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Pharmacist Education and Cancer: Attitudes and Perceptions of Clinicians Surrounding a Potential Role for Pharmacists in Clinical Pharmacogenomics

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Abstract

Objectives: Pharmacogenomics (PGx) is of increasing importance due to rising awareness of interpatient variability in drug response in conditions such as cancer. With the vision of implementing PGx testing as standard clinical practice in the near future, pharmacists are predicted to take on an active role. This study aims to explore clinician acceptance and value of pharmacy PGx roles as well as continue research into the barriers facing the implementation of clinical PGx and potential roles for pharmacy.

Methods: This study was done by literature review and semi-structured interviews comprising both closed and open-ended questions carried out in person by the researcher (Laura Hartley). This project was an extension of a project previously approved by the University of South Australia's Human Research Ethics Committee with a subsequent amendment to involve further researchers. Eleven clinicians involved in care of cancer patients at the Flinders Medical Centre (FMC) were interviewed, predominantly from the Flinders Centre for Innovation in Cancer (FCIC). The participant pool consisted of 2 surgeons, 8 physicians and 1 pathologist. Clinical and research expertise spanned the breadth of cancer phenotypes.

Data Analysis: This involved repetitive listening to audio recordings, studying of notes taken during the interview and continuous adaptation of common findings into themes. A thematic framework was created, the data coded and analysed using the one sheet of paper (OSOP) method. Following on, data was grouped into broader categories (axial coding) and anomalies identified so that the data would not be affected by the researcher's personal bias.

Results: Three main themes were identified - barriers to implementation of clinical PGx, pharmacy roles within PGx and clinician acceptance. Each theme was subdivided into the following categories: barriers - research aspects, practice issues and precedent. Roles - research, practical, pastoral/educational and administrative. Acceptance - positive, negative and the importance of multi-disciplinary working. Results indicate a positive attitude towards pharmacist involvement in PGx practice provided protocols and multi-disciplinary working are in place. The data also suggested that the relative lack of evidence for testing and timeline of testing are significant barriers to implementation in practice. A major role for pharmacy will be in the development of an evidence base, performing clinical PGx tests and championing the adoption of new PGx technologies in current practice.

Conclusion: This study was consistent with previous studies detailing the barriers facing clinical PGx implementation. The barrier perceived as most significant was the issue of insufficient evidence pertaining to clinical utility, validity and cost-effectiveness. Viewpoints raised during this study indicate that until the evidence base has been strengthened clinicians are unlikely to adopt PGx testing into their everyday practice regardless of who performs them. Roles for pharmacists were found to be largely consistent with previous findings although some additional roles were identified in protocol/guideline development and improving the evidence base. Overall, a positive attitude towards PGx roles for pharmacists was observed. Previous studies identified clinician acceptance of pharmacy roles as an important driver for the uptake of clinical PGx. This study provides support for the acceptance of the role of pharmacist-led PGx practice.

Keywords: *Pharmacogenomics; Pharmacogenetics; Pharmacogenomics; Metabolic profiling; PGx testing; Risperidone; Quetiapine*

Introduction

The Importance of Pharmacogenomics in Healthcare Practice

Pharmacogenomics (PGx) is the study of how alterations in the human genome affect the overall behaviour of drugs. Part of pharmacogenomics focuses on the effects of genomic variation in drug metabolising enzymes such as cytochrome P450 termed 'pharmacogenetics' [1,2]. The terms 'pharmacogenomics' and 'pharmacogenetics' are often used interchangeably - in this study, the terms 'pharmacogenomics', 'metabolic profiling' and 'pharmacogenomic testing' will be used to describe the utilisation of genomic technologies for the purposes of eliciting metabolising enzyme status in reference to commonly used drugs.

Genomic variations can lead to changes in both pharmacokinetics and pharmacodynamics. This study focuses on changes in the pharmacokinetic aspects of drug response, particularly alterations in metabolism. Changes in drug metabolism may lead to reductions in drug efficacy and safety subsequently increasing the risk and incidence of side effects or adverse drug reactions (ADRs) [3]. Genomic variations influencing pharmacokinetics are usually heritable and last a lifetime effectively prohibiting particular patients from receiving certain medications such as irinotecan and cetuximab unless the benefits grossly outweigh the risks (in severe cases, hospitalisation or death) [3]. This may be viewed as a lost opportunity for proven effective therapy [4].

Recent studies estimate that genetic variation accounts for 20-95% of interpatient treatment response variability [3]. As many as 7% of hospital admissions in Europe are thought to be due to ADRs [3] and since ADRs are one of the top five causes of death in the USA alone[3,5], it is reasonable to hypothesise that PGx testing prior to treatment will make a significant contribution to improving efficacy and safety profiles.

In some fields (e.g. cancer, organ transplantation and therapeutic drug monitoring [3,6]) the use of genetic markers was introduced into clinical practice years ago. In oncology, PGx markers relating to the pharmacodynamics of targeted therapies (e.g. KRAS for cetuximab and Her2 for trastuzumab) are regularly used to guide prescribing [7]. However, there are certain drugs which are known to be affected by variations in metabolising status but pre-emptive profiling is not carried out in practice. For example, irinotecan (a semi synthetic analogue of camptothecin used in colon cancer) states PGx information in its Summary of Product Characteristics (Appendix C) and in some cases on its packaging as well, yet routine testing for UDP-glucuronosyltransferase 1 (UGT1A1) variants is not performed [1]. The possible reasons for this are detailed later in the study.

Barriers to Clinical Implementation

There is substantial evidence to support the integration of clinical PGx in practice and a deeper understanding of the effects of genomic variation on drug response afforded by the increase in high throughput genomic technologies available has already contributed to the emergence of 'personalised medicines (PM)' in healthcare [8]. Despite the continuing expansion of simplified technologies establishing their place in clinical practice, there are multiple barriers to their success as prescribing tools.

A recent report described the introduction of PM as 'a disruptive innovation' which would require multiple changes to existing protocol and development of new business models to incorporate it into current practice [9]. The report also identifies that although the move towards PM has been foreseen for many years, the transition will be slow due to the multiple barriers preventing its establishment.

For the purpose of this study, the barriers to clinical implementation identified in the literature are broadly grouped into three categories- cost, evidence and education.

Cost Issues: The first issue of cost is reimbursement. PGx testing is expensive - according to a recent study, the cost of testing for variations in CYP2C9/VKORC1 for warfarin ranges from $199-500 [10] and UGT1A1 testing costs on average $375 [10,11]. The relative lack of cost-effectiveness studies is also a factor [10]. Although there are cost-effectiveness studies for some tests, in general the evidence base

is inconsistent, frequently oversimplified and often hypothetical [12]. Though initial expenses are likely to be substantial, testing may save money in the long-term by reducing ADR incidence [10,12], increasing patient productivity and reducing overall healthcare costs by imposing sensible restrictions on the use of expensive targeted therapies such as monoclonal antibodies [10,13].

A 2010 study showed that the likelihood of reimbursement was stronger if the test had strong evidence of clinical utility (addressed later in the study) and was recommended by professional bodies such as the National Institute for Health and Clinical Excellence [10]. Focusing on building a solid evidence base including cost-effectiveness studies for PGx tests may improve the chances of implementing clinical PGx but it will be time-consuming and costly to do [10,13]. The alternative (self-payment) may reduce the cost to healthcare facilities but not only does this risk the increase in use of direct-to-consumer tests which are often inconclusive at best [14], it also carries the risk of patient-healthcare professional (HCP) miscommunication, psychological distress and a whole host of other ethical and legal issues beyond the scope of this paper [14].

Evidence: It has been increasingly acknowledged that the demonstration of clinical utility and validity of PGx markers is an essential factor influencing the successful uptake of clinical PGx. Without strong evidence of clinical utility and validity, HCPs are less likely to accept testing into practice [13] and even though well thought out randomised controlled trials have afforded us the most useful evidence, the data is not always available [10,15]. Such data varies in strength depending on the technology [10] creating inconsistency in the evidence base and as such, uncertainty surrounding the adoption of such tests [16].

To illustrate - a recent study found that although many conditions have PGx markers, their expression is not always associated with the presence (or lack) of a drug response but rather their expression provides an indication of their influence on the natural disease course (a 'prognostic' factor rather than a 'predictive' factor) [15]. Furthermore, this study found that prognostic markers would not influence treatment choice (therefore they lack clinical utility) but predictive markers would provide a useful indication for treatment choice [15]. KRAS genotyping is an example of a predictive marker and used to guide the prescription of anti-EGFR (epidermal growth factor receptor) therapies (e.g. cetuximab) in metastatic colorectal cancer [15]. BRAF mutation testing acts as an example of a prognostic factor for the same indication [17]. Although the patient may benefit from anti-EGFR therapy, the marker is not routinely exploited to guide their prescription [15,17].

PGx in Pharmacy Practice and Education: Many consider the largest barrier facing clinical PGx to be HCP education. Studies have shown that at an undergraduate level, young HCPs (both medics and pharmacists) are not equipped with the skills necessary to take on new PGx roles before they graduate due to a lack of teaching on the topic [17-19]. Pharmacists are considered to be 'experts in drug therapy and management' and are responsible for ensuring the safe and effective use of medicines. As such it is likely that the role of PGx testing will fall to them to improve clinical outcomes [1,20]. A recent study has predicted that in the future, not only will pharmacists be expected to perform community based PGx services [3], order and interpret tests, make PGx-based prescription recommendations, they will also be expected to provide PGx training and education to other HCPs [1,20,21].

However, currently the majority of pharmacists are neither considered equipped by other HCPs nor do they consider themselves sufficiently prepared to perform these roles effectively [22,23]. One study identified those that possess the necessary skills have undergone further specialist training after university [23]. The same study identified clinician acceptance of these roles as a major driver encouraging the uptake of pharmacist-led clinical PGx [23]. An example of successful integration of clinical PGx testing can be seen at St Jude Children's Research Hospital, Memphis, USA. The pharmacist-led, hospital-based PGx service is performed alongside existing pharmacokinetics services [6]. The test results are sent to pharmacists for interpretation and this informs their therapy recommendations and changes. Another example is the integration of pharmacists into interpretation teams within companies specialising in genetics where they work in multi-disciplinary teams to analyse test results and provide advice and recommendations to clinicians [24]. In both cases, pharmacists are demonstrated to be highly flexible in the roles they perform.

Despite demonstrations of adaptability for both pharmacy and the corresponding technology, the comparative lack of HCPs with in-depth PGx knowledge has led to a deficiency in champions for the area [25]. There have been studies to suggest that the adoption of new technologies is based on the 'I will if you will' principle [25] and this indecision has led to delays in the implementation of PGx testing. It is predicted that educating our young HCPs will lead to the generation of champions for the area [25].

An Example in Clinical Context

One example of such a test which may be useful in clinical practice is that of eliciting CYP2C9 status. CYP2C9 is an enzyme involved in the metabolism of warfarin - an anticoagulant commonly used to prevent clotting events in pro-thrombotic conditions such as atrial fibrillation and ischaemic stroke [26,27]. A recent study ascertained that 15% variability in patient response is attributable to single nucleotide polymorphisms (SNPs) in the gene encoding Vitamin K Oxido-Reductase Complex 1 (VKORC1) and 18% is due to SNPs in the gene encoding CYP2C9 [28]. The same study also identified that pre-emptive PGx testing reduced the number of hospitalisations caused by ADRs (thromboembolisms and haemorrhage [25]) by 30% [28].

The test is able to identify whether a patient is homozygous for wild-type CYP2C9*1 (extensive metabolisers) or heterozygous (poor metabolisers) i.e. CYP2C9*1 plus one copy of CYP2C9*2/3 and is therefore useful to determine their starting dose of warfarin [28]. Patients who were heterozygous were shown to have a 50-75% decrease in their capacity to metabolise warfarin indicating that their starting dose should be lower than those homozygous for CYP2C9*1 [28]. Patients found to be either homozygous for or heterozygous to include CYP2C9*3/4/5 were advised to avoid warfarin, unless the benefits outweighed the risks of treating and no alternative was available, due to severely diminished capacity to handle warfarin.

Although this study identified useful information about warfarin starting doses and avoiding ADRs with initial treatment, it failed to demonstrate a difference in the time taken to achieve the target INR between the groups and also failed to demonstrate a change in need for a 6 month INR check [28] indicating that even though PGx testing may be useful for improving safety and efficacy, it will not have a great impact on the timescale or monitoring of treatment. However, a recent study identified that PGx-guided warfarin dosing shortened the time period to achieve the target INR by 8 days and this resulted in more patients staying within the therapeutic window [29] in addition to a lower incidence of over anti-coagulation events. The discrepancy between these two studies is thought to be one of the factors affecting the integration of routine warfarin profiling into clinical practice.

Examples of PGx Tests Currently Available

A handful of protein- and DNA-based PGx tests have been developed and subsequently approved for in vitro diagnostic use representing tangible deliverables of the many genomic studies that correlate genetic variation to interpatient variability in drug response [30].

In 2005, the Food and Drug Association approved the first PGx test designed to elicit CYP450 metabolising status (Amplichip™ CYP450 Test; Roche Molecular Systems, Inc. NJ, USA) [30]. The test is based on the Affymetrix microarray technology for genotyping 27 separate CYP2D6 alleles and 3 CYP2C19 alleles linked to different metabolising phenotypes [30]. This test is recommended but not necessary for drugs that act as substrates for CYP2D6 and 2C19 e.g. tricyclic antidepressants and opioids [31]. Select laboratories also perform other tests for select populations. For example, the HLA-B*1502 allele test for carbamazepine-induced Stevens-Johnson syndrome in patients of Asian descent [32,33]. The DMET™ Plus Panel (Affymetrix) covers a wide range of genetic variations including rare and common single nucleotide polymorphisms (SNPs), insertions and deletions, many of which are not assayed for by conventional SNP methods [30].

Other PGx tests are available for the identification of predictors of susceptibility to ADRs associated with antipsychotic medications such as risperidone and quetiapine [30]. The PhyzioType™ (Genomas Inc. CT, USA) system assesses a number of DNA markers using

a complex biostatistical algorithm to predict a patients' risk of developing potentially life-threatening ADRs such as antipsychotic-induced metabolic syndrome [30]. In 2011, the PhyzioType™ system received FDA approval for the diagnosis and prevention of pre-diabetic and metabolic side effects associated with second generation antipsychotics [34].

Literature Review

There have been multiple studies in the past few years assessing the barriers to and attitudes surrounding the integration of PGx testing into practice. Thus far, the studies have concluded that although there is great interest in and potential for pharmacy taking on the role of PGx testing, the profession is not currently knowledgeable enough to take the role on. A recent qualitative study in South Australia, conducted semi-structured interviews with 21 hospital pharmacists to assess their knowledge of PGx and its importance in every day practice [2]. The results showed that the interviewees were unsure about the importance of PGx and how to implement PGx testing into their practice.

Concurrently, a small scale study of the roles specialist pharmacists performed in PGx and assessment of the readiness of the profession to take on this role was conducted [35]. This study identified that although pharmacists performed a large range of roles within PM and were becoming more involved with PGx, as a whole the profession was not sufficiently educated enough for the integration of testing to be a success. The study also found that clinician acceptance (an unknown entity) was an important driver encouraging the uptake of PGx practice in pharmacy [23].

In conclusion, these select studies show that pharmacy is not ready to take on the role of PGx testing despite having the interest. There is a lot of uncertainty surrounding how these tests could be integrated into practice, whether they will be of value to patient care from both a clinical and cost-effectiveness perspective and until now, the studies have concentrated on a PGx role for pharmacists involving biomarker profiling in cancer. However, there have not been any studies assessing the potential role for pharmacists in metabolic profiling; an area where it is believed their involvement may have significant impact on the quality of patient care. Furthermore, there have been no studies investigating whether pharmacist involvement in any form of PGx testing (biomarker or metabolic profiling) would be accepted and perceived as valuable by the medical community.

Study Objectives

This project is a continuation of previous research investigating the barriers facing the integration of clinical PGx testing and roles pharmacy can perform within PGx and PM. This project aims to fill the gap identified by previous studies by investigating clinician acceptance of pharmacist assistance in the uptake and performing of metabolic profiling.

Methods

Data Gathering

This study was based on a set of 3 qualitative interview questions conducted by the researcher and focused on the following areas:

a. Whether a pharmacist role in PGx (particularly metabolic profiling) would be valued by clinicians
b. Whether metabolic profiling is being performed in the specialty area of the interviewee
c. Which tests, who is involved in carrying them out and potential roles for pharmacy
d. The problems facing implementation, whether pharmacy could help or not and why

Prior to the interview, information regarding the interviewees' area of specialty and seniority was gathered from searches on the Flinders University intranet. This information was checked with the participant at the start of the interview and any discrepancies noted. Those without such information were asked for this at the start of the interview. The structure of the interview was based loosely on the flow chart in appendix A with the identity of the next question prompted by the answer before it. Interviewees were encouraged to provide greater detail if their answers encouraged further discussion. Questions relating to demographics were asked first as an introduction to the study.

Participants were selected based on their location and involvement in a field of medicine where routine metabolic profiling would potentially make a significant impact. Participants were invited to take part in the study by email or verbal invitation via the Academic Supervisor (Prof R. McKinnon) and arrangements for face-to-face interviews were made by the researcher (Laura Hartley) via email. A participant information sheet and consent form was given to each of the interviewees to read and sign prior to starting the interview. All interviews were conducted during working hours at the FCIC/FMC.

The interviews were conducted between February and April 2014, audio-recorded and transcribed by the researcher by repetitive listening to the audio recordings (made on iPad and Dictaphone). The interviews were conducted in either a private meeting room or the participants' office and involved only the participant and researcher. During the interview, notes were taken to back up or clarify any answers given by the participant. There was no time limit given to the interview to encourage open discussion however the majority of interviews lasted no more than 15 minutes in total due to demanding work schedules.

As the study was an extension of previous research carried out by the FCIC, it was already approved by the University of South Australia's Human Research Ethics Committee and a new application was not needed. Amendments to the original ethics protocol were approved prior to data collection and made to include a new researcher, a new set of participants (clinicians) and to make changes to the interview questions, participant information sheet and consent form. The data gathering process continued until the point of data saturation and no new findings became apparent [36,37,38]. Participant personal information remained confidential - only information regarding area of specialty, years of practice in specialty area and research activity was recorded. The anonymous raw data included the audio recordings and transcripts and remain securely stored at the FCIC.

Data Analysis

Data analysis was carried out throughout the data collection stage [36]. Initially, this involved repetitive listening to the audio recordings and studying of notes taken by the researcher during the interviews. Any common findings derived from the initial stages of the data analysis process were documented and used to develop a list of main themes [2,36,39].

From this list, a thematic framework was created and categories identified based on the interview questions and any issues highlighted during the interview process [2,36]. The coding process was then carried out. During this stage, the transcripts and notes were read repeatedly and sections of the text ascribed to the main categories or themes e.g 'evidence' or 'pharmacist roles'. The text was also labelled with numerical or short text descriptions to aid identification of origin later on [36]. After all the data was coded, the text under each heading was analysed using the OSOP (one sheet of paper) method [36]. During this process, the sections of text were read and separate notes were made surrounding any issues that arose from the coded data and associated with the participants' identities [36]. Once completed, all the issues raised were grouped into broader categories, headings or themes (axial coding) [36]. Any contradictory evidence that stood out was identified so that the data analysis would not be affected by the researchers' personal bias [36,37] and bias was not introduced into the study.

Data analysis involved the continuous generation and adaptations of themes and categories [39]. Repetitive reading and reflecting on the results and quality of data aided deeper understanding and familiarisation [36]. The researcher was also aware the participants were from a different background (pharmacy student and clinician) [2,36].

Results

Demographics

11 qualified physicians were interviewed. Clinical experience ranged from registrar to specialist. Four participants had worked in their current specialist field for between 0 and 5 years, two between 6 and 10 years, two between 10 and 15 years and three for 15 years or more. Ten participants described themselves as 'research active', one did not. Of those that considered themselves research

active - seven participants spent between 0 and 5 hours per week on PGx and PM research, two between 11 and 15 hours per week and one 15 hours or more per week (the eleventh participant was considered 'research inactive' and was therefore not asked how many hours they spent on PGx and PM research)

Primary research interests were attributed to the following cancer categories: lung (1), gastrointestinal (oesophagus to colon) (3), haematological (1), pharmacology, targeted therapies and basic science (3), endocrine (including genitourinary, gynaecological and breast) (2) and pathology (1). All participants perform clinical duties at the FMC. 8/11 clinicians interviewed participate in roles involving PGx to some degree in three main areas: clinical practice, academia and/or research.

Findings

Based on the transcripts of the interviews, there were 3 major themes identified (Figure 1). The first theme identifies the main barriers believed to be preventing the integration of clinical PGx in the current setting, the second details potential pharmacy roles in metabolic profiling perceived as valuable by clinicians. The third theme considers clinician acceptance of pharmacist involvement in PGx.

Figure 1: *The three main themes identified from the raw interview data.*

Barriers to Implementation of Clinical PGx

The interview data identifies 3 main factors thought to be causing significant delays in the implementation of clinical PGx (Figure 2).

Research Aspects: 'Research Aspects' broadly covers issues identified at interview with the evidence base for PGx testing and cost. 10/11 clinicians interviewed identified the relative lack of evidence for PGx tests to be the main barrier to implementation in clinical practice. When examined further, the specific issues attained to lack of clinical utility and validity studies, inconsistency between perceived therapeutic benefit and clinical impact and unfamiliarity with the technology. 1/11 clinicians identified a possible solution to the problem (marked *).

Cost of testing was also identified to be a major contributing factor to the delays in implementation. 6/11 raised issues with cost-effectiveness and cost to the patient.

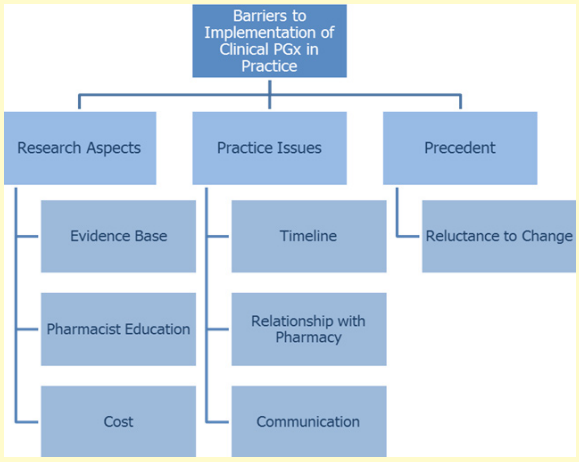

Figure 2: *A summary of the barriers facing the implementation of clinical PGx in practice identified at interview.*

Practice Issues: The topic of 'practice issues' describes the challenges associated with daily working practice and personnel and is subdivided into concerns surrounding PGx testing timelines, the relationship with pharmacy, how integration into practice could be done, communication and pharmacist education.

5/11 clinicians identified problems with the timeline of performing PGx tests in practice.

3/11 clinicians were concerned about the relationship with pharmacy, the attribution of responsibility and how these tests would be incorporated into busy clinical practices.

1/11 clinicians identified an issue with communication between colleagues in the public healthcare system.

1/11 clinicians identified an issue with pharmacist education

Precedent: The final sub-category identified was 'precedent'. 7/11 clinicians stated that current practice is based on following what has been successful previously and therefore the profession demonstrates a reluctance to adopt new technologies. 1/11 clinicians gave an example of such reversed practice (marked *).

Pharmacist Roles of Value

A total of 4 areas where pharmacist input would be of value to clinicians and their clinical practice was identified from the raw data (Figure 3).

Research Roles: 4/11 clinicians identified a role for pharmacy in developing the evidence base for PGx tests by performing clinical utility/validity, cost-effectiveness and bioavailability studies. 1/11 clinicians stated that the issue of insufficient evidence was not something that could be 'addressed on an individual level' but rather as a collective effort (marked *).

Practical Roles: 11/11 clinicians identified roles for pharmacy in the day to day running of PGx testing in clinics. This included roles such as ordering tests, filling out paperwork, getting consent, interpreting results and recommending drugs and dosages.

Pastoral and Educational Roles: 8/11 clinicians acknowledged a role for pharmacy in pastoral (e.g. patient advocate) and educational roles (e.g. PGx champion and HCP education).

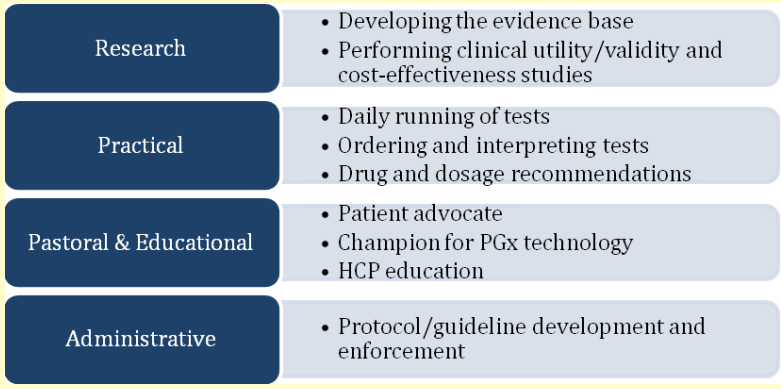

Figure 3: *A summary of roles that could be performed by pharmacy considered to be of value to clinicians identified at interview.*

Administrative Roles: 6/11 clinicians stated that pharmacy input into the development and enforcement of PGx protocols and guidelines would be of value to clinical practice.

Clinician Acceptance of Pharmacist Involvement in Clinical PGx

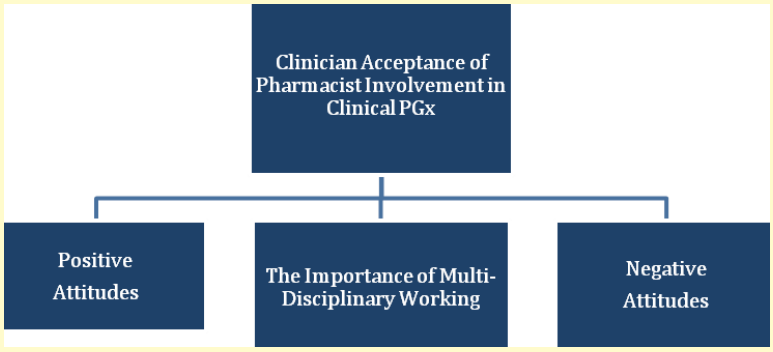

Figure 4: *A summary of the attitudes and perceptions of clinicians towards pharmacist involvement in PGx practice identified at interview.*

Attitudes: 11/11 clinicians appeared comfortable with pharmacist involvement in clinical PGx practice. 8/11 actively demonstrated a positive attitude. 0/11 clinicians demonstrated a negative attitude towards pharmacist involvement in metabolic profiling.

3.2.3.2 The Importance of Multi-Disciplinary Working in Clinical PGx: 6/11 clinicians interviewed highlighted the need for multi-disciplinary working in PGx practice. When examined further, multi-disciplinary working was needed to ensure the uptake of these tests into practice and to improve the education of all HCPs involved with the pharmaceutical management of patients.

Discussion

Analysis of Findings

Barriers: The problems facing the integration of clinical PGx in practice is a subject that has been addressed many times in the literature [2,5,16]. The main barriers identified by this study are consistent with those findings. The literature identified other possible barriers that were not mentioned in detail at interview - the issues of reimbursement [10] and pharmacist education [18]. Previous studies have suggested that currently, pharmacy is not sufficiently educated to participate in PGx practice therefore the issue of education was predicted to arise. However, only 1/11 clinicians queried it. A contradicting study [20] stated that the majority of pharmacy schools now include PGx in their curricula to varying degrees and a study conducted at the FMC identified that some of the resident pharmacists were knowledgeable enough and performed roles in PGx [35] therefore it is possible views about pharmacist education were obscured by the fact that it is not an issue at this institution.

One barrier not addressed by the literature but identified in the study was that of precedent. 7/11 clinicians interviewed stated that current prescribing practice is dictated by the successes of previous prescribing habits and therefore they perceive a reluctance to introduce new technologies which may or may not cause substantial time delays. As mentioned earlier, an American study [25] examined the way by which new technologies are adopted into practice and found that many were affected by the 'I will if you will' principle. These findings and the results of this study indicate that if metabolic profiling can be incorporated successfully into one department, the rest of the profession may follow.

The lack of sufficient evidence for testing and timeline of carrying out the tests were perceived to be the most important factors identified by this study preventing PGx implementation. Lack of evidence was also found to be the most expensive and time consuming barrier to overcome. However, the results indicate that until these issues are addressed metabolic profiling will not move forward into widespread clinical practice despite reassurances that it is a beneficial thing to do.

Roles for Pharmacists: Roles for pharmacists in PGx ascertained from the literature included interpreting PGx tests, choosing or making recommendations for drug therapy and counselling patients with regards to their PGx information [20,21,22] amongst other practical and pastoral roles. The findings from this study were largely consistent with those in the literature however other roles not addressed by the literature were also identified. These included administrative and research roles such as protocol/guideline development, and performing clinical utility, validity and cost-effectiveness analyses.

11/11 interviewees emphasised a potential role for pharmacy in the day-to-day running of metabolic profiling. One clinician highlighted this by demonstrating a good working relationship with a ward pharmacist who is already involved in practical and pastoral PGx roles such as carrying out select tests for gentamicin and methotrexate and acting as a patient advocate. The findings from this interview indicate that the haematology department may be an ideal location to trial the integration of these tests in clinical practice as an extension of current practice. The practical and pastoral/educational roles a pharmacist could perform found by this study are consistent with those suggested in the literature.

Attitudes and Perceptions: Until now there have been no studies investigating the clinician-pharmacist relationship with regards to PGx and therefore there are no studies to compare the results of this investigation to. In practice, there has long been perceived disquiet between clinicians and pharmacy for unknown reasons [40]. Appearing oblivious to this, 11/11 participants demonstrated a positive attitude towards practical PGx roles for pharmacists provided there were protocols and guidelines in place to ascertain the attribution of responsibility, scope and implications of testing. These same clinicians also identified an active role for pharmacists in strengthening the evidence base for PGx tests, a role which previously may have been left to industry implying their trust in the profession.

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interview indicate that the haematology department may be an ideal location to trial the integration of these tests in clinical practice as an extension of current practice. The practical and pastoral/educational roles a pharmacist could perform found by this study are consistent with those suggested in the literature.

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The study also further highlighted the importance of multi-disciplinary working (which was identified in an earlier study [35]) indicating that PGx testing should be a collaborative effort between all HCPs involved in the pharmaceutical care of a patient i.e. the clinicians, pharmacists and nurses so that the utilisation of PGx data and knowledge of PGx improves. This again contradicts the notion of an unsatisfactory working relationship between clinician and pharmacist and the FCIC itself is a perfect example of what medicine is capable of when HCPs work together. This result also appears to negate the barriers identified with practice issues such as communication and the relationship with pharmacy.

Despite the many perceived barriers facing the integration of metabolic profiling in practice found both in the literature and in this study, none of the participants demonstrated a negative attitude towards pharmacist involvement in PGx. The results indicate that the interviewees believe pharmacy to be well placed to perform practical and pastoral roles in PGx. Three viewpoints raised demonstrated the need for clinician involvement in PGx (both metabolic and biomarker profiling) furthering the importance of multi-disciplinary working - clinician input into the development of PGx protocols, the selection of tissues for PGx testing (where PGx markers relating to the pharmacodynamic of targeted therapies are concerned) and informing clinicians when a test has been done.

Limitations of the Study

There are several limitations affecting generalisability, objectivity and interpretation related to this study

Generalisability: The number of clinicians interviewed was a major limitation to the study. The small sample size may not be representative of a larger population and may affect the ability to generalise the results. This limitation was due to the time-frame of the study (which lasted 12 weeks inclusive of study design, data collection and data analysis) and the narrow inclusion criteria of the participants as well as their availability for interview. The limited sample size was not due to return of invitation as the study had a 100% return rate of acceptance. It was decided to interview clinicians from one location (FMC, Australia) to aid data collection and minimise time delays but this may have affected the generalisability of the results as practice may differ between hospitals and between countries (particularly between developed and developing countries where resources may be scarce). By only interviewing clinicians the study is also limited as it only describes the views of one profession involved in the pharmaceutical management of patients. Previous studies have investigated alternative viewpoints [35] however; nursing staff have yet to be consulted. Despite these limitations, the data collected was consistent with the findings identified by the literature. To improve the generalisability of the results and to ensure the results are representative of a larger population, a larger sample size is required covering the breadth of professions involved in patient pharmaceutical care across a range of countries.

Researcher Bias and Objectivity: 9/11 participants were involved in clinical, research and/or academic PGx roles. For this reason it is possible that the objectivity of the study was compromised. Effort was made to include clinicians with little knowledge of PGx and limited PGx roles, namely surgeons and pathologists, to minimise bias and increase objectivity.

Another limitation to the study may be its design and the interpretation of the interview findings. It is possible that both were influenced by the researchers own attitudes and assumptions, compromising the objectivity. Care was taken not to introduce any researcher bias into the study by asking objective open ended questions that did not prompt a subsequent subjective response from the researcher. The interview questions were checked by three separate sources to ensure no bias was introduced however; it is possible that the participants' response may have affected the way the researcher asked the next question.

The quality of recordings at times was affected by background noise. Care was taken to minimise this by using sound-proofed meeting rooms but constraints on clinicians' time sometimes necessitated the use of their offices instead.

Interpretation of Research: Despite recognition as a valuable source of research by many professions, qualitative research in itself may be a limitation. There is a common perception that qualitative research is not 'real research' [41] and therefore this may affect its credibility. Since this study looks at the attitudes towards and perceptions of a currently hypothetical role for pharmacists in clinical PGx, qualitative research was considered the best option as it is unrealistic to measure attitudes using qualitative parameters.

Conclusion

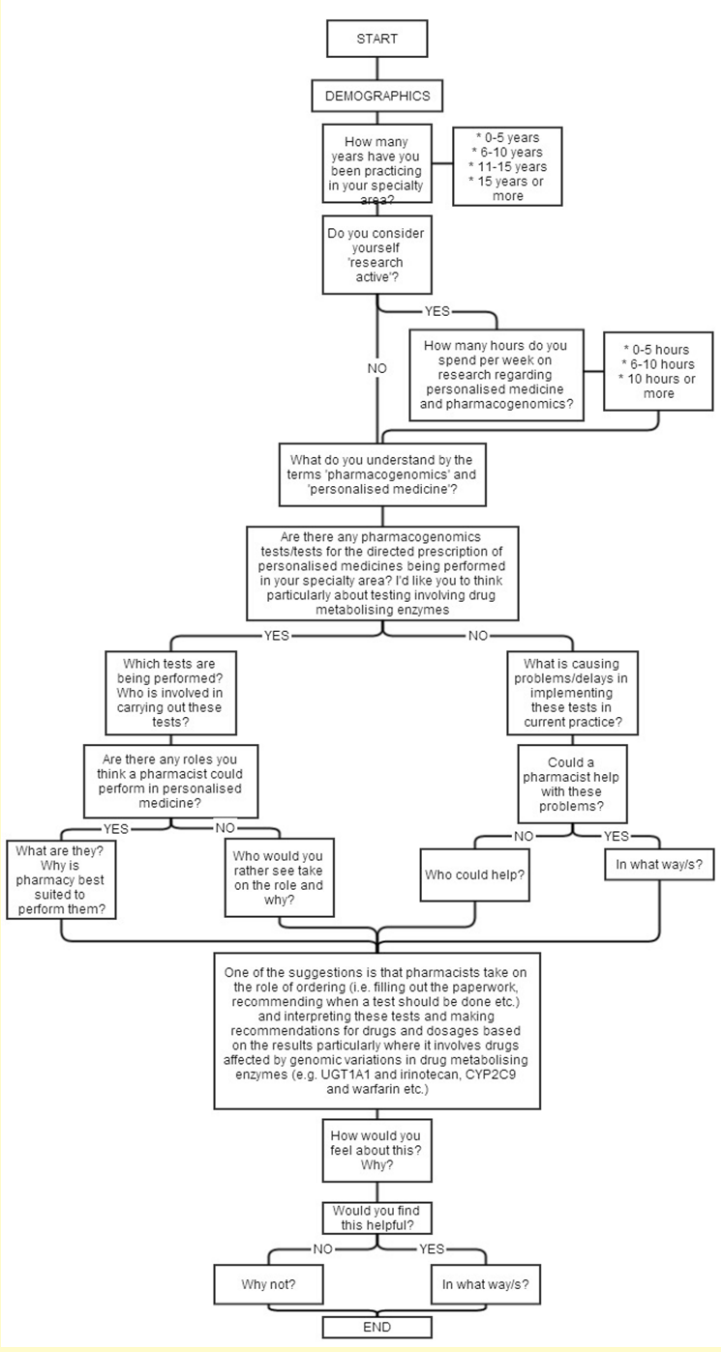
In conclusion, this study was found to be consistent with previous studies detailing the barriers to the implementation of clinical PGx in practice. The barrier perceived as the most significant was the issue of insufficient evidence pertaining to clinical utility, validity and cost-effectiveness. Viewpoints raised during this study indicate that until the evidence base has been strengthened clinicians are unlikely to adopt PGx testing into their everyday practice regardless of who performs them. Roles for pharmacists were found to be largely consistent with previous findings although some additional roles were identified in protocol/guideline development, enforcement and strengthening of the evidence base. Although there were foreseen conditions to these roles (multi-disciplinary working and protocolisation) overall, a positive attitude towards PGx roles for pharmacists was observed. Previous studies identified clinician acceptance of pharmacy roles as an important driver for the uptake of clinical PGx [35]. This study has acknowledged acceptance of the role of pharmacist-led PGx practice. A potential area for trial was identified in the haematology department where currently, they perform a higher number of PGx tests than any other department interviewed.

Since the number of participants in this study was small more interviews covering both the breadth of professions involved in the pharmaceutical care of patients and other settings such as the UK, USA and developing countries would need to be done in order to obtain more data and increase how representative the results are of a larger population.

Recent claims state that the 'substantive benefits of personalised medicine continue to elude us' and that the technological advances facilitate research but do not have an impact on patient outcomes [42], however; research into the implementation of PGx testing is ongoing. Future study may now focus on the nursing professions and patient viewpoints of PGx, how PGx testing could be incorporated into busy clinical practice, the support network and business models needed to ensure its success, the strengthening of the PGx evidence base and increasing the awareness amongst the healthcare community of the benefits of metabolic profiling as these are important drivers that will encourage pharmacists to take up roles in PGx.

Now the issue of clinician acceptance has been addressed, clinical PGx is closer to becoming a reality. Advancing PGx may provide a wide variety of new roles for pharmacists in practice [43] but predictably it will take time to integrate it in a way that is effective, undemanding and inherently beneficial to patient care [44].

Transcript of questions and flowchart used in the interviews



List of figures used in study

Figure 1: *major themes identified from the primary interview data analysis*

Figure 2: *a summary of the barriers to implementation of clinical PGx in practice identified at interview*

Figure 3: *a summary of the roles performed by pharmacists that are considered of value to clinicians identified at interview*

Figure 4: *a summary of the attitudes and perceptions of clinicians towards pharmacist involvement in clinical PGx practice identified at interview*

List of footnotes

a. page 8 - Comprehensive details are available in the original study papers (referenced). The ethical and legal considerations of PGx testing are outside the scope of this study

b. page 17 - 'specialist' taken to mean consultant, surgeon and includes participants with further specialist training such as pathologists

List of abbreviations

FCIC: Flinders Centre for Innovation in Cancer

FMC: Flinders Medical Centre

HCPs: Healthcare Providers/Professionals

PGx: Pharmacogenomics

PM: Personalised medicine

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