			relevant to the use of PGx tests			• The majority of respondents felt primarily responsible for informing patients about PGx tests for prescribed medications and deciding how to document PGx results. There was limited recognition of other healthcare professionals' roles in PGx testing, except for disease specialists.
Haga 2012	Pilot Study, 2012	NA	To assess attitudes toward PGx testing, ancillary disease risk information, and related clinical issues, we conducted a series of focus groups among health professionals.	Primary care Professionals and Genetic Professionals	United States	• Primary care physicians (PCPs) expressed general interest in pharmacogenomics (PGx) testing but had reservations about its practical application. Concerns included uncertain clinical benefits, insurance reimbursement challenges, potential treatment delays, and difficulties in communicating and interpreting ancillary genetic risks. • While PCPs felt a duty to disclose potential genetic risks to patients, geneticists believe it is not always necessary, emphasizing the complexity of genetic information, such as incomplete penetrance • To optimise the use of PGx testing, expanded educational programs, increased access to genetic experts, and clear clinical guidelines are essential.
Haga 2014	2014	General	Displays delivery models of pharmacogenomic screening for healthcare settings	Pharmacist	United States	• Current prescription-driven and pre-emptive PGx models are insufficient for widespread adoption, necessitating alternative delivery strategies. • Incorporating PGx into wellness programs, retail clinics, and whole genome sequencing offers potential avenues for broader access and utilization. • It is crucial to develop strategies that make testing more accessible and affordable to the general populations.
Haga 2017	Pilot study, 2017		To investigate provider utilization of pharmacist support in the delivery of pharmacogenetic testing in a primary care setting.	Primary care providers' and Pharmacists.	United States	• Two primary care clinics participated in the study. One clinic was provided with an in-house pharmacist and the second clinic had an on-call pharmacist. • The pharmacogenetic (PGx) training was well-received by most providers, who felt it equipped them to order and utilize PGx tests effectively. Providers with direct access to a pharmacist (in-house) were more likely to

						order PGx test and consult with the pharmacist compared to those with on-call pharmacist support. • Despite abnormal test results in a third of patients, only a small proportion of drug changes were made. While the in-house pharmacist model showed initial promise, long-term test utilisation was inconsistent. There is a need to explore potential barriers such as insurance, time constraints, or lack of in-house testing facilities.
Hajek 2022	2022	NA	To offer guidance to health systems developing genetic education programs that are appropriate to the needs of providers who are not genetic specialists.	Health Care Providers'	United States	• A 2-year genomics education program with quarterly web-based modules that were mandatory for all physicians and advanced practice providers was developed. • The training was effective and boosted healthcare providers' confidence in their genetic knowledge and ability to use genetics. • This demonstrates the potential of scalable digital education to enhance provider readiness in genomic medicine.
Herman 2014	Clinical trial, 2014	Non-diabetes patient under evaluation for obstructive coronary artery disease (CAD)	Assessing the benefits of gene expression score in the diagnosis of obstructive CAD	Physicians, nurses, and physician assistants	United States	• The Gene Expression Score (GES) effectively identifies patients without obstructive coronary artery disease (CAD), allowing for faster diagnosis and treatment of non-cardiac causes of chest pain. • Implementing GES in primary care can improve patient care by streamlining the diagnostic process and reducing unnecessary tests for low to intermediate-risk patients, especially women.
Hundertmark 2020	The thirteen-question survey, 2020	Pharmacist Knowledge from postgraduate education and training.	The primary objective of this survey was to determine how postgraduate education and training influence pharmacists' knowledge and attitudes toward	Pharmacist	United States	• Pharmacists with post graduate education were more likely to receive formal training on PGx, self-rated their knowledge higher, and respond favorably to PGx being offered through pharmacy services. Pharmacists with board certifications were more comfortable interpreting PGx results. • To effectively implement pharmacogenomic testing, leveraging pharmacists with postgraduate qualifications is recommended as a foundational step.

			pharmacogenomic testing.			Comprehensive educational initiatives are essential to equip all pharmacists with the necessary knowledge and skills.
Hutchcraft 2022	Single institution prospective cohort study, 2022.	Hereditary Disease	To assess the clinical utility of germline medical exome sequencing in patients recruited from a family medicine clinic and comparing the mutation frequency of hereditary predisposition genes to established general population frequencies.	Physicians	United States	• Germline genetic screening identified hereditary disease predispositions and actionable pharmacogenomic variants in patients. • While pharmacogenomic testing led to medication changes in a small number of cases, the study demonstrated the feasibility of integrating genetic screening into primary care. • Long-term integration of pharmacogenomic test results into electronic health records is crucial to maximize patient benefit.
Jablonski 2020	Sub analysis of a 1-year prospective Assessment of medication cost, 2019.	Psychiatric (Mental Illness).	Comparison of economic outcomes when elderly patients with neuropsychiatric disorders received psychotropic medications guided by a combinatorial pharmacogenomic (PGx) test.	Primary Care Providers'	United States	• Aligning medication with pharmacogenomic test results (congruent prescribing) significantly reduced annual drug costs for patients with neuropsychiatric disorders, especially in those aged 65 and older. • Congruent prescribing was associated with a reduction in the number of neuropsychiatric medications for older patients.
Jarvis 2022	Retrospective study, 20233	Older adult population	Evaluating a large real-world pharmacogenomic implementation to the comprehensive medication management system in the US	Pharmacist	United States	• A pharmacogenomics-enriched comprehensive medication management program reduced direct medical charges by approximately $7000 per patient (≥65 years) who are receiving benefits through a state retirement system over the first 32 months of a voluntary PGx-enriched comprehensive medication management program. • The program shifted healthcare resource utilization from acute care to primary care.

						• Medication risk assessment, patient-provider communication, and sustained positive healthcare trends support the program's effectiveness.
Kehr 2023	Single center, non-interventional, retrospective cohort study.	Older adults within an outpatient geriatric clinic.	The primary objective was to identify the proportion of patients who completed PGx testing. Secondary objectives included determining the proportion of patients with actionable PGx results, determining the proportion of patients with a baseline medication intervention within six months of completing PGx testing, and identifying barriers to not completing testing.	Pharmacist	United States	• Of 67 patients, 72% successfully completed PGx testing, with 72% having actionable PGx findings and 83% having a pharmacological intervention made thereafter. • Nineteen patients did not complete testing (28%), with the primary barrier being not having an appointment scheduled (63%).
Kennedy 2013	2013	Psychiatric patients	Feasibility of pharmacogenomic testing in primary care	Physician	Canada	• The integration of PGx reports for CYP450 variants has been well-received by both physicians and patients. • Successful integration of pharmacogenomic (PGx) testing for antidepressants and antipsychotics in primary care. • Demonstrated feasibility of delivering understandable and actionable PGx information to primary care providers. • Anticipated improved treatment outcomes through early-stage PGx testing.
Kimpton 2019	Retrospective study, 2019.	Exposure of patients to pharmacogenomic drugs retrospectively.	To investigate the longitudinal exposure of English primary care patients to pharmacogenomic	Practitioners	United Kingdom	• In English primary care, it's highly common for patients to be exposed to multiple pharmacogenomic drugs, with 60% receiving two or more and 18% receiving five or more over 2 years.

			drugs to inform the design of pre-emptive testing.			• Exposure to these drugs typically begins in early adulthood and increases with age. • Three pharmacogenes are responsible for over 95% of the prescribed pharmacogenomic drugs. • There is a lack of evidence on the clinical utility of PGx • These insights could guide the development of pre-emptive pharmacogenomic testing strategies for primary care.
Ladapo 2015	Prospective Muti-centric Observational Study, 2015	Coronary artery disease (CAD)	Assess the usage of blood gene expression diagnostic tests and their clinical benefit in confirming obstructive CAD in primary care.	Physician, nurse, phlebotomist, office manager	United States	• A personalized gene expression score (GES) significantly influenced primary care providers' cardiac referral decisions for patients with stable, nonacute chest pain. • Patients with low GES had a reduced likelihood of being referred for cardiac evaluationcompared to those with elevated GES.
Leger 2016	Retrospective study, 2016	HIV infection	Examination of genetic data with the efavirenz discontinuation from central nervous system adverse events in HIV primary care patients of Southeastern United States	Physician	United States	• Among 566 patients, 17.5% discontinued efavirenz within 12 months, with 5.1% stopping due to CNS symptoms. • Slow metabolizers had a significantly higher risk of discontinuing efavirenz for CNS symptoms. • The risk was notably stronger in Whites compared to Blacks.
Lemke 2017	Descriptive Study	NA	To explore primary care physicians, views of the utility and delivery of direct access to pharmacogenomics (PGx) testing in a community health system.	Primary Care Physicians	United States	• Benefits of PGx testing include reducing side effects, faster dose titration, enhanced shared decision-making, and offering psychological reassurance. • Challenges to address include privacy concerns, cost, insurance coverage, and the complexity of interpreting PGx test results.
Li 2014	Pilot Study, 2014.	Hyperlipidemia (Statin Therapy).	To improve statin adherence, it is tailored to an individuals' SLCO1B1*5	Physicians	United States	• Sharing pharmacogenetic test results with both patients and healthcare providers can influence medication adherence positively.

			genotype and addresses a major driver of statin adherence in the primary care population.			• This is achieved by increasing patients' understanding of their condition, alleviating medication concerns, and promoting collaborative decision-making. • Delivering SLCO1B1*5 results and recommendations through electronic medical records (EMR) is feasible in a primary care setting.
Luke 2021	Qualitative Descriptive Approach, 2021.	In this study, additional internal factors related to the capabilities, opportunities, and motivations of pharmacists that influence their ability to implement PGx testing were analyzed.	To further elucidate the factors influencing the integration of PGx testing by pharmacists in their practices, the BCW approach should be used to inform future intervention options to support pharmacists with this integration.	Pharmacists	Canada	• Pharmacists' professional identities, practice environments, self-confidence, and beliefs in PGx benefits influenced their ability to provide PGx-testing services. Potential interventions to enhance implement include preparing pharmacists for higher patient volumes, assisting with software and technology integration, and streamlining workflows and documentation.
Marzuillo 2014	A cross-sectional survey, 2014.	A self-administered questionnaire was used to carry out a cross-sectional survey of a random sample of Italian public health professionals.	To assess the knowledge, attitudes, and training needs of public health professionals in the field of predictive genetic testing for chronic diseases.	Public health practitioners	Italy	• Italian public health professionals have a positive attitude toward predictive genetic testing for chronic diseases but require additional training to enhance their methodological knowledge. • Knowledge increases with exposure to genetic testing during postgraduate training, continued medical education, and proficiency in English. • Adequate knowledge strongly predicts positive attitudes toward genetic testing from a public health perspective. • Physicians have lower knowledge levels but more public health-oriented attitudes compared to other professionals.
Massart 2022	2022	Public	Describe a precision medicine center using a multi-disciplinary care model in primary care settings	Physicians and pharmacists trained in genetics and	United States	• The clinic includes a primary care physician trained in genetics, a pharmacogenomics-specialized pharmacist, and two genetic counselors. • The clinic accepts referrals, conducts genetic and pharmacogenomic testing, and provides follow-up

				genetic counselors		care, with results and care plans shared back with referring clinicians. • Since its launch, the clinic has received 99 referrals, demonstrating the model's success in expanding access to genetic services and increasing clinician collaboration and awareness. • This innovative model may serve as a template for other health systems looking to offer precision medicine services in primary care.
Mills 2013	2013	Public	Key elements to communicate with patients before and when reporting pharmacogenomic data	Physician, pharmacist, and genetic counselor	United States	• Challenges: Low adoption due to unclear guidelines on who should order tests, when to order, and how to communicate results, combined with PCPs' limited familiarity with PGx testing. • Patient Preferences: Patients prefer receiving PGx results from trusted PCPs. • Pre-Test Communication: Key topics include the purpose of the test, risks/benefits, the genetic basis of PGx testing, and its future benefits for other treatments. • Post-Test Communication: Focus on clear communication of results, implications for future treatments, and providing summary letters or referrals as needed.
Mwale 2021	Qualitative interview/Semi-structured interviews with GPs as well as documentary analysis of policy/ 2021	N/A Genomic medicine in the NHS and practice implementation	To explore GPs, views on mainstreaming genomic medicine in the NHS and implications for their practice. To examine how visions of genomic futures in the NHS are conceived and received by GPs by engaging the	General practitioners (GPs)	United Kingdom	• Facilitators for PGx Implementation: policy documents present a positive vision of genomic medicine as a transformative technology, indicating its potential to improve diagnosis and treatment within the NHS; genomic medicine is seen as capable of providing personalized treatments and identifying genetic determinants of diseases, which can enhance patient care. • Barriers: many general practitioners (GPs) feel inadequately informed about genomics and its implications for clinical practice, resulting in skepticism regarding its relevance and applicability; current healthcare infrastructure lacks the necessary systems

			concept of "sociotechnical imaginaries." To undertake documentary analysis of publicly available policy documents relating to the mainstreaming of genomics, such as the Human Genomics Strategy Group (2012), the Chief Medical Officer of England's (2016) report, the Life Sciences Industrial Strategy (2020), and editorial material on NHSE and Genomics England websites provided an alternative official account of how genomic futures are imagined, presented, and enacted.			to effectively integrate genomic medicine into everyday clinical practice, hindering its implementation. GPs prioritize pressing patient care needs over genomic initiatives, viewing genomics as a low priority in light of existing challenges within primary care. Concerns about the complexities of genomic testing and its implications for patient expectations create anxiety among GPs, leading to reluctance in adopting genomics as a routine practice.
Natasha Petry 2019	The five Iâ€™sâ€™ as a template for other institutions seeking to start a "de novo" pharmacogen	Manuscript, 2019.	Describes our efforts to place pharmacogenomics in the hands of the primary care provider, integrating this information into a patient's healthcare over their lifetime.	Pharmacists, Nurses, Genetic Counselors, and other healthcare workers	United States	• Facilitator: A multidisciplinary team, including pharmacists, genetic counselors, and lab scientists, collaborates to integrate PGx into primary care. This team approach is supported by automated decision support systems that provide real-time alerts and recommendations based on established guidelines, helping healthcare providers make informed prescribing decisions for patients based on their genetic profiles.

	omics program.					• Barrier: Despite the advantages of PGx testing, limited provider knowledge about PGx remains a significant challenge. Many healthcare professionals lack adequate training in PGx, leading to difficulties in interpreting test results and implementing recommendations in clinical practice. Additionally, standardizing PGx testing processes and integrating them into electronic medical records (EMRs) pose operational challenges that can impede the widespread adoption of these personalized medicine approaches across healthcare systems.
O'Donnell 2017	Prospective	NA	To examine prospectively the impact of available pharmacogenomic information on physician prescribing behaviors.	Physicians	United States	• The clinical decision support (CDS) system utilized traffic light alerts (green for favorable, yellow for caution, and red for high risk) to communicate pharmacogenomic information to providers. • Analysis of 2,220 outpatient encounters showed that medications classified as high pharmacogenomic risk were changed significantly more often than those without such information. • Medications with cautionary pharmacogenomic information were also changed more frequently. • Improved decision-making to reduce patient risk through the integration of genomic medicine into clinical practice.
O'Shea 2022	A questionnaire study, 2022.	An anonymous, online questionnaire generated using Qualtrics® and circulated via social media and posters placed in eight participating community pharmacies was	To establish perceptions of pharmacogenomics (awareness, understanding, openness to availability, perceived benefits and concerns, willingness to pay, and service setting) and investigate if they differ between those	Community Pharmacists, Primary Healthcare Providers	Ireland	• Low awareness and knowledge of pharmacogenomics among the general population. • After being informed about pharmacogenomics, patients with chronic diseases were 2.17 times more likely to desire the availability of pharmacogenomic services compared to those without chronic conditions • Willingness to pay for pharmacogenomic testing was not influenced by chronic disease status. • Respondents preferred pharmacogenomic services to be offered in primary care settings rather than hospitals.

		conducted with Irish adults.	with and without chronic disease(s).			
Olander 2018	Survey, 2018.	NA	The primary objective of this survey was to ascertain primary care clinicians' perceptions of pharmacogenetic use and implementation in an integrated health system of metropolitan and rural settings across several states.	Primary Care Clinicians	United States	• Of the 90 respondents, (90%) of respondents felt uncomfortable ordering pharmacogenetic tests, and 76% were unsure about applying the test results in clinical practice. • 78% of respondents expressed interest in having pharmacogenetic testing available through Medication Therapy Management (MTM) services, although physician assistants showed less interest compared to nurse practitioners and medical doctors/doctors of osteopathy. • 95% of respondents indicated interest in a clinical decision support tool related to pharmacogenetic results. • Overall, primary care clinicians are hesitant to engage with pharmacogenetics; however, the positive attitude towards incorporating testing into MTM services presents an opportunity for pharmacists to enhance their practices.
Olson 2017	A prospective, randomised study	Neuropsychiatric Disorders	Pharmacogenetic testing holds promise as a personalised medicine tool by permitting individualization of pharmacotherapy in accordance with genes influencing therapeutic response, side effects, and adverse events. The authors evaluated the effect of outcomes for the patients diagnosed with neuropsychiatric	Clinicians	United States	• A prospective, randomized study was conducted with 237 patients at a community-based psychiatric practice, comparing PGx guided treatment with standard care. • More than half (53%) of patients in the control group experienced at least one adverse drug event, while only 28% of patients receiving PGx-guided medication management reported adverse events (P = .001). • Both groups showed improvements Neuropsychiatric Questionnaire (NPQ) and Symbol Digit Coding Test (SDC) scores, but no statistical difference. • Pharmacogenetic testing can enhance the tolerability of psychiatric drug therapy while maintaining similar efficacy compared to standard treatment.

			disorders of pharmacogenetics-guided treatment compared to the usual standard of care.			
Overkleeft 2020	A Bioinformatics Approach, 2020.	The illustration of the 4MedBOX system.	To provide a description of the Personal Genetic Locker project and show its utility through a use case based on open standards, which is illustrated by the 4MedBox system.	Primary care professionals	Netherlands	• Facilitators: The Personal Genetic Locker (PGL) Project provides an infrastructure for individuals to access and manage their genetic health data, enhancing personalized medicine. This includes clinical decision support systems that aid clinicians in treatment decisions, collaborative development with partners like 4MedBox, and a focus on establishing a strong ethical foundation to address the implications of genetic data use. • Barriers: The implementation of pharmacogenomics faces challenges such as the lack of clear guidelines for translating test results into clinical actions, trust issues regarding the reliability of non-standard genetic data, and the need for specialized training for healthcare providers. Additionally, ethical and legal concerns about consent and privacy must be addressed, alongside technological hurdles for data sharing and a need for greater public awareness of genetic research.
Papastergiou 2017	Open-label, non-randomised, Observational.	NA	To evaluate the feasibility of implementing personalised medication services into community pharmacy practice To assess the number of drug therapy problems identified as a result of pharmacogenomic screening	Pharmacists	Canada	• Pharmacists offered PGx screening as part of their professional services program. • A total of 100 patients participated in the program. • Common reasons for pharmacogenomic testing included ineffective therapy (43.0%), addressing adverse reactions (32.6%), and guiding therapy initiation (10.4%). • An average of 3.3 drug therapy problems related to pharmacogenomic testing were identified per patient, leading to pharmacist recommendations such as therapy changes (60.3%), dose adjustments (13.2%), drug discontinuations (4.4%), and increased monitoring (22.1%).

						• The study demonstrates community pharmacists' readiness to adopt pharmacogenomic screening, enabling them to enhance medication therapy management and provide personalized medication services.
Papastergiou 2021	Prospective, single-blind, randomised controlled design	Major depressive disorder and/or generalized anxiety disorder,	Impact of pharmacogenomics guided versus standard antidepressant treatment of depression and anxiety, implemented in three large community pharmacies.	Pharmacists	Canada	• 213 outpatients diagnosed with major depressive disorder and/or generalized anxiety disorder were randomized to receive either pharmacogenomics-guided treatment (n = 105) or standard antidepressant treatment (n = 108). • Participants receiving PGx-guided treatment demonstrated greater improvements in the primary outcome (depression) and two secondary outcomes (generalized anxiety and disability). • Treatment satisfaction improved similarly in both groups
Park 2007	Focus group Interviews	Smoking Cessation /Tobacco dependence	(a) to explore physicians' attitudes toward treatment strategies that include matching patients to smoking cessation treatment by genotype, and (b) to identify concerns that would need to be addressed prior to the clinical integration of a genetic test to tailor smoking cessation treatment.	Physicians	United States	• Physicians recognized the potential of genetically tailored treatment to improve smoking cessation efforts for patients trying to quit. • Several barriers to clinical integration were noted, including: misunderstandings by patients about the implications of genetic test results; potential misinterpretation of information related to racial differences in the prevalence of certain risk alleles; concerns about discrimination against patients undergoing genetic testing. • Physicians expressed heightened concerns when informed that the same genetic markers used for tailoring smoking treatment are also linked to a higher risk of nicotine addiction and other psychiatric disorders. • To effectively integrate genetic testing into routine practice, primary care physicians require additional educational resources and system support.
Prather 2022	Case Report/2022	Post CVA (Cerebro Vascular Accident)	Assessing the positive impact of personalised	Pharmacist	United States	• A 71-year-old female of European descent enrolled in a pharmacogenomics-enriched comprehensive

			medicine in post-CVA patients with idiopathic symptoms			medication management (PGx+CMM) program, following a cerebrovascular accident. • The PGx+CMM pharmacist utilized a clinical decision support system (CDSS) to review and adjust the patient's medication regimen, communicating recommendations to the prescribing physician. • Following the adjustments, the patient experienced rapid improvement in symptoms, indicating that they were likely due to medication side effects, while maintaining controlled blood pressure and cholesterol levels.
Rafi 2020	A Qualitative Study, 2020.	Semi-structured interviews were undertaken with 18 clinical participants (16 GPs and two other clinicians). All interviews were recorded and transcribed verbatim.	To explore the potential barriers, opportunities, and challenges facing the implementation of pharmacogenomics into primary care.	General practitioners	United Kingdom	• Barriers: Participants expressed concerns about the cost-effectiveness of implementing PGx in primary care, as well as ethical, legal, and social implications associated with the use of genomic information. • Opportunities: The increasing availability of direct-to-consumer testing presents an opportunity to drive awareness and understanding of PGx in primary care, emphasizing the need for education and workforce training. • Challenges: Key challenges identified include the need to educate the primary care workforce on PGx, address the economic and informatics aspects of implementation, and consider the potential impact on patients before integrating genomic testing into routine practice.
Rigter 2020	Focus group Interviews, Meetings, and Delphi Technique		To define actions, roles, and responsibilities for the implementation of pharmacogenetics by conducting a multi-phased stakeholder study.	pharmacists and primary care physicians	Netherlands	• Lack of evidence for the clinical utility of PGx was identified as a significant barrier to its integration into primary care. • Reimbursement policies and effective data registration and sharing are crucial for the routine application of PGx. • There is currently a lack of clarity regarding the division of roles and responsibilities between general practitioners and pharmacists in the context of PGx.

						• During an expert meeting, 16 actions were proposed across four areas (clinical utility, reimbursement, data registration and sharing, and roles and responsibilities), with nine actions remaining pertinent after a Delphi Study. • Participants exhibited low agreement on the prioritization of actions, highlighting different perspectives and the need for better alignment among stakeholders. • Effective and efficient implementation of PGx in primary care could be facilitated by coordinating independent initiatives among various stakeholders.
RodrÃ-guez-Escudero 2020	Pilot study, following a pre- and post-interventional experimental design, 2020	Psychiatry	aimed at demonstrating the benefit of incorporating PGx information into Comprehensive Medication Management (CMM) services.	Pharmacist	Puerto Rico	• Pharmacists created new Medication Action Plans (MAPs) for each patient based on PGx results, leading to personalized treatment recommendations. • Genetic variants affecting drug safety and effectiveness were identified in 96% of patients, prompting pharmacists to modify initial treatment recommendations. • Polymorphisms in key isoenzyme genes—CYP2D6 (83%), CYP2C19 (52%), and CYP2C9 (41%)—were identified among the patients. • Pharmacists identified 22 additional medication-related problems following PGx determinations, highlighting their role in comprehensive medication management (CMM).
Schwartz 2017	2017	Hyperlipidemia Hypertension Type 2 diabetes mellitus Hypothyroidism Vitamin D deficiency Allergic rhinitis Anxiety Gastroesophageal	The purpose of this study was to implement a clinical pharmacist-led MTM service within a primary care setting that is enhanced by 1) a clinical decision support system (CDSS) that includes a unique	Pharmacist	United States	• Patients enrolled in the study used an average of 12.1 (± 4.6) medications. • Average turnaround time for Medication Therapy Management (MTM) Plus consults was 11.7 (± 6.2) days. • Pharmacists identified a total of 138 medication-related problems (MRPs) during the consults. • Most frequent types of MRPs included drug-drug interactions (25.0%) and drug-gene interactions (DGIs; 24.6%).

		reflux disorder Major depressive disorder Insomnia	combination of medication risk mitigation factors, which aids the pharmacist in interpreting the medication profile, and 2) pharmacogenomics (PGx) testing			• Clinical pharmacist-led MTM Plus service in a primary care setting is feasible and effective. • DGIs are prevalent among older adults in family practice, and PGx testing can reveal additional MRPs that might otherwise be overlooked.
Sharma 2017	Validation Study, 2017.	Opioid Use Disorder.	To determine the predictability of aberrant behavior to opioids using a comprehensive scoring algorithm incorporating phenotypic and, more uniquely, genotypic risk factors.	Primary care Physicians	United States	• In a validation study involving 452 participants diagnosed with opioid use disorder (OUD) and 1,237 controls, the algorithm demonstrated 91.8% sensitivity in categorizing patients at high and moderate risk for OUD. • The sensitivity of the algorithm remained above 90% even with changes in the prevalence of OUD. • The algorithm effectively stratifies primary care patients into low-, moderate-, and high-risk categories, aiding in the identification of those requiring additional guidance, monitoring, or treatment adjustments.
Shields 2008	Survey, 2008	Smoking Cessation	To assess physicians' willingness to offer a new genetic test to tailor smoking treatment individually	Physicians	United States	• Physicians' likelihood of offering a new genetic test for tailoring smoking cessation treatment ranged from 69–78% across scenarios. • Their willingness significantly decreased when informed that the test could identify predisposition to nicotine addiction, differ by race, or have associations with other conditions. • The term "genetic" versus "non-genetic" significantly reduced the likelihood of physicians offering the test in all scenarios. Effective education for primary care physicians is essential for the successful integration of pharmacogenetic strategies for smoking treatment.
Shields 2008	2008	Drugs and Alcohol Addiction	To review challenges related to provider readiness.	Physicians	United States	• Key challenges to integrating pharmacogenetics into clinical practice include ensuring primary care physicians' preparedness, patients' willingness to

			To address physicians' knowledge of genetics and the barriers posed by complex genetic traits in particular. To document PCPs' actual experience in ordering and referring patients for genetic testing. Finally, To make recommendations for addressing these concerns and for facilitating the integration of pharmacogenetic treatment strategies for addiction into primary care practice.			undergo testing, the availability of resources and infrastructure, adequate financing and reimbursement, and robust privacy protections to prevent stigmatization and discrimination. • Training in clinical genetics, accurate knowledge of legal protections, and preparedness to counsel patients about genetic testing were all significant predictors for having ordered and/or referred a patient for genetic testing.
Silva 2021	Informatic and Bioanalytic method, 2021.	Chronic diseases such as antiepileptic, antiemetics, and antihypertensives.	To provide facile clinical decision support to inform and augment medication management in the primary care setting.	Pharmacists	United States	• PGx examines how individual genes, either alone or in combination with other genetic factors, impact drug responses. • PGx integrates pharmacology and genomics to create personalized, safe drug treatment plans based on an individual's genetic profile.A major challenge in PGx is the absence of comprehensive clinical-genomic databases that can link genotypes, drug dispensing data, and patient outcomes, hampering progress in the field.
Smith 2022	Prospective Cohort Study Design, 2022.	The general practitioners recruited 189 patients between October 2020 and March 2021. The	To assess the feasibility of collecting buccal samples by general practitioners (GPs) at private practices in Singapore within a	General practitioners	Singapore	• Seven GPs from six private practices in Singapore recruited 189 patients for pharmacogenetic testing, with all patients having at least one actionable genetic variant. • The prevalence of patients with two, three, or four variants was 37.0%, 32.8%, and 12.7%, respectively.

		sample size was calculated on the basis of allele frequencies from a similar primary care study in Canada.	usual consultation, incorporating the use of a pharmacogenetics-based medical decision support system to guide subsequent drug dosing.			• Potential medication alterations were identified using a Clinical Decision Support System. • Patients were accepting, and GPs were enthusiastic about the potential of pharmacogenetics to personalize medicine. • The study demonstrated the feasibility of pharmacogenetic testing in primary care
Srinivasan 2021	Open-ended, semi-structured interviews, 2021.	Patients who received positive genomic screening results.	To examine primary care providers (PCP) experiences in reporting genomic screening results and integrating those results into patient care.	Primary Care Providers	United States	• Of the 500 patients who underwent genomic screening, 67 received results indicating a genetic variant requiring clinical management. • PCPs valued genomic screening for its benefits to patients and their families and advocated for the inclusion of underrepresented minorities in genomic research. • Challenges identified by providers included maintaining patient contact over time, arranging follow-up care, and managing results with limited genetics expertise. • Ethical concerns were raised about offering genomic sequencing to patients who might not afford diagnostic testing or follow-up care due to financial constraints.
StSauver 2016	Survey, 2016.	A total of 159 clinicians within the Mayo Clinic primary care practice received email surveys with the aim of gaining insights into their views regarding the integration and application of pharmacogenomic testing within their clinical practice. These surveys were designed to	To describe early clinician experience with pharmacogenomics in the clinical setting.	Primacy Care Physicians	United States	• Of 90 clinicians, 52% did not expect to use or were unsure about using pharmacogenomic information in future prescribing practices. • 53% found pharmacogenomic alerts confusing, frustrating or difficult to navigate for additional information. • Only 30% of clinicians who received a CDS alert changed their prescription to an alternative medications. • The study suggests a general lack of clinician comfort with integrating pharmacogenomic data into primary care.

		evaluate the clinicians' sentiments regarding pharmacogenomics and to gauge their opinions on the usefulness of electronic pharmacogenomics clinical decision support (PGx-CDS) alerts.				
Swen 2012	Elderly patients over the age of 60, who were on multiple medications and had used at least one drug falling under specific Anatomical Therapeutic Chemical (ATC) codes, including within the previous two years, were chosen randomly for the study, 2012.	Patients were selected from the pharmacy records if they used at least one drug that CYP2D6 metabolizes or CYP2C19 and at least four additional drugs in the preceding two years.	To investigate the feasibility of pharmacy-initiated pharmacogenetic screening in primary care with respect to patient willingness to participate, quality of DNA collection with saliva kits, genotyping, and dispensing data retrieved from the pharmacy.	Pharmacists	Netherlands	• 58.1% of invited patients were willing to participate in the PGx screening study, indicating a high level of acceptance despite the screening not being tied to a specific clinical issue. • Pharmacy-initiated PGx screening is feasible in primary care, but challenges include difficulties in saliva production, particularly for patients on anticholinergic medications, and a 6.7% no-call rate for CYP2D6 on the AmpliChip.

Tanner 2018	A naturalistic, open-label, prospective study, 2018.	Major Depressive Disorder, Depression.	To evaluate the utility of combinatorial pharmacogenomics in patients with major depressive disorder in primary care and psychiatric care settings.\ To evaluate symptom improvement, response, and remission rates following treatment guided by combinatorial pharmacogenomic testing among patients with major depressive disorder enrolled in a large, prospective study.	Primary care physicians, psychiatrists	Canada	• A study involving 1,871 patients with Major Depressive Disorder (MDD). • Pharmacogenomic testing categorised medications based on gene-drug interactions, with Beck's Depression Inventory (BDI) scores assessed at baseline and follow-up. • Results showed a 27.9% reduction in depression symptoms, with a 25.7% response rate (≥50% decrease in BDI) and a 15.2% remission rate (BDI ≤10). • Patients treated by primary care providers had significantly better outcomes compared to those treated by psychiatrists, with higher symptom improvement, response, and remission rates. • Patients taking genetically congruent medications (with little or no gene-drug interactions) had a 31% relative improvement in response rate compared to those taking incongruent medications. • The study supports the use of pharmacogenomics in broader treatment settings, particularly in primary care.
Tiwari 2022	Rater-blinded, randomised, controlled trial, 2022	Depression	To evaluate the utility of the combinatorial pharmacogenomic test in a Canadian population, this trial was assessed in conjunction with a trial conducted in a U.S. population (GUIDED trial).	physicians	Canada	• Patients in the PGx guided-care arm showed greater symptom improvement (27.6% vs. 22.7%), response (30.3% vs. 22.7%), and remission rates (15.7% vs. 8.3%) compared to treatment as usual, though differences were not statistically significant. • Results suggest that combinatorial PGx testing can be a useful tool for guiding depression treatment within the Canadian healthcare system.
Turkmen 2023	The study analyzed up to 32 360 UK Biobank participants	Incident diagnosis of coronary heart disease, heart failure (HF), chronic kidney disease,	To estimate associations between reported pharmacogenetic variants and incident	General Practitioners	United Kingdom	• The study analyzed 32,360 UK Biobank participants prescribed dihydropyridine calcium channel blockers (dCCB) in primary care, focusing on 23 genetic variants. • Key findings include that carriers of the rs877087 T allele in the RYR3 gene had an increased risk of heart

	prescribed dCCB in primary care (from UK general practices, 1990â€"2017), 2022.	edema, and switching antihypertensive medication.	adverse events in a community-based cohort prescribed dihydropyridine calcium channel blockers.			failure (HF) with a hazard ratio of 1.13, although this was not significant after correction for multiple testing. • If rs877087 T allele carriers experienced the same treatment effect as non-carriers, the incidence of HF could potentially reduce by 9.2%. • Patients with rs10898815 in NUMA1 and rs776746 in CYP3A5 were more likely to switch to an alternative antihypertensive medication. • Other genetic variants studied did not show strong or consistent associations with adverse clinical outcomes.
vanderWouden 2016	Longitudinal, prospective cohort study, 2016.	DTC PGT consumers.	To describe the characteristics and perceptions of DTC PGT consumers who discuss their results with their PCP.	Primary Care Providers	United States	• 63% of respondents planned to share their pharmacogenomic results with their primary care provider (PCP), but only 27% did so at 6-month follow-up. • Common reasons for not sharing results included perceiving the test as not important enough (40%) or not having time (37%). • Among those who discussed their results with a PCP, 35% were very satisfied, while 18% were not satisfied at all. • Key Encounter Themes: Frequently mentioned themes included the actionability of results (32%), PCP engagement (25%), and lack of PCP engagement (22%).
vanderWouden 2019	The prospective pilot study, 2019.	In this study, Community pharmacists were provided the opportunity to request a panel of eight pharmacogenetics to guide drug dispensing within a clinical decision support system (CDSS) for 200	To quantify both the feasibility and the real-world impact of this approach in primary care.	Community pharmacists	Netherlands	• Community pharmacists used a panel of eight pharmacogenetics to guide drug dispensing for 200 primary care patients, with follow-up after an average of 2.5 years. • PGx-panel results were recorded in 96% of pharmacist and 68% of general practitioner electronic medical records (EMRs). • 97% of patients reused PGx-panel results for at least one new prescription, with 33% using it for up to four prescriptions. • 24.2% of these prescriptions had actionable drug-gene interactions (DGIs) that required pharmacotherapy adjustments.

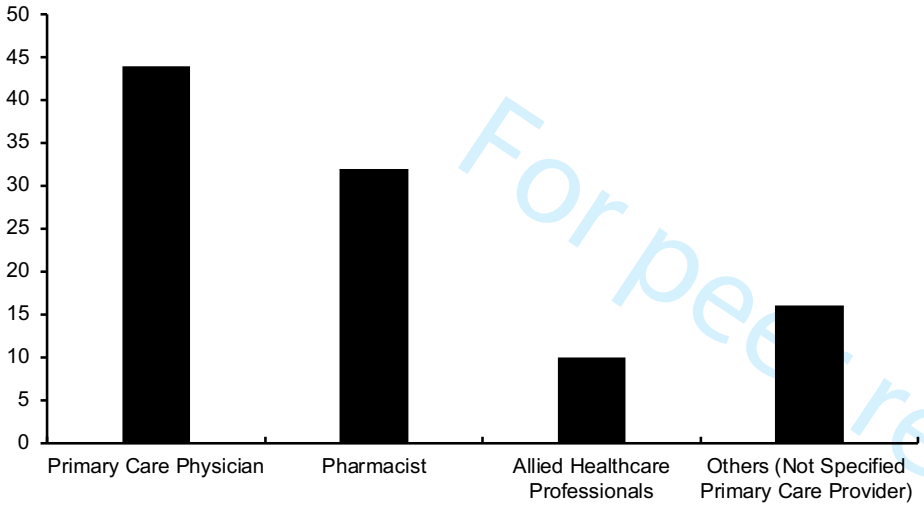
		primary care patients.				• No difference in healthcare utilization was observed between patients with and without actionable DGIs. • Pre-emptive panel-based pharmacogenetic testing is feasible and has a substantial real-world impact in primary care.
vanderWouden 2020	PREPARE study, 2020.	Enrollment of patients under their pharmacists who plan to initiate one of 39 drugs with a Dutch Pharmacogenetics Working Group (DPWG) recommendations.	To study pharmacists' perceived enablers and barriers for PGx panel-testing among pharmacists participating in a PGx implementation study.	Pharmacists	Netherlands	• Barrier: Unclear procedures for implementing PGx testing; undetermined reimbursement for PGx tests and consultations; insufficient evidence of clinical utility for PGx panel testing; infrastructure inefficiencies affecting implementation; limited knowledge and awareness of pharmacogenetics among healthcare professionals. • Enabler: Pharmacists' perceived role in delivering pharmacogenetics; belief in the clinical utility of pharmacogenetics. • Despite a strong belief in the benefits of pharmacogenetics, existing barriers hinder its implementation in primary care settings.
Vassy 2018	Qualitative Analysis, 2018.	Primary Care Physicians and their generally healthy patients undergoing genome sequencing	To illuminate how PCPs communicate different types of genome sequencing results and their management recommendations for those results of uncertain clinical utility.	primary care physicians	United States	• In a study of 48 PCP–patient visits, a "take-home" message (recommendation) was identified for each genomic result discussed, categorized into (1) continuing current management, (2) further treatment, (3) further evaluation, (4) behavior change, (5) remembering for future care, or (6) sharing with family members. Quantitative analysis revealed that continuing current management was the most common recommendation, accounting for 66% of all recommendations. Pharmacogenetics prompted recommendations to remember for future care in 79% of cases, while carrier status led to sharing with family members in 83% of instances. • Polygenic results frequently resulted in behavior change recommendations. For monogenic results, 25% of recommendations were for further evaluation.

						• Rationales for recommendations were based on patient context, family context, and scientific/clinical limitations of sequencing. • Overall, PGPs distinguished substantive differences among categories of genomic sequencing results and tailored their clinical recommendations accordingly.
Vassy 2020	Randomised trial, 2020.	Statin myopathy risk.	To determine the impact of delivering SLCO1B1 pharmacogenetic results to physicians on the effectiveness of atherosclerotic cardiovascular disease (ASCVD) prevention (measured by low-density lipoprotein cholesterol [LDL-C] levels) and concordance with prescribing guidelines for statin safety and effectiveness.	Physicians	United States	• The study involved 408 patients randomized into intervention (193 patients) and control (215 patients) groups to assess SLCO1B1 genotype effects on statin therapy. • 120 patients (29%) had a genotype indicating increased simvastatin myopathy risk; statin therapy was offered to 33.7% in the intervention group and 32.1% in the control group. • At 12 months, LDL-C reductions were noninferior between the intervention (-1.1 mg/dL) and control (-2.2 mg/dL) groups, with no significant difference in guideline-concordant statin prescriptions (6.2% vs. 6.5%). • Few documented cases of statin-associated muscle symptoms (SAMS) in both groups. • The findings suggest that reporting SLCO1B1 results did not adversely impact atherosclerotic cardiovascular disease prevention and may have led to avoiding simvastatin prescriptions for genetically at-risk patients
Weinstein 2020	A qualitative study, 2019.	Depression	To explore pharmacist and physician perspectives on the utility and critical considerations for designing a pharmacist-run pharmacogenomic service for depression in primary care.	Pharmacists	United States	• Pharmacogenomics can help tailor initial medication choices for patients with depression in primary care. • A pharmacist-driven pharmacogenomics service should start with pre-visit chart review and involve a collaborative, team-based approach with effective communication. • Trained pharmacists in partnership with outpatient physician practices are essential for interpreting pharmacogenomic results and recommending appropriate medications.

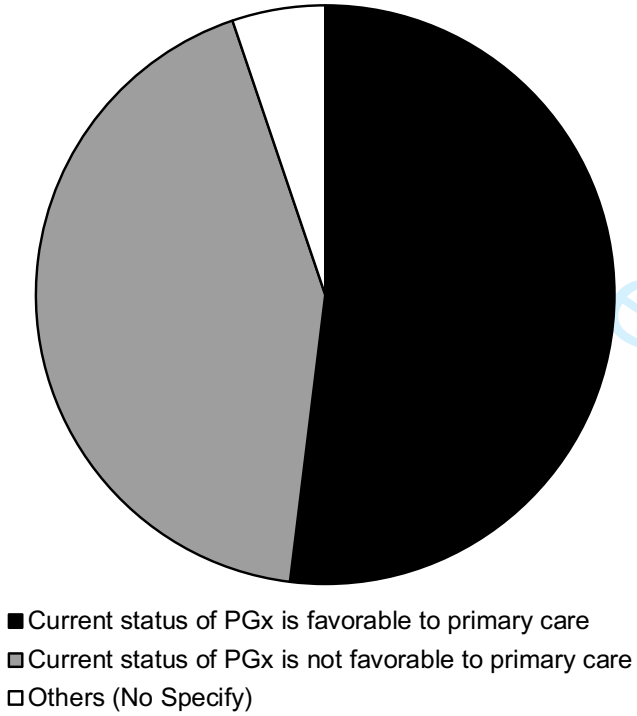
						• Successful implementation requires careful patient selection, engagement, and education. • Monitoring and follow-up care responsibilities will be shared among team members. • Ongoing education for healthcare professionals on interpreting and implementing pharmacogenomic data in depression treatment is essential.
Wildin 2022	Consolidated Framework for Implementation Research (CFIR), 2022.	Genetic Disease.	To review the barriers, solutions, and perceived gaps in the context of an implementation research framework.	Primary Care Provider	United States	• The pilot implementation of clinical genomic population health screening for any-health-status adults demonstrated feasibility, successfully translating prior research into clinical practice by centering primary care and using a clinically relevant gene panel. • Key strengths included engaging leadership, securing buy-in from clinical administration, involving diverse stakeholders, and leveraging existing workflows, alongside contracting with a commercial laboratory for testing and reporting. • Indirect measures of success showed continued volunteer participation from new primary care providers (PCPs), ongoing patient testing, and minimal complaints related to process and communication. • Barriers to scaling included underestimating the need for leadership engagement in health information technology (HIT), challenges with electronic health record (EHR) integration, and issues with tracking patient attribution. • Adaptations to the process, such as an EHR-plus-paper order method, increased the burden on clinic staff and contributed to backed process errors • Resilience was supported by the strong knowledge and experience of the implementation team and continued involvement of patient-focused advocates, despite disruptions like the COVID-19 pandemic and a cyberattack.

Williams 2016	Qualitative study, A top-down sampling method, 2016.	Alcohol use disorders	Qualitative interviews with primary care providers from 5 clinics in the Veterans Health Administration (VA) to assess their interest in using a genetic test to inform the treatment of alcohol use disorders with pharmacotherapy.	Primary Care Providers, physicians	United States	• Participants showed general interest in using genetic tests to aid in alcohol use disorder (AUD) treatment planning. • Perceived benefits of pharmacogenetic testing included aiding therapeutic choice and enhancing patient motivation and engagement in treatment. • Perceived drawbacks included potential limitations in pharmacotherapy benefits by narrowing the target population and negative impacts from "negative" test results. • Clinical utility was viewed with caveats, as its effectiveness would depend on prognostic accuracy and medication characteristics. • There was uncertainty about whether the test would influence clinical decision-making. • Pragmatic barriers to implementation included costs and the need for resources such as laboratory facilities.
Youssef 2021	A comprehensive analysis of a large community pharmacy database was conducted, in 2021.	A total of 56 drugs with 56 unique drug-gene interactions were included in the study for instance (Warffarin, Zuclopenthixol, Carbamazepine).	To quantitatively estimate the volumes of medicines impacted by the implementation of a population-level, pre-emptive pharmacogenetic screening program for nine genes related to medicines frequently dispensed in primary care in 2019.	Pharmacists	United Kingdom	• Actionable drug-gene interactions (DGI) were present in 19.1% to 21.1% of new prescriptions for these drugs, affecting approximately 5,233,353 to 5,780,595 prescriptions out of a total of 27,411,288 new prescriptions per year. • These actionable DGIs would necessitate increased monitoring, maximum ceiling dose precautions, or changes in drug regimen. • Immediate dose adjustments or changes in medication regimen accounted for 8.6% to 9.1% of the prescriptions with actionable DGIs. • The study highlights the frequent occurrence of actionable DGIs in UK primary care, indicating significant opportunities to optimize prescribing practices.

Supplementary File 3: Key stakeholders for the implementation of pharmacogenomics testing in the primary care settings.



Supplementary File 4: Opinion towards implementation of pharmacogenomics testing in the primary care settings



Supplementary File 5: Enablers and challenges of implementation of pharmacogenomics testing in primary care settings