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Configuring an implementation model for multi-drug pharmacogenomic testing in the NHS

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Abstract

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Backgrounds

Pharmacogenomic testing can improve patient outcomes through safer and more efficient dose and drug selection. Implementation of multi-drug pharmacogenomic testing in clinical care has been fragmented internationally and is largely absent within the NHS. The aim of this thesis was to develop and refine a programme theory using behaviour science for the implementation of multi-drug pharmacogenomic testing within an NHS context.

Methods

Underpinned by behavioural science, the research programme comprised three empirical studies. The first study modelled the impact of multi-drug pharmacogenomic testing in UK primary care, by estimating the occurrence of actionable drug gene interactions in daily practice, using first prescription volumes for 56 PGx drugs and phenotype frequency data. The second study involved a systematic review and narrative synthesis of the barriers and enablers to implementing multi-drug pharmacogenomic testing, using the TDF to map factors affecting prescriber, pharmacist, and patient behaviours. Finally, the third study was a qualitative exploration of the real-world implementation of multi-drug pharmacogenomic testing in the NHS, conducted using a case study methodology.

Results

Over 20% of all new prescriptions annually issued for 56 medicines in UK primary care had an actionable drug-gene interaction according to guidelines from the Dutch Pharmacogenetic Working Group and/or the Clinical Pharmacogenetics Implementation Consortium. A multi-drug pharmacogenomic testing programme which constitutes testing genetic variants in four genes (CYP2C19, CYP2D6,

SLCO1B1, HLA-B) would cover more than 95% of the potential drug-gene interactions occurring in UK primary care.

The systematic review found barriers to the implementation of multi-drug pharmacogenomic testing can be organised around four themes influencing behaviours of prescribers, pharmacists and patients. These are: IT infrastructure, Effort, Rewards and Unknown Territory. Barriers were most consistently mapped to TDF domains: memory, attention and decision-making processes, environmental context and resources, and belief about consequences. Pharmacists played a vital role in PGx testing implementation model and enabled prescribers to order and deliver PGx testing for patients.

Empirical data using a case study methodology of real-world implementation of multi-drug pharmacogenomic testing, found pharmacists were key drivers for PGx testing implementation model within an NHS context. Training to prepare health professionals to deliver and utilise PGx testing in clinical decision making, should focus on skills development and managing expectations of both patients and health professionals of what PGx testing can provide.

Conclusions

These three studies advance the understanding of implementing multi-drug pharmacogenomic testing by converging implementation science and genomic medicine. The modelling study provides researchers and policy makers with new knowledge to design a minimum drug-gene panel for a PGx testing panel relevant to the UK population. The multi-drug PGx testing implementation configuration informed by the systematic review and case study requires further modelling and feasibility testing to optimise before implementation across NHS settings.

Keywords: *pharmacogenomics, personalised medicine, implementation*

“Let the waters settle and you will see the moon and the stars mirrored in your own being.”

Rumi

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Glossary

ADR	Adverse Drug Reaction
AF	Atrial Fibrillation
BCT	Behaviour Change Technique
AS	Activity Score
BCW	Behaviour Change Wheel
BNF	British National Formulary
CASP	Critical Appraisal Skills Programme
CAT	Complexity Assessment Toolkit
CDSS	Clinical Decision Support System
CFIR	Consolidated Framework for Implementation Research
CNV	Copy number variants
COAG	Clarification of Optimal Anticoagulation through Genetics
COM-B	Capability Opportunity Motivation Behavioural Model
CPIC	Clinical Pharmacogenetics Implementation Consortium
CPNDS	Canadian Pharmacogenomics Network for Drug Safety
CVD	Cardiovascular Disease
DGI	Drug Gene Interaction
DOAC	Direct Oral Anticoagulant
DPWG	Dutch Pharmacogenetics Working Group
DTC	Direct To Consumer
DYPD	Dihydropyridine Dehydrogenase

EHR	Electronic Health Record
EM	Extensive Metaboliser
EU-PACT	EUropean Pharmacogenetics of AntiCoagulant Therapy
FDA	Food and Drug Administration
GIFT	Genetic Informatics Trial
GLH	Genomic Laboratory Hubs
GMA	Genomic Medicines Alliance
GP	General Practitioner
GPhC	General Pharmaceutical Council
GSK	Glaxo Smith Kline
HIV	Human Immunodeficiency Virus
HS	High sensitivity
IM	Intermediate Metaboliser
MRC	Medical Research Council
NASSS	Non-adoption, Abandonment, Scale-up, Spread, and Sustainability
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NIP	Nurse Independent Prescriber
NPT	Normalization Process Theory
NS	Normal Sensitivity
NT	Normal transporter
PD	Pharmacodynamic

PGx	Pharmacogenomic
PIP	Pharmacist Independent Prescriber
PK	Pharmacokinetic
PM	Poor Metaboliser
PM	Personalised Medicine
PPI	Activity score
PREPARE	Preemptive Pharmacogenomic Testing for Preventing Adverse Drug Reactions
PT	Poor transporter
PTTR	Percentage Time in Therapeutic Range
RAG	Red Amber Green
RCT	Poor metaboliser
RNPGx	French National Network 'Réseau' of Pharmacogenetics
SNP	Single nucleotide polymorphism
TDF	Theoretical Domains Framework
TPB	Theory of Planned Behaviour
TPP	Translational Pharmacogenetic Program
TRA	Theory of Reasoned Action
UK	United Kingdom
UM	Ultra-rapid Metaboliser
VTE	Venous Thromboembolism
WGS	Whole Genome Sequencing
WHO	World Health Organisation

5-FU	5-Flurouracil

Initials

DB	Debi Bhattacharya
AC	Allan Clark
DM	Doug Mellor
FP	Fiona Poland
RS	Ravi Sharma
SW	Sujata Walkerly
DW	David Wright
EY	Essra Youssef

Publications

1. **Youssef, E**., Buck, J. & Wright, D. Understanding pharmacogenomic testing and its role in medicine prescribing. 2020, *Nursing Standard*. 35, 7, p. 55-60.

2. **Youssef, E**. & Wright, D. Pharmacogenomic testing and its future in community pharmacy. 2020, *The Pharmaceutical Journal*. 304, 7933, p. 52-57.

3. Thornley, T., Esquivel, B., Wright, D. J., van den Dop, H., Kirkdale, C. L. & **Youssef, E**. Implementation of pharmacogenomic testing service through community pharmacy in the Netherlands: Results from an early service evaluation. 2021, *Pharmacy*. 9, 38.

4. **Youssef, E**., Kirkdale, C. L., Wright, D., Guchelaar, HJ. & Thornley, T. Estimating the potential impact of implementing pre-emptive pharmacogenetic testing in primary care across the UK. 2021, *British Journal of Clinical Pharmacology*. 87, 7, p. 2907-2925.

5. **Youssef, E**., Thornley, T., Wright, D. & Guchelaar, H-J. Pharmacogenetics: optimising prescribing in primary care. 2022, *Prescriber*. 33, 5, p. 10-13.

6. **Youssef, E**., Mellor, D., Walkerly, S. & Wright, D. Enhancing pharmacy practice doctoral research with patient and public involvement. 2022, *International Journal of Pharmacy Practice*. 30, 3, p. 288-291.

7. **Youssef, E**., Bhattacharya, D., Sharma, R. & Wright, D.J. A Theory-Informed Systematic Review of Barriers and Enablers to Implementing Multi-Drug Pharmacogenomic Testing. *Journal of Personalized Medicine*. 2022, 12,11, 1821.

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- Analysing Qualitative Data
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- Evaluation of behaviour change interventions

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1. Chapter 1: Background

1.1 Introduction

Since the start of the millennia, the terms: 'Personalised medicine'; 'Precision Medicine' and 'Individualised medicine' have proliferated in the literature (Johnson et al., 2021). Broadly these terms refer to a medical model where the provision of healthcare is more person-centred. The goal of this approach is to make medical decisions informed by a patient's individual characteristics, including clinical, social, or genetic factors. By considering these individual factors, the most appropriate treatment can be selected to achieve the desired outcome. From 2015, the National Health Service (NHS) England in the UK, has made personalised medicine a key priority in informing future healthcare provisions (Keogh, 2015).

Personalised medicine in conjunction with the existing evidence-based medicine approach to healthcare has the potential to transform the way clinicians and allied professionals prescribe medicines. 'Pharmacogenomic' testing is a form of genetic testing which informs prescribing and has a central role to play in personalised medicine (Pirmohamed, 2014).

This chapter provides a literature-based overview of the challenges associated with prescribing medicines, the potential role of pharmacogenomic testing to mitigate these risks and a summary of progress to date implementing pharmacogenomic testing in clinical practice. This background provides the research context necessary to frame and justify the empirical studies reported in this thesis that examined the potential implementation of multi-drug pharmacogenomic testing in a UK healthcare context.

1.2 Medicines

Worldwide, medicines are the most frequently administered medical intervention within health systems. Medicines are used in all age groups, ethnicities, and sexes to treat and manage the causes and symptoms of disease. Medicine usage differs between groups of people with different characteristics and is positively correlated with morbidity and age. The majority of all medicines are prescribed in primary

care, but hospital medications, over-the-counter medicines and dietary supplements all contribute to total drug consumption.

More than one billion prescription items were issued in primary care in England in 2019/20 a significant increase from the 813 million items dispensed in 2009/10 (NHSBSA, 2021). Globally, the sales of medicines have increased successively with an overall 3% compounded annual growth rate from 2014-2019. Drivers of this growth include introduction of new medicines, new medical recommendations to treat morbidity in advanced age, and increase in preventative medicine. Metabolic diseases related to changing lifestyles are also on the rise globally, with medicines used to treat diabetes and cardiovascular disease seeing significant increase in use over time. This trend in global medicines usage and spending is projected to continue to increase at a rate of 2-5% annually and expected to exceed 1.1 trillion dollars in 2024 (IQVIA, 2020).

Prescribing safe and effective medicines for patients comes with well-known challenges. Adverse drug reactions, medication ineffectiveness, polypharmacy and medicines non-adherence are ubiquitous scenarios observed in clinic. The effectiveness of medicines is variable with estimates suggesting most medicines are only 50%-75% effective (Spear et al., 2001). This is shown in Table 1.1 where the response rate of groups of medicines used to treat different disease are reviewed by Spear and colleagues.

Table 1-1 Response rates of patients to a major drug from a selected group of therapeutic areas(Spear et al., 2001)

Therapeutic area	Efficacy Rate (%)
Alzheimer's	30
Analgesics (Cox-2)	80
Asthma	60
Cardiac Arrhythmias	60
Depression (SSRI)	62
Diabetes	57
Hepatitis C virus	47
Oncology	25
Osteoporosis	48
Rheumatoid arthritis	50
Schizophrenia	60

When compounding the incidence of prescribing errors, estimates for the proportion of the population benefitting from their medicines is further reduced. In the UK, a review of the quality of medication use in primary care suggests that only 4-21% of patients achieve optimum benefit from their medicines (Garfield et al., 2009). This is further complicated by patient adherence to medicines. The World Health Organisation (WHO) estimates 50% of patients with long term conditions do not take their medicines as prescribed (Sabate, 2003).

Medication adherence is a complex behaviour and is defined as the extent to which a person's behaviour-taking medication corresponds with agreed recommendations from a care provider (Sabate, 2003). Reasons for non-adherence are complex and multi-factorial (Horne et al., 2005, Lindenfeld and Jessup, 2017, Lehane and McCarthy, 2007). Adherence poses a greater challenge when medication is employed as a long-term preventative measure, such as for hypertension or hypercholesterolaemia (Leslie et al., 2019). Patient perceived risk associated with their disease also plays a role with patient adherence to Human Immunodeficiency

Virus (HIV) medication being shown to be 5% higher than adherence to cardiovascular disease (CVD) medication. The number of medicines a patient is prescribed also affects adherence with non-adherence estimated at a rate of 6-55% in elderly 'polypharmacy' patients (Gray, Mahoney et al. 2001, Cárdenas-Valladolid, Martín-Madrazo et al. 2010, Pasina, Brucato et al. 2014).

Polypharmacy refers to a scenario where multiple medicines are concomitantly prescribed and is one of the drivers of increased medication use. A simple definition used within the literature, defines polypharmacy by a numerical threshold of five or medicines consumed regularly (Masnoon et al., 2017). The Medical Research Council National Survey for Health and Development published a report in 2018, which found nearly a quarter (22.8%) of individuals surveyed were taking more than 5 medicines at age 69 (n=5362). While increased medicines usage is often necessary in older adults with multiple co-morbidities, (Guthrie et al., 2015) polypharmacy is a risk factor for frailty, hospitalisation, cognitive problems, falls and mortality. (Fried et al., 2014)

'Inappropriate' polypharmacy refers to prescribing additional medicines with an unfavourable risk profile. Factors like age and morbidity change the benefit/risk profiles of medicines. In addition, higher numbers of medicines increase the risk of drug-drug interactions leading to problematic side-effects or adverse drug reactions (ADRs). A retrospectively designed study examining the incidence and characteristics of patients hospitalised due to ADRs in a large teaching hospital (n=3659), found the number of medicines to be a significant predictor of ADR related admission ($p<0.0001$; HR 1.14; 95% CI 1.09, 1.20) (Davies et al., 2009).

1.3 Adverse drug reactions

Adverse drug reactions are one of the mostly widely researched unintended consequences of prescribing medicines to treat illness. Incidence of ADR or hospital admission related ADR are outcome parameters often used to assess the safety of medicines and prescribing interventions. They can also sometimes impact the effectiveness of a medicine since ADR can affect a patient's medicines adherence.

Adverse drug reactions have been defined "as any undesirable effect of a drug beyond its anticipated therapeutic effect" (Pirmohamed et al., 1998). These effects can be classified in a number of ways. The most widely recognised system was proposed by Rawlins in 1981 and separates adverse drug reactions into two groups: Type A and Type B reactions.

Type A reactions are the most common adverse drug reactions accounting for approximately 80% of total ADRs reported. The cause of these reactions is an enhancement of the medicines primary pharmacological effect. These reactions are predictable and often the consequence of inappropriate dosage, especially when drug elimination is impaired physiologically (age/comorbidities/renal/liver function impairment), chemically (drug or food interaction) or environmentally (smoking).(Hoop et al., 2008, Pirmohamed et al., 1998, Rawlins, 1981) An example of a Type A reaction is hypotensive fall due to a high dose of antihypertensive medication. Since type A reactions are predictable, they can be attributed more directly to medication errors and are therefore preventable.

Type B reactions are adverse drug reactions described as 'idiosyncratic reactions' (Pirmohamed et al., 1998). Whilst the incidence rate is lower compared to type A reactions, type B reactions are important because they are often more serious and associated with death (Pirmohamed, 2004). Type B reactions are unpredictable with no widely accepted animal model in existence. They can be immediately severe or have a time delay, so while the initial response may be variable, re-challenge of the medicine can prove fatal (Park et al., 1992). In laymen terms, adverse drug reactions are often referred to as a drug allergy. A common example of a type B adverse drug reaction is a penicillin allergy.

Type B reactions are strongly related to genetic variations however the mechanisms behind some of these reactions is not yet fully understood (Hoop et al., 2008, Pirmohamed, 2004) .

Adverse drug reactions can have serious consequences. The largest prospective analysis of ADRs in the National Health Service (NHS) in England, reported that 6.5% (n=18,820) of all hospital admissions are related to ADRs (Edwards and Aronson,

2000).This broadly correlates with data pooled from similar studies in Europe and the USA (Howard, 2003, Leendertse et al., 2008, Kongkaew et al., 2008). The majority (72%) of hospital related ADRs were classified as avoidable through better prescribing and monitoring (Edwards and Aronson, 2000).

ADRs are also common once patients have been admitted to hospital. A study by Davies et al. 2009 prospectively analysed the rate of ADR within a NHS in-patient hospital setting over 6 months (n=3,695). They found 14.7% of inpatients experienced an ADR, and 50% of these ADRs were avoidable (Davies et al., 2009). Hospital in-patient ADRs were a significant cause of morbidity and increased the length of inpatient stay by an average of 0.25 days/patient admission episode (Davies et al., 2009).

Even when ADRs do not lead to hospitalisation, the physical and psychological effects experienced by patients can be burdensome. Side effects of medicines such as nausea and headaches, when chronic, can affect the patient in a way similar to symptoms of disease, contributing to medicines non-adherence (DiBonaventura et al., 2012).

ADRs represent a large burden to health care systems around the world. Classification systems for ADRs are useful from the perspective of judging whether an ADR was preventable or not. To reduce the incidence and severity of ADRs, prescribers must balance the benefits and risks of a medicine prior to initiating it. This is challenging due to the historical precedent within medicine which assumes patients with the same diagnosis will respond to a medicine in a similar way. In clinical settings, it is observable that patient variability in drug response is common. Often this unpredictability in a patient's drug response is likely to lead to prescribers adopting a cautious approach where medicines are trialled at the lowest dose and patients try multiple medicines or doses of a medicine until the 'right' one is found. This phenomenon is called 'trial and error' prescribing. Tailoring or 'personalising' medicines to the individual by identifying characteristics that predictably augment their drug response, could lead to better dose and treatment selection which translates to safer and more efficient prescribing.

1.4 Personalised medicine

'Personalised medicine' is a term that broadly encompasses various approaches to tailor healthcare through greater understanding of patient characteristics. (Culbertson et al., 2007) These characteristics could be related to a patient's diagnosis, genetic background, or other clinical or social features. As discussed earlier, replicating clinical trial results in patients in real-world settings is challenging. Adverse drug reactions, inefficacious medicines, and poor compliance with taking medicines are all undesirable first-order outcomes of prescribing due to patient variability in drug response. Personalised medicine (PM) seeks to understand the factors and mechanisms driving this variability in order to implement protocols that can match patients with medical treatments more safely and effectively (Mathur and Sutton, 2017). PM is closely linked to technological advancements in medicine, particularly genetics. Micro-array genetic sequencing technology refers to a micro-chip testing platform that allows high-volume, automated analysis of many pieces of DNA at one (Bumgarner, 2013). This type of genetic testing technology is used routinely within the NHS to support the diagnosis and management of many cancers (Brittain et al., 2017). Within PM, two terms exist for utilising genetic testing technologies to tailor medicines choice and dosing to the individual. These are: 'Pharmacogenetics' and 'Pharmacogenomics' and will be the focus of this programme of work.

1.4.1 Pharmacogenetics and Pharmacogenomics

The term 'pharmacogenetics' was first documented in the literature in 1956 and refers to the role of genetic inheritance relating to inter-individual variation in drug response (Carson et al., 1956). The discipline of pharmacogenetics emerged through experiments in the 1950s. Discoveries around this time included the link between glucose-6-phosphate dehydrogenase deficiency and haemolytic anaemia in individuals taking antimalarial drugs (Ecobichon and Kalow, 1963) and cholinesterase deficiency causing increased sensitivity to anaesthetic (Motulsky, 1957). The results from these and other experiments, were drawn together in a seminal paper by medical geneticist Arno Motulsky's, 'Drug Reactions, Enzymes and Biochemical

Genetics' (Motulsky, 1957). This paper was the first to conceptualise the idea that inherited defects in metabolism may explain individual differences in drug response (Gonzalez et al., 1988).

The discipline of pharmacogenetics grew in the decades after at a relatively slow pace, with gene-drug associations being extrapolated as researchers serendipitously identified them rather than actively searching for them. This changed in 1988, when Frank Gonzales and colleagues cloned the complementary DNA of the CYP2D6 gene, and found different variations in the gene, affected the functionality of the CYP2D6 enzyme (Wilkinson, 2005). CYP2D6 forms part of the cytochrome P450 enzyme family in the liver, which collectively metabolise most medicines in the body (The International, 2001). This discovery alongside, new molecular testing techniques yielded a significant breakthrough in the field of pharmacogenetics and led to the rapid expansion of discoveries involving other drug metabolising enzymes and transporters (Gonzalez et al., 1988). The completion of the human genome project in 2001, and advances in the gene-sequencing technologies, galvanising interest in pharmacogenetics from both public and commercial enterprise (Gurwitz and Manolopoulos, 2007).

Pharmacogenomics is a newer term that emerged in the late 1990's and was associated with industrial applications of genomics in drug discovery. In more recent years, it is used to describe the relationship between variants in large collection of genes, up to the whole genome and variable drug effects (Pirmohamed, 2014). The main distinction between the two terms is that pharmacogenetics is usually in reference to how variation in a single gene influences the response to a single drug whereas pharmacogenomics is a broader term that encompasses how all the genes (genome) can influence response to drugs (Mini and Nobili, 2009). In practice however, both terms are used interchangeably since pharmacogenomic research will often inform pharmacogenetic applications. An example of this is Abacavir, an anti-retroviral agent used in treatment of HIV (EMA, 2000). It was developed by GlaxoSmithKline (GSK) and received full marketing approval in Europe in 1999 (Hughes et al., 2008). Unfortunately it was associated with a potentially fatal hypersensitivity reaction that affects 2-9% of abacavir treated patients (Press, 2019).

GSK undertook several genome wide studies which found a strong association between HLA-B*5701 and the abacavir induced hypersensitivity reaction (Press, 2019). After replication of studies and a randomised controlled trial that found screening for this biomarker cost-effective, it has been adopted into routine practice in the UK. Testing for HLA-B*5701 before initiating abacavir is now mandated by the National Institute for Clinical Excellence (NICE) (Allen, 2000). In this way the HLA-B*5701 test can be considered as pharmacogenetic but developed through pharmacogenomic methods. This information however is unlikely to change or impact on the way doctors and pharmacists use the test. Given the interchangeability of the terms within the literature, and increased popular usage of the term 'pharmacogenomics', this thesis will use 'pharmacogenomics' or 'PGx' herein to describe genetic testing to inform prescribing.

1.4.2 Drug gene interactions

In order to understand pharmacogenomic testing and its clinical applications, it is important to first describe the nature of drug-gene interactions (DGI). An individual's drug response is the combination of the drugs effect on the body, and the body's effect on the drug. Pharmacodynamics (PD) or the drugs effect on the body, refers to the physiological processes that occur as a result of a drug binding to cell receptors within the body. The body's effect on a drug is referred to as pharmacokinetics (PK) which describes systems that promote the absorption, metabolism, and excretion of a drug. Collective knowledge of factors which alter an individual's PK/PD profile are used routinely in prescribing to 'personalise' medical management. For example, elderly patients are recommended to have reduced dosing of opioids due to age-related decline in the blood brain barrier which is leakier. This decline leads to more drug-binding to the opioid receptors in the brain compared to patients of a younger age taking the same dose. Medicines taken concomitantly can also affect each other through their individual effects on the body either through metabolism or competition for drug-binding at the target cell receptor. These effects are called drug-drug interactions and are managed routinely in practice.

Drug-gene interactions (DGIs) describe the genetic variants that underpin the PK or PD mechanisms influencing drug response. The most extensively studied DGI cover genetic variants responsible for production of the Cytochrome P450 family of drug metabolising enzymes in the liver. Whilst this family has 50 plus enzymes, the main effects are only seen in six enzymes which together metabolise 90% of drugs (Sim and Ingelman-Sundberg, 2010). Mutations in the genetic sequence coding for these genes can result in increased or decreased expression of these enzymes. The down-stream effect of increased CYP 450 enzyme activity is either decreased effectiveness of active drugs (as a result of de-activation of the drug) or increased toxicity of prodrugs (as a result of increased production of active metabolites). Below are two examples explaining the different scenarios.

Proton Pump Inhibitors (PPIs) omeprazole, lansoprazole and pantoprazole are all used commonly in primary and secondary care for management of disorders related to the PH of the stomach environment. Each of these medicines are primarily metabolised by the enzyme CYP2C19. Overwhelming evidence now indicates that individuals born with CYP2C19*17 version of this gene, have increased expression of the CYP2C19 enzyme, leading to increased metabolism of PPIs and subsequently decreased PPI plasma concentration (El Rouby et al., 2018). Due to the risk of therapeutic failure, two organisations now recommend higher dosing of PPIs in patients carrying this genetic variant (El Rouby et al., 2018).

Codeine is a pro-drug, which is metabolised by the CY2D6 enzyme into its active metabolite morphine. Several genetic variants of this gene conferring for rapid and ultra-rapid metabolism of codeine have been discovered and linked to increased codeine toxicity. As a result, the majority of organisations providing PGx prescribing guidelines recommend avoiding codeine in patients carrying the aforementioned CYP2D6 genetic variants.

PGx testing therefore offers additional information to the prescriber by illuminating drug-gene interactions to be considered along with other clinical factors to narrow drug and dose selection. Over one hundred DGIs have been reported by the most widely recognised repository of PGx information, PharmGKB (Abdullah-Koolmees et al., 2020) . Of these, the majority DGIs implemented have been within the field of

cancer therapy. The majority of cancer therapeutic agents target acquired genetic anomalies (somatic genome) and so are often approved with companion diagnostic genetic testing. The cost implications of genetic testing within cancer are therefore different to costs of prescribing medicines in other therapeutic areas. To narrow the scope of this thesis, the researcher explored the implementation of PGx testing of the inherited or germ-line genome and excluded cancer genomics or PGx testing of the somatic genome due to its specialised nature.

1.5 Clinical pharmacogenomic testing methods

Pharmacogenomic (PGx) testing encompasses several analytical methods of genetic testing. These may be done reactively in a case by case or drug by drug basis or pre-emptively in an anticipatory manner testing for single genetic variants (single nucleotide polymorphism, SNP) in multiple genes or whole genome sequencing. Different genetic testing techniques introduce different risks and benefits of testing, with implications for clinical implementation. The main genetic techniques underpinning PGx testing are described below.

1.5.1 SNP genotyping

SNP genotyping is the most common method employed by laboratories offering PGx testing both publicly and privately. Different techniques and equipment are offered by medical diagnostic technology companies like Illumina and Thermofisher, but the principle is the same in each (Kim and Misra, 2007). Patients DNA is extracted, and the gene of interest amplified through polymerase chain reaction. Gene copies are then tested for pre-specified SNPs at pre-specified gene locations. Advantages of SNP genotyping is it can test for a few or many SNPs simultaneously in a relatively short period of time, sometimes within hours if for a few genetic variants. The limitation of this genotyping technique is it only tests for pre-specified SNPs which means rarer SNPs that are important in certain ethnicities or those which are not yet understood are not included. Furthermore, SNP genotyping cannot look at copy number variants (CNVs) related to genes like CYP2D6. This may provide false reassurance of the PGx test result if a patient is

called a normal metaboliser in the event a rare genetic variant is missed (Kim and Misra, 2007).

1.5.2 Whole genome sequencing

Whole genome sequencing (WGS) uses next-generation sequencing technology to comprehensively analyse an individual's entire genome. Whereas SNP analysis will only look at pre-determined specific locations in DNA, whole genome sequencing will analyse the entire DNA materteral. WGS has an advantage over SNP genotyping because if new genetic variants of interest are discovered, SNP genotyping will have to be repeated. WGS on the other hand can be carried out once and the information stores and accessed retrospectively when newer SNPs of importance are identified in the future. This is particularly advantageous for PGx testing, as testing can be initiated prospectively, and data interrogated whenever new genetic variants are discovered. WGS can also detect copy number variants (CNVs), although this can still be challenging. Several limitations exist WGS including being significantly more expensive and time consuming compared to SNP analysis, as well as the risk of secondary findings. Secondary findings are the discovery of genetic variants that may contribute to discuss but is not the cause of the patients' current condition and reason for genetic testing. In addition, due to the homology between some genes of interest, there is a small risk of false positives with WGS as pseudo genes are reported. The accuracy of SNP genotyping is higher than WGS for PGx testing (Arbitrio et al., 2021). Both pharmacogenomic testing methods come with advantages and limitations. Both techniques, however, provide information that still needs translating from genetic results into practical guidance for clinical decision making.

1.6 Clinical pharmacogenomic testing interpretation

Converting genetic test results into clinical action was one of the first challenges reported by earlier adopters of pharmacogenomic testing. Two organisations emerged anticipating the necessity of PGx prescribing guidance: the Dutch Pharmacogenetics Working group (DPWG) and the Clinical Pharmacogenetics

Implementation Consortium (CPIC). Both organisations provide therapeutic recommendations to guide prescribers' selection and dosing of medicines in the presence of evidence-based drug gene interactions. A comparison of guidelines produced by both CPIC and DPWG for the same drug-gene interactions, shows a high rate of concordance, although differences are observed particularly with respect to dosing information. Both CPIC and DPWG employ different methodologies for curating their guidelines which accounts for differences in published recommendations (Krebs and Milani, 2019).

1.6.1 Dutch Pharmacogenetics Working Group

The Dutch Pharmacogenetics Working Group (DPWG) was established by the Royal Dutch Association for the Advancement of Pharmacy in 2004. The aim of the group was to make PGx information accessible to doctors and pharmacists during decision making processes within the usual clinical environment (Swen et al., 2008). The group originally consisted of 15 members from different disciplines and included pharmacists, physicians, pharmacologists, chemists, epidemiologists and toxicologist (Swen et al., 2008). The first output was a set of 26 PGx informed dosing/drug recommendations that were included in to the G-standard, an extensive electronic drug database that is used nationwide in the Netherlands for prescribing and dispensing medicines (Swen et al., 2008). Recommendations appear as clinical decision support alerts whenever a medicine that can be informed by PGx is prescribed or dispensed. The recommendations themselves are derived from an analysis of the existing literature, for gene-drug interactions that are supported by 'good quality' studies and also lead to clinically relevant outcomes. The recommendations are updated every three months where they are integrated into the G-Standard and currently cover over 80 drugs (Lunenburg et al., 2020). Pharmacists in the Netherlands have been able to order PGx testing independently from 2004 (Bank et al., 2018a). However, a national survey of Dutch pharmacists in 2011, showed only 14.7% had ordered a PGx test in the last 6 months of the survey (Bank et al., 2018a). No studies have reported on physician PGx ordering practices. The DPWG guidelines are being used in the PREPARE study, the largest prospective

PGx study investigating the cost-effectiveness and clinical utility of pre-emptive panel testing European populations (Krebs and Milani, 2019). Trial results are not yet published.

1.6.2 Clinical Pharmacogenetics Implementation Consortium

Clinical Pharmacogenetics Implementation Consortium (CPIC) is an international group of PGx experts that develop CPIC guidelines according to a standardised format. Drug and doing recommendations are divided into three categories: strong, moderate and weak, depending on the level of evidence underpinning the drug-gene interaction. Strong recommendations mean the evidence behind the DGI is high quality and desirable effects clearly outweigh the undesirable effects. Recommendations classified as 'moderate' mean there is close or uncertain balance as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects (Abdullah-Koolmees et al., 2020). CPIC have currently published twenty-six clinical PGx recommendation documents which cover a total of over eighty drug-gene interactions. CPIC guidelines are used by all sites in the USA, funded by the Translational Pharmacogenetic Program (TPP) in 2011 (Luzum et al., 2017). The TPP facilitated PGx testing implementation across six sites from primary and secondary care including: University of Maryland, University of Florida, Vanderbilt University, St Jude Children's Research Hospital, Ohio State University and Mayo Clinic. Within these programmes, point-of-care and pre-emptive PGx testing is conducted in all consenting patients (Luzum et al., 2017).

1.6.3 Other organisations

In addition to DPWG and CPIC, the Canadian Pharmacogenomics Network for Drug Safety (CPNDS), and the French National Network (Réseau) of Pharmacogenetics (RNPGx) also produce PGx recommendations (Picard et al., 2017). In contrast to DPWG and CPIC, CPNDS and RNPGx have published PGx recommendations for a significantly smaller number of drug-gene interactions (Bank et al., 2018b). Currently in the UK, there is yet no single set of NHS developed or adopted PGx guidelines. In order to implement clinical PGx testing in a UK healthcare setting, prescribes need PGx guidelines that are accessible, updatable, and clinically

relevant to decision making. For a publicly funded health system like the NHS, evidence supporting effectiveness and cost-effectiveness of PGx testing is necessary prior to any PGx guideline design and eventual adoption and implementation.

1.7 Benefits, limitations, and ethics of Pharmacogenomic testing

Whilst pharmacogenomic testing has the potential to provide many benefits for patients, it also has its limitations and risks. It is therefore important to discuss all issues and consequences related to the practical application of PGx testing, in order to avoid setting unrealistic expectations. These issues are discussed below.

1.7.1 Benefits of Pharmacogenomic testing

Benefits of pharmacogenomic testing focus on either improving patient safety, drug efficacy, or sometimes both, for example where patient adherence to taking medicines is affected by adverse effects e.g. antidepressant medication. As discussed previously, drug response is complex and drug-gene interactions (DGIs) are only one component of several interacting factors influencing patient response. Physiological factors (age, sex, pregnancy), pathological factors (disease states, kidney, and liver function), drug and food interactions (enzyme inducers or inhibitors) all individually and collectively influence drug efficacy and toxicity. The effect size of any one drug-gene interaction (DGI) on overall drug response is variable and depends on both the penetrance of the drug-gene relationship and number of interacting clinical factors present.

A pharmacogenomic scenario which demonstrates benefits of PGx testing quite clearly is the DGI: *HLA-B*57:01* and Abacavir. Abacavir is an antiretroviral agent used to achieve viral suppression and immunological improvement in patients with HIV infection. The genetic variant *HLA-B*57:01* has a high gene penetrance, which is to say the majority of individuals who carry this genetic variant will experience a severe allergic skin reaction upon taking Abacavir. In addition, the mechanism of action behind the *HLA-B*57:01* and Abacavir DGI is direct, therefore, no physiological factors, pathological factors or drug and food interactions affect the DGI (Mounzer et al., 2019). In a landmark prospective double-blind randomised

controlled trial of 1956 patients, PGx testing for *HLA-B*57:01* prior to initiating Abacavir proved to reduce incidence of Abacavir induced hypersensitivity adverse drug reactions both effectively and cost-effectively (Mallal et al., 2008).

Evidence demonstrating the benefits of prospective PGx testing to enhance safety and efficacy for other DGIs is not always as clear. This is demonstrated in the case of warfarin. Warfarin is an anti-coagulant used in the treatment of venous thromboembolism and prevention of stroke in atrial fibrillation. Dosing of warfarin can be challenging because of its narrow therapeutic window and difficulty in predicting individual dosing requirements. To date, three major randomised controlled trials (RCTs) have been performed investing the effect of PGx testing on warfarin prescribing. These trials were: COAG (Kimmel et al., 2013) , EU-PACT (Pirmohamed and Hughes, 2013) and GIFT (Kimmel et al., 2013). Table 1-2. summarises the key characteristics and outcomes of all three studies.

Table 1-2 Summary of major randomised controlled trials investigating clinical utility of PGx guided warfarin testing

	COAG(Kimmel et al., 2013)	**EU-PACT** (Pirmohamed and Hughes, 2013)	**GIFT**(Kimmel et al., 2013)
Sample size	1015	455	1600
Indication for warfarin	VTE+ AF	VTE + AF	Prevention of deep vein thrombosis post - elective hip and knee operations.
PGx arm	Algorithm (day 1-5) Genes: CYP2C9, VK0RC1	Algorithm (w/loading) (day 1-5) Genes: CYP2C9, VK0RC1	Algorithm (day 1-11) Genes: CYP2C9, VK0RC1, CYP4F2
Comparison arm	Clinical algorithm (day 1-5)	Standard loading dosing (by age) (day 1-3)	Clinical algorithm (day 1-11)
Blinding	Double	Single (patient)	Double
Primary outcome	PTTR (day 4/5-28)	PTTR (day 1-84)	Within 30 days: major bleed, INR ≥4, death. Within 60 days: venous thromboembolism
Result	No difference in PTTR No difference in time to INR No difference in > or < INR	Greater PTTR Fewer INR ≥4 Less time to INR Cost-effective from NHS perspective(76)	Less major bleeds** Fewer INR ≥4 No deaths in either group Fewer VTE events** Cost-effectiveness not assessed

**PTTR: Percentage time in therapeutic range. **not statistically significant as defined by P>0.05*

Two trials (9EU-PACT and GIFT) showed pre-emptive PGx testing and PGx guided prescribing of warfarin (compared to usual care, led to better therapeutic control. In

contrast, the COAG trial showed no differences between PGx testing and usual care. As seen in Table 1-2, differences in outcomes between the trials may be explained by differences in trial methodology and choice of outcomes. Since, completion of all three trials, a new therapeutic class of medicines (direct oral anticoagulants) has been released on to the market as an alternative to warfarin. These medicines do not require the same monitoring as warfarin and their mechanism of action means their therapeutic effects are more predictable. Therefore, the population of patients that are prescribed warfarin and may benefit from PGx testing is likely smaller now.

Evidence demonstrating clinical utility of PGx testing is also mixed for other drug-gene pairs. Clopidogrel is a medicine used in the management of stroke and cardiovascular disease. It is a pro-drug and requires biotransformation in the liver to its active metabolite by the enzyme CYP2C19.(Zhang et al., 2020) In a retrospective cohort study (n=3 670), patients carrying genetic variants coding for a poor CYP2C19 metaboliser status, were reported to be almost four times more likely to experience a sub-therapeutic antiplatelet response when treated with clopidogrel (Simon et al., 2009). Since then, prospective randomised controlled trials assessing the clinical utility of PGx testing of the CYP2C19 enzyme has returned ambiguous results. Tailored Antiplatelet Initiation to Lesson Outcomes due to Decreased Clopidogrel Response After Percutaneous Coronary Intervention (TAILOR-PCI) was a randomised controlled trial evaluating a PGx-guided strategy for choice and dosing of antiplatelet therapy compared with standard therapy among patients who underwent percutaneous coronary intervention (PCI) (Pereira et al., 2020). This was the largest trial to date (n=5,302) and failed to show a difference in the primary outcome between the PGx-guided group compared to standard therapy. Post-hoc analysis however showed a nearly 80% reduction in the rate of adverse effects in the first three months of antiplatelet treatment among patients who received PGx guided therapy compared to those who did not. Unfortunately, as this was not a pre-planned analysis, it is difficult to draw firm conclusions on the benefits of PGx testing in this area (Pereira et al., 2020).

Evidence supporting a pharmacogenomic testing approach to guide safer and more effective medication choices in psychiatry is promising. A systematic review and

meta-analysis of prospective randomised controlled trials found individuals receiving PGx guided medication were 1.7 times more likely to achieve symptom remission from major depressive disorder compared to usual care (Bousman et al., 2019b). One limitation of this review, however, was the heterogeneity of gene panels comprising the pharmacogenetic testing intervention initiated in each of the individual studies. Therefore, the benefits of PGx testing in psychiatry may not be realised by every gene panel.

Pharmacogenomic testing may also have value in improving patient medication adherence. A prospective non-randomised trial showed patient adherence to statin therapy at 6 months increased when tested and given knowledge about the effect of PGx gene (KIF6 gene) on statin drug effects (Charland et al., 2014). The personal nature of learning an individual's genetic likelihood towards a positive therapeutic effect may decrease patient concern and improve medication adherence. Further evidence is however needed to explore this effect.

1.7.2 Limitations of Pharmacogenomic testing

Pharmacogenomic testing in clinical care has several limitations which may impact its implementation. As described several times before, drug response is complex and PGx testing only illuminates the effect of one factor influencing drug response. Consequently, the degree to which PGx testing accurately predicts drug response is dependent on the degree to which overall drug response is influenced by this single drug-gene interaction. In practice, only a small proportion (7%) of all medicines licensed have a drug-gene interaction that is so pronounced as to predictably augment the drug response and make PGx testing clinically actionable (Relling and Evans, 2015).

Limitations of PGx testing are discussed below.

1.7.3 Potential for misleading results

As discussed in section 1.4, both whole genome sequencing (WGS) and single nucleotide polymorphism (SNP) testing methods of PGx testing, are unable to identify rare genetic variants. In a scenario, where PGx testing misses a rare genetic

variant, two clinical outcomes are possible. Firstly, the patient could be predicted to have a normal response to a medicine incorrectly, but they would still the have usual standards of care, so nothing is lost from PGx testing. Or secondly, they could entail prescription changes due to an incorrect result that the patient has an aberrant genotype, in which case they may have less favourable drug/dose choices compared to usual care. This risk is of particular concern for individuals from non-European heritage as there is less understanding of genetic variants in these populations (Tuteja and Limdi, 2016).

This leads to uncertainty over whether the results reported by one laboratory using a particular PGx panel can be repeated using a different companies' PGx panel. The Food and Drug Administration (FDA) in the USA initially authorised 23andMe to provide pharmacogenomic testing in 2018 but with confirmatory laboratory testing (Rubinstein and Pacanowski, 2021). This decision was met with confusion at the time, as effectively patients could be requested to pay for testing twice before treatment decisions are made. To address concerns over the accuracy of PGx testing results reported by laboratories, several initiatives are underway to agree a minimum set of actionable gene and alleles for panel testing (Lab, Bousman et al., 2019a).

1.7.4 Phenoconversion

It is well-documented that medicines can affect the metabolism of other medicines through induction or inhibition of drug metabolising enzymes. This phenomenon is referred to as 'phenoconversion' and complicates interpretation of PGx test results (Mostafa et al., 2021). For example, a patient carrying genetic variants conferring for normal metaboliser status of the CYP2D6 enzyme is predicted to have a typical response to codeine. However, if the patient concurrently takes the medicine paroxetine, which is a strong CYP2D6 inhibitor (Alfaro et al., 2000), then the patients CYP2D6 genotype-predicted phenotype will likely be converted to a poor metaboliser, resulting in diminished analgesia.

The incidence of phenoconversion in the population is predicted to be high, with incidence increasing in the presence of polypharmacy. A recent retrospective

cohort study of 137 elderly care acute inpatients with PGx testing performed, predicted medication induced phenoconversion increased the incidence on admission of CYP2D6 intermediate metabolisers by 11.7% and CYP2C19 intermediate metabolisers by 13.1%. Seventy five percent of the patients in this population were taking polypharmacy at admission (Mostafa et al., 2021).

At the moment the majority of PGx reports provide information on the predicted genotype and phenotype without considering phenoconversion. This is not unlike other resources that report on drug-drug interactions as pairs without considering all concurrent medicines, foods, or co-morbidities. There is also the challenge of accurately predicting the phenotype converted corrected phenotype. Where an individual is predicted to be a phenotype on opposing ends of the spectrum e.g. poor metaboliser or ultra-rapid metaboliser, the presence of an enzyme inducing or inhibiting agent may result in the phenoconversion to multiple potential phenotypes e.g. normal metaboliser or intermediate metaboliser. Therefore, when interpreting the impact of phenoconversion clinically, it will be optimal to draw on the expertise of a pharmacist utilising clinical pharmacology knowledge in combination with an understanding of patient response (efficacy and/or toxicity).

1.7.5 Ethical issues arising from Pharmacogenomic testing

Pharmacogenomic testing like other forms of genetic testing can have ethical implications. The Nuffield Council on Bioethics published a report in 2003, concerning the various ethical issues PGx testing may pose (Singh, 2003). Whilst the report was published at a time when clinical PGx testing was in its infancy, the ethical concerns remain, although some progress to mitigating the risk has been made. The individual ethical issues related to PGx testing and potential solutions are discussed in detail below.

1.7.5.1 Exacerbation of health inequalities

As discussed earlier, the frequency of genetic variants differs between geographic ancestral groups (Tonk et al., 2017). Therefore, PGx testing recommendations developed in one ancestral population may not be valid in another ancestral

population. Patients from ancestral populations that have been understudied may miss out on the benefits of PGx testing since genetic variants that are of relevance to these populations may be missed through testing. Additionally, through this same mechanism, there is also a potential for PGx testing to cause harm to patients. For example, in the COAG trial, described earlier, there was a statistically significant difference between African Americans and non-African Americans. African Americans fared worse with the pharmacogenetic algorithm than with the clinical algorithms (percent time in therapeutic range 35.2% vs.43.5%, respectively; adjusted mean difference, 8.3%; P = 0.01) (Kimmel, 2015). The gene variants informing the COAG PGx warfarin-dosing algorithm tested CYP2C9*2 and *3 and VKORC1 rs9923231 which do not describe the variety of warfarin drug response in individuals with African heritage. Since, the COAG trial genome-wide association studies investigating variants of interest in African-American adults related to warfarin drug response have been conducted and identified CYP2C9*5, *6 and *8 as occurring more frequently in these populations (Perera et al., 2013, Johnson et al., 2017). This problem can appear for both whole genome sequencing (WGS) and single nucleotide polymorphism (SNP) genotyping since while WGS will sequence the entire genome, the reporting of variants will only be for those where the functional effect on drug response is known. It is estimated that over 78% of participants in published genome wide associate studies (GWASs) are of European descent (Peterson et al., 2019), therefore the published guidance for variants with known functional effect will disproportionately favour those of a European heritage since the research has predominately been done within this group. This problem is not unique to pharmacogenomics but rather a feature of genetic research as a whole. To overcome this, collaborative efforts between different research groups worldwide are needed to generate large scale discovery cohorts of diverse ancestry expanding the diversity of the current reference panels (Peterson et al., 2019).

1.7.5.2 Confidentiality, privacy, and data protection

Privacy and data confidentiality of patient information is a key concern patients expressed which relate to pharmacogenetic testing (Peterson-Iyer, 2008). This is in

part related to prevailing narrative of 'genetic exceptionalism' which affects the acceptability and adoption of genetic testing technologies in health care systems. 'Genetic exceptionalism' is a term describing a belief that genetic information is fundamentally different from other forms of medical data. In part there are some features of genetic data that support this belief including the uniqueness of the data to the individual and the highly predictive nature of the information for example, susceptibility to disease. Genetic information may also be of interest to third parties like insurers and employers. However, in the context of pharmacogenomics, the emphasis on the genetic component can be unhelpful as the information given by the test does not give diagnostic information about a patient or their relative.

1.8 PGx testing clinical implementation landscape

Laboratories offering PGx testing exist in much of Europe, America, Australia and Canada as shown in Table 1-3. However, it is difficult to comment on whether any country in world has implemented PGx testing at a macro-healthcare level and integrated it to the point it is considered routine care. The Netherlands, has made the most progress in this respect. In 2005, two events occurred that facilitated the current infrastructure that supports modern day PGx testing in the Netherlands. First, the set-up of a specialist PGx laboratory at the University of Rotterdam (van Schaik and Ifcc Task Force on Pharmacogenetics: Prof. Dr. Maurizio Ferrari, 2013) that began providing testing for patients nationwide and secondly the formation of the 'Dutch Pharmacogenetics Working Group' (DPWG) (van Schaik and Ifcc Task Force on Pharmacogenetics: Prof. Dr. Maurizio Ferrari, 2013).

Other countries have not made the same progress in building supporting infrastructures for PGx implementation, although it is important to note the Netherlands has the advantage of a healthcare system organised around a single, central drug database (KNMP, 2022). Instead within other countries, PGx testing is largely contained to pockets of independent PGx adopter sites. Examples in the literature for Europe include La Paz University Hospital in Madrid, Spain (Borobia et al., 2018), Robert Bosch Krankenhaus Hospital in Stuttgart, Germany (Bio.ligis) and

Diakonhejemmet Hospital in Oslo, Norway (Jukic et al., 2019). Outside of these examples, there are companies that specialise in providing PGx testing interpretation services directly to the consumer (DTC). 'Consumer' in this respect could be the doctor or patient. These services act to provide an intermediate step to integrate PGx into clinical practise. However. there is limited reported information as to the rate of adoption of these services.

Table 1-3 Summary of examples for implementation of PGx worldwide.

Country	Example of implementation site(s)	Example of direct-to-consumer PGx testing companies
USA	Multiple	Multiple
Canada	-	BiogeniQ GeneYouIn
Australia	-	myDNA Life CNSDose
The Netherlands	University of Rotterdam	-
South Korea	Seoul National University Hospital	-
Norway	Diakonhejemmet Hospital	-
Portugal	-	CGC Genetics
Spain	La Paz University Hospital	AB Biotics
Germany	Robert Bosch Krankenhaus Hospital	-
Russia	-	Genotek Ltd.

1.9 Challenges to PGx testing implementation

Despite the benefits and progress made towards worldwide implementing pharmacogenomic testing, several challenges still remain for bringing widespread adoption and sustained implementation of pharmacogenomic testing in primary and secondary clinical care settings. Examples of these barriers to PGx testing implementation cover four broad domains: test-related, knowledge and education,

evidence and ethical social and legal. A summary of the key challenges under each of these themes are shown in Table 1-4.

Table 1-4 Examples of challenges to implementing PGx testing encountered across the world(Johnson, 2013, Relling and Evans, 2015).

Challenges	Description
Test-related	Lack of clarity for inclusion and exclusion criteria for testing Cost of testing Reimbursement for testing Increase in clinician workload Prolonged turnaround time for results Lack of testing infrastructure and data information storage Limited healthcare record interoperability
Knowledge and Education	Gaining laboratory expertise to interpret PGx results Healthcare professional's knowledge on PGx and result interpretation Lack of patient awareness and engagement Lack of clear guidelines for interpreting PGx information into actionable recommendations No validated drug decision support to support clinicians interpret PGx results
Evidence	Limited randomised controlled trial data supporting effectiveness and cost-effectiveness of a PGx guided treatment approach
Ethical, legal and social	Genetic discrimination Consent processes Implications for healthcare insurance

1.10 Implementing Pharmacogenomic testing in the UK

In 2012, the Department of Heath established a clinical transformation project called the 100,000-Genomes Project where National Health Service (NHS) patients with cancer and rare diseases would have their whole genome sequenced (Turnbull, 2018). In contrast to other population genomics studies, such as those in Iceland, Japan, Finland, Sweden and the Netherlands, the 100,000 Genomes Project, aimed to fully integrate genomic testing within existing routine healthcare pathways in the NHS (Trotman et al., 2022). Outputs from the project include a network of seven NHS funded regional genetics laboratories and clinical genetics departments launched in 2018. These centres provide equitable access to genomic testing across the NHS through the National Genomic Test directory which is regularly reviewed and updated (Trotman et al., 2022).

Currently pharmacogenomic testing in the national genomic test directory is focused on testing a small number of gene-drug pairs of the somatic genome to guide therapy choices for cancer and rare diseases, for example cystic fibrosis (Trotman et al., 2022). Examples of germline PGx testing are rare, although recently genetic variants coding the enzyme dihydropyridine dehydrogenase (DYPD) were introduced to guide safer dosing of 5-fluorouracil (5-FU), a chemotherapy agent (Trotman et al., 2022). All examples of PGx testing currently focus on a few high-risk drug-gene pairs and testing is initiated for a small group of patients in secondary and tertiary care. Compared to the over eighty medicines with PGx prescribing guidelines from CPIC or DPWG, PGx testing in the NHS is currently severely under-utilised.

To date only one study has explored PGx implementation in the UK. This study looked at the implementation of point-of-care genotype-guided warfarin dosing in three nurse-led anticoagulation clinics (Jorgensen et al., 2019). Questionnaires undertaken as part of the service evaluation found two thirds of nurses thought the genotyping approach interfered with the smooth running of the clinic. This highlights the importance of integrating new interventions into existing pathways smoothly, so as to enhance acceptability.

There is therefore limited research which considers how multi-drug PGx testing should be designed or best implemented within NHS primary and secondary care settings. With NHS policy driving the adoption of PGx testing and a genetic testing infrastructure put in place through the genomic medicine centres, it is now timely to research this area and support the development of personalised medicines and ensure patients get the best use of their medicines.

1.11 Summary and thesis outline

Pharmacogenomics is an evolving scientific discipline that aims to enhance the safety and efficiency of prescribing. Clinical application of pharmacogenomics through whole genome sequencing or single nucleotide polymorphism testing provides a mechanism to improve the safety and efficiency of medicines prescribing in the health economy.

This thesis described research exploring the design and implementation of a multi-drug pharmacogenomic testing intervention within an NHS context. The research sought to answer the following research questions:

1) What are the design components of a multi-drug pharmacogenomic testing panel that provides the potential for the most benefit for UK NHS patients?
2) What does the global literature report with respect to the current barriers and enablers to the implementation of multi-drug pharmacogenomic testing from a behavioural perspective of prescribers, pharmacists, and patients?
3) What are the locally relevant (UK) barriers and enablers to implement multi-drug pharmacogenomic testing, when considering behavioural perspectives of prescribers, pharmacists, and patients?
4) What are the key components necessary for the implementation of multi-drug pharmacogenomic testing in clinical care in the NHS?

The outline of thesis chapters is as follows:

Chapter Two justifies the selection of a behaviour change theory to frame the design and evaluation of multi-drug pharmacogenomic testing implementation. Different implementation theories and frameworks relating to the design and evaluation of complex interventions like pharmacogenomic testing are explored and their strengths and limitations appraised. The researcher presents the rationale for choosing a behaviour change framework over other implementation theories to underpin the approach to designing and evaluating studies included in the thesis.

Chapter Three begins with a brief introduction to critique the current literature surrounding the potential impact of pharmacogenomic testing in the UK. The researcher sets the parameters for research enquiry exploring the potential impact of pharmacogenomic testing to optimise prescribing in the UK with definitions for the terms 'impact' and 'optimise' explicitly stated. A novel methodology is designed to theoretically estimate the effect of pharmacogenomic testing implementation on prescribing in the UK. Methodology and outcome measures chosen are rationalised, with the strengths and limitations of the approach taken within the study, described fully. The findings of the study described through drug-gene pairs linked to the largest prescription volumes are evaluated and presented in how they relate to the thesis aims. Finally, recommendations for research directions to inform future policy considerations for implementing pharmacogenomic testing in the UK are described.

Chapter Four describes the existing literature on the implementation of pharmacogenomic testing and through a scoping search justifies the requirement for a systematic review in this area. The researcher presents the findings of the scoping search and explains how the results inform the methodology of a systematic review. The methods for a novel systematic review exploring the barriers and enablers to the implementation of pharmacogenomic testing using a behavioural framework are described. The findings of the systematic review are narratively synthesised and evaluated, exploring strengths and limitations of how the review relates to the thesis aims. Finally, it sets out recommendations for researchers, clinicians and policy makers interested in developing interventions to improve the uptake and sustained adoption of pharmacogenomic testing clinical implementation.

Chapter Five reports the design and conduct of PGx testing case study. The chapter reports on the process of designing a methodology for a study exploring the implementation of a commercial pharmacogenomic testing service in different NHS settings using case study methodology. Interviews were conducted post PGx testing delivery with health professionals and patients to identify local barriers and enablers to implementation within an NHS context. Qualitative analysis of the interviews was conducted in a two-step process: initially inductive thematic analysis of the interviews and then mapping to a behaviour change framework to identify the behavioural determinants underpinning the barriers to implementation.

Chapter Six considers the significance of the findings from all three studies in this programme of work and how they contribute to strengthening and extending current understandings of pharmacogenomic testing implementation in the UK. A pharmacogenomic testing intervention and implementation pathway for the NHS is proposed and the value of using behaviour change theory in designing and evaluating such an intervention is scrutinised. The implications for practice and further research are discussed.

2. Chapter 2: Theoretical approach to implementing pharmacogenomic testing.

2.1 Introduction

This chapter explains the rationale for choosing a theoretical underpinning to guide the design of studies included in this program of work. Thus far, 'a process of trial and error' by researchers and policy makers has guided the implementation of pharmacogenomic testing in a clinical setting. This may have contributed to the fragmented pharmacogenomic testing implementation landscape described in Chapter 1. This chapter introduces the concept of 'complex interventions' and applies this to multi-drug pharmacogenomic testing. The latest guidance from the Medical Research Council on developing, evaluating, and implementing complex interventions is explored. This chapter also sets out an initial logic model outlining constituents of a multi-drug pharmacogenomic testing implementation strategy. The logic model is visually represented as a schematic diagram showing a flow of activities. Several implementation theories, models and frameworks are drawn on to identify the relevant mechanisms within the logic model that lead to changes in patient outcomes.

The strengths and limitations of each of these approaches are evaluated in relation to implementing multi-drug pharmacogenomic testing in the NHS. The most applicable theoretical approach is chosen and justified with respect to the aim of this thesis. The chapter concludes by prioritising uncertainties highlighted through the logic model, justifying the design of three studies to address each key uncertainty.

2.2 Translating evidence

One of the goals of health service research is to develop new practices and models of care evidenced as effective and cost-effective. Translating these practices and models of care into health service practice requires change in the existing behaviours of healthcare professionals, patients, and carers (Davis and Taylor-Vaisey, 1997). If adopting a new practice conflict with established patterns of

behaviour or social/professional norms, then the care delivered to patients may overlook or omit recognised best practice. This can be defined as the 'translational gap' , which is the difference between evidence based medicine and the realities of healthcare practice (Masic et al., 2008). A study conducted in the USA found patients received on average 55% of recommended care and quality, varying by medical condition ranging from 79% of recommended care for senile cataracts to 11% of recommended care for alcohol dependence (McGlynn et al., 2003). In addition to the limited use of effective treatments, evidence indicates that around 20% to 30% of patients may receive unneeded care or potentially harmful care (Grol and Grimshaw, 2003). Historically, focus on improving uptake of evidence-based guidelines has been to 'inform and educate', however human behaviour is much more complex and the result of several influencing and interacting factors, all of which require consideration when developing interventions to change behaviour (Baker et al., 2015).

Implementation of pharmacogenomic testing is no exception to this. A pilot study in the UK investigating the implementation of three PGx informed warfarin anti-coagulation clinics, found nurses running the clinic perceived PGx testing as interfering with their workflow (Jorgensen et al., 2019). This is a prime example of a new practice disrupting usual clinical pathways thereby reducing acceptability of those adopting the practice. It is important to highlight the pharmacogenomic testing in the aforementioned pilot study was for a single drug within a single clinical context. Implementing multi-drug pharmacogenomic testing in NHS primary and secondary clinical care, increases complexity, making a theoretically underpinned approach to implementation even more important to translate knowledge to practice.

2.3 Complex interventions

Part of the challenge of implementing pharmacogenomic testing has been around how to characterise it as a healthcare intervention (Relling et al., 2010). As argued in Chapter 1, pharmacogenomic testing differs from genetic testing for disease risk, but also from clinical tests like renal function tests. Currently, pharmacogenomic testing as a novel health care intervention presents several points of uncertainty compared to biochemical and genetic clinical tests. These include indications for testing, timing of testing and short- and long-term outcomes of testing. Additionally, the genetic nature of pharmacogenomic testing raises ethical concerns over patient consent and privacy which maybe require more health care professional input and therefore represents a deviation from the usual practice of ordering biochemical tests. These components contribute to the complexity of pharmacogenomic testing as a health care intervention and justifies the assertion that it is an example of a 'complex intervention'. The Medical Research Council argues complex interventions as complex *because of properties of the intervention itself, such as the number of components involved; the range of behaviours targeted; expertise and skills required by those delivering and receiving the intervention; the number of groups, settings, or levels targeted; or the permitted level of flexibility of the intervention or its components* (Skivington et al., 2021*).*

Table 2-1. summarises some sources of complexity related to multi-drug pharmacogenomic testing. These sources of complexity influence the implementation of pharmacogenomic testing which will impact the benefits patients receive from testing.

Table 2-1 Pharmacogenomic testing and its sources of complexity.

Source of complexity	Description
Technology	• Pharmacogenomic testing is not a single technology. • Encompasses multiple distinct technologies used to identify a single or multiple variants of one or more genes. • No universally agreed standard for gene panel. • Testing from one laboratory is not always interchangeable with another test from another laboratory.
Patient population	• Impacts multiple drugs used to treat multiple conditions. • Often the patient population will have multiple co-morbidities which can complicate things further as co-existing disease states and medicines used to treat them interact in ways that are not always fully understood. • Patient acceptability and concerns over data privacy.
Regulatory complexity	• Genetic testing point of care devices are regulated as medical devices and need approval through organisations like the Medicines Health Regulatory Agency in the UK, European Medicines Agency in Europe, and FDA in the USA. • Laboratory genetic testing does not fall within this remit. Without a specific framework, there is a grey area over whether a prescriber's indemnity would cover this affect. • Guidelines are needed on how DNA is stored and information shared between providers.
Healthcare professionals	• Pharmacogenomic testing affects the prescribing of medicines which is governed by multiple health professionals including physicians, nurses, and pharmacists. • The roles these professionals have in the implementation of pharmacogenomic testing are different and interact.

Framing pharmacogenomic testing as a complex intervention and consequently utilising evidence based methodological approaches geared to the design, evaluation and implementation of complex interventions may improve the chances of effective adoption and sustaining its implementation. This is particularly important for implementation within a UK context, because of financial constraints associated with publicly funded central health care systems. In this way, the example of 'trial and error' fragmented implementation observed in the US where pharmacogenomic testing programs are largely confined to discreet academic medical centres is not suitable for implementation in the UK (Hippman and Nislow, 2019). Instead, a considered, pragmatic approach which comprehensively draws on current literature on developing, evaluating, and implementing complex interventions is more likely to produce a successful implementation process for pharmacogenomic testing that can be applied across NHS settings.

2.4 Developing, evaluating, and implementing complex interventions

The Medical Research Council (MRC) published guidance on the development and evaluation of complex interventions to improve health in 2004 (Medical Research Council, 2000), later updated in 2008 (Craig et al., 2008) and 2021 (Skivington et al., 2021) to reflect developments in theory and methods. The 2021 update sought to go beyond identifying whether an intervention is effective but rather whether it can be implementable, cost-effective, transferable, and scalable in real- world conditions (Skivington et al., 2021). This update places greater emphasis on theoretically deconstructing interventions into individual components enabling agreement on core elements to be delivered in different contexts. This approach allows implementation of complex interventions to be adapted for different contexts while maintaining the core intervention components which produce desired outcome changes. Attention, therefore, goes beyond the design of the intervention itself but also the conditions needed to fulfill its mechanisms of change and/or resources required to support intervention reach and impact in real-world implementation (Skivington et al., 2021). The MRC framework provides guidance

for researchers and policy makers, developing and evaluating complex interventions. This framework is shown in Figure 2-1.

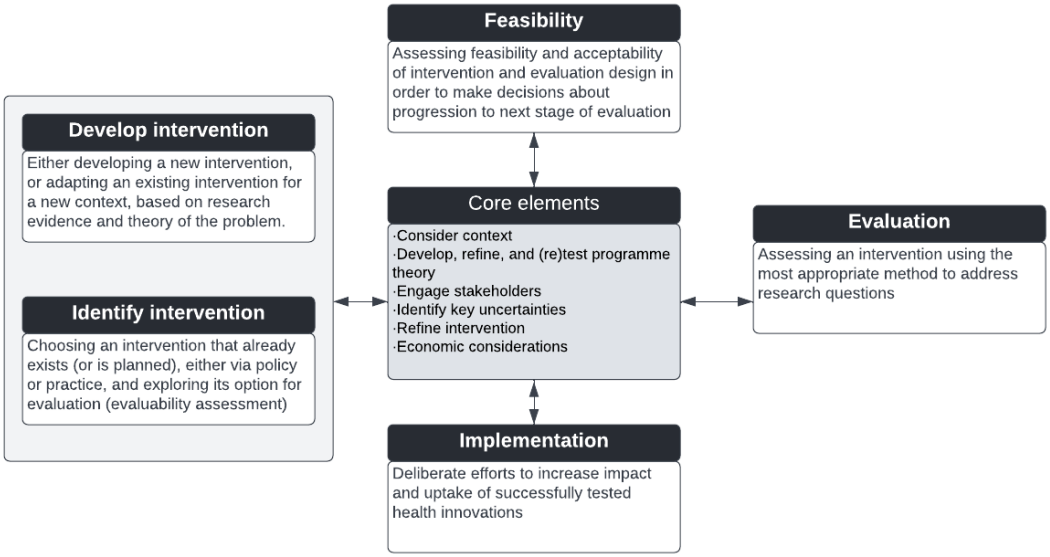


Figure 2-1 Key processes of the Medical Research Council guidance on developing and evaluating complex interventions [adapted from (Skivington et al., 2021)]

The new MRC framework consists of four phases: developing or identifying the intervention, feasibility testing, evaluation, and implementation. The phases are not linear, and a research programme might begin at any stage, depending on the key uncertainties about the intervention in question and repeating phases is preferred to automatic progression if key uncertainties remain unresolved (Skivington et al., 2021). For this programme of work, the absence of multi-drug pharmacogenomic testing within the NHS, dictates that this research will focus on the development stage in the MRC framework. The development stage comprises three areas. The first, is consulting the existing evidence base through a systematic review (and meta-analysis if applicable) to establish what has been done and whether changing one or more behaviours in a particular population is feasible and effective. Second,

is to provide a theoretical basis for the intervention and how it works to change outcomes. Thirdly, to model by testing potential design features of the intervention, aimed at optimizing and/or exploring intervention effects and costs.

One set of key elements underpins all stages of the MRC framework, Figure 2.1 presents this set of common elements to include: considering context, developing, and *refining programme theory*, engaging stakeholders, identifying key uncertainties, refining the intervention and economic considerations.

A programme theory will describe how researchers or policy makers expect an intervention to effect changes and under what conditions (Skivington et al., 2021). It therefore articulates the key components of the intervention and how they interact, the mechanisms of change, the features of the context expected to influence those mechanisms and how those mechanism might influence the context. A programme theory should ideally be developed at the start of a research project and involve diverse stakeholders, based on the relevant evidence and theory, and refined over successive phases. Logic models are a tool enabling researchers and policy makers to objectively visualize a service to make clear the assumptions and uncertainties around how, when and under what circumstances an intervention brings about changes in processes and outcomes. Programme theories can be visually represented through logic models as schematic diagrams showing how an intervention would theoretically work through the logical flow and links between the required inputs, activities and anticipated or desired outcomes and impact (Smith et al., 2020).

2.5 Multi-drug pharmacogenomic testing logic model

Figure 2-2. shows the initial programme theory represented visually by a logic model for implementing multi-drug pharmacogenomic testing. The literature review outlined in Chapter 1 and the researchers experiences talking to pharmacists delivering PGx pharmacy services in Australia informed the logic model. The researchers supervisory team reviewed the logic model and clarified

any assumptions shown in the model. There were several iterations of the logic model in the early stages and Figure 2-2 shows the version used in planning the studies included in this thesis. Table 2-2 summarises descriptions for each of its components of the logic model shown in Figure 2-2.

Table 2-2 Description of each component of the logic model representing implementation of multi-drug pharmacogenomic testing in the NHS.

Component	Descriptions
Activities and inputs	- Human, financial, organizational, community or system resources in any combination.
Mechanism	- Specific actions to be performed during the provision of a multi-drug pharmacogenetic testing service using the resources and targeting the outputs and outcomes
Outputs	- Represent what the activities will produce or create. - What multi-drug pharmacogenetic testing service delivers directly to the patient and other stakeholders
Outcomes	- Represent the changes and benefits that will be provided to the patients and other stakeholders. - The direct product of the outputs. - Divided into 'short- and medium-term outcomes' (up to 3 years) and 'long-term outcomes' (3–6 years)
Moderating factors	- Factors associated with the environment in which a multi-drug pharmacogenetic testing service is inserted

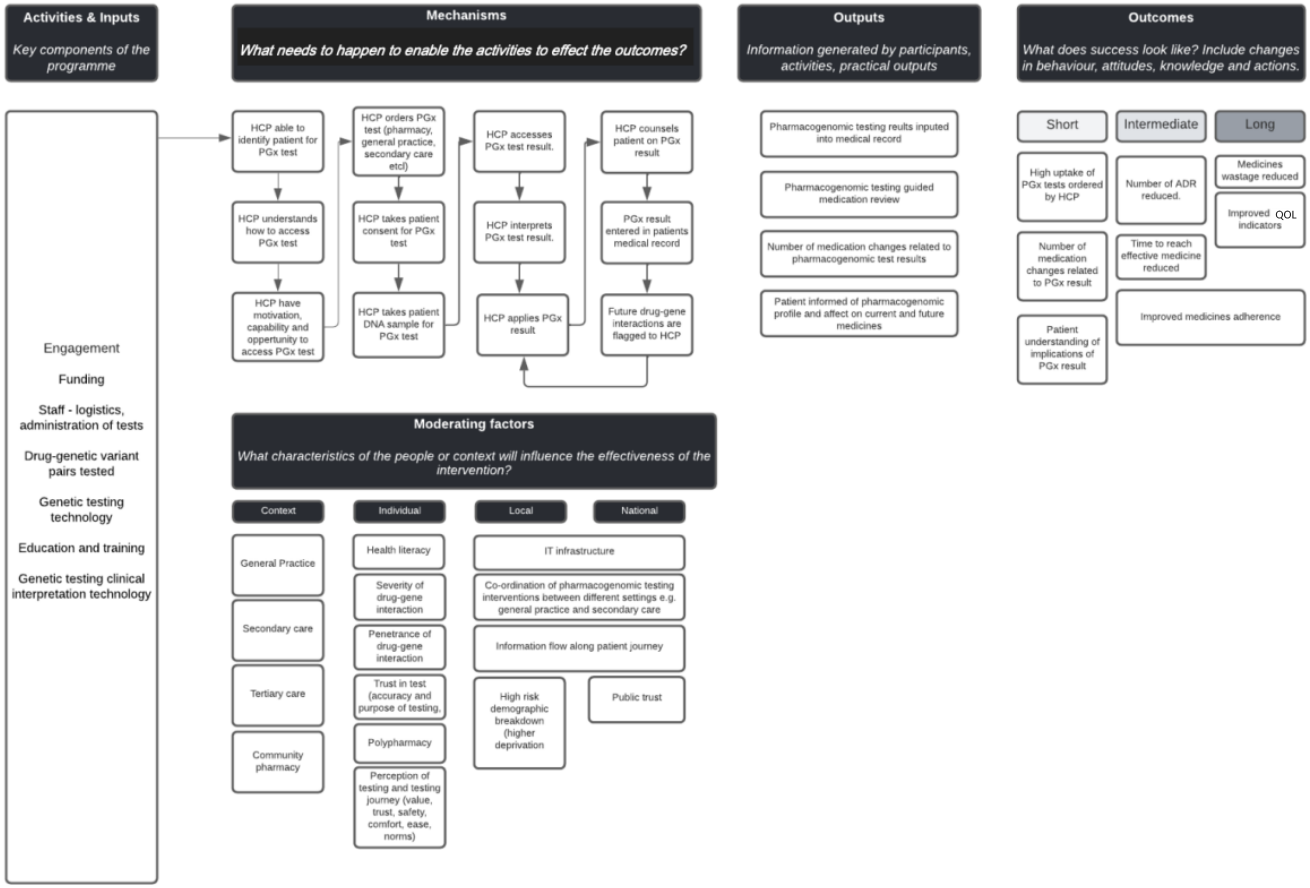


Figure 2-2 Logic model showing initial programme theory for implementing multi-drug pharmacogenomic testing in the NHS. HCP = Healthcare professionals, QOL = Quality of Life.

The literature review found that implementing multi-drug PGx testing in the NHS requires several resources, including support from policy makers, clinical and managerial personnel, funding for setup and delivery costs, additional staff for operational activities, and education and training. The drug-gene panel is also a critical resource needed for the PGx testing intervention.

The logic model shows specific actions health professionals take to deliver the PGx testing service, which was based on consultations with pharmacists in Australia who provided commercial PGx testing services. The health profession's specialty is not specified to reflect the different service models of PGx testing reported in Chapter 1, which may involve clinicians, pharmacists, or genetic counsellors.

The logic model also includes moderating factors that may affect implementation, such as the context in which PGx is implemented, funding availability, and public trust in institutions. These factors were identified in the literature review, and their impact on implementation is discussed in Chapter 1.

The logic model's outputs and outcomes were generated by the researcher with input from the supervisory team and are typical of health service research interventions.

The logic model highlighted several areas of uncertainty initially identified in Chapter 1 relating to implementing multi-drug pharmacogenomic testing. Table 2-3 outlines questions relating to these logic model areas.

Table 2-3 Uncertainties identify for each component of the logic model.

Area 1: Activities and inputs:	**Area 2: Mechanisms:**
• What type of stakeholder engagement is required? • What are the costs associated? • Which drug-gene pairs should be tested? • What type of technology is most suitable?	• Who are the health professionals involved? • What are the steps required? • What is the consent process? • Which steps are the most challenging? • What are the core steps?
Area 3: Moderating factors:	**Area 4: Outputs and outcomes**
• What is the effect of setting? • What factors influence which activities and how? • How acceptable are the activities to different stakeholders?	• What is the effect on patients? • How long are the effects sustained for? • Are there any unexpected outcomes?

As argued in Chapter 1, the aim of this programme of work is to address a gap in the literature and design a multi-drug pharmacogenomic testing implementation configuration in the NHS. This aim guided the areas of uncertainty to prioritize for this programme of work, which were: *'Area 1: Activities and inputs', 'Area 2: Mechanisms',* an *'Area 3 Moderating factors'.* The absence of an existing implementation model for multi-drug pharmacogenomic testing in the NHS, creates obstacles for designing and executing feasibility and evaluation work. Addressing this first requires developmental work is first needed to adapt a multi-drug pharmacogenomic testing intervention for an NHS context. The MRC guidance, shown in Figure 2-1, promotes considering development work alongside implementation work. Doing this would help avoid future translation limitations, seen where interventions are developed for environments like clinical trials, which are often disconnected from the complexity of real-world settings. Historically complex healthcare interventions intuitively developed through a trial and error have had variable success in sustaining adoption and implementation in the long term (Grol and Grimshaw, 2003). 'Theory' can be defined as a set of analytical

principles to structure, explain and guide understanding of observations (Nilsen, 2015). The MRC guidance, highlights progress in implementation science, in using a theoretical lens (Davies et al., 2010) to identify which moderating factors influence implementation. Some evidence suggests behaviour change interventions underpinned by theory are more likely to be effective than those which are solely empirically driven (Glanz and Bishop, 2010, Bluethmann et al., 2017).

The MRC guidance advocates using theory to understand how change is brought about, including the interplay of mechanisms and contexts. However, the MRC guidance does not advise on how to select and apply an appropriate theory. Consequently, researchers must determine for themselves the most appropriate theoretical lens for their programme theory by selecting from a plethora of health psychology, implementation and behaviour change theories, models and frameworks.

2.6 Theories, models, and frameworks

Theory has been defined as a set of analytical principles designed to structure, explain and aid understanding of observations (Wacker, 1998). Theories are built from relationships between dependent and independent variables within a domain where the theory applies, which can together explain or predict an outcome, such as a specific behaviour (Nilsen, 2015). They can also clarify causal mechanisms and the core components of an intervention, explaining how and why certain outcomes are achieved, thereby improving implementation. Additionally, a benefit to researchers using theory is they are explicit, open to question and examination and more consistent with accumulated knowledge when compared to beliefs and assumptions. In this way, theories can provide a meaningful context for individual pieces of empirical evidence and build an integrated body of knowledge when compared to other quantitative and qualitative inquiries.

A wide range of theories, models and frameworks are available to understand the influences on implementation including in health services processes. The complexity of healthcare and the multi-dimensional nature of influences and

relationships affecting implementation, means no single theory, model or framework is likely to address all aspects of the implementation process. However, explicit application of even a single appropriate theory, when compared to intuitive experience, can shorten the time needed to develop interventions, optimize their design and identify conditions of context for implementation to be adopted and sustained (Damschroder, 2020). The latest MRC guidance therefore advises researchers to understand and include existing implementation theory, models or frameworks in designing, developing, and evaluating complex interventions. The Chapter 1 literature review identified that pharmacogenomic testing has faced implementation challenges internationally. As we know this and given the lack of current multi-drug pharmacogenomic testing in NHS clinical care, using theory to conceptualise influences on implementation may help identify sources of uncertainties in the programme theory introduced earlier in this chapter. Furthermore, using a theoretical lens to help interpret and understand influences on the processes within the logic model, may clarify some casual mechanisms and identify core components of the intervention and how it may lead to changes in patient outcomes. This programme of research is developmental and focused on developing a multi-drug pharmacogenomic testing configuration for implementing in the NHS. Deploying a well-established theoretical lens, can inform activities later in the research cycle, like feasibility testing and evaluation especially as additional knowledge is accumulated with reference to such a consistent theoretical lens.

The plethora of theoretical approaches available in implementation science can complicate choosing one or more theories, models of frameworks to embed within a research programme. Nielsen has proposed a taxonomy which distinguishes different categories of theories, models and frameworks in implementation science (Nilsen, 2015). Figure 2-3 shows how the taxonomy divides theoretical approaches by their primary aims: describing and/or guiding the process of translating research into practice; then understanding and/or explaining what influences implementation outcomes; and finally evaluating implementation. A theoretical approach selected for this programme of work aims to understand and explain what influences multi-drug pharmacogenetic testing implementation outcomes

within the NHS. Without current examples of multi-drug pharmacogenetic testing models within the NHS, evaluating implementation would not be robust. Neither is a adopting a theoretical approach which seeks to describe or guide the process of translating research into practice, as examples of implementation do occur in other countries with varying degrees of success. Instead, a theoretical approach that guides understanding and explanation of influences on implementation outcomes through the logic model is desired, to identify the key components and mechanism for adapting and implementing multi-drug pharmacogenomic testing to bring about positive patient outcomes in different NHS settings.

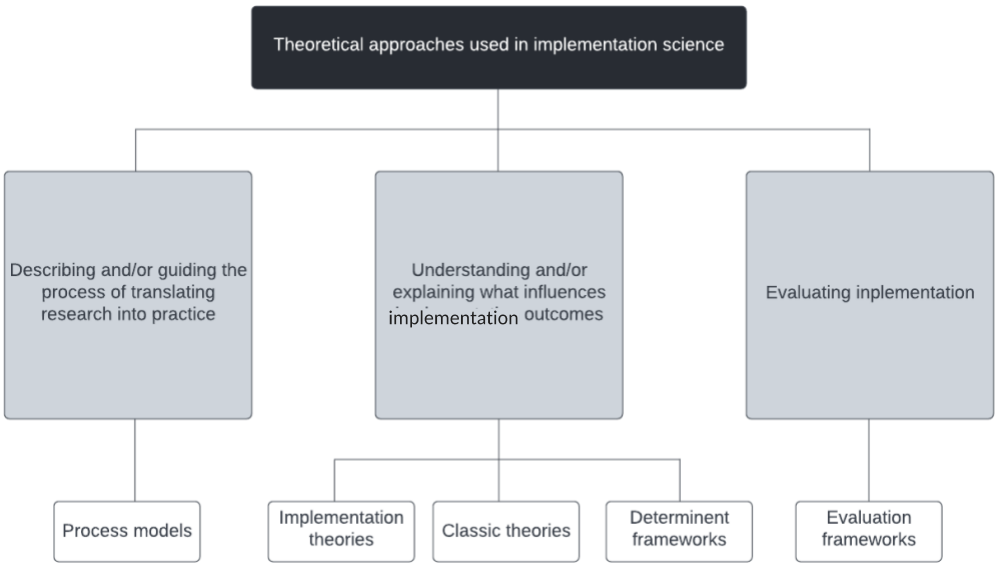


Figure 2-3 Aims for using theoretical approaches in implementation science and corresponding categories of theories, models and frameworks. (Adapted from (Nilsen, 2015))

Theoretical approaches which aim to understand and/or explain influences on implementation outcomes can be divided into classical theories, implementation theories and determinant frameworks (Nilsen, 2015). The following section describes each of these theoretical approaches, their origins, how they were developed and their strengths and limitations with respect to the aims of this research.

2.6.1 Classical theories in implementation research

'Classical theories' refers to theories established in the fields of psychology, sociology and organizational theory, 'borrowed' in developing and evaluating complex interventions, seen in Nielsen's taxonomy of theoretical approaches used in implementation science (Nilsen, 2015).

2.6.2 Behaviour change theories in implementation research

Behaviour within psychology is defined as an 'activity of an organism interacting with its environment' (Davis et al., 2015). Health psychology and behaviour change theory seeks to identify the variable underpinning decisions to perform a behaviour (Kwasnicka et al., 2016), providing a schematic of the mechanisms that may support the behaviour in real-life settings. Examples of psychological behaviour change theories commonly used in implementation science to study determinants of 'clinical behaviour' change include the Theory of Reasoned Action (Ajzen I. and Fishbein M, 1970), the Theory of Planned Behaviour (Ajzen, 2011) and the reasoned action approach (Fishbein and Ajzen, 2011).

Implementing multidrug pharmacogenomic testing in healthcare settings, requires changing existing behaviours of healthcare professionals and patients. Knowing which factors or determinants influence these behaviours is useful for addressing one of the uncertainties in the logic model, namely what and how moderating factors affect the mechanisms through which multi-drug pharmacogenomic testing effects changes in patient outcomes.

The Theory of Reasoned Action (TRA) was developed by social psychologists Fishbein and Ajzen in 1970 (Ajzen I. and Fishbein M, 1970). The theory assumes behaviour results from the intention to voluntarily perform a behaviour. Intention to perform a voluntary behaviour is influenced by a combination of attitudes towards a behaviour and subjective norms (Ajzen I. and Fishbein M, 1970). TRA has been used to examine multiple health behaviours, including predicting early sexual behaviour in adolescents (Doswell et al., 2011) and encouragement of pediatricians to get parents to vaccinate children (Roberto et al., 2011).

A criticism of TRA is it did not consider 'volitional control' i.e. whether or not an individual has control over the behaviour. Consequently, the theory was adapted to the Theory of Planned Behaviour (TPB) with an added component of 'perceived behavioural control (Ajzen, 2011). Perceived behavioural control is the belief in how easy or difficult performance of the behaviour is likely to be. Where TRA is used to explain voluntary behaviour, TPB can be used to study behaviour which may not be

completely under the control of the individual for a variety of reasons. TPB has been used to predict health-related behavioural intention, including exercise (Nguyen et al., 1997) and diet (Conner et al., 2003). TPB has progressed into the Reasoned Action Approach (Fishbein and Ajzen, 2011), which distinguishes pairs of sub-components of perceived behavioural control, to predict intention. The RAA may be more useful for predicting risk behaviours, in particular that there may be a more impulsive pathway to action for attitudes and norms (Conner et al., 2017).

Both TRA, TPB and RAA have a broad-reaching nature which makes them difficult to completely operationalize. Each theory purports to explain the determinants of behaviour but does not provide guidance on how to apply this knowledge to change behaviour to enhance successful implementation. The aim of this body of work, was to develop a multi-drug pharmacogenomic testing implementation configuration for the NHS, for this reason, these theories were deemed inappropriate to underpin the methods for this research.

2.6.3 Diffusion of innovation theory

Rogers's diffusion of innovations (Rogers E.M, 2003) is widely recognized as a social science theory developed to explain how an idea or innovation gains momentum and becomes adopted by a population or social system. The theory has two concepts. Firstly, the outcome of diffusion is that individuals adopt a new behaviour or product primarily with a key to adoption being a perception that the innovation is new and innovative. And secondly, the rate of adoption of the innovation will differ between individuals due to different characteristics. As such, adoption does not happen at once, but rather over time with some individuals more likely to embrace the innovation earlier than others (Kaminski J, 2011). The theory therefore emphasizes the importance of understanding the characteristics of the target population that will promote or impede adoption of the innovation. As shown in Figure 2-4, the theory has five established adopter categories, with suggested strategies for appealing interventions to them.

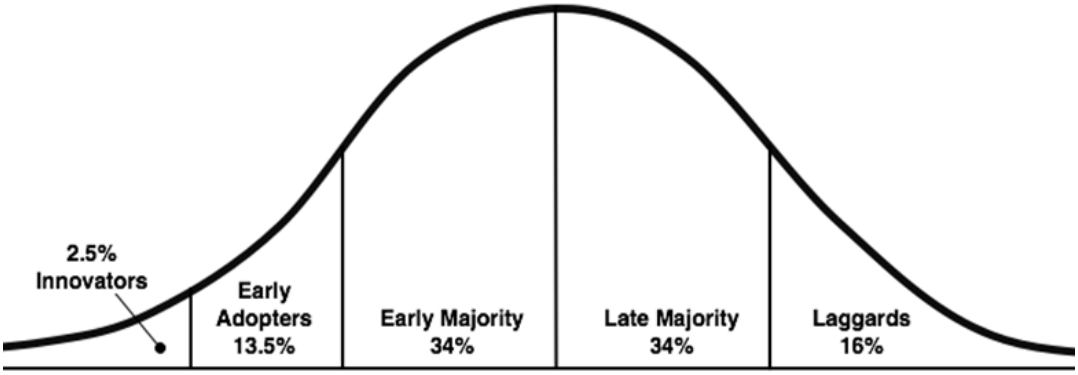


Figure 2-4 Diffusion of Innovation theory- adopter categories (Adapted from (Rogers E.M, 2003))

1. **Innovators**: These individuals are risk takers and take interest in new ideas. As these individuals are likely to want to be the first to try the innovation, very little is needed to appeal to them.
2. **Early adopters**: These are leaders who are aware for the need for change, making them comfortable adopting new innovations. Strategies that appeal to this group, include how-to manuals and information sheets on implementation.
3. **Early majority**: These are individuals who adopt new innovations before the average person but need some convincing. Strategies to appeal to this group include success stories and evidence of the innovation's effectiveness.
4. **Late majority**: This group are skeptical of change and only adopt an innovation after it has been tried by the majority. Strategies that appeal to this population include evidence of how other people have tried the innovation and successfully adopted it.
5. **Laggards**: This group is the most difficult to motivate due to their conservative and skeptical nature. Strategies that appeal to this population include statistics, fear appeals and peer pressure from other adopter groups.

Additionally, the theory also has five main factors that influence adoption of an innovation, with each factor influencing the five adopter categories to different extents. These are:

1 **Relative advantage**: degree to which an innovation is perceived to be superior to the idea, practice or product it replaces.
2 **Compatibility**: degree to which the innovation is aligned with the values, experiences and needs of the adopter population.
3 **Complexity**: perceived difficulty of the innovation to understand/or use by the adopter population.
4 **Triability**: extent to which the innovation can be tested or experimented with prior to adoption.
5 **Observability**: extent to which the innovation produces tangible results.

Within a healthcare context, Rogers diffusion of innovation theory has been used to study individual's adoption of new healthcare information technologies (Helitzer et al., 2003, Lee, 2004, van der Weide and Smits, 2004) and public health programmes like smoking cessation (McManus, 2013). The theory has been described as a macro-level theory (Lien and Jiang, 2017) taking a broader view of adoption of new practices across populations or groups. As a result, applying this theory within the context of implementing multi-drug pharmacogenomic testing in the NHS would not provide the level of detail necessary to identify and resolve the implementation problem experienced so far by those implementing pharmacogenomic testing. As seen in the logic model, (Figure 2.2), implementing multi-drug pharmacogenomic testing includes a series of behaviours involving multiple people. For this reason, Roger's Diffusion of Innovation theory is inappropriate as it fails to consider the influence of resources or social systems in supporting multiple new behaviours.

2.7 Implementation theories

Implementation theories are theories originating within the field of implementation science. These theories were designed with the intention to produce a robust set of conceptual tools enabling researchers and practitioners to identify, describe and explain important elements of implementation processes and their outcomes (May,

2013). The COM-B (Capability, Opportunity, Motivation and Behaviour) model (West and Michie, 2020) and the Normalization Process theory (May and Finch, 2009) are two such approaches commonly applied within health services research to enhance understanding and explain aspects of implementation.

2.7.1 COM-B model

The COM-B model (Michie et al., 2011) was developed by health psychologists Robert West, Maartje van Stralen and Susan Michie in 2011 and proposes that for a person to carry out a behaviour, three conditions must be met. These are that the person must have the psychological and physical ability to do so (**C**apability), have the social and physical opportunity to enact the behaviour (**O**pportunity), and want or need to carry out the behaviour more than other competing behaviours (**M**otivation). As each of these components interact, interventions must target one or more of these components to deliver and maintain effective behaviour change.

The 53dventage of the COM-B Model over a single theory of behaviour is that it encompasses several distinct explanatory components, thus adding additional potential influences on behaviour. Additionally, COM-B sits at the center of the Behaviour Change Wheel (BCW), a tool kit for designing behaviour change interventions. The Behaviour Change Wheel sets out nine broad categories of intervention that can be included in any behaviour change strategy: education, persuasion, incentivisation, coercion, enablement, training, restriction, environmental restructuring, and modelling (Michie et al., 2011). Combining the COM-B model in tandem with the BCW, gives researchers and policy makers the ability to not only identify implementation problems, but also the possible solutions to solve identified implementation problems.

2.7.2 Normalization Process theory

Normalization Process Theory (NPT) originated as a model, built from knowledge gained from empirical studies of implementing new technologies (McEvoy et al., 2014). It is concerned with understanding processes involved in what people ‘do’ and how they construct what they ‘do’ both as individuals and collectively, as part of a socially organized group (Murray et al., 2010).

NPT has been defined as a 'middle range theory' (Murray et al., 2010). Middle range theories are frameworks for understanding problems and for guiding the development of interventions in a practical sense. NPT can be used alongside other approaches. For example, a research group in Germany, developed an intervention manual to enhance self-care of patients with heart failure using both the COM-B model and Normalization Process Theory (Herber et al., 2018) .

NPT seeks to surface factors that can promote, or inhibit, the normalization of a set of practices, by identifying four core components to NPT to then examine in specific contexts: coherence; cognitive participation; collective action and reflexive monitoring. Each of the core components is described below:

- *Coherence*: the process and work of sense-making and understanding that individuals and organizations have to go through in order to promote or inhibit the routine embedding of a practice.
- *Cognitive participation*: the work that individuals and organizations have to do to enact the new practice.
- *Collective action*: is how people make the practice or behaviour work in reality, considering what they require to make it happen.
- *Reflexive monitoring*: the work inherent in the informal and formal appraisal of a new practice once it is in use, in order to assess its advantages and disadvantages, and which develops users' comprehension of the effects of a practice.

Carl May proposes that barriers and facilitators that promote or inhibit embedding of a practice or behaviour act on one or more of these four generative mechanisms. To achieve sustained change within a social context, both individuals and the collective need to continuously invest in actions that exert work on these mechanisms. NPT considers not only the actions of the individual and collective to be dynamic, but also the environment in which actions take place. Therefore, investment of individuals in embedding a behaviour or practice is influenced by the environment itself. For example, failure to refill alcohol sanitizer pumps in general practice surgeries leads to a deterioration in practitioners' hand hygiene.

Normalization Process Theory can be used from the initial development stage of an intervention to evaluation and has been used to develop interview schedules, coding and analytical frameworks, and guide interpretation and impact of research findings (May et al., 2018). A criticism of NPT is a focus on the agency of those involved in implementation, often conceptualized as the professional practitioners, as opposed to those who experience the effects of that agency (Segrott et al., 2017). In the context of pharmacogenomic testing implementation, this is of high importance, given the influence of pharmacists and patients, on clinicians pharmacogenomic testing behaviour (Veilleux et al., 2020).

2.7.3 Determinant frameworks

Determinant frameworks describe general types (classes or domains) of determinants hypothesized or found to influence implementation outcomes. Frameworks often incorporate a wide range of theories, allowing researchers to capture and evaluate more influences on single or group behaviour than they would with one theory alone. The determinant frameworks described and explored for their use in implementing multi-drug pharmacogenomic testing below are: the NASSS Framework and the Theoretical Domains Framework.

2.7.3.1 The NASSS Framework

The NASSS framework is an evidence-based framework for studying the **n**on-adoption and **a**bandonment of technologies by individuals and the challenges to the **s**cale-up, **s**pread and **s**ustainability of these technologies in health care organisations. Developed by Trisha Greenhalgh and Seye Ambimbola in 2019, the framework is designed as a sensitising device that incorporates and combines a range of existing theoretical perspectives on illness and disease, technology adoption, organisational change, and system change (Greenhalgh et al., 2017). The framework can be used to help construct a rich narrative of an unfolding technology programme and identify various uncertainties and interdependencies that need to be contained and managed if the program is to succeed. NASSS consists of seven domains, each of which may be simple (few components, predictable), complicated (many components, predictable) or complex (many

components interacting in a dynamic and unpredictable way). Table 2-4 contains descriptions for each of the domains.

Table 2-4 Domains in the NASSS Framework

Domain	Definition
Condition	- The condition of the person(s) to which the technology is targeting.
Technology	- Uncertainties associated with the technology - Can related to what the technology is; where it will come front; technology performance and dependability; technology's usability and acceptability. - The technical interdependencies and changes to organisational tasks and routines.
Value proposition	- The value the technology might generate for different groups of people. - Value may be financial, such as profit, or non-financial, such as control of symptoms.
Adopters	- Who is the technology intended for and what changes will it bring for them? - The implications for people who might be indirectly affected by the technology.
Organisations(s)	- The organisation implementing the technology's capacity to take on technological innovations.
Wider system	- The external conditions that could complicate adoption and spread of the innovation. - Examples could include the political and/or policy climate; professional bodies; patient organisations and lobbying groups; regulatory context; commercial context.
Embedding and adaption over time	- Flexibility that can be built into the technology to maximise future adaptability. - Ways in which organisations develop resilience to accommodate future system changes.

The NASSS framework considers the sustainability of implementing interventions in health care contexts which are dynamic and ever evolving. It can help explain the successes, failures, and challenges of implementing interventions, since failure is often linked to complexity across multiple NASSS domains. The NASSS framework has been used to evaluate technology-supported programmes including video outpatient consultations, pendant alarms worn around the neck (and or wrist) for care clients and a biomarker monitoring (weight, blood pressure, heart rate) in the form of tablet technology for health failure patients (Greenhalgh et al., 2018). All evaluations used in-depth longitudinal ethnographic study designs to generate rich descriptions of local technology supported innovations. At the time of researching different implementation frameworks, the NASSS Complexity Assessment Toolkit (CAT) had not been published. This toolkit contains a series of questions and prompts for the researcher, clinical, social worker, or patient to elicit reflections on uncertainties and complexities within each of the domains. The toolkit is intended to prompt conversations and bring together different stakeholders to create an action plan to design an implementation project considering measures to reduce or respond to complexity in the different domains (Greenhalgh et al., 2020).

The NASSS framework was not selected for this research project for two reasons. Firstly, the NASSS CAT had not been published at the time of researching different implementation frameworks. It was therefore difficult for the researcher to envision how to apply the NASSS framework in a rigorous manner. Secondly, the NASSS framework was designed for large scale implementation projects and used ethnographic study designs to elicit rich descriptions of the implementation challenges across the domains. It was not possible to use such a study design for this research project due to funding limitations. Only a small number of pharmacogenomic tests were available for use to the researcher which impeded the ability to design a large implementation study and utilize the NASSS framework in the manner it was designed for.

2.7.3.2 The Theoretical Domains Framework

The Theoretical Domains Framework (TDF) is an integrative framework of behaviour change theories developed through a collaboration between psychologists and health service researchers to provide access to non-behavioural scientists to select from a comprehensive theoretical framework (Atkins et al., 2017). The framework developed in 2005 is a synthesis of 33 behaviour change theories and 128 theoretical constructs, organised into 14 (Atkins et al., 2017), originally 12, theoretical domains. Each theoretical domain represents a determinant of behaviour, as seen in Table 2-5.

The TDF provides a theoretical lens through which to view the cognitive, affective, social and environmental influences on behaviour. It does not explain these relationships, but rather provides an initial foundation to understand behaviour by identifying influences or areas to target when designing interventions. Researchers can use the framework to structure methods of gathering evidence to identify the influences on behaviour within a context. This generates a 'behavioural diagnosis' which is a description of the influences targeted for change in designing interventions. The TDF fits well with the Behaviour Change Wheel (BCW) and COM-B model mentioned earlier in this chapter, with the domains of the TDF mapping onto the COM-B segments (Cane et al., 2012).

Table 2-5 The Refined Theoretical Domains Framework (Michie et al., 2005).

Domain/Definition	Constructs
Knowledge **An awareness of the existence of something**	– Knowledge (including knowledge of condition/scientific rationale) – Procedural knowledge – Knowledge of task environment
Skills **An ability or proficiency acquired through practice**	– Skills – Skills development – Competence – Ability – Interpersonal skills – Practice
Social/Professional Role and Identity **A coherent set of behaviours and displayed personal qualities of an individual in a social or work setting**	– Professional identity – Professional role – Social identity – Identity – Professional boundaries – Professional confidence – Group identity – Leadership – Organisational commitment
Belief about Capabilities **Acceptance of the truth, reality or validity about an ability, talent, or facility that a person can put to constructive use.**	– Self-confidence – Perceived competence – Self-efficacy – Perceived behavioural control – Beliefs – Self-esteem – Empowerment – Professional confidence
Optimism **The confidence that things will happen for the best or that desired goals will be attained.**	– Optimism – Pessimism – Unrealistic optimism – Identity
Belief about Consequences **Acceptance of the truth, reality, or validity about outcomes of a behaviour in a given situation.**	– Beliefs – Outcome expectancies – Characteristic of outcome expectancies – Anticipated regret – Consequents

Table 2.5 The Refined Theoretical Domains Framework continued (Michie et al., 2005).

Domain/Definition	Constructs
Reinforcement **Increasing the probability of a response by arranging a dependent relationship, or contingency, between the response and a given stimulus.**	– Rewards (proximal/distal, valued/not valued. Probably/improbable) – Incentives – Punishment – Consequents – Reinforcement – Contingencies – Sanctions
Intentions **A conscious decision to perform a behaviour or a resolve to act in a certain way.**	– Stability of intentions – Stages of change model – Transtheoretical model and stages of change
Goals **Mental representation of outcomes or end states that an individual wants to achieve**	– Goals (distal/proximal) – Goal priority – Goal/target setting – Goals (autonomous/controlled) – Action planning – Implementation intention
Memory, Attention and Decision Processes **The ability to retain information, focus selectively on aspects of the environment and choose between two or more alternatives.**	– Memory – Attention – Attention control – Decision making – Cognitive overload/tiredness
Environmental Context and Resources **Any circumstances of a persons' situation or environment that discourages or encourages the development of skills and abilities, independence, social competence, and adaptive behaviour.**	– Environmental stressors – Resources/ material resources – Organisational culture/climate – Salient events/critical incidents – Person x environment interaction – Barriers and facilitators

Table 2.5 The Refined Theoretical Domains Framework continued (Michie et al., 2005).

Domain/Definition	Constructs
Emotion **A complex reaction pattern, involving experimental, behavioural, and physiological elements, by which the individual attempts to deal with a personally significant matter or event.**	– Fear – Anxiety – Stress – Depression – Positive/negative affect – Burn-out
Behavioural Regulation **Anything aimed at managing or changing objectively observed or measured actions.**	– Self-monitoring – Breaking habit – Action planning

The TDF has been used to facilitate comprehensive assessment of determinants to health professionals' behaviour. A rapid systematic review of TDF-based qualitative studies in 2020, found 186 studies using healthcare professionals, patients and the public (McGowan et al., 2020). The TDF has been used in qualitative research, surveys, systematic reviews, feasibility and randomised studies and process evaluations (Francis et al., 2012).

The primary strength of the TDF is it presents a comprehensive set of underpinning psychology theories and constructs that allow health service researchers to access in a systematic way when designing behaviour change interventions. The broad range of theoretical domains enables identification of relevant beliefs which may be missed through an atheoretical or single theory approach. On the other hand, application of the TDF in a rigid manner, may lead to non-TDF-related factors being overlooked, For example, using purely deductive approaches in qualitative research may result in missing important contextual influences on behaviour and other potential changes in participants that may not be elicited if findings are contained within domains in the first instance (McGowan et al., 2020). This disadvantage may

be overcome by including an inductive approach within analysis of qualitative studies, particularly the initial coding of data so that non-TDF-related factors are not overlooked, and nuance and context are not lost.

2.8 Selected theoretical approach

The NPT, COM-B and TDF all could have been used to underpin this research project, although all approaches have their limitations, and no single theory, model or framework would cover all the constructs required for designing an implementation configuration for multi-drug pharmacogenomic testing in the NHS.

All three approaches have been operationalised in studies of healthcare implementation, providing a good foundation and knowledge base to access when incorporating theory in the design and methodologies of the studies in this programme of work. They can all be used as an organising lens for analysing, reporting, designing complex interventions, generating research questions, and designing tools to investigate and support implementation and process evaluations. Nonetheless, all three present tensions for researchers when fitting data into pre-determined categories, understanding construct or domain definitions clearly and mapping data accurately when data might be seen to fit into more than one category.

The COM-B model and the TDF are concerned with factors influencing an individual stakeholders' behaviour to be targeted for behaviour change when developing a new intervention. In contrast, NPT focuses on the process elements of implementation and work that is required of individual stakeholders and the impact of the collective to bring about 'normalization' of a new intervention. The absence of an existing defined multi-drug pharmacogenomic testing intervention in the NHS, positions this research at the micro-organizational level of implementation. At this stage, the priority is to develop a multi-drug pharmacogenomic testing intervention for small scale testing, therefore an approach which targeted individuals' healthcare behaviours would be more appropriate for this purpose.

In addition, at the time of selecting a theoretical lens, the authors of the COM-B and TDF were offering a summer school designed to equip researchers with the necessary skills to apply both theoretical approaches to their research. This course provided the researcher with confidence to use the COM-B and TDF with scientific rigour, enhancing the trustworthiness of the qualitative research findings.

The TDF was then selected over the COM-B because of its granularity which provided a mechanism to identify specific influences on health practitioners' behaviour in a more precise way. This would help in future stages of research, to inform selection of a smaller number of behaviour change technique that could be prioritized in designing behaviour change interventions which might enhance an implementation strategy for pharmacogenomic testing. The TDF could also be used like the COM-B with the Behaviour Change Wheel to develop and deliver a behaviour change strategy.

2.9 Implications for this programme of work

The following section briefly considers the design of three studies each addressing and progressing research questions identified in Chapter 1, clarifying uncertainties and assumptions presented in the programme theory represented by Figure 2-2 showing multi-drug pharmacogenomic testing implementation in the NHS. The next section describes each of the studies, the research gap they are designed to answer, the theoretical perspective and methods adopted to progress and build evidence, increasing knowledge of a theoretically informed, evidence-based implementation model for multi-drug pharmacogenomic testing in the NHS.

Both qualitative and quantitative research methods were used to address each uncertainty proposed by the initial logic model, seen in Figure 2-2. This is pictorially shown in figure 2-5 as four jigsaw pieces to represent the contribution of each study.

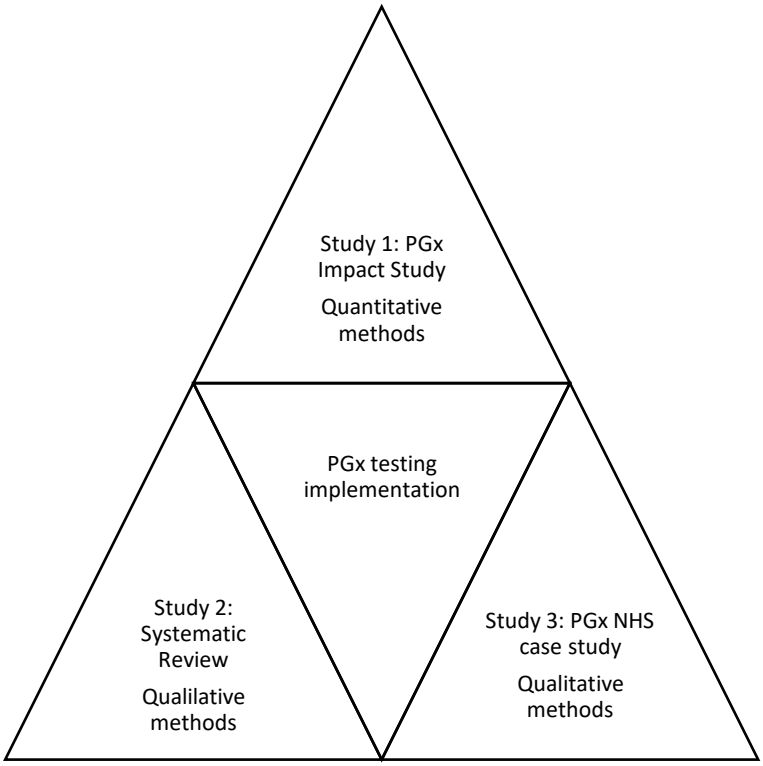


Figure 2-5 Overview of research methods used in the thesis

Study 1: PGx Impact Study. [Thesis, Chapter 3]

Research question addressed:

- What are the design components of a multi-drug pharmacogenomic testing panel that provides the potential for the most benefit for UK NHS patients?

This study addresses what the potential impact of multi-drug pharmacogenomic testing in a UK primary care context. A quantitative modelling approach is used, to estimate the volume of medicines annually prescribed in UK primary care that could be optimized through pharmacogenomic testing. Using the best available evidence, gene-drug pairs which affect the largest volume of prescriptions are identified. By identifying these gene-drug pairs, knowledge is gained with respect to the technology requirements of a multi-drug pharmacogenomic testing intervention.

Study 2: Systematic review [Thesis, Chapter 4]

Research question addressed:

- What does the global literature report with respect to the current barriers and enablers to the implementation of multi-drug pharmacogenomic testing from a behavioural perspective of prescribers, pharmacists, and patients?

This study identifies the behaviours and influences on behaviours relevant to the implementation of multi-drug pharmacogenomic testing in clinical settings. This study uses a systematic review methodology to examine the influences on the behaviour of prescribers, pharmacists and patients implementing multi-drug pharmacogenomic testing. These influences were mapped to the TDF to identify areas to target for behaviour change interventions, to improve the successful implementation of multi-drug pharmacogenomic testing.

Study 3: Case study of PGx implementation in the NHS [Thesis, Chapter 5]

Research question addressed:

- What are the locally relevant (UK) barriers and enablers to implement multi-drug pharmacogenomic testing, when considering behavioural perspectives of prescribers, pharmacists, and patients?

This study identifies the behaviours and influences on behaviours relevant to the implementation of multi-drug pharmacogenomic testing in NHS clinical settings. This study used a case study methodology offering practitioners in primary and secondary care a commercial multi-drug pharmacogenomic testing service for use in their clinical practice. Healthcare practitioners and patients were interviewed to add to the understanding of the local barriers to and enablers of behaviours related to implementing pharmacogenomic testing in the NHS.

2.10 Summary

Implementing complex interventions like multi-drug pharmacogenomic testing require careful consideration and substantial effort. Using theory to underpin implementation research, even in the development or adaptation of a new

intervention, provides a framework within which to optimise understanding of barriers and facilitators to successful implementation, and mechanism of why implementation succeeds or fails. After a review of the most relevant theoretical approaches, a framework approach using the Theoretical Domains Framework was selected, due to its emphasis on identifying the individual influences on health practitioners and patient behaviours which could be targeted for behaviour change interventions to improve successful implementation.

3. Chapter 3: Estimating the potential impact of implementing pre-emptive pharmacogenomic testing in primary care across the UK.

This chapter is derived from the following publication:

Youssef, E., Kirkdale CL, Wright DJ, Guchelaar H, Thornley T (2021) Estimating the potential impact of implementing pre-emptive pharmacogenetic testing in primary care across the UK. *British Journal of Clinical Pharmacology*. 87, 7, p. 2907-2925. **https://doi.org/10.1111/bcp.14704**

3.1 Introduction

This chapter will present the results of a modelling study estimating the impact of multi-drug pharmacogenomic testing in UK primary care. As reasoned in Chapter 1 and Chapter 2, one of the key uncertainties around implementing a pharmacogenomic (PGx) testing intervention in the NHS, is quantifying the scale of prescribing activity that could be optimised through PGx testing. Furthermore, the absence of a widely accepted pharmacogenomic testing panel, that covers commonly occurring drug-gene pairs relevant to a UK context presents a challenge to researchers and policy makers interested in adopting, implementing, and evaluating multi-drug pharmacogenomic testing interventions within the NHS.

As discussed in Chapter 1 pharmacogenomic testing is an umbrella term encompassing numerous genetic testing technologies and implementation configurations. Significant debate persists about the optimal timing and methodology for delivering pharmacogenomic testing in clinical care. In recent years, pre-emptive panel-based pharmacogenomic testing, where several drug-gene pairs are tested and information saved, in preparation of future prescriptions, has been proposed to offer the most economic strategy for clinical implementation. It is still unclear however when testing should be initiated, whether this be from childhood, early adulthood or for those with multiple morbidities given their proclivity to polypharmacy.

It is estimated that throughout an individual's lifetime, exposure to drug-gene interactions (DGI) is high. A recent study analysing the genetic variant frequencies for fourteen pharmacogenes in 487,409 participants in the UK biobank found 99.5% of individuals have a predicted atypical response to at least one drug (McInnes et al., 2020). Clinical guidelines advising management of these DGI are key to implementation. The international Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetic Working Group (DPWG) in the Netherlands have independently reviewed over 100 DGI and published therapeutic recommendations for 86 DGI (Barbarino et al., 2018) . Of these recommendations, a high proportion pertain to medicines initiated in primary care.

Kimpton and colleagues analysed prescribing patterns between 1993-2017, in a sample of 648,141 English primary care patients (Kimpton et al., 2019). They found exposure to PGx drugs, i.e. drugs with published drug-gene interactions (DGI) ,was high, with over 80% of patients being exposed to at least one PGx drug, and 58% exposed to more than or equal to two PGx drugs over a 20-year period. A limitation of this study was the inclusion of drugs which do not carry a published therapeutic recommendation, which means whilst the study shows exposure is high in primary care, it is unclear what the impact would be on prescribing (Kimpton et al., 2019). In the Netherlands, Banks and colleagues analysed dispensing data for initiated medicines in primary care with a DPWG therapeutic recommendation (Bank et al., 2019).They combined this information, with population incidence of aberrant phenotypes to estimate the impact of pre-emptively PGx testing the entire Dutch population. The authors found that nearly one in four new prescriptions for 45 PGx drugs had an actionable DGI, with one in nineteen new prescriptions requiring a dose adjustment or alternative drug choice (Bank et al., 2019).

The study reported here therefore sought to address gaps in the current evidence base and estimate the potential impact of PGx testing on prescribing activity, as well as informing the testing component for a multi-drug pharmacogenomic testing intervention and delivery considerations for implementation in UK primary care.

3.2 Aim

To estimate the impact of multi-drug pharmacogenomic testing annually on prescribing activity in UK primary care.

3.3 Objectives

1. To identify drug-gene pairs with published prescribing recommendations from CPIC and DPWG relevant to UK primary care.

2. To estimate the volumes of newly initiated medicines with PGx prescribing recommendations annually prescribed in UK primary care.

3. To analyse whether age affects exposure to drug-gene interactions.

4. To analyse whether frequency of drug-gene interaction varies by therapeutic class of drug.

5. To identify which genes underpin the most frequently occurring drug-gene interactions.

3.4 Ethics approval

The study was confirmed as a service evaluation by the University of East Anglia Faculty of Medicine and Health Sciences Research Ethics Committee (Reference: 2019/2020-080). The ethical approval letter is provided in Appendix 1.

3.5 Patient and Public Involvement

Two patient and public representatives assisted in the design of dissemination materials for the study (Youssef et al., 2022).

3.6 Methods

A project management group was convened comprising of academic supervisory team and an expert in pharmacogenomic research (Henk-Jan Gucheelar). The initial idea for the study was proposed by Tracey Thornley. The aim was to replicate the study by Bank and colleagues (Bank et al., 2019) where first time prescriptions issued in 2017/18 in the Netherlands were reviewed for drug-gene interactions as per guidelines from the Dutch Pharmacogenetics Working Group (DPWG). However, the methodology proposed by Banks was not possible to replicate for a UK context due to several differences between the Netherlands and UK. These differences included: the way prescribing data is collected in the Netherlands compared to the UK; access to pharmacogenomic variant frequency data for the UK; differences in medicines licensing and availability and lack of PGx guidelines endorsed in the UK. As a result, the researcher, proposed methods to overcome these challenges, which were overseen and reviewed by members of the project management group, who additionally monitored project progression.

3.1.1 Methodological Approach

The aim of this study required a methodological approach that could estimate with reasonable confidence the annual volume of prescribing activity that could in theory be optimised by pre-emptive pharmacogenomic testing. Neither prospective or retrospective study designs were appropriate given the absence of pharmacogenomic testing in the UK. Instead, a modelling approach was taken, with careful consideration given to each assumption feeding into the model, reducing where possible the degree of uncertainty introduced where data recorded for other reasons are combined.

3.1.2 Identification and selection of drugs and drug-gene interactions relevant to UK primary care

Medicines included in the analysis were those with PGx drug/dosing guidelines published by the DPWG and/or CPIC. In the absence of UK endorsed PGx guidelines, these organisations were chosen, because of their authority within the field of PGx. Guidelines published up to 31.03.2020 were identified through PharmGKB, which provides an up-to-date repository of gene-drug interactions and therapeutic recommendations published by DPWG, CPIC and other organisations (Barbarino et al., 2018).

Medicines were screened against a set of inclusion and exclusion criteria using the following UK based medicine resources: British National Formulary (BNF) (Joint Formulary Committee, 2020) , Martindale: the complete drug reference (Brayfield, 2020) and Openprescribing.net. (OpenPrescribing.net, 2020).

Inclusion criteria:

- Licensed in the UK
- Initiated or continued in primary care

Exclusion criteria:

- Specialist medicines requiring long term monitoring by secondary care prescribers.

As seen in Appendix 2, for each drug selected, only a single-gene interaction was included for analysis. Population frequency data for multiple concurrent aberrant phenotypes was unavailable, and thus to avoid overestimating the effect of PGx testing for a single drug, the phenotype frequency data were applied for the most impactful single gene. This was either the gene associated with phenotypes that led to more 'actionable' therapeutic recommendations e.g. choosing the gene with recommendations for 'direct action' over the gene with 'indirect action', or choosing the gene with the most frequently occurring aberrant phenotypes in the UK population. For example, the VKORC1 gene was selected over CYP2C9 and CYP4F2 genes when analysing the impact of PGx testing on warfarin, because VKORC1 gene aberrant variants account for a higher percentage of variation in warfarin dosing (30% vs 18% and 11% respectively) (Johnson et al., 2017) and occur more frequently in European populations compared to CYP2C9 and CYP4F2 (Shendre et al., 2018).

3.1.3 Classifying 'actionability' of therapeutic recommendations

CPIC and DPWG guidelines were reviewed for each selected DGI and therapeutic recommendations were labelled in a standard format as seen in Table 3-1.Where differences between CPIC and DPWG therapeutic recommendations occurred , (Bank et al., 2018b) both recommendations were considered and estimates for the overall impact were recorded as a range to reflect this. Additionally, both sets of guidelines were checked to see whether the therapeutic recommendations were dependent on specific patient factors, or concomitant medications.

Table 3-1 Therapeutic recommendations assigned ‘direct action’, ‘indirect action’ and ‘no action’.

	Direct Action	Indirect action	No action
Therapeutic Recommendation	Lower dose required at start therapy	Observe status of patient carefully	
	Higher dose required at start therapy	Optional lower dose required at start therapy	
	Switch to alternate drug at start therapy	Optional higher dose required at start therapy	
		Optional switch at start therapy	
		Guard against maximum dose	

3.1.4 Estimating number of new medicines with drug-gene interactions initiated in UK primary care

Total volumes of prescriptions for PGx drugs dispensed in primary care between 01.01.2019 and 31.12.2019 were extracted from national databases (HSC Business Services Organisation, 2020, NHS Wales, 2020, Public Health Scotland, 2020, OpenPrescribing.net, 2020). Dispensing patterns in a large UK pharmacy chain database were then analysed to estimate the proportion of medicines newly initiated as part of the total annual dispensing volumes for medicines relevant to UK primary care. To calculate rates, total and newly dispensed volumes for all relevant PGx drugs between 01.01.2018 and 31.12.2018 were extracted from the dispensing database. Newly dispensed drug volumes were defined as drugs which were dispensed for the first time in 12 months to the patient.

To obtain national estimates of new prescriptions for relevant PGx drugs, these proportions were applied to total primary care dispensing volumes between 01.01.2019 and 31.12.2019 for England, Scotland, Northern Ireland and Wales.

3.1.5 Estimating frequency of actionable phenotypes for relevant medicines initiated in UK primary care

Phenotypic frequency data for genes responsible for the most relevant drug-gene interactions were sought. For 6 genes (CYP2C9, CYP2C19, CYP2D6, SLCO1B1, TPMT, and VKORC1) and 3 genetic variants (HLA-B*57:01, HLA-B*15:02, and factor V Leiden) phenotypic data was obtained from an anonymised pool of 879 patients at the University of Liverpool, UK, as part of the "Preemptive Pharmacogenomic Testing for Preventing Adverse Drug Reactions" (PREPARE) study (Clinical trial.gov identifier: NCT03093818). The genetic test results for CYP2D6, CYP2C19, SCLO1B1, TPMT and VKORC1 were translated to actionable phenotypes (intermediate, poor, or ultra-rapid metaboliser) using DPWG guidelines (van der Wouden et al., 2017) . For the gene CYP2C19, haplotype was translated to phenotype (intermediate [activity score 1], intermediate [activity score 1.5], poor metaboliser), using CPIC guidelines to support application of therapeutic recommendation for non-steroidal anti-inflammatories (Theken et al., 2020) . (See Appendix 3) Phenotype frequencies for HLA-A*31:01, HLA-B*15:02 and HLA-B*58:01 were calculated using ethnicity incidence frequency tables (Barbarino et al., 2018) matched to UK census data 2011 similar to the methodology described by Fan and Bousman. 2019 (Fan and Bousman, 2020). (Appendix 4 contains estimates for UK phenotype incidence used in this study).

3.1.6 Estimating Impact

To estimate the potential impact of PGx testing on drugs newly initiated in the UK, the estimated newly initiated prescription volumes of relevant PGx drugs were multiplied by the percentage incidence of different actionable phenotypes to obtain estimates for prescription volumes of PGx drugs dispensed nationally that require a change in prescribing or monitoring.

3.7 Results

3.7.1 Identification of relevant pharmacogenomic drugs to UK primary care

A total of 56 drugs with 56 unique DGIs were included in the study. Figure 3-1 is a flowchart representing the selection process for medicines included in the study

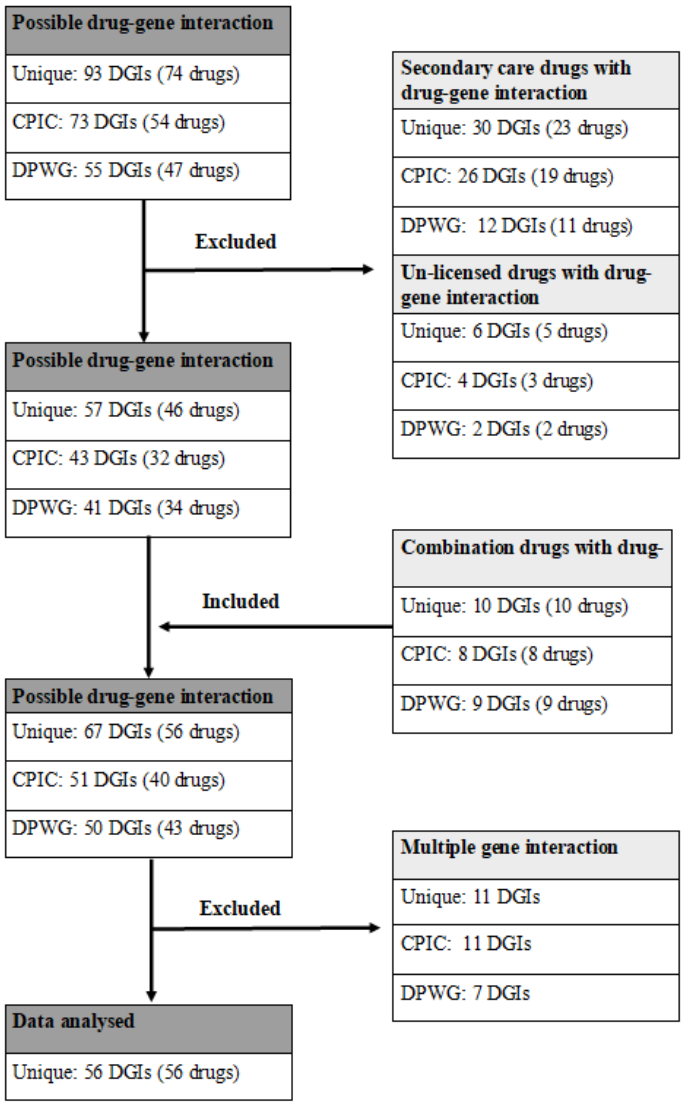


Figure 3-1 Drug-gene interactions (DGIs) included in study. Flowchart of DGIs and drugs selection process using Clinical Pharmacogenetics Implementation Consortium (CPIC) and Dutch Pharmacogenetics Working Group (DPWG) guidelines

3.7.2 Overall UK results

There were 27,411,287 estimated new prescriptions for 56 PGx drugs in 2019. (England: 22,264,390 items, Scotland 2,416,941 items, Wales 1,753,062 items, Northern Ireland 976,894 items). Table 3-2 shows the overall estimated newly initiated prescription volumes for 56 PGx drugs dispensed by community pharmacies in 2019. Table 3-3 shows a breakdown of UK drug volumes per actionable phenotype for each drug with published CPIC and or DPWG guidelines relevant to UK primary care. The full breakdown of drug volumes for each of the devolved nations is available in Appendix 5. Table 3-4 shows a breakdown of the estimated volume ranges of prescriptions dispensed in UK primary care in 2019 that require either direct or indirect action. Table 3-4 shows that between 5,233,353 to 5,780,595 of these prescriptions had an actionable therapeutic recommendation according to CPIC and/or DPWG guidelines. The variation in the two figures reflects the difference in actionability of prescribing recommendations between CPIC and DPWG.

Based on the data presented in this study, roughly one in five new prescriptions for one of these 56 PGx drugs newly initiated in the community requires a therapeutic intervention. These numbers are derived by dividing the lowest and highest estimates for volumes of prescriptions with actionable PGx recommendations by the estimated total volume of these prescriptions newly initiated annually in UK primary [5,233,353/27,411,287 and 5,780,595/27,411,287].

Should all patients in the UK with a new prescription for this selection of drugs have been pre-emptively genotyped for 9 genes (CYP2C19, CYP2C9, CYP2D6, F5,HLA-A, HLA-B, SLCO1B1, TPMT, VKORC1), then one in every eleven new prescriptions could be adjusted based on the genetic result. This frequency is the same across England, Northern Ireland, Scotland and Wales.

3.7.3 Frequency of exposure to pharmacogenomic drugs by therapeutic group

Table 3-5 shows the distribution of newly initiated PGx drugs dispensed in the UK in 2019 by therapeutic group. The PGx drugs with therapeutic recommendations (n=5,780,595) dispensed to UK patients in the largest volumes were for weak opioids (47.9%, n=2,766,128), antidepressants (30.9%, n=1,783,362) and proton pump inhibitors (5.7%, n=329,300).

For those medicines with a therapeutic recommendation requiring 'direct action' (n=2,500,283), the top three drug classes were the same but in a different order; antidepressant (49.5%, n=1,236,804), weak opioid (15.4%, n=385,638), proton pump inhibitors (13.1%, n=327,491).

3.7.4 Frequency of exposure to pharmacogenetic drugs by gene

Table 3-6 and 3-7 shows the distribution of newly initiated PGx drugs dispensed in the UK in 2019 by gene. Of the estimated 5,780,595 medicines with a therapeutic recommendation, four genes accounted for 95.8% of all DGI. 68.3% CYP2D6 (n=3,950,129), 20.1% CYP2C19 (n=1,159,040), 3.8% HLA-B (n=222,199) and 3.6% SLCO1B1 (n=208,462).

Of the estimated 2,500,283 prescription items dispensed in the UK with a recommendation for 'direct action', 61.3% (n=1,531,923) were affected by the CYP2D6, 25.0% (n=624,298) were CYP2C19 and 8.3% (n=208,462) were affected by the SLCO1B1 gene.

3.7.5 Frequency of exposure to pharmacogenetic drugs by age

Table 3-8 shows the age distribution of patients exposed to a PGx drug in 2018. Of the 4,439,352 patients in the community pharmacy database newly dispensed one of 56 PGx drugs, 61.9% (n=2,746,113) were between the ages 19-59. In those aged 0-18 years, exposure to an anti-infective PGx drug was most common (34.4%), whilst those aged between 19-49 years were more likely to be exposed to

antidepressants with a DGI. In age groups 50-115 years, exposure to proton pump inhibitors and analgesia were the most common sources for PGx exposure.

Table 3-2 Estimate of annual volume of PGx drugs newly initiated in UK primary care.

Drug	Estimate of volumes of PGx medicines newly initiated in primary care (2019)				
	England	Scotland	Wales	Northern Ireland	UK (total)
Acenocoumarol	1,107	26	27	5	1,165
Allopurinol	280,391	22,658	24,466	7,190	334,705
Amitriptylline	1,456,603	136,070	113,825	55,169	1,761,667
Ampicillin_flucloxacillin	4,663	243	64	94	5,064
Aripiprazole	90,819	5,680	7,215	2,643	106,357
Atomoxetine	12,830	1,417	968	829	16,044
Atorvastatin with concomitant CYP inhibitors	102,695	5,070	6,248	2,897	116,910
Azathioprine	43,786	5,547	2,939	1,801	54,073
Carbamazepine	93,188	8,277	6,371	3,252	111,088
Celecoxib	41,410	7,904	2,087	3,957	55,358
Citalopram	1,306,405	101,452	120,505	49,224	1,577,586
Clomipramine	14,210	2,139	1,193	484	18,026
Clopidogrel	462,092	40,163	30,422	11,663	544,340
Codeine	1,147,510	50,040	45,913	17,054	1,260,517

Table 3-2. Estimate of annual volume of PGx drugs newly initiated in UK primary care (continued).

Drug	Estimate of volumes of PGx medicines newly initiated in primary care (2019)				
	England	Scotland	Wales	Northern Ireland	UK (total)
Codeine_aspirin	72	9	5	2	88
Codeine_paracetamol	2,551,074	465,019	307,277	211,929	3,535,299
Codeine_ibuprofen	99	17	4	8	128
Codeine_paracetamol_buclizine	730	2,991	385	259	4,365
Codeine_paracetamol_caffeine	490	0	31	2	523
Doxepin	1,056	220	70	50	1,396
Escitalopram	154,094	9,115	4,773	11,362	179,344
Estrogen_contraceptives	1,316,077	132,871	64,667	57,844	1,571,459
Flecainide	25,056	1,522	1,772	380	28,730
Flucloxacillin	2,842,764	323,869	198,383	96,471	3,461,487
Flurbiprofen	0	70	45	38	153
Fluvoxamine	1,571	128	92	54	1,845
Haloperidol	56,980	4,523	3,727	2,326	67,556

Table 3-2. Estimate of annual volume of PGx drugs newly initiated in UK primary care (continued).

Drug	Estimate of volumes of PGx medicines newly initiated in primary care (2019)				
	England	Scotland	Wales	Northern Ireland	UK (total)
Ibuprofen	584,337	169,678	78,355	41,800	874,170
Ibuprofen_paracetamol	110	0	1	1	112
Imipramine	12,530	2,046	618	285	15,479
Lamotrigine	120,310	11,409	7,847	4,726	144,292
Lansoprazole	2,130,638	126,705	136,903	57,234	2,451,480
Meloxicam	69,546	9,345	4,278	4,425	87,594
Mercaptopurine	4,776	813	331	190	6,110
Metoprolol	17,253	1,532	830	461	20,076
Nortriptylline	80,164	9,632	3,288	1,955	95,039
Omeprazole	3,211,202	364,505	260,405	128,861	3,964,973
Ondansetron	81,088	10,221	4,616	10,181	106,106
Oxcarbazepine	5,005	342	225	88	5,660
Pantoprazole	99,827	4,468	4,922	9,217	118,434

Table 3-2. Estimate of annual volume of PGx drugs newly initiated in UK primary care (continued).

Drug	Estimate of volumes of PGx medicines newly initiated in primary care (2019)				
	England	Scotland	Wales	Northern Ireland	UK (total)
Paroxetine	74,841	6,949	7,348	2,400	91,538
Phenytoin	13,801	1,088	831	262	15,982
Piroxicam	1,758	201	93	244	2,296
Sertraline	2,094,199	170,666	173,404	93,388	2,531,657
Simvastatin	508,662	52,615	42,996	13,184	617,457
Simvastatin_ezetimibe	555	21	18	38	632
Simvastatin_fenofibrate	16	5	0	6	27
Tamoxifen	42,740	4,213	2,784	1,321	51,058
Tenoxicam	28	8	2	2	40
Tramadol	666,669	100,900	43,281	40,733	851,583
Tramadol_paracetamol	6,208	325	678	1,193	8,404
Trimipramine	887	61	59	25	1,032
Venlafaxine	289,694	30,099	22,516	24,245	366,554

Table 3-2. Estimate of annual volume of PGx drugs newly initiated in UK primary care (continued).

Drug	Estimate of volumes of PGx medicines newly initiated in primary care (2019)				
	England	Scotland	Wales	Northern Ireland	UK (total)
Voriconazole	137	54	28	2	221
Warfarin	132,250	11,423	12,554	3,194	159,421
Zuclopenthixol	7,387	577	377	246	8,587
Total	**22,264,390**	**2,416,941**	**1,753,062**	**976,894**	**27,411,287**

Table 3-3 Overview of the inferred drug-gene interactions among 56 PGx drugs with CPIC and/or DPWG guidelines, relevant to UK primary care

Drug	Phenotype	Estimated no. of drugs dispensed in UK (2019)	Recommendation	Ref Guideline
CYP2C19				
Citalopram	EM	1,038,547	No action	Both
	IM	415,060	Guard maximum daily dose	DPWG*
	PM	44,920	Lower dose required at start therapy	CPIC*
	UM	79,059	Switch to alternate drug at start therapy	CPIC*
Clopidogrel	EM	358,346	No action	Both
	IM	143,215	Switch to alternate drug at start therapy	Both
	PM	15,500	Switch to alternate drug at start therapy	Both
	UM	27,279	No action	Both
Escitalopram	EM	118,064	No action	Both
	IM	47,185	Guard maximum daily dose	DPWG*
	PM	5,108	Lower dose required at start therapy	CPIC*
	UM	8,987	Switch to alternate drug at start therapy	Both

Drug	Phenotype	Estimated no. of drugs dispensed in UK (2019)	Recommendation	Ref Guideline
CYP2C19				
Escitalopram	IM	644,979	No action	DPWG
	PM	69,803	No action	DPWG
	UM	122,854	Higher dose required at start therapy	DPWG
Omeprazole	EM	2,610,197	No action	DPWG
	IM	1,043,177	No action	DPWG
	PM	112,898	No action	DPWG
	UM	198,701	Higher dose required at start therapy	DPWG
Pantoprazole	EM	77,967	No action	DPWG
	IM	31,160	No action	DPWG
	PM	3,371	No action	DPWG
	UM	5,936	Higher dose required at start therapy	DPWG
Sertraline	EM	1,666,627	No action	Both
	IM	666,073	No action	Both
	PM	72,086	Guard maximum daily dose	DPWG
	UM	126,871	No action	Both

Drug	Phenotype	Estimated no. of drugs dispensed in UK (2019)	Recommendation	Ref Guideline
CYP2C19				
Trimipramine	EM	679	No action	CPIC
	IM	272	Optional lower dose required at start therapy	CPIC
	UM	51	Optional switch to alternate drug at start therapy	CPIC
	PM	30	Optional switch to alternate drug at start therapy	CPIC
Voriconazole	EM	145	No action	Both
	IM	58	Observe status of patient carefully	DPWG*
	PM	7	Switch to alternate drug at start therapy	CPIC
	UM	11	Switch to alternate drug at start therapy	CPIC
CYP2C9				
Celecoxib	EM	36,423	No action	CPIC
	IM (AS=1.5)	11,135	No action	CPIC
	IM (AS=1.0)	6,605	Optional lower dose required at start therapy	CPIC
	PM	1,195	Lower dose required at start therapy	CPIC
Flurbiprofen	EM	100	No action	CPIC
	IM (AS=1.5)	31	No action	CPIC

Drug	Phenotype	Estimated no. of drugs dispensed in UK (2019)	Recommendation	Ref Guideline
CYP2C9				
Flurbiprofen	IM (AS=1.0)	18	Optional lower dose required at start therapy	CPIC
	PM	4	Lower dose required at start therapy	CPIC
Ibuprofen	EM	575,163	No action	CPIC
	IM (AS=1.5)	175,827	No action	CPIC
	IM (AS=1.0)	104,305	Optional lower dose required at start therapy	CPIC
	PM	18,875	Lower dose required at start therapy	CPIC
Ibuprofen_ paracetamol	EM	75	No action	CPIC
	IM (AS=1.5)	22	No action	CPIC
	IM (AS=1.0)	13	Optional lower dose required at start therapy	CPIC
	PM	2	Lower dose required at start therapy	CPIC
Meloxicam	EM	57,633	No action	CPIC
	IM (AS=1.5)	17,618	No action	CPIC
	IM (AS=1.0)	10,451	Lower dose required start therapy	CPIC
	PM	1,892	Switch to alternate drug at start therapy	CPIC

Drug	Phenotype	Estimated no. of drugs dispensed in UK (2019)	Recommendation	Ref Guideline
CYP2C9				
Meloxicam	IM (AS=1.5)	3,215	Lower dose required at start therapy	CPIC
	IM (AS=1.0)	1,907	Lower dose required at start therapy	CPIC
	PM	345	Lower dose required at start therapy	CPIC
Piroxicam	EM	1,511	No action	CPIC
	IM (AS=1.5)	462	No action	CPIC
	IM (AS=1.0)	274	Switch to alternate drug at start therapy	CPIC
	PM	49	Switch to alternate drug at start therapy	CPIC
Tenoxicam	EM	27	No action	CPIC
	IM (AS=1.5)	8	No action	CPIC
	IM (AS=1.0)	4	Optional switch at start therapy	CPIC
	PM	1	Optional switch at start therapy	CPIC
Amitriptylline	EM	900,854	No action	Both
	IM	724,686	Lower dose at start therapy	Both
	PM	106,100	Switch to alternate drug at start therapy	CPIC
	UM	30,027	Switch to alternate drug at start therapy	CPIC

Drug	Phenotype	Estimated no. of drugs dispensed in UK (2019)	Recommendation	Ref Guideline
CYP2D6				
Aripiprazole	EM	54,386	No action	DPWG
	IM	43,752	No action	DPWG
	PM	6,406	Guard maximum daily dose	DPWG
	UM	1,813	No action	DPWG
Atomoxetine	EM	8,204	No action	Both
	IM	6,600	Observe status of patient carefully	Both
	PM	966	Observe status of patient carefully	Both
	UM	274	Observe status of patient carefully	Both
Clomipramine	EM	9,219	No action	Both
	IM	7,415	Lower dose at start therapy	DPWG*
	PM	1,086	Lower dose at start therapy	DPWG*
	UM	306	Higher dose required at start therapy	DPWG*
Codeine	EM	644,582	No action	Both
	IM	518,531	Observe status of patient carefully	Both
Drug	**Phenotype**	**Estimated no. of**	**Recommendation**	**Ref Guideline**

		drugs dispensed in UK (2019)		
CYP2D6				
Codeine	PM	75,917	Switch to alternate drug at start therapy	Both
	UM	21,487	Switch to alternate drug at start therapy	Both
Codeine_ aspirin	EM	45	No action	Both
	IM	37	Observe status of patient carefully	Both
	PM	5	Switch to alternate drug at start therapy	Both
	UM	1	Switch to alternate drug at start therapy	CPIC*
Codeine_ ibuprofen	EM	66	No action	Both
	IM	53	Observe status of patient carefully	Both
	PM	7	Switch to alternate drug at start therapy	Both
	UM	2	Switch to alternate drug at start therapy	Both
Codeine_ paracetamol	EM	1,807,824	No action	Both
	IM	1,454,294	Observe status of patient carefully	Both
	PM	212,921	Switch to alternate drug at start therapy	Both
	UM	60,260	Switch to alternate drug at start therapy	Both
Drug	**Phenotype**	**Estimated no. of drugs dispensed**	**Recommendation**	**Ref Guideline**

		in UK (2019)		
CYP2D6				
Codeine_ paracetamol_ buclizine	EM	2,233	No action	Both
	IM	1,795	Observe status of patient carefully	Both
	PM	263	Switch to alternate drug at start therapy	Both
	UM	74	Switch to alternate drug at start therapy	CPIC*
Codeine_ paracetamol_ caffeine	EM	266	No action	Both
	IM	216	Observe status of patient carefully	Both
	PM	32	Switch to alternate drug at start therapy	Both
	UM	9	Switch to alternate drug at start therapy	CPIC*
Doxepin	EM	713	No action	Both
	IM	575	Lower dose required at start therapy	DPWG*
	PM	84	Lower dose required at start therapy	DPWG*
	UM	24	Higher dose required at start therapy	DPWG*
Drug	**Phenotype**	**Estimated no. of drugs dispensed**	**Recommendation**	**Ref Guideline**

		in UK (2019)		
CYP2D6				
Flecainide	EM	14,692	No action	DPWG
	IM	11,818	Lower dose required at start therapy	DPWG
	PM	1,731	Lower dose required at start therapy	DPWG
	UM	489	Observe status of patient carefully	DPWG
Fluvoxamine	EM	942	No action	
	IM	759	No action	Both
	PM	112	Optional lower dose required at start therapy	CPIC
	UM	32	No action	Both
Haloperidol	EM	34,545	No action	DPWG
	IM	27,791	No action	DPWG
	PM	4,068	Lower dose required at start therapy	DPWG
	UM	1,152	Observe status of patient carefully	DPWG
Imipramine	EM	7,915	No action	DPWG
	IM	6,367	Lower dose required at start therapy	DPWG
Drug	**Phenotype**	**Estimated no. of drugs dispensed**	**Recommendation**	**Ref Guideline**

		in UK (2019)		
CYP2D6				
Imipramine	PM	932	Lower dose required at start therapy	DPWG
	UM	265	Higher dose required at start therapy	DPWG
Metoprolol	EM	10,267	No action	DPWG
	IM	8,258	Guard maximum daily dose	DPWG
	PM	1,209	Guard maximum daily dose	DPWG
	UM	342	Observe status patient carefully	DPWG
Nortriptyline	EM	48,600	No action	Both
	IM	39,096	Lower dose required at start therapy	Both
	PM	5,724	Switch to alternate drug at start therapy	CPIC
	UM	1,619	Switch to alternate drug at start therapy	CPIC
Ondansetron	EM	54,257	No action	CPIC
	IM	43,649	No action	CPIC
	PM	6,391	No action	CPIC
	UM	1,809	Switch to alternate drug at start therapy	CPIC
Drug	**Phenotype**	**Estimated no. of drugs dispensed**	**Recommendation**	**Ref Guideline**

		in UK (2019)		
CYP2D6				
Paroxetine	EM	46,808	No action	Both
	IM	37,656	No action	Both
	PM	5,514	Optional switch to alternate drug at start therapy	CPIC
	UM	1,560	Switch to alternate drug at start therapy	Both
Tamoxifen	EM	26,108	No action	Both
	IM	21,003	Switch to alternate drug at start therapy	Both
	PM	3,076	Switch to alternate drug at start therapy	Both
	UM	871	No action	Both
Tramadol	EM	435,468	No action	DPWG
	IM	350,310	Observe status of patient carefully	DPWG
	PM	51,289	Observe status of patient carefully	DPWG
	UM	14,516	Switch to alternative	DPWG
Tramadol_ paracetamol	EM	4,295	No action	DPWG
Drug	**Phenotype**	**Estimated no. of drugs dispensed**	**Recommendation**	**Ref Guideline**

		in UK (2019)		
CYP2D6				
Tramadol_ paracetamol	IM	3,458	Observe status of patient carefully	DPWG
	PM	507	Observe status of patient carefully	DPWG
	UM	144	Switch to alternative	DPWG
Venlafaxine	EM	187,442	No action	DPWG
	IM	150,788	Switch to alternate drug at start therapy	DPWG
	PM	22,076	Switch to alternate drug at start therapy	DPWG
	UM	6,248	Observe status of patient carefully	DPWG
Zuclopenthixol	EM	4,391	No action	DPWG
	IM	3,532	Lower dose required at start therapy	DPWG
	PM	518	Lower dose required at start therapy	DPWG
	UM	146	Observe status of patient carefully	DPWG
Factor V Leiden				
Estrogen_ contraceptives	Negative	1,507,391	No action	DPWG
	Positive	64,068	Switch to alternate drug at start therapy	DPWG
Drug	**Phenotype**	**Estimated no. of drugs dispensed**	**Recommendation**	**Ref Guideline**

		in UK (2019)		
HLA-A				
Carbamazepine	HLA-A*31:01 Negative	108,175	No action	CPIC
	HLA-A*31:01 Positive	2,913	Switch to alternate drug at start therapy	CPIC
HLA-B				
Allopurinol	HLA-B*58:01 Negative	329,397	No action	CPIC
	HLA-B*58:01 Positive	5,308	Switch to alternate drug at start therapy	CPIC
Ampicillin_	HLA-B*57:01 Negative	4,748	No action	DPWG
flucloxacillin	HLA-B*57:01 Positive	316	Observe status of patient carefully	DPWG
Flucloxacillin	HLA-B*57:01 Negative	3,245,385	No action	DPWG
	HLA-B*57:01 Positive	216,102	Observe status of patient carefully	DPWG
Lamotrigine	HLA-B*15:02 Negative	143,837	No action	DPWG
	HLA-B*15:02 Positive	455	Switch to alternate drug at start therapy	DPWG (
Oxcarbazepine	HLA-B*15:02 Negative	5,642	No action	CPIC
	HLA-B*15:02 Positive	18	Switch to alternate drug at start therapy	CPIC
Drug	**Phenotype**	**Estimated no. of drugs dispensed**	**Recommendation**	**Ref Guideline**

		in UK (2019)		
SLCO1B1				
Atorvastatin with concomitant CYP inhibitor	NT (521TT)	83,753	No action	DPWG
	NT (521TT)	83,753	No action	DPWG
	PT (521TC)	31,043	Switch to alternate drug at start therapy	DPWG
	PT (521CC)	2,114	Switch to alternate drug at start therapy	DPWG
Simvastatin	NT (521TT)	442,338	No action	CPIC
	PT (521TC)	163,957	Switch to alternative	CPIC
	PT (521CC)	11,162	Switch to alternative	CPIC
Simvastatin_ ezetimibe	NT (521TT)	453	No action	CPIC
	PT (521TC)	168	Switch to alternative	CPIC
	PT (521CC)	11	Switch to alternative	CPIC
Simvastatin_ fenofibrate	NT (521TT)	20	No action	CPIC
	PT (521TC)	7	Switch to alternative	CPIC
	PT (521CC)	0	Switch to alternative	CPIC
Drug	**Phenotype**	**Estimated no. of drugs dispensed**	**Recommendation**	**Ref Guideline**

		in UK (2019)		
TPMT				
Azathioprine	EM	49,101	No action	Both
	IM	4,911	Lower dose required at start therapy	Both
	PM	61	Switch to alternate drug at start therapy	Both
Mercaptopurine	EM	5,549	No action	Both
	IM	555	Lower dose required at start therapy	Both
	PM	6	Switch to alternate drug at start therapy	Both
VK0RC1				
Acenocoumarol	NS (1173CC/1639GG)	476	No action	DPWG
	NS (1173CT/-1639GA)	550	No action	DPWG
	HS (1173TT/-1639AA)	139	Lower dose required at start therapy	DPWG
Warfarin	NS (1173CC/ 1639GG)	65,176	No action	Both
	NS (1173CT/-1639GA)	75,288	No action	Both
	HS (1173TT/-1639AA)	18,957	Lower dose required at start therapy	Both

Table 3-4 Estimation for prescription volumes of primary care medicines in 2019 with CPIC and/or DPWG therapeutic recommendations.

	Volume of prescriptions with CPIC and/or DPWG guidelines dispensed in UK primary care 2019	
	Highest estimation	**Lowest estimation**
Direct action	2,500,283	2,354,058
Higher dose required at start therapy	328,086	327,491
Lower dose required at start therapy	912,492	846,005
Switch to alternate drug at start therapy	1,259,705	1,180,562
Indirect action	3,280,166	2,879,465
Guard maximum daily dose	550,204	137,987
Observe status of patient carefully	2,613,125	2,613,037
Optional lower dose required at start therapy	119,241	111,325
Optional switch drug at start therapy	5,595	1,697

Table 3-5 Distribution of newly initiated PGx drugs dispensed in the UK in 2019 by therapeutic group.

Therapeutic Class	Total volume of PGx drugs newly dispensed in UK		Total volume of PGx drugs with an 'actionable' therapeutic recommendation dispensed in UK		Total volume of PGx drugs with direct action therapeutic recommendation dispensed in UK	
	n	%	n	%	n	%
Analgesic	**6,680,630**	**24.4%**	**2,909,816**	**50.3%**	**418,380**	**16.7%**
NSAIDs	1,019,723	3.7%	143,688	2.5%	32,742	1.3%
Weak opioids	5,660,907	20.7%	2,766,128	47.9%	385,638	15.4%
Cardiovascular	**1,488,758**	**5.4%**	**410,120**	**7.1%**	**399,822**	**16.0%**
Antiarrhythmic	28,730	0.1%	14,038	0.2%	13,549	0.5%
Anticoagulant	160,586	0.6%	19,096	0.3%	19,096	0.8%
Antiplatelet	544,340	2.0%	158,715	2.7%	158,715	6.3%
Beta Blocker	20,076	0.1%	9,809	0.2%	0	0.0%
Statin	735,026	2.7%	208,462	3.6%	208,462	8.3%
Endocrinology	**1,571,459**	**5.7%**	**64,068**	**1.1%**	**64,068**	**2.6%**
Estrogenic contraceptive	1,571,459	5.7%	64,068	1.1%	64,068	2.6%
Gastrointestinal	**6,640,993**	**24.2%**	**329,300**	**5.7%**	**329,300**	**13.2%**
Antiemetic	106,106	0.4%	1,809	0.0%	1,809	0.1%
Proton pump inhibitor	6,534,887	23.8%	327,491	5.7%	327,491	13.1%
Immunosuppression	**60,183**	**0.2%**	**5,533**	**0.1%**	**5,533**	**0.2%**
Infections	**3,466,772**	**12.6%**	**216,494**	**3.7%**	**18**	**0.0%**
Antibiotic	3,466,551	12.6%	216,418	3.7%	0	0.0%
Antifungal	221	0.0%	76	0.0%	18	0.0%
Oncology	51,058	0.2%	**24,079**	**0.4%**	**24,079**	**1.0%**
Psychiatry/neurology	**7,116,729**	**26.0%**	**1,815,877**	**31.4%**	**1,253,775**	**50.1%**
Antidepressant	6,641,163	24.2%	1,783,362	30.9%	1,236,804	49.5%
Antiepileptic	277,022	1.0%	8,853	0.2%	8,853	0.4%
Antipsychotic	182,500	0.7%	15,822	0.3%	8,118	0.3%
Atomoxetine	16,044	0.1%	7,840	0.1%	0	0.0%

Table 3-5 Distribution of newly initiated PGx drugs dispensed in the UK in 2019 by therapeutic group (continued).

Therapeutic Class	Total volume of PGx drugs newly dispensed in UK		Total volume of PGx drugs with an 'actionable' therapeutic recommendation dispensed in UK		Total volume of PGx drugs with direct action therapeutic recommendation dispensed in UK	
Other	**334,705**	**1.2%**	**5,308**	**0.1%**	**5,308**	**0.2%**
Gout	334,705	1.2%	5,308	0.1%	5,308	0.2%
Total	**27,411,287**	**100.0%**	**5,780,595**	**100.0%**	**2,500,283**	**100.0%**

Table 3-6 Estimated volumes of medicines dispensed in 2019 with a CPIC and/or DPWG therapeutic guidelines recommending 'direct action'.

	England		Scotland		Wales		Northern Ireland		UK (Total)	
GENE	**DRUG VOLUME**	**(%)**	**DRUG VOLUME**	**(%)**	**DRUG VOLUME**	**(%)**	**DRUG VOLUME**	**(%)**	**DRUG VOLUME**	**(%)**
CYP2C19	522,225	25.5%	45,247	21.8%	38,875	24.3%	17,951	20.7%	624,298	25.0%
CYP2C9	28,281	1.4%	5,554	2.7%	2,637	1.6%	1,737	2.0%	38,209	1.5%
CYP2D6	1,240,041	60.6%	132,842	63.9%	99,592	62.2%	59,448	68.5%	1,531,923	61.3%
F5	53,657	2.6%	5,417	2.6%	2,636	1.6%	2,358	2.7%	64,068	2.6%
HLA-A	2,444	0.1%	217	0.1%	167	0.1%	85	0.1%	2,913	0.1%
HLA-B	4,842	0.2%	396	0.2%	414	0.3%	129	0.1%	5,781	0.2%
SLCO1B1	173,551	8.5%	16,367	7.9%	13,971	8.7%	4,573	5.3%	208,462	8.3%
TPMT	4,465	0.2%	585	0.3%	300	0.2%	183	0.2%	5,533	0.2%
VKORC1	15,858	0.8%	1,361	0.7%	1,496	0.9%	381	0.4%	19,096	0.8%
Total	**2,045,364**	**100.0%**	**207,986**	**100.0%**	**160,088**	**100.0%**	**86,845**	**100.0%**	**2,500,283**	**100.0%**

Table 3-7 Estimated volumes of medicines dispensed in 2019 with a CPIC and/or DPWG therapeutic recommendation.

	England		Northern Ireland		Scotland		Wales		UK (Total)	
GENE	DRUG VOLUME	(%)	DRUG VOLUME	(%)	DRUG VOLUME	(%)	DRUG VOLUME	(%)	DRUG VOLUME	(%)
CYP2C19	966,447	21.0%	36,560	15.7%	79,232	14.5%	76,801	19.8%	1,159,040	20.1%
CYP2C9	102,961	2.2%	7,202	3.1%	26,752	4.9%	12,240	3.2%	149,155	2.6%
CYP2D6	3,110,634	67.4%	174,928	75.3%	396,533	72.5%	268,034	69.0%	3,950,129	68.3%
F5	53,657	1.2%	2,358	1.0%	5,417	1.0%	2,636	0.7%	64,068	1.1%
HLA-A	2,444	0.1%	85	0.0%	217	0.0%	167	0.0%	2,913	0.1%
HLA-B	182,608	4.0%	6,158	2.6%	20,630	3.8%	12,803	3.3%	222,199	3.8%
SLCO1B1	173,551	3.8%	4,573	2.0%	16,367	3.0%	13,971	3.6%	208,462	3.6%
TPMT	4,465	0.1%	183	0.1%	585	0.1%	300	0.1%	5,533	0.1%
VKORC1	15,858	0.3%	381	0.2%	1,361	0.2%	1,496	0.4%	19,096	0.3%
Total	**4,612,625**	**100.0%**	**232,428**	**100.0%**	**547,094**	**100.0%**	**388,448**	**100.0%**	**5,780,595**	**100.0%**

Table 3-8 Age distribution of 4,439,352 patients in the community pharmacy database newly dispensed one or more of the selected 56 PGx drugs in 2018.

	Therapeutic class											
Age (years)	**Analgesia**	**Anti-infective**	**Cardiovascular**	**Antidepressant**	**Antipsychotic**	**Epilepsy**	**CNS- other**	**Contraceptive**	**Gastro-intestinal**	**Other**	**Total**	**Most common PGx drug group exposure**
<18	25.3%	34.4%	0.1%	9.5%	0.6%	0.6%	0.8%	18.7%	9.8%	0.2%	100.0%	Anti-infective
19-29	13.5%	12.0%	0.2%	31.3%	0.6%	0.9%	0.1%	26.9%	13.0%	1.5%	100.0%	Antidepressant
30-39	20.5%	12.1%	0.7%	29.8%	0.6%	0.8%	0.1%	12.6%	19.4%	3.3%	100.0%	Antidepressant
40-49	24.5%	10.9%	2.5%	28.8%	0.6%	0.7%	0.0%	2.7%	24.6%	4.7%	100.0%	Antidepressant
50-59	25.7%	10.2%	5.7%	24.1%	0.4%	0.5%	0.0%	0.1%	27.8%	5.4%	100.0%	Gastrointestinal
60-69	27.5%	10.2%	9.9%	17.0%	0.4%	0.4%	0.0%	0.0%	28.8%	5.7%	100.0%	Gastrointestinal
70-79	27.9%	11.4%	13.5%	13.9%	0.5%	0.4%	0.0%	0.0%	26.8%	5.5%	100.0%	Analgesia
80-89	27.7%	13.5%	15.4%	12.8%	1.0%	0.4%	0.0%	0.0%	24.5%	4.7%	100.0%	Analgesia
90-99	24.7%	16.8%	15.4%	12.2%	2.2%	0.3%	0.0%	0.0%	24.9%	3.4%	100.0%	Gastrointestinal
100-115	24.2%	20.7%	10.5%	10.5%	5.6%	0.3%	0.1%	0.4%	25.9%	1.8%	100.0%	Gastrointestinal

3.8 Discussion

This study addresses a key gap in the existing evidence base for the impact of pharmacogenomic testing in UK primary care by estimating the extent to which current prescribing could be optimised through multi-drug pharmacogenomic testing. Moreover, the study is strengthened by its quantification of potential direct and indirect prescribing interventions and, subsequent categorisation of recommendations by the two most prominent pharmacogenomic organisations. Together with existing literature describing the extent to which drug-gene interactions occur in UK primary care (Kimpton et al., 2019), and the most prominent gene variants underpinning these interactions, an indication of the need for and scope of a genetic testing panel comprising a multi-drug pharmacogenomic testing intervention is provided.

3.8.1 Main findings

The main findings demonstrate the high impact PGx testing could have on medicines prescribed across primary care in the UK. Based on the frequencies of actionable phenotypes for 6 genes from 879 patients and the estimated actionable phenotypes for 3 genetic variants from ethnicity census data, it is inferred that between 19.1% and 21.1% of the first prescriptions for these 56 PGx drugs would have an actionable DGI requiring direct or indirect intervention. If the UK population were pre-emptively tested for this panel of genes, then an estimated 8.6% to 9.2% of the first prescriptions for these 56 PGx drugs would require a direct intervention as per CPIC and/or DPWG guidelines.

The most common newly initiated PGx drugs with an actionable DGI were for weak opioids like codeine and tramadol, antidepressants and proton pump inhibitors. Four genes (CYP2D6, CYP2C19, HLA-B and SCLO1B1) accounted for 95.8% of all drugs initiated with an actionable DGI. Age demographics within a community pharmacy database suggest the type of PGx drug exposure changes with age. Patients under 50 years were more likely to be exposed to antidepressants and

anti-infectives with DGIs. In the over 50s, PGx exposure was more frequently attributed to gastrointestinal and analgesic medicines.

Using the community pharmacy database as reference, the number of unique patients newly dispensed at least one of the 56 PGx drugs selected in one year were identified. These numbers were extrapolated for the national prescription volumes to estimate between 3,741,848 patients and 4,133,126 patients annually in primary care could potentially benefit for PGx testing.

3.8.2 Comparison with other studies

The finding of this study that UK patients are frequently exposed to pharmacogenomic drugs in primary care is supported by recent studies from England and the Netherlands. Bank and colleagues in the Netherlands (Bank et al., 2019) investigated the prescribing of 45 drugs with a DPWG guidelines in primary care. They found that 23.6% of all new prescriptions of these drugs had an actionable DGI, with 5.4% requiring direct intervention in the form of drug/dose adjustment.

The results of this study were similar but with a higher frequency of DGI occurrence requiring direct intervention (9.2% vs 5.4%). This is likely due to differences in methodology. The study methodology included more PGx drugs, 56 drugs versus 45 drugs, due to the inclusion of both CPIC and DPWG therapeutic recommendations. Currently, the UK has no organisation responsible for publishing PGx prescribing guidelines. As a result, inclusion of both CPIC and DPWG therapeutic recommendations provides the broadest interpretation of potential impact on UK prescribing patterns.

Kimpton and colleagues (Kimpton et al., 2019) investigated the exposure of 648,141 English primary care patients to 63 drugs over a 25-year period of time. They found that 3 genes (CYP2C19, CYP2D6 and SCLO1B1) accounted for >95% of the common PGx drugs dispensed. The results of this study when restricted to PGx drugs associated with ‘direct action’ showed similar results with the same three genes accounting for 94.6% of PGx drug dispensing. A broader analysis of the study data

set of all DGI with any actionable recommendation, shows 95.8% DGI are affected by four genes (CYP2C19, CYP2D6, SLCO1B1, HLA-B). A strength of this study was the inclusion of phenotype frequency data, therefore our analysis supports the assertion that testing for CYP2C19, CYP2D6, SCLO1B1 and HLA-B, provides the biggest opportunity to optimise medicines dispensed in primary care due to the high incidence of actionable DGI for these genes occurring in the population.

3.8.3 Implementation of pharmacogenomic testing in the UK

NHS England have recently announced plans to adopt a pre-emptive PGx testing strategy for drug-gene pairs with the most evidence of clinical and cost-effectiveness (NHS England, 2020). The aim is for patients in the next ten years to be tested for a panel of genes and genetic variants, and to have these results recorded in their medical records, for healthcare professionals to access across primary and secondary care (NHS England, 2020).

This study demonstrates that at a population level PGx testing has a large impact on the prescribing of medicines in UK primary care, with approximately 5,780,595 prescriptions for medicines dispensed annually having an actionable DGI according to CPIC and/or DPWG guidelines. Of these affected medicines, more than 95% of DGIs were due to variants in CYP2C19, CYP2D6, SCL01B1 and HLA-B genes. To date, little has been published on which genes will be tested by the NHS England pre-emptive PGx testing panel. The results of this study can inform the design of drug-gene panel underpinning a multi-drug pharmacogenomic testing intervention for evaluation and implementation.

3.8.4 Strengths and limitations

This study addresses a key gap in the existing evidence base for the potential impact of multi-drug pharmacogenomic testing by estimating quantitatively the volume of prescriptions for medicines dispensed in UK primary care where prescribing could be optimised by PGx testing. These findings could help support a nationwide multi-drug pharmacogenomic testing programme in primary care by highlighting the annual exposure of patients to the PGx drugs.

A strength of this study is the inclusion of PGx medicines with CPIC and/or DPWG evidence-based published prescribing guidelines. Since there are no UK based PGx prescribing guidelines, this approach allowed capture of the widest possible outcomes of PGx testing. Where differences occurred between 'actionability' of recommendation, e.g. one body recommended direct action whilst the other recommended non-direct action or no action, both scenarios were included in the analysis to produce a range of volumes for drugs affected by particular phenotypes, minimising bias. Additionally, inclusion of DGIs with published therapeutic recommendations allowed for a more granular analysis of the quantitative impact on prescribing nationally.

This study is the first to estimate impact of PGx testing using UK phenotype frequency data. A comparison of a recent study analysing frequency of actionable PGx phenotypes of 487,409 participants in the UK biobank, showed similar incidence of phenotypes for CYP2D6, CYP2C19, SCLO1B1, TPMT and VKORC1 as used in this study (McInnes et al., 2020). The frequencies for F5 and HLA-B*57:01, used in our study are also comparable to other published studies (Pherwani et al., 2003, Martin et al., 2014).

For HLA-A*31:01, HLA-B*15:02, HLA-B*58:01, frequency was calculated based on ethnicity data taken from the UK census and published phenotype incidence per ethnicity provided by PharmGKB. There are several limitations to this approach. Firstly, UK census ethnicity categories differ from CPIC biogeographical groups. Secondly, the most recently reported UK census data is from 2011 and is based on self-reported ethnicity. As a result, this approach may lead to over or underestimation of the incidence of these genetic variants in the UK population. However, collectively these three genetic variants only account for four of the 56 PGx drugs included in the study.

The method used in this study to estimate the volumes of PGx drugs newly initiated in primary care has some limitations. Due to the structure of how dispensing data in the UK are reported by individual countries, data on annual volumes of medicines dispensed which are newly initiated is absent. To overcome this challenge, a large community pharmacy dispensing database was analysed to calculate what

percentage of total medicines dispensed were newly initiated. To do this, an assumption was made that medicines first dispensed within a one year time frame in the community pharmacy database were newly initiated in primary care. This may be an overestimation as a patient's newly dispensed medicine could have been dispensed earlier by another pharmacy. However, targeting only medicines which have been newly initiated also has its limitations, since there are opportunities to optimise medicines even when they have already been started through PGx testing; for example, earlier identification of side effects or safe guarding against maximum dosing.

Additional sources of limitations to consider include the lack of patient clinical data in our dispensing data sets. For several drugs, there may an overestimation of effect as therapeutic recommendations are based on the combination of both genetic results and patient clinical factors. PGx drugs included in our analysis affected by these conditions include clopidogrel, omeprazole, lansoprazole, pantoprazole, and oral hormonal contraceptives.

Furthermore, the method used in this study included a single gene interaction for each drug. For ten of the 56 PGx drugs (amitriptyline, azathioprine, carbamazepine, clomipramine, doxepin, imipramine, mercaptopurine, phenytoin, trimipramine and warfarin) included in our analysis, additional DGIs were excluded. This methodology therefore likely gives a conservative estimate of the impact of PGx testing for these drugs and may underestimate the overall impact of PGx testing in UK primary care.

3.9 Summary

In conclusion this modelling study demonstrates a high incidence of actionable drug gene interactions occurring in UK primary care. A small number of genes account for the majority of PGx drugs issued annually with an actionable prescribing recommendation. These findings could support health economic modelling, by identifying drug-gene pairs for implementation prioritisation in primary care.

4. Chapter 4: A theory informed systematic review of barriers and enablers to implementing multi-drug pharmacogenetic testing

This chapter is derived from the following publication:

Youssef, E., Sharma, R., Wright, D., & Bhattacharya D. A theory informed systematic review of barriers and enablers to implementing multi-drug pharmacogenomic testing. 2022, *Journal of Personalized Medicine*.12,11, 1821.
https://doi.org/10.3390/jpm12111821

4.1 Introduction

This chapter focuses on a systematic review, conducted in line with the development stage of the UK MRC framework for complex interventions (Skivington et al., 2021). The study reported here sought to address gaps in the evidence base in order to inform the implementation strategy for pharmacogenomic testing in the UK, that can be widely adopted in the NHS and maintained in different real-world clinical settings.

As discussed in chapter 2, pharmacogenomic testing represents a complex intervention. These types of interventions present challenges for researchers looking to evaluate and develop strategies for adopting and sustaining implementation in clinical settings. For example, the current gold standard evaluation approach for healthcare interventions is a definitive randomised controlled trial which historically does not allow researchers to distinguish between the active and inactive intervention components (Skivington et al., 2021). Failure to collect empirical data with the aim to understand the mechanisms of change through which intervention components are implemented and exert their effect, impacts post-trial outcomes of the intervention and long-term sustained adoption in real-life settings.

An emerging concept in developing and evaluating complex interventions, is the use of psychological theory to improve understanding of behaviour change processes. Within the field of pharmacogenomic testing, a great deal of work has been published on identifying factors affecting the clinical implementation of pharmacogenomic testing. As outlined in Chapter 1, these include barriers like cost, clinical guidelines, time and education. What has been missing from the literature, is a behavioural lens to the pharmacogenomic testing implementation problem faced by researchers, and policy makers. The following systematic review was designed and conducted to address this gap in the literature and provide empirical data using a theoretical lens to progress the field of pharmacogenomic testing implementation.

4.2 Research design and methodology

4.2.1 Scoping search

An initial scoping review was carried using in part the methodological framework devised by Arksey and O'Malley (Arksey and O'Malley, 2005). The purpose of the scoping review, was to:

1) To examine extent, range and nature of research activity related to research question.
2) To determine the value of undertaking a full systematic review e.g. feasibility (does any literature exist?) or relevance (has a systematic review already been conducted?)
3) To inform the search strategy, methodology and scope of a systematic review.

The scoping search was carried out in July 2019 using search terms (Table 4-1) in the electronic databases Ovid EMBASE and MEDLINE, PsychInfo, CINAHL Complete, Business Info and a modified strategy in PubMed

Table 4-1 Search terms for scoping search

Database	Ovid Embase and Medline	PsychInfo	CINAHL complete	Business Info	PubMed
Search terms	['pharmacogenetic* OR pharmacogenomic* OR pharmacogenetic testing OR pharmacogenomic testing] **AND** [implement* OR Experience* OR Qualitative OR Interview OR Focus group OR Ethnograph* OR Observation OR survey OR questionnaire]"	"['pharmacogenetic* OR pharmacogenomic* OR pharmacogenetic testing OR pharmacogenomic testing] **AND** [implement* OR Experience* OR Qualitative OR Interview OR Focus group OR Ethnograph* OR Observation OR survey OR questionnaire]"	"['pharmacogenetic* OR pharmacogenomic* OR pharmacogenetic testing OR pharmacogenomic testing] **AND** [implement* OR Experience* OR Qualitative OR Interview OR Focus group OR Ethnograph* OR Observation OR survey OR questionnaire]"	'['pharmacogenetic* OR pharmacogenomic* OR pharmacogenetic testing OR pharmacogenomic testing] **AND** [implement* OR Experience* OR Qualitative OR Interview OR Focus group OR Ethnograph* OR Observation OR survey OR questionnaire]	Key authors **AND** pharmacogenetic* OR pharmacogenomic* OR pharmacogenetic testing OR pharmacogenomic testing

After combining all the results and removing duplicates 197 papers remained. Through screening titles 57 papers were identified, which decreased to 30 after abstract screening.

The scoping review identified that the number of studies which used traditional qualitative research methods such as interviews, focus groups and ethnographies was low (1 interview, 1 focus group). Instead, the search strategy picked up 18 commentaries, where the authors described the processes and challenges their institutes encountered in setting up PGx testing pathways. Whilst these papers did not employ traditionally accepted research methodologies, the accounts did provide data informed by the real-world experiences of PGx testing which was lacking in other published interviews and focus groups that focused on a hypothetical perspective of PGx testing.

Another finding of the scoping review was the heterogeneity to which the term 'PGx testing' was applied in the literature. Table 4-2 shows the diversity and scope of different genetic testing and reporting which were under the umbrella term of 'PGx tests'.

Table 4-2 Range of genetic testing technologies under the umbrella term 'PGx testing'.

PGx test	Example of test used in clinical practice
Germ-line (inherited DNA) testing	
Singe gene-single drug	HLA-A*31:01- Abacivir
Multi gene-single drug	CYP2D6, CYP4F2, VKORC1- Warfarin
Single gene-multi drug	CYP2D6- anti-depressants, anti-psychotics, beta-blockers, analgesia
Multi-gene-multi-drug	Panel PGx testing e.g. CYP2C19, CYP2D6, TPMT etc employed in U-PGx trial(Manson et al., 2017)

This helped identify the scope of the systematic review, which was to look exclusively at the barriers and enablers to multi-drug PGx testing. The rationale for this is using a PGx test to inform the prescribing of only one drug may exist in an entirely different context where testing can be offered as a companion diagnostic, potentially only

affecting the behaviour of the initiating clinician. In addition, pre-emptive panel testing a group of genes is likely to be the most cost-effective testing method for health care systems (Manson et al., 2017) and therefore it would be prudent to focus the review on this. Paediatric PGx testing was also excluded, as testing was often offered as part of cancer genetic testing which comes with different implications regarding consent and incidental finding when compared to PGx testing in the adult population.

4.2.2 Aims and objectives

4.2.2.1 Aims and scope of study

To systematically identify all barriers and enablers to the clinical implementation of pharmacogenomic (PGx) testing. In this review, 'PGx testing' refers to the testing of germline (inherited) genetic information that impacts a patient's response to multiple medicines. This type of PGx testing could be in the form of testing variants of multiple genes or a single gene that affects the drug response of multiple medicines.

4.2.2.2 Objectives

1. To describe all candidate behaviours of prescribers, pharmacists and patients that occur when multi-drug PGx testing is implemented.
2. To identify influences (barriers and enablers) on each of these candidate behaviours.
3. To compare influences (barriers and enablers) on each of these candidate behaviours in different settings (primary vs secondary care).
4. To organise reported influences (barriers and enablers) to candidate behaviours in terms of the Theoretical Domains Framework (TDF)

4.2.2.3 Literature Search Strategy

A systematic search was conducted to identify relevant published studies that described the barriers and facilitators to the implementation of multi-drug PGx testing in healthcare settings. The review followed the general principles of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green, 2008) and ENTREQ (Enhancing Transparency in Reporting the Synthesis of Qualitative Research (Tong et al., 2012). A protocol was developed and registered on the International Database of Prospectively Registered Systematic Reviews (PROSPERO) on 22nd September 2020. The review registration number is CRD42019150940. The protocol was developed by the thesis researcher (EY) under the guidance and assistance of the supervisory team David J Wright (DJW) and Debi Bhattacharya (DB). A copy of the study's protocol is provided in Appendix 6.

The following electronic databases were searched on 25th November 2019 and updated on 10th June 2022:

- MEDLINE (Ovid)®
- EMBASE (Ovid)®
- PubMed
- CINAHL (EBSCOhost)
- PsycInfo

The search strategy was grouped into three main concepts using the PICO tool shown in table 4-3. Search terms were developed in MEDLINE (Ovid)® and adapted for use in other databases using thesaurus terms and free-text terms. The full list of search terms used in each database is included in Appendix 7. Search results were limited by two filters: English language and publication type: journal.

Table 4-3 Search terms used in MEDLINE (Ovid)® organised around PICO concepts. ('P' AND 'I' AND 'O')

PICO header	Search terms (adapted for each database)
Population 'P'	Exp Patients [MeSH] OR Public.tw OR "service-user*".tw OR "service user*".tw OR consumer*.tw OR customer*
Intervention 'I'	Exp Pharmacogenomic testing [MeSH] OR "PGx".tw OR Pharmacogenomic*.tw OR Pharmacogenetic*.tw
Comparator 'C'	Not applicable
Outcome 'O'	Implementation.tw OR adoption.tw OR barrier*.tw OR enabler*.tw OR facilitator*.tw OR challenge*.tw OR opportunit*.tw perceive*.tw OR perception*.tw OR value*.tw OR perspective*.tw OR view*.tw OR experience*.tw OR need*.tw OR attitude*.tw OR belie*.tw OR opinion*.tw OR feel*.tw OR know*.tw OR understand*.tw OR EXP qualitative research OR interview*.tw OR qualitative.tw OR qualitative analysis.tw OR focus group*.tw OR survey*.tw OR questionnaire*.tw OR ethnograph*.tw OR observation*.tw

Additionally, reference lists of all studies included for final analysis and those of related systematic reviews identified by this search were also manually inspected to identify further studies with relevance to this review. Authors of studies were contacted by email where necessary to enquire about missing data.

4.2.3 Software to manage references

Search results of the various databases were exported into the reference manager Endnote 7.2.1, where duplicates were identified, recorded, and removed.

4.2.4 Inclusion/ Exclusion Criteria

Inclusion criteria

Studies were included from this review when they met any of the following criteria:

Study Design/Characteristics:

- Original research published in a peer review journal with a qualitative component (e.g. interviews, focus groups, ethnography, survey)
- Case studies/series, commentaries, descriptive articles published in peer review journals that describe real-world experiences of implementation.
- No publication date restrictions
- Published in English language

Participants:

- Adults who have had multi-drug pharmacogenetic testing
- Any healthcare professional involved in the care of above patients

Intervention:

- Multi-drug pharmacogenetic testing

Setting:

- Primary care
- Community
- Pharmacy
- Outpatient clinics
- Hospitals
- Acute/Secondary care
- Mental health
- Nursing/ care/ residential homes

Outcome:

- Factors which hinder or prevent clinical implementation of pharmacogenetic testing
- Factors which promote/support clinical implementation of pharmacogenetic testing

Exclusion criteria

Studies were excluded from this review when they met any of the following criteria:

Study Design:

- Systematic reviews
- Published in a non-English language
- Unable to retrieve full text

Study Participant:

- Patients < 18 years of age who receive multi-drug pharmacogenetic testing
- Adults receiving whole genome sequencing
- Adults receiving single-drug pharmacogenetic testing
- Adults receiving pharmacogenetic testing of somatic genome

Language

Only studies written in the English language were included in this review.

4.2.5 Screening and selection

Search results were checked for eligibility in relation to the research question, the whole process of results screening was carried out in three consecutive stages as described below:

- Title screening: initial screening of titles against the inclusion criteria to identify potential papers for abstract retrieval.
- Abstract screening: screening of abstracts to identify papers for full text retrieval.
- Full text assessment: assessment of full papers for inclusion.

Title screening, abstract screening and full text assessment were all carried out independently by two reviewers: the thesis author (EY) and Ravi Sharma (RS), to check their eligibility against the inclusion and exclusion criteria (Appendix 8). The findings were compared, and discrepancies resolved by discussion. Inter-rater agreement was measured using Cohen's kappa coefficient for every stage of screening.

4.2.6 Data extraction and synthesis

A data extraction template was specifically designed using Microsoft Excel to extract data from eligible studies (Appendix 9).

The data extraction form was piloted using a representative sample of studies. Data from each eligible study was independently extracted by EY, and then it was independently checked by a second reviewer (DB) to verify accuracy and completeness of all data extracted. Framework analysis with the TDF as an a priori framework was used to map determinants to the behaviours of prescribers, pharmacists and patients related to implementation of PGx testing. Table 4.4 shows descriptions of each of the TDF domains in the context of PGx test implementation.

Figure 4-1. shows the data synthesis process. Extracted data items were first grouped into behaviour descriptions. If the data item did not adequately correspond to an existing behavioural description, a new behaviour description was created. Next, data items related to barriers or enablers to each behaviour description were extracted and mapped to domains in the TDF. Determinants were then coded by who reported them: prescribers, pharmacists, or patients both directly or indirectly through author interpretations. Finally, the determinants were grouped into overarching themes (Gale et al., 2013) and the findings described narratively.

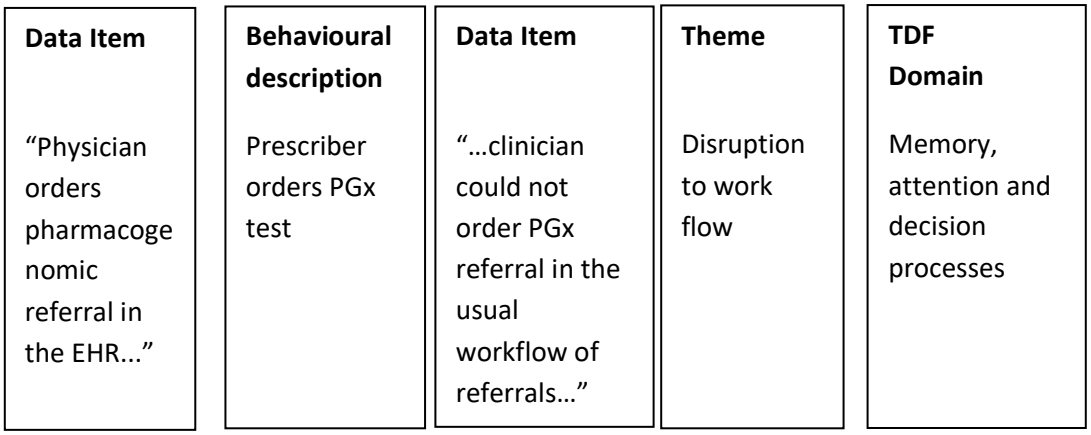


Figure 4-1 Data synthesis example.

Table 4-4 TDF domains in context

TDF domain	TDF domain definition (Cane et al., 2012)	Definition in context
Knowledge	An awareness of the existence of something.	Awareness of pharmacogenomics by prescribers, pharmacists and patients.
Skills	An ability or proficiency acquired through practice.	The ability or proficiency prescribers, pharmacists or patients have acquired to use pharmacogenomics through practice.
Social/Professional Role and Identity	A coherent set of behaviours and displayed personal qualities of an individual in a social or work setting.	The perceived professional role and personal identity of prescribers, pharmacists and patients in relation to using pharmacogenomics.
Belief about capabilities	Acceptance of the truth, reality or validity about an ability, talent, or facility that a person can put to constructive use.	Perception of prescribers, pharmacists and patients about their own capability to use pharmacogenomics.
Optimism	The confidence that things will happen for the best or that desired goals will be attained.	The confidence, or otherwise, of prescribers, pharmacists or patients around the use of pharmacogenomics in their practice.
Belief about consequences	Acceptance of the truth, reality or validity about outcomes of a behaviour in a given situation.	Belief of prescribers, pharmacists or patients about the value of using pharmacogenomics in their practice.

Table 4-4. TDF domains in context (continued).

TDF domain	TDF domain definition (Cane et al., 2012)	Definition in context
Reinforcement	Increasing the probability of a response by arranging a dependent relationship, or contingency between the response and a given stimulus.	Incentives, rewards, sanctions, reinforcement from any level, including patient feedback, clinician perspectives, funding, external views
Intentions	A conscious decision to perform a behaviour or a resolve to act in a certain way.	Intentions of prescribers, pharmacists and patients to consider using pharmacogenomics in their practice.
Goals	Mental representations of outcomes or end states that individual wants to achieve.	Perceptions by prescribers, pharmacists and patients that pharmacogenomics can be potentially used in their practice.
Memory, Attention and Decision Processes	The ability to retain information, focus selectively on aspects of the environment and choose between two or more alternatives.	The ability for prescribers, pharmacists and patients to remember to consider using pharmacogenomics.
Environmental Context and Resources	Any circumstances of a persons' situation or environment that discourages or encourages the development of skills and abilities, independence, social competence, and adaptive behaviour.	Any circumstance of the organisations situation or environment that discourages or encourages the ability of prescribers, pharmacists or patients to use pharmacogenomics in practice including independence, social competence and adaptive behaviour.

Table 4-4. TDF domains in context (continued).

TDF domain	TDF domain definition (Cane et al., 2012)	Definition in context
Social Influences	Those interpersonal processes that can cause individuals to change their thoughts, feelings or behaviours.	Interpersonal interactions within and outside the organisation that can influence the thoughts, feelings or behaviours of prescribers, pharmacists or patients in relation to the use of pharmacogenomics.
Emotions	A complex reaction pattern, involving experimental, behavioural, and physiological elements, by which the individual attempts to deal with a personally significant matter or event.	Feelings by prescribers, pharmacists or patients related to the use of pharmacogenomics in their practice.
Behavioural Regulation	Anything aimed at managing or changing objectives observes or measured actions.	Anything prescribers, pharmacists or patients have proactively created to help make decisions about and make change in using pharmacogenomics.

4.2.7 Quality assessment

A range of quality assessment tools (Centre for Evidence Based Management (Center for Evidence Based Management, 2014); The Critical Appraisal Skills Programme CASP Qualitative checklist (Critical Appraisal Skills Programme, 2022) and Critical appraisal of survey (Centre for evidence based management, 2022), were used according to the study designs (Kroopnick, 2013).

4.3 Results

The following section describes the findings and interpretations from the papers included in the systematic review.

4.3.1 Reporting

A PRISMA flow chart, which is a preferred method for reporting results of systematic reviews (Moher et al., 2009) was selected to report the findings of this systematic review, and to summarise the results obtained throughout the full process of studies' screening. The chart shows the numbers of studies identified in each stage as well as the number of duplicates recognised and removed. Reasons for exclusion are also provided alongside the PRISMA chart, specifically for studies excluded at both the abstract and the full text screening stages.

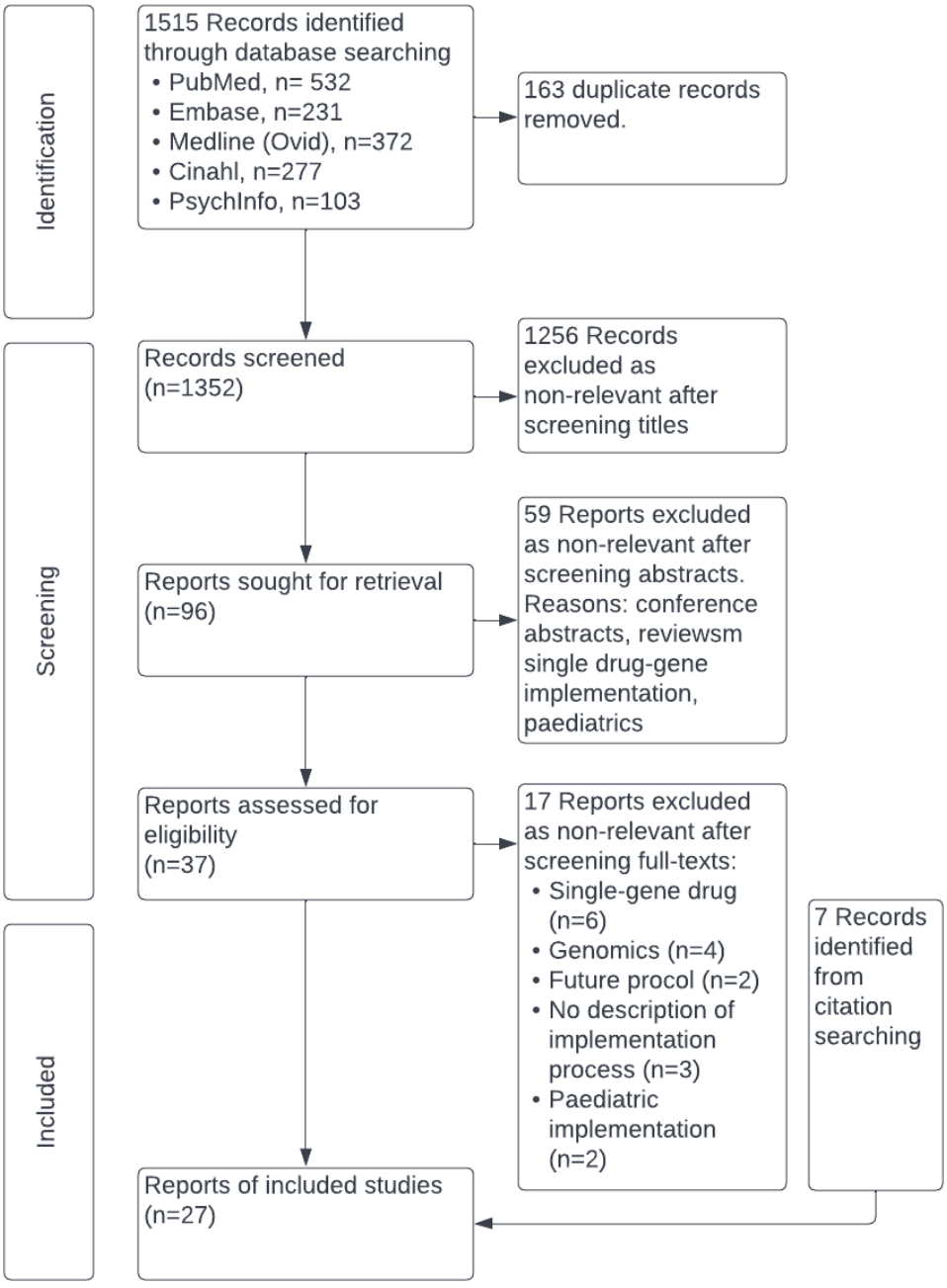


Figure 4-2 PRISMA flow diagram. PRISMA= Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

4.3.2 Main results

The systematic search identified 1515 citations, of which 20 studies met all of the inclusion criteria. The bibliographies of these studies that were identified by the search were independently checked by EY, and an additional seven studies met the inclusion criteria. All of the additional studies were confirmed for eligibility by a second independent reviewer (RS), therefore a total of 27 studies were included in this review.

The primary reasons for exclusion at full-text screening were implementation of single drug/gene pair testing rather than multi-drug or being unable to isolate the reported barriers and enablers to pharmacogenomic implementation from those for wider genomic implementation.

The results of inter-rater agreement between reviewers were as follows:

- Title screening stage: the calculated Cohen's Kappa coefficient = 0.87, which indicated almost perfect agreement among the two reviewers.
- Abstract screening stage: the calculated Cohen's Kappa coefficient= 0.72, which indicated substantial agreement among the two reviewers.
- Full text assessment: the calculated Cohen's Kappa coefficient = 0.78, which indicated substantial agreement among the two reviewers (Viera and Garrett, 2005)

4.3.3 Characteristics of studies

Table 4-5 summarises the characteristics of the twenty-seven included articles all of which were from high income countries and primarily the United States (n=23, 85%). Both primary and secondary care settings were represented. Seventeen articles explored behaviours of prescribers (O'Donnell et al., 2012, Bielinski et al., 2014, Levy et al., 2014, Formea et al., 2015, Haga et al., 2015, Dawes et al., 2016, Dunnenberger et al., 2016, Eadon et al., 2016, St Sauver et al., 2016b, Rosenman et al., 2017, Dressler et al., 2019, Ho et al., 2022, Tuteja et al., 2021, Arwood et al., 2020, Marrero et al., 2020, Bain et al., 2018, Borden et al., 2019, Unertl et al., 2015), fifteen explored behaviours of the pharmacist (Dawes et al., 2016, Haga et al., 2015, Levy et al., 2014,

Dunnenberger et al., 2016, Swen et al., 2012b, Moaddeb et al., 2015a, Arwood et al., 2020, Bright et al., 2020, Haga, 2021, Lanting, 2020, Liko et al., 2021, Marrero, 2020, Tuteja et al., 2021, van der Wouden et al., 2020, Martin et al., 2022) and seven explored patient behaviours (Bielinski et al., 2017, Bielinski et al., 2014, Rosenman et al., 2017, Moaddeb et al., 2015a, Dressler et al., 2019, Lanting, 2020, Martin et al., 2022). Most of the included studies collected data via document analysis and surveys. There were no differences in reported barriers and enablers between different study designs. Table 4-6 described the quality of the included studies. The majority (40%) of the studies were of moderate quality, 30% were of high quality and 30% were of low quality.

4.3.4 Target behaviour areas

Four implementation stages were described across the reports. These stages are shown in Table 4-7. Each implementation stage incorporated multiple behaviours of which the 'facilitating test' stage comprised the most activities

.

Table 4-5 Summary of included studies

Study (Year) Country	Objective	Study design	Study setting	Methods used	Actor
Bain et al. (2018) USA	To determine the feasibility of implementing a pharmacist-led pharmacogenomics (PGx) service.	Feasibility Study.	Primary care. (community pharmacy).	Document analysis.	Prescriber.
Formea et al. (2015) USA	To describe experiences of implementing pharmacogenomics education in a large, academic healthcare system.	Descriptive case study.	Primary care.	Senior stakeholder observation.	Prescriber.
Bielinski et al. (2017 USA	To assess patient experiences and understanding of pharmacogenomics and pharmacogenomics educational materials.	Service evaluation.	Secondary care.	Survey.	Patient.
Dawes et al. (2017) Canada	To assess the ability to obtain and genotype saliva samples and determine levels of use of a pharmacogenomic decision support tool.	Prospective cohort study.	Primary care.	Document analysis.	Prescriber, Pharmacist.

Table 4-5 Summary of included studies (continued)

Study (Year) Country	Objective	Study design	Study setting	Methods used	Actor
O'Donnell et al. (2012) USA	To describe an institutional pharmacogenomics-implementation project.	Descriptive case study.	Secondary care.	Senior stakeholder observation.	Prescriber.
Haga et al. (2015) USA	To assess the feasibility of a combined pharmacist-delivered medication therapy management (MTM) with pharmacogenetic (PGx) testing.	Feasibility study.	Primary care.	Document analysis, survey.	Prescriber, Pharmacist.
Borden et al. (2019) USA	To understand whether pharmacogenomic results are discussed between patient and provider and whether medication recall is impacted by pharmacogenomic testing.	Service evaluation.	Primary care.	Survey.	Prescriber.
Levy et al. (2014) USA	To describe the key requirements to ensure a successful and enduring PGx implementation within a large healthcare system.	Descriptive case study.	Secondary care.	Senior stakeholder observation.	Prescriber, Pharmacist.

Table 4-5 Summary of included studies (continued)

Study (Year) Country	Objective	Study design	Study setting	Methods used	Actor
Dunnenberger et al. (2016) USA	To describe the development and implementation of a multidisciplinary pharmacogenomics clinic within a community-based medical genetics program.	Descriptive case study.	Secondary care.	Senior stakeholder observation.	Prescriber, Pharmacist.
Swen et al. (2012) Netherlands	To investigate the feasibility of pharmacy-initiated pharmacogenetic screening in primary care.	Feasibility study.	Primary care.	Document analysis, survey.	Pharmacist.
Bielinski et al. (2014) USA	To report the design and implementation of a pre-emptive pharmacogenomics (PGx) testing programme.	Descriptive case study.	Primary care, Secondary care.	Survey.	Patient.
Eadon et al. (2016) USA	To describe the formation of a pharmacogenomics consultation service at a safety-net hospital, which predominantly serves low-income, uninsured, and vulnerable populations.	Descriptive case study.	Secondary care.	Document analysis, Senior stakeholder observation.	Prescriber.

Table 4-5 Summary of included studies (continued)

Study (Year) Country	Objective	Study design	Study setting	Methods used	Actor
Unertl et al. (2015) USA	To describe the knowledge and attitudes of clinicians participating in a large pharmacogenomics implementation program.	Process evaluation.	Primary care, Secondary care.	Interviews.	Prescriber.
St Sauver et al. (2016) USA	To summarise and describe early clinician experience with pharmacogenomics in the clinical setting.	Service evaluation.	Secondary care.	Survey.	Prescriber.
Rosenman et al. (2017) USA	To describe challenges and potential solutions based on a pharmacogenomic testing programme.	Descriptive case study.	Secondary care.	Senior stakeholder observation.	Prescriber, Patient.
Moeddeb et al. (2015) USA	To characterise the experiences and feasibility of offering pharmacogenetic (PGx) testing in a community pharmacy.	Feasibility study.	Primary care (community pharmacy).	Document analysis.	Pharmacist, Patient.

Table 4-5 Summary of included studies (continued)

Study (Year) Country	Objective	Study design	Study setting	Methods used	Actor
Dressler et al. (2019) USA	To assess the feasibility and perspectives of pharmacogenetic testing in rural, primary care physician practices.	Feasibility study.	Primary care.	Survey.	Prescriber, Patient.
Arwood et al. (2020) USA	To describe the development, workflow, and early implementation challenges associated with a pharmacist pharmacogenetic testing clinic.	Service evaluation.	Secondary care.	Document analysis, Senior stakeholder observation.	Prescriber, Pharmacist.
Bright et al. (2020) USA	To evaluate the implementation processes relating to a pharmacist pharmacogenetic testing consult service.	Service evaluation.	Secondary care.	Document analysis, Senior stakeholder observation.	Pharmacist.
Haga et al. (2021) USA	To assess pharmacist experiences with delivering pharmacogenetic testing in independent community pharmacies.	Process evaluation.	Primary care.	Survey, Document analysis, semi-structured interviews.	Pharmacist.

Table 4-5 Summary of included studies (continued)

Study (Year) Country	Objective	Study design	Study setting	Methods used	Actor
Lanting et al. (2020) Netherlands	To identify barriers and facilitators to the implementation of an outpatient pharmacogenetic screening service.	Process evaluation.	Secondary care.	Survey, interviews, focus group.	Pharmacist, Patient.
Liko et al. (2021) USA	To describe the implementation of a pharmacist-provided pharmacogenomic testing service at an academic medical centre.	Descriptive case study.	Secondary care.	Senior stakeholder observation.	Pharmacist.
Marrero et al.(2020) USA	To describe the transition from implementing single-gene testing to a pre-emptive panel-based pharmacogenetic testing service.	Descriptive case study.	Secondary care.	Senior stakeholder observation.	Prescriber, Pharmacist.
Tuteja et al. (2021) USA	To evaluate the approaches taken by early adopters to implement a clinical pharmacogenetic testing service.	Service evaluation.	Primary care, Secondary care.	Survey.	Prescriber, Pharmacist.

Table 4.5 Summary of included studies (continued)

Study (Year) Country	Objective	Study design	Study setting	Methods used	Actor
Van der Wouden et al. (2020) Netherlands	To identify pharmacists' perceived barriers and enablers facilitating the implementation of pharmacist-initiated pharmacogenetic testing in primary care.	Service evaluation.	Primary care.	Interview, Survey.	Pharmacist.
Ho et al. (2021) USA	To characterise clinician perceptions, practices, preferences and barriers to integrating pharmacogenomics in a single pharmacogenomic clinic.	Service evaluation.	Secondary care.	Survey.	Prescriber.
Martin et al. (2022) USA	To assess the perspectives and experiences of patients participating in a pharmacist-led PGx service.	Service evaluation.	Tertiary care.	Semi-structured interviews.	Patient, Pharmacist.

Table 4-6 Quality of included studies

High quality (n=8)	Moderate quality (n=11)	Low quality (n=8)
Dawes et al.(2017)	Bain et al.(2018)	Formea et al. (2015)
Unertl et al.(2015)	Bielinski et al. (2014)	O'Donnell et al. (2012)
Swen et al. (2012)	Bielinski et al.(2017)	Levy et al. (2014)
Haga et al. (2021)	St. Sauver et al.(2016)	Dunnenberger et al.(2016)
Lanting et al. (2020)	Moeddeb at al.(2015)	Eadon et al. (2016)
Van der Wouden (2020)	Dresser et al.(2019)	Rosenman et al. (2017)
Ho et al. (2021)	Haga et al. (2015)	Liko et al. (2021)
Martin et al. (2022)	Borden et al. (2019)	Marrero et al. (2020)
	Arwood et al.(2020)	
	Bright et al. (2020)	
	Tuteja et al. (2021)	

Table 4-7 Barriers and enablers reported for each target behavioural area.

Implementation Step	Description of Behaviour	Theme	TDF Domain	Perspective	Reported Barrier	Reported Enabler
Ordering test	Prescriber orders PGx test	IT Infrastructure	Memory, attention, and decision making	Prescriber	Disruption to workflow (Dunnenberger et al., 2016)	No data available
					Logistics/ease of use (Dressler et al., 2019)	No data available
		Effort	Memory, attention, and decision making	Prescriber	Perceived additional workload of test (Dunnenberger et al., 2016, Rosenman et al., 2017)	No data available
					Paperwork (Haga et al., 2021)	No data available
			Skills	Prescriber	Unclear procedures (van der Wouden et al., 2020)	Previous exposure to PGx (Liko et al., 2021, Bain et al., 2018)
			Social/Professional role and identity	Prescriber	Language of result reporting (Unertl et al., 2015)	No data available
			Optimism	Prescriber	Perceived complexity of PGx (Unertl et al., 2015)	No data available
			Other	Prescriber	Content and form of training (Unertl et al., 2015)	No data available
					Low clinician engagement (St Sauver et al., 2016a)	No data available
		Rewards	Belief about consequences	Prescriber	No data available	Prescriber perceived value of testing (Dressler et al., 2019),(Bain et al., 2018)

Table 4-7 Barriers and enablers reported for each target behavioural area.(continued)

Implementation Step	Description of Behaviour	Theme	TDF Domain	Perspective	Reported Barrier	Reported Enabler
Ordering test	Prescriber orders PGx test	Rewards	Environmental context and resources	Prescriber	Demand/supply for service (Dunnenberger et al., 2016)	No data available
				Prescriber	Disruption to workflow due to time delay for results (Bielinski et al., 2017)	No data available
		Unknown territory	Belief about capabilities	Prescriber	Perceived confidence to order test (Unertl et al., 2015)	No data available
			Memory, attention, and decision making	Prescriber	Liability of incidental findings (Rosenman et al., 2017)	Ability to recognise drug–gene pairs (Bielinski et al., 2017, Eadon et al., 2016)
			Skills	Prescriber	Prescriber knowledge of who to test (Dressler et al., 2019, Ho et al., 2022)	No data available
			Environmental context and resources	Prescriber	Reimbursement (van der Wouden et al., 2020, Ho et al., 2022)	No data available
			Knowledge	Prescriber	Knowledge gap when to order test (Bain et al., 2018)	No data available
				Prescriber	Awareness of availability of testing (Ho et al., 2022)	No data available
			Other	Prescriber	Availability of guidelines (Ho et al., 2022)	No data available

Table 4-7 Barriers and enablers reported for each target behavioural area.(continued)

Implementation Step	Description of Behaviour	Theme	TDF Domain	Perspective	Reported Barrier	Reported Enabler
Ordering test	Pharmacist orders PGx test	Effort	Environmental context and resources	Pharmacist	Reimbursement (Haga, 2021, Ho et al., 2022)	No data available
		Rewards	Social/Professional role and identity	Pharmacist	No data available	Pharmacist expert knowledge (van der Wouden et al., 2020, Martin et al., 2022)
			Belief about consequences	Pharmacist	No data available	Pharmacist's perceived value of testing (Martin et al., 2022, Ho et al., 2022)
		Unknown territory	Knowledge	Pharmacist	Awareness of availability of testing (Ho et al., 2022)	No data available

Table 4-7 Barriers and enablers reported for each target behavioural area.(continued)

Implementation Step	Description of Behaviour	Theme	TDF Domain	Perspective	Reported Barrier	Reported Enabler
Facilitating the test	Patient gives consent to PGx test	Rewards	Belief about consequences	Patient	Perceived risk of discrimination (Dunnenberger et al., 2016) Perceived utility of test (Rosenman et al., 2017, Moaddeb et al., 2015a)	No data available
			Optimism	Patient	Pessimism about test utility (Moaddeb et al., 2015a)	Perception of the test will be useful (Dressler et al., 2019, Haga et al., 2021, Lanting, 2020) Confidence in pharmacist knowledge (Haga et al.,2015, Martin et al., 2022)
		Unknown territory	Emotion	Patient	Perceived risk of discrimination (Dunnenberger et al., 2016)	No data available
				Patient	Concerns about data privacy (Rosenman et al., 2017)	No data available
				Patient	Perceived implications for family members (Dunnenberger et al., 2016)	No data available
				Patient	Perceived risk of discrimination (Dunnenberger et al., 2016)	No data available

Table 4-7 Barriers and enablers reported for each target behavioural area.(continued)

Implementation Step	Description of Behaviour	Theme	TDF Domain	Perspective	Reported Barrier	Reported Enabler
Facilitating the test	Patient gives consent to PGx test	Unknown territory	Emotion	Patient	Concerns about data privacy (Rosenman et al., 2017)	No data available
			Environmental context and resources	Patient	Information technology interoperability (Bain et al., 2018)	No data available
	Pharmacist shares report with prescriber	IT Infrastructure	Environmental context and resources	Prescriber, Pharmacist	Information technology interoperability (Bain et al., 2018)	No data available

Table 4-7 Barriers and enablers reported for each target behavioural area.(continued)

Implementation Step	Description of Behaviour	Theme	TDF Domain	Perspective	Reported Barrier	Reported Enabler
Facilitating the test	HCP counsel's patient on PGx result	Effort	Environmental context and resources	Prescriber, Pharmacist	Prescriber and pharmacist access to central prescribing system (Bain et al., 2018, Martin et al., 2022)	No data available
		Rewards	Environmental context and resources	Patient	No data available	Patient access to report results (Marrero et al., 2020)
		Unknown territory	Skills	Prescriber	No data available	Prescriber experience with PGx (Borden et al., 2019)
Interpretating the test	Pharmacist interprets PGx results	Effort	Social/Professional role and identity	Prescriber, Pharmacist	No data available	Pharmacist expert knowledge (Arwood et al., 2020, Bright et al., 2020, Dunnenberger et al., 2016)
	Prescriber interprets PGx result	Effort	Memory, attention, and decision making	Prescriber	No data available	Electronic workflow alert for drug–gene pairs (Eadon et al., 2016)
			Emotion	Prescriber	Negative perception of CDS (St Sauver et al., 2016b)	No data available
		IT Infrastructure	Social/Professional role and identity	Prescriber	No data available	Pharmacist expert knowledge (van der Wouden et al., 2020)

Table 4-7 Barriers and enablers reported for each target behavioural area.(continued)

Implementation Step	Description of Behaviour	Theme	TDF Domain	Perspective	Reported Barrier	Reported Enabler
Application of the test	Prescriber applies PGx result	Effort	Memory, attention and decision making	Prescriber	Location of results (Marrero et al., 2020)	No data available
		IT Infrastructure	Environmental context and resources	Prescriber	No data available	CDS alert at point of prescribing (Formea et al., 2015, Lanting, 2020, Liko et al., 2021)
		Rewards	Belief about capabilities	Prescriber	Prescriber perceived lack of capability to apply results (O'Donnell et al., 2012)	No data available
			Belief about consequences	Prescriber	Perceived severity of drug–gene interaction (St. Sauver et al., 2016)	Perceived utility of PGx testing (Borden et al., 2019)
			Social influences	Prescriber	Perceived utility of drug–gene pairs in certain clinical specialties (O'Donnell et al., 2012)	No data available
		Unknown territory	Environmental context and resources	Prescriber	Prescriber liability (Eadon et al., 2016)	No data available
			Knowledge	Prescriber	Knowledge gap on how to apply PGx results (Bain et al., 2018, O'Donnell et al., 2012)	No data available

4.3.5 Themes

Figure 4-3 illustrates the four themes that emerged from the data with corresponding TDF domains. Ten of the fourteen TDF domains were represented in the barriers and enablers grouped under the four themes. These themes covered all stages of the implementation cycle and were IT Infrastructure, Effort, Rewards and Unknown Territory.

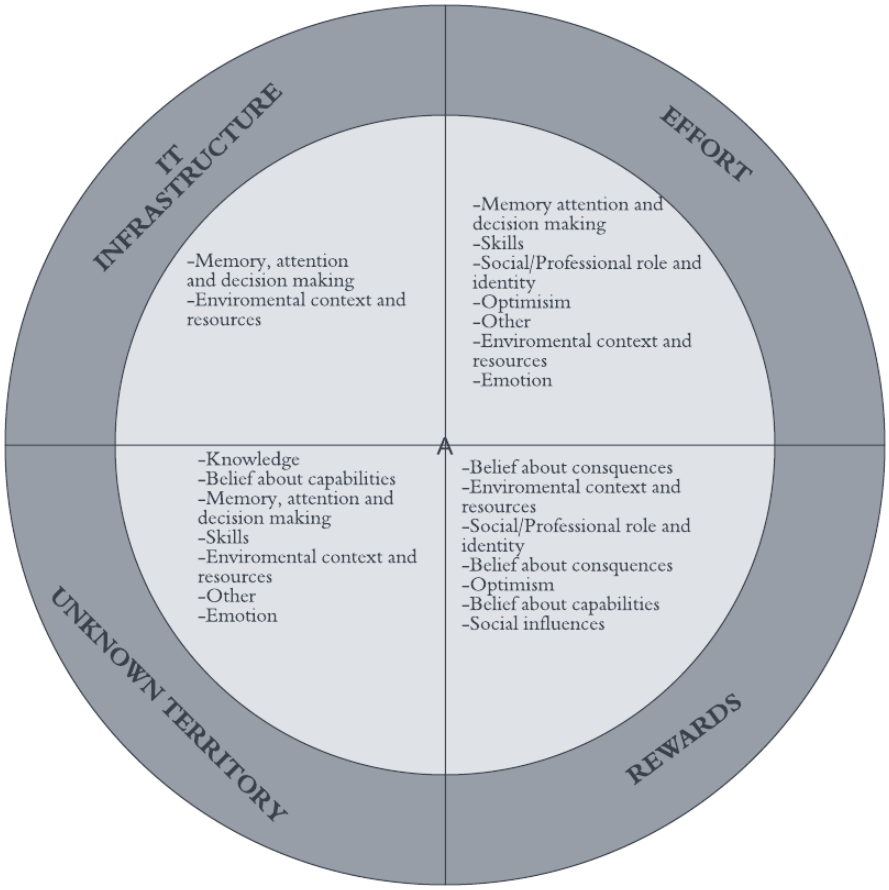


Figure 4-3 Four overarching themes emerged from the barriers and enablers extracted from the included papers. These themes (outer ring) are linked to TDF domains (inner four quadrants)

4.3.5.1 IT infrastructure

All implementation stages had barriers and enablers related to the extent to which local information technology systems were adapted. The majority of the barriers and enablers within this theme were mapped to two TDF domains: 'Memory, attention and decision making' and 'Environmental context and resources'.

Several papers reported ways in which technology was or could be utilised to reduce the cognitive burden on prescribers using PGx testing. Five studies (Dressler et al., 2019, Dunnenberger et al., 2016, Eadon et al., 2016, Lanting et al., 2020, Liko et al., 2021) reported how an inability to order PGx testing through usual IT workflows presented a barrier to prescribers ordering behaviours. In the latter implementation stages, uploading genotyping reports on the electronic medical record in a searchable format, enabled prescribers to interpret PGx results (Eadon et al., 2016).

IT systems interoperability represented a major barrier to pharmacists within PGx testing roles. A feasibility study investigating the implementation of a pharmacist-led PGx testing service to community-based medical centres reported how pharmacists directly sent PGx results to the prescriber via an online server and the pharmacy record. Whilst this method was feasible for this setting, the inability of pharmacists to access a central electronic medical record impacted the pharmacist recommendations (Bain et al., 2018). Furthermore, modelling this IT structure in other settings may be challenging. For example, a descriptive case study describing PGx implementation in a large academic centre reported holding PGx data on multiple IT systems led to poor trackability of lifetime genetic results (Formea et al., 2015). A survey of patients undergoing pharmacogenomic testing through a pharmacist-led pharmacogenomic clinic showed patients preferred for test results to be incorporated in the medical record so other medical providers had access, facilitating PGx-guided decision making (Martin et al., 2022).

Designing IT PGx workflows that are intuitive to end users is also important. One US study investigating the implementation of PGx testing in a health system serving both primary and secondary care reported how IT workflows integrating PGx were co-designed by pharmacists, physicians, and nurses (Levy et al., 2014).

4.3.5.2 Effort

The cognitive, physical, and emotional effort to undertake behaviours necessary for implementation was a major theme of the studies included. Effort affected most of the behaviours across the implementation stages and was reported in more than half of the papers included (64%, n = 16/27).

Barriers and enablers affecting cognitive effort were most likely to be mapped to the 'Memory, attention and decision making' TDF domain. Electronic prompts in the form of PGx clinical decision support tools enabled prescribers to order PGx testing for patients (Eadon et al., 2016) as well as enabling the interpretation and application of PGx test results by prescribers and pharmacists (Dunnenberger et al., 2016, Eadon et al., 2016, Formea et al., 2015, Bain et al., 2018). Health professionals pre-existing procedural competence meant that behaviours such as prescribers and pharmacists collecting DNA samples and sending them to a laboratory for testing were of low cognitive effort and easily implemented (Dawes et al., 2016, Swen et al., 2012a, van der Wouden et al., 2020).

Physical effort emerged as a barrier to patients consenting to PGx testing. A survey of patients who had taken part in a PGx testing programme in the US reported nearly half of the participants (42%) (n = 869) were unwilling to incur out-of-pocket costs for PGx testing (Bielinski et al., 2017). This was also found in a service evaluation of a US hospital implementing PGx testing, where reimbursement of testing was a significant barrier to patient engagement (Arwood et al., 2020). In addition to cost, DNA collection methods also represented a physical effort barrier to patient behaviours related to PGx implementation (Eadon et al., 2016, Swen et al., 2012a). A

feasibility study exploring a community pharmacy implementation model in the Netherlands, found saliva sampling to be challenging for certain groups of patients due to comorbidities or concurrent medicines (Swen et al., 2012a). This could be overcome by restructuring the environment and providing additional resources for example offering multiple DNA collection methods of blood, and saliva (Eadon et al., 2016, Liko et al., 2021).

Electronic prompts were reported to reduce the cognitive effort of prescribers ordering, interpreting, and applying PGx results. The introduction of these alerts within clinical workflows was sometimes perceived negatively, and doctors reported alert fatigue if electronic prompts appeared indiscriminately for every patient (St Sauver et al., 2016b, Unertl et al., 2015). Prescribers in primary care perceived PGx testing as complex and too specialised to use in their own practice, and this was exacerbated by unfamiliar nomenclature used in reporting results (Unertl et al., 2015). Emotional effort was, therefore, a complex theme that covered multiple TDF domains: 'Social/professional role and identity'; 'Emotion', and 'Optimism'.

4.3.5.3 Rewards

Rewards as a theme described factors which were perceived by prescribers, pharmacists, or patients as a positive outcome to PGx testing. 'Optimism' and 'Belief about consequences' were the two most frequently mapped TDF domains for determinants under this theme. Patients' reported optimism for a pharmacist PGx delivery model enabled patient consent behaviours within these implementation models (Haga et al., 2015, Martin et al., 2022). Optimism on the part of the patient that the PGx testing would help their medical management enabled patient consenting behaviours (Dressler et al., 2019, Haga et al., 2021, Lanting et al., 2020, Marrero, 2020) whereas pessimism on the part of the patient about the utility of PGx testing prevented these behaviours (Moaddeb et al., 2015b). Optimism also impacted behaviours of prescribers related to PGx implementation. The perceived clinical utility or value for money of the test impacted whether a prescriber would

order or apply a PGx test. Primary care physicians interviewed as part of a feasibility study investing PGx implementation in a rural US setting found the cost of PGx testing was a barrier to initiating testing suggesting a poorer perceived cost–benefit ratio (Dressler et al., 2019). In contrast, a survey of prescribers at a tertiary center in the US reported favourable attitudes to the perceived clinical utility of testing enabling PGx testing applications (Borden et al., 2019).

Belief about consequences emerged as both a barrier and enabler to prescriber behaviours related to PGx implementation. This determinant centred on the prescriber's perceptions about the clinical utility of PGx testing and was augmented by the clinical relevance of the drug–gene pairs implemented locally through the frequency or severity of drug–gene interactions encountered (O'Donnell et al., 2012, St Sauver et al., 2016b).

Turnaround time between testing and receiving results was also reported as a barrier to prescriber ordering behaviours (Dunnenberger et al., 2016). This was overcome in several US implementation sites through environmental restructuring to enable a pre-emptive PGx testing approach (Bielinski et al., 2014, O'Donnell et al., 2012).

4.3.5.4 Unknown territory

The novelty of PGx testing affected all stages of the implementation cycle but manifested as primarily a barrier at the initial stage of prescriber and pharmacist ordering behaviour. General knowledge of PGx and identifying patients for testing were reported as barriers to prescribers and pharmacist ordering behaviours (Dressler et al., 2019, O'Donnell et al., 2012, Ho et al., 2022, Unertl et al., 2015). In addition, a survey of prescribers and pharmacists at a tertiary centre with an established pharmacogenomic testing program, stated the greatest barrier to using PGx testing was an absence of established or clear guidelines for interpreting and applying results (Ho et al., 2022).

The lack of general PGx experience by prescribers affected prescriber confidence in using PGx. Prescribers were reported to hold negative beliefs about their capability to use PGx, consequently affecting their behaviours involving ordering, interpreting, and applying PGx information in clinical care (O'Donnell et al., 2012, Unertl et al., 2015). Prescribers who had prior exposure to PGx information were reported to be more informed and confident in undertaking behaviours relating to PGx simply through experience (Bright et al., 2020, Borden et al., 2019).

In a backdrop of legal uncertainty two PGx implementation sites in the US, adopted a team approach to PGx interpretation, with a specific consult group managing and taking responsibility for liability associated with incidental findings (Eadon et al., 2016, Rosenman et al., 2017). It was not reported in these studies whether the drive for liability protections came from the prescribers themselves or the organisation.

4.4 Discussion

4.4.1 Main findings

To the authors best knowledge, this is the first systematic review in the context of pharmacogenomic testing to focus on barriers and enablers to the behaviours of prescribers, pharmacists, and patients, relating to implementation in primary and secondary care and subsequently map them to the theoretical domain framework.

In line with previous research, information technology was identified as both a barrier to and an enabler of implementation (Amare et al., 2018). A recent structured scoping review of pharmacogenetic testing programs using the consolidated framework for implementation research (CFIR) found that IT solutions are currently unable to support pharmacogenomic-guided prescribing at the interface between primary and secondary care. This was a persistent problem to wider adoption and implementation (McDermott et al., 2022). At the individual level, we found that clinical decision support systems (CDSS) when linked to the electronic health record (EHR) in particular, enabled initiation and application of PGx testing through the

mechanism of environmental restructuring and prompting prescriber PGx-related behaviours. The importance of well-designed CDSS alerts has been well-documented with the Dutch Pharmacogenetics Working Group describing one the earliest examples of implementing CDSS alerts in a national electronic prescribing and medicines surveillance system (Swen et al., 2011). Since then, the Clinical Pharmacogenetics Implementation Consortium's (CPIC) Informatics Working Group has provided best practice suggestions for integrating pharmacogenomics CDSS for clinical delivery (Hoffman et al., 2016). Whilst our findings are not necessarily novel, given that IT interoperability (Roosan et al., 2020) and CDSS design (Hinderer et al., 2017) have been the subject of extensive research, our linking to behavioural change theory may provide better direction for the future design and evaluation of effective CDSS which incorporate behavioural change techniques (Michie et al., 2013).

Prescriber and pharmacist views on the clinical utility and cost-effectiveness modulated their perceptions of the rewards of PGx testing. This finding corroborated a recent systematic review exploring barriers and enablers of PGx testing in primary care which also found the domain 'belief about consequences' was an important driver for primary care physicians' adoption of PGx testing (Qureshi et al., 2022). Our findings show this domain influences physicians in secondary care and pharmacists in both settings. Our findings are also strengthened by excluding studies which consider attitudes towards PGx testing from a theoretical perspective.

Healthcare systems represent complex environments comprising multiple interacting components that are evolving dynamically and are interdependent (Greenhalgh, 2018). PGx clinical implementation strategies often demanded new models of care thus adding to the complexity and effort required by people within the system to adapt and sustain PGx testing. The more a new intervention such as PGx demands different processes within an organisation, the more effort is required of the existing workforce, and the less likely it is to be taken up and sustained (Greenhalgh et al., 2017). These new models of care were dominated by pharmacist-led models of implementation. The large emotional effort on the part of physicians

to implement PGx testing arising from unfamiliarity and complex processes, led to them feeling that it did not align with their professional role and identity. This misalignment may be the driver for the more prominent pharmacist roles reported (Hayward et al., 2021) which has been facilitated by advocacy for this role from pharmacy professional bodies in the US (American Society of Health-System Pharmacists, 2021). In contrast, medical professional statements have been confusing. For example, while Clopidogrel FDA labelling recommends alternative therapy in patients identified as CY2C19 poor metabolisers (FDA, 2021). The American College of Cardiology Foundation, American Heart Association, and the Society for Cardiovascular Angiography and Interventions guidelines recommend against routine PGx testing in all percutaneous intervention patients (Lawton et al., 2022). Inconsistencies in messaging may negatively influence prescriber attitudes to PGx testing as professional associations play a key role in shaping the professional role and identity of their members (Montgomery and Oliver, 2016).

Panel pre-emptive PGx testing is often cited as the most suitable model for implementing routine PGx testing in clinical care (Cavallari et al., 2018). The reasons underpinning this predominantly centre around cost-effectiveness, with the aggregate effect of PGx testing on health outcomes being more favourable in a pre-emptive multiple drug–gene testing scenarios over a patient's lifetime than through a single drug–gene reactive testing scenario(Verbelen et al., 2017). Several studies demonstrate how common drug–gene interactions are in a wide range of populations (Youssef et al., 2021, Kimpton et al., 2019, Lunenburg et al., 2021, Chanfreau-Coffinier et al., 2019). However, each of these studies whilst describing a panel pre-emptive pharmacogenomic test uses different drug–gene pairs and guidelines for hypothetical implementation. This reflects wider discord over which genetic variants comprise a panel PGx testing approach that maximises clinical impact and is equitable and fair. There is yet no consensus over what a standardised panel is, however, there have been a few recent papers that have suggested prototypes for implementation in different contexts (Blagec et al., 2018, Bousman et

al., 2019a). In this way, despite over two decades of research, implementation efforts of PGx testing in clinical care are challenged by the evolving, dynamic definitions of what PGx testing is and its constituent parts. As a result, the belief among health professionals that PGx testing is a novelty remains since familiarity with one form of testing may not translate to easing the use of another. This is perhaps reflected by the absence of endorsement for PGx testing by professional organisations (Turner et al., 2020) and complicated by the activities of private companies in this space.

4.4.2 Implications for future research

The majority of articles included in this review focused on the barriers and enablers to the prescriber and pharmacist behaviours related to implementation. The barriers and enablers were predominately described through author interpretations recounted in narrative descriptions of implementation rather than primary data derived through traditional qualitative research methods. None of the articles used implementation frameworks or theory which introduces a degree of uncertainty to our findings.

Future research exploring determinants of the behaviours of physicians, pharmacists, and patients in real-world PGx implementation settings would be strengthened through use of rich qualitative research methods and a theoretical lens. This would support the understanding of context-specific barriers and enablers (for example in primary verses secondary care) and develop evidence-based, theory informed interventions for the most appropriate implementation configuration.

4.4.3 Strengths and Limitations

A number of elements exist that strengthen the confidence with the findings of this systematic review The review followed the standard approach to systematic reviews outlined by the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green, 2008) and ENTREQ (Enhancing Transparency in Reporting the Synthesis of Qualitative Research) guide (Tong et al., 2012). The

results of this review were based on searching for the best available evidence by using a comprehensive search methodology with a combination of complementary key words that were used to systematically search all related databases. The scoping review preceding the systematic review, assisted in developing an inclusion and exclusion criteria that helped in selecting related studies from the vast number of articles initially identified. The search was made more comprehensive by hand-searching the bibliographies of all included studies, so that all potentially eligible and published studies could be identified. No restriction on the year of publication was made in this review, in order to run an extensive search to capture all possible evidence regarding implementation of multi-drug pharmacogenomic testing across the years. Moreover, unlike other systematic reviews identifying the barriers and enablers to pharmacogenomic testing implementation (Qureshi et al., 2022, Dominic et al., 2021) this review uses a theoretical framework and only includes studies describing real-world implementation rather than conceptual understanding of what challenges may be encountered when implementing pharmacogenomic testing.

Limitations to this review relate to both the individual articles and review methodology. As discussed previously, almost all articles included described the authors' interpretation of barriers and enablers verses first-person accounts of prescriber, pharmacist, and patients. To capture the full breadth of available real-world data, articles with high risk of bias such as descriptive case studies were included. However, their findings were often reflected in studies with low risk of bias. Only articles published in the English language were included due to resource constraints, leading to possibly rejecting some high-quality studies not written in English.

4.5 Summary

Multi-drug pharmacogenomic testing represents a complex intervention. Framing implementation through a behavioural science lens provides insight into the key determinants driving prescriber, pharmacist and patient behaviours relating to PGx testing. Memory, attention, and decision making; beliefs about consequences and environmental context and resources underpinned the main barriers to behaviours related to PGx testing implementation. Theory-based implementation interventions targeting these domains, may progress efforts for widespread PGx adoption and sustainability.

Chapter 5: A case study of pharmacogenomic testing in the NHS.

4.6 Introduction

Chapter 1 described the international pharmacogenomic testing landscape and key drivers behind translating pharmacogenomic research into clinical practice. These included new technologies such as faster, cheaper genetic testing laboratory techniques, and clinical decision support programmes using evidence based pharmacogenomic prescribing recommendations. Despite these advancements, the usage of pharmacogenomic testing worldwide is still restricted to academic research centres in the USA, Australia and the Netherlands and widespread clinical implementation is a problem.

Previous approaches to analyse the PGx implementation problem have collected data on barriers and enablers to implementation at a macro level, lacking detail locating who, when and where do these barriers and enablers appear during the PGx testing process. From an implementation science perspective, these approaches lack the necessary detail to 'diagnose' the implementation problem adequately and may have impeded progress to address and resolve these implementation problems. This is particularly relevant to PGx testing which has several components of complexity, as described in Table 2.1 in Chapter 2.

Chapter 2, described the importance of applying theory when developing and implementing complex interventions. Using theory here aims to enable researchers to isolate mechanisms and processes of change occurring when new interventions are adopted, implemented, and sustained within systems. The Theoretical Domains Framework (TDF) is an integrative framework of behaviour change theories organised into 14 domains (Cane, O'Connor et al. 2012). The TDF was selected as the theoretical lens underpinning the development of a multi-drug pharmacogenomic testing intervention. Identifying the individual behavioural influences on health practitioners and patient behaviours related to implementing multi-drug pharmacogenomic testing provides the theoretical understanding to enable successful implementation.

Chapter 4 explored barriers and enablers to implementing multi-drug pharmacogenomic testing from a behavioural perspective. The systematic review and narrative synthesis included studies from several countries including North America, Canada and the Netherlands and included pharmacists, doctors and patients across primary and secondary care settings. The systematic review identified several behaviours relating to the implementation of multi-drug pharmacogenomic testing and the barriers and enablers to each of these behaviours at an individual and organisational level.

This chapter addresses an evidence gap found through the systematic review: a lack of empirical real-world data for multi-drug pharmacogenomic testing implementation in an NHS context. This chapter describes a study which designed a testing pathway for a multi-drug pharmacogenomic testing intervention to optimise prescribing within contrasting NHS settings in England. This used an exploratory case study design to explore the barriers and enablers to implementing multidrug-pharmacogenomic testing relevant to an NHS context. Barriers and enablers were then mapped to domains within the TDF to prioritise behaviours and associated domains for behaviour change.

The qualitative nature of this exploratory case study design required a change in voice in the thesis writing from a passive, general voice to an active voice. High quality qualitative research that is credible and trustworthy relies on reflexivity (Jootun et al., 2009). Reflexivity in research is a process of dynamically including viewpoints and experiences in developmental accounts of the research process itself, to include the viewpoints and experiences of the researcher in actively conducting the research and to distinguish and identify different voices and actions (Olmos-Vega et al., 2022). From this point, this chapter is therefore written in the first-person from my perspective as the researcher.

4.7 Aim

To understand prescriber, pharmacist, and patients' perceptions of barriers and enablers to implementing multi-drug pharmacogenomic testing within an NHS context.

4.8 Objectives

1. Describe the design for identifying how a multi-drug pharmacogenomic testing intervention may be implemented within an NHS context.
2. Describe what training and for whom may be required to implement multi-drug pharmacogenomic testing within an NHS context.
3. Describe barriers and enablers to multi-drug pharmacogenomic testing implementation for prescribers, pharmacist and patients within an NHS context.
4. Identify what TDF domains may be relevant to prescribers', pharmacists' and patients' behaviours which relate to implementing multi-drug pharmacogenomic testing within an NHS context.

4.9 Ethical Approvals

I obtained ethical and governance approval from the UK Health Research Authority. The study protocol and ethical and governance approval letters are provided in Appendix 10 and 11. I found the most challenging aspect of the first ethics committee meeting was explaining how PGx testing would be used by health professionals and evidencing that health professionals would have the necessary indemnity cover to use the PGx test in the clinical care of patients. I addressed these issues by providing written information from each of the participating NHS trusts to establish that the prescribers professional indemnity would cover the use of the PGx test as the prescriber would still be using their clinical judgement. I also amended the protocol to explain in more explicit terms how the health professionals would use the PGx test, including outlining more clearly the inclusion and exclusion criteria.

4.10 Patient and Public Involvement

I worked with two lay representatives to design study materials and discuss approaches to patient recruitment. I did this because I identified through the systematic review that one of the barriers to PGx testing was patient acceptability around genetic testing. I therefore sought PPI input to ensure the patient voice was present throughout the research process in an attempt to pre-empt what some of the patient recruitment issues might be and resolve them ahead of study enrolment. Through a series of online meetings over Microsoft Teams, I worked with SW and DM to produce participant information sheets, research invitation letters and consent forms (Youssef, Mellor et al. 2022) (Appendix 12-16,18 and 19). SW also roleplayed an interview with me to refine the topic guide in preparation for the patient interviews. My work with the lay representatives was influential to securing ethical approval as the original ethical committee required an additional patient information sheet that SW and DM helped design through several iterations.

4.11 Methods

The systematic review provided information to begin conceptualizing and describing what behaviours prescribers, pharmacists and patients commonly engage with when pharmacogenomic testing is implemented. These common behaviours were grouped within four implementation stages:

1) Ordering pharmacogenomic testing
2) Facilitating pharmacogenomic testing
3) Interpreting pharmacogenomic test results
4) Actioning pharmacogenomic test results

These stages and corresponding behaviours provided the outline of an implementation loop that can occur when PGx testing is initiated. Once results are available the loop is reinitiated by prescribers as new medicines PGx testing can inform on are prescribed, triggering health professional behaviours related to interpreting and actioning pharmacogenomic test results. This loop helps optimise

the safety and efficiency of future medicines initiated for the patient by a prescriber.

Most studies included in the systematic review described PGx test implementation from the perspective of researchers providing narrative accounts of the process of introducing and implementing pharmacogenomic testing within their setting. The conclusions drawn from the systematic review, provide a starting point for researchers and policy makers looking to implement PGx testing, but lack the detail about the complex causal pathways through which PGx testing brings about changes in patient outcomes. Furthermore, the systematic review did not include any studies which described multi-drug pharmacogenomic testing within an NHS context. Health services research increasingly recognizes that complex interventions need to be considered in relation to their context of use as separating interventions from context of use is not easy nor useful (Paparini, Green et al. 2020). Consequently, there is a need for credible evidence of how multi-drug pharmacogenomic testing may be implemented within an NHS setting.

To address these objectives, I sought a methodological approach that could provide useful, actionable evidence for decision makers across the NHS, to implement multi-drug pharmacogenomic testing in their local settings and populations. I therefore chose a case study research approach as it provides a means to explore in-depth a complex phenomenon in its natural or 'real-life' setting.

5.6.1 Case Study Research

Case study research is a research approach in which the investigator explores a bounded system (a case) or multiple systems (collective) to explore an event or phenomenon in its natural context and in depth (Crowe, Cresswell et al. 2011). Case studies are conceptualised in terms of the bounded phenomena of interest rather than in terms of fixed specific data collection methods (Yin 2018). This research design helped me focus on, explore, and so to understand holistically how and why healthcare professionals and patients accommodate and engage with multi-drug pharmacogenomic testing in their 'natural' settings.

The first step in conducting case study research is therefore to "define the case and bound the case" (Yin 2018). Defining the case means to define the constituents of the case clearly and specifically, whether this is persons, places, or organization of phenomena. Bounding the case defines its scope: what is and is not included in the case, whether from time, structure, or other perspectives.

In the present research, I defined the case study by people and space. I defined the relevant actors as the health professionals ordering and carrying out testing, and those patients receiving testing. I defined space as those enclosed systems within different clinical settings in NHS primary and secondary care, where pharmacogenetic testing could be carried out. I limited the scope of the study to the perspectives of the people within the boundaries of the different clinical settings because the primary research aim here was to understand healthcare professional- and patient-perceived barriers and enablers to implementing multi-drug pharmacogenomic testing.

My first step was to identify and recruit stakeholders willing to engage with me and design 'pathways' for PGx testing implementation. I described 'pathways' to stakeholders as the patient journey through time and space in a healthcare setting to accessing and receiving PGx testing. Before discussing with stakeholders, I spent some time in Australia with the principal pharmacists of myDNA Life, who were providing the PGx testing service for this study. This discussion gave me appropriate language to describe clearly and precisely each of the PGx testing activities required by healthcare professionals to deliver PGx testing to patients. My discussions with stakeholders, equipped me to formulate a pathway at each of the chosen healthcare sites by capitalising on local knowledge of existing clinical processes within their respective sites.

This study consisted of two phases. In Phase 1 I identified and facilitated the development of PGx testing pathways in diverse contrasting NHS sites, to act as contained 'cases'. Healthcare professionals at each of these sites were given access to a multi-drug pharmacogenomic test to be used on patients under their direct clinical care. Once all the patients had been recruited and received PGx testing at

each of the sites, Phase 2 was initiated. Phase 2 involved conducting semi-structured interviews with health care professionals and patients who took part in Phase 1, to identify their perspectives on barriers and enablers to multi-drug pharmacogenomic testing within each case study.

5.6.2 PGx service set up

5.6.2.1 The intervention

As described in Chapter 1, multi-drug pharmacogenomic testing is not a single, discrete piece of technology, instead it is a testing process which includes four key components shown in Figure 5-1.

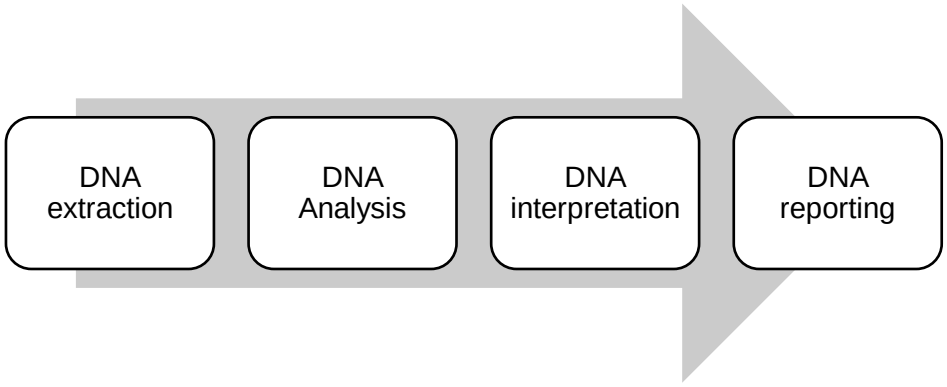


Figure 0-1 PGx testing process

A commercial pharmacogenomic (PGx) testing service provided by myDNA Life Australia was used as the PGx testing intervention in this study as it provided all four key components of the testing process. A brief description of each component in the testing process is provided below.

DNA Extraction

A cheek swab sample is collected from the patient using a CE accredited device to ensure DNA remains stable during transport to laboratories in Australia for testing. The cheek swab sample may be collected by the patient themselves, or a healthcare professional can do this for the patient in person. This is a simple procedure, and I was informed by the company that this is nearly always performed

correctly by patients. In the event that the DNA sample collected is inadequate, the company will contact the patient and healthcare professional and request a second sample. I spoke to the lead pharmacist at myDNA Life and was assured this was very rarely required.

Each sample contains a barcode which must be registered online with the patient details creating a secure online portal for the prescriber, pharmacist and patient to access results. Once collected, the registered sample is sent in a pre-paid envelop to a secure warehouse in West Drayton. Shipping to Australia was triggered when sufficient swabs were received by the warehouse location. The company provides a commercial lifestyle genetic testing service in the UK, which ensured GDPR compliance for data transfer and supported ethical approval.

DNA analysis

Once DNA was extracted from the buccal swabs, it was analysed for common variants in nine genes encoding the enzymes: CYP2C9, CYP2C19, CYP2D6, CYP3A5, CYP1A2, CYP3A4, VKORC1 and the drug transported SLCO1B1.

Table 5.1 compares genes relevant to drug prescribing in UK primary care as explained in Chapter 3, against the gene and gene variants covered by myDNA. The genetic variants (alleles) shown in Table 5-1 were from a paper by Van der Wouden et al (2019) who make recommendations for 'PGx passport', a complete set of actionable gene variant alleles to be used in tandem with DPWG guidelines (Swen et al., 2011, van der Wouden et al., 2019).

myDNA Life analysed 5 out of 9 genes reported in Chapter 3 as relevant to UK primary care. However, one of the key findings from chapter 3, was that four genes (CYP2C19, CYP2D6, SLCO1B1, HLA-B) are responsible for >95% of all drug-gene interactions predicted to occur annually in UK primary care (Youssef et al., 2021). If we compare the impact by looking at the three genes which myDNA also covers (CYP2C19, CYPD6 and SLCO1B1) then screening for variants in these genes could potentially optimise the prescribing of 91.9% of all medicines annually newly initiated in UK primary care.

Table 0-1 Comparison of myDNA test coverage vs PGx genes relevant to UK primary care

Gene	Alleles											
CYP2C9	*2	*3	*5	*11	*17							
CYP2C19	*2	*3	*4A/B	*5	*6	*8	*9	*10	*17			
CYP2D6	*xN	*3	*4	*5	*6	*8	*9	*10	*14A	*14B	*17	*41
F5	1691 G>A											
HLA-A	*31:01											
HLA-B	*15:02	*15:11	*57:01	*58:01								
SLCO1B1	*5	*15	*17									
TPMT	*2	*3A	*3B	*3C								
VKORC1	-1639 G>A	1173 C>T										
CYP1A2	*3											
CYP3A4	*5											

*Grey= Covered by myDNA, Pink=not covered by myDNA, Blue= covered by myDNA but not included in the PGx Impact Study (Youssef et al., 2021). *Genes relevant to UK Primary care as determined by results from Chapter 3.*

Whilst myDNA does not test all of the genetic variants recommended by the PGx-passport, the genetic variants tested cover 95% of known variant alleles in European populations for CYP2D6, 99% for CYP2C19 and 96% for CYP2C9 (Mostafa et al., 2021).

DNA Interpretation

The myDNA Life clinical team assesses peer reviewed and published pharmacogenomic prescribing resources to create an automated clinical algorithm that translates genetic variants into clinically actionable information for over 80 medicines. Where differences occur between guidelines for example CPIC and DPWG, the advice to the prescriber is harmonised and referenced to include both recommendations.

DNA Reporting

A team of physicians, pharmacists, and molecular geneticists' quality control a clinical interpretation report which references clinical recommendations of CPIC and DPWG as well as primary PGx literature. This report is sent to the prescriber and pharmacist via the online portal within 10 working days of receiving the swab. The report uses a RAG (Red, Amber, Green) reporting system for clinical recommendations, with the aim to make interpretation easier for healthcare professionals.

Healthcare professional training

Each prescriber and pharmacist involved in PGx testing at each of the sites recruited undertook the relevant online training package developed by myDNA. The company provided two training packages: one for pharmacists and one for clinicians. These were not translated to a UK setting as they were available in English and had been used by the company in countries other than Australia, like the USA, Canada and Malaysia. I watched both online training packages before the study began and found them to be suitable for UK health professionals because they assumed little prior knowledge of PGx testing.

Training took no more than one hour to complete and covered the following topics with the aim to prepare health professionals to deliver a PGx testing service:

- Ensure that patient consent is informed, and concerns are appropriately addressed
- Collect the buccal sample and patient information for the myDNA test registration
- Pharmacogenomic testing and how it relates to prescribing

Before the online training, recruited prescribers and pharmacists had the opportunity to self-test their genetics by using the myDNA PGx testing service on themselves. As the PGx testing has several steps from ordering the test to receiving the results, I thought it was important the healthcare professional had a detailed

understanding of the patient's journey. In addition, the healthcare professional would also be able to practise how to collect a cheek swab sample, register the test kit and interpret the test report before doing this for patients. The systematic review found that one of the barriers to ordering PGx testing was prescribers' lack of prior experience with PGx testing. I mapped this barrier to the corresponding TDF domain of skills which can be targeted by offering instructions on how to perform the behaviour and opportunities to practise the behaviour or behavioural rehearsal (Carey et al., 2019). I also provided information to the healthcare professionals on the research design and answered any general questions they had regarding PGx testing.

5.6.2.2 Study population

Prescribers who had completed the online PGx training, identified patients under their direct care who met the following inclusion/exclusion criteria.

Inclusion criteria

- Adult male and female patients aged 18 years or older at the time of enrolment. No upper age limit specified.
- Able to read, write and speak English.
- Under the immediate care of registered prescriber who has completed PGx training provided by myDNA.
- Able to give consent.
- Prescribed at least one medicine that can be informed by the myDNA test.
- History of adverse drug reactions/ side effects/ or lack of therapeutic benefit from medicines prescribed past and present.

Exclusion criteria

- Under the age of 18 years.
- Unable to provide consent due to capacity.
- Palliative (expected life expectancy <12 months).
- People undergoing mental health crisis.

5.6.3 Case Study Selection

Table 5-2 provides outline descriptions of each of the characteristics of each case study. To identify and recruit case study sites, I initially gave a presentation about the study concept at a medicine's optimisation group of East Anglia meeting. This group consists of academics at the University of East Anglia, patient, and public representatives, medics and pharmacists from hospital and primary care. Initially two principal pharmacists at two different hospitals in the East of England and a stroke consultant at another hospital also in the East of England contacted me after the presentation showing interest in accessing the PGx tests as part of the study. I arranged a meeting with the pharmacists and stroke consultants separately to explain the myDNA PGx testing process and the study objectives. I then negotiated with each of the healthcare professionals, through a series of in-person meetings and email correspondence the details of a PGx testing 'pathway' in their respective clinical settings. Identifying these pathways enabled me to detail who at each of the sites would do what activities, when and where in relation to patients accessing PGx testing. These details bounded the individual case study sites.

To recruit case study sites in primary care, I contacted colleagues in my research department who were able to identify contacts at two local general practices: a GP, and pharmacist independent prescriber. I organised a meeting with senior clinical representatives at each of the sites, to present details of the study. After negotiating the details of which HCP would do which activities with the PGx testing pathways in each of the settings, the final two cases were chosen as shown in Table 5-2.

Table 0-2 Case study characteristics

Case study	Details of setting	Healthcare professionals involved	Target patient recruitment	Data collection	Data analysis
Mental Health hospital Site A	Outpatient department, Community hospital	Pharmacist independent prescriber, Nurse independent prescriber	10	Semi-structured interviews post-intervention with healthcare professionals and patients. Researcher (EY) reflexive narrative account.	Inductive thematic analysis with behavioural framework component.
Hospital Site B	Cardiology in patient ward, Community hospital	Cardiology medical consultant, Senior hospital prescribing pharmacist	5		
Hospital Site C	Acute Stroke in patient ward, Teaching hospital	Stroke medical consultant, Rotational hospital pharmacist	5		
General practice Site A	General practice	General practice doctor, Pharmacist independent prescriber	5		
General practice Site B	General practice and community pharmacy	General practice doctor, Community pharmacist	5		

5.6.4 Data collection

I collected data in two forms: my narrative account and interview. My narrative account is a written summary of my reflections during the process of designing the

study and negotiating with stakeholders to develop the PGx testing pathways at each healthcare setting which formed the case studies. This data provides detailed qualitative insights into the methods, and my decision-making when choosing the methodology and methods design and carrying out the study. This data is particularly important to distinguish within the context of this study, as the PGx test intervention was provided as part of the research and not an existing intervention within each of the case studies selected. Therefore, my role as the researcher and the research subjects namely the healthcare professionals and patients, were interactively linked and the findings therefore sensitive to this context. My narrative account helps to provide credibility for the findings, by providing details to help present as authentic as possible a picture of the phenomena from my observed experience (Noble and Smith 2015).

The second form of data I collected was interviewing healthcare professionals and patients' post-multi-drug pharmacogenomic testing delivery. The systematic review findings showed that barriers to PGx testing implementation arose mostly around the prescriber behaviour to order PGx testing. Taking this into account, I developed a semi-structured topic guide informed by the systematic review of barriers and enablers to the implementation of multi-drug pharmacogenomic testing reported in Chapter 4 (Youssef et al., 2021). I designed a topic guide to ensure consistency across the interviews (Appendix 17).

I designed the guiding questions in the semi-structured topic guide with the aim to elicit participant's views regarding the following three areas:

1. Healthcare professional and patients' perceptions of multi-drug pharmacogenomic testing in their setting.
2. Healthcare professional and patients' perceived barriers to implementing multi-drug pharmacogenomic testing in their setting.
3. Healthcare professional and patients' perceived enablers to implementing multi-drug pharmacogenomic testing in their setting.

I designed questions and probes to elicit barriers and enablers to implementing multi-drug pharmacogenomic testing within all 14 TDF domains. Prior to initiating the interviews, I sought feedback on the topic guide from an expert in qualitative research methodology (FP) and expert in use of the TDF (DB). I amended the topic guide based on the feedback I received. The changes I made in the topic guide included the following:

1) Changing the style of the questions so they are less direct and intimidating to the patient. For example, instead of starting a question with *"What do you think about…"* I changed it to "Could you tell me about…".
2) Removing closed questions in favour of more open questions

I also piloted the topic guide with a mock interview with one of the PPI representatives (SW). I created an actor's brief for SW where a patient had a PGx test which explained why she had an adverse reaction to one of her antidepressants. The actor's brief is available in Appendix 20.

At the end of the mock interview, I asked for feedback from the PPI representative on their experience as an interviewee and my performance as an interviewer. Based on the PPI representatives' feedback and my own reflections from conducting the interview, I made further changes to the topic guide. These changes included more structuring questions to navigate the interview and check the participant had finished expressing their answers fully. Having a mock interview with the PPI representative would be even more important for a telephone interview as I could only communicate with the patient verbally, and would not be able to observe non-verbal communication cues that indicated they understood the question or were bored etc. I agreed with this feedback as it could enhance the trustworthiness of the telephone interviews and amended the topic guide accordingly. Additionally, during the practice interview with the PPI representative, she asked me a question pretending to be the patient about how long her newly prescribed medicine would take to work. During the course of the mock interview, I caught myself shifting into pharmacist mode instead of interviewer mode and explaining that antidepressants will take around 6 weeks to see an effect. I mentally

noted this lapse during the interview and discussed it at the end of the interview with SW. She suggested changing the introduction before the start of the interview to explain clearly to the patient despite my professional background I would be exclusively present in the interview as a researcher. I took her suggestion on board and amended the interview topic guide. Additionally, I made some notes for myself with prompts if a participant asked a medical question during the course of the interview, reminding them of my role and advising them to contact their medical provider.

I also learned through piloting the topic guide a 30-minute telephone interview was feasible for sufficient discussions. I opted to undertake telephone interviews over in person interviews from a pragmatic perspective. The impact of Covid-19 meant health professionals and patients were encouraged to maintain social distancing where possible. Well-planned telephone interviews can gather data comparable to those held face-to-face, whilst enabling the inclusion of groups that are isolated, geographically dispersed, or stigmatised (DeJonckheere and Vaughn, 2019, Novick, 2008). Telephone interviews also have advantages over face-to-face interviews in terms of reducing interviewer effects, lowering the tendency to socially desirable responses and reducing research costs (Lavrakas, 1987). I conducted telephone interviews between July and August 2022. Written, informed consent was obtained from participants at the beginning of each phone interview. To prepare the interview, I undertook training in qualitative research methodology and principles and practice of behaviour change.

5.6.5 Sampling

I planned to use a purposive sampling technique to guide selection of patients to interview. This is a sampling technique in which the research participants are chosen to represent a range of beliefs and experiences that the researcher believes will be relevant (Kuper et al., 2008). I planned to collect information from patients who expressed an interest to participate in the research on a form as seen in Appendix 15. From the patient pool of interview volunteers, I planned to select patients to identify the uniqueness of each case study from a heterogenous sample,

as well as common patterns that emerge from the sample to capture the core experiences and central, shared aspects of experiences. I aimed to collect a maximum of 12 patient interviews, on the assumption that 30 patients would be recruited across the five case studies and 10 health care professional interviews, on the assumption that all five case studies would go ahead. This number of interviews is in line with usual qualitative sampling practices (Guest et al., 2006).

5.6.6 Quality in Qualitative Research

The approach to ensuring quality is qualitative research is distinct from that of quantitative research (Johnson et al., 2020). Where quantitative research uses statistically-related terminology to appraise research such as internal validity, external validity and generalisability, these terms are much less applicable in qualitative research which seeks to rigorously identify differences and diversity in plural ideas, views and experiences, even in single instances (Santiago-Delefosse et al., 2016). Therefore, qualitative research is assessed for quality and rigour in terms of 'trustworthiness', which requires the conduct and reporting of research to be transparent and auditable (Guba, 1981). Here, terminology such as credibility, transferability, dependability, confirmability and authenticity are used (Guba, 1981). To address credibility, the researcher should attempt to demonstrate as true a picture of the phenomenon presented. To enable transferability, sufficient detail of the context of the qualitative study should be provided to allow the reader to determine whether the context of the study allows findings to translate to similar contexts. For confirmability, the researcher should demonstrate the findings are clearly derived from the data. For dependability which is analogous to the consistency and reliability of the finding and the degree to which research procedures are documented, an audit trail should be maintained of the data, methods, and decisions (Nyirenda et al., 2020). These aspects of trustworthiness are achieved in qualitative research through triangulation and reflexivity.

Triangulation refers to the use of multiple methods or data sources in qualitative research to develop a comprehensive understanding of phenomena. Triangulation can be used to indicate verification or completeness of the data, which is important

in ensuring qualitative research enables multiple realities to be recognized (Nyirenda et al., 2020). I employed triangulation in the data analysis in this study to offer a more comprehensive picture of each of the case studies by treating my written reflexive observations and the interview transcripts as two different data sources.

While objectivity is prioritized in quantitative research and is sought through mechanisms like blinding, subjectivity is intrinsic in qualitative research which recognizes multiple realities (Elliott et al., 1999). Qualitative research is therefore reflexive as the researcher is part of the research and not just observer but an instrument in the research process. Reflexivity is the self-aware analysis of the interconnectedness between the researchers and the object of the research (Elliott et al., 1999). Qualitative researchers must therefore be aware and acknowledge the factors which may influence their behaviour throughout the research process. This involves exploring the researcher's relationship with subject matter. A strategy I adopted to record and acknowledge my own interaction with the qualitative data collected was through keeping a reflexive researchers diary through the entire research process. Initially before any data collection, I documented my specific beliefs and issues relating to the subject matter. Being actively aware of these preconceptions facilitated me to make them transparent during the data collection and analysis process. After each interview, I also reflected on and documented learning from the discussions and research process.

5.6.7 Data Analysis

I conducted data analysis of each of the cases in two stages. Firstly, I looked over my reflective diary, study documentation, email and written correspondence to produce a researcher narrative account of setting up and monitoring the running of the PGx testing service in each of the cases. Secondly, I undertook data analysis of the interview data in two phases: 1) thematic analysis and 2) Mapping to the TDF. I then triangulated both data sources to characterise each of the cases and identify barriers and enablers to implementing PGx testing in the NHS.

5.6.7.1 Interview data analysis steps

I transcribed verbatim all interviews and removed participant identifiers to anonymised them. I then checked the accuracy of transcriptions against the audio files twice, which aided in familiarisation with the data. Analysis was an ongoing process and assisted by qualitative analysis software NVivo 12(QSR International, Melbourne, Australia).

I undertook data analysis of each of the interviews and collectively in these two steps:

1. Thematic analysis to identify participant-stated determinants (barriers and enablers) to practitioner, pharmacist and patient behaviours involved in implementing multi-drug pharmacogenomic testing.
2. Mapping all identified determinants in step 1, to the TDF.

Phase 1: Thematic analysis

I initially analysed the data through the five commonly-found steps of thematic analysis :data familiarisation, generating initial codes, searching for themes, review theses, defining and naming themes initially-described by Braun and Clarke (Braun and Clarke, 2006). Thematic analysis took place first to ensure resultant themes were not constricted to the pre-defined TDF domains.

Step 1: Data familiarisation

I reread the transcripts several times to help familiarise myself with the breadth and depth of their content. During this process I made informal notes on my initial ideas for relevant coding categories and referred to these during later phases of the analysis.

Step 2: Generating initial codes

I coded inductively, initially identifying data describing the behaviours of health professionals and patients related to the implementation of PGx testing. Data extracts describing barriers or enablers to these behaviours were coded inclusively, i.e. relevant text surrounding the phenomena of interest was retained, to ensure continuing attention to features of context. Two researchers experienced in

qualitative research (FP) and behaviour change (DB) research reviewed a sub-set of the codes and associated data extracts for consistent credibility.

Step 3, 4, and 5: Searching for themes, reviewing themes, and defining themes

I sorted the codes by considering how different codes could be combined to form overarching themes and sub-themes. I collated all relevant data extracts within themes identified through inductive reasoning and then refined these to identify the data as meaningfully coherent within each theme. Finally, themes were defined in order to convey the essence of what they were commonly about, to present them for analysis.

Phase 2: Mapping all determinants to health professional and patient behaviour related to multi-drug pharmacogenomic testing to the TDF.

I re-read the transcripts and mapped all inductive codes from the phase 1 thematic analysis to the relevant TDF domains. The TDF domain definitions were used to guide this mapping and organised the coded data within each domain into barriers and enablers. DB checked the mapping for consistent credibility, and I resolved any disagreements through discussion.

4.12 Results

5.7.1 Researcher's reflexive narrative account

I found the process of recruiting healthcare professionals for my study challenging. My background at the start of my PhD was a clinical hospital pharmacist with three years post-qualification experience and a post-graduate diploma in clinical pharmacy. When I applied for the PhD, I had little knowledge on pharmacogenomics or personalised medicine other than the idea that it held the promise of being able to find the 'right drug, at the right time, for the right person' based on the person's genetics. Once I joined my PhD programme in October 2018, I began to read around the subject for my literature review to discover what was clinically achievable and deliverable with the technology available, finding this to be more modest than I had initially thought. Additionally, while I had knowledge of the

scientific literature that underpinned the technology, namely how the drug-gene pairs are discovered, what laboratory techniques are used to detect the gene variants and what types of studies inform the evidence behind the published prescribing recommendations, I found limited literature that described the practical on-the-ground implementation of pharmacogenomic testing. In addition, the PGx testing service I was providing to the stakeholders was designed for community pharmacies in Australia who were responsible for performing the test but did not action the result in the way a medical doctor will.

I observed some common challenges in my process of securing interest from stakeholders from all settings, described below. Later, I will discuss in more depth the process of securing interest from stakeholders in each of the settings: primary care, secondary care, and mental health.

Managing healthcare professional expectations on what the test can offer

I found managing expectations on what value PGx testing could provide in patient care to be one of the more challenging aspects of negotiations with healthcare professionals because health professionals lacked knowledge on PGx testing. Nearly all the healthcare professionals I approached about my study, had never used, or received training on pharmacogenomic testing. The resources I had from myDNA covered which drug-gene interactions the PGx test would report on but did not describe the nature of this information. As seen in modelling study reported on in Chapter 3, 'actionability' of drug-gene interactions differs widely with some requiring immediate dose or drug change (direct action) and others requiring additional monitoring or dose capping (indirect action). This made negotiations sometimes challenging as the list could be misleading because it did not distinguish between the evidence underpinning each of the drug-gene interactions. For example, the evidence underpinning the drug-gene interaction of proton pump inhibitors is only relevant for the indication of H Pylori eradication or erosive oesophagitis. Proton pump inhibitors are one of the most prescribed medicines in both primary and secondary care, however most of these prescriptions are for indications other than H Pylori infection or erosive oesophagitis. Therefore, a

healthcare professional who views the list, may think: ' I have lots of patients on proton pump inhibitors for acid reflux, this might help me optimise prescribing for them', but the reality is if the majority of their patients are prescribed PPIs for indications other than H Pylori infection or severe erosive oesophagitis, then the test will not be relevant to them.

Initially I wrestled with the problem of how to describe the value of PGx testing as both a researcher and pharmacist. On the one hand as a researcher, I was keen not to engineer a context where PGx testing was only viewed as useful by healthcare professionals as it was important that the 'reality' of what PGx testing is, was experienced by the healthcare professionals. However, as a pharmacist I was resistant to the idea of putting another healthcare professional in a situation where they would receive information on a patient's genetics showing a predicted potential aberrant response to a medicine, but no clear information on how to manage this. Later in the research when I became more familiar with PGx testing, I viewed the risk of health professionals receiving a patient's genetic results of unknown significance as a low-risk event, as it became clear to me that healthcare professionals would simply revert to normal prescribing guidance. Consequently, in research decision making processes, I informed the health professionals interested in joining my study that the PGx test would inform on medicines outside of their clinical speciality and allowed them to decide how to manage these clinical scenarios.

The aim of the study was to understand what a PGx testing pathway would look like within an NHS setting. However, as part of the study a PGx testing pathway also had to be set up, so this was also considered part of the research by the NHS ethics committee. Therefore, for the NHS Ethics application I had to create an inclusion criterion for healthcare professionals to choose patients for the PGx testing. As the test was to be part of the patients' clinical care and would require additional time from the patient to consent to testing, and share information, I stated one of the inclusion criteria as that the test should be ordered if the prescriber judged the patient could benefit from PGx testing. This was still a broad inclusion criterion

because I as the researcher was interested in what influences healthcare professionals to order PGx testing the patients.

To support my ability to negotiate with healthcare professionals, so they could be fully informed on how the test might be able to optimise prescribing in their usual clinical practice, I spent some time familiarising myself with published CPIC and DPWG guidelines. The myDNA test informs on around 80 drugs, however with my own experience as a pharmacist, I was able reduce my workload of literature searching by focusing on the medicines I could see were most frequently prescribed in each of the specialities I approached. Once familiar with the literature, in the conversations with healthcare professionals I presented the list of the medicines the myDNA test could provide information on and then asked which of those medicines were of most interest to the healthcare professionals. I was able to give them further information at that point in the conversation on what kind of information the test would provide for that medicine. At this point when I could see the healthcare professional had a clearer picture of what kind of information the test could provide, thereby managing their expectations and the patients.

Minimising additional work required of health professionals delivering the PGx testing service

It was not feasible to design a PGx test intervention from scratch for piloting within the time constraints of the PhD. Therefore, I had to adapt as much as possible the existing PGx testing service from myDNA to an NHS context. This was somewhat challenging, as the myDNA testing service was based in Australia and designed to be a direct-to-consumer genetic testing service. This testing model relies on a patient highly motivated to undertake PGx testing even willing to pay for their own genetic test. Consequently, the process of registering each kit online and sending the sample in the post require additional work of the patient which someone who has paid for the kit may find more acceptable.

To reduce the risk of health professionals over-selecting patients with high health literacy levels and self-motivation, I therefore wrote into the protocol that the health professionals could carry out these activities on behalf of the patient. Later

with the impact of COVID-19, I gave the health professionals both options: either they could register the kits and collect the saliva swab samples themselves from the patient; or they could send a pack with the kits and information to the patients home where they would carry out these activities themselves.

In each of the settings, I tried to separate the activities relating to facilitating the PGx testing process to allied professionals rather than the primary prescriber. My perception at the time was that a hospital consultant or general practioners would be less willing to be part of the study if they had to undertake the time consuming, but not technical aspects of PGx testing service delivery. Instead, where possible I aimed to restrict the activities of the prescribers to activities requiring their clinical judgement like selecting the patients and interpreting and applying the PGx results within the clinical decision-making processes. My initial stakeholder conversations at the medicines optimisation group indicated pharmacists were more likely to express enthusiasm for the PGx testing as a potentially useful concept and were more likely to offer to undertake the activities relating to service delivery. As a result, where possible, I negotiated with stakeholders at each of the sites to identify a service delivery pathway that incorporated both clinicians and pharmacists.

NHS Ethics process

The process of securing NHS Ethical approval was prolonged and challenging due to the novelty of the technology and the company who provided the PGx testing service being based in Australia. I initially approached the NHS ethics process with the mindset that the study would be a service evaluation, and the research component would be the qualitative element of interviewing a sample of the healthcare professionals and patients post-PGx testing service delivery. My rationale was a medical doctor could order a PGx test for a patient privately and therefore even though I was giving access to the PGx testing service to prescribers, I did not want to be involved in how they would use the tests but rather understand their experiences post PGx testing delivery. This approach was not supported by the NHS Health Research Authority ethics review because myDNA Life did not offer at the time a PGx testing service in the UK, although it had all the necessary legal

approvements to do so. As a result, the protocol underwent multiple iterations to include descriptions of the planned health care professional and patient activities in the process of the service delivery. This was not ideal, as I wanted to research how the health professionals adapt the PGx testing service delivery model to their setting through their experiences. The ethics committee however did not allow this because they interpreted a risk to participants to the study using a technology in the care of patients that is novel and outside of their routine practice without clear procedures. Therefore, to minimise this risk, I had to write clearly in my protocol how the health professionals would deliver the service before they even had a chance to practise using the PGx test themselves.

Ethical approval for the study was initially denied by the REC because the ethics committee was not satisfied that the health professional participants were being given comprehensive-enough instructions on how to deliver the PGx testing service in their setting. In addition, the ethics committee wanted details as to whether the health professional's professional liability and indemnity insurance would cover them using PGx testing in the clinical care of their patients and how they would use the test in their clinical decisional making. I also found it difficult to explain the function of the PGx test in providing additional information to be integrated by the prescriber in the clinical decision-making process of choosing medicines and doses, rather than a companion diagnostic that would instruct whether the prescriber would choose or avoid a certain medicine. To respond to the feedback from the ethics committee, I amended the protocol to include more inclusion/exclusion requirements to guide health professional selection of patients and locations for where activities pertaining to service delivery would take place. I also obtained written confirmation that prescriber's liability and indemnity insurance would cover them using the test as it was not a substitution for clinical decision making and prescribers are able to order this type of testing privately for patients already.

Mental Health Trust Hospital Site A

The Principal Pharmacist from the Mental Health Trust Hospital Site A was one of the first to show interest in the study. She was enthusiastic and responded

promptly to my email, to arrange a meeting on site with a Pharmacist Independent Prescriber (PIP) who would be the principal investigator at the hospital. At the first meeting, both the principal pharmacist and PIP were very enthusiastic about enabling the study, had researched on pharmacogenomic testing and made the link between genetic testing and drug metabolism. As they had some basic knowledge of pharmacogenomic testing made it easier to discuss how the test might be used in their setting. I found the expectations of the PIP and principal pharmacist, the easiest to manage as they were aware of how the test worked and the information, they would receive to guide prescribing. The conversations I had with the PIP, told me that they were saying that side effects were often the most common reason a patient would stop an anti-depressant or anti-anxiolytic, suggesting any test might at least indicate to the health professionals which medicines to avoid and narrow the list of prescribing options was useful. Here is an extract from my reflexive diary following my initial meeting with the Principal Pharmacist and PIP from The Mental Health Trust.

"I had a meeting today with [PIP] at the City Anchorage. He was really enthusiastic about the [PGx] testing and has already spoken to some of the consultants about using the test in patients they know now. He framed the DNA testing as finding out about the patient's drug metabolism and all of their patients take medicines the test can inform on." (Researcher reflexive diary entry 25.01.2019)

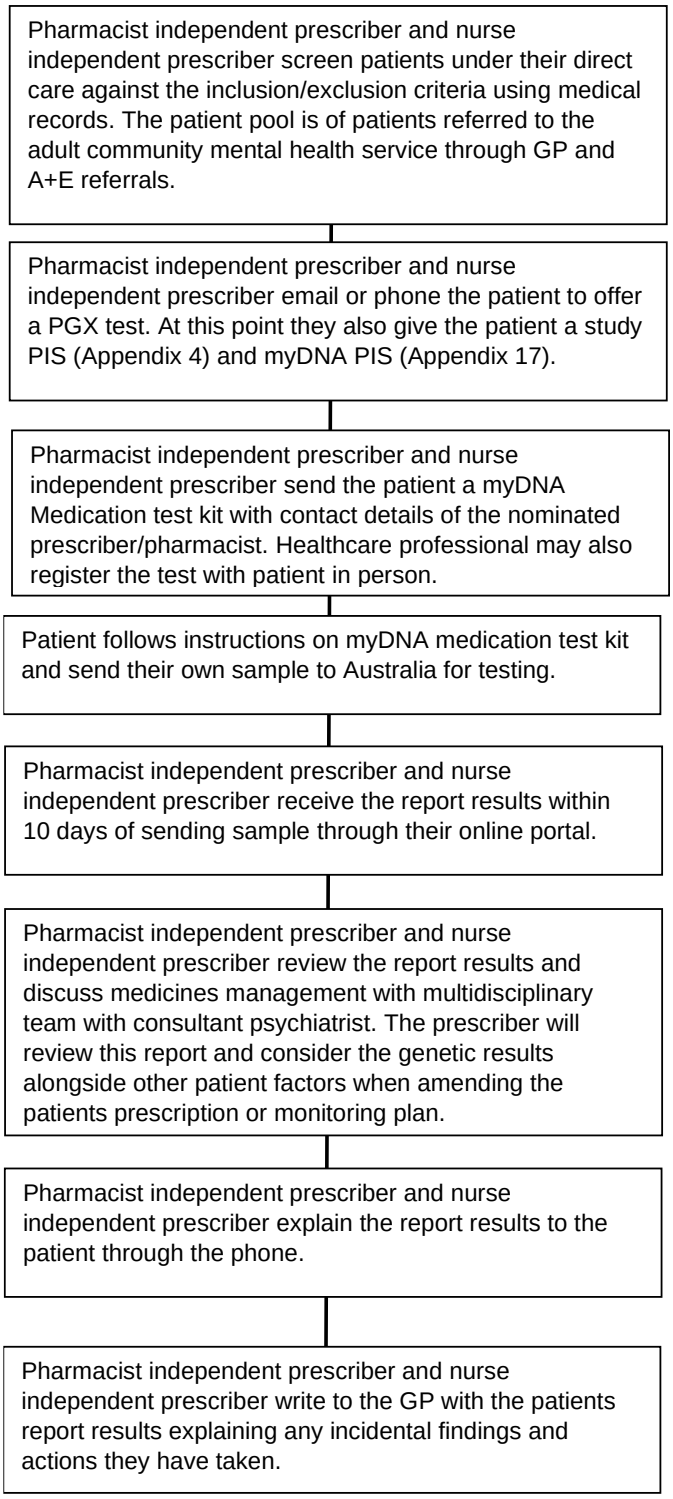
This PIP's framing of PGx testing as drug metabolism DNA testing demonstrates technical knowledge of PGx testing which I did not encounter with stakeholders from the other settings.

I noted in my researcher diary that I perceived the PIP to be enthusiastic about the study as they asked lots of questions about PGx and for references so they could read more about the topic. They were also prompt in replying to email correspondence and took initiative to identify the key research contacts at their site and introduce me early in the research process, which I think was a key driver to securing approvals for the study at mental health site before the other sites. As this quote indicates, the PIP had already started to describe the concept of the study to

the consultants, recognising they would need their buy-in to support the study. When I expressed to the PIP that he showed more interest and motivation for the study versus other healthcare professionals I approached to describe the study, he noted that within the area of mental health, there was little guidance to help selection of medicines. He explained that often what determines whether someone remains on a medicine, is the absence of side effects, of which there were few clinical tests they could use to predict this. Therefore, the promise that PGx testing. could provide a method to narrow the number of medicines, a prescriber could select for a patient was a huge advantage to the PIP to help optimise prescribing. After the meeting, I arranged a follow up with the PIP and the mental health team consisting of nurse independent prescribers and consultants to discuss the study and how the service could be delivered in their setting. Figure 5.2 sets out the PGx testing service delivery pathway for the mental health trust.

The pharmacist independent prescriber and nurse independent prescriber elected for a model where they would carry out all the PGx testing activities themselves, from consenting the patient, to registering the kit, interpreting the report, and counselling the patient. This was in line with their usual practice as each practitioner often worked independently with the care of their patient lists, with input from the weekly multidisciplinary team meetings.

Figure 0-2 Summary of PGx testing pathway at mental health trust hospital site A



Secondary Care

I found recruiting case study leads from hospitals to be the most challenging. I saw this as mainly because the facilitative activities required the health professionals to deliver the PGx testing service delivery. The 'facilitation' activities involved were time intensive, creating a barrier in negotiations as I found the medical consultants who were interested in doing the PGx testing in principle but did not perceive they had the additional time carry out these activities. One of the aims of this study was to describe the design of how multi-drug pharmacogenomic testing may be implemented within an NHS context. I was therefore interested in an implementation model that would be scalable for wider implementation which would therefore require acceptability from medical consultants.

My experience as a hospital pharmacist, had made me aware of how doctors order clinical tests during ward rounds. Typically, the doctor would document the required clinical blood test in the notes, order the test on the computer system and speak to the patients' nurse to collect the sample and send off to the laboratory. The 'facilitation' steps of the myDNA PGx testing service presented a deviation from the standard clinical test pathway. Based on the literature, and experience I gained from observing the PGx testing model in Australia, I identified that a hospital pharmacist could undertake some of the facilitative behaviours like registering the testing kits, collecting the patient sample and consent, and posting the sample. When I talked to the consultant about this idea, they judged a consultant/pharmacist PGx delivery model to be acceptable, with the consultant identifying the patients for recruitment.

I identified two hospitals as potential case studies. Hospital Site B was a small general hospital and Hospital Site C was a larger teaching hospital, both located in the East of England.

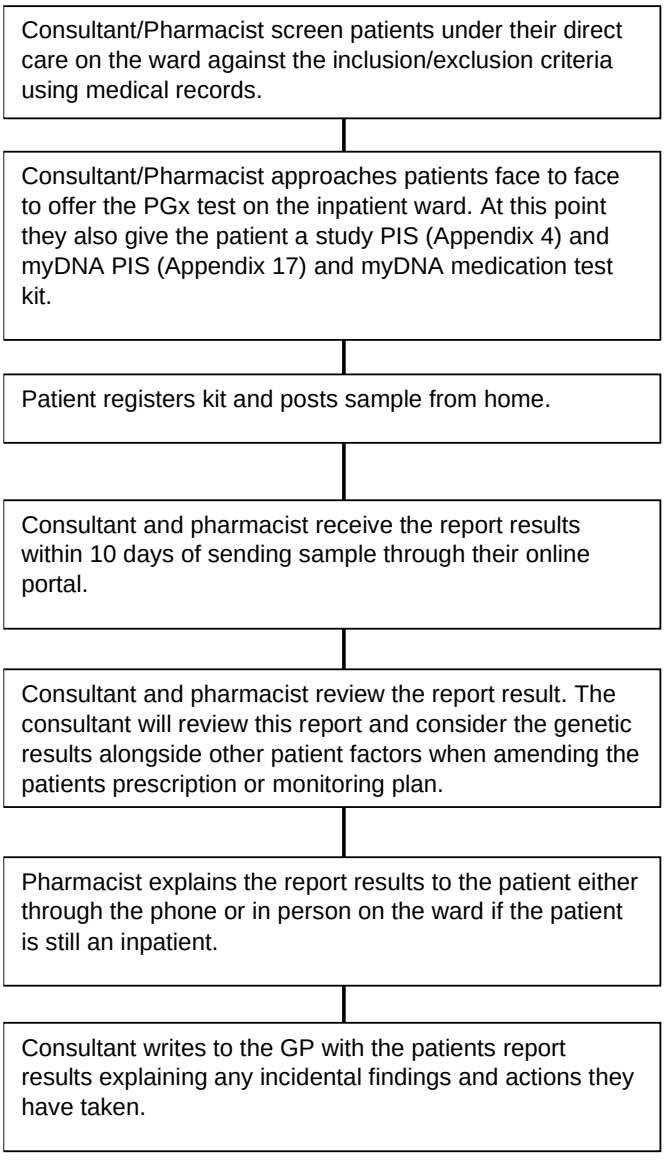
I identified Hospital Site B through the principal pharmacist who contacted me after I presented the concept of the study at the medicine's optimisation group of East Anglia. This group consisted of consultants, GPs, pharmacists, patients, and academics looking to build research collaborations in the Norfolk area. I had a meeting with the principal pharmacist and showed him the list of medicines the PGx test could inform on. I found it was easier to organise the medicines into therapeutic groups and identify specialities that would frequently initiate these medicines. Through the meeting with the principal pharmacist, we identified two areas: cardiology and gastroenterology. The principal pharmacist then contacted different consultants in these specialities' cardiology consultant expressed an interest in using the test in the heart failure outpatient clinic. The clinic had a pharmacist independent prescriber who would work with the consultant to deliver the PGx testing service. The pharmacist and consultant would work in tandem to interpret the DNA results and the consultant would make the prescribing decision. The pharmacist would contact the patient's GP and highlight any drug gene interactions and what actions had been taken.

The second site was a large university teaching hospital (Hospital Site C). I was initially approached by the elderly care consultant who was interested in being part of the study, because the test informed on medicines, he saw routinely prescribed in his patient population. The elderly care consultant was particularly interested in using the PGx test to support deprescribing by identifying medicines that were sub-optimally prescribed. Unfortunately, after talking through the online registration and consent process, the elderly care consultant expressed it may be challenging to recruit patients who may not have the capacity to consent themselves online to the test. He suggested instead I work with a stroke consultant and made the necessary introductions. The stroke consultant was interested in using the PGx test to support prescribing of anti-platelets and also antidepressants post-stroke. I was concerned about the use of the test prior to prescribing, as there would be an estimated delay of two weeks for results reporting. I emphasised this to the stroke consultant, who felt even with the delay the results would be useful from a medicines review perspective and to identify patients who had previous therapeutic failure with the

anti-platelet medicine clopidogrel. Much like Hospital Site B, a ward pharmacist would work with the stroke consultant and carry out the facilitative activities necessary to deliver the PGx test service.

Unfortunately, due to COVID-19, after securing NHS ethical approvals and local hospital trust agreements, both hospitals sites B and C pulled out of the study as all research activities were halted to prioritise urgent patient care

Figure 0-3 Summary of PGx testing pathway for secondary care



Primary Care

I faced similar challenges in recruiting primary care sites as I did secondary care sites, namely negotiating with GPs what time commitments were necessary to deliver the PGx testing service. Again, proposing a clinician/ pharmacist model for PGx test service delivery was considered by GPs and pharmacists alike as acceptable.

For the general practice site A, I was approached by a teacher pharmacist practitioner in my department at the University. This person also worked part-time as a pharmacist independent prescriber (PIP) at general practice site A, conducting medicines reviews. The PIP had heard about the study through word of mouth in the department and approached me in-person for further details. I arranged a meeting with both the PIP and GP interested in PGx testing and negotiated a model where the PIP would offer the PGx test delivery service as part of their role conducting medicines reviews. The GP would oversee these activities, working with the PIP to identify patients to recruit and reviewing the PIPs actions based on the PGx test report results. Both the PIP and GP wanted to use the PGx test to guide prescribing for patients who had tried multiple antidepressants unsuccessfully.

For general practice site B, I was approached by a GP from the medicine's optimisation group of East Anglia. The practice did not employ a pharmacist but was located closely to a community pharmacy and had good relations with the pharmacy manager at the community pharmacy. I arranged a meeting with both the GP and community pharmacist, and they proposed a model where the GP would identify patients suitable for testing and signpost them to the community pharmacy where the pharmacist would take consent and register a PGx test kit. The community pharmacist would then arrange a follow up appointment with the patient where they review the report that has been discussed with the GP and counsel the patient on any changes to the prescribing or monitoring of the medicines based on the report.

Figure 5.4 summarises the PGx testing service delivery pathway for primary care. Unfortunately, due to COVID-19 disruption, after securing NHS ethical approvals and local agreements, both general practices pulled out as all research activities were halted to prioritise urgent patient care.

Figure 0-4 Summary of PGx testing pathway for primary care (general practice 1)

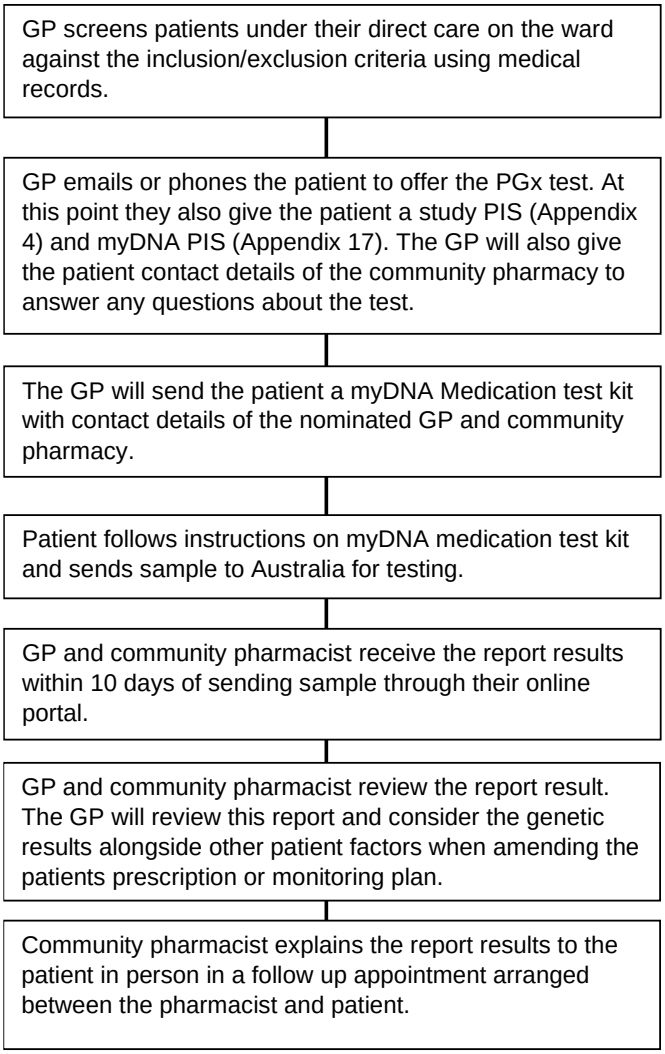
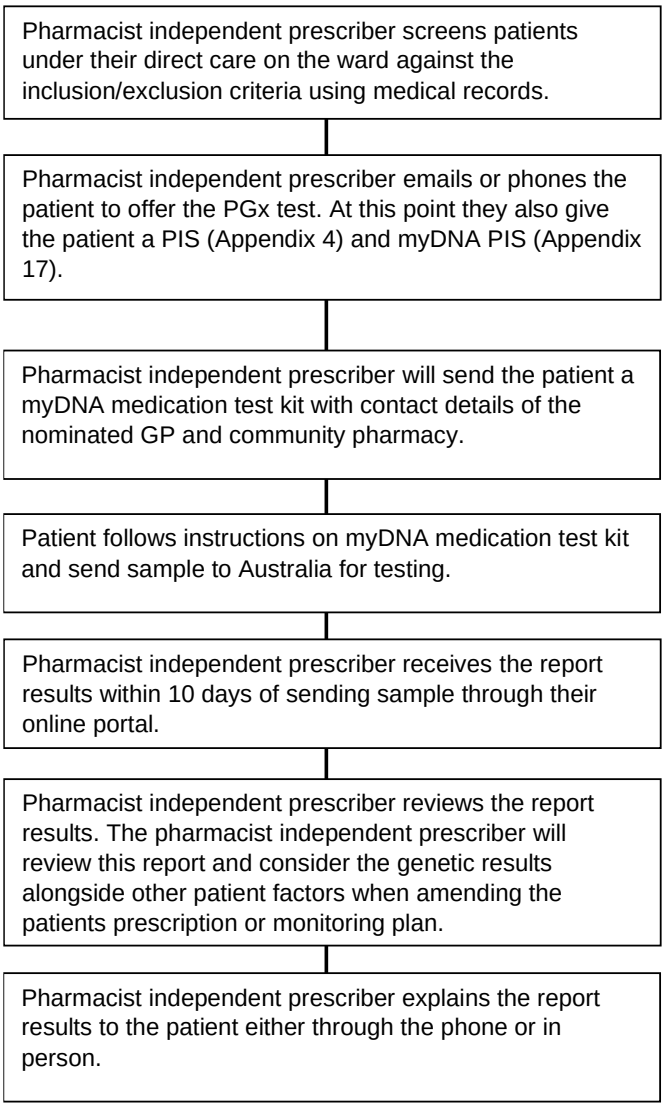


Figure 0-5 Summary of PGx testing pathway for primary care (general practice 2)



5.7.2 Case Study Interviews

5.7.2.1 Sample

Principal investigators in all five case studies gave their expression of interest and support for the study, which enabled me to secure approval from the NHS Health Research Authority to carry out the study with NHS patients. However, the timing of the NHS ethics approval coincided with the COVID-19 lockdown. These lockdown effects were sustained over the next two years as all the sites dealt with

consequences of COVID-19 such as the second wave of infections which occurred between November 2020-March 2021 and then vaccination rollouts in November 2020- March 2021 and then vaccination from September 2021. As a result, only the mental health trust hospital site A was able to support the study, with the other case studies dropping out at various dates, shown in Table 5-3, due to staffing shortages and existing workloads.

Table 0-3 Table showing the dropout and completion timelines for each case study.

Case study	NHS Ethics approval	Local Approvals (Capability and Capacity)	Dropout date	Reason for dropout
Mental Health hospital Site A	17.03.2020	26.03.2021	n/a	n/a
Hospital Site B		Declined	10.01.2021	Stroke department unable to engage with study due to patient care demands in post-COVID recovery period.
Hospital Site C		Declined	08.02.2022	Pharmacy department unable to engage with the study due to staffing issues in post-COVID recovery period.
General practice Site A		17.06.2021	14.21.2021	GP unable to support due to work pressures due to COVID-19 vaccinations.
General practice Site B		17.06.2021	08.11.2021	GP unable to support due to work pressures due to COVID-19 vaccinations.

Only the mental health trust participated fully in this study to provide all components of a complete single case study for analysis. The pharmacist independent prescriber (PIP) and nurse independent prescriber recruited ten patients to have PGx testing. All healthcare professionals and patients who received PGx testing were invited to participate in interviews. I obtained consent and interviewed all the health professionals recruited at the mental health trust for the study which were a pharmacist independent prescriber (PIP) and a nurse independent prescriber. From the 10 patients who had received PGx testing at the mental health trust, one patient expressed interest and gave consent for an interview which I subsequently conducted. To encourage recruitment of patient interviews I submitted an amendment to NHS HRA ethics board, to increase the value of the gift card reward for research participation from £10 to £20. However, no additional patients volunteered to be interviewed. Table 5.3 shows a summary of the interview participant characteristics. Details of how I managed and analysed the interview data are included in Section 5.6.6.

Table 0-4 Summary of interview participants' characteristics

Participant	Group	Interview length
1	Pharmacist Independent prescriber	35 mins
2	Patient	28 mins
3	Nurse Independent prescriber	26 mins

5.7.2.2 Thematic analysis

Four overarching themes emerged from the inductive analysis:

1. Process
2. Expectations
3. Effort
4. Unknown territory

Table 5-5 summarises the different themes and sub-themes for each together with a definition of each theme. These themes were derived inductively from the discussion of interviewee perspectives on health professional and patient enacted PGx testing related behaviours. The themes can be seen to identify both barriers and enablers to PGx testing implementation at an individual level and group levels. I discuss each of these themes in more detail in the following sub-sections.

Table 0-5 Summary of overarching themes

	Description of theme (including definitions) and sub-themes
Process	The series of progressive and interdependent activities required of healthcare professionals and patients to access pharmacogenomic testing. • Complicated registration system • Computer system incompatible for allied professionals • Patient technological competence • Cheek swab sample is simple • Time delay for results • Pharmacogenomic testing in principle is simple to deliver • Healthcare professional existing workload • Additional workload associated with testing
Expectations	The relationship between beliefs of healthcare professionals around what PGx testing can deliver in relation to optimizing drug and dose selection, and how PGx testing is used in practice. • Pharmacogenomic testing reduces time to the right drug • Healthcare professionals perceived patient agency in shared decision making • Disillusionment • Positive attitude to pharmacogenomic testing • Face to face setting for counselling patients on results • Function of pharmacogenomic testing • History of side effects with medicines • Cost of pharmacogenomic testing

Effort	The additional cognitive work that healthcare professionals must exert to successful complete clinical activities to deliver pharmacogenomic testing. • Prescriber self-reported confidence to judge patient health literacy • Existing clinical judgement to select patients • Practioners confidence to counsel patient • RAG results reporting system
Unknown territory	Uncertainties, doubts, and fears relating to the consequences of pharmacogenomic testing. • Lack of criteria for testing • Perception that pharmacogenomic testing is scientifically complex • Healthcare professional experience self-testing • Patient selection • Poor GP engagement with secondary care • Lack of widespread training for PGx • Signposting resources

Process

The theme of 'process' emerged in all three participant interviews. 'Process' as a theme referred to the activities required of health professionals and patients to access pharmacogenomic testing. These activities related to delivering the PGx testing service rather than clinical activities of using the test results in the clinical management of patients.

Features of the PGx testing service delivery process were reported by all three interview participants as acting as barriers to implementing pharmacogenomic testing in the mental health setting. The health professional participants described the registration process as complicated, time consuming and a barrier to ordering PGx testing for patients. The next quote highlights how the mental health pharmacist independent prescriber viewed the registration process as a physical barrier to implementing PGx testing.

"it's very geared up for (pause) general practice it's, it seems to be very geared up for doctors, so everybody and they put me through his. My name is Doctor [pharmacist independent prescriber]... Yeah, it's not really geared up for non-medical prescribers and I don't think it's really geared up for secondary care. And it was all set-up to be your results will go back to your GP and (pause) stuff like that (pause) and yeah, it was. It was a bit tricky…" (Participant 1, Pharmacist independent prescriber)

The myDNA online registration system template was designed for doctors, so the pharmacist independent prescriber (PIP) was recorded on the system as doctor. Also, only the pharmacist independent prescriber was recorded as a registered myDNA trained provider, so the nurse independent prescriber had to register patients under the PIP's name. The language used in the patient consent form also described the results as being returned to the patient's doctor rather than 'prescriber' which were the roles of the pharmacist or nurse independent prescribers. These features of the online registration system created confusion for patients, so the pharmacist independent prescriber and nurse independent prescriber had to dedicate more time to registering the patients on the system in person rather than if they had given the patients the myDNA medication kit, to register themselves at home. This limited the time available to recruit patients, with health professional participants commenting that the additional workload required for them to deliver the PGx testing service was a strain on their already-high workload.

The PGx testing cascade of activities was initiated by the independent prescribers identifying and ordering PGx testing for patients. Both the pharmacist independent prescriber and patient expressed how the additional delay for returning results was a barrier to patient consent. The PIP viewed recruitment as an easy process in theory because the PGx testing would be suitable for most of the large pool of patients he saw. However, this delay seemed to raise challenges as he assumed most patients would be unwilling to wait so long for their results. The patient participant corroborated this, perceiving the delay in getting results as time she wasted being on the wrong medicines.

The DNA collection method could act as an enabler to healthcare professionals ordering PGx testing and patients consenting to PGx testing . All participants interviewed indicate that the cheek swab DNA collection method can be acceptable to patients, requiring little specific skill to carry out.

Expectations

The theme of 'expectations' refers to the relationship between what healthcare professionals believed PGx testing could deliver for optimizing drug and dose selection, and how PGx testing is used in practice. The theme emerged across all participant interviews.

Generally, participants at the single mental health trust expressed positive attitudes towards PGx testing. They said they believed PGx testing could make the prescribing process more efficient by reducing the time needed for a patient to achieve therapeutic benefits from their medicines or avoid side effects. The patient participant with a history of depression, described how a history of side effects to medicines was a driver for her consenting to PGx testing. The following quote demonstrates this view for this patient view.

"Well, I had the test obviously because like I said I was so sensitive to medication. I couldn't get a medication that was (pause) that was right for me." (Participant 2, Patient)

The health professionals identified the difficulty of managing a patient's expectations regarding PGxtesting's ability to determine the "correct" medicine for the individual. This health professional participant's assumption, led to some selection bias. Where healthcare professionals recruited patients they deemed competent to understand the nuance of pharmacogenomic testing as a tool to help the prescriber select a medicine in partnership with the patient. This health professionals' expectation encouraged health professionals to choose to counsel the patient on their results face-to-face rather than on the phone.

Despite both the pharmacist independent prescriber and nurse independent prescriber selecting only patients they deemed having good health literacy and reporting the PGx test results in a face-to-face setting, the sub-theme 'disillusionment' emerged from across all interviews. The patient participant had endured a long wait for their PGx test results, only for their report to show that the medicine where she experienced side effects was in the 'green' category and therefore she reported she perceived the test achieved nothing new.

Disillusionment as a sub-theme also emerged for health professional participants in two ways. Firstly, as frustration with the delay to return PGx testing results which the health professional perceived as leading to disappointment on the patient's part. This is reflected in the quote below from the mental health pharmacist independent prescriber' account.

"We're gonna use this really great futuristic system to help you choose the best possible medication for you…but we don't know how long it will take to get results...with our kind of patients they're not the most acutely unwell people with mental illness, but they're not people who want to be waiting a couple of months…"(Participant 1, Pharmacist independent prescriber)

Secondly, health professionals themselves reported disappointment when presented with the PGx results, as the test did not provide guidance in selecting between medicines in a similar drug category. Instead, the pharmacist and nurse independent prescribers learned through the experience of testing, to utilise the

test to assist in decision making by highlighting medicines to avoid rather than guiding selecting of medicines in the first instance.

This mismatch between health professionals' and patients' expectations of PGx testing and the function or role of PGx testing in the clinical setting may have contributed to participants reporting scepticism as to whether the intervention would be cost-effective in all prescribing scenarios.

Effort

The theme of 'effort' appeared in all participant interviews at the mental health trust and was related to barriers and enablers across all the implementation stages: ordering, facilitating, interpreting and application of PGx test. 'Effort' in this context referred to the cognitive work of healthcare professionals so as to carry out the clinical activities involved in delivering PGx testing.

Health care professionals perceived a patient's degree of health literacy moderating the ease with which they can communicate effectively the role of PGx testing in prescribing medicines. Health professionals used their experience and rapport with patients to select those patients who were most likely to understand the nuance of how PGx testing could help. The next quote demonstrates how the pharmacist independent prescriber viewed the relationship between a patient's health literacy and potential unintended consequences of PGx testing.

"…if you're not careful, you can give a patient the impression that it's a magic test that's gonna tell you the perfect drug that's gonna have no side effects and its gonna cure everything and if you've got somebody who has no health literacy, that's what they're gonna think this is."(Participant 1, Pharmacist independent prescriber)

The cognitive effort to counsel patients about PGx testing was perceived as less when the patient had a high degree of health literacy or was familiar with PGx testing. The nurse independent prescriber described using the PGx test in a patient who had visited Australia several times and seen the PGx testing advertised there.

When asking about the training provided by myDNA to deliver the service the nurse and pharmacist independent prescribers stated little information in the training was given on how to interpret PGx testing, however they did not see this as creating a barrier to interpreting and applying the PGx results. They found the RAG [red, amber, green] system of prescribing recommendations simple to understand and could synthesise the PGx key information quickly. This suggested this as an enabler possibly reducing the cognitive work demanded by the health professionals in interpreting and applying the PGx results.

Unknown territory

Finally, the theme 'unknown territory' emerged through all three participant interviews. 'Unknown territory' referred to the health care professional and patient perceiving uncertainties, doubts and fears relating to the consequences of pharmacogenomic testing.

Within the wider context of the NHS, the absence of multi-drug pharmacogenomic testing led to health professionals acknowledging PGx testing was unknown territory for them. As part of the training, health professionals were offered PGx testing themselves, which was received positively, de-mystifying the PGx testing process. Health professionals reported being more confident as a result of the activity, in selecting patients for PGx testing. Health professionals did however, report concern about how other less experienced colleagues would use PGx testing in the clinical care of patients. A sub-theme that emerged from health professional interviews was uncertainty about patient access to testing and criteria for testing. In the following quote, the nurse independent prescriber suggested that the genetic component of PGx testing could cause psychological harm in some patient groups within the mental health setting.

" Some people have paranoid schizophrenia, think they've got, like, microchips in their head and stuff… And then if we are asking them, oh, we take your DNA. I think that could cause distress to some of them."(Participant 3, Nurse independent prescriber)

When asked whether there should be narrower criteria for who can have PGx testing, the nurse independent prescriber commented that more restricted criteria may exclude patients who may be most in need of PGx testing.

"I think because, you know, they take some, for want of a better word, heavy duty medication antipsychotics with, you know, huge side effects. Maybe you know these side effects are debilitating for some people. And so they're the people that [PGx testing] probably it would be better suited for. So, I think there needs to be just better processes around the recruitment." (Participant 3, Nurse independent prescriber)

Instead, the health professionals in the mental health setting saw processes around recruitment where patients are referred to specialists with pharmacogenomic training as a better solution than generalists to ensure access to testing confers more benefits vs harms. For example, as part of the protocol for this study, health professionals would inform the patients GP of the patients PGx results and any action that was taken. The health professionals never received any correspondence from the GP regarding the patient's PGx testing and were seen as being disengaged. This may reflect the lack of widespread training for PGx testing in the NHS.

Finally, despite the initial novelty of PGx testing, the health professionals found their experiences of using the testing, as helping them gain confidence to apply PGx testing more routinely in their practice. They saw signposting PGx resources in the patients' results as a basis for increasing their confidence in using the results.

5.7.2.3 TDF themes

All inductive codes (sub-themes) within the four themes were later mapped to ten TDF domains. These codes are presented within their respective domains, according to whether they were barriers or enablers to behaviours relating to PGx testing implementation, in table 5-6. Codes in the themes 'Expectations' and 'Unexpected territory' were mapped to six different TDF domains, whereas codes in the themes 'Process' and 'Effort' were only mapped to 3 different TDF domains.

As shown in Table 5-6, participants most commonly related barriers to implementation to the TDF domain 'Environmental context and resources'. Health professionals and patients found the PGx testing pathway process to be time intensive and complex. The online registration system contributed to digital exclusion, with health professionals selecting younger patients they assessed as having the necessary digital skill level to complete the online tasks for DNA kit registration. These barriers affected the behaviour of health professionals ordering PGx testing for patients due to the technology characteristics of the PGx testing intervention disrupting the workflow of health professionals.

The TDF domain, 'Emotion' represents a complex reaction pattern by which an individual attempts to deal with a personally significant matter or event. Health professionals and patients reported disillusionment and unmet expectations with the function of PGx testing and service delivery elements. Despite the optimism healthcare professionals and patients initially had believing PGx testing would optimise prescribing in the first instance, the contribution PGx testing played in the mental health case study was more modest. This potentially reflects deficiencies in the training package provided used by health professionals in the study, which focused more on service deliver rather than the application of PGx testing in the clinical setting. Prioritising the domain 'emotion' in the training package by reframing PGx testing as providing assistive support for clinical decision making could reduce the perception of disappointment from testing on both the patient and health professionals' part.

A key driver for implementing multi-drug pharmacogenomic testing was expressed as both health professionals and patients easily able to gain the practical and clinical skills necessary to carry out PGx related behaviours like collecting a DNA sample and applying the PGx results. These skills were gained by the health professionals through self-testing prior to using the PGx test in clinical care which suggests even modest prior exposure to PGx testing can make a significant contribution to use of PGx testing in clinical care.

Table 0-6 Thematic analysis barrier and enabler to PGx implementation related behaviours mapped to ten TDF domains. *Ph (Pharmacist independent prescriber), *N (Nurse independent prescriber), Pt (Patient).

Stage	Behaviour	Theme	Sub-theme [Barrier (B), Enabler (En)]	Source	TDF domain
Ordering	Prescriber orders PGx test	Process	Complicated registration system (B)	Ph, N	Environmental context and resources
			Computer system incompatible for allied professionals (B)	Ph + N	Environmental context and resources
			Patient technology competence (B)	Ph	Environmental context and resources
			Delay for results (B)	Ph + N	Environmental context and resources
			PGx in principle is simple to deliver (En)	Ph + N	Belief about consequences
			Existing workload (B)	N	Environmental context and resources
			Additional workload associated with testing (B)	Ph	Environmental context and resources
		Expectations	PGx reduces time to right drug (En)	N	Optimism
			Perception Patients agency in SDM (En)	Ph	Social influences
			Positive attitude to PGx testing (En)	Ph + N	Optimism
			Disillusionment (B)	Ph	Emotion
			Function of PGx (B)	Ph	Emotion
			Cost (B)	Ph	Environmental context and resources

Table 5-6 Thematic analysis barrier and enabler to PGx implementation related behaviours mapped to ten TDF domains. *Ph (Pharmacist independent prescriber), *N (Nurse independent prescriber), Pt (Patient). [Continued].

Stage	Behaviour	Theme	Sub theme [Barrier (B), Enabler (En)]	Source	TDF domain
Ordering	Prescriber orders PGx test	Effort	Prescriber confidence judging health literacy (En)	Ph + N	Belief about capabilities
			Existing clinical judgement to select patients (En)	Ph	Skills
		Unknown territory	Lack of criteria for testing (B)	Ph	Memory, attention and decision making
			PGx testing is scientifically complex (B)	N	Belief about capabilities
			Patient selection (B)	N	Belief about consequences
			HCP self-testing (En)	Ph + N	Skills
Facilitating	HCP collects patients DNA	Process	Cheek swab sample is simple (En)	Ph + N + Pt	Skills
		Expectations	/	/	/
		Effort	/	/	/
		Unknown territory	/	/	/

Table 5-6 Thematic analysis barrier and enabler to PGx implementation related behaviours mapped to ten TDF domains. *Ph (Pharmacist independent prescriber), *N (Nurse independent prescriber), Pt (Patient). [Continued].

Stage	Description of behaviour	Theme	Sub theme [Barrier (B), Enabler (En)]	Source	TDF domain
Facilitating	HCP counsels patients on PGx result	Effort	Practitioner confidence to counsel (En)	Ph	Belief about capabilities
			RAG system reporting (En)	Pt	Memory, attention, and decision processes
		Unknown territory	/	/	/
	Patient gives consent to PGx test	Process	Complicated registration system (B)	Pt	Environmental context and resources
			Delay for results (B)	Pt	Environmental context and resources
			Cheek swab sample is simple (En)	Pt	Skills
		Expectations	Previous SEs with medicines (En)	Pt	Belief about consequences
			E	Pt	Emotion
		Effort	/	/	/
		Unknown territory	/	/	/

Table 5-6 Thematic analysis barrier and enabler to PGx implementation related behaviours mapped to ten TDF domains. *Ph (Pharmacist independent prescriber), *N (Nurse independent prescriber), Pt (Patient). [Continued].

Stage	Description of behaviour	Theme	Sub theme [Barrier (B), Enabler (En)]	Source	TDF domain
Interpreting	Prescriber interprets PGx test	Process	/	/	/
		Expectations	/	/	/
		Effort	RAG rating system (En)	Ph	Memory, attention, and decision processes
		Unknown territory	Signposting resources (En)	Ph	Memory, attention, and decision processes
Application	Prescriber applies PGx test result	Process	/	/	/
		Expectations	/	/	/

Table 5-6 Thematic analysis barrier and enabler to PGx implementation related behaviours mapped to ten TDF domains. *Ph (Pharmacist independent prescriber), *N (Nurse independent prescriber), Pt (Patient). [Continued].

Stage	Description of behaviour	Theme	Sub theme [Barrier (B), Enabler (En)]	Source	TDF domain
Application	Prescriber applies PGx test	Effort	Existing clinical experience (En)	Ph	Skills
		Unknown territory	Poor GP engagement with secondary care (B)	Ph	Social influences
			Lack of widespread training for PGx (B)	N + Pt	Knowledge
			HCP self-testing (En)	Ph	Skills

4.13 Discussion

5.8.1 Main findings

This study reports on the relatively novel experience of those involved in developing and delivering a multi-drug pharmacogenomic testing intervention within four partial case studies and one full case study across different NHS clinical settings. To my knowledge, this is the first study to report on the real-world implementation of multi-drug pharmacogenomic testing within an NHS context. These results therefore add to an innovative field of work, offering insights into some of challenges that can occur when developing and delivering multi-drug PGx testing services within the UK.

Out of the five case studies initially selected to deliver multi-drug PGx testing, only one was fully realized which was the mental health case study. What distinguished the mental health case study from the partial case studies in general practice and hospital was the innovator features the principal pharmacist and pharmacist independent prescriber (PIP) principal investigator exhibited when compared to other healthcare professionals in the other partial case studies who exhibited early adopter features. In Rogers diffusion of innovation theory, he describes innovators as individuals who take interest in new ideas and want to be the first to try and innovation, with very little needed to appeal to them (Rogers E.M, 2003). In contrast early adopters while comfortable adopting new innovations need much more persuasion, in the form of how-to manuals and information sheets on implementation. Through my reflective account, I noted that the PIP in the mental health setting was far more proactive in securing institutional support for the study from the consultant and research leads within the mental health trust. This aided me in securing the necessary ethical and research capacity and capability approvals ahead of the other partial case studies. A possible reason for the mental health PIPs increased motivation to implement PGx testing compared to prescribers in the partial case studies is that PGx testing is perceived as more valuable within the mental health speciality compared to other clinical specialities. Medication is the

standard of care for most debilitating psychiatric illnesses, however many medicines commonly used to treat these illnesses have substantial adverse drug reaction and side effect profiles. In addition, it often takes four to six weeks to show an adverse effect leading to considerable healthcare expenditure and patient suffering (Virelli et al., 2021), therefore the value of PGx testing may be seen as higher within the mental health speciality.

This study indicates multi-drug PGx testing models may need to differ between primary and secondary care settings. A similarity between implementation models in the four partial case studies and mental health case studies was the collaborative nature between pharmacists and doctors. This finding is corroborated in the systematic review (Chapter 4) and in the wider literature (Hayward et al., 2021) which shows pharmacists can flexibly fill variable roles within PGx testing models. Such roles can include supporting medical prescribers, also reported in the systematic review (Chapter 4) encompassing behaviours like counselling patients before and after PGx testing, obtaining DNA samples and consent from patients and interpreting PGx test results for medical prescribers (Youssef et al., 2021). The literature also shows pharmacists fill more active roles in PGx testing models, including behaviours like initiating PGx testing for patients and actioning results as part of patient medication reviews (Hayward et al., 2021, Youssef et al., 2021).

A unique finding from this study was in identifying the role of pharmacist independent prescribers (PIP) as key actors in implementing PGx testing. The roles of PIPs within four of the implementation models were active, undertaking actions which included initiating PGx testing, interpreting and actioning PGx test results for patients. This finding perhaps reflects the differences in pharmacist professional roles in the UK as compared with the USA where the majority of pharmacist integrated PGx testing models have been reported (Hayward, 2021). The UK is unique worldwide, in enabling pharmacists, nurses and allied health professionals to prescribe medicines independently of a doctor's input since non-medical prescribing legislation has been passed (Graham-Clarke et al., 2019). In 2020, the General Pharmaceutical Council (GPhC) proposed major reforms in the pharmacy

undergraduate course curriculum integrating prescribing skills within a 5 year degree, so pharmacy students can independently prescribe upon graduation (D Rudkin, 2020).

While the findings of this study alone must be interpreted with caution, when examined alongside the systematic review findings (Chapter 4), wider literature, and existing legislative pharmacist powers in the UK, PIP led PGx testing models may be a viable option for widespread implementation. Compared to medical doctor/ pharmacist collaborations, PIPs can prescribe medicines directly rather than advising on the safe and effective use of medicines. As a result, they can manage a patient's medicines independently of a medical doctor and so could carry out all actions within a PGx testing model. This is advantageous from an implementation perspective as interventions to encourage uptake of PGx testing related behaviours only need to target the behaviour of one individual- PIP, rather than multiple staff members, which would have increased complexity. While these findings must be treated with caution, the PIP PGx testing model described within a single mental health setting nonetheless shows that this type of PGx testing model can be feasible.

Within the literature, education and training for healthcare professionals is a frequently reported barrier to implementing multi-drug pharmacogenomic testing (Hayward et al., 2017, McDermott et al., 2022, Youssef et al., 2021). As only one of the five case studies progressed into phase 2, where PGx testing was delivered, the findings which now follow must be considered with caution. Within the context of this study, health professional interviewees reported the myDNA Life online training package as adequately preparing them to deliver PGx testing. In addition to the training package, healthcare professionals in the mental health trust case study were also offered self PGx testing which they both undertook prior to delivering PGx testing for patients. Healthcare professional interviewees reported self-testing as a training activity which enhanced their perceived confidence in their capability to deliver PGx testing for patients. This finding is supported by another study conducted in the US which reported on the experiences of doctors within a single

primary care health system who received complimentary pharmacogenomic direct access kits through a pilot program (Lemke et al., 2017). Participants in this study reported undergoing PGx self-testing as a teaching tool was a helpful way to gain first-hand knowledge of the testing and results process which translated to doctors providing better and more concrete information to patients regarding testing and decision-making. Health care professional education and training packages incorporating behaviour change techniques (BCTs) targeting the TDF domain 'Skills' may be more effective than traditional approaches focused on enhancing PGx knowledge, to enable prescribers to initiate and ultilise PGx testing in patient care. Examples of BCTs linked to the 'Skills' TDF domain include 'Instruction on how to perform behaviour', 'Behavioural practice/rehearsal' and 'Graded tasks' (Carey et al., 2019). Within a National PGx testing roll out, it is unlikely to be feasible to provide all health care professionals with a PGx test to self-test with as a teaching tool. Instead, it may be more feasible at a national level to deliver teaching activities using role play where healthcare professionals practice choosing patients for PGx testing, or interpreting PGx test results may suffice in replicating the benefits of self-testing seen in this study and others.

From the healthcare professional interviews, the mental health case study indicated that the most significant barriers to PGx testing occur at the ordering stage. The theme 'Process' emerged with healthcare professionals indicating the online registration process and turnaround time for PGx reporting as negatively influencing their ability to recruit patients for PGx testing. This finding corroborates with those in the systematic review (Chapter 4) which also reported that most barriers to implementation occur in the initial stage of the prescriber ordering a PGx test. This could indicate that implementation strategies that prioritise the prescriber ordering PGx testing as a target behaviour may be more successful for wide-spread adoption and sustained implementation, as it seems this behaviour is seen as central to bringing the desired change in clinical practice. Again, like the findings of the systematic review, barriers to this behaviour could be mitigated through environmental restructuring, streamlining the PGx ordering process and turnaround time so it is more efficient and integrated in the existing workflows.

In contrast with findings from the systematic review, the TDF domain 'memory, attention and decision processes' were not reported as a barrier to PGx testing ordering behaviour in this study. This may reflect the small number of patients the health professionals were asked to recruit in this study which meant health professionals could dedicate more time per patient to interpret and discuss PGx test results. To upscale the process, behaviour change techniques to address the domain memory, attention and decision making through the design of streamlined clinical decision support are likely to be needed.

The sub-theme of disillusionment with PGx testing, emerged through healthcare professional interviews. The small number of PGx tests available to each of the healthcare professionals in the mental health trust may have also contributed to this view. While at a population level more than 95% of individuals carry at least one genetic variant that predicts an aberrant response to at least one medication (McInnes et al., 2021), the rate at which a healthcare professional is likely to amend prescribing based on PGx test results is much lower. As shown in the Chapter 3 (Youssef et al., 2021), between 1 in 8 and 1 in 9 medicines with PGx published guidelines, newly initiated in primary care are predicted to require an amendment in prescribing. Therefore, it is less surprising that healthcare professionals in the mental health trust using PGx testing reactively versus pre-emptively in only 5 patients each, reported a discord between expectations of PGx testing and the form of PGx testing delivered during the study. These findings indicate a pre-emptive rather than reactive PGx testing implementation model However, using PGx testing in patients with polypharmacy may increase the likelihood of PGx testing optimizing prescribing.

Finally, a major challenge I encountered in this study was securing NHS ethical approval, which delayed the study start date. The initial ethical committee rejected the study as they perceived PGx testing as a novel technology despite its use in many other countries. This response could not, therefore be seen to be well-founded in evidence. Nonetheless this response, required me to make amendments in the research which impacted on the results. For example, the PGx testing

pathways had to be agreed before the empirical testing and this discouraged health care professionals from actively adapting the intervention to their clinical setting. 'Genetic exceptionalism' which posits that genetic information is distinct from other types of health data and therefore requires additional and distinctive safety guards to be put in place (Relling et al., 2010) may have contributed to the resistance I observed from the ethical committee to provide a favourable opinion for the study. This challenge may be mitigated when PGx testing is adopted nationally in the NHS.

5.8.2 Strengths and limitations

This is the first study which has investigated the potential implementation of multi-drug pharmacogenomic testing in primary and secondary care NHS settings. This study contributes to the published evidence base by adding research-based information to this under-researched area and provides insights for policy makers and researchers on the characteristics of the process of implementing multi-drug pharmacogenomic testing within the NHS.

A strength of this study is in applying behavioural science theory to identify and understand the barriers and enablers to implementing multi-drug pharmacogenomic testing as seen by healthcare professionals and patients. This has provided specific information to illuminate ways of using behaviour change techniques to address barriers to implementation which may enable more successful sustained adoption.

There were also some limitations. Firstly, the impact of COVID-19, greatly limited case study site recruitment. Despite my securing full NHS and local ethical approvals to carry out the study, four of the five case studies did eventually not go ahead when my research activities were stopped due to COVID-19. The sample size for the study was therefore much smaller and less diverse than anticipated, which may have limited the range of findings that could be generated and their transferability to the wider population. Additionally, for those interviewed, there

was a greater risk of recall bias as it was not possible to conduct interviews with participants immediately following PGx testing.

4.14 Summary

This exploratory study used case study methodology to develop PGx testing models in different NHS contexts and to describe the experiences of health care professionals delivering PGx testing and patients receiving PGx testing. The findings indicate that PGx testing models utilising pharmacist independent prescribers may improve uptake of PGx testing due to the alignment of behaviours and the professional role of pharmacists. Pre-emptive PGx testing models may be more acceptable to health care professionals and patients as they eliminate a time delay for results which can potentially cause distress to patients. Due to COVID-19, only one of the five case studies developed, delivered PGx testing to patients, thereby limiting transferability. Further qualitative studies, particularly in-depth case studies using multiple data collection methods to ascertain the distinctive and relevant components in PGx testing implementation in different NHS settings were seen to be feasible, informative, and potentially useful in generating further new knowledge.

Chapter 6: Overall discussion

6.1 Introduction

As discussed in the introduction, pharmacogenomic testing can enhance the safety and efficiency of prescribing, thereby addressing a huge public health burden associated with adverse drug reactions and trial and error prescribing. Reducing the cost of genetic sequencing technologies helps gradually realise the promise of pharmacogenomic testing within the NHS inches closer. This thesis is timely in addressing some of the key uncertainties of researchers and policy makers interested in implementing pharmacogenomic testing in the UK.

The purpose of this concluding chapter is to firstly summarise principal findings from the previous chapters. Secondly, evaluate the studies as a whole with respect to the strengths and limitations of this research. Thirdly discuss the main findings with respect to the wider literature. Fourthly present an updated logic model for a multi-drug PGx testing implementation configuration for an NHS context and finally conclude with recommendations for future research.

6.2 Revisiting the aims and research questions

The overall aim of the research, as stated in section 1.11, was to explore the design, and implementation of a multi-drug pharmacogenomic testing intervention within an NHS context, guided by the MRC framework for complex interventions (Skivington et al., 2021). The research was guided by four research questions:

1. What are the design components of a multi-drug pharmacogenomic testing panel that provides potentially the most benefit for UK NHS patients?
2. What does the global literature report with respect to current barriers and enablers to implementing multi-drug pharmacogenomic testing from a behavioural perspective of prescribers, pharmacists, and patients?
3. What are the locally relevant (UK) barriers and enablers to implementing multi-drug pharmacogenomic testing, when considering behavioural perspectives of prescribers, pharmacists, and patients?

4. What are the key components necessary for the implementation of multi-drug pharmacogenomic testing in clinical care in the NHS?

The first research question was addressed in Study One (Chapter 3). This study was a modelling study estimating the impact of multi-drug pharmacogenomic testing in UK primary care by identifying the volumes of newly initiated medicines with actionable drug-gene interactions as identified by CPIC and DPWG published guidelines. This study was designed to explore what design components of a multi-drug PGx testing intervention provide potentially the most benefit to UK NHS patients.

The second research question was addressed in Study Two (Chapter 4). This study was a systematic review and narrative synthesis of published evidence on influences on behaviours of prescribers, pharmacists and patients implementing multi-drug pharmacogenomic testing. This study aimed to identify the barriers and enablers to implementing multi-drug PGx testing from the behavioural perspective of prescribers, pharmacists, and patients.

The third research question was addressed in Study Three (Chapter 5). This study describes the process of implementing a multi-drug pharmacogenomic testing service within an NHS context using a case study design. This study aimed to identify what locally relevant barriers and enablers to implementing multi-drug PGx testing can occur from the perspective of prescribers, pharmacists, and patients in the NHS.

The fourth and final research questions is addressed in this discussion chapter where the key points from the earlier chapters are revisited and brought together in an updated logic model. This updated logic model summarises the key components key components necessary for implementing multi-drug pharmacogenomic testing in clinical care in the NHS.

6.3 Strengths and limitations of this programme of work

The strengths and limitations associated with the three empirical studies are discussed within the respective chapters (Chapters 3-5). The strengths and limitations related to the overall work presented in this thesis are discussed below.

A key strength of this work is that it followed guidelines by the Medical Research Council (MRC) for the development of complex interventions (Skivington et al., 2021). These guidelines divide complex intervention research into four phases: development or identification of the intervention, feasibility, evaluation, and implementation. A research programme may begin at any phase depending on the key uncertainties about the intervention in question, to be resolved. Chapter 1 began describing a review of the literature, identifying, and prioritising the research gaps and key uncertainties. Chapter 2 contained an overview of different theoretical approaches to implementation, developing a logic model which brought the evidence base and theory together to describe the envisaged configuration of multi-drug pharmacogenomic implementation. This logic model illustrated the purpose and content of a multi-drug PGx testing intervention to reduce adverse drug reactions and improve prescribing efficiency. From observing this logic model, three empirical studies, reported in Chapter 3, 4, and 5, were designed to try and address uncertainties summarised in the logic model. Using the framework helped ensure findings of this research reporting on the implementation of multi-drug PGx testing in the NHS were grounded theoretically. Evidence suggests that interventions grounded in theory are more effective than those with no theoretical bases (Glanz and Bishop, 2010).

Furthermore, applying behavioural science theory to understand the behaviours of prescribers, pharmacists and patients which underpin the implementation of multi-drug pharmacogenomic testing can improve future implementation efforts. When developing interventions to change behaviour, there is a need for high specificity in terms of what the behaviour is and who is their target (Michie et al., 2018). Not specifying how the behaviour is characterised and who is identified as the target of behaviours, may result in many barriers and enablers and no directions for using

this knowledge, making an already-complex health system more complex. Rather than developing interventions to target the behaviours of multiple practitioners within the multidisciplinary team to facilitate better adoption and implementation of multidrug pharmacogenomic testing, according to the systematic review and case study efforts should be focused on developing interventions tailored to the determinants of the prescribers ordering PGx testing.

Securing external funding from the Harold and Marjorie Moss Trust supported activities to facilitate meaningful patient and carer involvement throughout the programme of work through funding DM (patient who had been prescribed polypharmacy) and SW (carer of a patient prescribed polypharmacy) to work with EY. DM and SW had a significant impact on key decisions taken throughout the studies described in this thesis and peer reviewed publication (Youssef et al., 2022). For example, DM and SW provided support in the interpretation of data collected in the systematic review (Chapter 4) regarding patient perspectives on consenting to testing. Additionally, DM and SW played an active role in designing the format and content the patient information materials for the case study reported in Chapter 5 which supported the NHS ethical approval application by ensuring that the distinctive voices of patients and carers could be seen to be central to this research.

The peer review process afforded by publication of two of the three empirical studies comprising this thesis (Chapter 3, and Chapter 4) contributed distinctively to refining the research methods, analysis, and interpretation of key findings from studies one and two and can therefore be seen to be a core strength in the work of this thesis.

The comprehensive use of qualitative research methods was a strength to this research. Qualitative methods have been reported to contribute to developing and evaluating complex interventions [Corrigan et al., 2006]. In this thesis, qualitative findings from the systematic review and narrative synthesis in Chapter 4, and the partial case studies and mental health case study in Chapter 5, helped illuminate some of the nature of and reasons for behaviours underpinning multi-drug pharmacogenomic testing and the barriers to each of these behaviours. Qualitative

methods are therefore seen to be crucial for further refining the implementation of PGx testing as they have been seen to be useful for examining the mechanisms of change which lead to the intervention outcomes.

The limitation associated with the programme of work as a whole is the likely limited generalisability of the findings and thus potentially the proposed implementation model for multi-drug pharmacogenomic testing summarised in the logic model. The methodology of the systematic review and narrative synthesis reported on in Chapter 4 included any published reports describing real-world implementation of multi-drug PGx testing. As a result, the findings are derived for articles describing authors' interpretation of barriers and enablers versus first-person accounts of prescriber, pharmacist, and patients, which introduces bias to the findings. Furthermore, only articles published in the English language were included due to resource constraints, leading to possibly rejecting some high-quality studies not written in English. The empirical study described in Chapter 5 was undertaken in a single mental health trust in the East of England, which further limits generalizability.

6.4 Key findings

To the authors knowledge, this is the first piece of work to have approached the topic of multi-drug PGx testing implementation using systematically and empirically driven methodology. As justified in Chapter 2, PGx testing is an example of a complex healthcare intervention (Skivington et al., 2021). However, in the literature there is a clear absence of studies that systematically adopt a complex intervention framework to develop and implement a PGx testing intervention. A lack of robust theory to guide intervention development and implementation of PGx testing interventions has been a key limitation of the existing literature.

This thesis contributes to the evidence base on multi-drug PGx testing implementation by combing mixed research methods with theory informed implementation science to explore real-world experiences of healthcare professionals delivering PGx testing. The combination of novel quantitative

methodology and implementation science is a distinctive feature of this thesis. A range of findings from the three research studies have the potential to shape a future multi-drug PGx testing intervention for use with NHS primary care. The following section describes the key findings from this thesis and contextualises them within the wider literature to inform a multi-drug PGx testing implementation configuration for use in the NHS.

6.4.1 PGx drug-gene testing panel design requirements

One of the key uncertainties to implementing PGx testing in the National Health Service (NHS) in the UK, is identifying a drug-gene panel that covers the most common drug-gene interactions in the UK population. As described in Chapter 1, pharmacogenomic testing is not a single technology, but instead a range of analytical techniques to identify variants of genes associated with the metabolism or transport of drugs. Internationally there is a lack of consensus on a standard pharmacogenomic testing panel that is comprehensive and provides useful information for prescribers to optimise prescribing of medicines for patients.

A theoretical study in the Netherlands designed a pharmacogenomic testing panel, called a "PGx passport," to optimize the prescribing of commonly prescribed drugs. The panel covers 58 gene variants of 14 genes (van der Wouden et al., 2019). While the study provides recommendations for testing gene variants that occur in at least 1% of any ethnic population, reducing the risk of health inequalities, there are limitations to this approach. The "PGx passport" only includes medicines that can be optimized using Dutch Pharmacogenetic Working Group guidelines, which may exclude medicines relevant to the UK and governed by CPIC guidelines, limiting the impact of pharmacogenomic testing.

Consequently, the first study in this thesis used a quantitative modelling approach to identify drug-gene pairs relevant to UK primary care and estimate the impact of multi-drug pharmacogenomic testing by identifying the volumes of newly initiated medicines with actionable drug-gene interactions as identified by CPIC and DPWG published guidelines. Findings from this study indicated that a pre-emptive multi-

drug pharmacogenomic testing panel of 9 genes (CYP2C19, CYP2C9, CYP2D6, F5,HLA-A, HLA-B, SLCO1B1, TPMT, VKORC1) would affect roughly one in five prescriptions for 56 commonly prescribed newly initiated medicines in UK primary care annually, translating to roughly 4 million patients and 6 million prescriptions (Youssef et al., 2021). A similar study in the Netherlands estimates that 23.6% of prescriptions for 45 drugs with DPWG guidelines initiated in the Netherlands could be optimised by PGx testing (Bank et al., 2019) with 5.4% requiring direct intervention in the form of drug/dose adjustment.

The modelling study reported on in Chapter 3, showed the most commonly initiated PGx drugs with actionable drug gene interactions were for weak opioids like codeine and tramadol, antidepressants, and proton pump inhibitors. A pre-emptive pharmacogenomic testing panel that was limited to testing for variants in only four genes (CYP2D6, CYP2C19, HLA-B and SCLO1B1) would have picked up 95.8% of all the drug-gene interactions identified by the wider panel testing for variants in 9 genes. Another study investigating the exposure of 648,141 English primary care patients to 63 drugs over a 25-year period of time (Kimpton et al., 2019) found a similar result with three PGx genes (CYP2C19, CYP2D6 and SCLO1B1) accounting for >95% of the common PGx drugs dispensed. It should be noted that the study by Kimpton and colleagues included medicines without published PGx prescribing guidelines and did not incorporate phenotype frequency data. Therefore, the results may overestimate the impact of a PGx panel limited to screening gene variants of three PGx genes.

A strength of the study presented in Chapter 3, is it only included medicines with published CPIC and or DPWG guidelines, thereby maximising the utility of PGx testing as only drug-gene variants the prescriber can act on are included. A second advantage of this study is it incorporated UK phenotype frequency data thereby personalising the panel for a UK population. An advantage of this approach is that the number of patients carrying actionable variants within the proposed PGx testing panel is maximised while theoretically reducing costs associated with a more extensive testing panel. Further cost-effectiveness analysis is needed to evaluate the proposed pre-emptive PGx testing panel, however the findings from

this study can contribute to the design and scope of a NHS multi-drug pharmacogenomic testing panel.

6.4.2 PGx testing implementation defined through behaviours

As identified in Chapter 2, PGx testing is a complex intervention. The approach of this thesis was to explore the implementation of PGx testing was using behavioural science and the Theoretical Domains Framework. This involved characterising implementation of PGx testing by identifying the target behaviours and influences on them that occur during implementation. These factors can therefore be addressed to change behaviour, increasing adoption and sustained implementation of multi-drug PGx testing. The first step was therefore to identify the actors who has to change their behaviour in order to implement multi-drug PGx testing.

The scoping search conducted prior to the systematic review and narrative synthesis reported in Chapter 4, identified key actors to implementing multi-drug PGx testing as prescribers, pharmacists, and patients. This corresponds with other reviews that take a behavioural perspective to implementing PGx testing, which also explore barriers and enablers physicians, pharmacists and patients adopting PGx testing (Qureshi et al., 2022, Jameson et al., 2021).

The systematic review went on to identify twenty-seven papers describing the real-world implementation of multi-drug PGx testing involving either/and prescribers, pharmacists, and patients. Implementation behaviours occurred in four stages: ordering, facilitating, interpreting, and actioning PGx testing. While the papers in the systematic review all described implementation of multi-drug PGx testing in countries outside of the UK, the findings from the four partial case studies and mental health case study in Chapter 5 indicate implementation in the UK also follows these stages.

The findings of a systematic review and a mental health case study suggest that the main barriers to implementing pharmacogenetic (PGx) testing are related to the initial stage of prescriber ordering. These barriers include lack of knowledge and skills on which patients to test and how to order the tests, disruption to existing

workflows, and perceptions of clinical utility, cost-effectiveness, and reimbursement. Both studies suggest that strategies to change prescriber behaviour and increase their likelihood of ordering PGx testing for patients may improve overall implementation efforts of multi-drug PGx testing. It is important to note that the data collected and reported on in both studies may be biased towards the prescriber perspective compared to the pharmacist and patient perspective. In the systematic review only seven of the twenty-seven papers reported on the patient perspective and the patient perspective was only explored in the mental health case study, not the four other partial case studies. With this in mind, further research may be needed to confirm these findings.

6.4.3 Barriers and enablers to prescribers implementing multi-drug PGx testing

There are several barriers and enablers to the implementation of PGx testing by prescribers. Prescriber behaviours relating to implementation were characterised through the systematic review and mental health case study as occurring in the ordering, interpretating, and actioning implementation phases of PGx testing. As described before, barriers to the prescriber ordering PGx testing can be considered as the most significant in influencing overall implementation of PGx testing.

The systematic review findings indicate addressing the TDF domains of 'environmental context and resources' and 'memory, attention and decision making' may increase the likelihood of prescribers ordering PGx testing. Strategies to broadly address these domains include improving interoperability of IT system between different care settings and designing timely and direct clinical decision support systems to help prescribers order and interpret PGx testing. These findings must be considered cautiously as the none of the studies included in the systematic review incorporated a behavioural science lens in the collection, analysis or reporting of the studies. Therefore, the findings from the systematic review while coded to the TDF by two separate researchers, are based on incomplete data and are indicative rather than conclusive.

A lack of adequate education and training for prescribers was also reported in the systematic review and mental health case study as barrier to prescribers ordering PGx testing for patients, interpreting PGx test results and making medication changes as a result of PGx testing. None of the papers included in the systematic review discussed in detail what training and education requirements were necessary to facilitate the prescribers PGx testing related behaviours. This was instead partially addressed Chapter 5 where two non-medic prescribers were questioned about their experiences of training in a single mental health case study. Within the context of this study, prescriber interviewees reported self-testing as a training activity enhanced their perceived confidence in their capability to deliver PGx testing for patients and is corroborated by a separate USA study (Lemke et al., 2017).

Prescriber education and training packages incorporating behaviour change techniques (BCTs) targeting the TDF domain 'Skills' may be more effective than traditional approaches focused on enhancing PGx knowledge, to enable prescribers' behaviour to initiate and ultilise PGx testing in patient care. Examples of BCTs linked to the 'Skills' TDF domain include 'Instruction on how to perform behaviour', 'Behavioural practice/rehearsal' and 'Graded tasks' (Carey et al., 2019). It may be more feasible at a national level to deliver teaching activities using role play where healthcare professionals practice choosing patients for PGx testing, or interpreting PGx test results may suffice in replicating the benefits of self-testing seen in this study and others.

Finally, a unique finding from this thesis is the role of non-medical prescribers, specifically pharmacist-independent prescribers in PGx testing implementation within the NHS compared to the rest of the world. Within the systematic review and wider literature (Qureshi et al., 2022, Kim et al., 2020) prescribers in relation to PGx testing implementation predominately refers to medical doctors. However, as reported in the systematic review medical doctors often perceive a large emotional effort to order PGx testing relating to perceptions of PGx testing as complex and mismatched with their professional role and identity. This misalignment may be driver for more more prominent pharmacist roles reported (Hayward et al., 2021)

internationally describing PGx testing implementation. Rather than utilising pharmacists to positively influence medical doctors to order and action PGx testing, a model where pharmacists can circumvent this and order and action PGx testing independently as non-medical prescribers may be a preferable model for implementation. From a behavioural science perspective, a PIP model of implementation is also preferable since it involves changing the behaviour of a single actor rather than multiple actors, which can make implementation planning more complex.

Three of the partial case studies and full mental health case study reported on in chapter 5 show it is possible and may be preferable to adopt a PIP-led PGx testing implementation model within the NHS. The UK is unique worldwide, in enabling pharmacists to prescribe medicines independently of a doctor's input with further post-graduate education (Graham-Clarke et al., 2019). This however is proposed to change with major reforms in the pharmacy undergraduate education enabling pharmacist to prescribe upon graduation (D Rudkin, 2020) thereby substantially upskilling the workforce to potentially deliver all PGx testing behaviours.

6.4.4 Barriers and enablers to pharmacists implementing multi-drug PGx testing

The barriers and enablers to pharmacists implementing multi-drug PGx testing are not as well-defined in this thesis when compared to barriers and enablers to prescribers. As a result the following section will describe some of the potential barriers and enablers to pharmacists implementing PGx testing.

Fifteen out of the twenty-seven articles included in the systematic review reported on pharmacist behaviours involved in the implementation of PGx testing. The majority of these behaviours occurred in the facilitation and interpretation phases of PGx test implementation including pharmacists taking counselling patients pre and post PGx testing, collecting DNA samples from patients and interpreting PGx test results for medical doctors. Much like prescribers, the biggest potential barriers to pharmacists implementing PGx testing related to the TDF domains: environmental context and resources and memory attention and decision making.

Improving the interoperability between pharmacy IT systems and the prescribers IT systems so pharmacists have access to the patient's full medical history can improve the confidence of pharmacists to interpret PGx test results and advise prescribers and patients. Clinical decision support systems can prompt pharmacists to advice prescribers to initiate PGx testing for a patient and action past PGx test results when new medicines are initiated.

A potential factor that could enable pharmacists implementing PGx testing is the alignment between this type of testing and the perceived social and professional role of pharmacists. According to the systematic review, both internal (within the pharmacy profession) and external (from outside the profession) perceptions of pharmacists as experts in medicine can help increase pharmacists' confidence in carrying out PGx testing behaviours. In addition, doctors may trust pharmacists' judgement more when it comes to interpreting PGx test results because of their expert knowledge, and patients may be more likely to trust and follow the advice of pharmacists when it comes to consenting to testing and understanding their test results. Unfortunately, it was not possible to confirm this finding mental health case study reported in Chapter 5 as this used a pharmacist independent prescriber in the PGx testing model. Further research is therefore required to confirm barriers and enablers to pharmacists implementing PGx testing within an NHS context.

6.4.5 Patient perceived barriers and enablers to multi-drug PGx testing implementation

Unfortunately, a weakness of the empirical work of this thesis is identifying with confidence the patient perceived barriers and enablers to multi-drug PGx testing implementation. The following section therefore discusses some of the potential patient perceived barriers and enablers that can occur when PGx testing is implemented in the NHS.

Only seven out of the twenty-seven papers included in a systematic review reported on patient behaviours related to implementing PGx testing. This included only one behaviour, which was patients consenting to PGx testing. Potential barriers to patients consenting to PGx testing were mostly related to emotions and

beliefs about the consequences of testing, such as concerns about data privacy, the impact on relatives, and the risk of discrimination. Patients who were optimistic that PGx testing could improve their doctor's or pharmacist's ability to select the right medicines for them were more likely to consent to testing. These factors also emerged in an interview with a patient in a mental health case study who said her motivation for having PGx testing was that it could help manage her illness by identifying a medicine that would work for her without side effects. Unfortunately, the patient in the mental health case study felt that PGx testing did not help her and was left with unmet expectations. The findings from the systematic review and mental health case study highlight the potential importance of pre- and post-PGx test counselling for patients to manage their expectations of testing and alleviate concerns about genetic discrimination and privacy. Patient needs and preferences regarding counselling for PGx testing from their healthcare provider have been explored in another qualitative meta-study, which found that patients generally have high expectations for PGx testing counselling, while levels of "genome-based health literacy" among the general public are relatively low (Veilleux et al., 2020). There is therefore a gap in how PGx pre- and post-test counselling should be delivered when PGx testing is implemented within the NHS.

6.5 Revised Logic model

This section addresses the final research question from this thesis which is to identify and describe the key components necessary for the implementation of multi-drug PGx testing in the NHS. This is addressed by summarising the overall findings from this PhD within a logic model updated using the thesis study findings for a multi-drug PGx testing configuration for implementation in the NHS.

By comparing the original logic model (shown in Chapter 2) to the updated logic model (shown in Figure 6-1), several differences can be seen. The updated logic model has a narrower scope and provides more detailed information on the implementation of multi-drug PGx testing in the NHS, based on empirical studies conducted in the thesis.

One major difference between the two logic models is that the original logic model's components "mechanisms" and "moderating factors" are replaced by "inputs" and "contexts" in the updated logic model. The thesis finds that both medical and non-medical prescribers and pharmacists are likely to be involved in implementing PGx testing in the NHS, and the updated logic model reflects this by focusing on factors relevant to these healthcare professionals specifically.

The moderating factors in the original logic model were broader and covered barriers and enablers that may affect PGx testing implementation generally. In the updated logic model, the domains of the TDF that map the barriers and enablers affecting the behaviors of prescribers, pharmacists, and patients are visually represented.

However, since multi-drug pharmacogenomic testing is a novel intervention within the NHS, some aspects of the findings used to inform the updated logic model are incomplete and require feasibility testing and process evaluation in create a complete model. Therefore, this section discusses the components of the updated logic model seen in Figure 6-1, based on current guidelines, wider research, and the findings from this research.

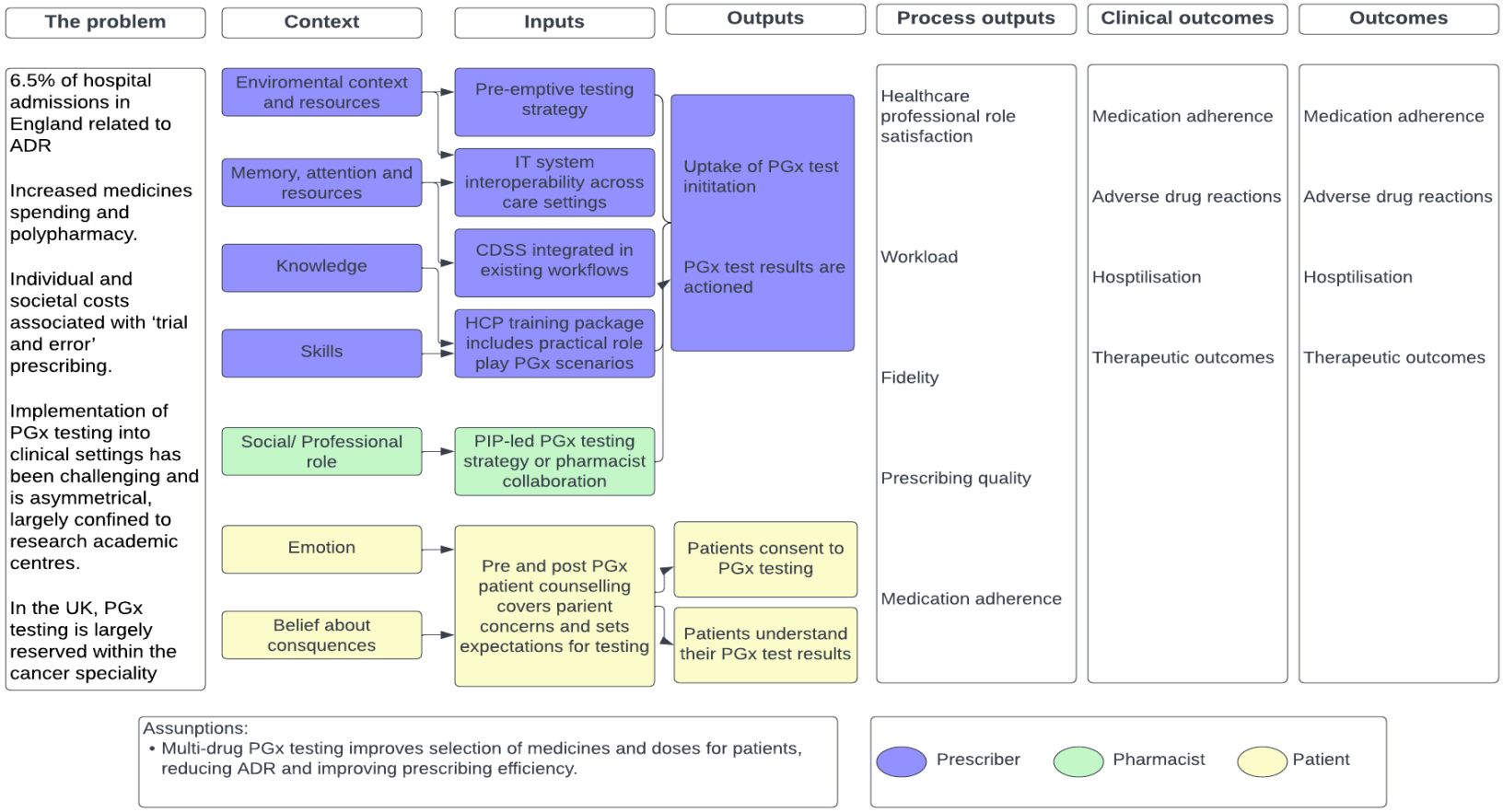


Figure 0-1 Updated Logic model of PGx testing implementation configuration within the NHS.

6.5.1 Reframing the research problem

A review of the literature, conducted at the beginning of the PhD and reported in Chapter 2, highlighted how despite the benefits of PGx testing in terms of reducing ADR and improving efficiencies in prescribing, implementation in a clinical setting has been slow and non-linear (Chapter 1). Establishing a threshold of evidence demonstrating clinical utility and cost-effectiveness has been one of the key barriers to implementing PGx testing (Relling, 2015). Since beginning this PhD, evidence demonstrating PGx guided prescribing to be superior to usual care has grown for multiple clinical specialties (Zhu et al., 2021, Karamperis et al., 2021, Jiang et al., 2022, Jarvis et al., 2022). Additionally, findings from the PGx modelling (Chapter 3) show the rate of drug-gene interactions occurring within the UK population is high with PGx testing potentially optimizing the prescribing of 1 in 5 PGx medicines newly initiated in primary care.

A significant development which occurred during the course of this PhD is the launch of the Genomic Medicine Service and seven Genomic Medicines Alliances (GMAs) across England. These GMAs bring together multidisciplinary teams with clinical, digital, and operational expertise to improve regional coordination of care and collaborative working practices between community-based services and hospitals, physical and mental health services and between health and social care. The combination of the GMS and GMAs provides a robust infrastructure to support equitable access to genomic medicine across NHS settings in England. There is therefore now a need to identify PGx testing implementation models which this thesis delivers.

6.5.2 Context and Inputs

The updated logic model shows the TDF domains affecting the behaviour of prescriber, pharmacists and patients the most, with potential strategies to overcomes this. An example of a solution identified through the systematic review and indicated by the mental health case study was improving information technology interoperability which addresses the TDF domain of ‘Environmental

context and resources, encouraging the prescriber to order PGx testing for a patient.

Incorporation of behaviour change techniques (BCTs) that target the TDF domains shown under context in the updated logic model may lead to more successful implementation of PGx testing. It was not within the scope of the studies conducted and methodologies used within this thesis to ascertain which behaviour change technique should be selected for consideration when implementing PGx testing.

A new finding from the empirical work of this research which was not clear in the original logic model was the role of pharmacists in PGx testing. The findings indicate pharmacists perceiving PGx testing behaviours as aligning with their professional role. Additionally, the findings indicate acceptability of pharmacists delivering PGx testing is high among patients and medical doctors.

The NHS Long term plan supports the provision of prescribing pharmacist within primary care networks to deliver medicines management and care of those with long-term conditions. Pharmacists within primary care networks are already responsible for carrying out medicines' reviews, particularly for patients with polypharmacy. PGx testing could therefore be combined with the existing medicines review enhancing the service provided by pharmacists in primary care.

6.5.3 Outputs and Outcomes

The studies in this thesis were not designed to explore outcomes of PGx testing therefore the updated logic model is comprised of information from the literature review in Chapter 1 rather than empirical findings from the three studies. Outcomes of PGx testing and the mechanism by which PGx testing brings about these changes in outcomes, requires further research in the form of process evaluation.

In the short-term prescribers and pharmacists would aim to increase uptake of PGx testing, utilising PGx test results to make medication changes. As indicated in the mental health case study, prescribers may need to deliver PGx test results in person

to the patient, to ensure expectations of PGx testing are managed and patient concerns are addressed.

In the medium term it is expected that the number of adverse drug reactions is reduced, and number of medical visits reduced as medicine selections are optimised through PGx testing. Patients' adherence to medicines adherence may also be improved through improved tolerability to medicines, or psychologically through the idea of personalising medicines. These mechanisms were not investigated in this thesis and need require further research to ascertain.

Finally in the long-term it is expected that PGx testing will reduce medicines wastage and improve quality of life indicators for patients. Again, further feasibility testing is required to explore any unwanted outputs from PGx testing and the mechanisms underpinning these.

6.6 Implications for future research

Studies conducted and reported on in this thesis, add more information to the literature regarding implementation of multi-drug pharmacogenomic testing in the NHS, however, there is still a dearth or research in this area, and more studies are needed in the future to address several uncertainties raised through the course of this research and explore this field in more details. The following text provides recommendations for future research.

6.5.1 Case study in non-mental health NHS clinical settings

As discussed earlier in this chapter and chapter five, a limitation of this thesis is the empirical qualitative data investigating the experiences healthcare professional and patients of implementing PGx testing in the NHS is limited to a single mental health case study in the East of England. Therefore, the findings may not be generalizable to other NHS settings. As a result, a future research recommendation will be to conduct further in-depth, comparative case studies of PGx implementations in different primary and secondary care settings in multiple localities. Within these case studies, multiple data collection methods should be used to ascertain the

distinctive and relevant components in PGx testing implementation in different NHS settings.

6.5.2 Feasibility study

The next step recommended by the MRC is to conduct feasibility testing to assess both the effectiveness and cost-effectiveness of implementing the proposed PGx testing implementation configuration in the NHS. The feasibility study would consider factors such as uptake and retention rates and should include a process evaluation to examine the reach of the intervention in terms of the characteristics of the population accessing the service. This is of utmost importance in terms of PGx testing, given the potential for exacerbating health inequalities identified in Chapter 1.

The process evaluation would also examine the feasibility of implementation and the fidelity of the intervention model. This describes the ability of health care professionals to consistently deliver PGx testing in accordance to a PGx testing service specifications and the acceptability of the intervention from the perspective of doctors, pharmacists and patients. Additionally, the suitability and acceptability of the proposed outcome measures to patients, commissioners, and other healthcare providers will also be established.

6.7 Final conclusions

- PGx testing can optimise prescribing in 1 in 5 newly prescribed medicines with PGx guidelines in UK primary care. This would translate to roughly 4 million patients in the UK.
- The biggest barriers to PGx testing implementation occur at the initial stage, impeding the behaviour of the prescriber to order multi-drug PGx testing for a patient.
- A number of strategies including improving IT infrastructure and interoperability, developing effective CDSS and utilising pharmacists in PGx testing implementation models, can enable prescribers to order PGx testing.

- The multi-drug PGx testing implementation configuration developed in this thesis remains to be optimised by selecting and modelling Behaviour Change Techniques. This will help determine which Behaviour Change Techniques may actively change behaviours of prescribers, pharmacist, and patients and how to optimise reach.
- The optimised multi-drug PGx testing implementation configuration will require further testing in a time sensitive case study in non-mental health settings, then a feasibility study and definitive trial to ultimately determine whether it is effective and cost-effective in changing prescriber and pharmacist behaviour to adopt PGx testing and the patient consequences for reducing adverse drug reactions and optimised prescribing.

References

ABDULLAH-KOOLMEES, H., VAN KEULEN, A. M., NIJENHUIS, M. & DENEER, V. H. M. 2020. Pharmacogenetics Guidelines: Overview and Comparison of the DPWG, CPIC, CPNDS, and RNPGx Guidelines. *Front Pharmacol,* 11**,** 595219.

AJZEN, I. 2011. The theory of planned behaviour: reactions and reflections. *Psychol Health,* 26**,** 1113-27.

AJZEN I. AND FISHBEIN M 1970. The prediction of behavior from attitudinal and normative variables. *Journal of Experimental Psychology,* 6**,** 466-87.

ALFARO, C. L., LAM, Y. W., SIMPSON, J. & ERESHEFSKY, L. 2000. CYP2D6 inhibition by fluoxetine, paroxetine, sertraline, and venlafaxine in a crossover study: intraindividual variability and plasma concentration correlations. *J Clin Pharmacol,* 40**,** 58-66.

ALLEN, D. R. 2000. Pharmacogenetics and the practice of medicine. *Nature,* 405**,** 857-865.

AMARE, A. T., SCHUBERT, K. O., TEKOLA-AYELE, F., HSU, Y. H., SANGKUHL, K., JENKINS, G., WHALEY, R. M., BARMAN, P., BATZLER, A., ALTMAN, R. B., AROLT, V., BROCKMOLLER, J., CHEN, C. H., DOMSCHKE, K., HALL-FLAVIN, D. K., HONG, C. J., ILLI, A., JI, Y., KAMPMAN, O., KINOSHITA, T., LEINONEN, E., LIOU, Y. J., MUSHIRODA, T., NONEN, S., SKIME, M. K., WANG, L., KATO, M., LIU, Y. L., PRAPHANPHOJ, V., STINGL, J. C., BOBO, W. V., TSAI, S. J., KUBO, M., KLEIN, T. E., WEINSHILBOUM, R. M., BIERNACKA, J. M. & BAUNE, B. T. 2018. Association of the Polygenic Scores for Personality Traits and Response to Selective Serotonin Reuptake Inhibitors in Patients with Major Depressive Disorder. *Front Psychiatry,* 9**,** 65.

AMERICAN SOCIETY OF HEALTH-SYSTEM PHARMACISTS. 2021. *ASHP Statement on the Pharmacist's Role in Clinical Pharmacogenomics* [Online]. Available: https://www.ashp.org/-/media/assets/policy-guidelines/docs/statements/pharmacists-role-clinical-pharmacogenomics.ashx [Accessed 20.03.2023].

ARBITRIO, M., SCIONTI, F., DI MARTINO, M. T., CARACCIOLO, D., PENSABENE, L., TASSONE, P. & TAGLIAFERRI, P. 2021. Pharmacogenomics Biomarker Discovery and Validation for Translation in Clinical Practice. *Clin Transl Sci,* 14**,** 113-119.

ARKSEY, H. & O'MALLEY, L. 2005. Scoping studies: towards a methodological framework. *International Journal of Social Research Methodology,* 8**,** 19-32.

ARWOOD, M. J., DIETRICH, E. A., DUONG, B. Q., SMITH, D. M., COOK, K., ELCHYNSKI, A., ROSENBERG, E. I., HUBER, K. N., NAGOSHI, Y. L., WRIGHT, A., BUDD, J. T., HOLLAND, N. P., MASKA, E., PANNA, D., ELSEY, A. R., CAVALLARI, L. H., WIISANEN, K., JOHNSON, J. A. & GUMS, J. G. 2020. Design and early implementation successes and challenges of a pharmacogenetics consult clinic. *Journal of Clinical Medicine,* 9(7)**,** 1-18.

ATKINS, L., FRANCIS, J., ISLAM, R., O'CONNOR, D., PATEY, A., IVERS, N., FOY, R., DUNCAN, E. M., COLQUHOUN, H., GRIMSHAW, J. M., LAWTON, R. & MICHIE, S. 2017. A guide to using the Theoretical Domains Framework of behaviour change to investigate implementation problems. *Implement Sci,* 12**,** 77.

BAIN, K. T., SCHWARTZ, E. J., KNOWLTON, O. V., KNOWLTON, C. H. & TURGEON, J. 2018. Implementation of a pharmacist-led pharmacogenomics service for the Program of All-Inclusive Care for the Elderly (PHARM-GENOME-PACE). *Journal of the American Pharmacists Association,* 58**,** 281-289.e1.

BAKER, R., CAMOSSO-STEFINOVIC, J., GILLIES, C., SHAW, E. J., CHEATER, F., FLOTTORP, S., ROBERTSON, N., WENSING, M., FIANDER, M., ECCLES, M. P., GODYCKI-CWIRKO, M., VAN LIESHOUT, J. & JAGER, C. 2015. Tailored interventions to address determinants of practice. *Cochrane Database Syst Rev***,** CD005470.

BANK, P. C., SWEN, J. J. & GUCHELAAR, H. J. 2018a. A nationwide cross-sectional survey of pharmacy students on pharmacogenetic testing in The Netherlands. *Pharmacogenomics,* 19**,** 311-319.

BANK, P. C. D., CAUDLE, K. E., SWEN, J. J., GAMMAL, R. S., WHIRL-CARRILLO, M., KLEIN, T. E., RELLING, M. V. & GUCHELAAR, H. J. 2018b. Comparison of the Guidelines of the Clinical Pharmacogenetics Implementation Consortium and the Dutch Pharmacogenetics Working Group. *Clinical Pharmacology and Therapeutics,* 103**,** 599-618.

BANK, P. C. D., SWEN, J. J. & GUCHELAAR, H. J. 2019. Estimated nationwide impact of implementing a preemptive pharmacogenetic panel approach to guide drug prescribing in primary care in The Netherlands. *BMC Med,* 17**,** 110.

BARBARINO, J. M., WHIRL-CARRILLO, M., ALTMAN, R. B. & KLEIN, T. E. 2018. PharmGKB: A worldwide resource for pharmacogenomic information. *Wiley Interdiscip Rev Syst Biol Med,* 10**,** e1417.

BIELINSKI, S. J., OLSON, J. E., PATHAK, J., WEINSHILBOUM, R. M., WANG, L., LYKE, K. J., RYU, E., TARGONSKI, P. V., VAN NORSTRAND, M. D., HATHCOCK, M. A., TAKAHASHI, P. Y., MCCORMICK, J. B., JOHNSON, K. J., MASCHKE, K. J., ROHRER VITEK, C. R., ELLINGSON, M. S., WIEBEN, E. D., FARRUGIA, G., MORRISETTE, J. A., KRUCKEBERG, K. J., BRUFLAT, J. K., PETERSON, L. M., BLOMMEL, J. H., SKIERKA, J. M., FERBER, M. J., BLACK, J. L., BAUDHUIN, L. M., KLEE, E. W., ROSS, J. L., VELDHUIZEN, T. L., SCHULTZ, C. G., CARABALLO, P. J., FREIMUTH, R. R., CHUTE, C. G. & KULLO, I. J. 2014. Preemptive genotyping for personalized medicine: design of the right drug, right dose, right time-using genomic data to individualize treatment protocol. *Mayo Clin Proc,* 89**,** 25-33.

BIELINSKI, S. J., ST SAUVER, J. L., OLSON, J. E., WIELAND, M. L., VITEK, C. R., BELL, E. J., MC GREE, M. E., JACOBSON, D. J., MCCORMICK, J. B., TAKAHASHI, P. Y., BLACK, J. L., CARABALLO, P. J., SHARP, R. R., BEEBE, T. J., WEINSHILBOUM, R. M., WANG, L. & ROGER, V. L. 2017. Are patients willing to incur out-of-pocket costs for pharmacogenomic testing? *Pharmacogenomics J,* 17**,** 1-3.

BIO.LIGIS. *German hospital Robert-Bosch-Krankenhaus Stuttgart and Bio.ligis GIM Integrate pharmacogenetics into clinical practice-a milestone for personalised medicine* [Online]. [Accessed 10.10.2021].

BLAGEC, K., KOOPMANN, R., CROMMENTUIJN - VAN RHENEN, M., HOLSAPPEL, I., VAN DER WOUDEN, C. H., KONTA, L., HONG, X., STEINBERGER, D., JUST, E., SWEN, J. J., GUCHELAAR, H.-J., SAMWALD, M. & XU, H. 2018. Implementing pharmacogenomics decision support across seven European countries: The Ubiquitous Pharmacogenomics (U-PGx) project. *Journal of the American Medical Informatics Association,* 25**,** 893-898.

BLUETHMANN, S. M., BARTHOLOMEW, L. K., MURPHY, C. C. & VERNON, S. W. 2017. Use of Theory in Behavior Change Interventions. *Health Educ Behav,* 44**,** 245-253.

BORDEN, B. A., GALECKI, P., WELLMANN, R., DANAHEY, K., LEE, S. M., PATRICK-MILLER, L., SORRENTINO, M. J., NANDA, R., KOYNER, J. L., POLONSKY, T. S., STADLER, W. M., MULCAHY, C., KAVITT, R. T., RATAIN, M. J., MELTZER, D. O. & O'DONNELL, P. H. 2019. Assessment of provider-perceived barriers to clinical use of pharmacogenomics during participation in an institutional implementation study. *Pharmacogenetics and Genomics,* 29**,** 31-38.

BOROBIA, A. M., DAPIA, I., TONG, H. Y., ARIAS, P., MUNOZ, M., TENORIO, J., HERNANDEZ, R., GARCIA GARCIA, I., GORDO, G., RAMIREZ, E., FRIAS, J., LAPUNZINA, P. & CARCAS, A. J. 2018. Clinical Implementation of Pharmacogenetic Testing in a Hospital of the Spanish National Health System: Strategy and Experience Over 3 Years. *Clin Transl Sci,* 11**,** 189-199.

BOUSMAN, C., MARUF, A. A. & MÃ¼LLER, D. J. 2019a. Towards the integration of pharmacogenetics in psychiatry: a minimum, evidence-based genetic testing panel. *Current Opinion in Psychiatry,* 32**,** 7-15.

BOUSMAN, C. A., ARANDJELOVIC, K., MANCUSO, S. G., EYRE, H. A. & DUNLOP, B. W. 2019b. Pharmacogenetic tests and depressive symptom remission: a meta-analysis of randomized controlled trials. *Pharmacogenomics,* 20**,** 37-47.

BRAUN, V. & CLARKE, V. 2006. Using thematic analysis in psychology. *Qualitative Research in Psychology,* 3**,** 77-101.

BRAYFIELD, A. 2020. *Martindale: The Complete Drug Reference (online)* [Online]. Available: https://about.medicinescomplete.com [Accessed 10.09.2020].

BRIGHT, D., SAADEH, C., DEVUYST-MILLER, S., SOHN, M., CHOKER, A. & LANGERVELD, A. 2020. Pharmacist consult reports to support pharmacogenomics report interpretation. *Pharmacogenomics and Personalized Medicine,* 13**,** 719-724.

BRITTAIN, H. K., SCOTT, R. & THOMAS, E. 2017. The rise of the genome and personalised medicine. *Clin Med (Lond),* 17**,** 545-551.

BUMGARNER, R. 2013. Overview of DNA microarrays: types, applications, and their future. *Curr Protoc Mol Biol,* Chapter 22**,** Unit 22 1.

CANE, J., O'CONNOR, D. & MICHIE, S. 2012. Validation of the theoretical domains framework for use in behaviour change and implementation research. *Implement Sci,* 7**,** 37.

CAREY, R. N., CONNELL, L. E., JOHNSTON, M., ROTHMAN, A. J., DE BRUIN, M., KELLY, M. P. & MICHIE, S. 2019. Behavior Change Techniques and Their Mechanisms of Action: A Synthesis of Links Described in Published Intervention Literature. *Ann Behav Med,* 53**,** 693-707.

CARSON, P. E., FLANAGAN, C. L., ICKES, C. E. & ALVING, A. S. 1956. Enzymatic Deficiency in Primaquine-Sensitive Erythrocytes. *Science,* 124**,** 484-485.

CAVALLARI, L. H., LEE, C. R., BEITELSHEES, A. L., COOPER-DEHOFF, R. M., DUARTE, J. D., VOORA, D., KIMMEL, S. E., MCDONOUGH, C. W., GONG, Y., DAVE, C. V., PRATT, V. M., ALESTOCK, T. D., ANDERSON, R. D., ALSIP, J., ARDATI, A. K., BROTT, B. C., BROWN, L., CHUMNUMWAT, S., CLARE-SALZLER, M. J., COONS, J. C., DENNY, J. C., DILLON, C., ELSEY, A. R., HAMADEH, I., HARADA, S., HILLEGASS, W. B., HINES, L., HORENSTEIN, R. B., HOWELL, L. A., JENG, L. J., KELEMEN, M. D., LEE, Y., MAGVANJAV, O., MONTASSER, M., NELSON, D. R., NUTESCU, E. A., NWABA, D. C., PAKYZ, R. E., PALMER, K., PETERSON, J. F., POLLIN, T. I., QUINN, A. H., ROBINSON, S. W., SCHUB, J., SKAAR, T. C., SMITH, D. M., SRIRAMOJU, V. B., STAROSTIK, P., STYS, T. P., STEVENSON, J. M., VARUNOK, N., VESELY, M. R., WAKE, D. T., WECK, K. E., WEITZEL, K. W., WILKE, R. A., WILLIG, J., ZHAO, R. Y., KREUTZ, R. P., STOUFFER, G. A., EMPEY, P. E., LIMDI, N. A., SHULDINER, A. R., WINTERSTEIN, A. G. & JOHNSON, J. A. 2018. Multi-site Investigation of Outcomes with Implementation of CYP2C19 Genotype-Guided Antiplatelet Therapy after Percutaneous Coronary Intervention. *JACC Cardiovasc Interv,* 11**,** 181-91.

CENTER FOR EVIDENCE BASED MANAGEMENT 2014. Critical Appraisal Checklist for a Meta-Analysis or Systematic
Review.

CENTRE FOR EVIDENCE BASED MANAGEMENT. 2022. *Critical Appraisal of a Survey* [Online]. [Internet]. Available: https://www.cebma.org/wp-content/uploads/Critical-Appraisal-Questions-for-a-Survey.pdf [Accessed 20.06.2022].

CHANFREAU-COFFINIER, C., HULL, L. E., LYNCH, J. A., DUVALL, S. L., DAMRAUER, S. M., CUNNINGHAM, F. E., VOIGHT, B. F., MATHENY, M. E., OSLIN, D. W., ICARDI, M. S. & TUTEJA, S. 2019. Projected Prevalence of Actionable Pharmacogenetic Variants and

Level A Drugs Prescribed Among US Veterans Health Administration Pharmacy Users. *JAMA Netw Open,* 2**,** e195345.
CHARLAND, S. L., AGATEP, B. C., HERRERA, V., SCHRADER, B., FRUEH, F. W., RYVKIN, M., SHABBEER, J., DEVLIN, J. J., SUPERKO, H. R. & STANEK, E. J. 2014. Providing patients with pharmacogenetic test results affects adherence to statin therapy: Results of the Additional KIF6 Risk Offers Better Adherence to Statins (AKROBATS) trial. *Pharmacogenomics Journal,* 14**,** 272-280.
CONNER, M., KIRK, S. F., CADE, J. E. & BARRETT, J. H. 2003. Environmental influences: factors influencing a woman's decision to use dietary supplements. *J Nutr,* 133**,** 1978S-1982S.
CONNER, M., MCEACHAN, R., LAWTON, R. & GARDNER, P. 2017. Applying the reasoned action approach to understanding health protection and health risk behaviors. *Soc Sci Med,* 195**,** 140-148.
CRAIG, P., DIEPPE, P., MACINTYRE, S., MICHIE, S., NAZARETH, I., PETTICREW, M. & MEDICAL RESEARCH COUNCIL, G. 2008. Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ,* 337**,** a1655.
CRITICAL APPRAISAL SKILLS PROGRAMME. 2022. *10 Questions To Help You Make Sense of Qualitative Research. CASP Qual Checklist* [Online]. [Internet]. Available: https://caspuk.net/wp-content/uploads/2018/03/CASP-Qualitative-Checklist-Download.pdf [Accessed 20.03.2023].
CULBERTSON, A. W., VALENTINE, S. J. & NAYLOR, S. 2007. Personalised medicine: Technological innovation and patient empowerment or exuberant hyperbole? *Drug Discovery World,* 8**,** 18-31.
D RUDKIN, K. R., T PATTERSON, A EVANS, R M PARR, C HARRISON 2020. Reforms to the initial education and training of pharmacists.
DAMSCHRODER, L. J. 2020. Clarity out of chaos: Use of theory in implementation research. *Psychiatry Res,* 283**,** 112461.
DAVIES, E. C., GREEN, C. F., TAYLOR, S., WILLIAMSON, P. R., MOTTRAM, D. R. & PIRMOHAMED, M. 2009. Adverse Drug Reactions in Hospital In-Patients: A Prospective Analysis of 3695 Patient-Episodes. *PLoS ONE,* 4**,** e4439-e4439.
DAVIES, P., WALKER, A. E. & GRIMSHAW, J. M. 2010. A systematic review of the use of theory in the design of guideline dissemination and implementation strategies and interpretation of the results of rigorous evaluations. *Implement Sci,* 5**,** 14.
DAVIS, D. A. & TAYLOR-VAISEY, A. 1997. Translating guidelines into practice. A systematic review of theoretic concepts, practical experience and research evidence in the adoption of clinical practice guidelines. *Cmaj,* 157**,** 408-16.
DAVIS, R., CAMPBELL, R., HILDON, Z., HOBBS, L. & MICHIE, S. 2015. Theories of behaviour and behaviour change across the social and behavioural sciences: a scoping review. *Health Psychol Rev,* 9**,** 323-44.
DAWES, M., ALOISE, M. N., ANG, J. S., CULLIS, P., DAWES, D., FRASER, R., LIKNAITZKY, G., PATERSON, A., STANLEY, P., SUAREZ-GONZALEZ, A. & KATZOV-ECKERT, H. 2016. Introducing pharmacogenetic testing with clinical decision support into primary care: a feasibility study. *CMAJ Open,* 4**,** E528-E534.
DEJONCKHEERE, M. & VAUGHN, L. M. 2019. Semistructured interviewing in primary care research: a balance of relationship and rigour. *Fam Med Community Health,* 7**,** e000057.
DIBONAVENTURA, M., GABRIEL, S., DUPCLAY, L., GUPTA, S. & KIM, E. 2012. A patient perspective of the impact of medication side effects on adherence: results of a cross-sectional nationwide survey of patients with schizophrenia. *BMC Psychiatry,* 12**,** 20-20.

DOMINIC, T., JOSEPH, S., SAAD, M., PARK, T. & MUZUMDAR, J. 2021. The attitudes and confidence of pharmacists in the United States or Canada Regarding Pharmacogenomic Testing: a systematic review. *JACCP Journal of the American College of Clinical Pharmacy,* 4(9)**,** 1255.

DOSWELL, W. M., BRAXTER, B. J., CHA, E. & KIM, K. H. 2011. Testing the theory of reasoned action in explaining sexual behavior among African American young teen girls. *J Pediatr Nurs,* 26**,** e45-54.

DRESSLER, L. G., BELL, G. C., ABERNATHY, P. M., RUCH, K. & DENSLOW, S. 2019. Implementing pharmacogenetic testing in rural primary care practices: a pilot feasibility study. *Pharmacogenomics,* 20**,** 433-446.

DUNNENBERGER, H. M., BISZEWSKI, M., BELL, G. C., SEREIKA, A., MAY, H., JOHNSON, S. G., HULICK, P. J. & KHANDEKAR, J. 2016. Implementation of a multidisciplinary pharmacogenomics clinic in a community health system. *Am J Health Syst Pharm,* 73**,** 1956-1966.

EADON, M. T., DESTA, Z., LEVY, K. D., DECKER, B. S., PIERSON, R. C., PRATT, V. M., CALLAGHAN, J. T., ROSENMAN, M. B., CARPENTER, J. S., HOLMES, A. M., MCDONALD, C. A., BENSON, E. A., PATIL, A. S., VUPPALANCHI, R., GUFFORD, B. T., DAVE, N., ROBARGE, J. D., HYDER, M. A., HAAS, D. M., KREUTZ, R. P., DEXTER, P. R., SKAAR, T. C. & FLOCKHART, D. A. 2016. Implementation of a pharmacogenomics consult service to support the INGENIOUS trial. *Clin Pharmacol Ther,* 100**,** 63-6.

ECOBICHON, D. J. & KALOW, W. 1963. THE EFFECTS OF SIALIDASE ON PSEUDOCHOLINESTERASE TYPES. *Canadian Journal of Biochemistry and Physiology,* 41**,** 969-974.

EDWARDS, I. R. & ARONSON, J. K. 2000. Adverse drug reactions: definitions, diagnosis, and management. *The Lancet,* 356**,** 1255-1259.

EL ROUBY, N., LIMA, J. J. & JOHNSON, J. A. 2018. Proton pump inhibitors: from CYP2C19 pharmacogenetics to precision medicine. *Expert Opin Drug Metab Toxicol,* 14**,** 447-460.

ELLIOTT, R., FISCHER, C. T. & RENNIE, D. L. 1999. Evolving guidelines for publication of qualitative research studies in psychology and related fields. *Br J Clin Psychol,* 38**,** 215-29.

EMA. 2000. *Public Statement on Abacavir - Ziagen - on hypersensitivity reactions and resporatory symptoms* [Online]. Available: https://www.ema.europa.eu/en/news/public-statement-ziagen-abacavir-important-safety-information-hypersensitivity-reactions-respiratory [Accessed 20.03.2023].

FAN, M. & BOUSMAN, C. A. 2020. Estimating the Potential Impact of CYP2C19 and CYP2D6 Genetic Testing on Protocol-Based Care for Depression in Canada and the United States. *Mol Neuropsychiatry,* 5**,** 27-33.

FDA. 2021. *Table of Pharmacogenomic Biomarkers in Drug Labeling* [Online]. Available: https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling [Accessed 21.03.2023].

FISHBEIN, M. & AJZEN, I. 2011. *Predicting and Changing Behavior,* New York, Psychology Press.

FORMEA, C. M., NICHOLSON, W. T. & VITEK, C. R. 2015. An inter-professional approach to personalized medicine education: one institution's experience. *Per Med,* 12**,** 129-138.

FRANCIS, J. J., O'CONNOR, D. & CURRAN, J. 2012. Theories of behaviour change synthesised into a set of theoretical groupings: introducing a thematic series on the theoretical domains framework. *Implement Sci,* 7**,** 35.

FRIED, T. R., O'LEARY, J., TOWLE, V., GOLDSTEIN, M. K., TRENTALANGE, M. & MARTIN, D. K. 2014. Health Outcomes Associated with Polypharmacy in Community-Dwelling Older Adults: A Systematic Review. *Journal of the American Geriatrics Society,* 62**,** 2261-2272.

GALE, N. K., HEATH, G., CAMERON, E., RASHID, S. & REDWOOD, S. 2013. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. *BMC Medical Research Methodology,* 13.

GARFIELD, S., BARBER, N., WALLEY, P., WILLSON, A. & ELIASSON, L. 2009. Quality of medication use in primary care--mapping the problem, working to a solution: a systematic review of the literature. *BMC Med,* 7**,** 50.

GLANZ, K. & BISHOP, D. B. 2010. The role of behavioral science theory in development and implementation of public health interventions. *Annu Rev Public Health,* 31**,** 399-418.

GONZALEZ, F. J., SKODAT, R. C., KIMURA, S., UMENO, M., ZANGER, U. M., NEBERT, D. W., GELBOIN, H. V., HARDWICK, J. P. & MEYER, U. A. 1988. Characterization of the common genetic defect in humans deficient in debrisoquine metabolism. *Nature,* 331**,** 442-446.

GRAHAM-CLARKE, E., RUSHTON, A., NOBLET, T. & MARRIOTT, J. 2019. Non-medical prescribing in the United Kingdom National Health Service: A systematic policy review. *PLoS One,* 14**,** e0214630.

GREENHALGH, T. 2018. How to improve success of technology projects in health and social care. *Public Health Res Pract,* 28.

GREENHALGH, T., MAYLOR, H., SHAW, S., WHERTON, J., PAPOUTSI, C., BETTON, V., NELISSEN, N., GREMYR, A., RUSHFORTH, A., KOSHKOUEI, M. & TAYLOR, J. 2020. The NASSS-CAT Tools for Understanding, Guiding, Monitoring, and Researching Technology Implementation Projects in Health and Social Care: Protocol for an Evaluation Study in Real-World Settings. *JMIR Res Protoc,* 9**,** e16861.

GREENHALGH, T., WHERTON, J., PAPOUTSI, C., LYNCH, J., HUGHES, G., A'COURT, C., HINDER, S., FAHY, N., PROCTER, R. & SHAW, S. 2017. Beyond Adoption: A New Framework for Theorizing and Evaluating Nonadoption, Abandonment, and Challenges to the Scale-Up, Spread, and Sustainability of Health and Care Technologies. *J Med Internet Res,* 19**,** e367.

GREENHALGH, T., WHERTON, J., PAPOUTSI, C., LYNCH, J., HUGHES, G., A'COURT, C., HINDER, S., PROCTER, R. & SHAW, S. 2018. Analysing the role of complexity in explaining the fortunes of technology programmes: empirical application of the NASSS framework. *BMC Med,* 16**,** 66.

GROL, R. & GRIMSHAW, J. 2003. From best evidence to best practice: effective implementation of change in patients' care. *The Lancet,* 362**,** 1225-1230.

GUBA, E. G. 1981. Criteria for assessing the trustworthiness of naturalistic inquiries. *Ectj,* 29.

GUEST, G., BUNCE, A. & JOHNSON, L. 2006. How Many Interviews Are Enough? *Field Methods,* 18**,** 59-82.

GURWITZ, D. & MANOLOPOULOS, V. G. 2007. Personalized Medicine. Elsevier.

GUTHRIE, B., MAKUBATE, B., HERNANDEZ-SANTIAGO, V. & DREISHCULTE, T. 2015. The rising tide of polypharmacy and drug-drug interactions:population database analysis 1995-2010. *BMC Medicine,* 13**,** 1-10.

HAGA, S. B., MILLS, R., MOADDEB, J., LIU, Y. & VOORA, D. 2021. Independent community pharmacists' experience in offering pharmacogenetic testing. *Pharmacogenomics and Personalized Medicine,* 14**,** 877-886.

HAGA, S. B., MOADDEB, J., MILLS, R., PATEL, M., KRAUS, W. & ALLEN LAPOINTE, N. M. 2015. Incorporation of pharmacogenetic testing into medication therapy management. *Pharmacogenomics,* 16**,** 1931-41.

HAGA, S. B. M., R.: MOADDEB, J.: LIU, Y.: VOORA, D. 2021. Independent community pharmacists' experience in offering pharmacogenetic testing. *Pharmacogenomics and Personalized Medicine,* 14**,** 877-886.

HAYWARD, J., BISHOP, M., RAFI, I. & DAVISON, V. 2017. Genomics in routine clinical care: what does this mean for primary care? *Br J Gen Pract,* 67**,** 58-9.

HAYWARD, J., MCDERMOTT, J., QURESHI, N. & NEWMAN, W. 2021. Pharmacogenomic testing to support prescribing in primary care: a structured review of implementation models. *Pharmacogenomics,* 22**,** 761-776.

HAYWARD, J. M., J.: QURESHI, N.: NEWMAN, W. 2021. Pharmacogenomic testing to support prescribing in primary care: A structured review of implementation models. *Pharmacogenomics,* 22(12)**,** 761-777.

HELITZER, D., HEATH, D., MALTRUD, K., SULLIVAN, E. & ALVERSON, D. 2003. Assessing or predicting adoption of telehealth using the diffusion of innovations theory: a practical example from a rural program in New Mexico. *Telemed J E Health,* 9**,** 179-87.

HERBER, O. R., ATKINS, L., STORK, S. & WILM, S. 2018. Enhancing self-care adherence in patients with heart failure: a study protocol for developing a theory-based behaviour change intervention using the COM-B behaviour model (ACHIEVE study). *BMJ Open,* 8**,** e025907.

HIGGINS, J. P. & GREEN, S. 2008. Cochrane handbook for systematic reviews of interventions.

HINDERER, M., BOEKER, M., WAGNER, S. A., BINDER, H., UCKERT, F., NEWE, S., HULSEMANN, J. L., NEUMAIER, M., SCHADE-BRITTINGER, C., ACKER, T., PROKOSCH, H. U. & SEDLMAYR, B. 2017. The experience of physicians in pharmacogenomic clinical decision support within eight German university hospitals. *Pharmacogenomics,* 18**,** 773-785.

HIPPMAN, C. & NISLOW, C. 2019. Pharmacogenomic Testing: Clinical Evidence and Implementation Challenges. *J Pers Med,* 9.

HO, T. T., GIFT, M. & ALEXANDER, E. 2022. Prioritizing pharmacogenomics implementation initiates: a survey of healthcare professionals. *Per Med,* 19**,** 15-23.

HOFFMAN, J. M., DUNNENBERGER, H. M., KEVIN HICKS, J., CAUDLE, K. E., WHIRL CARRILLO, M., FREIMUTH, R. R., WILLIAMS, M. S., KLEIN, T. E. & PETERSON, J. F. 2016. Developing knowledge resources to support precision medicine: principles from the Clinical Pharmacogenetics Implementation Consortium (CPIC). *J Am Med Inform Assoc,* 23**,** 796-801.

HOOP, J. G., ROBERTS, L. W., GREEN HAMMOND, K. A. & COX, N. J. 2008. Psychiatrists' attitudes regarding genetic testing and patient safeguards: a preliminary study. *Genet Test,* 12**,** 245-52.

HORNE, R., WEINMAN, J., BARBER, N. & ELLIOTT, R. 2005. Concordance, adherence and compliance in medicine taking Report for the National Co-ordinating Centre for NHS Service Delivery and Organisation R & D (NCCSDO). *National Co-ordinating Centre for NHS Service Delivery and Organisation R & D***,** 1-331.

HOWARD, R. L. 2003. Investigation into the reasons for preventable drug related admissions to a medical admissions unit: observational study. *Quality and Safety in Health Care,* 12**,** 280-285.

HSC BUSINESS SERVICES ORGANISATION. 2020. *Prescription cost analysis 2019 at Northern Ireland Level* [Online]. Available: http://www.hscbusiness.hscni.net/services/3125.htm [Accessed 31.03.2020].

HUGHES, A. R., SPREEN, W. R., MOSTELLER, M., WARREN, L. L., LAI, E. H., BROTHERS, C. H., COX, C., NELSEN, A. J., HUGHES, S., THORBORN, D. E., STANCIL, B., HETHERINGTON, S. V., BURNS, D. K. & ROSES, A. D. 2008. Pharmacogenetics of hypersensitivity to abacavir: From PGx hypothesis to confirmation to clinical utility. *Pharmacogenomics Journal,* 8**,** 365-374.

IQVIA 2020. Global Medicine Spending and Usuage Trends.

JAMESON, A., FYLAN, B., BRISTOW, G. C., SAGOO, G. S., DALTON, C., CARDNO, A., SOHAL, J. & MCLEAN, S. L. 2021. What Are the Barriers and Enablers to the Implementation of Pharmacogenetic Testing in Mental Health Care Settings? *Front Genet,* 12**,** 740216.

JARVIS, J. P., PETER, A. P., KEOGH, M., BALDASARE, V., BEANLAND, G. M., WILKERSON, Z. T., KRADEL, S. & SHAMAN, J. A. 2022. Real-World Impact of a Pharmacogenomics-Enriched Comprehensive Medication Management Program. *J Pers Med,* 12.

JIANG, S., MATHIAS, P. C., HENDRIX, N., SHIRTS, B. H., TARCZY-HORNOCH, P., VEENSTRA, D., MALONE, D. & DEVINE, B. 2022. Implementation of pharmacogenomic clinical decision support for health systems: a cost-utility analysis. *Pharmacogenomics J,* 22**,** 188-197.

JOHNSON, J. A. 2013. Pharmacogenetics in clinical practice: how far have we come and where are we going? *Pharmacogenomics,* 14**,** 835-43.

JOHNSON, J. A., CAUDLE, K. E., GONG, L., WHIRL-CARRILLO, M., STEIN, C. M., SCOTT, S. A., LEE, M. T., GAGE, B. F., KIMMEL, S. E., PERERA, M. A., ANDERSON, J. L., PIRMOHAMED, M., KLEIN, T. E., LIMDI, N. A., CAVALLARI, L. H. & WADELIUS, M. 2017. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Pharmacogenetics-Guided Warfarin Dosing: 2017 Update. *Clin Pharmacol Ther,* 102**,** 397-404.

JOHNSON, J. L., ADKINS, D. & CHAUVIN, S. 2020. A Review of the Quality Indicators of Rigor in Qualitative Research. *Am J Pharm Educ,* 84**,** 7120.

JOHNSON, K. B., WEI, W. Q., WEERARATNE, D., FRISSE, M. E., MISULIS, K., RHEE, K., ZHAO, J. & SNOWDON, J. L. 2021. Precision Medicine, AI, and the Future of Personalized Health Care. *Clin Transl Sci,* 14**,** 86-93.

JOINT FORMULARY COMMITTEE. 2020. *British National Formulary* [Online]. Available: http://www.medicinescomplete.com [Accessed 10.09.2020].

JOOTUN, D., MCGHEE, G. & MARLAND, G. R. 2009. Reflexivity: promoting rigour in qualitative research. *Nurs Stand,* 23**,** 42-6.

JORGENSEN, A. L., PRINCE, C., FITZGERALD, G., HANSON, A., DOWNING, J., REYNOLDS, J., ZHANG, J. E., ALFIREVIC, A. & PIRMOHAMED, M. 2019. Implementation of genotype-guided dosing of warfarin with point-of-care genetic testing in three UK clinics: a matched cohort study. *BMC Med,* 17**,** 76.

JUKIC, M. M., SMITH, R. L., HASLEMO, T., MOLDEN, E. & INGELMAN-SUNDBERG, M. 2019. Effect of CYP2D6 genotype on exposure and efficacy of risperidone and aripiprazole: a retrospective, cohort study. *The Lancet Psychiatry,* 6**,** 418-426.

KAMINSKI J 2011. Diffusion of Innovation Theory. *Canadian Journal of Nursing Informatics,* 6.

KARAMPERIS, K., KOROMINA, M., PAPANTONIOU, P., SKOKOU, M., KANELLAKIS, F., MITROPOULOS, K., VOZIKIS, A., MULLER, D. J., PATRINOS, G. P. & MITROPOULOU, C. 2021. Economic evaluation in psychiatric pharmacogenomics: a systematic review. *Pharmacogenomics J,* 21**,** 533-541.

KEOGH, B. 2015. NHS England Board Paper: Personalised Medicine Strategy. 1-5.

KIM, S. & MISRA, A. 2007. SNP genotyping: technologies and biomedical applications. *Annu Rev Biomed Eng,* 9**,** 289-320.

KIM, W. Y., KIM, H. S., OH, M. & SHIN, J. G. 2020. Survey of physicians' views on the clinical implementation of pharmacogenomics-based personalized therapy. *Transl Clin Pharmacol,* 28**,** 34-42.

KIMMEL, S. E. 2015. Warfarin pharmacogenomics: current best evidence. *J Thromb Haemost,* 13 Suppl 1**,** S266-71.

KIMMEL, S. E., FRENCH, B., KASNER, S. E., JOHNSON, J. A., ANDERSON, J. L., GAGE, B. F., ROSENBERG, Y. D., EBY, C. S., MADIGAN, R. A., MCBANE, R. B., ABDEL-RAHMAN, S. Z., STEVENS, S. M., YALE, S., MOHLER, E. R., FANG, M. C., SHAH, V., HORENSTEIN, R. B., LIMDI, N. A., MULDOWNEY, J. A. S., GUJRAL, J., DELAFONTAINE, P., DESNICK, R. J., ORTEL, T. L., BILLETT, H. H., PENDLETON, R. C., GELLER, N. L., HALPERIN, J. L., GOLDHABER, S. Z., CALDWELL, M. D., CALIFF, R. M. & ELLENBERG, J. H. 2013. A Pharmacogenetic versus a Clinical Algorithm for Warfarin Dosing. *New England Journal of Medicine,* 369**,** 2283-2293.

KIMPTON, J. E., CAREY, I. M., THREAPLETON, C. J. D., ROBINSON, A., HARRIS, T., COOK, D. G., DEWILDE, S. & BAKER, E. H. 2019. Longitudinal exposure of English primary care patients to pharmacogenomic drugs: An analysis to inform design of pre-emptive pharmacogenomic testing. *Br J Clin Pharmacol,* 85**,** 2734-2746.

KNMP. 2022. *The G-Standaard: the medicines standard in healthcare* [Online]. Available: https://www.knmp.nl/producten/gebruiksrecht-g-standaard/informatie-over-de-g-standaard/the-g-standaard-the-medicines-standard-in-healthcare [Accessed 03.03.2022].

KONGKAEW, C., NOYCE, P. R. & ASHCROFT, D. M. 2008. Hospital Admissions Associated with Adverse Drug Reactions: A Systematic Review of Prospective Observational Studies. *Annals of Pharmacotherapy,* 42**,** 1017-1025.

KREBS, K. & MILANI, L. 2019. Translating pharmacogenomics into clinical decisions: do not let the perfect be the enemy of the good. *Hum Genomics,* 13**,** 39.

KROOPNICK, M. 2013. AM last page. The MCAT exam: comparing the 1991 and 2015 exams. *Acad Med,* 88**,** 737.

KUPER, A., LINGARD, L. & LEVINSON, W. 2008. Critically appraising qualitative research. *BMJ,* 337**,** a1035-a1035.

KWASNICKA, D., DOMBROWSKI, S. U., WHITE, M. & SNIEHOTTA, F. 2016. Theoretical explanations for maintenance of behaviour change: a systematic review of behaviour theories. *Health Psychol Rev,* 10**,** 277-96.

LAB, P. *PRIME: Pharmacogenomics for the prevention of adverse drug reactions in mental health* [Online]. Available: https://www.psychpgxlab.com/projects/prime [Accessed 03.03.2022].

LANTING, P., DRENTH, E., BOVEN, L., VAN HOEK, A., HIJLKEMA, A., POOT, E., VAN DER VRIES, G., SCHOEVERS, R., HORWITZ, E., GANS, R., KOSTERINK, J., PLANTINGA, M., VAN LANGEN, I., RANCHOR, A., WIJMENGA, C., FRANKE, L., WILFFERT, B. & SIJMONS, R. 2020. Practical barriers and facilitators experienced by patients, pharmacists and physicians to the implementation of pharmacogenomic screening in Dutch outpatient hospital care-an explorative pilot study. *Journal of Personalized Medicine,* 10(4)**,** 1-13.

LANTING, P. D., E.: BOVEN, L.: VAN HOEK, A.: HIJLKEMA, A.: POOT, E.: VAN DER VRIES, G.: SCHOEVERS, R.: HORWITZ, E.: GANS, R.: KOSTERINK, J.: PLANTINGA, M.: VAN LANGEN, I.: RANCHOR, A.: WIJMENGA, C.: FRANKE, L.: WILFFERT, B.: SIJMONS, R. 2020. Practical barriers and facilitators experienced by patients, pharmacists and physicians to the implementation of pharmacogenomic screening in Dutch outpatient hospital care-an explorative pilot study. *Journal of Personalized Medicine,* 10(4)**,** 1-13.

LAVRAKAS, P. J. 1987. *Telephone survey methods: Sampling, selection, and supervision.*, Sage Publications.

LAWTON, J. S., TAMIS-HOLLAND, J. E., BANGALORE, S., BATES, E. R., BECKIE, T. M., BISCHOFF, J. M., BITTL, J. A., COHEN, M. G., DIMAIO, J. M., DON, C. W., FREMES, S. E., GAUDINO, M. F., GOLDBERGER, Z. D., GRANT, M. C., JASWAL, J. B., KURLANSKY, P. A., MEHRAN, R., METKUS, T. S., JR., NNACHETA, L. C., RAO, S. V., SELLKE, F. W., SHARMA, G., YONG, C. M. & ZWISCHENBERGER, B. A. 2022. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation,* 145**,** e18-e114.

LEE, T.-T. 2004. Nurses' adoption of technology: application of Rogers' innovation-diffusion model. *Applied Nursing Research,* 17**,** 231-238.

LEENDERTSE, A. J., EGBERTS, A. C. G., STOKER, L. J. & VAN DEN BEMT, P. M. L. 2008. Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. *Archives of Internal Medicine,* 168**,** 1890-1896.

LEHANE, E. & MCCARTHY, G. 2007. An examination of the intentional and unintentional aspects of medication non-adherence in patients diagnosed with hypertension. *Journal of Clinical Nursing,* 16**,** 698-706.

LEMKE, A. A., HUTTEN SELKIRK, C. G., GLASER, N. S., SEREIKA, A. W., WAKE, D. T., HULICK, P. J. & DUNNENBERGER, H. M. 2017. Primary care physician experiences with integrated pharmacogenomic testing in a community health system. *Per Med,* 14**,** 389-400.

LESLIE, K. H., MCCOWAN, C. & PELL, J. P. 2019. Adherence to cardiovascular medication: a review of systematic reviews. *J Public Health (Oxf),* 41**,** e84-e94.

LEVY, K. D., DECKER, B. S., CARPENTER, J. S., FLOCKHART, D. A., DEXTER, P. R., DESTA, Z. & SKAAR, T. C. 2014. Prerequisites to implementing a pharmacogenomics program in a large health-care system. *Clin Pharmacol Ther,* 96**,** 307-9.

LIEN, A. S. & JIANG, Y. D. 2017. Integration of diffusion of innovation theory into diabetes care. *J Diabetes Investig,* 8**,** 259-260.

LIKO, I., CORBIN, L., TOBIN, E., AQUILANTE, C. L. & LEE, Y. M. 2021. Implementation of a pharmacist-provided pharmacogenomics service in an executive health program. *American Journal of Health-System Pharmacy,* 78(12)**,** 1094-1103.

LINDENFELD, J. & JESSUP, M. 2017. 'Drugs don't work in patients who don't take them' (C. Everett Koop, MD, US Surgeon General, 1985). *European Journal of Heart Failure,* 19**,** 1412-1413.

LUNENBURG, C., THIRSTRUP, J. P., BYBJERG-GRAUHOLM, J., BAEKVAD-HANSEN, M., HOUGAARD, D. M., NORDENTOFT, M., WERGE, T., BORGLUM, A. D., MORS, O., MORTENSEN, P. B. & GASSE, C. 2021. Pharmacogenetic genotype and phenotype frequencies in a large Danish population-based case-cohort sample. *Transl Psychiatry,* 11**,** 294.

LUNENBURG, C., VAN DER WOUDEN, C. H., NIJENHUIS, M., CROMMENTUIJN-VAN RHENEN, M. H., DE BOER-VEGER, N. J., BUUNK, A. M., HOUWINK, E. J. F., MULDER, H., RONGEN, G. A., VAN SCHAIK, R. H. N., VAN DER WEIDE, J., WILFFERT, B., DENEER, V. H. M., SWEN, J. J. & GUCHELAAR, H. J. 2020. Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene-drug interaction of DPYD and fluoropyrimidines. *Eur J Hum Genet,* 28**,** 508-517.

LUZUM, J. A., PAKYZ, R. E., ELSEY, A. R., HAIDAR, C. E., PETERSON, J. F., WHIRL-CARRILLO, M., HANDELMAN, S. K., PALMER, K., PULLEY, J. M., BELLER, M., SCHILDCROUT, J. S., FIELD, J. R., WEITZEL, K. W., COOPER-DEHOFF, R. M., CAVALLARI, L. H., O'DONNELL, P. H., ALTMAN, R. B., PEREIRA, N., RATAIN, M. J., RODEN, D. M., EMBI, P. J., SADEE, W., KLEIN, T. E., JOHNSON, J. A., RELLING, M. V., WANG, L., WEINSHILBOUM, R. M.,

SHULDINER, A. R., FREIMUTH, R. R. & PHARMACOGENOMICS RESEARCH NETWORK TRANSLATIONAL PHARMACOGENETICS, P. 2017. The Pharmacogenomics Research Network Translational Pharmacogenetics Program: Outcomes and Metrics of Pharmacogenetic Implementations Across Diverse Healthcare Systems. *Clin Pharmacol Ther,* 102**,** 502-510.

MALLAL, S., PHILLIPS, E., CAROSI, G., MOLINA, J. M., WORKMAN, C., TOMAZIC, J., JAGEL-GUEDES, E., RUGINA, S., KOZYREV, O., CID, J. F., HAY, P., NOLAN, D., HUGHES, S., HUGHES, A., RYAN, S., FITCH, N., THORBORN, D., BENBOW, A. & TEAM, P.-S. 2008. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med,* 358**,** 568-79.

MANSON, L. E., VAN DER WOUDEN, C. H., SWEN, J. J. & GUCHELAAR, H. J. 2017. The Ubiquitous Pharmacogenomics consortium: making effective treatment optimization accessible to every European citizen. *Pharmacogenomics,* 18**,** 1041-1045.

MARRERO, R. J., CICALI, E. J., ARWOOD, M. J., EDDY, E., DEREMER, D., RAMNARAIGN, B. H., DAILY, K. C., JONES, D., COOK, K. J., CAVALLARI, L. H., WIISANEN WEITZEL, K., LANGAEE, T., NEWSOM, K. J., STAROSTIK, P., CLARE-SALZER, M. J., JOHNSON, J. A., GEORGE, T. J. & COOPER-DEHOFF, R. M. 2020. How to Transition from Single-Gene Pharmacogenetic Testing to Preemptive Panel-Based Testing: A Tutorial. *Clinical Pharmacology and Therapeutics,* 108(3)**,** 557-565.

MARRERO, R. J. C., E. J.: ARWOOD, M. J.: EDDY, E.: DEREMER, D.: RAMNARAIGN, B. H.: DAILY, K. C.: JONES, D.: COOK, K. J.: CAVALLARI, L. H.: WIISANEN WEITZEL, K.: LANGAEE, T.: NEWSOM, K. J.: STAROSTIK, P.: CLARE-SALZER, M. J.: JOHNSON, J. A.: GEORGE, T. J.: COOPER-DEHOFF, R. M. 2020. How to Transition from Single-Gene Pharmacogenetic Testing to Preemptive Panel-Based Testing: A Tutorial. *Clinical Pharmacology and Therapeutics,* 108(3)**,** 557-565.

MARTIN, J. L., LEE, Y. M., CORBIN, L. W., COLSON, R. & AQUILANTE, C. L. 2022. Patients' perspectives of a pharmacist-provided clinical pharmacogenomics service. *Pharmacogenomics,* 23**,** 463-474.

MARTIN, M. A., HOFFMAN, J. M., FREIMUTH, R. R., KLEIN, T. E., DONG, B. J., PIRMOHAMED, M., HICKS, J. K., WILKINSON, M. R., HAAS, D. W., KROETZ, D. L. & CLINICAL PHARMACOGENETICS IMPLEMENTATION, C. 2014. Clinical Pharmacogenetics Implementation Consortium Guidelines for HLA-B Genotype and Abacavir Dosing: 2014 update. *Clin Pharmacol Ther,* 95**,** 499-500.

MASIC, I., MIOKOVIC, M. & MUHAMEDAGIC, B. 2008. Evidence based medicine - new approaches and challenges. *Acta Inform Med,* 16**,** 219-25.

MASNOON, N., SHAKIB, S., KALISCH-ELLETT, L. & CAUGHEY, G. E. 2017. What is polypharmacy? A systematic review of definitions. *BMC Geriatrics,* 17**,** 1-10.

MATHUR, S. & SUTTON, J. 2017. Personalized medicine could transform healthcare. *Biomed Rep,* 7**,** 3-5.

MAY, C. 2013. Towards a general theory of implementation. *Implement Sci,* 8**,** 18.

MAY, C. & FINCH, T. 2009. Implementing, Embedding, and Integrating Practices: An Outline of Normalization Process Theory. *Sociology,* 43**,** 535-554.

MAY, C. R., CUMMINGS, A., GIRLING, M., BRACHER, M., MAIR, F. S., MAY, C. M., MURRAY, E., MYALL, M., RAPLEY, T. & FINCH, T. 2018. Using Normalization Process Theory in feasibility studies and process evaluations of complex healthcare interventions: a systematic review. *Implement Sci,* 13**,** 80.

MCDERMOTT, J. H., WRIGHT, S., SHARMA, V., NEWMAN, W. G., PAYNE, K. & WILSON, P. 2022. Characterizing pharmacogenetic programs using the consolidated framework for implementation research: A structured scoping review. *Front Med (Lausanne),* 9**,** 945352.

MCEVOY, R., BALLINI, L., MALTONI, S., O'DONNELL, C. A., MAIR, F. S. & MACFARLANE, A. 2014. A qualitative systematic review of studies using the normalization process theory to research implementation processes. *Implement Sci,* 9**,** 2.

MCGLYNN, E. A., ASCH, S. M., ADAMS, J., KEESEY, J., HICKS, J., DECRISTOFARO, A. & KERR, E. A. 2003. The quality of health care delivered to adults in the United States. *N Engl J Med,* 348**,** 2635-45.

MCGOWAN, L. J., POWELL, R. & FRENCH, D. P. 2020. How can use of the Theoretical Domains Framework be optimized in qualitative research? A rapid systematic review. *Br J Health Psychol,* 25**,** 677-694.

MCINNES, G., LAVERTU, A., SANGKUHL, K., KLEIN, T. E., WHIRL-CARRILLO, M. & ALTMAN, R. B. 2020. Pharmacogenetics at Scale: An Analysis of the UK Biobank. *Clin Pharmacol Ther*.

MCINNES, G., LAVERTU, A., SANGKUHL, K., KLEIN, T. E., WHIRL-CARRILLO, M. & ALTMAN, R. B. 2021. Pharmacogenetics at Scale: An Analysis of the UK Biobank. *Clin Pharmacol Ther,* 109**,** 1528-1537.

MCMANUS, A. 2013. Health promotion innovation in primary health care. *Australas Med J,* 6**,** 15-8.

MEDICAL RESEARCH COUNCIL 2000. A framework for development and evaluation of RCTs for complex interventions to improve health. Health Services and Public Health Research Board.

MICHIE, S., JOHNSTON, M., ABRAHAM, C., LAWTON, R., PARKER, D. & WALKER, A. 2005. Making psychological theory useful for implementing evidence based practice: a consensus approach. *Quality and Safety in Health Care,* 14**,** 26-33.

MICHIE, S., RICHARDSON, M., JOHNSTON, M., ABRAHAM, C., FRANCIS, J., HARDEMAN, W., ECCLES, M. P., CANE, J. & WOOD, C. E. 2013. The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. *Ann Behav Med,* 46**,** 81-95.

MICHIE, S., VAN STRALEN, M. M. & WEST, R. 2011. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. *Implement Sci,* 6**,** 42.

MICHIE, S., WEST, R., SHEALS, K. & GODINHO, C. A. 2018. Evaluating the effectiveness of behavior change techniques in health-related behavior: a scoping review of methods used. *Transl Behav Med,* 8**,** 212-224.

MINI, E. & NOBILI, S. 2009. Pharmacogenetics: Implementing personalized medicine. *Clinical Cases in Mineral and Bone Metabolism,* 6**,** 17-24.

MOADDEB, J., MILLS, R. & HAGA, S. B. 2015a. Community pharmacists' experience with pharmacogenetic testing. *Journal of the American Pharmacists Association: JAPhA,* 55**,** 587-594.

MOADDEB, J., MILLS, R. & HAGA, S. B. 2015b. Community pharmacists' experience with pharmacogenetic testing. *J Am Pharm Assoc (2003),* 55**,** 587-594.

MOHER, D., LIBERATI, A., TETZLAFF, J., ALTMAN, D. G. & G., P. 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLOS Medicine,* 6**,** e1000097.

MONTGOMERY, K. & OLIVER, A. L. 2016. A Fresh Look at How Professions Take Shape: Dual-directed Networking Dynamics and Social Boundaries. *Organization Studies,* 28**,** 661-687.

MOSTAFA, S., POLASEK, T. M., SHEFFIELD, L. J., HUPPERT, D. & KIRKPATRICK, C. M. J. 2021. Quantifying the Impact of Phenoconversion on Medications With Actionable Pharmacogenomic Guideline Recommendations in an Acute Aged Persons Mental Health Setting. *Front Psychiatry,* 12**,** 724170.

MOTULSKY, A. G. 1957. DRUG REACTIONS, ENZYMES, AND BIOCHEMICAL GENETICS. *Journal of the American Medical Association,* 165**,** 835-835.
MOUNZER, K., HSU, R., FUSCO, J. S., BRUNET, L., HENEGAR, C. E., VANNAPPAGARI, V., STAINSBY, C. M., SHAEFER, M. S., RAGONE, L. & FUSCO, G. P. 2019. HLA-B*57:01 screening and hypersensitivity reaction to abacavir between 1999 and 2016 in the OPERA((R)) observational database: a cohort study. *AIDS Res Ther,* 16**,** 1.
MURRAY, E., TREWEEK, S., POPE, C., MACFARLANE, A., BALLINI, L., DOWRICK, C., FINCH, T., KENNEDY, A., MAIR, F., O'DONNELL, C., ONG, B. N., RAPLEY, T., ROGERS, A. & MAY, C. 2010. Normalisation process theory: a framework for developing, evaluating and implementing complex interventions. *BMC Med,* 8**,** 63.
NGUYEN, M. N., POTVIN, L. & OTIS, J. 1997. Regular exercise in 30- to 60-year-old men: combining the stages-of-change model and the theory of planned behavior to identify determinants for targeting heart health interventions. *J Community Health,* 22**,** 233-46.
NHS ENGLAND. 2020. *National Genomic test directory* [Online]. Available: https://www.england.nhs.uk/publication/national-genomic-test-directories/ [Accessed 10.09.2020].
NHS WALES. 2020. *Prescription Cost Analysis* [Online]. Available: https://nwssp.nhs.wales/ourservices/primary-care-services/general-information/data-and-publications/prescription-cost-analysis/ [Accessed 31.03.2020].
NHSBSA 2021. Number of prescription items dispensed in pharmacies in England from 2006/07 to 2020/21.
NILSEN, P. 2015. Making sense of implementation theories, models and frameworks. *Implement Sci,* 10**,** 53.
NOVICK, G. 2008. Is there a bias against telephone interviews in qualitative research? *Res Nurs Health,* 31**,** 391-8.
NYIRENDA, L., KUMAR, M. B., THEOBALD, S., SARKER, M., SIMWINGA, M., KUMWENDA, M., JOHNSON, C., HATZOLD, K., CORBETT, E. L., SIBANDA, E. & TAEGTMEYER, M. 2020. Using research networks to generate trustworthy qualitative public health research findings from multiple contexts. *BMC Med Res Methodol,* 20**,** 13.
O'DONNELL, P. H., BUSH, A., SPITZ, J., DANAHEY, K., SANER, D., DAS, S., COX, N. J. & RATAIN, M. J. 2012. The 1200 patients project: creating a new medical model system for clinical implementation of pharmacogenomics. *Clin Pharmacol Ther,* 92**,** 446-9.
OLMOS-VEGA, F. M., STALMEIJER, R. E., VARPIO, L. & KAHLKE, R. 2022. A practical guide to reflexivity in qualitative research: AMEE Guide No. 149. *Med Teach***,** 1-11.
OPENPRESCRIBING.NET 2020. EBM DataLab. University of Oxford.
PARK, B. K., PIRMOHAMED, M. & KITTERINGHAM, N. R. 1992. Idiosyncratic drug reactions: a mechanistic evaluation of risk factors. *British Journal of Clinical Pharmacology,* 34**,** 377-395.
PEREIRA, N. L., FARKOUH, M. E., SO, D., LENNON, R., GELLER, N., MATHEW, V., BELL, M., BAE, J. H., JEONG, M. H., CHAVEZ, I., GORDON, P., ABBOTT, J. D., CAGIN, C., BAUDHUIN, L., FU, Y. P., GOODMAN, S. G., HASAN, A., ITURRIAGA, E., LERMAN, A., SIDHU, M., TANGUAY, J. F., WANG, L., WEINSHILBOUM, R., WELSH, R., ROSENBERG, Y., BAILEY, K. & RIHAL, C. 2020. Effect of Genotype-Guided Oral P2Y12 Inhibitor Selection vs Conventional Clopidogrel Therapy on Ischemic Outcomes After Percutaneous Coronary Intervention: The TAILOR-PCI Randomized Clinical Trial. *JAMA,* 324**,** 761-771.
PERERA, M. A., CAVALLARI, L. H., LIMDI, N. A., GAMAZON, E. R., KONKASHBAEV, A., DANESHJOU, R., PLUZHNIKOV, A., CRAWFORD, D. C., WANG, J., LIU, N., TATONETTI,

N., BOURGEOIS, S., TAKAHASHI, H., BRADFORD, Y., BURKLEY, B. M., DESNICK, R. J., HALPERIN, J. L., KHALIFA, S. I., LANGAEE, T. Y., LUBITZ, S. A., NUTESCU, E. A., OETJENS, M., SHAHIN, M. H., PATEL, S. R., SAGREIYA, H., TECTOR, M., WECK, K. E., RIEDER, M. J., SCOTT, S. A., WU, A. H. B., BURMESTER, J. K., WADELIUS, M., DELOUKAS, P., WAGNER, M. J., MUSHIRODA, T., KUBO, M., RODEN, D. M., COX, N. J., ALTMAN, R. B., KLEIN, T. E., NAKAMURA, Y. & JOHNSON, J. A. 2013. Genetic variants associated with warfarin dose in African-American individuals: a genome-wide association study. *The Lancet,* 382**,** 790-796.

PETERSON, R. E., KUCHENBAECKER, K., WALTERS, R. K., CHEN, C. Y., POPEJOY, A. B., PERIYASAMY, S., LAM, M., IYEGBE, C., STRAWBRIDGE, R. J., BRICK, L., CAREY, C. E., MARTIN, A. R., MEYERS, J. L., SU, J., CHEN, J., EDWARDS, A. C., KALUNGI, A., KOEN, N., MAJARA, L., SCHWARZ, E., SMOLLER, J. W., STAHL, E. A., SULLIVAN, P. F., VASSOS, E., MOWRY, B., PRIETO, M. L., CUELLAR-BARBOZA, A., BIGDELI, T. B., EDENBERG, H. J., HUANG, H. & DUNCAN, L. E. 2019. Genome-wide Association Studies in Ancestrally Diverse Populations: Opportunities, Methods, Pitfalls, and Recommendations. *Cell,* 179**,** 589-603.

PETERSON-IYER, K. 2008. Pharmacogenomics, ethics, and public policy. *Kennedy Institute of Ethics journal,* 18**,** 35-56.

PHERWANI, A. D., WINTER, P. C., MCNAMEE, P. T., PATTERSON, C. C., HILL, C. M., CONNOLLY, J. K. & MAXWELL, A. P. 2003. Is screening for factor V Leiden and prothrombin G20210A mutations in renal transplantation worthwhile? Results of a large single-center U.K. study. *Transplantation,* 76**,** 603-5.

PICARD, N., BOYER, J. C., ETIENNE-GRIMALDI, M. C., BARIN-LE GUELLEC, C., THOMAS, F., LORIOT, M. A. & FRENCH NATIONAL NETWORK OF, P. 2017. Pharmacogenetics-based personalized therapy: Levels of evidence and recommendations from the French Network of Pharmacogenetics (RNPGx). *Therapie,* 72**,** 185-192.

PIRMOHAMED, M. 2004. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *Bmj,* 329**,** 15-19.

PIRMOHAMED, M. 2014. Personalized pharmacogenomics: predicting efficacy and adverse drug reactions. *Annu Rev Genomics Hum Genet,* 15**,** 349-70.

PIRMOHAMED, M., BRECKENRIDGE, A. M., KITTERINGHAM, N. R. & PARK, B. K. 1998. Fortnightly review: Adverse drug reactions. *BMJ,* 316**,** 1295-1298.

PIRMOHAMED, M. & HUGHES, D. A. 2013. Pharmacogenetic tests: The need for a level playing field. *Nature Reviews Drug Discovery,* 12**,** 3-4.

PRESS, J. F. C. 2019. *Abacavir* [Online]. Available: https://bnf.nice.org.uk/drug/abacavir.html#preTreatmentScreeningInformation [Accessed 10.10.2021].

PUBLIC HEALTH SCOTLAND. 2020. *Prescriptions in the Community* [Online]. Available: https://www.opendata.nhs.scot/dataset/prescriptions-in-the-community [Accessed 31.03.2020].

QURESHI, S., LATIF, A., CONDON, L., AKYEA, R. K., KAI, J. & QURESHI, N. 2022. Understanding the barriers and enablers of pharmacogenomic testing in primary care: a qualitative systematic review with meta-aggregation synthesis. *Pharmacogenomics,* 23**,** 135-154.

RAWLINS, M. D. 1981. Clinical pharmacology. Adverse reactions to drugs. *Br Med J (Clin Res Ed),* 282**,** 974-6.

RELLING, M. V., ALTMAN, R. B., GOETZ, M. P. & EVANS, W. E. 2010. Clinical implementation of pharmacogenomics: overcoming genetic exceptionalism. *The Lancet Oncology,* 11**,** 507-509.

RELLING, M. V. & EVANS, W. E. 2015. Pharmacogenomics in the clinic. *Nature,* 526**,** 343-50.

RELLING, M. V. E., W. E. 2015. Pharmacogenomics in the clinic. *Nature,* 526**,** 343-50.

ROBERTO, A. J., KRIEGER, J. L., KATZ, M. L., GOEI, R. & JAIN, P. 2011. Predicting pediatricians' communication with parents about the human papillomavirus (hpv) vaccine: an application of the theory of reasoned action. *Health Commun,* 26**,** 303-12.

ROGERS E.M 2003. *Diffusion of Innovations,* New York, Free Press.

ROOSAN, D., HWANG, A., LAW, A. V., CHOK, J. & ROOSAN, M. R. 2020. The inclusion of health data standards in the implementation of pharmacogenomics systems: a scoping review. *Pharmacogenomics,* 21**,** 1191-1202.

ROSENMAN, M. B., DECKER, B., LEVY, K. D., HOLMES, A. M., PRATT, V. M. & EADON, M. T. 2017. Lessons Learned When Introducing Pharmacogenomic Panel Testing into Clinical Practice. *Value Health,* 20**,** 54-59.

RUBINSTEIN, W. S. & PACANOWSKI, M. 2021. Pharmacogenetic Gene-Drug Associations: FDA Perspective on What Physicians Need to Know. *American family physician,* 104(1)**,** 16-19.

SABATE, E. B., PATRICIA 2003. Adherence to Long-Term Therapies: Evidence for Action. *J Nurs Scholarsh.***,** 207.

SANTIAGO-DELEFOSSE, M., GAVIN, A., BRUCHEZ, C., ROUX, P. & STEPHEN, S. L. 2016. Quality of qualitative research in the health sciences: Analysis of the common criteria present in 58 assessment guidelines by expert users. *Soc Sci Med,* 148**,** 142-51.

SEGROTT, J., MURPHY, S., ROTHWELL, H., SCOURFIELD, J., FOXCROFT, D., GILLESPIE, D., HOLLIDAY, J., HOOD, K., HURLOW, C., MORGAN-TRIMMER, S., PHILLIPS, C., REED, H., ROBERTS, Z. & MOORE, L. 2017. An application of Extended Normalisation Process Theory in a randomised controlled trial of a complex social intervention: Process evaluation of the Strengthening Families Programme (10-14) in Wales, UK. *SSM Popul Health,* 3**,** 255-265.

SHENDRE, A., DILLON, C. & LIMDI, N. A. 2018. Pharmacogenetics of warfarin dosing in patients of African and European ancestry. *Pharmacogenomics,* 19**,** 1357-1371.

SIM, S. C. & INGELMAN-SUNDBERG, M. 2010. The Human Cytochrome P450 (CYP) Allele Nomenclature website: a peer-reviewed database of CYP variants and their associated effects. *Human Genomics,* 4**,** 278-278.

SIMON, T., VERSTUYFT, C., MARY-KRAUSE, M., QUTEINEH, L., DROUET, E., MENEVEAU, N., STEG, P. G., FERRIERES, J., DANCHIN, N., BECQUEMONT, L., FRENCH REGISTRY OF ACUTE, S. T. E. & NON, S. T. E. M. I. I. 2009. Genetic determinants of response to clopidogrel and cardiovascular events. *N Engl J Med,* 360**,** 363-75.

SINGH, D. 2003. Ethical issues of pharmacogenetics must be addressed, says Nuffield Council. *BMJ,* 327**,** 701.

SKIVINGTON, K., MATTHEWS, L., SIMPSON, S. A., CRAIG, P., BAIRD, J., BLAZEBY, J. M., BOYD, K. A., CRAIG, N., FRENCH, D. P., MCINTOSH, E., PETTICREW, M., RYCROFT-MALONE, J., WHITE, M. & MOORE, L. 2021. A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance. *BMJ,* 374**,** n2061.

SMITH, J. D., LI, D. H. & RAFFERTY, M. R. 2020. The Implementation Research Logic Model: a method for planning, executing, reporting, and synthesizing implementation projects. *Implement Sci,* 15**,** 84.

SPEAR, B. B., HEATH-CHIOZZI, M. & HUFF, J. 2001. Clinical application of pharmacogenetics. *Trends in Molecular Medicine,* 7**,** 201-204.

ST SAUVER, J. L., BIELINSKI, S. J., OLSON, J. E., BELL, E. J., MC GREE, M. E., JACOBSON, D. J., MCCORMICK, J. B., CARABALLO, P. J., TAKAHASHI, P. Y., ROGER, V. L. & ROHRER VITEK, C. R. 2016a. Integrating pharmacogenomics into clinical practice: promise vs reality. *Am J Med,* 129**,** 1093-1099.e1.

ST SAUVER, J. L., BIELINSKI, S. J., OLSON, J. E., BELL, E. J., MC GREE, M. E., JACOBSON, D. J., MCCORMICK, J. B., CARABALLO, P. J., TAKAHASHI, P. Y., ROGER, V. L. & ROHRER VITEK, C. R. 2016b. Integrating Pharmacogenomics into Clinical Practice: Promise vs Reality. *Am J Med,* 129**,** 1093-1099 e1.

ST. SAUVER, J. L., BIELINSKI, S. J., OLSON, J. E., BELL, E. J., MC GREE, M. E., JACOBSON, D. J., MCCORMICK, J. B., CARABALLO, P. J., TAKAHASHI, P. Y., ROGER, V. L. & ROHRER VITEK, C. R. 2016. Integrating Pharmacogenomics into Clinical Practice: Promise vs Reality. *American Journal of Medicine,* 129**,** 1093-1099.e1.

SWEN, J. J., NIJENHUIS, M., DE BOER, A., GRANDIA, L., MAITLAND-VAN DER ZEE, A. H., MULDER, H., RONGEN, G. A., VAN SCHAIK, R. H., SCHALEKAMP, T., TOUW, D. J., VAN DER WEIDE, J., WILFFERT, B., DENEER, V. H. & GUCHELAAR, H. J. 2011. Pharmacogenetics: from bench to byte--an update of guidelines. *Clin Pharmacol Ther,* 89**,** 662-73.

SWEN, J. J., VAN DER STRAATEN, T., WESSELS, J. A., BOUVY, M. L., VLASSAK, E. E., ASSENDELFT, W. J. & GUCHELAAR, H. J. 2012a. Feasibility of pharmacy-initiated pharmacogenetic screening for CYP2D6 and CYP2C19. *Eur J Clin Pharmacol,* 68**,** 363-70.

SWEN, J. J., VAN DER STRAATEN, T., WESSELS, J. A. M., BOUVY, M. L., VLASSAK, E. E. W., ASSENDELFT, W. J. J. & GUCHELAAR, H. J. 2012b. Feasibility of pharmacy-initiated pharmacogenetic screening for CYP2D6 and CYP2C19. *European Journal of Clinical Pharmacology,* 68**,** 363-370.

SWEN, J. J., WILTING, I., GOEDE, A. L. D., GRANDIA, L., MULDER, H., TOUW, D. J., BOER, A. D., CONEMANS, J. M. H., EGBERTS, T. C. G., KLUNGEL, O. H., KOOPMANS, R., WEIDE, J. V. D., WILFFERT, B., GUCHELAAR, H. J. & DENEER, V. H. M. 2008. Pharmacogenetics: From Bench to Byte. *Clinical Pharmacology & Therapeutics,* 83**,** 781-787.

THE INTERNATIONAL, S. N. P. M. W. G. 2001. A map of human genome sequence variation containing 1.42 million single nucleotide polymorphisms. *Nature,* 409**,** 928-933.

THEKEN, K. N., LEE, C. R., GONG, L., CAUDLE, K. E., FORMEA, C. M., GAEDIGK, A., KLEIN, T. E., AGUNDEZ, J. A. G. & GROSSER, T. 2020. Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for CYP2C9 and Nonsteroidal Anti-Inflammatory Drugs. *Clin Pharmacol Ther,* 108**,** 191-200.

TONG, A., FLEMMING, K., MCINNES, E., OLIVER, S. & CRAIG, J. 2012. Enhancing transparency in reporting the synthesis of qualitative research: ENTREQ. *BMC medical research methodology,* 12**,** 181.

TONK, E. C. M., GURWITZ, D., MAITLAND-VAN DER ZEE, A. H. & JANSSENS, A. C. J. W. 2017. Assessment of pharmacogenetic tests: Presenting measures of clinical validity and potential population impact in association studies. *Pharmacogenomics Journal,* 17**,** 386-392.

TROTMAN, J., ARMSTRONG, R., FIRTH, H., TRAYERS, C., WATKINS, J., ALLINSON, K., JACQUES, T. S., NICHOLSON, J. C., BURKE, G. A. A., GENOMICS ENGLAND RESEARCH, C., BEHJATI, S., MURRAY, M. J., HOOK, C. E. & TARPEY, P. 2022. The NHS England 100,000 Genomes Project: feasibility and utility of centralised genome sequencing for children with cancer. *Br J Cancer,* 127**,** 137-144.

TURNBULL, C. 2018. Introducing whole-genome sequencing into routine cancer care: the Genomics England 100 000 Genomes Project. *Ann Oncol,* 29**,** 784-787.

TURNER, R. M., NEWMAN, W. G., BRAMON, E., MCNAMEE, C. J., WONG, W. L., MISBAH, S., HILL, S., CAULFIELD, M. & PIRMOHAMED, M. 2020. Pharmacogenomics in the UK National Health Service: opportunities and challenges. *Pharmacogenomics,* 21**,** 1237-1246.

TUTEJA, S. & LIMDI, N. 2016. Pharmacogenetics in Cardiovascular Medicine. *Curr Genet Med Rep,* 4**,** 119-29.

TUTEJA, S., SALLOUM, R. G., ELCHYNSKI, A. L., SMITH, D. M., ROWE, E., BLAKE, K. V., LIMDI, N. A., AQUILANTE, C. L., BATES, J., BEITELSHEES, A. L., CIPRIANI, A., DUONG, B. Q., EMPEY, P. E., FORMEA, C. M., HICKS, J. K., MROZ, P., OSLIN, D., PASTERNAK, A. L., PETRY, N., RAMSEY, L. B., SCHLICHTE, A., SWAIN, S. M., WARD, K. M., WIISANEN, K., SKAAR, T. C., VAN DRIEST, S. L., CAVALLARI, L. H. & BISHOP, J. R. 2021. Multisite evaluation of institutional processes and implementation determinants for pharmacogenetic testing to guide antidepressant therapy. *Clinical and Translational Science.*

UNERTL, K. M., FIELD, J. R., PRICE, L. & PETERSON, J. F. 2015. Clinician perspectives on using pharmacogenomics in clinical practice. *Personalized Medicine,* 12**,** 339-347.

VAN DER WEIDE, M. & SMITS, J. 2004. Adoption of innovations by specialised nurses: personal, work and organisational characteristics. *Health Policy,* 68**,** 81-92.

VAN DER WOUDEN, C. H., CAMBON-THOMSEN, A., CECCHIN, E., CHEUNG, K. C., DAVILA-FAJARDO, C. L., DENEER, V. H., DOLZAN, V., INGELMAN-SUNDBERG, M., JONSSON, S., KARLSSON, M. O., KRIEK, M., MITROPOULOU, C., PATRINOS, G. P., PIRMOHAMED, M., SAMWALD, M., SCHAEFFELER, E., SCHWAB, M., STEINBERGER, D., STINGL, J., SUNDER-PLASSMANN, G., TOFFOLI, G., TURNER, R. M., VAN RHENEN, M. H., SWEN, J. J., GUCHELAAR, H. J. & UBIQUITOUS PHARMACOGENOMICS, C. 2017. Implementing Pharmacogenomics in Europe: Design and Implementation Strategy of the Ubiquitous Pharmacogenomics Consortium. *Clin Pharmacol Ther,* 101**,** 341-358.

VAN DER WOUDEN, C. H., PAASMAN, E., TEICHERT, M., CRONE, M. R., GUCHELAAR, H. J. & SWEN, J. J. 2020. Assessing the Implementation of Pharmacogenomic Panel-Testing in Primary Care in the Netherlands Utilizing a Theoretical Framework. *J Clin Med,* 9.

VAN DER WOUDEN, C. H., VAN RHENEN, M. H., JAMA, W. O. M., INGELMAN-SUNDBERG, M., LAUSCHKE, V. M., KONTA, L., SCHWAB, M., SWEN, J. J. & GUCHELAAR, H. J. 2019. Development of the PGx-Passport: A Panel of Actionable Germline Genetic Variants for Pre-Emptive Pharmacogenetic Testing. *Clin Pharmacol Ther,* 106**,** 866-873.

VAN SCHAIK, R. H. & IFCC TASK FORCE ON PHARMACOGENETICS: PROF. DR. MAURIZIO FERRARI, P. D. M. N. P. D. M. P. P. D. H.-J. G. P. D. R. V. S. 2013. Clinical Application of Pharmacogenetics: Where are We Now? *Ejifcc,* 24**,** 105-12.

VEILLEUX, S., BOUFFARD, M. & BOURQUE BOULIANE, M. 2020. Patient and Health Care Provider Needs and Preferences in Understanding Pharmacogenomic and Genomic Testing: A Meta-Data Analysis. *Qual Health Res,* 30**,** 43-59.

VERBELEN, M., WEALE, M. E. & LEWIS, C. M. 2017. Cost-effectiveness of pharmacogenetic-guided treatment: are we there yet? *Pharmacogenomics J,* 17**,** 395-402.

VIERA, A. J. & GARRETT, J. M. 2005. Understanding interobserver agreement: the kappa statistic. *Fam Med,* 37**,** 360-3.

VIRELLI, C. R., MOHIUDDIN, A. G. & KENNEDY, J. L. 2021. Barriers to clinical adoption of pharmacogenomic testing in psychiatry: a critical analysis. *Transl Psychiatry,* 11**,** 509.

WACKER, J. G. 1998. A definition of theory: research guidelines for different theory-building research methods in operations management. *Journal of Operations Management,* 16**,** 361-385.

WEST, R. & MICHIE, S. 2020. A brief introduction to the COM-B Model of behaviour and the PRIME Theory of motivation. *Qeios*.

WILKINSON, G. R. 2005. Drug metabolism and variability among patients in drug response. *N Engl J Med,* 352**,** 2211-21.

YOUSSEF, E., KIRKDALE, C. L., WRIGHT, D. J., GUCHELAAR, H. J. & THORNLEY, T. 2021. Estimating the potential impact of implementing pre-emptive pharmacogenetic testing in primary care across the UK. *Br J Clin Pharmacol,* 87**,** 2907-2925.

YOUSSEF, E., MELLOR, D., WALKERLY, S. & WRIGHT, D. J. 2022. Enhancing pharmacy practice doctoral research with patient and public involvement. *Int J Pharm Pract,* 30**,** 288-291.

ZHANG, Z., CHEN, M., ZHANG, L. & ZHAO, Q. 2020. The impact of cytochrome 450 and Paraoxonase polymorphisms on clopidogrel resistance and major adverse cardiac events in coronary heart disease patients after percutaneous coronary intervention. *BMC Pharmacology and Toxicology,* 21**,** 1.

ZHU, Y., MORIARTY, J. P., SWANSON, K. M., TAKAHASHI, P. Y., BIELINSKI, S. J., WEINSHILBOUM, R., WANG, L. & BORAH, B. J. 2021. A model-based cost-effectiveness analysis of pharmacogenomic panel testing in cardiovascular disease management: preemptive, reactive, or none? *Genet Med,* 23**,** 461-470.

Appendices

Appendix 1 Ethical approval letter for PGx modelling study (Chapter 3).

NORWICH MEDICAL SCHOOL

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Essra Youssef

PHA

2nd April 2020

Dear Essra

Project Title: Estimating the potential impact of implementing pre-emptive pharmacogentic testing in community pharmacy across the UK

Reference: 2019/20-080

I have reviewed the submission of your above proposal and I can confirm that it is considered to be a Service Evaluation. There are no issues of confidentiality or harm to participants and I am happy to approve the study by light touch review.

Please could you ensure that any amendments to either the protocol or documents submitted are notified to us in advance and also that any adverse events which occur during your project are reported to the Committee. Please could you also arrange to send us a report once your project is completed.

Approval by the FMH Research Committee should not be taken as evidence that your study is compliant with GDPR and the Data Protection Act 2018. If you need guidance on how to make your study GDPR compliant, please contact your institution's Data Protection Officer.

I would like to wish you good luck with your project.

Yours sincerely

Prof Alastair Forbes
Chair
FMH Ethics Committee

COVID-19: *The FMH Research Ethics Committee procedures remain as normal. Please note that our decisions as to the ethics of your application take no account of Government measures and UEA guidelines relating to the coronavirus pandemic and all approvals granted are, of course, subject to these. If your research is COVID-19 related it will naturally be expedited. If the current situation means that you will have to alter your study, please submit an application for an amendment in the usual way.*

Appendix 2: List of drugs with additional drug-gene interactions not assessed (Chapter 3).

Drug	Drug-gene interaction estimated	Additional drug-gene interactions not estimated
Acenocoumarol	VKORC1	
Allopurinol	HLA-B	
Amitriptylline	CYP2D6	CYP2C19
Ampicillin_flucloxacillin	HLA-B	
Aripiprazole	CYP2D6	
Atomoxetine	CYP2D6	
Atorvastatin with concomitant CYP inhibitors	SLCO1B1	
Azathioprine	TPMT	NUDT15
Carbamazepine	HLA-B	HLA-A
Celecoxib	CYP2C9	
Citalopram	CYP2C19	
Clomipramine	CYP2D6	CYP2C19
Clopidogrel	CYP2C19	
Codeine	CYP2D6	
Codeine_aspirin	CYP2D6	
Codeine_paracetamol	CYP2D6	
Codeine_ibuprofen	CYP2D6	CYP2C9
Codeine_paracetamol_buclizine	CYP2D6	
Codeine_paracetamol_caffeine	CYP2D6	
Doxepin	CYP2D6	CYP2C19
Escitalopram	CYP2C19	
Estrogen_contraceptives	F5	
Flecainide	CYP2D6	
Flucloxacillin	CYP2C9	

Flurbiprofen	CYP2C9	
Fluvoxamine	CYP2D6	
Haloperidol	CYP2D6	
Ibuprofen	CYP2C9	
Ibuprofen_paracetamol	CYP2C9	
Imipramine	CYP2D6	CYP2C19
Lamotrigine	HLA-B	
Lansoprazole	CYP2C19	
Meloxicam	CYP2C9	
Mercaptopurine	TPMT	NUDT15
Metoprolol	CYP2D6	
Nortriptylline	CYP2D6	
Omeprazole	CYP2C19	
Ondansetron	CYP2D6	
Oxcarbazepine	HLA-B	
Pantoprazole	CYP2C19	
Paroxetine	CYP2D6	
Phenytoin	HLA-B	CYP2C9
Piroxicam	CYPC9	
Sertraline	CYP2C19	
Simvastatin	SLC01B1	
Simvastatin_ezetimibe	SLC01B1	
Simvastatin_fenofibrate	SLC01B1	
Tamoxifen	CYP2D6	
Tenoxicam	CYP2C9	
Tramadol	CYP2D6	
Tramadol_paracetamol	CYP2D6	
Trimipramine	CYP2D6	CYP2C19
Venlafaxine	CYP2D6	

Voriconazole	CYP2C19	
Warfarin	CYP2C19	CYP4F2, VK0RC1
Zuclopenthixol	CYP2D6	

Appendix 3: Estimate of proportion (%) of newly initiated medicines as a proportion of overall dispensing (Chapter 3)

Drugs	Proportion of medicines newly initiated as part of overall dispensing in one year (%)
Acenocoumarol	5.02%
Allopurinol	4.63%
Amitriptyline	10.44%
Ampicillin_Flucloxacillin	79.45%
Aripiprazole	7.66%
Atomoxetine	11.20%
Atorvastatin	4.52%
Atorvastatin with CYP	0.22%
Azathioprine	5.39%
Carbamazepine	4.11%
Celecoxib	13.61%
Citalopram	9.26%
Clomipramine	6.23%
Clopidogrel	4.54%
Codeine TOTAL	23.21%
Codeine_paracetamol TOTAL	17.01%
Codeine_ibuprofen	15.05%
Codeine_Paracetamol_buclizine	20.73%
Codeine_paracetamol_caffeine	13.90%
Doxepin	4.40%
Escitalopram	12.42%
Estrogen_contraceptives	35.72%
Flecainide	5.85%
Flucloxacillin	75.01%
Flurbiprofen	26.88%
Fluvoxamine	7.01%
Haloperidol	17.23%
Ibuprofen	34.20%
Ibuprofen_paracetamol	53.19%
Imipramine	8.28%
Lamotrigine	4.00%
Lansoprazole	7.98%
Meloxicam	13.57%
Mercaptopurine	7.30%
Metoprolol	4.45%
Nortriptyline	12.34%
Omeprazole	10.11%
Ondansetron	32.45%
Oxcarbazepine	4.60%
Pantoprazole	7.57%

Paroxetine	5.67%
Phenytoin	1.98%
Piroxicam	11.17%
Sertraline	12.53%
Simvastatin	2.33%
Simvastatin_ezetimibe	3.07%
Simvastatin_fenofibrate	66.67%
Tamoxifen	6.40%
Tenoxicam	4.54%
Tramadol	11.00%
Tramadol_paracetamol	12.74%
Trimipramine	2.96%
Venlafaxine	6.24%
Voriconazole	29.79%
Warfarin	1.88%
Zuclopenthixol	6.65%
Total Unique Patients (Newly initiated at least one PGx drug)/Total volume of new PGx scripts	71.5%

Estimate of the frequency at which new prescriptions are issued for selected medicines as a proportion of the overall total prescription issued annually. Percentages were calculated using a large community pharmacy database. Dispensing volumes were extracted for 56 PGx drugs dispensed between 01.01.2018-31.12.2018. Medicine items which were issued for the first time to the patient in 12 months were classified as 'new medicine'.

Appendix 4: Overview of PGx variants and phenotype assignment (Chapter 3)

Gene	Haplotype	Phenotype	Frequency (decimal)	Frequency (percentage)
CYP2D6	*1/*3 (xN) *1/*4, xN *10/*10 *10/*41 *17/*17 *17/*41 *3/*41 *3/*9 *4/*10 *4/*41 *4/*9 *41/*4, xN *41/*41 *5/*41 *5/*9 *6/*10 *6/*41 *9/*10 *9/*41 *9/*9 wildtype/*3 wildtype/*4 wildtype/*4 or *4/*10 wildtype/*5 wildtype/*6	IM	0.411	41.14% (SE +/- 1.65%)
CYP2D6	*3/*4	PM	0.060	6.02%

	*4/*4 *4/*4xN *4/*5 *4/*6 *4/*6, xN *5/*5			(SE +/- 0.80%)
CYP2D6	*1xN	UM	0.017	1.70% (SE +/- 0.43%)
SLCO1B1	wildtype/*5	Decreased function	0.266	26.55% (SE +/- 1.48%)
SLCO1B1	*5/*5	Poor Function	0.018	1.81% (SE +/- 0.45%)
TPMT	wildtype/*3A or *3B/*3C wildtype/*2 wildtype/*3C	Intermediate metaboliser	0.091	9.08% (SE +/- 0.97%)
TPMT	*3A/*3A	Poor metaboliser	0.001	0.11% (SE +/- 0.11%)
VKORC1	1173C>T/1173C>T	-1639AA (1173TT)	0.119	11.89% (SE +/-1.09%)
VKORC1	wildtype/1173C>T	-1639GA (1173CT)	0.472	47.23% (SE +/- 1.68%)
VKORC1	wildtype/wildtype	-1639GG (1173CC) wildtype	0.409	40.88% (SE +/- 1.65%)
CYP2C9	wildtype/*11 *1/*2	IM (AS=1.5)	0.201	20.11% (SE +/- 1.35%)
CYP2C9	*2/*2 *1/*3	IM (AS=1)	0.119	11.93% (SE +/- 1.09%)

CYP2C9	*2/*3 *3/*3	PM (AS=0)	0.0216	2.16% (SE +/- 0.49%)
CYP2C19	*2/*17 *8/*17 *9/*17 wildtype/*10 wildtype/*10 wildtype/*3 wildtype/*4 wildtype/*8	IM	0.263	26.31% (SE +/- 1.49%)
CYP2C19	*2/*2 *2/*9 *4B/*2	PM	0.028	2.85% (SE +/- 0.56%)
CYP2C19	*17/*17	UM	0.050	5.01% (SE +/- 0.74%)
F5	1691G>A/1691G>A wildtype/1691G>A wildtype/wildtype	F5 Positive	0.041	4.08% (SE +/- 0.67%)
HLA-B	wildtype/HLA-B*5701 wildtype/wildtype	HLA-B*5701-POSITIVE	0.062	6.24% (SE +/- 0.81%)

Table 1. PGx variant frequencies and phenotype assignment for Liverpool population in PREPARE study

Gene	Haplotype	Phenotype	Frequency (decimal)	Frequency (percentage)
HLA-A	/	HLA-A*31:01 POSITIVE	0.026	2.62%
HlA-B		HLA-B*15:02 POSITIVE	0.003	0.32%
HlA-B	/	HLA-B*58:01 POSITIVE	0.016	1.59%

Table 2. PGx variant frequency estimates for UK population

Calculation for PGx variant frequency estimates for UK Population

HLA allele	African Allele Frequency	African American Allele Frequency	Caucasian (European + North American) Allele Frequency	Middle Eastern Allele Frequency	East Asian Allele Frequency	South/Central Asian Allele Frequency	Americas Allele Frequency	Oceanian Allele Frequency
HLA-A*31:01	0.52	0.98	2.84	1.11	3.34	2.20	6.43	0.67
HLA-B*15:02	0.00	0.10	0.04	0.06	6.88	4.64	0.16	5.37
HLA-B*57:01	0.79	0.10	3.23	1.70	0.90	4.49	1.55	1.11
HLA-B*58:01	5.54	3.89	1.32	2.43	6.13	4.54	1.11	2.30

Table 1. Frequencies of HLA-B and HLA-A variants in major race/ethnic groups. From CPIC (https://cpicpgx.org/guidelines/guideline-for-carbamazepine-and-

CPIC ethnic categories	UK Census ethnic groups	Frequency of UK ethnic population (A)	Frequency HLA-A*31:01 in CPIC ethnic categories (B)	Frequency Estimate HLA-A*31:01 in UK (A*B)	Frequency HLA-B*15:02 in CPIC ethnic categories [C]	Frequency Estimate HLA-B*15:02 in UK (A*C)	Frequency HLA-B*58:01 n CPIC ethnic categories (D)	Frequency Estimate HLA-B*58:01 in UK (A*D)
Caucasian (European + North American)	White	0.871	2.84	0.0247364	0.04	0.0003484	1.32	0.0114972
/	Gypsy/Traveller/Irish traveller	0.001	/	/	/	/	/	/
/	Mixed/Multiple ethnic groups	0.02	/	/	/	/	/	/
South/Central Asian	Asian / Asian British: Indian	0.024	/	/	/	/	/	/
	Asian / Asian British: Pakistani	0.019	/	/	/	/	/	/
	Asian / Asian British: Bangladeshi	0.007	/	/	/	/	/	/
	Total Asian	0.05	2.2	0.0011	4.64	0.00232	4.54	0.00227
East Asian	Asian / Asian British: Chinese	0.007	3.34	0.0002338	6.88	0.0004816	6.13	0.0004291
/	Asian / Asian British: Other Asian	0.014	/	/	/	/	/	/
African	Black / African / Caribbean / Black British	0.03	0.52	0.000156	0	0	5.54	0.001662

/	Other Ethnic Group	0.009	/	/	/	/	/	/
Middle Eastern	/	/	1.11	/	/	/	/	/
Americas	/	/	6.43	/	/	/	/	/
Oceanian	/	/	0.67	/	/	/	/	/
UK estimate frequency				0.0262262		0.00315		0.0158583
UK estimate frequency (%)				2.62%		0.32%		1.59%

Table 2. UK demographic mapped to ethnicity.

Appendix 5: Overview of the inferred drug-gene interactions among 56 PGx drugs with CPIC and/or DPWG guidelines, relevant to UK primary care (Chapter 3).

Drug	Phenotype	Estimated number of drugs dispensed in 2019					Recommendation	Ref Guide line
		England	Scotland	Wales	Northern Ireland	UK TOTAL		
CYP2C19								
Citalopram	EM	860,026	66,787	79,330	32,404	1,038,547	No action	Both
	IM	343,712	26,692	31,705	12,951	415,060	Guard maximum daily dose	DPWG *
	PM	37,198	2,889	3,431	1,402	44,920	Lower dose required at start therapy	CPIC*
	UM	65,469	5,084	6,039	2,467	79,059	Switch to alternate drug at start therapy	CPIC*
Clopidogrel	EM	304,202	26,439	20,027	7,678	358,346	No action	Both
	IM	121,575	10,567	8,004	3,069	143,215	Switch to alternate drug at start therapy	Both
	PM	13,158	1,144	866	332	15,500	Switch to alternate drug at start therapy	Both
	UM	23,157	2,013	1,525	584	27,279	No action	Both

Escitalopram	EM	101,442	6,000	3,142	7,480	118,064	No action	Both
	IM	40,542	2,398	1,256	2,989	47,185	Guard maximum daily dose	DPWG *
	PM	4,388	260	136	324	5,108	Lower dose required at start therapy	CPIC*
	UM	7,722	457	239	569	8,987	Switch to alternate drug at start therapy	Both
Lansoprazole	EM	1,402,630	83,411	90,125	37,678	1,613,844	No action	DPWG
	IM	560,566	33,336	36,019	15,058	644,979	No action	DPWG
	PM	60,667	3,608	3,898	1,630	69,803	No action	DPWG
	UM	106,775	6,350	6,861	2,868	122,854	Higher dose required at start therapy	DPWG
Omeprazole	EM	2,113,980	239,958	171,428	84,831	2,610,197	No action	DPWG
	IM	844,861	95,901	68,512	33,903	1,043,177	No action	DPWG
	PM	91,435	10,379	7,415	3,669	112,898	No action	DPWG
	UM	160,926	18,267	13,050	6,458	198,701	Higher dose required at start therapy	DPWG
Pantoprazole	EM	65,718	2,941	3,240	6,068	77,967	No action	DPWG
	IM	26,264	1,176	1,295	2,425	31,160	No action	DPWG
	PM	2,842	127	140	262	3,371	No action	DPWG

	UM	5,003	224	247	462	5,936	Higher dose required at start therapy	DPWG
Sertraline	EM	1,378,642	112,351	114,155	61,479	1,666,627	No action	Both
	IM	550,979	44,902	45,622	24,570	666,073	No action	Both
	PM	59,630	4,860	4,937	2,659	72,086	Guard maximum daily dose	DPWG
	UM	104,948	8,553	8,690	4,680	126,871	No action	Both
Trimipramine	EM	585	40	38	16	679	No action	CPIC
	IM	233	16	16	7	272	Optional lower dose required at start therapy	CPIC
	UM	44	3	3	1	51	Optional switch to alternate drug at start therapy	CPIC
	PM	25	2	2	1	30	Optional switch to alternate drug at start therapy	CPIC
Voriconazole	EM	90	35	19	1	145	No action	Both
	IM	36	14	7	1	58	Observe status of patient carefully	DPWG *
	PM	4	2	1	0	7	Switch to alternate drug at start therapy	CPIC
	UM	7	3	1	0	11	Switch to alternate drug at start therapy	CPIC
CYP2C9								

Celecoxib	EM	27,246	5,200	1,373	2,604	36,423	No action	CPIC
	IM (AS=1.5)	8,329	1,590	420	796	11,135	No action	CPIC
	IM (AS=1.0)	4,941	943	249	472	6,605	Optional lower dose required at start therapy	CPIC
	PM	894	171	45	85	1,195	Lower dose required at start therapy	CPIC
Flurbiprofen	EM	0	46	30	24	100	No action	CPIC
	IM (AS=1.5)	0	14	9	8	31	No action	CPIC
	IM (AS=1.0)	0	8	5	5	18	Optional lower dose required at start therapy	CPIC
	PM	0	2	1	1	4	Lower dose required at start therapy	CPIC
Ibuprofen	EM	384,468	111,640	51,554	27,501	575,163	No action	CPIC
	IM (AS=1.5)	117,531	34,128	15,760	8,408	175,827	No action	CPIC
	IM (AS=1.0)	69,722	20,246	9,349	4,988	104,305	Optional lower dose required at start therapy	CPIC
	PM	12,616	3,664	1,692	903	18,875	Lower dose required at start therapy	CPIC
Ibuprofen_	EM	73	0	1	1	75	No action	CPIC

paracetamol	IM (AS=1.5)	22	0	0	0	22	No action	CPIC
	IM (AS=1.0)	13	0	0	0	13	Optional lower dose required at start therapy	CPIC
	PM	2	0	0	0	2	Lower dose required at start therapy	CPIC
Meloxicam	EM	45,758	6,148	2,816	2,911	57,633	No action	CPIC
	IM (AS=1.5)	13,988	1,880	860	890	17,618	No action	CPIC
	IM (AS=1.0)	8,298	1,115	510	528	10,451	Lower dose required start therapy	CPIC
	PM	1,502	202	92	96	1,892	Switch to alternate drug at start therapy	CPIC
Phenytoin	EM	9,080	716	547	172	10,515	No action	CPIC
	IM (AS=1.5)	2,776	219	167	53	3,215	Lower dose required at start therapy	CPIC
	IM (AS=1.0)	1,647	130	99	31	1,907	Lower dose required at start therapy	CPIC
	PM	298	23	18	6	345	Lower dose required at start therapy	CPIC
Piroxicam	EM	1,156	133	61	161	1,511	No action	CPIC
	IM (AS=1.5)	354	40	19	49	462	No action	CPIC

	IM (AS=1.0)	210	24	11	29	274	Switch to alternate drug at start therapy	CPIC
	PM	38	4	2	5	49	Switch to alternate drug at start therapy	CPIC
Tenoxicam	EM	18	5	2	2	27	No action	CPIC
	IM (AS=1.5)	6	2	0	0	8	No action	CPIC
	IM (AS=1.0)	3	1	0	0	4	Optional switch at start therapy	CPIC
	PM	1	0	0	0	1	Optional switch at start therapy	CPIC
Amitriptylline	EM	744,854	69,582	58,207	28,211	900,854	No action	Both
	IM	599,194	55,974	46,823	22,695	724,686	Lower dose at start therapy	Both
	PM	87,727	8,195	6,855	3,323	106,100	Switch to alternate drug at start therapy	CPIC
	UM	24,828	2,319	1,940	940	30,027	Switch to alternate drug at start therapy	CPIC
CYP2D6								
Aripiprazole	EM	46,441	2,904	3,689	1,352	54,386	No action	DPWG
	IM	37,360	2,337	2,968	1,087	43,752	No action	DPWG
	PM	5,470	342	435	159	6,406	Guard maximum daily dose	DPWG

	UM	1,548	97	123	45	1,813	No action	DPWG
Atomoxetine	EM	6,560	725	495	424	8,204	No action	Both
	IM	5,278	583	398	341	6,600	Observe status of patient carefully	Both
	PM	773	85	58	50	966	Observe status of patient carefully	Both
	UM	219	24	17	14	274	Observe status of patient carefully	Both
Clomipramine	EM	7,267	1,094	610	248	9,219	No action	Both
	IM	5,845	880	491	199	7,415	Lower dose at start therapy	DPWG *
	PM	856	129	72	29	1,086	Lower dose at start therapy	DPWG *
	UM	242	36	20	8	306	Higher dose required at start therapy	DPWG *
Codeine	EM	586,795	25,588	23,478	8,721	644,582	No action	Both
	IM	472,044	20,585	18,887	7,015	518,531	Observe status of patient carefully	Both
	PM	69,111	3,014	2,765	1,027	75,917	Switch to alternate drug at start therapy	Both
	UM	19,560	853	783	291	21,487	Switch to alternate drug at start therapy	Both

Codeine_ aspirin	EM	37	4	3	1	45	No action	Both
	IM	30	4	2	1	37	Observe status of patient carefully	Both
	PM	4	1	0	0	5	Switch to alternate drug at start therapy	Both
	UM	1	0	0	0	1	Switch to alternate drug at start therapy	CPIC*
Codeine_ ibuprofen	EM	50	9	2	5	66	No action	Both
	IM	41	7	2	3	53	Observe status of patient carefully	Both
	PM	6	1	0	0	7	Switch to alternate drug at start therapy	Both
	UM	2	0	0	0	2	Switch to alternate drug at start therapy	Both
Codeine_ paracetamol	EM	1,304,527	237,794	157,130	108,373	1,807,824	No action	Both
	IM	1,049,419	191,292	126,403	87,180	1,454,294	Observe status of patient carefully	Both
	PM	153,644	28,007	18,506	12,764	212,921	Switch to alternate drug at start therapy	Both
	UM	43,484	7,926	5,238	3,612	60,260	Switch to alternate drug at start therapy	Both
Codeine_	EM	374	1,530	197	132	2,233	No action	Both

paracetamol_ buclizine	IM	300	1,230	158	107	1,795	Observe status of patient carefully	Both
	PM	44	180	23	16	263	Switch to alternate drug at start therapy	Both
	UM	12	51	7	4	74	Switch to alternate drug at start therapy	CPIC*
Codeine_ paracetamol_ caffeine	EM	250	0	15	1	266	No action	Both
	IM	202	0	13	1	216	Observe status of patient carefully	Both
	PM	30	0	2	0	32	Switch to alternate drug at start therapy	Both
	UM	8	0	1	0	9	Switch to alternate drug at start therapy	CPIC*
Doxepin	EM	540	112	36	25	713	No action	Both
	IM	434	91	29	21	575	Lower dose required at start therapy	DPWG *
	PM	64	13	4	3	84	Lower dose required at start therapy	DPWG *
	UM	18	4	1	1	24	Higher dose required at start therapy	DPWG *
Flecainide	EM	12,813	778	906	195	14,692	No action	DPWG

	IM	10,307	626	729	156	11,818	Lower dose required at start therapy	DPWG
	PM	1,509	92	107	23	1,731	Lower dose required at start therapy	DPWG
	UM	427	26	30	6	489	Observe status of patient carefully	DPWG
Fluvoxamine	EM	803	65	46	28	942	No action	
	IM	646	53	38	22	759	No action	Both
	PM	95	8	6	3	112	Optional lower dose required at start therapy	CPIC
	UM	27	2	2	1	32	No action	Both
Haloperidol	EM	29,137	2,313	1,906	1,189	34,545	No action	DPWG
	IM	23,440	1,861	1,533	957	27,791	No action	DPWG
	PM	3,432	272	224	140	4,068	Lower dose required at start therapy	DPWG
	UM	971	77	64	40	1,152	Observe status of patient carefully	DPWG
Imipramine	EM	6,407	1,046	316	146	7,915	No action	DPWG
	IM	5,154	842	254	117	6,367	Lower dose required at start therapy	DPWG

	PM	755	123	37	17	932	Lower dose required at start therapy	DPWG
	UM	214	35	11	5	265	Higher dose required at start therapy	DPWG
Metoprolol	EM	8,823	784	425	235	10,267	No action	DPWG
	IM	7,097	630	341	190	8,258	Guard maximum daily dose	DPWG
	PM	1,039	92	50	28	1,209	Guard maximum daily dose	DPWG
	UM	294	26	14	8	342	Observe status patient carefully	DPWG
Nortriptyline	EM	40,993	4,926	1,681	1,000	48,600	No action	Both
	IM	32,977	3,962	1,353	804	39,096	Lower dose required at start therapy	Both
	PM	4,828	580	198	118	5,724	Switch to alternate drug at start therapy	CPIC
	UM	1,366	164	56	33	1,619	Switch to alternate drug at start therapy	CPIC
Ondansetron	EM	41,465	5,226	2,360	5,206	54,257	No action	CPIC
	IM	33,357	4,205	1,899	4,188	43,649	No action	CPIC
	PM	4,884	616	278	613	6,391	No action	CPIC
	UM	1,382	174	79	174	1,809	Switch to alternate drug at start therapy	CPIC

Paroxetine	EM	38,271	3,553	3,757	1,227	46,808	No action	Both
	IM	30,787	2,859	3,023	987	37,656	No action	Both
	PM	4,507	419	443	145	5,514	Optional switch to alternate drug at start therapy	CPIC
	UM	1,276	118	125	41	1,560	Switch to alternate drug at start therapy	Both
Tamoxifen	EM	21,855	2,154	1,424	675	26,108	No action	Both
	IM	17,582	1,733	1,145	543	21,003	Switch to alternate drug at start therapy	Both
	PM	2,574	254	168	80	3,076	Switch to alternate drug at start therapy	Both
	UM	729	72	47	23	871	No action	Both
Tramadol	EM	340,910	51,596	22,132	20,830	435,468	No action	DPWG
	IM	274,243	41,507	17,804	16,756	350,310	Observe status of patient carefully	DPWG
	PM	40,152	6,077	2,607	2,453	51,289	Observe status of patient carefully	DPWG
	UM	11,364	1,720	738	694	14,516	Switch to alternative	DPWG
Tramadol_ paracetamol	EM	3,174	165	346	610	4,295	No action	DPWG
	IM	2,554	134	279	491	3,458	Observe status of patient carefully	DPWG

	PM	374	20	41	72	507	Observe status of patient carefully	DPWG
	UM	106	6	12	20	144	Switch to alternative	DPWG
Venlafaxine	EM	148,139	15,391	11,514	12,398	187,442	No action	DPWG
	IM	119,170	12,382	9,262	9,974	150,788	Switch to alternate drug at start therapy	DPWG
	PM	17,447	1,813	1,356	1,460	22,076	Switch to alternate drug at start therapy	DPWG
	UM	4,938	513	384	413	6,248	Observe status of patient carefully	DPWG
Zuclopenthixol	EM	3,777	295	193	126	4,391	No action	DPWG
	IM	3,039	237	155	101	3,532	Lower dose required at start therapy	DPWG
	PM	445	35	23	15	518	Lower dose required at start therapy	DPWG
	UM	126	10	6	4	146	Observe status of patient carefully	DPWG
Factor V Leiden								
Estrogen_ contraceptives	Negative	1,262,420	127,454	62,031	55,486	1,507,391	No action	DPWG

	Positive	53,657	5,417	2,636	2,358	64,068	Switch to alternate drug at start therapy	DPWG
HLA-A								
Carbamazepine	HLA-A*31:01 Negative	90,744	8,060	6,204	3,167	108,175	No action	CPIC
	HLA-A*31:01 Positive	2,444	217	167	85	2,913	Switch to alternate drug at start therapy	CPIC
HLA-B								
Allopurinol	HLA-B*58:01 Negative	275,944	22,299	24,078	7,076	329,397	No action	CPIC
	HLA-B*58:01 Positive	4,447	359	388	114	5,308	Switch to alternate drug at start therapy	CPIC
Ampicillin_ flucloxacillin	HLA-B*57:01 Negative	4,372	228	60	88	4,748	No action	DPWG
	HLA-B*57:01 Positive	291	15	4	6	316	Observe status of patient carefully	DPWG
Flucloxacillin	HLA-B*57:01 Negative	2,665,289	303,650	185,998	90,448	3,245,385	No action	DPWG

	HLA-B*57:01 Positive	177,475	20,219	12,385	6,023	216,102	Observe status of patient carefully	DPWG
Lamotrigine	HLA-B*15:02 Negative	119,931	11,373	7,822	4,711	143,837	No action	DPWG
	HLA-B*15:02 Positive	379	36	25	15	455	Switch to alternate drug at start therapy	DPWG (not live)
Oxcarbazepine	HLA-B*15:02 Negative	4,989	341	224	88	5,642	No action	CPIC
	HLA-B*15:02 Positive	16	1	1	0	18	Switch to alternate drug at start therapy	CPIC
SLCO1B1								
Atorvastatin with concomitant CYP inhibitor	NT (521TT)	73,569	3,632	4,476	2,076	83,753	No action	DPWG
	PT (521TC)	27,269	1,346	1,659	769	31,043	Switch to alternate drug at start therapy	DPWG
	PT (521CC)	1,857	92	113	52	2,114	Switch to alternate drug at start therapy	DPWG
Simvastatin	NT (521TT)	364,398	37,693	30,802	9,445	442,338	No action	CPIC
	PT (521TC)	135,068	13,971	11,417	3,501	163,957	Switch to alternative	CPIC
	PT (521CC)	9,196	951	777	238	11,162	Switch to alternative	CPIC

Simvastatin_ ezetimibe	NT (521TT)	398	15	13	27	453	No action	CPIC
	PT (521TC)	147	6	5	10	168	Switch to alternative	CPIC
	PT (521CC)	10	0	0	1	11	Switch to alternative	CPIC
Simvastatin_ fenofibrate	NT (521TT)	12	4	0	4	20	No action	CPIC
	PT (521TC)	4	1	0	2	7	Switch to alternative	CPIC
	PT (521CC)	0	0	0	0	0	Switch to alternative	CPIC
TPMT								
Azathioprine	EM	39,760	5,037	2,669	1,635	49,101	No action	Both
	IM	3,976	504	267	164	4,911	Lower dose required at start therapy	Both
	PM	50	6	3	2	61	Switch to alternate drug at start therapy	Both
Mercaptopurine	EM	4,337	738	301	173	5,549	No action	Both
	IM	434	74	30	17	555	Lower dose required at start therapy	Both
	PM	5	1	0	0	6	Switch to alternate drug at start therapy	Both
VK0RC1								
Acenocoumarol	NS (1173CC/	452	11	11	2	476	No action	DPWG

	1639GG)							
	NS (1173CT/-1639GA)	523	12	13	2	550	No action	DPWG
	HS (1173TT/-1639AA)	132	3	3	1	139	Lower dose required at start therapy	DPWG
Warfarin	NS (1173CC/ 1639GG)	54,068	4,670	5,132	1,306	65,176	No action	Both
	NS (1173CT/-1639GA)	62,456	5,395	5,929	1,508	75,288	No action	Both
	HS (1173TT/-1639AA)	15,726	1,358	1,493	380	18,957	Lower dose required at start therapy	Both

***gene-drug interactions with difference in the actionability of recommendations between CPIC and DPWG.**

***EM* extensive/normal metaboliser, *IM* intermediate metaboliser, *PM* poor metaboliser, *UM* ultra-rapid metaboliser, *NT* normal transport activity, *PT* poor transport activity, *NS* normal sensitivity, *HS* high sensitivity, *AS* activity score**

Appendix 6: Systematic review protocol (Chapter 4)

Systematic review

1. * Review title.

Give the working title of the review, for example the one used for obtaining funding. Ideally the title should state succinctly the interventions or exposures being reviewed and the associated health or social problems. Where appropriate, the title should use the PI(E)COS structure to contain information on the Participants, Intervention (or Exposure) and Comparison groups, the Outcomes to be measured and Study designs to be included.

A qualitative systematic review of barriers and enablers to clinical implementation of pharmacogenetic testing.

2. Original language title.

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

3. * Anticipated or actual start date.

Give the date when the systematic review commenced, or is expected to commence.
18/11/2019

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.
31/03/2020

5. * Stage of review at time of this submission.

Indicate the stage of progress of the review by ticking the relevant Started and Completed boxes. Additional information may be added in the free text box provided.
Please note: Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. Should evidence of incorrect status and/or completion date being supplied at the time of submission come to light, the content of the PROSPERO record will be removed leaving only the title and named contact details and a statement that inaccuracies in the stage of the review date had been identified.
This field should be updated when any amendments are made to a published record and on completion and publication of the review. If this field was pre-populated from the initial screening questions then you are not able to edit it until the record is published.

The review has not yet started: No

Review stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here (e.g. Funded proposal, protocol not yet finalised).

6. * Named contact.

The named contact acts as the guarantor for the accuracy of the information presented in the register record.

Essra Youssef

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Ms Youssef

7. * Named contact email.

Give the electronic mail address of the named contact.

e.youssef@uea.ac.uk

8. Named contact address

Give the full postal address for the named contact.

University of East Anglia, Norwich Research Park, Norwich, NR4 7TJ

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

07412001675

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

University of East Anglia

Organisation web address:

https://www.uea.ac.uk/pharmacy/people/profile/e-youssef

11. * Review team members and their organisational affiliations.

Give the title, first name, last name and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong.

Miss Essra Youssef. University of East Anglia
Professor David Wright. University of East Anglia
Dr Debi Bhattacharya. University of East Anglia

12. * Funding sources/sponsors.

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Include any unique identification numbers assigned to the review by the individuals or bodies listed.

Not applicable.

13. * Conflicts of interest.

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members.

15. * Review question.

State the question(s) to be addressed by the review, clearly and precisely. Review questions may be specific or broad. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS where relevant.

What are the barriers and enablers to clinical implementation of multi-drug pharmacogenetic (PGx) testing?

16. * Searches.

State the sources that will be searched. Give the search dates, and any restrictions (e.g. language or publication period). Do NOT enter the full search strategy (it may be provided as a link or attachment.)

Two strategies will be applied in the search for eligible studies:

1)Identification of published studies.

The following electronic databases will be searched for published studies- MEDLINE (via OVID); EMASE (via OVID); CINAHL (via EBSCO); PsycINFO (via EBSCO) and PubMed Central.

The search terms will be grouped into three main concepts using the PICO tool. Search terms will be developed in MEDLINE (via OVID) and adapted for use in other databases using thesaurus terms and free-text terms.

POPULATION: Exp Patients [MeSH] OR Public.tw OR "service-user*".tw OR "service user*".tw OR consumer*.tw OR customer*

INTERVENTION: Exp Pharmacogenomic testing [MeSH] OR "PGx".tw OR Pharmacogenomic*.tw OR Pharmacogenetic*.tw

COMPARATOR: Not applicable

OUTCOME: Implementation.tw OR adoption.tw OR barrier*.tw OR enabler*.tw OR facilitator*.tw OR challenge*.tw OR opportunit*.tw perceive*.tw OR perception*.tw OR value*.tw OR perspective*.tw OR view*.tw OR experience*.tw OR need*.tw OR attitude*.tw OR belie*.tw OR opinion*.tw OR feel*.tw OR know*.tw OR understand*.tw OR EXP qualitative research OR interview*.tw OR qualitative.tw OR qualitative analysis.tw OR focus group*.tw OR survey*.tw OR questionnaire*.tw OR ethnograph*.tw OR observation*.tw

No date or country restrictions will be added to ensure a maximum capture of study titles.

2)Reference lists and correspondence.

The reference lists titles of all included studies will be searched to identify any additional papers suitable for inclusion.

Once the definitive list of papers is obtained, all first authors of selected papers will be contacted to establish if they are aware of any further research (ongoing, published or unpublished) that has not already been identified through the search.

17. URL to search strategy.

Give a link to a published pdf/word document detailing either the search strategy or an example of a search strategy for a specific database if available (including the keywords that will be used in the search strategies), or upload your search strategy.Do NOT provide links to your search results.

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Do not make this file publicly available until the review is complete

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

The implementation of multi-drug pharmacogenetic testing in different clinical settings.

19. * Participants/population.

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.

Inclusion criteria:

- Adults who have had multi-drug germ-line pharmacogenetic testing
- Any healthcare professional involved in the care of above patients

Exclusion criteria:

- Participants 18 years of age who receive multi-drug pharmacogenetic testing
- Adults receiving whole genome sequencing

- Adults receiving single-drug pharmacogenetic testing

- Adults receiving pharmacogenetic testing of somatic genome

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the nature of the interventions or the exposures to be reviewed.

Intervention: Multi-drug pharmacogenetic/ pharmacogenomic (PGx) testing

In this review, 'PGx testing' refers to the testing of germline (inherited) genetic information that impacts a patient's response to multiple medicines. This type of PGx testing could be in the form of testing variants of multiple genes or testing variants of a single gene that affects the drug response of multiple medicines.

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

No control.

22. * Types of study to be included.

Give details of the types of study (study designs) eligible for inclusion in the review. If there are no restrictions on the types of study design eligible for inclusion, or certain study types are excluded, this should be stated. The preferred format includes details of both inclusion and exclusion criteria.

Study design/characteristics:

Inclusion criteria:

• Original research published in a peer review journal with a qualitative component (e.g. interviews, focus groups, ethnography, survey)

• Case studies/series, commentaries, descriptive articles published in peer review journals that describe real-world experiences of implementation of multi-drug pharmacogenetic testing.

Exclusion criteria:

• Systematic reviews

23. Context.

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

Studies describing PGx testing in the following settings will be included/excluded from this review:

Inclusion criteria:

• Primary care

• Community

• Pharmacy

• Outpatient clinics

• Hospitals

• Acute/Secondary care

• Mental health

• Palliative care

• Nursing/care/residential homes

Exclusion criteria:

• No setting will be excluded as this study is looking at implementation of PGx testing in all settings.

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

To identify barriers and enablers to the clinical implementation of multi-drug pharmacogenetic testing.

Timing and effect measures

Not applicable to this review.

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state 'None' or 'Not applicable' as appropriate to the review

1) Barriers and enablers at each stage of the PGx testing process: 1)Prescriber initiates PGx testing for a patient, 2)Prescriber orders a PGx test for a patient, 3)Patient consents to PGx testing, 4)Collection of a genetic sample from the patient, 5)Interpretation of PGx test results by the prescriber and pharmacist, 6)Application of PGx test result by the prescriber and pharmacist, 7)Communication of PGx test results to the patient, 8)Incorporation of PGx test results into the patients medical record. Any additional barriers/identified at a stage of the PGx testing process not specified on the outset will also be captured so as to not constrain the results. These will be captured in a 'Other' category.

2) Compare primary (participant reported) and secondary (authors interpreted) barriers and enablers to clinical implementation of PGx testing.

3) Barriers and enablers to the implementation of PGx testing from the perspective of prescribers, pharmacists and patients.

4) Barriers and enablers to the implementation of PGx testing in different settings (primary vs secondary care).

5) Organise reported barriers and enablers in terms of domains of the Theoretical Domains Framework.

Timing and effect measures

Not applicable to this review.

26. * Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

Titles and abstracts of studies identified during the search (and those from additional sources) will be screened by two independent reviewers for eligibility. Full texts of potentially eligible studies will be retrieved and independently assessed against inclusion/exclusion criteria by two reviewers. At each stage, Cohens Kappa will be calculated to measure level of agreement. A verbal consensus process will be used to resolve any discrepancies between review authors, with no requirement for a third reviewer.

The following information will be extracted from included studies: Study design, setting (primary care, community, pharmacy, outpatient clinic, hospital, acute/secondary care, mental health), country, and participants (prescribers, pharmacists, patients) and recorded in a piloted data extraction tool in microsoft excel.

27. * Risk of bias (quality) assessment.

Describe the method of assessing risk of bias or quality assessment. State which characteristics of the studies will be assessed and any formal risk of bias tools that will be used.

No studies will be excluded based on quality as our aim is to identify barriers and enablers to the implementation of PGx testing as comprehensively as possible. The quality assessment will be undertaken for the purposes of characterising included studies. The Critical Appraisal Skills Programme CASP Qualitative checklist [1] and Critical appraisal of survey [2] will be used to critically appraise qualitative studies and surveys respectively. The lead review author (EY) will undertake critical appraisal of all studies. The second review author (DW) will independently complete a critical appraisal of a 20% sample of included studies.

References:

1)Critical Appraisal Skills Programme (CASP). 10 Questions To Help You Make Sense of Qualitative Research. CASP Qual Checkl [Internet]. Available from: https://caspuk.net/wp-content/uploads/2018/03/CASP-Qualitative-Checklist-Download.pdf

2)Center for, Evidence Based Management. Adapted from Crombie, The Pocket Guide to Critical Appraisal; the critical appraisal approach used by the Oxford Centre for Evidence Medicine, checklists of the Dutch Cochrane Centre, BMJ editor's checklists and the checklists of the EPPI Centre. [Internet]. [cited 2018 Aug 1]. Available from: http://www.cebma.org/wp-content/uploads/Critical-Appraisal-Questions-for-aSurvey.pdf

28. * Strategy for data synthesis.

Provide details of the planned synthesis including a rationale for the methods selected. This **must not be generic text** but should be **specific to your review** and describe how the proposed analysis will be applied to your data.

A narrative synthesis will be applied to summarise the evidence, heterogenity and context of studies explored descriptively rather than quantatively. Coding will happen in two stages. First quotes indicating a barrier or enabler to different steps involved in the clinical implementation of PGx testing will be extracted from the included studies and recorded in a Microsoft excel spreadsheet. We define steps involved in the clinical implementation of PGx testing as: 1)Prescriber initiates PGx testing for a patient, 2)Prescriber orders a PGx test for a patient, 3)Patient consents to PGx testing, 4)Collection of a genetic sample from the patient, 5)Interpretation of PGx test results by the prescriber and pharmacist, 6)Application of PGx test result by the prescriber and pharmacist, 7)Communication of PGx test results to the patient, 8)Incorporation of PGx test results into the patients medical record. Any additional barriers/identified at a stage of the PGx testing process not specified on the outset will also be captured so as to not constrain the results. These will be captured in a 'Other' category. Each of the barriers/ enablers (determinants) identified at each of the steps described above will be mapped onto the following TDF domains:1) Knowledge, 2)Skills, 3)Social Influences, 4)Memory, attention and decision processes, 5) Behavioural regulation, 6) Professional/Social role and Identity, 7)Beliefs about Capabilities, 8)Belief about consequences, 9) Optimism, 10)Intentions, 11)Goals, 12)Emotions, 13)Environmental Context and Resources, and 14) Reinforcement.[1] Any determinants that do not fit into the existing domains will be categorised as 'Others' domain.[2]

References:

1)Cane J, O'Connor D, Michie S. Validation of the theoretical domains framework for use in behaviour change and implementation research. Implement Sci [Internet]. 2012;7(37). Available from: https://implementationscience.biomedcentral.com/articles/10.1186/1748-5908-7-37

2)Taylor N, Lawton R, Conner M. Development and initial validation of the determinants of physical activity questionnaire. Int J Behav Nutr Phys Act [Internet]. 2013 Jun;10:74. Available from: https://ijbnpa.biomedcentral.com/articles/10.1186/14795868-10-74

29. * Analysis of subgroups or subsets.

State any planned investigation of 'subgroups'. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach.

We will perform three different subgroup analysis of the data

1) Compare primary (participant reported) and secondary (authors interpreted) themes of barriers and enablers to clinical implementation of PGx testing.

2) Explore the barriers and enablers to the implementation of PGx testing from the perspectives of

prescribers, pharmacists and patients if data available.

3) Explore any differences in reported barriers and enablers to implementation of PGx testing between primary and secondary care settings if data available.

30. * Type and method of review.

Select the type of review and the review method from the lists below. Select the health area(s) of interest for your review.

Type of review

Cost effectiveness
No

Diagnostic
No

Epidemiologic
No

Individual patient data (IPD) meta-analysis
No

Intervention
No

Meta-analysis
No

Methodology
No

Narrative synthesis
Yes

Network meta-analysis
No

Pre-clinical
No

Prevention
No

Prognostic
No

Prospective meta-analysis (PMA)
No

Review of reviews
No

Service delivery
No

Synthesis of qualitative studies
Yes

Systematic review
Yes

Other
No

Health area of the review

Alcohol/substance misuse/abuse
No

Blood and immune system
No

Cancer
No

Cardiovascular
No

Care of the elderly
No

Child health
No

Complementary therapies
No

Crime and justice
No

Dental
No

Digestive system
No

Ear, nose and throat
No

Education
No

Endocrine and metabolic disorders
No

Eye disorders
No

General interest
No

Genetics
No

Health inequalities/health equity
No

Infections and infestations
No

International development
No

Mental health and behavioural conditions
No

Musculoskeletal
No

Neurological
No

Nursing
No

Obstetrics and gynaecology
No

Oral health
No

Palliative care
No

Perioperative care
No

Physiotherapy
No

Pregnancy and childbirth
No

Public health (including social determinants of health)
No

Rehabilitation
No

Respiratory disorders
No

Service delivery
No

Skin disorders
No

Social care
No

Surgery
No

Tropical Medicine
No

Urological
No

Wounds, injuries and accidents
No

Violence and abuse
No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.
English

There is not an English language summary

32. * Country.

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved.
England

33. Other registration details.

Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. (N.B. Registration details for Cochrane protocols will be automatically entered). If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

34. Reference and/or URL for published protocol.

Give the citation and link for the published protocol, if there is one

Give the link to the published protocol.

Alternatively, upload your published protocol to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

No I do not make this file publicly available until the review is complete

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.

Do you intend to publish the review on completion?

Yes

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords will help users find the review in the Register (the words do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

pharmacogenetic testing; pharmacogenomic testing; implementation; pharmacogenomics;

pharmacogenetics

37. Details of any existing review of the same topic by the same authors.

Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38. * Current review status.

Review status should be updated when the review is completed and when it is published. For newregistrations the review must be Ongoing.
Please provide anticipated publication date

Review_Ongoing

39. Any additional information.

Provide any other information the review team feel is relevant to the registration of the review.

40. Details of final report/publication(s).

This field should be left empty until details of the completed review are available.

Give the link to the published review.

Appendix 7: Systematic review search strategy (Chapter 4)

PICO tool[a]	Search terms					
	General term	PubMed	Ovid EMBASE	Ovid MEDLINE	CINAHL complete	PsychInfo
P	Healthcare setting	Primary Health Care [MeSH] OR Secondary Care [MeSH] OR General Practice [MeSH] OR Hospitals [MeSH] OR Pharmacy [MeSH]	Exp Health care delivery [Emtree] OR Exp Primary health care [Emtree] OR Exp Medical care [Emtree] OR Exp health care facility [Emtree] OR EXP Secondary health care [Emtree] OR Exp Pharmacy [Emtree] OR Exp hospital pharmacy [Emtree]	Exp Primary Health Care [MeSH] OR Exp Secondary Care [MeSH]; OR Exp General Practice [MeSH];OR Exp Hospitals [MeSH] OR Exp Pharmacy [MeSH]	Exp "Health care delivery" OR TX hospital* OR TX pharmacy	MJ "health care service*" OR MA "Secondary Care "[MeSH]; OR MA "General Practice" [MeSH];OR MA Hospitals [MeSH] OR MA Pharmacy [MeSH]
I	PGx testing by doctor or pharmacist or experienced by patient	[Pharmacogenomic testing [MeSH] OR "PGx".tw; "Pharmacogenetic testing".tw OR Pharmacogenomic*.tw OR Pharmacogenetic*.tw] AND [Physicians [MeSH] OR Pharmacists [MeSH] OR Patients [MeSH] OR Public.tw OR	[Exp Pharmacogenetic testing [Emtree] OR "PGx".tw OR Pharmacogenomic$.tw OR Pharmacogenetic$.tw] AND [Exp Physician [Emtree] OR Exp Pharmacist [Emtree] OR Exp patient [Emtree] OR Public.tw OR "service-user$".tw OR "service user$".tw	[Exp Pharmacogenomic testing [MeSH] OR "PGx".tw; "Pharmacogenetic testing".tw OR Pharmacogenomic*.tw OR Pharmacogenetic*.tw] AND [Exp Physicians [MeSH] OR Pharmacist*.tw OR Exp Patients [MeSH]	[AB Pharmacogenetic* OR AB pharmacogenomic* OR AB "PGx"] AND [TX physician* OR TX pharmacist* OR TX nurse* OR MH patients OR TX public OR TX "service user*" OR TX "service-user*"]	[MA "Pharmacogenomic testing" [MeSH] OR AB "PGx" OR AB "Pharmacogenetic testing" OR AB Pharmacogenomic* OR AB Pharmacogenetic*] AND [MA Physicians [MeSH] OR MA Pharmacists [MeSH] OR Patients [MeSH]

		"service-user*".tw OR "service user*".tw OR consumer.tw OR consumers.tw OR customer.tw OR customers]	OR consumer$.tw OR customer$.tw	OR Public.tw OR "service-user*".tw OR "service user*".tw OR consumer*.tw OR customer*]		OR TX Public OR TX "service-user*" OR TX "service user*"]
C	n/a					
O	Implementation captured through the perspective of those who have experience of testing	Implementation.tw OR adoption.tw OR perceive.tw OR perceiving.tw OR perception.tw OR perceptions.tw OR value.tw OR values.tw OR perspective.tw OR perspectives.tw OR view.tw OR views.tw OR experience.tw OR experiences.tw OR need.tw OR needs.tw OR attitude.tw OR attitudes.tw OR belief.tw OR beliefs.tw OR opinion.tw OR opinions.tw OR feelings.tw OR understand.tw	Implementation.tw OR adoption.tw OR perceive$.tw OR perception$.tw OR value$.tw OR perspective$.tw OR view$.tw OR experience$.tw OR need$.tw OR attitude$.tw OR belie$.tw OR opinion$.tw OR feel$.tw OR know$.tw OR understand$.tw	Implementation.tw OR adoption.tw OR perceive*.tw OR perception*.tw OR value*.tw OR perspective*.tw OR view*.tw OR experience*.tw OR need*.tw OR attitude*.tw OR belie*.tw OR opinion*.tw OR feel*.tw OR know*.tw OR understand*.tw	TX Implementation OR TX perceive* OR TX perception* OR TX satisf* OR TX value* OR TX perspective* OR TX view* OR TX experience* OR TX opinion* OR TX TX "consumer satisfaction" OR TX belie* OR MH "patient satisfaction"	TX Implementation OR TX perceive* OR TX perception* OR TX satisf* OR TX value* OR TX perspective* OR TX view* OR TX experience OR TX opinion* OR TX belie* OR MJ "Client attitudes"
[a]('P' AND 'I' AND 'O') Footnote: * is a truncation symbol to retrieve terms with a common root within CINAHL Plus and MEDLINE. $ is a truncation symbol to retrieve terms with a common root within EMBASE.						

Appendix 8: Abstract screening tool (Chapter 4).

Author(s)	Study ID	Title	Accepted (yes / No)	Reason for rejection

Appendix 9: Data Extraction tool (Chapter 4).

Quote	Behaviour code	Factor affecting Implementation Code	Factor affecting Implementation Quote	Barrier/Enabler	Whose behaviour?	Source	TDF	Intervention to overcome this	BCT	Other

Appendix 10: Protocol for PGx case study (Chapter 5)

PGx Clinical Pathway Development Study protocol

Study name: **Pharmacogenetic Clinical Pathway Development Study**

Version	3.2
Date	5th July 2022
Sponsor	University of East Anglia
IRAS/HRA reference	273748

Name	Essra Youssef
Role and Affiliation	PhD applicant and pharmacist School of Pharmacy, Faculty of Science University of East Anglia, Norwich Research Park, Norwich, NR4 7TJ Tel: 01603 591996 E-mail: E.Youssef@uea.ac.uk
Signature	

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Glossary of abbreviations and terms

ADR	Adverse Drug Reaction
DME	Drug Metabolising Enzyme
HCP	Health Care Professional
HRA	Health Research Authority
MRC	Medical Research Council
PD	Pharmacodynamics
PK	Pharmacokinetics
PGx	Pharmacogenetics
PIS	Patient Information Sheet
PPI	Patient and Public Involvement

Roles and responsibilities

Pharmacogenetic Clinical Pathway Development Study steering committee roles (and expertise)

Essra	Youssef	Chief investigator (PhD applicant and pharmacist)
Doug	Mellor	Lay representative
Sujata	Walker	Lay representative
David	Wright	Academic supervisor (Feasibility and randomised controlled trial design)
Debi	Bhattacharya	Academic supervisor (Behaviour change research)
Fiona	Poland	Academic supervisor (Qualitative research methods)
Allan	Clark	Academic supervisor (Statistics)

1 Abstract

Background

Medicines are the main health intervention in western healthcare systems. Whilst they do provide benefits, inter-individual differences can lead to lower treatment efficacy and adverse drug reactions (ADR). Response to medicines is influenced by a variety of physiological, environmental and genetic factors. 'Pharmacogenetics', shortened to PGx is an emerging discipline that analyses how genes affect an individual's drug response. The aim of PGx testing is personalising therapy to maximise therapeutic benefit and avoid ADR. This technology is available in the USA, Australia, Canada, and parts of Europe but as of yet is only privately available in the UK. Consequently, very little is known about a model for implementing PGx testing within a NHS context.

Aims

The aim of this study is to explore and develop new clinical pathways for PGx test delivery in hospital, general practice and mental health. To achieve this, a group of clinicians will be provided with access to a PGx testing service to use in thirty patients. The proposed output is the knowledge gained to support future implementation strategies for PGx testing at a national level.

Methods

Pathways for PGx testing delivery will be explored and developed at each site through discussion with relevant stakeholders (clinicians and pharmacists). All healthcare professionals involved in the testing pathways will undergo PGx training that is relevant to their role. Training will enable healthcare professionals to identify patients likely to benefit from testing, take patient consent and explain results to patients. Post PGx test delivery, all healthcare professionals and a sample of patients will be interviewed to examine the clinical pathways through their experiences.

2 Background and Rationale

Medicines

Medicines represent the most frequent medical intervention in health systems around the world and are a source of significant expenditure. Spending on prescription medicines in England alone was £18.2 billion in 2017/18, representing an increase of 40% from 2010/11 (£13b).(1) Despite the monetary and societal investment we place in medicines to prevent, treat and cure illness and disease- they do not always work.

Many patients are unable to fully benefit from their first recommended treatment. The efficacy rate for most drugs is estimated to be between 30-50%.(2) Patients can respond differently to the same drug and dose (quantity of drug). Sometimes the effective drug dose in one person can lead to a serious adverse drug reaction (ADR) in another. ADRs alone contribute to 1 in 16 hospital admissions in England and 4% of total bed capacity.(3)

Unpredictability of drug response leads to a 'trial and error' approach to prescribing. This generates multiple consultations delaying achievement of therapeutic goals and creating medicine waste.

What governs drug response?

Drug response is influenced by a variety of physiological, environmental and genetic factors.(4) Inter-individual variation in drug response can be located to two branches of pharmacology. The first is 'Pharmacokinetics (PK)' which encompasses all effects of the body on the drug. When a drug enters the body, it follows an identical process of absorption, distribution, metabolism and elimination. A medicines' affect relies on it being in the circulatory system at the optimum concentration and period of time to exert its intended effect. Below this threshold a lack of efficacy is observed and beyond it, toxicity may take effect. Interventions to augment any one or more of these parameters, can affect the concentration of drug in circulation and in turn therapeutic efficacy. (Table 1)

PK parameters	**Definition**	**Example intervention**
Absorption	Rate and extent to which the drug is absorbed by the body.	Taking a drug before food if absorption is reduced by presence of food in the gut
Distribution	Rate and extent to which drug is distributed in tissues and fluids distinct from the site of absorption.	Certain drugs cannot be given to pregnant women because they can pass onto the foetus
Metabolism	Rate and extent to which drug is broken down in the liver either to its active form or to inactive form to be eliminated.	Avoiding drug interactions where one drug inhibits the metabolism of the other.
Elimination	Rate and extent to which drug and its metabolites are removed from the body.	Reducing dose in presence of reduced kidney function

Table 1. Summary of pharmacokinetic parameters

The second branch is 'Pharmacodynamics (PD)' which is the physiological effect of the drug on the body. This occurs as a result of the drug binding or interacting with a molecule in the body called a 'drug receptor'. When a drug binds to this molecule, it elicits a biochemical reaction that leads to a physiological response. For example, antihypertensive medicines bind to target molecules in the kidneys leading to a reduction in overall blood pressure.

'Pharmacogenetics (PGx)' is newly emerging discipline that analyses genetic polymorphisms that alter these PK/PD parameters. Polymorphisms refers to different

versions of a gene called ‘alleles’. These are inherited from parents and code for the expression of the gene. For example, a gene codes for eye colour and the combination of alleles will determine whether blue or brown eyes are expressed. In pharmacogenetics alleles are analysed for genes that are responsible for a component of drug response. The most extensively studied example includes polymorphisms in genes coding drug metabolising enzymes (DME) in the liver. Variations in these genes lead to four different categories for activity: poor metaboliser, intermediate metaboliser, extensive metaboliser and ultra-rapid metaboliser.(5) Prominent examples of the clinical applications of DME status include personalising the prescribing of antidepressants, pain medicines and warfarin.(6)(7)(8)

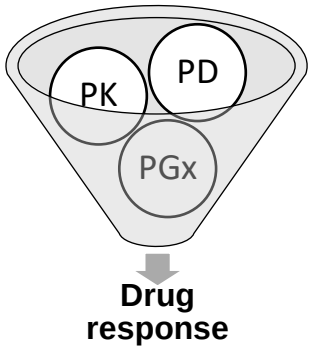

Figure 1. Diagram demonstrating the different components influencing drug response

PGx information alongside known PK, PD characteristics of the drug and patient may offer the opportunity to optimise medicines by ‘personalising’ drug choice, dose and monitoring. In this way PGx testing provides additional information for the prescriber to consider when balancing possible risks against benefits of prescribing a drug.

Implementation of PGx testing in health systems

Internationally PGx testing can be considered in a pre-implementation phase, there are no national pre-emptive PGx screening programmes in existence to date. There is however, PGx testing available in many countries although this is fragmented and largely isolated to academic centres.(9)(10) Outside of these centres, direct-to-consumer tests are available however uptake has been modest largely due to lack of reimbursement by health insurance providers.(9)

Within the literature, a number of barriers to PGx testing implementation have been cited including:

- Lack of knowledge and training(11–23)
- Absence of guidelines within a clinical workflow(11,14,16,18,21,24)
- Absence of clinical decision support tools(11,14,17,19,23–30)
- Quality of existing evidence base(18,24,31,32)

- Lack of perceived utility(14,23,24,31–33)
- Concerns about confidentiality and discrimination(12,17,24,25,31,34)

To address these barriers a number of organisations have emerged, most notably the Dutch Pharmacogenetics Working Group (DPWG) and the Clinical Pharmacogenetics Implementation Consortium (CPIC).(35)(36) Both these organisation develop evidence-based PGx therapeutic recommendations to support clinical decision making when PGx test results are known. They do not however make recommendations for when PGx testing should be performed.

This is due to a lack of randomised controlled trials (RCT) demonstrating the effectiveness and cost-effectiveness of a PGx approach over usual care in drugs other than warfarin and abacavir.(8)(37) PGx therapeutic recommendations for medicines used in pain relief, cardiovascular disease, diabetes and mental health disorders, are supported by smaller retrospective studies. This is similar to those which underpin current dosing recommendations in kidney or liver disease.(38)

To address the evidence barrier, two large programmes of work are underway. The first is the PREPARE randomised cross-over trial, involving 8,000 patients across seven European countries.(39) This trial is investigating whether pre-emptive PGx testing (before initiation of medicine) of a panel of genes leads to an overall reduction in the incidence of adverse drug reactions (ADR). A pre-emptive PGx testing programme is also in place at St Jude Children's Research Hospital in the US. This is evaluating the effectiveness of incorporating PGx data in electronic health records for almost 5,000 paediatric patients.(40)

Whilst these studies will help clarify the clinical utility derived from pre-emptive PGx testing, a number of uncertainties remain. These include, which patient groups would maximally benefit from testing, at which stage testing should be implemented and whether testing on a reactive basis provides benefit.

Expressed need for this research and policy context

The current and historic research approach has been evaluating PGx testing from a pre-emptive perspective. However, PGx testing may also have a role in optimising existing medicines therapy, particularly in patients with polypharmacy. Polypharmacy, commonly defined as taking five or more medicines (41) is a global health problem associated with lower rates of adherence, (42) increased risk of adverse drug reactions, avoidable hospital admissions, falls and mortality.(43)(44)(45)

Within the UK, the Kings fund in 2012 identified that 22% of patients were prescribed over five medicines at any one time and 5.8% were prescribed ten or more medicines.(46) As the population ages, the incidence rate is likely to increase. The response in England to the challenges posed by polypharmacy has been to support a policy of medicines optimisation.(47) Medicines optimisation is a 'person-centred approach to the safe and effective use of medicines'.(41) PGx testing may facilitate medicines optimisation through the personalisation of medicines and doses in patients with existing polypharmacy.

This study forms the first in a larger programme of work to evaluate the effectiveness and cost-effective of PGx testing for medicines optimisation in polypharmacy. Because PGx testing is a complex intervention, organisations such as the Medical Research Council recommend developing interventions systematically before testing them.(48) Current research on the implementation of PGx testing in the UK is limited by its hypothetical perspective.(49)(50)(51) This study will address this gap, by conducting a qualitative service evaluation of PGx testing to build the evidence for how PGx testing should be delivered and how to integrate it into existing clinical pathways for future studies. This work also has wider applications for PGx test service design and implementation in the NHS which has been identified as a priority by the UK government.(52)

3 Aims and objectives

The aim of this project is to develop acceptable and efficient Pharmacogenetic (PGx) testing clinical pathways.

The objectives, with respect to Pharmacogenetic (PGx) testing in patients in primary, secondary and mental health settings, are to:

- Describe the barriers and facilitators associated with PGx testing.
- Identify how best to consent patients and complete their details to enable testing to be performed
- Identify what changes in existing clinical pathways are necessary for facilitating PGx testing
- Identify which healthcare professionals should be involved at each stage of the process
- Describe training requirements for the different members of the team involved in PGx testing
- Describe healthcare professional acceptability
- Identify process, clinical and economic measures related to the intervention
- Identify any unintended consequences
- Identify which patients are believed to most likely to benefit

4 Study design and methods

4.1 The intervention

The PGx testing service used in this study is provided by myDNA Life Australia. myDNA Life is an Australian genetic interpretation company that offers personalised advice on medicines (Appendix 1),diet and fitness. The rationale for using a commercially available

PGx testing service is to address logistical barriers to implementation identified in the literature. The myDNA Life PGx testing service includes a CE accredited device for DNA collection (Appendix 2), online PGx training package for prescribers and pharmacists, nationally accredited laboratories for DNA analysis (53) and a clinical interpretation report that references international recognised recommendations by CPIC and DPWG (Appendix 3). In addition, from a data protection point of view, myDNA Life is already registered in the UK and is GDPR compliant.

The PGx test involves a trained healthcare professional (HCP) or patient using a cheek swab to collect DNA (Appendix 2). This swab is then sent in a pre-paid envelop to a secure warehouse in West Drayton. Shipping to Australia is triggered once enough swabs are received by the warehouse location. Each swab is labelled with a unique registration code which is used to register patient details creating a secure online portal for the prescriber, pharmacist and patient to access results. DNA is extracted and analysed only for common variants in nine PGx genes. The results are then used to prepare a clinical interpretation report by a team of physicians, pharmacists and molecular geneticists referencing clinical recommendations of CPIC and DPWG as well as primary PGx literature.(Appendix 3) This report is sent to the prescriber and pharmacist via the online portal within 10 working days of receiving the swab. The prescriber/pharmacist will then explain the results to the patient before the patient is able to access their results via their own patient portal.

4.2 Healthcare professional training

Prescribers in contrasting primary and secondary care settings (GP practice, Hospital and Mental Health Trust) will have access to PGx testing kits.(Appendix 2) Key stakeholders will be approached to develop a testing pathway at each site. Each prescriber and pharmacist involved in PGx testing will undertake the relevant online training package developed by myDNA. Two training packages are available, one for pharmacists and another for prescribers. These have not been translated to a UK setting.

Training should take no more than 1 hour to complete and will cover the following:

- Ensure that patient consent is informed and concerns are appropriately addressed
- Collection of the buccal sample and patient information for the myDNA test
- Interpret the test result and relate it to prescribing choice

A brief overview of the research process will also be included.

Before the online training, recruited prescribers and pharmacists will have the opportunity to use the test on themselves. This will be a valuable learning experience for the

prescriber/pharmacist to understand each step in detail of the testing process and report interpretation. This will be facilitated by the chief investigator (EY).

4.3 Study Population

Prescribers on completion of the PGx training will identify patients under their direct care who meet the inclusion/exclusion criteria. This will be different in each setting. In general practice and the mental health setting, the prescriber will screen patients through their computer records. In hospital the prescriber will screen patients on the inpatient ward using the hospital medical notes.

In general practice and the mental health setting the prescriber will approach patients several ways: sending a letter/email to the patient or contacting the patient over the phone. In hospital the prescriber will approach the patient on the inpatient ward. This initial approach comprises of the prescriber explaining the study and the myDNA service. The prescriber will also give the patient a project PIS (Appendix 4) and a myDNA PIS (Appendix 17). The project PIS explains to the patient that they will be contacted post-results to be invited to participate in the research by being interviewed. The PIS will make it clear that participation in the research is optional and non-participation will in no way affect their care.

In general practice and the mental health setting, patients who have read the project PIS (Appendix 4) and myDNA PIS (Appendix 17). And expressed an interest in having the PGx test, will be posted a single myDNA medication test kit within two weeks of notice of interest. The test kit will include a cheek swab kit, instructions (Appendix 19) on how to take a cheek swab sample and details of the patients nominated prescriber and pharmacist (if applicable). The nominated prescriber and pharmacist will be the health professional who recruits the patient. The patient will collect their cheek swab sample themselves. The patient will also register the myDNA medication test kit to themselves and their nominated prescriber and pharmacist (if applicable). The myDNA test kit registration is online, and takes the patient through a series of questions that they complete. Patients complete a consent form to have their DNA analysed by myDNA. Registration of the kit online by the patients is necessary, so that the results are returned to the patient and their nominated prescriber. myDNA will have records of the prescribers and pharmacists in the UK who have completed the online training. Their details will appear to the patient on a scroll bar list, to reduce the risk of patients entering the wrong prescribers' details. myDNA will not process the DNA sample until the patient enters details of a prescriber or pharmacist that has completed the myDNA training.

In hospital once the consultant has obtained an expression of interest from the patient, the ward pharmacist will then take consent for the myDNA test and collect a cheek swab sample on the ward. Depending on the availability of the PGx trained ward pharmacist, this could happen immediately or within a week of the consultant obtaining an expression of interest from the patient.

The myDNA PIS and consent forms have not been translated to a UK setting as myDNA Australia will be analysing the samples and must do so in accordance with their own

consent. In terms of the suitability of the existing materials, over 20,000 patients have used these in Australia and Canada and with English being the common language, we do not anticipate any ambiguity in patients understanding of materials.

4.3.1 Inclusion/exclusion criteria

Inclusion Criteria

- Adult male and female patients aged 18 years or older at the time of enrolment. No upper age limit specified.
- Able to read, write and speak English.
- Under the immediate care of registered prescriber who has completed PGx training provided by myDNA
- Able to give consent
- Prescribed at least one medicine that can be informed by the myDNA test (Appendix 1)
- History of adverse drug reactions/ side effects/ or lack of therapeutic benefit from medicines prescribed past and present.

Exclusion Criteria

- Under the age of 18 years
- Unable to provide consent due to capacity
- Palliative (expected life expectancy <12 months)
- People undergoing mental health crisis

At this stage it is not necessary for patients to be prescribed 5 or medicines. This stage is about developing pathways for delivering the test at each site that are efficient and acceptable to the healthcare professionals and patients.

4.3.2 Testing process/service delivery

Through discussion with stakeholders (prescribers and pharmacists) at all sites, potential pathways have been proposed for PGx test service delivery to minimise disruption to current practice (Appendix 6). This has involved utilising pharmacists in each of the sites to explain what the genetic test is to the patient and explaining report results to patients. By

assigning these activities to pharmacists, the time of the prescriber is more suitably used for report interpretation.

myDNA consent and cheek swab collection

In all sites, myDNA consent and cheek swab collection will be obtained face-to-face with the patient on site. In the general practice pathways this will be either in a consultation room at the surgery or a consultation room in the community pharmacy. In the mental health setting this will be in a consultation room at the hospital. In hospital this will be on the inpatient ward. In all instances, the pharmacist or prescriber will explain the myDNA testing process and obtain consent for testing from the patient online (Appendix 5). The pharmacist or prescriber will collect a sample of cheek cells from the patient (Appendix 2) and seal this in an opaque pre-addressed envelope along with patient contact details (name, phone number, DOB).

DNA storage/transfer

The pharmacist or prescriber will store the patients' cheek swab sample in a locked cabinet or drawer in a secure room on the premises of which it was collected and post the sample within 24 hours of collection. In the hospital setting, this will be in the pharmacy offices. In general practice this will be in the consultation room. At the mental health setting, this will be in the offices of the prescribers.

Samples are posted to a secure warehouse in West Drayton (myDNA Life, 361 Stockley Close, West Drayton, Middlesex, UB7 9BL) using business reply post. From here, samples are then shipped periodically to myDNA laboratories (12 River Street South Yarra, VIC, Australia 3141) for analysis. The management of the warehouse and shipping of samples to Australia is undertaken by MNX Global Logistics. The process of transferring the DNA sample to the UK warehouse and then shipping samples to Australia is currently used by myDNA Life in the UK for the lifestyle genetics test sold through Lloyds pharmacy.

Personalised medicine report review

The report with the patients' genetic results and interpretation will be uploaded electronically onto the prescribers' online portal. Where a pharmacist has taken consent from the patient for the myDNA test, a copy of the report will also be uploaded onto the pharmacists' online portal. The prescriber will review this report and consider the genetic results alongside other patient factors when amending the patients prescription or monitoring plan. This will be covered by the myDNA PGx training.

Explaining results to patients and follow-up

The patients nominated pharmacist or prescriber will contact the patient to explain the results over the phone within a week of reviewing results. This explanation will include explaining the genetic results and any changes in the prescribing or monitoring of the patients current medicines influenced by the genetic results. The only exception to this will be in the hospital setting. In the unlikely situation, that the patient is still an inpatient on the ward, the ward pharmacist will explain the results to the patient in person.

In the hospital and mental health setting the prescriber will also share a copy of the report (PDF) with the patients GP. In the event of an incidental finding i.e. the genetic result identifies the patient could have an unfavourable response to a medicine which is not in the secondary care prescribers speciality, then the secondary care prescriber will write to the patients GP to inform them specifically of this result and any action the secondary care prescriber has taken to mitigate this i.e asking the patient about side effects related to this medicine.

The pharmacist or prescriber who has explained the results of the PGx test over the phone will post a copy of 'Request to destroy stored DNA sample' (Appendix 18) within a week of explaining the results. This ensures the sample will be destroyed. In the event that a patient does not sign the 'Request to destroy stored DNA sample' form within two weeks of receiving it, the prescriber or pharmacist will contact myDNA on the patients behalf to have the patients DNA sample destroyed.

4.4 Qualitative service evaluation

Qualitative methodologies offer the most appropriate way to elicit people's beliefs, knowledge and the meanings they ascribe to their experiences.(54) In this study these methods will be used to examine what barriers and enablers exist to service delivery, implementation and use.

Semi-structured interviews have been chosen over focus groups for their strength in generating in depth and rich data.(54) Topic guides for HCP and patients will obtain views regarding recruitment, experiences of delivering and receiving different aspects of the intervention, impact on prescribing behaviour, medicines taking, and any unintended consequences.

4.4.1 Prescriber and Pharmacist interviews

Post-PGx test service delivery, the chief investigation (CI) will send an email to each of the prescribers and pharmacists, inviting them to participate in a telephone interview (Appendix 7). The email will also have a "Participation Information Sheet" (PIS) attached (Appendix 8) and consent form (Appendix 9). Participants who return a completed consent form will be contacted by the CI to agree a time and place that is convenient for the interview to take place. At the start of the interview the CI will email the interviewee a copy of the consent form with both the interviewer and interviewees signatures. A semi-structured topic guide (Appendix 10) will be used to facilitate the interview. The topic guide may be altered slightly in an iterative process, following experiences of initial interviews.

4.4.2 Patient interviews

A maximum of 12 patients who had the test will be recruited for a 30 minute telephone interview. Patients will receive an invitation letter through email or post from their Consultant/GP (Appendix 11) within a week of having their test results returned. If no response, patients will receive one more invitation letter a month after the first letter is sent. Those who are interested will contact the CI directly via phone or email. The CI will collect patient specific details on an interview expression of interest form (Appendix 12).

This form will be used as a screening tool so that the CI has the necessary information to develop a sampling strategy for interviewing patients. Those selected for interview will be sent a participant information sheet (Appendix 13) and consent form (Appendix 14) via post or email. Once the completed consent form is received, the CI will contact the patient within two working days to identify whether the patient is still interested and arrange a time for the interview. Patients will have up to a month from receiving the posted PIS and consent form to decide whether to participate or not. The telephone interview will be guided by an iterative topic guide (Appendix 15).

Once the interview has taken place, the CI will post a gift voucher to the patient. Once all the interviews have taken place, any patients who expressed interest and were unable to be interviewed due to constraints in data collection will be sent a thank you/regret letter (Appendix 16)

4.5 Discontinuation/Withdrawal of Participants from Study

Participants for interview are able to withdraw at any point before or during the interview. Once the interview has taken place participants will be unable to access or change the information provided up to the point of withdrawal. This stipulation is stated in the participant information sheets.

If a patient loses capacity to consent to storage of their DNA sample at any point during this study, then the prescriber who has ordered the PGx test will contact myDNA on the patients behalf to request the patients DNA sample is destroyed.

5.1 Sampling

All prescribers and pharmacists will be invited to interview if possible. The limiting factor will be prescriber and pharmacist consent to be interviewed by the chief investigator (CI).

Theoretical sampling will be used to guide selection of patients for interview. This is a sampling technique that involves sampling individuals whom the researcher predicts (based on theoretical models or previous research) to add new perspective to those already represented in the sample. (55) The CI will collect information from patients interested in an interview on a form (Appendix 12). From these patients will be selected based on the testing pathway used to explore the acceptability of test delivery. A maximum of 12 interviews with patients will be sought in line with usual qualitative practices.(56)

5.2 Interview timeline

Prescribers and pharmacists involved in delivering the PGx test will be invited to have an interview as soon at the testing kits at each of the sites have been used. This will capture the immediate experiences of prescribers and pharmacists using the PGx test. This is important to minimise recall biases in the data collection.

To minimise the disruption to prescriber and pharmacist schedules, each participant will be consulted regarding the most suitable arrangements that will consider their work

commitments. The interviews will take place in a suitable room at the participants' workplace.

Patients will be invited for an interview by their consultant/GP through post/e-mail a week within a week of PGx results being explained. Patients who are interested will contact the CI directly. At this point the CI will talk to the patient on the phone and take details to help with the sampling strategy (Appendix 12). The CI will post the patient a PIS (Appendix 13) and consent form (Appendix 14). Participants who complete the consent form will be contacted by the CI within two working days or receiving this form to arrange a time for a telephone interview. The interview will take place within two weeks of receiving informed consent for the telephone interview.

5.3 Logistics

Prescriber/Pharmacist: The interviews will be expected to last 30 mins over the phone. The researcher will record the interview by putting the phone on loud speaker in a private room within UEA.

Patient: The interview will be expected to last 30 mins and will be done through the phone at a time that is convenient for the patient. The researcher will record the interview by putting the phone on loud speaker in a private room within UEA.

5.4 Data Management

The semi-structured interviews will be audio recorded and transcribed verbatim by the CI. Participants' identities will be anonymised during the transcription phase. This will involve removing any identifiable information.

All data collected from participants will remain confidential. All data collected from participants will be securely stored at UEA in a locked filing cabinet. Audio recorded data will be downloaded onto a secure, password protected computer at UEA and files deleted from the audio recording device.

Participants' personal data will be destroyed following the end of the CI's PhD. The research data will be destroyed after 10 years of research publication as per University of East Anglia policy. Management of data will comply with the Data Protection Act 2018 with respect to data storage, processing and destruction.

5.5 Data Analysis

The first process in analysis will be thematic analysis. The CI will undertake thematic analysis of the data. Data will be coded with themes and organised using NVivo qualitative software. The codes of (at least) the first two pages of each transcript will be checked by a member of the supervisory team to ensure coding is being undertaken correctly.(57)

Once thematic analysis has been performed, the themes will be mapped to the theoretical domains framework (TDF).(58) The TDF is a framework of behaviour change theories organised into 14 theoretical domains with each domain representing a determinant of behaviour including 'knowledge', 'skills', 'emotions', 'professional role and identity', and

'environmental context and resources'. The TDF has been successfully applied to the development of practitioner behaviour change interventions as each domain is linked to a taxonomy of 93 Behaviour Change Techniques (BCTs)(59). Data analysis using this framework approach will support PGx testing intervention development for future feasibility testing.

6 Study administration and ethical issues

6.1 Day to day management of the study

Day to day management of the study will be coordinated by the CI. The CI will meet weekly with the primary academic supervisor (DW) and at least once monthly with the management group. The chief investigator (EY) will meet on ad hoc basis with other members of the management group if needed to resolve day to day issues.

6.2 Timelines

Activities	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7
Prescriber/ Pharmacist training							
Prescriber/pharmacist PGx self-test							
PGx testing service delivery							
Patient sent request for interviews							
Patient interviews							
Prescriber/pharmacist interviews							

6.3 Sponsorship

This study is sponsored by the University of East Anglia as part of a three year PhD.

6.4 Patient and Public Involvement

The researcher (EY) has worked with Doug Mellor and Sujata Walker in the design of this research. AD is a lay representative and has reviewed all the patient and public paperwork and provided feedback which has been acted on by the researcher. AD will continue to provide feedback for the duration of this project and will be involved in the design of future studies for this programme of work.

6.5 Ethics

A favourable opinion will be sought from the UK Health Departments Research Ethics Service NHS REC and HRA approval for the study protocol, informed consent forms and other relevant documents.

Before any site can enrol patients into the study, the PI will ensure that appropriate approvals from each of the study sites. Specific arrangements on how to gain approval from participating organisations are in place and comply with the relevant guidance.

For any amendment to the study, the PI will submit information to the appropriate body in order for them to issue approval for the amendment. The researcher will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

7 Dissemination and Outcome

The dissemination plan is designed to reach all relevant stakeholders to inform the policy debate around pharmacogenetic testing implementation and the models for pharmacogenetic testing delivery. The full dissemination plan will be designed by the steering committee with input from the medicines optimisation group East Anglia during the course of the study. This will include peer reviewed academic papers, conference presentations and presentations and outputs targeting stakeholder groups.

We will also produce a lay summary of the findings and disseminate this amongst the participants of the study via e-mail/post.

8 References

1. Ewbank L, Omojomolo D, Sullivan K, McKenna H. The rising cost of medicines to the NHS: what's the story. King's Fund [Internet]. 2018;(April):1–345. Available from: https://www.kingsfund.org.uk/publications/rising-cost-medicines-nhs

2. Spear BB, Heath-Chiozzi M, Huff J. Clinical application of pharmacogenetics. Trends Mol Med. 2001;7(5):201–4.

3. Pirmohamed M. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. Bmj [Internet]. 2004;329(7456):15–9. Available from: http://www.bmj.com/cgi/doi/10.1136/bmj.329.7456.15

4. Ahmed S, Zhou Z, Zhou J, Chen SQ. Pharmacogenomics of Drug Metabolizing Enzymes and Transporters: Relevance to Precision Medicine. Genomics, Proteomics Bioinforma [Internet]. Beijing Institute of Genomics, Chinese Academy of Sciences and Genetics Society of China; 2016;14(5):298–313. Available from: http://dx.doi.org/10.1016/j.gpb.2016.03.008

5. Wilkinson GR. Drug Metabolism and Variability among Patients in Drug Response. 2014;2211–21.

6. Rosenblat JD, Lee Y, McIntyre RS. The effect of pharmacogenomic testing on response and remission rates in the acute treatment of major depressive disorder: A meta-analysis. J Affect Disord [Internet]. Elsevier B.V.; 2018;241(April):484–91. Available from: https://doi.org/10.1016/j.jad.2018.08.056

7. Linares OA, Daly D, Linares AD, Stefanovski D, Boston RC. Personalized oxycodone dosing: Using pharmacogenetic testing and clinical pharmacokinetics to reduce toxicity risk and increase effectiveness. Pain Med (United States). 2014;15(5):791–806.

8. Pirmohamed M, Burnside G, Eriksson N, Jorgensen AL, Toh CH, Nicholson T, et al. A Randomized Trial of Genotype-Guided Dosing of Warfarin. N Engl J Med [Internet]. 2013 Dec 12;369(24):2294–303. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1311386

9. Klein ME, Parvez MM, Shin J-G. Clinical Implementation of Pharmacogenomics for Personalized Precision Medicine: Barriers and Solutions. J Pharm Sci [Internet]. 2017 Sep;106(9):2368–79. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0022354917303209

10. Dunnenberger HM, Crews KR, Hoffman JM, Caudle KE, Broeckel U, Howard SC, et al. Preemptive Clinical Pharmacogenetics Implementation: Current Programs in Five US Medical Centers. Annu Rev Pharmacol Toxicol [Internet]. 2015 Jan 6;55(1):89–106. Available from: http://www.annualreviews.org/doi/10.1146/annurev-pharmtox-010814-124835

11. Bank PC, Swen JJ, Guchelaar HJ. A nationwide survey of pharmacists' perception of pharmacogenetics in the context of a clinical decision support system containing pharmacogenetics dosing recommendations. Pharmacogenomics. 2017;18(3):215–25.

12. Alejielat R, Ejielat Z, Andrawes S, Mhaidat NM. An evaluation of the knowledge, opinions, expectations and concerns toward pharmacogenomics among Jordanian pharmacists. Per Med. 2016;13(2):143–54.

13. Elewa H, Alkhiyami D, Alsahan D, Abdel-Aziz A. A survey on the awareness and attitude of pharmacists and doctors towards the application of pharmacogenomics and its challenges in Qatar. J Eval Clin Pract. 2015;21(4):703–9.

14. Johansen Taber KA, Dickinson BD. Pharmacogenomic knowledge gaps and educational resource needs among physicians in selected specialties. Pharmgenomics Pers Med. 2014;7(1):145–62.

15. Bernhardt BA, Zayac C, Gordon ES, Wawak L, Pyeritz RE, Gollust SE. Incorporating direct-to-consumer genomic information into patient care: attitudes and experiences of primary care physicians. Per Med [Internet]. 2012 Sep;9(7):683–92. Available from: https://www.futuremedicine.com/doi/10.2217/pme.12.80

16. Hinderer M, Boeker M, Wagner SA, Lablans M, Newe S, Hülsemann JL, et al. Integrating clinical decision support systems for pharmacogenomic testing into clinical routine- a scoping review of designs of user-system interactions in recent system development. BMC Med Inform Decis Mak. 2017;17(1):1–15.

17. Schwartz EJ, Issa AM. The role of hospital pharmacists in the adoption and use of pharmacogenomics and precision medicine. Per Med. 2017;

18. Overby C, Erwin A, Abul-Husn N, Ellis S, Scott S, Obeng A, et al. Physician Attitudes toward Adopting Genome-Guided Prescribing through Clinical Decision Support. J Pers Med [Internet]. Multidisciplinary Digital Publishing Institute; 2014 Feb 27 [cited 2018 Oct 29];4(1):35–49. Available from: http://www.mdpi.com/2075-4426/4/1/35

19. Katsanis S, Minear M, Vorderstrasse A, Yang N, Reeves J, Rakhra-Burris T, et al. Perspectives on Genetic and Genomic Technologies in an Academic Medical Center: The Duke Experience. J Pers Med [Internet]. Multidisciplinary Digital Publishing Institute; 2015 Apr 3 [cited 2018 Oct 29];5(2):67–82. Available from: http://www.mdpi.com/2075-4426/5/2/67

20. Luzum JA, Luzum MJ. Physicians' attitudes toward pharmacogenetic testing before and after pharmacogenetic education. Per Med. 2016;13(2):119–27.

21. Owusu Obeng A, Fei K, Levy K, Elsey A, Pollin T, Ramirez A, et al. Physician-Reported Benefits and Barriers to Clinical Implementation of Genomic Medicine: A Multi-Site IGNITE-Network Survey. J Pers Med [Internet]. Multidisciplinary Digital Publishing Institute; 2018 Jul 24 [cited 2018 Oct 29];8(3):24. Available from: http://www.mdpi.com/2075-4426/8/3/24

22. Frick A, Benton CS, Scolaro KL, McLaughlin JE, Bradley CL, Suzuki OT, et al. Transitioning pharmacogenomics into the clinical setting: Training future pharmacists. Front Pharmacol. 2016;7(AUG).

23. Amara N, Blouin-Bougie J, Bouthillier D, Simard J. On the readiness of physicians for pharmacogenomics testing: an empirical assessment. Pharmacogenomics J [Internet]. 2018 Mar 13;18(2):308–18. Available from: http://www.nature.com/doifinder/10.1038/tpj.2017.22

24. De Denus S, Letarte N, Hurlimann T, Lambert JP, Lavoie A, Robb L, et al. An evaluation of pharmacists expectations towards pharmacogenomics. Pharmacogenomics. 2013;14(2):165–75.

25. Tuteja S, Haynes K, Zayac C, Sprague JE, Bernhardt B, Pyeritz R. Community pharmacists' attitudes towards clinical utility and ethical implications of pharmacogenetic testing. Per Med. 2013;10(8):793–800.

26. Haga SB, Mills R, Moaddeb J, Allen Lapointe N, Cho A, Ginsburg GS. Patient experiences with pharmacogenetic testing in a primary care setting. Pharmacogenomics. 2016;17(15):1629–36.

27. Just KS, Steffens M, Swen JJ, Patrinos GP, Guchelaar HJ, Stingl JC. Medical education in pharmacogenomics—results from a survey on pharmacogenetic knowledge in healthcare professionals within the European pharmacogenomics clinical implementation project Ubiquitous Pharmacogenomics (U-PGx). Eur J Clin Pharmacol. European Journal of Clinical Pharmacology; 2017;73(10):1247–52.

28. Hinderer M, Sebastian A, Hülsemann JL. Pharmacogenomics pharmacogenomic clinical decision support. 2017;18:773–85.

29. Shishko I, Almeida K, Silvia RJ, Tataronis GR. Psychiatric pharmacists' perception on the use of pharmacogenomic testing in the mental health population. Pharmacogenomics. 2015;16(9):949–58.

30. Haga S, Burke W, Ginsburg G, Mills R, Agans R. Primary care physicians' knowledge of and experience with pharmacogenetic testing. Clin Genet. 2012;82(4):388–94.

31. Chan CYW, Chua BY, Subramaniam M, Suen ELK, Lee J. Clinicians' perceptions of pharmacogenomics use in psychiatry. Pharmacogenomics [Internet]. 2017 Apr;18(6):531–8. Available from: https://www.futuremedicine.com/doi/10.2217/pgs-2016-0164

32. Cohen J, Wilson A, Manzolillo K. Clinical and economic challenges facing pharmacogenomics. Pharmacogenomics J [Internet]. Nature Publishing Group; 2013;13(4):378–88. Available from: http://dx.doi.org/10.1038/tpj.2011.63

33. Owusu-Obeng A, Weitzel KW, Hatton RC, Staley BJ, Ashton J, Cooper-Dehoff RM, et al. Emerging roles for pharmacists in clinical implementation of pharmacogenomics. Pharmacotherapy. 2014;34(10):1102–12.

34. Baker K, Dumas B. Pharmacogenomics Impressions of pharmacogenomic testing among Certified Registered Nurse. 2016;17:593–602.

35. van Schaik RH, IFCC Task Force on Pharmacogenetics: Prof. Dr. Maurizio Ferrari (IT), Prof. Dr. Michael Neumaier (GER), Prof. Dr. Munir Pirmohamed (UK), Prof. Dr. Henk-Jan Guchelaar (NL), Prof. Dr. Ron van Schaik (NL). Clinical Application of Pharmacogenetics: Where are We Now? Ejifcc [Internet]. 2013;24(3):105–12. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27683445%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC4975184

36. Johnson J, Caudle K, Gong L, Whirl-Carrillo M, Stein C, Scott S, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Pharmacogenetics-Guided Warfarin Dosing: 2017 Update. Clin Pharmacol Ther [Internet]. 2017 Sep;102(3):397–404. Available from: http://doi.wiley.com/10.1002/cpt.668

37. Mallal S, Phillips E, Carosi G, Molina J-M, Workman C, Tomažič J, et al. HLA-B*5701 Screening for Hypersensitivity to Abacavir. N Engl J Med [Internet]. 2008 Feb 7;358(6):568–79. Available from: http://www.nejm.org/doi/abs/10.1056/NEJMoa0706135

38. Pirmohamed M, Hughes DA. Pharmacogenetic tests: The need for a level playing field. Nat Rev Drug Discov [Internet]. Nature Publishing Group; 2013;12(1):3–4. Available from: http://dx.doi.org/10.1038/nrd3921

39. Ubiquitous Pharmacogenomics. PREPARE: Preventing Adverse Drug Reactions-study overview [Internet]. [cited 2019 Apr 23]. Available from: http://upgx.eu/study/

40. Hoffman JM, Haidar CE, Wilkinson MR, Crews KR, Baker DK, Kornegay NM, et al. PG4KDS: A model for the clinical implementation of pre-emptive pharmacogenetics. Am J Med Genet Part C Semin Med Genet [Internet]. 2014 Mar;166(1):45–55. Available from: http://doi.wiley.com/10.1002/ajmg.c.31391

41. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. BMC Geriatr. BMC Geriatrics; 2017;17(1):1–10.

42. Kardas P, Lewek P, Matyjaszczyk M. Determinants of patient adherence : a review of systematic reviews. 2013;4(July):1–16.

43. Nguyen JK, Fouts MM, Kotabe SE, Lo E. Polypharmacy as a risk factor for adverse drug reactions in geriatric nursing home residents. Am J Geriatr Pharmacother [Internet]. 2006 Mar;4(1):36–41. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1543594606000031

44. Gomez C, Vega-Quiroga S, Bermejo-Pareja F, Medrano MJ, Louis ED, Benito-Leon J. Polypharmacy in the Elderly: A Marker of Increased Risk of Mortality in a Population-Based Prospective Study (NEDICES). Gerontology [Internet]. 2014 Dec 6;61(4):301–9. Available from: https://www.karger.com/Article/FullText/365328

45. Richardson K, Bennett K, Kenny RA. Polypharmacy including falls risk-increasing medications and subsequent falls in community-dwelling middle-aged and older adults.

Age Ageing [Internet]. 2015 Jan 1;44(1):90–6. Available from: https://academic.oup.com/ageing/article-lookup/doi/10.1093/ageing/afu141

46. Duerden M PR. Polypharmacy and medicines optimisation: making it safe and sound. Kings Fund [Internet]. 2013;1–68. Available from: http://www.kingsfund.org.uk/publications

47. Heaton J, Britten N, Krska J, Reeve J. Person-centred medicines optimisation policy in England: an agenda for research on polypharmacy. Prim Health Care Res Dev [Internet]. 2017 Jan 16;18(1):24–34. Available from: http://www.journals.cambridge.org/abstract_S1463423616000207

48. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M, et al. Developing and evaluating complex interventions: The new Medical Research Council guidance. Int J Nurs Stud [Internet]. Elsevier Ltd; 2008;50(5):587–92. Available from: http://dx.doi.org/doi:10.1136/bmj.a1655

49. Wright AJ, Sutton S, Armstrong D, Aveyard P, Kinmonth AL, Marteau TM. Factors influencing the impact of pharmacogenomic prescribing on adherence to nicotine replacement therapy: A qualitative study of participants from a randomized controlled trial. Transl Behav Med. 2018;8(1):18–28.

50. Fargher EA, Eddy C, Newman W, Qasim F, Tricker K, Elliott RA, et al. Patients' and healthcare professionals' views on pharmacogenetic testing and its future delivery in the NHS. Pharmacogenomics. 2007;8(11):1511–9.

51. The Royal Society. Pharmacogenetics dialogue. 2005;

52. Keogh B. NHS England Board Paper: Personalised Medicine Strategy. 2015;(Paper: PB.24.09.15/05):1–5.

53. myDNA Life. Pharmacogenomic Testing [Internet]. 2019. Available from: https://www.mydna.life/pharmacogenomic-testing/

54. Ritchie J, Lewis J, Nichols CM, Ormston R. Qualitative Research Practice: A Guide for Social Science Students and Researchers. London: SAGE Publications Ltd; 2014.

55. Kuper A, Lingard L, Levinson W. Critically appraising qualitative research. BMJ [Internet]. 2008 Aug 7;337(aug07 3):a1035–a1035. Available from: http://www.bmj.com/cgi/doi/10.1136/bmj.a1035

56. Guest G, Bunce A, Johnson L. How Many Interviews Are Enough? Field methods. 2006 Feb;18(1):59–82.

57. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol. 2006 Jan;3(2):77–101.

58. Michie S, Johnston M, Abraham C, Lawton R, Parker D, Walker A. Making psychological theory useful for implementing evidence based practice: A consensus approach. Qual Saf Heal Care. 2005;14(1):26–33.

59. Atkins L, Francis J, Islam R, O'Connor D, Patey A, Ivers N, et al. A guide to using the Theoretical Domains Framework of behaviour change to investigate implementation problems. Implement Sci. Implementation Science; 2017;12(1):77.

Appendix 11: Ethical approval of PGx case study (Chapter 5).

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Ms Essra Youssef
School of Pharmacy
University of East Anglia Norwich Research Park
NR4 7TJ

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17 March 2020

Dear Ms Youssef

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Pharmacogenetic (PGx) Clinical athway Development Study: Version 2.0**
IRAS project ID:	**273748**
Protocol number:	**Not available**
REC reference:	**19/IEC08/0062**
Sponsor	**University of East Anglia**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The standard conditions document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **273748**. Please quote this on all correspondence.

Yours sincerely,
Kathryn Davies

Approvals Specialist

Email: approvals@hra.nhs.uk

Copy to: *Ms Maya Kumar*

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Insurance and indemnity letter]	1.0	07 November 2019
Interview schedules or topic guides for participants [HCP interview topic guide]	2.0	10 October 2019
Interview schedules or topic guides for participants [Patient interview topic guide]	2.0	10 October 2019
IRAS Application Form [IRAS_Form_11112019]		11 November 2019
Letter from funder [Funder acceptance letter]	1.0	09 August 2019
Letters of invitation to participant [HCP interview invitation email]	2.0	10 October 2019
Letters of invitation to participant [Patient interview invitation letter]	2.0	10 October 2019
Organisation Information Document [Organisation information document]	3.0	31 January 2020
Other [Patient thank you/regret letter/email]	3.0	06 January 2020
Other [Response to Ethics provisional outcome]	1.0	06 February 2020
Other [Response to Ethics favourable opinion]	1.0	28 February 2020
Other [Example of myDNA report]	2.0	10 October 2019
Other [myDNA consent form]	2.0	10 October 2019
Other [Summary of service delivery pathways]	2.0	22 October 2019
Other [Patient interview expression of interest form]	2.0	10 October 2019
Other [myDNA test PIS]	2.0	10 October 2019
Other [myDNA patient request to destroy DNA sample]	2.0	10 October 2019
Other [Cover letter]	1.0	06 November 2019
Other [Ethics unfavourable opinion letter]	1.0	30 September 2019
Other [myDNA quick reference list]	2.0	10 October 2019
Other [myDNA testing kit]	2.0	10 October 2019
Participant consent form [HCP interview consent form]	4.0	28 February 2020
Participant consent form [Patient interview consent form]	4.0	28 February 2020
Participant information sheet (PIS) [Study PIS]	3.0	06 January 2020
Participant information sheet (PIS) [HCP interview PIS]	4.0	28 February 2020
Participant information sheet (PIS) [Patient interview PIS]	4.0	28 February 2020
Research protocol or project proposal [PGx clinical pathway development study protocol]	3.0	06 January 2020
Schedule of Events or SoECAT [HRA schedule of events]	2.0	24 October 2019
Summary CV for Chief Investigator (CI) [Essra Youssef CV]	1.0	12 August 2019
Summary CV for student [Essra Youssef CV]	1.0	12 August 2019
Summary CV for supervisor (student research) [David Wright CV]	1.0	12 August 2019
Summary CV for supervisor (student research) [Allan Clark CV]	1.0	12 August 2019
Summary CV for supervisor (student research) [Debi Bhattacharya CV]	1.0	12 August 2019
Summary CV for supervisor (student research) [Fiona Poland CV]	1.0	12 August 2019

IRAS project ID	273748

Information to support study set up

The below provides all parties with information to support the arranging and confirming of capacity and capability with participating NHS organisations in England and Wales. This is intended to be an accurate reflection of the study at the time of issue of this letter.

Types of participating NHS organisation	Expectations related to confirmation of capacity and capability	Agreement to be used	Funding arrangements	Oversight expectations	HR Good Practice Resource Pack expectations
No Honorary Research Contracts, Letters of Access or pre-engagement checks are expected for local staff employed by the participating NHS organisations. Where arrangements are not already in place, research staff not employed by the NHS host organisation undertaking any of the research activities listed in the research application on NHS premises would be expected to obtain a Letter of Access based on standard DBS checks and occupational health clearance.	Research activities should not commence at participating NHS organisations in England or Wales prior to their formal confirmation of capacity and capability to deliver the study.	An Organisation Information Document has been submitted and the sponsor is not requesting and does not expect any other site agreement to be used.	Study funding will be provided to sites as per the Organisational Information Document	A Principal Investigator should be appointed at study sites	All sites will perform the same research activities therefore there is only one site type.

Other information to aid study set-up and delivery

This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales in study set-up.
The applicant has indicated that they do not intend to apply for inclusion on the NIHR CRN Portfolio.

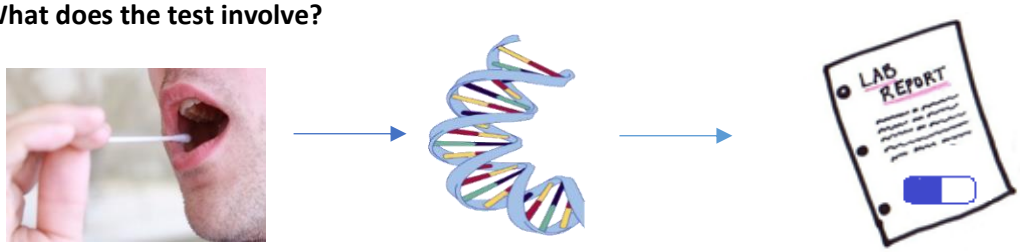
Appendix 12: Patient participant information sheet for PGx case study (Chapter 5).

Pharmacogenetic (PGx) Clinical Pathway Development Study

Participant Information Sheet

The University of East Anglia (UEA) is providing a genetic test for your medicines, which your doctor/pharmacist/nurse has offered you. Researchers at the University are interested in how such tests can be given to patients. The UEA is not involved in deciding who is offered the test or in your individual test result, the UEA is only interested in your experience of using the test.

What does the test involve?



This test involves you giving a sample of cells from the inside of your cheek. This is done using a swab, which looks like a cotton bud. The top of the swab is used to rub the inside of your cheek to collect the cells.

Your sample will then be sent to myDNA Laboratories in Australia where it will be tested. The report with your genetic results will be e-mailed to your doctor/pharmacist/nurse and the information contained may help them select medicines better suited for you.

Your pharmacist or nurse may change your existing medicines or prescribe new medicines based on your genetic results. **It will be up to the doctor/pharmacist/nurse looking after you, in discussion with you, to decide whether or not to make these changes, taking into account other factors related to your medical history.** Your hospital clinician will send the genetic report to your GP but will inform you of this.

Because this test is being offered as part of UEA study, your doctor/ pharmacist/nurse will ask you to complete a form to have your sample destroyed after you have received your genetic results. This is to prevent any further testing of your genetic sample. If at any point you are unable to do this on your own, your doctor/ pharmacist/nurse will complete this form on your behalf.

What is the research?

After you have your genetic results, your pharmacist or nurse will **invite** you on behalf of the UEA research team, to have a telephone interview. The interview will be about your

experience having this genetic test. This will be arranged at a time that is convenient for you. **You may have the genetic test and not take part in the interview. Your willingness to undertake an interview will be entirely up to you and does not affect whether you will be given the test or not.**

You do not have to take part and you may withdraw from the study at any time without stating a reason. This will not affect your legal rights, medical treatment or social care in any way.

If you have any concerns about the study please contact [redacted]

About the researcher carrying out the study:

Hi,

My name is Essra. I am a qualified pharmacist and PhD applicant in the School of Pharmacy at the University of East Anglia.

This research study is part of my PhD thesis looking at ways genetic testing can help the prescribing of medicines in a practical way.

If you would like any information or a brief chat about this research, then please get in touch by phone or email.

Essra Youssef, MPharm, MRPharmS

Phone: 01603 592035 (Mon-Fri 9-4pm)

Email: e.youssef@uea.ac.uk

Appendix 13: Healthcare professional participant invitation letter (Chapter 5).

Subject Heading: Invitation to participate in telephone interview for the 'PGx Clinical Pathway Development Study'

Dear [Insert name]

My name is Essra Youssef and I am a PhD student based at the University of East Anglia. As part of my PhD, I am conducting a piece of research around pharmacogenomic (PGx) testing in UK practice. Specifically, I am exploring how PGx testing can be delivered in a range of healthcare settings and what barriers and facilitators exist to its implementation within such contexts.

As an individual who been involved in the care of patients who had the myDNA Life PGx test, I would like to invite you to take part in a telephone interview in order to explore your experiences of using the service. I very much hope you will consider participating. The attached participant information sheet and consent form provides further information on the research study.

If you are interested in participating, please respond to this email (e.youssef@uea.ac.uk) and indicate that you would like to take part.

If you would prefer not to be contacted further regarding involvement in this research, please reply to this email requesting not to be contacted further.

Please email your response by [insert date one week from email date].

If you have any questions, please don't hesitate to get in touch either via phone or email.

I look forward to hearing from you.

Best wishes,

Essra Youssef

Research Pharmacist I School of Pharmacy I Faculty of Science

University of East Anglia, Norwich Research Park, Norwich, NR4 7TJ

Tel: 01603 591973 I E-mail: e.youssef@uea.ac.uk I Office: CAP 01.109

Appendix 14: Interviewee participant invitation letter for patient (Chapter 5).

PGx Clinical Pathway Development Study

Participant Information Sheet

I would like to invite you to take part in a research study. This study is being run and sponsored by the University of East Anglia. Before you decide whether you would like to participate, I would like you to understand why the research is being done and what it would involve for you.

What is the project about?

The aim of this study is to evaluate the implementation of a pharmacogenomic testing service across different NHS settings: Primary and Secondary Care. In order to capture this information, telephone interviews will be conducted with the different healthcare professionals who were involved in delivering the testing service. The views and opinions represent the findings of the study that will be formally presented as a part of a doctoral thesis, in publications to peer reviewed journals and at conference.

Why have I been invited?

You have been invited to take part in this research because of your involvement with delivering a Pharmacogenomic testing service.

Do I have to take part?

You are not obliged to participate. If you agree to take part then we will ask you to sign a consent form. You are however free to withdraw from the study at any time, without giving a reason. If you would prefer to receive no further contact regarding this study then please email Essra Youssef at e.youssef@uea.ac.uk and state that you do not wish to be contacted further regarding this research.

What will happen to me if I take part?

Please note that participation in this study will not have any effect on your role. All participants will be asked to sign a consent form to indicate if they agree to participate. The telephone interview is expected to last 30 minutes at a convenient time for you.

What will you ask me about?

You will be asked about your experiences and involvement in delivering PGx testing to patients. You will not be asked to talk about anything that you do not wish to talk about. However, if for any reason you do feel uncomfortable at any point during the interview, you are free to stop without giving a reason.

What will happen to my interview data?

The telephone interview will be recorded on a voice recorder to enable an accurate recording of your thoughts and experience. The researcher will listen to all recordings and transcribe them so that an accurate record of the interview is available for analysis. Your name and other individual characteristics will be changed in the transcription so that you will not be identifiable in any way in this study or subsequent reports.

What are the possible benefits of becoming involved in this project?

There is no direct benefit to taking part. The results of this study will provide us with information on barriers and enablers to the implementation of PGx testing and help us design a feasibility study exploring the role of PGx testing in polypharmacy.

What are the possible disadvantages of becoming involved in this project?

Other than the time taken to participate, no other disadvantages are envisioned to you taking part.

Will I be able to be identified from this interview?

Everything you tell the interviewer will stay confidential. Your identity will be anonymised in the transcript and in any publications or presentations based on this research.

What if I reveal sensitive information during the interview?

You will be asked to refrain from using names and identifiers if relating to patients, carers, yourself, family members or colleagues. If sensitive information is revealed, this will be discussed with you and any potential action reviewed by the researcher with their supervisory team.

How will my data be stored?

The electronic anonymised transcript will be stored on a password protected computer. Anonymised paperwork relating to this study will be stored securely in the School of Pharmacy at the University of East Anglia.

Long-term data for this research will be stored in a secure room on a password protected computer at the University of East Anglia (UEA) for 10 years and disposed of in accordance with UEA's data management protocol. All procedures for the handling, processing, storage and destruction of data are compliant with the Data Protection Act 2018.

How will we use information about you?

We will need to use information from you for this research project. This information will include your name and contact details. People will use this information to do the research or to check your records to make sure that the research is being done properly. We will keep all information about you safe and secure. Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

Will you let me know the results of the study?

Yes. We will send you a summary of the results of the study within 6 months of the study finishing.

What are your choices about how your information is used?

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have. To safeguard your rights, we will use the minimum personally-identifiable information possible.

We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

Where can you find out more about how your information is used?

You can find out more about how we use your information at:

- Contacting HRA at www.hra.nhs.uk/information-about-patients/
- Contacting UEA Data Protection Team dataprotection@uea.ac.uk

Will I be compensated for taking part?

No, but your workplace will be paid for your time, enabling you to take time out of your working day to be interviewed.

What happens next if I would like to participate?

If you would like to be interviewed, please email e.youssef@uea.ac.uk, stating that you would like to participate in an interview. From there, a suitable date, time will be arranged.

Who has reviewed the study?

This study has been reviewed and approved by a NHS Health Research Authority committee.

Who is sponsoring this study?

The University of East Anglia is the sponsor for this study based in the United Kingdom. We will be using information from you in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. The University of East Anglia will keep identifiable information about you for 10 years after the study has finished.

Further information and contact details

If you would like further information please contact the researched Essra Youssef, School of Pharmacy, UEA (e.youssef@uea.ac.uk /01603 591973)

What if you have concerns or complaint regarding the study?

If you have a complaint about how you were approached or how the interview was conducted please contact [redacted]

Appendix 15: Patient interview expression of interest form (Chapter 5).

PGx Clinical Pathway Development Study'

Patient Expression of Interest Form

Forename		
Surname		
Status		
Address and Postcode		
Email address **(Optional)**		
Date of Birth		Gender: ☐ Male ☐ Female ☐ Prefer not to say
Main telephone number		
Alternative telephone number		
Date of receiving myDNA test results		
Name and address of where you had the testing?		

How did you receive your myDNA test results? ☐ In person ☐ Via phone call

Who explained your myDNA test results? ☐ Doctor ☐ Nurse ☐ Pharmacist

Due to possible demand for this study, we cannot guarantee that you will be contacted for an interview.

Please return to Essra Youssef, School of Pharmacy, Faculty of Science, University of East Anglia, Norwich Research Park, Norwich, NR4 7TJ

Appendix 16: Interviewee consent form (Chapter 5).

Participant Consent Form Participant ID: ..... [to be completed by the researcher]

Study Title: **Pharmacogenetic (PGx) Clinical Pathway Development Study**

Researcher: Essra Youssef

	Please **initial** box
1. I confirm that I have been given a copy of the participant information sheet (Version 5.0 – dated 05.07.2022) for the above study, which I have read.	☐
2. I was given the opportunity to ask questions and discuss any concerns with the researcher.	☐
3. I understand that my participation is voluntary, and I can withdraw at any time without giving a reason - this will not affect my treatment or care in anyway.	☐
4. I understand that the interview will be audio-recorded so that what I will say can be accurately recorded. I understand that the interview will remain confidential and that I will not be identified in any way in any reports or publications. I agree to my anonymous quotations being used in the research report.	☐
5. I understand I will not have access to the audio recording or transcript of the interview.	☐
6. I understand that any transcripts will be kept on a password-protected computer in a locked cabinet and will only be accessible to relevant research staff.	☐
7. I agree to take part in the above study.	☐

Name of participant	Signature	Date	Signature

[The following to be completed by the researcher]

Name of person receiving consent form	Date	Signature

Please sign and send both copies to the researcher in the pre-paid envelope addressed to Essra Youssef, School of Pharmacy, Faculty of Science, University of East Anglia, Norwich Research Park, Norwich, NR4 7TJ. The researcher will return one copy to yourself with the £10 amazon gift voucher to the address provided. The other copy will be kept in a confidential research file.

Appendix 17 : Topic guide (Chapter 5).

Prior to interview starting	• Introduce self • We are looking to do a piece of research based on the thoughts and experiences of using the myDNA test. • You have been asked to take part in this interview because you had a myDNA test. • I would like to record the session so that I can focus on what you're saying without the need to make a lot of notes, though I may make a few notes if I need to. • It's important to remember when answering and discussing questions that there are no right or wrong answers, please just be yourself and speak as honestly as possible. • Please refrain from talking about specific patients, or aspects of your working life which may not be appropriate in this setting. • Anything that is said within the session will be treated confidentially, your responses will be stored in an anonymous format, and so your name will not appear in any report. • The session should take approximately 30 minutes. I will set a timer to make sure it won't take more than that. • Are there any questions before we begin?	Organise paperwork (consent form and information sheet) Two Dictaphones Spare batteries Notebook Paper and pens
Switch on recording device	• Can you please confirm your name for the recording?	

Main Questions	**Potential Probes**	**Notes**
How did you learn about the test/service?	- Who told you and what was there role? - Where were you told? - How much time did it take from being told about the service/test to you actually having the test? - Did you feel you were approached at the right time and right setting?	

Could you tell me about your experience of having the test?	- Why did you have the test? - Were the health professionals delivering the testing able to answer your questions? - What do you feel are the positives and negatives to testing?	
Could your doctor/pharmacist/nurse done anything different to improve your experience of having this test?	- Did you feel you were given clear enough information about the test? - Did you feel you had enough time to ask any questions at each stage?	
Could you share some of your experiences of receiving your test results?	- Did you understand your result? - Did you have any questions and were these answered well in your opinion? - Have you used your web portal since?	

Closing Statements
Is there anything you feel you wish to add? Thank you very much for your time. I will now end the recording.

Appendix 18: Patient thank you regret letter (Chapter 5).

Dear XXXXXXXX,

Hello my name is Essra. I am a researcher based at the University of East Anglia (UEA) and I am involved in a 3 year research project looking at a type of genetic testing known as ‘Pharmacogenetic’ that can be carried out to help doctors prescribe medicines that are more tailored.

I am writing to thank you for the interest you have down in joining the ‘PGx Clinical Pathway Development Study’. Unfortunately, due to the high amount of people who have also said they would like to be involved in this study, I am unable to include you in the study.

Once again thank you for your interest and if you have any questions, please don’t hesitate to get in touch either through phone/email or letter.

Best wishes,

Essra Youssef

Research Pharmacist I School of Pharmacy I Faculty of Science

University of East Anglia, Norwich Research Park, Norwich, NR4 7TJ

Tel: 01603 591996 I E-mail: E.Youssef@uea.ac.uk

Appendix 19: Patient instructions on how to register PGx test kit (Chapter 5)

INSTRUCTIONS (please read carefully)

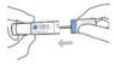
To ensure accurate results, please do not eat, drink or smoke 30 minutes prior to swabbing.

1. Peel open the foil pouch enclosed. Open the swab tube by pressing the upper part of the cap with your thumb. Remove the swab by holding the white cap.

Do not touch the swab head with your fingers as you risk sample contamination.

2. Insert the swab head between cheek and lower gums. Roll the swab for 30 seconds. Repeat this process on your other cheek.

3. Place the swab back into tube. Press firmly until you hear a click.



4. Using a pen, fill in your details on the barcoded sticker and adhere to the swab tube as directed.
The top part is for you to keep.

5. Visit **www.mydna.life/register** and register your DNA sample using the barcode number provided.

6. Put your swab tube back inside the pouch and fold to close.

7. Place pouch in the enclosed reply paid envelope and post it to us.

ALL DONE!
You will be notified once we have received your sample and your report(s) are ready.

IMPORTANT INFORMATION

Your nominated pharmacist is: Leo Boswell

Please ensure you register your swab online at www.myDNA.life/register

Unregistered swabs will not be processed.

Appendix 20: Actors brief (Chapter 5)

Patient brief

Jane Smith. 34 years old. Norwich

Jane was referred to Leo (pharmacist prescriber) from the GP as she had tried two antidepressants (citalopram and sertraline) with no help. She has been newly diagnosed with anxiety and depression 6 months ago. Citalopram made her nauseous and sertraline gave her nightmares.

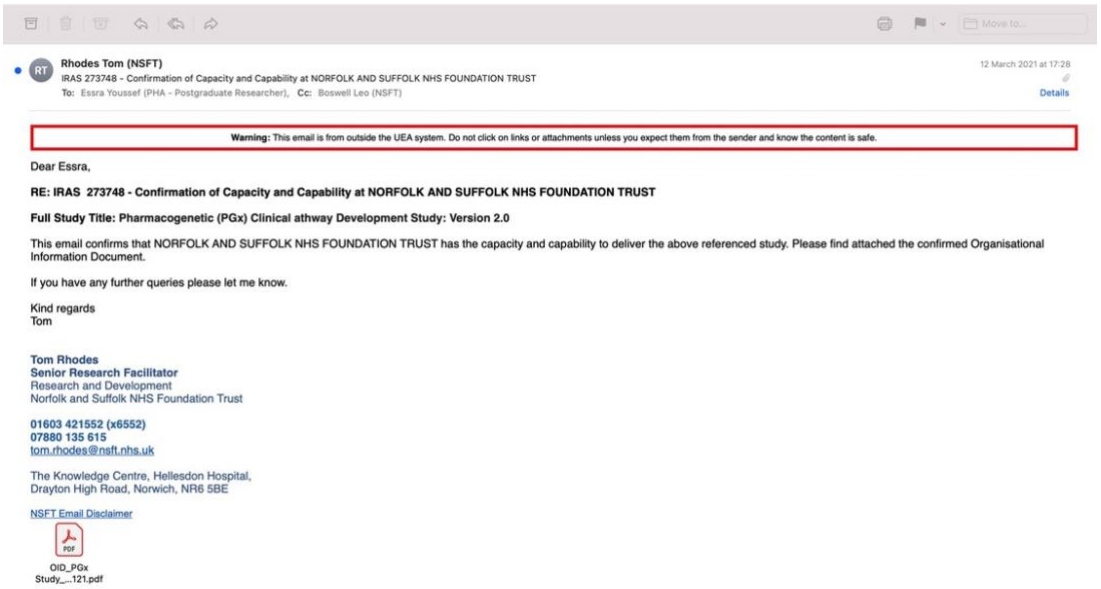
She saw Leo in person at the clinic. After reviewing her medicines, he explained that they could offer a genetic test to help look at how she processed medicines, and this might help pick a better medicine for her. She agreed as it sounded interesting, and she wanted a better treatment. At the same clinic visit, Leo gave her a testing kit and some information about the study.

When she got home, she followed the instructions and provided a saliva sample. She also completed the online registration and sent her sample in the post.

About three weeks later, Leo rang her and explained the results. Her results showed she didn't process citalopram and sertraline like everyone else. The levels in her blood are higher than normal which made her sick and gave her nightmares. Instead, Leo recommended a new drug- mirtazapine. She's just started it and she's hopeful it will work because its better for her body.

She thought the test was good, but it took too long to get the results. She thinks all patients should have this when their born and then the doctors can look up the results when they need to.

Appendix 21: Capability and Capacity Mental Health Trust (Chapter 5)



Rhodes Tom (NSFT)
IRAS 273748 - Confirmation of Capacity and Capability at NORFOLK AND SUFFOLK NHS FOUNDATION TRUST
To: Essra Youssef (PHA - Postgraduate Researcher), **Cc:** Boswell Leo (NSFT)

12 March 2021 at 17:28
Details

Warning: This email is from outside the UEA system. Do not click on links or attachments unless you expect them from the sender and know the content is safe.

Dear Essra,

RE: IRAS 273748 - Confirmation of Capacity and Capability at NORFOLK AND SUFFOLK NHS FOUNDATION TRUST

Full Study Title: Pharmacogenetic (PGx) Clinical athway Development Study: Version 2.0

This email confirms that NORFOLK AND SUFFOLK NHS FOUNDATION TRUST has the capacity and capability to deliver the above referenced study. Please find attached the confirmed Organisational Information Document.

If you have any further queries please let me know.

Kind regards
Tom

Tom Rhodes
Senior Research Facilitator
Research and Development
Norfolk and Suffolk NHS Foundation Trust

01603 421552 (x6552)
07880 135 615
tom.rhodes@nsft.nhs.uk

The Knowledge Centre, Hellesdon Hospital,
Drayton High Road, Norwich, NR6 5BE

OID_PGx Study_...121.pdf