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Exploring the potential impact of collaborative medicines optimisation involving pharmacogenomic testing and general practice pharmacists in primary care in Ireland

A thesis submitted to the University of Dublin, Trinity College for the degree of Doctor of Philosophy

By

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Declaration

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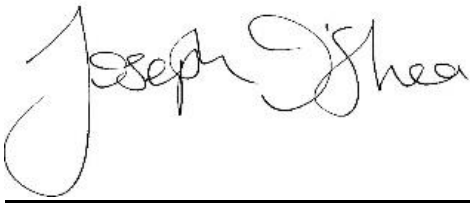

Joseph O'Shea

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“They say no plan survives first contact with implementation.

I’d have to agree.”

– Andy Weir, The Martian

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PS, look at the wall

Summary

Introduction

People are living longer, but not necessarily in better health. The ageing population coupled with the rise in chronic conditions has led to many older people being prescribed polypharmacy, which may not always be appropriate. Medicines optimisation, a patient-centred process, strives for the best clinical outcomes by ensuring the safe and effective use of medicines through medication reviews. However, this necessitates greater collaboration among healthcare professional to individualise care, monitor outcomes closely, review medications more frequently and support patients when needed. Current medical practice often applies the same dose to all individuals based on population studies, overlooking individual differences. Precision medicine, in contrast, seeks to customise pharmacotherapy to individual patients, acknowledging variability in drug response. The study of genetics has been widely applied in precision medicine, and one of the emerging applications is pharmacogenomic-informed pharmacotherapy, which tailors drug selection and dosing based on a patient's genetic profile.

Methods

A systematic review was conducted to determine the effectiveness of pharmacogenomic interventions in improving outcomes derived from consensus-based core outcome sets in adult patients with multimorbidity and prescribed polypharmacy in all healthcare settings to inform the implementation of pharmacogenomic-guided therapy in clinical practice. A cross-sectional questionnaire study was performed to identify the potential opportunities and challenges of implementing pharmacogenomic testing in Ireland based on the previously unexplored views of those with multimorbidity and polypharmacy, those with a single chronic disease, and those without existing medical conditions. A retrospective study was undertaken using data from the STOP-HF cohort (comprised of Irish patients over the age of 40, with one or more risk factors for developing heart failure) to investigate the potential impact of pharmacogenomic testing. Finally, a qualitative semi-structured interview study was caried out with stakeholders involved in a medicines optimisation service, developed as part of the project to integrate a pharmacist into general practice, to establish their views of the service and the incorporation of pharmacogenomics.

Results

The results of the systematic review indicated that once the scope extends beyond single drug-gene interactions, there is limited available evidence. Nevertheless, pharmacogenomic testing was shown to be an effective intervention for improving outcomes in this vulnerable patient cohort, reducing the incidence of adverse drug reactions, reducing healthcare utilisation and costs, and improving clinical decision-making. The questionnaire study provided a comprehensive account of the views of the Irish public regarding pharmacogenomic testing. It was shown that respondents with a chronic disease were more than twice as likely to value pharmacogenomic service availability than those without existing medical conditions. In the retrospective longitudinal study of patients with cardiovascular risk factors, multimorbidity, and polypharmacy, a high level of exposure to medications with potential for drug-gene interactions was observed. Statins accounted for the majority of these interactions; patients receiving a statin were genotyped for SLCO1B1 and ABCG2 no function alleles. A significant association between poor statin transporter function phenotype and progression of heart failure was found, highlighting an opportunity for routine genotyping to reduce the risk of heart failure. The qualitative interview study determined stakeholders' perceptions towards pharmacists working in general practice to provide a telepharmacy collaborative medicines optimisation service in Irish primary care. Barriers and facilitators to the service and considerations around the incorporation of pharmacogenomics into the service were identified. This study demonstrated the feasibility and acceptability of a general practice pharmacist working remotely.

Conclusions

The culmination of research presented in this thesis provides a comprehensive exploration of the impact pharmacogenomic interventions could have for patients with multimorbidity and prescribed polypharmacy in the context of medicines optimisation. Notably, prior to this research, no published studies had examined the implementation of pharmacogenomic testing in Ireland. Furthermore, the development of a telepharmacy collaborative medicines optimisation service involving a general practice pharmacist in primary care constituted a pioneering and substantial contribution to practice-based research. Rather than attempting to address all aspects of pharmacogenomic testing in a single research project, this thesis identifies opportunities for future research.

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Published manuscripts

1) **O'Shea J**, Ledwidge M, Gallagher J, *et al.* Pharmacogenetic interventions to improve outcomes in patients with multimorbidity or prescribed polypharmacy: a systematic review. 2022. *The Pharmacogenomics Journal*.
   doi: 10.1038/s41397-021-00260-6.
2) **O'Shea J**, Ryan C, Gallagher J, *et al.* Public perceptions of pharmacogenomic services in Ireland - Are people with chronic disease more likely to want service availability than those without? A questionnaire study. 2022. *Exploratory Research in Clinical and Social Pharm*acy.
   doi: 10.1016/j.rcsop.2022.100182.
3) Johnson L, Youssef E, **O'Shea J**, *et al.* Estimating the prevalence of potential and actionable drug-gene interactions in Irish primary care: A cross-sectional study. 2024. *British Journal of Clinical Pharmacology*.
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Manuscripts submitted, awaiting publication

1) **O'Shea J**, Ryan C, Gallagher J, *et al.* Collaborative medicines optimisation service involving a general practice pharmacist in Irish primary care (COMPASS): a SEIPS-based interview study. *British Journal of General Practice*.
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3) **O'Shea J**, Ryan C, Gallagher J, *et al.* Statin SLCO1B1 and ABCG2 genotypes and progression of heart failure: A retrospective longitudinal report from the St Vincent's Screening TO Prevent HF (STOP-HF) cohort. *European Journal of Heart Failure*.

Conference presentations

Published conference abstracts

1) **O'Shea J**, Gallagher J, Ryan C, *et al.* Statin SLCO1B1 and ABCG2 genotypes and progression of pre-heart failure: a report from the St. Vincent's screening to prevent heart failure (STOP-HF) trial. 2023. European Society of Cardiology 365.
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Conference presentations

1) **O'Shea J**, Ryan C, Gallagher J, *et al.* COllaborative Medicines oPtimisAtion Service involving a general practice pharmaciSt (COMPASS) in Irish primary care: a SEIPS based interview study.
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   Award: Best Poster Presentation Award
2) **O'Shea J**, Ledwidge M, Gallagher J, *et al.* Pharmacogenetic interventions to improve outcomes in patients with multimorbidity or prescribed polypharmacy: a systematic review.
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Abbreviations and acronyms

ACC	American College of Cardiology
ADE	Adverse drug event
ADME	Absorption, distribution, metabolism, or elimination
ADR	Adverse drug reaction
AHA	American Heart Association
BMI	Body mass index
BNP	B-type natriuretic peptide
CAD	Coronary artery disease
CDM	Chronic Disease Management
CDS	Clinical decision support
CI	Confidence interval
COMPASS	COllaborative Medicines oPtimisAtion Service involving a general practice pharmaciSt
COREQ	Consolidated Criteria for Reporting Qualitative Research
CP	Community pharmacist
CPIC	Clinical Pharmacogenetics Implementation Consortium
CR	Cristín Ryan
CRP	C-reactive protein
CVD	Cardiovascular disease
CYP	Cytochrome P450

DPS	Drugs Payment Scheme
DPWG	Dutch Pharmacogenetic Working Group
DTC	Direct-to-consumer
EMA	European Medicines Agency
ESC	European Society of Cardiology
FDA	The US Federal Drug Agency
GMS	General Medical Services
GP	General practitioner
GPP	General practice pharmacist
GPVC	General practitioner Visit Card
HCP	Healthcare professional
HF	Heart failure
hs-CRP	High-sensitivity C-reactive protein
HSE	Health Service Executive
JO'S	Joseph O'Shea
LAVI	Left atrial volume index
LDL-C	Low density lipoprotein cholesterol
LTI	Long Term Illness
LVD	Left ventricular dysfunction
LVDD	Left ventricular diastolic dysfunction

LVH	Left ventricular hypertrophy
LVSD	Left ventricular systolic dysfunction
LVEF	Left ventricular ejection fraction
LVMI	Left ventricular mass index
MACE	Major adverse cardiovascular event
MeSH	Medical Subject Headings
MI	Myocardial infarction
ML	Mark Ledwidge
MRP	Medication-related problem
NHS	National Health Service
NICE	National Institute For Health And Care Excellence
NNT	Number Needed to Treat
NP	Natriuretic peptide
OR	Odds ratio
PCNE	Pharmaceutical Care Network of Europe
PCRS	Primary Care Reimbursement Service
PharmGKB	The Pharmacogenomics Knowledge Base
PharmVar	The Pharmacogene Variation Consortium
PREPARE	Pre-Emptive Pharmacogenetic Testing for Preventing Adverse Drug Reactions
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis

PSI	Pharmaceutical Society of Ireland
RoB 2	Risk of Bias 2.0 tool
ROBINS-I	Risk of Bias in Non-Randomised Studies – of Interventions tool
SAMS	Statin-associated musculoskeletal symptoms
SEIPS	Systems Engineering Initiative for Patient Safety
SmPC	Summary of Product Characteristics
START	Screening Tool to Alert to Right Treatment
STOP-HF	The St. Vincent's Screening To Prevent Heart Failure programme
STOPP	Screening Tool of Older Persons' Prescriptions
TILDA	The Irish Longitudinal Study on Ageing
UK	United Kingdom
US	United States
WHO	World Health Organisation
WTP	Willingness to pay

Chapter 1

Introduction

1. Chapter 1: Introduction

1.1. The ageing population

It is widely acknowledged that the population is ageing worldwide. With declining birth rates and increasing life expectancy, the global population is undergoing a major demographic shift [1]. This increase in average life span and change in global age structure towards an ageing society is a major success for medical and public health systems. However, it also presents new challenges for public health policy to ensure that healthy life expectancy is increased rather than just life expectancy [2]. Over the coming years the largest rate of growth is expected in older adults, a population group commonly defined as those aged 65 years and over. By 2050, the number of older people worldwide is expected to increase two-fold to 1.5 billion [1]. In Ireland, this proportion is predicted to rise from approximately 720,000 (14.6%) to over one and a half million (26.6%), between 2020 and 2050 (see Figure 1.1) [1].

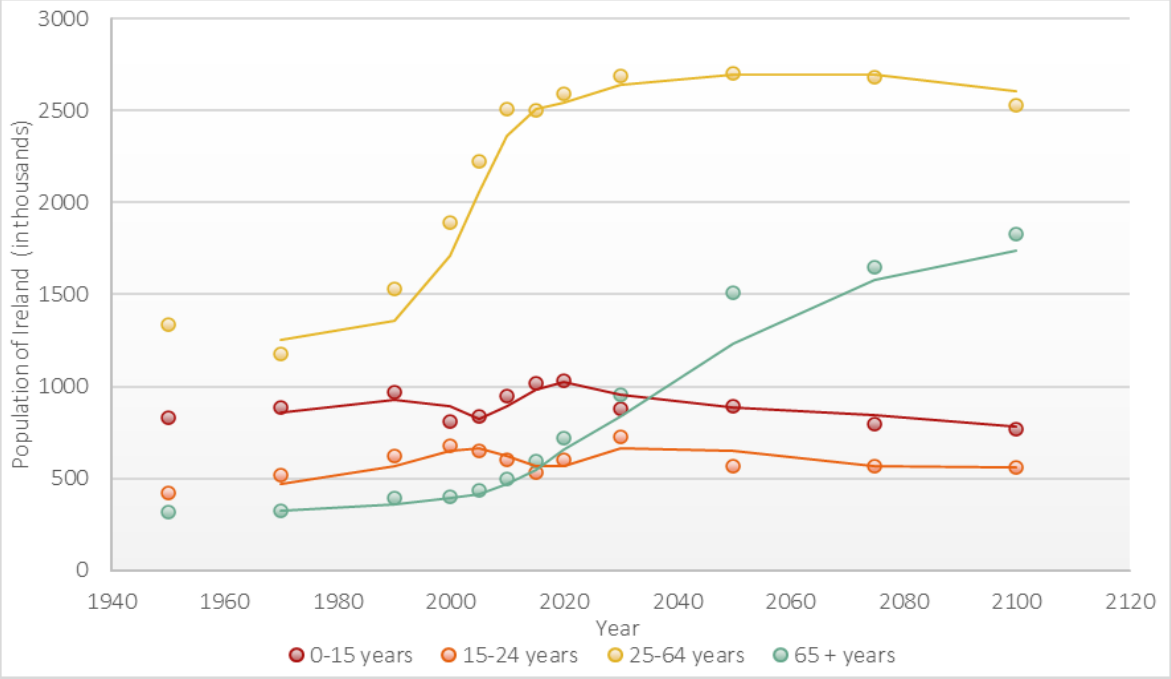

Figure 1.1. Ireland's projected population figures by age category from 1950 to 2100 (adapted from [1])

These demographic trends indicate the future challenges to healthcare delivery in Ireland. People may be living longer, but not necessarily in better health [3]. The once predominant health concern of acute infections as the major disease burden on society has been replaced by noncommunicable diseases [4]. Noncommunicable diseases, more commonly referred to

as chronic diseases or chronic conditions, tend to affect the individual for a long period and are the result of genetic, physiological, environmental, and behavioural factors [5]. Examples of the most common causes of death in older adults globally include coronary heart disease, stroke, chronic lower respiratory disease, and malignant neoplasms [6]. These types of conditions are described as chronic or long-term conditions, *i.e.*, those that can be controlled through pharmacological and non-pharmacological treatments, but a cure is currently unavailable [7].

A growing older population will require innovative policy approaches to enable healthier, happier and economically solvent extended life spans [8]. In Ireland, 65 year old males and females have a life expectancy of 15.8 and 19.4 years respectively [9], of which 11.3 and 12.5 years are expected to be healthy life years (years that a person aged 65 years is expected to live in a healthy condition) [10]. It should be noted that the level of pressure on any healthcare system attributable to advancing age will be highly dependent upon the state of health of persons in old age. Decline in health will add to the existing pressures on healthcare system resources, especially as the incidence of multimorbidity and accompanying polypharmacy (defined below) increases with the progressive improvement in life expectancy.

1.2. Multimorbidity

1.2.1. Definition of multimorbidity

Multimorbidity is commonly defined as the co-existence of two or more chronic conditions [11]; however, there is no agreement on the most appropriate definition [12]. A systematic review of multimorbidity definitions concluded that most include the occurrence of multiple diseases, predominantly with a cut-off of two or more conditions [13]. The term comorbidity has been used interchangeably to describe multimorbid patients; however, it is now accepted that comorbidity describes the presence of other conditions in addition to an index condition, with the latter generally deemed to be of greatest importance, as opposed to multimorbidity where any condition could be included [14, 15]. Multimorbidity is a more useful term that is used to describe patients who suffer from two or more long-term conditions as it does not place greater emphasis on any one condition [15]. This thesis uses the co-existence of two or more chronic conditions as the definition for multimorbidity.

1.2.2. Prevalence of multimorbidity

Although multimorbidity is seen in all age groups, evidence suggests multimorbidity is the norm rather than the exception in older adults in Ireland and is consistent with the notion that the additional life-years constitute an additional opportunity for acquiring other chronic conditions [4, 16-18]. With advancing age, people are at a greater risk of experiencing chronic conditions as the human body undergoes a number of physiological changes in all organ systems. For example, blood pressure increases, atherosclerosis develops, cardiac output decreases, lung function is impaired, creatinine clearance reduces, and blood glucose progressively elevates [19].

The prevalence of multimorbidity in Irish adults aged ≥50 years is estimated to be between 50-73% [20-22]. A recent systematic review by Chowdhury *et al.* demonstrated that 51% of the adult population above 60 years of age worldwide had multimorbidity, while the overall global prevalence was 37.2% [23]. Furthermore, multimorbidity was found to be more prevalent in women than men (39.4% versus 32.8%) [23]. An association was also found between multimorbidity and socio-economic status, demonstrating that people from low socio-economic areas are more likely to experience multimorbidity [23, 24].

1.2.3. Potential consequences of multimorbidity

The issue of multimorbidity is a common one and presents many challenges. With growing economic pressures, healthcare services will have to adapt to meet the complex care needs of older people with multimorbidity, whose healthcare requirements are more intricate than other patient groups [25]. In Ireland, the mean number of primary care consultations and hospital out-patient visits increase significantly with increasing numbers of chronic conditions [20]. Treatment of multimorbidity comprises 79% of medicines prescribed [26], 78% of general practitioner (GP) consultations [17], and 64% and 70% of outpatient and inpatient hospital admissions respectively [27]. Consequently, multimorbidity comprises a significant amount of the total healthcare costs for primary and secondary care among Irish patients aged ≥50 years [20].

In 2021, The Irish Longitudinal Study on Ageing (TILDA) explored the association between multimorbidity and out-of-pocket healthcare expenditure [28]. In this study of community-

dwelling adults aged 50 years and older in Ireland, differences in out-of-pocket healthcare expenditure were found between those with and without multimorbidity. The results show that having multimorbidity in Ireland increases an individual's likelihood of having out-of-pocket healthcare expenditure by 20%, and leads to higher financial burden, particularly for those in more socioeconomically disadvantaged groups. Individuals with multimorbidity spent more on average per annum (€806.8 for two conditions, €885.8 for three or more conditions) than individuals with no conditions (€580.3) [28]. Eligibility for free healthcare and heavily subsidised medicines greatly reduces these out-of-pocket healthcare costs.

Despite the widely reported risks associated with multimorbidity, there is currently a lack of evidence of effective interventions to manage multimorbidity appropriately [7]. Such risks include functional and physical decline; a higher rate of mortality, healthcare utilisation and costs, medication use and potentially inappropriate prescribing; and a decrease in quality of life [16, 17, 20, 29-34]. The pharmacological management of numerous co-existing chronic conditions is often complex, challenging the traditional approach taken to treat individual conditions separately [35]. Attending multiple healthcare professionals (HCPs) to treat multimorbidity often results in the prescribing of multiple medications, commonly termed polypharmacy.

1.3. Polypharmacy

1.3.1. Definition of polypharmacy

An inevitable consequence of multiple chronic conditions is treatment with multiple medications. Where multiple medicines are concomitantly prescribed, this is often referred to as polypharmacy [36]. Although the concept of polypharmacy was first discussed in the literature over 150 years ago, there is still no consensus on how best to operationalise the definition [37]. Most commonly, polypharmacy definitions include numerical thresholds such as being on at least four or five regular medications [36, 38]. However, as a new definition is yet to be agreed, the most common definition of 'concomitant ingestion of four or more medications' has been used throughout this thesis to denote polypharmacy. Rankin *et al.* used this definition in a Cochrane review which investigated the effectiveness of interventions to improve appropriate polypharmacy [36].

The concept of multiple medication use has taken on a distinctly negative tone in geriatric practice due to the inherent increased risk of adverse drug events (ADEs) [39, 40]. Given the increase in multimorbidity and the fact that clinical guidelines advocate for the prescribing of multiple medicines in the treatment and management of chronic conditions [41], the viewpoint that polypharmacy is always negative should be avoided. Polypharmacy is often clinically indicated and beneficial in specific conditions (*e.g.,* hypertension, diabetes mellitus) and patient populations (*e.g.,* patients with multimorbidity). It is therefore increasingly being recognised that polypharmacy can be entirely appropriate in treating older patients with multimorbidity and has been described as a 'necessary evil' [37]. As noted by Guthrie *et al.* [40], polypharmacy is "potentially problematic rather than always inappropriate".

Increasingly, the term 'appropriate polypharmacy' has been adopted, distinguishing between the use of many and too many medicines in light of the clinical context in which medications are prescribed to patients [42, 43]. Appropriate polypharmacy can be defined as 'prescribing for individuals with complex or multiple conditions where medicine use has been optimised and prescribing aligns with best evidence' [44]. In the World Health Organisation's (WHO) third global patient safety challenge titled Medication Without Harm [45], polypharmacy and specifically appropriate medication use is identified as a major priority [43, 46]. Thus, the indication of a medication and its potential for patient harm should be evaluated. Conversely, inappropriate prescribing occurs when medications are no longer indicated or effective, their existing or potential harms outweigh the benefits [47], and/or clinically indicated medicines are omitted [48].

1.3.2. Prevalence of polypharmacy

Although prevalence estimates vary across countries, polypharmacy in older people is recognised as a widespread global issue that poses risks of medication-related harm and safety risks to patients [36]. Several cross-sectional analyses have identified numerous different parameters associated with an increase in the prevalence of polypharmacy. Increasing age, female gender, a higher number of chronic conditions, lower wealth, physical inactivity, obesity, and poorer self-rated health are positively associated with the incidence of polypharmacy [40, 49-53].

In Ireland, several estimates of polypharmacy prevalence in older people have been published. Moriarty *et al.* showed that from 1997 to 2012, the prevalence of polypharmacy (≥ 5 medicines) in people ≥65 years increased from 17.8% to 60.4% [53]. These rates were twice as high as those shown by Richardson *et al.*, reporting polypharmacy in 31% in those aged 65-74 years, rising to 37% in those ≥75 years [54]. Tatum *et al.* showed polypharmacy was evident in 68.2% of adults aged 65-69 years and increased again to 82.6% for adults aged 75 years and over [55]. Moreover, these studies demonstrated polypharmacy is not just a burden of the older population, with a substantial number of people in the 45-64 years group also affected. In this age group, Moriarty *et al.* demonstrated an increased prevalence of polypharmacy from 8.3% to 30.2% over the study period [53]. Richardson *et al.* found 19% of the 50-64 year age group was experiencing polypharmacy [54], whilst Tatum *et al.* reported 38.6% of those aged 45-54 years had polypharmacy [55].

Similar findings have been reported in other European countries [49]. A recent cross-sectional analysis of data from the Survey of Health, Ageing and Retirement in Europe database, showed that polypharmacy is a highly prevalent condition across the older population with rates between 26.3-39.9% across 17 European countries [49]. The prevalence of polypharmacy increased as the age groups increased: 25.3% adults aged 65-74 years were prescribed polypharmacy, increasing to 36.4% between 75-84 years and 46.5% in adults ≥85 years [49].

1.3.3. Potential consequences of polypharmacy

Given the negative consequences associated with multimorbidity, it is no surprise that polypharmacy patients may experience various undesirable outcomes as a result of receiving multiple medications. These effects may present as increased risk of hospitalisations and falls, poorer functional status, and higher morbidity and mortality rates [52, 56-60]. Additionally, patients with polypharmacy often know too little about their medications and have difficulties with treatment compliance [61]. Polypharmacy is believed to cause unnecessary health expense for both patients and healthcare systems alike [60], and is associated with potentially inappropriate prescribing and a number of adverse clinical outcomes that may affect patient safety mediated through medication-related problems (MRPs) and prescribing cascades [34, 40, 60, 62, 63].

MRPs are circumstances during pharmacological treatment that potentially or actually interfere with optimal care outcomes [64], which can manifest as drug-related morbidity or mortality if no action is taken [65]. They are common among polypharmacy patients and can cause adverse effects (adverse drug reactions (ADRs) and ADEs), drug-drug interactions, medication non-adherence, and inappropriate and/or under-use of treatments [66]. An ADR is any undesirable effect of a medication beyond its anticipated therapeutic effects occurring during clinical use (Section 1.3.5) [67]. In contrast, an ADE is an untoward occurrence after exposure to a medication that is not necessarily caused by the medication [67]. To combat ADEs, patients may be prescribed inappropriate, unnecessary, or potentially hazardous medications; this is generally referred to as a prescribing cascade [68, 69].

Age-related physiological changes affect how the body responds to and handles medications (pharmacodynamics and pharmacokinetics respectively), complicating prescribing in older patients as they are more prone to ADEs [69, 70] (Table 1.1). As a result, finding the balance between aggressively treating diseases and avoiding MRPs in older patients is a challenge [42]. Ensuring that prescribing is evidence-based is imperative to achieving appropriate polypharmacy, particularly in older patients with multimorbidity [43]. Whilst a medication may be appropriate at the time of prescribing, the ongoing appropriateness must be ensured through regular medication reviews (Section 1.5).

Table 1.1. Age-related physiological changes pertaining to pharmacokinetic and pharmacodynamic function (adapted from [69, 70])

Pharmacokinetic changes	
Absorption	Decreased acidity and function of mucosal cells in the stomach ▪ Potentially affects absorption of some drugs that require an acidic environment Altered motility of the gastrointestinal tract ▪ May negatively affect the absorption of oral medications, but the effects are proposed to be minimal due to the large surface area of the gastrointestinal tract
Distribution	Reduction in total body water ▪ Results in a smaller distribution volume and thus a higher and potentially toxic concentration of some drugs Increase in the body fat percentage ▪ May prolong the effects of lipophilic drugs while prolonging the elimination half-life Reduction in serum albumin ▪ Results in less drug binding to serum proteins and more drug circulating in the serum with increasing risk of toxicity
Metabolism	Hepatic blood flow and liver mass decreases ▪ Results in decreased first pass metabolism and so more drug is available in the bloodstream
Elimination	Renal function decreases ▪ Results in prolonged half-life, and higher concentrations, of drugs or metabolites
Pharmacodynamic changes	
Sensitivity	Physiological changes to the organ systems of an older person are generally considered to increase sensitivity to drugs ▪ Therefore, reduced doses are generally recommended when prescribing medications to this group

1.3.4. Determinants of drug response

Drug response is highly variable between individuals, resulting in 40-70% of patients exhibiting a lack of efficacy or ADRs from pharmacotherapy [71, 72]. Inconveniently, drug response is difficult to predict since it is affected by multiple determinants (Table 1.2) [73-76]. Two conceptual pathways describe an organism's overall response to drug exposure.

Firstly, there is pharmacokinetic variability in the processes (absorption, distribution, metabolism, or elimination (ADME)) modulating delivery of drug and active metabolites to and removal from their site(s) of action [76]. This variability explains why different patients require different doses to achieve the same systemic exposure. The sources of pharmacokinetic variability, especially related to a person's phenotype and genotype, are usually well characterised, and their impact is addressed in prescribing information [74]. The impact of phenotype is extensively studied for most drugs, such as age, presence of food, organ failure, and concomitant medication [74].

Secondly, there is pharmacodynamic variability in the relationship between systemic exposure and effect. This variability describes why patients respond differently to the same exposure and need different exposures to achieve the same effect. In contrast to pharmacokinetic variability, pharmacodynamic variability, which often accounts for the majority of response variability [77], is much less well understood [74]. As a result, identifying the true causes of observed differences in drug response and the correlations among them can be challenging [73]. To further complicate prediction, these factors may affect one another, and their interactions may vary across drugs. With advances in technology, DNA testing to help predict drug response is becoming more tenable (Section 1.6) [78].

Table 1.2. Sources of variability in drug response (adapted from [74])

Pharmacokinetic variability			
Subject phenotype	Weight Body surface area Microbiome	Age Organ function	Ethnicity Gender
Subject genotype	Polymorphisms in metabolising enzymes or transporters		
Disease phenotype	Expression levels of drug target	Disease response or progression over time	Indirect treatment effects (*e.g.,* derepressing CYP450s)
Lifestyle and environment	Concomitant medications	Diet	Smoking
Other	Adherence	Drug formulation and route of administration	Dosing regimen
Pharmacodynamic variability			
Subject genotype	Polymorphisms in drug target or downstream pathway Off-target polymorphisms indicating risk of adverse effects		
Disease phenotype	Heterogeneity of disease mechanisms		
Disease genotype	Driver mutations of disease heterogeneity		

1.3.5. Benefit and burden of pharmacotherapy

In a historical context, innovations in pharmacotherapy have been revolutionary in increasing life expectancy and improving quality of life [79]. However, while drug treatment is often successful, the presentation of ADRs and the lack of efficacy as a result of unsuccessful or inappropriate pharmacotherapy is a significant burden for individual patients and society as a whole. ADRs are a significant cause of excess morbidity and, in some cases, mortality. ADRs also lead to patient dissatisfaction with their care and have been shown to be a risk factor for future non-compliance with medications [80]. Additionally, ADRs can mimic disease leading to potentially inappropriate investigations and treatments (*i.e.,* prescribing cascade) [67].

It has been largely observed that older adults are particularly prone to develop such reactions and experience hospitalisation as a result; among the main reasons would be age-related physiological changes, the presence of multimorbidity, and polypharmacy. Oscanoa *et al.* suggest approximately one in ten older adult (> 60 years) hospital admissions were attributable to ADRs and possibly preventable in most cases [81]. Kongkaew *et al.* demonstrated a higher rate of hospitalisation in older patients (> 60 years) as compared to those aged 17-60 years; median ADR prevalence rate 10.7% and 6.3% respectively [82].

ADRs are a preventable cause of significant economic burden. The Irish National Adverse Events Study quantified the prevalence, nature, and cost of adverse events in Irish hospitals [83]. Of the 3,177 admissions reviewed (1,574 in 2009 and 1,603 in 2015), 12.2% of all hospital admissions in 2009 involved an adverse incident, increasing to 14% in 2015 [83]. With 390,000 hospital admissions in 2015, this would extrapolate to 54,000 admissions being associated with one or more adverse events [83]. The resulting economic burden has been estimated to be €4,700 per adverse event for the hospital stay alone (median stay of 5.6 days), which when extrapolated nationally would equate to an annual cost of hospital-based adverse events for adult inpatients of €190 million for 2015 [83].

In parallel, lack of efficacy also results in a significant burden. However, data quantifying patient and societal burden is scarce. Nevertheless, one can conclude its magnitude by inspecting the number needed to treat (NNT) which offers a measurement of the impact of a medication by estimating the number of patients that need to be treated to prevent one additional negative outcome [84]. NNTs lower than five are rare and are more commonly above 10, implying that the large majority of patients will not benefit from drug treatment and may experience harm from untreated disease [84]. Ineffective drug treatment is a major cause of squandered healthcare expenditure; in the United States (US) alone, it has been estimated that at least a third of the money that is spent on prescription medications is wasted, amounting to more than $100 billion a year [85].

1.4. Healthcare in Ireland

1.4.1. Healthcare system in Ireland

Ireland has a dual healthcare system, consisting of both private and public healthcare options in both primary and secondary care [86]. Responsibility for policy and strategy rests with the Department of Health while the Health Service Executive (HSE) regulates the government funded health services [87]. The public healthcare system in Ireland is primarily government funded with general taxation forming 77% of the funding. Non-government expenditure is financed by voluntary health contributions, *i.e.,* private health insurance (12%) and out-of-pocket payments (11%) [88]. Out of every €100 spent on healthcare in 2021, €37 was spent in hospitals, €21 in out-patient healthcare providers (mainly GPs and dentists), €17 on long-term residential facilities (nursing homes and residential disability services), and €11 in retailers of medical goods (mainly pharmacies) [88].

All residents are technically eligible for public healthcare; however, there are variations in cost, coverage, and access depending on one's income, geographic location, and length of time it takes to receive care [89]. The Irish health service is hospital-oriented with most of the public expenditure and public servants in the acute hospitals, while primary care receives less funding and comprises mainly private contractors. In addition, this two-tier healthcare system gives preferential access to hospital care to those who have private health insurance; people who can pay privately or have private health insurance receive diagnoses and treatments quicker in hospitals because they can afford the monthly premiums [89, 90]. About 47% of the population have private health insurance but it contributes only about 12% of all health spending [88, 91]. Those who cannot afford private health insurance must often face long waiting lists [92]. Details of the complicated nature of coverage in the Irish healthcare system are explained in Figure 1.2 and Figure 1.3.

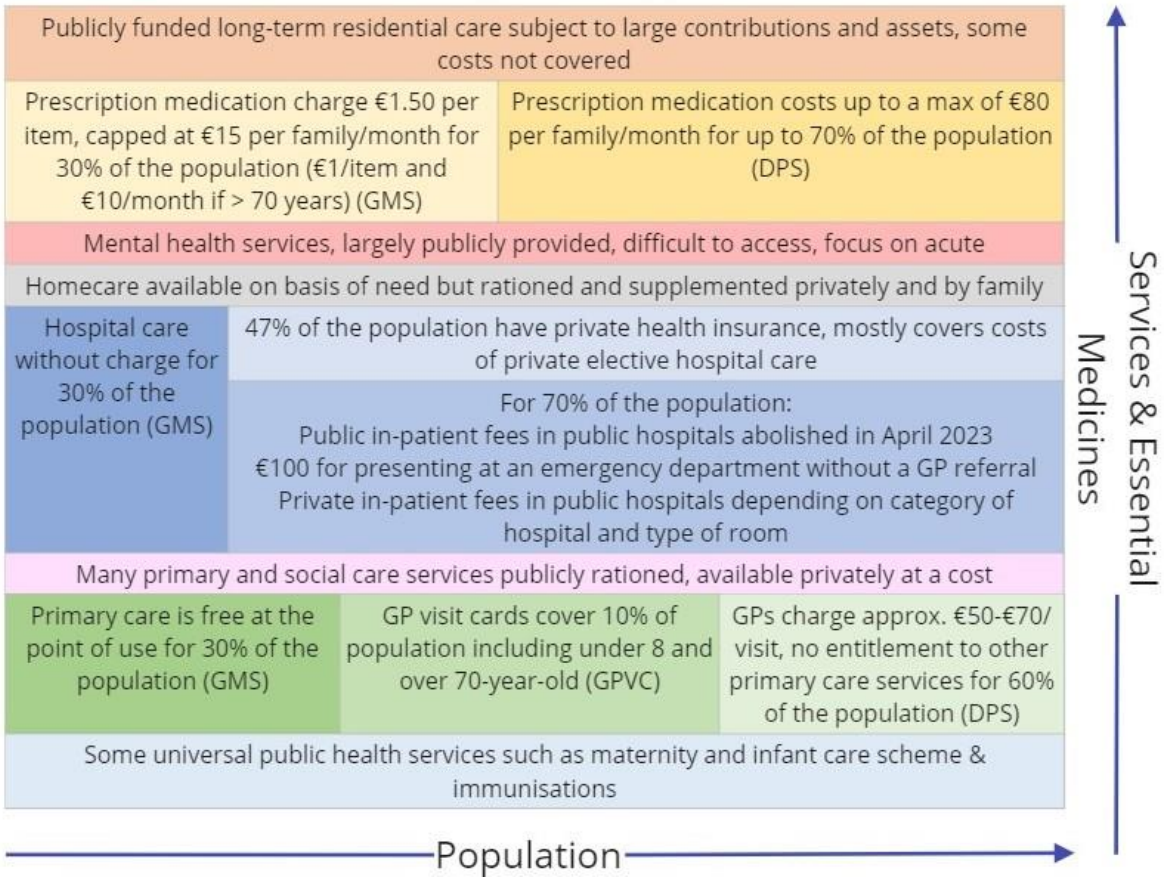

Figure 1.2. Coverage for care in Ireland, 2023

GMS General Medical Services, *GPVC* GP visit card, *DPS* Drugs Payment Scheme, *LTI* Long Term Illness.

Primary care services, such as general practice, pharmacy, and dentistry, have a contract with the HSE to provide public services but may also provide private services. In both primary and hospital settings, publicly and privately financed care is often administered by the same staff using the same facilities [90]. This has led to public healthcare resources for services provided by the HSE often being utilised for patients paying privately and as such, public patients may have to wait longer for a specific service [86]. Unusually in a high income country and European context, Ireland is the only Western European country that does not offer universal coverage of primary care [93]. There has been consensus among all groups in society that there should be universal health coverage and that the service should be focused on prevention rather than treatment [86]. In 2017, a policy called Sláintecare was agreed, detailing a ten-year plan for health reform aiming to establish a universal, single-tier health service and reorientate the health system towards integrated primary care [94-96] (Figure 1.4).

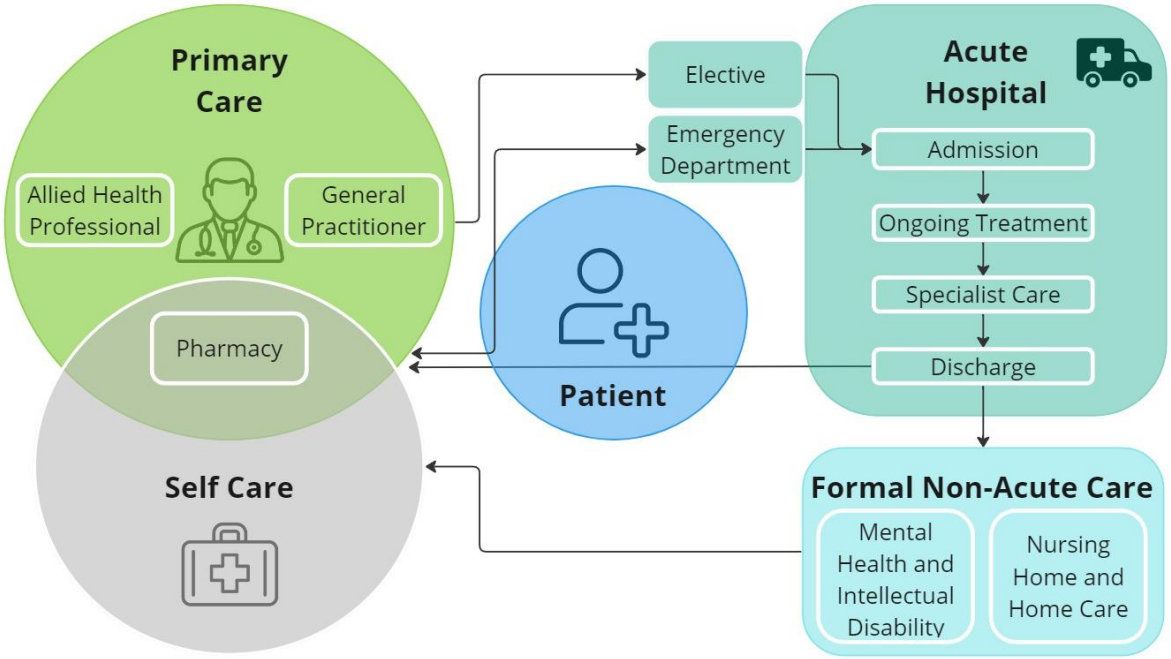

Figure 1.3. Outline of patient care journey (adapted from [97])

1.4.2. Healthcare schemes in Ireland

Various government healthcare schemes exist under which healthcare is provided mainly free-of-charge with some small co-payments [98]. The HSE Primary Care Reimbursement Service (PCRS) is responsible for making payments to HCPs, like GPs and pharmacists, for free or reduced-cost services they provide to the public across a range of primary care schemes [98]. During 2022, PCRS payments and reimbursements amounted to approximately €3,813.62 million under the following schemes: General Medical Services (GMS); Drugs Payment Scheme (DPS); Long Term Illness (LTI); Dental Treatment Services Scheme; European Economic Area; High Tech Arrangements; Primary Childhood Immunisation; Health (Amendment) Act 1996; Opioid Substitution Treatment Scheme; and Health Service Executive Community Ophthalmic Services Scheme [98]. The PCRS notes the following number of eligible persons per scheme in 2022: GMS 1,568,379, GP visit card (GPVC) 535,741, DPS 1,654,375, and LTI 332,967 [99], from a population of 5,149,319 people based on figures from the Central Statistics Office in 2022 [100].

Entitlement to healthcare is subject to a complex system of eligibility categories. Full eligibility is granted to patients primarily on an income basis under the GMS scheme and with some (ill-defined) discretion to award cards where the absence of a card may cause undue hardship [98]. There are separate eligibility criteria for the GMS scheme depending on the patient's age and living situation [101]. Patients who are granted full eligibility are given a GMS card which entitles them to free GP services, public hospital services, dental, optical, and aural services, maternity and infant care services, and community care and social services [98]. In addition, prescription item fees are subsidised; €1.50/item dispensed to a maximum €15/month reduced to €1/item and a maximum €10/month for people ≥70 years [98].

About a third (30%) of the population have medical cards under the GMS scheme [99]. This costs the HSE an average payment to pharmacies of €750.51 per person for prescription medications [98]. A small proportion of those above the income threshold for a medical card are entitled to a GPVC which provides free GP visits only [98]. The same eligibility criteria exist for GPVC as GMS cards except the income thresholds for a GPVC are higher than those for a GMS card. In August 2023, GPVCs were extended to all children under the age of 8, as well as those ≥70 years. The remainder of the population (approximately 60%) pay the full cost associated with GP care but are entitled to subsidised public hospital care as of April 2023 [102].

The rest of the population (approximately 70%) have to pay between €50-€70 for each GP visit. Patients without a GMS card may apply for a DPS card to receive financial protection for prescription medications. With a DPS card, a patient pays up to €80 a month for prescription medications after which the cost is covered by the HSE (approximately 30% of the population have a DPS card, costing the HSE on average €311.47 per person) [86, 98, 99]. For patients that do not exceed €80/month, they are simply under a private scheme. The LTI scheme is also available, which provides the necessary medicines and/or appliances for a schedule of 16 illnesses free-of-charge irrespective of income (*e.g.,* diabetes and epilepsy) [98]. Approximately 6% of the population have an LTI card, costing the HSE on average €1,497.49 per person [98].

1.4.3. Primary care in Ireland

As health systems heave under growing populations and changing demographic profiles, the impetus to innovate and deliver a more efficient and accessible primary health care service has occupied the minds of governments and healthcare planners [95, 103]. A strong primary care system is considered the cornerstone in health systems for delivering effective, safe, and patient-centred care [104]. Research constantly indicates robust association between primary care and lower costs, better utilisation patterns, and reduced mortality [105, 106]. In primary care, the policies and operation of the public health service are determined at a national level and then administered through regional offices.

General practitioners

General practice plays a central role in the delivery of primary care services [107]. As the first point of contact for most individuals' interactions with the health service, the role of the GP is crucial in providing professional quality care [103, 108]. General practice is fundamental to delivering timely, high-quality, accessible healthcare. International evidence shows that healthcare systems with strong primary care have better, more equitable population health outcomes and are cost effective [105]. General practices range from solo practitioners to large primary care centres, with teams of over twenty staff with a practice manager, administrative staff, general practice nurses and GPs [109].

In Ireland, the majority of GPs are self-employed private practitioners. Due to a lack of a central register for GPs and the nature of practice in Ireland with GPs operating independently, information about both GP numbers and the volume of general practice consultations is difficult to ascertain [107, 110]. The Irish College of General Practitioners, the professional body for GPs in Ireland, estimates that 4,187 GPs are actively practising in Ireland [109]. However, general practice is under serious strain [109]. As the population grows, the demand for healthcare grows in tandem [109]. In the next ten years, the demand for primary care is forecast to rise by 46% [111]. In 2020, it was estimated that GPs undertake an average of 29 consultations per day or over 21 million consultations per year [110]. In 2018, the Organisation for Economic Co-operation and Development reported that Ireland has one of the lowest levels of doctors per capita in Europe, at 2.9 per 1,000 citizens. With 24% of these doctors being GPs, this equates to an average number 0.69 GPs per 1,000

population [112]. There are not enough GPs to meet the current or future needs of our expanding and ageing population with highly complex care needs [109]. Furthermore, along with the global demographic, the GP population is also ageing, with 14% of practising GPs now ≥65 years [110, 113]. To meet demand, a 37% increase in the primary care workforce is required [111].

General practices are under significant pressure [109]. The normal GP working day is 10 hours on average, with GPs spending an average 13.7 minutes per consultation. Two hours of clinical consultations generates a further hour of administrative work [110]. GPs are working longer days, exacerbating workload pressures, fuelling burnout and impairing recruitment, worsening the GP workforce deficit in Ireland [109]. Compared to the United Kingdom (UK) and other European countries, more Irish GPs experience emotional exhaustion, a contributing factor to burnout [114]. One solution proposed is the integration of pharmacists into general practice (Section 1.4.4) [109].

Pharmacists practising in the community pharmacy setting

In order to operate in Ireland, community pharmacies register as a retail pharmacy business with the Pharmaceutical Society of Ireland (PSI). The PSI, as the regulator of 4,785 pharmacists practising in the community pharmacy setting and 1,982 community pharmacies in 2022 [115], is responsible for the health, safety and wellbeing of patients and the public. In support of lifelong learning and development, the PSI established a core competency framework for pharmacists, detailing the professional role of a pharmacist. Patient-centred care is fundamental to this role [116] (Table 1.3 and Section 1.5.2). The role of the pharmacist has grown significantly in recent decades due to evolving patient and economic needs, and significant progressions and changes in medicines, technology and regulation [97].

The conventional activities of the profession primarily focused on the dispensing and supply of medicines, while interaction with other HCPs was somewhat limited. Nowadays, pharmacists are also responsible for ensuring the rational and cost-effective use of medicines, promoting healthy living, delivering public health initiatives, and improving clinical outcomes by actively engaging in direct patient care and collaborating with many healthcare disciplines. Pharmacists are experts in medications and have the knowledge to reduce prescribing errors and optimise patient's medication-related outcomes [103].

Table 1.3. Professional role of the pharmacist in Ireland (adapted from [116])

Domain	Competency	
1. Personal	1.1	Demonstrates leadership
	1.2	Confidently makes sound decisions and solves problems
	1.3	Establishes and maintains collaborative working relationships
	1.4	Communicates effectively
2. Professional	2.1	Applies a 'person-centred' approach
	2.2	Practises legally and ethically
	2.3	Commits to lifelong learning and development
	2.4	Adapts to change and innovation
	2.5	Commits to evidence-based practice
3. Organisation and management skills	3.1	Manages self
	3.2	Manages within the workplace
	3.3	Manages resources and finance
	3.4	Contributes to continuous quality improvement and risk management
4. Pharmacy care	4.1	Manufactures and compounds medicines
	4.2	Manages the medicines supply chain
	4.3	Dispenses, supplies, and administers medicines
	4.4	Provides patient consultations and counselling
	4.5	Reviews and manages medicines
	4.6	Leads for safety
	4.7	Provides medicines information and education
5. Public health	5.1	Participates in population health initiatives
	5.2	Engages in health promotion activities

In their 2016 report on future pharmacy practice in Ireland, the PSI emphasise the radical changes the profession will face as it moves toward providing services and playing a greater role in health promotion and disease prevention to meet the population's health needs [97]. With this expanding scope of practice, pharmacists are being recognised as key stakeholders in providing individualised patient care. The future trajectory of the profession looks to enhance this activity through collaborative, multidisciplinary practice and independent pharmacist prescribing to optimise medicines management in partnership with patients [97].

As the vast majority of prescriptions are either initiated or repeated in general practice, primary care is the gateway to safe and high-quality pharmaceutical care. Pharmacists, who are trained as 'medication experts', should take the lead in supporting the safe and effective use of medicines. However, several factors impede community pharmacists (CPs) taking on such a role. Due to the time and workload demand of facilitating timely dispensing of

medications, CPs have limited time to spend on pharmacy services such as performing clinical medication reviews [117]. The reimbursement of pharmacy services is another major hurdle [86]. Limited access to patient medical records further restricts CPs' ability to optimally contribute to the quality of pharmaceutical care.

While the role of the pharmacist has undergone a paradigm shift over the years from the compounding and dispensing of medicines towards the provision of patient-centred pharmaceutical care [117], further utilisation of their skillset is required to meet the rising demand for healthcare delivery in primary care. Combining clinical skills with medication knowledge offers opportunities for pharmacists to take integral responsibility for the pharmaceutical care provided in primary care [118]. This could enable pharmacists to contribute significantly to managing workloads in general practice and hence demonstrate the pharmacy profession as a beneficial addition to the skill-mix in general practice [118].

1.4.4. Collaborative primary care

As age, morbidity and number of medications rise, so too do all types of consultations in general practice. The rise in general practice healthcare utilisation has not been matched by a corresponding growth in the workforce capacity, with GPs concerned about both patient and doctor safety in this context [119]. High workload and job stress are associated with lower practice performance and more negative patient experiences [120]. This is a significant problem with the potential to cause harm to patients and GPs. Several frameworks and strategies have been introduced to try to ameliorate healthcare in Ireland. Sláintecare is one such healthcare reform policy adopted by the government with eight fundamental principles (Figure 1.4). Included is the implementation of integrated care programmes focused on long-term conditions and older people to provide appropriate and effective primary care [95, 96].

General practice may be at a crossroads regarding a sustainable model of care. Enhanced HCP collaboration is required to individualise care, monitor outcomes more carefully, review medicines more frequently and support patients when needed. To alleviate pressures that GPs face and provide a multi-skilled task force, pharmacists have been integrated into practice teams in several health systems internationally. In 2016, the National Health Service (NHS) in England ran a successful national pilot scheme of general practice pharmacists (GPPs). With more than 8,500 pharmacists now working in general practice as of July 2023,

they have a vital role in patient care [121]. General practices with a higher proportion of older adults more likely to have complex care needs and be at risk of inappropriate polypharmacy tend to integrate greater numbers of pharmacists [122].

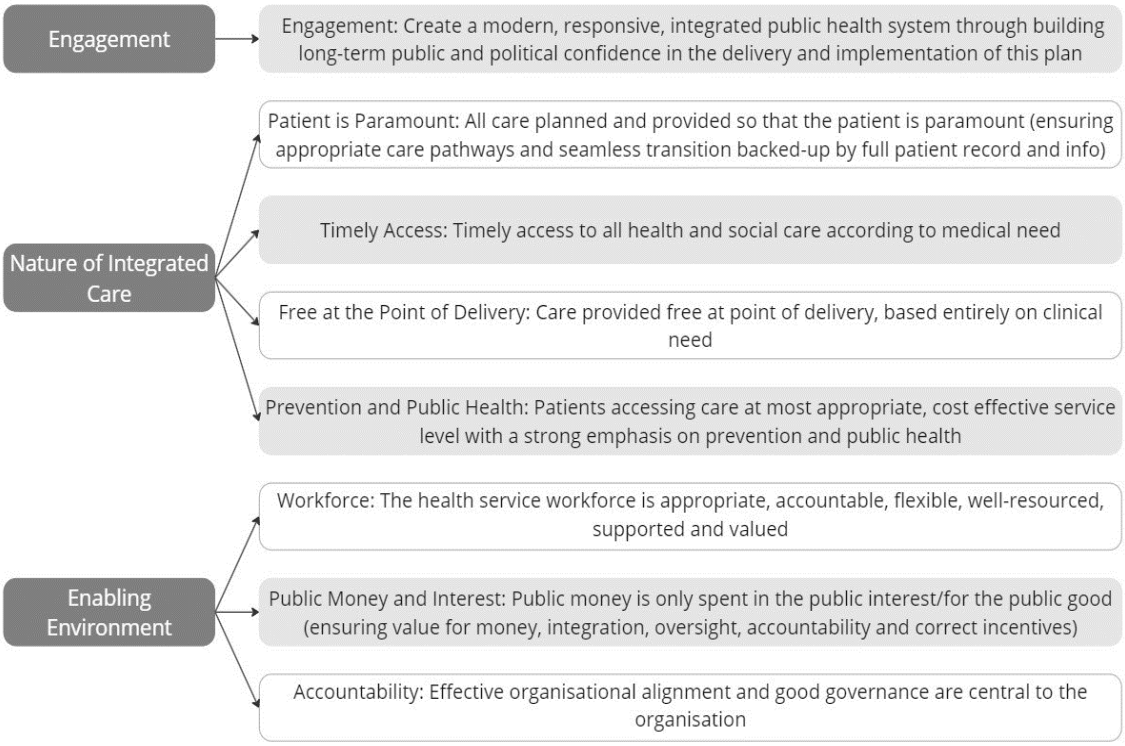

Figure 1.4. The eight fundamental principles of Sláintecare (adapted from [96])

Pharmacists have a range of responsibilities within practices, from providing clinical services to performing administrative duties. Clinical services that pharmacists provide include operating minor ailment clinics, face-to-face polypharmacy medication reviews, managing and prescribing for long-term conditions and addressing medication adherence [123]. The role of a pharmacist also includes providing education, dealing with hospital discharge letters, detecting and managing ADRs, overseeing audits and being a point of contract for medicine-related enquiries [124]. By taking on routine tasks, pharmacists are increasing the capacity of general practices, thereby increasing patient access, reducing prescribing errors and increasing strategic prescribing.

The impact of pharmacists in general practice has been extensively documented. Existing literature identifies the benefits of GPPs, with GPs valuing the medication expertise provided by pharmacists [125]. There is also agreement that pharmacists relieve workload pressures in general practice [126]. A systematic review further revealed a reduction in MRPs and improvements in appropriate medicines use and patient clinical outcomes, most notably in cardiovascular disease (CVD) and diabetes [127]. Moreover, observations have seen an additional benefit of cost-effectiveness and reductions in medication-related hospitalisations due to pharmacist interventions [128-130].

The model of GPPs may provide advantages over a community pharmacy service; for example co-location, access to medical records to inform appropriateness of recommendations, the potential for communication and discussion of the pharmacist's recommendations, and reduced fragmentation of care [131-134]. The GPP will not be distracted by dispensing, logistics, human resource management and other managerial tasks, enabling the GPP to focus on improving patients' pharmacotherapy. Finally, an inclusion of independent GPP prescribers can release an average five hours of direct GP time per week, adding further value to the multidisciplinary team [135]. Consequently, pharmacists with prescribing qualifications have a positive impact on alleviating general practice pressure. Studies integrating GPPs are beginning to emerge in Irish primary care [136, 137].

1.5. Medicines optimisation

1.5.1. Definition of medicines optimisation

Medicines optimisation has been variously defined by the National Institute for Health and Care Excellence (NICE), Royal Pharmaceutical Society and NHS England as a patient-centred process, aimed at ensuring the best clinical outcomes for patients through safe and effective use of medicines [138-141]. It can be described as a process, approach or a concept that incorporates many aspects of improving medication use and is fundamental to addressing the challenges posed by multimorbidity and polypharmacy. While it is clinician-driven, shared decision-making is essential, seeking to use the best available evidence to guide decisions about the care of the individual patient in line with their preferences [140]. As such, it may require compromise between the HCP's goals regarding medication and the goals and preferences of the patient [139].

Medicines optimisation differs from medicines management in a number of ways but most importantly it focuses on improved outcomes through medication reviews (defined below) and patient-centredness rather than systems and processes [139]. Medicines optimisation is the responsibility of all clinical professionals involved in improving the health of patients through medicines. It involves identifying patients at risk of preventable MRPs; understanding the evidence for the effectiveness, risks, and benefits of prescribing and deprescribing medicines; and recognising opportunities for lifestyle changes and nonmedical therapies to reduce the need for medicines [138, 142]. It can occur at any point along the patient care pathway, such as during prescription ordering and delivery, prescribing, dispensing, administration, medication review, provision of advice and counselling [139].

The Royal Pharmaceutical Society suggest four guiding principles for medicines optimisation: (i) aim to understand the patient's experience; (ii) evidence-based choice of medicines; (iii) ensure medicines use is as safe as possible; and (iv) make medicines optimisation part of routine practice [138]. This guidance goes on to describe goals to improve the use of medicines, which have been concisely described by NHS England as follows: improve their outcomes; take their medicines correctly; avoid taking unnecessary medicines; reduce wastage of medicines; and improve medicines safety [141].

1.5.2. Patient-centred care

The risks and benefits of treatments, as well as patient preferences, should be carefully taken into consideration when making decisions about treatments. Efforts to optimise multimorbidity and polypharmacy should adopt a patient-centred approach [143-146]. The Institute of Medicine defines patient-centred care as [147]: "Providing care that is respectful of, and responsive to, individual patient preferences, needs and values, and ensuring that patient values guide all clinical decisions." There is active collaboration and shared decision-making between patients and HCPs to design and manage a customised and comprehensive care plan [148]. As such, the patient-centred nature of medicines optimisation is apparent.

Clinical guidelines "systematically bring together evidence regarding a single condition or group of related conditions, and provide recommendations for patient management based on the evidence where it exists and consensus where it does not" [35]. Clinical guidelines help to standardise health practices and play an important role in improving healthcare for people with long-term conditions [35]. However, most guidelines only focus on a single condition and are therefore not always reflective of the population with the condition. In people with multimorbidity, current guideline recommendations rapidly cumulate to drive polypharmacy, without providing guidance on how best to prioritise recommendations [35]. Such prioritisation requires the exercise of clinical judgement and meaningful engagement with patient preferences.

The NICE guideline on multimorbidity management recognises the limitations of single-disease guidelines (generally drawn from people without multimorbidity and taking comparatively fewer medications). Consequently, NICE recommend tailoring the approach to caring for patients with multimorbidity and promoting shared decision-making with patients [41]. The WHO emphasised the importance of refining healthcare systems to enable safer primary care for those with multimorbidity; through personalisation of treatments, and by combining best available evidence with clinical knowledge and judgement [143]. The WHO advises that patient care needs to be proactive and anticipatory, taking a life cycle approach and including preventive care for those at risk of developing multiple conditions [143].

1.5.3. Medication review

As stated above in Section 1.4.1, the healthcare system in Ireland is not conjoined which can make medicines optimisation difficult for HCPs. Encompassed within medicines optimisation, medication reviews are crucial to promote patient-centred care and safe and rational use of medicines. According to the Pharmaceutical Care Network of Europe (PCNE), a medication review is defined as a structured evaluation of a patient's medicines with the aim of optimising medicines use and improving health outcomes. This entails detecting MRPs and recommending interventions [149]. The PCNE classification of medication reviews considers the type and source of available information, with the most advanced form of medication review supported by medication history, patient interview, and clinical data [149].

Medication review is an umbrella term encompassing a number of interventions with an overall aim to improve the quality, safety and appropriate use of medicines [150]. The three types of review described by Medicines Partnership have become widely cited: prescription review, compliance and concordance review, and clinical medication review (Table 1.4). Medication review is a diagnostic intervention which aims to identify problems for action by the HCP, patient, or both and can also be regarded as an educational intervention to support patient knowledge and adherence [150].

Medication reviews can be conducted by any HCP with the relevant knowledge of medications, including public nurses, GPs, and pharmacists. Medication reviews can range from an opportunistic unstructured review to a more in-depth review involving discussions with patients, which have a more patient-centred approach. Patients with different needs require different types of review, and their needs may change over time. Though others may also benefit from medication review, NICE recommends that multimorbidity, polypharmacy and frailty should be prioritised [140]. Outcomes include understanding the patient experience and preferences, facilitating improved adherence, or stopping ('deprescribing') medicines.

Deprescribing has been defined as 'the process of withdrawal of an inappropriate medication, supervised by a HCP with the goal of managing polypharmacy and improving outcomes' [151]. This is particularly relevant to patients with polypharmacy as the risk of medication-related harm increases with the number of medications prescribed [140]. Stopping or reducing medicines is a collaborative process requiring careful clinical consideration, with a need to balance issues such as potential loss of clinical benefit and increased patient anxiety, against reductions in medication burden, errors and ADRs [152].

Dose reduction and therapeutic substitution may be more accurately considered a part of optimal prescribing and not specifically deprescribing [153]. Additionally, dose reduction does not fit the aim of reducing polypharmacy. However, interventions focusing on improving prescribing appropriateness by deprescribing fail to consider inappropriate prescribing in its entirety. Inappropriate prescribing does not only encompass over-prescribing (prescribing of more drugs than clinically necessary) and mis-prescribing (incorrect prescribing of a necessary drug), but it also includes under-prescribing (failure to prescribe a clinically indicated drug) [46, 154]. Under-prescribing is common in older patients and the associated clinical consequences pose safety risks to patients [155].

Table 1.4. Three types of medication reviews (adapted from [149, 150, 156])

Type	Scope	Method
Prescription review *PCNE classification – simple*	Practical medicines management issues (*e.g.,* anomalies, changed items) that can improve the clinical and cost-effectiveness of medicines and patient safety, usually with one specific purpose in mind; includes medication reconciliation	▪ Usually without patient present ▪ Possibly with access to patient's medical notes ▪ Possibly includes all prescription but not complementary and OTC medicines
Compliance and concordance review *PCNE classification – intermediate*	Explore medicine taking including the patient's pattern of medicine taking and beliefs about medicines (medicine-taking behaviour); should be conducted at agreed intervals for patients with multimorbidity and polypharmacy	▪ Usually with patient present ▪ Possibly with access to patient's medical notes ▪ Includes all prescription and complementary and OTC medicines
Clinical medication review *PCNE classification – advanced*	Holistic review considering treatment in the context of the patient's underlying condition and symptoms; conducted when a patient requests or at agreed intervals, if ADRs occur, or if a patient stops taking a prescribed medicine (*e.g.,* CDM)	▪ With patient present ▪ With access to patient's medical notes and laboratory test results ▪ Includes all prescription and complementary and OTC medicines

Abbreviations: *ADRs* adverse drug reactions, *CDM* Chronic Disease Management, *OTC* over-the counter, *PCNE* Pharmaceutical Care Network of Europe

1.5.4. Medication review guidelines

There are various models of medication reviews published that can be used to assist HCPs in both primary and secondary care. In the guidelines on medicines optimisation, NICE recommends conducting structured medication reviews in older patients, patients with polypharmacy, and patients with chronic conditions [140]. The medication review should consider the patient's and carer's views about medicines, including any concerns, problems and understanding. The person delivering the medication review should examine all the patient's medicines including prescribed medicines, over-the-counter medicines, and complementary medicines. The reviewer should consider the safety, efficacy, and

appropriateness of medicines for a given patient. The reviewer should also check whether a patient has any risk factors that can lead to ADRs and whether monitoring is required [140].

At present, there is no consensus on the type of HCP most appropriate to conduct a medication review; however, the HCP should have the knowledge and skills to deliver a review. That includes technical knowledge of medication management, knowledge of therapeutic use of medicines, and appropriate communication skills to engage the patient in the discussion about medicines [140]. The Scottish Government's Polypharmacy Model of Care Group published guidance outlining a seven-step structured process for conducting medication reviews with patients receiving polypharmacy [144]. The '7-steps' promote individualised care and partnership between HCPs and patients to make shared decisions that will ensure their medicines are safe and appropriate (Table 1.5) [144]. In this process, the reviewer investigates what is important to the patient, medicines that may be essential, ineffective, unnecessary, or harmful, and opportunities for cost minimisation, resulting in a medicines plan that agrees with and is centred on the patient [144].

The Bristol Medication Review Model developed by integrating common themes identified in existing studies with a patient-centred approach provides a framework for standardised delivery of structured reviews. In this model, information is gathered about a patient's medications (reconciliation, adherence, patient's understanding) and decisions are made based on an evaluation of under-treatment, unnecessary medicines, and possible harmful prescribing [145]. An expert panel from the American Geriatrics Society developed a set of guiding principles on the management of older patients with multimorbidity, outlining a patient-centred approach to ensure safe and appropriate medicine use [146]. Furthermore, the Ariadne principles can support decision-making specifically during general practice consultations involving multimorbidity. These principles advocate spending time to assess the patient's priorities and goals, rather than being driven by disease-focused processes and outcomes [157]. This model places the setting of realistic treatment goals at the centre of the multimorbidity consultation, achieved via thorough patient assessment, prioritising health problems, considering patient preferences, and individualising care [157]. These recommendations have been consolidated to promote patient-centred care (Figure 1.5).

Table 1.5. The six domains of 'The 7 Steps Medication Review' (adapted from [144])

Domain	Steps	Process
Aims	1. What matters to the patient?	Review diagnoses and identify therapeutic objectives
Need	2. Identify essential drug therapy	Identify essential drug (not to be stopped without specialist advice)
	3. Does the patient take unnecessary drug therapy?	Identify and review the (continued) need for drugs
Effectiveness	4. Are therapeutic objectives being achieved?	Identify the need for adding/ intensifying drug therapy in order to achieve therapeutic objectives
Safety	5. Does the patient have or at risk of ADRs/side effects? Does the patient know what to do if they're ill?	Identify patient safety (drug-disease interactions, drug-drug interactions, high risk drugs) and ADR (specific symptoms/markers, cascades, cumulative adverse drug effects) risk
Cost-effectiveness	6. Is drug therapy cost-effective?	Identify unnecessarily costly drug therapy
Patient-centredness	7. Is the patient willing and able to take drug therapy as intended?	Does the patient understand the outcomes of the review? Ensure drug therapy changes are tailored to patient preferences Agree and communicate plan

Abbreviations: *ADR* adverse drug reaction

Figure 1.5. Structured approach for evaluating and managing patients with multimorbidity (adapted from [140, 145, 146, 157])

1.5.5. Effectiveness of medication review

Pharmacists are the HCP with the widest knowledge of medicines and the potential complexities associated with the increasing use of medicines. Therefore, pharmacists have a critical role to play within the health system to ensure the rational use of medicines by maximising the benefits and minimising the potential for patient harm [97]. The effectiveness of pharmacist-led medication review has been examined in several systematic reviews and meta-analyses. Favourable results were demonstrated for a range of clinical outcomes (primarily driven by attainment of biomarker targets for blood pressure, glycosylated haemoglobin, cholesterol, as well as reduction in Framingham risk score) and some measures of quality use of medicines (number and appropriateness of medications, medication adherence and resolution of MRPs) [127, 158-160].

In a systematic review exploring the effect of medication review as an isolated intervention, Huiskes *et al.* found a lack of effect of medication reviews on mortality and hospitalisations, quality of life, and economical outcome measures [161]. However, hard outcomes such as mortality and hospitalisations are often not the primary focus of medication review studies. Huiskes *et al.* suggest that if the aim of a medication review is to decrease mortality or prevent patients from being admitted to hospitals, one should select a population with high risk of any of these events [161]. While Huiskes *et al.* demonstrated that a patient-centred model of medication review has an effect on most medication-related outcomes [161], Rankin *et al.* could not determine if interventions to improve appropriate polypharmacy, such as reviews of patients' prescriptions, resulted in substantial clinical improvement [36]. The authors of this Cochrane review concluded that pharmaceutical care (promoting the correct use of medicines by identifying, preventing, and resolving MRPs) may slightly reduce the number of potential prescribing omissions. However, it was unclear whether these interventions improve medication appropriateness or reduce the number of potentially inappropriate medicines [36].

A pilot study in 2012 suggested that a medication review service involving collaboration between pharmacists and GPs would be feasible in Ireland; however, the HSE did not proceed with further evaluation or development [162]. Consequently, pharmacists offer the service themselves without remuneration; however, there has been no review of the extent of the provision nor the quality of the service [86]. The electronic patient medication records used in community pharmacies not only records the patient's medicines, but also other pertinent information noted following discussions with patients and prescribers. However, this opportunistic prescription review may not reveal patient's preferences and problems, particularly with long-term medicines and when the patient reports overall satisfaction with their treatment [162]. A structured, systematic, and patient-centred approach may be achieved through collaborative multidisciplinary medicines optimisation in primary care.

1.6. Pharmacogenomics

In medicine, as it is performed today, the optimal population dose as determined in clinical trials is applied to all individuals. For a medication to be the right treatment, it needs to be provided at the right dose. However, since the population is heterogeneous, the optimal individual dose is not equal to the optimal population dose for all individuals and therefore leads to variability in drug response (Figure 1.6). For instance, at the population dose some individuals will be non-responders and some will develop adverse effects [74]. The former may be able to respond to and tolerate higher doses, while the latter may respond well to lower doses [74]. Dealing with this variability has been a reality of pharmacotherapy for as long as medicines have been available. In many diseases, clinical practice is to adjust doses until a target effect is achieved [74].

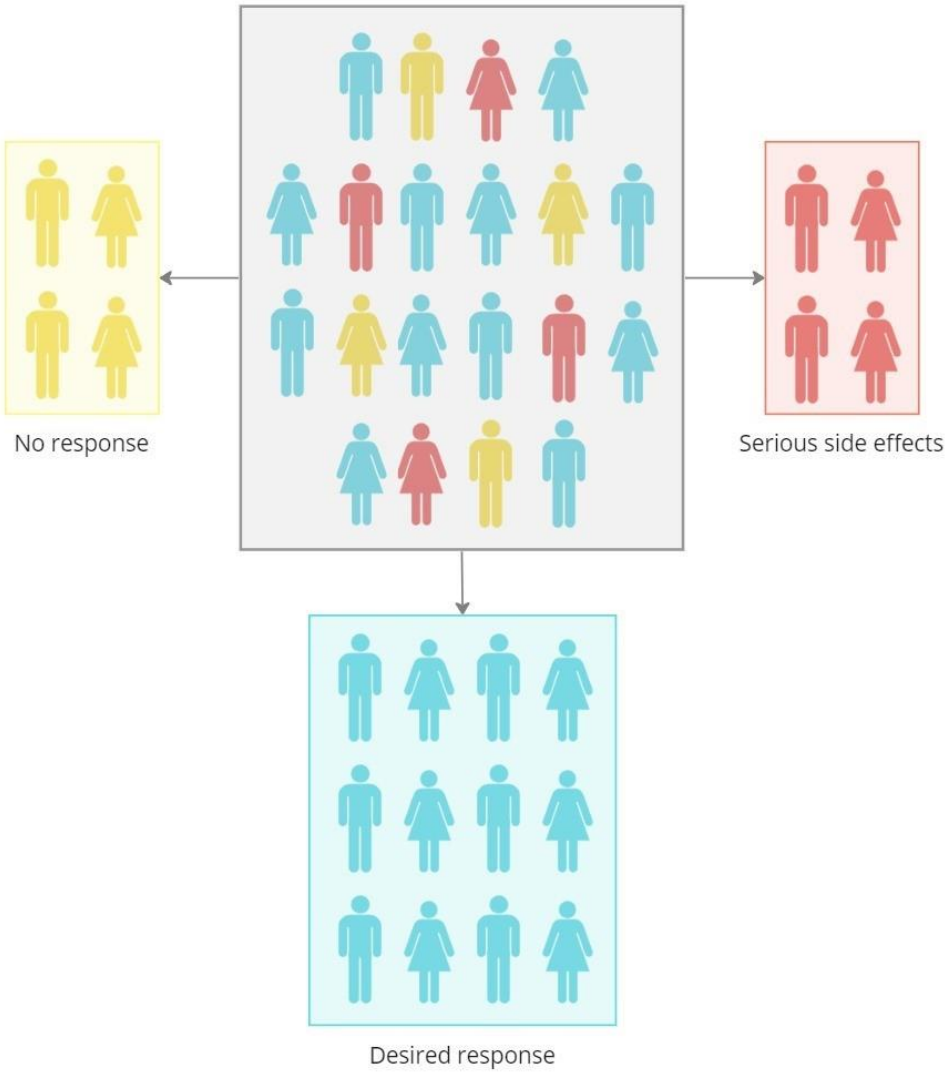

Figure 1.6. Variability in drug response

1.6.1. Definitions

As opposed to population-based application, precision medicine (personalised, individualised, or stratified medicine) aims to individualise application of pharmacotherapy in an effort to optimise the risk-benefit ratio [74, 163]. The terms 'precision', 'personalised', 'individualised', and 'stratified' medicine are close relatives of pharmacogenomics (Table 1.7). However, these are broader terms which also cover non-genetic factors [164]. Precision medicine involves the utilisation of individual patient characteristics (genetic, biomarker, phenotypic or psychosocial characteristics) to enable the classification of patients into subpopulations that differ in susceptibility to a particular disease or in response to a specific treatment. As a result, it is possible to distinguish a given patient from others with similar clinical presentations, facilitating the individualisation of medical treatments [163].

The study of genetics has been widely applied in precision medicine, and one of the emerging applications is pharmacogenomic-informed pharmacotherapy, tailoring drug selection and dosing to the patient's genetic features. Pharmacogenomics promises to shift healthcare from a "one size fits all" model to a precise and personalised regimen. It utilises an individual's germline genetic profile to identify those who are at higher risk for potentially ineffective and/or harmful drugs [76, 165-167]. Consequently, pharmacogenomic testing offers HCPs the opportunity to act prospectively rather than retrospectively, using genetic information to individualise and optimise pharmacotherapy prior to initiation [167, 168]. The ultimate goal of pharmacogenomics is to prescribe the right medication at the right dose to the right individual at the right time [168].

The terms pharmacogenetics and pharmacogenomics are often used interchangeably [169]. While the former term is largely used in relation to variation in a single gene affecting variability in relation to one specific medicine (or group of medicines), the latter is a broader term that encompasses all genes in the genome that may determine drug response [170]. Because actionable pharmacogenomic variants are ubiquitous and germline pharmacogenomic results are life-long, recent trends of investigations on determinants of drug response have shifted from individual drug-gene pair-based pharmacogenetics to a panel of pharmacogenomic markers [171, 172]. However, for simplicity, this thesis treats pharmacogenetics and pharmacogenomics as synonymous.

1.6.2. Genetic prediction of drug response

As previously mentioned in Section 1.3.4, interindividual variability in drug response is driven by several extrinsic and intrinsic factors. Genetic variations are being increasingly recognised among these factors that lead to changes in the activity or availability of drug metabolising enzymes, receptors, channels, and other proteins involved in drug pharmacokinetics and pharmacodynamics [75]. It is estimated that 15–30% of drug response variability is caused by genetic polymorphisms [72]. Moreover, Ingelman-Sundberg suggested that up to 10-20% of ADRs may be due to genetic factors, either in whole or in part [173]. The field of pharmacogenomics aims to define these genetic mechanisms. While the earliest examples of pharmacogenomic variability involved variability in pharmacodynamic processes [76], pharmacodynamic drug targets have not been studied to the same extent as pharmacokinetic sources of variation [74, 76, 167].

Pharmacodynamically, genetic variation in drug target proteins (receptors, enzyme active sites, intracellular signalling proteins) may alter drug potency for its effector protein, and therefore affect its efficacy [76]. There are few examples of polymorphisms in target receptors that have led to recommendations that impact drug choice or dose selection. For example, the risk of malignant hyperthermia on exposure to inhaled anaesthetics or succinylcholine is mediated by variants in RYR1 or CACNA1S [174]. Pharmacodynamic variation also influences warfarin effects; VKORC1 encodes the vitamin K epoxide reductase protein, the target enzyme of warfarin. A common variant of VKORC1 (c.-1639G>A, rs9923231) is significantly associated with warfarin sensitivity and patients with one or two copies of –1639A require progressively lower warfarin doses than –1639G/G homozygotes [175].

Pharmacokinetically, the impact of genotype is understood for many drugs whose ADME involves polymorphic metabolic enzymes or transporters [74]. The intended drug response is expected when plasma drug concentrations are above the therapeutic and below the toxic thresholds. An individuals' plasma concentration at a particular dose is determined by proteins involved in the ADME of the drug, which are encoded in DNA. Genetic variation within these ADME genes may cause variation in protein functionality, *i.e.,* yielding proteins with increased, normal, reduced, or loss-of-function. The resultant phenotypes are ultra-

rapid, normal, intermediate, and poor metaboliser respectively, affecting drug plasma concentration and resulting in altered drug response [78].

Therefore, an individual's germline genetic variation is a particularly promising predictive factor that can enable drug response prediction. In this regard, cytochrome P450 (CYP) genes are of particular importance as the CYP genes are highly polymorphic and are responsible for metabolising a substantial number of drugs [176]. Fifty-seven active CYP genes were identified through the work of the Human Genome Project. Of these, the isoforms belonging to the CYP1, 2, and 3 families mediate 70-80% of all phase I-dependent (oxidative) metabolism of clinically used drugs [173]. While there are many CYP genes of interest when it comes to drug metabolism, currently CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, and CYP4F2 have been evaluated to determine specific dosing guidelines [177-180] (see Section 1.6.3 and Table 1.6).

Four different CYPs (CYP2D6, CYP2C9, CYP2C19, and CYP3A4) have particularly important roles in the oxidative metabolism of a range of different drugs and are each encoded by different genes [164]. All are subject to well-studied genetic polymorphisms. In the case of CYP2D6 and CYP2C19, significant proportions of the population completely lack one of these enzymes due to the presence of inactivating genetic polymorphisms in both copies of the gene [181]. Conversely, some individuals may have higher than normal CYP2D6 or CYP2C19 activity (aforementioned ultra-rapid metabolisers). In the case of CYP2D6, this is due to one or more additional copies of the gene being present and for CYP2C19, the presence of polymorphisms resulting in increased gene expression [181].

1.6.3. Pharmacogenomic guidelines

Translation of pharmacogenomic test results into actionable data in clinical practice is now well established, aiding clinical decision making by HCPs. Several international organisations have developed evidence-based pharmacogenomic guidelines providing actionable, genotype-based prescribing recommendations for well-known drug-gene interactions [177-180]. The Dutch Pharmacogenetics Working Group (DPWG) and the Clinical Pharmacogenetics Implementation Consortium (CPIC) are the leading scientific consortia in the field of pharmacogenomics. The DPWG was founded by the Royal Dutch Pharmacists Association (KNMP) in 2005 to develop clear guidelines for HCPs on how to interpret and apply pharmacogenomic test results. The DPWG is multidisciplinary and includes clinical pharmacists, physicians, clinical pharmacologists, clinical chemists, epidemiologists, and toxicologists [182].

In parallel, the CPIC was established in 2009 as a shared project between the Pharmacogenomics Knowledge Base (PharmGKB) and the Pharmacogenomics Global Research Network. PharmGKB is a resource of pharmacogenomic variants [177], and the Pharmacogenomics Global Research Network is a network of investigators conducting pharmacogenomics research as well as numerous clinical trials [183]. The CPIC was created to address the need for very specific guidance for clinicians and laboratories so that pharmacogenomic tests could be used wisely in the clinic [184]. The DPWG and CPIC have been developing guidelines for over 15 years, with over 200 drug-gene interactions reviewed to date [178, 179]. The DPWG and CPIC have published actionable pharmacogenomic recommendations for 63 and 105 individual drug-gene interactions respectively (Table 1.6) [177]. Of these recommendations, a high proportion pertain to medicines prescribed in primary care.

Table 1.6. Drug-gene pairs with actionable prescribing recommendations from the CPIC and the DPWG (adapted from [177])

Gene	Drug(s)
CYP2C9	Celecoxib, flurbiprofen, fluvastatin, fosphenytoin, ibuprofen, lornoxicam, meloxicam, phenytoin, piroxicam, siponimod, tenoxicam, warfarin
CYP2C19	Amitriptyline, citalopram, clomipramine, clopidogrel, dexlansoprazole, doxepin, escitalopram, imipramine, lansoprazole, omeprazole, pantoprazole, sertraline, trimipramine, voriconazole
CYP2D6	Amitriptyline, aripiprazole, atomoxetine, brexpiprazole, clomipramine, codeine, desipramine, doxepin, eliglustat, flecainide, fluvoxamine, haloperidol, hydrocodone, imipramine, metoprolol, nortriptyline, ondansetron, paroxetine, pimozide, propafenone, risperidone, tamoxifen, tramadol, trimipramine, tropisetron, venlafaxine, vortioxetine, zuclopenthixol
SLCO1B1	Atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin
ABCG2	Allopurinol, rosuvastatin
CYP2B6	Efavirenz, sertraline
CYP3A4	Quetiapine
CYP3A5	Tacrolimus
CYP4F2	Warfarin
VKORC1	Acenocoumarol, phenprocoumon, warfarin
Factor V Leiden	Hormonal contraception
HLA-A	Carbamazepine
HLA-B	Abacavir, allopurinol, carbamazepine, flucloxacillin, fosphenytoin, lamotrigine, oxcarbazepine, phenytoin
NUDT15, TPMT	Azathioprine, mercaptopurine, tioguanine
MT-RNR1	Amikacin, gentamicin, kanamycin, paromomycin, plazomycin, streptomycin, tobramycin
DPYD	Capecitabine, flucytosine, fluorouracil, tegafur
IFNL3	Peginterferon alfa-2a, peginterferon alfa-2b, ribavirin
UGT1A1	Atazanavir, irinotecan
G6PD	Dapsone, methylene blue, nitrofurantoin, pegloticase, primaquine, rasburicase, tafenoquine, toluidine blue
CFTR	Ivacaftor
CACNA1S, RYR1	Desflurane, enflurane, halothane, isoflurane, methoxyflurane, sevoflurane, succinylcholine

Pharmacogenomic information is also reflected in drug labels developed by regulatory agencies. Additional sources of information regarding the pharmacogenomics of medications are the Summary of Product Characteristics (SmPC) approved by the European Medicines Agency (EMA) and other agencies, as well as drug labels approved by the US Federal Drug Agency (FDA) [185]. The number of medications with pharmacogenomic information in their SmPC or label has increased over the years due to regulatory guidelines and policy [186]. The labels of 15% of EMA and FDA drugs include pharmacogenomic information to inform prescribing [180, 187]. The FDA has a list of 517 gene-drug associations that have been included in drug labels [180], and its table of pharmacogenomic associations lists 121 drug-gene interactions [188]. In addition, the PharmGKB is a comprehensive pharmacogenomics resource with curated and graded evidence of combinations of drugs and genes, including drug label annotations and clinical guideline annotations [189]. PharmVar, a centralised data repository, provides high-quality data on pharmacogene variation [190].

These guidelines and drug labels have, in part, facilitated global recognition and clinical acceptability of pharmacogenomic testing. This is exemplified by numerous institutions and health systems across Europe, North America, Canada, and Asia that have implemented pharmacogenomic testing [191, 192], and an exponential growth in direct-to-consumer (DTC) pharmacogenomic testing options [193]. However, harmonisation in pharmacogenomic drug labelling between different regulatory agencies is lacking because of differing views on actionability and differences in legal statuses and clinical practice [194].

While pharmacogenomic testing laboratories have been established across many countries, the practice is not yet embedded in routine clinical practice across primary and secondary care settings. Attempts are being made to develop its use; for example, the NHS Improvement and Genomics England recently announced plans to implement pre-emptive pharmacogenomic panel testing in the UK by 2025 [195]. There are also examples of pharmacogenomic testing adoption at the national level via electronic prescribing and dispensing systems (*e.g.,* the Netherlands) [196], and pharmacogenomic identification card systems (*e.g.,* Taiwan and Thailand) [197].

1.6.4. Approaches to pharmacogenomic testing

Significant debate persists regarding the optimal timing and methodology of testing for delivering pharmacogenomic testing in clinical care to maximise utility and convenience for patients [165, 198-200]. Pharmacogenomic testing is offered using three main approaches: reactive, point-of-care, and pre-emptive (Figure 1.7). Specifically, there has been divergence on whether testing should be performed in a reactive manner for a gene(s), with implications for a single drug at the time it is prescribed, or pre-emptively using a panel-based approach prior to drug prescribing [165]. With pre-emptive testing, genotype information for potentially hundreds of pharmacogenes is readily available in the patient's medication record to inform future drug therapy.

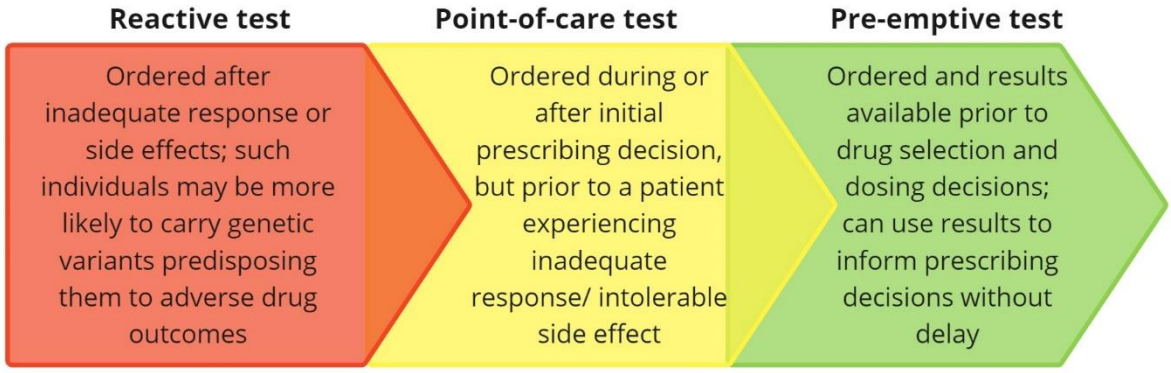

Figure 1.7. Pharmacogenomic testing approaches

There are also three types of pharmacogenomic tests: single gene tests, multi-gene (panel) tests, and combinatorial tests. Single gene tests include one or multiple genetic variants (alleles) in a single gene that is associated with efficacy or tolerability of a drug or group of drugs, multi-gene tests include genetic variants in multiple genes, while a combinatorial test is a special type of multi-gene panel test that uses proprietary algorithms to translate test results into prescribing decisions [198]. Although some of these combinatorial pharmacogenomic tests demonstrate positive findings [201, 202], the drug selection and dosing recommendations may differ when compared to recommendations based on published pharmacogenomic-based prescribing guidelines by the CPIC and the DPWG or pharmacogenomic information on drug labels (*e.g.,* FDA and EMA) [203-205].

Many HCPs who have implemented pharmacogenomics have done so on a basis with the benefit of increased probability the genetic test result will be applied by the clinician as the prescribing decision is linked to the performance of the pharmacogenomic test [199]. Conversely, reactive testing has several disadvantages, such as high expense and a test turnaround time that may be too slow to be useful for initial prescribing decisions [199]. In the point-of-care approach, immediate drug selection and dosing is not informed by testing; however, it does provide an opportunity to adjust the prescription upon receipt of the test results [198]. Test turnaround time, which can range from several days to weeks, impacts the effectiveness and appropriateness of this approach.

In contrast, the pre-emptive approach is less reliant on test turnaround time as testing is offered and the results available prior to drug therapy initiation [198]. As a result, HCPs can use an individual's pharmacogenomic test results to inform prescribing decisions without delay. Besides, the pharmacogenomic test data can be used as a lifetime predictive tool for drug safety and efficacy. It has also been suggested that delivering pharmacogenomic testing through a pre-emptive panel-based approach as opposed to reactive single-gene approach is more cost-effective and practical [200, 206, 207]. Consequently, pre-emptive testing is emerging as a best practice, supported by the significant prevalence of clinically actionable genetic variants and widespread use of drugs with potential pharmacogenomic relevance [165].

Although the minor allele frequencies of specific variants in the genes are low and range from approximately 0.1–5·0%, testing for a panel that consists of multiple actionable variants in the 12 most important pharmacogenes identifies at least one actionable genotype in 90–95% of individuals across multiple populations [199, 208]. When pharmacogenomics is adopted in such a model, it has been estimated that 25% of all incident prescriptions will have a relevant drug-gene interaction. In this study, pharmacogenomic test results and clinical recommendations were returned within seven days [172]. Furthermore, pharmacogenomic testing is offered by commercial and non-commercial entities. Both are mostly performed in an accredited clinical laboratory (*e.g.,* International Organisation for Standardisation 15189) [198].

In the US alone, 76 commercial laboratories offer pharmacogenomic testing and testing in about 50 medical centres or health systems worldwide [191, 193]. However, commercial and non-commercial entities often differ in the model used to offer pharmacogenomic testing. There are two types of models: DTC and gatekeeper model; the former allows consumers to access their genetic information through an online service without the intermediary of a HCP [209], whereas the latter requires referral from a HCP prior to commencing the pharmacogenomic test [198]. Commercial laboratories have adopted both models [210], but medical centres exclusively employ the gatekeeper model wherein the tests are interpreted by physicians, pharmacists, nurses, or genetic counsellors either individually or as part of a multidisciplinary team [211]. Nevertheless, there is a consensus that HCPs, preferably those who know the patient's history, should be involved in the ordering and interpretation of a pharmacogenomic test [212].

Despite the promise of and progress in the field of pharmacogenomics to achieve precision medicine, it is still not routinely applied in patient care. It is imperative that primary care HCPs and healthcare systems as a whole are prepared to face the reality of increasing consumer and clinician access to precision medicine data and use healthcare resources to apply pharmacogenomic data in an informed, efficient, and evidence-based manner that compliments routine patient care [213]. To facilitate implementation of pharmacogenomics into the UK NHS, the Royal College of Physicians and the British Pharmacological Society produced a report [214]; a set of recommendations adapted to make them relevant for any healthcare system is presented in Box 1.1. The role of pharmacy in implementing and delivering pharmacogenomics services is illustrated in Box 1.2. Furthermore, the Royal Pharmaceutical Society stressed the importance of a comprehensive workforce strategy and fully resourced genomics education and training related to clinical pharmacogenomics competency requirements in line with all multidisciplinary professionals involved in the delivery of pharmacogenomics [215].

Box 2.1: Recommendations for the implementation of pharmacogenomics in clinical practice [214]

- Clinical implementation of pharmacogenomics should occur in both primary and secondary care settings, as well as in specialised centres, and should reflect the wide range of drugs that have actionable pharmacogenomic recommendations.
- One model might be to start with a small number of drug–gene pairs and gradually increase to a comprehensive service.
- Appropriate funding is needed for implementing a pharmacogenomic clinical service; active efforts should be made from the beginning to ensure that the service does not exacerbate health inequalities.
- Services should include standards for test turnaround times, flexibility in the type of technology used depending on the gene-drug pair, and standards for reporting, storing, and incorporating the test results in the patient medication record.
- The pharmacogenomic service should be adaptable — that is, able to modify and refine the available tests based on new evidence.
- A comprehensive education and training package that is relevant to all involved HCPs should accompany the implementation of a pharmacogenomic service.
- Support for clinicians should be provided as pharmacogenomic testing is rolled out; including clinical decision support (CDS) systems, to minimise errors and maximise cost efficiency.
- There should be consideration around expanding and clearly defining roles of existing staff to incorporate pharmacogenomics and medicines optimisation.
- The pharmacogenomic service should undergo continuous audit and evaluation, leading to the development of a learning health system that maximises patient benefits.
- A pharmacogenomic service should be accompanied by funding for research — not only biomedical research, but also research into ethical, legal, and social issues.
- Clear lines of communication should be established with healthcare managers, patient representative bodies, the public and the media.

Box 1.2: The evidence-based role of pharmacy in implementing and delivering pharmacogenomics services [215].

- Raising awareness and promoting the use of pharmacogenomics in the healthcare setting.
- Members of multidisciplinary teams for better integration of pharmacogenomics.
- Identifying patients who would benefit from pharmacogenomic testing *e.g.,* during medication reviews.
- Providing information and advice to patients and the public on pharmacogenomics due to their accessible position at the patient interface.
- Establishing, choosing, recommending, and ordering pharmacogenomic tests.
- Performing pharmacogenomic sampling and testing.
- Pharmacogenomic data collection, analysis, and management.
- Making recommendations on pharmacotherapy based on pharmacogenomic test results.
- Medicines optimisation, therapeutic drug monitoring and dose adjustment based on pharmacogenomic test results.
- Providing advice to patients on how their genetic material will be used and how test results may affect current or future treatment.
- Educating other HCPs on pharmacogenomics.
- Developing and interpreting pharmacogenomic processes, guidelines, and other publications.
- Supporting, contributing, and leading research in the area of pharmacogenomics.
- Contributing to pharmacogenomics networks and committees.
- Helping the development of infrastructure and creating pharmacogenomics technologies for implementation in the healthcare sector.

Table 1.7. Definition of terms used

Term	Definition
Multimorbidity	The co-existence of two or more chronic conditions [11]
Polypharmacy	The concomitant ingestion of four or more medications [36]
Appropriate polypharmacy	Prescribing for individuals with complex or multiple conditions where medicine use has been optimised and prescribing aligns with best evidence [44]
Deprescribing	The process of withdrawal of an inappropriate medication, supervised by a healthcare professional with the goal of managing polypharmacy and improving outcomes' [151]
Medication review	A structured evaluation of a patient's medicines with the aim of optimising medicines use and improving health outcomes. This entails detecting MRPs and recommending interventions [149]
Medicines optimisation	Medicines optimisation is a patient-centred process, aimed at ensuring the best clinical outcomes for patients through safe and effective use of medicines; it can be described as a process, approach or a concept that incorporates many aspects of improving medication use [138-141]
Precision medicine	This term broadly encompasses all approaches to tailoring medical treatment to the individual characteristics of each patient. It integrates genetic, environmental, and lifestyle information to predict and treat disease more accurately. Precision medicine is generally considered analogous to personalised, individualised and stratified medicine [163]
Personalised medicine	This term is often used interchangeably with precision medicine, personalised medicine focuses on customising healthcare based on individual genetic profiles, as well as other personal information like lifestyle and environment [216]
Individualised medicine	This term is very similar to personalised medicine and is often used synonymously. However, it can emphasise a broader range of factors beyond genetics, including individual preferences, behaviours, and environmental influences
Stratified medicine	This approach involves categorising patients into subgroups or 'strata' based on specific characteristics, such as genetic markers or clinical features, and tailoring treatments to these subgroups. It is a step towards more individualised care but not as tailored to the individual as personalised medicine [217]
Pharmacogenomics	This field studies how genes affect a person's response to medications. Pharmacogenomics is a broader term that encompasses all genes in the genome that may determine drug response [170]
Pharmacogenetics	A subset of pharmacogenomics, pharmacogenetics specifically focuses on how variations in a single gene affect a person's response to one specific medicine (or group of medicines) [170]

1.7. Justification for research

As outlined above, there has been a marked increase in multimorbidity and associated polypharmacy with the change in global age structure toward an ageing population, increasing the likelihood of patients suffering from adverse effects from their medicines. ADRs constitute a serious and growing health problem, especially for older patients. Polypharmacy and potentially inappropriate prescribing are well known risk factors for ADRs. New pragmatic studies are needed to address the complex interplay of patient and clinical factors and to further examine the impact of drug-drug, drug-disease, and drug-gene interactions (pharmacogenomics) on the occurrence of ADRs. Patients at highest risk of inappropriate polypharmacy are those with the greatest frailty, those prescribed the most medicines, and those taking high risk medicines.

The subsequent rise in general practice healthcare utilisation as age, morbidity and number of medications rise has not been matched by a corresponding growth in the workforce capacity. To alleviate pressures faced by GPs, pharmacists have been integrated into practice teams in several health systems internationally. Holistic, patient-centred reviews are important to optimise medication use, reduce ADRs, prevent hospitalisation and enhance overall patient outcomes. However, existing tools do not examine or incorporate drug-gene interactions. Prior to this research, there had been no published investigations into the implementation of pharmacogenomic testing in Ireland or collaborative GPP telepharmacy medicines optimisation in primary care. Building on established guidelines (the CPIC and the DPWG), drug-gene interactions in contemporary, multimorbid, polypharmacy patients in Ireland was examined. Using this research, it is anticipated that the existing medicines optimisation process will be remodelled to incorporate pharmacogenomics for the benefit of patients.

1.7.1. Research aims and objectives

The overall aim of the research outlined in this thesis was to establish the impact pharmacogenomic testing could have for patients with multimorbidity and prescribed polypharmacy, and the role of pharmacists collaborating with HCPs in primary care in relation to a medicines optimisation service incorporating genetic information into patient-centred medication reviews.

The key objectives of this research project were to:

- Identify, analyse, and evaluate the effectiveness of pharmacogenomic interventions designed for adults with multimorbidity and prescribed polypharmacy across various healthcare settings, with a focus on examining their development, implementation, genetic underpinnings, and impact on economic, clinical, and humanistic outcomes.
- Explore the feasibility of implementing pharmacogenomic testing into Ireland's healthcare system by examining public awareness, receptiveness to pharmacogenomic service availability, factors affecting testing decision, willingness to pay, and preferred access methods.
- Investigate the impact of pharmacogenomic testing in the Irish STOP-HF patient population with cardiovascular risk factors by determining the prevalence of abnormal SLCO1B1 and ABCG2 phenotypes and their influence on the progression of pre-heart failure and new-onset symptomatic heart failure amongst patients exhibiting altered systemic statin exposure due to poor function phenotypes.
- Implement a telepharmacy collaborative medicines optimisation service in Irish primary care, led by a general practice pharmacist, utilising Lean methodology. Assess key stakeholders' perspectives on the service, including barriers and facilitators, analyse the patient journey through the service, gather stakeholder opinions on integrating pharmacogenomic testing, and create a service process map that incorporates identified barriers and facilitators.

1.7.2. Research framework

In this thesis, the Medical Research Council's framework for the design and evaluation of complex interventions was applied to guide the development and implementation of pharmacogenomic interventions as part of medicines optimisation within primary care settings in Ireland [218]. This framework provides a systematic approach for designing and evaluating complex interventions (*i.e.,* comprising multiple interacting components and targeting multiple levels of influence). The updated guidance provides a comprehensive framework for developing and evaluating complex interventions. Key points include emphasising the importance of theory-driven intervention development, clarifying the role of pilot and feasibility studies, highlighting the iterative nature of intervention development, emphasising the importance of context, and providing guidance on process evaluation and implementation [218]. Additionally, the framework underscores the significance of stakeholder involvement and the need for ongoing adaptation throughout the intervention development process. Figure 1.8 outlines the research conducted in this thesis.

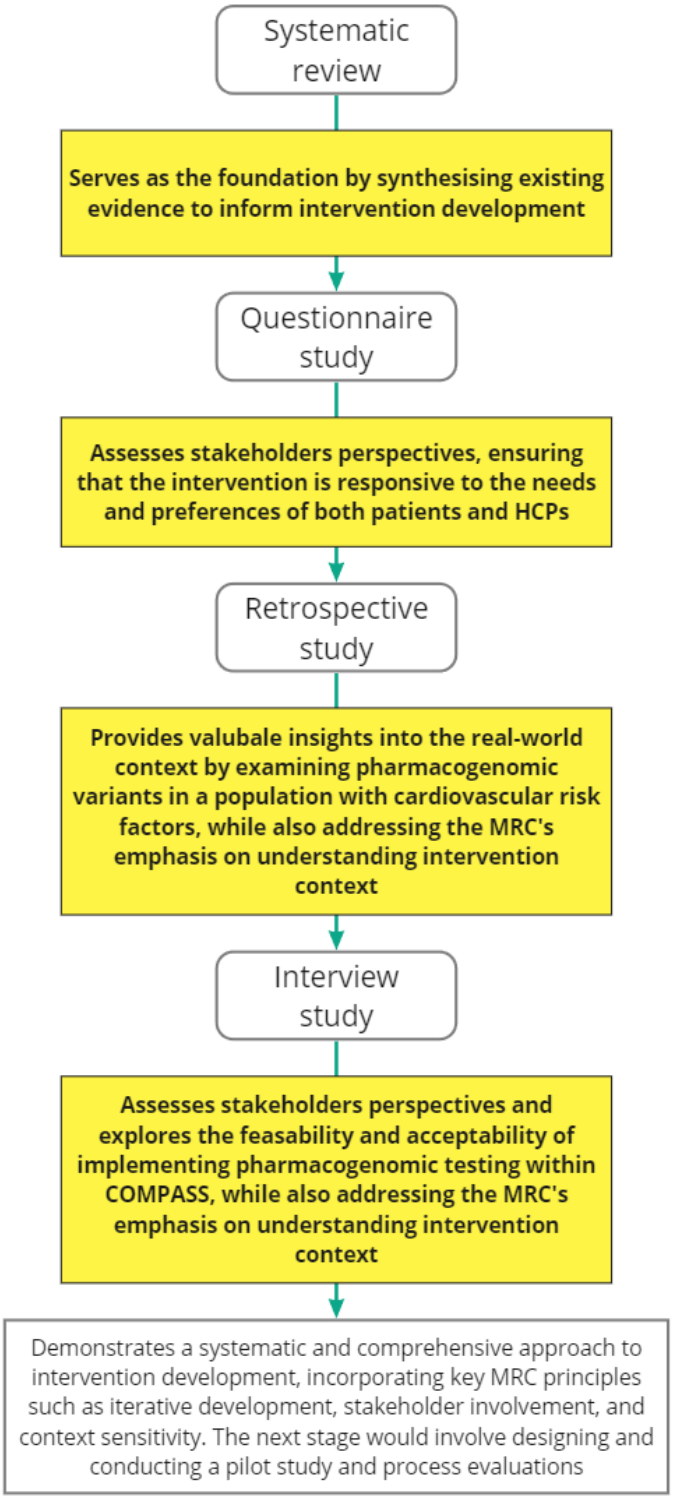

Figure 1.8. Research outline

Abbreviations: *COMPASS* collaborative medicines optimisation service involving a general practice pharmacist, *HCP* healthcare professional, *MRC* Medical Research Council

1.8. Overview of thesis chapters

This introductory chapter outlines the ongoing issues and problems associated with multimorbidity and polypharmacy in an ageing population, as well as evidence-based approaches to address them. Important background information was provided not only in justifying the current research but also in identifying an evidence-based intervention that would be amenable to pharmacist delivery. To address the key research objectives stated above, the project was divided into four phases. The findings from each phase are outlined in Chapters 2-5 of this thesis:

Chapter 2: Presents the systematic review that identified all randomised, non-randomised, observational, and non-comparative studies involving adults with multimorbidity and/or prescribed polypharmacy in all healthcare settings to determine the effectiveness of pharmacogenomic interventions to improve outcomes derived from consensus-based core outcome sets for multimorbidity and polypharmacy. Included studies were assessed for risk of bias.

Chapter 3: Presents the findings of a national questionnaire, which addresses a notable gap in the literature in terms of the Irish public's perceptions of and attitude towards pharmacogenomic testing. We hypothesised that perceptions of pharmacogenomics would significantly differ based on the view of those with and without chronic disease(s). Furthermore, the results from a cross-sectional study using pharmacy claims data to estimate the prevalence of potential and actionable drug-gene interactions are briefly discussed.

Chapter 4: Presents the findings from a retrospective analysis in the STOP-HF cohort, exploring the association between abnormal statin transporter function phenotypes (SLCO1B1 and ABCG2) and the progression of pre-heart failure and new-onset symptomatic heart failure. Moreover, the exposure of >1,200 patients to medications with a potential drug-gene interaction in an Irish community setting were assessed.

Chapter 5: Presents an overview of the collaborative medicines optimisation service involving a general practice pharmacist in Irish primary care (COMPASS) developed using Lean methodology as part of the Irish Research Council's Employment-Based Programme. The findings of an interview study exploring the views of stakeholders (patients, GPs, and

CPs) on COMPASS, the integration of pharmacists into general practice, and the incorporation of pharmacogenomic testing into COMPASS were assessed with barriers and facilitators to the service identified using the SEIPS 3.0 model.

Chapter 6: Summarises the key findings of the research presented in each chapter. The overall limitations of the research undertaken are outlined and recommendations are provided for future research that would assist the implementation of pharmacogenomic testing in Ireland, as well as the development of GPPs' role in primary care and medicines optimisation.

Chapter 2

Pharmacogenomic interventions to improve outcomes in patients with multimorbidity or prescribed polypharmacy:

A systematic review

2. Chapter 2: Systematic review

2.1. Introduction

This chapter focuses on a systematic review, developed in accordance with the Preferred Reporting Items for Systematic review and Meta-analysis (PRISMA) statement and using methods established by the Cochrane Collaboration [219-221]. As discussed in Chapter 1 (Section 1.1), people are living longer but not necessarily in better health. As such, older adults may have multiple chronic health conditions (multimorbidity) which may require multiple medications, leading to the prescribing of polypharmacy. Polypharmacy is associated with a number of adverse clinical outcomes that may affect patient safety.

Medication review as part of medicines optimisation may help to improve medication use in these patients. The study reported here sought to address gaps in the current evidence base and inform the development of a novel complex intervention incorporating pharmacogenomics to improve medicines optimisation in adult patients with multimorbidity and prescribed polypharmacy. As mentioned in Chapter 1 (Section 1.6), pharmacogenomics informed prescribing is one of the first applications of genomics in medicine [222]. Variation in drug efficacy or safety has detrimental effects on patient outcomes and leads to increased costs to resource-constrained healthcare systems.

Genetic variation in the regulatory and coding regions of genes involved in determining drug response (pharmacogenes) is common in the human population [199, 208]. In addition, drugs whose response is affected by pharmacogenomic variation are commonly used in clinical practice. For example, in the UK, 58% of patients were prescribed at least one drug affected by polymorphisms in actionable pharmacogenes [223]. Furthermore, as individuals age, they are more susceptible to diseases requiring pharmacotherapy; therefore, almost 90% of patients >70 years of age will be exposed to at least one drug with pharmacogenomic prescribing guidance [223].

Pharmacogenomic testing promises to personalise medicine by using an individual's genetic makeup, which predicts drug response, to guide optimal drug and dose selection [165]. This removes the traditional 'trial and error' approach of prescribing medications, thereby

promising safer, more effective and cost-effective pharmacotherapy [167, 224]. Pharmacogenomic testing is likely to take the form of a multi-gene panel, which can offer better value than multiple single tests as costs and processing times fall. Although pharmacogenomics has largely been a focus for academic research over the past few decades, policy makers are now increasingly interested in the role of pharmacogenomics in improving patient outcomes, which might enable implementation into clinical practice [194].

2.1.1. Overview of the current evidence base

A wide range of systematic reviews (and meta-analyses) have explored the effectiveness of pharmacogenomic interventions across different clinical conditions, pharmacotherapies, population groups, and settings. Predominantly, these reviews have focused specifically on single drug-gene or disease-gene pairs. As mentioned in Chapter 1 (Section 1.6.3), the DPWG and the CPIC are the two most widely recognised expert groups involved in the development of pharmacogenomic clinical guidelines.

In their guideline development process, the CPIC and the DPWG conduct systematic literature searches to identify candidate drug-gene interactions and compile and evaluate the evidence supporting the interaction [225]. Some examples include reviews focused specifically on the effectiveness of pharmacogenomic-guided psychotropic (antidepressant, antipsychotic and anxiolytic) [226-229], analgesic [230, 231], anticoagulant [175], antiplatelet [232], anticonvulsant [233, 234], antineoplastic [235], proton pump inhibitor [236], and statin therapy [237].

Countless studies incorporating pharmacogenomic testing have been performed in recent years, yielding a substantial body of knowledge on gene-based variations affecting individual drug susceptibility. However, most of these studies focused on the associations between specific genes and a single drug or disease. Several randomised controlled trials have provided gold-standard evidence for the clinical utility of single drug-gene pharmacogenetic tests to: guide dosing for warfarin [238], proton pump inhibitors [239], non-steroidal anti-inflammatories and opioids [240], and thiopurines [241], and guide the drug selection of clopidogrel [242], simvastatin [243], and abacavir [244].

Additionally, several prospective cohort studies have been performed indicating the clinical utility of single drug-gene pharmacogenomic tests to guide drug selection of carbamazepine [245] and allopurinol [246]. The foregoing studies may be perceived as a proof-of-concept supporting the clinical utility of pre-emptive pharmacogenomic testing and may therefore also be applied to other drug-gene interactions, for which evidence of the same rigour may lack [247, 248].

The level of evidence needed to support the use of pharmacogenomics in routine clinical practice remains controversial [247-250]. Some argue for randomised controlled trial data, demonstrating clinical utility of pharmacogenomic testing over standard, non-genotype guided care, prior to its implementation into routine care [251, 252]. Others counter that a degree of genetic exceptionalism seems to exist [253], and the perceived mandatory requirement for prospective evidence to support the clinical validity of pharmacogenomic testing is inappropriate and excessive [247, 248]. Notably, in that regulators and clinicians accept the concept of modifying drug doses in kidney or liver impairment based on pharmacokinetic modelling, but not when the variation is due to pharmacogenes that have the same impact on drug exposure [248].

Furthermore, many argue that, randomised controlled trials in this area may be impractical for several reasons: i) randomised controlled trials are costly; ii) there is a lack of generalisability of many trials given the strict inclusion and exclusion criteria; iii) ethical issues might arise in dosing participants with known functional variants; iv) many genetic variants have low population allele frequencies, trials with large sample sizes would be needed, which might not be feasible because of both cost and recruitment difficulties; and v) trials that take into account multimorbidity and polypharmacy (the focus of this systematic review), as well as multiple drug-gene associations in the elderly, are difficult to design [194, 249, 250]. In the absence of randomised controlled trials, pragmatic trials and observational studies are often used as evidence supporting the use of pharmacogenomics in patient care [254].

An emerging consensus is pharmacogenomic testing implementation needs to embrace a pre-emptive approach [200, 207]. Practically, this approach could mean that a patient requiring a pharmacogenomic test for a particular drug-gene pair would be genotyped using a genetic panel containing a number of pharmacogenes. The results could then be stored in the patient medication record for future use if and when a patient requires another drug for which response might be subject to pharmacogenomic variation. Evidence from clinical implementation of pre-emptive pharmacogenomic panels is already showing tremendous potential. When as few as five gene-drug pairs were considered, a pre-emptive genotyping panel yielded actionable variants in >90% of patients in the Pharmacogenomic Resource for Enhanced Decisions in Care and Treatment (PREDICT) programme at Vanderbilt University Medical Centre [208]. Herein, the implementation of a pre-emptive pharmacogenomic panel avoided the use of nearly 15,000 individual pharmacogenomic tests (if done reactively) [208].

Although the literature suggests that drug-gene and drug-drug-gene interactions are prevalent and clinically relevant [208, 255, 256], pharmacogenomics is not considered in the WHO, NICE and Scottish guidelines for multimorbidity and polypharmacy management [41, 143, 144], and is rarely applied as part of medicines optimisation despite its potential [257]. Furthermore, two Cochrane reviews investigating interventions to improve outcomes for patients with multimorbidity and prescribed polypharmacy were found to have uncertain effectiveness [36, 258]. Smith *et al.* demonstrated little or no difference to healthcare utilisation, small improvements in patient-reported outcomes, and slightly enhanced patient-related health behaviours and provider behaviour in their Cochrane review, concluding that there are uncertainties about the effectiveness of these strategies [258]. Rankin *et al.* found that interventions to improve the appropriate use of polypharmacy had little or no effect on healthcare utilisation, MRPs, and quality of life, uncertain effects on medication appropriateness, and some reduction in the number of potential prescribing omissions [36]. However, neither of these Cochrane reviews identified interventions involving pharmacogenomics as the intervention or indeed a component of the intervention.

It has been recognised that a 'one-size-fits-all' approach is unlikely to improve the care of those with multimorbidity and prescribed polypharmacy, and so the development of a complex intervention (with multiple interacting components) to address this problem is justified. Consequently, pharmacogenomics may have a role in improving the current approaches to medication usage, with potential for improving appropriate polypharmacy and preventing MRPs. Most of the currently available pharmacogenetic evidence focuses on individual drug-gene pairs. However, given the shift in implementation from reactive testing for single drug-gene pairs to pre-emptive panels that cover multiple drug-gene pairs [200, 207], that actionable genetic variants are ubiquitous [208], and results of germline pharmacogenomic tests are life-long [171], a multi-pharmacogenomic approach was considered more relevant for patients receiving multiple medicines to treat several long-term conditions.

Nevertheless, the effectiveness of multi-gene, multi-drug, multi-disease pharmacogenomic interventions in adults with multimorbidity and prescribed polypharmacy is yet to be established. This systematic review aimed to establish the efficacy of such interventions in all healthcare settings, and to inform the implementation of pharmacogenomic-guided therapy into clinical practice.

2.2. Aims and objectives

2.2.1. Aim

The overall aim of this systematic review was to determine the effectiveness of pharmacogenomic interventions in improving economic, clinical, and humanistic outcomes derived from consensus-based core outcome sets in adults with multimorbidity or prescribed polypharmacy in all healthcare settings, and to inform the implementation of pharmacogenomic-guided therapy into clinical practice.

2.2.2. Objectives

The objectives were to:

- Identify studies which explicitly applied a multi-gene, multi-drug, multi-disease pharmacogenomics intervention in the care of adults (aged 18 years or older) who were multimorbid (two or more chronic conditions) and prescribed polypharmacy (four or more medications)
- Examine how the pharmacogenomic interventions were developed and designed and propose a model for its implementation
- Determine the genetic variants that underpinned these interventions
- Determine how the intervention was implemented (*e.g.,* setting, provider)
- Identify and assess the outcomes measured and compare to the core outcome sets for studies in multimorbidity and polypharmacy
- Establish the effectiveness of pharmacogenomic interventions in improving economic, clinical, and humanistic outcomes in adults prescribed polypharmacy.

2.3. Research design and methodology

2.3.1. Protocol

This systematic review followed a protocol developed using methods established by the Cochrane Collaboration. This protocol was registered with PROSPERO, the International Prospective Register of Systematic Reviews (registration number CRD42020178126). The review findings have been reported in accordance with the PRISMA 2020 statement [219, 220]. (See completed PRISMA checklist in Appendix 2.1).

2.3.2. Eligibility criteria

2.3.2.1. Types of studies

Study inclusion was based on the Cochrane EPOC Checklist (which included randomised trials, non-randomised trials, controlled before-after studies, and interrupted time series analyses) [259], as well as observational and non-comparative studies. Relevant protocols could be included once completed. Ideally, systematic reviews should include the highest level of primary evidence available, *i.e.,* randomised controlled trials, but in cases such as this where limited evidence is anticipated or the concepts and recommendations are relatively novel, the next best level of evidence should be considered to help answer the research question. Thus, broad study designs were included to ensure a comprehensive report on the available literature was produced. Any study not written in the English language was excluded as reviewers did not have extensive knowledge of other languages, and funding was not available to support translation costs.

2.3.2.2. Types of interventions

Interventions delivered in all healthcare settings (*e.g.,* primary care, secondary care), provided by any HCP were considered for inclusion. Any type of intervention involving multi-gene, multi-drug, multi-disease pharmacogenomic-guided treatment was considered for inclusion. Therefore, studies involving single gene, single drug, single disease pharmacogenetic interventions were excluded.

2.3.2.3. Types of participants

Studies were included if the participants were 18 years of age or older and had two or more chronic conditions or were prescribed on average four or more medicines (the definition of multimorbidity and polypharmacy stated previously in Chapter 1 [36, 258]; Section 1.2.1 and Section 1.3.1 respectively). As the focus of this review is the effectiveness of pharmacogenomic screening in the care of patients with multimorbidity or prescribed polypharmacy, documentation of these parameters was required. Studies focusing on patients with malignancy, palliative care, human immunodeficiency virus and hepatitis were excluded from this review as these conditions require specialist attention.

2.3.2.4. Types of outcomes measures

Increasing emphasis is being placed on the importance of 'core outcome sets' as an agreed and standardised set of outcomes that should be measured and reported, as a minimum, in all trials in a specific clinical area [260]. Core outcome sets are intended to ensure that selected outcomes are relevant to key stakeholders and to overcome problems with heterogeneity in outcome measurements that have hindered the pooling of data in systematic reviews. Ongoing work as part of the COMET (Core Outcome Measures in Effectiveness Trials) initiative is seeking to establish rigorous methods for developing core outcome sets [260, 261]. Consensus-based core outcome sets for trials of interventions aimed at improving the appropriateness of polypharmacy in older people in primary care and multimorbidity research have been published [262, 263].

To be eligible, studies had to include at least two outcomes derived the aforementioned core outcome sets [262, 263]. In brief, Smith *et al.* developed a core outcome set for multimorbidity research, consisting of 17 outcomes over five groups. The three priority outcomes in the multimorbidity set included health-related quality of life, mental health, and mortality [263]. For trials aimed at improving the appropriateness of polypharmacy in older people in primary care, Rankin *et al*. produced a core outcome set consisting of 16 outcomes across six themes, with seven priority outcomes (medication appropriateness, medication regimen complexity, medication side effects, quality of life, mortality, serious ADRs and falls) [262]. Table 2.1 provides a combination of the two core outcome sets.

Table 2.1. Combination of the core outcome sets for multimorbidity and polypharmacy (adapted from [262, 263])

Themes	Outcomes
Clinical outcomes	Mortality*
	Mental health*
Health systems-related outcomes	Healthcare utilisation (GP visits, hospital admissions)
	Healthcare costs
	Quality of healthcare (patient-rated)
Patient knowledge and behaviour	Patients' knowledge
	Self-rated health
	Self-management behaviour
	Self-efficacy
Medication-related outcomes	Medication appropriateness*
	Serious ADRs*
	Medication regimen complexity*
	Medication side effects*
	Adherence
	Clinically significant drug interactions
	The number of 'regular' medicines prescribed
	Therapeutic duplication, prescribing errors
Patient-related outcomes	Quality of life/health-related quality of life*
	Falls*
	Treatment/medication burden
	Cognitive function
	Physical function
	Activities of daily living function
	Physical activity
Consultation-related outcomes	Communication
	Shared decision making
	Prioritisation

* = priority outcomes - all studies should consider them and then consider the others depending on the individual study. Abbreviations: *ADR* adverse drug reaction, *GP* general practitioner

2.3.3. Search strategy

A systematic search of six electronic databases covering the medical and pharmaceutical peer-reviewed literature was undertaken (PubMed, Embase, Cochrane CENTRAL, CINAHL, AMED, and PsycINFO) from each database's inception to the search date (April 2020), using both free text terms and Medical Subject Headings (MeSH) that were devised in accordance with the subject librarian for the School of Pharmacy and Pharmaceutical Sciences in Trinity College Dublin, Mr Andrew Jones. Search terms focused on keywords and controlled vocabulary related to 'pharmacogenetics', 'pharmacogenomics', 'multimorbidity' and 'polypharmacy'. No restriction was placed on the language of publication in the search; however, studies not published in the English language were excluded.

The search strategy for each of the databases is provided in Appendix 2.2. The search terms were adapted according to each database, and where applicable, variations and truncations were applied (all keywords were indexed to suitable thesaurus). Ongoing or unpublished trials were searched for on the following trial registry sites: ClinicalTrials.gov, the EU Clinical Trials Register, and the WHO International Clinical Trials Register. The 'grey literature' (*e.g.,* Government reports and theses available from the Irish Health Service Executive's repository Lenus and Trinity College Dublin's open-access repository TARA) was searched to identify any other relevant studies. The reference lists of eligible papers, identified through the electronic search, were hand-searched.

2.3.4. Study selection

Study selection involved a two-phase screening and eligibility determination process by two reviewers independently through Covidence [264]. The search results were combined and duplicated were removed. After removal of duplicates on EndNote® (the reference manager) and Covidence® (an online tool developed to streamline the systematic review process), the PhD Candidate Joseph O'Shea (JO'S) and Prof. Cristín Ryan (CR) independently screened titles and abstracts of each search result for relevancy. References were screened and sorted into 'yes' (the study is eligible), 'maybe' (eligibility is unclear from the title and abstract alone), or 'no' (the study is ineligible) categories within the Covidence® platform. If information from a paper appeared missing, or the full article was not available, study authors were contacted to request the article, or an interlibrary loan requested.

Following this, the full-text papers of articles categorised as 'yes' and 'maybe' were retrieved and assessed for inclusion by two independent reviewers (JO'S, Catherine Keenan (CK)). Any disagreements over study inclusion in both stages of screening were discussed and between the two reviewers for that article, and if agreement could not be reached, it was discussed with a third reviewer (Prof. Mark Ledwidge (ML)). To address the research question, included studies assessed the impact of pharmacogenomic testing on patient outcomes derived from the aforementioned core outcome sets in patients with multimorbidity and/or prescribed polypharmacy.

2.3.5. Data extraction

Data extraction forms were pre-defined and developed *a priori*, following an example from the Cochrane Collaboration. The data extraction form was piloted independently by two reviewers (JO'S and CK), using two agreed studies and modifications were discussed and agreed. Refinements were made before using the data extraction form to extract data from the remaining studies. Data extraction was conducted by two reviewers independently (JO'S, CK). Any disagreement, for any component of data analysis, was resolved through consensus and recourse to a third reviewer (ML). Data extracted included authors, country of study, study design, population characteristics, average number of medicines and conditions, intervention type, intervention content, length of follow-up, type of outcome(s), and the study findings and conclusion(s). The data extraction form used in this systematic review is available in Appendix 2.3.

2.3.6. Quality assessment

The reviewers (JO'S, CR) conducted independent risk of bias assessments on all included studies using tools developed by the Cochrane Collaboration. The Cochrane Risk of Bias 2.0 (RoB 2) and Risk of Bias in Non-randomised Studies – of Interventions (ROBINS-I) tools were used to assess randomised and non-randomised studies respectively [265, 266]. The RoB 2 tool provides a framework for assessing the risk of bias against five domains: (i) the randomisation process; (ii) deviations from the intended interventions; (iii) missing outcome data; (iv) measurement of the outcome; and (v) selection of the reported result. Each domain contains numerous questions which require an answer from five possible options (i) yes, (ii) probably yes, (iii) no, (iv) probably no, or (v) no information. The answers were cumulated to

provide each domain with a risk of bias judgement of low/high/some concerns. The judgements of each domain then provided an overall risk of bias of low/high/some concerns for the entire study.

ROBINS-I contains seven domains: (i) bias due to confounding; (ii) bias in selection of participants into the study; (iii) bias in classification of interventions; (iv) bias due to deviations from intended interventions; (v) bias due to missing data; (vi) bias in measurement of outcomes; and (vii) bias in selection of the reported result. Similar to RoB 2, each domain in ROBINS-I includes several questions with five possible responses of (i) yes, (ii) probably yes, (iii) probably no, (iv) no, or (v) no information. Each domain was then rated as having a low/moderate/serious/critical level of bias or no information. The judgement of each domain was then combined to provide an overall risk of bias judgement of low, moderate, serious, critical or no information. Studies were not excluded based on the risk of bias assessment. The risk of bias figures were generated using robvis, a web app designed for visualising risk of bias assessments performed as part of a systematic review [267]. The tool creates traffic light plots of the domain-level judgments for each individual result formatted according to the risk of bias assessment tool used to perform the assessments (*e.g.,* RoB 2 and ROBINS-I).

2.3.7. Data analysis

An in-depth narrative synthesis of studies meeting the inclusion criteria was conducted. Narrative synthesis involves combining the findings of multiple studies using a textual approach to create a summary and explain the findings from the included studies [268].The method of narrative synthesis is used when substantial methodological and clinical heterogeneity between studies render studies non-amenable to meta-analysis. Tables were prepared for the extracted data. Studies noted as ongoing in the published systematic review have been reassessed and included in this chapter if completed. A consensus approach was taken to develop the process model (Section 2.4.5); following data extraction, the results were discussed, and process agreed to by the research team (JO'S, CR and ML).

2.4. Ethical standards

Ethical approval was not a requirement for this systematic review; nevertheless, ethical standards were applied in numerous forms to ensure the accuracy, integrity, and quality of the research. The protocol was developed in line with PRISMA-P [269, 270] and was reported in PROSPERO, see section 2.3.1 above, ensuring the PhD candidate and members of the review team were clear with the work undertaken. Transparency of study protocol and subsequent results is an important aspect of conducting a systematic review [271]. The study findings have been published in The Pharmacogenomics Journal [272], which includes reference to the protocol on PROSPERO, and acknowledgement of all researchers involved in the review.

2.5. Results

2.5.1. Search results

Electronic searches of the databases and hand searching of reference lists of the included studies identified 12,433 records. Following removal of duplicate records, 10,725 titles and abstracts were screened. Of these, 10,623 studies did not meet the inclusion criteria, and were excluded. A total of 102 full text articles were retrieved and assessed for eligibility. Based on the inclusion criteria, 15 articles were identified as eligible, and 87 articles were excluded. Reasons for exclusion can be found in the PRISMA Flow Diagram (see Figure 2.1) and in the Characteristics of Excluded Studies table (Appendix 2.4).

Fifteen studies were eligible for inclusion, one which is still ongoing. Therefore, the narrative synthesis included 14 studies [172, 273-285]: six non-comparative studies [278, 280-284], three observational studies [277, 279, 285], and five randomised controlled trials [172, 273-276]. Meta-analysis was not suitable for the randomised studies due to the clinical and methodological diversity in these studies owing to variability in the outcomes assessed. A descriptive overview of the included studies is presented in the next section along with a narrative summary outlining how each study reported the use of pharmacogenomics to improve economic, clinical, and humanistic outcomes for patients with multimorbidity and prescribed polypharmacy.

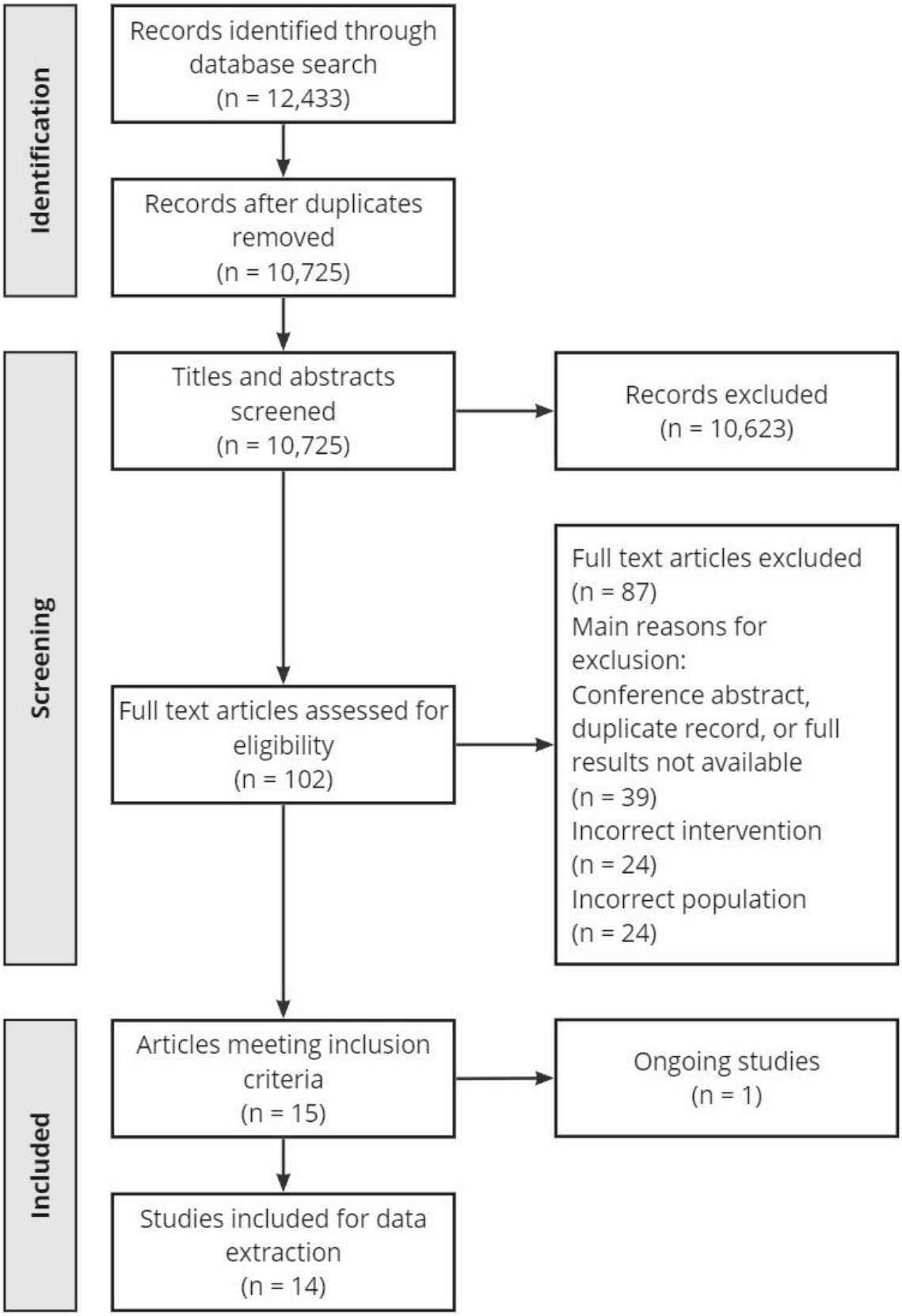

Figure 2.1. PRISMA flow diagram of the literature searching process

2.5.2. Description of included studies

Fourteen studies investigated panel-based pharmacogenomic interventions in adults with multimorbidity and prescribed polypharmacy. A summary of the characteristics of included studies is presented below in Table 2.2. Studies frequently omitted counts of chronic conditions and the definition of polypharmacy varied across studies. The average number of medications per patient was reported. The studies were predominantly US-based [273, 275-281, 283, 284], with the remainder conducted in Canada [282] and Europe (Austria, Germany, Greece, Italy, the Netherlands, Slovenia, Spain, and the UK) [172, 274, 285]. The comparative studies often used a control group untested for pharmacogenomics [172, 273, 275, 277], or the control group was tested and the results withheld [274, 276]. In the nested case-control and cross-sectional study, each participant underwent pharmacogenomic testing; in the former, comparisons were made between cases with frequent and controls with infrequent hospitalisations [279], while the latter made comparisons against a group lacking drug-gene interactions [285].

The included studies predominantly took place in primary care, except for one study assessing the impact of pharmacogenomic profiling on in-hospital prescribing [281]. The majority of the included studies involved explicit pharmacist-led medication management with recommendations forwarded to patients' physicians. Mean age ranged from 57 to 78 years, the proportion of males ranged from 31-67%, the mean number of conditions and medications ranged from 5-8 and 4-20 respectively, and most participants were of Caucasian ethnicity (67-99%). Similarities were evident in the genetic testing approach, with a core panel consisting of CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5 and VKORC1. Variants and SNPs analysed differed considerably overall. Genes unrelated to drug ADME were also tested; for example, HTR2A (5-hydroxytryptamine (serotonin) receptor 2a), a gene of interest in psychiatry and neurology. The most extensive panel was used by Swen *et al.* (50 germline-variant alleles located within 12 genes). Various CDS systems were employed: UPGx GIMS [172], YouScript [273, 275, 277], GENETWORx [278, 279], IDgenetix [276, 284], GeneYouIn [282], uMETHOD Health [280], Genomic Prescribing System [281], and PRIMER [283].

Table 2.2. Description summary of included studies

Source	Study design	Study description	Participants	Mean no. of comorbidities	Mean no. of medications
Randomised trials					
Elliott 2017 [273] United States	Randomised controlled trial	IG: Pharmacist-led MTM on patients undergoing PGx testing followed by development of DDI, DGI and DDGI risk profiles using YouScript CDST. PGx test results and prescribing suggestions forwarded to physicians. CG: Comparisons made against an untested group who received usual care (standard pharmacist MTM). Genes: CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5 and VKORC1.	Older polypharmacy patients IG = 57 CG = 53	Not reported	IG = 11.6 CG = 11.8
Just 2021 [274] Germany	Randomised controlled trial	IG: Age, renal function, genotyping results, potential DDIs, and results of the HAS-BLED and the CHA2DS-VASc scores were used to create an individualised risk assessment leaflet that was sent to the patients' GP. CG: Received standardised risk assessment and a look-a-like leaflet, in which single points were mentioned, but in a general and non-personalised way (standard of care). Genes: CYP2C9, CYP2C19 and VKORC1.	Older (aged 60 years and over) multimorbid patients IG = 167 CG = 173	Not reported; >2 concomitant diseases required for inclusion	Only reported the median number of medications IG = 13 CG = 13
Kim 2018 [275] United States	Randomised trial (post-hoc analysis)	IG: Pharmacist-led MTM using YouScript with and without PGx (IG1 and IG2 respectively). IG1 underwent PGx testing followed by development of DDI, DGI and DDGI risk profiles. PGx test results and prescribing suggestions forwarded to their physicians. IG2 (untested for PGx) was used to assess	Polypharmacy patients IG1 = 58 IG2 = 180	IG1 = 6.5 ± 2.8 IG2 = 6.6 ± 2.6	IG1 = 11.5 ± 4.1 IG2 = 11.5 ± 4.3

Source	Study design	Study description	Participants	Mean no. of comorbidities	Mean no. of medications
		effect of CDST alone. CG: Comparisons made against an untested group who received usual care (standard pharmacist MTM). Genes: CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5 and VKORC1.	CG = 104	CG = 6.2 ± 2.2	CG = 11.2 ± 3.8
Saldivar 2016 [276] United States	Randomised trial (non-comparative results)	All patients tested; those with passing results randomised to IG or CG (results listed only for IG). IG: Pharmacist-led MTM using IDgenetix to generate DDI and DGI recommendations. PGx test results and prescribing suggestions forwarded to their physicians. CG: PGx results withheld. Genes: CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, VKORC1, CYP1A2, HTR2A, HTR2C, SLC6A4, SLC6A2, COMT, OPRM1, SLCO1B1, MTHFR, F2 and F5.	Patients in a long-term care facility n = 132	Not reported	12.0
Swen 2023 [172] Austria, Greece, Italy, the Netherlands, Slovenia, Spain, and the UK	Cluster-randomised crossover implementation study	IG: PGx test results available to HCP on a CDST and Medication Safety Code cards for patients. Adherence to DPWG guidelines was not mandatory and left to the discretion of the treating HCP. CG: Patients received standard clinical care and a plastic card indicating their participation in the PREPARE study. CG patients were genotyped after completion of follow-up. Patients in both groups were contacted at regular intervals to collect data on the occurrence and severity of ADRs. Genes: CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A5, DPYD, F5, HLA-B, SLCO1B1, TPMT, UGT1A1 and VKORC1	Adult patients with a first prescription for a DPWG actionable drug IG = 3,342 CG = 3,602	Not reported	IG = 6.85 ± 5.8 CG = 8.83 ± 7.1

Source	Study design	Study description	Participants	Mean no. of comorbidities	Mean no. of medications
Non-randomised trials (observational and non-comparative studies)					
Brixner 2016 [277] United States	Non-concurrent cohort study	IG: Pharmacist-led MTM on patients undergoing PGx testing followed by development of DDI, DGI and DDGI risk profiles using YouScript CDST. PGx test results and prescribing suggestions forwarded to their physicians. CG: Comparisons made against an untested historical cohort (matched on key variables via a propensity score method). Genes: CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5 and VKORC1.	Older polypharmacy patients IG = 205 CG = 820	Not reported	4.0*
Finkelstein 2016 [278] United States	Non-comparative case series study	Participants offered PGx testing by their treating physician to optimise their therapy. GENETWORx was used for analysis. The testing facility provided detailed findings reports and basic education materials explaining the general principles of PGx testing. Genes: CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5 and VKORC1.	Older polypharmacy patients n = 3	7.0	20.3
Finkelstein 2016 [279] United States	Nested case-control study	Cases: chosen from eligible patients with high rates of hospitalisations. Controls: included eligible patients with infrequent hospitalisations matched to cases on age, race, ethnicity, and chronic disease score. PGx testing performed on all patients. GENETWORx used for the analysis. The testing facility provided PGx reports and education materials explaining the general principles of PGx testing. DGI severity was confirmed by an independent pharmacist review. Genes: CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5 and VKORC1.	Older polypharmacy patients IG = 6 CG = 6	IG = 8.2 ± 1.2 CG = 8.2 ± 2.0	IG = 14.3 ± 5.3 CG = 14.0 ± 2.9

Source	Study design	Study description	Participants	Mean no. of comorbidities	Mean no. of medications
Keine 2019 [280] United States	Non-comparative case series study	Patients with a family history of Alzheimer's disease, mild cognitive decline or mild Alzheimer's disease were enrolled. The uMethod Health precision medicine platform was used to analyse DDIs DGIs, anticholinergic burden and depression-inducing drugs. PGx prescribing suggestions reviewed by a physician and forwarded to patients. Genes: Gene panel is not detailed.	Older polypharmacy patients n = 295	Not reported	11.5
Lee 2019 [281] United States	Non-comparative case series study	Genotyped 1200 Patients Project participants analysed for hospitalisations (n = 20) to examine medication changes, actionable PGx information and potential prescribing actions using CPIC, FDA and Genomic Prescribing System CDST PGx information. Genes: CYP2C9, CYP2C19, CYP2D6, CYP4F2, VKORC1, SLCO1B1, KIF6, GNB3, LTC4S, ADD1 and GLCCI1.	Polypharmacy outpatients n = 867	7.6	8.9
Papastergiou 2017 [282] Canada	Non-comparative case series study	Pharmacists trained in PGx enrolled patients they thought would benefit from the service. Geneyouin provided the tests and evidence-based reports (CPIC and FDA) highlighting patients' metabolic profiles and risk medications. PGx test results and prescribing suggestions forwarded to physicians. Genes: CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, VKORC1, CYP1A2, OPRM1 and SLCO1B1.	Community pharmacy patients n = 100	Not reported	4.9
Reynolds 2017 [283] United States	Non-comparative case series study	Physicians ordered PGx testing for eligible patients; genotypes were correlated to predicted phenotypes on the PRIMER report. Pharmacists performed MTM (DDIs and DGIs) and ranked the severity of interactions. PGx test results and prescribing suggestions forwarded to physicians.	Polypharmacy patients n = 705	Not reported	12.0

Source	Study design	Study description	Participants	Mean no. of comorbidities	Mean no. of medications
		Genes: CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, VKORC1, CYP1A2, SLC6A4, COMT, OPRM1, SLCO1B1, F2, F5 and MTHFR.			
Sugarman 2016 [284] United States	Non-comparative case series study	Pharmacist-led MTM using IDgenetix to generate DDI and DGI recommendations. PGx test results and prescribing suggestions forwarded to their physicians. Genes: CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, VKORC1, CYP1A2, HTR2A, HTR2C, SLC6A4, SLC6A2, COMT, OPRM1, SLCO1B1, and MTHFR.	Patients in a long-term care facility n = 112	Not reported	19.0
Van der Wouden 2019 [285] The Netherlands	Cross-sectional study	Pharmacists requested PGx tests for eligible patients to guide therapy. DPWG guidelines provided the recommendations that were sent to pharmacists and physicians. PGx data was saved in both electronic medical records for future use; follow-up was 2.5 years. Patients put into three groups: (1) did not encounter a DGI or encountered a DGI and HCP (2) adhered or (3) did not adhere to guidelines. Genes: CYP2C9, CYP2C19, CYP2D6, CYP3A5, SLCO1B1, TPMT, VKORC1 and DPYD.	Community pharmacy patients G1 = 138 G2 = 49 G3 = 9	G1 = 4.4 ± 2.4 G2 = 4.9 ± 2.6 G3 = 4.4 ± 2.3	G1 = 3.9 ± 3.4 G2 = 4.0 ± 2.9 G3 = 4.4 ± 3.0

Abbreviations*: ADR* adverse drug reaction, *CDST* clinical decision support tool, *CG* control group, *CPIC* Clinical Pharmacogenetics Implementation Consortium, Dutch Pharmacogenetic Working Group, *DDI* drug-drug interaction, *DDGI* drug-drug-gene interaction, *DGI* drug-gene interaction, *ED* emergency department, *FDA* U.S. Food and Drug Administration, *G* group, *HCP* healthcare professional, IG intervention group, *MTM* medication therapy management, *PGx* pharmacogenomic, *OASIS* Outcome and Assessment Information Set; * D. Brixner contacted; estimated the majority were on four or more medications

2.5.3. Summary of results

The included studies reported on the impact of pharmacogenomic interventions on healthcare utilisation, healthcare costs, the incidence of ADRs, and clinical decision-making. The highest level of evidence for the utility of pre-emptive genotyping and the largest sample size was provided by Swen *et al.'s* Pre-emptive Pharmacogenomic Testing for Preventing Adverse Drug Reactions (PREPARE) study. PREPARE was a prospective study in seven European centres with almost 7,000 patients randomly allocated to either standard care (n = 3,602) or genotype-guided care (n = 3,342) [171, 172]. The pharmacogenomics panel utilised in the trial tested for 44 variants in 12 genes relevant for 42 drugs [286].

Four studies investigated the impact of pharmacogenomic interventions on healthcare utilisation. Reductions in hospitalisations and emergency department visits were observed following genetic testing and medicines optimisation [273, 277]. Brixner *et al.* reported reductions in hospitalisations and emergency department visits by 40% ($p < 0.05$) and 70% ($p < 0.001$) respectively [277], while Elliott *et al.* found reductions of 52% ($p < 0.01$) and 42% ($p < 0.05$) respectively [273]. A 47% increase in outpatients visits ($p < 0.0001$) in patients undergoing pharmacogenomic testing was reported by Brixner *et al.* [277]. Elevated rates of hospitalisation in older patients with pharmacogenomic polymorphisms was recorded by Finkelstein *et al.* ($p < 0.05$) [279]. Van der Wouden *et al.* found no significant differences in healthcare utilisation [285].

Estimated improvements in healthcare costs were reported in several studies. Brixner *et al.* found the cost of genetic testing was nearly or completely offset by savings resulting from decreased healthcare utilisation using mean and median national data. Using the mean, savings of $1,132 per patient were made, while the median resulted in savings of $788 during the 16-week follow-up [277]. Elliott *et al.* modelled cost saving based on Medicare average all-cause readmission and emergency department cost, yielding savings of $4,382 per patient in 8 weeks prior to the cost of intervention [273]. Two studies performed in long-term care facilities estimated cost savings of approximately $1,430 and $3,000 over 2.3 years (average length of stay) [276, 284]. Swen *et al.* will report their cost-effectiveness analysis in an upcoming paper, hypothesising that panel-based pre-emptive pharmacogenomic testing is likely to be the most cost-effective method for implementing pharmacogenomics [172].

Actionable pharmacogenomic polymorphisms were ubiquitous. The potential for enhanced medication safety through drug interaction management was demonstrated, with up to seven gene-based drug interaction recommendations per patient [273, 275-285]. Elliott *et al.* and Swen *et al.* reported most patients carried at least one aberrant CYP variant [172, 273]; of the 6,944 patients enrolled in the PREPARE study by Swen *et al.*, 93.5% carried at least one actionable variant; 48% of whom carried three or more actionable variants. Reynolds *et al.* identified drug-gene interactions in 78% of their participants [283]. Sugarman *et al.* reported medication change reasons were exclusively genetic in 28% of patients.

For patients whose medications remained unchanged, a high proportion of genetic variations that could impact future prescriptions was observed [284]. [172]. Swen *et al.* provided patients with a Medication Safety-Code card containing their pharmacogenomic results, which can be used by other HCPs during subsequent prescriptions by scanning the QR code on the card [172]. Van der Wouden *et al.* identified targets for pharmacogenomic testing, reporting the number of newly initiated prescriptions with potential drug-gene interactions increases with age and number of comorbidities and comedications, but this was not statistically concluded [285]. Lee *et al.* suggested inpatient prescribing could be informed by pre-emptive genotyping those at risk of hospitalisation (older patients prescribed polypharmacy), as many prescriptions initiated in hospital included pharmacogenomic medications [281].

The primary outcome measure in the study by Swen *et al.* was the effect of pre-emptive panel-based pharmacogenomic testing on patient-reported ADR prevalence. The results showed that genotype-guided care reduced ADRs by 30%, providing the first randomised evidence of the utility of pharmacogenomic panel-based testing [172]. The incidence of ADRs increased with higher reported numbers of drug allergies and comedications. Conversely, the German IDrug study by Just *et al.* involving older patients with multimorbidity and prescribed polypharmacy randomised to receive an individual risk assessment (including drug-drug interactions and pharmacogenomics) (n = 167) or a standardised risk assessment (without individualised information) (n = 173) found pharmacogenomic testing had no impact on the occurrence of ADRs [274]. However, the calculated sample size of the IDrug study was not met [287].

Clinical decision-making appeared reinforced by the interventions. Physicians followed between 30-79% of the MRP recommendations [172, 273, 275, 277, 282, 283]. Swen *et al.* demonstration a high level of adoption of the DPWG recommendations; overall 70% of recommendations were accepted by the physicians and pharmacists [172]. Swen *et al.* achieved systematic education of the HCPs active through an educational programme. Associations were found between physician acceptance and recommendation seriousness [275, 277] and if the recommendation involved pharmacogenomics [282].

Van der Wouden *et al.* demonstrated the importance of accurate record keeping to maintain the value of genetic testing. Within 2.5 years, a mean of 2.71 drugs for which results were available were prescribed; 24% of these were actionable drug-gene interactions. Pharmacists were found to be better able to record pharmacogenomic data than GPs (96% vs. 68%) [285]. Clinical outcomes, while prioritised in the core outcome sets [262, 263], were only described in Elliott *et al.* [273]. A statistically insignificant reduction in mortality was reported; however, the study was not powered for mortality and included this outcome post-hoc. Select quality metrics (such as pain, depression, and anxiety) and the number of falls were also recorded, demonstrating relatively small differences [273].

2.5.4. Risk of bias

The risk of bias assessment is detailed in Appendix 2.5 and summarised in Figure 2.2 and Figure 2.3. RoB 2 was used for four randomised studies [172, 273-275], while ROBINS-I was used for two non-randomised studies [277, 285]. The study by Saldivar *et al.* was designed as a randomised trial; however, it is an "initial assessment" and provides non-comparative results [276]. Similarly, the case-control study by Finkelstein *et al.* did not compare the effect of the intervention received [279]. It was not possible to assess non-comparative studies because it is a prerequisite in ROBINS-I that there is a comparative study. Non-comparative studies were considered at critical risk of bias mostly due to confounding factors [266].

Overall, the risk of bias ranged from moderate/some concerns to high risk. Using RoB 2, the article by Swen *et al.* was found to be at low risk of bias, that by Kim *et al.* and Just *et al.* had some concerns, while Elliott *et al.'s* research paper was noted as high risk of bias (Figure 2.2). Lack of blinding was considered to produce a low risk of bias due to the nature of genetic testing [172, 273-275]. Missing outcome data generated some concerns; owing to the post-hoc design of Kim *et al.*, the calculated sample size not being met in Just *et al.*, and the post-hoc addition of outcomes to Elliott *et al.* [273, 275]. The overall high risk of bias judgement in Elliott *et al.* was due to the post-hoc amendments [273].

The two studies assessed by ROBINS-I (Brixner *et al.* and van der Wouden *et al.*) were noted as moderate risk of bias (Figure 2.3). Brixner *et al.* adequately controlled for confounding using propensity scores [277], while patient factors were uncontrolled in van der Wouden *et al.* [285]. Selection of participants was based on prior-agreed inclusion criteria [277, 285]; however, follow-up and start of intervention may not have coincided in van der Wouden *et al.* [285]. Intervention groups were clearly defined, with no deviations or loss to follow-up reported. Measurement of outcomes had a moderate risk of bias (could be influenced by knowledge of intervention received) [277, 285].

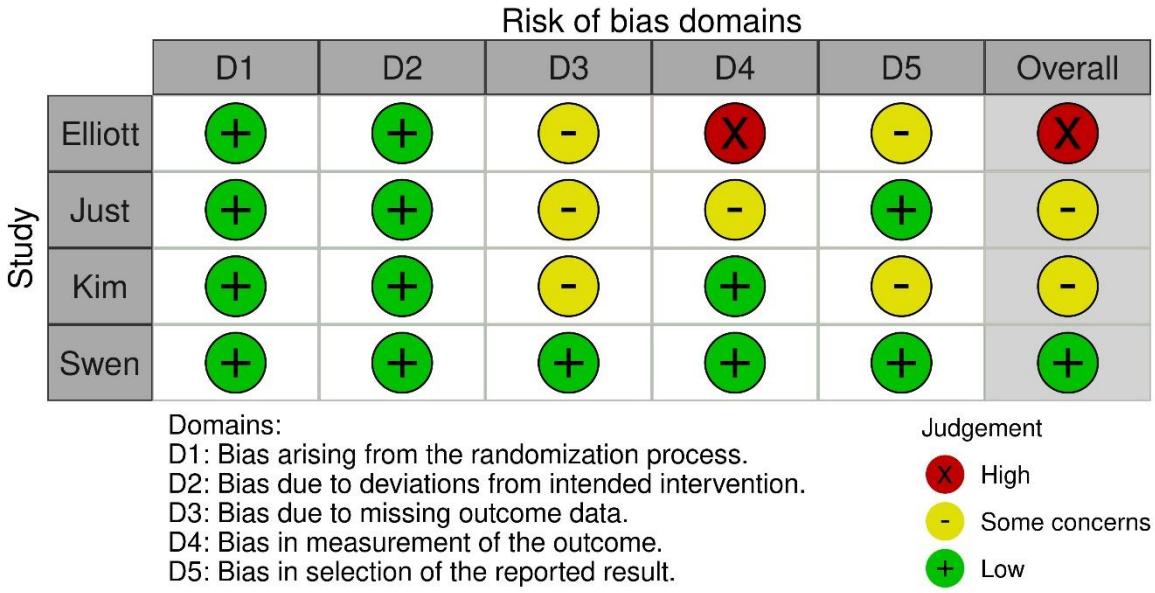

Figure 2.2. Risk of bias (RoB 2) plot of the domain-level judgements for randomised studies [172, 273-275]

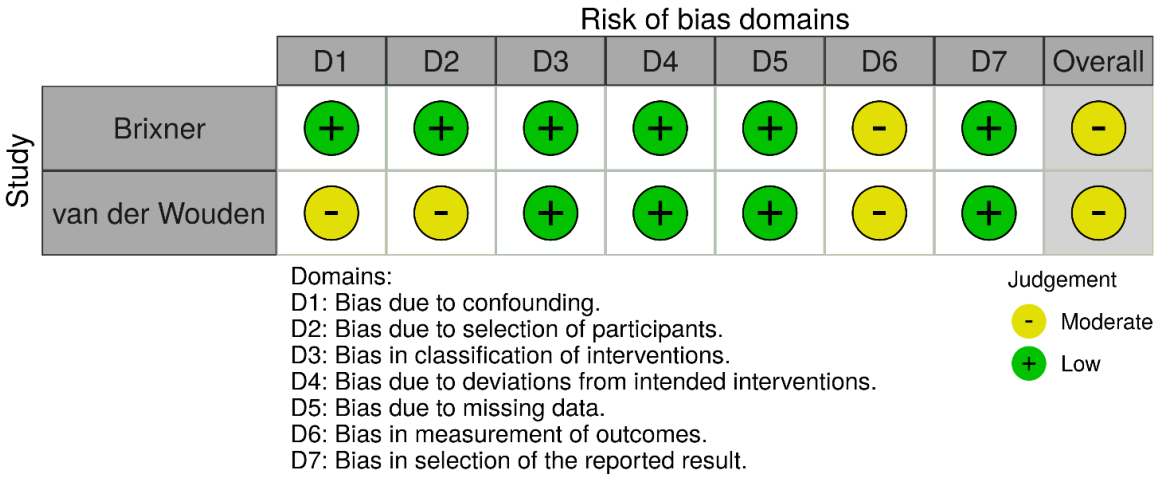

Figure 2.3. Risk of bias (ROBINS-I) plot of the domain-level judgements for non-randomised studies [277, 285]

2.5.5. General process model

To aid the development of future pharmacogenomic interventions, a process diagram derived from the steps described in each of the included studies was produced (see Figure 2.4). This pharmacogenomic general process model outlines the steps required for a pharmacogenomic intervention that can prompt medicines optimisation, patient benefit, and reduction in adverse events. This list of steps is not intended to be inclusive or prescriptive; specific clinical needs and workflow vary among healthcare settings. The steps and considerations can be adapted to individual care structures, patient needs and clinical priorities.

2.5.6. Summary of ongoing studies

Originally, the systematic review published in The Pharmacogenomics Journal had three ongoing studies [272]. Swen *et al.* and Just *et al*. has since completed their studies and have been incorporated into the included studies. While the other trial by Quinn *et al.* was eligible for inclusion, this study had not been completed by the time this report was written [288].

In the US, Quinn *et al.* (NCT04120480) are conducting a pharmacist-led randomised controlled trial involving high-risk patients prescribed polypharmacy randomised to receive pharmacogenomic-guided treatment or usual care to determine clinical and economic effectiveness [288]. The investigators hypothesise that pharmacogenomic testing and pharmacist review of medication appropriateness will lower one-year healthcare utilisation and costs compared to controls. Outcomes include healthcare utilisation, costs, medication changes, medication congruence and adherence. The study is currently active but not recruiting, with 600 patient enrolled. The estimated completion date is December 2024.

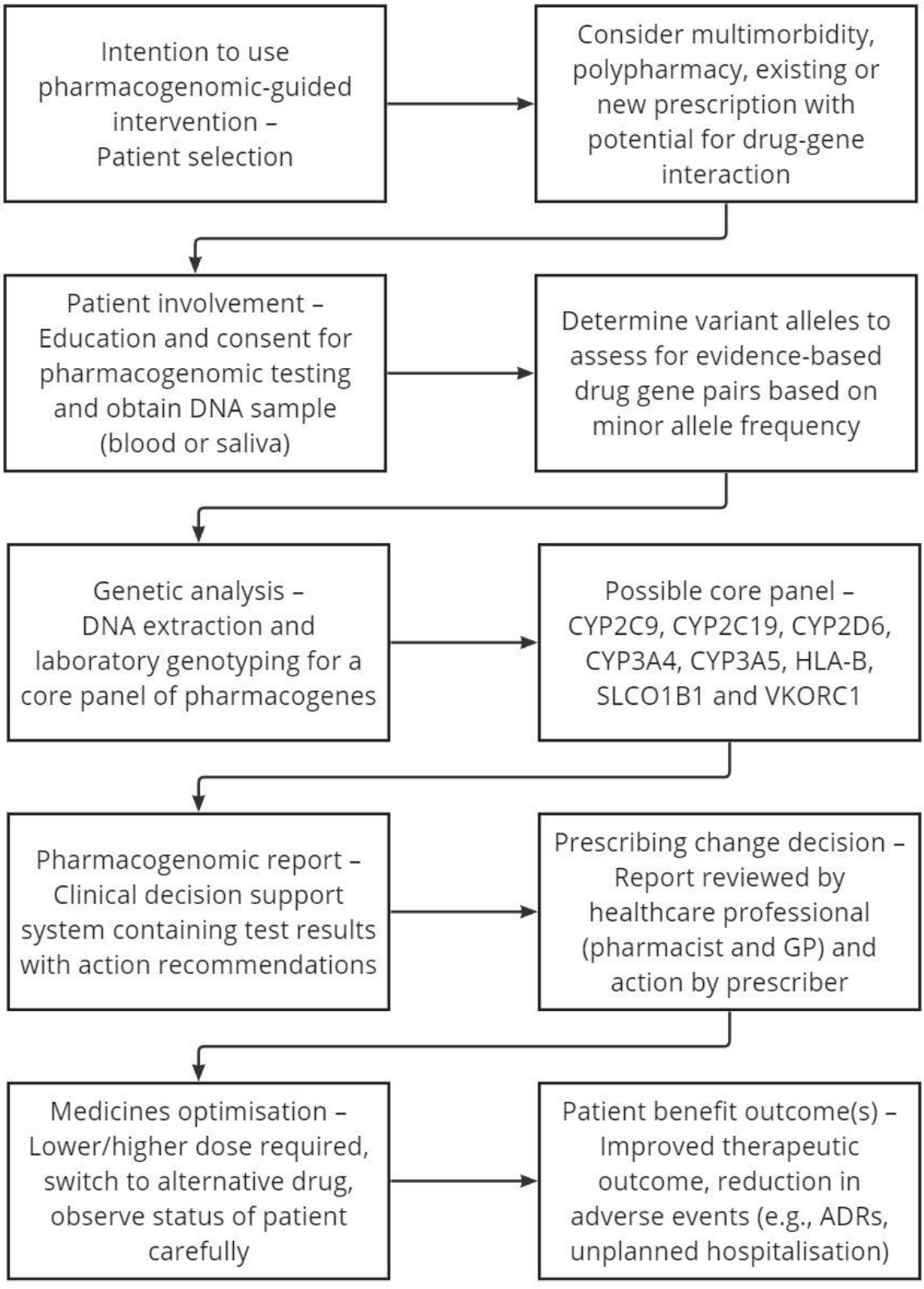

Figure 2.4. General process model for pharmacogenomic testing as an intervention

Abbreviations: *ADR* adverse drug reaction, *GP* general practitioner

2.6. Discussion

This systematic review is the first of its kind; previous systematic reviews have focused specifically on the effectiveness of single drug-gene or disease-gene pairs pharmacogenomic interventions across different clinical conditions, pharmacotherapies, population groups, and settings. This systematic review demonstrates that once the scope of the review extends beyond single drug-gene interactions there is limited available evidence. Pharmacogenomic testing in patients with multimorbidity and/or prescribed polypharmacy appears to have little coverage in the literature. Following retrieval of 10,725 records, fifteen studies were eligible for inclusion (one of which is ongoing). The included studies demonstrated the impact pharmacogenomic interventions could have for patients with multimorbidity and prescribed polypharmacy by reducing the incidence of ADRs, reducing healthcare utilisation and costs, and identifying at-risk patients to improve clinical decision-making.

In recent years, mounting evidence has supported the hypothesis that pharmacogenomic testing can have a positive impact on health outcomes and advance the development of precision medicine [165, 200]. Several institutions in the US, such as Vanderbilt University Medical Centre [208], St. Jude Children's Research Hospital [289], and the Mayo Clinic [290], have already established programmes to incorporate pre-emptive pharmacogenomic testing into clinical practice. Herein, a novel narrative synthesis of studies was presented focussing on the effectiveness of multi-drug, multi-gene pharmacogenomic interventions in the management of those with multimorbidity and/or prescribed polypharmacy.

2.6.1. Effectiveness of the interventions

The included studies by Swen *et al.* and Elliott *et al.* provide evidence from randomised controlled trials in favour of the incorporation of pharmacogenomic testing in primary care to improve outcomes for patients with multimorbidity and prescribed polypharmacy [172, 273]. While Elliott *et al.* provides evidence in a small, selected population (n = 110) [273], Swen *et al.'s* study, recently published in The Lancet, was a randomised, multi-centre trial of almost 7,000 patients seeking care in multiple therapeutic areas [172]. Swen *et al.*, demonstrated a 30% decrease in clinically relevant ADRs. Additionally, acceptance of pharmacogenomic guideline-based recommendations was high, with a 70% adoption rate

[172]. Elliott *et al.* demonstrated that comprehensive medicines optimisation delivered by clinical pharmacists, incorporating a six gene panel pharmacogenomic test along with an appropriate CDS system (YouScript®), versus usual care (drug-drug interaction screening with recommendations acted on according to clinical judgement) considerably reduced re-hospitalisations and emergency department visits. This resulted in healthcare utilisation cost savings and improved healthcare [273]. Brixner *et al.* reported similar findings [277]. Kim *et al.* and Reynolds *et al.* found pharmacogenomic testing in the management of patients prescribing polypharmacy identified more serious MRPs in comparison to those identified in the absence of patient-specific pharmacogenomic information, enabling the detection of potential problems that would not be identified through standard medicines optimisation [275, 283].

Saldivar *et al.* demonstrated the opportunity for healthcare savings solely from medicines optimisation when incorporating pharmacogenomic testing in the management of patients prescribed polypharmacy [276]. The case-control study by Finkelstein *et al.* showed an association between high hospitalisation rates and pharmacogenomic polymorphism in older adult patients prescribed polypharmacy [279]. Lee *et al.'s* findings supported this association, and discovered in these hospitalised older patients prescribed polypharmacy, initiation of new prescriptions with pharmacogenomic drugs was frequent [281]. Lee *et al.* suggest targeting this group for pre-emptive genotyping to facilitate the delivery of highly relevant information to inform inpatient prescribing [281]. Papastergiou *et al.* demonstrated the readiness of CPs to adopt pharmacogenomic screening into practice and their ability to leverage this technology to positively affect medicines optimisation for patients prescribed polypharmacy [282]. Sugarman *et al.* concluded that pharmacogenomic testing resulted in a 38% increase in the number of patients prescribed polypharmacy with medication change opportunities compared with traditional medication review, and modelled drug cost savings exceeded testing costs within the first year [284].

As evident by much of the search results being published in just the past decade, pharmacogenomics is an emerging field. The PREPARE study by Swen *et al.* is a landmark trial that sheds light on the value of pharmacogenomic testing for clinical utility and medication safety [172]. It is the first study to show the feasibility and benefits of a pharmacogenomic-panel strategy and provides evidence to support large-scale implementation of panel-based pharmacogenomics testing to make drug therapy increasingly safe. Swen *et al.'s* PREPARE study spanned numerous healthcare settings (hospitals, outpatient clinics, and pharmacies) in several European countries, using a 12 pharmacogene panel test that identified at least one actionable genetic variation in 93.5% of the population [172]. This finding supports other published studies including the Vanderbilt PREDICT study [208] and the Mayo-Baylor RIGHT 10K study [291] where pharmacogenomics was found to be relevant to the majority of the studied population.

Given the constraints under which health services operate, evidence of cost-effectiveness of pharmacogenomic testing is important. Fortunately, evidence of the cost-effectiveness of individual pharmacogenomic tests is increasing [292, 293], including a panel-based approach [294]. Most published studies evaluating cost and pharmacogenomic testing for genes with CPIC guidelines determined that pharmacogenomic-guided treatment was cost-effective or cost-saving [293]. This resonates with the findings of our systematic review; however, we await the findings of the cost-effect analysis of the PREPARE study for further clarification [172]. Consequently, pharmacogenomics may have a role in improving the current approaches to medication usage, with potential for preventing MRPs through medicines optimisation. Further good quality evidence in diverse, real-world patient populations will enable us to establish the true efficacy and utility of multi-medicine pharmacogenomics in personalised patient care, and to advance the discovery and development of appropriate patient outcome improvement strategies.

2.6.2. Heterogeneity of study designs

The heterogeneity of study designs employed in the area of pharmacogenomics should be considered. Lack of evidence from gold standard randomised controlled trials is frequently cited as a reason to delay implementation, despite a substantial evidence base and published guidelines. This necessity has been challenged; many argue that the perceived mandatory

requirement for prospective evidence to support the clinical validity of a pharmacogenomic test, prior to its implementation into routine care, is inappropriate and unreasonable [247, 248, 295, 296]. Of course, evidence of clinical utility is needed before implementing a pharmacogenomic test. However, confirmation of utility cannot be achieved solely by waiting for randomised controlled trials, which are at the top of the evidence hierarchy [249].

To enable implementation, all types of evidence should be considered and evaluated, such as the smaller-scale, non-randomised clinical studies, and strong observational evidence included in this systematic review [249, 297, 298]. Although observational data, that are very common in pharmacogenomics, can be prone to confounding and various biases [297, 299], they do have advantages over randomised controlled trials. Pragmatic and observational trials are conducted in the context of clinical practice, enhancing their generalisability, and they may be less costly than randomised controlled trials [300]. While the conclusions that can be drawn from included studies using such alternative designs are limited [276-285], pharmacogenomics should be viewed as a patient safety intervention, and randomised controlled trials are not always performed for many widely used patient safety strategies [301]; notable examples being dose adjustments based on renal dysfunction, liver dysfunction, drug interactions, and other patient-specific characteristics [254].

In conclusion, classical randomised controlled trials with large sample sizes, such as Swen *et al.'s* PREPARE study [171, 172], have a valid place in the evaluation of healthcare interventions. However, our understanding of how well pharmacogenomic interventions will work in routine practice for patients with multimorbidity and prescribed polypharmacy would likely be enhanced by greater focus on methodological triangulation (gaining a greater understanding of a research question by studying it from different perspectives using different methodologies) to integrate evidence from different perspectives [300]. Pragmatic and observational studies have an important role to play in evaluating healthcare interventions to ensure that they are fit for purpose in routine clinical practice settings [300].

2.6.3. Implications for future research and practice

This systematic review provides various considerations for future studies. Implementation of pharmacogenomics into clinical practice has been slow, and pharmacogenomic testing has largely been restricted to certain specialist centres [302]. Reasons include a perceived lack of clarity on clinical utility and cost-effectiveness, inability to access tests, lack of knowledge on how to interpret and act on results, concerns about disruption to the normal clinical pathway, and worries over confidentiality issues [303]. This review provides insight into several of these barriers, highlighting evidence on the effectiveness of pharmacogenomic interventions to reduce healthcare utilisation and costs and improve patient outcomes. Hurdles to implementing pharmacogenomic testing as part of medicines optimisation will be explored further in Chapter 3 and Chapter 5.

The implementation of pharmacogenomic testing into clinical practice needs to be actively pursued. To this end, the Royal College of Physicians and the British Pharmacological Society produced a report with recommendations to facilitate its implementation [214]. These recommendations were presented in Chapter 1 (Section 1.6.4); the need for appropriate funding, CDS systems, HCP education and training, and clear lines of communication were highlighted. As shown in this systematic review, the incorporating pharmacogenomic testing into routine patient care will require multidisciplinary expertise, including HCPs to coordinate patients' genetic results with their medications, specialists in health economics, as well as ethical, legal, and social expertise to ensure that inequalities are not exacerbated [194].

The current approach to medicines optimisation usually does not incorporate pharmacogenomics as a cause of MRPs. This studies included in this systematic review demonstrated that pharmacogenomics is indeed a source of MRPs, constituting a new dimension to conventional drug interaction assessment processes. Moreover, patients prescribed polypharmacy are susceptible to phenoconversion; the mismatch between the genotype-based prediction of CYP450-mediated drug metabolism and the true capacity of an individual to metabolise drugs due to nongenetic factors [304]. Phenoconversion can result from the use of concomitant medication (there are over ninety drugs known to inhibit CYP enzyme activity [305]), comorbidities, or other factors such as smoking [304]. The effect of phenoconversion may differ per genotype [304].

In a retrospective analysis of over 20,000 patients referred for pharmacogenomic testing, Hocum *et al.* reported that 47% of interactions involving genes were significant (*i.e.,* changing the medication regimen or adjusting the dose recommended) and can lead to side effects and ADRs [306]. In this study, 24.6% of these interactions were drug-gene interactions while 22.4% were drug-drug-gene interactions [306]. The sheer number of patients with risk phenotypes (up to 93.5% with one aberrant CYP variant and 48% with three or more [172]), as well as the prevalence of drug-gene interactions (up to seven gene-based drug interaction recommendations per patient identified in this systematic review) and drug-drug-gene interactions suggests that pharmacogenomic testing in all patients prescribed polypharmacy may be beneficial, regardless of patient age. Future studies should focus on the use of CDS systems using algorithms to account for drug-drug-gene interactions.

This area of clinical systems and pathways needs more work in terms of pharmacogenomics implementation [194]. This step will require country-specific expertise in implementation science. For healthcare systems with limited electronic health infrastructure, the "Medication Safety Code card" used by Swen *et al.* may be a viable option to make pharmacogenomic data and CDS available [171, 307]. This card is part of a mobile-based CDS system that is independent of existing information technology infrastructures, and after scanning the quick response code, enables retrieval of patient-relevant pharmacogenetic dosing guidelines [307]. For the widespread utility of pharmacogenomics, CDS systems that combine at a minimum drug-drug, drug-gene, and drug-drug-gene interactions during the optimisation process are crucial. Further consideration around alert fatigue is also relevant.

Future studies should incorporate additional factors such as herbal medicines, diet, and drug-disease interactions, duration of treatment considerations, and potentially inappropriate medications. To investigate the appropriateness of prescribed medications, various validated screening tools exist that can be used to improve the quality and safety of prescriptions for older patients, such as the Screening Tool of Older Persons' Prescriptions (STOPP) and Screening Tool to Alert to Right Treatment (START) that highlights potentially inappropriate medications and potential prescribing omissions [308, 309]. These tools also currently lack pharmacogenomic consideration [257]. An approach combining validated screening tools with these peer-reviewed and evidence-based pharmacogenomic guidelines could be used to improve outcomes in patients with multimorbidity and prescribed polypharmacy.

A collaborative, primary care approach involving GPs, pharmacists, and patients was shown to underly pharmacogenomic interventions. Appropriately trained pharmacists demonstrated their ability to take a prominent role in the clinical application of pharmacogenomics, an opinion that is supported by the American Society of Health-System Pharmacists [310]. Reasons for this include their expertise in medicines (knowledge of pharmacokinetics and pharmacodynamics [311]) and dedication to medication surveillance, the unique resource they provide to health systems and patients, the continued expansion in the scope of pharmacy practice, and their readiness to implement pharmacogenomics [282]. This is supported by the majority of studies included in this review involving pharmacist-led medication management and pilot studies performed in pharmacy settings [312-316].

Although genetic testing in pharmacy practice may be appropriate, comprehensive educational programmes, such as continuing professional development courses, would be required to improve pharmacists' knowledge, readiness and comfort in applying pharmacogenomics in their approach to patient-centred care [317, 318]. For instance, in the US, a survey of 101 CPs determined the majority of CPs are interested in incorporating personalised medicine services into their practices, but they require further education to do so [319]. The ability to record the results of pharmacogenomic tests in the patient's medication record to inform current and future prescribing is a pivotal facilitator to clinical

utility and cost-effectiveness [285]. Consequently, the role of the pharmacist in interventions adhering to pharmacogenomic guidelines employing CDS systems should be investigated.

Another barrier to the implementation of pharmacogenomics is that some clinicians and payers consider some amount of trial and error to be an inevitable part of medication use, especially for less expensive medications [320]. To embrace pre-emptive pharmacogenomics, this mind set must shift from accepting poor prescribing outcomes toward preventing harm and using all available information to select the right medication at the right dose for the right patient from the first prescription. Additionally, Munir Pirmohamed recommends that the implementation of pharmacogenomics should be accompanied by continuous monitoring in real-world practice so that the process is continually refined to optimise patient outcomes [194].

2.6.4. Strengths and limitations

This review is the first to investigate the effectiveness of pharmacogenomic interventions to improve outcomes for patients with multimorbidity and/or prescribed polypharmacy and has identified a gap in the literature focusing on such interventions in this patient cohort. This review is strengthened by its pragmatic focus, examining the effectiveness of multi-drug pharmacogenomic-guided therapy in the care of those with multimorbidity or prescribed polypharmacy compared with the established literature focusing on one singular drug, disease, or limited drug-gene combinations. The search strategy was developed in consultation with Trinity College's subject librarian and applied to six databases to provide an extensive search. This coupled with the range of study types included in the predefined inclusion and exclusion criteria ensure a wide range of studies could be captured in this review (10,725 titles and abstracts were screened as part of this review). This review placed no restriction on geographical region, enabling us to have a broader view of pharmacogenomic interventions internationally. Our review is also strengthened by the robust methodology used. This systematic review was developed in accordance with the PRISMA statement and Cochrane tools were used to assess the risk of bias.

This study has some limitations to consider. Firstly, only a narrative analysis was performed due to significant heterogeneity in the articles included. Thus, the results only provide a high-level representation of the impact of pharmacogenomic testing in patients with multimorbidity and/or prescribed polypharmacy. Second, we are constrained by the sparsity of evidence available on the efficacy of pharmacogenomics in this area. The dearth of gold-standard randomised controlled trial evidence in this area necessitated the need to include observational studies and non-comparative studies. Thirdly, as noted previously, there is no consensus on the definition of polypharmacy. This review defined polypharmacy as four or more medicines; therefore, studies that defined polypharmacy as less than four, or the average number of medications prescribed per patient was less than four, were excluded. In studies reporting the averages, it is possible that a subset of the study participants could be prescribed less than four medicines. Fourthly, this review was limited to articles published in the English language. Finally, studies undertaken in multimorbid populations with a specific focus on a single drug or drug class were not included.

2.7. Conclusion

The incorporation of pharmacogenomic testing into the medicines optimisation process could have significant benefits for health service providers and for patients by reducing healthcare utilisation and healthcare costs, enhancing identification of clinically significant drug interactions and ADRs, and improving clinical decision-making. We found limited evidence on the efficacy of pharmacogenomic interventions to improve outcomes in patients with multimorbidity or prescribed polypharmacy due to a lack of methodologically robust, high-quality studies, small sample sizes, and relatively short follow-up durations. However, the landmark PREPARE study by Swen *et al.* and the small, randomised study by Elliott *et al.* provided encouraging results using a multi-gene, multi-disease, multi-drug pharmacogenomic approach as part of medicines optimisation [172, 273]. Using methodological triangulation, we conclude that pharmacogenomic-guided therapy holds promise for individualising therapy.

Chapter 3

Public perceptions of pharmacogenomic services in Ireland - are people with chronic disease more likely to want service availability than those without?

A questionnaire study

3. Chapter 3: Pharmacogenomics questionnaire

3.1. Introduction

As outlined in Chapter 1, HCPs have long cared for patients through provision of individualised, patient-centred therapeutic plans; however, little attention has been given to the unique role of a patient's genetic profile in driving therapeutic success or failure. In this regard, pharmacogenomic testing supports precision approaches to prescribing by enhancing identification of potentially ineffective and/or harmful drugs, thereby improving drug therapy efficacy and reducing the incidence of adverse drug responses [171, 321, 322]. The systematic review presented in Chapter 2 demonstrated that the use of pharmacogenomic interventions in medicines optimisation for patients with multimorbid chronic disease and polypharmacy could have significant benefits [272]. Most notably, the landmark PREPARE randomised controlled trial by Swen *et al.* involving close to 7,000 patients, in multiple healthcare settings across seven countries, demonstrated that pharmacogenomic testing reduced a patient's chance of significant ADR by one-third compared to a patient who received treatment as usual [172].

As noted in Chapter 1, medicines optimisation is a patient-centred approach aimed at ensuring the best clinical outcomes for patients through the safe and effective use of medicines [138-140]. Medicines optimisation incorporates many aspects of improving medication use and is fundamental to addressing the challenges posed by multimorbidity and polypharmacy [138-140]. However, current approaches to medicines optimisation do not incorporate pharmacogenomics and the scientific evidence base for application of pharmacogenomics amongst patients with chronic diseases, multimorbidity and polypharmacy is limited [272]. In the outpatient setting, the American Pharmacists Association issued a paper supporting the CP's role in the implementation of pharmacogenomics through medicines optimisation services [323]. The similarities in focus between medicines optimisation (optimising therapeutic outcomes for patients) and pharmacogenomics (identifying drug-gene interactions for an individual patient) were highlighted, and the pharmacist was cited as a logical HCP to integrate pharmacogenomics into practice [323].

While studies have explored public understanding of and attitudes towards pharmacogenomics [320, 324-334], few studies specifically investigated the views of people with chronic diseases. Pharmacogenomics remains at the forefront of precision medicine and is gaining momentum in healthcare delivery internationally, with various completed and ongoing implementation studies in the US, Canada, Europe, and Asia (largely limited to specialist secondary and tertiary care settings) [171, 321, 322]. Pharmacogenomic testing can be pre-emptive to provide genetic data for medicines optimisation at point of initial prescribing, or reactive in response to treatment failure or an ADR. The use of a pre-emptive multigene panel has the potential to provide a lifetime's worth of test results applicable to multiple drugs and is emerging as a best practice [199, 291, 310]. This approach to pharmacogenomic testing could have a high impact on medicines prescribed across primary care.

For instance, Youssef *et al.* analysed a large community pharmacy database in the UK and found approximately 20% of all new prescriptions for 56 pharmacogenomic drugs newly initiated in primary care require a therapeutic intervention according to guidelines published by the CPIC and the DPWG [256]. Four genes (CYP2C19, CYP2D6, HLA-B and SLCO1B1) accounted for 95.8% of all drugs initiated with an actionable drug-gene interaction, affecting commonly prescribed drugs such as codeine, citalopram, allopurinol and simvastatin respectively [177, 256]. Youssef *et al.* concluded that should the UK population be pre-emptively tested for their panel of genes, primary care prescribing will be significantly affected, as approx. 9% of the first prescriptions for these 56 drugs would require a direct intervention as per CPIC and/or the DPWG guidelines [256]. Kimpton *et al.* also demonstrated that exposure of primary care patients in the UK to pharmacogenomic drugs is extremely common [223]; 8-in-10 patients were exposed to at least one pharmacogenomic drug over a 20-year period, with pharmacogenomic drugs comprising 16% of all drugs prescribed during that time. Three pharmacogenes (CYP2C19, CYP2D6 and SLCO1B1) accounted for >95% of these common pharmacogenomic drugs [223].

Consequently, as precision medicine grows, it is anticipated that the demand for HCPs in primary care to apply principles of pharmacogenomics in practice will rise sharply [335-337]. Much of the interest in pharmacogenomic and other genomic tests has been driven

at the patient level by growth in the DTC genetic testing marketing [210], which is expected to reach €8.17 billion by 2030 [338]. This uptake in patient and provider interest in pharmacogenomic testing has been particularly notable in the primary care setting, where importantly, most prescribing and dispensing of medicines occurs [339]. Thus, there is a need to upskill the primary care workforce at large to improve its genetic literacy [340]. Nevertheless, regulators have raised concerns about the interpretation and integration of DTC pharmacogenomic tests into routine healthcare [341, 342].

In accordance with this, the Mayo-Baylor RIGHT 10K Study revealed nearly universal patient applicability of pre-emptive testing, but implementation required extensive integrated institution-wide human and software resources [291]. This study involved collaboration between the Mayo Clinic and the Baylor College of Medicine Human Genome Sequencing Center in the US to generate DNA sequence data for 10,077 patients who receive their healthcare from the Mayo Clinic. For 13 pharmacogenes of interest (including CYP2C19, CYP2D6, HLA-B and SLCO1B1) 79% of participants were found to carry clinically actionable variants in three or more genes. This study strongly suggests that pre-emptive pharmacogenomic panel implementation can be useful clinically, especially if delivered at the point-of-care when medicines are prescribed, and that it would apply to almost every patient [291].

The current literature demonstrates that many primary care HCPs including physicians and pharmacists are hopeful about the role of pharmacogenomics in enhancing the care of their patients [343, 344]. However, in spite of increasing accessibility of pharmacogenomic testing and its potential to personalise drug therapies and guide the use of many medications commonly prescribed in primary care (*e.g.,* selective serotonin reuptake inhibitors, tricyclic antidepressants, codeine, tramadol, statins), its application in routine patient care remains limited [336, 337, 345, 346]. Multiple barriers to pharmacogenomics implementation specifically within primary care are often highlighted (Figure 3.1) [347-351]. It is envisaged that overcoming these barriers will provide the impetus for the widespread adoption of pharmacogenomic guidelines (such as those published by the CPIC and the DPWG), enabling the realisation of the potential of pharmacogenomic testing in primary care [171].

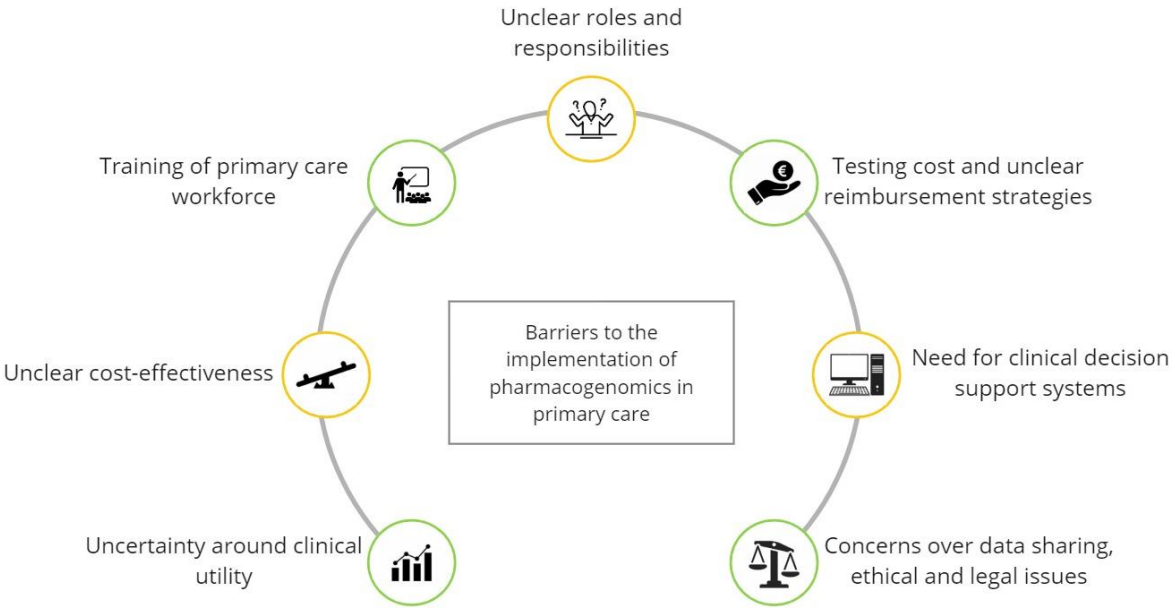

Figure 3.1. Barriers to the implementation of pharmacogenomics in primary care

Patient perceptions are important during the development and implementation of a new clinical service as they can help guide both service development as well as individual clinician practices. Having that perspective in the early stages of adopting a new clinical service may help drive changes in development and implementation. Ultimately, a pharmacogenomic test can be understood as diagnostic information and also information that is proprietary to the patient; thus, some ethical questions arise, and the patient's perception is absolutely essential to promoting pharmacogenomic initiatives. Reported patient perceptions of medicines optimisation services suggest that patients value medicines optimisation services but expressed concerns around privacy and necessity of medicines optimisation service provision [352].

Regarding pharmacogenomics, studies from the US reported varying public and patient awareness of pharmacogenomics (48-88%) but high level of interest in using a pharmacogenomic service (81-83%) [324, 325, 333]. Patients' attitudes towards pharmacogenomics were generally very positive [333], while others would be more willing to use a pharmacogenomics service if it was paid for by their health insurance company

[325]. Concerns have been raised regarding the potential for discrimination, the personal implications of additional risk information, and the practical issues of cost and follow-up care [328]. In Germany, the UK and Australia, the public are generally supportive of pharmacogenomic testing, but expressed additional concerns regarding patient autonomy, the unavailability of suitable drugs based on genetic makeup, and storage and privacy of genetic information [326, 327, 329].

Participants of an Icelandic study were concerned that drugs developed based on pharmacogenomics would be more expensive and result in greater health disparities [334]. In Spain, the majority of participants in a questionnaire study preferred storing pharmacogenomic results in patient medication records rather than in electronic sources and highly agreed with the possibility of carrying their results on a portable card [353]. In a Canadian study assessing the attitudes of healthy individuals and patients with a chronic disease (heart failure and heart transplant recipients) towards pharmacogenomics, most participants stated that they would accept pharmacogenomic testing and expressed high hopes regarding its potential applications. Overall, interest for pharmacogenomics was shared equally among the three groups; although healthy individuals were more concerned about the possibility of employer and insurance provider discrimination and were more worried about confidentiality issues [354].

While the abovementioned studies on perceptions of pharmacogenomics provide crucial information, there is potential for transition in perceptions owing to the shifting nature of the public's familiarity with genetic testing and continual declines in its expense [355]. Furthermore, some of these earlier studies were conducted prior to the release of pharmacogenomic-based guidelines from the CPIC and the DPWG. Finally, there was a notable lack of previously published research exploring the views of the public of Ireland on pharmacogenomic testing.

3.2. Aims and objectives

3.2.1. Aim

The aim of the present study was to identify the potential opportunities and challenges of implementing pharmacogenomic testing in Ireland based on the previously unexplored views of those with multimorbidity/polypharmacy, a single chronic disease, and those without existing medical conditions. We hypothesised that perceptions of pharmacogenomics would significantly differ based on the view of those with and without chronic disease(s). This study was to serve as a baseline for identifying areas of potential exploration within the wider context of the overall research project.

3.2.2. Objectives

The specific objectives were to:

- Identify participants' awareness and knowledge of pharmacogenomics
- Establish participants' openness to availability of pharmacogenomic services in Ireland
- Ascertain the factors that would positively and negatively influence their decision to have a pharmacogenomic test (perceived benefits and concerns)
- Determine how much respondents would be willing to pay for such a service
- Identify participants' accessibility to healthcare to inform about preferred location(s) and provider(s) for pharmacogenomic services.

3.3. Research design and methodology

3.3.1. Rationale for choice of methodology

Qualitative methods, such as semi-structured interviews that will be explored in Chapter 5, differ in their intended purposes from quantitative methods, such as questionnaires [356]. In-depth data for the purposes of interpreting, understanding and contextualising participants' perspectives can be gathered using qualitative methods, whereas quantitative methods are concerned with generalising findings, establishing causal explanations, and making predictions. The opportunity for large-scale sampling of the public using a questionnaire data was important for the purpose of the current study as it provided the potential for generalising the research findings to the wider population in Ireland [357]. This would not be possible with a qualitative approach as sample sizes are necessarily small, owing to the time and resources required for qualitative research.

Questionnaires offer other distinct advantages which also accounted for the selection of this research method in the current study [356]. For example, questionnaires can be completed by respondents in their own time and at their own pace. This was of particular importance as the questionnaire was conducted during the COVID-19 pandemic which precluded close contact with respondents. These were considerations of particular importance in the current study as the research sought to engage the public and questions inquired into their healthcare and personal opinions.

3.3.2. MPharm research project

The research was undertaken as part of an MPharm project to promote research, analysis, teamwork and presenting skills. The PhD candidate co-supervised this research project, conceptualised the idea, organised and applied for ethical approval, curated the data, and conducted the formal analysis presented in this chapter. For their research project, the MPharm students conducted a separate analysis and report. As part of this project, the posters used for distributing the questionnaire (Section 3.3.4) were displayed on site in participating pharmacies in which the MPharm students involved in this study were completing their internships.

3.3.3. Questionnaire design

The questions were designed to take into account the existing literature on patient perceptions of pharmacogenomics [320, 324-334], and to build upon the results of the systematic review described in Chapter 2 which concluded that more work is needed on pharmacogenomic testing as part of medicines optimisation for patients with multimorbidity and prescribed polypharmacy [272]. Very little pharmacogenomics research has been published to date in Ireland. As a result, perceptions of pharmacogenomic testing in Ireland constitutes a specific gap in the literature. In the questionnaire, pharmacogenomic testing was defined as 'the use of genetic information to tailor pharmaceutical treatments to an individual' [169], and information provided on where it is performed, testing methods and types, and examples of pharmacogenomic medications.

The questionnaire consisted of four subsections with 58 questions overall: (1) demographics (11 questions), (2) healthcare experiences and accessibility (17 questions), (3) pharmacogenomics (7 questions), and (4) factors associated with choosing to have a pharmacogenomic test (23 questions) (Appendix 3.1). To ensure respondents were not identifiable, the 'anonymise responses' setting was enabled from the outset. Consent was required at the beginning of the questionnaire to proceed. Most questions required respondents to either choose from fixed-response options (Section 1-3) or rate their response to particular statements using five-point Likert scales (Section 4). A small number of questions with open-ended responses were also included. The participants did not have to complete every question to proceed and could cease participation at any stage.

The questionnaire was piloted within the School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin, to assess the questionnaire's face validity and content validity [358]. Face validity involved an informal review of the questionnaire by non-experts to assess its clarity, comprehensibility, and appropriateness for the target group. Content validity involved a formal assessment by subject experts to determine the appropriateness of content and identify any misunderstandings or omissions. No issues arose with completion of the questionnaire and no additions were recommended. Several questions were

reworded for readability. It was estimated that it would take approximately 15-20 minutes to complete the questionnaire.

In Section 2 of the questionnaire, respondents were asked questions relating to their healthcare. To ascertain the proportion of patients with multimorbidity and polypharmacy, respondents were asked to answer yes/no to having any long-term medical conditions and taking any regular medications prescribed by their doctor. If respondents answered yes, they were asked to specify the quantity of each to enable identification of multimorbidity and polypharmacy. Free text options were provided to capture the types of conditions and prescribed medications. Respondents' utilisation of Irish government medication schemes was also assessed, such as the GMS, DPS and LTI schemes. Healthcare schemes in Ireland are outlined in Chapter 1 (Section 1.4.2). Given the national focus of this questionnaire, it was not validated for use outside of Ireland.

3.3.4. Questionnaire distribution

This study consisted of an anonymous, self-administered, cross-sectional, online questionnaire generated using Qualtrics® [359]. Qualtrics® is a survey software tool used to design, send, and analyse surveys online. Posters with a QR code linked to the Qualtrics® online questionnaire were displayed on the social media pages of the researchers and the School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin, and on-site in participating pharmacies (Appendix 3.2). Patient advocacy groups were tagged on the social media posts, promoting a broader scope of participants to be reached.

The questionnaire went live in April 2021 and remained open for four weeks. Weekly reminders were posted on social media to promote recruitment. To be eligible to participate in this study, it was required that respondents be over the age of 18 and living in Ireland. Furthermore, given the online nature of the questionnaire, a certain degree of IT literacy and internet access was required to participate. An introductory cover page and consent section (Appendix 3.3) preceded the questionnaire. The participant information leaflet (Appendix 3.4) was linked in this introductory section also prior to the participants answering the questions.

3.3.5. Sample size

Based on data from the Tailored Antiplatelet Therapy Following Percutaneous Coronary Intervention (TAILOR-PCI) study, we assumed that 77% of patients would be interested in pharmacogenomic services [360]. It was hypothesised respondents with chronic disease would be more interested in pharmacogenomic services than those without existing conditions owing to their frequent experience with medications and healthcare services. Without existing data to support this hypothesis, it was assumed those with chronic disease would be at least 15% (relatively) more interested in pharmacogenomic services.

The State of Health in the EU country health profile for Ireland showed nearly three in ten Irish adults (28%) reported having at least one chronic disease in 2019 [361]. Therefore, respondents without existing conditions were considered likely to outnumber those with chronic disease and a 2:1 enrolment was used. For a desired power of 0.80 and Type I error rate of 0.05, we estimated that at least 336 evaluable responses were required (112 with chronic disease and 224 without any existing medical conditions) using the ClinCalc sample size calculator.

3.3.6. Data analysis

All viable data were coded for and entered into the computer program SPSS (v27.0) for statistical analysis. Standard descriptive analyses (frequencies (n) and proportions (%)) were used to summarise the questionnaire responses. Missing data (*i.e.,* unanswered questions) in individual questionnaires were coded as such and omitted from the analysis. The percentage values quoted are based on the number of respondents to individual questions. To investigate if perceptions differ amongst those with a chronic disease, these respondents were subdivided into multimorbidity/polypharmacy and single chronic disease based on their responses to the presence and quantity of conditions and prescribed medicines (described in Section 3.3.3).

Cross-tabulations (chi-square (χ^2) test) and multiple linear regression analyses were performed to investigate whether chronic disease status (multimorbidity/polypharmacy, single chronic disease, no existing medical condition) had any impact on pharmacogenomic awareness, openness to availability, perceived benefits/risks, and willingness to pay (WTP).

Shapiro-Wilk test was used to verify normality of the data. There were several instances in which, on account of small numbers of respondents selecting particular responses on the five-point Likert scales, it was necessary to merge response categories to meet the criteria of a valid χ^2 test. Where the presented results of χ^2 tests are based on amended response categories they are marked accordingly (*i.e.,* ^ merged responses). If after merging, the assumption of relatively large sample sizes was not met (*i.e.,* expected frequencies of at least 5 for the majority (80%) of cells), the likelihood ratio was used to determine statistical significance. To correct for possible overestimation of the χ^2 value when testing two variables that each have two categories, Yate's Continuity of Correction was used to assess statistical significance.

Bivariate and multivariate analyses were conducted, with the former comparing those with chronic disease to those without (independent sample t-test), while the latter involved comparisons between those with multimorbidity/polypharmacy, a single chronic disease, and respondents without existing conditions (one-way ANOVA). Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were then computed, using a significance level of 5% for all statistical tests. A small number of questions with open-ended responses were also included. These responses were manually reviewed, and content analysis conducted.

3.4. Ethical approval

Ethical approval was granted by the School of Pharmacy & Pharmaceutical Sciences Research Ethics Committee in March 2021 (Ref. 2021-02-01) (Appendix 3.5). The study findings have been published in Exploratory Research in Clinical and Social Pharmacy [362], which includes acknowledgment of all researchers involved in this study.

3.5. Results

3.5.1. Responses

A total of 421 respondents started the questionnaire, with complete responses obtained from 354 of these respondents. The participants did not have to complete every question to proceed and could cease participation at any stage; thus, the proportions quoted in this section are based on the number of respondents to individual questions. The majority of respondents (50%, n = 209) heard about the questionnaire by word of mouth, followed by social media (35%, n = 147) and an unspecified 'other' method (8%, n = 36). Only 28 respondents (7%) were recruited from a participating pharmacy. On average, the questionnaire took 15 minutes to complete.

3.5.2. Demographics

Respondents' demographics details are shown in Table 3.1. Statistically significant results of cross-tabulations that were performed between questionnaire responses on the basis of respondents' demographics are outlined in Section 3.5.2.3.

3.5.2.1. Sample representativeness

Based on comparison with national gender and age data from the Central Statistics Office Census of the Population 2016 [363], the sample of respondents was not representative of the wider population of Ireland (Table 3.2).

3.5.2.2. Respondent characteristics

Respondents were 72% female (n = 303), between 25 and 64 years (63%, n = 265), and predominantly of European descent (94%, n = 396). Respondents with a chronic disease were older than those without existing medical conditions (median age 35 vs 30 years, $p < 0.001$). Furthermore, multimorbid chronic disease and/or polypharmacy respondents were older than their single chronic disease counterparts (median age 50 vs 30 years, $p < 0.001$). Understandably, respondents with multimorbidity/polypharmacy were more likely to be receiving medications under a government scheme (GMS, DPS, LTI) than single chronic disease patients ($p < 0.001$). The multimorbidity/polypharmacy group had the highest number of respondents receiving medications under the DPS and GMS scheme.

Table 3.1. Demographic characteristics of questionnaire respondents by chronic disease status

	%Overall	%NCD (n = 301)	%CD (n = 120)	P [a]	%SCD (n = 65)	%MMPP (n = 55)	P [b]
Education (n = 421)				0.604			0.034*
At least a college degree	77.9	78.7	75.8		84.6	65.5	
Less than a college degree	22.1	21.3	24.2		15.4	34.5	
Job status (n = 401)				0.530			0.702
Employed	84.0	83.2	86.4		87.3	85.1	
Unemployed	16.0	16.8	13.6		12.7	14.9	
Health-related profession (n = 421)				0.723			0.219
Yes	50.1	50.8	48.3		55.4	40.0	
No	49.9	49.2	51.7		44.6	60.0	
Health insurance (n = 419)				0.831			0.279
Yes	74.7	74.2	75.8		81.5	69.1	
No	25.3	25.8	24.2		18.5	30.9	
Life insurance (n = 419)				1.000			0.980
Yes	40.8	40.8	40.8		40.0	41.8	
No	59.2	59.2	59.2		60.0	58.2	
Government scheme (n = 418)				<0.001*			<0.001*
DPS	22.5	18.1	33.3		23.1	45.5	
GMS	8.85	6.71	14.2		6.15	23.6	
LTI	1.91	0.00	6.67		6.15	7.27	
No scheme	66.7	75.2	45.8		64.6	23.6	

* Significant at $p < 0.05$, [a] Independent t-test for variables with two groups, [b] ANOVA for variables with more than two groups, *CD* chronic disease, *GMS* general medical services scheme, *LTI* long-term illness scheme, *MMPP* multimorbid chronic disease and/or polypharmacy, *NCD* no chronic disease, *SCD* single chronic disease

Table 3.2. Sample representativeness

	Respondents (n = 421)		National data (n = 3,510,039)		P [c]
Gender	%	N	%	N	Test statistic
Female	72	303	51	1,790,374	< 0.001*
Male	28	118	49	1,719,665	
Age	%	N	%	N	Test statistic
18-24	34	144	9	331,208	
25-64	63	265	73	2,541,264	< 0.001*
>65	3	12	18	637,567	

* Significant at $p < 0.05$, [c] χ^2 test

3.5.2.3. Cross-tabulations of respondents' demographics and questionnaire responses

As shown in Table 3.3, significantly higher proportions of female respondents work/worked in a health-related profession compared to males. Male respondents were less likely to take daily medications prescribed by their doctor on a regular basis and to have stopped taking a medicine in the past due to side effects.

Table 3.3. Cross-tabulations between gender and questionnaire responses

What is your gender?				
Health-related profession	Female	Male	N	P [c]
Yes	77.3%	22.7%	210	0.021*
No	66.7%	33.3%	211	
Regular medications	Female	Male	N	P [c]
Yes	77.4%	22.6%	159	0.016*
No	65.5%	34.5%	235	
Stopped a medicine due to side effect(s)	Female	Male	N	P [c]
Yes	78.3%	21.7%	115	0.038*
No	67.0%	33.0%	261	

* Significant at $p < 0.05$, [c] χ^2 test

Statistically significant differences were also found between age of various respondents' demographics (Table 3.4). A significantly higher proportion of respondents aged 18-24 years were found to be unemployed and not in possession of life insurance. Compared to respondents aged 25-64 years and ≥65 years, significantly fewer 18–24-year-old respondents had a long-term medical condition and rated their health status as average or poor. A significantly higher proportion of those aged 25-64 years had an annual household income between €100,001-€140,000. Conversely, a significantly higher proportion of respondents aged 18-24 years were receiving <€20,000 per annum.

Table 3.4. Cross-tabulations between age and questionnaire responses

What age are you?					
Employed	18-24	25-64	≥65	N	P [c]
Yes	29.1%	70.6%	0.3%	337	< 0.001*
No	71.9%	26.6%	1.6%	64	
Income*	18-24	25-64	≥65	N	P [c]
< €20,000	54.5%	42.4%	3.0%	33	
€20,001 - €60,000	38.9%	56.3%	4.8%	167	
€60,001 - €100,000	30.6%	67.7%	1.6%	124	0.003*
€100,001 - €140,000	32.6%	67.4%	0.0%	46	
≥ €140,001	15.2%	82.6%	2.2%	46	
Life insurance	18-24	25-64	≥65	N	P [c]
Yes	16.4%	80.7%	2.9%	171	< 0.001*
No	46.8%	50.8%	2.4%	248	
Chronic conditions	18-24	25-64	≥65	N	P [c]
Yes	25.0%	70.0%	5.0%	120	0.008*
No	38.2%	60.4%	1.5%	275	
Health status*	18-24	25-64	≥65	N	P [c]
Excellent or good	36.5%	61.4%	2.0%	342	0.043*
Average or poor	19.2%	76.9%	3.8%	52	

* Significant at $p < 0.05$, [c] χ^2 test

3.5.3. Healthcare characteristics

Respondents' healthcare characteristics are shown in Table 3.5. Thirty percent of respondents had at least one long-term medical condition (n = 120). Multimorbidity was present in 39% of these respondents (n = 47). Forty percent of participants regularly take medications (n = 159); 13% of whom experience polypharmacy (n = 21). Eighty-seven percent of respondents characterised their health status as excellent or good (n = 342), which is comparable with national reports of self-rated health status [364, 365]. However, respondents with chronic disease and multimorbidity/polypharmacy had poorer perceptions of their health ($p < 0.001$).

Forty-six percent of respondents had experienced a side effect from a medicine before (n = 166); of those, 70% categorised the side effect as mild (n = 127) and 31% had stopped taking the medication (n = 115). Overall, 31% had stopped taking a medication due to perceived ineffectiveness (n = 117). Moreover, respondents with chronic disease and multimorbid chronic disease and polypharmacy had greater reported side effects ($p < 0.001$) and non-persistence due to side effects ($p = 0.005$) and inefficacy ($p < 0.001$). Fourteen respondents (4%) were previously hospitalised due to a MRP (*e.g.,* side effects).

Table 3.5. Healthcare characteristics by chronic disease status

	%Overall	%NCD (n = 274)	%CD (n = 120)	P [a]	%SCD (n = 65)	%MMPP (n = 55)	P [b]
Multimorbidity (n = 120)				-			<0.001
≥2 long-term conditions	39.2	0.0	39.2		0.0	85.5	
1 long-term condition	60.8	0.0	60.8		100	14.5	
Polypharmacy (n = 163)				0.004			<0.001
≥ 4 regular medicines	12.9	2.99	19.8		0.00	38.8	
< 4 regular medicines	87.1	97.0	80.2		100	61.2	
Health status (n = 394)				<0.001			<0.001
Excellent	42.6	50.0	25.8		43.1	5.45	
Good	44.2	42.7	47.5		41.5	54.5	
Average	12.2	6.93	24.2		15.4	34.5	
Poor	1.02	0.36	2.50		0.00	5.45	
Previous medical test to guide treatment (n = 298)				<0.001			<0.001
Yes	33.9	24.5	52.0		40.0	66.0	
No	66.1	75.5	48.0		60.0	34.0	
Experienced a side effect (n = 362)				<0.001			<0.001
Yes	45.9	38.1	62.6		61.3	64.2	
No	54.1	61.9	37.4		38.7	35.8	
Stopped a medicine due to side effects (n = 376)				0.019			0.005
Yes	30.6	26.6	39.3		31.2	49.1	
No	69.4	73.4	60.7		68.8	50.9	
Stopped a medicine due to inefficacy (n = 373)				0.007			<0.001
Yes	31.4	26.8	41.4		28.6	56.6	
No	68.6	73.2	58.6		71.4	43.4	

* Significant at $p < 0.05$, [a] Independent t-test for variables with two groups, [b] ANOVA for variables with more than two groups, *CD* chronic disease, *MMPP* multimorbid chronic disease and/or polypharmacy, *NCD* no chronic disease, *SCD* single chronic disease

3.5.4. Perceptions of pharmacogenomic testing

Respondents' perceptions of pharmacogenomics (awareness, knowledge, openness to pharmacogenomic services, and likelihood to test) by chronic disease status are shown in Table 3.6. To address the aims and objectives of this study, in this section participants' perceptions of pharmacogenomic testing in Ireland is reported under pharmacogenomics awareness and knowledge, the perceived value of a pharmacogenomic testing service (openness to pharmacogenomic services in Ireland), and the perceived benefits and risks of pharmacogenomic testing.

3.5.4.1. Pharmacogenomics awareness and knowledge

Respondents' awareness of pharmacogenomics was low (44%, n = 166) (Table 3.6). The majority of respondents with and without a chronic disease were unaware of pharmacogenomics prior to the questionnaire (57% and 56% respectively). These differences were not found to be statistically significant ($p = 0.939$), regardless of adjusting for age and gender (OR 1.18, [95% CI 0.74–1.87]). However, 86% of respondents were aware that genetics could have an impact on the effectiveness of their medications (n =218). Overall, respondents' understanding of pharmacogenomics and its application in healthcare (pharmacogenomics knowledge) was poor or very poor (55%, n = 212). Of those who had heard of pharmacogenomic testing, 77% reported their understanding of its applications in healthcare was excellent or good (n = 84) ($p < 0.001$).

Table 3.6. Pharmacogenomic awareness, knowledge, experience, openness, and likelihood to test by chronic disease status

	%Overall	%NCD (n = 269)	%CD (n = 118)	P [a]
Pharmacogenomics awareness (n = 382)				0.939
Yes	43.5	43.8	42.7	
No	56.5	56.2	57.3	
Pharmacogenomics knowledge (n = 386)				0.123
Excellent	8.03	9.33	5.08	
Good	18.7	17.5	21.2	
Fair	18.4	15.7	24.6	
Poor	27.7	28.4	26.3	
Very poor	27.2	29.1	22.9	
Aware genetics could have an impact medication efficacy (n = 253)				0.909
Yes	86.2	85.7	87.2	
No	13.8	14.3	12.8	
Previous genetic test (n = 371)				0.053
Yes	9.70	7.60	14.8	
No	90.3	92.4	85.2	
Open to pharmacogenomic services (n = 387)				0.055
Yes	75.5	72.1	83.1	
No	2.07	2.23	1.69	
Don't know	22.5	25.7	15.3	
Likelihood to test if receiving a medication that may be affected by genetics (n = 387)				0.290
Very likely	67.7	64.7	74.6	
Somewhat likely	25.6	27.5	21.2	
Not very likely	4.91	5.58	3.39	
Not at all likely	1.81	2.23	0.85	

[a] Independent t-test for variables with two groups, *CD* chronic disease (includes MMPP multimorbid chronic disease and/or polypharmacy and SCD single chronic disease), *NCD* no chronic disease

Awareness of pharmacogenomics between those with and without a chronic disease was not found to be statistically significant (p = 0.939) (Table 3.6), regardless of adjusting for age and gender (OR 1.18, [95% CI 0.74–1.87]). Pharmacogenomics awareness was associated with age (18-24 years), a college degree, current/previous employment in a health-related profession, and experience with medication side effects. As shown in Table 3.7, those over the age of 24 were less likely to have heard of pharmacogenomic testing as compared with those between the ages of 18-24 years. Conversely, respondents with a college degree, experience in a health-related profession, and with a history of side effects were more likely to have heard of pharmacogenomic testing. Chronic disease status was not associated with knowledge of the applications of pharmacogenomics in healthcare (p = 0.123) (Table 3.6). As shown in Table 3.8, understanding of the applications of pharmacogenomics in healthcare was associated with several factors.

Table 3.7. Association between pharmacogenomics awareness and questionnaire responses

Have you ever heard of pharmacogenomic testing?				
Age^	Yes	No	N	P [c]
18-24	57.0%	43.0%	128	
25-64	36.9%	63.1%	244	< 0.001*
≥65	30.0%	70.0%	10	
Education	Yes	No	N	P [c]
At least a college degree	49.5%	50.5%	299	< 0.001*
Less than a college degree	21.7%	78.3%	83	
Health-related profession	Yes	No	N	P [c]
Yes	68.1%	31.9%	191	< 0.001*
No	18.8%	81.2%	191	
Experienced a side effect	Yes	No	N	P [c]
Yes	55.6%	44.4%	162	< 0.001*
No	35.6%	64.4%	191	

Table 3.8. Association between pharmacogenomics knowledge and questionnaire responses

How would you rate your understanding of how pharmacogenomics can be used in healthcare? ^				
Age^	Excellent or good	Poor or very poor	N	P [c]
18-24	43.2%	56.8%	111	
25-64	27.4%	72.6%	197	0.010*
≥65	14.3%	85.7%	7	
Education	Excellent or good	Poor or very poor	N	P [c]
At least a college degree	36.9%	63.1%	241	0.006*
Less than a college degree	18.9%	81.1%	74	
Health-related profession	Excellent or good	Poor or very poor	N	P [c]
Yes	54.7%	45.3%	148	< 0.001*
No	13.2%	86.8%	167	
Experienced a side effect	Excellent or good	Poor or very poor	N	P [c]
Yes	44.4%	55.6%	126	0.003*
No	27.2%	72.8%	162	
Pharmacogenomics awareness	Excellent or good	Poor or very poor	N	P [c]
Yes	77.1%	22.9%	109	< 0.001*
No	8.0%	92.0%	201	

^ merged responses, * Significant at $p < 0.05$, [c] χ^2 test

3.5.4.2. Perceived value of pharmacogenomic services

General information was provided about pharmacogenomic testing followed by a question on openness to pharmacogenomic services (perceived value). Overall, the majority of respondents (76%, n = 292) valued pharmacogenomic services, while 22% of respondents were unsure (n = 87). Very few respondents (2%, n = 8) were opposed to pharmacogenomic service availability (Table 3.6). As shown in Table 3.9, receptiveness to pharmacogenomic services in Ireland was associated with several factors. Perceived value of pharmacogenomic services in Ireland was associated with several factors including a college degree ($p = 0.044$), current/previous employment in a health-related profession ($p = 0.018$), experience with medical tests to guide medication therapy ($p = 0.030$), history of medication side effects ($p = 0.013$), previous genetic test ($p = 0.039$), and awareness and understanding of pharmacogenomics and its applications in healthcare ($p < 0.001$).

The majority of respondents with and without a chronic disease were open to pharmacogenomic services (83% and 72% respectively) ($p = 0.055$). Adjusting for age and gender, respondents with a chronic disease were 2.17 times more likely ([95% CI, 1.23–4.00], $p < 0.001$) to want pharmacogenomic service availability than respondents without existing conditions. This result was driven by significant age and gender adjusted increases in positive responses from those with multimorbidity and polypharmacy versus respondents without any chronic disease (OR 2.46, [95% CI, 1.13–6.00], $p = 0.033$), rather than those with a single chronic disease only (OR 1.96, [95% CI, 0.97–4.29], $p = 0.074$). Similarly, there was a high level of interest in testing if the respondent was receiving a medication that may be affected by their genetics, with 65% of respondents without existing conditions and 75% of chronic disease respondents selecting ‘very likely’ to have a test in this instance ($p = 0.290$) (Table 3.6).

Table 3.9. Association between openness to the availability of pharmacogenomic services and questionnaire responses

Do you think pharmacogenomic services should be offered in Ireland?					
Education	Yes	No	Don't know	N	P [c]
At least a college degree	77.2%	2.6%	20.1%	303	0.044*
Less than a college degree	69.0%	0.0%	31.0%	84	
Health-related profession	Yes	No	Don't know	N	P [c]
Yes	80.8%	2.6%	16.6%	193	0.018*
No	70.1%	1.5%	28.4%	194	
Previous medical test	Yes	No	Don't know	N	P [c]
Yes	85.0%	1.0%	14.0%	100	0.030*
No	71.5%	2.1%	26.4%	193	
Experienced a side effect	Yes	No	Don't know	N	P [c]
Yes	82.4%	1.8%	15.8%	165	0.013*
No	69.3%	2.1%	28.6%	192	
Pharmacogenomics awareness	Yes	No	Don't know	N	P [c]
Yes	85.5%	2.4%	12.0%	166	< 0.001*
No	69.0%	1.9%	29.2%	216	
Pharmacogenomics knowledge^	Yes	No	Don't know	N	P [c]
Excellent or good	87.4%	2.9%	9.7%	103	< 0.001*
Poor or very poor	67.9%	1.4%	30.7%	212	
Previous genetic test	Yes	No	Don't know	N	P [c]
Yes	91.7%	2.8%	5.6%	36	0.039*
No	73.7%	2.1%	24.2%	335	

^ merged responses, * Significant at $p < 0.05$, [c] χ^2 test

Almost all of the respondents (93%, n = 361) were likely or very likely to have a pharmacogenomic test performed if they were receiving a medication with potential to be affected by their genetics (Table 3.6). Three-quarters of those with a chronic disease had a high level of interest in testing for this purpose versus 65% respondents without an existing medical condition; however, this difference was also not found to be statistically significant (p = 0.290). As shown in Table 3.10, likelihood to have a pharmacogenomic test was associated with several factors. Those earning between €60,001-€100,000, taking daily prescribed medications, aware of the effect genetics can have on medications, and those who are open to pharmacogenomic services in Ireland were more likely to have a pharmacogenomic test if indicated.

Table 3.10. Association between likelihood to have a pharmacogenomic and questionnaire responses

If you knew one of the medications you take could potentially be affected by your genes, how likely are you to use a pharmacogenomic testing service? ^				
Income^	Likely	Not likely	N	P [c]
< €20,000	92.0%	8.0%	25	
€20,001 - €60,000	90.3%	9.7%	155	
€60,001 - €100,000	98.3%	1.7%	116	0.035*
€100,001 - €140,000	88.1%	11.9%	42	
≥ €140,001	95.6%	4.4%	45	
Regular medications	Likely	Not likely	N	P [c]
Yes	96.8%	3.2%	155	0.041*
No	90.9%	9.1%	231	
Aware genetics impacts medications	Likely	Not likely	N	P [c]
Yes	95.9%	4.1%	218	0.035*
No	89.9%	10.1%	169	
Open to pharmacogenomic service availability in Ireland	Likely	Not likely	N	P [c]
Yes	96.2%	3.8%	292	
No	62.5%	37.5%	8	< 0.001*
Don't know	86.2%	13.8%	87	

^ merged responses, * Significant at $p < 0.05$, [c] χ^2 test

3.5.4.3. Perceived benefits of pharmacogenomic testing

Respondents were asked about their perceived benefits of pharmacogenomic testing after learning about each specific use/benefit (*e.g.,* to predict their risk of a side effect, to optimise their medicines) (Figure 3.2). Most respondents (65-95%) expressed interest in pharmacogenomic testing for the various purposes presented (strongly agree and agree) which was not associated with chronic disease status. Interest in pharmacogenomic testing was highest in order to select the most effective medicine for their condition and was similar amongst those with and without a chronic disease (94% and 95% respectively) ($p = 0.348$). Additional benefits captured by the free text option included: reduce costs (for patients and payers); reduce hospitalisation (due to side effects and inefficacy); more efficient use of resources (reduce waste); improve standard of care (reduce trial and error and drug interactions, improve timing and adherence); improve understanding (of self and interactions, peace of mind, control, confidence).

Openness to availability of pharmacogenomic services in Ireland was associated with agreeing to have a pharmacogenomic test for several of the potential uses, including to predict a serious side effect, reduce the number of prescribed medicines, to optimise current and future medicines, and interest in the test being reimbursed by the respondents' insurance plan ($p < 0.05$). Interestingly, a similar level of agreement was found between those with and without experience in a health-related profession and agreeing to have a pharmacogenomic test for any of the potential benefits or risks presented in this questionnaire. An exception was found for a pharmacogenomic test to predict mild/moderate side effects. Those who work/worked in a health-related profession were more likely to disagree with testing in this scenario ($p = 0.025$).

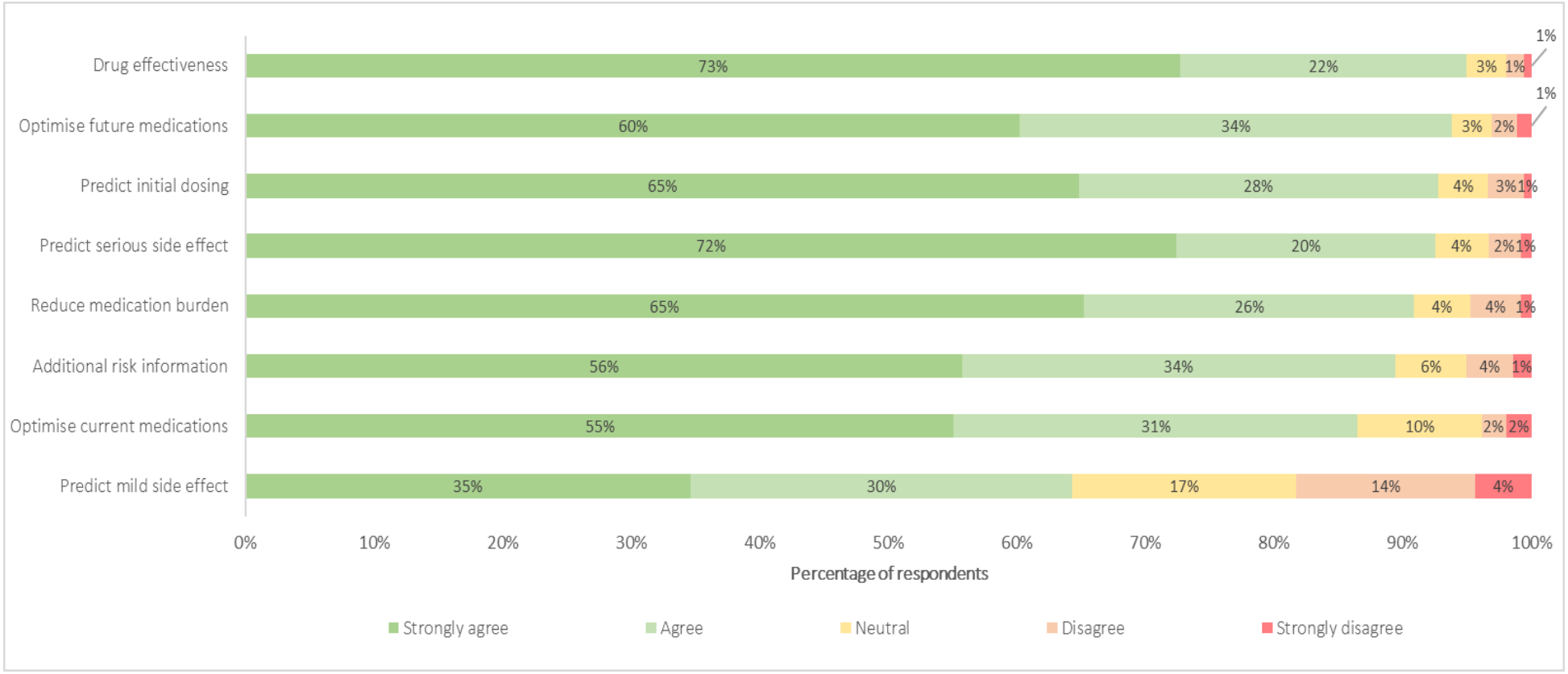

Figure 3.2. Bar charts of respondents' likelihood to have a pharmacogenomic test for certain benefits/uses

Likelihood assessed using a 5-point Likert scale, where 1 = strongly agree (green), 5 = strongly disagree (red).

3.5.4.4. Perceived risks of pharmacogenomic testing

Conversely, respondents were asked about their perceived risks/concerns of pharmacogenomic testing (Figure 3.3). Respondents expressed varying concern (15-61%) for the risks presented (strongly agree and agree) which was also not associated with chronic disease status. In contrast, respondents expressed most concern for expensive pharmacogenomic tests (63% and 60% of those with and without a chronic disease respectively) ($p = 0.418$). Additional risks/concerns captured by the free text option included: test accessibility, efficiency, quality, and invasiveness; HCP education; disclosure to employer, insurance and mortgage provider; and genetic information ownership and consent.

Respondents with less than a college degree were more likely to be concerned about a pharmacogenomic test that involves a blood sample and may result in incidental findings ($p < 0.05$). Additionally, respondents who were unsure about or opposed to the availability of pharmacogenomic testing in Ireland were more likely to have concerns with all the potential risks of pharmacogenomic testing presented except for a test that requires a blood sample and a test that may be expensive ($p < 0.05$). Respondents who were unlikely to have a pharmacogenomic test if taking a medication with potential to be affected by their genetics were more likely to disagree with the uses of pharmacogenomic testing and agree with the risks ($p < 0.05$).

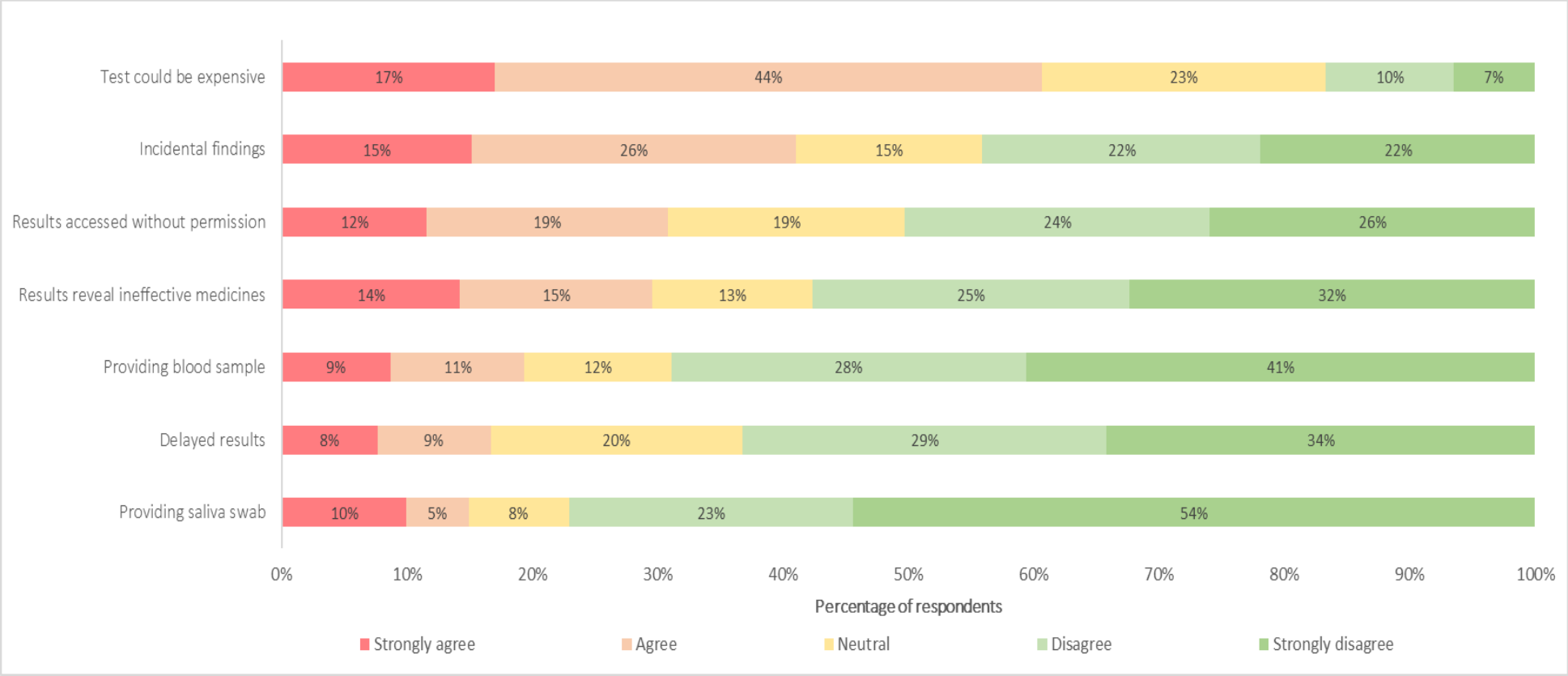

Figure 3.3. Bar charts of respondents' likelihood to have a pharmacogenomic test for certain risks/concerns

Likelihood assessed using a 5-point Likert scale, where 1 = strongly agree (green), 5 = strongly disagree (red).

3.5.5. Willingness-to-pay for pharmacogenomic services

Respondents' WTP for pharmacogenomic testing was assessed for three scenarios (Figure 3.4). As shown, between 81-86% of respondents would not surpass the €100 price mark for all the pharmacogenomic tests listed. A small proportion of respondents (12-16%) would be willing to pay a maximum price of €250 for each of the tests, and even fewer (1-4%) willing to spend beyond €500 for pharmacogenomic testing. Annual household income was associated with respondents' WTP (Table 3.11 and Figure 3.5-Figure 3.7). Overall, the higher earners were willing to pay more for the different types of pharmacogenomic tests ($p < 0.05$, χ^2 test). Those earning ≥ €140,001 were consistently willing-to-pay a maximum price of €250 for the different types of pharmacogenomic test. Furthermore, respondents with poorer perceptions of their health were more likely to pay the maximum price (€750) for pre-emptive and whole-genome sequencing tests ($p = 0.003$). Experience with stopping a medicine due to side effects ($p = 0.021$) and inefficacy ($p = 0.003$) was associated with WTP for reactive and pre-emptive testing.

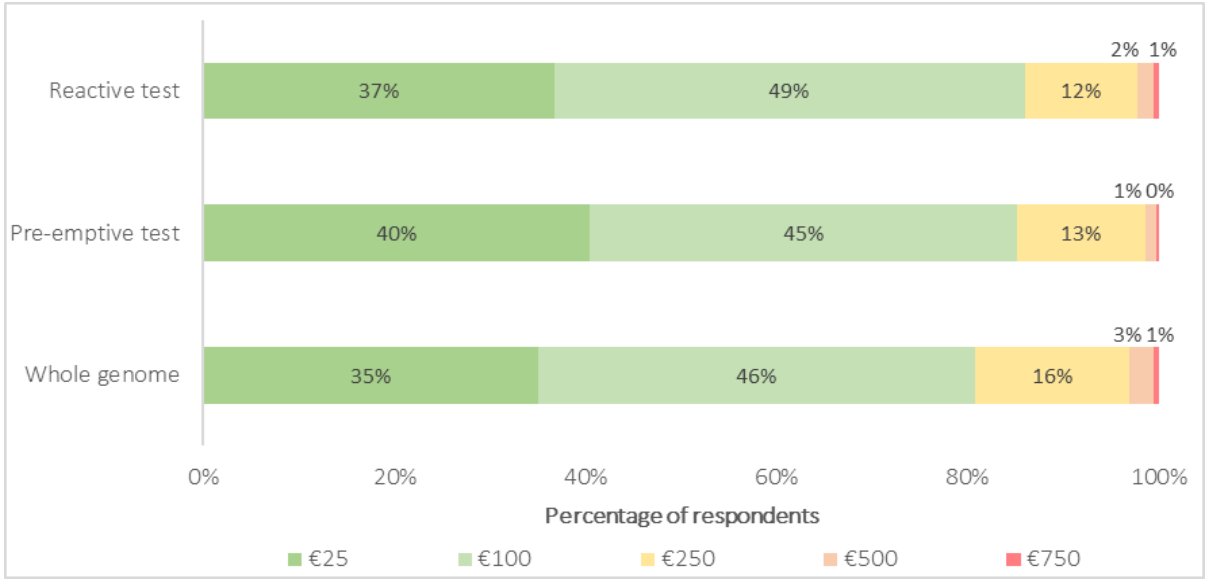

Figure 3.4. Bar charts of respondents' willingness to pay for the different types of pharmacogenomic tests

Reactive pharmacogenomic testing was defined as a test in response to unexplained side effects, pre-emptive as a test to ensure suitable medication use before those medicines are indicated, and whole genome sequencing as a test to ensure suitable medication use and also provide additional risk information.

Table 3.11. Association between respondents' willingness to pay for the different types of pharmacogenomic tests and annual household income

Reactive pharmacogenomic test WTP							
Income ^	€25	€100	€250	€500	€750	N	P [c]
< €20,000	42.9%	52.4%	4.8%	0.0%	0.0%	21	
€20,001 - €60,000	41.3%	48.3%	8.4%	2.1%	0.0%	143	
€60,001 - €100,000	32.4%	55.6%	12.0%	0.0%	0.0%	108	0.004*
€100,001 - €140,000	42.5%	47.5%	7.5%	2.5%	0.0%	40	
≥ €140,001	22.0%	36.6%	31.7%	4.9%	4.9%	41	
Pre-emptive pharmacogenomic test WTP							
Income ^	€25	€100	€250	€500	€750	N	P [c]
< €20,000	50.0%	50.0%	0.0%	0.0%	0.0%	20	
€20,001 - €60,000	44.6%	42.4%	11.5%	0.7%	0.7%	139	
€60,001 - €100,000	41.1%	43.9%	14.0%	0.9%	0.0%	107	0.007*
€100,001 - €140,000	37.5%	57.5%	2.5%	2.5%	0.0%	40	
≥ €140,001	22.0%	39.0%	36.6%	2.4%	0.0%	41	
Whole-genome sequencing WTP							
Income ^	€25	€100	€250	€500	€750	N	P [c]
< €20,000	55.0%	40.0%	5.0%	0.0%	0.0%	20	
€20,001 - €60,000	40.4%	44.0%	10.6%	3.5%	1.4%	141	
€60,001 - €100,000	31.5%	47.2%	19.4%	1.9%	0.0%	108	0.004*
€100,001 - €140,000	29.3%	63.4%	4.9%	2.4%	0.0%	41	
≥ €140,001	22.0%	36.6%	39.0%	2.4%	0.0%	41	

^ merged responses, * Significant at $p < 0.05$, [c] χ^2 test, *WTP* willingness to pay

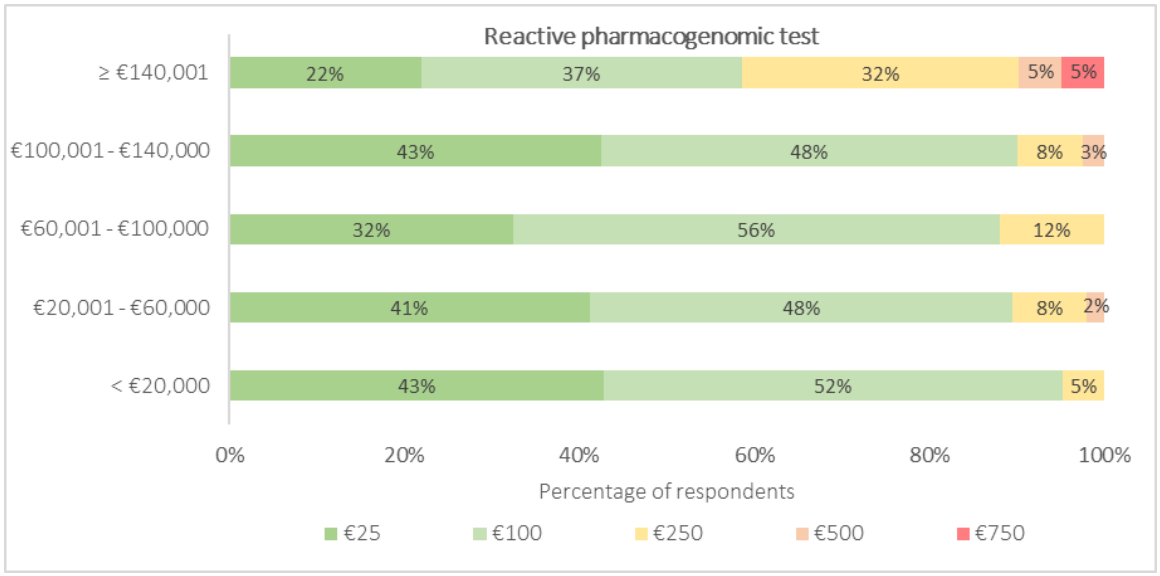

Figure 3.5. Bar charts of willingness-to-pay for a reactive pharmacogenomic testing by annual household income

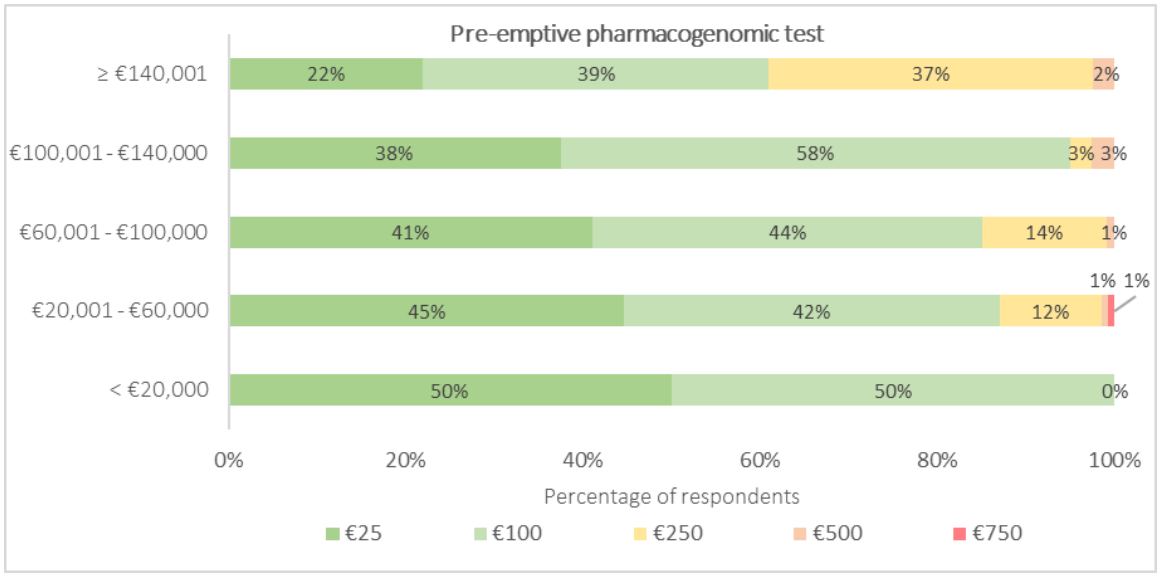

Figure 3.6. Bar charts of willingness-to-pay for a pre-emptive pharmacogenomic testing by annual household income

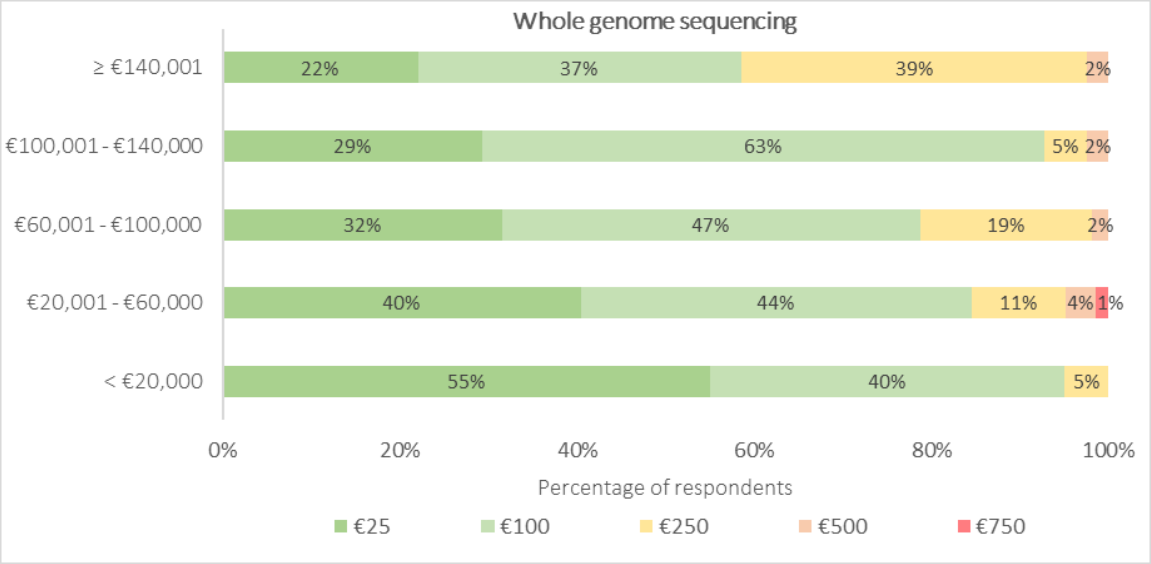

Figure 3.7. Bar charts of willingness-to-pay for whole genome sequencing by annual household income

Experience with stopping a medicine due to side effects (p = 0.021) and inefficacy (p = 0.003) was associated with WTP for reactive and pre-emptive testing. Those who were aware of pharmacogenomics were willing to spend more for pre-emptive (p < 0.001) and whole genome sequencing pharmacogenomic testing (p = 0.004). Respondents classifying their understanding of the applications of pharmacogenomic testing in healthcare as excellent or good were willing to pay more for a pre-emptive pharmacogenomic test (p = 0.004). Those who experienced a medication-related hospitalisation (*e.g.,* due to side effects) were also willing to pay more for reactive and pre-emptive pharmacogenomic tests (p < 0.05). Chronic disease status was not associated with WTP for reactive and pre-emptive pharmacogenomic tests (Table 3.12). Interestingly, respondents without any chronic disease were willing to incur more costs for whole-genome sequencing than patients with a chronic disease (p = 0.009). A high level of interest in insurance reimbursement for pharmacogenomic testing was shown, which was not affected by chronic disease status (p = 0.067) (Table 5).

Table 3.12. Respondents' willingness to pay for the different types of pharmacogenomic test (reactive, pre-emptive, whole-genome sequencing) and level of agreement with insurance reimbursement by chronic disease status

	%Overall	%NCD (n = 246)	%CD (n = 111)	P [a]
Reimbursed by insurance (n = 351)				0.067
Strongly agree	59.3	57.4	63.3	
Agree	26.5	30.2	18.3	
Neutral	10.8	8.68	15.6	
Disagree	1.71	1.65	1.83	
Strongly disagree	1.71	2.07	0.92	
Reactive test WTP (n = 357)				0.582
€25	36.7	34.1	42.3	
€100	49.3	50.8	45.9	
€250	11.8	12.6	9.91	
€500	1.68	1.63	1.80	
€750	0.56	0.81	0.00	
Pre-emptive test WTP (n = 351)				0.101
€25	40.5	37.6	46.8	
€100	44.7	46.3	41.3	
€250	13.4	15.3	9.17	
€500	1.14	0.83	1.83	
€750	0.28	0.00	0.92	
Whole genome sequencing WTP (n = 354)				0.009*
€25	35.0	32.8	40.0	
€100	45.8	46.3	44.5	
€250	16.1	19.3	9.09	
€500	2.54	1.64	4.55	
€750	0.56	0.00	1.82	

* Significant at $p < 0.05$, [a] Independent t-test for variables with two groups, CD chronic disease (includes MMPP multimorbid chronic disease and/or polypharmacy and SCD single chronic disease), NCD no chronic disease, WTP willingness to pay

3.5.6. Preferences for location and provider of pharmacogenomic services

3.5.6.1. Healthcare setting for pharmacogenomic services

Respondents were more interested in a pharmacogenomic service provided in the primary care setting (community pharmacy or general practice), rather than hospital setting. In relation to accessibility to healthcare services in Ireland, respondents were asked how often they attend and how long it takes to get to their local pharmacy and GP. On average, it takes respondents 8 minutes to reach their local community pharmacy, and 16 minutes to attend their regular prescriber. In further analyses, community pharmacies were found to be frequented more often than general practice, with 55% of respondents attending their local community pharmacy at least monthly (n = 233). In comparison, a similar proportion of respondents (54%, n = 228) attend their GP once yearly or less frequently, while very few respondents (9%, n = 36) attend at least once a month. Understandably, respondents with chronic disease attend both community pharmacy ($p < 0.001$) and general practice ($p = 0.011$) more frequently than respondents without any chronic disease. Furthermore, a significantly higher proportion of those with multimorbidity and polypharmacy attend both settings more frequently than single chronic disease respondents ($p < 0.001$). Overall, 73% of respondents selected community pharmacy as the most convenient healthcare service to them (n = 288).

3.5.6.2. Healthcare professional to provide pharmacogenomic testing services

Respondents were positive about community-based pharmacogenomics services, with 44% (n = 170) expressing a preference for CPs to be responsible for pharmacogenomic testing, 32% (n = 124) preferring GPs, and 20% (n = 77) preferring a hospital HCP. Choice of HCP to provide pharmacogenomic services was not associated with chronic disease status ($p = 0.646$). In addition, 4% (n=16) selected the 'other' option, which included collaboration between primary care HCPs and specialists/specialised centres with understanding of pharmacogenomics. As shown in Table 3.13, HCP to provide pharmacogenomic testing services was associated with several factors Those with experience in a health-related profession were less likely to choose general practice. Conversely, those opposed to pharmacogenomic testing in Ireland were more likely to choose GPs. Respondents with awareness of pharmacogenomics preferred hospital settings compared to those without.

Table 3.13. Association between pharmacogenomic service provider/setting and questionnaire responses

If a pharmacogenetics service was provided in Ireland, what healthcare professional do you think should provide this service?					
Health-related profession	CP	GP	HHCP/Other	N	P [c]
No	41.2%	40.2%	18.6%	194	0.001*
Yes	46.6%	23.8%	29.5%	193	
Most convenient healthcare service	CP	GP	HHCP/Other	N	P [c]
Community pharmacy	49.1%	29.3%	21.6%	283	
General practice	30.9%	40.4%	28.7%	94	0.015*
Hospital or other	22.2%	33.3%	44.4%	9	
Pharmacogenomics awareness	CP	GP	HHCP/Other	N	P [c]
Yes	42.8%	24.1%	33.1%	166	< 0.001*
No	44.9%	38.0%	17.1%	216	
Open to pharmacogenomic service availability in Ireland	CP	GP	HHCP/Other	N	P [c]
Yes	46.6%	31.8%	21.6%	292	
No	0.0%	75.0%	25.0%	8	0.006*
Don't know	39.1%	28.7%	32.2%	82	

^ merged responses, * Significant at $p < 0.05$, [c] χ^2 test, *CP* Community pharmacist, *GP* General practitioner, *HHCP* Hospital healthcare professional

3.6. Discussion

The current questionnaire provides a comprehensive and up-to-date account of a sample of Irish peoples' views regarding pharmacogenomic testing. At the time that this questionnaire was issued, there had been no previously published research in this area. We hypothesised that perceptions of pharmacogenomics would significantly differ based on the view of those with and without chronic disease(s). It was shown that respondents with chronic disease were more than twice as likely to value pharmacogenomic service availability than respondents without existing medical conditions, when adjusted for age and gender. Furthermore, it appears that this was driven more by preferences of those with multimorbid chronic disease and polypharmacy than with single chronic disease. Our findings serve to address an important deficit in the literature as the views of chronic disease patients versus respondents without any chronic disease on pharmacogenomic testing had yet to be explored. Therefore, this study served to address this shortfall and provided important information to guide the direction of the overall research project.

3.6.1. Demographics

Based on comparison with national gender and age data, the sample of respondents was not representative of the wider population of Ireland. Furthermore, the respondent demographics of the questionnaire were not equally dispersed in many categories. Almost all respondents were of European ancestry (94%), and the majority were employed (84%), had some type of college degree (78%), and had health insurance (75%). Females comprised 72% of respondents, and approximately 50% of respondents work or previously worked in a health-related profession. The sample consisted predominantly of respondents between the ages 25-64 years (63%, n = 265). Older and younger adults were under- and over-represented in this study respectively. Given this demographic information, the findings of this study may not be representative of the general Irish population (Table 3.2).

This result may be due to the fact that the questionnaire was distributed electronically via social media and word of mouth for the majority of respondents (85%, n = 356). Nevertheless, in Ireland, the majority of the population has access to the internet in their homes (92% of individuals have used the internet within the previous three months) [366],

and social media is a common source of communication (79% of the total population use social media) [367]. Hence, we do not think that the distribution method in itself has introduced a severe bias in representation. The observed bias is more likely to be due to interest, ability, and availability of time. Age- and gender-adjustment was performed in our analysis to remove confounding caused by these parameters.

3.6.2. Perceptions of pharmacogenomics

Despite the lack of sample representativeness, the findings provide valuable insights into a sample of Irish peoples' perceptions of pharmacogenomic testing. Pharmacogenomics is still an evolving discipline and will undoubtedly undergo further developments over the coming years to enhance clinical utility and subsequent patient outcomes. As the pharmacogenomics evidence base expands and prior to its evolution into routine clinical implementation, it is crucial to ascertain the user's perception of utility, barriers, and impetus to this new, holistic approach to healthcare delivery.

Pharmacogenomics services are predominantly delivered in specialist settings, yet the majority of medical care is provided in the community or primary care setting. With increased implementation across specialist secondary and tertiary care settings and into primary care in the US, Canada, Australia, and in other European countries, it is possible that a larger proportion of Irish people will begin to hear about these tests. At present, pharmacogenomic testing is not yet commonplace in Ireland. Consequently, it was unsurprising that the overall awareness of pharmacogenomic testing was low (44%, n = 166). Interestingly, approximately one third of respondents who work/worked in a health-related profession had not heard about pharmacogenomics prior to the questionnaire (32%, n = 61). Our findings also suggest that while over half of the respondents were not confident in their understanding of pharmacogenomics, the majority have a high level of interest and positive perceptions of its potential benefits to improve drug therapy outcomes, which were similar amongst those with and without chronic conditions.

Over 90% of participants indicated they would be interested (strongly agree and agree) in pharmacogenomic testing to optimise their medicines, enhance prescribing, predict their risk of serious adverse events, and to reduce their medication burden. Thus, reflecting the findings of the Mayo-Baylor RIGHT10K Study survey of 4,624 patients in which almost all

respondents (94.6%) felt that pharmacogenomic testing would help them avoid exposure to medication that might be harmful [291]. Respondents demonstrated greatest concern when it came to the cost of pharmacogenomic testing. A majority of respondents expressed a preference for health insurance coverage for pharmacogenomics services and few people were willing to pay more than €100 for the service. Respondents also expressed concerns over the potential for ancillary risk information and unauthorised access to their test results. Thus, strict incidental findings and data sharing policies need to be put into place that provide security for patients and enable data to be shared among HCPs caring for the patient without and privacy issues.

3.6.2.1. Multimorbidity and polypharmacy

The present study builds on the systematic review presented in Chapter 2, which concluded that more work is needed on pharmacogenomic testing as part of medicines optimisation for multimorbid chronic disease and polypharmacy patients [272]. Limited data suggest pharmacogenomic testing could have significant benefits for healthcare providers and patients by reducing healthcare utilisation and costs, enhancing drug interaction identification, and improving clinical decision-making. More robust, high-quality evidence was provided by Swen *et al.* (PREPARE) which demonstrated that pharmacogenomic testing resulted in a 30% decrease in clinically relevant ADRs [172].

In this questionnaire study, respondents with chronic conditions and multimorbid chronic disease and polypharmacy were found to be older and were more likely to report medication adverse effects and non-persistence, which may have influenced their perceived value of pharmacogenomic services. While respondents with chronic disease were more than twice as likely to value pharmacogenomic service availability than respondents without existing medical conditions, this result was driven more by the preferences of those with multimorbidity and prescribed polypharmacy than those with a single chronic disease. Although older people with multimorbidity and prescribed polypharmacy are under-represented in this study, multimorbidity was prevalent in this younger population. A cross-sectional analysis of TILDA data collected in 2016 found that 36.8% of adults aged 50-59 years had two or more chronic conditions [28]. Consequently, there is an unmet need for pharmacogenomic information to be incorporated into

medicines optimisation for patients with multimorbidity and prescribed polypharmacy in primary care, regardless of patient age.

3.6.3. Preferences for location and provider of pharmacogenomic services

The primary care setting is a logical clinical entry point for pharmacogenomic testing. GPs and CPs in primary care are an initial point of access into the healthcare system, focus on preventive care, treat a wide variety of illnesses, and communicate frequently with patients and other HCPs [213]. They are ideally positioned to identify patients who may need a pharmacogenomic test, order necessary tests, and document and communicate test results to patients and other HCPs [213]. Participants in this questionnaire study largely agreed with this notion, favouring the delivery of services in the community setting as opposed to hospital settings. To enable the implementation of pharmacogenomic testing and resultant medicines optimisation in primary care, a collaborative approach involving GPs, pharmacists and patients will be necessary.

Particular interest was shown for pharmacogenomic testing in the community pharmacy, perhaps enhanced by ease of access to this healthcare setting. Moreover, only 7% of respondents were recruited from participating pharmacies; thus, respondents were not under undue influence to select this setting for pharmacogenomic testing. While incorporating pharmacogenomic testing in primary care is consistent with the evolution of this practice area, this progression has not yet reached independent pharmacist prescribing in Ireland. Therefore, in an Irish community pharmacy pharmacogenomic service provision model, GPs will be relied upon to make pharmacogenomic test results actionable in conjunction with CPs. Such models have been investigated and demonstrate promise [282, 312, 313, 368, 369]. While the high level of interest in pharmacogenomic testing is encouraging, this may not translate to high uptake due to the cost of testing, where reimbursement will undoubtedly have an impact. Although pharmacists internationally are incorporating pharmacogenomics into their practices, this study highlighted the need for further education as well as concerns around patient health privacy [319, 344, 370, 371].

3.6.3.1. Pharmacogenomics education in primary care

Pharmacogenomics implementation is highly dependent on its general acceptance among patients and HCPs, which is one of the most influential prerequisites for successful implementation. A recent systematic review by Hansen *et al.* examining the attitudes of patients, GPs, and pharmacists towards pharmacogenomic testing in primary care emphasised lack of knowledge as an important barrier to the implementation of pharmacogenomic testing in clinical practice [372]. Rogausch *et al.* found that approximately 40% of patients could not comprehend the full consequences of a pharmacogenomic test [326]. In a small cohort of patients recruited from a community pharmacy in the US, Gibson *et al.* demonstrated 52% of respondents were unfamiliar with pharmacogenomics (compared to 56% in our study) [325]. Selkirk *et al.* showed 61% of GPs felt uncertain about how to incorporate pharmacogenomics in their practice [373].

Other studies found that GPs needed more information and education on pharmacogenomics, including interpreting results [346, 374]. To this end, Haga *et al.* demonstrated general practice-based pharmacists can increase the likelihood of pharmacogenomic test utilisation [374]. Conversely, Hansen *et al.* also demonstrated that pharmacists did not feel competent in pharmacogenomic counselling [372]. Despite this, a majority of CPs were interested in personalised medicine and were motivated to implement and provide pharmacogenomic services [319]. The Mayo-Baylor RIGHT10K study found that a collaborative primary care approach entailing the involvement of pharmacogenomic-trained pharmacists acting as a conduit between the data, physicians and patients, information technology support for the development of CDS tools and alerts, and effective multidisciplinary pharmacogenomic education programs were all required for the successful implementation of pharmacogenomics [291]. In the PREPARE study, an educational programme that included online modules, educational videos, brochures, and an interactive educational game was established for the systematic education of the HCPs active in the implementation of pharmacogenomics during the study [172].

The exigent need for pharmacogenomics education was mirrored in the present study and reflects the intensive work required to implement a pharmacogenomics program in practice [291]. At present, pharmacogenomic testing is not yet commonplace in Ireland.

Consequently, it was unsurprising that the overall awareness and knowledge of pharmacogenomic testing was low (44% and 55%). Nevertheless, this unfamiliarity with pharmacogenomics is a source of concern given the high proportion of respondents in a health-related profession in our study (50%). Approximately one third of these respondents were unaware of pharmacogenomics, and 45% rated their understanding of its applications in healthcare as poor or very poor. Therefore, major educational efforts for HCPs, as well as the public, are required for pharmacogenomics implementation in routine care [372, 375].

Such educational efforts should include informing HCPs and patients about pre-emptive pharmacogenomic testing, raising awareness of alternative and best methods of treatments, and aiding understanding and interpretation of the benefits and limitations of the genetic information provided [376]. Comprehensive continuing professional development courses for HCPs, such as those that developed in the Pharmacists: Personalized Medicine Experts study [317], and the Mayo-Baylor RIGHT 10K program [291], may help by improving knowledge, readiness, and expertise in applying pharmacogenomics to patient care [317, 318]. Furthermore, incorporation of pharmacogenomics and personalised medicine education into the curricula of health science faculties is vital to address the lack of preparedness in the primary care workforce and to prevent education creating a bottleneck in the implementation of personalised medicine [347, 377-379].

Moreover, significant research and service development is required for the implementation of pharmacogenomics in routine patient care. To this end, the Royal Pharmaceutical Society issued a statement on the role of pharmacy in pharmacogenomics, asserting that pharmacogenomics is a natural expansion of the role of the pharmacist and the pharmacy team [215]. In this report, the Royal Pharmaceutical Society highlights that pharmacists are key professionals working on the frontline of healthcare and are experts in medicines [215]. Pharmacists' unique training in science and healthcare enables them to articulate complex medicines issues in a patient-friendly way; therefore, pharmacists are well equipped to play an integral part in the development of pharmacogenomics [215].

The role of pharmacy in implementing and delivering pharmacogenomics services was presented in Box 1.2 in Chapter 1 (Section 1.6.4) [215]. As members of a multidisciplinary team, pharmacists could raise awareness, educate other HCPs on pharmacogenomics, and promote better integration of pharmacogenomics. Through medication reviews, pharmacists could identify patients who would benefit from pharmacogenomic testing and provide information and advice to patients on this service [215]. Furthermore, the Royal Pharmaceutical Society stressed the importance of a comprehensive workforce strategy and fully resourced genomics education and training related to clinical pharmacogenomics competency requirements in line with all multi-disciplinary professionals involved in the delivery of pharmacogenomics [215].

Consequently, the findings of this study underline the need for more research on the implementation of community-based pharmacogenomic services for people with multimorbidity and polypharmacy. As with any novel medical intervention, the effective translation of new clinical tools such as pharmacogenomic testing will be substantially influenced by the local environment or context in which they will be used. Decisions regarding the use of new innovations are influenced by both patient and healthcare provider factors such as attitudes, understanding, interest, perceived value, and cost [380]. The views of CPs, GPs, and patients regarding collaborative medicines optimisation incorporating pharmacogenomics need to be investigated to identify barriers, facilitators, and future improvement strategies.

3.6.4. Willingness-to-pay for pharmacogenomic services

Our results indicate that while a majority of respondents are interested in pharmacogenomic testing, there is a desire for health insurance co-funding of the service. A large proportion would not be willing to pay more than €100, below the typical price for pre-emptive testing. This may be due to the fact that pharmacogenomic effects are not something a patient can physically feel, making it difficult for patients to incur costs regardless of perceiving the benefits. The presence of a chronic disease did not result in respondents being willing to incur greater costs. Conversely, patients without any chronic disease were willing to pay more for whole-genome sequencing. This could be an incidental finding, but it could also suggest those with chronic diseases are concerned about discovering their risk for an additional disease, while those without existing conditions are more open to these findings.

New research on the implementation of pharmacogenomics in practice suggests that there may be potential benefits of whole-genome analyses [291]. However, this work also underlines high costs of delivering pre-emptive whole-genome testing and the professional resources required to integrate this information into the process of medicines optimisation. Indeed, the FDA have insisted that the interpretation of even more basic DTC genotype-based pharmacogenomic tests must involve HCP input [341, 342]. Unsurprisingly, we observed that respondents' financial situation was a key driver of a willingness to incur any out-of-pocket costs for pharmacogenomic testing. These findings add evidence to the concern that future benefits of pharmacogenomics may be disproportionately allocated to those with more financial resources [349]. However, our findings demonstrate a high level of interest in pharmacogenomic testing reimbursement and support the need for more data on the clinical and health-economic benefits of widespread pre-emptive pharmacogenomic testing. It is also clear that more work is needed to avoid widening health disparities among patients with economic vulnerability.

3.6.5. Potential impact of pharmacogenomic testing in Irish primary care

The systematic review described in Chapter 2 demonstrated that pharmacogenomic variants are ubiquitous and clinically relevant. The results from Chapter 3 demonstrated the receptivity of a sample of Irish people to the availability of pharmacogenomic services to improve patient outcomes through individualised pharmacotherapy. The potential impact of pharmacogenomic testing on prescribing in primary care in the UK was provided in Section 3.1; however, there is a dearth of data on the prevalence of drug-gene interactions in Irish primary care. To contextualise the perceptions on pharmacogenomics gleaned in this questionnaire study, a cross-sectional analysis using pharmacy GMS claims data from the HSE-PCRS in the community setting was undertaken to estimate the prevalence of drug-gene interactions in Irish primary care. The PhD candidate is a co-author on this paper currently under peer-review by the British Journal of Clinical Pharmacology.

The HSE-PCRS data has been used extensively in research for different purposes. Cooper *et al.* used PCRS data to establish the prevalence of potentially inappropriate prescribing, finding it to be common in middle-aged people with the risk of potentially inappropriate prescribing increasing with polypharmacy [381]. Kim *et al.* measured medication adherence in older community-dwelling patients with multimorbidity using PCRS data, finding 31% of older patients with multimorbidity were non-adherent to their medication [382]. Finally, Mattsson *et al.* will use this data to evaluate the prescribing of analgesic and sedative medications, in particular opioids and benzodiazepines, to inform regulation and use of these controlled drugs to maximise benefits for patients [383].

The volume of first time and total dispensings of 46 pharmacogenomic drugs between 01-01-2021 and 31-12-21 were extracted from the GMS database and analysed to estimate the national prevalence of total dispensings and incidence of first time dispensings with potential drug-gene interactions according to the CPIC and the DPWG guidelines. This study involved analysis of pharmacogenetic haplotypes and phenotypes for 14 genes (CFTR, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A5, CYP4F2, DPYD, IFNL3, NUDT15, SLCO1B1, TPMT, UGT1A1, and VKORC1). The first time and total dispensing volumes of relevant drugs were multiplied by the percentage frequency of actionable phenotypes (obtained primarily

from the UK Biobank) for relevant genes to estimate the incidence of actionable drug-gene interactions, categorised according to actionability, as used by Youssef *et al.* [256].

Nearly one fifth (19.8%, n = 12,443,637) of all medicines prescribed to patients enlisted in the GMS were found to have a potential drug-gene interaction. On application of phenotype frequencies, it was estimated that nearly one in five dispensings of these drugs (18.9%, n = 2,349,055) had a drug-gene interaction requiring direct (*e.g.,* dose or drug change) or indirect action (*e.g.,* monitoring). One in thirteen (7.4%, n = 139,169) patients who received a medicine for the first time required an immediate change in drug regimen or dose adjustment, based on evidence-based guidelines [178, 179]. Similar to Kimpton *et al.*, three genes accounted for >95% of all actionable drug-gene interactions (CYP2C19, CYP2D6 and SLCO1B1).

This study found a high prevalence of actionable drug-gene interactions prescribed to the GMS population in Irish primary care using HSE-PCRS data. Three genes account for the majority of drug-gene interactions with actionable therapeutic recommendations. This study identifies therapeutic areas of primary care prescribing that should be targeted to prevent ADRs and therapeutic failures resulting from drug-gene interactions and demonstrates a role for pre-emptive testing and testing of patients already prescribed routine medicines. It was beyond the scope of this cross-sectional analysis to investigate the prevalence of drug-gene interactions in patients with multimorbidity and prescribed polypharmacy; this will be examined in Chapter 4.

3.6.6. Strengths and limitations

In light of the notable lack of previously published research which has sought to explore the views of Irish people on pharmacogenomic testing, the findings of this questionnaire address an important deficit in the literature. In contrast to the current study, as the first known national questionnaire on the subject of pharmacogenomics, various studies have been published in other countries such as the UK, Canada, and the US. No incentive was offered as part of this study; adding to the value of the insights provided as honest and reliable accounts of respondents' views on matters relating to pharmacogenomic testing. Furthermore, the fact that the questionnaires could be completed by respondents in their own time and at their own pace was of particular importance [356]. Additionally, the potential bias in responses that may result from direct contact with researchers was avoided using an online questionnaire, which was important as we sought to engage the public and enquire into their healthcare and personal opinions.

The present work has a number of limitations. Firstly, its small sample size may not fully represent the broader Irish population. This necessitates caution when interpreting the findings, which offer insights into a segment of Irish individuals but may not reflect the views of the general public. The sample was predominantly aged 25-64 years, with older adults (≥ 65 years) under-represented, possibly due to the online dissemination method which may have been less accessible to this age group. Consequently, older people with multimorbidity and polypharmacy are under-represented, despite their potentially significant experience with medication side effects and medications impacted by pharmacogenomics. On the other hand, the sample may be more reflective of middle-aged individuals with multimorbidity. Additionally, the respondent pool was skewed towards those with higher levels of education, higher income, and healthcare backgrounds, which may have influenced the generally positive responses towards pharmacogenomics. Nonetheless, the study offers valuable perspectives and contributes to the understanding of attitudes towards pharmacogenomics within the sample surveyed. Secondly, response bias is likely; respondents participating in this study are characteristically different from those who did not. Owing to the anonymous format of the questionnaire, it was not possible to assess or conduct follow-up evaluation with non-respondents.

Thirdly, the data collected in this study was self-reported by respondents and not verified with general practice or pharmacy records. Fourthly, the promotion of the questionnaire on the social media pages of the researchers' and the School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin, may have contributed to the over-representation of young adults (students) and those with a background in a health-related profession. Fifthly, 84% of the surveys (n = 354) were fully completed. It is likely the time taken to complete the questionnaire was a barrier for some respondents, thus limiting the results generated. Furthermore, the COVID-19 pandemic presented various unexpected challenges mainly in the data collection stage. Face-to-face recruitment in participating community pharmacies was significantly limited, accounting only for 7% of respondents. Finally, the views of healthcare workers on pharmacogenomics were not specifically assessed in this study. More work is required to ensure that the needs and preferences of a broader range of people with chronic disease are accounted for in the development, implementation, and evaluation of pharmacogenomic services. Although the sample may not necessarily be representative, the findings provide valuable insights into the opinions of a sample of the Irish population on pharmacogenomics.

3.7. Conclusion

The findings provide valuable insights into the views, experiences, and knowledge of a sample of the Irish population regarding pharmacogenomic testing, as well as considerations for implementing such services in Ireland. The data indicate strong support for pharmacogenomic testing among the sample, particularly those with multimorbidity and polypharmacy, highlighting an unmet need for its integration into medicines optimisation. However, the potential benefits of pharmacogenomic tests must be weighed against concerns such as test costs, incidental findings, and genetic data privacy. To build on these insights, it would be beneficial to design a well-structured, representative questionnaire that encompasses a broader and more diverse sample of the Irish population. This approach would provide a more comprehensive understanding of stakeholder views and address potential challenges in the delivery and implementation of pharmacogenomic testing in Irish primary care in Ireland, ultimately ensuring better patient safety and care.

Chapter 4

Statin SLCO1B1 and ABCG2 genotypes and progression of heart failure:

A retrospective longitudinal report from the St Vincent's Screening TO Prevent HF (STOP-HF) cohort

4. Chapter 4: STOP-HF retrospective analysis

4.1. Introduction

As noted in Chapter 1, ageing around the world poses a global challenge. The phenomenon of ageing has led to a substantial increase in chronic conditions, consequently increasing the prevalence of multimorbidity. The pharmacological management of numerous co-existing chronic conditions is often complex and inevitably leads to treatment with polypharmacy. In patients with multimorbidity, the drug-drug interactions and drug-disease interactions may leave them particularly vulnerable to adverse events, especially in the senior and frail [384]. Studies have found that multimorbidity leads to poor quality of life [31], increased use of healthcare [17, 20], greater complexity regarding clinical treatment and patient management [16, 34], and an increase in mortality [29, 32, 385]. Cardiovascular disease (CVD) is a major cause of morbidity worldwide and remains the foremost cause of preventable death; accounting for 17.9 million deaths in 2019, representing 32% of all global deaths [386]. CVD was estimated to cost the EU economy €210 billion annually in 2015, of which 53% (€110 billion) was due to healthcare costs [387]. There are a host of risk factors for the development of CVD, such as hypertension, dyslipidaemia, diabetes, obesity, smoking and alcohol consumption. In Europe, one in four people have at least one of these risk factors [387].

Hypercholesterolaemia is a risk factor for both fatal and non-fatal CVD events in people with and without a past CVD, and lowering cholesterol is an important target for pharmacotherapy [388]. Lipid-modifying agents are widely recommended to reduce lipid levels and to prevent atherosclerotic CVD [389-391]. Statins (3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors) are the most studied drugs in cardiovascular prevention and are the first-choice agent to reduce high blood cholesterol. In the past decade, the use of statins in the primary prevention (patients at risk of CVD but who have not yet had an event) and secondary prevention (patients with known CVD) of CVDs has increased globally. The use of statins in secondary prevention for patients with established CVD is generally uncontroversial, but debate remains about their use for primary prevention [392]. The controversy centres on uncertainty about whether the benefits of statins outweigh

the harms and whether widespread statin use can be justified from a societal perspective [393].

Given the robust evidence of efficacy and safety for statins from multiple randomised controlled trials, their share of lipid-modifying agent use has increased over time. A cross-sectional analysis using monthly pharmaceutical sales data in 83 counties found an estimated 145.8 million people (2.6% of the global population) used statins in 2018 [394]. Statins were the most commonly used class of lipid-modifying agent and experienced the largest average growth from 2008 to 2018 (compound annual growth rate of 5.19%) [394]. In 2023, atorvastatin was the most commonly prescribed product according to HSE-PCRS data across the GMS and DPS patient population [395]. In 2021, approximately €33 million was spent annually in Ireland on statins in State-funded purchases alone (*i.e.,* GMS, DPS and LTI schemes) [396]. While the ageing population in high-income countries has been cited as a driver of increased utilisation of statins, increasing treatment intensification rather than population ageing was almost exclusively responsible for this rise [397]. There is some evidence that statins are underused in certain sections of the population [398-400], and that statins are not targeted at those most likely to benefit [401, 402].

A cross-sectional analysis of TILDA data on a nationally representative sample of community dwelling adults aged 50 years and older in Ireland demonstrated almost one-third of these adults receive statin therapy [403]. Almost two-thirds of these took statins for the primary prevention of CVD. Importantly, the prevalence of statin utilisation was found to increase with age, frequency of GP visits, and polypharmacy; controlling for indication, a person receiving five or more medicines (excluding statins) was more likely to be taking a statin [403]. An Irish study found that the prevalence of polypharmacy in those over 65 years in 2012 was 60%, and that statins were the drug category prescribed to the highest number of individuals [53]. Another study reported that lipid-modifying drugs were the most commonly reported medication class (69%), along with antithrombotics, used by those reporting polypharmacy [54]. In a study in primary care settings in Quebec, among 971 participants 31.9% of all participants were prescribed polypharmacy; statins constituted the most commonly prescribed medication in this study, with approximately 30% of patients taking a statin for primary prevention [384].

4.1.1. Statins in heart failure

Heart failure (HF) is a complex clinical syndrome characterised by debilitating symptoms, a particularly poor quality of life, frequent hospitalisations, and reduced survival [404]. It also exerts a substantial drain on healthcare resources. The incidence of HF is typically associated with underlying CVD and its prevalence is on the rise due to an ageing population: from around 1% for those aged <55 years to >10% in those aged ≥70 years [405]. With an increasing number of patients, HF is becoming a major worldwide public health problem which requires a global response. Optimal medical management of HF is becoming increasingly more complex. The concomitant use of evidence-based medication at the highest tolerated dose is advocated for by international guidelines published by the European Society of Cardiology (ESC) and the American College of Cardiology/American Heart Association (ACC/AHA) [405, 406]. Subsequently, polypharmacy is now the new norm in the management of HF, which is compounded by additional prescriptions older patients tend to receive for their comorbidities [407, 408]. Consequently, therapies which reduce the risk of developing HF are highly desirable [409]. Dyslipidaemia increases the risk of incident HF independent of its association with myocardial infarction (MI) [410], for which statin therapy is a potential corrective action [405].

Statins are one of the most prescribed medications worldwide with established use for individuals with CVD [392]; a number of large-scale clinical trials have demonstrated that statins substantially reduce cardiovascular morbidity and mortality in both primary and secondary prevention [411-413]. Notwithstanding these observations, the use of statins in patients with existing HF is disputed [414]. This controversy mainly stems from the results of two large scale studies of patients with symptomatic stage C HF with reduced ejection fraction, CORONA and GISSI-HF [415, 416]. Both trials examined the effect of rosuvastatin on mortality and morbidity in patients with established HF [415, 416]. Although treatment was well tolerated, a significant effect of statin therapy on the predetermined endpoints was not shown, despite a marked reduction in low-density lipoprotein cholesterol (LDL-c) and high-sensitivity C-reactive protein (hs-CRP) [415, 416], contrasting with the positive results observed in many smaller randomised and non-randomised studies [417].

As a result, the 2021 ESC guideline on the treatment of HF makes no recommendation on the use of statin therapy in patients with HF without other indications for their use [405]. Ultimately, the question of whether statin therapy is indicated in patients with established HF without hypercholesterolaemia remains unanswered and outside the scope of this study. The main objective of this study was to compare progression of asymptomatic HF and new-onset symptomatic HF amongst patients with aberrant SLCO1B1 and ABCG2 statin transporter phenotypes that alter systemic exposure to statins (Section 4.1.2). Asymptomatic HF includes those at risk for HF (stage A) and patients with pre-HF (stage B).

Pre-HF refers to the early stages of the disease, where subtle changes occur before the onset of clinical HF symptoms. Pre-HF is being recognised as an important stage for recognition of future risk of HF [406, 418-420]. Identifying individuals who are in a trajectory to develop HF also provides a crucial opportunity for the prevention of HF. Detecting pre-HF can be difficult due to its asymptomatic nature, often leaving patients oblivious of their deteriorating cardiac health [419]. The prevalence of pre-HF is estimated to be five to ten times higher than symptomatic HF, ranging from 11-43% with higher estimates found in older patients, in men, and in those with hypertension [421]. Patients with asymptomatic HF can present with structural or functional cardiac abnormalities including left ventricular (LV) remodelling (including low LV ejection fraction (LVEF) and LV hypertrophy (LVH; a LV mass index (LVMI) that exceeds the normal range)), and LV systolic and diastolic dysfunction (LVSD and LVDD) [405, 406, 419-421].

Patients with structural cardiac dysfunction but without clinical symptoms are usually undetected unless imaging assessment such as echocardiography is performed [421]. There is increasing evidence for the use of natriuretic peptide (NP) biomarkers, such as B-type NP (BNP) and N-terminal pro-BNP, to detect the presence or severity of HF with a high diagnostic accuracy. The use of BNP as a biomarker in the diagnosis of HF has been included in HF guidelines, including the diagnosis of asymptomatic HF and pre-HF [405, 406, 420]. The diagnosis of HF with reduced ejection fraction requires the presence of symptoms and/or signs of HF and a reduced ejection fraction (LVEF ≤40) [405]. The diagnosis of HF with preserved ejection fraction remains challenging. To facilitate broad clinical application, the ESC guideline for the diagnosis of HF recommends a pragmatic approach that should include

the following: i) signs and symptoms of HF; ii) an LVEF ≥50%; and iii) objective evidence of cardiac structural and/or functional abnormality consistent with the presence of LVDD/raised LV filling pressures (left atrial enlargement reflects chronically elevated LV filling pressures; predicted using the left atrial volume index (LAVI)), including raised NPs [405].

When compared with patients with common forms of cancer, patients with HF have very similar case-fatality rates (59% versus 58% within 5 years) and are associated with similar premature life-years lost [422]. This underlines the necessity to move the needle to earlier detection and prevention in HF very similar to cancer prevention [419]. The ability to detect a higher risk of HF can be achieved through screening programmes, such as the St Vincent's Screening to Prevent Heart Failure (STOP-HF) programme (Section 4.3.1) [418, 423]. Once pre-HF is identified, controlling cholesterol levels is one of the many essential steps to reduce the risk of HF [406]; several studies have demonstrated that statins reduce HF incidence [424-430]. Statin therapy has been conclusively shown to reduce the risk of MI in primary and secondary prevention populations by lowering LDL-c [411, 431]. Since many cases of HF are consequent to MI [432], statins could potentially prevent the development of HF by reducing first and recurrent injurious myocardial events [409]. Subsequently, guidelines published by the ESC and ACC/AHA recommend primary prevention of HF with statin therapy [405, 406].

However, it is possible that statin therapy may influence the development of HF by other mechanisms (pleiotropic effects, *i.e.,* exerting multiple pharmacological properties) such as reduced inflammation, improved endothelial function, reduced thrombogenicity, improved autonomic function, and improved LV function [417, 433-438]. The syndrome of HF is characterised by increased levels of circulating inflammatory mediators, which have been implicated in the pathogenesis of HF [439]. Statins have been shown to decrease the number of inflammatory cells in atherosclerotic plaques and to possess other anti-inflammatory properties [440]. They have been proven to act as anti-inflammatory agents that slow the progression of disease [433, 438, 441, 442]. This is especially important given the role of inflammation in the formation of atherosclerotic plaques [435, 436, 438, 443].

In the Scandinavian Simvastatin Survival Study, 4,444 patients with coronary heart disease without evidence of HF were randomised to placebo or simvastatin 20-40 mg/day. In this study, simvastatin reduced the incidence of HF with a risk reduction of 21% ($p < 0.015$) and

also reduced the number of hospitalisations and deaths associated with HF [424]. In their study of 1,410 patients, Aronow *et al.* reported a risk reduction of 26% in the incidence of HF in patients treated with statins versus those treated with no lipid-lowering drug ($p < 0.001$) [425]. In the A to Z trial, among 4,497 patients randomised to placebo or simvastatin 40 mg/day for one month followed by 80 mg/day thereafter following acute coronary syndrome, the risk of new-onset symptomatic HF was reduced by 28% in the statin group ($p = 0.04$) [426].

The PROVE IT-TIMI 22 study randomised 4,162 patients hospitalised for acute coronary syndrome (MI or high-risk unstable angina) to either intensive statin therapy (atorvastatin 80 mg) or moderate statin therapy (pravastatin 40 mg) [427]. Treatment with atorvastatin 80 mg significantly reduced the risk of development of HF by 45% ($p = 0.008$). This benefit was independent of recurrent MI, suggesting that intensive statin therapy lowers the risk of HF independently of its ability to reduce recurrent ischaemic injury [427]. The Treating to New Targets trial randomised 10,001 patients with stable coronary heart disease to treatment with atorvastatin 80 mg or 10 mg/day, and reported a 41% and 13% risk reduction in HF hospitalisations in patients with and without a history of HF respectively [428]. Similar to the PROVE IT-TIMI 22 study, this benefit did not appear to be mediated through a reduction in preceding ischaemic events; the authors suggested pleiotropic properties may be responsible for the beneficial effects of statin therapy in preventing HF hospitalisations [428].

In the IDEAL study, 8,888 patients with a history of MI were randomised to receive simvastatin 20 to 40 mg/day or atorvastatin 80 mg/day [429]. More intensive LDL-c lowering with atorvastatin 80 mg was associated with a 26% decrease of new-onset HF ($p = 0.03$). Furthermore, HF without preceding MI was decreased by 27% ($p = 0.03$) [429]. In the 20-year follow-up of WOSCOPS, treatment with pravastatin 40 mg versus placebo was associated with a 35% reduction in HF hospitalisation in the statin arm ($p = 0.01$) [430]. Finally, reduction in HF as an outcome has been reported in a meta-analysis of 14 trials of statin-based LDL lowering with a risk reduction of 10% [409]. Therefore, the postulation that statins are only beneficial for HF prevention in high-risk patients by preventing MI events is not supported by the evidence [438]; in those without an intervening MI, the benefits of statins to prevent HF were the most striking which could be due to pleiotropic mechanisms [409].

4.1.2. Pharmacogenomic guidelines

As outlined in the previous chapters, there is increasing interest in the concept of personalised medicine, also known as precision medicine or genomic medicine, whereby therapies with the best response and highest safety margin are uniquely tailored to the individual. Personalised medicine has the potential to overcome various challenges, such as adverse reactions to medicines, common medicines not being effective in treating large numbers of patients, and rising healthcare costs due to more prevalent chronic diseases in an ageing population [194]. Personalisation involves considering one's genetic, biomarker, phenotypic or psychosocial characteristics to facilitate the individualisation of treatments and ensure better patient care [444, 445]. Such methods contrast with the conventional 'one-size-fits-all' approach, in which disease treatment and prevention strategies are developed for the 'average patient'. An area of genomic medicine known as pharmacogenomics is a major component in the quest for personalised medicine. While the origin of modern pharmacogenomics can be traced back over 50 years [165], significant progress in the field has been made within the last decade alone. Countless pharmacogenomic studies have been performed in recent years, yielding a substantial body of knowledge on gene-based variations affecting individual drug susceptibility.

The systematic review presented in Chapter 2 demonstrated that the use of pharmacogenomic interventions in medicines optimisation for patients with multimorbidity and prescribed polypharmacy could have significant benefits [272]. The results from Chapter 3 established that Irish public in general, and more specifically those with multimorbidity and prescribed polypharmacy, are strongly supportive of pharmacogenomic testing to improve patient outcomes through individualised pharmacotherapy. Furthermore, the cross-sectional analysis of HSE-PCRS data briefly presented in Chapter 3 (Section 3.6.5) found a high prevalence of actionable drug-gene interactions prescribed to the GMS population in Irish primary care. In this study, statins (affected by genetic variations in SLCO1B1) accounted for 12.5% (n = 46,200) of first time dispensing of medicines with actionable drug-gene interactions and 25.1% (n = 588,702) of all medicines with drug-gene interactions dispensed in 2021. Therefore, for patients who are currently receiving or are candidates for statin therapy, pharmacogenomic test results may provide additional useful information [237].

Clinical guidelines advising management of drug-gene interactions are essential for the implementation of pharmacogenomics. As outlined in Chapter 1, the CPIC was formed to disseminate freely available, peer-reviewed, and detailed gene/drug clinical practice guidelines that enable the translation of genetic test results into actionable prescribing decisions [178, 225]. In addition, the DPWG was established with the objective of developing pharmacogenomic recommendations based on systematic review of the literature [179, 225]. Furthermore, the FDA now requires submission of pharmacogenomic data to be included in the labelling of drugs and maintains a list of FDA-approved drugs with pharmacogenomic information in their labelling [446]. Pharmacogenomic information is also reflected in the SmPC approved by the EMA [187, 447]. However, mention of pharmacogenomics in drug labels may lack definite actionable guidance compared to the genotype-based prescribing recommendations from the CPIC/DPWG who have published guidance for 105 and 63 drug-gene interactions respectively [177]. A large proportion of these recommendations relate to medicines commonly initiated in primary care, and several specialist medicines (Table 4.1).

The CPIC recently reviewed genetic variants of the statin transporter genes SLCO1B1 (solute organic anion transporter family member 1B1, also known as OATP1B1) and ABCG2 (adenosine triphosphate-binding cassette G2) that can affect statin disposition and the risk for statin-associated musculoskeletal symptoms (SAMS) [237]. Studies have found that statin use can be associated with adverse effects; the most common statin-related ADR is skeletal muscle toxicity which can manifest as SAMS [448]. SAMS include a range of clinical entries from the most common (1 in 10 to 1 in 100), myalgia; less common (1 in 100 to 1 in 1,000), myopathy; and rare (1 in 1,000 to 1 in 10,000), rhabdomyolysis [449, 450]. Based on extrapolation from dose-response and drug-drug interaction data, most SAMS cases are likely statin concentration-dependent due to direct statin myotoxicity [451]. The frequency of SAMS is high in clinical practice, and although it is described as mild, SAMS frequently leads to statin discontinuation, thus leading to higher cholesterol levels and a higher risk for CVD if statins are not reinitiated [452-454].

The protein product of the SLCO1B1 gene, facilitates the hepatic uptake of all statins [455]. Decreased function of this transporter decreases hepatocellular concentrations of statins, resulting in lower efficacy for reducing LDL-c, and increases systemic exposure to statins, the

putative causal factor underlying the link to SAMS [456]. ABCG2 encodes the efflux transporter, also known as breast cancer resistance protein, that modulates the absorption and disposition of rosuvastatin. Loss-of-function variants in the SLCO1B1 and ABCG2 transporter genes increase SAMS risk and may require adjustment according to CPIC recommendations (summarised in Table 4.2). Some studies have also suggested that loss of function transporter gene variants can also influence efficacy of statin therapy [172, 237]. However, these associations are incompletely understood and have largely focused on LDL-c endpoints. Apart from this, while the proposed benefit of SLCO1B1 and ABCG2 testing is the avoidance of SAMS, it is worth noting that no study has empirically demonstrated the impact of SLCO1B1 and ABCG2 pharmacogenomic testing on cardiovascular events [457].

To date, we are not aware of any study which has investigated the progression of HF amongst patients with aberrant SLCO1B1 and ABCG2 statin transporter phenotypes. In the 12-gene panel PREPARE study by Swen *et al.,* SLCO1B1 accounted for 29.9% of drug-gene interactions requiring a change to standard-of-care drug treatment per the DPWG guidelines [172]. For first prescriptions for a drug that had an actionable recommendation in the DPWG guidelines, the highest numbers were observed for atorvastatin (204 [28.5%] of 716) [172]. Consequently, analysis of these pharmacogenes may help improve the overall safety, adherence, and efficacy of statin therapy [172, 237, 454]. Given the strong association between polypharmacy and statin use, the morbidity associated with CVD, an increased incidence of HF as the population ages, and evidence suggesting that statin therapy can prevent the development of HF, the effect of SLCO1B1 and ABCG2 genotyping in a patient population with cardiovascular risk factors was explored. We hypothesised that patients with a poor statin transporter function phenotype would be at greater risk of progression of asymptomatic HF and incidence of new-onset symptomatic HF.

Table 4.1. An overview of drug-gene pairs prescribed in Irish primary care with actionable prescribing recommendations and their anticipated effects when used to guide dose and drug selection (adapted from [177-179])

Gene	Drug(s)	Reduced side effect risk	Improved efficacy
ABCG2	Allopurinol		✓
	Rosuvastatin	✓	
CYP2B6	Sertraline	✓	
CYP2C9	NSAIDs (celecoxib, ibuprofen, meloxicam, piroxicam)	✓	
	Fluvastatin	✓	
	Fosphenytoin, phenytoin	✓	
	Warfarin	✓	
CYP2C19	SSRIs (citalopram, escitalopram, sertraline)	✓	✓
	TCAs (amitriptyline, clomipramine, imipramine, trimipramine)	✓	✓
	Clopidogrel		✓
	PPIs (lansoprazole, omeprazole, pantoprazole)		✓
CYP2D6	SSRIs (fluvoxamine, paroxetine)	✓	✓
	TCAs (amitriptyline, clomipramine, imipramine, nortriptyline, trimipramine)	✓	✓
	Antipsychotics (aripiprazole, brexpiprazole, haloperidol, risperidone, zuclopenthixol)	✓	✓
	Other antidepressants (venlafaxine, vortioxetine)	✓	✓
	Atomoxetine		✓
	Opioids (codeine, tramadol)	✓	✓
	CVD (flecainide, metoprolol, propafenone)	✓	✓
	Ondansetron		✓
	Tamoxifen		✓
CYP3A4	Quetiapine	✓	✓
CYP3A5	Tacrolimus	✓	✓
CYP4F2	Warfarin	✓	
F5	Oestrogen contraceptive agents	✓	
HLA-A	Carbamazepine	✓	

Gene	Drug(s)	Reduced side effect risk	Improved efficacy
HLA-B	Allopurinol	✓	
	Anticonvulsants (carbamazepine, fosphenytoin, lamotrigine, oxcarbazepine, phenytoin)	✓	
	Flucloxacillin	✓	
NUDT15	Thiopurines (azathioprine, mercaptopurine, tioguanine)	✓	
SLCO1B1	Statins (atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin)	✓	
TPMT	Thiopurines (azathioprine, mercaptopurine, tioguanine)	✓	
VKORC1	Warfarin	✓	

Abbreviations: *CVD* cardiovascular disease, *CYP* cytochrome P450, *F5* Factor V Leiden, *NSAID* non-steroidal anti-inflammatory drug, *PPI* proton pump inhibitor, *SSRI* selective serotonin reuptake inhibitor, *TCA* tricyclic antidepressant. Note: anticipated effects may vary depending on metaboliser status for the gene of interest.

Table 4.2. Dosing recommendations for statins based on SLCO1B1 and ABCG2 phenotypes (adapted from [237])

	SLCO1B1							ABCG2
Phenotype	Atorvastatin	Fluvastatin	Lovastatin	Pitavastatin	Pravastatin	Simvastatin	Rosuvastatin	Rosuvastatin
Decreased function	Start on ≤40 mg/day *	Prescribe desired starting dose ¥	Prescribe alternative §	Start on ≤2 mg/day *	Prescribe desired starting dose ¥	Prescribe alternative §	Prescribe desired starting dose ¥	Prescribe desired starting dose
Poor function	Start on ≤20 mg/day *	Start on ≤40 mg/day ₸	Prescribe alternative ᴿ	Start on ≤1 mg/day *	Start on ≤40 mg/day ₸	Prescribe alternative ᴿ	Start on ≤20 mg/day *	Start on ≤20 mg/day *

* Possible increased risk of myopathy above these doses; if higher doses needed for desired efficacy, consider combination therapy (i.e., statin plus non-statin), ¥ Possible increased risk of myopathy especially for doses of fluvastatin and pravastatin >40 mg/day and rosuvastatin >20 mg/day, § Limiting dose to ≤20 mg/day if therapy warranted, ₸ If 40 mg/day tolerated and higher potency needed, consider higher dose (possible increased risk of myopathy >40 mg/day), alternative statin, or combination therapy, ᴿ Low statin-associated musculoskeletal symptoms risk with rosuvastatin 20 mg/day

4.2. Aims and objectives

4.2.1. Aim

The aim of this retrospective longitudinal study was to investigate the potential impact of pharmacogenomic testing in the Irish STOP-HF patient population with cardiovascular risk factors (stage A and stage B HF), but without symptomatic HF (stage C HF).

4.2.2. Objectives

The objectives were to:

- Standardise the pharmacogenomic-based prescribing recommendations from the CPIC and the DPWG and determine which SLCO1B1 variants to test for
- Establish the prevalence of multimorbidity and polypharmacy in the STOP-HF population
- Investigate the exposure of the STOP-HF cohort to drugs with a potential for drug-gene interactions and their impact on outcomes (controlling for multimorbidity and polypharmacy)
- Determine the prevalence of aberrant SCLO1B1 and ABCG2 statin transporter phenotypes in the STOP-HF population
- Compare progression of pre-HF and new-onset symptomatic HF (stage C) amongst patients with aberrant SLCO1B1 and ABCG2 statin transporter phenotypes that may alter systemic exposure to statins

4.3. Research design and methodology

A retrospective, longitudinal study was performed using data from the STOP-HF population. The study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies of the EQUATOR network [458].

4.3.1. Description of the STOP-HF programme

This retrospective longitudinal study involved analysis of patient data from the STOP-HF programme. STOP-HF is an ongoing, prospective, longitudinal study population in Ireland. This section provides background information on the programme.

4.3.1.1. Background

Improved risk stratification and identification of patients at higher risk of HF and other cardiovascular events is of little utility unless tailored interventions can be employed to reduce an individual's risk. The need for such an intervention was the genesis of the landmark STOP-HF study. In this a pragmatic, prospective randomised trial, the authors measured BNP levels in patients with established CVD but without HF, and employed an intensive, multi-factorial cardiovascular management strategy in those deemed to be high risk [423]. The cohort included subjects with risk factors for the development of HF (stage A HF) and subjects with structural heart abnormalities but without signs and symptoms of HF (stage B HF). Patients were referred to the STOP-HF programme between 2005 and 2009, with 39 participating practices in the catchment area of St Vincent's University Hospital, Dublin, Ireland [423]. Patients were randomly assigned to BNP-driven collaborative care between community physicians and specialist cardiology services or to the control group receiving routine primary care physician management [423]. This intervention was shown to reduce rates of new-onset HF, asymptomatic LV dysfunction (LVD), and emergency hospitalisations for major adverse cardiovascular events (MACE). A subsequent analysis demonstrated cost-effectiveness [459]. As a result of the positive findings of the STOP-HF trial, that have been included in European, American and Canadian guidelines for HF [460-462], the programme continues as a clinical screening service carried out in St. Michael's Hospital, Dublin [463].

The STOP-HF programme, an extension of the STOP-HF trial, adopts a more personalised, biomarker-enabled approach to risk prediction, wherein NPs are used to identify those patients most at risk of HF and other cardiovascular events and targeted risk reduction interventions are then directed toward high-risk individuals [423]. Furthermore, STOP-HF offers a valuable opportunity to monitor for new-onset HF over time in a broad community population, based on longitudinal follow-up of an at-risk cohort [464]. The use of biomarkers such as BNP, troponin 1 and CRP as adjuncts to traditional cardiovascular risk assessment is an important example of personalised medicine used to identify patients who will most benefit from certain interventions [465, 466]. The data available from this cohort has the potential to validate further aspects of personalised medicine, such as pharmacogenomic testing. This programme can provide insight into associations between statin transporter gene variants and progression of HF over time.

4.3.1.2. Patient eligibility for inclusion in STOP-HF

As per the research study, patients aged ≥40 years with one or more risk factors for developing HF who provide written informed consent to participate are eligible to utilise the STOP-HF service [423, 463]. The eligible risk factors include hypertension, hypercholesterolaemia, diabetes, coronary artery disease, arrhythmia, valvular disorders, peripheral vascular disease, angina, LVH, and previous myocardial infarction. Exclusion criteria for participation in the STOP-HF service include individuals under the age of 40, individuals with no risk factors for developing HF, failure or unwillingness to provide written informed consent, and patients with known symptomatic HF.

4.3.1.3. STOP-HF intervention

Patients attend the clinical screening service at intervals determined by the patient's risk status based on their BNP results at last clinic visit. BNP levels are categorised as satisfactory (<20 pg/mL), medium (20-49 pg/mL), or high (≥50 pg/mL), yielding recommendations for three, two or one yearly reviews respectively [463]. Participants with a BNP level of 50 pg/mL or higher undergo Doppler echocardiography and review by a cardiologist at each visit. At each clinic visit, the patient is seen by a nurse and/or cardiologist who perform a number of assessments as outlined below. All participants receive further coaching, emphasising

individual risk status and the importance of adherence to medication and healthy lifestyle behaviours [423, 463]. The patient's GP is also provided with details of the study visit.

Medication history

At the first clinic visit, the nurse or cardiologist obtained the patient's complete medical history. At subsequent visits, a nurse or cardiologist obtained information regarding new medical conditions, changes to medications, and details of any hospitalisations or medical procedures. Details of any changes are confirmed with the patient's GP or pharmacist.

Vital signs, height, and weight

Blood pressure and pulse measurements were assessed at every visit. Blood pressure was measured in the non-dominant arm using a standard sphygmomanometer with an appropriate size cuff in the sitting position after five minutes of rest. Height in centimetres (cm) was measured at the first clinic visit. Body weight (to the nearest 0.1 kilogram (kg) in indoor clothing without shoes) was measured at each study visit. This was used to calculate the patient's body mass index.

Laboratory measurements

Peripheral blood samples and plasma for biomarkers were drawn at each study visit. Serum BNP from the peripheral circulation was measured using a point-of-care test. Lipid, glucose, renal and liver profiles were performed in St. Michael's Hospital laboratory or St. Vincent's Hospital, depending on the availability of the test. Sample processing and analysis were done according to local standard operating procedures. Kidney function was assessed by calculating eGFR using the MDRD equation.

Echo Doppler studies

Echocardiography was performed on all subjects at the baseline visit. Thereafter, echocardiography was performed at each study visit for those with BNP ≥50 pg/mL. For those with BNP <50 pg/mL, echocardiography was not performed unless deemed clinically necessary by the cardiologist. Echocardiography was performed by a designated, experienced echocardiographer. The following parameters were reported: LVEF, LVMI, LAVI, E wave deceleration time, E/e', and tissue Doppler imaging.

4.3.2. Study population

A total of 1,247 patients with CV risk factors, but without symptomatic HF, from the STOP-HF follow up programme (described in Section 4.3) [423], consented to participate in this retrospective, longitudinal report. Patients provided informed consent to genetic analyses and longitudinal follow-up. A subset of 947 patients receiving statin therapy at any point over the study follow-up period were genotyped. Excluded from the overall analysis were those with baseline diagnoses of HF, and those not taking a statin from the subset analysis.

4.3.3. Study procedure

Data collection was undertaken a nurse and/or cardiologist in the STOP-HF team who perform a number of assessments as outlined below. The STOP-HF follow-up programme baseline visit included clinical history; clinical assessment; biochemical, cardiovascular, and metabolic medications; and Doppler-echocardiography assessment. Cardiometabolic assessment included evaluation of blood pressure, lipids, glucose, and creatinine. All patients underwent phlebotomy for isolation of genomic DNA from whole blood samples using the MagNA Pure 96 high-throughput instrument. Participating patients consented to scheduled clinic follow-up at intervals of 1 to 3 years, depending on risk determined by BNP levels.

At the final STOP-HF follow-up programme visit, all patients underwent repeat clinical, cardiometabolic, biochemical, and Doppler echocardiography assessment. Doppler echocardiography was performed by an experienced cardiac echocardiographer in the STOP-HF unit. The assessment provided information on progression of LVD, including progression of LVSD and LVDD as well as progression of structural abnormalities (SA; *i.e.,* LAVI and LVMI). Assessment of LVDD involved evaluation of the ratio of mitral inflow velocities and tissue Doppler analysis of early diastolic mitral annular velocity at the lateral wall (E/e'). Table 4.3 provides the definition of several terms used in this chapter.

Data on comedications, comorbidities, clinical outcomes, and hospitalisations (cardiovascular and non-cardiovascular related) were available at baseline and follow-up for participants in the STOP-HF programme. Comprehensive data cleansing was performed by the PhD candidate on the medication and comorbidity data for each participant at both timepoints. Medication entries were formatted under columns titled INN, ATC classification,

medication dose, and medication frequency. Drugs with a pharmacogenomic recommendation according to the CPIC and the DPWG guidelines were identified in this database.

4.3.4. Genotyping

For each patient (n = 947), genomic DNA was isolated from whole blood samples using the MagNA Pure 96 high-throughput instrument, Genotyping for each sample was performed on the Illumina Infinium Global Screening Array v3.0 platform with standard quality control measures, in collaboration with Genuity Science (Ireland) Ltd. Genotype data were exported using Illumina Studio in VCF 4.2 format before extraction of patient-level genotype for SLC1OB1 and ABCG2 gene variant using Bcftools-1.10.2. ABCG2 (421C>A) and SLCO1B1 (*5, *9, *14, *15, *20, *23, *31, *46, *47) variants were genotyped using ABCG2 rs2231142 (G>T) and the following SLC1OB1 SNPs: rs373327528 (G>A), rs2306283(A>G), rs11045819 (C>A), rs4149056 (T>C), rs59502379 (G>C), rs34671512 (A>C).

These rsID numbers were identified using the Pharmacogene Variation (PharmVar) Consortium, a central repository for pharmacogenetic variation, cataloguing allelic variation of genes impacting drug metabolism, disposition, and response. Identified genetic variants were converted to their respective phenotypes. For SLCO1B1, an individual was classified as having decreased function if they possessed one normal or increased function allele and one no-function allele (*e.g.,* *1/*5). Poor function was indicated by the presence of two no-function alleles (*e.g.,* *5/*5). For ABCG2, an individual was categorised as having decreased function if they had one normal function allele and one decreased function allele (*e.g.,* c.421 C/A). Poor function was defined by the presence of two decreased function alleles (*e.g.,* c.421 A/A).

Due to substantial similarities in CPIC and DPWG guidelines on the same drug-gene interaction, there are ongoing efforts to harmonise the two [225]. The PhD candidate standardised the pharmacogenomic-based recommendations from the CPIC and the DPWG (Appendix 4.1) and consolidated a list of variants based on the gene panels used by the included studies in the systematic review presented in Chapter 2 (Appendix 4.2). Information on the alleles tested for in this study was collected across the following headings, including variant position, effect on protein, PharmVar notation, dbSNP rsID, functional status, minor

allele frequency, GRCh38 HGVS and variant call format (specifies the format of a text file used in bioinformatics for storing gene sequence variations), and collated onto a single spreadsheet (Appendix 4.2). Alleles with a confirmed aberrant phenotype on PharmVar were included, while those with normal, unknown, or unassigned function were omitted. This approach led to the inclusion of a greater number of SLCO1B1 variants than in the PREPARE study by Swen *et al.*, who only tested for *5 and *15.

4.3.5. Study outcomes

The outcomes of this study were threefold. Firstly, the exposure of the STOP-HF population to drugs with a potential for drug-gene interactions and associations between exposure and outcomes such as hospitalisation (all-cause and MACE hospitalisations) and death were explored (controlling for polypharmacy and multimorbidity). MACE was defined as emergency hospitalisation for any of the following: arrhythmia, transient ischemic attack, stroke, myocardial infarction, peripheral or pulmonary thrombosis/embolus, or HF. Secondly, the incidence of aberrant SLCO1B1 and ABCG2 phenotypes in this population and genotype associations with blood pressure, lipid levels, glucose, LVEF, lateral E/e', LAVI, LVMI, hospitalisation (all-cause and MACE hospitalisations) and death were assessed. Finally, the main objective of this study was to evaluate differences between statin transporter (SLCO1B1 and ABCG2) phenotype and progression of HF. Progression of HF is defined as new onset symptomatic HF and/or progression of LVSD and/or progression of LVDD (Table 4.3). The combination of progression of HF and SA (LAVI, LVH and LVMI parameters in Table 4.3) in this asymptomatic population was also evaluated.

Table 4.3. Definition of terms

Term	Definition
Heart failure	A clinical syndrome consisting of cardinal symptoms (*e.g.,* breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (*e.g.,* elevated jugular venous pressure, pulmonary crackles, and peripheral oedema) caused by structural and/or functional cardiac abnormality [405]
Hypercholesterolemia	TC >5.0 mmol/L (4.5 mmol/L in high-risk patients) and/or LDL-C >3.0 mmol/L (2.5 mmol/L in high-risk patients) or receiving lipid-lowering therapy
Hypertension	SBP ≥140 mm/Hg and/or DBP ≥90 mm/Hg and patient is medicated for ≥1month)
Left ventricular hypertrophy	LVMI >125 g/m^2 in males and >110 g/m^2 in females
Progression of LVDD	Follow-up E/e' (ratio of mitral inflow velocities and tissue Doppler analysis of early diastolic mitral annular velocity at the lateral wall) lateral >13 with an increase of 2 from baseline to follow-up
Progression of LVSD	Follow-up EF <50% with a reduction of at least 5% from baseline to follow-up
Progression of SA	LAVI >34 mL/m^2 and 3.5 mL/m^2+ increase from baseline to follow-up; LVMI 20 g/m^2+ increase from baseline to follow-up
Stage A HF	Individuals with no structural damage to the heart but who are at high risk for developing HF due to risk factors such as hypertension, diabetes, obesity, CAD, family history of cardiomyopathy, etc.
Stage B HF	Patients with asymptomatic HF with cardiac structural or functional defined as meeting one or more of the following criteria: a) LAVI >34 ml/m^2 or, b) EF <50%, or c) LVH
Stage C HF	Symptomatic HF with cardiac structural or functional abnormalities and symptoms such as shortness of breath, fatigue, oedema, etc.
Stage D HF	Patients with HF who remain symptomatic despite maximal therapy

Abbreviations: *BMI* body mass index, *CAD* coronary artery disease, *DBP* diastolic blood pressure, *EF* ejection fraction, *HF* heart failure, *LAVI* left atrial volume index, *LDL-C* low-density lipoprotein cholesterol, *LVDD* left ventricular diastolic dysfunction, *LVH* left ventricular hypertrophy, *LVMI* left ventricular mass index, *LVSD* left ventricular systolic dysfunction, *SA* structural abnormality, *SBP* systolic blood pressure, *TC* total cholesterol

4.3.6. Data analysis

All statistical analyses were performed using SPSS, version 28.0. All continuous variables were tested for normality using the Shapiro-Wilk Test of Normality, and by examining the histogram and normal Q-Q plots for the variables of interest. Non-normally distributed variables were presented as medians with 25^{th} and 75^{th} percentiles and between groups comparisons of these variables performed using the Mann-Whitney U Test (two categories). Categorical variables are presented as counts and percentages and comparisons between groups were made using Pearson's Chi-square (χ^2) test. Odds ratios (ORs) with 95% confidence intervals (CIs) were reported. Missing data were coded as such and omitted from the analysis. A P value <0.05 was considered statistically significant. Multivariable binary logistic regression analysis was used to predict the probability of a categorical outcome with two possible levels (*e.g.,* prescribed a medication with a potential for drug-gene interactions). SLCO1B1 and ABCG2 decreased and poor function phenotypes were assessed with normal function phenotypes as controls. Multivariable binary logistic regression analysis using the stepwise method was performed to examine the association between statin transporter phenotype and the categorical determinants of progression of HF variables (LVDD, LVSD, its individual components), and hospitalisation (all-cause and MACE) and death. In addition to estimating the unadjusted effects for outcomes, models were created controlling for variables such as age, BNP, systolic blood pressure and heart rate. Multicollinearity was assessed among the variables being controlled for by calculating the Variance Inflation Factor (VIF). The VIF values for all variables were found to be <5, indicating that multicollinearity was not a concern for the variables included in the binary logistic regression models.

4.4. Ethical approval

Written, informed consent was obtained for all patients included in this study (Appendix 4.3). The patient information leaflet used to consent patients is provided in Appendix 4.4. The study protocol was approved by the St Vincent's University Hospital Ethics Committee and conformed to the principles of the Declaration of Helsinki (Appendix 4.5). The STOP-HF clinic nurse enrolled consecutive patients and obtained written informed consent. The material transfer agreement between the Heartbeat Trust and TCD is provided in Appendix 4.6.

4.5. Results

A total of 1,247 subjects at risk for HF (stage A) or with pre-HF (stage B) were included in the study and genotyped for SLCO1B1 and ABCG2 variants. Among these, 947 patients from the STOP-HF programme were on statin therapy at some point during the median study follow-up period of 4.5 years (IQR: 3.0, 5.8) (analyses shown in Section 4.5.3 to Section 4.5.5).

4.5.1. Demographics

The main demographic, medical, clinical, echocardiographic, and biochemical characteristics of the whole study population (n = 1,247) are presented in Table 4.4. The median (IQR) patient age was 66.2 years (58.2-72.9) and 51.2% (n = 639) of participants were male. A total of 980 (78.6%) patients were classified as having a history of dyslipidaemia at baseline, 948 (76.0%) had hypertension, and 512 (41.1%) had diabetes. On average, patients in this population (n = 1,247) were being treated with six medications at baseline; 355 patients (28.5%) were prescribed less than four medicines, 795 (63.8%) between four to 10 medicines, and 97 (7.8%) more than 10 medicines. Understandably, over the study period (on average 4.7 years) more patients entered the ≥65 years age group (n = 911 patients at follow-up). On average, patients were being treated with seven medicines at follow-up; 221 patients (17.7%) were prescribed less than four medicines, 832 (66.7%) between four to 10 medicines, and 194 (15.6%) more than 10 medicines.

Information on diagnoses from patients' medical records were retrospectively collected to calculate the Charlson Comorbidity Index (CCI) score for each patient at baseline and follow-up. The median (IQR) CCI score was 3 (2-4) at baseline and 4 (2-5) at follow-up. A total of 753 patients (60.4%) had a CCI score ≥3 at baseline and 921 (73.9%) at follow-up. Using the CCI scores, 10-year survival was calculated ($10\ year\ survival = 0.983\text{^}(e^{CCI\ x\ 0.9})$). The median (IQR) 10-year survival was 77.5 (53.4-90.2) at baseline and 53.39 (21.4-90.2) at follow-up. Patients with a higher CCI score (3 or higher) had significantly greater odds of progression of pre-HF, developing new-onset symptomatic HF, all-cause hospitalisation, emergency hospitalisation for MACE, and death (p <0.001) at follow-up compared to those with lower CCI scores adjusted for age.

Table 4.4. Overall patient baseline characteristics (N = 1,247)

	All (N = 1,247)
Age, median (IQR)	66.2 (58.2-72.9)
Male, n (%)	639 (51.2)
Polypharmacy, n (%)	892 (71.5)
Multimorbidity, n (%)	986 (79.1)
Cardiometabolic phenotype, median (IQR)	
BMI, kg/m^2	28.34 (25.6-32.0)
SBP, mmHg	136 (124-149)
DBP, mmHg	81 (74-89)
Pulse pressure, mmHg	54 (44-64)
Heart rate, bpm	70 (62-78)
TC, mmol/L	4.5 (3.9-5.2)
LDL, mmol/L	2.3 (1.9-3.0)
HDL, mmol/L	1.2 (1.0-1.6)
TG, mmol/L	1.5 (1.0-2.2)
eGFR, mL/min	76.4 (65.0-89.4)
Glucose, mmol/L	6.0 (5.2-7.7)
BNP, pg/mL	21.5 (9.3-52.0)
Cardiovascular disease history, n (%)	
Dyslipidaemia	980 (78.6)
Hypertension	948 (76.0)
Diabetes mellitus	512 (41.1)
Myocardial infarction	120 (9.6)
Angina	83 (6.7)
Echocardiographic parameters, median (IQR)	
EF, %	66.0 (62.0-72.0)
LAVI, mL/m^2	24.7 (20.9-30.1)
LVMI, g/m^2	92.0 (79.8-107.9)
E/e’	8.2 (6.5-10.2)

	All (N = 1,247)
Medications, n (%)	
Statin	947 (75.9)
ACE inhibitor	361 (28.9)
ARB	315 (25.3)
Beta-blocker	403 (32.3)
Ca^{2+}-channel blocker	339 (27.2)
Diuretic	326 (26.1)
Oral antidiabetic	382 (30.6)
Insulin	50 (4.0)
Aspirin	680 (54.5)
Antiplatelet	696 (55.8)
Warfarin	39 (3.1)
NOAC	21 (1.7)

Abbreviations: *ACE* angiotensin converting enzyme, *ARB* angiotensin receptor blocker, *BMI* body mass index, *BNP* B-type natriuretic peptide, *bpm* beats per minute, *Ca^{2+}* calcium, *DBP* diastolic blood pressure, *DF* decreased function, *EF* ejection fraction, *HDL* high-density lipoprotein, *LAVI* left atrial volume index, *LDL* low-density lipoprotein, *LVMI* left ventricular mass index, *NF* normal function, *NOAC* novel oral anticoagulant, *PF* poor function, *SBP* systolic blood pressure, *TC* total cholesterol, *TG* triglycerides

A total of 682 patients (54.8%) were aged 65 years or older. As shown in Table 4.5, older patients (aged ≥65 years) experienced higher rates of polypharmacy and multimorbidity than their younger counterparts (<65 years of age) (p <0.001). Diagnoses included in this analysis were dyslipidaemia, hypertension, diabetes mellitus, history of stroke, transient ischaemic attack and myocardial infarction, angina, ischaemic heart disease, atrial fibrillation, chronic renal failure, deep vein thrombosis, pulmonary embolism, valvular heart disease, and arrhythmia. Furthermore, older patients were more likely to be prescribed a medication with a potential drug-gene interaction per the CPIC/DPWG guidelines (p <0.001). These findings at baseline are mirrored at follow-up.

Table 4.5. Patient medication and comorbidity characteristics according to age at baseline and follow-up (n = 1,247)

	<65 years	≥65 years	P value
Baseline	n = 565	n = 682	
Male, n (%)	289 (51.2)	351 (51.4)	0.953 [a]
No. medicines, mean (±SD)	4.9 (3.2)	6.2 (3.2)	<0.001 [b]
Polypharmacy, n (%)	351 (62.1)	541 (79.3)	<0.001 [a]
No. comorbidities, mean (±SD)	2.2 (1.1)	2.7 (1.3)	<0.001 [b]
Multimorbidity, n (%)	415 (73.5)	571 (83.7)	<0.001 [a]
Potential DGI, n (%)	394 (69.7)	557 (81.7)	<0.001 [a]
Follow-up	n = 378	n = 869	
Male, n (%)	201 (53.3)	438 (50.4)	0.368 [a]
No. medicines, mean (±SD)	5.7 (3.6)	7.6 (3.7)	0.000* [b]
Polypharmacy, n (%)	260 (68.8)	766 (88.1)	<0.001* [a]
No. comorbidities, mean (±SD)	2.2 (1.0)	2.8 (1.4)	<0.001* [a]
Multimorbidity, n (%)	287 (75.9)	753 (86.7)	<0.001* [a]
Potential DGI, n (%)	292 (77.2)	744 (85.6)	<0.001* [a]

[a] χ^2 test, [b] Mann-Whitney U test, *DGI* drug-gene interaction

4.5.2. Exposure to drugs with a potential for drug-gene interactions and outcome measures

4.5.2.1. Overall prevalence of potential drug-gene interactions

The overall prevalence of potential drug-gene interactions per the CPIC/DPWG guidelines prescribed in the STOP-HF population in Irish primary care at baseline and follow-up are shown in Table 4.6. The proportion of these drug-gene interactions categorised under statin, other cardiology medicines (*i.e.,* clopidogrel, flecainide, metoprolol, propafenone and warfarin), proton pump inhibitors (PPIs), central nervous system (CNS; *i.e.,* antidepressants, antipsychotics, anticonvulsants), analgesics (*i.e.,* opioids, NSAIDs, anti-gout), and others (*i.e.,* immunosuppressants, antibacterials) are shown in Figure 4.1 and Figure 4.2. At baseline, 951 (76.3%) patients were prescribed 1,484 medications with a potential drug-gene interaction per the CPIC/DPWG guidelines from the list shown in Table 4.1 (1.6 drug-gene interactions per patient). The number of patients with potential drug-gene interactions increased to 1036 (83.1%) from baseline to follow-up; with patients prescribed 1,806 medications with potential drug-gene interactions (1.7 drug-gene interactions per patient).

Table 4.6. Overall prevalence of potential drug-gene interactions per the CPIC/DPWG guidelines prescribed in the STOP-HF population in Irish primary care at baseline and follow-up

	Potential DGI at baseline (n = 1,484)		Potential DGI at follow-up (n = 1,806)	
Drug	n	%	Drug	n
Allopurinol	36	2.4%	63	3.5%
Amitriptyline	18	1.2%	25	1.4%
Atorvastatin	496	33.4%	501	27.7%
Azathioprine	3	0.2%	3	0.2%
Carbamazepine	6	0.4%	6	0.3%
Celecoxib	8	0.5%	10	0.6%
Citalopram	45	3.0%	60	3.3%
Clomipramine	2	0.1%	2	0.1%
Clopidogrel	48	3.2%	47	2.6%
Codeine	24	1.6%	53	2.9%
Escitalopram	25	1.7%	32	1.8%

Flecainide	3	0.2%	6	0.3%
Flucloxacillin	0	0.0%	2	0.1%
Fluvastatin	5	0.3%	4	0.2%
G03C	14	0.9%	10	0.6%
Haloperidol	0	0.0%	1	0.1%
Ibuprofen	13	0.9%	20	1.1%
Imipramine	2	0.1%	2	0.1%
Lamotrigine	3	0.2%	5	0.3%
Lansoprazole	57	3.8%	82	4.5%
Meloxicam	11	0.7%	4	0.2%
Metoprolol	16	1.1%	16	0.9%
Omeprazole	121	8.2%	180	10.0%
Ondansetron	0	0.0%	1	0.1%
Pantoprazole	65	4.4%	113	6.3%
Paroxetine	12	0.8%	7	0.4%
Phenytoin	1	0.2%	1	0.1%
Pravastatin	93	6.3%	83	4.6%
Propafenone	2	0.1%	0	0.0%
Quetiapine	5	0.3%	7	0.4%
Risperidone	0	0.0%	3	0.2%
Rosuvastatin	174	11.7%	242	13.4%
Sertraline	4	0.3%	16	0.9%
Simvastatin	69	4.7%	68	3.8%
Tacrolimus	6	0.4%	8	0.4%
Tamoxifen	0	0.0%	2	0.1%
Tramadol	25	1.7%	33	1.8%
Trimipramine	1	0.2%	1	0.1%
Venlafaxine	18	1.2%	25	1.4%
Warfarin	53	3.6%	62	3.4%

Abbreviations: *DGI* drug-gene interaction

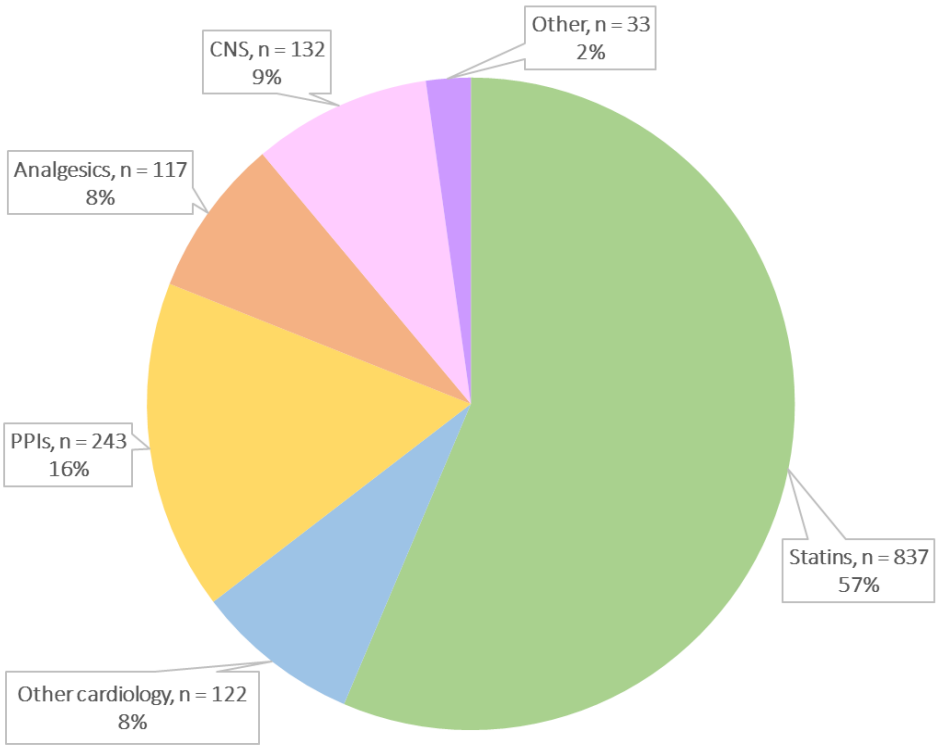

Figure 4.1. Categorised potential drug-gene interactions at baseline (n = 1,484)

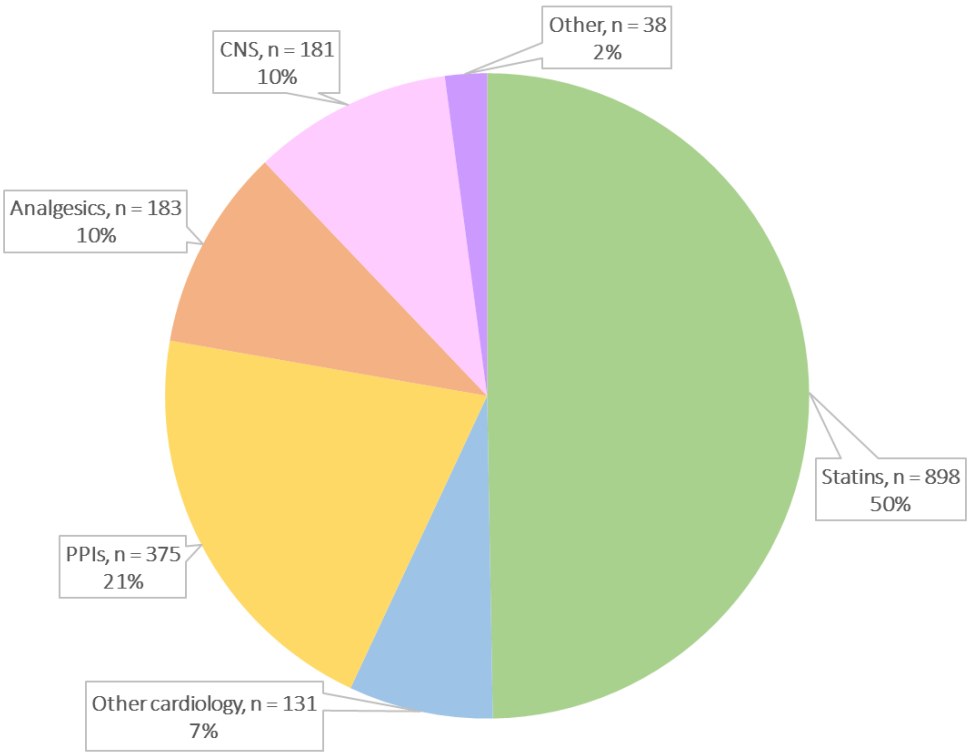

Figure 4.2. Categorised potential drug-gene interactions at follow-up (n = 1,806)

4.5.2.2. Polypharmacy and multimorbidity

The proportion of patients prescribed a medication with a potential drug-gene interaction by polypharmacy status (not prescribed polypharmacy, prescribed polypharmacy (four to 10 medicines), and prescribed excessive polypharmacy (more than 10 medicines)) at baseline and follow-up are shown in Figure 4.3 and Figure 4.4 respectively. In multivariable binary regression analysis, the risk of exposure to a medication with a potential drug-gene interaction at baseline increased with patient age (≥65 years) (OR 1.5 [95% CI 1.1, 1.9], p = 0.013), and the presence of multimorbidity (OR 3.1 [95% CI 2.2, 4.3], p <0.001) (list of included conditions shown in Section 4.5.1) and polypharmacy (OR 3.4 [95% CI 2.5, 4.7], p <0.001). At follow-up, the risk of exposure to a medication with a potential drug-gene interaction was no longer associated with age (p = 0.561) but was higher in those with multimorbidity (OR 2.7 [95% CI 1.9, 3.9], p <0.001) and prescribed polypharmacy (OR 4.8 [95% CI 3.3, 6.8], p <0.001) in multivariable binary regression analysis.

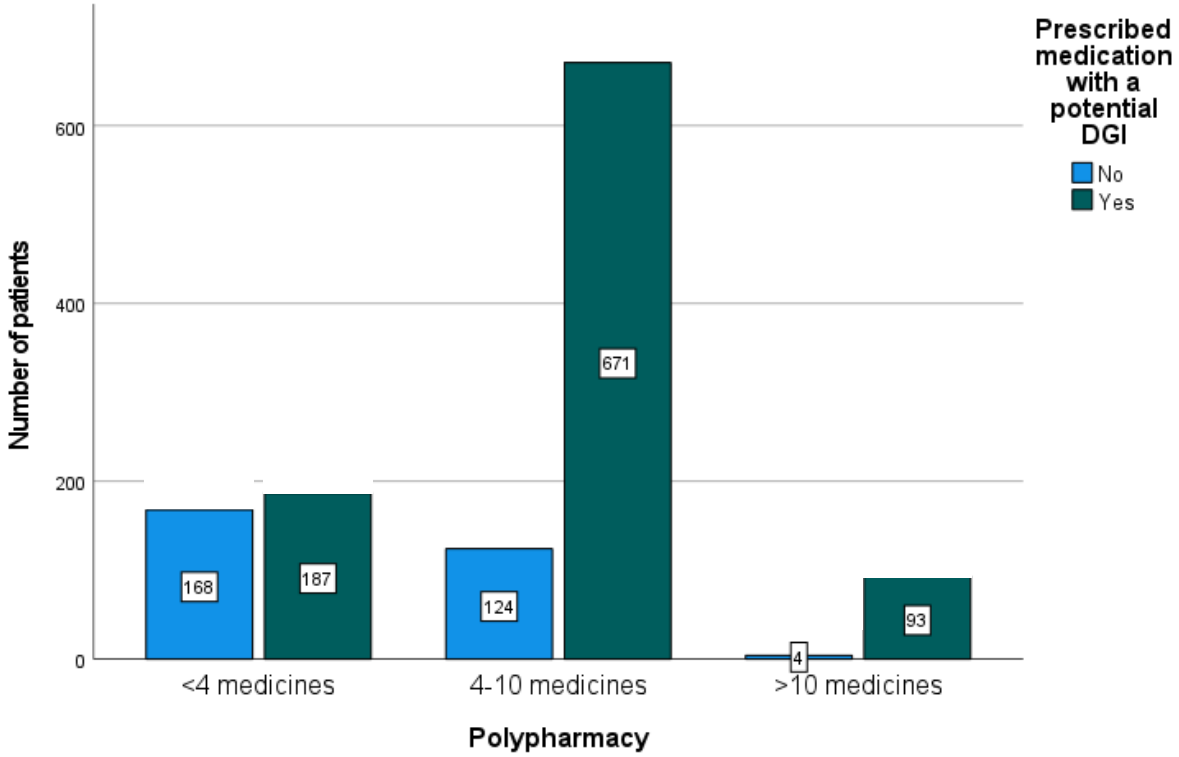

Figure 4.3. Bar chart potential drug-gene interactions by polypharmacy at baseline (n = 1,247)

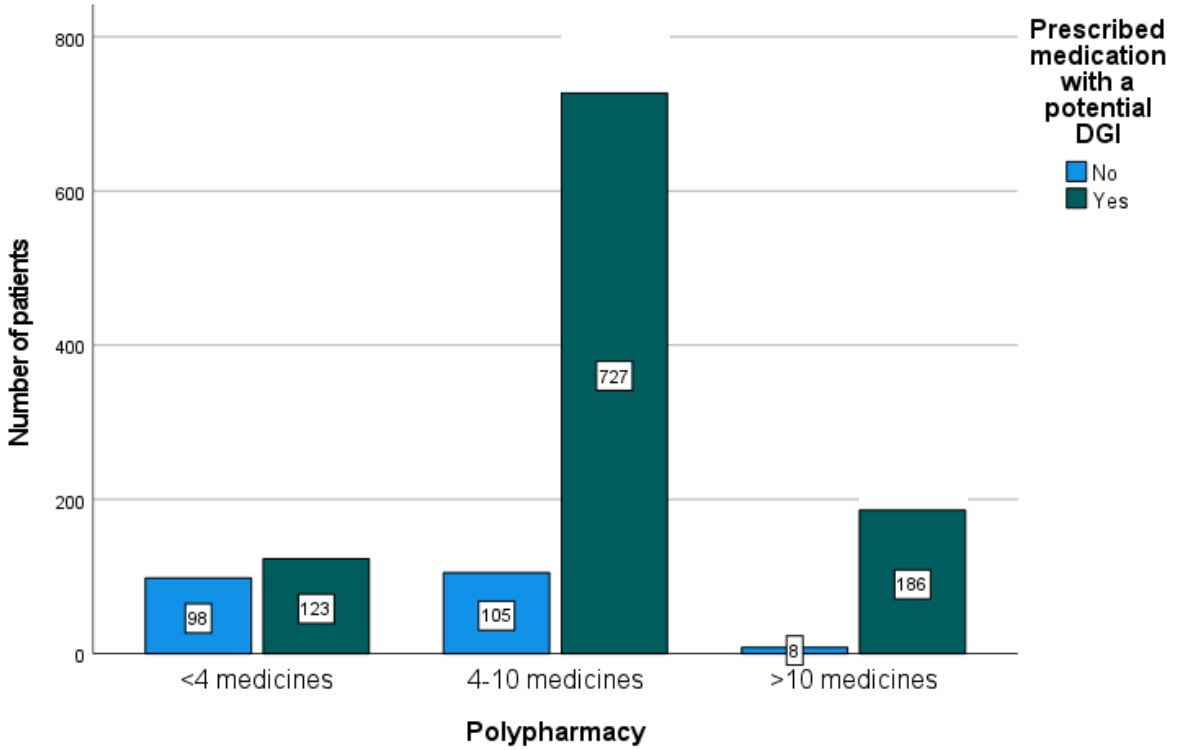

Figure 4.4. Bar chart potential drug-gene interactions by polypharmacy at follow-up (n = 1,247)

4.5.2.3. Outcome measures

To dissociate the contribution of multimorbidity and polypharmacy to outcomes associated with the exposure of patients to medications with potential for drug-gene interactions, multivariable binary regression analysis was conducted. Controlling for age, multimorbidity and polypharmacy, exposure to drugs with a potential for drug-gene interactions was not found to be associated with all-cause hospitalisation (p = 0.080), emergency hospitalisation for MACE (p = 0.135), mortality (p = 0.223), and emergency hospitalisation for MACE or death (p = 0.090) at follow-up (Table 4.7).

Table 4.7. Association between exposure to drugs with potential for drug-gene interactions and outcome measures (controlling for age, multimorbidity and polypharmacy)

Model	B (SE)	OR (95% CI)	P value
All-cause hospitalisation			
Potential DGI	0.366 (0.209)	1.44 (0.96, 2.17)	0.080
Age	0.043 (0.007)	1.04 (1.03, 1.06)	<0.001*
Polypharmacy	0.291 (0.220)	1.34 (0.87, 2.06)	0.187
CVD MM	0.372 (0.214)	1.45 (0.95, 2.21)	0.082
MACE hospitalisation			
Potential DGI	0.555 (0.371)	1.74 (0.84, 3.61)	0.135
Age	0.032 (0.011)	1.03 (1.01, 1.05)	0.003*
Polypharmacy	0.460 (0.397)	1.56 (0.73, 3.45)	0.247
CVD MM	1.788 (0.599	5.98 (1.85, 19.34)	0.003*
Mortality			
Potential DGI	0.780 (0.640)	2.18 (0.62, 7.65)	0.223
Age	0.92 (0.022)	1.10 (1.05, 1.14)	<0.001*
Polypharmacy	0.896 (0.775)	2.45 (0.54, 11.19)	0.248
CVD MM	-0.902 (0.465)	0.406 (0.16, 1.01)	0.052
MACE hospitalisation or mortality			
Potential DGI	0.555 (0.327)	1.74 (0.92, 3.31)	0.090
Age	0.044 (0.010)	1.05 (1.03, 1.07)	<0.001*
Polypharmacy	0.522 (0.360)	1.69 (0.83, 3.41)	0.146
CVD MM	0.979 (0.366)	2.22 (1.08, 4.55)	0.030*

* significant at p <0.05. Abbreviations: *CVD MM* cardiovascular disease multimorbidity (list of included diagnoses in Section 4.5.1), *DGI* drug-gene interaction, *MACE* major adverse cardiovascular event

4.5.3. Genotyped cohort demographics

The main demographic, medical, clinical, echocardiographic, and biochemical characteristics for the subset of the STOP-HF population receiving statin therapy and genotyped for SLCO1B1 and ABCG2 (n = 947) are presented in Table 4.8. Patients with a SLCO1B1 and ABCG2 poor statin transporter function phenotype had significantly higher median systolic blood pressure (142 [131;156] vs 135 [123;147] mmHg, p = 0.019) pulse pressure (61.5 ± 19.2 vs. 55.7 ± 16.4 mmHg, p = 0.070), and E/e' (8.1 [6.6-10.1] vs 9.4 [7.7-10.6], p = 0.032) measurements compared with the normal statin transporter function phenotype group. Additionally, prevalence of hypertension was significantly higher for poor versus normal function phenotype patients (poor 90.9% vs normal 76.0%, OR 3.0 [95% CI 1.1, 8.5], p = 0.031). In the entire cohort (n = 947), phenotypes did not differ in terms of BMI, BNP, total cholesterol, HDL-c, LDL-c, triglyceride, and glucose levels as shown in Table 4.8.

Table 4.8. Patient baseline characteristics according to SCLO1B1/ABCG2 phenotype

	Normal function (n = 661)	Decreased function (n = 242)	Poor function (n = 44)	P value PF vs NF	P value DF vs NF
Age, median (IQR)	67.0 (59.7-72.8)	66.9 (59.5-74.5)	64.6 (58.7-69.3)	0.136 [a]	0.563 [a]
Male, n (%)	351 (53.1)	130 (53.7)	20 (45.5)	0.325 [b]	0.869 [b]
Polypharmacy, n (%)	512 (77.5)	184 (76.0)	34 (77.3)	0.977 [b]	0.652 [b]
Multimorbidity, n (%)	570 (86.2)	207 (85.5)	41 (93.2)	0.189 [b]	0.789 [b]
Cardiometabolic phenotype, median (IQR)					
BMI, kg/m^2	28.5 (25.8-32.0)	28.9 (26.0-32.2)	27.6 (24.8-31.1)	0.354 [a]	0.309 [a]
SBP, mmHg	135 (123-147)	136 (126-149)	142 (131-156)	0.019* [a]	0.188 [a]
DBP, mmHg	81 (74-88)	80 (73-89)	83 (72-92)	0.216 [a]	0.583 [a]
Pulse pressure, mmHg	54 (44-64)	55 (46-65)	56 (50-66)	0.070* [a]	0.092 [a]
Heart rate, bpm	69 (60-77)	69 (62-76)	70 (62-81)	0.796 [a]	0.730 [a]
TC, mmol/L	4.3 (3.7-5.0)	4.4 (3.8-5.1)	4.4 (4.0-5.0)	0.410 [a]	0.310 [a]
LDL, mmol/L	2.2 (1.8-2.8)	2.3 (1.7-2.9)	2.2 (1.8-3.0)	0.763 [a]	0.443 [a]
HDL, mmol/L	1.20 (1.0-1.6)	1.2 (1.0-1.6)	1.2 (1.0-1.4)	0.976 [a]	0.696 [a]
TG, mmol/L	1.50 (1.1-2.2)	1.6 (1.0-2.2)	1.7 (1.0-2.4)	0.610 [a]	0.809 [a]
eGFR, mL/min	76.1 (64.5-87.8)	75.8 (65.0-90.2)	74.6 (65.2-87.5)	0.913 [a]	0.659 [a]
Glucose, mmol/L	6.0 (5.2-7.6)	6.0 (5.3-7.9)	5.7 (5.2-7.4)	0.412 [a]	0.229 [a]

	Normal function (n = 661)	Decreased function (n = 242)	Poor function (n = 44)	P value PF vs NF	P value DF vs NF
BNP, pg/mL	21.5 (9.0-53.7)	23.4 (10.6-51.7)	24.5 (12.8-60.5)	0.322 [a]	0.575 [a]
Cardiovascular disease history, n (%)					
Dyslipidaemia	593 (89.7)	225 (93.0)	42 (95.5)	0.217 [b]	0.137 [b]
Hypertension	509 (77.0)	178 (73.6)	40 (90.9)	0.031* [b]	0.282 [b]
Diabetes mellitus	277 (41.9)	105 (43.4)	16 (36.4)	0.470 [b]	0.690 [b]
Myocardial infarction	77 (11.6)	31 (12.8)	4 (9.1)	0.606 [b]	0.634 [b]
Angina	50 (7.6)	21 (8.7)	6 (13.6)	0.149 [b]	0.582 [b]
Echocardiographic parameters, median (IQR)					
EF, %	66.0 (61.0-72.0)	66.0 (62.0-71.0)	65.5 (60.0-72.3)	0.431 [a]	0.870 [a]
LAVI, mL/m^2	25.0 (21.1-30.5)	24.9 (20.6-29.6)	24.5 (21.9-35.0)	0.445 [a]	0.382 [a]
LVMI, g/m^2	92.0 (79.8-107.8)	94.9 (80.7-110.7)	100.7 (84.4-112.7)	0.082 [a]	0.292 [a]
E/e’	8.1 (6.6-10.1)	8.6 (6.6-10.6)	9.4 (7.7-10.6)	0.032* [a]	0.213 [a]
Medications, n (%)					
Statin	661 (100)	242 (100)	44 (100)	1.000	1.000
ACE inhibitor	205 (31.0)	75 (31.0)	8 (18.2)	0.073 [b]	0.995 [b]
ARB	163 (24.7)	57 (23.6)	12 (27.3)	0.698 [b]	0.732 [b]
Beta-blocker	227 (34.3)	81 (33.5)	20 (45.5)	0.135 [b]	0.807 [b]

	Normal function (n = 661)	Decreased function (n = 242)	Poor function (n = 44)	P value PF vs NF	P value DF vs NF
Ca^{2+}-channel blocker	181 (27.4)	67 (27.7)	14 (31.8)	0.524 [b]	0.928 [b]
Diuretic	175 (26.5)	57 (23.6)	14 (31.8)	0.438 [b]	0.374 [b]
Oral antidiabetic	207 (31.3)	89 (36.8)	11 (25.0)	0.380 [b]	0.122 [b]
Insulin	21 (3.2)	7 (2.9)	1 (2.3)	0.738 [b]	0.827 [b]
Aspirin	396 (59.9)	148 (61.2)	25 (56.8)	0.686 [b]	0.734 [b]
Antiplatelet	405 (61.3)	153 (63.2)	25 (56.8)	0.558 [b]	0.593 [b]
Warfarin	21 (3.2)	7 (2.9)	2 (4.5)	0.621 [b]	0.827 [b]
NOAC	13 (2.0)	2 (0.8)	1 (2.3)	0.888 [b]	0.235 [b]

[a] Mann-Whitney U test, [b] χ^2 test, * significant at p <0.05. Abbreviations: *ACE* angiotensin converting enzyme, *ARB* angiotensin receptor blocker, *BMI* body mass index, *BNP* B-type natriuretic peptide, *bpm* beats per minute, *Ca^{2+}* calcium, *DBP* diastolic blood pressure, *DF* decreased function, *EF* ejection fraction, *HDL* high-density lipoprotein, *LAVI* left atrial volume index, *LDL* low-density lipoprotein, *LVDD* left ventricular diastolic dysfunction, *LVMI* left ventricular mass index, *LVSD* left ventricular systolic dysfunction, *NF* normal function, *NOAC* novel oral anticoagulant, *PF* poor function, *SBP* systolic blood pressure, *TC* total cholesterol, *TG* triglycerides

4.5.4. Phenotype frequencies and lipid levels

A total of 947 subjects at-risk for HF or with pre-HF were included in the study and genotyped for SLCO1B1 and ABCG2 variants. Taking into account recommended dosing of statins based on SLCO1B1 and ABCG2 phenotype using the CPIC guidelines [237], 661 (69.8%) patients were classified as having normal/increased statin transporter function, 242 (25.6%) were classified as decreased function, and 44 (4.7%) were classified as having poor function (Figure 4.5). The phenotypic frequencies of SLCO1B1 were: 71.3% (n = 675) normal/increased function, 25.9% (n = 245) decreased function, and 2.9% (n = 27) poor function. For ABCG2, a total of 76.2% (n = 722), 22.0% (n = 208) and 1.8% (n = 17) had normal, decreased, and poor function phenotype respectively.

Patients with a poor function phenotype (n = 44) were receiving atorvastatin (n = 33, 75%), rosuvastatin (n = 9, 21%), simvastatin (n = 1, 2%) or pravastatin therapy (n = 1, 2%). For five patients taking atorvastatin (11.4%), the dose prescribed exceeded CPIC recommendations (>20 mg/day) (Table 4.2); three of these patients were already receiving combination therapy to lower their lipid levels. Ten patients were prescribed atorvastatin 20 mg/day and five patients rosuvastatin 20 mg/day; if higher doses are needed to control their lipid levels, combination therapy with a non-statin medication would be advised. In the entire genotyped cohort (n = 947), phenotypes did not differ in terms of total cholesterol, LDL-c, HDL-c, and triglyceride levels at baseline and follow-up, as shown in Table 4.9.

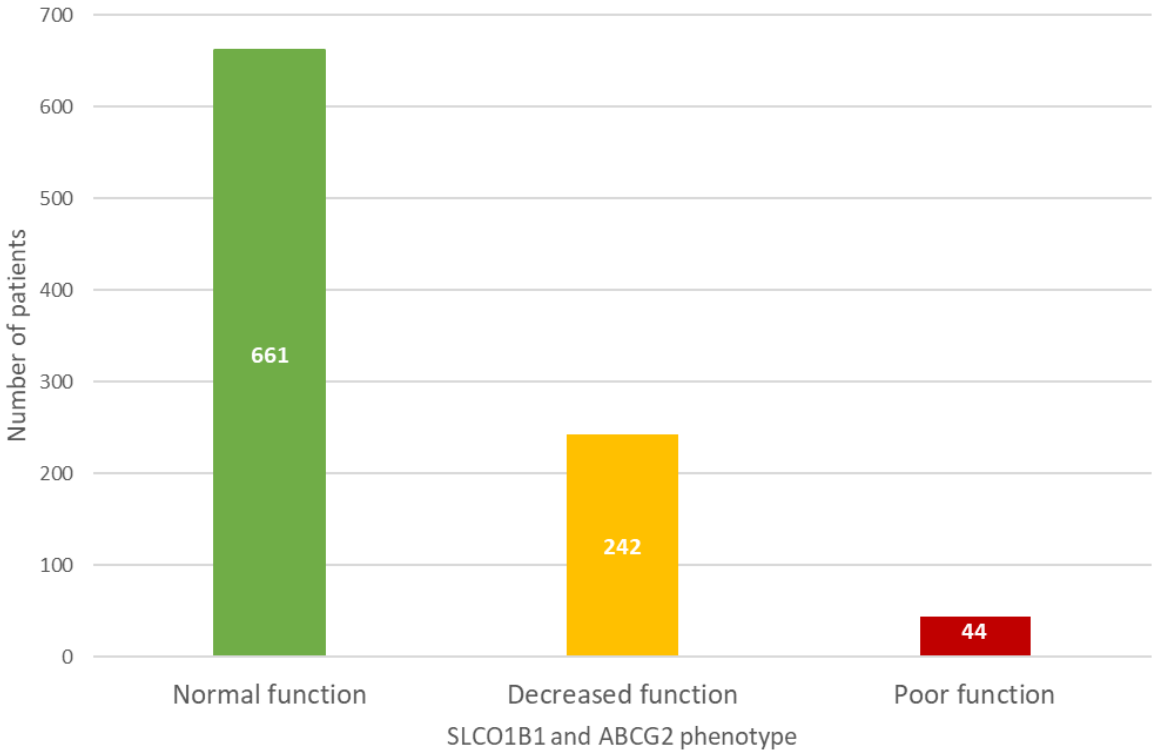

Figure 4.5. Distribution of SLCO1B1 and ABCG2 phenotypes in the STOP-HF population (n = 947)

Table 4.9. Lipid profile comparison at baseline and follow-up according to SLCO1B1 and ABCG2 phenotype

	NF (n = 661)	DF (n = 242)	PF (n = 44)	P value PF vs NF	P value DF vs NF
Lipid profile at baseline (mmol/L), median (IQR)					
TC	4.3 (3.7-5.0)	4.4 (3.8-5.1)	4.4 (4.0-5.0)	0.410	0.310
LDL	2.2 (1.8-2.8)	2.3 (1.7-2.9)	2.2 (1.8-3.0)	0.763	0.443
HDL	1.2 (0.9-1.6)	1.2 (1.0-1.6)	1.2 (1.0-1.4)	0.976	0.696
TG	1.5 (1.1-2.2)	1.6 (1.0-2.2)	1.7 (1.0-2.4)	0.610	0.809
Lipid profile at follow-up (mmol/L), median (IQR)					
TC	4.2 (3.7, 4.9)	4.3 (3.8, 4.9)	4.2 (3.6, 4.6)	0.555	0.519
LDL	2.2 (1.8, 2.7)	2.2 (1.7, 2.7)	2.0 (1.6, 2.4)	0.077	0.990
HDL	1.3 (1.0, 1.6)	1.3 (1.0, 1.6)	1.3 (1.0, 1.7)	0.297	0.374
TG	1.5 (1.0, 2.1)	1.5 (1.0, 2.2)	1.3 (1.1, 2.1)	0.937	0.750

All tests were Mann-Whitney U test. Abbreviations: *DF* decreased function, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *NF* normal function, *PF* poor function, *TC* total cholesterol, *TG* triglycerides

4.5.5. Doppler echocardiography and outcome measures

The SLCO1B1 and ABCG2 genotyped cohort of patients (n = 947) were analysed for progression of LVSD (defined as EF <50% with a reduction of at least 5% from baseline to follow-up), progression of LVDD (defined as E/e' >13 with an increase of at least 2 from baseline to follow-up), progression of SA (LAVI >34 mL/m^2 and at least a 3.5 mL/m^2 increase from baseline to follow-up; LVMI >125 g/m^2 in males and >110 g/m^2 in females with an increase of at least 20 g/m^2 baseline to follow-up).

4.5.5.1. Univariate analyses

Doppler echocardiography (Table 4.10) showed that lateral E/e' at baseline is significantly greater amongst those with poor statin transporter function versus normal statin transporter function (p = 0.032); however, this increase was not found to be significant at follow-up (p = 0.082). In the median (IQR) 4.5 years (3.0-5.8) of follow-up for the genotyped cohort, univariate analyses found that the incidence of new-onset symptomatic HF, LVSD and LVDD was higher in the poor versus normal statin transporter function phenotype patients, but these differences were not found to be statistically significant (p = 0.170, p = 0.122 and p = 0.057 respectively). Univariate analyses did not yield any associations between poor or decreased statin transporter phenotype in regard to new-onset hospitalisation versus patients with a normal statin transporter phenotype. Additionally, mortality was not different among phenotypes.

Progression of LVD (LVSD and LVDD) was significantly higher in the poor versus normal statin transporter function phenotype group (OR 2.2 [95% CI 1.0, 4.9], p = 0.037). For the composite endpoint of new-onset symptomatic HF/LVD progression (LVSD and LVDD), patients with a poor statin transporter function versus normal demonstrated elevated rates (OR 2.6 [95% CI 1.3, 5.3], p = 0.005) in the χ^2 analysis. Furthermore, poor statin transporter function was associated with new-onset symptomatic HF/progression of LVD/progression of SA (LAVI, LVMI) (OR 2.4 [95% CI 1.3, 4.4], p = 0.006) compared to patients with a normal statin transporter function in the χ^2 analysis. These variables will be examined further in the next section using binary logistic regression. The results of the adjusted multivariable binary logistic regression analyses and the incidence of progression of asymptomatic stage A and stage B HF and new-onset symptomatic HF are summarised in Figure 4.6.

Table 4.10. Doppler echocardiography and outcome measures at baseline and follow-up according to SLCO1B1 and ABCG2 phenotype

	Normal function (n = 661)	Decreased function (n = 242)	Poor function (n = 44)	P value PF vs NF	P value DF vs NF	N
Echocardiographic parameters, median (IQR)						
EF at baseline	66.0 (61.0-72.0)	66.0 (62.0-71.0)	65.5 (60.0-72.3)	0.431 [a]	0.870 [a]	947
EF at follow-up	67.0 (62.0-72.0)	66.0 (62.0-71.0)	68.5 (62.0-73.0)	0.715 [a]	0.493 [a]	947
LAVI at baseline	25.0 (21.1-30.5)	24.9 (20.6-29.6)	24.5 (21.9-35.0)	0.445 [a]	0.382 [a]	942
LAVI at follow-up	26.0 (22.1-32.0)	26.0 (22.7-33.3)	26.8 (22.6-35.5)	0.479 [a]	0.929 [a]	942
LVMI at baseline	92.0 (79.8-107.8)	94.9 (80.7-110.7)	100.7 (84.4-112.7)	0.082 [a]	0.292 [a]	947
LVMI at follow-up	93.5 (78.8-109.2)	92.8 (78.6-107.9)	97.1 (86.9-115.4)	0.185 [a]	0.819 [a]	947
E/e' at baseline	8.1 (6.6-10.1)	8.6 (6.6-10.6)	9.4 (7.65-10.6)	0.032* [a]	0.213 [a]	944
E/e' at follow-up	8.6 (6.9-10.7)	8.4 (7.0-10.6)	9.7 (7.23-12.0)	0.082 [a]	0.715 [a]	944
Outcome measure, n (%)						
LVSD progression	18 (2.7)	3 (1.2)	3 (6.8)	0.122 [b]	0.190 [b]	947
LVDD progression	51 (7.7)	20 (8.3)	7 (15.9)	0.057 [b]	0.783 [b]	944
LVD progression	68 (10.3)	22	9 (20.5)	0.037* [b]	0.598	944
SA progression	123 (18.6)	48 (19.8)	11 (25.0)	0.303 [b]	0.679 [b]	943
New-onset stage C HF	20 (3.0)	11 (4.5)	3 (6.8)	0.170 [b]	0.267 [b]	947
HF or LVD progression	82 (12.4)	31 (12.8)	12 (27.3)	0.005* [b]	0.866 [b]	944

	Normal function (n = 661)	Decreased function (n = 242)	Poor function (n = 44)	P value PF vs NF	P value DF vs NF	N
HF or LVD or SA progression	172 (26.0)	65 (26.9)	20 (45.5)	0.006* [b]	0.795 [b]	940
Death	17 (2.6)	12 (5.0)	0 (0.0)	0.282 [b]	0.072 [b]	947
Emergency hospitalisation for MACE	64 (9.7)	32 (13.2)	6 (13.6)	0.396 [b]	0.126 [b]	947
Emergency hospitalisation for MACE and death	77 (11.6)	40 (16.5)	6 (13.6)	0.692 [b]	0.053 [b]	947
All-cause hospitalisation	182 (27.5)	72 (29.8)	10 (22.7)	0.488 [b]	0.511 [b]	947

[a] Mann-Whitney U test, [b] χ^2 test, * significant at p <0.05. Abbreviations: *EF* ejection fraction, *HF* heart failure, *LAVI* left atrial volume index, *LVDD* left ventricular diastolic dysfunction, *LVMI* left ventricular mass index, *LVSD* left ventricular systolic dysfunction, *MACE* major adverse cardiovascular event, *SA* structural abnormality

4.5.5.2. Binary logistic regression analyses

The results from the binary logistic regression models for the association between SLCO1B1 and ABCG2 phenotype and LVSD, LVDD, SA and LVD progression, the composite endpoint new-onset symptomatic HF or LVD progression, and the composite endpoint new-onset symptomatic HF/progression of LVD/progression of SA and are shown in Table 4.11. Various models were run using the stepwise method. A lack of association was found in the unadjusted and adjusted binary logistic regression analyses examining the relationship between SLCO1B1 and ABCG2 statin transporter function phenotype and progression of LVSD, LVDD and SA, and the incidence of new-onset symptomatic HF. For the association between statin transporter function phenotype and LVD progression, in the unadjusted model, patients with a poor function phenotype were 2.2 times more likely to demonstrate LVD progression versus those with a normal function phenotype ($p = 0.042$). However, this model only explained 1% (Nagelkerke R^2) of the variance in this composite endpoint. Controlling for the aforementioned factors, the final model explained 9% of the variance and correctly classified 89.2% of cases; however, SLCO1B1 and ABCG2 phenotype no longer had a statistically significant effect on LVD progression ($p = 0.066$).

Progression of LVD was combined with occurrence of new-onset symptomatic HF in the next analysis. In the unadjusted model, patients with a poor statin transporter function phenotype were 2.6 times more likely to develop new-onset symptomatic HF/LVD progression versus those with a normal function phenotype ($p = 0.007$); however, this model only explained 1.7% of the variance. Controlling for the aforementioned factors, the final model explained 15% of the variance and correctly classified 86.6% of cases. Patients with a poor versus normal statin transporter function phenotype were 2.7 times more likely to develop new-onset symptomatic HF/LVD progression ($p = 0.010$). For the composite endpoint of new-onset symptomatic HF/progression of LVD/SA, patients with a poor versus normal statin transporter function phenotype were 2.35 times more likely to have this outcome in the unadjusted model ($p = 0.007$). However, this model only explained 1.4% of the variance in this composite endpoint. Controlling for the aforementioned factors, the final model explained 26.6% of the variance and correctly classified 72.6% of cases. Patients with a poor statin transporter function phenotype were 2.7 times more likely to develop new-onset symptomatic HF/LVD progression/SA progression ($p = 0.005$) versus normal function.

Table 4.11. Association between SLCO1B1 and ABCG2 poor function phenotype and progression of pre-HF and new-onset symptomatic HF at follow-up

Model	Nagelkerke R^2	B (SE)	OR (95% CI)	P value
LVSD progression (n = 705)				
Unadjusted model	0.011	0.961 (0.644)	2.61 (0.74, 9.24)	0.136
Adjusted model	0.140	0.767 (0.762)	2.15 (0.48, 9.58)	0.314
LVDD progression (n = 703)				
Unadjusted model	0.010	0.813 (0.437)	2.26 (0.96, 5.31)	0.063
Adjusted model	0.082	0.838 (0.458)	2.31 (0.94, 5.67)	0.067
SA progression (n = 702)				
Unadjusted model	0.002	0.371 (0.362)	1.45 (0.71, 2.95)	0.305
Adjusted model	0.267	0.446 (0.416)	1.56 (0.69, 3.53)	0.284
New-onset symptomatic HF (n = 705)				
Unadjusted model	0.008	0.852 (0.640)	2.35 (0.67, 8.23)	0.183
Adjusted model	0.139	0.896 (0.710)	2.45 (0.61, 9.85)	0.207
LVD progression (n = 703)				
Unadjusted model	0.010	0.804 (0.395)	2.24 (1.03, 4.85)	**0.042***
Adjusted model	0.092	0.776 (0.422)	2.17 (0.95, 4.96)	0.066
New-onset symptomatic HF or LVD progression (n = 705)				
Unadjusted model	0.017	0.970 (0.358)	2.64 (1.31, 5.33)	**0.007***
Adjusted model	0.150	1.007 (0.392)	2.74 (1.27, 5.90)	**0.010***
New-onset symptomatic HF or LVD progression or SA progression (n = 705)				
Unadjusted model	0.014	0.852 (0.316)	2.35 (1.26, 4.35)	**0.007***
Adjusted model	0.266	0.986 (0.353)	2.68 (1.34, 5.35)	**0.005***

* significant at p <0.05. Model adjusted for age, BMI, BNP, CVD MM, HR, and SBP. Abbreviations: *BMI* body mass index, *BNP* B-type natriuretic peptide, *CVD MM* cardiovascular disease multimorbidity (list of included diagnoses in Section 4.5.1), *HF* heart failure, *HR* heart rate, *LVD* left ventricular dysfunction (*LVSD* left ventricular diastolic dysfunction and *LVDD* left ventricular systolic dysfunction), *SA* structural abnormality (left atrial volume index and left ventricular mass index), *SBP* systolic blood pressure

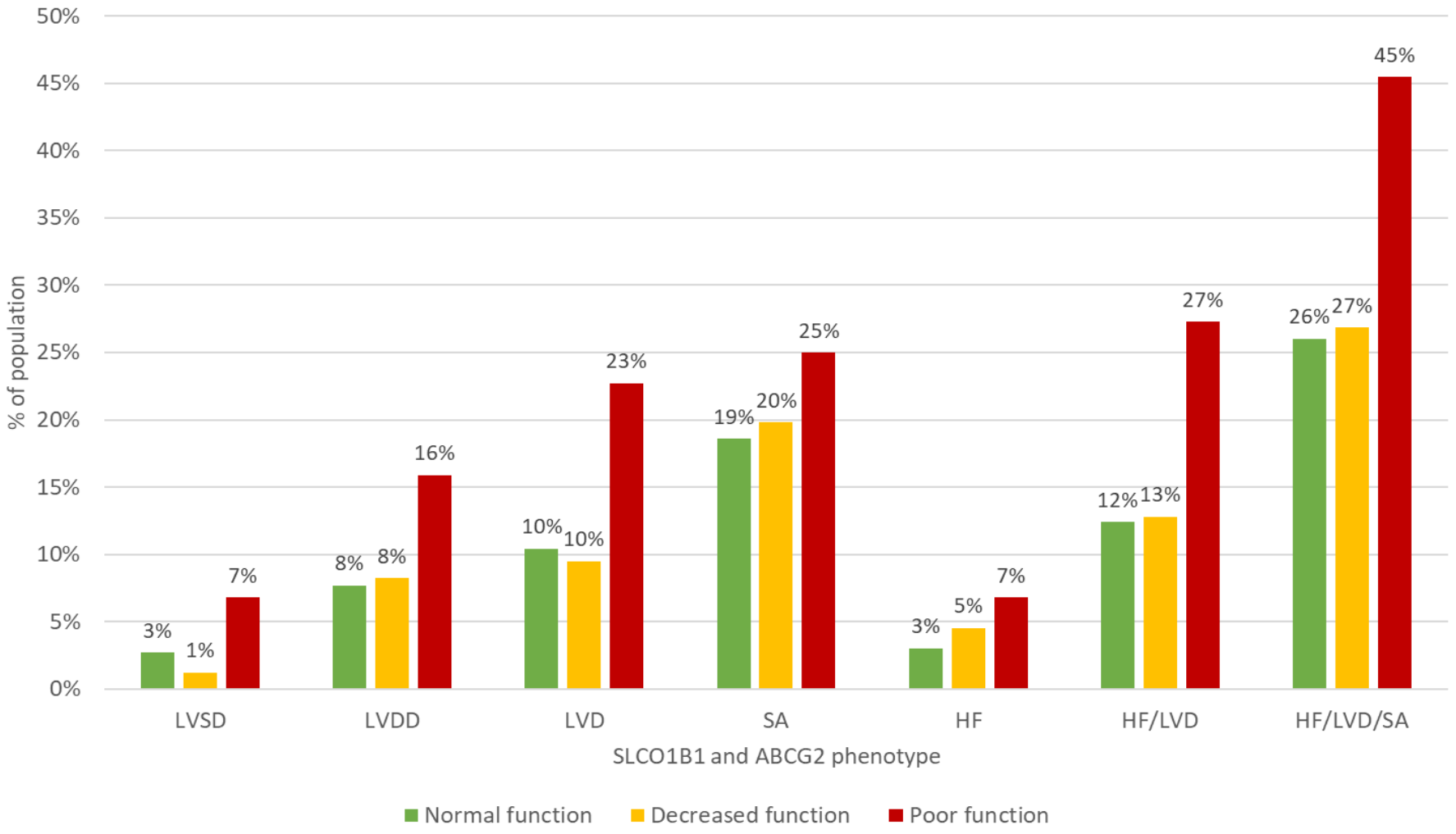

Figure 4.6. Incidence of HF outcomes over follow-up period by SLCO1B1 and ABCG2 phenotypes in the STOP-HF population

4.6. Discussion

4.6.1. Summary of the main findings

In this retrospective longitudinal study of patients with cardiovascular risk factors (stage A and stage B HF), multimorbidity and polypharmacy in the STOP-HF programme, we observed a high level of exposure to medications with potential for drug-gene interactions according to pharmacogenomic guidelines published by the CPIC and the DPWG. Statins accounted for 57% and 50% of these interactions at baseline and follow-up respectively. Patients receiving statin therapy at any point over the study 4-year follow-up period were genotyped for SLCO1B1 and ABCG2 no function alleles and phenotyped accordingly; 26% of patients carried one no function allele (decreased function phenotype) and 5% carried two no function alleles (poor function phenotype). With a median age of 66 years, the STOP-HF population was shown to be an older patient cohort with multimorbidity and prescribed polypharmacy. Understandably, increasing number of medicines to treat patients' comorbidities was linked with elevated risk of receiving a medication with potential for drug-gene interactions.

Our study is the first to investigate progression of pre-HF and new-onset symptomatic HF amongst patients with aberrant SLCO1B1 and ABCG2 statin transporter phenotypes that may alter systemic exposure to statins. The benefits of incorporating pharmacogenomic information as part of prescribing statins may have benefits beyond maximising the risk/benefit of statin therapy. This study suggests that there is an association between poor statin transporter phenotype and elevated risk of progression of pre-HF (left ventricular dysfunction and cardiac structural abnormalities) and new-onset symptomatic HF. However, it also suggests that there is no association between decreased statin transporter phenotype and progression of pre-HF and occurrence of new-onset symptomatic HF. It is important to note that the evolution of the condition over time could potentially alter this finding, and future research may reveal different associations as the disease progresses. While further work may be needed to confirm these data in other populations, our study suggests that routine SLCO1B1 and ABCG2 genotyping may help to identify patients receiving statin therapy with cardiovascular risk factors at greater risk of HF progression.

4.6.2. Comparison with existing literature

Various trials have documented the efficacy and safety of statin therapy [467-470]; however, there is a relative dearth of data from the major lipid-lowering trials on the effects of statin therapy on HF since most trials excluded patients with this syndrome [471]. Some of these trials allow us to look at incident HF (Section 4.1.1) [424-430]. Collectively, these trials provide reasonable evidence that statin use can prevent or delay the onset of HF. This therapeutic link was based on the supposition that statins prevent MI and consequent cardiac damage and so reduce the risk of developing reduced ejection fraction HF. The current study was underpowered to assess this relationship as the number of patients with new-onset MI was low. A meta-analysis on the effect of statin therapy on HF events by Preiss *et al.* reported significant reductions in non-fatal MI and HF hospitalisations [409]. The former finding is not surprising [411]; however, the latter observation is intriguing considering neither a reduced risk of non-fatal MI or a decrease in LDL-c were correlated with the reduced risk of HF hospitalisation [409]. Consequently, it is possible that statins may influence the development of HF through other mechanisms [417, 433-438].

The use of medicines for primary prevention in patients with multimorbidity was addressed by a key recommendation in the NICE Guidelines in 2016 as 'Be aware that the management of risk factors for future disease can be a major treatment burden for people with multimorbidity and should be carefully considered when optimising care' [41]. However, even in primary prevention, discontinuing statins while maintaining other drug therapies may increase the long-term risk of fatal and non-fatal cardiovascular outcomes. In a large cohort study of patient aged 65 years or older exposed to polypharmacy, discontinuation of statin therapy while maintaining antihypertensive, antidiabetic, and antiplatelet drug therapies was found to increase the long-term risk of cardiovascular hospital admission, all-cause emergency admission, and all-cause mortality compared with those who maintained all drug therapies, including statins [472]. This occurred in younger and older patients, men and women, patients with mild or severe clinical profiles, and irrespective of whether statins were prescribed as primary or secondary cardiovascular prevention. Furthermore, this risk was highest for those with HF [472].

To achieve the desired effect of statin therapy, optimal adherence is necessary. However, in older patients, adherence to medication can be particularly challenging due to factors such as polypharmacy and increased susceptibility to adverse events [473]. For example, a patient on five to nine medicines has about 50% probability of experiencing a drug-drug interaction and this increases to 100% when the number of medicines exceeds 20 [60]. In addition, metabolism enzymes become less functional at advanced ages, resulting in increased statin concentrations and higher likelihood of drug-drug interactions. Side effects are also common when more medications are used, with up to 40% of hospitalisations in older patients attributable to ADEs [60]. As a result, increasing polypharmacy has frequently been correlated with poor statin adherence [474]. A systematic review on adherence and persistence among statin users aged 65 years and over reported suboptimal statin use among older patients, with 40% non-adherent at one year and more than one-third discontinuing treatment by three years [475]. This is notable for a population at increased risk of cardiovascular events in whom 82% of cardiovascular-related deaths occur [476].

The issue of statin non-adherence may be exacerbated by drug-gene interactions. Pharmacogenomic variants in the SLCO1B1 and ABCG2 genes can impact statin disposition and tolerability during statin therapy. The CPIC provide therapeutic recommendations for statins based on these genes with the goal of improving the overall safety, adherence, and efficacy of statin therapy [237]. The therapeutic recommendations predominantly apply to a new or a revision (dose or type) to statin prescription. However, given the vast number of patients receiving statin therapy in the STOP-HF programme and the retrospective nature of this report, an important issue to consider is how to manage statin therapy in these patients. The genotype results indicate that in some patients they are in a higher risk category (moderate or high SAMS risks) based on the currently prescribed statin. For patients at moderate risk who have already been on a stable statin and dose for at least 4 weeks without symptoms suggestive of SAMS, and for patients at high risk who have been taking their statin therapy for at least one year without any negative effects, then it is deemed safe to continue that statin therapy long-term [237]. It is worth noting that other factors such as increased statin dose, drug interactions, advanced age, small BMI, female gender, metabolic comorbidities (*e.g.,* hypothyroidism), and intense physical exercise are known to influence a patient's risk for developing SAMs [448, 477, 478].

Consequently, one potential benefit of SLCO1B1 and ABCG2 testing may be a reduction in the incidence of SAMS, by identifying those at significant risk and recommending lower statin dose, an alternative statin with lower SAMS risk, or combination therapy with a non-statin rather than dose escalation. However, the current study lacked patient data on medication adherence and adverse effects such as SAMS. Furthermore, patient lipid profile data in the STOP-HF population did not demonstrate a difference between those with normal, decreased, or poor function; overall, median lipid profile values within the optimal levels were found. As the study cohort consisted of subjects enrolled in the STOP-HF follow-up study, almost half of the subjects were part of the STOP-HF trial, which included a control group receiving usual care and an intervention arm that received collaborative care between primary care physician and cardiovascular specialist based on BNP plasma level. Patients involved in this programme may receive more intensive care than the general population. For instance, the Irish cohort of the DA VINCI study did not achieve 2019 ESC/EAS LDL-c goals, highlighting the disparity between dyslipidaemia management in clinical practice in Ireland compared with guideline recommendations [479].

4.6.3. Implications for future research

As this study represents the inaugural identification of this finding, we are limited to speculate regarding the underlying reasons for the observed outcome. To this end, the pleiotropic effects (*i.e.,* non-LDL-c lowering) exerted by statins may explain why patients with a poor statin transporter function phenotype were 2.7 times more likely to develop pre-HF progression and new-onset symptomatic HF compared to those with a normal function phenotype in this study despite the two groups demonstrating no differences in cholesterol levels. Clinical evidence suggests statin therapy can reduce the risk of development of HF and HF hospitalisations [424-430]. Although a reduction in LDL-c is the major effect of statin therapy, a number of studies have suggested that statins may exert salutary effects in patients at risk of HF by virtue of their pleiotropic properties that may influence the pathophysiology of HF to confer survival and further outcomes benefits [417, 433-438]. Notably, hydrophilic statins (rosuvastatin, and pravastatin) may not show these pleiotropic actions to the same extent as lipophilic statins (atorvastatin, simvastatin, and fluvastatin). Bonsu *et al.* found that lipophilic vs hydrophilic statins were associated with greater treatment effects on cardiac function and inflammatory markers [441].

It is not known whether statin transporter genes are related to progression of pre-HF in those without symptomatic HF. SLCO1B1 is a liver-specific transporter protein that plays a crucial role in the uptake of statins into hepatocytes. Statins are primarily metabolised in the liver, where they exert their lipid-lowering effects. Individuals with a poor statin transporter function phenotype have reduced uptake of statins into the liver, leading to lower intracellular concentrations of statins. This reduces the efficacy of statin therapy in lowering cholesterol levels, which could potentially contribute to the progression of atherosclerosis and increase the risk of HF; however, this does not appear to be the case in the current study. Increased exposure to statin-related adverse effects, such as myopathy and rhabdomyolysis, may further compromise cardiac function and contribute to the risk of HF; however, we lacked data on SAMS to assess this hypothesis.

Besides inhibition of HMG-CoA reductase, statins are known to improve endothelial function, ameliorate inflammation in the setting of HF, attenuate myocardial remodelling, and reduce cardiac arrhythmias [417, 434-438, 443], all of which may reduce progression of HF [417, 434]. These additional benefits are primarily thought to arise because of inhibition of the synthesis of isoprenoid intermediates (farnesyl pyrophosphate and geranylgeranyl phosphate) of the mevalonate pathway which affect multiple biochemical signalling pathways [480]. These isoprenoid intermediates mediate the activation of various signalling molecules via the prenylation of small guanosine triphosphate (GTP) binding proteins: Rho, Ras, and Rac [417, 433-436, 439]. Rho is involved in the activation of inflammatory cytokines, inducing nuclear factor kappa B (NF-$\varkappa$B) and activator protein (AP)-1 activation. NF-$\varkappa$B is an important transcription factor that is responsible for the activation of a variety of inflammatory pathways [434, 435, 439]. Statins decrease NF-$\varkappa$B activation by decreasing the levels of oxidative stress within cells. With respect to AP-1, statins have been shown to reduce the expression of c-Jun, one of the two proteins that comprises the AP-1 complex [435]. Ras proteins regulate cell proliferation and hypertrophy, whereas Rac are involved in reactive oxygen species generation via nicotinamide adenine dinucleotide phosphate oxidase activation.

By inhibiting HMG-CoA reductase, statins decrease isoprenoid production which consequently leads to a dose-dependent downregulation of the signalling pathways mediated by Rho, Ras and Rac [417, 433-436, 439]; thus exerting cholesterol-independent

effects such as enhancement of endothelial function (inhibition of Rho protein increasing nitric oxide production and decreasing endothelin I), decrease in proinflammatory cytokines (inhibition of Rho and Rac proteins, NF-$\varkappa$B, and AP-1), and the attenuation of ventricular remodelling (inhibition of Ras, Rho and Rac, reducing the hypertrophic response to improve left ventricular function). All of these factors play a critical role in HF progression and prognosis [417, 434, 439]. By inhibiting the NF-$\varkappa$B pathway, statins decrease the transcription of pro-inflammatory genes, including the gene encoding CRP [481, 482]. CRP is a non-specific marker of inflammatory diseases produced predominantly by hepatocytes in response to proinflammatory cytokines, such as interleukin-6 [436], and is recognised as an independent risk predictor of CVD [433]. Several studies have demonstrated significant reductions in CRP upon treatment with statins [483]. Meta-analyses by Li *et al.* and Zhang *et al.* respectively demonstrated that CRP levels independently predict all-cause and cardiovascular mortality risk in the general population and that statin therapy was associated with a decrease in CRP in patients with congestive HF [442, 484].

Other anti-inflammatory effects of statins may not be dependent on their uptake into the liver; it is possible that the anti-inflammatory effect of statins in patients with a poor statin transporter function phenotype may still be preserved through their actions on extrahepatic tissues and cells. Further research is required to fully understand the impact of SLCO1B1 polymorphisms on the anti-inflammatory effect of statins and their implications for cardiovascular risk reduction. With reduced hepatocellular uptake of statins in patients with a poor statin transporter function phenotype, the pleiotropic effects of statins via inhibition of the mevalonate production and activation of downstream inflammatory signalling pathways may be diminished, leading to less favourable cardiovascular risk profile and an increased risk of HF progression. More work is needed to confirm the findings of the present study in larger datasets and to understand whether the effect on progression of pre-HF and incidence of new-onset symptomatic HF is related to adherence, pharmacological effects of poor statin transporter function phenotype, and/or pleiotropic effects of statins considering inflammatory markers.

4.6.4. Limitations

The present study has several limitations. First, this is a retrospective, observational study and we cannot exclude the possibility that unmeasured variables may have introduced bias or confounding into our study. Second, the findings of this study depended on data that were entered into a clinical database and not collected research. Since the data was not collected in a predesigned proforma as per the specific requirement of the study, some data was inevitably missing. For instance, we lacked data on patient medication adherence, adverse effects to medications (*e.g.,* SAMS) and inflammatory markers (*e.g.,* CRP) to investigate the potential of the anti-inflammatory pleiotropic property of statins and their possible impact on HF pathophysiology. Third, the results from this study are from a single centre in the east of Ireland and thus are not generalisable to other populations. Finally, participants in the STOP-HF programme may receive more intensive care than the general population. The number of events in the overall STOP-HF population may be lower than expected due to the participation of patients in a collaborative specialist-family medicine chronic disease management programme. Further observational studies in larger cohorts of subjects at risk of HF are warranted to confirm the association between the SLCO1B1 and ABCG2 poor statin transporter function phenotype and progression of LVD and incidence of new-onset symptomatic HF.

4.6.5. Actions taken based on findings

Following the analysis conducted on the STOP-HF cohort, it was ensured that any necessary actions related to the findings were considered. Upon consultation with the Principal Investigator of the STOP-HF cohort, it was confirmed that patients had consented to their blood samples being stored for future analysis and genetic testing (Appendix 4.3 and Appendix 4.4). Importantly, the results from these genetic tests are intended solely for research purposes. Consequently, these results will not be shared with the patients, their doctors, nor will they be recorded in the patients' medical charts. Therefore, there was no need to disclose any findings directly to the patients. This process ensures compliance with ethical standards and respects the confidentiality and anonymity of the participants while facilitating ongoing and future research endeavours.

4.7. Conclusion

Among subjects at risk for HF (stage A and B HF), the SLCO1B1 and ABCG2 poor statin transporter function phenotype is associated with progression of pre-HF and incidence of new-onset symptomatic HF. The results from this study support the concept that statin therapy could exert protective cardiovascular effects in subjects at risk of HF and routine SLCO1B1 and ABCG2 genotyping may help to identify patients with cardiovascular risk factors at greater risk of HF progression. Importantly, our findings lay the foundation for future clinical studies aimed to test the role of genetic testing and therapy as part of more personalised HF prevention.

Chapter 5

Collaborative medicines optimisation service involving a general practice pharmacist (COMPASS) in Irish primary care:

A SEIPS-based interview study

5. Chapter 5: COMPASS interview study

5.1. Introduction

As outlined in Chapter 1, demographic projections suggest that the populations of all countries are ageing. By 2050, over one fifth of the world's population will be 60 years or older [485]. A growing older population will require a more holistic and integrated approach to healthcare delivery and medicines optimisation to promote healthier extended life spans [8]. As a result of the ageing population, along with advancements in public health and modern medicine, increasing morbidity and use of medications are expected. With growing economic pressures, healthcare services will have to adapt to meet the complex care needs of older people with multimorbidity and those prescribed polypharmacy, whose healthcare requirements are more intricate than other patient groups [25, 486]. Appropriate medication use is of particular importance [46], and polypharmacy has been identified as a major priority by the WHO in its third Global Patient Safety Challenge: Medication Without Harm [45, 487].

Primary care bears most of the burden in the front-line management of patients with multimorbidity prescribed polypharmacy. Due to workforce shortages and the complex nature of managing these patients, which is further compounded by competing clinical priorities and conflicting guidelines, GPs are confronted by excess pressure and workloads [25, 488-490]. This is a significant problem with the potential to cause harm to patients and GPs as high workload and job stress are associated with lower practice performance and more negative patient experiences [120]. General practice must be supported to develop its capacity to provide patient-centred, individualised healthcare to an ageing population with rising rates of multimorbidity and polypharmacy.

Several frameworks and strategies have been introduced to attempt to reform healthcare in Ireland, *e.g.,* Sláintecare. The implementation of integrated care programmes focused on long-term conditions and older people to provide appropriate and effective primary care is central [95, 96]. While the HSE's Enhanced Community Care programme to increase community healthcare services and to reduce pressure on secondary care is a worthy goal, there are significant obstacles. GP capacity and recruitment continues to be an issue, and is

likely to remain so, even with the investment announced as part of the €130 million agreement between the Irish Medical Organisation and the Government on the extension of GPVC eligibility [491, 492].

Pharmacists have been introduced into general practice (*i.e.,* general practice pharmacists; GPPs) to provide a multi-skilled task force and alleviate some of the increasing stresses faced by GPs [135, 489, 493, 494]. In the UK, the Clinical Pharmacists in General Practice scheme was introduced as part of the Five Year Forward Review by the NHS England to address the staff shortage in general practice in 2015 [495]. From 2015 to 2019, the scheme expanded with funding increasing from £15 million to £112 million to support the expansion of the general practice workforce, which included the employment of 460 clinical pharmacists in the first phase of the scheme and a further 1500 clinical pharmacist posts in April 2019 [122]. In July 2019, the new GP five-year contract framework was launched to support Primary Care Networks recruit up to an additional 20,000 staff to work in primary care teams, including clinical pharmacists [496]. As of December 2023, data from NHS England reveals a total of 9,873 pharmacy professionals working in general practice and Primary Care Networks [497].

Additionally, every general practice in Northern Ireland now has a pharmacist as an integral part of their clinical team, working alongside GPs and other HCPs to improve the safety and quality of prescribing and improve patient outcomes [498]. In Northern Ireland, GPPs are involved in a wide range of tasks in which they use their clinical knowledge and expertise to achieve better health outcomes for the population from the use of medicines. For instance, managing patient medication reviews and hospital discharge information, ensuring efficient use of health service funding for medicines and appropriate use of medicines, and promoting high quality, safe prescribing while relieving work pressures on other clinical staff working the general practice [499]. While uncommon in Ireland, two recent pilot studies found GPP integration is feasible and can improve prescribing safety and deprescribing efforts [136, 137].

As outlined in Chapter 1, medicines optimisation encompasses many aspects of improving medication use and is fundamental for enhancing the management of patients with multimorbidity and prescribed polypharmacy [139, 144, 500]. In medicines optimisation, GPPs collaborate with GPs, CPs, and patients on numerous tasks such as medication reviews, medication reconciliation, managing repeat prescriptions, and providing medicines information to ensure patients get the best clinical outcomes from their medicines [138-140]. Although evidence on the impact of medication reviews on clinical outcomes is lacking [36], a reduction in MRPs and the number of prescribed drugs have been demonstrated [161, 501, 502]. While polypharmacy is often clinically indicated and beneficial in specific conditions and patient populations, medication review and subsequent deprescribing if indicated is particularly relevant in this cohort as the risk of MRPs increases with the number of medications prescribed [140]. Additionally, patients prescribed polypharmacy often know too little about their medications and have difficulties with treatment compliance [61].

The EU funded iSIMPATHY (Implementing Stimulating Innovation in the Management of Polypharmacy and Adherence Through the Years) project sought to ensure the most sustainable use of medicines for patients by training pharmacists and other HCPs to deliver patient-centred medication reviews and embedding a shared decision-making approach to managing polypharmacy [503]. This project used a multidisciplinary collaborative approach to deliver pharmacist-led medication reviews using the 7-Steps methodology (detailed in Section 1.5.4) [144, 503]. A total of 6,481 patients participated in iSIMPATHY medication reviews. A number of key benefits were obtained by utilising the 7-Steps approach: 82% of interventions were rated clinically significant, while 4% of interventions potentially prevented major organ failure, ADRs or incidents of similar clinical importance; the appropriateness of medicines improved in 92% of reviews, with an average reduction of one medicine; direct cost savings of £13,100 and a potential total of £168,800 savings from avoided healthcare utilisation per 100 review; patients reported better understanding of their medicines, improved adherence and experienced less harm; and an average of 7.4 Quality-Adjusted Life Years were gained per 100 patients [503]. The iSIMPATHY medication reviews in the Republic of Ireland were carried out in primary care where the pharmacists worked in the general practice and/or remotely, with most reviews being provided via telephone [503].

Consequently, collaborative medication reviews as part of medicines optimisation involving general practice pharmacists can achieve better patient safety and system outcomes within the economic resources available [503]. Furthermore, the integration of pharmacists into the general practice team facilitates primary care collaboration and communication, enables access to medical records, and reduces the fragmentation of care [131, 132, 134, 504]. However, the GPP need not be present in the same geographical location as the GP [503]. A recent systematic review showed consistency between remotely integrated and co-located GPPs to improve prescribing appropriateness and reduce the number of per-patient medications [505]. Studies outside Ireland have demonstrated that GPPs can positively affect prescribing quality, emergency department use, healthcare costs, patient outcomes, and GP capacity primarily through medicines optimisation and in some cases prescribing medicines [127, 131, 504-508]. Regarding clinical outcomes, GPP interventions have been associated with significant improvements in blood pressure, glycosylated haemoglobin, cholesterol, and cardiovascular risk [127].

Following the recent advances in pharmacogenomics, patient-centred medicines optimisation should be expanded to include consideration of individual's genetic variation. As noted in Chapter 1, pharmacogenomics informed prescribing is one of the first applications of genomics in medicine [222, 509], promising to personalise medicine by using an individual's genetic makeup, which predicts drug response, to guide optimal drug and dose selection [165, 166]. This may help remove some of the traditional "trial and error" approach of drug prescribing, resulting in safer, more effective, and cost-effective drug treatment [167, 510]. For innovations such as pharmacogenomic testing to be sustainably integrated in healthcare, it is known that changes in culture, structure, and practice are required. The insights of a key stakeholder, the service provider (GP or CP in primary care), on pharmacogenomic testing and its various characteristics (*e.g.,* timing, type, genetic variants) will be invaluable in the process of paving the road for the implementation of pharmacogenomics in clinical practice.

As discussed in Chapter 2, the use of pharmacogenomic interventions in medicines optimisation for patients with multimorbidity and polypharmacy could have significant benefits [272]. In Chapter 3, the public's support and interest in pharmacogenomic testing was described. This was especially the case for people with chronic disease, who were over two times more likely to value pharmacogenomic services than those without any chronic disease. Furthermore, gene-based drug interactions were shown to be prevalent and clinically relevant in Irish primary care. As noted in Chapter 4, the STOP-HF cohort, an older patient population with multimorbidity and prescribed polypharmacy, demonstrated a high prevalence of potential drug-gene interactions. In this population with cardiovascular risk factors, statins were commonly prescribed. Genotyping for SLCO1B1 and ABCG2 variants that can affect statin disposition and adverse events during statin therapy found that patients with a poor function statin transporter function phenotype were at elevated risk of progression of pre-HF and incidence of new-onset symptomatic HF.

5.2. COllaborative Medicines oPtimisAtion Service involving a general practice pharmaciSt (COMPASS)

It is critical to inspect the complexity of our healthcare system and the competing priorities amongst GPs, CPs and patients, and work to align our focus to effectively manage patients. The combined knowledge and experience of these stakeholders are required to ensure patients' treatments are optimised to achieve their preferred outcomes. Thus, a novel, **co**llaborative **m**edicines o**p**timis**a**tion **s**ervice involving alliance between a general practice pharmaci**s**t (PhD candidate) and the healthcare staff within the general practice (namely GPs, practice nurses and physician assistants) was established (hereafter, the service is referred to as COMPASS). Under the Irish Research Council's Employment-Based Programme, the PhD candidate was employed as a GPP in a CHO Area 5 teaching general practice with a track record of participating in practice research. Eight GPs, several nurses, phlebotomists, physician assistants and support staff were employed in this practice.

The PhD candidate (a pharmacist) was able to work remotely with the general practice using a work laptop with the practice management software Socrates® installed to provide a part-time telepharmacy service (up to 15 hours per week) from June 2021 to December 2023. The role of the GPP in COMPASS was informed by the interaction between patients and

healthcare in Irish primary care. The GPP received referrals from members of the general practice team via Socrates® and had access to patients' electronic medical records; enabling the GPP to view the patient's past medical history, pathology, specialist correspondence, previous medicines, and biochemical monitoring. As the GPP worked remotely, contact with patients and CPs was predominantly via telephone. Communication with CPs was also facilitated by access to the practice Healthmail address.

COMPASS was developed using Lean methodology. Lean is derived from the Toyota production system, a system originally used to increase efficiency in manufacturing companies [511]. More recently, Lean methodology has also been identified as an effective strategy to promote patient safety, patient satisfaction, and the delivery of efficient, high-quality healthcare [512, 513]. Lean adds value to the patients' experience and is based on respect for people and continuous improvement [513]. Lean healthcare starts by reviewing a healthcare process to determine what is of value to the patient, *i.e.,* activities that enhance healthcare quality and promote patient well-being towards a better outcome [514].

Correspondingly, Lean healthcare helps identify waste, *i.e.,* anything other than the minimum amount of equipment, space, or staff time essential to add value to a product or service [515]. As a result, Lean healthcare classifies activities into value-added or non-value-added [512]. Value-added activities contribute directly to patient needs, whereas non-value-added activities take unnecessary time, space, or resources [512]. Consequently, Lean methodology is a team-based problem-solving approach designed to address current challenges faced by healthcare organisations [513]. This methodology provides a means of integrating improvement into standardised workflow and decreases healthcare cost, eliminates wastes, and rejects redundancies.

COMPASS was developed during the COVID-19 pandemic, where virtual consultations were becoming the norm, due to restrictions on attendance in general practices. The Lean approach to service development was used in order to foster a dynamic and effective GPP-GP relationship with patient-centred care at its core. This approach to the service development was agreed by all stakeholders, to allow rapid service development in line with the changing healthcare landscape. It allowed for progressive changes to the service, and processes within that service, to be made continuously following feedback and reflections

from all stakeholders. Weekly discussions were held amongst the primary care team on Zoom®, which provided opportunities to discuss priorities for the practice, to increase GPP involvement in the practice, and address challenges encountered by the GPP and the primary care team with COMPASS. These meetings were held for the duration of the PhD candidate's employment as a GPP to ensure continuous practice improvement was maintained.

COMPASS focused on addressing stakeholders' concerns, in which the medicines optimisation processes were required to improve the current workflow rather than add extraneous complexity that would have diminished uptake. This was further compounded by the proposition of incorporating pharmacogenomics into COMPASS to enhance the personalisation of medicines optimisation. However, implementation of pharmacogenomic testing as part of COMPASS is yet to be achieved and was outside the scope of the current study.

COMPASS developed over 30 months encompassed a range of pharmacy activities, some of which involved direct contact with patients and others that were supportive roles for the GPs. With regards to patient-facing roles, these included undertaking medication reviews with patients and medication reconciliation at transitions of care. Non-patient facing roles included activities such as advising GPs and CPs on therapeutic substitution when medicines were in short supply and resolving prescription queries. These priorities were in line with the WHO Global Patient Safety Challenge: Medication Without Harm to address patient harm due to medicines [516]. Priorities for action were high-risk situations, polypharmacy, and transition of care. The components of COMPASS developed using Lean methodology are described in Section 5.2.1 to Section 5.2.4.

5.2.1. Medication review

GPs referred eligible multimorbid patients prescribed polypharmacy (≥4 medicines) for GPP-led medication review via tasks on Socrates®. Additionally, GPs referred patients involved in the Chronic Disease Management (CDM) programme on a reactive case-by-case basis for GPP review after the availability of biochemical and clinical test results and prior to the patient's appointment with the GP. The CDM programme involves two reviews per year for patients who have a GMS, GPVC or Health Amendment Act card and have a specified chronic disease (*e.g.,* cardiovascular disease, chronic obstructive pulmonary disease, asthma, and diabetes). The patient-centred medication reviews within COMPASS lasted approximately 45-60 minutes. During each review, numerical data were gathered in Excel documenting patient age and number of conditions, medications, recommendations, and accepted recommendations. Following each medication review, a summary of the findings and relevant suggestions were reported to the GP to act upon using their own clinical judgement.

A medication review form was developed for GPP-led medication review (Table 5.1), incorporating advice on a holistic patient-centred approach using the 7-Steps review process from the Polypharmacy Guidance Realistic Prescribing tool [144]. The medication review form was piloted with three pharmacists in the School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin. The holistic, collaborative GPP-GP-patient medication reviews within COMPASS followed a structured, stepwise process (Figure 5.1), focussing on seven domains:

i. Review prescriber's concern (*i.e.,* reason for referral), identify therapeutic objectives and review patient priorities and concerns
ii. Review diagnoses and assess drug therapy for valid indications and adherence to identify essential drug therapy
iii. Review the need for unnecessary drugs – consider deprescribing medications that may cause harm or are no longer providing benefit or reducing dose
iv. Identify if therapeutic objectives are being met (*e.g.,* recent clinical measurements and biochemical results) and whether drug therapy should be added or intensified
v. Identify patient safety risks (*e.g.,* Stockley's Interaction Checker, high-risk prescribing, and potentially inappropriate prescribing) and adverse effects

vi. Assess for cost-effective prescribing

vii. Ensure patient-centredness by making sure the plan is communicated clearly to patients and their GP and CP are according with the patient's preferences

Clinical judgement, taking into account the patient's perspective and contextual factors, was used to identify instances of potentially inappropriate prescribing and opportunities for deprescribing medications that may cause harm or are no longer providing benefit. Factors considered when determining medication appropriateness included its indication, dose, duration, and risk of MRPs. Guidelines published by deprescribing.org and Primary Health Tasmania were reviewed to assist with deprescribing [517, 518]. To enable a more rounded approach to medication review, standard instruments for measuring prescribing appropriateness such as STOPP/START and Beers' Criteria were not central [519, 520]. A holistic polypharmacy review will often result in an element of deprescribing, but stopping medicines was not the primary driver of these medication reviews, as the patient's preferences were equally important.

Table 5.1. COMPASS medication review form

Patient ID				
Name		DOB		
Background				
Prescriber concern(s)				
Patient questions	Do you have any concerns at the moment?			
	How do you take your medicines?			
	What assistance do you require?			
	Do you have any other health issues?			
	Do you take any other medications (*e.g.,* OTC, herbal)?			
	Do you understand the purpose of this review process and what it entails?			
	Do you require technique demonstration?			
Biochemistry/clinicals	BP	Lipids	Smoker	Alcohol
	BMI	HbA_{1c}	Renal	Liver
Interactions (high priority, actionable)				
Drug-drug	Note interactions with "dosage adjustment or close monitoring is required" per Stockley's Interaction Checker: Note interactions with "give guidance about possible adverse effects and/or consider some monitoring" per Stockley's Interaction Checker:			
Potential drug-gene				
Potential drug-kidney				
Potential drug-liver				
Recommendations and Summary				
Summary	Provide prioritised prescribing recommendations (numbered)			
Outcome				
Follow-up				

Table 5.1 (cont'd). COMPASS medication review form

Current medicines (including OTC and herbal)		Link to an active diagnosis	Patient-knowledge of indication?	Patient-reported indication	Used as prescribed?	Adherence				Side effects?	Is this medicine essential?	Patient view on deprescribing (if relevant)	General comments relating to advice, side effects and other issues
						Always	Frequent	Seldom	Never				
1	Name Dosage		☐Yes ☐No		☐Yes If no, specify:					☐Yes ☐No	☐Yes ☐No		
2	Name Dosage		☐Yes ☐No		☐Yes If no, specify:					☐Yes ☐No	☐Yes ☐No		
3	Name Dosage		☐Yes ☐No		☐Yes If no, specify:					☐Yes ☐No	☐Yes ☐No		

Abbreviations: *OTC* over-the-counter

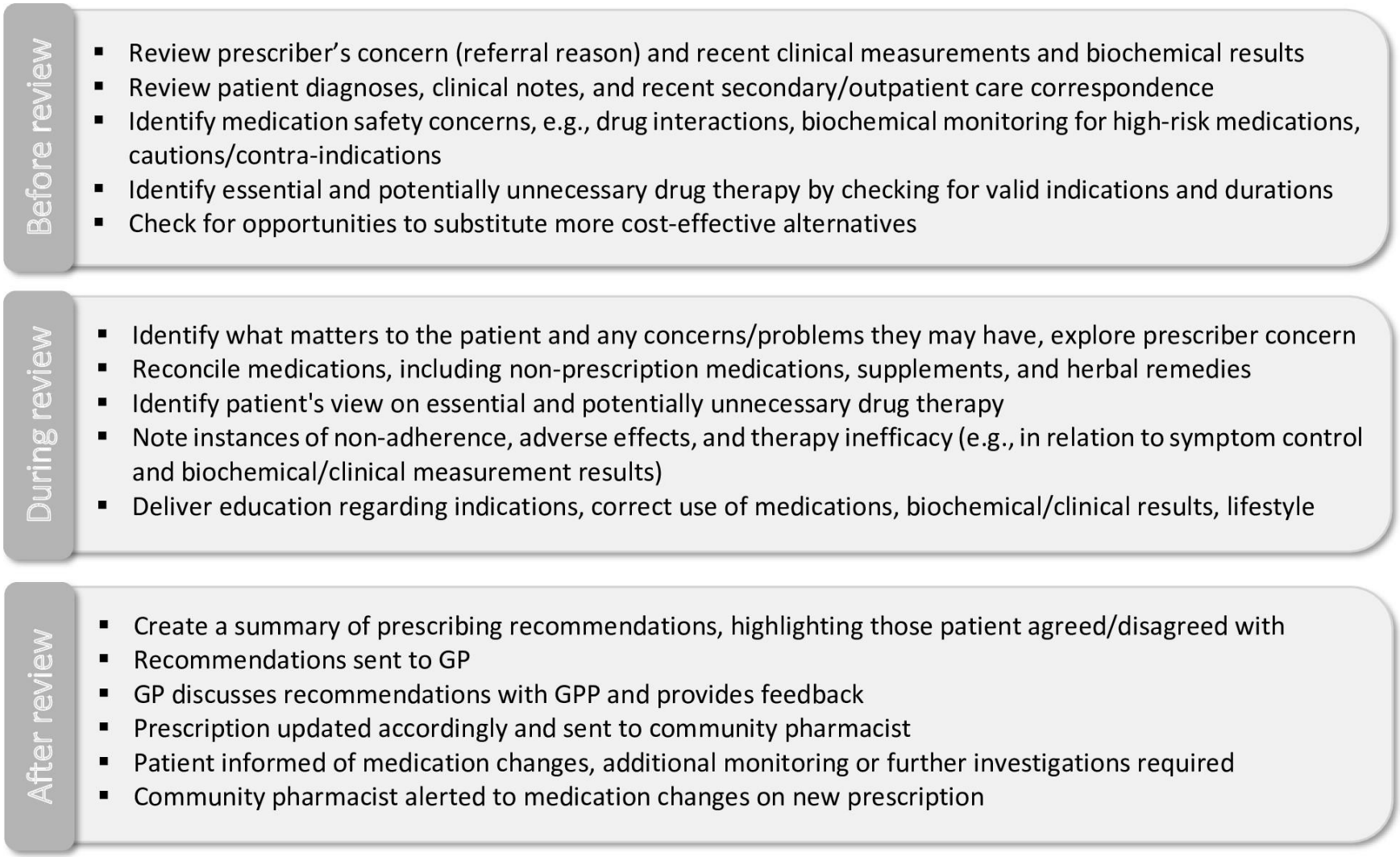

Figure 5.1. COMPASS medication review process

5.2.2. Medication reconciliation at transitions of care

The transition of patients with chronic and complex diseases from hospital to the community is a critical time. Medication discrepancies arising at care transitions are prevalent and are linked with ADEs [521]. More than 40% of medication errors result from inadequate medication reconciliation at care transitions [522]. Medication reconciliation is a conscientious, patient-centred, inter-professional process that supports optimal medicines management [523]. To prevent medication errors, the GPP performed medication reconciliation at transitions to build a complete list of a patient's medicines, check them for accuracy, and reconcile and document any changes with the goal of providing the correct medications to the patient. This process involved contacting hospital prescribers to clarify ambiguity and rectify problems with discharge prescriptions and CPs to confirm any changes.

Medication discrepancies are unexplained differences in documented medication regimens across different sites of care [524]. Knowledge-based mistakes, especially about the dose of the drug and the patient's comorbidities, are a common cause of prescribing errors in hospital inpatients [525]. Lack of training and lack of experience of the prescriber have been described as error-provoking conditions [525]. Oftentimes, hospital prescribers attempt to prescribe the patient's regular medicines on the discharge prescriptions but do not capture an accurate list. It is then unsure if omissions are intentional or not, necessitating contact with the prescriber to ensure medicines are not stopped in error. Contacting prescribers in the hospital setting can be a challenging and time-consuming task but is essential in order to complete these transition of care reviews; however, this is time that the GP and CP do not have to take away from their core daily activities.

5.2.3. Therapeutic substitution

Over time in the practice, a demand became apparent for pharmacist-led therapeutic substitution; the practice of replacing a patient's prescription drug with a chemically different drug that is expected to have the same clinical effect. The alternative drug may be within the same class or from another class with assumed therapeutic equivalence. Medication shortages that are unfortunately common necessitate the need for alterations to be made to a patient's prescription. In Ireland, the majority of shortages (>50%) are caused by manufacturing delays, which aligns with what is observed across the EU where quality and manufacturing issues were found to cause 51% of shortages [526]. According to the Medicines Shortages Lists populated and monitored by the Health Products Regulatory Authority in Ireland, there are currently 280 medications in short supply; unexpected increase in demand is a common cause [527]. This list showed an 86% increase in shortages from 2022 to 2023, rising from 178 to 332 [528]. Adding to the gravity of the situation, the number of medicines with just one supplier has also seen a dramatic spike, now reaching >44% of all medicines in short supply, significantly above the EU-wide average of 25% [528].

While the Department of Health stressed that there are numerous alternatives available to ensure continuity of care, therapeutic substitution is not straight-forward at present [526]. With expert knowledge of medicines but without prescribing rights, pharmacists are relied upon to suggest such alternatives to the patient's GP but cannot act until a new prescription is furnished to enable the patient to continue treatment with a therapeutically equivalent medication. For patients presenting to their community pharmacy to collect their prescription, they may need to return to their GP for an alternative prescription for an available product, or the pharmacist needs to contact the GP on the patient's behalf to organise a prescription. To alleviate GP and CP pressure whilst still acting within the constraints placed around therapeutic substitution in Ireland, a therapeutic substitution process was developed that GPs in the practice were asked to opt-in for. In this process, CPs alerted the GPP to the shortage via Healthmail (the electronic prescribing system used in Ireland) and could suggest an alternative. The GPP independently identified an alternative, checking for availability in the community pharmacy if necessary. The GPP then prepared the prescription on Socrates® for the GP to sign prior to sending electronically to the CP.

5.2.4. Prescription queries

Resolving prescription queries for both GPs and CPs was a major part of COMPASS (categorised under medication reconciliation, prescription appropriateness, and repeat prescribing queries). With the advent of Healthmail in Ireland and access to the GP practice management software, the GPP was able to address prescription queries from any stakeholder involved in the primary care of patients in an agile, flexible, and responsive manner. Medication reconciliation in this instance did not involve a transition of care, but entailed checking a patient's medication to ensure their list of medicines was correct without a full medication review of the patient to avoid medication errors such as omissions, duplications, dosing errors, and drug interactions. Prescription appropriateness queries involved investigating concerns around appropriate doses and durations of treatment, side effects, and medication coverage under Irish government schemes. Repeat prescribing consisted of queries around necessity and timeliness of prescribing as well as appropriateness of controlled drugs prescriptions. There are a number of requirements in order for a controlled drug prescription to be legally valid under the Misuse of Drugs Regulations 2017; repeat prescribing of Schedule 2 and 3 controlled drugs, which is not allowed under the legislation, was a common issue. An overview of the tasks conducted by the GPP within COMPASS is provided in Figure 5.2.

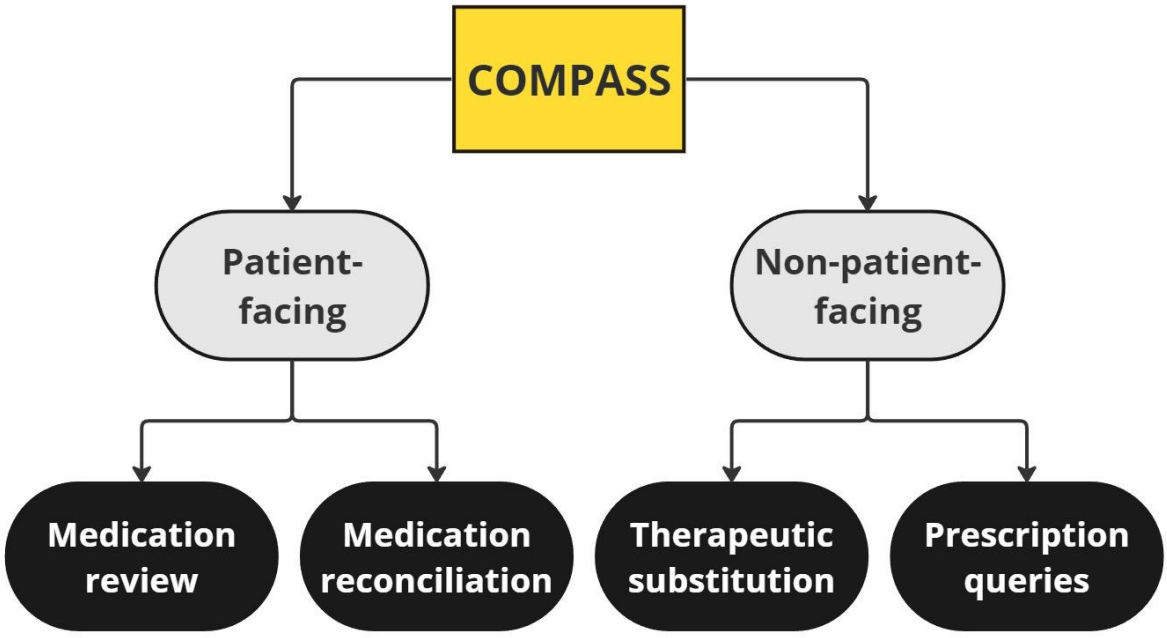

Figure 5.2. Overview of COMPASS activities

5.3. Aims and objectives

5.3.1. Aim

Considering the novelty of COMPASS, the aim of this study was to establish key stakeholders' (GPs, CPs, and patients) views of the service. A secondary aim was to determine stakeholders' perceptions of incorporating pharmacogenomic testing into COMPASS.

5.3.2. Objectives

The specific objectives were to:

- Map the patient's journey through COMPASS using all stakeholders' perspectives
- Establish the views of stakeholders (barriers, facilitators, and future improvement strategies) regarding COMPASS and specifically the involvement of pharmacists in general practice, and
- Determine stakeholders' views on incorporating pharmacogenomics into COMPASS
- Develop a process map for COMPASS incorporating the barriers and facilitators identified from the stakeholder interviews to improve the service in the future

5.4. Research design and methodology

A qualitative semi-structured interview study was undertaken with GPs, CPs, and patients in primary care in Ireland where the PhD candidate provided COMPASS (Section 5.2). Semi-structured interviews are an effective method to collect qualitative, open-ended data and to explore participants' thoughts, feelings, and beliefs about a particular topic [529]. Furthermore, medication reviews as part of medicines optimisation are considered complex healthcare interventions because they consist of consecutive steps and are usually conducted by an interprofessional team [530]. Complex healthcare interventions are difficult to evaluate with solely quantitative methods, hence qualitative research using semi-structured interviews was conducted [531]. The study was reported according to the Consolidated Criteria for Reporting Qualitative Research (COREQ) checklist [532].

5.4.1. Study population and setting

Only stakeholders (GPs, CPs, and patients) who took part in COMPASS were eligible for to take part in the interview study (Section 5.2). All GPs and patients were from the same general practice surgery in Ireland, while all CPs who were consulted within the service were eligible to take part.

5.4.2. Sampling and recruitment

Purposive, convenience and snowball sampling was used in the recruitment of GPs, patients and CPs respectively [533]. Potential GP interviewees who participated in COMPASS were identified by the GPP. A list of patients who underwent a medication review as part of COMPASS was provided to their GP who assessed patient availability and willingness to participate in this study. Phone numbers and email addresses for patients are kept on their patient medication record and accessible to the HCP involved in their care. If consent was given by the patient to their GP to receive an invitation to participate in this study, the PhD candidate then contacted the patients. The researcher contacted CPs involved in the care of patients consented for interview using publicly available contact details to assess their interest in participating in the study. Selected CPs had varying previous interaction with the GPP as part of COMPASS.

Participation for all interviewees was voluntary, and those interested were sent an invitation letter (Appendix 5.1), participant information leaflet (Appendix 5.2) and consent form (Appendix 5.3) via email. Potential participants were followed up seven days after the invitation was sent if no response was received. Upon return of consent forms, interview dates and times were set. Interviews were conducted by the researcher between August and October 2022. Participants did not receive payment for taking part in this study.

5.4.3. Topic guide development

Separate topic guides were developed for patients and HCPs (GPs and CPs) (Appendix 5.4 and Appendix 5.5 respectively). Topic guides were informed by published literature on barriers and facilitators to GPP integration into general practice [534-536], medicines optimisation [537-540], and pharmacogenomic testing [343, 362, 541]. The topic guides were piloted with two HCPs with qualitative research experience in the School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin. A Patient Public Involvement advisor was involved in co-designing the patient topic guide.

The topic guides focussed on three sections: (i) COMPASS, (ii) integrating pharmacists into general practice, and (iii) the potential for incorporating pharmacogenomics into COMPASS. As shown in Figure 5.2, medication review and medication reconciliation involved direct contact with the patient (via telephone), while therapeutic substitution and resolution of prescription queries generally did not involve patient contact. Therefore, the primary focus of this qualitative study was on the patient-facing components of COMPASS. Clarifying questions about COMPASS and probes around the work system elements were utilised to help identify barriers and facilitators. Topic guides underwent an iterative developmental process, where data analysis was performed in tandem with data collection. This allowed for key themes/concepts identified through the analysis to be further explored with subsequent participants. All interview topic guides were theoretically based on the Systems Engineering Initiative for Patient Safety (SEIPS) 3.0 model, as explained below (Section 5.4.4).

5.4.4. The SEIPS model

The SEIPS model is a well-regarded theoretical model that provides a framework for integrating human factors and ergonomics in healthcare quality and patient safety improvement [542-544]. The first version of the SEIPS model was published in 2006 by Carayon *et al.* [542]. In response to a shift in the healthcare system toward a patient-centred model of care, SEIPS 2.0 was developed [543], primarily to address the work done by patients, families and other non-professionals (*i.e.,* active engagement in health-related activities for example medication taking and symptom monitoring, scheduling appointments, consuming information about health and communicating with HCPs). SEIPS 3.0 expands upon SEIPS 2.0, mainly by focusing attention on the patient journey as it unfolds over time and space, describing their interactions with different healthcare workers, often belonging to different organisations [544]. In the SEIPS 3.0 model, the patient journey is defined as 'the spatial-temporal distribution of patients' interactions with multiple care settings over time' [544].

The SEIPS model seeks to explain work system designs from a human factors and patient safety perspective by adopting a 'whole system' approach. All versions of the model depict three major components, the work system, processes and outcomes [545]. SEIPS focuses on the interactions of five related work system components (people, tasks, tools and technology, environment, and organisational conditions), and how these impact on 'outcomes' to support evaluation, planning and research activities [544, 545]. In different visual representations of the SEIPS model [542, 543], the work system and process are displayed separately. However, it is important to emphasise that the work system and process are intractably related and are two different perspectives on the same object, *i.e.,* the work done by HCPs, patients, and caregivers [544].

In the SEIPS model, the person is the centre of the work system, and interactions amongst work system elements are designed to support performance and safety and avoid negative outcomes, such as stress and preventable patient harm [542]. Therefore, in applying a SEIPS model with the patient at the centre of the work system (in this case, COMPASS), deficiencies in healthcare systems that can impair the patient's capacity to receive high quality safe care (and facilitators to support people in the work system) may be identified. This contributes to the design of systems and processes for delivering patient-centred care [542].

A key component of examining the patient journey using SEIPS 3.0 is the focus on the patient experience [544].The patient journey map provided a means to visualise the internal and external factors affecting patient flow and the different paths patients must take throughout COMPASS in order to achieve their care goals. Across healthcare settings, these interactions were influenced by the external environment in which these work system elements were embedded. Work systems were identified for each stakeholder involved in COMPASS (GPPs, GPs, CPs, and patients). Using feedback from the stakeholders on COMPASS, the service can be redesigned to improve the patient journey and subsequent outcomes.

The SEIPS model has been applied in a variety of settings to optimise healthcare workflow efficiency, identify barriers, and to improve patient safety outcomes [546-549]. Wooldridge *et al.* used SEIPS to model three primary care processes, namely pre-visit planning, patient outreach, and follow-up, to understand and analyse healthcare processes systematically and identify specific areas of improvement [546]. Mundt *et al.* interviewed members from primary care clinics in an effort to model and understand team-based primary care [547]. Using the SEIPS model to identify safety hazards in general practice, Bowie *et al.* designed a safety checklist to improve safety systems and processes in the general practice work system [548]. Werner *et al.* mapped medication management for older adults' hospital-to-skilled-home-healthcare transitions using the SEIPS 2.0 model and highlighted the importance of a process-level view of healthcare delivery occurring across system boundaries [549].

5.4.5. Data management

Following consent, all interviews were conducted via telephone, recorded, and transcribed verbatim via transcription service. Transcripts were checked for accuracy and to remove any identifiers. All interviews were audio recorded with the consent of the participant, as per consent form (Appendix 5.3). To ensure anonymity and confidentiality, each participant was assigned a two-digit identification number reflecting the group from which the participant was associated (*e.g.,* GP01, CP01, P01, where GP = General Practitioner, CP = Community Pharmacist, and P = Patient). During the data collection phase, the data was pseudonymised. A password-protected Excel file stored on the PhD candidate's Trinity College Dublin OneDrive account accessed via their password-protected computer contained the participants' name, contact number, email address and anonymity code. This key was deleted within seven days of the final interview taking place to render the data (transcripts labelled with the anonymity code) anonymous by leaving no link between the anonymity code on the transcript and the participant to whom that data related.

5.4.6. Data analysis

The patient journey through COMPASS was mapped prior to the identification of improvement strategies. Transcripts were imported and managed in NVivo (version 12), a software programme used for qualitative and mixed-methods research. Data analysis was performed in parallel with data collection by the PhD candidate. Barriers and facilitators to COMPASS were identified from the transcripts and coded according to the SEIPS 3.0 model [544].

Thematic analysis was performed following the step-by-step guide published by Braun *et al.* [550], which contained the following phases:

i. Familiarisation with the data
ii. Generate initial codes
iii. Search for themes
iv. Review themes
v. Define and name themes; and
vi. Produce the report including a selection of illustrative data and quotations.

Thematic analysis was a recursive process (*i.e.,* an iterative process in a series of repeatable steps), with movement back and forth throughout the phases listed above [550]. For instance, via data analysis and consensus within the research team, new emergent themes appeared which replaced the original themes. A random sample of transcripts was analysed by a second member of the research team. Themes were reviewed and refined by discussion within the research team.

The SEIPS model and Braun and Clarke's reflexive thematic analysis were used together in a blended approach to enhance the comprehensiveness of the analysis. While SEIPS 3.0 provided a structural framework to identify and code barriers and facilitators within the work system, thematic analysis allowed for a deeper exploration of the data to generate nuanced themes and patterns. The integration of these approaches enabled a detailed work-systems analysis of COMPASS, GPP integration into general practice, and considerations around the incorporation of pharmacogenomic testing into COMPASS was generated.

To assist in selecting aspects of COMPASS to address, a SEIPS-based process map was produced using Miro to depict the relevant subset of work system factors whose interactions were thought to be meaningful [545]. This blended analytical approach ensured a thorough and multi-faceted understanding of the data, combining the systematic rigour of the SEIPS model with the flexibility and depth of thematic analysis.

5.5. Ethical approval

Ethical approval was granted by the School of Pharmacy and Pharmaceutical Sciences Research Ethics Committee in March 2022 (Ref. 2021-12-02) (Appendix 5.6).

5.6. Results

5.6.1. Demographic data

In total, 15 interviews were undertaken (involving six CPs, five GPs and four patients; participant details shown in Table 5.2). The GPs reported seeing on average 32 patients per day. Four CPs interviewed were supervising pharmacists, while the remaining two were support pharmacists. Each CP had a co-working CP, with overlap present in two-thirds of cases. CPs were responsible for the care of patients interviewed in this study and had previously interacted with the GPP in varying capacities (mainly therapeutic substitution and medication reconciliation). Patients were older adults with multimorbidity and prescribed polypharmacy.

Table 5.2. Characteristics of participants

Key Characteristics	
Gender (n = 15)	N (%)
Male	7 (47)
Female	8 (53)
Patients (n = 4)	Median (IQR)
Age in years	66 (62, 70)
Number of medications	15 (10, 19)
Number of chronic conditions	9 (7, 11)
General practitioners (n = 5)	Median (IQR)
Years as a general practitioner	12 (4, 25)
Community pharmacists (n = 6)	Median (IQR)
Years as a community pharmacist	5.5 (2-25)
Number of daily prescription items	300 (225, 338)
Number of co-working technicians	3 (2, 3)
Average interview duration (n = 15)	Time (mean)
Patient	49 mins
Community pharmacist	41 mins
General practitioner	54 mins

Abbreviation: *IQR* interquartile range

5.6.2. Patient journey through COMPASS

Prior to the identification of stakeholder-informed barriers and facilitators to COMPASS, the patient experience and interactions with multiple work systems/processes and their elements in COMPASS were described in a patient journey map (Figure 5.3). This figure describes a host of primary care interactions for the patient journey through COMPASS and the roles of the GPP previously described in Section 5.2; namely medication review (green pathway), medication reconciliation (red pathway), resolution of prescription queries (purple pathway), and therapeutic substitution (blue pathway).

5.6.3. Main themes from thematic analysis

The SEIPS-based barriers and facilitators to COMPASS are described within the main themes of patient-centred care (Section 5.6.4); impact on healthcare (Section 5.6.5); collaboration and communication (Section 5.6.6); and day-to-day practicalities (Section 5.6.7). A summary of these SEIPS-based barriers and facilitators are provided in Table 5.3 and Table 5.4 respectively and are supported by illustrative quotations in the relevant section under each theme. Due to the multidimensionality of participants' quotations, some quotations may map to more than one SEIPS element.

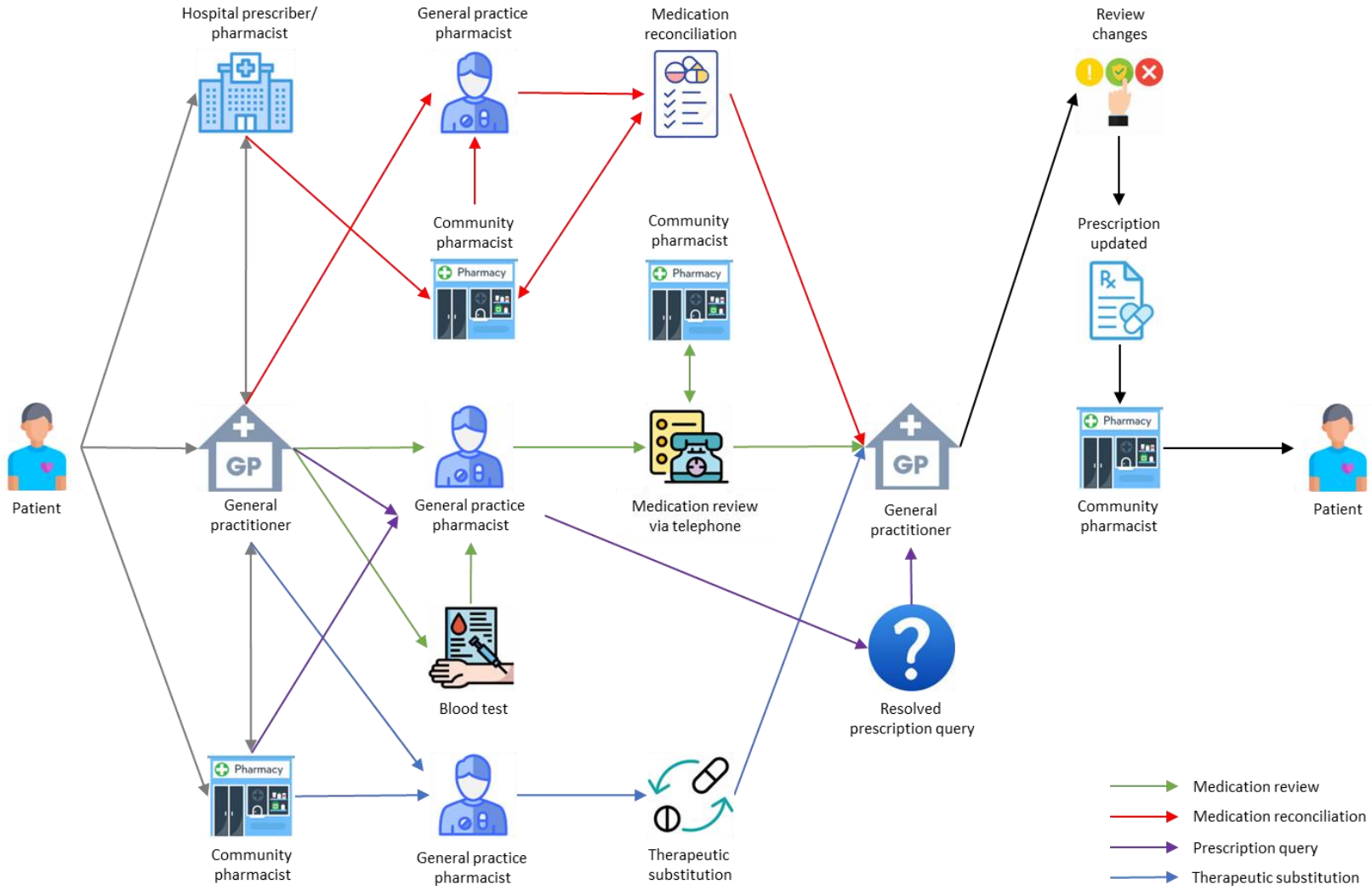

Figure 5.3. Mapping the patient journey in COMPASS

5.6.3.1. Summary of barriers

Table 5.3. Barriers to COMPASS using SEIPS 3.0 work system elements [544]

Patient-centred care	
Person	Lack of medication-related awareness and knowledge
	HCP perceived patient lack of interest in medication reviews
	Reluctance for medication changes
	Awareness of GP time constraints influencing consultations
	Lack of understanding of the GPP's role and availability
Task	Imbalance of information between patients and HCPs
	Onus on patient to raise queries in relation to their medicines
	Patients stopping medicines without informing their HCPs
	Complexity of review associated with multimorbidity and polypharmacy
Tools and technology	Lack of medication review resources for patients and HCPs alike
Organisation	Rigidity in medication review interval
	Areas of GP and CP expertise (GPs' pharmacological competence)
Environment	Challenges with shared decision-making
	Mixed opinions on a fee for service
Impact on healthcare	
Person	Challenges with patient health literacy
	Patient understanding of medication reviews
Task	Challenges with deprescribing, requires GP commitment
	GPP lacks access to GP suite applications and pharmacy suppliers
	Medication reconciliation is a time-consuming task
Tools and technology	Patients unable to self-elect for GPP review
	Lack of a GPP webpage on the general practice site to define GPP role and promote awareness
Outcomes	Other aspects of GPP role prioritised over medication reviews, *e.g.,* medication reconciliation and therapeutic substitution
Collaboration and communication	
Person	CP frustration with reliance to bridge communication gaps between the hospital and general practice

Tasks	CP challenges with contacting GPs
	Myriad medication review suggestions for GP to act on
	Lack of GP feedback on review recommendations acceptance
	Lack of GPP-CP communication on medication changes following review
	Prescribing discrepancies and miscommunication across levels of care (*i.e.,* secondary and primary care upon hospital discharge)
	GP responsible for hospital prescription transcription
Tools and technology	Lack of a central patient medication record
	Fallible paper-based system in hospital
Organisation	Complexity of care, many HCPs involved inter and intra levels of care
	Lack of effective interdisciplinary communication in primary care
	Lack of multidisciplinary practice in primary care
	Challenges associated with relationships/trust with locum GPs/CPs
	Challenges associated with hospital prescribers' experience and unfamiliarity with the patient
	GP reluctance to amend a colleagues' patients' medicines
Day-to-day practicalities	
Task	GP and CP time pressure impeding ability to perform thorough reviews
	GP and CP strenuous workload
	Absence of a formal medication review process in primary care
Tools and technology	Abundance of clinical information available to GPs but not CPs that lends itself to effective review
	Challenges with medication reviews via telephone for specific populations, *e.g.,* hearing impairment
Organisation	Uncertainty around full-time GPP requirement
Environment	Novelty of GPP role in Ireland, poor understanding
	Space to accommodate GPPs
	Advantages of co-location over remote working to enhance rapport between GPP and general practice team
	CP concern with GPP role given current pharmacist shortages
	Lack of funding for medication reviews and contractual concerns

Abbreviations: *CP* community pharmacist/pharmacy, *GP* general practitioner/practice, *GPP* general practice pharmacist, *HCP* healthcare professional

5.6.3.2. Summary of facilitators

Table 5.4. Facilitators of COMPASS using SEIPS 3.0 work system elements [544]

Patient-centred care	
Person	GP openness to sharing prescribing decisions with GPP
	Patient perspective to tailor medication review process
Task	Additional GPP roles, *e.g.,* formulary development and approval processes
	Reviews for specific populations, *e.g.,* CDM and nursing home patients
Tools and technology	Appropriateness of medication review via telephone in general
	Medication review resources for patients and HCPs alike
Organisation	Areas of GP and CP expertise (CPs' pharmacological competence)
	Define GPP role to improve stakeholders' understanding
Impact on healthcare	
Person	Patient empowerment through education
Task	Patients valued individualised medication reviews
	GPP supporting GPs with difficult conversations with patients
	Document recommendations from review on file for future reference
	GP commitment to deprescribing
	COMPASS creates manageable actionable tasks for GPs, prioritised recommendations
	Medication reconciliation at transitions of care to avoid medication-related harm
Tools and technology	GPP webpage to define role and promote awareness
	Allow patients to self-elect for GPP medication review
	Recent blood test results to inform the review
	Provide an updated medicines list with indications and cautions
Organisation	Prescribing paradigm shift in hospitals (*e.g.,* only note medication changes instead of repeating patient's full prescription)
	Identification of a responsible person in the hospital to contact in relation to transition of care review queries
Outcomes	COMPASS encourages evidence-based, safer prescribing
	Improved medication adherence and patient safety

	Creates a sense of support and reassurance for GPs, additional safety net when prescribing
	Reduced healthcare costs through COMPASS
Collaboration and communication	
Person	Patient-HCP professional relationship and trust
	Valued GP-CP relationship; improved safety and efficiency of practice
	Utilisation of appropriate GP and CP skillset to enhance patient care
	GPs valued pharmacists' pharmacological competence
	CPs attest to own knowledge in relation to medicines
	GPP-CP collegiality, mutual understanding, and experience
Tasks	Thoroughness of GPP review appreciated by GPs
	GPP familiarity with community pharmacy solutions, drug schemes and product availability
	Timely hospital discharge letters to both GPs and CPs
Tools and technology	HCP communication via Healthmail
	Linked prescribing databases (central patient medication record)
Organisation	Progressive culture of collaboration with GPPs in general practice
	Continuity of care, attending a regular GP and CP
	Effective multidisciplinary practice with clear lines of communication
	Independent GPP review, mitigate potential for tension from GPs correcting another's work
	GPP impartialness that can compensate for GPs own inclinations and background knowledge on patients
	Expanded roles and services boosts profile of general practice
	Hospital pharmacist review at discharge
Environment	Introduction of pharmacist-led therapeutic substitution and prescribing
	Demonstrates value of the pharmacy profession in primary care
Outcomes	Assisting management of multimorbid polypharmacy patients
	Improved GP workload and time available
	Improved interdisciplinary practice in primary care
Day-to-day practicalities	
Task	Medication review believed to be a fundamental role of the pharmacist

	Upskill technicians and physician assistants to alleviate pressures faced by GPs and CPs
Tools and technology	Medication review via telephone save on space for practice and costs for patients (*e.g.,* in terms of travel)
	GPP access to complete patient information on GP practice management software
Organisation	GPP availability and task turnaround in a part-time role valued
Environment	Expansion of GPP role in primary care, GPs would like to more reviews conducted
	GPP training/internships and GP mentors
	Remote working lends itself to enhanced suitability for smaller and more remote practices
	Funding/reimbursement to increase service capability for COMPASS

Abbreviations: *CDM* chronic disease management, *CDSS* clinical decision support system, *COMPASS* collaborative medicines optimisation service involving a general practice pharmacist, *CP* community pharmacist/pharmacy, *GP* general practitioner/practice, *GPP* general practice pharmacist, *HCP* healthcare professional

5.6.4. Patient-centred care

5.6.4.1. Person

Several CPs and GPs thought patients' health literacy relating to medicines, affecting the patient's ability to understand and use information to inform health-related decisions, was barrier to conducting effective medication reviews and sharing decision-making.

"It's not all that easy… a lot of people are elderly… it's very difficult to describe the tablets because a lot of them are just white… without kind of visual aid it's not all that easy." CP04

Most GPs and CPs perceived a lack of interest by patients in their own medicines (*e.g.,* poor understanding of pharmacotherapy indication) and healthcare decisions.

"You'd be surprised how many people that don't realise why they're taking a certain medication." CP01

Several CPs and GPs noted an inversely proportional relationship between patient awareness of their medications' indications and the number of medicines required to manage their condition(s).

"Trying to manage polypharmacy takes up a lot more time… communication sometimes can be a big issue as well… a lot of patients probably may not know what medications they are on or sometimes why they are on them… access to a pharmacist or somebody with expertise and knowledge in medications would be really useful in these situations." GP05

Most GPs and CPs felt patients demonstrate an underappreciation for medication reviews, impacting their tendency to incorporate such reviews in their approach to patient-centred care.

"Patients tend not to appreciate the value of medication reviews. They come in with their own issues and don't realise… that we need to focus on their medications as well as a separate issue. They just think you just hit a repeat button and go." GP03

"Patients lack appreciation of the importance of medicines optimisation… they see it as a waste of time… can I not just hit print and send it off?" GP04

Several stakeholders described negative attitudes of patients towards medication changes, specifically deprescribing medications. Interviewees explained patients often do not like change and felt that patients might be reluctant or have no incentive to stop medicines, particularly those that they had taken for a long time.

"It's much easier to start a medication than to stop it… resistance from patients as well to stopping." GP01

Satisfaction with the current medication regime and therefore reluctance to have anyone change it was common in the medication reviews as part of COMPASS. Consequently, patient-centred deprescribing can be difficult to achieve. Some patients reflected an awareness of GPs' time constraints and felt this impacted on their GPs approach to discussing their medicines in the necessary detail.

"I find going to the doctor, you realise you have only something like ten minutes… very aware I'm talking too long here… and somebody else is waiting for to get in… that you're delaying the doctor." P02

Unfamiliarity with the GPP role was common amongst patients and several CPs. This may lead to hesitancy in interacting with the GPP on the patient's behalf. Role definition was considered important to prevent confusion amongst patients, who may traditionally think the principal role of the pharmacist is to dispense medications.

"I find it [GPP medication review] easier now because I've spoken to you before. But the first time, I suppose I was taken aback a bit. I didn't know you were with the surgery." P04

However, patients noted this uncertainty was alleviated once context was given and the medication review commenced. Openness to the GPP following the initial review was reported. Patients also noted the benefits of medication reviews for other patients, particularly those prescribed polypharmacy and with poor understanding of their medicines.

"It would be good if other patients had access [to a GPP], I think it'd help a lot of people." P03

"Every doctor in there should make their patients aware of your availability. I think that's a fantastic idea… if someone like myself, who is on several different medicines, who has several

different problems, can actually coordinate his medicine, and feel comfortable that he's not gonna get into a mess… I think it's a huge valuable addition to the surgery." P01

One patient who receives prescriptions from several prescribers in both primary and secondary care was pleased to be offered an opportunity for an evaluation of their medicines together within the wider clinical context.

"It's basically double-checking, because there is so many people giving me prescriptions." P01

5.6.4.2. Task

One GP thought addressing the patient-HCP information imbalance by providing context and test results in advance of appointments and medication reviews is important to promote shared decision-making.

"It's [reviews and changes] a bit unequal or unbalanced because I have more information than they do… I try to give people information before the appointment… that can work better because they're prepared then." GP02

Some GPs and CPs felt that patients bear the responsibility of raising particular concerns in relation to their medicines, for example, ADRs and stopping medications.

"I probably won't keep asking about side effects… I kind of rely on patients… if they don't say I'm getting side effects from X, I'll just roll over the script." GP02

Such instances of patients experiencing ADRs and/or stopping medications may not be reported to the patient's GP or CP. Medication review as part of COMPASS provides an opportunity to promote transparency through the identification of these issues.

"If I feel I don't need to keep taking something, I don't take it… so they [GPs and CPs] kind of wonder what I'm at… I'd probably wait until my next review to inform the GP." P02

GPs cited challenges with medication reviews for older patients with multimorbidity and those prescribed polypharmacy, noting the importance of GPP assistance in this regard and in identifying specific populations to review.

"When you have an elderly patient with multiple comorbidities and you are trying to review ten or twelve medications it becomes much more complicated." GP05

Some CPs and GPs suggested additional GPP activities to improve patient care, *e.g.,* formulary development, approval processes (*e.g.,* phasing prescriptions, oral nutritional supplements, post-herpetic neuralgia therapy) and reviewing specific patient populations (*e.g.,* patients in nursing homes, patients receiving methotrexate and novel oral anticoagulants therapy).

"Practice prescribing would be really good… there are certain high-risk medications where pharmacists' views could be helpful, e.g., methotrexate and NOACs… a practice formulary could be a useful tool to try to harmonise people… the pharmacist would have a really good overview in terms of accessibility, price, and tolerability." GP03

GPs thought GPP involvement in CDM reviews was important given the structured nature of the appointments and the volume of information to be assessed in a timely manner.

"I think the model where a lot of the patients are people who we refer to you because they have particular issues and the CDM reviews work very well." GP03

5.6.4.3. Tools and technology

Patients attested to the method of performing medication reviews via telephone, saving not only on space in the practice, but also costs for the patient in terms of travel costs to the surgery.

"That [medication review via telephone] was ideal for me because, you know, it costs to travel… it's available to everybody so why not make use of it." P01

Patients with frailty or mobility issues also supported the medication reviews via telephone as part of COMPASS.

"That [medication review via telephone] is exactly what would benefit me because again mobility and I don't drive." P04

Development of medication review resources such as visual aids and flyers in the practice for was identified as an opportunity to improve understanding of COMPASS.

"If the resources were there for the consultation… I suppose its information gathering and that could be done anywhere… like the ICGP have a guide on haemochromatosis and how to interpret it and what to do with the results. So I think when something becomes commonplace then you kind of have a resource document." GP05

5.6.4.4. Organisation

Patients identified CP and GP areas of expertise, noting that CPs to have more medication-related knowledge than GPs.

"If I had a query about my medicines, I'd probably go to the pharmacist… I'd rely on his expertise, to check stuff for me. I wouldn't imagine the GP would be aware of everything I'm taking." P01

The current implementation of medication reviews in primary care may not reflect the needs of patients. Some patients disapproved of reviews at predetermined intervals and thought they should be available upon request.

"I think that I've been taking medication for so long that I have learned not to just take something without asking and finding out about it… it's like when I go to the doctor like I wouldn't be afraid to sort of ask about it [review of medicines]." P02

Whereas GPs and CPs correlated review frequency with patient complexity (review every two-three months and six-twelve months for complex and stable patients respectively).

"I suppose the more complex patients need more regular review, sometimes even more often than six months, you know, sometimes every three months… but maybe somebody very, very stable, I think sometimes a year can be fine". GP01

5.6.4.5. Environment

While the importance of shared decision-making in medication reviews was recognised by some HCPs, they noted it was challenging to incorporate in practice. Interaction with aforementioned factors under the person work system element such as patient motivation and health literacy impede the extent of incorporating shared decision-making in consultations.

"It's [shared decision-making] a tricky one… I try and negotiate with patients… for instance, I might be saying look, I'll try not to put you on a medication here, what can you give me? We'll see where we are… we haven't succeeded and met our targets and now we're on medication… if they had come in four months ago and I gave them a four-month script, I kind of know they're compliant… so in some ways, I've had that negotiation already, I probably won't even go into the issue of decision-making; I'll just repeat the script." GP02

Patients recognised the importance of medication reviews but were mixed in their opinion on out-of-pocket expenditure for the service. Placing this financial burden on patients requires consideration; with the preponderance of GMS patients and multimorbidity and polypharmacy, funding systems need to be established so that access to essential healthcare can be maximised for those with greater need.

"Well I would pay for it [medication reviews as part of COMPASS] … I would figure it would be like, I don't know, probably similar to a doctor's consultation… you're a professional as much as a doctor, you should be paid for it." P01

"It just depends how much it is… at the moment things are a bit tough… if it was available on medical cards, it would be fantastic, but it doesn't sound like it's going to be." P03

5.6.5. Impact on healthcare

5.6.5.1. Person

GPs felt COMPASS could help patients gain greater control and responsibility over their healthcare decisions and actions by improving their understanding of and compliance with their pharmacotherapy.

"Patient education… access to a practice pharmacist with expertise and knowledge in medications… the patient having a better understanding of their medications, the reasons for them, compliance, and how to use them properly… they can have a massive determinant on patient outcomes." GP05

GPs and CPs emphasised the importance of improved patient responsibility and organisation for their healthcare needs, which can be promoted through COMPASS. Some GPs cited that patients may contact their GP once they have run out of their medication to get an appointment, which affects the quality of the consultations they receive. Similarly, patients may wait until they have run out of medication before ordering their prescription in the pharmacy.

"The patients also can say "well I'm out of my tablets", you know. Well then you need to see someone soon. We're a bit too soft on patients. I was saying, well that's your job you know, you need to let us know and allow two or three weeks of a lead in time to get a standard appointment here. We end up then maybe just trying to do whatever's quickest to get the job done and that's not ideal." GP02

5.6.5.2. Task

Interviewed patients saw no reason to refuse a medication review themselves, regarding it as a good opportunity to clear any doubts, discuss medicines appropriateness, and provide reassurance and co-ordination of their healthcare. CPs and GPs also highlighted the importance of interventions like those provided within COMPASS.

"If someone like myself, who is on several different medicines… can actually coordinate his medicine, and feel comfortable… I think it's a huge valuable addition to the surgery." P01

"I suppose the more checks and balances that there are on the system the more well our patients become and the better looked after they feel." CP03

"The patients respond very positively to it… they are quite appreciative of someone taking the time to go through their medications, help understand things, and identify issues." GP05

GPs explained prioritising and documenting prescribing recommendations made by the GPP within COMPASS improved adoption of prescribing recommendations, particularly when gradual reduction prior to discontinuation is required and as patient receptivity to prescribing changes evolves with time.

"In an ideal world we would make changes overnight… some recommendations are very easy to integrate… others take a little bit of time or may not be appropriate right then, but I think it's always good to have them there [on file]." GP05

GPs highlighted the importance of medication reviews within COMPASS producing manageable, actionable tasks in a prioritised manner, so the process does not exacerbate an already demanding workload.

"I suppose it doesn't create any work for me as such, where sometimes people try and help and they nearly raise so many questions that you're like, oh I need to get the patient back in and go through all of this with them… you've not only made a suggestion, but you've taken it that step further to see, well is that realistic and is the patient going to do that… it definitely reduces my workload even if it generates the conversation." GP01

GPs recognised that GPP suggestions to change medications may need to be implemented over time; therefore, GP commitment to deprescribing and monitoring are crucial for adoption of GPP recommendations.

"The medicine reviews are very good… it's great to have a direction and a plan. You might do one change now and review it and then another change. So just it's great to have a kind of action plan." GP04

GPs felt supported by GPP in navigating difficult conversations with patients, *e.g.,* about stopping/tapering medications causing dependence.

"[The GPP] could be the one to put the compromise to them as easily as me… that you negotiate and say, "look if you can cut back on the codeine-based products maybe it'll improve your constipation"… those kind of trade-offs I think could be better discussed between a pharmacist and the patient." GP02

CPs and GPs emphasised the importance of medication reconciliation at the transition point to avoid medication-related harm whilst acknowledging this complicated task can be time consuming.

"Issues are exceptionally common… it does cause a lot of problems but having said that… it's the one occasion where we actually do go through someone's medication and look at it very thoroughly because you're generally thrown by what's come out of the hospital." CP04

5.6.5.3. Tools and technology

Patients and GPs thought a webpage providing information about COMPASS and the role of the GPP within this service could improve the service, especially if patients were able to request a review themselves.

"The [general practice] has its own website… it could be adding a webpage about the GPP with information for patients… patients that would like a review themselves could book in that manner that would take pressure off GPs you know feeling the need to refer." GP03

Some patients stated that their experience with COMPASS would have been improved if they had a better understanding of the process; prior communication with patients was considered helpful to avoid misconceptions and anxiety related to the withdrawal of medicines which could be achieved through the likes of the aforementioned webpage.

"A publicly accessible website would be a great idea, that's a fabulous idea, because it just allays people's fears… [people from the area] seem to be very suspicious and they like to be forewarned (laughs)." P01

Up-to-date blood tests results were considered important for generating recommendations in the medication reviews as part of COMPASS and to reduce GP workload, which are available for the CDM medication reviews.

"*It's [medication review] easier when you have the bloods to hand. So it's an efficient manner to go through it I suppose." GP05*

"During CDM, people are coming in as part of that to get their repeat prescription so, and you have their recent bloods to hand." GP01

Some GPs and CPs thought providing an updated list of medicines (with indications and associated cautions) was important to improve patient awareness and facilitate accurate transfer of information.

"An up-to-date list of medicines and cautions… so that patients know what they are doing and then we both have a record of what medications they are on, and patients are kind of more in the know." CP01

One GP recognised appropriate prescribing tools (*e.g.,* STOPP/START [519] and Beers' Criteria [520]) as too cumbersome to implement regularly, citing inclusion in CDS systems as an opportunity.

"I don't use them that much, but like the STOPP/START criteria and Beers' criteria… looking at medicines optimisation, particularly in older people. I know they're there but I actually, I don't really use them that often… it's not like streamlined, that's annoying." GP01

5.6.5.4. Organisation

GPs and CPs recommended changes to prescribing habits in secondary care to address the issue of omissions on discharge prescriptions necessitating communication with hospital prescribers to confirm intentions.

"The most difficult thing is the omissions - were the medicines meant to be stopped or was it just that they omitted to add it to a prescription? It's usually somebody that doesn't know the patient just transcribing that prescription out." GP04

An existing opportunity to reduce CPs and GP workload upon discharge is a simple box at the bottom of hospital prescriptions to note medication changes. At present, primary care HCPs cannot rely upon this box alone if hospital prescribers attempt to inaccurately repeat the patient's regular list of medications.

"More often than not you know there's the comment box where it should be mentioned if something is discontinued… a lot of the time that's not filled out and then you are kind of wondering was it just omitted accidently or was it intentional… definitely it adds time pressure and to the workload." CP06

One GP described that there isn't necessarily an onus on hospital prescribers to repeat the patients list of medicines.

"I mean they don't have to write down the full list… nobody ever told me or there was never kind of a precedent that you had to just regurgitate the list... it's such a mess, the discharge prescriptions." GP01

Additionally, identification of a responsible person in the hospital to contact directly in relation to hospital discharge concerns was identified as an opportunity to improve transition of care. The hospital pharmacist could play this role.

"Communication between hospital pharmacists and CPs might be a help." GP05

5.6.5.5. Outcomes

Shared decision-making with patients to agree to medication changes and set realistic goals in relation to deprescribing, and prioritisation of the recommendations sent to the GP by the GPP prior to implementation were identified as a facilitator to the medication reviews within COMPASS.

"I suppose it doesn't create any work for me as such… you've not only made a suggestion, but you've taken it that step further to see, well is that realistic and is the patient going to do that… it definitely reduces my workload even if it generates the conversation." GP01

However, GPs valued the GPP's prescribing recommendations as the reviews would likely enhance patient safety through the reduction of unnecessary polypharmacy and ADRs, leading to improvements in patient medication adherence.

"You can tell the amount of work that has gone into the review. It massively increases patient safety… it reduces the risk of errors in prescribing. And prescribing errors are such a big component of adverse outcomes in healthcare at the moment." GP05

"It's [medication review] not just good, it's necessary… I felt reassured about what I was or wasn't taking… and that everything is coordinated and in tune." P02

Some GPs were surprised by the amount of potential MRPs identified by the GPP. GPs said despite their best intentions and capabilities, they can make errors and having a GPP may help to encourage safer prescribing and reduce medication errors.

"You flagged a lot of potential interactions… it's been a real eye opener for me… I think how many scripts come across your desk in a typical week and how long it takes to sort them because it's quite a lot of work, and we do appreciate it." GP02

Furthermore, GPs indicated that the GPP was an invaluable source of information, ensuring that GPs were receiving evidence-based recommendations.

"I suppose we're just getting very like up-to-date evidenced based information into whether it's queries or review of medications." GP01

Some GPs found the GPP helped create a sense of support and reassurance when prescribing and provided an additional safety net, even if the review process did not generate any prescribing recommendations.

"It kind of gives me confidence that I've had a quick look at those, and I didn't think there was anything major so I'm glad that [the GPP] didn't find anything major as well... it's another safety thing that you can feel more reassured in your own practice." GP04

However, workload pressure and time constraints sometimes prevented GP referral for medication reviews, leading to prioritisation of therapeutic substitution, medicines reconciliation, and general queries.

"I find the medicines optimisation reviews great… I know I should probably be sending you more of them… you definitely take away and reduce the workload in terms of discharge summaries [medication reconciliation] and dealing with community pharmacies in terms of what's available stock wise or what's appropriate [therapeutic substitution and resolution of prescription queries], so I think it's really, really valuable." GP01

Some GPs and CPs thought about the potential for reduced patient and government spend on medications with COMPASS via reduction in unnecessary medications and more financially prudent prescribing.

"I think it [medication review] has reduced costs hugely in terms of the drug bill… medications that aren't needed… I think it's well worth the investment and time that it takes for the long-term effect that you get from it." GP03

5.6.6. Collaboration and communication

5.6.6.1. Person

Interviewees mentioned interpersonal and communication skills as important for establishing trust with patients and for managing relationships with others on primary care teams.

"I felt the first day like I spoke to you, you were very approachable, so I hope you stay there for a long time to come." P02

As shown in Figure 5.3, the patient journey throughout COMPASS is complex, with many different HCPs responsible for their care. Patients had confidence in their regular GP and CP and regarded the trusting relationship with them as a good basis for a successful patient care.

"I feel that he [the GP] is looking after me, like I'm important to him. I'm not just a number on a piece of paper … if you know somebody, that's so different … I suppose I'm lucky in that I have had a pharmacist and a doctor that I could always talk to." P02

"I go into the same pharmacy all the time and I know the pharmacist now … he's a lovely guy, … I pass everything through him … every prescription I get … he double-checks and triple-checks ,and he has corrected a couple of them so far." P01

Utilisation of appropriate GP and CP skillsets to enhance patient care was identified as an opportunity. One CP described the specific set of skills and expertise both professions have, but that patients will receive the most benefit when there is a convergence in primary care.

"I think when both professions play to their strengths it makes a massive difference for patients… when you've got the medicines expert and the diagnoses, physiology expert really playing together and working for the best outcome for a patient, they will get better care than when the sum of the parts are going into it." CP03

All interviewees attested to the pharmacological competence of pharmacists, citing previous experiences with CPs in which they demonstrated extensive knowledge on medications, including interactions, monitoring and costs.

"If a pharmacy ever rings me, 19 times out of 20 I've made a hash of something." GP02

"A pharmacist has a lot more knowledge regarding pharmacology and medicines than a doctor does. They spend a lot more time doing it." GP05

CPs self-identified as medicines experts and believed they have adequate clinical knowledge and skills to provide medication reviews or have the motivation to obtain the necessary skills.

"It's only a pharmacist really that can occupy that role [medication review]… because I think we [CPs] have spent so long dealing with the medicines and GPs spent so long dealing with the diagnoses, I think that we should play to our strengths... I think that's one of the really important roles of a pharmacist is to be that expert to provide the advice on the medicines… it'd be very difficult to sign anyone else up to do it." CP04

GPs felt their own knowledge was less extensive, relying on CPs in this regard to improve patient safety.

"The relationship with the pharmacy, in general it's very good because I rely on the pharmacist to cover my ass... very rarely the opposite happens that the pharmacy needs me to cover their ass because they gave the dose wrong. That's so uncommon. I actually find it a very sort of reassuring check." GP02

CPs expressed frustration with being relied upon to bridge communication gaps between the hospital and general practice. Some CPs would like the hospital to send the prescription electronically to the GP, while others would like the onus to be put on the patient to be responsible for their prescriptions.

"Then the other problem you get … is emailing on the hospital prescriptions [to the GP]. Like in general we wouldn't have, and we've kind of started now like emailing hospital scripts to the GPs … prior to that we hadn't been doing it because we put the onus on the patient to sort their own medicines." CP04

CPs recognised a sense of collegiality with the GPP, describing a feeling of mutual understanding and enhanced communication with the GPP.

"It's someone on the same level who gets what you're doing on a day-to-day basis, and you can talk to them in a way that they will sort of get and understand the struggle that we have of sourcing stuff." CP02

5.6.6.2. Task

Some CPs and GPs agreed that feedback on prescribing recommendations and meetings for critical reflection may improve COMPASS. The challenges faced by CPs in contacting GPs was noted by some.

"The relationship with GPs does vary, but generally quite good. Not that we have a bad relationship with any surgeries but just some can be hard to contact, or you know they can be less responsive than others because obviously they are under pressure as well." CP06

Confirmation of accepted recommendations could lead to greater involvement of CPs in the process, preventing confusion upon receipt of an updated prescription.

"I think with the busyness of the surgeries it might be that your approval comes back as a prescription." CP03

GPs appreciated the thoroughness of GPP reviews, referencing knowledge, time and workload barriers inhibiting their ability to perform a similar review in practice.

I think the optimisations are great, you just go through them in such detail… I don't think I would do as good a job as you do at the medicines review." GP01

Furthermore, GPs and CPs valued the GPP's familiarity with community pharmacy solutions, drug schemes and product availability.

"As a pharmacist you have the knowledge of product availability, that mightn't be readily available to the likes of the GP … I do think you're well placed there to do that." CP06

As patients move between healthcare providers and settings, discrepancies and miscommunication in clinical records are common. HCPs highlighted the primary-secondary care interface as an error prone area, where errors are likely to occur on discharge prescriptions. Patients with multimorbidity and polypharmacy are likely to have incomplete or incorrect medicines lists.

"I think confusion with hospital prescriptions is far too common and I think it's actually quite avoidable." CP03

“The complex hospital script… they wouldn’t bother putting at the bottom what’s added in, what’s changed, what’s reduced - it’s a real riot… they’re the ones I baulk at.” GP02

The challenges associated with medication reconciliation in primary care are compounded by the inaccessibility of prescribers in the hospital setting. CPs reported reviewing hospital discharge prescriptions under time pressure prior to dispensing; upon identification of an error, resolution is difficult to achieve as prescribers may be uncontactable.

“That’s one thing that we've spent so much time on … you ring the hospital, it takes you forever to actually get through to somebody, then they need to go looking for the answer… a lot of the time it's a really simple answer and it's the answer you expected, but you could spend like two or three days trying to get in contact with somebody and the patient is just waiting to be like told what's happening.” CP05

The duration of medications prescribed in the hospital was another source of confusion for GPs, stemming from poor communication from the hospital with both the patient and primary care prescriber.

“Sometimes something is prescribed in the hospital setting appropriately but then they might only see that specialist once or twice… sometimes it's not clear, is this lifelong - what's the kind of longer-term plan, you know, in ten years’ time, in twenty years’ time, when they're still coming to see us, should they still be on these.” GP01

5.6.6.3. Tools and technology

Several CPs alluded to instances of poor communication with general practice, with phone calls taking up considerable time.

“I know it's a function of the fact that there's so many patients and not enough doctors, but it's very, very difficult to contact a GP surgery by phone anymore and it really is only through email that you can do.” CP04

CPs and GPs singled out the handwritten and paper-based system in Irish hospitals as a source of error.

"So it's a really tricky … the handwriting also gets in the way … I can't read it. That's getting so unsafe too, you know. It's fraught with potential dangers." GP02

CPs and GPs cited Healthmail (the electronic prescribing system in Ireland; Healthmail was used by the CPs to communicate with the GPP within COMPASS) effectively improved communication inter- and intra-levels of care.

"I do think Healthmail definitely makes communication a good bit easier because before Healthmail it was all phone calls and you're waiting to get a call back… and it's just very time consuming." CP01

The use of electronic prescribing through Healthmail in secondary care would also alleviate the concern faced by CPs around sharing hospital prescriptions with patients' GPs.

"It's frightening to think that sometimes it is down to the pharmacist to send a copy of the script as a reference because they [GPs] are not in the know at all." CP01

Additionally, an electronic system would reduce the transcription burden and improve transparency of private patients' medications for GPs.

"If they're GMS, then I need to transfer every script and that's a bit of a pain in the ass … I'm not too sure why the GP is the best person doing that… it's quite tedious transcribing." GP02

CPs and GPs thought combining fragmented healthcare through a central patient medication record would enhance collaboration and communication by improving the transfer of information between and within settings.

"A summary care record is a massive barrier I think for having these interventions be meaningful in the community because even GPs can be left in the dark when secondary care is involved... ideally a full model of electronic prescriptions will come… uploaded to a central location and can be pulled to any pharmacy where the patient presents, and that record is available for the GP practice also." CP03

Although, CPs and GPs considered this an aspiration rather than a reality in the future of their practice.

"In theory I think it would be very useful but in practice, I don't know, we are probably a bit off that point yet … I would say we have more important things at the moment that could be done in Ireland in the healthcare system. It might not be the priority." CP06

5.6.6.4. Organisation

The strongest on-going interaction was between the GPP and the GP in the delivery of COMPASS (medication review, medication reconciliation, therapeutic substitution, and prescription queries) (Figure 5.4). Other relationships were not as strong; CPs do not refer patients for medication review and patients may not be directly involved in tasks relating to therapeutic substitution. Medication reconciliation referred to the GPP by GPs and CPs oftentimes involved GPP communication with secondary care without patient involvement.

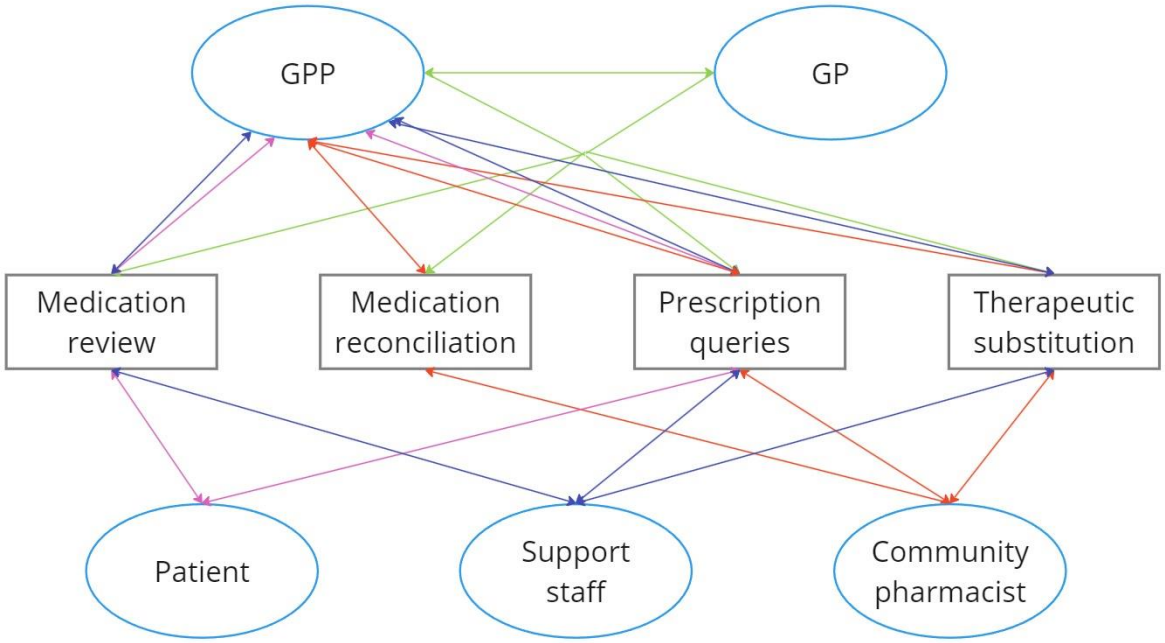

Figure 5.4. Diagrammatic representation of GPP interactions with stakeholders through tasks

Stakeholders are represented with ovals; tasks are represented with rectangles. GPP interactions are colour coded (GP: green, CP: red, patient: pink, support staff (general practice nurses, phlebotomists, physician assistants, administrators, practice manager): purple).

As mentioned, the patient journey in healthcare is complex. For patients, attending a regular CP and a regular GP was important for continuity of care.

"I feel that he [GP] is looking after me, like I'm important to him… if you know somebody, that's so different… I'm lucky in that I have had a pharmacist and a doctor that I could always talk to." P02

"I go into the same pharmacy all the time and I know the pharmacist now… he's a lovely guy… I pass everything through him." P01

However, inevitably another HCP (*e.g.,* a co-working or locum GP or CP) could be responsible for their care at some point generating concerns for all stakeholders.

"One doctor has said something or started something and then they go back to their regular GP maybe the next time and that will be stopped again… causes a bit of confusion." CP02

Some interviewees raised concerns about locum pharmacists in relation to developing relationships, familiarity with patients and trusting prescribing recommendations.

"We wouldn't really have a good relationship [locum pharmacist] because it is a different one every time we go… to be dealing with one pharmacist would be just fantastic" P03

"Relationships can be difficult for a pharmacist you mightn't know as well. Some patients see a lot of locums and that can be difficult for both the locum and for ourselves." GP03

While the importance of teamwork and trusting relationships was recognised, some interviewees acknowledged a lack of multidisciplinary practice in primary care.

"I personally think multidisciplinary practice is invaluable because of the different prisms by which you look at patients, prescriptions and solving problems… GPs have a very specific set of skills, and there are things that only GPs should do… there are things that only pharmacists can do and understand… and there are things that both professionals can share… we should play to our strengths, but that's not always the case in primary care." CP06

The incorporation of a GPP was considered an effective means of improving collaboration and communication in primary care but would require effective GPP teamwork skills and a progressive general practice culture for implementation.

"There's a bit of a gap between pharmacy into the GP, there doesn't seem to be a way to directly get in touch or to communicate directly. So I do think the likes of [GPPs] are ideally placed there to liaise back and forth." CP01

"Teamwork would be the valuable part of what you [GPP] would be involved in… it feels like there's somebody on our side… rather than just doing something and guessing oh, I think that will be okay, I might get the GPP to have a look at this… instead of doing a prescription of some sort and hoping it's okay." GP04

Some GPs reported hesitancy to review and alter the medications of a colleague's patient, citing barriers such as their understanding of the patient's treatment history and the potential for conflict by correcting someone else's work.

"A lot of us, we kind of shy away from making any big changes… say maybe you should see the doctor who knows you best before we're making this big of a change." GP04

It was noted that this reluctance to make changes to medications the GP did not prescribe themselves extends beyond primary care into secondary care.

"The GP is the last guy to sign off a script. But it may feature drugs from a cardiologist and a psychiatrist... I'm thinking where do I stop? Where can I cut? Because I don't control the psychiatry drugs... it's difficult, you end up sort of being aware of the risk." GP02

One GP thought independent GPP reviews would mitigate this potential for tension.

"It's hard to say to another colleague like, well what you prescribed there was incorrect… whereas if you kind of come along from a medicines optimisation view, it's a nicer way to do it." GP01

Furthermore, some GPs thought the impartialness of the GPP to compensate for their own inclinations and background knowledge on patients was important.

"People do have different knowledge basis… when you have been looking at the same person like for a long time you can't see the wood for the trees... whereas if you're looking at something fresh, you've no biases or anything towards that person… you'll always find

something that I haven't noticed, just like for a second pair of eyes or a more specialist pair of eyes." GP01

GPs thought expanded roles and services such as GPPs and COMPASS improves the profile of the practice encouraging retention of current patients and promoting attendance of new patients.

"We have a social prescriber, practice pharmacist, physician associate and hopefully a second on the way, you know all these things help definitely in selling a profile of the practice." GP02

GPs empathised with prescribers in the hospital setting, citing that they are usually inexperienced, unfamiliar with the patient, and reliant upon patients and primary care teams to provide the patient's current medicine list.

"In fairness they [hospital prescribers] must dread the scripts… you get this patient who's been discharged, and no one has done the discharge script and the guy is dragged up on call, he doesn't know the patient and he's asked to transcribe from the kardex." GP02

"I find that it's usually the most junior member of the team who does the discharge summary and the discharge prescription… there's loads of mistakes all the time. Now, we're not completely blame free - we have to make sure that the letters that we are sending to the hospital are an up to date, accurate list of medications. But often things are left off or they're put on and you're never sure, is it a mistake or is it on purpose." GP01

Some interviewed CPs and GPs reported that hospital pharmacists generally are not involved in medication reconciliation at hospital discharge. One GP cited that when present, their review of the patient's medicines is highly beneficial.

"I suppose some hospitals have ward-based pharmacists, which has been really helpful because they will reconcile the patients' medications with their pharmacy or their GP practice and highlight anything that was omitted or, you know, the doses which are incorrect, to the team on the ward and then the kardex can be changed appropriately." GP01

The established communication pathways between HCPs, and their failings, were underlined by interviewees as barriers. Delays in the transfer of information from secondary to primary care are common. GPs are reliant upon CPs to provide a copy of patients' discharge

prescriptions as the hospital can take several weeks to forward the information to the GP. Timely discharge letters and prescriptions to CPs and GPs was identified as an opportunity.

"I wasn't aware that the hospital doctors don't really liaise with the GP as quickly as they probably should." CP01

"When there's communication between secondary care and primary care it's not always the best… it's difficult sometimes to have a seamless transfer between secondary and primary care." GP05

5.6.6.5. Environment

Similar frustrations were voiced by GPs and CPs, recognising that pharmacists have the competence, knowledge, and experience to resolve therapeutic substitution queries themselves.

"If a drug is in short supply, in general the pharmacist will know what alternatives there are and will be well competent to prescribe it … I find some of that quite frustrating … they don't need to make a phone call." GP02

CPs described that although solutions to medicines shortages are relatively easy to obtain, this process is encumbered by legislatively necessary, although practically unnecessary, communication and time demands.

"I just email him and say look, there's a short, can I give this instead, and he says yes or no… it's so difficult to contact the surgery, there's no point in trying to ring them… and then if you email in, emails often get lost... it's not ideal situation at all." CP04

An opportunity to improve therapeutic substitution would be to enable pharmacists to substitute a prescription item and alert the GP to the change. Until such time that legislation facilitates this process, GPP-assisted therapeutic substitution was identified as an effective approach for both the CPs and GPs involved.

"It [GPP-assisted therapeutic substitution] made the last few months a lot easier… you need someone to relay information back otherwise it just doesn't get addressed and you're waiting

to hear back about certain queries and that could go on for weeks… once I send it to you, it just gets sorted." CP01

Some CPs thought GPs may feel threatened by the expansion of pharmacists' roles, especially regarding the ability to prescribe; however, GPs were more open to the suggestion than CPs anticipated.

"I think we just need to trust pharmacists to be able to make a lot of these decisions… a pharmacist has a lot more knowledge regarding pharmacology and medicines than a doctor does. They spend a lot more time doing it. I think I'd be quite happy to trust a pharmacist to make that decision… I think it just would make everyone's life a bit easier. And it would be a more efficient use of every healthcare professionals time." GP05

Several GPs and CPs believed that it would be very beneficial for the GPP to be a prescriber, further saving GP time by reducing workload duplication. Some GPs said their view on pharmacist prescribing was influenced by their experience with other nonmedical prescribers and believed appropriate training would be needed.

"I think there's definitely a role for pharmacist prescribing, like same way there is the role for a nurse prescribing… there's a training that's signed off, and they are trained in a specialised area." GP01

CPs thought it was important to demonstrate the value of the pharmacy profession and attested to the merits of expanded roles for pharmacists such as GPPs and pharmacist prescribing for patient safety and to alleviate pressures faced by general practice. However, concerns such as time available, lack of prescribing training, and access to more thorough clinical information were raised.

"I think it's very valuable for the profession to demonstrate the value that we can have in taking workload off the GP, because I think even taking a 10-minute period out of a GP's day can make a massive difference to their workload. If we do some of the clinical thinking for them and provide solutions rather than just ask questions, I think that's a much better way for pharmacists to work." CP03

Some CPs felt a role in general practice may improve their sense of job satisfaction, due to a reduction in dispensing duties and administrative tasks, and the desire for enhanced flexibility and utilisation of more clinical knowledge.

"It's obviously a generational thing now… looking at non-pharmacists, their roles seem to be a lot more flexible now, whereas pharmacies don't really offer that flexibility in working conditions and your working hours… it's not particularly attractive." CP04

5.6.6.6. Outcomes

GPs were supportive of the GPP role to improve their workload and time available through medication review, medication reconciliation, therapeutic substitution, and the resolution of prescription queries.

"They're very complex, serious reviews that took you a few hours to sort out… for me that would have been virtually impossible… what we're trying to do is trying to deliver the highest quality that we can within the constraints of what we work in, and I think that the practice pharmacist really helps with doing that." GP04

Furthermore, GPs said COMPASS helped to improve the management of patients with multimorbidity and prescribed polypharmacy. In these patients, medication reviews are more complex, compounding time and workload pressure in these consultations for GPs.

"One of the barriers to medicines optimisation is obviously the number of medications… it takes a lot of time to go through them and gets quite complex… [COMPASS] makes a significant impact I think in terms of being able to implement the changes… you bring a different perspective in terms of understanding what are the patient's concerns as well as the actual pharmacology and sides effects." GP03

The lack of effective interdisciplinary communication in primary care was identified as a barrier by CPs. The GPP's position to bridge communication gaps and improve understanding across primary care was valued by CPs and GPs.

"Obviously your work has a big impact as well in terms of acting as sort of a go between community pharmacy, someone who understands what the issues are on both sides. So that really has made a big difference both for us and for them." GP03

5.6.7. Day-to-day practicalities

5.6.7.1. Task

Although interviewed CPs and GPs recognised the value of medication reviews, implementation was considered impractical for GPs seeing 32 patients/day in ideally 12-minute consultations and CPs dispensing anywhere between 200-475 prescription items/day.

"We are all busy, so I think time constraints are always a matter… we only have so many hours in the day so certainly trying to manage polypharmacy takes up a lot more time than dealing with single one item prescriptions." GP05

"The fact you just don't have the time for it [medication reviews] really puts you off doing it at all, to be honest." CP04

Some GPs and CPs described the challenges posed by reviewing patients with multimorbidity and prescribed polypharmacy on top of an already strenuous workload.

"The length of conversations is getting longer and longer. The number of issues being raised is getting more complex… the number of diseases we're treating is getting more complex… pharmacology is getting more complex… there's a lot to squeeze into what is a 12-minute consult." GP02

"Polypharmacy is always going to be tricky. I suppose you have to engage your brain a little bit more and we are not trained pharmacists. I suppose you need to acknowledge that maybe you don't have a complete knowledge of everything." GP05

Challenges are also present for patients with regards to the management of multimorbidity in secondary care. One patient who attends specialists for different conditions in various hospitals described the complexity of this process.

"I have clots in me leg, I go to [X] for that. And then I have the heart problem, so [Y]'s dealing with that. And then I have the arthritis and [Z]'s is dealing with that… I could be in a hospital somewhere once a month." P01

Interviewees noted the importance of regular medication review; however, the types of review and the frequency at which they are conducted varies. With the exception of the CDM programme, a formal medication review process is absent in primary care.

"I suppose it would happen probably more informally throughout the day… it's more likely to happen I suppose in certain cohorts of patients… the CDM is probably the closest thing to a formal structure that we are operating at the moment." GP05

CPs and GPs generally conduct prescription reviews and medication reconciliation on a reactive basis, typically focussing on new or changed medicines, or patient-reported issues (such as inefficacy or side effects).

"There's nothing formal, as in we will do those activities [medication review] every now and again… I don't think at community pharmacy level in Ireland at the moment we have that proactive approach, like the medicines use review service in the UK is an opportunity." CP03

While their pharmacological competence lends itself to medication reviews, CPs indicated role reform would be required for systematic implementation in community pharmacies.

"I think CPs can make time for what they consider important. So they consider you know the piece work of dispensing and government income from GMS important." CP03

Taking into account GPs' and CPs' time and workload constraints that impacts their ability to conduct thorough medication reviews with patients in practice, a separate role such as the GPP conducting medication reviews as part of COMPASS was considered important.

"I'd be fairly confident that any practice pharmacist like you would be able to demonstrate the difference you've made to patients in terms of the amount of more hours you can put in front of a GP. Because they don't need to see a GP because you've taken the workload off… I would be really surprised if you can't demonstrate an awful lot of cost and certainly some time savings for GPs which is what they need." CP03

To alleviate existing pressures in primary care, the responsibility of pharmacy technicians and physician assistants could be enhanced. One CP referenced accuracy checking pharmacy technicians in the UK who are accredited to perform the final accuracy check of dispensed items clinically screened by the CP to spare pharmacist time.

"There has to be a pharmacist involved in the clinical and accuracy check. One of the most immediate things I think this country could do is… for accuracy checking by technicians rather than by pharmacists… would release a lot more time for pharmacists to be patient facing and offer more point of contact services that only pharmacists can do." CP03

5.6.7.2. Tools and technology

Within this structure of multidisciplinary practice, unclear lines of responsibility in relation to medicines reviews was a barrier elucidated by participants. While CPs identified as medicines experts, the abundance of clinical information available to GPs that is absent in community pharmacy lends itself to effective medication reviews.

"I think it's probably best to have the likes of yourselves [GPPs] to do the check with the prescriber… because we don't have the full picture at the end of the day, we don't know what the tests came back as." CP01

Interviewees attested to the method of performing medication reviews via telephone, saving on space in the practice and costs in terms of travel for the patient.

"The telephone review works quite well… it's always nice to be face-to-face but that involved a room and involves the patient coming in. It also means for patients, some of them are quite elderly or quite frail, not coming in can be an advantage… I think a lot of it can be done by telephone." GP02

Although, there may be issues depending on the auditory perception capability of the patient being reviewed as part of COMPASS.

"It might be a case of in-person has a role and benefit, if there's issues with communication say an elderly patient who maybe has difficulty hearing or communicating." GP05

5.6.7.3. Organisation

GPs and CPs were impressed with the GPP's availability and resolution of queries in a part-time role and cited the process of task referral to the GPP via the general practice software and Healthmail was suitable.

"I think we've been surprised by your availability… I mean it's happened a few times where I have reviewed a person in the morning session and before lunchtime, I'd be contacted by you with an alternative medication. I wouldn't expect that kind of turnaround." GP05

"To be honest the fact that you'd be taking all these queries, as in I can just send them to yourselves and you can sort them in the space of three or four days, I'm happy out. That's taking a massive load off my shoulders to be honest." CP01

GPs were unclear whether a full-time or part-time GPP role would be best. The former would enable more activities to be undertaken, promote greater awareness of the role, and enhance relationship development, while the latter may be necessary depending on workload.

"I suppose the only barrier to you is that you're not like 24/7… I know that you will get to review their medicines or queries but you're not online Monday to Friday all day… but I also don't know if you need a pharmacist available like, you know, nine to five. But let's say, logging on like once a session." GP01

The possibility of sharing GPPs between practices was suggested.

"I can just see a huge area in the future where somebody, like yourself [GPP], can be in Limerick and reviewing medicines for people in Gweedore, Bantry or Gorey for instance." GP02

5.6.7.4. Environment

Several stakeholders expressed desire for the Irish health service to become more like other countries' with pharmacists integrated into general practice teams and medicines reviews mandated and funded.

"I honestly didn't understand the role and how actually similar it would have been to what I would have come across in the UK working as practice-based pharmacist." CP03

Interviewees highlighted the novelty of GPPs in Ireland and valued defining the role to minimise unnecessary overlap and to enhance understanding and utilisation by all stakeholders.

"It's nice to have a pharmacist like you in that role for us CPs… but the problem is there's no pharmacists to have the role you perform rolled out countrywide." CP06

Interviewees found it acceptable that GPs should delegate parts of medicines optimisation to GPPs; however, CPs also highlighted their own limitations, proposing undergraduate internships in general practice, software training, designated GP mentors, and postgraduate education requirements.

"Even if it was available, and I could train to do it… I think it's something I would like to be able to do, but again it's a time barrier… even though I'm sure it'd be extremely beneficial to the whole health system." CP04

"I was attached to a GP practice, and we had access to the care records. We could see all the interventions that had happened with the patient and had really good overarching clinical governance in terms of patient plans and you could work within your sphere of competency… it was very clear where you had to hand over… I had GP mentors to help me prescribe." CP03

Within the practice, GPs would like to see more reviews conducted, but agree that it is a matter of manpower and workload that would require a targeted role. Defining the scope of practice of the GPP was identified as an opportunity.

"I think it would be encouraging that patients would automatically have a medication review by the pharmacist, but it's a case of manpower. It's a huge workload and can't be done by one person." GP05

"It would be good if other patients had access [to a GPP], I think it'd help a lot of people." P03

All CPs believed that these reviews should be part of the future of pharmacy, though fundamental changes to the existing pharmacy workforce in Ireland would be required.

"Whenever you've got medicines … I think you have to have a pharmacist flying the flag for either the profession or the patient or both … pharmacy should be at the table no matter where it is … I genuinely believe that the pharmacist is the expert … somebody has got to champion the patient and generally it will be whoever is at the point of supply." CP03

In general, space to accommodate GPPs was thought to be a key barrier to their integration but less so for GPs practising in a larger practice.

"We would be tight on rooms. If we were to employ a pharmacist I don't know where we'd put them… I think remote working is a much more scalable option that has ability to make impact… any practice, big or small, has the ability to undertake these sort of reviews." GP03

Several stakeholders thought that a GPP working remotely to provide COMPASS negated concerns such as space requirements, and lends itself to enhanced suitability for smaller and more remote practices.

"I think this general practice pharmacist thing could be replicated in lots and lots of other practices and you wouldn't need to be limited by location." GP01

Nevertheless, the GPP's physical presence on site was also considered important to enhance rapport, ensure accessibility, and enable a more diverse range of tasks be performed.

"I think a huge amount of it can be done virtually. I suppose when you are in a room with someone it's a bit easier to develop rapport and a relationship as opposed to onscreen." GP05

"There needs to be like some kind of collegiality in terms of the people that you would be making recommendations to. I personally would find it hard to build relationships solely remotely." CP03

GPs thought it would not be too difficult to integrate pharmacists into general practice given the movement towards multidisciplinary teams in primary care. However, one CP felt that the emergence of a new role for pharmacists would exacerbate existing pressures faced by the workforce with staff shortages.

"I imagine it [COMPASS] is a very good idea if there's enough pharmacists… the manpower crisis in pharmacies at the moment, it's just not something that is likely to be implemented… I can only see that as a pharmacist gone out of community pharmacy really, another blow." CP04

The opportunistic prescription review conducted by CPs associated with dispensing may not involve patients or reveal their concerns to the same extent as medication reviews as part of

COMPASS. The perception of whether there is a mandate for a new service was considered an important aspect of acceptance of a service.

"Medicines optimisation would be more important in the UK where they're contracted, you have to demonstrate that you do it whereas I think it's an expectation that you do it in Ireland and isn't necessarily reflected in any kind of contract." CP03

Medication reviews as part of COMPASS were not seen as a priority in community pharmacy, but more of an 'in an ideal world' matter. CPs explained that for services such as medication reviews to be viable in their practice and widely established, funding and contractual concerns would need to be addressed.

"It's great that it's [medication review] being looked at but I wouldn't be overly hopeful that this particular aspect is… something that we would be paid for. But I wouldn't know any pharmacist that doesn't do it as part of their practice." CP04

One GP was cognisant of this need for the evolution of the pharmacy workforce and funding to increase service capability, enabling pharmacists to conduct medicines optimisation in their practice in the interest of patient-centred care.

"In the last couple of years with vaccination and COVID especially, I think it's shown that pharmacists are very valuable and are ready to evolve roles… if a separate role for a clinical pharmacist conducting reviews was part of the contract, and the pharmacists were paid in the community for doing that, I think that would be quite beneficial … if that was rolled out nationally, I think it has potential for a huge improvement in patient outcomes and patient care." GP05

5.6.8. Incorporating pharmacogenomic testing into COMPASS

5.6.8.1. Person

Regarding pharmacogenomic testing, interviewees demonstrated poor awareness and understanding. Some patients expressed anxiety, fear and worry toward pharmacogenomic testing that may yield addition disease risk information.

"Well the genetics thing is, again I'm probably a bloody boomer attitude, you know, what you don't know, sometimes you're better off not knowing." P01

"That's something that'll take people quite a while to get used to… I don't think many people in the beginning would avail of it." P02

Interviewees were unfamiliar with the different types of pharmacogenomic test and their implications for patients. Nevertheless, there was a professional interest and general curiosity in pharmacogenomics.

"I love a break from the whole checking off scripts, so I love these services that come in… it's all about expanding the role and making use of pharmacists… I'd be happy to say that it would be a benefit to the role and probably would improve job satisfaction." CP01

Some patients believed pharmacogenomic testing would yield helpful information as part of COMPASS, not only giving them peace of mind in relation to their pharmacotherapy, but also for their children regarding disease risk information.

"I'd be up for it anyway, I think it's a great idea… a step forward like that in medicine is a good thing… this testing can only make it safer and, you know, at the end of the day that's what it's all about… I would use the test in a sense to basically warn the next generation." P01

An identified opportunity for pharmacogenomic testing was patients with a suspected personal history, for example, a history of unexplained side effects or ineffective therapy that could be due to genetic factors.

"It would be fantastic. We certainly have situations where you're surprised if a patient is getting side effects with a medication, then with other patients they're usually very well

tolerated… or people not responding to medication that other people would have responded to… if it leads to more targeted prescribing it would be very good." GP04

Some CPs and GPs expressed interest in a pharmacogenomics service, although they lacked confidence in their expertise at present to incorporate it as part of their practice.

"It is very novel, and I think it might sometimes solve a few head scratching problems… when we can't understand why something isn't working the way you expect… instead of it being kind of idiopathic and writing it off, we might have access now to understand why that particular combination isn't working and what might work better… it's exciting and appropriate, but I wouldn't have a lot of expertise in it." CP03

It was noted by some GPs and CPs that the value of testing will differ greatly across subsets of the population they cover, considering income and health-consciousness factors that would influence patient willingness-to-pay for pharmacogenomic testing.

"I think at €300 perhaps it would be a barrier. I think there is a cohort there that it would appeal to, people who are very proactive about their health, and have the income and resources to afford it." GP05

5.6.8.2. Task

Several interviewees were interested in pharmacogenomic testing to optimise pharmacotherapy and its potential for enhanced patient trust in medical therapies. GPs also considered the potential for medical intervention and monitoring with pharmacogenomic testing important.

"You always treat the patient in front of you and each patient is going to have a specific genetic makeup… it makes sense for the experts in medicine to be expert in what works best for a set of gene patterns… if we can optimise medicine and we can understand how to do it in a better way by doing a genomic profile then we should do." CP03

"Knowing if the medication is going to work or that you may need a higher or lower strength would make patients a lot more comfortable long term." GP05

While CPs and GPs appreciated the potential benefits of pharmacogenomic-informed prescribing and dispensing, barriers such as time and workload pressures, inadequate training, and funding and contractual concerns may prohibit the notion of pharmacogenomics becoming part of their practice.

"I think it makes a lot of sense. Am I looking forward to another layer of complexity, maybe not, but I'm not against it in principle… I suppose I am conscious we have a lot of different things going into the mix particularly as the patient gets a bit older… so how that [pharmacogenomic testing] comes in, the way it's displayed, the way you're informed, and at what point in your decision making it comes in, that would need to be good. " GP02

While interviewed CPs and GPs admitted their understanding of pharmacogenomics was poor, they sought appropriate demonstration of evidence (clinical benefit and cost-effectiveness) for the use of pharmacogenomics in patient care. Some interviewees thought that once the benefits are apparent, pharmacogenomics would be easier to implement.

"I think there's two factors. One is trying to figure out how it will fit in to practice. There's a lot of data coming in already so people could be turned off... people will need to see a benefit to it, you need to have clear indications for it and where it'll fit in. I think then secondly people will need education… what is the benefit, where is it useful, and where it can add value… it's about clinical impact is what it will all come down to." GP03

Additionally, one GP described challenges with HCPs being unprepared at present to address patient queries in relation to pharmacogenomics that may arise in their practice as a result of DTC testing.

"I had a woman come in, she had some sort of genetic sequencing done and came in and said, I have such and such a gene… I was like, okay, that means nothing to me, and she said, it's means I'm higher risk for melanoma, renal cell carcinoma and something else… I didn't know what else to do with that information and I don't think the consultants did either." GP01

5.6.8.3. Tools and technology

Furthermore, some CPs and GPs considered the need for appropriate CDS systems and centralised prescribing systems to facilitate the integration of pharmacogenomics into their practice as the patient medication record is currently unprepared.

"Pharmacogenomic testing naturally could come after the implementation of something like a centralised medical record. It would then be very useful, if everything else was already built up." CP06

Interviewees thought that flexible methods to obtain samples for pharmacogenomic testing was important, with a preference demonstrated for the least invasive method providing equivalent accuracy.

"I'd say mouth swab or saliva… because the blood, for me, I've more holes than a colander… they're constantly taking bloods. I think if it was just a mouth swab, like I'd be all up for that, it's not intrusive." P01

One GP said that ultimately a pharmacogenomic testing service should be provided in the setting that best suits the patient and has the appropriate infrastructure to store genetic data.

"I suppose it's whatever environment where a patient feels safe and trusts… I think it can absolutely be done in community pharmacy. Provided the resources for storing any kind of clinical material and personal information is secure and is trusted. It could happen in GP practice… so where's best to do it? I'm not sure." GP05

5.6.8.4. Organisation

HCPs felt the need for pharmacogenomics education and training to enhance their knowledge and level of comfort with this novel aspect of patient care. For example, education could be provided in the form of postgraduate programmes or continuous professional development courses.

"I think both CPs and GPs would require training. It's something that pharmacists probably have more knowledge of, but obviously if something like this was to be rolled out, I certainly would need more training on it." CP06

"If I had an opportunity to do a pharmacogenomics course, I'd be more than interested… I don't think I'd be particularly comfortable at going through a genomic report. I just don't think I have the knowledge or expertise to deal with that at the moment." GP05

Interviewee-reported methods for patient education were less transparent; one GP explained that through HCP training in pharmacogenomics, CPs and GPs could educate their patients.

"It's complex enough and I think if the doctor doesn't understand it, the patient definitely won't understand it and if you're gonna be providing that service, then you need to be able to answer all the follow-up questions and know how to interpret their results." GP01

HCP motivation to provide pharmacogenomic services varied. As a result, CPs and GPs identified unclear lines of responsibility in relation to service provider and setting for the implementation of pharmacogenomic testing.

"I'd be happy to say that community pharmacies are ideally placed [to provide pharmacogenomic testing]… it probably would make sense for it to be in maybe a pharmacy setting as opposed to a GP given that they are so out the door dealing with patients." CP01

"It sounds to me kind of like it's something that would start in general practice… and maybe would trickle down to us." CP05

Owing to the barriers previously mentioned, some interviewees considered a separate role, such as the GPP, may be best suited to facilitate pharmacogenomic service provision in primary care.

"If it was the case that they send the results to us, we interpret them, we recommend a dose and then it goes back, that obviously would take like a lot more time for us… you wouldn't manage that somewhere that has one pharmacist… that would be a whole other person's job." CP05

"I think it would be best they're part of the system… I don't think it should be a separate sort of a system… that test then might be interpreted by a practice pharmacist like yourself and we are given a report which will guide us as to what might be the most appropriate approach." GP03

5.6.8.5. Environment

Regarding the cost associated with pharmacogenomic testing, some patients related this expense to other healthcare expenditures that constitute part of their care.

"I'm used to paying for everything… if I need it [pharmacogenomic testing] and if it's going to do good, like why wouldn't I pay for it." P02

"There used to be a food intolerance test, and it wasn't even that accurate… people were happy to pay minimum €120 and it could range all the way up to €360… I think the likes of this type of testing service [pharmacogenomic testing] is definitely more beneficial for a lot more people." CP01

One GP considered it important to keep up to date with advances such as pharmacogenomic testing and to review international practices and react accordingly nationally.

"It is certainly the better way to be looking at things… the likes of the UK and America, they always seem to be that little bit more ahead and it probably has been shown that its more beneficial to go down the road like that [implementing pharmacogenomic testing]… just to get the full picture and tailor it towards the person themselves." GP01

Some interviewees thought other healthcare issues should be prioritised over the implementation of pharmacogenomics, for instance, raising the basic level of prescribing in Ireland, adequate staffing in pharmacies and general practices, and a centralised prescribing system.

"My hesitation is that I think it's [pharmacogenomic testing] very like the thin edge of the wedge kind of stuff… there are GP practices out there that are just in terrible states… I think there might be more bang for their buck in general to try and bring up the basic level of prescribing in Ireland rather than trying to do like something very fancy." GP01

"In theory I think it would be very useful but in practice, I don't know, we are probably a bit off that point yet… I would say we have more important things at the moment that could be done in Ireland in the healthcare system. It might not be the priority." CP06

Interviewees desired pharmacogenomic test cost coverage, through public funding or insurance reimbursement, but were unsure how realistic this notion may be.

"If it was available on medical cards, it would be fantastic, but it doesn't sound like it's going to be." P03

"On the flip side, if you are able to show there's a cost saving to introduce something like this… it's something that could potentially be funded publicly through the HSE to improve or reduce demand on the health system." GP05

While interviewees valued the potential benefits of pharmacogenomic testing, there was a desire for legislative safeguards, particularly in relation to patient data, prior to its implementation. To address these concerns, an appropriate regulatory framework for ethical conduct of pharmacogenomic testing, informed patient consent, and strong data protection was advocated for.

"Once your genetic information is there, it's there, and it's there for a long time and there's no guarantee of rules and regulations around the control of it like won't change and you've no idea who would be allowed to get access to it in the future." CP04

This regulatory framework and patient education may assist alleviating concerns in relation to employer, insurer, and mortgage provider disclosure of pharmacogenomic test results.

"Concerns around employer, insurance, and mortgage provider discrimination… it's one of those things that's quite easy for people to latch onto and to go to the extreme version of it… I think you would need a strong educational campaign for the public so that there isn't any fear to have it done." GP05

Additionally, one CP recognised the potential for cost-savings through reductions in ADRs and ineffective therapy by assessing a patient's genotype using pharmacogenomic testing as part of COMPASS.

"I think in the long run that's gonna save people time and money, that you're taking something that is actually suitable for you and at the right doses… you can see like if somebody is gonna get adverse effects or anything like that, you can probably minimise those kind of things." CP05

5.6.9. COMPASS process map

The findings from the above sections were synthesised to create COMPASS process map. The process for patients, GPPs, GPs and CPs in their respective work systems are described pre-, mid-, and post-COMPASS in Figure 5.5, Figure 5.6, and Figure 5.7 respectively. The process map can be used to explain COMPASS while simultaneously depicting problems or patterns that need to be addressed for implementation, thus enabling identification of specific areas for improvement. The groundwork of the map projects the flow of processes within COMPASS, tasks of the care team (patient, CP, GP, GPP), and interactions that were reported from the interview data to act as barriers or facilitators to the process (barriers are shown in red whilst facilitators are shown in green). Barriers and facilitators were linked to the SEIPS work system elements (*P* person, *Ta* task, *TT* tools and technology, *O* organisation, *E* environment, and *Ou* outcomes).

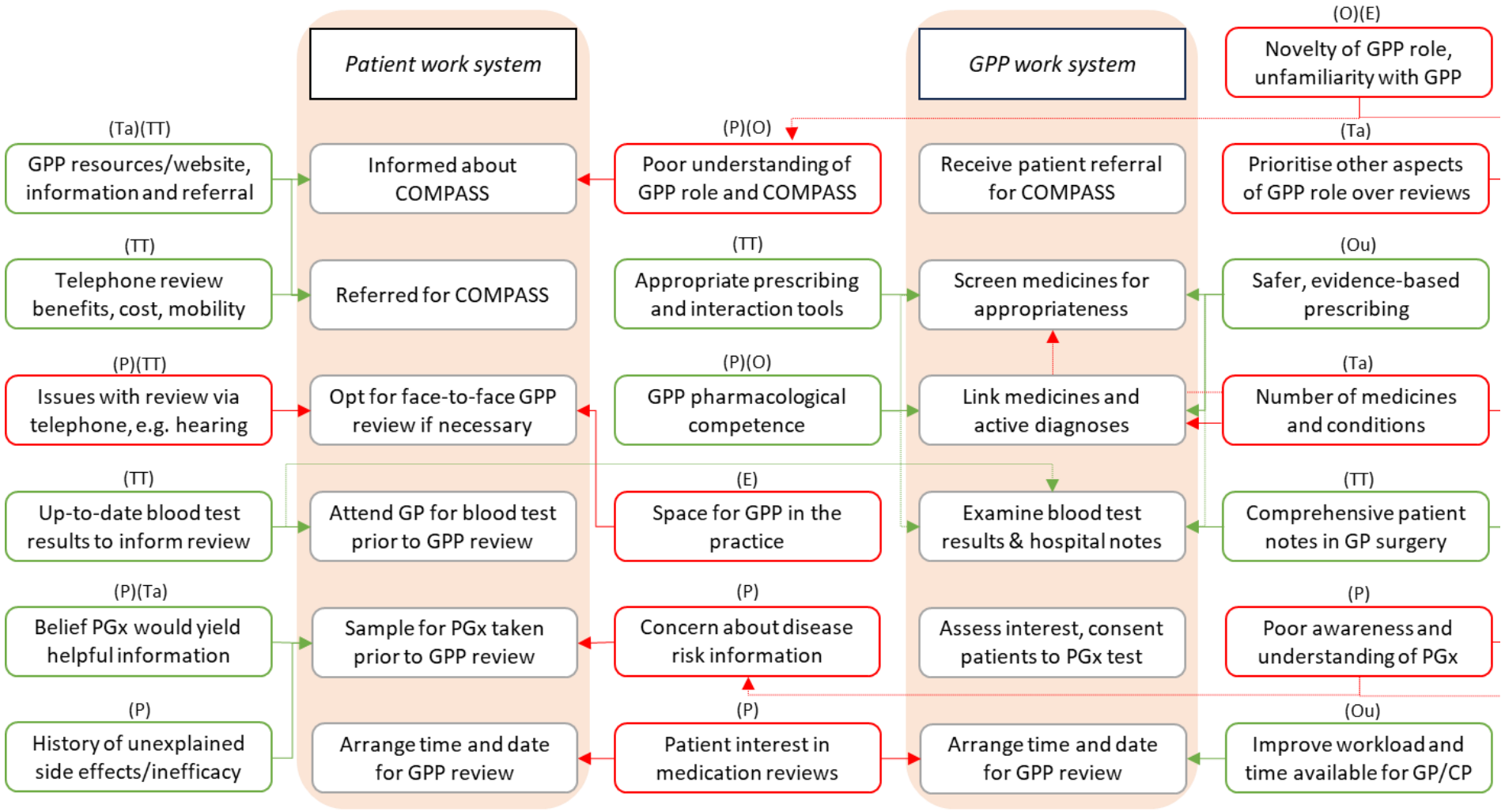

Figure 5.5. Pre-COMPASS process map describing the steps taken in each work system and their associated barriers and facilitators

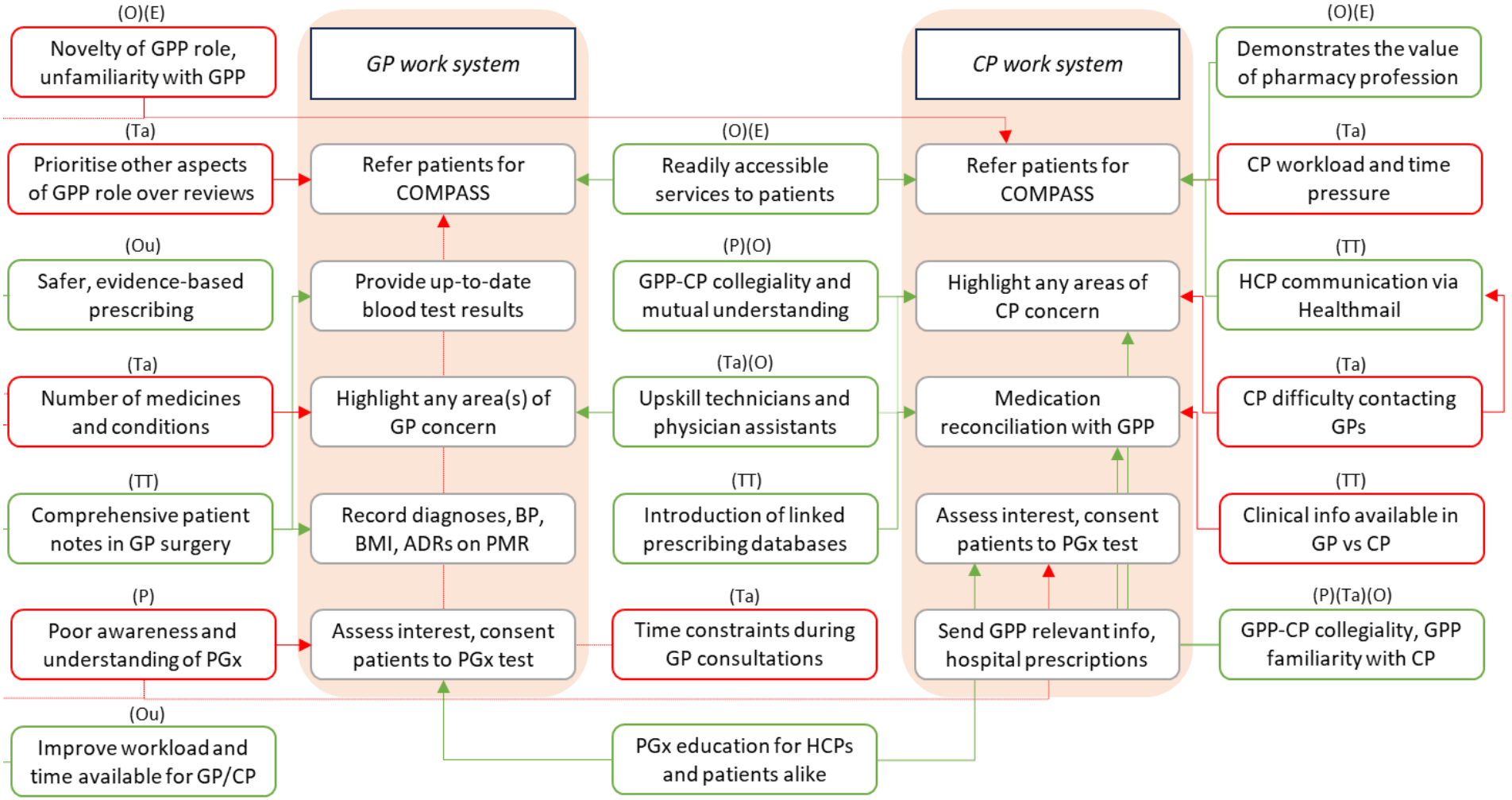

Figure 5.5 (cont'd). Pre-COMPASS process map describing the steps taken in each work system and their associated barriers and facilitators

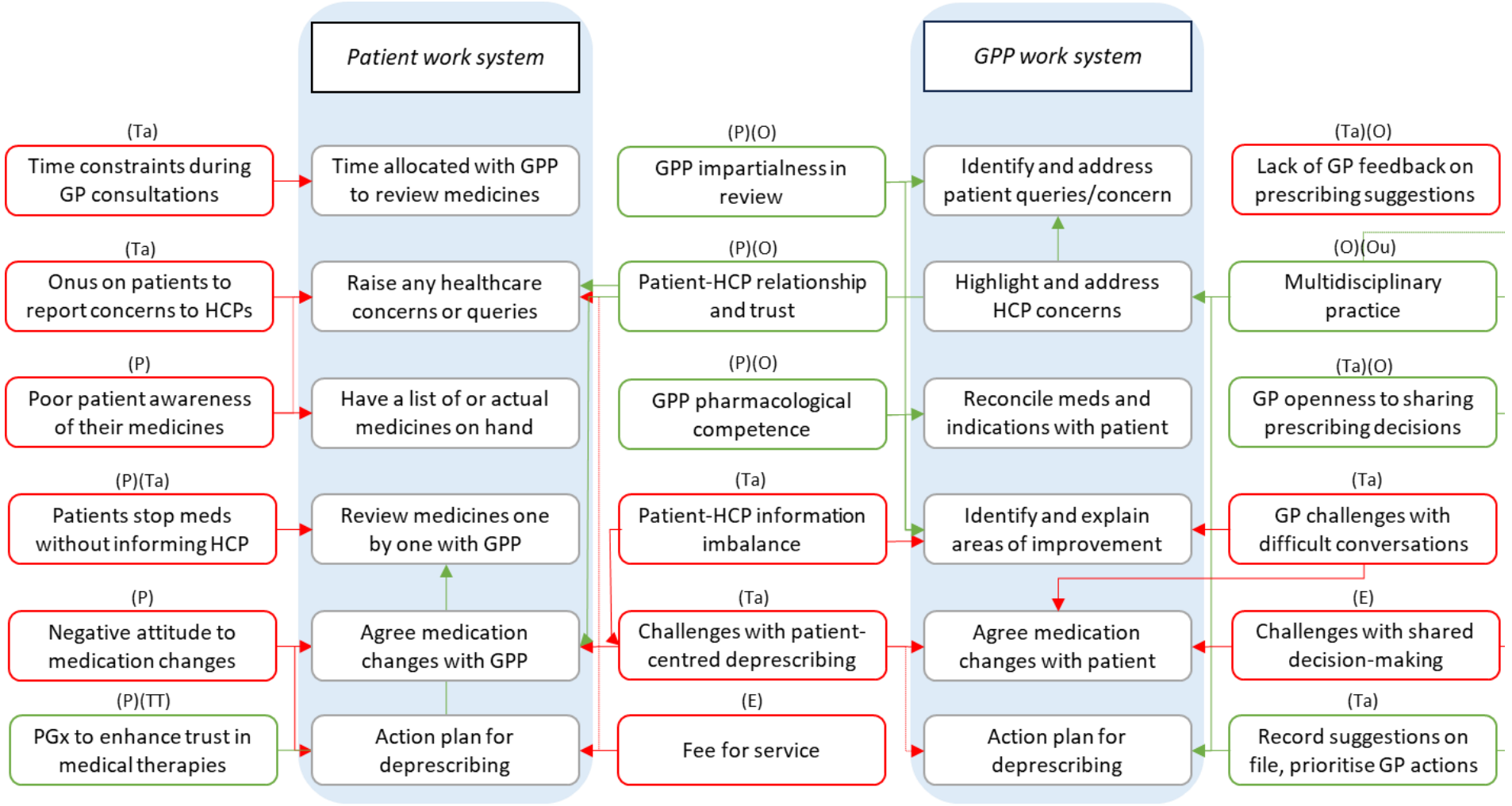

Figure 5.6. Mid-COMPASS process map describing the steps taken in each work system and their associated barriers and facilitators

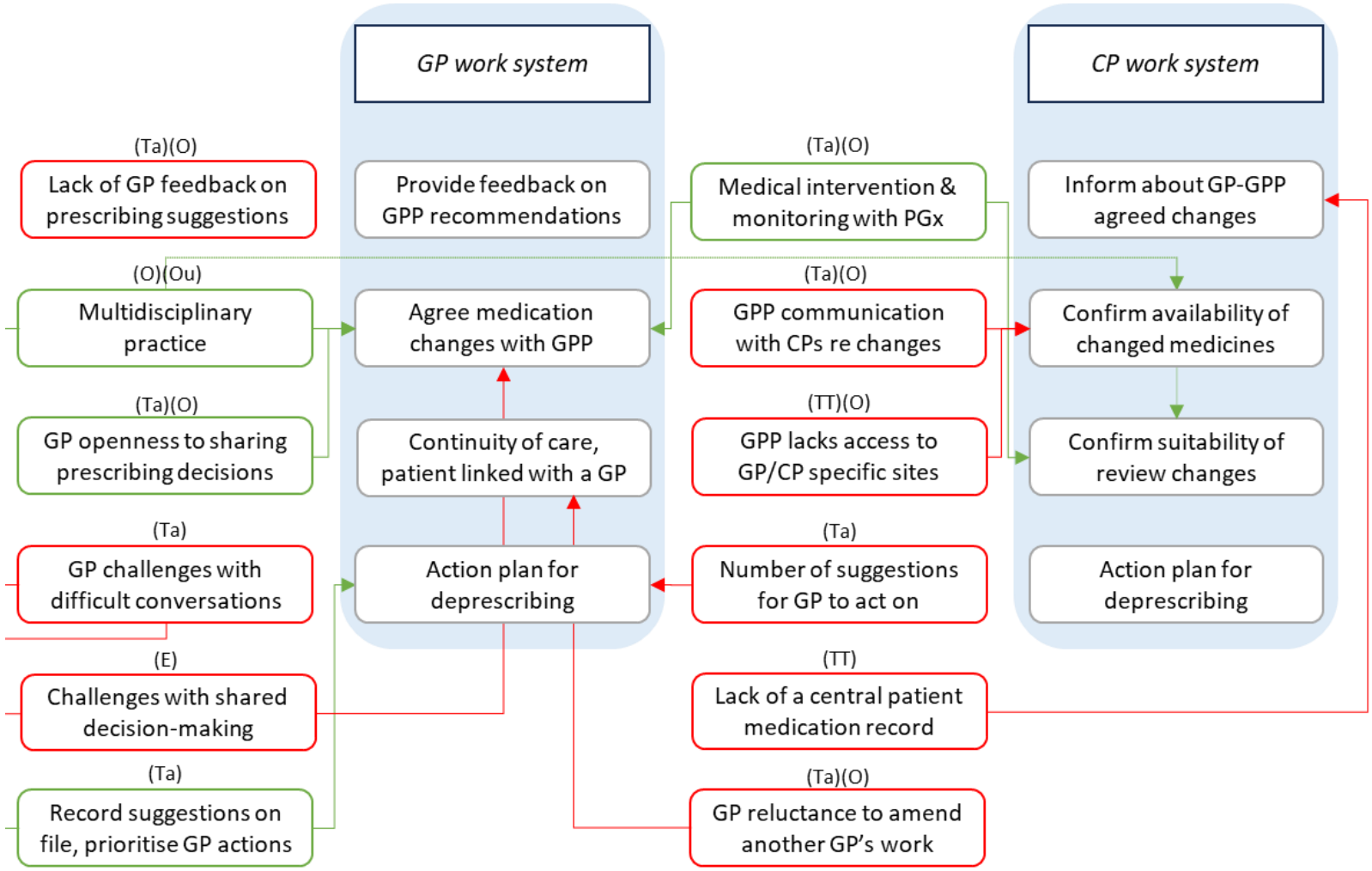

Figure 5.6 (cont'd). Mid-COMPASS process map describing the steps taken in each work system and their associated barriers and facilitators

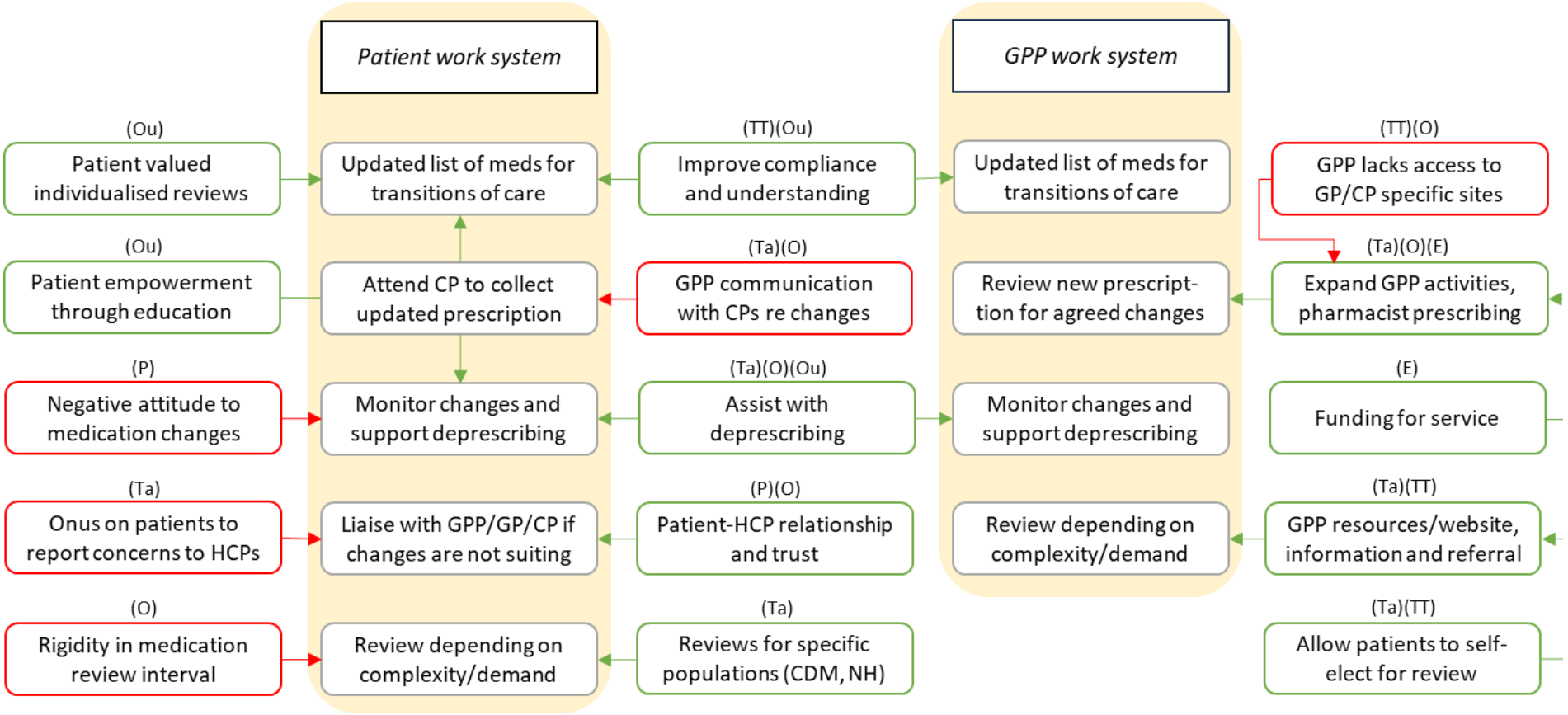

Figure 5.7. Post-COMPASS process map describing the steps taken in each work system and their associated barriers and facilitators

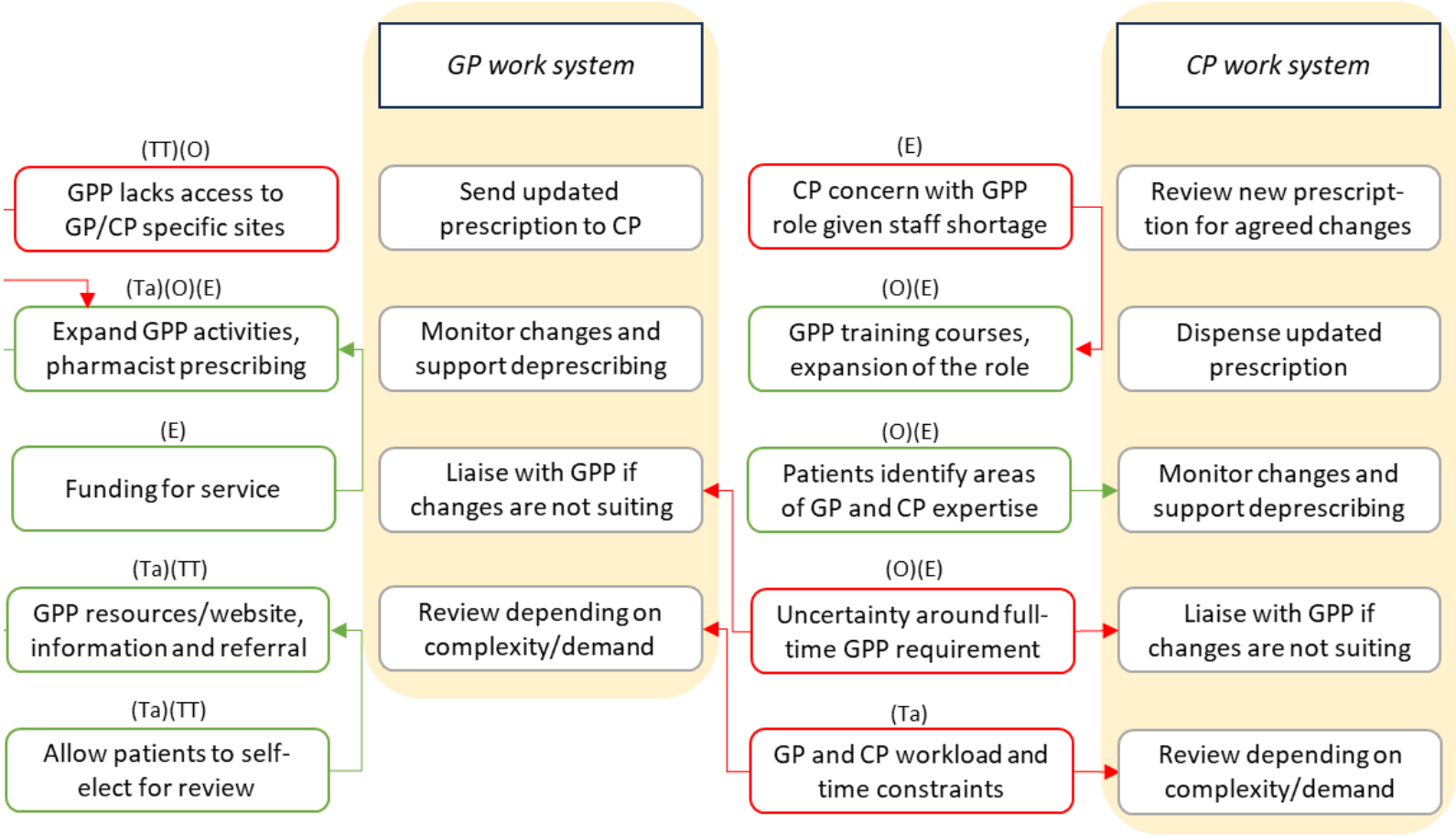

Figure 5.7 (cont'd). Post-COMPASS process map describing the steps taken in each work system and their associated barriers and facilitators

5.7. Discussion

This novel qualitative interview study is the first to focus on determining stakeholders' (GPs, CPs, and patients) perceptions towards pharmacists working in general practice to provide a telepharmacy collaborative medicines optimisation service (COMPASS) in Irish primary care. The service entailed a blend of activities with and without direct patient contact. Using the SEIPS model, barriers and enablers to COMPASS and considerations around the incorporation of pharmacogenomic testing into COMPASS were identified. Stakeholders interviewed were broadly optimistic about pharmacists working in general practice, collaborating to deliver patient-centred care to improve outcomes for patients and HCPs alike. The feasibility of a GPP working remotely and aspects that required further attention to ensure better and continuing integration of remote GPPs into general practice were elucidated, considering day-to-day practicalities. To enhance the service provided, process maps were produced.

Furthermore, the experience of stakeholders in primary care upon discharge of patients from secondary care was described. Overall, GPs and CPs generally expressed frustrations with the poor existing communication pathways, a fallible paper-based system, and the task of reconciling and transcribing hospital discharge prescriptions. Additionally, perceptions on the implementation of pharmacogenomic testing was also assessed. Interviewees raised several concerns about the implementation of pharmacogenomics, including but not limited to HCP and patient education, data protection and thorough consent process, CDS systems, and the cost of testing.

In relation to therapeutic substitution, there was agreement that pharmacists should be permitted to deal with shortages of medicines. To this end, the Health (Miscellaneous Provisions) Bill 2024 to amend the Health Act 1970 and the Irish Medicines Board Act 1995 is currently before the Dáil Éireann [551]. Part of this amendment concerns management of medicines shortages via the introduction of therapeutic substitution protocols and related actions that will help to mitigate the impact of medicines shortages. Therapeutic substitution protocols would allow pharmacists to supply a specified therapeutic alternative medicinal product in limited circumstances where there is a shortage of a medicine in strict compliance with approved protocols specific to a known or anticipated shortage [551]. This amendment

will utilise the expertise of pharmacists and enable them to be agile in responding to medicines shortages, enhancing the therapeutic substitution component of the service.

5.7.1. Comparison with existing literature

This study's findings share broad similarities with the existing literature regarding the barriers and facilitators to integrating pharmacists into general practice [125, 534, 536, 552-555]. In contrast to a studies in Australia and England which revealed tensions between CPs and GPPs stemming from professional hierarchy and competing, business-related interests [555, 556], this study demonstrated good relationships and mutual support between the HCPs. The importance of strong relationships has been identified as a key component to GPPs working in primary care [557]. A central strength of this study was the universal feedback of teamwork and strong relationships between the GPs and pharmacists. Participants reported that the interdisciplinary environment of the general practice enabled enhanced collaboration and communication compared to traditional pharmacy services, as reported elsewhere [558].

Given the novelty of GPPs in Ireland, participants feared that patients would not understand the difference between GPPs and CPs, which is consistent with other studies [126, 536, 559, 560]. Our findings indicated that patients were unaware of the pharmacist's presence in the general practice and unclear how to contact the GPP. When they did interact with the GPP, patients highly appreciated the quality of care they received. Previous research in the UK has also reported unawareness due to the absence of relevant communication from practices, including patients not realising they had a consultation with a GPP, and confusion between community and general practice-based pharmacists' roles [493, 561]. A lack of well-defined roles has been identified as an obstacle to patient awareness, demand, and uptake of pharmacist services in general practice and community settings [125, 557, 562]. The need to inform the wider public about the GPP's existence, what services they provide and how to access them was elucidated. Moreover, the need to properly inform stakeholders about the roles and responsibilities of GPP was emphasised.

A key finding of this study was that CPs and GPs recognised the importance of patient-centred, collaborative medication reviews to improve patient outcomes by addressing non-adherence and inappropriate prescribing [563-565]. However, due to high workload pressures and time constraints, most medication reviews undertaken by CPs and GPs in practice are hastily conducted and entail little to no patient involvement [566]. Thus, the time available for GPPs to conduct medication reviews as part of their role was invaluable. Furthermore, treating the multimorbidity of an increasingly ageing population inevitably involves more complex prescribing and associated review and follow-up [125]; hindered by the fragmentation of healthcare across the primary–secondary care interface, challenges in delivering patient-centred care, barriers to shared decision-making, and the inadequacy of guidelines and evidence-based medicine [567, 568]. Hence, it is unsurprising that GPs valued the medication expertise of the GPP in managing these patients through COMPASS.

There is evidence from both this study and others that patients recognise the pressures faced in general practice and are pleased to accept resolution through the availability of new roles [560]. Patients felt GPP consultations were good quality, in concert with findings from other studies [560, 569]. Similar to a questionnaire study investigating patient views about a patient-centred GPP-led polypharmacy medication review service in England [570], patients found the reviews helpful, most understood their medicines better since the review, and it provided an opportunity to address patients' concerns about their medicines. Patients reported benefits from longer medication review appointments, feeling they were not rushed, and that their conditions were being considered holistically. A qualitative semi-structured interview study in German primary care demonstrated that patients regard medication reviews as beneficial and have expectations around indications and interactions being assessed [539]. As shown in Table 5.1, medication reviews as part of COMPASS addressed these concerns.

The findings are consistent with other studies suggesting that additional roles in general practice can make unique contributions to the team [560, 571]. GPPs are ideally placed to use their skills and knowledge to help the GP practices liaise with CPs as reported elsewhere [559]. GPs believe pharmacists' expertise, the safety net they provide by checking for medication errors, and communication skills are fundamental enablers [125, 536, 552, 572].

GPs also valued their direct access to the medication expertise of the GPP when they had queries relating to an individual patient or when they needed support understanding a piece of work such as clinical guidelines, demonstrating trust in the pharmacist which concurs with another interview study in England [125]. This finding mirrored those of Canadian GPs, who noted the benefit of feeling more secure as a result of being able to consult with a pharmacist [573].

Overall, GPs referred to a noticeable reduction in workload for them and a general positivity across the practice about the impact of the GPP through COMPASS. The potential for GPPs to add to their workload by creating additional queries/tasks has been previously raised [125]; however, GPs were not concerned by this as even though prescribing recommendations from COMPASS may generate the need for a patient consultation, this was important to improve patient safety. Evidence has shown that GPPs provide valuable services to ease the burden on GPs and improve medicines optimisation and patient care [125, 534, 536]. Considering 10% of hospital admissions among older people are the result of ADRs of prescribed medications, with approximately 70% potentially avoidable, these findings are reassuring [574].

Mirroring other studies in this area, funding, infrastructure, and workload balance for this type of role appear to be universal barriers to implementation. The use of a telepharmacy service to support medicines optimisation in primary care was found to be a viable option for certain patient groups [575], bypassing the infrastructure barrier. Such interventions are growing in popularity with several potential benefits on patient outcomes and costs [576]. While qualitative evidence from England indicates that pharmacist-led polypharmacy medication reviews are a positive experience for older individuals [570], it would appear patients may be reluctant to attend an additional in-person appointment for the purpose of pharmacist review. Cardwell *et al.* reported that face-to-face pharmacist-led medication reviews yielded a low response rate in their pilot study [136], likely due to the high treatment burden and frequent routine visits to HCPs experienced by patients with multimorbidity and prescribed polypharmacy. Improved prior communication and information around the intended purpose and potential benefits of medication reviews may enhance patient engagement and improve patient experience and outcomes [537].

There was less clear agreement on future GPP roles in relation to prioritised services linked to GP workload, co-location, and time configuration. GPP reliance on referrals from the GP to provide clinical services to patients was acknowledged; as previously reported, such services ideally would be readily accessible to patients [555]. Nevertheless, as shown in recent pilot studies in Ireland, integrating pharmacists into general practice is feasible and an effective means of improving prescribing safety and implementing deprescribing [136, 137]. While GPs reported an increase in their workload post-GPP medication review, GPs felt this was worthwhile as the reviews identified and resolved various issues [554].

Additionally, similarities with the iSIMPATHY Project were apparent in which complex patients with multimorbidity and prescribed polypharmacy underwent GPP review [572]. Stakeholders reported the reviews were very acceptable, improved medicines appropriateness, and provided a significant return on investment [572]. Moreover, the feasibility of sharing GPPs between practices was demonstrated [572]. The GPs in this study valued the role of the GPP and recommended that all practices should have a pharmacist.

5.7.2. Implications for practice

This study demonstrated a range of views and experiences attesting to the value pharmacists can add to the general practice team through COMPASS and what is required to ensure efficient integration. The primary care crisis and the way that GPPs can release capacity for GPs and CPs and use their expertise to fill a gap in the primary care team to improve patient-centred care, collaboration, communication, and quality use of medicines was established. There was good agreement across the stakeholders that GPPs were beneficial in broadly supporting the shared goal of improving patient care through medicines optimisation. Overall, patients indicated that they did not clearly understand the role of a GPP but did personally find the interaction pleasant. The major benefit of the GPP role is improving accessibility and adding unique expertise to general practice.

In keeping with international literature [126], there was enthusiasm and willingness among most of the pharmacists for new, extended roles in primary care. The development of extended roles depends upon a number of factors, including role definition, professional boundaries, and the willingness of GPs to delegate tasks. Promotion of the role among pharmacists, primary care teams, patients, and policymakers is likely to encourage training

in general practice roles. This in turn could help to reduce uncertainty regarding definitions of the role, and to fuel pharmacists' primary care-based career aspirations. Furthermore, this study revealed that GPPs would need clinical skills to allow them to undertake their role and the confidence required to use these skills.

Unlike other countries, there are no formal training pathways or programmes for GPPs in Ireland. The introduction of education to prepare pharmacists for a role in general practice was considered important, whether that be during the pharmacist's undergraduate or postgraduate training. The importance of pharmacists spending time in general practices during their training with GP mentors was highlighted [553], such as formal training via the Primary Care Pharmacy Education Pathway in England which entails workplace-based training in practices (including prescribing training) [577]. Several stakeholders thought the GPP role would be enhanced by pharmacist prescribing within clearly defined competencies, for which a core set of clinical skills required by GPP prescribers has been published [578]. Moreover, the Minister for Health in Ireland has recently established an expert task force to support the expansion of pharmacist roles inclusive of prescribing [579].

To improve collaborative working between GPs and GPPs, face-to-face meetings are recommended to develop a trusting relationship [534]. However, co-location is not necessarily essential for GPs and GPPs to value, learn from and utilise the other's expertise. For instance, the PINCER trial demonstrated the effectiveness of a pharmacist-led information technology intervention for reducing medication errors in 72 general practices [128]. There is currently no structured funding model to support the GPP role, one of the major barriers to implementation and uptake of the role [552, 555]. The cost of employing a GPP and who should pay for that was identified as a future challenge. Several stakeholders perceived that government funding would be essential to widely establish the role. Future work should be undertaken to raise awareness of the role and its benefits, to develop training programmes inclusive of pharmacist prescribing, and to evaluate the feasibility of sharing a GPP with multiple practices to provide telepharmacy services.

Furthermore, while the NHS England plan to incorporate pharmacogenomics in primary care by 2025 [195], there is currently no plan for the implementation of pharmacogenomics in Ireland. As a result, it was unsurprising that participants demonstrated poor awareness and

understanding of pharmacogenomics. Reflecting the findings from Chapter 3, the exigent need for pharmacogenomics education for HCPs and patients alike was demonstrated for pharmacogenomics implementation in routine care. Despite recognising the potential benefits of pharmacogenomic testing, GPs' and CPs' receptivity to incorporating pharmacogenomic services into their practice was affected by the aforementioned time and workload pressures, inadequate training, and funding concerns. Furthermore, participants identified unclear lines of responsibility in relation to pharmacogenomic testing and considered a separate role, such as a GPP, may be a solution.

Challenges to describing the role of the practice pharmacist exist. Uncertainty about the utility of pharmacists within an integrated medical team can stem from perceptions of pharmacists as solely being a dispenser of medicines or a retailer [504]. Furthermore, adoption of roles such as medication reviews that are currently conducted in varying degrees by members of the general practice team could be viewed by some as a threat. However, allowing the pharmacists to assume the lead in these roles would enable established team members to focus on their core roles while making best use of the pharmacist's unique skill set [504]. Additionally, the absence of dedicated and sustainable funding to facilitate the integration of pharmacists into general practice stands as a barrier [552, 580].

5.7.3. Strengths and limitations

The qualitative design used in the current study allowed for an in-depth understanding of stakeholders' experience with COMPASS and perceptions on pharmacist integration into general practice and the implementation of pharmacogenomics as part of this service. The reporting of this qualitative study was in line with the COREQ checklist. The involvement of multidisciplinary contributors (HCPs, non-HCPs, and Patient Public Involvement advisor) for methodology development and refinement enhanced the rigour of this study and the robustness of its findings. A gatekeeper was used for patient recruitment in this study to address the possible conflicting role of the GPP also being the researcher. The views of older patients with multimorbidity and prescribed polypharmacy were captured in this interview study. A further strength is the iterative approach with analysis of earlier interviews informing the focus of later interviews. A range of views were captured with sufficient data saturation achieved to offer findings a conceptual depth, with key stakeholders from the primary care team and patients in the analysis. The number of participants from those involved in the service willing to take part in the study was also a strength. Our analysis of barriers and facilitators using the SEIPS 3.0 model provides detailed information for professionals or organisations, regionally or nationally, to develop multifaceted implementation strategies for improving the implementation of COMPASS.

A number of limitations should be noted. First, recruitment was limited to one geographical region. There may also have been an element of volunteer bias amongst our sample as those who agreed to participate may have been more enthusiastic and interested in research. The use of a pre-identified framework for analysis may have limited the potential breadth of responses. Finally, this is a qualitative study that does not make claims to generalisability but provides possible explanations for observed phenomena.

5.7.4. Reflexivity section

As the primary researcher conducting this study, I recognise that my background as a GPP significantly influenced both the data collection and analysis processes. My professional experience provided me with deep insights into the healthcare system and the operation of services like COMPASS, which informed my understanding of participant responses. This insider knowledge enabled me to engage with the material on a nuanced level, yet it also brought specific perspectives and potential biases to the research. During the interviews, I was acutely aware of the potential for social desirability bias, where participants might provide responses they believed I wanted to hear. My role as a GPP could have influenced their willingness to discuss certain issues, particularly those related to pharmacy practices or healthcare delivery. To mitigate this, I made concerted efforts to create an open and non-judgmental environment, emphasising the importance of candid feedback. I used neutral language and encouraged participants to share both positive and negative experiences.

In analysing the data, I employed a reflexive thematic analysis approach as outlined by Braun and Clarke. This involved not just a systematic coding process but also continuous self-reflection on my positionality and its impact on the research. I documented my thoughts, decisions, and evolving understanding throughout the analysis in NVivo. This practice was crucial in helping me remain aware of my assumptions and how they might influence the coding and theme development. Discussions with the research team played a pivotal role in challenging my perspectives and ensuring a more balanced interpretation of the data. By incorporating feedback from team members with diverse backgrounds, I aimed to enhance the credibility and trustworthiness of the findings. These collaborative sessions helped to surface different viewpoints and reduce the risk of my professional subjective influences overshadowing the analysis. Overall, this reflexivity section aims to provide transparency about my role and influence in the research process. It acknowledges the subjective nature of qualitative research and the steps taken to address potential influences. By reflecting on my position as a researcher who works in the field, I hope to offer a clear account of how my background both enriched and shaped this study.

5.8. Conclusion

In conclusion, GPs, CPs, and patients involved in COMPASS were broadly optimistic regarding aspects of pharmacists working in general practices and the potential outcomes of collaborative medicines optimisation for patients (particularly those with multimorbidity and prescribed polypharmacy) and HCPs alike, which appear to be timely given current pressures in general practice. This research has created greater understanding of the feasibility of a GPP working remotely providing a telepharmacy service and offers considerations about if and where pharmacogenomic testing could play a role in COMPASS. There are a number of recommendations based on the results of this study that have the potential to inform successful integration of pharmacists into general practice considering day-to-day practicalities and to enhance the service provided. Given the anticipation for GPP integration in Ireland following its success internationally and in Northern Ireland, primary care stakeholders must prepare for this role to be expanded.

Chapter 6

General discussion

6. Chapter 6 – General discussion

6.1. Introduction

The research presented in this thesis has focused on the potential implementation of pharmacogenomic interventions as part of medicines optimisation. Through a multi-faceted approach, the studies presented sought to assess the effectiveness and potential implications of pharmacogenomic services, particularly focusing on patients with multimorbidity and those prescribed polypharmacy (Section 6.2). Despite the high prevalence of multimorbidity and polypharmacy, there exists a notable dearth of evidence regarding optimal management strategies for these patients [581]. Furthermore, prior to this research, no published studies had examined the potential impact of pharmacogenomic testing in an Irish patient cohort with multimorbidity and prescribed polypharmacy. Focusing on the evidence gathering phase of the Medical Research Council's framework for the design and evaluation of complex interventions (Section 1.7.2) [218], the research followed a systematic process to guide the development and future implementation of pharmacogenomic interventions as part of medicines optimisation within primary care settings in Ireland. Overall, this research contributes valuable insights into the potential integration of pharmacogenomic interventions into primary care settings, offering a roadmap for future investigations and informing policy decisions aimed at optimising medicines and improving patient outcomes. This chapter provides a general discussion of the thesis, highlighting the key findings and implications for further research, policy, and practice.

6.2. Key findings of this thesis

The overall aim of the research outlined in this thesis was to establish the potential impact pharmacogenomic testing could have for patients with multimorbidity and prescribed polypharmacy. A collaborative medicines optimisation service was developed to explore the role of a pharmacist integrated into general practice conducting patient-centred medication reviews and the potential role of pharmacogenomic testing as part of this service. Each component of the data presented in this thesis addresses different aspects of this research project's aim. Collectively, they provide a comprehensive exploration of pharmacogenomic interventions in the context of medicines optimisation in primary care.

Chapter 1 introduces the topics of multimorbidity, polypharmacy, medicines optimisation and pharmacogenomic testing. A systematic review was conducted to identify studies that employed a pharmacogenomic intervention as part of medicines optimisation with the aim of improving outcomes in patients with multimorbidity and prescribed polypharmacy in all healthcare settings and to determine the effectiveness of these interventions (Chapter 2). A cross-sectional questionnaire study was undertaken to identify the potential opportunities and challenges of implementing pharmacogenomic testing in Ireland based on the views of the public (Chapter 3). A retrospective longitudinal study was performed to examine specific pharmacogenomic variants in an Irish patient population with cardiovascular risk factors and their influence on the progression of pre-HF and new-onset symptomatic HF amongst patients exhibiting altered systemic statin exposure due to poor function phenotypes (Chapter 4). In the final study, a qualitative semi-structured interview study was conducted to evaluate the views of GPs, CPs, and patients on COMPASS in Irish primary care and to determine their perceptions on the incorporation of pharmacogenomic testing into this service (Chapter 5). The main findings arising from each of these studies are discussed in further detail within this section.

6.2.1. Polypharmacy and multimorbidity

The systematic review (Chapter 2) served as the foundation by synthesising and evaluating the existing evidence base for pharmacogenomic testing in patients with multimorbidity and prescribed polypharmacy to inform assessment and development of the intervention [218]. The key objective of this study was to identify, analyse, and evaluate the effectiveness of pharmacogenomic interventions in this patient population, with a focus on examining their development, implementation, genetic underpinnings, and impact on economic, clinical, and humanistic outcomes. The included studies predominantly took place in primary care. Evidence supporting the effectiveness of pharmacogenomic interventions to improve outcomes for patients with complex health needs was provided [272]. In this population, pharmacogenomic interventions were shown to enable the detection of MRPs that would not be identified through standard medicines optimisation, reducing the incidence of ADRs, hospitalisations, and emergency department visits. Furthermore, the heterogeneity in study designs and outcomes across the literature was highlighted. While randomised controlled trials were lacking, we included broad study designs to comprehensively report on the available literature.

The questionnaire study (Chapter 3) builds on the systematic review, which concluded that more work is needed on pharmacogenomic testing as part of medicines optimisation for patients with multimorbidity and those prescribed polypharmacy. Chapter 3 served to explore the feasibility of implementing pharmacogenomic testing into Ireland's healthcare system by examining public awareness, receptiveness to pharmacogenomic service availability, factors affecting testing decision, willingness to pay, and preferred access methods [362]. This study revealed strong public support for pharmacogenomic testing, particularly among those with chronic diseases, highlighting the unmet need for its incorporation in medicines optimisation. It was hypothesised that perceptions of pharmacogenomics would significantly differ based on the view of those with and without chronic disease(s); we found that respondents with chronic disease were more than twice as likely to value pharmacogenomic service availability than respondents without existing medical conditions. Furthermore, it appeared that this was driven more by the preferences of patients with multimorbidity and polypharmacy than those with a single chronic disease.

The differential preferences observed underscored the importance of tailoring healthcare interventions to meet the diverse needs of patient populations.

The retrospective longitudinal study (Chapter 4) provided significant clinical insights by examining specific pharmacogenomic variants in an older patient population with multimorbidity and prescribed polypharmacy, aligning with the overall aim of this research project. A key objective of this study was to investigate the exposure of the STOP-HF cohort to medications with a potential for drug-gene interactions and their impact on outcomes. Patients with multimorbidity and prescribed polypharmacy were found to be over three times more likely to be prescribed a medication with potential for drug-gene interactions. Furthermore, this study provided evidence for the prescription of statin therapy in primary cardiovascular prevention; discontinuation of statins in older patients exposed to polypharmacy with cardiovascular risk factors may elevate their risk of progression of HF and new-onset symptomatic HF. Finally, the qualitative interview study (Chapter 5) assessed key stakeholders' perspectives on COMPASS. GPs valued GPP support, referring patients with complex health needs to COMPASS for GPP-led patient-centred medication review [144]. Patients were appreciative of the quality of care received and were pleased to be offered an opportunity for an evaluation of their medicines within the wider context of their care.

6.2.2. Understanding pharmacogenomics

The questionnaire study presented in Chapter 3 aligned with the aim of the research project, establishing the potential acceptance and demand for pharmacogenomic services in the primary care setting. This study offered valuable insights into patient perspectives to guide the development of patient-centred interventions. At present, pharmacogenomic testing is not yet commonplace in Ireland. Consequently, it was unsurprising that the overall awareness of pharmacogenomic testing in this study was low. While over half of the respondents were not confident in their understanding of pharmacogenomics, the majority were supportive of pharmacogenomic testing, demonstrating positive perceptions of its potential benefits to improve pharmacotherapy outcomes, which were similar amongst those with and without chronic conditions. An unmet need for the incorporation of pharmacogenomic testing into medicines optimisation processes was identified in this study; however, respondents expressed concern regarding the cost of testing and a desire for coverage of these services.

The retrospective longitudinal study presented in Chapter 4 examined specific pharmacogenomic variants (SLCO1B1 and ABCG2) in patients with cardiovascular risk factors, directly addressing the aim of evaluating pharmacogenomic interventions in patients with complex health needs. This study offered important clinical insights into the potential utility of genetic testing beyond guiding medication management decisions. In this study, a high level of exposure to medications with potential for drug-gene interactions was demonstrated. Importantly, a poor statin transporter function phenotype was significantly associated with progression of pre-HF and new-onset symptomatic HF. While further work may be needed to confirm these data in other populations, this retrospective analysis suggests that routine SLCO1B1 and ABCG2 genotyping may help to identify patients receiving statin therapy with cardiovascular risk factors at great risk of HF progression. Poor awareness and understanding of pharmacogenomics were also observed in Chapter 5. Interviewees were unfamiliar with the different types of pharmacogenomic tests and their potential implications for patients. Nevertheless, there was a professional interest and general curiosity in pharmacogenomics.

6.2.3. Virtual general practice pharmacist

The development and implementation of a telepharmacy collaborative medicines optimisation service led by a GPP in Irish primary care was outlined in Chapter 5. Although it was not set up as a research project, COMPASS signifies a substantial contribution to novel service provision. The aim of qualitative interview study presented in Chapter 5 was to assess key stakeholders' perspectives on COMPASS (including barriers and facilitators identified using the SEIPS 3.0 model), analyse the patient journey through the service, gather stakeholder opinions on integrating pharmacogenomic testing, and create a service process map that incorporates identified barriers and facilitators.

While pharmacogenomic testing may enhance services like COMPASS by enabling more personalised medicines optimisation, it should not be seen as a silver bullet solution. Instead, it should be integrated into a broader pharmaceutical care and medicines optimisation strategy. Such a strategy should include a range of tools and approaches, including clinical judgement, patient education, and regular medication reviews, to ensure holistic and effective patient care. Pharmacogenomics can offer valuable insights into how patients might respond to certain medications, but its true value is realised when integrated with other clinical practices to optimise therapeutic outcomes and minimise adverse effects.

Although COMPASS does not currently focus on pharmacogenomic testing, this chapter remains consistent with the overarching aim of this thesis to improve medicines optimisation in primary care, particularly for patients with complex health needs. Initially, it was intended that pharmacogenomics would be integrated into COMPASS and examined further in a prospective study. However, difficulties were encountered in securing a laboratory collaboration and obtaining the necessary funding to pursue this integration (Section 6.5 and Section 6.6). Despite these setbacks, this study represents a critical step in gauging the feasibility and scalability of integrating novel medicines optimisation services into routine clinical practice.

By engaging stakeholders and soliciting feedback on the COMPASS delivery model, the study adhered to the Medical Research Council’s emphasis on stakeholder involvement and context sensitivity [218]. A diverse range of views and experiences highlighted the value that pharmacists can add to the general practice team through COMPASS, as well as the

requirements for ensuring their efficient integration. The primary care crisis and the way that GPPs can release capacity for GPs and CPs and use their expertise to fill a gap in the primary care team to improve patient-centred care, collaboration, communication, and quality use of medicines was established. There was good agreement across the stakeholders that GPPs were beneficial in broadly supporting the shared goal of improving patient care through medicines optimisation. The GPP improved accessibility and added unique expertise to general practice; however, a lack of a well-defined GPP role was identified as an obstacle for patient awareness.

Additionally, stakeholders' perceptions on the integration of pharmacogenomic testing into medicines optimisation services were explored. While interest in the availability of pharmacogenomic testing to optimise pharmacotherapy was shown, HCPs lacked confidence in their expertise at present to incorporate it as part of their practice. The findings shed light on the logistical hurdles and resource limitations associated with implementing such interventions within existing healthcare frameworks, necessitating adjustments to current workflows and processes. Unclear lines of responsibility in relation to service provider and setting for the implementation of pharmacogenomic testing was shown. To this end, GPPs could play a pivotal role in ensuring seamless integration of pharmacogenomics. Additionally, GPPs could contribute to research and quality improvement initiatives aimed at assessing the impact of pharmacogenomic testing on patient outcomes and refining implementation strategies.

6.3. Justification for research

Focusing on patients with multimorbidity and polypharmacy in this research project was not only logical but imperative for several reasons. Firstly, with the ageing population, the prevalence of morbidity and medication usage is expected to rise, underscoring the relevance of studying this patient demographic [582]. Secondly, patients with multimorbidity and polypharmacy face complex healthcare needs, navigating multiple chronic conditions and medications, which can pose significant challenges for both patients and healthcare providers alike [486]. Thirdly, this population is particularly vulnerable to ADRs due to the potential for drug-drug interactions, drug-disease interactions, and individual variations in drug metabolism [486]. Fourthly, despite the high prevalence of multimorbidity and polypharmacy, there exists a notable dearth of evidence regarding optimal management strategies for these patients [581]. Traditional clinical trials often exclude such complex patients, leading to a lack of generalisability of study findings to real-world clinical practice [486]. Thus, by focusing on this demographic, this research project aimed to address a critical gap in the literature and provide essential evidence to guide clinical decision-making. Finally, improving medication management and treatment outcomes in this vulnerable cohort holds the potential to significantly impact healthcare outcomes and resource utilisation positively.

The proposal to incorporate pharmacogenomic testing into medicines optimisation was grounded in several compelling reasons. Pharmacogenomic testing enables the customisation of medication regimens based on an individual's genetic profile, offering personalised treatment approaches that optimise therapeutic outcomes and minimise the risk of ADRs, thereby enhancing patient safety [194]. By tailoring medication regimens to patient's genetic profiles, pharmacogenomic testing has the potential to improve pharmacotherapy efficacy, leading to enhanced treatment outcomes and symptom management. While upfront costs may be incurred, pharmacogenomic testing has the potential for long-term cost savings by reducing medication-related adverse events, hospitalisation, healthcare utilisation, and associated costs [293, 510, 583]. Moreover, pharmacogenomic testing aligns closely with the principles of medicines optimisation by enhancing the quality, safety, and effectiveness of pharmacotherapy. Medicines optimisation aims to ensure that patients receive the right medications, at the right doses,

for right duration, with the overarching goal of maximising therapeutic outcomes while minimising the risk of ADRs and treatment-related complications [138, 139]. Pharmacogenomic testing complements medicines optimisation in several key ways. Recognising that patients respond differently to medications due to individual factors such as genetics, age, comorbidities, and concomitant medications, pharmacogenomics testing enables personalisation of treatment, risk reduction, and optimisation of treatment outcomes by tailoring medication regimens based on patients' genetic profiles. This individualised approach maximises treatment efficacy and minimises potential MRPs, aligning with the core tenets of medicines optimisation.

Incorporating pharmacogenomic testing into medicines optimisation necessitates collaboration among multiple HCPs [584]. As shown in COMPASS, additional roles such as GPPs can play a pivotal role given the existing workload and time constraints on HCPs in primary care. Pharmacists possess specialised knowledge and training in pharmacotherapy and medication management that makes them well-suited to support medicines optimisation services [138]. Pharmacogenomic testing may introduce new complexities and considerations for patients regarding their medication regimens; pharmacists already play a crucial role in educating patients about the implications of their pharmacotherapy and providing counselling on medication adherence and potential drug interactions. By leveraging their expertise in this area and bolstering it with training on pharmacogenomics, pharmacists could interpret genetic test results, provide personalised prescribing recommendations, and collaborate with other HCPs to optimise treatment regimens for individual patients. Acting as central coordinators, GPPs could facilitate communication between healthcare teams and ensure effective integration of pharmacogenomic information into clinical decision-making processes, thereby enhancing patient care and treatment outcomes.

6.4. Limitations

The strengths and limitations associated with the individuals phases of this research have been described in the preceding chapters. In the systematic review presented in Chapter 2, there was a notable lack of randomised controlled trial data specifically demonstrating the effectiveness of pharmacogenomic interventions to improve outcomes in patients with multimorbidity and those prescribed polypharmacy. Several factors contribute to this lack of randomised controlled trial data; for instance, the complexity of this patient population, ethical considerations, sample size and power, and the requirement for extended follow-up periods and careful consideration of clinical endpoints to evaluate the long-term effectiveness and sustainability of pharmacogenomic interventions in this population. In the questionnaire study presented in Chapter 3, the online dissemination method may have limited the generalisability of the findings to broader patient populations. The COVID-19 pandemic presented various unexpected challenges mainly by prohibiting face-to-face recruitment. Future research should aim to recruit more diverse and representative samples to ensure validity and reliability of the results. Moreover, qualitative methods, such as focus groups, could complement this study by providing a deeper understanding of patients' perceptions, beliefs, and experiences related to pharmacogenomic testing and personalised medicine.

In Chapter 4, the retrospective design and reliance on data entered into a clinical database and not collected in research may have introduced biases and confounding variables that could impact the validity and generalisability of the findings. Future research should aim to address these limitations by prospectively collecting comprehensive clinical and genetic data in larger, more diverse patient populations to provide more robust evidence regarding the predictive utility and clinical impact of pharmacogenomic testing. In Chapter 5, it is worth noting that the focus of the qualitative interview study on a single healthcare system in Ireland may constrain the generalisability of the findings to other contexts and settings. Additionally, there may also have been an element of volunteer bias amongst our sample as those who agreed to participate may have been more enthusiastic and interested in research. Therefore, future research endeavours should strive to replicate and validate these findings in diverse healthcare settings to ascertain their applicability and broader relevance.

It is important to acknowledge that prospective pharmacogenomic testing was not included in this thesis. The absence of collaboration and funding for a prospective pilot study to implement pharmacogenomic testing as part of medicines optimisation constituted the primary limitation of the overall research. Instead, the focus was on laying the groundwork and building the necessary foundation for future studies to incorporate prospective pharmacogenomic testing into medicines optimisation practices within the primary care setting in Ireland. While prospective pharmacogenomic testing holds promise for personalised medicines approaches, its implementation involves various logistical and methodological challenges beyond the scope of this thesis. These hurdles include establishing standardised protocols for genetic testing, ensuring timely access to test results, integrating genetic information into clinical decision-making processes, and evaluating the impact of pharmacogenomic-guided interventions on patient outcomes.

By acknowledging the absence of prospective pharmacogenomic testing in this thesis, we recognise the importance of incremental progress and iterative development in research endeavours. Rather than attempting to address all aspects of pharmacogenomic testing in a single research project, this thesis focused on conducting foundational research, such as systematic reviews, questionnaire studies, retrospective analyses, and evaluation of a collaborative medicines optimisation service, to build the necessary evidence base and infrastructure for future studies to incorporate prospective pharmacogenomic testing. Additionally, the COVID-19 pandemic resulted in setbacks. During the pandemic, COMPASS referral and uptake was affected as the general practice was consumed by COVID-19 related appointments and vaccination services.

6.5. Recommendations for future research

To further elaborate on the findings of the exploratory research presented in this thesis, there are several recommendations that should be investigated in future research. Overall, this thesis made significant strides in advancing our understanding of pharmacogenomic interventions and established the groundwork for future research aimed integrating pharmacogenomic interventions within primary care settings. The systematic review, questionnaire study, retrospective analysis of the STOP-HF population, and evaluation of COMPASS provided valuable insights into the feasibility, acceptability, and potential impact of pharmacogenomic testing in improving medicines optimisation processes and patient outcomes. Nevertheless, several limitations persist, highlighting areas for further investigation.

The inability to conduct prospective pharmacogenomic testing due to logistical constraints as part of this research project underscores the need for future endeavours to explore the feasibility and impact of real-world implementation. Identifying barriers, such as the lack of collaboration and funding, emphasises the need for research and development funding to support forthcoming studies in this area. Moving forward, a pilot study in real-world clinical settings built upon this foundation-laying research will further enrich the evidence base for pharmacogenomic interventions and guide future implementation efforts within primary care, in line with the principles of the Medical Research Council's framework [218]. A pilot study can encompass various research methodologies, including mixed-methods, randomised controlled trials, or process evaluations to assess the feasibility, acceptability, and potential effectiveness of and barriers to pharmacogenomic interventions in improving medicines optimisation and patient outcomes before undertaking a larger-scale study.

Leveraging the findings and insights generated from this thesis, future research can design and implement prospective pharmacogenomic testing initiatives for patients with complex health needs in primary care to address the remaining challenges and limitations, ultimately advancing the field of personalised medicine and improving patient outcomes in clinical practice. Moreover, conducting a prospective pharmacogenomic medicines optimisation service interventions study, incorporating a randomised controlled trial design with three study arms, would offer a robust evaluation of the intervention's efficacy and cost-

effectiveness. This study could compare outcomes among patients receiving usual care, those undergoing standard medicines optimisation interventions, and those receiving medicines optimisation incorporating pharmacogenomic testing. Lastly, comprehensive pharmacoeconomic evaluations would provide critical evidence on the economic value and sustainability of implementing a pharmacogenomic medicines optimisation service in primary care. Cost-effectiveness analyses could assess the incremental benefits and costs of pharmacogenomic testing compared to standard care or medicines optimisation alone, considering factors such as test costs, healthcare utilisation, MRPs, and long-term health outcomes. Additionally, conducting in-depth focus group studies with key stakeholders involved in a pharmacogenomic medicines optimisation service would provide invaluable insights into their experiences, perspectives, and priorities.

6.6. Recommendations for practice

The findings presented in this thesis hold substantial implications practice in pharmacogenomics and medicines optimisation, especially in primary care settings. Firstly, it is imperative to address the need for the development, assessment, and implementation of comprehensive educational programmes focusing on pharmacogenomics and medicines optimisation for both patients and HCPs in primary care settings. These programmes should encompass a wide array of topics, ranging from the fundamental concepts of pharmacogenomics, such as genetic variation in drug metabolism and response, to practical strategies for integrating pharmacogenomic testing into clinical decision-making processes. Evidence suggests that integrating pharmacogenomics education into HCP curricula can significantly enhance knowledge and awareness in this field [585]. The means of delivering an educational initiative should be tailored in accordance with the targeted audience and their needs. Educational initiatives could include interactive workshops, seminars, online modules, and educational materials tailored to the specific needs and preferences of different stakeholders. By fostering greater awareness, understanding, and uptake of pharmacogenomic testing and personalised medicine approaches, these educational initiatives could play a pivotal role in facilitating the integration of pharmacogenomics into routine clinical practice.

Secondly, the establishment of collaboration links with accredited laboratories or setting up an in-house laboratory facility equipped to conduct pharmacogenomic analyses and interpret genetic test results represents a critical step forward. This infrastructure is paramount in ensuring the efficient and precise processing of genetic samples, while maintaining stringent quality control measure to uphold the integrity of the data obtained. Moreover, having access to expert interpretation of the test results is indispensable, as it provides HCPs with invaluable insights into the potential implications of genetic variations on drug metabolism and response. Collaboration with genetic counsellors could further enhance the value of pharmacogenomic testing by facilitating effective communication of test results to both HCPs and patients. By leveraging the expertise of genetic counsellors, HCPs can ensure that patients receive clear and comprehensive explanations of their test results, empowering them to make informed decisions about their treatment options. During

this process, efforts should be made to develop standardised protocols and guidelines for integrating pharmacogenomic testing into routine clinical practice, ensuring equitable access and optimal outcomes for all patients.

Thirdly, integrating CDS systems that incorporate pharmacogenomic prescribing recommendations from established guidelines such as the CPIC and the DPWG is crucial for enhancing and standardising the implementation of pharmacogenomic testing in clinical practice. These CDS systems can serve as valuable tools to support HCPs in interpreting genetic test results and translating them into actionable prescribing recommendations at the point of care. These systems can provide real-time alerts or prompts when relevant genetic variants are identified, offering guidance on appropriate medication selection, dosing adjustments, and monitoring strategies based on patients' genetic profiles. Moreover, CDS systems can help overcome barriers related to HCP's knowledge gaps and time constraints by providing readily accessible and user-friendly tools for interpreting pharmacogenomic test results, minimising disruption and maximising utility. Additionally, these systems can support the previously mentioned education and training initiatives by providing links to relevant resources, guidelines, and educational materials, further enhancing the competence and confidence of HCPs in pharmacogenomic-based prescribing.

Finally, this thesis highlights the importance of stakeholder engagement and collaboration in developing and implementing complex interventions, like medicines optimisation and pharmacogenomic testing in primary care, to aid understanding of the practical challenges and opportunities inherent in real-world clinical practice. The collaborative medicines optimisation service developed as part of this research project could be expanded to encompass other healthcare systems in Ireland, enabling collaboration with additional HCPs, practices, and primary care networks to broaden the reach of the research. Thus, enabling a more diverse patient population to benefit from personalised medicines optimisation approaches. This expansion could involve strategic partnerships with healthcare organisations, professional associations, and government agencies to facilitate implementation and sustainability across different healthcare settings.

6.7. Implications for policy

The findings presented in this thesis have significant implications for policy in the field of pharmacogenomics and medicines optimisation, particularly within primary care settings; although further research as outlined in Section 6.5 is required. The culmination of evidence derived from our systematic review (Chapter 2) not only corroborates the effectiveness of pharmacogenomic interventions but also highlights an opportunity to enhance outcomes for patients dealing with the complexities of multimorbidity and polypharmacy. Furthermore, the insights gleaned from the questionnaire study (Chapter 3), underscoring patient receptivity toward pharmacogenomic services as part of medicines optimisation, suggest a palpable demand for integrating pharmacogenomic testing into primary care practice in Ireland. NHS England will create eight genomic networks of excellence (partnerships between the NHS, academia, and industry) with £15 million of funding over the next two years to develop evidence and models of adoption of genomic advances and technology applications in the NHS [586]. A dedicated network focused on pharmacogenomics and medicines optimisation will be one of the eight networks, which will aim to develop the rollout of pharmacogenomics and medicines optimisation in the NHS. It is important for policymakers to consider developing a vision for the integration of pharmacogenomics in Ireland to build momentum in this space.

Reflecting on these considerations, policymakers should consider devising frameworks conducive to the seamless integration of medicines optimisation and pharmacogenomic services into guidelines and policies, with the overarching goal of optimising medication management, mitigating ADRs, and ensuring equitable access for patients. This may involve developing guidelines for the appropriate use of pharmacogenomic testing and establishing reimbursement mechanisms to facilitate its widespread adoption in primary care. Wide adoption of medicines optimisation and pharmacogenomics requires specific policy changes, such as formally recognising medicines optimisation as a core healthcare priority, integrating medicines optimisation into existing healthcare quality standards and clinical guidelines, investing in workforce training and interprofessional collaboration models, implementing health information technology solutions, establishing financial incentives and reimbursement mechanisms, and launching public awareness campaigns.

A pathway for such integration may lie with the HSE's Medicines Management Programme, which champions safe, effective, and cost-effective prescribing [587]. By incorporating medicines optimisation and pharmacogenomics into this strategic framework, the HSE stands to fortify its commitment to personalised, patient-centred care and pharmacovigilance. Furthermore, pharmacogenomics aligns closely with the principles and objectives outlined in Sláintecare, Ireland's national healthcare reform strategy [96]. By incorporating pharmacogenomic testing into healthcare practices, Sláintecare's emphasis on patient-centred care is reinforced through tailored treatment plans that consider patients' genetics, ensuring medications are both effective and well-tolerated. Additionally, pharmacogenomics supports Sláintecare's goal of integrated care by providing standardised genetic information that can be shared among HCPs across different settings, promoting continuity of care and improving patient outcomes. Pharmacogenomic testing can also contribute to Sláintecare's preventative care agenda by enabling pre-emptive adjustments to medication regimens, averting potential ADRs and complications. Another overlap is Sláintecare's vision of modernising healthcare delivery and improving population health outcomes; the integration of pharmacogenomics will foster innovation and technological advancement within the Irish healthcare system.

The retrospective analysis (Chapter 4) of an older patient population with multimorbidity and polypharmacy shed light on the pronounced prevalence of medication regimens with potential for drug-gene interactions. Moreover, the discerned association between poor statin transporter phenotype and heightened risk of HF progression in this cohort with cardiovascular risk factors highlights the potential of pharmacogenomics in pre-emptive, preventative healthcare interventions. Identifying individuals who are in a trajectory to develop HF provides a crucial opportunity for the prevention of HF. Our study suggests that routine SLCO1B1 and ABCG2 genotyping may help to identify patients receiving statin therapy with cardiovascular risk factors at greater risk of HF progression. This fortuitous alignment with the HSE's Integrated Care Programme for the Prevention and Management of Chronic Diseases (ICPCD) presents a unique opportunity to recalibrate the approach toward chronic disease prevention and management, aligning with the ICPCD's ethos of patient-centred, integrated care provision [588].

The need for comprehensive educational programmes for both HCPs and patients, as elucidated in this thesis, warrants policy support to develop and implement educational initiatives aimed at enhancing the knowledge and awareness of pharmacogenomics. Synchronising with continuing professional development programmes for doctors are pharmacists, such initiatives can cultivate a proficient healthcare workforce poised to navigate the nuances of medicines optimisation and pharmacogenomics. Under the Medical Practitioners Act 2007, all doctors who are registered with the Medical Council of Ireland are required to maintain their professional competence in line with requirements set by the Medical Council [589]. Similarly, the Pharmacy Act 2007 requires that all pharmacists must undertake continuing professional development, in line with the PSI's requirements, including that they must maintain a record of their lifelong learning and demonstrate evidence of this on request [590]. Additionally, efforts should be made to educate patients about the benefits of pharmacogenomic testing and medicines optimisation, empowering them to make informed decisions about their treatment options.

The development and evaluation of the telepharmacy COMPASS (Chapter 5) accentuate the feasibility of GPPs working remotely in primary care and identified aspects that require further attention to ensure enhanced integration of pharmacists into general practice. These findings resonate with the HSE's Enhanced Community Care programme [591], advocating for enhanced services in primary care settings, and harmonise with the overarching vision of Sláintecare to increase community health services and reduce pressure on hospital systems [592]. Policymakers and healthcare leaders may explore opportunities to expand and scale up remote medicines optimisation services, leveraging pharmacogenomic testing to personalise medication management and improve therapeutic outcomes for patients with complex healthcare needs. Policymakers and healthcare organisations may need to invest in workforce development initiatives to build capacity among HCPs, provide training in pharmacogenomics, and establish collaborative models of care to facilitate the delivery of personalised medicine approaches in primary care settings.

While evidence on the clinical utility and cost-effectiveness of pharmacogenomic interventions as part of medicines optimisation (Section 6.5) may be required before instigating policy reform, the identification of barriers to prospective pharmacogenomic

testing, such as lack of collaboration and funding, highlights the need for research and development funding to support future studies in this area. Policymakers and funding agencies are encouraged to prioritise such endeavours by allocating resources to support prospective pharmacogenomic testing initiatives, including pilot studies, feasibility trials, and implementation research, to generate robust evidence and inform policy decisions regarding the adoption and reimbursement of pharmacogenomic services in primary care. In tandem, the Health Information and Quality Authority could consider conducting a health technology assessment, furnishing independent evidence to support decision-making based on a finite budget [593]. Health technology assessment is a multidisciplinary research process that collects and summarises information on the clinical effectiveness and safety, cost-effectiveness and budget impact, organisational and social aspects, and ethical and legal issues pertaining to health technologies such as pharmacogenomic testing [593]. The information presented in this assessment may be used to support decisions about the implementation of pharmacogenomics at the national level.

Policymakers and professional organisations should consider developing guidelines and quality standards delineating the implementation framework for pharmacogenomic testing in primary care in Ireland, including recommendations for test selection, interpretation of results, and integration into clinical decision-making processes. By outlining standardised protocols and best practice recommendations, coherence and quality in the delivery of pharmacogenomic services can be ensured across disparate healthcare settings, improving patient outcomes and generating confidence in personalised medicine approaches. In summation, the findings from the thesis have important implications for policy and practice, highlighting the potential benefits of integrating pharmacogenomic testing into medicines optimisation practices in primary care settings. Crucially, they furnish actionable insights for policymakers, healthcare leaders, and practitioners charting a course towards the adoption and implementation of personalised medicine approaches.

6.8. Conclusion

The research presented in this thesis offers a comprehensive investigation into the potential impact of pharmacogenomic interventions in patients with multimorbidity and prescribed polypharmacy within the context of medicines optimisation, with a focus on the role of pharmacists in Irish primary care. Through a systematic review, questionnaire study, retrospective longitudinal study, and evaluation of a telepharmacy service, key insights have been synthesised regarding the effectiveness, challenges, and opportunities surrounding pharmacogenomic testing for medicines optimisation in this patient population. While barriers to prospective pharmacogenomic testing were identified, including collaboration and funding limitations, recommendations for future research include educational programmes, collaboration with accredited laboratories, integration of CDS systems, and exploration of prospective testing initiatives. Collaboration among policymakers, healthcare leaders, and researchers is essential to address these barriers and integrate pharmacogenomic services into primary care. Implications for policy and practice include devising frameworks for integration, establishing reimbursement mechanisms, and investing in workforce training and health information technology. Prioritising research funding, conducting health technology assessments, and developing guidelines for implementation are crucial steps for policymakers. Healthcare organisations can expand telepharmacy services and establish collaborative care models to facilitate personalised medicine approaches. Overall, this thesis contributes to the growing evidence base supporting the integration of pharmacogenomic interventions into primary care medicines optimisation, offering pathways for policymakers, healthcare leaders, and HCPs to enhance patient outcomes and confidence in pharmacogenomic interventions.

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Appendices

Appendix 2.1. PRISMA checklist

Section/topic	#	Checklist item	Page
TITLE			
Title	1	Identify the report as a systematic review.	51
ABSTRACT			
Abstract	2	N/A	N/A
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	53
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	57
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	58
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	61
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	61
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	61
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if	62

Section/topic	#	Checklist item	Page
		applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	59
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	59
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	62
Effect measures	12	Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.	63
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis.	63
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	63
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	63
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	63
	13e	Describe any methods used to explore possible causes of heterogeneity among study results	63
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A

Section/topic	#	Checklist item	Page
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	62
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	64
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	64
Study characteristics	17	Cite each included study and present its characteristics.	66
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	75
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots.	67
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	72
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	N/A
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	75
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	75

Section/topic	#	Checklist item	Page
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	79
	23b	Discuss any limitations of the evidence included in the review.	81
	23c	Discuss any limitations of the review processes used.	87
	23d	Discuss implications of the results for practice, policy, and future research.	83
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	58
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	58
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	N/A
Competing interests	26	Declare any competing interests of review authors.	N/A
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	N/A

Appendix 2.2. Search strategies

PubMed

1	“pharmacogenetics"[Text Word]
2	"pharmacogenetic variants"[Text Word]
3	"pharmacogenetic testing"[Text Word]
4	"genetic testing"[Text Word]
5	"precision medicine"[Text Word]
6	"personalised medicine"[Text Word]
7	"personalized medicine"[Text Word]
8	"pharmacogenomics"[Text Word]
9	"genetic variation"[Text Word]
10	"genetic polymorphism"[Text Word]
11	"clinical enzyme tests"[Text Word]
12	"hematological tests"[Text Word]
13	"haematological tests"[Text Word]
14	"buccal swabs"[Text Word]
15	"cheek swab"[Text Word]
16	or/1-15
17	multimorbid*[Text Word]
18	multi-morbid*[Text Word]
19	multi morbid*[Text Word]
20	"multiple chronic conditions"[Text Word]
21	"multiple chronic diseases"[Text Word]
22	"multiple chronic illnesses"[Text Word]
23	chronic condition*[Text Word]
24	chronic disease*[Text Word]
25	chronic illness*[Text Word]
26	"chronic care"[Text Word]
27	chronic syndrome*[Text Word]
28	chronic disorder*[Text Word]
29	"multidisease"[Text Word]
30	multi-disease[Text Word]
31	multiple condition*[Text Word]
32	multiple disease*[Text Word]
33	multiple illness*[Text Word]
34	multiple syndrome*[Text Word]
35	multiple disorder*[Text Word]
36	comorbid*[Text Word]
37	co-morbid*[Text Word]
38	co morbid*[Text Word]
39	"polypharmacy"[Text Word]
40	"polymedication"[Text Word]
41	"polytherapy"[Text Word]
42	polypharma*[Text Word]
43	multiple medic*[Text Word]
44	chronic medic*[Text Word]
45	long term medic*[Text Word]
46	multiple drug*[Text Word]
47	concomitant medic*[Text Word]
48	concurrent medic*[Text Word])
49	or/17-48
50	full text[sb]
51	16 and 49 and 50

EMBASE

1	pharmacogenetics:ti,ab,kw
2	'pharmacogenetic variant':ti,ab,kw
3	'pharmacogenetic testing':ti,ab,kw
4	'genetic screening':ti,ab,kw
5	'precision medicine':ti,ab,kw
6	'personalised medicine':ti,ab,kw
7	'personalized medicine':ti,ab,kw
8	pharmacogenomics:ti,ab,kw
9	'genetic variation':ti,ab,kw
10	'genetic polymorphism':ti,ab,kw
11	'clinical enzyme tests':ti,ab,kw
12	'hematological tests':ti,ab,kw
13	'haematological tests':ti,ab,kw
14	'buccal swabs':ti,ab,kw
15	'cheek swab':ti,ab,kw
16	or/1-15
17	multimorbid*:ti,ab,kw
18	'multi morbid*':ti,ab,kw
19	'multiple chronic conditions':ti,ab,kw
20	'multiple chronic diseases':ti,ab,kw
21	'multiple chronic illnesses':ti,ab,kw
22	'chronic condition*':ti,ab,kw
23	'chronic disease*':ti,ab,kw
24	'chronic illness*':ti,ab,kw
25	'chronic care':ti,ab,kw
26	'chronic syndrome*':ti,ab,kw
27	'chronic disorder*':ti,ab,kw
28	multidisease:ti,ab,kw
29	'multi disease':ti,ab,kw
30	'multiple condition*':ti,ab,kw
31	'multiple disease*':ti,ab,kw
32	'multiple illness*':ti,ab,kw
33	'multiple syndrome*':ti,ab,kw
34	'multiple disorder*':ti,ab,kw
35	comorbid*:ti,ab,kw
36	'co morbid*':ti,ab,kw
37	polypharmacy:ti,ab,kw
38	polymedication:ti,ab,kw
39	polytherapy:ti,ab,kw
40	polypharma*:ti,ab,kw
41	'multiple medic*':ti,ab,kw
42	'chronic medic*':ti,ab,kw
43	'long term medic*':ti,ab,kw
44	'multiple drug*':ti,ab,kw
45	'concomitant medic*':ti,ab,kw
46	'concurrent medic*':ti,ab,kw
47	or/17-46
48	16 and 47

CENTRAL – Cochrane Central Register of Controlled Trials search strategy

#1 MeSH descriptor: [Pharmacogenetics] explode all trees

#2 MeSH descriptor: [Pharmacogenomic Variants] explode all trees

#3 MeSH descriptor: [Pharmacogenomic Testing] explode all trees

#4 MeSH descriptor: [Genetic Testing] explode all trees

#5 MeSH descriptor: [Precision Medicine] explode all trees

#6 personalised medicine:ti,ab,kw

#7 personalized medicine:ti,ab,kw

#8 pharmacogenomics:ti,ab,kw

#9 MeSH descriptor: [Genetic Variation] explode all trees

#10 MeSH descriptor: [Polymorphism, Genetic] explode all trees

#11 MeSH descriptor: [Clinical Enzyme Tests] explode all trees

#12 MeSH descriptor: [Hematologic Tests] explode all trees

#13 haematological tests:ti,ab,kw

#14 buccal swabs:ti,ab,kw

#15 cheek swabs:ti,ab,kw

#16 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15

#17 multimorbid*:ti,ab,kw

#18 multi-morbid*:ti,ab,kw

#19 multi morbid*:ti,ab,kw

#20 MeSH descriptor: [Multiple Chronic Conditions] explode all trees

#21 multiple chronic diseases:ti,ab,kw

#22 multiple chronic illnesses:ti,ab,kw

#23 chronic condition*:ti,ab,kw

#24 chronic disease*:ti,ab,kw

#25 chronic illness*:ti,ab,kw

#26 chronic care:ti,ab,kw

#26 chronic syndrome*:ti,ab,kw

#28 chronic disorder*:ti,ab,kw

#29 multidisease:ti,ab,kw

#30 multi-disease:ti,ab,kw

#31 multiple condition*:ti,ab,kw

#32 multiple disease*:ti,ab,kw

#33 multiple illness*:ti,ab,kw

#34 multiple syndrome*:ti,ab,kw

#35 multiple disorder*:ti,ab,kw

#36 comorbid*:ti,ab,kw

#37 co-morbid*:ti,ab,kw

#38 co morbid*:ti,ab,kw

#39 MeSH descriptor: [Polypharmacy] explode all trees

#40 polymedication:ti,ab,kw

#41 polytherapy:ti,ab,kw

#42 polypharma*:ti,ab,kw

#43 multiple medic*:ti,ab,kw

#44 chronic medic*:ti,ab,kw

#45 long term medic*:ti,ab,kw

#46 multiple drug*:ti,ab,kw

#47 concomitant medic*:ti,ab,kw

#48 concurrent medic*:ti,ab,kw

#49 #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48

#50 #16 and #49

CINAHL – Cumulative Index to Nursing and Allied Health Literature; AMED – The Allied and Complimentary Medicine Database; and PsycInfo

S1 TI (pharmacogenetics OR pharmacogenetic variants OR pharmacogenetic testing OR genetic testing OR precision medicine OR personalised medicine OR personalized medicine OR pharmacogenomics OR genetic variation OR genetic polymorphism OR clinical enzyme tests OR hematological tests OR haematological tests OR buccal swabs OR cheek swab) OR AB (pharmacogenetics OR pharmacogenetic variants OR pharmacogenetic testing OR genetic testing OR precision medicine OR personalised medicine OR personalized medicine OR pharmacogenomics OR genetic variation OR genetic polymorphism OR clinical enzyme tests OR hematological tests OR haematological tests OR buccal swabs OR cheek swab)

S2 TI (multimorbid* OR multi-morbid* OR multi morbid* OR multiple chronic conditions OR multiple chronic diseases OR multiple chronic illnesses OR chronic condition* OR chronic disease* OR chronic illness* OR chronic care OR chronic syndrome* OR chronic disorder* OR multidisease OR multi-disease OR multiple condition* OR multiple disease* OR multiple illness* OR multiple syndrome* OR multiple disorder* OR comorbid* OR co-morbid OR co morbid* OR polypharmacy OR polymedication OR polytherapy OR polypharma* OR multiple medic* OR chronic medic* OR long term medic* OR multiple drug* OR concomitant medic* OR concurrent medic*) OR AB (multimorbid* OR multi-morbid* OR multi morbid* OR multiple chronic conditions OR multiple chronic diseases OR multiple chronic illnesses OR chronic condition* OR chronic disease* OR chronic illness* OR chronic care OR chronic syndrome* OR chronic disorder* OR multidisease OR multi-disease OR multiple condition* OR multiple disease* OR multiple illness* OR multiple syndrome* OR multiple disorder* OR comorbid* OR co-morbid OR co morbid* OR polypharmacy OR polymedication OR polytherapy OR polypharma* OR multiple medic* OR chronic medic* OR long term medic* OR multiple drug* OR concomitant medic* OR concurrent medic*)

S3 S1 AND S2

Limiters – Full text; exclude MEDLINE records

Expanders – Apply related words

Search modes – Boolean/Phrase

Appendix 2.3. Data extraction form

Reference ID	Characteristics of study								
	Title	Author	Publication year	Country of study origin	Study dates	Clinical setting	Inclusion criteria	Exclusion criteria	Follow-up duration

Reference ID	Participant demographics							
	Mean age of participants (intervention and control)	% male (intervention and control)	Ethnicity (intervention and control)	Socioeconomic status (intervention and control)	Mean no. of conditions (intervention and control)	Mean no. of medications (intervention and control)	No. of patients recruited (intervention and control)	No. of patients lost to follow up (intervention and control)

Reference ID	Intervention design and delivery								
	Study type (e.g. RCT, NRCT)	Number of study sites	Description of intervention	Pharmacogenetic component(s) of the intervention	Description of control	Intervention setting	Sample size calculation	Mode of delivery (e.g. face-to-face)	Provider (who delivered the intervention)

Reference ID	Intervention design and delivery (cont'd)								
	Intervention duration	Clinical outcomes	Health systems-related outcomes	Medication-related outcomes	Patient-related outcomes	Patient knowledge and behaviour outcomes	Consultation-related outcomes	Other outcomes	Timing of outcome measurement

Reference ID	Study findings								
	Results 1	Results 2	Results 3	Results 4	Results 5	Authors comments	Study's reported limitations	Funding	Conflicts of interest

Reference ID	Risk of bias assessment – ROB 2						
	Bias arising from the randomisation process	Bias due to deviations from the intended intervention	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Other bias	Overall risk of bias

Reference ID	Risk of bias assessment – ROBINS-I								
	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from the intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Other bias	Overall risk of bias

Appendix 2.4. Characteristics of excluded studies

Study	Reason for exclusion
Al-Zubiedi 2009[1]	Conference abstract: full-text study retrieved ([2])
Altar 2015[3]	Wrong patient population: no evidence of multimorbidity or polypharmacy
Anderson 2007[4]	Wrong patient population: no evidence of multimorbidity or polypharmacy
Anderson 2010[5]	Wrong patient population: no evidence of multimorbidity or polypharmacy
Barley 2014[6]	Wrong intervention: intervention lacked a pharmacogenetics component
Bielinski 2014[7]	Protocol: full-text study retrieved ([8])
Bielinski 2014[7]	Duplicate: duplicate protocol for a retrieved full-text study ([8])
Biskupiak 2015[9]	Conference abstract: full-text study retrieved ([10])
Biskupiak 2015[11]	Duplicate: duplicate conference abstract for a retrieved full-text study ([10])
Boels 2017[12]	Wrong intervention: intervention lacked a pharmacogenetics component
Bradley 2018[13]	Wrong patient population: no evidence of multimorbidity or polypharmacy
Brown 2017[14]	Wrong patient population: no evidence of multimorbidity or polypharmacy
Brown 2020[15]	Conference abstract: full-text study retrieved ([16])
Burnette 2012[17]	Wrong intervention: no intervention
Cervantes 2019[18]	Conference abstract: full-text study unobtainable
Charland 2012[19]	Conference abstract: full-text study retrieved ([20])
Charland 2014[20]	Wrong intervention: intervention involved a single drug-gene interaction
Chenoweth 2014[21]	Wrong intervention: intervention lacked a pharmacogenetics component
Clarke 2011[22]	Wrong intervention: intervention involved a single drug-gene interaction
DiFrancia 2019[23]	Wrong patient population: patients with malignancy, HIV, HCV and HBV

Study	Reason for exclusion
Dorfman 2013[24]	Wrong intervention: no intervention
Emmelhainz 2018[25]	Conference abstract: full-text study unobtainable
Forester 2020[16]	Wrong patient population: no evidence of multimorbidity or polypharmacy
Frank 2019[26]	Wrong intervention: intervention lacked a pharmacogenetics component
Freeman 2017[27]	Conference abstract: full-text study unobtainable
French 2010[28]	Wrong intervention: intervention involved a single drug-gene interaction
Gibbs 2019[29]	Duplicate: duplicate conference abstract for an unobtainable full-text study ([30])
Greden 2018[31]	Conference abstract: full-text study retrieved ([32])
Greden 2019[32]	Wrong patient population: no evidence of multimorbidity or polypharmacy
Greden 2019[33]	Duplicate: duplicate conference abstract for a retrieved full-text study ([32])
Greden 2019[34]	Duplicate: duplicate conference abstract for a retrieved full-text study ([32])
Guchelaar 2017[35]	Conference abstract: full-text study unobtainable as study is ongoing ([36])
Hall-Flavin 2012[37]	Wrong patient population: no evidence of multimorbidity or polypharmacy
Hall-Flavin 2013[38]	Wrong patient population: no evidence of multimorbidity or polypharmacy
Harada 2017[39]	Wrong intervention: intervention involved a single drug-gene interaction
Herbert 2017[40]	Duplicate: duplicate protocol for a retrieved full-text study ([41])
Herbert 2018[42]	Protocol: full-text study retrieved ([41])
Holland 2019[43]	Wrong intervention: intervention lacked a pharmacogenetics component
Jain 2017[44]	Conference abstract: full-text study unobtainable
Jaspers 2019[45]	Conference abstract: full-text study unobtainable
Ji 2016[8]	Wrong patient population: no evidence of multimorbidity or polypharmacy

Study	Reason for exclusion
Keine 2018[46]	Wrong intervention: intervention lacked a pharmacogenetics component
Kennedy 2018[47]	Wrong intervention: no intervention
Kimmel 2013[48]	Conference abstract: full-text study retrieved ([49])
Kimmel 2013[49]	Wrong intervention: intervention involved a single drug-gene interaction
Kosti 2018[50]	Wrong intervention: no intervention
Lamont 2018[51]	Wrong intervention: intervention lacked a pharmacogenetics component
Lee 2016[52]	Conference abstract: full-text study retrieved ([53])
Leroux 2018[54]	Wrong intervention: intervention lacked a pharmacogenetics component
Mayhew 2017[55]	Conference abstract: full-text study excluded during screening process ([56])
NCT01184300 2010[57]	Protocol: full-text study retrieved ([58])
NCT01633957 2012[59]	Protocol: full-text study retrieved ([60])
NCT02428660 2015[61]	Protocol: full-text study retrieved and included ([62])
NCT03537547 2018[63]	Protocol: full-text study unobtainable (trial terminated)
NCT03597165 2018[64]	Protocol: full-text study retrieved ([65])
Paul 2017[66]	Conference abstract: full-text study unobtainable
Pérez 2016[67]	Conference abstract: full-text study retrieved ([68])
Pérez 2017[68]	Wrong patient population: no evidence of multimorbidity or polypharmacy
Pink 2014[2]	Wrong patient population: no evidence of multimorbidity or polypharmacy
Ray 2015[69]	Conference abstract: full-text studies retrieved ([3, 70-72])
Roberts 2012[58]	Wrong intervention: intervention involved a single drug-gene interaction
Roe 2018[73]	Conference abstract: full-text study unobtainable

Study	Reason for exclusion
Roth 2013[74]	Wrong intervention: intervention lacked a pharmacogenetics component
Ruano 2020[75]	Wrong patient population: no evidence of multimorbidity or polypharmacy
Shickh 2019[65]	Wrong patient population: patients with malignancy
Sutherland 2017[76]	Wrong intervention: intervention lacked a pharmacogenetics component
Sweet 2017[77]	Wrong patient population: no evidence of multimorbidity or polypharmacy
Sylvia 2014[78]	Wrong intervention: intervention lacked a pharmacogenetics component
Tanner 2018[41]	Wrong patient population: no evidence of multimorbidity or polypharmacy
Tiwari 2019[79]	Conference abstract: full-text studies retrieved ([41, 72])
Tylee 2012[80]	Protocol: full-text study retrieved ([6])
vanBronswijk 2019[81]	Wrong intervention: intervention lacked a pharmacogenetics component
VanDeventer 2017[82]	Conference abstract: full-text study retrieved ([14])
Vassy 2014[83]	Wrong patient population: no evidence of multimorbidity or polypharmacy
Walker 2019[84]	Conference abstract: full-text study unobtainable
Winkelmann 2001[85]	Wrong patient population: no evidence of multimorbidity or polypharmacy
Winner 2013[70]	Wrong patient population: no evidence of multimorbidity or polypharmacy
Winner 2013[71]	Wrong patient population: no evidence of multimorbidity or polypharmacy
Winner 2015[72]	Wrong patient population: no evidence of multimorbidity or polypharmacy
Wu 2019[30]	Conference abstract: full-text study unobtainable
Xu 2018[60]	Wrong patient population: no evidence of multimorbidity or polypharmacy
Zastrozhin 2018[86]	Wrong patient population: no evidence of multimorbidity or polypharmacy

Study	Reason for exclusion
Zastrozhin 2019[87]	Wrong intervention: intervention involved a single drug-gene interaction
Zastrozhin 2019[88]	Conference abstract: full-text study retrieved ([87])
Zastrozhin 2019[89]	Duplicate: duplicate conference abstract for a retrieved full-text study ([87])
Zastrozhin 2019[90]	Duplicate: duplicate conference abstract for a retrieved full-text study ([87])
Zintchouk 2016[91]	Wrong intervention: intervention lacked a pharmacogenetics component

Appendix 2.5. Risk of bias assessments

Elliott *et al.* [92]

Risk of bias – RoB 2		
Bias	Authors' judgement	Support for judgement
Bias arising from the randomisation process	Low risk of bias	Randomly assigned to intervention and control groups; baseline differences did not suggest any issues; allocation sequence was random and concealed
Bias due to deviations from the intended intervention (assignment)	Low risk of bias	Open-label trial; no concern due to the nature of the study; the principles of an intention-to-treat analysis were followed
Bias due to missing outcome data	Some concerns	Outcome assessment appears to have been conducted for each participant; presence of missing data and a sensitivity analysis was not conducted
Bias in measurement of the outcome	High risk of bias	The method of measuring the outcome seems appropriate and was the same across two groups; outcome assessors were aware of the intervention received; post-hoc amendments to outcomes with inclusion and exclusion; death was incorporated as a component of the primary endpoint post-hoc
Bias in selection of the reported result	Some concerns	The prespecified analysis plan was amended post-hoc; unclear if the reported effect estimates were selected on the basis of results from multiple outcome measurements
Other bias	None to report	None to report
Overall risk of bias		High risk of bias The trial is judged to be at high risk of bias in at least one domain for this result

Just *et al.* [93]

Risk of bias – RoB 2		
Bias	Authors' judgement	Support for judgement
Bias arising from the randomisation process	Low risk of bias	Randomly assigned to intervention and control groups; baseline differences did not suggest any issues; allocation sequence was random and concealed
Bias due to deviations from the intended intervention (assignment)	Low risk of bias	In general, patients and GPs were blinded for the study group; however, it is likely blinding became less effective when enrolling a high number of patients; the principles of an intention-to-treat analysis were followed
Bias due to missing outcome data	Some concerns	Data appears to be available for all participants; protocol publicly available; trial registry lists outcomes that are missing: healthcare utilisation, costs, medication changes, and quality of life
Bias in measurement of the outcome	Some concerns	The use of trigger lists and that the fact that the calculated sample size of the study was not met affected the measurement of the outcome; measurement could have differed between groups with GPs and their staff reporting different experiences with the trigger lists
Bias in selection of the reported result	Low risk of bias	Data that produced the results analysed for the primary outcome were in accordance with a pre-specified analysis plan finalised before the outcome data were available
Other bias	None to report	None to report
Overall risk of bias		Some concerns The trial is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain

Kim *et al.* [62]

Risk of bias – RoB 2		
Bias	Authors' judgement	Support for judgement
Bias arising from the randomisation process	Low risk of bias	Allocation sequence was random and concealed; participants assigned to groups based on birth year; marginally significant baseline difference showing greater number of ADRs in the PGx group than the other two arms (p = 0.06)
Bias due to deviations from the intended intervention (assignment)	Low risk of bias	Open-label trial; no concern due to the nature of the study; post-hoc analysis – high drop-out from the PGx arm resulted in reassignment of participants to control as the intention-to-treat analysis did not provide insight into the utility of the PGx service; deviations unlikely to have affected the outcome
Bias due to missing outcome data	Some concerns	Data appears to be available for all participants; protocol not publicly available; trial registry lists outcomes that are missing: number of ADRs, QoL, major event risk reduction; loss to follow-up not reported
Bias in measurement of the outcome	Low risk of bias	Unblinded pharmacists conducted initial medication review session; however, baseline differences were not statistically significant; Blinded pharmacists conducted secondary outcome (level of seriousness) measurement
Bias in selection of the reported result	Some concerns	Trial registry shows deviations from intended outcomes in the published work; however, it is a post-hoc analysis; unclear if the reported effect estimates were selected on the basis of results from multiple outcome measurements (different scales for severity ratings could be used)
Other bias	None to report	None to report
Overall risk of bias		Some concerns The trial is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain

Swen *et al.* [94]

Risk of bias – RoB 2		
Bias	Authors' judgement	Support for judgement
Bias arising from the randomisation process	Low risk of bias	Allocation sequence was random and concealed; countries randomised to start with either PGx or standard care and then swap; small but statistically significant baseline difference between study and control group observed for global health score and number of comedications
Bias due to deviations from the intended intervention (assignment)	Low risk of bias	Open-label trial; no concern due to the nature of the study; no deviations from the intended intervention; appropriate analysis used to estimate the effect of assignment to intervention
Bias due to missing outcome data	Low risk of bias	Intention-to-treat analysis performed; gatekeeping analyses performed to prevent dilution of the effect of the intervention; protocol publicly available; losses to follow-up listed for both groups
Bias in measurement of the outcome	Low risk of bias	Patient-reported adverse drug reactions collected during scheduled visits with research nurse that were not objectified by use of laboratory tests or physical examinations; however, causality analysis of the adverse drug reactions using a validated tool performed
Bias in selection of the reported result	Low risk of bias	Data that produced the results analysed for the primary outcome were in accordance with a pre-specified analysis plan finalised before the outcome data were available
Other bias	None to report	None to report
Overall risk of bias		Low risk of bias

Brixner *et al.* [10]

Risk of bias – ROBINS-I		
Bias	Authors' judgement	Support for judgement
Bias due to confounding	Low risk of bias	Control group propensity score matched to intervention group by age, gender, D'Hoore-Charlson comorbidity index score for specific morbidities, and for high-risk CYP450 medications
Bias in selection of participants into the study	Low risk of bias	Participants selection satisfactory (patients were included based on prior-agreed inclusion criteria); control group patients matched to intervention group patients on key characteristics; start of follow-up and start of intervention coincides for most participants
Bias in classification of interventions	Low risk of bias	Intervention groups clearly defined, with a prospective intervention group and retrospective control group; classification of intervention status unlikely to have been affected by knowledge of the outcome
Bias due to deviations from the intended intervention	Low risk of bias	No deviations from the intended intervention (intervention as per trial registry); protocol not publicly available
Bias due to missing data	Low risk of bias	Data appears to be available for all participants; no information on loss to follow-up
Bias in measurement of outcomes	Moderate risk of bias	No evidence of blinding or outcome/participant exclusion; outcomes reported on as per trial registry; outcome assessments may have differed between groups, with different resources available for data collection in the intervention and control group
Bias in selection of the reported result	Low risk of bias	There is sufficient evidence that reported outcomes arise from intended outcomes, analyses and cohorts based on the PGx intervention
Other bias	None to report	None to report
Overall risk of bias		Moderate risk of bias The study is sound for a non-randomised study but cannot be considered comparable to a well-performed randomised trial

van der Wouden *et al.* [95]

Risk of bias – ROBINS-I		
Bias	Authors' judgement	Support for judgement
Bias due to confounding	Moderate risk of bias	Potential for confounding (groups not controlled for patient factors); the impact of PGx confounded when patients are on multiple medications/have multiple comorbidities (increased likelihood of finding a useful effect); there is no missing information on identified potential confounding variables.
Bias in selection of participants into the study	Moderate risk of bias	Participants selection satisfactory (patients were included based on prior-agreed inclusion criteria); follow-up and start of intervention may not coincide for most participants (mean follow-up duration of 2.5 years); adjustment techniques used to correct for presence of selection biases
Bias in classification of interventions	Low risk of bias	Intervention groups clearly defined; there are no deviations from intervention and knowledge of intervention will have no impact on outcome; only one intervention group with stratification into groups performed for comparisons
Bias due to deviations from the intended intervention	Low risk of bias	No deviations from intended intervention are reported
Bias due to missing data	Low risk of bias	Due to the cross-sectional nature of the study, no patients were lost to follow-up
Bias in measurement of outcomes	Moderate risk of bias	Outcome measure could be influenced by knowledge of intervention received; differences could not be concluded due to high healthcare professional adherence to guidelines
Bias in selection of the reported result	Low risk of bias	There is sufficient evidence that reported outcomes arise from intended outcomes, analyses and cohorts based on the PGx intervention
Other bias	None to report	None to report
Overall risk of bias		Moderate risk of bias The study is sound for a non-randomised study but cannot be considered comparable to a well-performed randomised trial

Appendix 3.1. Questionnaire

SECTION 1: DEMOGRAPHICS

1) What is your gender?

☐ Male ☐ Female ☐ Prefer not to say ☐ Other (please specify)

2) What age are you?

☐ 18-24 years old ☐ 25-34 years old ☐ 35-44 years old ☐ 45-54 years old

☐ 55-64 years old ☐ 65-74 years old ☐ 75-84 years old ☐ 85 years or older

☐ Prefer not to say

3) How would you describe your ethnicity?

☐ European ☐ African ☐ Asian ☐ Prefer not to say ☐ Other (specify)

4) What is your highest level of education?

☐ Primary education ☐ Leaving Certificate ☐ University degree ☐ Masters/PhD

☐ Prefer not to say ☐ Other (please specify)

5) Which of these best describes your job status at the end of 2020?

☐ Employed ☐ Unemployed ☐ Retired ☐ Prefer not to say

6) Have you worked in a health-related profession?

☐ Yes ☐ No ☐ Prefer not to say

7) What is your household's annual income?

☐ < €20,000 ☐ €20,001 - €40,000 ☐ €40,001 - €60,000 ☐ €60,001 - €80,000

☐ €100,001 - €120,000 ☐ €120,001 - €140,000 ☐ €140,001 +

☐ Prefer not to say

8) Do you have private health insurance?

☐ Yes ☐ No ☐ Prefer not to say

9) Do you have life insurance?

☐ Yes ☐ No ☐ Prefer not to say

10) Do you currently receive your medication(s) under any of the following schemes?

☐ General Medical Services ☐ Long-Term Illness scheme ☐ Drugs Payment Scheme

☐ High Tech ☐ Health Amendment Act ☐ None of the above

☐ Prefer not to say

11) How did you hear about this survey?

☐ Social media ☐ In a recruiting pharmacy ☐ Word of mouth

☐ Prefer not to say ☐ Other (please specify)

SECTION 2: HEALTHCARE

12) How long does it take you to reach your local pharmacy? _____ (mins)

☐ Prefer not to say

13) Approximately, how often do you visit your local pharmacy? ☐ Less than monthly ☐ Monthly

☐ Every 3 months ☐ Every 6 months ☐ Once yearly ☐ Prefer not to say ☐ Other (please specify)

14) How long does it take you to reach your regular prescriber? _____ (mins) ☐ Prefer not to say

15) In which of the following settings is your regular prescriber? (Please tick all that apply)

☐ General practitioner ☐ Specialised clinic ☐ Hospital ☐ Prefer not to say

☐ Other (please specify)

16) Approximately, how often do you visit your general practitioner?

☐ Less than monthly ☐ Monthly ☐ Every 3 months ☐ Every 6 months

☐ Once yearly ☐ Prefer not to say ☐ Other (please specify)

17) What healthcare service is most convenient to you?

☐ Community pharmacy ☐ General practice ☐ Primary care clinic

☐ Hospital/Outpatients ☐ Prefer not to say ☐ Other (please specify)

18) Do you have any long-term medical conditions?

☐ Yes ☐ No ☐ Prefer not to say

If YES, please specify how many: _____

19) Which of the following therapeutic area(s) describes your medical condition(s)? (Tick all that apply)

☐ Cardiovascular ☐ Respiratory ☐Central nervous system

☐ Endocrine ☐ Musculoskeletal and joint ☐ Gastro-intestinal

☐ Urinary tract ☐ Immune system ☐ Malignancy

☐ Skin ☐ Renal ☐ Liver

☐ Prefer not to say ☐ Other (please specify)

20) How would you rate your health status?

☐ Excellent ☐ Good ☐ Average ☐ Poor ☐ Prefer not to say

21) Do you take any regular medications that are prescribed by your doctor on a daily basis?

☐ Yes ☐ No ☐ Prefer not to say

If YES, please specify how many: _____

Please list the medicines you take daily: _____

☐ Prefer not to say ☐ Not applicable

22) How would you rate your adherence to your medical treatment?

☐ Excellent ☐ Good ☐ Average ☐ Poor ☐ Prefer not to say

☐ Not applicable

23) When was the last change to your medication?

☐ Less than a month ago ☐ 1-3 months ago ☐ 4-6 months ago

☐ 7-9 months ago ☐ 10-12 months ago ☐ More than 12 months ago

☐ Not applicable ☐ Prefer not to say

24) Has a medical test ever guided your treatment (e.g., kidney or liver function)?

☐ Yes ☐ No ☐ Don't know ☐ Prefer not to say

25) Have you ever experienced a side effect from a medicine before?

☐ Yes ☐ No ☐ Don't know ☐ Prefer not to say

If YES, how would you categorise it?

☐ Mild ☐ Moderate ☐ Severe ☐ Prefer not to say ☐ N/A

26) Have you ever stopped taking a medicine because of a side effect you experienced?

☐ Yes ☐ No ☐ Don't know ☐ Prefer not to say ☐ N/A

If YES, was this based on doctor's recommendations?

☐ Yes ☐ No ☐ Don't know ☐ Prefer not to say ☐ N/A

27) Have you ever stopped taking a medicine because you felt it was not helping your condition?

☐ Yes ☐ No ☐ Don't know ☐ Prefer not to say ☐ N/A

If YES, was this based on doctor's recommendations?

☐ Yes ☐ No ☐ Don't know ☐ Prefer not to say ☐ N/A

28) Have you ever experienced a medication-related hospitalisation (e.g. due to side effects)?

☐ Yes ☐ No ☐ Prefer not to say

SECTION 3: PHARMACOGENOMICS

29) Have you ever heard of pharmacogenetic or pharmacogenomic testing?

☐ Yes ☐ No ☐ Don't know ☐ Prefer not to say

30) How would you rate your understanding of how pharmacogenomics can be used in healthcare?

☐ Excellent ☐ Good ☐ Fair ☐ Poor ☐ Very poor

☐ Prefer not to say

31) Have you ever had a genetic test?

☐ Yes ☐ No ☐ Don't know ☐ Prefer not to say

32) Do you think pharmacogenomic services should be offered in Ireland?

☐ Yes ☐ No ☐ Don't know ☐ Prefer not to say

33) If a pharmacogenomic service was provided in Ireland, what healthcare professional do you think should provide this service?

☐ Community pharmacists ☐ General practitioners

☐ Healthcare professionals based in the hospital setting

☐ Other (please specify) ☐ Prefer not to say

34) If you knew that your genetics could affect a medication you take, how likely would you be to use the genetic testing service?

☐ Very likely ☐ Somewhat likely ☐ Not very likely ☐ Not at all likely

☐ Prefer not to say

35) Do you feel that your genetics impacts your medications?

☐ Yes ☐ No ☐ Don't know ☐ Prefer not to say

SECTION 4: FACTORS ASSOCIATED WITH TAKING A PHARMACOGENOMIC TEST

36) Please indicate your level of agreement with the following statements (1= strongly agree, 2 = agree, 3 = neutral, 4 = disagree, 5 = strongly disagree).

I would like to get a pharmacogenomic test to:

a)	Predict my risk of experiencing a mild-moderate side effect (e.g., drowsiness, dizziness)	1	2	3	4	5
b)	Predict my risk of experiencing a serious side effect (e.g., heart failure or seizures)	1	2	3	4	5
c)	Select the most effective medicine to treat my illness	1	2	3	4	5
d)	Select the most appropriate dose and strength of medicine to treat my illness	1	2	3	4	5
e)	Reduce the number of medicines prescribed to me	1	2	3	4	5

Please state any other benefits having a pharmacogenomic test might have:

_____

37) Please indicate your level of agreement with the following statements (1= strongly agree, 2 = agree, 3 = neutral, 4 = disagree, 5 = strongly disagree)

I am concerned about getting a pharmacogenomic test because:

a)	The test might involve providing a saliva swab	1	2	3	4	5
b)	The test might involve providing a blood sample	1	2	3	4	5
c)	The test results are not available immediately	1	2	3	4	5
d)	I don't know who will be accessing my samples and test results	1	2	3	4	5
e)	The test could be expensive	1	2	3	4	5
f)	The test results might reveal that I have additional risk factors for another disease that I was unaware of	1	2	3	4	5
g)	The test might reveal that my current medication doesn't work for me	1	2	3	4	5

Please state any other concerns you may have:

_____

38) Please indicate your level of interest with the following statements (1= extremely interested, 2 = interested, 3 = neutral, 4 = not interested, 5 = not interested at all)

I am interested in getting a pharmacogenomic test:

a)	To help ensure I take the best available medicines for my current medical conditions	1	2	3	4	5
b)	To help ensure medicines I will receive in the future are the best medicines for me	1	2	3	4	5
c)	That also reveals additional risk information (e.g., risk of developing a certain disease)	1	2	3	4	5

d)	From my local community pharmacy	1	2	3	4	5
e)	From my local GP surgery	1	2	3	4	5
f)	From the nearest hospital to me	1	2	3	4	5
g)	That enables me to carry a card in my wallet/purse with the test results on it	1	2	3	4	5
h)	If the cost of testing is reimbursed by my insurance plan	1	2	3	4	5

39) If pharmacogenomic tests were available, what would be the maximum out-of-pocket cost you would be willing to pay for:

a)	A test in response to unexplained side effects	€25	€100	€250	€500	€750
b)	A test to ensure suitable medication use before those medicines are needed	€25	€100	€250	€500	€750
c)	A test to ensure suitable medication use before those medicines are needed and provide additional risk information	€25	€100	€250	€500	€750

Appendix 3.2. Poster for questionnaire study

Appendix 3.3. Questionnaire introduction and consent

INTRODUCTION

Thank you for your interest in this questionnaire.

We are undertaking a research study to understand people's preferences about using genetic tests to guide the choice of medications prescribed to them. Genetic tests are used in other countries for this purpose but are not commonly available in Ireland.

The information gathered will be used to help us understand if and how patients would like genetic tests to guide the choice of medications prescribed.

You do not have to take part in this study, it is entirely voluntary. If you decide to take part, there will be no adverse consequences. You can change your mind and opt-out at any time.

This survey should take approximately 15 minutes to complete and is broken down into the following four sections: (1) Demographics, (2) Healthcare, (3) Pharmacogenomics, and (4) Factors associated with choosing to take a pharmacogenomics test.

Please review the Participant Information Leaflet for more information.

CONSENT

There are five sections. Each section has a statement and asks you to tick the relevant box if you agree. Please ask any questions you may have when reading each of the statements by contacting the Principal Investigator Prof. Cristín Ryan: cristin.ryan@tcd.ie

Thank you for participating.

Please tick the box if you agree with the statement. All boxes need to be ticked in order to consent and proceed with the survey.

☐ I confirm I have read and understood the Information Leaflet for the above study. The information has been fully explained to me and I have been able to ask questions, all of which have been answered to my satisfaction.

☐ I understand that this study is entirely voluntary, and if I decide that I do not want to take part, I can stop taking part in this study at any time without giving a reason. I understand that deciding not to take part will not affect my future medical care. I understand that my survey data is anonymous and cannot be withdrawn after submission.

☐ I know how to contact the research team if I need to, and I understand that if I email the research team (for more information or to take part in the study) that the emails will be retained for seven years, in accordance with data protection legislation, after which the emails will be permanently deleted.

☐ I agree to take part in this research study having been fully informed of the risks, benefits and alternatives which are set out in full in the Information Leaflet which I have been provided with.

☐ I understand that to protect my anonymity any comments that I submit should not include any personal identifiable information.

Appendix 3.4. Questionnaire participant information leaflet

A questionnaire study investigating the Irish public's attitude towards pharmacogenomic testing

Site	School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin
Principal Investigator(s) and Co-Investigator(s) (insert names, titles and contact details)	Professor Cristín Ryan, MPharm, PhD, PGCHET, FHEA, Cristin.ryan@tcd.ie Mr Joseph O'Shea, MPharm, MPSI, Osheaj5@tcd.ie Claire Anne O'Brien, MPharm student, obriec64@tcd.ie Conor Morris, MPharm student, morrisc4@tcd.ie Eoin Dwyer, MPharm student, dwyereo@tcd.ie James McLaughlin, MPharm student, mclaugja@tcd.ie Laura Fitzpatrick, MPharm student, lafitzpa@tcd.ie Maire O'Meara, MPharm student, omearam3@tcd.ie Sarah Kelly, MPharm student, kellys81@tcd.ie Sophie Knox, MPharm student, knoxso@tcd.ie
Study Organiser/ Sponsor (if applicable)	Trinity College Dublin
Data Controllers	Trinity College Dublin
Data Protection Officer	Data Protection Officer Secretary's Office Trinity College Dublin Dublin 2

You are being invited to take part in a survey. The study is being conducted over the internet by Joseph O'Shea.

Before you decide whether you wish to take part, please read this information sheet carefully. Ask Joseph O'Shea any questions you may have. Don't feel rushed or under pressure to make a quick decision. You should understand the risks and benefits of taking part in this study so that you can make a decision that is right for you. You may wish to discuss it with your family, friends, or GP.

This leaflet has five main parts:

Part 1 – The Study

Part 2 – Data Protection

Part 3 – Costs, Funding and Approval

Part 4 – Future Research

Part 5 – Further Information

Part 1 – The Study

Why is this study being done?

We are doing this study to help us understand what patients and the public think of taking a genetic test to help guide the choice of medicine prescribed to you. It does not involve taking a genetic test, it involves answering questions about what you think of these tests. Data from the study will help us to understand patients' preferences about genetic tests to help guide the choice of medicines prescribed and if this is something that patients would like to be part of their care.

Why have I been invited to take part?

You are invited to take part if you are 18 years of age or over, understand the English language, and provide consent to participate. We would like to know what you think about using pharmacogenetic tests to guide the choice of medicines prescribed to you.

Do I have to take part? Can I withdraw?

You do not have to take part in this study, it is entirely voluntary. If you decide to take part, there will be no adverse consequences. You can change your mind and opt-out at any time. If you decide not to take part or to opt-out, it won't affect your current or future research participation or practice. If you decide to opt-out, you can do this by not completing the survey.

What happens if I change my mind?

You can change your mind about taking part at any time. Your future care or participation in other researcher studies will not be affected by a decision to withdraw. Please note, submitted surveys (whether completed or not) cannot be withdrawn as they are anonymous. No personal data will be gathered throughout this study, apart from the email address that you may have used to contact us for more information or to take part in the study. For participants who contacted the research team via email, these emails will be retained in line with data protection legislation. We will destroy your email address after seven years beyond completion of the study. We will not be able to link survey responses with any individual or email address.

How will the study be carried out?

The study will involve the online completion of a survey. If you decide to take part, a link to participate has been provided to you either via social media, or by email. You should click on this link which will bring you straight to the survey. The survey will be available for completion over a four-week period from 12th April – 10th May. General reminders to complete the survey will be circulated on a weekly basis. We will not know if you have already completed the survey, and if you have, you will be asked not to complete it again.

What will happen to me if I decide to take part?

If you decide to take part in this study, you will be sent a link to the survey in an email. Click on the link, and this will bring you to the questions in the survey. You will be asked to tick a box noting your consent for completing the survey, and there will also be instructions to guide you in how to complete the survey. The survey will take approximately 15 minutes to complete.

What will happen to my data?

Data will be analysed and used to inform further studies and also the provision of genetic tests to patients to guide the selection of medicines to treat their conditions. Results from the study will be published in academic journals and may also be presented at national and international conferences. Data storage and backup will comply with the data protection rules in health research:

- Responses to surveys will not be linked to email addresses.
- If any personal identifiers are provided while completing the survey, these will be removed, and de-identified.
- Data will be electronically stored and backed-up.
- All electronic computerised data throughout the study will be stored in a limited access OneDrive folder through Trinity College Dublin and encrypted password-protected laptop/computer.
- All electronic computerised data will be electronically backed up onto a Trinity College Dublin encrypted server.
- All data will be stored until the end of the study. Then it will be kept in an encrypted Trinity College Dublin server where it will be retained for seven years post study completion and will then be permanently deleted.
- Access to the data will be limited to the research team. The PhD candidate, Joseph O'Shea, will be responsible for ensuring data security under the supervision of Prof. Cristin Ryan.

Are there any benefits to taking part in this research?

Taking part in this study will not directly benefit you. However, the information you provide us will be used to help us inform the long-term provision of genetic tests to help guide the choice of medicines prescribed to you. This is a long-term research project, so the benefits of the research may not be seen for several years. By participating, you are helping to advance science and medicine for future generations.

Are there any risks to me or others if I take part?

There are no identified risks of taking part in this study, apart from losing the time taken to complete the questionnaire. You might feel inconvenient or uncomfortable in providing your opinion. However, questions will be general in nature and will not assess your own personal behaviour. Please note, there will be an opt out option for each question on the questionnaire, and you are free to cease participation at any time.

Health Information (Data); There is a very slight risk that a connection to your identity could be made, but this is highly unlikely. Great care will be taken to ensure the confidentiality of all data and the risk to participants of a breach of confidentiality is considered very low.

Will I be told the outcome of the study? Will I be told the results of any tests or investigations performed as part of this study that relate to me?

The results of the study will be reported in medical/scientific journals and disclosed at medical/scientific conferences. No information which reveals your identity will be disclosed.

Part 2 – Data Protection

What information about me (personal data) will be used as part of this study? Will my medical records be accessed?

Prior to completing the questionnaire: The only information we will have is the email address you used to contact study investigators for more information. No personal data will be collected. Medical records will not be accessed. No identifiable data will be collected in the survey, and data completed in the survey will not be linked to any email address.

What will happen to my personal data?

The only personal data that we will have will be the email address you use to contact us for further information about the study or to take part. This will be electronically stored on the researchers' Trinity College Dublin (TCD) email for seven years, then will be destroyed and permanently deleted. The retention period is in line with the GDPR.

Data from completed surveys will also be electronically stored and saved in a limited access OneDrive and Microsoft Teams folder in Trinity College Dublin and encrypted password-protected TCD computer for the study period, and will also be backed up onto TCD encrypted server. Data will be destroyed and permanently deleted seven years after study completion.

Who will access and use my personal data as part of this study?

Access to the data will be limited to the research team: Joseph O'Shea (PhD student), MPharm students involved (Claire Anne O'Brien, Conor Morris, Eoin Dwyer, James McLaughlin, Laura Fitzpatrick, Maire O'Meara, Sarah Kelly, Sophie Knox and the academic supervisor (Prof. Cristín Ryan).

Will my personal data be kept confidential? How will my data be kept safe?

Your privacy is important to us. We take many steps to make sure that we protect your confidentiality and keep your data safe. Here are some examples of how we do this:

Personal data type	Media format	Storage details
Contact email address	Electronic data (online)	The email addresses of those who contact the recruiting researchers for the study (JO'S and CR) will be retrievable from their respective TCD emails
Survey responses	Electronic document (.xlsx)	The electronic excel sheet will be stored and saved in a limited-access OneDrive and Microsoft Teams folder through TCD staff facility and encrypted password-protected TCD computer. Data will also be backed up onto the TCD encrypted servers

Note: Email addresses will not be linked to the survey responses.

- A data protection risk assessment was applied to this study identified that this study is low risk in terms of personal data processing.
- The research team members have successfully completed the required training on data protection law.
- All collected data will be anonymised. The results of the study will be reported in medical/scientific journals and disclosed at medical/scientific conferences and thesis dissertation. No information which reveals your identity will be disclosed.
- If something did go wrong or a data protection breach was suspected, a report will be submitted to the Data Protection Officer in Trinity College Dublin and comply with legislation regarding a suspected Data Protection breach.

What is the lawful basis to use my personal data?

By law,[1] we can use your personal information for scientific research[2] (in the public interest[3]). We will also ask for your explicit consent to use your data as a requirement of the Irish Health Research Regulations.

What are my rights?

You are entitled to:

- The right to access to your data and receive a copy of it
- The right to restrict or object to processing of your data
- The right to object to any further processing of the information we hold about you (except where it is de-identified)
- The right to have inaccurate information about you corrected or deleted
- The right to receive your data in a portable format and to have it transferred to another data controller
- The right to request deletion of your data

By law you can exercise the following rights in relation to your personal data, unless the request would make it impossible or very difficult to conduct the research. You can exercise these rights by contacting the Trinity College Data Protection Officer, Secretary's Office, Trinity College Dublin, Dublin 2, Ireland. Email: dataprotection@tcd.ie. Website: www.tcd.ie/privacy.

[1] The European General Data Protection Regulation (GDPR)
[2] *Article 9(2) (j))*
[3] *(Article 6(1)(e)*

Part 3 – Costs, Funding and Approval

Has this study been approved by a research ethics committee?

Yes, this study has been approved by the School of Pharmacy and Pharmaceutical Sciences Research Ethics Committee. Approval was granted on 29th March 2021, reference number 2021-02-01.

Who is organising and funding this study? Will the results be used for commercial purposes?

The research is being undertaken by a team of researchers in the School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin, including a PhD student and MPharm students, guided by a Principal Investigator. This research is not being funded by any organization. The researcher is not being paid for recruiting participants for this study. The results will not be used for commercial purposes.

Is there any payment for taking part? Will it cost me anything if I agree to take part?

No, we are not paying patients to take part in the study.

Part 4 – Future Research

Will my personal data and/or biological material be used in future studies?

Your data will not be used in future studies.

Part 5 – Further Information

Who should I contact for information or complaints?

If you have any concerns or questions, you can contact:

- Principal Investigator: Prof Cristín Ryan; cristin.ryan@tcd.ie
- PhD Student: Joseph O'Shea; osheaj5@tcd.ie
- Data Protection Officer, Trinity College Dublin: Data Protection Officer, Secretary's Office, Trinity College Dublin, Dublin 2, Ireland. Email: dataprotection@tcd.ie. Website: www.tcd.ie/privacy.

Under GDPR, if you are not satisfied with how your data is being processed, you have the right to lodge a complaint with the Office of the Data Protection Commission, 21 Fitzwilliam Square South, Dublin 2, Ireland. Website: www.dataprotection.ie.

Will I be contacted again?

No, you will not be contacted again.

Appendix 3.5. Questionnaire study ethical approval

Coláiste na Tríonóide, Baile Átha Cliath
Trinity College Dublin
Ollscoil Átha Cliath | The University of Dublin

Joseph O'Shea,
School of Pharmacy and Pharmaceutical Sciences,
Trinity College Dublin,
Dublin 2.

Ref. 2021-02-01

29 March 2021

Dear Joseph,

Re: A questionnaire study investigating the Irish public's attitude towards pharmacogenomic testing

I am pleased to inform you that the above project now has approval from the School of Pharmacy and Pharmaceutical Sciences Research Ethics Committee.

You are reminded that any significant deviation from the research description in the application requires approval from the School of Pharmacy and Pharmaceutical Sciences Research Ethics Committee before implementation.

Please also note the reporting requirements outlined on the Committee's website (http://pharmacy.tcd.ie/research/SoPPS_REC.php), in particular the need for:

- An immediate report in writing (by email to pharmacy.ethics@tcd.ie) of any serious or unexpected adverse events on participants, or unforeseen events that might affect the benefits/risks ratio as outlined in the application.
- Annual reports (report form on the Committee's website).
- An end of project report (report form on the Committee's website).

Please quote the reference number 2021-02-01 in any further correspondence.

Yours sincerely,

S. Ryder

Sheila Ryder,
Chairperson,
School of Pharmacy and Pharmaceutical Sciences Research Ethics Committee.

Sheila Ryder
Chairperson
Research Ethics Committee
School of Pharmacy and Pharmaceutical Sciences

Panoz Building, East End 4/5,
Trinity College,
Dublin 2, Ireland.

Tel. +353 1 896 2786
E-mail pharmacy.ethics@tcd.ie
http://pharmacy.tcd.ie/research/SoPPS_REC.php

Síle Ní Mharcaigh
Cathaoirleach
Coiste um Eitic Thaighde
Scoil na Cógaisíochta agus na nEolaíochtaí Cogaisíochta

Foirgneamh Panoz, An Taobh Thoir 4/5,
Coláiste na Tríonóide,
Baile Átha Cliath 2, Éire.

Teil. +353 1 896 2786
R-phost pharmacy.ethics@tcd.ie
http://pharmacy.tcd.ie/research/SoPPS_REC.php

Appendix 4.1. Consolidated pharmacogenomic recommendations from the CPIC and the DPWG to inform statin therapy [96-98]

In the interest of standardisation, a similar approach to Youssef *et al.* for formatting the guidelines was employed [99]; i.e., direct action meaning lower dose, higher dose, or alternative drug required and indirect action defined as optional dose or drug change, guarding against maximum doses and patient monitoring required. The CPIC and the DPWG guidelines were reviewed and their recommendations categorised in a standard format to assess drug-gene interactions. The CPIC and the DPWG published recommendations show a high rate of concordance; however, as a result of different guideline development methods used by these two consortia, differences between the published guidelines exists. Classification of recommendations in a standard format was informed by the level of evidence associated with a recommendation by the respective publisher. The CPIC rates the level of evidence on a three-point (optional-moderate-strong) scale [100], while the DPWG reviews the level of evidence and the level of clinical relevance on separate scales using a five point (0-4) and seven-point (AA-F) scale derived from the National Cancer Institute's Common Toxicity Criteria respectively [101].

The CPIC recommendations with a moderate or strong level of evidence have a moderate or high preponderance of evidence in favour of changing prescribing, and genetic information should be used, while an optional level indicates the evidence is weak with little conflicting data, and genetic information could be used to change prescribing. For all three recommendations, alternative therapies or dosing are highly likely to be safe and effective [100]. For the DPWG recommendations, the level of evidence of the drug-gene interaction indicates the quality of the evidence found in literature, with 0 demonstrating the lowest evidence and 4 the highest evidence. The clinical relevance of the potential adverse drug event, decreased therapeutic response, or other clinical effect resulting from the drug-gene interaction was scored on a seven-point scale with AA having the lowest impact and F the highest impact [101].

The levels of evidence reported by the DPWG were converted to the CPIC scale, with level 4 classified as strong, level 3 as moderate, and levels 0-2 as optional. If the level of evidence differed, the DPWG clinical relevance score was considered in the harmonisation process, with the lower level of evidence decided upon if the clinical relevance was AA-A and the higher level of evidence for the other clinical relevance rating. For example, if the CPIC rated a drug-gene interaction as optional, and the DPWG rated the same interaction as 3AA, the optional level was chosen; whereas, if the DPWG rated the interaction as 3C, the moderate level would be chosen. Recommendations with 'direct action' were those with a moderate or strong rating. Classification as 'indirect action' depended on the level of evidence being optional, or based on the recommendation type. Where disparities arose between the CPIC and the DPWG recommendations [102], both recommendations were considered and combined in ranges where appropriate. Additionally, the guidelines were checked to see whether the recommendations were dependent on specific patient factors, or concomitant medications.

Drug (When?)	Biomarker	Phenotype or Genotype (Who?)	Source (Where?)	Action (What?)	Therapeutic Recommendation (How?)	Further information (Why?)
Atorvastatin	SLCO1B1	521 CC or TC (rs4149056)	DPWG	Switch to alternate drug Observe status of patient carefully	If patient has additional significant risk factors for statin-induced myopathy: Prescribe an alternative not metabolised by SLCO1B1, such as fluvastatin Additional risk factors include advanced age, small body mass index, female gender, metabolic comorbidities, and vigorous physical exercise If alternative is not option or patient has no additional risk factors: Can take but advise patient to contact doctor in event of muscle symptoms	Increased risk of myopathy due to reduced metabolism resulting in higher PCs of active
Atorvastatin	SLCO1B1	IM *1/*5, *1/*15, *5/*6, *15/*10, *5/*43	CPIC	Lower dose required Optional switch to alternate drug Guard against maximum dose	Prescribe ≤ 40mg as a starting dose and adjust doses of atorvastatin based on disease-specific guidelines (possible increased risk for myopathy especially for 40mg dose). If dose > 40mg needed for desired efficacy, consider combination therapy (i.e., atorvastatin plus non-statin guideline directed medical therapy).	Increased risk of myopathy due to reduced metabolism resulting in higher PCs of active

Drug (When?)	Biomarker	Phenotype or Genotype (Who?)	Source (Where?)	Action (What?)	Therapeutic Recommendation (How?)	Further information (Why?)
Atorvastatin	SLCO1B1	PM *5/*5, *5/*15, *15/*15	CPIC	Lower dose required Optional switch to alternate drug Guard against maximum dose	Prescribe ≤ 20mg as a starting dose and adjust doses of atorvastatin based on disease-specific guidelines. If dose >20mg is needed for desired efficacy, consider rosuvastatin or combination therapy (i.e., atorvastatin plus non-statin guideline directed medical therapy).	Increased risk of myopathy due to reduced metabolism resulting in higher PCs of active
Fluvastatin	SLCO1B1	IM *1/*5, *1/*15, *5/*6, *15/*10, *5/*43	CPIC	Guard against maximum dose	Prescribe desired starting dose and adjust doses of fluvastatin based on disease-specific guidelines (possible increased risk for myopathy especially with doses >40mg per day).	Increased risk of myopathy due to reduced metabolism resulting in higher PCs of active
Fluvastatin	SLCO1B1	PM *5/*5, *5/*15, *15/*15	CPIC	Lower dose required Optional switch to alternate drug Guard against maximum dose	Prescribe ≤ 40mg per day as a starting dose and adjust doses of fluvastatin based on disease-specific guidelines (possible increased risk for myopathy especially with doses >40mg per day). If patient is tolerating 40mg per day but higher potency is needed, a higher dose (> 40mg) or an alternative statin (e.g., rosuvastatin 20 mg) or combination therapy (i.e. fluvastatin plus non-statin	Increased risk of myopathy due to reduced metabolism resulting in higher PCs of active

Drug (When?)	Biomarker	Phenotype or Genotype (Who?)	Source (Where?)	Action (What?)	Therapeutic Recommendation (How?)	Further information (Why?)
					guideline directed medical therapy) could be considered.	
Lovastatin	SLCO1B1	IM *1/*5, *1/*15, *5/*6, *15/*10, *5/*43	CPIC	Switch to alternate drug Lower dose required	Prescribe an alternative statin depending on the desired potency. If lovastatin therapy is warranted, limit dose to ≤20mg/day.	Increased risk of myopathy due to reduced metabolism resulting in higher PCs of active
Lovastatin	SLCO1B1	PM *5/*5, *5/*15, *15/*15	CPIC	Switch to alternate drug	Prescribe an alternative statin depending on the desired potency.	Increased risk of myopathy due to reduced metabolism resulting in higher PCs of active
Pitavastatin	SLCO1B1	IM *1/*5, *1/*15, *5/*6, *15/*10, *5/*43	CPIC	Lower dose required Optional switch to alternate drug Guard against maximum dose	Prescribe ≤ 2mg as a starting dose and adjust doses of pitavastatin based on disease-specific guidelines (possible increased risk for myopathy especially for doses > 1mg). If dose > 2mg needed for desired efficacy, consider an alternative statin (e.g. rosuvastatin 20 mg) or combination therapy (i.e. pitavastatin plus non-statin guideline directed medical therapy).	Increased risk of myopathy due to reduced metabolism resulting in higher PCs of active

Drug (When?)	Biomarker	Phenotype or Genotype (Who?)	Source (Where?)	Action (What?)	Therapeutic Recommendation (How?)	Further information (Why?)
Pitavastatin	SLCO1B1	PM *5/*5, *5/*15, *15/*15	CPIC	Lower dose required Optional switch to alternate drug Guard against maximum dose	Prescribe ≤ 1mg as a starting dose and adjust doses of pitavastatin based on disease-specific guidelines. If dose > 1mg needed for desired efficacy, consider an alternative statin or combination therapy (i.e. pitavastatin plus non-statin guideline directed medical therapy).	Increased risk of myopathy due to reduced metabolism resulting in higher PCs of active
Pravastatin	SLCO1B1	IM *1/*5, *1/*15, *5/*6, *15/*10, *5/*43	CPIC	Guard against maximum dose	Prescribe desired starting dose and adjust doses of pravastatin based on disease-specific guidelines (possible increased risk for myopathy with pravastatin especially with doses > 40mg per day).	Increased risk of myopathy due to reduced metabolism resulting in higher PCs of active
Pravastatin	SLCO1B1	PM *5/*5, *5/*15, *15/*15	CPIC	Lower dose required Optional switch to alternate drug Guard against maximum dose	Prescribe ≤ 40mg as a starting dose and adjust doses of pravastatin based on disease-specific guidelines (possible increased risk for myopathy especially with pravastatin doses > 40mg). If patient is tolerating 40mg dose but higher potency is needed, a higher dose (> 40mg) or an alternative statin or combination therapy (i.e. pravastatin	Increased risk of myopathy due to reduced metabolism resulting in higher PCs of active

Drug (When?)	Biomarker	Phenotype or Genotype (Who?)	Source (Where?)	Action (What?)	Therapeutic Recommendation (How?)	Further information (Why?)
					plus non-statin guideline directed medical therapy) could be considered.	
Rosuvastatin	SLCO1B1	IM *1/*5, *1/*15, *5/*6, *15/*10, *5/*43	CPIC	Guard against maximum dose	Prescribe desired starting dose and adjust doses of rosuvastatin based on disease-specific and specific population guidelines (possible increased risk for myopathy especially for doses > 20mg).	Increased risk of myopathy due to reduced metabolism resulting in higher PCs of active
Rosuvastatin	SLCO1B1	PM *5/*5, *5/*15, *15/*15	CPIC	Lower dose required Optional switch to alternate drug Guard against maximum dose	Prescribe ≤ 20mg as a starting dose and adjust doses of rosuvastatin based on disease-specific and specific population guidelines. If dose > 20mg needed for desired efficacy, consider combination therapy (i.e. rosuvastatin plus non-statin guideline directed medical therapy).	Increased risk of myopathy due to reduced metabolism resulting in higher PCs of active
Rosuvastatin	SLCO1B1	rs4149056 CC	FDA	Observe status of patient carefully	Results in higher systemic concentrations	Potential impact on pharmacokinetic properties only This interaction is a low level of evidence

Drug (When?)	Biomarker	Phenotype or Genotype (Who?)	Source (Where?)	Action (What?)	Therapeutic Recommendation (How?)	Further information (Why?)
Rosuvastatin	ABCG2	PM c.421 A/A (rs2231142)	CPIC	Lower dose required Optional switch to alternate drug Guard against maximum dose	Prescribe ≤ 20mg as a starting dose and adjust doses of rosuvastatin based on disease-specific and specific population guidelines. If dose > 20mg needed for desired efficacy, consider an alternative statin or combination therapy (i.e., rosuvastatin plus non-statin guideline directed medical therapy).	Unknown risk of myopathy and increased lipid-lowering effects due to increased exposure
Simvastatin	SLCO1B1	IM *1/*5, *1/*15, *5/*6, *15/*10, *5/*43	CPIC	Switch to alternate drug Lower dose required	Prescribe an alternative statin depending on the desired potency. If simvastatin therapy is warranted, limit dose to < 20mg/day.	Increased risk of myopathy due to reduced metabolism resulting in higher PCs of active
Simvastatin	SLCO1B1	PM *5/*5, *5/*15, *15/*15	CPIC	Switch to alternate drug	Prescribe an alternative statin depending on the desired potency.	Increased risk of myopathy due to reduced metabolism resulting in higher PCs of active
Simvastatin	SLCO1B1	rs4149056 TC	CPIC and DPWG	Switch to alternate drug Lower dose required	Use a lower dose; reduce the dose to 40 mg/day maximum; advise patient to report muscle symptoms In the event of treatment failure or	Increased risk of myopathy (intermediate) due to reduced

Drug (When?)	Biomarker	Phenotype or Genotype (Who?)	Source (Where?)	Action (What?)	Therapeutic Recommendation (How?)	Further information (Why?)
				Guard against maximum dose Observe status of patient carefully	toxicity, prescribe an alternative, such as pravastatin, rosuvastatin or fluvastatin Consider monitoring creatinine phosphokinase levels and additional risk factors for statin-induced myopathy Avoid combining the statin with OATP1B1 inhibitors (susceptible of increasing the exposure to statins)	metabolism resulting in higher PCs of active
Simvastatin	SLCO1B1	rs4149056 CC	CPIC and DPWG	Switch to alternate drug Lower dose required Guard against maximum dose Observe status of patient carefully	Use a lower dose; reduce the dose to 20 mg/day maximum; advise patient to report muscle symptoms (DPWG do not advise a dose reduction) In the event of treatment failure or toxicity, prescribe an alternative, such as pravastatin, rosuvastatin or fluvastatin Consider monitoring creatinine phosphokinase levels and additional risk factors for statin-induced myopathy Avoid combining the statin with OATP1B1 inhibitors (susceptible of increasing the exposure to statins)	Increased risk of myopathy (high) due to reduced metabolism resulting in higher PCs of active

Appendix 4.2. Consolidated list of SLCO1B1 and ABCG2 genetic variants

Gene	Allele	Variant Position	Effect on Protein	dbSNP rsID	Functional Status	MAF
ABCG2	c.421 A/A	88131171G>T	N/A	rs2231142	Decreased function	0.12
SLCO1B1	*5/*15/*17	21178615T>C	V174A	rs4149056	Decreased function	0.22
SLCO1B1	*5	21178615T>C	V174A	rs4149056	No function	0.12
SLCO1B1	*9	21205999G>C	G488A	rs59502379	No function	0.01
SLCO1B1	*14	21176879C>A	P155T	rs11045819	Increased function	0.12
SLCO1B1	*14	21176804A>G	N130D	rs2306283	Increased function	0.62
SLCO1B1	*15	21178615T>C	V174A	rs4149056	No function	0.12
SLCO1B1	*15	21176804A>G	N130D	rs2306283	Increased function	0.62
SLCO1B1	*20	21239042A>C	L643F	rs34671512	Increased function	0.05
SLCO1B1	*23	21172776G>A	G71R	rs373327528	No function	<0.01
SLCO1B1	*31	21205999G>C	G488A	rs59502379	No function	0.01
SLCO1B1	*31	21176804A>G	N130D	rs2306283	Increased function	0.62
SLCO1B1	*46	21178615T>C	V174A	rs4149056	No function	0.12
SLCO1B1	*46	21222355C>T	R580X	rs71581941	No function	<0.01
SLCO1B1	*47	21200544C>G	P336R	rs72559747	No function	<0.01

Appendix 4.3. The St. Vincent's Screening to Prevent Heart Failure (STOP-HF) follow-up programme consent form

St. Vincent's Healthcare GROUP LIMITED

ELM PARK, DUBLIN 4
HEART FAILURE UNIT, ST. VINCENT'S AND ST. MICHAEL'S HOSPITALS

The STOP HF Follow Up Programme - Consent Form

Name: .....

Address: .....

Date of Birth: .....

I confirm that I have read and understand the participants' information guide for the STOP HF Follow-Up Programme dated 7.11.13 2013.

I have been given the opportunity to ask questions and all of my questions have been answered.

I feel that I have received enough information about this programme.

I understand that my participation is entirely voluntary and that I am free to withdraw at any time without my medical care or legal rights being affected.

I agree that information pertaining to my health may be collected from my General Practitioner and my hospital records.

By signing this form, I agree that the data collected for the study can be used for research, presentation and publication, preserving my anonymity.

I understand that my General Practitioner and /or consultant will be informed of any relevant findings or changes to my treatment.

I agree that all my blood that has been taken and will be stored at each visit can be used for the purpose of medical research, including genetic testing and future unspecified use subject to approval by an Ethics Committee.

I agree that my anonymised blood and medical data can be sent to central research facilities outside of Ireland.

_____	_____	_____
Signature of Participant	**Date**	**Name in block capitals**
_____	_____	_____
Signature of Practitioner	**Date**	**Name in block capitals**

Appendix 4.4. The STOP-HF follow-up programme patient information leaflet

ELM PARK, DUBLIN 4
HEART FAILURE UNIT, ST. VINCENT'S AND ST. MICHAEL'S HOSPITALS

The St Vincent's Screening To Prevent Heart Failure (STOP-HF) Follow-Up programme

PARTICIPANTS' INFORMATION LEAFLET

NAME OF PRINCIPAL INVESTIGATORS:
Professor Kenneth McDonald MD, FRCPI (Consultant Cardiologist), Dr Chris Watson, University College Dublin and Dr. Mark Ledwidge (Research Director) Heartbeat Trust and St Vincent's Heart Failure Unit.

INTRODUCTION
Heart Failure is a medical condition that can result if not properly managed in a reduced quality of life and shortened life expectancy. It is a very common problem throughout the world and affects approximately 100,000 people in Ireland. Many more are at risk of developing this problem and it is this group who are the focus of the STOP HF (screening to prevent heart failure) follow-up programme run by Professor Ken McDonald (Consultant Cardiologist) and The Heartbeat Trust (a registered charity) team.

The STOP HF programme was started as a research programme in 2004 and results show that using blood screening and collaborative care between the hospital and the general practitioner (GP) can reduce heart failure and other serious cardiovascular events. Since 2011, it is a clinical screening programme monitoring those with risk factors for heart failure and defining their risk by the use of a blood test known as Natriuretic Peptide (NP). NP is a protein that is released from the heart when it is under stress or strain. People with risk factors for developing heart failure and in particular those with high blood pressure, high cholesterol, diabetes or a prior heart attack are invited to partake. All participants are actively cared for by their GP and if necessary referred to a consultant for further investigations. Those with a BNP > 50pg/ml will be reviewed by a specialist doctor.

WHAT IS THE PURPOSE OF THIS STUDY?
The Heartbeat Trust is working with other specialist centres throughout the world in an effort to improve detection and prevention of heart failure. Together, it is hoped to identify new "biomarkers" or blood tests that can help further improve detection and prevention of heart failure.

WHO IS ORGANISING AND FUNDING THIS RESEARCH?
This study is sponsored by the European Commission and the Heartbeat Trust and is being conducted in Ireland by St. Vincent's University Healthcare Group and University College Dublin.

WHAT IS THE ROLE OF ST. VINCENT'S UNIVERSITY HEALTHCARE GROUP, THE HEARTBEAT TRUST AND UNIVERSITY COLLEGE DUBLIN'S IN THIS STUDY:
St. Vincent's University Hospital, the Heartbeat Trust and University College Dublin are working with other specialist research centres throughout Europe in an effort to improve detection and prevention of heart failure. It is believed that a collaborative approach to research in this area will be the fastest and most effective way to improve patient care. This will require sharing our information with our European colleagues to create a large research population.

WHY HAVE I BEEN CHOSEN?

You have been chosen because you have risk factors for heart failure (e.g. high blood pressure, high cholesterol, high triglycerides, diabetes and / or overweight).

WHAT WILL HAPPEN IF I VOLUNTEER?

Your participation is entirely voluntary. You will also receive an assessment every one to three years depending on the NP result. Assessment includes taking a history of your risk factors for heart failure, your up to date medical and surgical history, medications being taken, and assessment of any symptoms you may have. You will have your blood pressure, heart rate, weight and abdominal girth taken. You will also have an electrocardiogram (ECG) and echocardiogram (a scan of your heart) done.

The information that we have gathered about you and the results of the investigations carried out during your hospital visits may be sent anonymously to a central database outside Ireland. Your data will be coded in a way that it will be impossible to identify you.

If you agree to participate, and you are a participant in another research programme, we may use some of the blood samples we have in storage belonging to you. Otherwise, you will be requested to donate a blood sample of 3 tablespoons in total along with a saliva and a urine sample, all of which will be stored for the duration of the study. This blood will be taken for analysis of NP, non-fasting cholesterol and non-fasting glucose (results will be given to you at the time of your visit). At intervals, we may take blood for U&E, HBA1c and fasting lipid testing (we will inform you if you need to fast when making your appointment to attend). Some of your blood will also be stored for further analysis and genetic testing.

When we store parrticipant samples, it is called a “biobank”, which is very useful for research. Occasionally, some samples will be sent anonymously from the hospital to a central “biobank” in outside of Ireland. These central storage facilities are safe places with specialised personnel. If other “biomarkers” come along that could be better than those we have at the moment we can test for them too. Only authorised personnel involved in this research will be allowed to analyse the samples. Your sample will be used for “biomarker” analysis. Your sample will be anonymous and you will not be identifiable with the sample, except by the team in St. Vincent’s University Healthcare Group. The results of the genetic tests are for research purposes only and will not be shared with you, your GP or noted in your medical chart.

All participants are educated in how best to manage their risk factors for heart failure including diet and lifestyle.

Information pertaining to your health may at intervals be collected from your General Practitioner (GP) and your hospital records

DO I HAVE TO TAKE PART AND WHAT HAPPENS IF I DO NOT AGREE TO PARTICIPATE?

Your participation is entirely voluntary. If you choose not to participate in the STOP-HF follow up study your medical care, your participation in other research studies and your rights will not be affected in any way. If you initially decide to take part you can subsequently change your mind without difficulty. Furthermore your doctor may decide to withdraw you from the study if he/she feels it is in your best interest.

ARE THERE ANY BENEFITS FROM MY PARTICIPATION?

You will not benefit directly from taking part in this study but the information that may be obtained may provide further knowledge of this condition and could improve future healthcare approaches.

ARE THERE ANY RISKS INVOLVED IN PARTICIPATING?

The only risk involved is related to the taking of your blood samples Having blood taken from a vein involves very little risk other than mild discomfort, bruising, feeling faint or fainting. On very rare occasions bleeding, infection, clot formation and / or nerve damage can occur but these complications are extremely rare. The risks of any other investigations and / or treatments recommended as a result of any abnormalities detected will be thoroughly explained to you

CONFIDENTIALITY

Your identity and data at all times will remain confidential. A study number will identify you. Your name will not be published or disclosed to anyone. Only authorised trained personnel within the hospital will have access to your identifiable data and samples. Data will be collected as usual in the paper based record and the secure database of the Heartbeat Trust and St. Vincent's Heart Failure Unit. The data will also be stored in an electronic case report form (eCRF). The data will be encrypted and stored on secure servers. It may be shared anonymously with centres outside of Ireland.

INSURANCE

Your doctors are adequately insured by virtue of their participation in the clinical indemnity scheme in the unlikely event of a study related injury. You will not be paid for taking part in this study. No expenses can be covered for taking part in this study.

HAS THIS STUDY BEEN REVIEWED BY AN ETHICS COMMITTEE?

The St. Vincent's Healthcare Group, Ethics and Medical Research Committee have reviewed and approved this study.

HOW TO CONTACT US

Many thanks for taking the time to read this. If you have queries / questions in relation to the study, please do not hesitate to ask us or contact us. Phone (01) 2713072

Appendix 4.5. The STOP-HF follow-up programme ethical approval

St. Vincent's Healthcare GROUP LIMITED

UCD DUBLIN

Ethics and Medical Research Committee
ELM PARK, DUBLIN 4
Tel. (01) 2214117 Fax (01) 2214428
email: joan.mcdonnell@ucd.ie or jacinta.mcmanus@ucd.ie

5th December, 2013.

Professor K. McDonald,
Consultant Cardiologist,
St. Vincent's University Hospital,
Elm Park,
Dublin 4.

Re: The STOP HF Screening Programme. Letter dated 15th November 2013. Amendment Notification Form signed and dated 15/11/13. PIL/Consent dated 7/11/13. Change of study title to "'STOP-HF Follow Up Programme".

Dear Professor McDonald,

The above amendment was reviewed at the Ethics and Medical Research Committee meeting held on Wednesday 4th December 2013.

This amendment was approved.

Yours sincerely,

Dr. E. McKone,
Chairman,
Ethics and Medical Research Committee.

cc Ms E. Tallon, Research Nurse, Heart Failure Unit, St. Michael's Hospital.

Appendix 4.6. STOP-HF material transfer agreement

The Provost, Fellows, Foundation Scholars, and the other members of Board, of the College of the Holy and Undivided Trinity of Queen Elizabeth near Dublin

and

Heartbeat Trust Company Limited by Guarantee

MATERIALS AND DATA TRANSFER AGREEMENT

This Agreement is made by and between

(1) **Heartbeat Trust CLG**, with an address at 3 Crofton Terrace, Dun Laoghaire, Co. Dublin (the "**Provider**" and "**HBT**"); and

(2) **The Provost, Fellows, Foundation Scholars, and the other members of Board, of the College of the Holy and Undivided Trinity of Queen Elizabeth near Dublin**, with an address at College Green, Dublin 2, Ireland. ("**Recipient**" and "**TRINITY**").

(hereinafter collectively referred to as "**Parties**" or individually as "**Party**").

Whereas:

A. HBT acting through Professor Mark Ledwidge is the custodian of certain Material as set out in Schedule 2, and Data related to the STOP-HF biomarker and STOP-HF pharmacogenomic studies as more particularly outlined in Schedule 1 to this Agreement ("**Data**");

B. TRINITY acting through Professor Cristin Ryan has approached HBT and requested that the Material and associated Data be transferred to the Recipient for the purpose of research and teaching, including joint HBT/TRINITY PhD research of Ms Claire Sweeney and Mr Joseph O'Shea as more particularly described in Schedule 1 ("**Purpose**");

C. HBT is willing to make the Material and Data available to Recipient for the Purpose subject to the terms and conditions of this Agreement;

D. Both Parties acknowledge that the Data is Anonymised (as defined below) to the Recipient but Pseudonymised to the Provider.

In consideration of the mutual promises and covenants herein, and for other good and valuable consideration, the receipt and sufficiency of which is hereby acknowledged, the Parties agree as follows:

1. Interpretation

1.1 *Definitions.* In this Agreement (and the background recitals above), unless the context requires otherwise or unless otherwise specified the following words shall have the following meanings:

Anonymised	shall mean Personal Data rendered anonymous in such a way that the Data Subject is not identifiable.

Confidential Information	shall mean but not be limited to all information (including, without limitation, the Data, and any and all related documentation, know-how, trade secrets, or business or research plans) that is provided by HBT to or otherwise made available to the Recipient in connection with this Agreement.
Data	shall mean all data shared by HBT under the terms of this Agreement as identified in Schedule 1.
Effective Date	shall mean the date of the last Party to sign this Agreement.
FOIA	shall mean the Irish Freedom of Information Act 2014, as amended, revised, modified or replaced from time to time.
Intellectual Property (IP)	shall mean all intellectual property of any description including Know-How, copyright, trademarks, database rights, design rights, patents, utility models, and applications for, and the right to apply for any of the foregoing items.
Material	shall mean the biomaterials shared by HBT under the terms of this Agreement as identified in Schedule 2.
Know-How	shall mean any unpatented technical information (including, without limitation, information relating to inventions, discoveries, concepts, methodologies, models, research, development and testing procedures, the results of experiments, tests and trials, manufacturing processes, techniques and specifications, quality control data, analyses, reports and submissions) that is not in the public domain.
Person	Shall mean a natural or legal person, public authority, agency or other body.
Personal Data	shall mean any information relating to an identified or identifiable natural person ('**Data Subject**'); an identifiable natural person is one who can be identified, directly or indirectly, in particular by reference to an identifier such as a name, an identification number, location data, an online identifier or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that natural person; For the avoidance of doubt Pseudonymised Data is Personal Data.

Pseudonymised	shall mean Personal Data which has been processed in such a manner that the Personal Data can no longer be attributed to a specific Data Subject without the use of additional information, provided that such additional information is kept separately and is subject to technical and organisational measures to ensure that the Personal Data are not attributed to an identified or identifiable natural person.
Results	shall mean all information, results, know-how, and New Data (as defined in Clause 6.3) arising from the Purpose that is created or developed, as a result of the use of the Data.

1.2 *Construction.* In this Agreement, unless the context requires otherwise:

(a) the headings are used for convenience only and shall not affect its interpretation;

(b) references to persons shall include incorporated and unincorporated persons; references to the singular include the plural and vice versa; and references to either gender include the other and the neuter;

(c) references to Clauses and Schedules mean clauses of, and schedules to, this Agreement;

(d) references in this Agreement to termination shall include termination by expiry;

(e) where the word "including" is used it shall be understood as meaning "including without limitation";

(f) time shall be construed by reference to time in Ireland;

(g) 'this Agreement' mean the Clauses of, and the Schedules to, this Agreement, all of which shall be read as one document; and

(h) 'business day' shall be construed as a reference to a day (other than a Saturday or Sunday) on which the banks are generally open for business in Ireland.

1.3 If any ambiguity or question of intent or interpretation arises, this Agreement shall be construed as if drafted jointly by the Parties and no presumption or burden of proof shall arise favouring or disfavouring any Party by virtue of the authorship of any of the provisions of this Agreement.

2. Licence of Data and Material

2.1 The Parties agree that the Data and Material is Anonymised to the Recipient.

2.2 Subject to the terms and conditions of this Agreement, HBT hereby grants to the RECIPIENT a non-exclusive, revocable, non-transferable, fully paid up licence to use the Data and Material solely for the Purpose and for no other purpose, for a period commencing on the Effective Date and ending on 1 September 2024 (**"Term"**) unless terminated earlier in accordance with this Agreement. The Term may be extended as mutually agreed in writing by the Parties.

2.3 Following the Effective Date, HBT shall use reasonable efforts to provide RECIPIENT with sufficient amounts of Material, as available, for RECIPIENT for the Purpose. The amount and sufficiency of Material provided cannot be guaranteed.

2.4 RECIPIENT shall keep the Material in a secure place at RECIPIENT scientist's laboratory at all times and the RECIPIENT shall ensure that no-one other than the RECIPIENT scientist and RECIPIENT authorised personnel have access to it.

2.5 RECIPIENT acknowledges that the Material being supplied may have unknown characteristics and may potentially contain viruses, latent viral genomes or other infectious agents. RECIPIENT warrants that it has the knowledge and ability to safely handle any Material supplied to it and agrees to use prudence and care in the use, handling, storage, transportation, containment, and disposal of the Material and all derivatives thereof. All costs and expenses associated with such protective measures shall be borne by RECIPIENT.

3. Recipient Obligations

3.1 Recipient shall not:

3.1.1 sell, transfer, supply, distribute or release any of the Data or Material to any third party, without the prior written consent of HBT;

3.1.2 use the Data or Material for any commercial purpose nor make any commercial or other gain from the Data or Material nor seek to obtain any protection of any Intellectual Property which may be contained in Data or Material;

3.1.3 use the Data or Material for any other purpose other than the Purpose; and/or

3.1.4 seek to identify the donors of Materials or any Data Subjects that may be linked to the Data nor contact any such donors or Data Subjects.

3.2 Recipient shall:

3.2.1 use the Material in accordance with good laboratory practice, and the highest standards of skill and care, and RECIPIENT shall comply with all applicable laws and regulations governing the transportation, keeping, use or disposal of the Material;

3.2.2 use appropriate safeguards to prevent use of the Material other than as provided for by this Agreement;

3.2.3 ensure that any agent, including any subcontractors or research personnel under the supervision of the Recipient, to whom it provides or makes available the Material, and/or Data agrees in writing to the same restrictions and conditions that apply throughout this Agreement.

4. Security and Confidentiality of the Data

4.1 Recipient shall at all times be responsible for ensuring the Data is stored securely.

4.2 The Data provided under this Agreement shall be considered the Confidential Information of HBT. Recipient shall use appropriate administrative, physical and technical safeguards to ensure

the security of the Personal Data and guard against unauthorised access thereto or disclosure thereof or loss or destruction while in its custody.

4.3 RECIPIENT shall ensure that all personnel who have access to and/or process the Data are obliged to keep the Data confidential.

4.4 RECIPIENT shall immediately report to HBT any use or disclosure of Data not provided for by this Agreement of which Recipient becomes aware.

4.5 The obligations of confidentiality and limited use under this clause shall not extend to any information:

(a) the RECIPIENT possessed before HBT disclosed it to the RECIPIENT; or

(b) is or becomes publicly known, other than as a result of breach of the terms of this Agreement by the RECIPIENT or by anyone to whom the RECIPIENT disclosed it; or

(c) the RECIPIENT obtains from a third party, and the third party was not under any obligation of confidentiality to HBT with respect to the Confidential Information; or

(d) the RECIPIENT can show (as demonstrated by its written records or other reasonable evidence) has been independently developed by any of the RECIPIENT'S employees or authorised persons who have not had any direct or indirect access to, or use or knowledge of, the Confidential Information.

5. Freedom of Information

5.1 The Parties shall cooperate in the handling and disposal of any requests made to either of them under the FOIA or the equivalent laws and regulations applicable to the Data in Recipient's place and country.

6. Intellectual Property and Publication

6.1 All title and ownership of the Data and Material, shall remain with HBT. All title and ownership of Results shall remain with TRINITY.

6.2 RECIPIENT shall grant HBT a non-exclusive, non-transferable, perpetual, worldwide, royalty-free licence to use Results that are created by RECIPIENT for non-commercial internal research purposes only.

6.3 RECIPIENT shall promptly notify HBT of any new developments or patentable findings or inventions resulting from RECIPIENT'S use of Data and/or Material (**"New Data")** and shall provide Professor Mark Ledwidge or any alternative person nominated by the HBT in writing with a copy of any New Data generated by it including but not limited to all raw data.

6.4 If RECIPIENT desires to publish any Results in a scientific publication, RECIPIENT will provide Professor Mark Ledwidge or the nominee with a copy of any manuscript or abstract disclosing such results prior to submission thereof to a publisher or to any third party not less than ninety (90) days prior to any public disclosure for his review. In no event should any such publication

disclose Confidential Information without prior written approval from HBT. The RECIPIENT shall make the necessary acknowledgements regarding the source of Data and Materials in any publication which mentions same. Authorship shall be accredited to the relevant Party where applicable, in accordance with the usual academic custom.

7. Warranties and Undertakings

7.1 Each Party acknowledges that, in entering into this Agreement, it does not do so in reliance on any representation, warranty or other provision except as expressly provided in this Agreement, and any conditions, warranties or other terms implied by statute or common law are excluded from this Agreement to the fullest extent permitted by law.

7.2 Each Party warrants to the other that it has full power and authority and has taken all necessary actions and obtained all authorisations, and licences, to allow it to enter into this Agreement.

7.3 RECIPIENT warrants and undertakes that no effort shall be made to identify the donor of Materials or any Data Subjects that may be linked to the Data either alone or in conjunction with any other information. Should RECIPIENT inadvertently identify such donor or Data Subject it shall notify HBT immediately, and it shall not reveal this information to any other Person.

8. Liability and Disclaimer

8.1 The Material is provided by HBT on an "AS IS" basis and the Material is understood to be of an experimental nature. All Material is being provided WITHOUT WARRANTY OR REPRESENTATIONS (INCLUDING but not limited to: FITNESS FOR A PARTICULAR PURPOSE, ACCURACY, EFFICACY, COMPLETENESS, CAPABILITIES OR SAFETY, AND ALL WARRANTIES AND REPRESENTATIONS WITH RESPECT TO THE MATERIAL WHETHER EXPRESS OR IMPLIED ARE HEREBY EXCLUDED TO THE GREATEST EXTENT PERMISSIBLE BY LAW .

8.2 HBT takes no responsibility for the accuracy, currency, reliability and correctness of the Data, nor the accuracy, currency, reliability and correctness of links or references to other information sources and disclaims all warranties in relation to such Data, links and references to the maximum extent permitted by law.

8.3 RECIPIENT agrees neither HBT nor its employees, servants or agents shall have any liability whether in contract, tort, statute or otherwise in connection with HBT's supply or Recipient's use, storage, handling and/or disposal of the Data and Material. RECIPIENT uses or relies on the Data and Material at its own risk. RECIPIENT hereby indemnifies HBT and shall keep HBT indemnified against all liabilities, losses, damages costs or expenses (including but not limited to direct, indirect or consequential losses, loss of profit, loss of reputation, suffered or incurred by HBT arising out of or in connection with any Claims and Losses made against it in relation to any breach by Recipient of its obligations. For the purposes of this Agreement (i) "Claims" shall mean all demands, claims, proceedings, penalties, fines and liability (whether criminal or civil), in contract, tort, negligence or otherwise and (ii) "Losses" shall mean all losses, including without limitation financial losses, damages, legal costs and other expenses of any nature whatsoever

8.4 Each Party shall maintain in full force and effect during the term of this Agreement, such insurance coverage arrangements as it deems appropriate and applicable, at its own costs, to cover its own acts and activities under this Agreement.

9. Termination

9.1 Either Party may terminate this Agreement upon thirty (30) day's written notice to the other Party.

9.2 Upon expiration or termination of this Agreement for any reason, Recipient shall, as requested by HBT, destroy or return all Data provided pursuant to this Agreement. Licence to use any such Data shall terminate on expiry or termination.

9.3 The provisions of this clause, and in addition clauses 6, 7, 8, 10 and to the extent applicable 11, shall survive the termination or expiry of this Agreement.

10. Dispute Resolution

10.1 The Parties shall make every reasonable effort to resolve all issues fairly by negotiation.

10.2 In the event that the dispute has not been settled amicably within sixty (60) days, it shall be submitted for mediation by a mediator or other appropriate independent third-party expert agreed by the Parties or, in default of agreement, appointed by the Centre for Dispute Resolution in Dublin. The cost of any such mediator or expert shall be borne equally by the Parties.

10.3 For the avoidance of doubt, however, nothing in this Clause 10 shall prevent or delay a Party from applying to a court of competent jurisdiction for the purposes of seeking injunctive relief provided that there is no delay in the prosecution of that application.

11. General

11.1 *Amendments.* This Agreement may only be amended in writing signed by duly authorised representatives of the Parties.

11.2 *Independent contractors.* The relationship of HBT to Recipient shall be that of independent contractor. This Agreement is not intended to, and does not, create any contract of employment or other legal relationship between the Parties.

11.3 *Sub-contracting.* Recipient shall ensure that any agent, including a sub-contractor, to whom it provides the Data agrees in writing to the same restrictions and conditions that apply throughout this Agreement.

11.4 *Assignment.* Neither Party may assign, mortgage, charge or otherwise transfer any or all of its rights and obligations under this Agreement except to its Affiliates without the prior written agreement of the other Party.

11.5 *Entire agreement.* This Agreement, including its Schedules, sets out the entire agreement between the Parties relating to its subject matter and supersedes all prior oral or written agreements, arrangements or understandings between them relating to such subject matter.

11.6 *Notices.* All notices given by either Party to the other pursuant to this Agreement shall be in writing and may be delivered by pre-paid post, registered courier or by hand to:

	HBT Contact:	TRINITY Contact:
Name	Professor Mark Ledwidge	Dr. Gordon Elliott
Title	Research Director	Senior Patents and Licensing Manager
Address	Heartbeat Trust, 3 Crofton Terrace, Dun Laoghaire, Co Dublin	Trinity Research and Innovation, O'Reilly Institute, Trinity College Dublin, Dublin 2, Ireland

Any such notice, if so given, shall be deemed to have been served:

(a) if sent by hand, when delivered;

(b) if sent by post or courier, one business day after posting.

11.7 *Further action.* Each Party agrees to execute, acknowledge and deliver such further instruments, and do all further similar acts, as may be necessary or appropriate to carry out the purposes and intent of this Agreement.

11.8 *Severability.* If the whole or any part of a provision of this Agreement is or becomes illegal, invalid or unenforceable under the law of any jurisdiction, that shall not affect the legality, validity or enforceability under the law of that jurisdiction of the remainder of the provision in question or any other provision of this Agreement and the legality, validity or enforceability under the law of any other jurisdiction of that or any other provision of this Agreement.

11.9 *Costs.* Each Party shall pay its own costs in connection with or incidental to the preparation, negotiation and execution of this Agreement.

11.10 *Counterparts and Signatures.* This Agreement may be executed in counterparts all of which taken together shall constitute one single agreement between the Parties. Transmission of an executed counterpart of this Agreement by e-mail (in PDF, JPEG or other agreed format) shall take effect as delivery of an executed counterpart of this Agreement. If e-mail method of delivery is adopted, without prejudice to the validity of the agreement thus made, each Party shall provide the others with the original of such counterpart as soon as reasonably possible thereafter.

11.11 *Announcements.* Neither Party shall make any press or other public announcement concerning any aspect of this Agreement or make any use of the name of the other Party in connection with or in consequence of this Agreement, without the prior written consent of the other Party.

11.12 *Law and jurisdiction.* This Agreement and any non-contractual obligations arising out of or in connection with this Agreement shall be governed by and construed in accordance with the laws of Ireland and each Party agrees to submit to the exclusive jurisdiction of the Irish courts.

Agreed by the Parties through their authorised signatories:

SIGNED For and on behalf of
TRINITY

Signed

Name: Dr. Gordon Elliott
Title: Senior Patents and Licensing Manager
Date: 20 MAY 2021

SIGNED For and on behalf of
Heartbeat Trust Company Limited by Guarantee

Signed

Name: Prof Mark Ledwidge
Title: Research Director
Date:

Schedule 1

Data and Purpose

processing/sharing of personal data between separate data controllers	
Data Provider	Heartbeat Trust Company Limited by Guarantee
Data Recipient	The Provost, Fellows, Foundation Scholars, and the other members of Board, of the College of the Holy and Undivided Trinity of Queen Elizabeth near Dublin
Purpose	The Recipient will clean the medication and co-morbidity data of the population and further analyze the data for drug-drug, drug-disease and drug-gene interactions and medication appropriateness using clinical risk predictors as part of Joseph O'Shea's PhD research project. In addition, the Recipient will analyse the data for biomarker predictors of outcomes as part of Claire Sweeney's research project.
Duration of the Processing	30th Sept 2020 to 1st September 2024
The type of Data being shared by Provider	Please select one or more from the following: • Health
The nature and purpose of the processing by Recipient	Describes the type of processing being performed on Personal Data. Examples include: • Collection of data • Organisation of data • Adaptation of data • Alteration of data • Storage of data • Consultation of data
The categories of Data Subjects	Please select one or more from the following: • Research subject • Patient

Schedule 2

Materials

Materials	Plasma, serum and extracted DNA samples from ongoing STOP-HF and prospective stage C HF study with data for biomarker analyses
Cost recovery Fee	To Be Waived, for the purposes of research.
Recipient Shipping Details	Trinity Translational Medicine Institute, on behalf of the School of Pharmacy and Pharmaceutical Sciences

Appendix 5.1. Interview invitation letter

Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

Invitation letter

Dear [insert participant's name],

We are undertaking a research study to inform the development of a personalised, collaborative medicines optimisation service involving general practitioners, pharmacist advisors, community pharmacists and patients. The research team involves collaboration between Mr Joseph O'Shea, Prof. Mark Ledwidge, Dr Joe Gallagher and Prof. Cristín Ryan.

I am contacting you to formally invite you to participate in the study. You have been selected due to your involvement in the medicines optimisation service. We are looking forward to your feedback on the service and your thoughts on a more personalised review incorporating genetic testing. Please find attached the Participant Information Leaflet which provides information on the study.

All study data will be processed in compliance with the General Data Protection Regulations, 2018, and the Health Research Regulations, 2018. The study has been approved by the School of Pharmacy and Pharmaceutical Sciences Research Ethics Committee in Trinity College Dublin.

I would be grateful if you could complete and return the attached consent form via email to osheaj5@tcd.ie, cristin.ryan@tcd.ie or mark.ledwidge@ucd.ie (an electronic signature will suffice), or via post to the School of Pharmacy and Pharmaceutical Sciences, Trinity College.

Please let me know of two possible times (and date/s) that would be suitable for you to participate in an interview. The interview should last approximately 30 minutes but you will be free to stop the interview at any time. If you decide not to take part or to withdraw, it will not affect your current or future care or research participation. If you have any questions, please do not hesitate to contact me at osheaj5@tcd.ie.

Yours sincerely,

Joseph O'Shea
BScPharm, MPharm, PGCert, MPSI
PhD Candidate
School of Pharmacy and Pharmaceutical Sciences
Trinity College Dublin 2

Mark Ledwidge, PhD, DPS, MPSI
Professor (Adjunct)
School of Pharmacy and Pharmaceutical Sciences
Trinity College Dublin 2

Appendix 5.2. Interview participant information leaflet

Participant Information Leaflet

Site	School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin
Principal Investigator(s) and Co-Investigator(s)	Co-Principal Investigators: Cristin Ryan (cristin.ryan@tcd.ie) Mark Ledwidge (mark.ledwidge@ucd.ie) Joe Gallagher (jgallagher@ucd.ie) Co-Investigator: Joseph O'Shea (joe.oshea@thepalmssurgery.com)
Data Controllers	Trinity College Dublin
Data Protection Officer	Data Protection Officer Secretary's Office Trinity College Dublin Dublin 2

You are being invited to take part in a research study conducted by the School of Pharmacy and Pharmaceutical Sciences in Trinity College Dublin (TCD). Before you decide whether you would like to take part, it is important that you take time to understand why this research is being conducted and what will be asked of you should you agree to participate. Please read the following information and contact the PhD Candidate (Mr. Joseph O'Shea, joe.oshea@thepalmssurgery.com) if you have any questions. Contact details can be found at the end of this leaflet.

This leaflet has four main parts:

Part 1 – The Study

Part 2 – Data Protection

Part 3 – Costs, Funding and Approval

Part 4 – Further Information

Part 1 – The Study

Why is this study being done?

Caring for patients with multiple long-term conditions and multiple medicines can be a challenge. A service with the patient at the centre and focused on safe and effective use of medicines may optimise care. This is called 'medicines optimisation'. For this to work well, community pharmacists and general practitioners need to work together. This can help personalise patient care, monitor outcomes more carefully, review medicines more frequently and support patients when needed.

Everyone responds to medicines differently. Some people may have unwanted effects, some may have no response at all. Genes can have a role in determining how your body reacts to a medicine. 'Pharmacogenomics' is a field of medicine that uses genetic information to optimise drug response and minimise side effects. In England, pharmacogenomics will be included in primary care by 2025. However, there is currently no such plan in Ireland. As a result, medicines optimisation does not incorporate this extra element.

This study aims to investigate a medicines optimisation service, with general practitioners and community pharmacists working together to ensure the most appropriate treatment. With this in mind, we are interested in the inclusion of pharmacogenomics in medicines optimisation.

Why have I been invited to take part?

You have been invited to take part in this study because you have been involved in practice pharmacist-led service to optimise your medicines. For patients, this involved receiving additional care from a pharmacist working with your general practitioner, who reviewed your medicines and offered you the chance to raise any concerns with your medicines. For those responsible for patient care (general practitioners and community pharmacists), this involved referring patients to the service, reviewing the medication change recommendations as a result of the medicines optimisation service, and implementing some changes. We would like to know your views on the medicines optimisation service to see what you think might help improve the service, or what might hinder it.

We will also be looking at a more personalised medicines service taking into account genetic information or a person's "genes". We want to see how genetic information can be incorporated into the medicines optimisation service, and again what might help or hinder this process. We want to set out a roadmap of how this service works and can be improved, and identify where genetic information could be included. This will help inform how this service could look in Ireland.

Do I have to take part? Can I withdraw?

Participation in the study is completely voluntary and the decision to not take part in the study will have no adverse consequences. If you decide to take part, you do not have to answer any questions that you do not wish to answer. If you decide to withdraw during the interview, you will not be penalised - any data that you have provided up to the point of withdrawal will not be used in the research and your data will be destroyed immediately. You are free to withdraw from the study after your interview also, up until your data has been analysed. If you decide not to take part or to withdraw, it will not affect your current care or future research participation.

How will the study be carried out?

Following contact with your general practitioner or community pharmacist and having expressed your interest in participating, you will be invited to participate in this study by a member of the research team. This Participant Information Leaflet accompanies a formal invitation and consent form. When you have read this document and returned the consent form to the research team member who contacted you, a date and time will be agreed to conduct the interview. The interview will last approximately an hour, although this may vary between individuals and will be conducted via telephone (recorded using a Dictaphone) or Microsoft Teams (recorded via Microsoft Teams).

At the beginning of each interview, a brief introduction to the research activities will be given, and full verbal consent obtained before recording and beginning the interview. At the time of interview, you will be informed of your rights (confidentiality, anonymity, data protection, freedom to stop and withdraw participation) (discussed below in this leaflet also). During the interview, you will be asked about your experience with the practice pharmacist medicines

reviews, your view on the practice pharmacist role, and your thoughts on using pharmacogenomics to inform prescribing. We will ask you what you thought worked well with the service and how it can be improved, and identify any benefits or concerns you might see with pharmacogenomic testing.

Interviews conducted via telephone will be transcribed (typed word-for-word) by the interviewer and for interviews conducted via Microsoft Teams (a virtual video platform), the transcribe function will be turned on to allow transcriptions to be carried out. These will be checked for accuracy and identifiers (such as your name) removed to anonymise the data.

What will happen to my data?

Your name and contact information (telephone number and email address) will be gathered in order to conduct the interview. This information will be kept in a password-protected Excel file ("key") on the researchers' TCD OneDrive account. The key also contains an anonymity code. During the data collection phase, the data will be pseudonymised. Once data analysis commences (within seven days of the final interview), the key will be deleted, rendering the data anonymous. The anonymity code from this Excel file will be used to label transcripts and recordings. Once the key is deleted, researchers will be unable to link your transcripts to you. You may request a copy of your transcript or withdraw your interview up until data analysis when the pseudonymised key is deleted. All interview transcripts will be anonymous and confidential, meaning that all identifiable information will be removed during transcription.

Data will be electronically stored on a password-protected laptop/computer and electronically backed up onto a TCD encrypted server. Interview recordings will be downloaded onto the researchers' TCD OneDrive account from Microsoft Teams or uploaded from the Dictaphone and stored securely. The interview recording held on Microsoft Teams and the Dictaphone will then be deleted as soon as possible after the interview. The interview recordings stored on the researchers' TCD OneDrive account will be stored for seven years and then deleted. Only the interviewers will have access to the recordings. The other research team member (Dr Joe Gallagher) will only have access to anonymised interview transcripts. The research team includes Joseph O'Shea (PhD Candidate), Prof. Mark Ledwidge (Co-Principal Investigator), Dr Joe Gallagher (Co-Principal Investigator) and Prof. Cristín Ryan

(Co-Principal Investigator). Joseph O'Shea will be responsible for ensuring data security under the supervision of the co-principal investigators (CR/ML/JG).

All consent forms will be stored securely on JO'S's TCD OneDrive account, each in a password-protected. Consent forms must be stored for seven years, after which they will be deleted by CR. All anonymized transcripts will be stored on the researcher's TCD OneDrive account, again each in a password-protected document and deleted after the study has concluded. Any published research will not be attributable to you. As TCD is the sponsor for this study, they will act as the data controller. Data will be analysed and used to inform further studies and the provision of pharmacogenomic tests to patients to guide the selection of medicines to treat their conditions. Results from the study will be published in an academic journal and may also be presented at national and international conferences.

Are there any benefits to taking part in this research?

Participation in this study may be beneficial for you, as you will have the chance to express your views and give feedback on a new way of making medicine personalised for each patient, which may contribute to better patient care.

Are there any risks to me or others if I take part?

There are no identified risks of taking part in this study, apart from losing the time taken to complete the interview. You might feel inconvenient or uncomfortable in providing your opinion. However, you do not have to answer any questions you do not wish to answer, and you are free to stop participating at any time.

Will I be told the outcome of the study? Will I be told the results of any tests or investigations performed as part of this study that relate to me?

The results of the study will be reported in medical/scientific journals and disclosed at medical/scientific conferences. No information which reveals your identity will be disclosed.

Part 2 – Data Protection

What information about me (personal data) will be used as part of this study? Will my medical records be accessed?

Your name and contact information (telephone number and email address) will be gathered in order to conduct the interview. This information will be kept in a password-protected Excel file ("key") on the researchers' TCD OneDrive account. The key also contains an anonymity code. During the data collection phase, the data will be pseudonymised. Once data analysis commences, the key will be deleted, rendering the data anonymous. The anonymity code from this Excel file will be used to label transcripts and recordings.

Once the key is deleted, researchers will be unable to link your transcripts to you. You may request a copy of your transcript or withdraw your interview up until data analysis when the pseudonymised key is deleted. All interview recording will be anonymous and confidential, meaning that all identifiable information will be removed during transcription.

What will happen to my personal data?

The data collected in this study will be processed only as necessary to achieve the objective of the study. Consent and anonymous transcripts will be kept for seven years in line with 2018 Health Research Regulations. After this, the responses will be destroyed. Data collected in this study will not be used for any future studies.

Who will access and use my personal data as part of this study?

Access to the data will be limited to the research team: Joseph O'Shea (PhD Candidate), Prof. Mark Ledwidge (Co-Principal Investigator), Dr Joe Gallagher (Co-Principal Investigator) and Prof. Cristín Ryan (Co-Principal Investigator). Only the research team will have access to your name and other personal information. The PhD candidate, Joseph O'Shea, will be responsible for ensuring data security under the supervision of the co-principal investigators (CR/ML/JG). The pharmacist members of the research team (JO'S, CR, ML) will be the only ones reviewing interview recordings, while the rest of the research team (JG) will have access to the anonymised transcripts.

Will my personal data be kept confidential? How will my data be kept safe?

Your identity will remain confidential. Transcripts will be anonymised. Information gained from the study including identifiable information such as consent forms/emails will be stored securely the researchers' secure TCD OneDrive accounts. Consent and transcripts will be securely stored for seven years and then destroyed, in line with current GDPR and Health Research Regulations 2018.

What is the lawful basis to use my personal data?

By law,[4] we can use your personal information for scientific research[5] (in the public interest[6]). We will also ask for your explicit consent to use your data as a requirement of the Irish Health Research Regulations.

What are my rights?

You are entitled to:

- Stop the interview at any time.
- The right to access your data and receive a copy of it
- The right to restrict or object to processing of your data
- The right to object to any further processing of the information we hold about you
- The right to have inaccurate information about you corrected or deleted
- The right to receive your data in a portable format and to have it transferred to another data controller
- The right to request deletion of your data

By law you can exercise the following rights in relation to your personal data unless the request would make it impossible or very difficult to conduct the research. You can exercise

[4] The European General Data Protection Regulation (GDPR)
[5] *Article 9(2) (j))*
[6] *(Article 6(1)(e)*

these rights by contacting the study Principal Investigator [Prof. Mark Ledwidge, School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin, Dublin 2, Ireland. Email: mledwidg@tcd.ie] or the Trinity College Data Protection Officer, Secretary's Office, Trinity College Dublin, Dublin 2, Ireland. Email: dataprotection@tcd.ie. Website: www.tcd.ie/privacy.

Part 3 – Costs, Funding and Approval

Has this study been approved by a research ethics committee?

Yes, this study has been approved by the School of Pharmacy and Pharmaceutical Sciences Research Ethics Committee. Approval was granted on 28/03/2022.

Who is organising and funding this study? Will the results be used for commercial purposes?

The research is being undertaken by a team of researchers in the School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin. This research is funded by an Irish Research Council Employment-Based Postgraduate Scholarship. The researcher is not being paid for recruiting participants for this study. The results will not be used for commercial purposes.

Part 4 – Further Information

Who should I contact for information or complaints?

If you have any questions about the research, now or later, please contact: Mr. Joseph O'Shea, PhD Candidate, School of Pharmacy and Pharmaceutical Sciences, Panoz Institute, Trinity College Dublin, Dublin, D02 PN40. Email: joe.oshea@thepalmssurgery.com

If you wish to make a complaint about the research, you can contact Prof. Mark Ledwidge (mledwidg@tcd.ie) or the Data Protection Officer, Trinity College Dublin: Data Protection Officer, Secretary's Office, Trinity College Dublin, Dublin 2, Ireland. Email: dataprotection@tcd.ie. Website: www.tcd.ie/privacy.

If you have concerns about how your information is being used, please contact: Data Protection Commission, 21 Fitzwilliam Square, Dublin 2, D02 RD28. Website: www.dataprotection.ie, Telephone: +353 761 104 800

Appendix 5.3. Interview consent form

Following contact with Joseph O'Shea and having expressed your interest in participating this consent form accompanies a participant information leaflet and invitation letter. When you have read the leaflet and returned this consent form to Joseph O'Shea (joe.oshea@thepalmssurgery.com) a date and time will be agreed to conduct the interview. There are 2 sections in this form. Please initial the box if you agree with the statement. You must sign and date below as the participant. Please feel free to contact Joseph O'Shea if there is something you do not understand. Thank you for participating.

Section 1	
General	*Initials*
I confirm that I have read and understood the information leaflet for the above study. The information has been fully explained to me and I have been able to ask questions, all of which have been answered to my satisfaction.	
I understand that this study is entirely voluntary, and if I decide that I do not want to take part, I can stop participating at any time without giving a reason.	
I understand that I will not be paid for taking part in this study.	
I know how to contact the research team if I need to.	
I agree to take part in this research study having been fully informed of the risks, benefits and alternatives which are set out in full in the information leaflet which I have been provided with.	
I agree to being contacted by researchers (by email and telephone) as part of this research study.	
Data processing	*Initials*
I understand that personal information about me will be protected in accordance with the General Data Protection Regulation.	
I understand that there are no direct benefits to me from participating in this study.	
I understand that I can request a copy of the text of my interview from the research team to review before data analysis has begun.	
I understand that I can request to withdraw my interview from the research team before data analysis has begun.	
I understand that my personal information will be confidential and stored safely. I am aware that I will not be identified in any of the findings.	
I understand that an interview will be recorded and that anonymous quotations may be used in the reports or outputs from this study.	

I understand that I can stop taking part in this study, up until the point when my data has been analysed, without giving a reason.	

Section 2			
Participant name		**Researcher name**	
Participant signature		**Researcher signature**	
Date		**Date**	

To be completed by the Principal Investigator or nominee.

I, the undersigned, have taken the time to fully explain to the above participant the nature and purpose of this study in a way that they could understand. I have explained the risks and possible benefits involved. I have invited them to ask questions on any aspect of the study that concerned them. I have given a copy of the information leaflet and consent form to the participant with contacts of the study team.

Researcher name	
Title and qualifications	
Signature	
Date	

Appendix 5.4. Interview topic guide - patients

- Hello. Thanks for making the time to talk with me today. I'm Joe O'Shea.
- I work from home helping the Palms Surgery as a **practice pharmacist**. In this role, I talk to patients about their medicines.
- You are being interviewed because you have been involved in this service. You were referred by your GP (name).
- In this service, I look at the medicines you are prescribed. I check for side effects and any other issues you may have. I also try to help improve how your medicines work for you. For example, changing a medicine or changing how often you might take it. In these reviews, your concerns and preferences as the patient are important.
- Now I am speaking to patients to **get your feedback on this service**.
- I am also interested in what you think about using genetic testing to help prescribing. Some people have differences in their genes that can affect how they respond to medicines. So, genetic testing may be important.
- Your feedback will help develop a new way for practice pharmacists to review medicines. We hope this will improve how people respond to their medicines and improve their health.
- The interview should last approximately **30 minutes**. There are some important study details in the **information leaflet** that was sent to you. Anything you say will be kept completely **confidential**. You will not be identified in any way. You can **stop the interview at any time**. Finally, the interview will be **recorded** so that we have an accurate and detailed account.
- The recording will be saved on a password-protected computer. Only those immediately involved in the research study will listen to them. The recording will be typed up word-for-word and the information made **anonymous**.
- There are **no right or wrong answers**. We would like your own **views and opinions, both positive and negative**. Your honest feedback will be very important in refining this service

for future testing. If you would prefer **not to answer** a question, let me know and we can move on.

- Have you **any questions** about the study or do you need me to clarify anything before we start the interview?
- If it's OK, I will start the recording now?" [Start recording interview]

[Demographic information: Note participant gender, age, drug scheme, number of medicines and number of medical conditions from their patient medication record]

In the first set of questions, I'd like to ask you to:

1. Tell me about your healthcare experiences over the past 6-12 months. (P)

- PROMPTS

a) Can you describe how you get your medicines? (From getting a prescription to getting the medicines) (P)

- How **often do you visit** your community pharmacy, GP, hospital prescriber? (T)
- How do you **order your medicines** from the pharmacy? (T)
- Is it difficult to collect your medicines? (T)
- Can you describe your **involvement** in healthcare decisions before your review? (P)
- What effects (if any) did **COVID-19** have on your healthcare experiences? Any positives that you can think of? (P)
- **If carer**, how is the relationship between carer and patient? (P)

b) How does your community pharmacist help you with your medicines and healthcare? (T)

- Have you experienced **any difficulties** with your community pharmacist? (O)
- How would you describe your **relationship with your community pharmacist**? (O)
- Do you feel supported and understood? (O)

c) How does your GP help you with your medicines and healthcare? (T)

- Have you experienced **any difficulties** with your GP? (O)
- How would you describe your **relationship with your GP**? (O)
- Do you feel supported and understood? (O)

d) Do you see more than one GP in the Palms?

- **If so**, tell me about your experience? (O) (E.g., rapport, GP understanding, patient satisfaction, etc.)
- **How many different GPs** do you think you have seen in the past year? (O)
- Can you describe **any issues** you may have experienced? (P)
- **If no**, how do you think you would feel about this? (P)

e) Can you tell me about your experience with seeing prescribers in different settings for instance, in the hospital? (O)

- How do you find having to see **multiple different doctors**? (O)
- Can you describe **any issues and benefits** you may have experienced? (P) (E.g., changes to prescription in hospital not adequately communicated or documented causing confusion for pharmacist and/or GP) (Drill into transition of care concerns)

f) What has it been like **taking your medicines** in the past year? (T)

- Can you tell me about your experience (if any) with **unwanted effects** from medicines before your review? (P)
- Have you ever **stopped a medicine** because of an **unwanted effect** you experienced? Have you ever stopped a medicine for **any other reason**? (P)
- Have you **ever stopped a medicine and not told** your GP or pharmacist? (P)
- Have you experienced **any other issues** with your medicines, e.g., supply? (P)

Moving on from your healthcare experiences in the last year, I would like you to:

2. Tell me about your experience with the practice pharmacist? (PR) I will ask more detailed questions about the encounter in a little while.

- PROMPTS

a) What can you remember from your medication review with the practice pharmacist? (PR)

b) Can you tell me about the effect (if any) that the medicines review service had on your overall healthcare? (OU)

- What has it been like **managing your medicines** since the review? Has the review improved how you take your medicines? (OU)
- If **remembering to take your medicines** was an issue before, did this improve with the review? (OU)
- Has there been **improvements** in your blood pressure, blood sugars, weight, sleep, energy etc.? (OU)
- Were **changes made** to your medications? **How long** did it take for changes to come into effect? (OU)
- What effect (if any) did the medicines review have your **ability to take your medicines as prescribed** by your GP? (OU)
- Have you experienced **any unwanted effects** from medicines since the review? (OU)
- **How frequently** do you think your medicines should be **reviewed**? (PR)
- Do you think it affected your **satisfaction with your healthcare**? (OU)
- Who do you think would **benefit** from these reviews? (OU)

c) Can you describe what you thought was good about the medicines review, and what could be improved upon? (PR)

- What do you think about the kind of **healthcare advice** the practice pharmacist provided? (T)
- Were there any questions you asked in the review that you might have been **afraid** to ask your GP? (T)
- Do you think it would have been good to have **access to information on the review process before the review**? (PR)
- If so, what way would you like to receive this information? (E.g., webpage, FAQ)
- Would you like to be able to **provide feedback** after the review? (PR)
- Was there **enough time** dedicated to the review? Did you feel rushed? (PR)
- Were you **comfortable** discussing with the practice pharmacist? Were you able to discuss in **private**? (E)

d) Can you describe your involvement in decisions during your review? (PR)

- What would **influence your involvement** in medicines reviews? (PR)
- Can you describe how you feel about **expressing your opinion** about the medicines you receive? (P)
- What do you think needs to happen so that your **voice is heard**? (P)

e) What are your thoughts on medicines review by phone? (TT)

- What would be **your preferred way to communicate** with a practice pharmacist? (TT)
- Would it be better if the pharmacist was there in person? (T)

f) Can you tell me what you would think about having to pay for this service? (PR)

- If it is something you would pay for, how much would you be **willing to pay**? E.g., €10, €20, €30, €40, €50 (PR)

Next, I would like to ask you to:

3. Briefly tell me about your thoughts on the practice pharmacist role. (T)

- PROMPTS

a) Based on the issues you discussed and to improve the process as a whole, how do you think pharmacists working within GP surgeries can help?

   - Can you describe any **advantages** that pharmacists working within GP surgeries could have? (PR)
   - Can you describe any **disadvantages** that pharmacists working within GP surgeries could have? (PR)
   - If multiple people involved in your care was an issue, what do you think about adding another person into this (the practice pharmacist)? (P)
   - *Try to link back to their own journey and what impact this might have.*
   - Can you **describe the knowledge/skills** you think pharmacists have that make them suited for a role in medicines optimisation? (P)
   - Do you think **other patients should have access** to a practice pharmacist to help optimise their medicines? (PR)
   - Do you think Palms patients should be made aware of this service? (PR)

b) Do you have any other suggestions about what the practice pharmacists did well, or what they can improve upon? (PR)

c) Can you describe how you think communication is between those responsible for your healthcare? (O)

   - Have you seen your healthcare professionals having a hard time communication? (E.g., multiple GPs, hospital doctors and primary care, GPs and pharmacists etc.)
   - What do you think led to that? (O)
   - What do you think leads to **effective communication**? (O)
   - Describe the effect (if any) that the practice pharmacist had on **communication.** (OU)

We previously mentioned a more personalised medicines review taking into account your genes. This could help show how you might respond to certain drugs. Genetic testing is performed in other countries such as the UK, the US, Canada and Australia, but is currently not included in medicines optimisation in Ireland. We would like to know:

4. What you think about using your genes or genetic information to help with your medicines review. (T)

- PROMPTS

a) Should genetic services be provided for patients as part of optimising medicines? (T)

   - If so, **who do you think should provide** genetic testing and why? (E)
   - What do you think about a **general practice pharmacist being responsible for providing genetic testing**? (O)
   - With your consent, should this **information be shared** amongst the people providing your care? Who should receive this information? (E)
   - Do you think it would affect your **satisfaction with your healthcare**? (OU)
   - Would you like to learn more about genetic testing to optimise your medicines? (PR)
   - If so, what would be your **preferred learning format**? (E.g., face-to-face, online) (PR)

b) What benefits do you think genetic testing can have in the prescribing of medicines? (OU)

   - E.g., predict risk of side effects, select the most effective medicines, select most appropriate dose and strength (OU)

c) Can you tell me what concerns you might have with genetic testing to optimise your medicines? (PR)

- E.g., cost, data protection, unexpected findings, sample provision, test turnaround time, mortgages/employer/insurance company discrimination, disclosure of results to family if additional risk information present (PR)
- What would make you **feel more at ease** with genetic testing to optimise your medicines? (P)
- Are you comfortable with your **genetic test results being stored** in the same way as your medical history? (TT)

d) What would influence your decision to get a genetic test? (P)

- Can you tell me what you would think about having to **pay for this service**? (PR)
- If it is something you would pay for, **how much** would you be willing to pay? E.g., €50-€100, €100-€200, €200-€300 (PR)
- Do you think genetic tests should be **covered by your health insurance**? (P)
- Your genes can be tested using a **blood sample, saliva sample or a mouth swab**. What would be your preferred method, and why? (TT)

CONCLUDING COMMENTS:

That brings us to the end of the interview. Is there anything else you would like to add?

Thank you very much for taking the time to speak to me today. [Stop recording]

Appendix 5.5. Interview topic guide – healthcare professionals

- Hello. Thanks for making the time to talk with me today. I'm Joe O'Shea.
- I work with the Palms Surgery as a **practice pharmacist** as part of my PhD with the School of Pharmacy at Trinity College Dublin.
- I work remotely in this role, supporting the surgery with activities such as medicines optimisation reviews, reviewing and reconciling hospital discharge prescriptions, assisting therapeutic substitution, and resolving general queries.
- You are being interviewed because one of your patients has been reviewed as part of this service.
- You may not have heard from one of the practice pharmacists directly, but we would still like to hear your opinion on the service.
- The main aim of this service was to optimise the patient's medicines. This means checking that the patient is taking the right medicines in the right way so that they get the most out of them.
- Medicines optimisation is different to medication reviews in that the patient is present for the review and involved in decision-making.
- These reviews may have involved stopping some medicines as well as starting others, in addition to advice on lifestyle changes, non-medical therapies and social clubs.
- Now we are speaking to patients and those responsible for their care **to explore their views of and experiences with the practice pharmacist service**. Medicines optimisation is an important part of the service that we would like to develop further with your feedback.
- We are also interested in your thoughts on a more personalised review taking into account a patient's genes. This might be important because some people have differences in their genes that can affect how they respond to their medicines. This is called **pharmacogenomics**.

- We plan to use the information gathered in this study to see if we can develop a new way for practice pharmacists to review medicines. We hope this will improve how people respond to their medicines and improve their health.
- The interview should last approximately **an hour**. There are some important study details in the **information leaflet** that was sent to you. Namely, anything you say will be kept completely **confidential**, you will not be identified in any way, and you can **stop the interview at any time**.
- Finally, the interview will be **recorded** so that we have an accurate and detailed account. The recording will be typed up word-for-word and the information made **anonymous**.
- There are **no right or wrong answers**. We would like your own **views and opinions, both positive and negative**. Your honest feedback will be very important in refining this service for future testing. If you would prefer **not to answer** a question, let me know and we can move on.
- Have you **any questions** about the study before we start the interview? If it's OK, I will start the recording now?" [Start recording interview]

In the first set of questions, I'd like to ask about you and your current work.

1. Demographic information.

Community pharmacists

a) How long have you been practicing as a pharmacist? (P)

b) What is your current position in the pharmacy? (E)

c) On average, how many prescription items do you dispense per day in your pharmacy? (T)

d) How many pharmacists work in your pharmacy? Is there ever overlap? (E)

e) How many technicians work in your pharmacy? (E)

f) What non-dispensing services does your pharmacy provide? (T)

General practitioners

a) How long have you been practicing as a general practitioner? (P)

b) On average, how many patients do you see per day? (T)

c) How many doctors work in your practice? (E)

d) On a typical weekday, how many other doctors are on with you? (E)

Next, I'd like to ask you about medicines optimisation reviews, meaning reviews where the patient is present and involved in decision-making. This is compared medicines reviews when checking a prescription when prescribing/dispensing which may not involve the patient.

2. Can you tell me about your experience with medicine optimisation reviews? (T)

- PROMPTS

g) Do you conduct medicines optimisation reviews in your practice? (PR)

  - Can you describe the medicine review process? (T)
  - Are medicine reviews a **priority in your practice**? (T)
  - What is **patient involvement** like in these reviews and decision-making? (PR)
  - What do you think would help encourage shared decision-making? (TT)
  - How do you **feel about reviewing patients'** medicines? (P)
  - What about when patients are **receiving 10 or more medicines**? (P)
  - **How often** do you think patients should have their medicines reviewed? (T)
  - What effects does a patient seeing multiple different prescribers in the same practice have? (O)

h) How would you describe your relationship with your local community pharmacists/GPs? (O)

  - What role do you think pharmacists have in medicines optimisation? (E)
    i. How you feel about **providing recommendations** to prescribers? (T)
    ii. What is **prescriber feedback** on these recommendations like? (T)
    iii. How do you think recommendations and feedback should be **communicated**? (T)
  - What role do you think GPs have in medicines optimisation? (E)

i. How do you feel about **providing feedback** on prescribing recommendations from pharmacists? (T)

i) Can you think of any barriers to medicine optimisation reviews in your practice? (T)

- Can you describe **work environment conditions that might help or hinder you** performing medicines reviews? (E)
- Can you think of **any resources** that might be of assistance here? (TT)

j) What do you think would help improve medicine optimisation reviews in your practice? (PR)

- What effect do you think **financial remuneration** would have in your practice? (E)

Moving on from medicines reviews in general, I would like you to:

3. Tell me about your experience with the practice pharmacist, if any? (PR)

- PROMPTS

a) Can you describe your experience with the medicine optimisation reviews conducted by the practice pharmacist? (PR)

   - What has the **referral process** looked like? Do you think this is suitable? (T)
   - What do you think about the **recommendations** the practice pharmacist made? (T)
   - **What advantages and disadvantages** did the medicines review have for you or your patients? (OU)
   - What effect (if any) did this have on your **workload, stress, time available**? (OU)
   - What do you think would **help improve** the medicine reviews? (PR)

b) Can you describe your experience with hospital discharge reconciliation conducted by the practice pharmacist? (PR)

   - Can you describe **any benefits or effects** you have noticed in managing patients who attend **multiple different prescribers** in **different settings**? (OU)
   - What do you think would **help improve** this process? (PR) (E.g., hospital discharge prescriptions, should they just note medicines that are changed/stopped, electronic system vs paper)

c) What are your thoughts on the assistance provided by the practice pharmacist for general queries? (PR)

   - Can you describe **any benefits or effects** you have noticed? (OU)
   - What do you think would **help improve** this process? (PR)

Next, I would like to ask you to:

4. Tell me what you think about the practice pharmacist role.

- PROMPTS

a) What do you think about the current utilisation of pharmacists in primary care? (E)

- What **knowledge/skills** do you think pharmacists have that make them suited for a role in general practice? Do you think **further training** is needed? (P)

b) What is your opinion on the practice pharmacist role? (E)

- Do you think it **adds value**? (OU)
- What other activities do you think the practice pharmacist could assist with? (T)
- Do you have any thoughts on **pharmacist-led therapeutic substitution**? (PR)
- Going beyond this, what about **pharmacist prescribing rights**? (PR) (Defensive practice, legal and regulatory barriers)
- Do you think **other patients should have access to a practice pharmacist** to help optimise their medicines? (PR)

c) What are your thoughts on the remote nature of the practice pharmacist? (E)

- What would be your **preferred way to communicate**? (TT)
- Do you think **co-location of staff** would help or hinder this process? (E)
- What are your thoughts on **medicines review by phone**? (TT)
- What are your thoughts on the practice pharmacist's **availability**? (O)

We previously mentioned a more personalised medicines review taking into account a patient's genetic information. "Pharmacogenomics" is the use of this information to determine how patients might respond to certain drugs. Pharmacogenomic testing is performed in other countries such as the UK, the US, Canada, and Australia, but is currently not included in medicines optimisation here in Ireland. We would like to know:

5. What you think about using patients' genetic information to help with prescribing and medicines reviews.

- PROMPTS

e) Can you describe your understanding of how pharmacogenomics can be used in healthcare? (P)

- Have you completed any training on pharmacogenomics, e.g. third level studies, CPD, online course? (P)
- Do you think **training** is needed here? (T) If so, what would be your **preferred learning format**? (E.g., face-to-face, online)
- Can you describe how you currently would **feel about** receiving, interpreting, advising upon, and storing **genetic test results**? (TT)
- Do you think the PMR would enable **storage** of patients' genetic test results? Would an **add-on or an additional tool** be needed? (TT)

f) Should genetic services be provided for patients as part of optimising medicines? (PR)

- If so, **who** do you think should provide genetic testing and **why**? (E)
- What do you think about a **general practice pharmacist being responsible for providing genetic testing** and liaising between general practice and community pharmacy? (O)
- Do you think it would affect your **job satisfaction**? (OU)
- What would **influence your decision to participate** in a genetic testing service? (P)

- Can you think of **any resources** that might be of assistance here? (TT)
- Can you **describe work environment conditions** might help or hinder you here? (E)

g) What benefits do you think genetic testing can have in the prescribing of medicines? (OU)

- E.g., predict risk of side effects, select the most effective medicines, select most appropriate dose and strength (OU)

h) Can you tell me what concerns you might have with genetic testing to optimise patients' medicines? (PR)

- E.g., cost, data protection, unexpected findings, sample provision, test turnaround time, employer/insurance company discrimination (PR)
- Do you think this is something patients would pay for? (E)
- Genetic tests can be performed using a **blood sample, saliva sample or a mouth swab**. What would be your **preferred method**, and why? (TT)
- What effect would **test cost coverage** by private health insurance or medical card have? (E)

CONCLUDING COMMENTS:

That brings us to the end of the interview. Is there anything else you would like to add?

Thank you very much for taking the time to speak to me today. [Stop recording]

Appendix 5.6. Interview study ethical approval

Coláiste na Tríonóide, Baile Átha Cliath
Trinity College Dublin
Ollscoil Átha Cliath | The University of Dublin

Joseph O'Shea,
School of Pharmacy and Pharmaceutical Sciences,
Trinity College,
Dublin 2.

Ref. 2021-12-02

28th March 2022

Dear Joseph,

Re: A human factors approach to personalised medicines optimisation involving pharmacist advisors in Irish primary care: A qualitative study

I am pleased to inform you that the above project now has ethical approval from the School of Pharmacy and Pharmaceutical Sciences Research Ethics Committee (SoPPS REC).

You are reminded that any significant deviation from the research description in the application requires approval from the SoPPS REC before implementation.

Please also note the reporting requirements outlined on the Committee's website (http://pharmacy.tcd.ie/research/SoPPS_REC.php), in particular the need for:

- An immediate report in writing (by email to pharmacy.ethics@tcd.ie) of any serious or unexpected adverse events on participants, or unforeseen events that might affect the benefits/risks ratio as outlined in the application.
- Annual reports (report form on the Committee's website).
- An end of project report (report form on the Committee's website).

As a researcher, you must also ensure that you comply with all applicable legislation, including any relevant provisions concerning data protection and health and safety.

Please quote the reference number 2021-12-02 in any further correspondence.

We wish you success with your research.

Yours sincerely,

Sheila Ryder,
Chairperson,
School of Pharmacy and Pharmaceutical Sciences Research Ethics Committee.

Sheila Ryder
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Síle Ní Mharcaigh
Cathaoirleach
Coiste um Eitic Thaighde
Scoil na Cógaisíochta agus na nEolaíochtaí Cogaisíochta

Foirgneamh Panoz, An Taobh Thoir 4/5,
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