Title: understanding the barriers and enablers of pharmacogenomic testing in primary care: A qualitative systematic review with meta-aggregation synthesis

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Abstract

Introduction: Pharmacogenomic testing can indicate which drugs may have limited therapeutic action or lead to adverse effects, hence guiding rational and safe prescribing. However, in the UK and other countries, there are still significant barriers to implementation of testing in primary care.

Objective: This systematic review presents the barriers and enablers to the implementation pharmacogenomics in primary care setting.

Methods: MEDLINE, EMBASE, PsycINFO and CINAHL databases were searched through to July 2020 for studies that reported primary qualitative data of primary care professionals and patient views. Following screening, data extraction and quality assessment, data synthesis was undertaken using meta-aggregation based on the theoretical domain's framework (TDF). Confidence in the synthesised findings relating to credibility and dependability was established using CONQual. Eligible papers were categorised into six TDF domains - knowledge; social and professional roles; behavioural regulation; beliefs and consequences; environmental context and resources; and social influences.

Results: From 1669 citations, eighteen eligible studies were identified across seven countries, with a sample size of 504 participants including both primary care professionals and patients. From the data, fifteen synthesised statements, all with moderate CONQual rating emerged. These categories range from knowledge, awareness among Primary Care Physicians and patients, professional relationships, negative impact of PGx, belief that PGx can reduce adverse drug reactions, clinical evidence, cost effectiveness, informatics and reporting issues and social issues.

Conclusions: Through use of TDF, fifteen synthesised statements provide policymakers with valuable recommendations for the implementation of pharmacogenomics in primary care. In preparation, policymakers need to consider the introduction of effective educational strategies for both PCPs and patients to raise knowledge, awareness, and engagement. The actual introduction of PGx will require reorganisation with decision support tools to aid use of PGx in primary care, with a clear delegation of roles and responsibilities between general professionals and pharmacists supplemented by a local pool of experts. Further policy makers need to address the cost effectiveness of pharmacogenomics and having appropriate infrastructure supporting testing and interpretation including informatic solutions for utilising pharmacogenomic results.

Introduction

The use of pharmacogenomics (PGx) testing to provide information on drug selection and dosing in routine clinical practice has been steadily increasing.[1,2,3,4] PGx offers optimisation of a patient's pharmacotherapy by increasing medication effectiveness, reducing drug related toxicity, and reducing healthcare costs.[3,5,6] While significant progress has been made in establishing PGx in secondary and tertiary care settings[3], the implementation of PGx testing in primary care, where the majority of drug prescriptions[7] are written, is less well established[1]. The evidence of the benefits to medicine management in these settings is growing[8] and it is estimated that one in four primary care patients take at least one medication with a genetic variation that could benefit from PGx testing.[9] Countries including the USA, Canada and The Netherlands have more developed systems, however they also report challenges to the widespread utilisation of PGx.[10,11]

Several studies have investigated the barriers and enablers for implementation of PGx in primary care.[10,11,12, 13, 14, 15] The most commonly identified barriers in clinical practice were lack of PGx skills and knowledge amongst HCP [3, 12,16,17,18,19], lack of decision support tool to aid interpreting results,[3,10,12,20,21,22] lack of clarity of professional roles and responsibilities between primary care clinicians[3,] and perceived lack of clinical evidence to support use of PGx testing. [3,4,10,12,15,16,17,19,23,24.] Barriers to policy implementation have also been identified and include lack of evidence for the cost effectiveness of PGx testing[1,4,8,26], lack of leadership to develop policy and guidance for PGx prescribing[16] ethical, legal and social barriers,[3,12,15] and reimbursement issues.[15,16,17,18,19] Enablers identified included a general interest in PGx testing[27], that PGx testing could guide drug choice [27], and recommendations for use from a colleague[27].

More deeper understanding of the barriers and enablers have been exposed by qualitative studies. For example, infrequent experience with personalized medicines[27], professional reliance on personal experience to navigate PGx care pathways[28], and how relationships with genetic specialists and clinics are managed.[27] Systematic reviews of perceived barriers [29,30] have been reported, but these reviews focus upon the provision of genetic services in primary care and not specifically PGx testing. However, a recent structured review by Hayward et al[57] of existing implementation models for PGx testing provided an insight into the factors which influence PGx testing in primary care. These included pre-test counselling, role of the pharmacist, data integration into the electronic medical record and point-of-care clinical decision support systems. Two other systematic reviews of doctor's and pharmacists' knowledge, attitude, and practice toward pharmacogenomics[27,31], were limited to survey findings. In this review, we seek to present synthesised statements of the barriers and enablers to the implementation of PGx testing in primary care by conducting a systematic review with meta-aggregation of qualitative studies. Use of a theoretical framework for this systematic review will provide focus for the synthesised evidence-based statements to better inform policy and practice strategies to enhance the uptake of PGx in primary care.

Materials and methods

The methods for this qualitative synthesis are described below. The Enhancing Transparency of Reporting the synthesis of Qualitative research (ENTREQ)[33] checklist for this review has been followed and is presented in Supplementary Table 1.

Search strategy

A comprehensive, systematic search strategy was used to identify all available primary qualitative studies. Systematic searches of the following database's were undertaken (RA & SQ) - Medline, EMBASE, PsycoInfo and CINAHL to identify relevant articles. The full search strategy is available in Supplementary Table 2.

Selection criteria

The PICo mnemonic was used to develop the search strategy.

Population: participants included primary care healthcare professionals including doctors, pharmacists and nurses, policy makers and patients.

Phenomena of interest: the use of PGx testing.

Context: only papers reporting primary qualitative data were included. Questionnaires and surveys were not included in this systematic review. Papers reporting both quantitative and qualitative data were included if the qualitative data could be independently extracted.
Settings: Studies reporting primary qualitative data on the views and perspectives of healthcare professionals, patients and the wider public, and service commissioners on the barriers and enablers to utilising PGx information to aid therapeutic decision making were selected for inclusion. Studies were not restricted for inclusion by country.

A search strategy was developed by the authors in collaboration with an Information Specialist. An initial search for articles was conducted in July 2018, but then updated March 2020 by RA. Studies were limited to those which reported qualitative data on the barriers and enablers for the implementation of PGx in primary care and were eligible for inclusion in the meta-synthesis. Studies which reported surveys or questionnaire data or not primarily based or related to primary care practice were excluded from the meta-synthesis.

Quality appraisal
The Critical Appraisal Skills Programme (CASP) [34] qualitative checklist was used to determine the methodological strengths and limitations of the included studies. The checklist contains 10 questions, thus providing rapid evaluation of studies. Questions were scored 0, 1 or 2, reflecting to what extent information from the paper answered each question. (0=no criteria fulfilled or can't tell; 1=some criteria fulfilled; 2= all criteria fulfilled). Papers where then rated low, medium, or high quality based on the following scoring system: high =18-20; medium= 14-17; low quality ≤14. Details and results of the quality appraisal for all included studies can be found in Supplementary Table 3.

Data extraction
Descriptive and methodological information about each paper was extracted into an excel table devised by LC. Two researchers independently reviewed and extracted all information under the results, discussion, and conclusion sections of each paper (SQ, LC) and in the case of ambiguity of data with regards to relevance to the research question, both researchers reached an agreement after full discussion. The emerging barriers and enablers were then coded into 6 out of 14 Theoretical Domains Framework (TDF) domains by the main researchers (SQ) and independently checked by a second researcher (AL). Only six domains were used, as these were the only ones that were supported by the data extracted from our papers.

This study used the TDF as a framework.[35]. TDF is a synthesis of 33 theories of behaviour and behaviour change clustered into 14 domains[35]. These 14 domains include knowledge, skills, social/professional role and identity, beliefs and capabilities, optimism, beliefs about consequences, reinforcement, intentions, goals, memory, attention and decision processes, environmental context and resources, social influences, emotion, and behavioural regulation. To effect change within organisations, there is a requirement for change in the behaviour of individuals or systems. Changing behaviour requires an understanding of the influences on behaviour in the context in which they occur.[36] This framework has been applied across a range of healthcare systems to influence healthcare behaviours.[36] The following six domains have been used to categorise the extracted data for this systematic review:

1. Knowledge
2. Social and professional roles
3. Behavioural regulation
4. Beliefs about consequences
5. Environmental context and resources
6. Social influences

Data synthesis
The data was synthesised through use the use of meta-aggregation, which involves aggregation of findings to generate a set of statements. This was achieved through assembling the findings and categorising these

findings based on similarity in meaning. These categories were then subjected to a synthesis to produce a set of findings.

Confidence in findings

We used the CONQUal approach to rate confidence in the synthesized findings. Based on the answers to the 5 Joanna Briggs Institute[56] questions we rated each paper as high, moderate, low, or very low[37]. Initially each synthesized finding was ranked as high and was downgraded based on assessments of dependability and credibility.

Dependability[37] – the dependability score was based on whether the critical appraisal scores fulfilled the following five dependability domains: Congruity between the research methodology and
1. the research question or objectives, 2. the methods used to collect data and 3. the representation and analysis of data. 4. A statement locating the researcher culturally or theoretically. 5. The influence of the researcher on the research, and vice-versa.
All studies started with a 'high' ranking. No downgrading was performed when 4-5 of the domains were met. Downgrading by one level occurred when the included studies met 2-3 of the domains (from high to moderate). Downgrading by two levels occurred when only 0-1 of these domains were met i.e., from high to low.

Credibility[37] – assesses the 'findings'. Credibility assesses the congruency between the author's interpretation and the supporting data. Each finding extracted from the paper was evaluated with a level of credibility based on the following ranking scale:

1. Unequivocal (findings accompanied by an illustration that is beyond reasonable doubt and therefore not open to challenge).
2. Equivocal (findings accompanied by an illustration lacking clear association with it and therefore open to challenge).
3. Unsupported (findings are not supported by the data).

We quality scored each paper using the CASP rating and the 5 JBI questions for dependability. The credibility was rated through assessing whether each extracted finding was accompanied by an interpretation which was either illustrated by the findings, lacked clear association, or was not supported.[37]

Results

Through our search strategy, 1,669 unique citations were generated. After title and abstract review, 147 citations underwent full-text article review, independently by three reviewers (SQ, LC, RK), to assess their eligibility based on the pre-specified inclusion criteria. 129 papers were excluded at this stage, common reasons for rejection included the paper reported survey data, only conference abstracts were available, it was not possible to extract data, the paper focused upon direct-to-consumer testing kits, the paper reported on other aspects of genetic testing, or the paper did not specifically relate to primary care PGx testing. A total of 18 studies, which met the inclusion criteria were included in the qualitative synthesis. (Figure 1). At each stage any disagreement between the three researchers was discussed and consensus reached (SQ, LC and RA).

<< Insert Figure 1 >>

Quality appraisal

The CASP quality appraisal scores for the 18 papers ranged from 14 to 19 out of 20, with six papers rated as high and 12 as medium. (Supplementary Table 3). All studies included a clear statement of the aims of the qualitative studies and explicit statement of findings, including linking the results to the original research question.

Characteristics of included studies

Approximately 504 participants were included from the 18 studies; this is because two studies did not state a definitive sample size [7,14] with the latter study stating, "an average of 7 primary care clinicians included at the five sites." We have taken this to be 35 participants for this study.[7] Of the reported participants the majority (270 (54%)) comprised primary care professionals (PCPs), with 186 (37%) patient's participants and 48 (9%) pharmacists were included. Not all studies reported the male to female breakdown of participants; but from those reported, males comprised 139 and females 210. 10 studies originated from the USA, 3 from Canada, 1 UK, 1 Australia, 2 The Netherland and 1 was a multicentre study based in 4 European countries. 7 of the 18 included studies reported patients views on pharmacogenomic testing. Full characteristics of the included papers and samples are presented in table 1.

<< Insert table 1 >>

Synthesised findings

We used the TDF to organise the barriers and enablers through an iterative process. All qualitative data from the 18 papers were initially extracted and categorised into barriers and enablers (Supplementary table 4). The data was then coded into 6 theoretical domains of the TDF: knowledge; social and professional roles; behavioural regulation; beliefs and consequences; environmental context and resources; and social influences. Table 2 shows the extracted barriers (B) and enablers (E) categorised as per the selected TDF domains. The extracted findings from each category were then analysed by two researchers (SQ and AL) to produce sixteen synthesised findings.

<< Insert table 2 >>

The summary of the extracted findings, categories and credibility ratings are included in Supplementary Table 5. A summary of the synthesised findings is presented in Table 3- CONQUal summary of findings.

<< Insert table 3 >>

TDF Domain 1: Knowledge

Twenty-five findings were categorised in the knowledge domain that informed five categories (Supplementary Table 5). These five categories include lack of genetic knowledge, limited experience with PGx, education and training, patient's lack of genetic knowledge and general interest in PGx testing. These five categories informed synthesised finding 1.

Synthesised Finding 1 mapped to the Knowledge domain:

- If pharmacogenomic knowledge, awareness and engagement of primary care professionals can be improved through effective undergraduate and postgraduate education programmes and if patients are appropriately engaged with the process, then primary care pharmacogenomic testing uptake is likely to increase.

TDF Domain 2: Social and professional roles

Fifteen findings were categorised in the social and professional roles domain that informed three categories (Supplementary Table 5). These include skill mix, pool of experts and professional relationships. These three categories informed synthesised findings 2 and 3.

Synthesised Findings 2 and 3 regarding professional role and responsibilities, mapped to social and professional roles domain:

- Better engagement with pharmacogenomics testing can be achieved if there is a clear division of

responsibility between Primary Care Professionals – one of the potential ways forward could be GPs making the diagnosis and the pharmacist choosing the appropriate drug through use of pharmacogenomics testing. This finding is presented as one possible solution for professional roles and responsibilities.

- If a more comprehensive model for GP-pharmacist responsibility and engagement with patients is developed, then this could improve the uptake of pharmacogenomics testing in primary care. Furthermore, the process can be facilitated by a committee of local pharmacogenomics experts to guide decision making.

TDF Domain 3: Behavioural regulation

Sixteen findings were categorised in the behavioural regulation domain that informed five categories. (Supplementary Table 5). These include negative impact of PGx, patient views, behavioural change, reliance on genetic testing and medical mistrust. These five categories informed synthesised findings 4 and 5.

Synthesised Findings 4 and 5 regarding "countering negative concerns about pharmacogenomics", mapped to behavioural regulation domain:

- If learning about the potential benefits and limitations of pharmacogenomics testing is made clearer for Primary Care Professionals and if patient expectations are managed effectively, then the benefits of pharmacogenomics testing in primary care can be more easily realised.

- If there is greater awareness and understanding between Primary Care Professionals that pharmacogenomics testing is complimentary rather than a substitute for current clinical decision-making, then this will increase their confidence and competence in using pharmacogenomics testing in primary care.

TDF Domain 4: Beliefs about consequences

Twenty-five findings were categorised in the beliefs about consequences domain that informed three categories. (Supplementary Table 5). These include reduces adverse drug reactions and reduces trial and error. These two categories informed synthesised finding 6.

Synthesised Finding 6 & 7 regarding positive impact of pharmacogenomics mapped to "beliefs about consequences" domain:

- If patients and Primary Care Professionals recognised the potential for pharmacogenomics testing to reduce adverse drug reactions and trial-and-error aspect of prescribing, then this will facilitate the uptake of pharmacogenomics testing in primary care.

- One of the benefits of genetic information collated for pharmacogenomics testing is related to whether a person will be susceptible to adverse drug reactions or not.

TDF Domain 5: Environmental context and resources

Fifty-two findings were categorised in the environmental context and resources domain that informed eleven categories. (Supplementary Table 5). These include electronic health record (EHR) implementation, workflow issues, reporting results, ordering/ interpreting tests, cost concerns, limitations, ancillary findings, technical issues, clinical utility, guideline development/accessibility and decision making. These eleven categories informed synthesised finding 7, 8, 9, 10, 11, 12 and 13.

Synthesised Findings 8, 9, 10, 11, 12 and 13 regarding the practical implementation of pharmacogenomics mapped to environmental context and resources domain:

- If pharmacogenomics results can be implemented and incorporated into the normal workflow patterns at the point of prescribing and if results are easily comprehensible, then uptake by Primary Care Professionals in primary care can be improved.

- If policy makers and commissioners invest in cost-effective models for pharmacogenomics testing (where the benefit of testing outweighs the cost of the test), then this will help minimise inequities between low and high socio-economic patient groups and facilitate the uptake of pharmacogenomics testing in primacy care.

- If pharmacogenomics test results, which offer valid and reliable information are used to aid decision-making during prescribing, then this will facilitate the uptake of pharmacogenomics testing in primary care.

- If the infrastructure around pharmacogenomics testing is strengthened such that results can be accessed in a timely manner and a prompt alerts the clinician to the availability of the results, then the uptake of pharmacogenomics in primacy care can be increased.

- If more specific guidance is produced for Primary Care Professionals, highlighting when pharmacogenomics testing is appropriate. For example, if guidelines were produced by national bodies such as NICE or MHRA, which build upon international guidance produced by CPIC or DPWG, then Primary Care Professionals would be reassured of the evidence base for pharmacogenomics recommendations, and this could lead to increase uptake of pharmacogenomics testing in primacy care.

- If Primary Care Professionals have successfully used pharmacogenomics or have personal experience of undertaking a pharmacogenomics test, then they are more likely to use pharmacogenomics testing for their patients in the future.

TDF Domain 6: Social influences

Thirteen findings were categorised in the social influence's domain that informed four categories. (Supplementary Table 5). These include employment discrimination, confidentiality/privacy of data, abuse of test results, and social inequities. These four categories informed synthesised finding 14 and 15.

Synthesised Findings 14 and 15 regarding ethico-legal implications of pharmacogenomics mapped to the social influence's domain:

- Reassurance that genetic information is kept confidential, and this would not adversely affect a person’s employment or insurance rights, then the patients are going to be more receptive to pharmacogenomics testing.

- If the perceived benefit for the use of pharmacogenomics amongst primary care patients is promoted, then this will facilitate the uptake of pharmacogenomics testing in primacy care.

Discussion

This study utilises synthesised findings from qualitative PGx primary care studies. Our systemic review produced fifteen synthesised statements from 18 papers, assimilating the barriers and enablers to the implementation of PGx testing in primary care to formulate actionable policy recommendations. These include the use of effective educational strategies to raise the knowledge, awareness, and engagement of

PCPs in PGx testing. Further the educational strategies should explain the benefits of using PGx testing - including reduction of adverse drug reactions, reduction of the trial-and-error model of prescribing and the knowledge that PGx testing is complimentary rather than a substitute for current decision-making in the prescribing process. Development of a comprehensive model with a division of responsibility between the GP and the pharmacist, supplemented by a local pool of experts is seen as a facilitator. Further important elements for the uptake of PGx testing included the cost of the test, so as not to disadvantage lower socio-economic groups. Further implementation will be enhanced by confidence in the evidence-base for PGx clinical guidelines. Finally, the infrastructure supporting results turnaround times is an important element to incorporate PGx test results into their normal workflow patterns, with results presented in an easily understandable format. The barriers and enablers highlighted in this study have been stated in previous studies.[14,23,32.] However, it is poignant to note that despite the advances in pharmacogenomic technology, the same barriers, (e.g., knowledge gap) are still pivotal to preventing PGx uptake.

This study has important implications for policymakers and healthcare professionals when considering what actions are needed for the implementation of PGx testing in primary care. This study also has important implications for primary care patients, which include raising their knowledge and awareness of testing through engagement.

Strengths and limitations

The main strength of this systematic review and meta-aggregation are the clear evidence-based statements which have been synthesised to inform policy and practice. Further all 18 papers were either classed as moderate or high as per the CASP quality rating.

A limitation of this review is that most included studies were from USA, where the healthcare system operates under an insurance-based system; therefore, these findings may not be transferable to other healthcare setting. Three studies in the review were from the perspective of a nationally funded healthcare system, one from the UK and two from The Netherlands. Although both Dutch and UK have nationally funded healthcare systems, PGx has been integrated into The Netherlands in primary care, whilst PGx strategies are still emerging in UK, and so careful consideration of the results would be needed for countries which have emerging PGx strategies. Further limitation was no data from low- or middle-income countries was included in this review, therefore transferability to such setting may not be applicable. Also, none of the included studies utilised ethnography as a method of qualitative data collection.

Future research should include more qualitative studies from low- and middle- income countries and utilise ethnography methodology in developed primary care system, thereby producing rich qualitative data. Further area for research should include the development of appropriate clinical decision support systems (CDSS) that facilitates use of PGx information at the point of prescribing and, ideally, integrating this information with other factors routinely considered in the prescribing decision-making process, such as co-medications and comorbidities. In the UK at least, the widespread and early adoption of electronic medical patient records in primary care, which are provided by only a handful of service providers (e.g., EMIS and SystemOne), provide a pre-existing technological infrastructure to build pharmacogenomic CDSS into.

Overall conclusion

This qualitative systematic review presents fifteen synthesised statements for policymakers with valuable recommendations that need addressing prior to implementation of pharmacogenomics in primary care. In this review we have identified a pathway for the implementation of pharmacogenomics in primary care. In preparation, policymakers need to consider the introduction of effective educational strategies for both PCPs and patients to raise knowledge, awareness, and engagement. The actual introduction of PGx will require reorganisation with decision support tools to aid use of PGx in primary care, with a clear delegation of roles and responsibilities between PGs and pharmacists supplemented by a local pool of experts. Further policy makers need to address the cost effectiveness of pharmacogenomics and having appropriate infrastructure supporting testing and interpretation including IT solutions for utilising pharmacogenomic results.

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Competing interests – SQ, AL, RKA, LC, JK and NQ have no competing interests.

Table 1: Characteristics of included studies and JBI & CASP quality assessment.

Citation	Context	Data collection method	Country	Participant's characteristics	Sample size	Sample characteristics	Setting	JBI Quality assessment					Overall score	CASP rating
								1	2	3	4	5		
Park[38] et al, 2006	Exploration of primary care physician's attitudes about the strengths of and barriers to using genetic testing to match patients to optimal nicotine replacement therapy.	Focus groups	USA	Primary Care Physicians	27	16 M & 11 F. Mean age 36 years (Range: 29-57 yrs)	Academic medical centers, Primary care academic faculty meetings	Y	Y	Y	N	N	Moderate	Medium
Dressler[39] et al, 2019	To reveal additional 'real-life' barriers to the implementation of PGx, that have not already been identified (cost, education and training were addressed in the study)	Phone interviews	USA	Primary Care Physicians	4 PCPs = 4[a]	Not stated	Rural primary care practices	Y	Y	U	N	N	Moderate	Medium
Williams[40] et al, 2016	To assess primary care providers interest in using a genetic test to inform treatment of alcohol use disorder with pharmacotherapy at Veterans Health Administration clinics	Interviews	USA	Primary Care Clinicians with prescribing privileges	24 MD = 19, Dr Osteopathy =1, nurse practitioners = 4	11 M & 13 F. Mean age 48 years (Range: 29-65 years)	5 primary care clinics associated with large VA medical facility	Y	Y	Y	U	N	Moderate	High
Lemke[41] et al, 2017	To explore PCP views of the utility and delivery of **direct access** to PGx testing in a community health system. Direct access – provider-ordered PGx test, mailed to the pt and results returned by PCP by telephone, in-person, mail etc.	Interviews	USA	Primary Care Physicians	15 PCPs =15	6 M & 9 F. Mean age: not stated	NorthShore University Health System - four hospital community health system in north suburban Chicago	Y	Y	Y	Y	Y	High	High
Frigon[42] et al, 2019	To understand the perceptions of PCPs, pharmacists and pts on the implementation of PGx testing in clinical practice	Focus groups	Canada	Primary Care Physicians, pharmacists, and patients	64 PCP = 23, Pharm =11 pts = 30	PCPs: 6 M and 17 F Mean age: not asked Pharmacists: 2 M and 9 F Mean age: not asked Patients:	PCPs invited through regional department of general medicine. Community pharmacists invited through regional department of pharmaceutical services and	Y	U	Y	N	N	Moderate	Medium

						9 M and 21 F Mean age: 50.3 years (Range 19-78 years)	convenience sampling and snowball recruitment strategies. Patients through same regions general population through convenience sampling following public announcements through social media and leaflets.							
Carroll[43] et al, 2016	To assess primary care providers' (PCPs') experiences with, perceptions of, and desired role in personalized medicine, with a focus on cancer.	Focus groups	Canada	Family practitioners, nurses, nurse practitioners, physician assistants, family medicine resident other	51 PCPs=51	11 M and 34 F[b]. Mean age 44 years (range: 23-65 years)	Urban and rural interprofessional primary care team practices in Alberta and Ontario.	Y	Y	Y	N	N	Moderate	Medium
Chase[44] et al, 2017	Examines some of the barriers to clinical decision support system for precision medicine	Interviews	USA	Primary Care Clinicians	≈35	Not stated	5 primary care sites varying between community clinics to large academic medical centers.	Y	Y	Y	Y	U	High	High
Unertl[45] et al, 2015	To describe the knowledge and attitudes of clinicians participating in a large PGx implementation program	Interviews	USA	Primary Care Providers Cardiologist	15 PCP = 6, cardiologist = 9	Not stated	Vanderbilt University Medical Center	Y	Y	Y	N	N	Moderate	Medium
Haga[46] et al 2012	To explore each group's attitudes about the use of PGx testing, potential for ancillary information, role of genetics experts, and sharing of PGx information among healthcare professionals	Focus groups	USA	Primary Care Professionals Physician assistant, nurse practitioners,	21	6 M and 15 F. Mean age: not recorded	Physicians from Duke -affiliated primary care clinics invited. Geneticists practicing at Duke	Y	Y	Y	N	N	Moderate	Medium

				family medicine (MDs) Internists, medical geneticists, genetic counsellors			uni medical center also invited."							
Harding[47] et al, 2019	The purpose of this study was to explore genetics in primary care from the perspective of both rural and urban PCPs	Interviews Focus groups	Canada	Primary Care Providers	29 n=10 interview n=19 focus group Interview group: - health care administrator =1, clinical geneticist = 1, nurse practitioner =1, public health administrator = 1, genetic counsellors =2, and PCPs =4 Focus group: - urban PCPs = 5 rural PCPs= 14	Interview group – not stated Focus group - age range 30-60 years	Rural and urban Canadian PCP	Y	Y	Y	N	N	Moderate	Medium
Lee[48] et al, 2017	To explore the attitudes and perceptions of pharmacogenomics among genotyped patients actively participating in an institutional pharmacogenomic implementation project, compared with that of a control group receiving traditional care	Focus groups	USA	Patients	22	11 M and 11 F. Mean age 59.5 years (range: 40-77 years)	Institutional pharmacogenomic implementation study	Y	Y	Y	N	N	Moderate	High

Rafi[49] et al 2020	To identify potential barriers, challenges and opportunities to implementation of PGx into UK General Practice	Interviews	UK	GPs and non-medic	18 GPs =16 scientific curator =1 Public health med researcher = 1	M and F – not stated GP modal age 50-59 years Scientific curator age 30-39 years Public health Med researcher age 50-59 years	Primary care	Y	U	Y	N	N	Moderate	medium
Rigter[50] et al, 2020	To define actions, roles, and responsibilities for implementation of pharmacogenetics by conducting a multi-phased stakeholder study. Stakeholders such as pharmacists, primary care physicians, patients, scientists, and policy makers were invited to discuss thresholds and opportunities for next steps in the implementation of pharmacogenetics in primary care in the Netherlands. Mixed method	Reporting only Focus groups Interviews	The Netherlands	GPs Pharmacists Patients	49[c] GP = 8, Pharmacist = 22 Pts = 19	28 M and 21 F. Mean age 46.7 years (range: 17-68 years)	Primary care - comprising an urban environment, a rural environment, and a "mixed" region.	Y	U	Y	Y	N	Moderate	Medium
Barr[51], 2008	To explore the range of factors that may impinge upon public and service user acceptability of the pharmacogenomics of antidepressants	Focus groups	Multi-centred UK, Poland, Denmark Germany	Patients	Not stated	Not stated	General public and mental health service users from four European sites	Y	Y	Y	Y	Y	High	Medium
Issa[52] et al, 2009	Examining patients' understanding and knowledge of personalized medicine and the process of decision-making regarding pharmacogenomics and targeted therapeutics and how patients value receiving pharmacogenomics-based personalized health care relative to the standard models of diagnosing and prescribing treatments.	Focus groups	USA	Patients	32	17 M and 15 F. Mean age: not stated (range: 25-64 years)	Outpatient clinics at The Methodist Hospital	Y	U	Y	N	N	Moderate	Medium
De Marco[53] et al, 2010	Views on Personalized Medicine: Do the Attitudes of African American and White Prescription Drug Consumers Differ?	Focus groups	USA	Patients	48		2 clinics and a family practice centre at a large public medical	Y	Y	U	Y	N	Moderate	Medium

							center in a central North Carolina city							
Haddy[54] et al, 2010	To investigate the current opinions and experiences of consumers with regard to medication use and side effects. It also explored what they understood by the term "Personalized Medicine" and whether they had any concerns regarding the use of genetics to determine medication selection. Consumers' opinions on the storage of medical and genetic information were also investigated.	Focus groups	Australia	Patients	35	9 M and 26 F. Mean age: not stated (range: 18->60 years)	Members of the general public	Y	Y	Y	Y	N	High	High
Van Der Wouden[55] et al, 2020	The primary aim was to identify pharmacists perceived remaining barriers preventing and enablers facilitating implementation of pharmacist initiated PGx in primary care.	Interviews	The Netherlands	Pharmacists (Involved in PREPARE study)	15	7M and 8 F Mean age 38.5 (Range: 25-59)	Community pharmacy	Y	Y	Y	N	U	Moderate	High

ConQual criteria for assessing confidence. The following five questions to confirm the dependability of the results.
1. Is there congruity between the research methodology and the research question or objectives?
2. Is there congruity between the research methodology and the methods used to collect data?
3. Is there congruity between the research methodology and the representation and analysis of data?
4. Is there a statement locating the researcher culturally or theoretically?
5. Is the influence of the researcher on the research, and vice-versa, addressed?
The letter denotes the ratings for each study (N = No, U = Unclear, Y = Yes).
(Ref: Munn Z, Porritt K, Lockwood C, Aromataris E, Pearson A. Establishing confidence in the output of qualitative research synthesis: the ConQual approach. BMC Med Res Methodol. 2014 Sep 20; 14:108. doi: 10.1186/1471-2288-14-108. PMID: 25927294; PMCID: PMC4190351.)

Table 2: Categories and findings including barriers and enablers across the included papers. Barriers (B) and enablers (E)

Knowledge (An awareness of the existence of something)	
Category	**Finding**
Lack of genetic knowledge (B)	Lack of knowledge and awareness [39,42,4347,49,39,50,]
	HCP PGx knowledge and awareness [55]
	Profound lack of knowledge of direct-to-consumer genetic tests[43]
Limited experience with PGx (B)	Personal unfamiliarity with genomic medicine[44]
	Limited encounters with genetics in practice [47]
	limited experience with personalized medicine [43]
	Level of comfort with genetic testing [47]
	Varying level of knowledge [44,45]
	Preparation and knowledge [45]
Training and education (B)	Lack of genomic education [42]
	PGx/Genetic education [47,49, 41]
	Education [47]
	Resources/support [47]
	Rapidly changing PGx knowledge and need for continuing education [45]
	Patient and provider education material [41]
	Pt education material – for frequent Q&As [45]
	Policies for responsibilities and ownership of PGx data [45]
Patients lack of genetic knowledge (B)	Unfamiliar with term PGx [52]
General interest in PGx testing (E)	Greater role for genetics [47]
	Shifting patterns of work to allow new advances [47]
	General interest in PGx testing[48]
	Potential of using PGx [49]
	Positive attitude towards PGx[51]
	PGx test results rapidly obtained to be valuable [42]
	Perceived role in delivering PGx [55]
Social and professional roles (A coherent set of behaviours and displayed personal qualities of an individual in a social or work setting)	
Category	**Finding**
Skill mix (B)	More access for pharmacists (and other HCP) to genetic information[54]
	Pharmacists to have major role in PGx [42]
	Division of responsibility [50]
	PCP's role in personalised medicine [43]
	PCP role - education, counselling, testing and referrals to specialists [47]
Pool of experts (B)	Pool of experts in general practice [49]
	Need for buddy or connection into a genetic service [43]
Professional relationships (E)	Relationship with healthcare professional [48]
	high regard for physicians who adopted pharmacogenomics[48]
	Relationship with healthcare professional [48]
	Opportunities for pharmacists [50]
	Patient–doctor relationship[39,43]
	Acting upon PGx and reporting to patients [55]
	Pharmacist added value and learning by doing [55]
	Professional interaction improvement [55]
Behavioural regulation (Anything aimed at managing or changing objectively observed or measured actions)	
Category	**Finding**
Negative impact of PGx (B)	Adverse impact resulting from negative results [40]
	Repercussions of positive test result – labelled, stigmatized, develop

	fatalistic perceptions [38]
	Anxiety about genetic information [42]
	Ambivalence – depression and genetic research (targeted PGx research and meds designed to treat) [51]
	Impact on patient perspectives and shared decision-making [49]
Patient views (B)	Consumer demand [52]
	Conflation of disease risk and drug reaction[51]
	Concerns when starting a new medication [48]
	Therapeutic benefit[48]
Behavioural change (B)	Patients use a positive test result as rationalization for giving up[38]
	Managing results expectations[41]
	Reluctant to change current practice[50]
Reliance on genetic testing (B)	Reliance on genetic test rather than patient history[38]
	Undermining the importance of psychological and behavioural determinants of both smoking/quitting[38]
	incentive to use medicines instead of conversation therapy[51]
Medical mistrust (B)	Medical mistrust by marginalised population (pt. view)[53]
Beliefs about consequences (Acceptance of the truth, reality, or validity about outcomes of a behaviour in a given situation)	
Category	**Finding**
Reduces adverse drug reactions (E)	Avoid adverse drug reactions[41]
	Reduce side effects[41]
	Improve compliance through less side effects[41]
	Reduction of adverse events[42]
	Concept of individualized medicine[44]
	Adverse effects[46]
	Tolerate adverse effects[48]
	Value of PGx testing in primary care[49]
	Reduce adverse effects[51]
	Reduction of adverse drug effects[52]
	Reduces adverse effects[53]
	Pharmacotherapy improvement[55]
Reduces trial and error (E)	Aid in therapeutic choice[40]
	Increase patient's confidence in their care[40]
	Reduce trial and error[53]
	Improved effectiveness[52]
Patient benefit (E)	Patient motivation[38,40]
	Benefit patients who had exhausted other treatment options[38]
	Improve patient adherence to treatment[40]
	Relieve patients of personal blame[38]
	Use as preventative tool through raising patient awareness[38]
	Create a placebo effect for patients[40]
	Quick access to results, cost effective options[38]
	Implications for future medication management[39]
	Competitive edge[39]
Environmental Context and Resources (Any circumstance of a person's situation or environment that discourages or encourages the development of skills and abilities, independence, social competence, and adaptive behaviour)	
Category	**Finding**
EHR implementation (B)	Priority for EHR implementation[44]
	Clinical decision support in EMR[39]
Workflow issues (B)	Translating results into clinical decisions[45]
	PGx integrated into EMR – integrating electronic alerts[42]
	Workflow issues for CDS, unwilling to have interruptions on their workflow[44]

Reporting results (B)	Clearer layout[41]
	Information overload[45]
	electronic capture of genomic information[49]
Ordering/interpreting tests (B)	Ordering and interpreting tests [38,45]
	Ability to understand and explain PGx test results [41,45,46]
	Specific training to report PGx results[41]
	Interpreting genetic information[38]
	Unclear procedures outside of the study[55]
Cost concerns (B)	Cost of PGx testing[39, 40, 41, 42, 44, 45, 47, 48, 50, 52, 53,
	Cost effectiveness[47, 49]
	Who pays?[44, 45,52, 54]
	Insurance coverage[41, 42]
	Insurance loading (paying extra premiums based on personal medical data)[49]
	Insurability and costs[52]
	Undetermined reimbursement for test and consult[55]
Limitations (B)	Limitations /implications of genetic testing[47]
	Concerns about consenting to PGx test[48]
	Population level benefits limited by reducing target population[40]
Ancillary findings (B)	Dealing with ancillary findings[46,48]
Technical issues (B)	Restricted time constraints[38, 41, 46]
	Accessibility of PGx test results/ Easily accessible personalized med tools [43,46]
	Flexible testing options[41]
	Turnaround times [40, 41]
	When and whom to test?[50]
	Access to testing (pt. view)[52]
	pre-emptive vs reactive[39]
	Pre-emptive[50]
	Technical issues[41]
Clinical utility (B)	Lack of evidence - clinical utility[50, 55]
	Need for evidence[44]
	Utility dependent on prognostic accuracy[40]
	No incremental utility over standard care[40]
	Clinical utility of tests[40,52]
	Accuracy of the test[48]
Guideline development/accessibility (B)	Accessible PGx guideline[42]
	Lack of genetic referral guidelines[43]
	Guidance document[39]
	Infrastructure inefficiencies (guideline factors, incentives, and resources)[55]
Decision-making (E)	Another aspect of clinical decision making[40]
	Guiding primary care medical decision-making[41]
	Individualize medication treatments[41]
	Informed decision making[41]
	Efficient decision making[41]
	Increased patient autonomy[41]
	Follow-up[55]
	Less fear and anxiety about trying a new medication[41]
	Valuable tool in the future[41]
Social influences **Those interpersonal processes that can cause individuals to change their thoughts, feelings, or behaviours)**	
Category	**Finding**
Employment discrimination (B)	Genetic information not shared with employers[54,54]
	Insurance, employment discrimination[53]

	Genetic discrimination and confidentiality[38]
	Health insurance, employment discrimination, and stigma[38]
Confidentiality/privacy of data (B)	Information stored in a confidential manner [42, 54]
	Storage and future use of information[52]
	Disclosure, privacy, and confidentiality[52]
	Data and privacy concerns[41]
	Privacy and personal pharmacogenomic information (pt. view)[48]
	Data ownership responsibility and liability[45]
Abuse of test results (B)	Test information not used in a harmful manner to patients[38]
	Use of information over time[39]
Social inequalities (B)	Social inequalities[42]

Table 3 - CONQUal summary of findings

	Title: the barriers and enablers of PGx testing in primary care: a review of qualitative evidence **Population:** primary care healthcare professionals including doctors, pharmacists and nurses, policy makers and patients. **Phenomena of interest:** the use of PGx testing **Context:** only papers reporting primary qualitative data were included. **Settings:** primary care setting.				
	Synthesised findings	**Type of research**	**Dependability**	**Credibility**	**CONQual score**
Knowledge	If pharmacogenomic knowledge, awareness and engagement of primary care professionals can be improved through effective undergraduate and postgraduate education programmes and if patients are appropriately engaged with the process, then primary care pharmacogenomic testing uptake is likely to increase.	Qualitative	Moderate	Equivocal	Moderate
Social and professional roles	Better engagement with pharmacogenomics testing can be achieved if there is a clear division of responsibility between Primary Care Professionals - GPs making the diagnosis and the pharmacist choosing the appropriate drug through use of pharmacogenomics testing. If a more comprehensive model for GP-pharmacist responsibility and engagement with patients is developed, then this could improve the uptake of pharmacogenomics testing in primary care. Furthermore, the process can be facilitated by a committee of local pharmacogenomics experts to guide decision making.	Qualitative	Moderate	Equivocal	Moderate
Behavioural regulation	If learning about the potential benefits and limitations of pharmacogenomics testing is made clearer for Primary Care Professionals and if patient expectations are managed effectively, then the benefits of pharmacogenomics testing in primary care can be more easily realised.	Qualitative	Moderate	Equivocal	Moderate
	If there is greater awareness and understanding between Primary Care Professionals that pharmacogenomics testing is complimentary rather than a substitute for current clinical decision-making, then this will increase their confidence and competence in using pharmacogenomics testing in primary care.	Qualitative	Moderate	Unequivocal	Moderate
Beliefs about consequences	If patients and Primary Care Professionals recognised the potential for pharmacogenomics testing to reduce adverse drug reactions and trial-and-error aspect of prescribing, then this will facilitate the uptake of pharmacogenomics testing in primary care.	Qualitative	Moderate	Equivocal	Moderate
	If the perceived benefit for the use of pharmacogenomics amongst primary care patients is promoted, then this will facilitate the uptake of pharmacogenomics testing in primacy care.	Qualitative	Moderate	Equivocal	Moderate
Environmental Context and Resources	If pharmacogenomics results can be implemented and incorporated into the normal workflow patterns at the point of prescribing and if results are easily comprehensible, then uptake by Primary Care Professionals in primary care can be improved.	Qualitative	Moderate	Equivocal	Moderate
	If policy makers and commissioners invest in cost-effective models for pharmacogenomics testing (where the benefit of testing outweighs the cost of the test), then this will help minimise inequities between low and high socio-economic patient groups and facilitate the uptake of pharmacogenomics testing in primacy care.	Qualitative	Moderate	Equivocal	Moderate
	If pharmacogenomics test results, which offer valid and reliable information are used to aid decision-making during prescribing, then this will facilitate the uptake of pharmacogenomics testing in primary care.	Qualitative	Moderate	Unequivocal	Moderate

	If the infrastructure around pharmacogenomics testing is strengthened such that results can be accessed in a timely manner and a prompt alerts the clinician to the availability of the results, then the uptake of pharmacogenomics in primacy care can be increased.	Qualitative	Moderate	Unequivocal	Moderate
	If more specific guidance is produced for Primary Care Professionals, highlighting when pharmacogenomics testing is appropriate. For example, if guidelines were produced by national bodies such as NICE or MHRA, which build upon international guidance produced by CPIC or DPWG, then Primary Care Professionals would be reassured of the evidence base for pharmacogenomics recommendations, and this could lead to increase uptake of pharmacogenomics testing in primacy care.	Qualitative	Moderate	Equivocal	Moderate
	If Primary Care Professionals have successfully used pharmacogenomics or have personal experience of undertaking a pharmacogenomics test, then they are more likely to use pharmacogenomics testing for their patients in the future.	Qualitative	Moderate	Equivocal	Moderate
Social influences	One of the benefits of genetic information collated for pharmacogenomics testing is related to whether a person will be susceptible to adverse drug reactions or not. Reassurance that genetic information is kept confidential, and this would not adversely affect a person's employment or insurance rights, then the patients are going to be more receptive to pharmacogenomics testing.	Qualitative	Moderate	Equivocal	Moderate

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram. Pharmacogenomic testing