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Estimating the cost-utility associated with multi-gene panel testing to avoid adverse drug reactions

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Estimating the cost-utility associated with multi-gene panel testing to avoid adverse drug reactions

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SUMMARY

Adverse drug reactions (ADRs) are an unintentional result of pharmaceutical therapy for some patients. They can have a substantial effect on patient mortality and morbidity, with the capacity to inflict large cost and resource implications on the health services. Many of these reactions could be likely avoidable with genetic testing, which has been acknowledged by worldwide medicine agencies and implemented for a handful of drugs.

This thesis applies an economic model to assess the cost-utility of a multi-gene panel test to avoid adverse drug reactions, using a combination of cost-effective genes contained within a panel test. This technology profiles a patient's genetic susceptibility to ADRs and may have the ability to limit lifetime adverse drug reactions, saving on cost accumulation and improving patient health.

A decision-analytic framework was adopted to determine the cost-utility of several gene panel combinations. This involved combining the cost and QALY outcomes of previous economic evaluations for single-gene testing to avoid adverse drug reactions and estimating the cost-utility of single-gene testing for associations lacking economic evidence.

Using the base-case scenario (ICER/QALY <£20,000, cost of test £30) on a multi-gene panel including 14 drug-gene associations, multi-gene panel testing was found to be cost-effective in patients eligible for carbamazepine (*HLA-A*31:01*), abacavir (*HLA-B*57:01*), mercaptopurine (*TPMT*), Clopidogrel (*CYP2C19*), warfarin (*CYP2C9*), phenytoin (*HLA-B*15:02*) and irinotecan (*UGT1A1*). This panel resulted in a cost-saving of £35 and a QALY gain of 0.0077.

This evidence suggests that prospectively testing using a panel test of genes within and beyond the HLA family (and returning the incidental findings for pre-emptive use) is a cost-effective method to avoid adverse drug reactions in the relevant disease groups.

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DECLARATION

I hereby declare that this thesis is the results of my own investigations, except where otherwise stated. All other sources are acknowledged by bibliographic references. This work has not previously been accepted in substance for any degree and is not being concurrently submitted in candidature for any degree unless, as agreed by the University, for approved dual awards.

Yr wyf drwy hyn yn datgan mai canlyniad fy ymchwil fy hun yw'r thesis hwn, ac eithrio lle nodir yn wahanol. Caiff ffynonellau eraill eu cydnabod gan droednodiadau yn rhoi cyfeiriadau eglur. Nid yw sylwedd y gwaith hwn wedi cael ei dderbyn o'r blaen ar gyfer unrhyw radd, ac nid yw'n cael ei gyflwyno ar yr un pryd mewn ymgeisiaeth am unrhyw radd oni bai ei fod, fel y cytunwyd gan y Brifysgol, am gymwysterau deuol cymeradwy.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

6-MP - 6-Mercaptopurine

ABC-HSR - Abacavir Hypersensitivity Reaction

ACMG - American College of Medical Genetics

ADE - Adverse Drug Event

ADME - Absorption, Distribution, Metabolism and Elimination

ADR - Adverse Drug Reaction

AE - Adverse Event

AWMSG - All Wales Medicines Strategy Group

CBA - Cost-Benefit Analysis

CEA - Cost-Effectiveness Analysis

CHEERS - Consolidated Health Economic Evaluation Reporting Standards

CI - Confidence interval

CI - Confidence Interval

CPIC - Clinical Pharmacogenetics Implementation Consortium

CUA - Cost-Utility Analysis

DILI - Drug-Induced Liver Inflammation

DMET - Drug Metabolizing Enzymes and Transporters

DNA - Deoxyribonucleic Acid

DoTs - Dose relatedness, Timing and patient Susceptibility

eMC - Electronic Medicines Compendium

EQ-5D - EuroQol questionnaire (5 Dimensions)

FDA - Food and Drug administration

FDA - Food and Drug Administration

FVL - Factor V Leiden

G6PD - Glucose-6-Phosphate Dehydrogenase

GBP - Great British Pound

HCSC - Health Canada (Santé Canada)

HIV - Human Immunodeficiency Virus

HLA - Human Leukocyte Antigen

HRQoL - Health Related Quality of Life

HTA - Health Technology Assessment

ICER - Incremental Cost-Effectiveness Ratio

MHRA - The Medicines & Healthcare products Regulatory Agency

NGS - Next-Generation Sequencing

NHS - National Health Service

NHS EED - National Health Service Economic Evidence Database

NICE - The National Institute for Health and Care Excellence

NIHR - National Institute for Health Research

NPV - Negative Predictive Value

ONS - Office for National Statistics

OR - Odds Ratio

PGRN - Pharmacogenetics Research Network

PIL - Patient Leaflet Information

PMDA - Pharmaceutical and Medicines Devices Agency

POLG - DNA Polymerase Gamma

PPV - Positive Predictive Value

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-analysis

RCT - Randomised Control Trial

SD - Standard Deviation

SF-6D - Short Form Health Survey (6 Dimensions)

SJS - Steven-Johnson Syndrome

SMC - Scottish Medicines Consortium

SPC - Summary of Product Characteristics

TEN - Toxic Epidermal Necrolysis

TPMT - Thiopurine-S-Methyltransferase

TTO - Time-Trade Off

UGT - UDP-glucuronosyltransferase

VBP – Value-based price

WHO - World Health Organisation

WTP - Willingness to Pay

1. INTRODUCTION

1.1 INTRODUCTION TO THESIS

Within the health sector demand continues to exceed supply with the development of new health technologies, an ageing population, a rise in expectations and the ability to provide treatment for a wider range of diseases, all of which contribute to the escalation in healthcare costs. With finite resources and without the ability to finance all, the introduction of one health intervention may mean there are fewer resources to provide for other amenities (Kobelt, 2013). Recent developments in precision medicine have enabled pharmaceutical treatment individualization to improve efficacy and reduce costs.

Some pharmaceutical interventions can cause undesirable and costly adverse effects which in some cases may outweigh the benefits. The expenditure on adverse drug reactions in the NHS has been estimated to be £98.5 million per annum, consuming 181,626 bed-days, directly causing 712 deaths and contributing to a further 1708 deaths during hospitalisation (Elliot et al., 2018), estimated to cause 6-7% of hospital admissions (Pirmohamed, 2004). However, developments in the utility of pharmacogenetic testing to guide prescribing suggest that up to 70% of these harmful reactions might be avoidable (Pirmohamed, 2004), enabling healthcare professionals to identify a safe and effective dose on an individual patient basis.

Genetic testing to avoid adverse drug reactions is particularly useful for some drug-gene associations, with some leading to clinical implementation due to their effects on both patient health outcomes and NHS expenditure (e.g. *HLA-B*57:01* in retroviral therapy of HIV by abacavir). With the catalogue of drug-gene associations expanding exponentially, avoiding adverse drug reactions and mapping out a patient's risk for future adverse drug reactions is more feasible than ever before. This thesis explores the cost-utility of multi-gene panel tests containing a range of drug-gene associations to avoid adverse drug reactions and assess the value-based price (VBP) to the NHS. The introduction of this thesis will explore the concept of health economics, economic modelling and pharmacogenetic testing to avoid adverse drug reactions and will explore the literature available on the economic impact associated with this.

1.2 INTRODUCTION TO HEALTH ECONOMICS

The overall aim of health economics is concerned with how best to allocate scarce resources to maximise health benefit, which in turn requires trade-offs between the various healthcare goals to be achieved. This raises discussions as to which area of healthcare is most deserving. The benefit of using resources to provide one service will inevitably remove the opportunity for that resource to be invested in a best alternative – this is known as opportunity cost (Elliott, & Payne, 2005).

The costs of new medicines and health technologies need to be justified in relation to their benefits. Sometimes the benefits forgone exceed those which are gained with the new intervention, which if approved would lead to inefficient allocation of resources. Investigating the cost-effectiveness of new interventions can assist policy makers such as the National Institute for Health and Care Excellence (NICE), the All Wales Medicines Strategy Group (AWMSG) and the Scottish Medicines Consortium (SMC) in the appraisal of new interventions. Although the criteria which decision makers may consider when appraising interventions does go beyond the economic outcomes, it offers critical insights into the impact of implementation on budget.

Economic evaluations within healthcare typically involve the systematic assessment of costs and consequences of alternative healthcare interventions, treatments or technologies to aid in efficient decision making (Drummond et al., 2005). A range of economic evaluations have been developed to help address the issues concerned with healthcare efficiency, by providing reliable economic evidence on technical efficacy, health gain and identification of cost implications. These assist in identifying interventions which maximise health gain and distribute budget most efficiently, with the ultimate objective of each analysis to improve health whilst being conscious of limited resources.

In the UK, economic evaluations have become a formalized requirement in the appraisal of new interventions by the policy makers. The NICE guide to the methods of health technology appraisal (2013) acknowledges that incorporating economic evaluations in guideline development elucidates the use of economic evaluation to not only estimate resource consequences, but the benefits and harm of alternative courses of action on resource use considering patient outcomes. Economic analysis is also required in AWMSG and SMC appraisal (AWMSG, 2018; SMC, 2018).

1.3 ECONOMIC ANALYSIS USED IN HEALTH TECHNOLOGY ASSESSMENT

Under circumstances where the outcomes or consequences of different interventions vary between one or more health outcomes, economic evaluation can be used to compare interventions to most efficiently achieve objective X (Drummond, 1997). There are different methods to achieve this objective which assess different variables of health technology impact.

Cost-effectiveness analysis is known by economists as the assessment of *"X" efficiency*, where the associated interventions are compared in terms of cost per unit outcome of consequence (Jefferson, Demicheli and Mugford, 1996). This method of economic analysis measures the health benefit of a new intervention in natural units e.g. life years gained, or adverse drug reactions avoided by comparing the costs and benefits of each intervention.

A limitation to the use of this is the inability to compare health interventions where natural effects are measured in different units (Jakubiak-Lasocka & Jakubczyk, 2014). This makes it particularly difficult to assess the cost-effectiveness of interventions between different areas of healthcare. To overcome this issue, a cost-utility analysis can be applied and is a common approach. A cost-utility analysis is a modification of the cost-effectiveness analysis which measures an intervention's effect on health using a utility-based measure such as quality adjusted life years (QALY). This allows health gain to be measured in transferrable units for the comparison of different healthcare interventions across disease areas.

Another option in the health technology assessment (HTA) process for public health interventions in the UK and for all interventions in some countries such as in supplementary analysis in the Netherlands (van Gils et al., 2017) (where the proposed intervention has important societal implications which extend beyond the health outcomes of the patients and beyond that of the healthcare system), is cost-benefit analysis (CBA) (Drummond et al., 2005).

This type of analysis places monetary values on inputs (costs) and outcomes which allows for interventions to be compared based on economics alone. CBA assesses the intrinsic value of an intervention (if benefits exceeds costs the intervention is worth doing). The results of this analysis can indicate the appeal of an intervention independently of a comparison to alternatives.

1.3.1 USING UTILITY IN HEALTH TECHNOLOGY ASSESSMENT

QALYs are the preferred health outcome measure by NICE, AWMSG and SMC in the UK for health technology assessment. For the calculation of QALYs, preference weights such as those from the UK tariff (Karlsson et al., 2011), are assigned to different health states (i.e. health state utility) over the duration of time spent in a given state. Utility is derived from the preference for different health states on a scale where 0 represents death and 1 represents perfect health, although some utility measures allow for states worse than death (negative utility). Changes in utility are considered equivalent regardless of the area on the scale (e.g. an increase from 0.2 to 0.3 is considered equivalent to an increase from 0.6 to 0.7) which is a much-debated concept (Whitehead &Ali, 2010).

The generation of value sets for health utility measurement involves individuals assessing and valuing different health states using preference-based measures (McDonough & Tosteson, 2007). Examples of this are the time-trade off (TTO) and standard gamble approaches which have been used to generate value sets for the commonly used EQ-5D and SF-6D questionnaires. These questionnaires comprise of different dimensions to assess total health including mobility, self-care, pain/discomfort, anxiety/depression and ill health etc. Each dimension combines to generate a score, reflecting a health state. Questionnaires are usually incorporated into routine data collection and are given to patients receiving the intervention to clarify differences in utility of the intervention versus no intervention or the best alternative.

QALYs are calculated by multiplying the value of preference of being in a health state and the length of time spent within that state. For example, if the health state of a given disease or condition is considered to have half the utility of being in full health (0.5) and the duration in this health state was 4 years, this is equivalent to 2 QALYs. There are limitations to using the QALY such as the ethical considerations, methodological issues and theoretic assumptions (Pettitt et al., 2016). Discussions have included as to whether every QALY is of equal value (Whitehead and Ali, 2010). Despite its limitations, the QALY is still regarded by NICE as the most robust method of measuring health benefit.

Based on cost utility analysis, an intervention is deemed productively efficient in the comparison against another intervention, if it results in higher (or equal) benefits at lower cost. This allows both productive efficiency and allocative efficiency to be addressed using a single

measure of health benefit, enabling diverse healthcare interventions to be compared (Palmer et al., 1999). Therefore, the intervention associated with the largest utility consequence with the lowest cost is likely to be the most cost-effective option. Health outcomes can be measured between different interventions with the same clinical outcome or between entirely different areas of healthcare with a different outcome focus. This imposes the need for transferrable measures of health which can be applied to all health states (or HRQoL), considering duration and severity.

1.3.2 The incremental cost-effectiveness ratio

The Incremental Cost-Effectiveness Ratio (ICER) is calculated by dividing the intervention incremental costs by the incremental QALYs, this gives a monetary value to be compared with the health agency threshold.

$$ICER = \frac{Costs_{intervention} - Costs_{comparator}}{QALYs_{intervention} - QALYs_{comparator}}$$

The ICER is used to compare with the willingness to pay (WTP) for a unit of effect, that is, the threshold to make a final recommendation (Jakubiak-Lasocka & Jakubczyk, 2014). Where AWMSG, SMC and NICE are confronted with a strategy that is more efficient than standard practice but which imposes increased costs, it must then be decided whether there is an increase in health (compared with standard practice) from the increase in expenditure (Rawlins and Culyer, 2004). This is where the ICER is most useful.

AWMSG, SMC and NICE use an ICER threshold to compare the cost-effectiveness of different interventions. This is a (non-absolute) threshold but in general, the most plausible threshold used to determine cost-effectiveness is below £20,000 per QALY, although accepting an intervention as a cost-effective strategy requires economic modelling and estimates around ICER uncertainty.

ICERs above £20,000 per QALY, up to £30,000 per QALY, necessitate for explicit evidence of assessed uncertainty, improvement on current service and substantial health gain. Above this threshold, rising to £50,000 per QALY and even higher, £100,000 to £300,000 per QALY for certain treatments that extend life at the end of life, and highly specialized technologies –

the evidence supporting this intervention needs to be increasingly strong. The thresholds are used as a guide to allow efficient use of NHS resource and is an estimate of the health forgone as services are displaced (McCabe, Claxton & Culyet, 2008). Uncertainty in costs and QALYs can affect the ICER value and therefore must be tested using a sensitivity analysis - allowing for decision makers to understand the cost and utility implications on the ICER if these vary.

1.3.3 COSTS INVOLVED IN ECONOMIC ANALYSIS

Direct costs characterize the value of all goods, services, and other resources consumed by providing health care, dealing with side effects or other current and future consequences of health care. Conversely, the indirect costs are costs accumulated as a secondary effect of the intervention or disease, such as the loss of productivity due to absence from work.

Indirect costs vary between individuals and interventions, are difficult to quantify and are often outside the perspective of payers and are therefore omitted from most economic analyses (Weintraub, 2003). Costs can also arise for patients and other agencies at different stages of intervention implementation. An intervention may be cost-effective in the long term but not deemed value for money in the short term (NICE, 2013), where costs are likely to be incurred.

1.3.4 ECONOMIC MODELLING

Economic evaluations are often conducted alongside randomised trials, providing precise evidence to evaluate cost-effectiveness and an unbiased interpretation of tangible costs involved and corresponding utility (QALYs). However, for health technology assessment the totality of effects may not be contained within a randomised trial due to single trials generally having limited time-frames and a lack of resources to assess all possible clinical and economic consequences. It may take several years to assess the full impact an intervention has on health, this is where the use of economic modelling can advise on possible future benefit by extrapolation of costs and utility. Economic modelling can provide estimated costs and benefits of a strategy which may have continued implications past the point of intervention (Briggs, Claxton & Sculpher, 2011).

The purpose of decision modelling is to synthesize estimated data on intervention clinical efficacy, costs, quality of life and health state valuation to determine the relative cost-

effectiveness of an intervention beyond the capacity of a randomised control study. Economic models can utilise inputs from different methods of research, such as; observational studies and meta-analyses,. These methods allow for collective results from individual studies to be included and point estimates to be made and modelled from, providing a larger spectrum of studies for the model to display outputs closest to the truth.

Decision trees are the simplest technique used in decision-analytical modelling. They represent a clinical pathway, where costs and utilities of different outcomes are branched off from a decision node. Each decision node characterizes a strategy with alternative events at the end of each pathway. The alternatives branched off from the node must be mutually exclusive and the probabilities must sum to 1.

Markov modelling can be used to simulate the transition between different health states using a technique to analyse repeated events, which is most applicable for modelling the outcome of clinical problems with continued risk. Markov models consist of a finite number of defined health states, each having descriptive costs and utilities attached which continues in cycles. They run on the assumption that the probability of a patient making a transition is independent of their past movement through the Markov model and therefore the Markov model has no memory. One cycle of the model can represent a time frame, such as one year. The model can show predicted development throughout time until all patients are in an absorbing state. The absorbing state represents a state which can be entered but cannot be left (e.g. death) (Briggs and Sculpher, 1998).l

1.4 Adverse drug reactions

1.4.1 The burden of adverse drug reactions

Adverse drug reactions (ADRs) are described by the World Health Organisation as "*a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function*" (WHO, 1972). ADRs range in severity and have a substantial effect on patient mortality and morbidity which can inflict large cost and resource implications on the health services. The most severe being Steven-Johnsons Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN),

which typically manifest as fever, malaise, blistering of skin, epidermolysis, erosions to the mucosa and ultimately involves systemic infection. The impact of this ADR has the potential to become fatal with the more extreme of these cutaneous ADRs (TEN) with 30-50% mortality. This causes extensive treatment involving high cost implications, with one case estimated at nearly £30,000 (Plumpton et al., 2015). Other less acute ADRs can still have explicit effects on healthcare expenditure, particularly for ADRs associated with common drugs (such as bleeding events in Warfarin therapy) where the population receiving treatment is vast and the potential ADR population is great. Effective intervention strategies may be able to considerably reduce the risk of ADRs and reduce NHS costs. The NICE costing statement suggests potentially adverse drug reaction-related admissions cost the NHS over £500 million annually (NICE, 2015).

In a large UK study of 18,820 patients, over a 6-month period there were 1225 admissions directly relating to ADRs to two NHS hospitals in Merseyside, accounting for 6.5% of acute admissions within these hospitals (Pirmohamed, 2004). Patients with an ADR stayed a median of 8 bed days in hospital, with each day spent admitted costing between £1917 and £9274. The projected cost per annum to the NHS for admissions alike was £446 million, a significant economic impact for ADRs of which 72% were suggested to be avoidable.

The increased length of stay due to ADRs was also reflected in Davies et al (2009), a small study which found ADRs occurring following hospital admissions directly increased length of stay in 26.8% of patients, by an average of 0.25 days per admission episode. This study also identified a large percentage thought to have been avoidable (n=52/91, 57%). More recently, Wu et al (2010) analysed trends in hospitals of England between 1999 and 2008. This study described 557,978 ADR-associated admissions over this time period, which represented 0.9% of total hospital admissions. Over this period the annual number of ADRs increased from 42,453 to 75,076, which could reflect the lack of contemporary interventions successfully reducing ADRs, an aging population (who are more susceptible), polypharmacy, increased prescribing and a rapid rate in drug development and drug repurposing.

1.4.2 Classification of adverse drug reactions

ADRs can be classified into two types; A and B. With type A being dose-dependent and predictable and type B being unpredictable and not dependent on dosage (Rawlins and Thompson, 1977). Type A constitutes approximately 80% of ADRs (Ritter, 2008). In recent time this classification of ADRs has been challenged due to overlapping - where ADRs may have characteristics of both types. Aronson and Ferner (2003) proposed a three-dimensional classification system which includes other criteria affecting an ADR's classification; pharmacological reaction and its dose dependence, time and severity, properties of the individual and other biological differences that contribute to a patient's susceptibility. This classification is called DoTS and focuses on dose relatedness, timing and patient susceptibility.

Dose relatedness refers to the dosage at which the toxic effects may occur and the nature of this dosage. Adverse events may occur following supra-therapeutic dosages (toxic reactions), standard dosage (collateral effects) and reactions at a subtherapeutic dosage (hyper-susceptibility).

Reactions which occur at any time throughout the course of a treatment are known as time independent reactions. Typically, they occur when the drug concentration changes at the site of action or when the pharmacological response is altered without a change in concentration. Reactions may also be dependent on time, these are divided into sub groups – rapid, first dose, early, intermediate, late and delayed.

Susceptibility is the third dimension of DoTS: the risk of adverse reactions differs throughout the population. This may be due to variation in genetics, sex, age, physiological variation, disease stage and other exogenous factors. The risk of an ADR may be a multifactorial combination of the variables mentioned, although genetic testing for ADR susceptibility can improve patient care and reduce costs associated with ADRs. Genetic testing opens the possibility for patients who have a risk allele to an ADR to be identified prior to prescription and having their treatment pathway altered accordingly, allowing for ADR to be prevented. This supports drugs being retained which are of high value clinically.

1.4.3 PHARMACOLOGY OF ADRS

Previously ADRs were viewed as unpredictable and unavoidable consequences of pharmacotherapy but strategies to assess patient risk and reduce ADRs have been developed. Through assessment of dosing errors, non-adherence and risk factors associated with pharmaceutical therapy, ADRs can now be managed by several approaches. Another significant contribution to ADRs is genetics and their involvement with pharmacokinetics, pharmacodynamics and susceptibility to hypersensitivity responses. The genetic contribution to ADRs is not yet entirely understood – it varies between drugs and there is high inter-patient variability often resulting in different outcomes (Khan, 2016).

ADRs which have been linked to a genetic polymorphism may be a product of poor metabolism, immune-mediated responses and drug hypersensitivity. The recognised hypersensitivity reaction in antiretroviral medication, abacavir, results in a potentially fatal CD8+ T cell mediated response where the drug has been found to bind non-covalently to an antigen-binding groove on *HLA-B*57:01*. This process alters the peptides presented by Human Leukocyte Antigen (HLA) to the CD8+ T cells so they are no longer recognized as 'self' and an immune mediated response is activated (Alfirevic and Pirmohamed, 2010). For patients without this HLA variant, abacavir is mostly metabolised normally and is an effective antiretroviral therapy. Immune-mediated hypersensitivity reactions occur with several other drug-gene associations including; *HLA-B*15:02* and carbamazepine, oxcarbazepine, phenytoin; *HLA-A*31:01* and carbamazepine (Pirmohamed, Ostrov & Park, 2015).

Some patients may have deficiencies in the metabolic processing of drugs, causing a build-up of unmetabolised product. Phase I metabolic pathway disturbances involve ADRs related to *cytochrome P450* enzymes, responsible for metabolising around 25% of drugs (Wolf and Smith, 1999). Variants in these drug-metabolising enzymes, particularly the polymorphism in the gene encoding *CYP2D6*, cause for poor metabolism and increased risk of ADRs. Because of polymorphisms in *cytochrome P450* enzymes this causes for a range of enzyme phenotypes. In poor metaboliser (PM) phenotypes, the plasma concentrations of a pharmaceutical may potentially become toxic causing a range of different ADRs. An example of this is patients with *CYP2C9* PM receiving warfarin for heart related disease. As this drug is solely metabolised by *CYP2C9*, clearance of warfarin is reduced which increases the plasma

concentration and causes increased anticoagulation, leaving patients at higher risk of bleeding events. There is large inter-patient variation in metabolism of warfarin depending on their genotype therefore genetic testing for *CYPC29* polymorphisms and monitoring of drug concentrations may decrease patient risk of bleeding (Cavallari, Jeong & Bress, 2011). Phase II metabolic pathway disturbances effect enzymes in a similar way such as *thiopurine methyltransferase* (*TPMT*) and *UDP-glucuronosyltransferase (UGT)1A1* gene polymorphisms; causing a range of ADR's, the most prevalent being myelotoxicity.

1.5 Methods to prevent adverse drug reactions

1.5.1 Precision medicine

Precision medicine in pharmacogenetics is an approach to healthcare which utilizes modern technologies in genetic profiling to analyse the molecular opportunity for optimizing therapeutic benefit (Weinshilboum & Wang, 2017). Interventions are tailored to sub-groups within disease populations, where a therapeutic benefit has been found from genetic profiling to guide pharmaceutical therapy. Genetic information can be used to direct therapy more appropriately, reducing the risk of adverse effects by either exclusion of a pharmaceutical or monitoring of therapeutic response.

In a clinical setting, genetic testing may advise the treatment of a patient on an individual basis, which can cause different economic outcomes based on the advice following a test result. There are different ways in which the same genetic test can be used, for example the diagnosis of an ADR, identifying a patient's need for further monitoring or the absolute exclusion of a drug from a patients' regimen (Alfirevic and Pirmohamed, 2015).

The diagnosis of an ADR can allow for advised patient drug withdrawal as with drug-induced liver inflammation (DILI) in patients receiving flucloxacillin. *HLA-B*57:01* has a high negative predictive value (NPV) for DILI in these patients, therefore a patient presenting with DILI that tests negative for the genetic variant can continue flucloxacillin as it would suggest flucloxacillin is not the causative agent and further investigation can be carried out on other prescribed medications (Daly et al., 2009).

Excluding a drug is another outcome of genetic testing which can decrease the risk of ADRs. This may not be easily managed for some drugs due to the dispute between benefit and harm, such as with the drug clozapine and cytochrome P450 genetic testing to avoid toxicity, which is a last-line treatment for schizophrenia after other drugs have been exhausted (Kane and Correll, 2010). There are pharmaceuticals which are highly beneficial and cost effective and excluding the drug would pose a greater opportunity cost on other areas of health than ADRs. Without excluding, genetic testing may allow for dosage alteration and monitoring to maintain the therapeutic benefit whilst reducing risk of toxicity.

Alfirevic and Pirmohamed (2017) suggest the criteria for a drug to be excluded: there must be other available drugs with a similar pharmacological effect, a high NPV, similar efficacy and no risk of a severe ADR. In instances where there are no available alternative drugs, the dosage must be altered to allow for drug monitoring depending on the outcome of the genotype, the NPV must be high with regards to allele and ADR association. This allows for the drug to produce therapeutic benefits with a reduced risk of toxicity. Notably, if the positive predictive value (PPV) of a gene to an ADR is low or there is no alternative treatment strategy, then genotyping to avoid ADRs may not be cost-effective as the risk of not may not outweigh the benefit of the drug.

The monitoring of patients and excluding of drugs comes at a cost. In the case of excluding a drug, the alternative drug may be more expensive or less effective resulting in an increase in cost per QALY gained. When the allele prevalence is low there may be many patients tested (generating additional cost) simply to identify one patient who is at increased risk - or when the ADR is rare, many patients may be denied optimal treatment in order to prevent a small population from the ADR.

Sometimes the decision to monitor a drug will be based on the strength of evidence of the association but also may be on the balance of risk when considering efficacy (or lack of efficacy) of other available treatments. Where an alternative drug is available offering similar efficacy for the same indication and no risk of severe ADR, the drug in question could be excluded from a patient's regime and the alternative drug used. For drugs where no alternative is available the drug could be given at a reduced dose and monitored in order to produce therapeutic benefits without toxicity.

Genetic susceptibility testing related to avoiding ADRs is currently implicated in the UK for some drug-gene associations whether as a requirement prior to prescription (e.g. *HLA-B*57:01* and abacavir) or a recommendation (e.g. *TPMT* and mercaptopurine). Other genetic tests may be recommended in certain populations or are merely informative of possible outcomes of drug-therapy, and other suggestions for genetic testing are not fully understood therefore not recommended as part of routine care. A systematic review of drugs associated with ADRs suggested 59% of 27 drugs were identified as being metabolised by at least one enzyme with a variant allele of a known error of metabolism (Phillips et al., 2001). Although the routine use of precision medicine in healthcare may be seen as a contemporary way to improve effective treatment, it needs be accompanied with reliable evidence of efficacy and cost-effectiveness for decision makers to agree on incorporation into clinical practice.

An example of this is warfarin, an anticoagulant for the prevention of embolic strokes within atrial fibrillation patients. Warfarin works by inhibition of *VKORC1*, an important enzyme in the vitamin K cycle for stimulating the coagulation cascade. However, inhibition of the vitamin K cycle may also lead to increased risk of haemorrhage, meaning that warfarin has a low therapeutic index. As the drug targets *VKORC1*, genetic variation in this gene can affect the risk of haemorrhaging. Moreover, warfarin is metabolized via *CYP2C9*, which is also subject to genetic polymorphism. Poor metabolism leading to increased drug concentration can also risk bleeding events, requiring that warfarin must be carefully monitored in patients with genetic variation in either *VKORC1* or *CYP2C9* (Flockhart et al., 2008). Variant alleles may have differential expressivity and penetrance between individuals and may have a variety of effects including adverse drug reactions and reduced drug efficacy.

A feature of genetic susceptibility is the sensitivity and specificity of the gene-drug association with the ADR. There are many studies which have assessed the sensitivity of pharmacogenes, where a high NPV suggests a strong correlation between carriers of the allele and a high or absolute risk of ADR. A 2008 US study, of 130 white and black HIV patients suffering from an abacavir hypersensitivity reaction, found the *HLA-B*57:01* gene to be 100% sensitive to the ADR (Saag et al., 2008) and as a result of this study and other confirmatory work - genotyping is mandatory prior to prescribing abacavir within FDA guidelines. This is an example of where a drug would be excluded from use in patients who are genetically susceptible. For some pharmacogenes, the sensitivity has been found to be lower and therefore may not need total

exclusion, rather just careful monitoring of the drug depending on the availabilities of other treatments.

Gene frequency is another important factor when considering the viability of genotyping and its cost-effectiveness, as patients from different ethnic backgrounds will have genetic variation causing some populations to be more susceptible to ADRs. This is seen in the Han Chinese population receiving carbamazepine, who are frequent carriers of *HLA-B*15:02* – a marker for severe cutaneous ADRs (Chung et al., 2004). More relevant to the UK population is abacavir hypersensitivity and *HLA-B*57:01* - where the risk of a severe cutaneous reaction has been strongly associated with the allele with a NPV of 100% and PPV of 46% (Mallal et al., 2008). The gene frequency for this allele is higher in the UK population (3%) than in others, which makes genetic testing very clinically relevant to the NHS (allelefrequencies.net).

Genotype testing strategies are now emerging into clinical practice, a component of precision medicine to assess the presence of biomarkers which can inform clinicians on possible patient response. The frequency of these reactions and the cost implications have been assessed in few UK studies, although there are many associations which need further research. But with developments in precision medicine, genetic data will become more readily available with whole-exome and whole-genome sequencing which has the possibility to be embedded in a patient's medical records. This means previously established genomic data can be used pre-emptively to improve individualisation of medicine (Alfirevic and Pirmohamed, 2016).

1.5.2 Pharmacogenetic testing recommendations

Pharmacogenetics is an innovative aspect of healthcare evolution which concerns genetic diversity in relation to drug exposure and clinical observations of a chemical compound efficacy and safety profile with an inborn error of metabolism or an acquired phenotype (Scott, 2011). Pharmacogenetics can be clinically observed, leading to enhanced precise tailoring of pharmacological therapy to improve efficiency. This may be through diversifying diagnostics and therapies, dissociating from the 'one-size-fits-all' approach and improving healthcare utility. As genetic factors may affect 20-95% of drug responses, gene-guided therapy can have a significant impact on healthcare (Fragoulakis and Mitropoulou, 2015). Clinical implementation of pharmacogenetic testing has been introduced in diagnostics and efficacy throughout different areas of medicine, and for some drug-gene associations genetic testing has

been found to be an effective method to reduce risk of suffering an ADR and in turn, has become an integral part of prescribing (e.g. Abacavir an *HLA-B*57:01*).

There are more than 250 labels (or Summary of Product Characteristics, SPCs) within the pharmacogenomics knowledge resource – PharmGKB. This database contains pharmacogenetic information approved by any of the four major health agencies; the U.S. Food and Drug Administration (FDA), the Pharmaceutical and Medicines Devices Agency (PMDA), Health Canada (Santé Canada) (HCSC) and European Medicines Agency (EMA). These health agencies are responsible for the scientific evaluation of new and existing medicine quality, safety and efficacy. Drug approval involves an extensive process assessing evidence relating to therapeutic indications and adverse drug reactions from randomised control studies (RCTs) and regulators have the ability to approve or reject based on the evidence provided by the manufacturer (Bighelli and Barbui, 2013). Drugs which later (once in routine use) show a poor safety profile can be withdrawn, labels can also be edited as further evidence is generated.

Drugs which have pharmacogenetic information in the SPC have significant evidence suggesting there is strong linkage between the pharmacogenetic information and the ADR. The patient information leaflet (PIL) is a concise requirement which summarises information from the SPC and includes a description of indications and usage, dosage, administrations and strengths, contraindications, warning and precautions, adverse reactions, drug interactions and use in specific population. The SPC is a legal document approved as part of the marketing authorisation and is used as a source of information for the prescriber on how the medicine should be used. Where applicable, contained within the label is the pharmacogenetic information which may describe the level at which pharmacogenetic testing is necessitated or whether there is merely a known association. This is published as guidance for prescribers once approved by the health agencies.

There are four ways in which pharmacogenetic testing can be implemented which is explicit in the SPC and presented on the Pharmacogenomics Knowledge Base (PharmGKB) biomarker database (PharmGKB.org, 2017) as testing required, recommended, actionable and informative (Table 1). This includes genetic testing, functional protein assays, cytogenetic studies etc and may specify patient populations for which genetic testing should be considered. Each pharmacogenetic annotation comes from a health agency, either the EMA, FDA, PMDA or

HCSC. Each of these agencies have their own recommendation for the target population, these recommendations may therefore differ between agencies.

Table 1: pharmacogenetic testing implementation legend on the PharmGKB database; required, recommended, actionable and informative. Explanation below of SPC description for legend categorisation. (pharmgkb.org, 2017).

Required	**Recommended**	**Actionable**	**Informative**
SPC states testing is necessary prior to drug administration	SPC suggests pharmacogenetic testing should be considered, but not obligatory	SPC contains information about changes in efficacy, dosage and toxicity due to gene/protein/chromosomal variants.	SPC contains information on drug metabolism or pharmacodynamics but does not suggest that the variation will have an adverse or different response to those without this variation.

An example of a required pharmacogenetic test is in relation to abacavir treatment, developed to treat people infected with HIV-1. Initial exploratory retrospective studies described a genetic association between *HLA-B*57:01* and abacavir hypersensitivity reaction (ABC-HSR) found to affect between 2–9% of patients (Hughes et al., 2008). The exploratory studies into the genetic association were initially developed following indication of ABC-HSR in a small population of patients and the early epidemiological analyses of clinical trial data, which found the risk of ABC-HSR was increased between ethnicities. This caused for a retrospective review of the drug by medicine agencies.

The PREDICT-1 trial assessed the clinical utility of genetic testing for *HLA-B*57:01* to reduce ABC-HSR in HIV patients and was designed as a randomized, blinded, prospective study. The

study monitored the occurrence of ABC-HSR over a 6-week period of abacavir initiation in 1578 subjects. For patients with confirmed ABC-HSR, the *HLA-B*57:01* allele had a PPV of 47.9% and an NPV of 100%. This study found that prospective testing reduced the incidence of ABC-HSR by 44% (Mallal et al., 2008). Across all medicine agencies the genetic testing of *HLA-B*57:01* is now required prior to prescribing abacavir for the treatment of HIV-1 and is the most successful of pharmacogenetics tests (so far) in becoming clinically implemented and a requirement for prescribing. This is due to its clinical utility at reducing the risk of ABC-HSR and reducing the cost implications associated with treating this.

Other drug-gene associations have been more challenging to clinically implement, such as the thiopurine methyltransferase variation in patients with autoimmune disease when treated with azathioprine and mercaptopurine – an association for which testing is recommended. Thiopurine drugs have been well-documented for myelosuppressive effects on haemopoietic cells. Although current UK guidelines recommend prospective *TPMT* genetic testing, it is only a mandatory procedure in children and young adults on the acute lymphoblastic leukaemia (ALL) 2011 trial protocol (Lennard, 2014). A 2007 survey suggested *TPMT* testing (either by genotype or phenotype) was used by 67% of health professionals in the UK prior to prescription (Fargher et al., 2007) but there was very little use of the genotype test for *TPMT* variant alleles, possibly reflecting the lack of test availability.

Although there have been studies which acknowledge the links between pharmacogenes and the risk of ADR, medicine agencies will only consider clinical implementation of a genetic test if the strength of the association has conclusive evidence (Walk, 2010). Grouped data analysis on the *UGT1A1**28 association with irinotecan and the ADRs neutropenia and severe diarrhoea, found the PPV to be 50% and NPV between 90-95%. The outcome was that the *UGT1A1**28 should not be used solely to exclude use of the drug, rather to aid in patient information in order to effectively monitor the patient and prescribe an appropriate dosage relating to their genotype. (FDA, 2004; Shah, 2005).

The introduction of clinical implementation of pharmacogenetic information to avoid ADRs has not been significant considering the time frame of precision medicine. The delay in clinical implementation of pharmacogenetics may be associated with the several barriers, such as; turnaround time, cost of test, clinician uncertainty and discomfort in delivering information (Johnson et al., 2012). With precision medicine to avoid ADRs, understanding the clinical

value can be challenging. Shah & Shah (2012) described the barriers to precision medicine as the lack of data on ADRs in the wider community, primarily due to genetic susceptibility, lack of ADR mechanism understanding, the relationship between safety and efficacy and the difficulty of improving safety with the possibility of reduced efficacy.

1.5.3 Multi-gene panel testing to prevent ADRs

Multi-gene panel tests refer to the combination of genes tested for simultaneously and provide genetic information for the initial drug and indication and also report incidental findings. In the context of ADRs, incidental findings are genetic results unrelated to the indication for which the genetic test was requested, but which may be clinically significant in the patient's lifetime (Wolf et al., 2008).

This concept of a panel of genes all screened using a single test has the potential of being extremely efficient, with one draw of blood or saliva sampling and with no or minimal additional costs. This single test will provide information to be used at the time of results (prospectively) and which can be returned as incidental findings and used in the future without the need for repeat testing (pre-emptively). Pre- and post-testing genetic counselling may however be more extensive due to result interpretation and explanation (Harris, Kelly & Wyatt, 2012).

Multi-gene panels have been most successful within oncology but the commercial market for this includes gene panels for neurological disorders, metabolic disease, heart disease and pharmacogenetics (Medical Genetics Centre, 2018). With multi-gene panels for ADRs, a single gene may affect pharmacokinetics or pharmacodynamics of more than one drug equally, the pharmacokinetics (or pharmacodynamics) of one drug may be influenced by more than one gene. Panels can offer a more efficient use of a DNA sample by facilitating the pre-emptive availability of genetic information in a single sample.

Current genetic panel tests for ADRs include the Drug Metabolizing Enzymes and Transporters (DMET™) which provides pharmacogenetic information to avoid/manage ADRs and increase treatment efficacy providing information on 1936 ADME (absorption, distribution, metabolism and elimination) genetic variants in one assay (Fernandez et al., 2012). This assay is not however informative on all ADR relating genes such as HLA and is not currently used to

determine the ADR profile of patients in a clinical setting rather experimental applications of personalized medicine (Sissung, English, Venzon, Figg & Deeken, 2010).

PGxOne ™ Plus is a similar panel test commercially available in the UK offering genetic analysis of 200 variations within 50 genes, not all of which directly relate to the risk of adverse drug reaction (some genes are to guide more appropriate therapy such as the Oestrogen Receptor Modulator (ESR)). This panel includes different HLA loci alleles such as *B*58:01* for hypersensitivity reaction with abacavir. Although the panel test is available on the market, it is yet to be incorporated into the NHS and may currently have a bigger market in other healthcare systems such as US or a commercial market, due to the large amount of genetic information contained, which would have to be returned to the patient (increasing costs). Panel testing for ADRs is not currently implemented in the NHS which may be due, in part, to a lack of economic evidence.

Panel cost-effectiveness may be driven by many factors, one of which is the association between the indications relating to the pharmacogenes (or disease linkage), some diseases may be closely correlated with the development of other diseases. The progression of HIV has become one of interest, as it carries an association with infection of the central nervous system and neurological effects of the virus. Seizures and epilepsy are a common development in patients with HIV, often occurring in the advanced stages of immunosuppression, with a reported incidence as high as 11% (Holmberg et al., 1995; Kellinghaus et al., 2008; Wong et al., 1990). Due to the immunocompromising effect of HIV (causing progressive failure of a patient's immune system), patients are more susceptible to infections with neurological complications such as acute and chronic meningitis and encephalitis. A panel test could therefore provide genetic information on drug-gene associations which is likely to be used in a HIV patients lifetime.

Another disease which links the incidental findings of prospective testing for *HLA-B*57:01* (when obtained via panel testing) is severe fungal infection in HIV patients. The *CYP2C19* allele can increase risk of toxicity when antiretroviral drugs, atazanavir or ritonavir are co-administered with voriconazole, a treatment for severe fungal infection. Annually, severe fungal disease will affect 0.6-4% of the HIV population (Pegorie, Denning, Welfare, 2016). The *CYP2C19* genotype may be a relevant incidental finding of the panel which would be used to prospectively test for *HLA-B*57:01* prior to abacavir initiation.

With chronic diseases such as epilepsy, patients may experience a plateau effect of pharmaceutical therapy over time or may require trying several different pharmaceuticals before optimising seizure control. A prospective gene-panel could be considered useful in this scenario when changing onto other anti-epileptic drugs. If the other available genetic associations relating to such pharmaceuticals have previously been tested for, the information is instantly accessible at no extra cost, to advise and guide therapy.

1.5.4 Economics of pharmacogenetic testing to prevent ADRs

Genetic testing for pharmacogenes associated with ADRs aims to improve cost-effectiveness of pharmacological therapy with a personalised approach. It is therefore vital to assess whether information from genomic technologies provides value for money, in terms of the relative costs and consequences compared with established best practice for both i) single-gene testing and ii) multi-gene panel testing/genomic sequencing.

Pharmacogenetic testing has the potential to reduce the costs associated with serious adverse drug reactions, particularly those that require hospitalisation (Ross, Anand, Joseph & Paré, 2012). To obtain valid, accurate, and relevant estimates of cost-effectiveness, reliable economic studies are required. Cost-effectiveness evidence is usually required to advise on the clinical implementation of genetic testing services. Such evaluations may incorporate a sensitivity analysis of costs, to assess the sensitivity in cost-effectiveness for different assumptions (e.g. cost of test, drug costs etc.). For pharmacogenetic interventions, the likely cost-effectiveness threshold is between £20,000 and £30,000 per QALY (NICE, 2013) (section 1.4.2). ICER calculations may compare e.g. testing vs routine procedure, depending on the context of the pharmacogenetic test.

1.5.4.1 Single-gene testing cost-effectiveness

Economic evidence has found pharmacogenetic testing to prevent ADRs improves health outcomes and cost-effectiveness in different countries and healthcare systems. Plumpton et al (2015) reviewed published economic evaluations of pharmacogenetic tests that aimed to prevent or reduce the incidence of ADRs. This included tests for genetic variations associated with an individuals' susceptibility to either an ADR (where an alternative prescription would be appropriate) or to being outside of a treatment's therapeutic window (where changes to dose would reduce the risk of toxicity). The authors found economic evidence pertaining to

a range of genetic polymorphisms; *HLA-B*57:01*, *HLA-B*58:01*, *HLA-B*15:02*, *HLA-A*31:01*, *TPMT*, *UGT1A1**28, *CYP2C9, VKORC1, CY2C19, A1555G, C6777T, MTHFR, Factor V Leiden (FVL), 5-HTTLPR.*

1.5.4.2 MULTI-GENE PANEL TESTING/SEQUENCING COST-EFFECTIVENESS

The concept of multi-gene panel testing is implemented in other areas of medicine such as in testing for hereditary oncology predispositions, for instance, women at increased risk of developing ovarian and/or breast cancer. This panel includes 19 genes of clinical relevance (Crawford et al., 2017). Hamblin et al., (2017) validated a 46 gene cancer panel costing £339 per patient. Using NHS costing this study reported the test to be less expensive than two or three single gene tests. However, implementation of panel testing in the NHS for ADRs is not yet practiced, which may be due to the limited data on the value of panel testing in this capacity.

This concept of returning genetic information from panel testing/sequencing for ADRs has been evaluated in the following economic evaluations: Alogaz, Durham and Kasirajan (2016): a study which assessed the cost-effectiveness of one-time genetic testing for ADRs and Bennette et al (2014) who assessed the cost-effectiveness of returning incidental findings of genetic sequencing.

Alogaz, Durham and Kasirajan (2016) used a Markov model to follow a cohort of asymptomatic 40-year olds screened using one-time genetic testing for ADR associations. This study was based on genes associated with ADRs contained within the FDA biomarker list (FDA, 2015) and considered *CYP2C19, CYP2D6, CYP2C9, VKORC1, CYP3A4* and *CYP3A5* along with reimbursed genes by Medicare. The result of this Markov model for the base-case implied that testing a group of 40-year olds and following them until death would produce an ICER of $53,680 per additional QALY of genetic testing versus no testing, which is slightly above the US ICER threshold of $50,000/QALY. The ICERs for the one-time genetic testing study were most sensitive to the probability of death due to ADR, reduction of ADR due to genetic testing, mean ADR risk and cost of genetic testing.

An important feature of the Bennette et al (2014) study is interest in the cost-effectiveness of incidental findings from unrelated screening initiation in three hypothetical cohorts (cardiomyopathy, colorectal cancer patients and healthy patients).

The study developed a decision-analytic model to assess the lifetime costs and QALYs associated with returning incidental findings of Next Generation Sequencing (NGS). NGS is a method used to sequence entire genomes or can be constrained to specific areas of interest e.g. a whole exome or small numbers of individual genes (Behjati & Tarpey, 2013). In the decision model, individuals undergoing genomic sequencing can either receive or not receive the incidental findings and the incremental differences between these strategies are measured (with regards to cost and QALYs). The probability of receiving specific incidental findings was based on disease prevalence estimates.

Incidental findings in this study refer to genetic information which is unrelated to the initial sequencing indication but may be clinically significant and useful in the future. This analysis focused on returning incidental findings of NGS of 7 conditions (for which the genomic parameters have high penetrance and clinical actionability); Romano & Ward Long QT Syndromes, malignant hyperthermia susceptibility, arrhythmogenic right ventricular cardiomyopathy, hypertrophic cardiomyopathy, dilated cardiomyopathy, lynch syndrome, hereditary breast and ovarian cancer and familial hypercholesterolemia.

Returning incidental findings to cardiomyopathy patients returned an ICER of $44,800 per QALY gained, increasing costs by $896,000 and increasing QALYs by 20 years. This study projected that testing of generally healthy individuals is not likely to be cost-effective unless the price of NGS falls below $500.

This was one of the first studies to assess the cost-effectiveness of returning incidental findings and provides evidence of clinical efficacy along with an economic advantage to implementing genome sequencing into clinical practice. The results of this evidence suggest there is benefit in certain cohorts of patients for genome sequencing, which is an important finding to conduct further work to assess other methods of genetic testing and returning incidental findings for cost-effectiveness.

1.5.4.3 COST-EFFECTIVENESS OF MULTI-GENE PANEL TESTING: PLUMPTON ET AL., 2018

The concept of returning incidental findings was adopted similarly in the Plumpton et al (2018) study which provided methodology for assessing the cost-effectiveness of multi-gene panel testing to avoid ADRs. Plumpton et al used a decision-analytic model to provide an economic assessment of multi-gene panel testing in the context of ADRs. The cost-effectiveness of the panel was determined by extracting data on the incremental cost and QALYs of pharmacogenetic testing vs routine treatment strategies from previous economic analyses. The incremental cost and QALYs of incidental findings were then calculated following methodology from Bennette et al (2015) (Section 1.4.4.2).

This study reported a case study of a panel test inclusive of *HLA-A*31:01* prior to prescription of carbamazepine and *HLA-B*58:01* prior to prescription of allopurinol. This panel of two genes was assessed for cost-effectiveness with regards to the benefits of reporting incidental findings, to prove the context of single-gene tests being cost-effective pre-emptively when incorporated in a panel. At a test cost of £50, the ICER was £13,464 per QALY gained. *HLA-A*31:01* was cost effective as a single gene test, *HLA-B*58:01* was not. The study identified that when *HLA-B*58:01* is incorporated into a panel test it becomes cost-effective to pre-emptively test. Conclusively, this study developed methodology allowing for the cost-effectiveness assessment of multi-gene panels.

Cost-effectiveness was also illustrated by a multi-gene panel including *HLA-A*31:01, HLA-B*15:02, HLA-B*57:01, HLA-B*58:01, HLA-B* (158T) and *HLA-DQB1* (126Q). The conclusion of this analysis was that if the findings for all alleles are acted upon the HLA test saved £378 and had a QALY gain of 0.0069. When analysing the panel test compared with no testing, prospective use of the panel was cost-effective in patients eligible for abacavir (*HLA-B*57:01*), carbamazepine (*HLA-A*31:01*) and clozapine (*HLA-B (158T)* and *HLA-DQB1 (126Q)*) but not for carbamazepine (*HLA-B*15:02*) or allopurinol (*HLA-B*58:01*).

The present study aimed to build on this, extending the genes contained within the panel to also include genes beyond the HLA family using the methodology to assess cost-effectiveness of multi-gene panels developed by Plumpton et al (2018).

1.5.4.4 Development of a cost-effective multi-gene panel to avoid ADRs

MC Diagnostics (MCD) is a specialist molecular diagnostics company with expertise in the automation of multiplexed molecular assays and custom designed image analysis interpretation software. They are interested in developing multi-gene panel tests which are cost-effective to the NHS by reducing ADRs through genetic testing. This test works by hybridizing DNA to immobilized probes at the bottom of a microwell plate, producing a colorimetric reaction which detects the presence of positive probes. The MCD match software then interprets the presence of alleles related to diverse drug reactions and produces an ADR profile for each patient sample.

This multiplex assay will initially be marketed to the NHS and other healthcare providers in the UK and Europe and has the capacity to incorporate a limited number of genes. It is essential for product implementation that this panel increases overall health and can be marketed at a reasonable (that is, value-based) price. The value-based price of a panel test relates to the price at which the panel has an ICER of <£20,000/QALY and therefore is a cost-effective strategy for the NHS to consider.

1.6 Aims and Objectives

The primary aim of this thesis was to conduct a cost-utility analysis of multi-gene panel testing to prevent adverse drug reactions, in terms of cost per QALY gained, from the perspective of the NHS in the UK. A further aim of this study was to apply a decision-analytic framework to assess the cost-effectiveness of different gene-panel configurations at various test costs.

To achieve this, there were several objectives.

i) Identify, categorise and prioritise drug-gene associations to prevent ADRs from the PharmGKB database.
ii) Assess the PharmGKB extracted drug-gene associations for previously conducted economic evidence by extracting data from the Plumpton et al (2015) systematic review and updating this review to 2017.
iii) Calculate single-gene cost-effectiveness estimates for relevant drug-gene associations without economic evidence.

iv) Extract data on incremental cost and QALYs, from previous economic analyses and the single-gene cost-utility estimates, to model the cost-effectiveness of a multi-gene panel using a previously developed decision-analytic meta-model.
   - Perform scenario analysis using different gene-panel combinations and test costs.
   - Perform sensitivity analysis on the base-case scenario using a 10,000 Monte Carlo simulation.

The use of a cost-utility analysis was appropriate for this study to assess the cost-effectiveness of multi-gene panel testing. This allows the utility-based measure (QALY) to be used in the comparison of single-gene testing or no genetic testing, compared with multi-gene panel-testing, in the event this evidence is used in HTA appraisal. This is also beneficial when assessing the opportunity cost of implementing multi-gene panel testing and allows this to easily be compared with the displacement of other healthcare services.

2. METHODS

2. 1 MODELLING AND ECONOMIC ANALYSIS OF MULTI-GENE PANEL TESTING

2.1.1 INTRODUCTION

The previous chapter explored the use of health economics and economic modelling in implementing pharmacogenomic testing methods, reviewing previous economic evidence and the current requirement for genetic testing prior to prescription to avoid adverse drug reactions. This chapter describes the adaption of a previously developed decision-analytic meta-model which was designed to assess the long-term cost-effectiveness of multi-gene panel testing to avoid adverse drug reactions.

This meta-model builds on previous work from Plumpton et al (2018), combining economic evidence of single-gene testing to assess the cost utility of multi-gene panel testing. Different scenarios of gene-panel combinations were then applied to the meta-model to assess the cost-effectiveness of different panel test configurations and also, using a base-case scenario gene-panel, identify the proportion of test scenarios where the panel test was cost-effective to use the information prospectively for each gene on the panel.

2.1.2 OVERALL APPROACH

The economic model within this study was employed to answer policy questions regarding multi-gene panel testing. The first policy question was to understand whether multi-gene panel testing (including genetic polymorphisms outside of the HLA family) is cost-effective when returning additional genetic information relating to ADRs (incidental findings). The second policy question this study aimed to answer was which genes provided a cost-effective combination as a panel test, considering the different incidental findings being returned with each panel scenario.

The presumption of multi-gene testing is that one genetic test is initially requested to provide genetic information to be used at that point of time. The difference between single-gene and panel testing for ADRs is that a panel will provide a risk allele profile, which has the possibility to inform a patient's treatment - in the incidence they are diagnosed with a disease which requires a drug with a genetic predisposition to an ADR. This information would have been previously recorded at the point of prospective testing (i.e. used pre-emptively). In practice this

allows for prevention of adverse drug reactions over a patient's lifetime with one genetic test offering guidance on excluding or monitoring on an individual basis.

The commercial aspect of this study aimed to assess the value-based price of each multi-gene panel test to the NHS (as defined in section 1.5.4.4) for each combination of genes. This would then provide the product developers with a threshold (with regards to the panel ICER; incremental cost/incremental QALYs) where the product is no longer cost-effective to the NHS (>£20,000/QALY). The value-based price was calculated by increasing the price per test within the economic model until using the panel was no longer cost-effective to any of the disease groups. To show the contrast between the price per test where the panel is viable for one disease group and all disease groups, the maximum panel price was also calculated. This was calculated by increasing the panel test from £0 to the price at which the panel was no longer cost-effective to test for all genes on the panel prospectively. This outlined the maximum price per test for which the panel could be cost-effective to all disease groups.

2.1.3 Model concept

The concept of the model was taken from Bennette et al (2014), where a decision-analytic model was created to project the lifetime health outcomes and costs associated with genetic sequencing of ACMG-recommended list of genes. The Bennette et al (2014) study concluded that the ACMG policy for returning results (Green et al., 2013) could be cost-effective and beneficial to patients of specific populations receiving genomic sequencing (section 1.5.4.2). This model was adapted by Plumpton et al (2018) to calculate the economic benefit of returning incidental findings to pre-emptively advise on ADR profiles for HLA genotypes (section 1.5.4.3). In the present study, the methodology of the Bennette et al (2014) model concept adaptation by Plumpton et al was adopted - applying the method of returning incidental findings from a multi-gene meta-model to a wider range of genetic polymorphisms and incorporating genes beyond those of the HLA family.

Conceptually, the model reports a panel ICER (calculation detailed below), which can be defined as the incremental cost/incremental QALY associated with multi-gene panel testing (figure 1). This is calculated using incremental costs and QALYs associated with prospectively testing for a gene within the panel and incorporates the effect on both cost and QALYs of returning the incidental findings, weighting this by the probability of suffering from a further

disease where incidental findings of the multi-gene panel test would be useful (i.e. another gene on the panel).

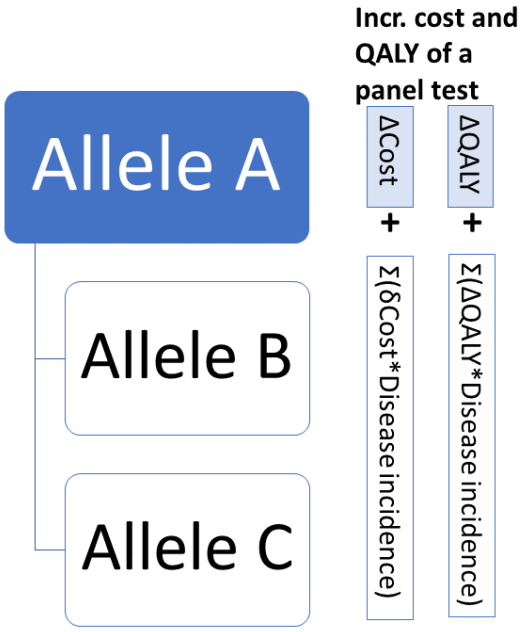

Figure 1: Illustration of how to calculate the incremental cost and QALY of a multi-gene panel test using a 3-gene panel.

The incremental costs of returning the incidental findings to provide pre-emptive information are the same as that with prospective testing - however the cost of the test is recovered by the prospective test. The incremental QALYs associated with pre-emptive testing are the same as for prospective prevention – in that the ADR is avoided. The genes contained within the panel which are secondary to the initial request for testing are considered opportunistic as patients were undergoing genetic testing for an ADR associated gene which is unrelated to the drug being prescribed, and condition it is being prescribed for (worked example in figure 2).

$$ICERPanel = \frac{CostPanel}{QALYPanel}$$

$$ICERPanel = (CostTest + \delta\, cost + cost(incidental\ findings))/\ (\Delta\ QALY + QALY(incidental\ findings))$$

CostTest = Cost of genotyping test

δ cost = incremental cost of prospective test (with the cost of test removed)

cost (incidental findings) = cost of returning incidental findings (weighted by disease incidence of each drug indication)

QALY (incidental findings) = QALYs of returning incidental findings (weighted by disease incidence of each drug indication)

Δ QALY = incremental QALY of prospective test (with the cost of test removed)

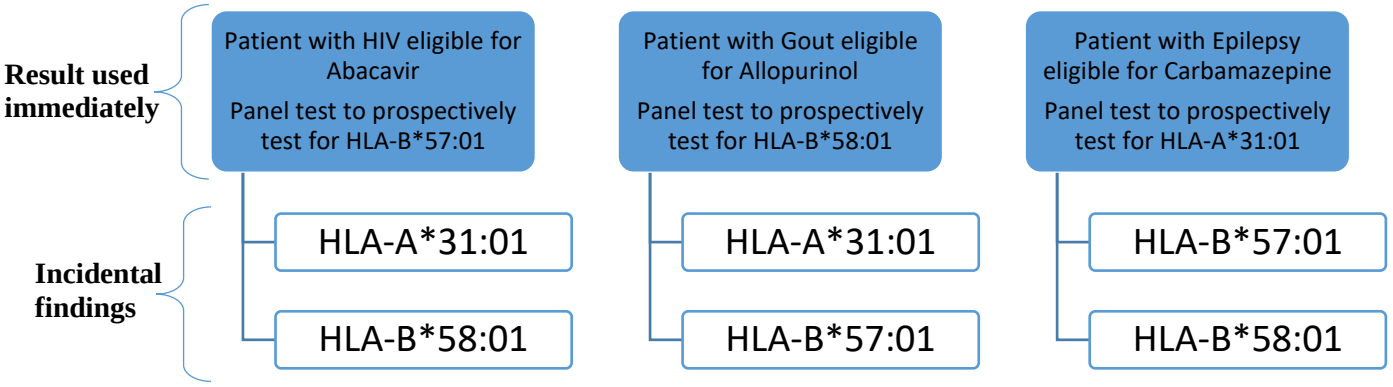

Figure 2: This figure illustrates a 3-gene panel displaying 3 possible options for allele A (Figure 1) (prospective genotyping, using a panel scenario). The overall panel result is a combination of these three starting points. For each panel configuration, the model applied a sensitivity analysis using a Monte Carlo simulation (10,000 replications) to assess how each gene within the panel can be used as the prospective test, pre-emptively or neither (with regards to their cost-effectiveness when used as such).

2.1.4 Model structure

A meta-model (decision-analytical model) was used, this is a compilation of evidence obtained from several other economic models from previous work (section 2.3) and from estimated cost-utility analyses of single-gene testing (this methodology is outlined in section 2.5). This approach is an explicitly quantitative approach to decision making under uncertainty. This method was used to quantify the impact of cost and utility on a theoretical group of patients who have additional genetic information pre-emptively returned after prospectively receiving genetic testing for an ADR related pharmacogene. The aim of the model was to produce a realistic outcome of pharmacogenetic multi-gene panel testing, from which mean costs and effects (QALYs) could be estimated.

To calculate this, the same methodology was followed as described in Plumpton et al (2018). This study used the Bennette et al (2014) calculation for incremental costs and QALYs of incidental findings - weighting the incremental cost $\delta Cost_{x, y, z}$ (minus the cost of genotyping) and $\Delta QALY_{x, y, z}$ by the probability of initiating drug y for indication z. The probability of initiating drug y for indication z was calculated using annual UK incidences, derived from the literature (section 2.6.5) and applied to the UK population.

2.1.5 Model assumptions

For the model to calculate an estimate of cost-effectiveness for each combination of genes, this necessitated some assumptions for simplification purposes or because the data was not in the correct format.

- Every new incidence of each disease would be treated first-line with the therapy relating to the drug-gene association.
- Patients within disease groups are at the same stage of their disease and with similar prognosis (as some diseases get progressively worse as in the case of some cancers).
- The incidence of all disease and gene frequency is the same in all patients entering the model as the general population e.g. a patient with epilepsy has the same incidence of suffering with gout in the future as a patient with HIV.
- Another assumption was involved in the conflicting evidence as to whether a positive allele should cause for a drug to be entirely excluded from a patient's treatment regime or whether it should be dose reduced and/or monitored to assess risk of toxicity. This

study assumed all patients positive for the risk allele had the drug excluded and were treated with a different drug.

- Each patient was assumed to be of the same age. Specifying age was not appropriate as the different diseases have different average age of onset, which will be varied in each of the economic analyses included in the meta-model - therefore reflecting one age was not appropriate.
- There was an assumption made regarding the storing of genetic information over a lifetime, this cost was assumed to be recovered in incremental costs and QALYs associated with the multi-gene panel test.
- The model timeframe was over a pragmatic lifetime horizon, this was the frequently used timeframe in the economic evidence used to populate the model (appendix 1) and therefore was the most appropriate.

The assumptions included in the model are as transparent as possible, assessing and evaluating and understanding the risk of bias involved in these.

2.2 Review and categorization of pharmacogenetic information containing summary of product characteristics.

In order to aid in the decision-making pathway with respect to prioritisation strategies for the development of a multi-gene panel test for ADRs, the identification of all medicines for which pharmacogenetics information is included in the Summary of Product Characteristics (SPC) was required, which could then inform the model described previously in section 2.1.

The PharmGKB database is a comprehensive resource which combines and disseminates knowledge on the impact of genetic variation on drug response, for the use of clinicians and researchers. It contains over 600 drugs with 130 pharmacokinetic or pharmacodynamic pathways resulting in almost 500 clinical annotations within the SPC (PharmGKB.org, 2017).

For genetic variants within this database, where evidence on drug-gene associations is sufficient, pharmacogenetic information is listed in the SPC (www.medicines.org.uk/emc) and in some circumstances testing is clinically implemented. All associations within the PharmGKB database have some level of pharmacogenetic annotation, with varying degrees of

advice on testing requirements. These recommendations are informed by an extensive evidence review by international medicine agencies (FDA, EMA, PMDA, HCSC).

2.2.1 PHARMGKB SEARCH STRATEGY

This study focuses solely on the associations as listed in the PharmGKB database, which advises whether genetic testing is required, recommended, actionable or informative. For inclusion in the panel-test cost utility analysis the drug-gene combinations required a "1A" level of evidence. This indicates the endorsement of this association in the CPIC (Clinical Pharmacogenetics Implementation Consortium) guidelines or implementation at Pharmacogenetics Research Network (PGRN). This enabled the identification of drug-gene pairs for which there is a strong level of clinical evidence which therefore may have impact when incorporated into a panel test.

To differentiate the clinical annotations contained within the SPC, a screening process was initiated to determine the pharmacogenes that have information on a change in efficacy, dosage or toxicity which related to the possibility of an ADR (figure 3).

Drugs which had pharmacogenetic information in their SPC appearing under 'warnings and precautions' and/or 'adverse reactions' and/or 'contraindications sections' and contained toxicity information with a known ADR were included in the initial database of pharmacogenes. The list of drug labels containing pharmacogenetic information was arranged by priority of testing to provide an interface for economic investigation.

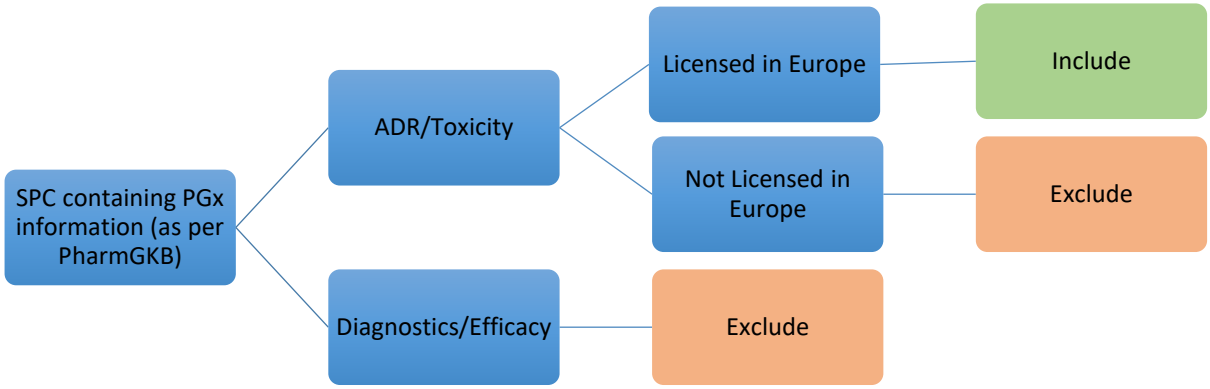

Figure 3: Describes the methodology to include drug-gene associations as per the information on PharmGKB to restrict to ADR related pharmacogenes licensed in Europe.

Drug-gene associations which aided in diagnostics or efficacy alone were not included in this study and associations related to a pharmaceutical which has over-the counter availability were also excluded due to the inability to regulate the usage. This relates to not being able to monitor how many over-the-counter treatments are purchased for which conditions and over-the-counter drug availability is not a context in which a pharmacogenetic test would be implemented to reduce the risk of ADR.

Once the ADR related genetic associations were extracted from the database, further stages of screening were then applied. This was to ensure the most relevant associations to the European population were filtered - due to the multi-gene panel tests commercial development focusing on a European market.

Pharmaceuticals were checked for licensing within Europe, the license refers to the ability for the drug to be sold and marketed. Only drugs which were licensed in Europe were included. The European Medicine Agency (EMA) website provided information on the licensing status for most drugs, allowing for confirmation of Europe licensing (www.ema.europa.eu/ema).

For the more recently developed drugs, drugs which are authorised through national procedures and medicines still in development, licensing information was not available. In this case the Electronic Medicines Compendium (eMC) was used, which is another recognized database of the UK licensing status of pharmaceuticals using both the Medicines & Healthcare products Regulatory Agency (MHRA) and EMA guidance.

In the Plumpton et al., 2018 focusing on HLA pharmacogenetic testing to avoid ADRs, associations with European allele frequencies of <1% were to be excluded. The present study included gene frequencies below this to extend the possible combinations in the gene panel, as low frequency alleles may still be cost-effective when returned as incidental findings or prospectively screened.

2.3 Systematic review update of economic evidence of pharmacogenetic testing

In order to estimate the cost-utility of a multi-gene panel it needed to be established which genes were cost-effective prospectively and which may not be prospectively cost-effective but do become of value when incorporated into a multi-gene panel. Identifying genetic predispositions prospectively can accurately predict the outcome of a patient and prevent the ADR through either drug choice or drug dose.

There were two scenarios involved in populating the meta-model to assess the cost effectiveness of a genetic panel previously described in section 2.1.5. These stages were dependant on the availability and plausibility of research conducted on the cost-effectiveness of testing for the pharmacogenetic associations (figure 4). Data could be extracted directly for input into the meta-model where economic evidence of single-gene cost-effectiveness was available. For the associations where testing is ‘required’ or ‘recommended’ as per PharmGKB database without economic evidence for single-gene cost-effectiveness, an estimation was calculated. This therefore made updating the systematic review an integral part of this study to find evidence for input.

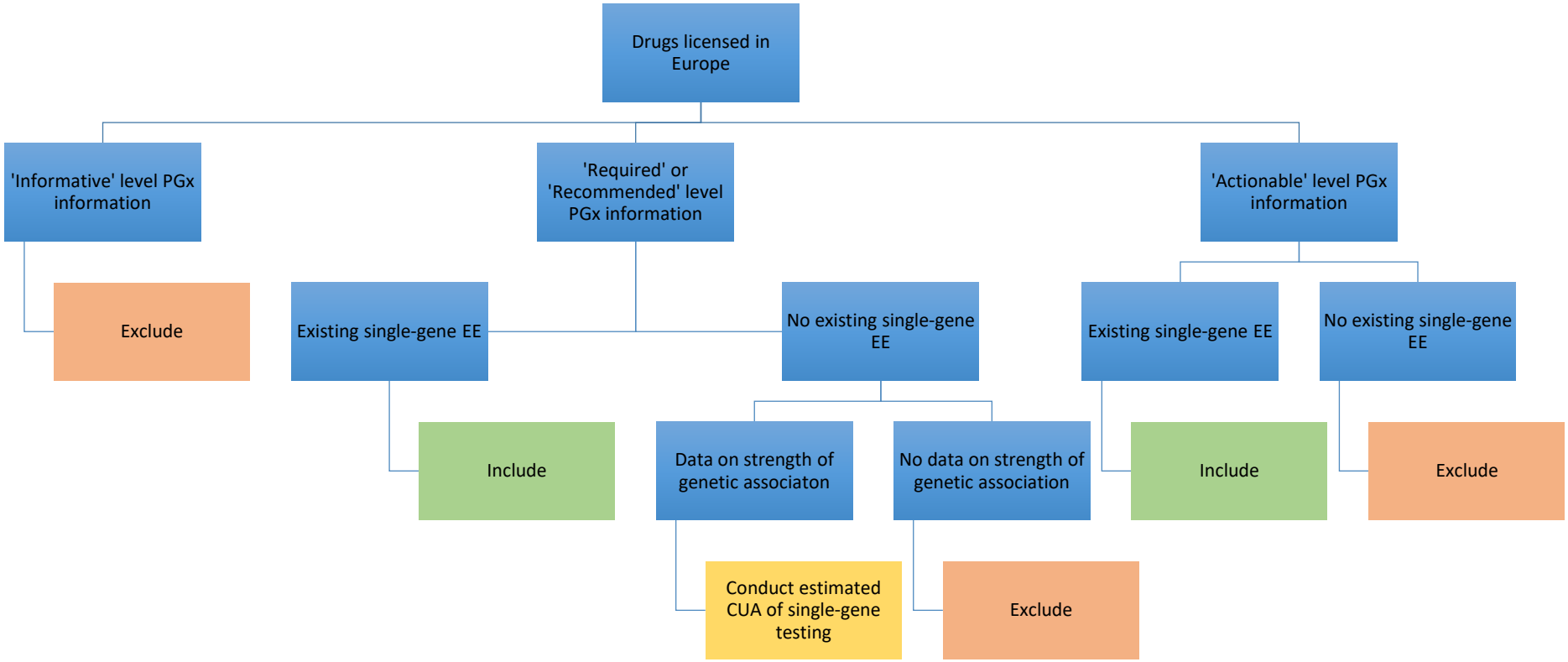

Figure 4: Process of data extraction or data generation for inclusion in decision-analytic meta-model to assess Cost-Utility of multi-gene panel testing.

EE= Economic Evidence, CUA= Cost-Utility Analysis

Single-gene testing economic analyses were important to foresee value of individual genes and obtain data on cost and utility data to inform the meta-model. The use of previously conducted economic analyses allowed for extensive robust evidence on all relevant implications on cost and utility to be incorporated into the panel test economic model.

The 2016 systematic review by Plumpton et al provided analysis of quality, costs and effectiveness for the economic evaluations available on single-gene pharmacogenetics testing for prevention of adverse drug reactions. The conclusions of this study were that the evidence available for abacavir, allopurinol, irinotecan and clopidogrel and their pharmacogenetic markers suggests adoption of routine testing into practice should be considered. Evidence for several other markers; 6-MP, azathioprine, cisplatin, methotrexate, warfarin and SSRIs had variation between individual study results.

To populate the meta-model as part of the present study, a search was conducted for previously published single-gene economic analysis to update the findings of the Plumpton et al (2016) systematic review for genes relevant to the PharmGKB database to 2017.

2.3.1 Search strategy

The search strategy employed in the present study followed previous work by Plumpton et al (2016) in their systematic review of Pharmacogenetics for prevention of ADRs (appendix 2). However, only economic analyses for the genes contained within the PharmGKB database were searched for, due to the testing annotations from the SPC.

This earlier systematic review searched Embase, MEDLINE and NHS EED for economic evidence. To extend this research to present day PubMed was used which incorporates other databases including MEDLINE. NHS EED literature updates were ceased from March 2015 which allowed for PubMed to be the most suitable database for the literature search, as it contains both databases previously searched in the Plumpton et al (2016) study.

2.3.2 Study selection and inclusion criteria

This study updated the findings of the 2016 systematic review by Plumpton et al to 2017, including only gene-drug associations to ADRs extracted from the PharmGKB database

(appendix 3). The search was conducted for inclusion of papers from June 2015 up to November 2017 and was inclusive of full economic evaluations, with preference to a cost-utility analysis comparing standard care with a genetic testing for pre-disposed susceptibility to the ADR.

2.3.3 Data extraction

Results extracted from the economic evaluations included the cost of test, cost year and currency, incremental cost and incremental QALY, this was presented as summarized version in comparison to the Plumpton et al (2016) systematic review, which was more detailed.

Due to the intention to use extracted data to inform a further economic model, the time frame of the study being evaluated was also noted. The time frame should be appropriate and reflect a period of time which makes it possible to encompass all important cost and utility differences (appendix 1).

2.3.4 Quality of reporting assessment

Data quality is important when used in an economic model, which is provided by large sample sizes, appropriate study design, and limited missing data. A screening process was undertaken to critically appraise the methodological value, risk of bias and transparency of the included studies. Critical appraisal in model-based cost-utility analysis is essential as they can be utilized in aiding decision making by assessing transparency.

The Plumpton et al (2016) systematic review gave a reporting quality review score which followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guideline. CHEERS is a 24-item checklist which is a practical tool for critical appraisal and can assist in examining reporting quality of economic evaluations (Husereau et al., 2013). When extending the systematic review evidence to the present data the CHEERS checklist was used. Reporting quality was considered ‘high’ if 20 out of 24 items were included. The quality of studies further informed parameter selection for the economic modelling work by providing a systematic framework for selecting from multiple similar studies (where applicable) based on study quality.

In reporting this review, the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) was followed (Liberati, et al., 2009). PRISMA is a checklist of 27 items to improve reporting of systematic reviews and meta-analysis (Moher, 2009).

2.3.5 Presentation of results

Results are presented as individual summaries of each study and include extracted data on costs and QALYs. Results are reported as individual study outcomes regarding pharmacogenetic testing to avoid ADRs. The results of the update are presented with the studies selected from the Plumpton et al (2016) systematic review for use within the economic model of the present study.

2.4 Selecting studies to inform cost-effectiveness of panel

Studies which performed an economic analysis from a UK NHS perspective were prioritised. For pharmacogenetic associations without a UK economic analysis, where possible the subsequent economic analyses included were from European studies (being the next most relevant population). For the remaining pharmacogenetic associations, available economic analyses outside of Europe were used which provided data on costs and QALYs from different populations. Although allele frequencies, costs and QALYs might not be parallel with the UK, the data used was extracted from well conducted extensive research studies using genetic testing and standard treatment as the comparator. Finally, in cases where there were no existing economic evaluations, an estimated single-gene cost-utility analysis was conducted following the methods outlined in Section 2.5.

Economic evaluations were chosen using the method described in the diagram below (figure 5). Studies were prioritised based on study quality as assessed by methods in chapter 2.3.4. In the event there were several studies of similar size and quality, the most recent was prioritized. This was applicable where the requirements of the model could be extracted (incremental costs and QALYs). If the incremental costs and QALYs were not provided, then the next most recent study was used. Using the most recently published study is applicable to this study as the accumulation of evidence is very much time-dependant in the field of precision medicine.

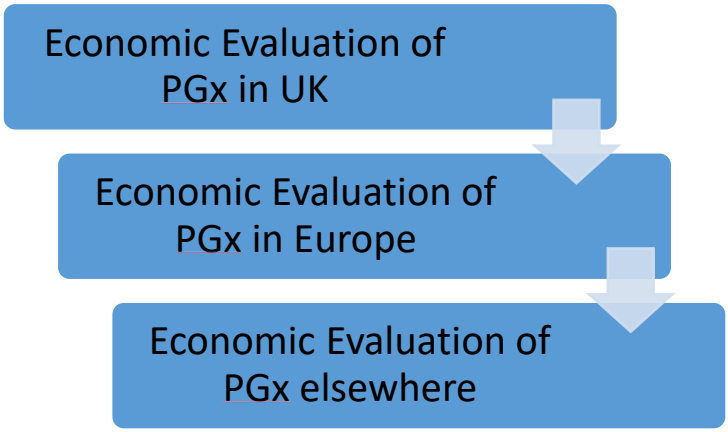

Figure 5: Flow chart of the study selection for use in economic analysis of multi-gene panel testing to prevent adverse drug reactions (PGx = pharmacogenetics).

2.5 Estimating single-gene testing cost-utility

To estimate the cost-utility of a multi-gene panel test, inputs from previously conducted economic analyses of single-gene tests for the associations shortlisted from the database were needed to populate the model. For several of the drug-gene combinations where testing is 'required' or 'recommended' there was no economic evidence of single-gene cost-effectiveness. In this instance an estimation of genetic testing cost-effectiveness was calculated using figures from previously conducted economic analyses, comparing the drug with a comparator along with other cost, utility and prevalence inputs. For the associations where testing is suggested as 'actionable' without previously conducted economic analyses (n= 82) an estimated cost-utility analysis was not conducted.

2.5.1 Calculating pharmacogenetic testing cost-utility estimates

The basis of this calculation is to compare the costs and utilities of testing and giving alternative medication with a patient suffering from the ADR considering the PPV and allele prevalence. The calculation is descriptive of the process followed by an allele positive patient under the exclude regimen (Plumpton et al., 2018).

Excluding a drug, the incremental cost of genetic testing can be estimated by breaking down costs associated with single-gene testing and weighting this by allele prevalence and the PPV:

Cost of genotyping, excluding the drug associated (if positive for the allele) with an ADR and treating with an alternative:

$$A = \text{CostTest} + \text{P(x)} * (1 - \text{PPV}) * \Delta\,\text{Costalternative}$$

Cost of treating with drug z and suffering from the ADR is weighted by the PPV:

$$B = \text{P(x)} * \text{PPV} * \text{CostADR}$$

Therefore, the following equation estimates the cost of single-gene testing:

$$\Delta\,\text{Cost}x, y, z = A - B$$

or

$$\Delta\text{Cost}x, y, z = \text{CostTest} + \text{P(x)} * (1 - \text{PPV}) * \Delta\,\text{Costalternative} - \text{P(x)} * \text{PPV} * \text{CostADR}$$

CostTest = Cost of genotyping test
P(x) = Probability of allele x
1-PPV = Probability of not suffering from the ADR with the allele
Δ Costalternative = Incremental cost of treating indication y with an alternative treatment to drug z
CostADR = Cost of the ADR

The corresponding calculation for incremental QALY associated with genetic testing can similarly broken down:

The QALY associated with testing for the genotype, excluding the drug associated (if positive) with an ADR and treating with an alternative:

$$C = \text{P(x)} * (1 - \text{PPV}) * \Delta\text{QALYalternative}$$

The QALY associated with treating with drug z and suffering from the ADR is weighted by the PPV:

$$D = \text{P(x)} * \text{PPV} * \text{QALYADR}$$

Therefore, the following equation estimates the cost of single-gene testing:

$$\Delta QALY x, y, z = C - D$$

or

$$\Delta QALY x, y, z = P(x) * (1 - PPV) * \Delta QALY alternative - P(x) * PPV * QALY ADR$$

P(x) = Probability of allele x
1-PPV = Probability of not suffering from the ADR with the allele
ΔQALYalternative = QALY associated with of treating indication y with an alternative treatment to drug z
QALY ADR = QALY associated with suffering from the ADR

Each of the inputs weight the calculation to reflect the incremental cost and utility of genetic testing to avoid an ADR and the use of alternative treatments, against the risk associated with an ADR and the cost related to this. This calculation uses the allele prevalence of the target population (Europe) and PPV to include probability of ADR to weight the calculation realistically.

The single-gene incremental QALY was calculated using a structure which compared the two treatment methods - testing positive for the allele and providing alternative therapy against the other option of all patients being initiated on the drug weighted by the risk allele prevalence, the PPV and the QALY decrement of having the ADR. The QALY decrement was taken from published literature and was calculated from the control QALY minus the ADR group QALY. Where the control QALY was not available the UK average was used. ADR QALYs were used from drugs which differed in indication as these were the only available resource. An ICER could then be calculated to compare screening with no screening. This was done by calculating incremental cost/incremental QALY.

The inputs to this calculation are the incremental cost of the alternative drug, the ADR cost, the cost of the genetic test, PPV (from sensitivity and specificity calculations, section 2.5.4) probability of the allele in the UK population, QALY associated with the ADR and QALY associated with the alternative treatment. These inputs were directly extracted from the published literature and used in the calculation.

2.5.2 Literature search on strength of genetic association

A further literature search was conducted to confirm the genetic association strength which allowed data to be extracted for use within the estimated single-gene cost-utility analysis. This data was needed to calculate the PPV to weight the single-gene testing cost effectiveness estimate as described in section 2.5.1. The prevalence inputs included the PPV previously calculated from data associating the genes to an ADR (methods outlined in section 2.6.5 and 2.6.6).

To provide genetic association data for the estimated calculation of cost-utility, the literature was searched for evidence of a pharmacogenetic relationship involving the initiation of a serious immunological response such as SJS/TEN, haemolysis, neutropenia, thrombotic events, hepatotoxicity and other adverse reactions. This search was conducted using the NICE evidence search (www.evidence.nhs.uk, 2017) and PubMed using the gene with the Boolean 'AND' operator with the associated pharmaceutical and its corresponding pharmacogene related to ADR risk (appendix 4).

2.5.3 Study selection and inclusion criteria

The abstract of each study from the full search was screened to decide whether the article met the inclusion criteria. They were then systematically selected by most robust methodology, with systematic reviews and meta-analyses the most appropriate for this type of evaluation (Figure 6) as they offer robust methodology by the review and collation of several studies, to produce a result by consensus. Where this was not available, RCTs were used.

Data used in the model should be as robust as possible, the traditional view of evidence is hierarchical as structured in the evidence pyramid (Figure 6), with systematic reviews (SRs) and randomized control trials (RCTs) thought to be the most robust.

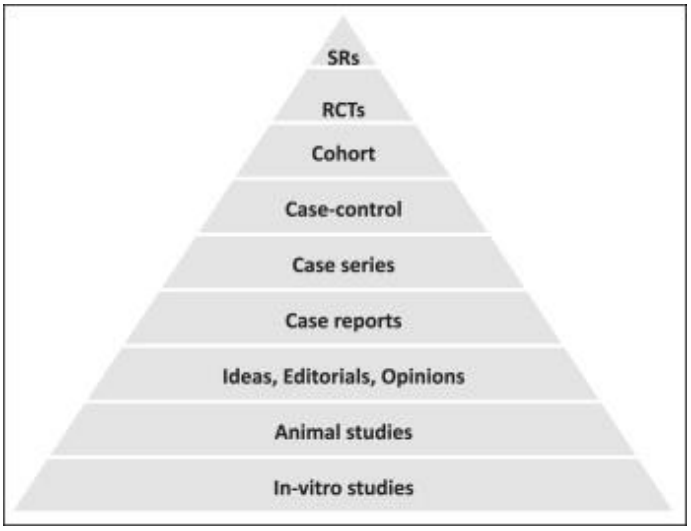

Figure 6: An illustration of the hierarchical structure of the evidence pyramid. (Reproduced from Pandis, 2011)

Studies from a UK perspective were prioritized due to the nature of the present study and its focus on the UK healthcare system. Multiple studies within this selection were then chosen by which possessed the largest sample size, most recently conducted and had most robust methodology.

Where no studies from a UK perspective, appropriate population or setting were available - a large study conducted on a European population succeeded for selection. The requirement of a European population was important to understand allele frequencies within the target population, as this will vary between different regions of the world. Subsequent to this, review studies from outside of Europe were accepted.

Following this prioritization strategy, individual studies of the genetic association were used although the sample size is considerably lower than that of a systematic review. This can affect reliability of population representation as the small sample size may not reflect the ADR and gene prevalence due to possibility of bias in both selection and population.

2.5.4 Data extraction for allele association

Data was extracted on the following study characteristics: year of publication, drug, disease, population, genotype, and A) number of patients allele positive (ADR group); B) number of

patients allele positive (no ADR group); C) number of patients allele negative (ADR group) and D) number of patients allele negative (no ADR group).

This data was used to confirm the association of each gene with a severe ADR (severe ADRs in section 2.5.2). From the published data, the sensitivity and specificity were calculated where:

$$Sensitivity = \frac{A}{A + C}$$

$$Specificity = \frac{D}{D + B}$$

The sensitivity refers to the ability of the allele to predict the risk of ADRs. It is the proportion of patients who experience the ADR, who test positive for the allele. The specificity is the proportion of patients who do not experience the ADR, who do not have the allele.

2.5.5. ADR AND ALLELE PREVALENCE

Each ADR frequency in patients receiving treatment is an important factor for cost-utility analysis. This helps to analyse how much the individual ADR impacts on the NHS and whether the testing of a pharmacogenetic association is of economic benefit, when weighting the calculation.

The eMC contains the SPC, which provides information on all adverse events associated with each drug based on clinical trials that the pharmaceutical company has carried out (Medicines.org.uk, 2017). The average incidence for severe ADRs for each drug were taken from this material for use in the estimated economic analysis.

The PPV and NPV were then calculated for input into the estimated cost-utility analysis of testing. The PPV is used to indicate the probability of suffering from the ADR if a patient is allele positive. The NPV is the probability of not suffering from the ADR if a patient is allele negative.

$$PPV = sensitivity * ADR\ prevalence / \big(sensitivity * ADR\ prevalence + (1 - specificity) * (1 - ADR\ prevalence)\big)$$

$$NPV = specificity * (1 - ADR\ prevalence)/(specificity * ((1 - ADR\ prevalence) + (1 - sensitivity) * (ADR\ prevalence))$$

Another factor which can be used to evaluate the requirement for genetic testing and its cost-effectiveness, is marker frequency in the population. This is important as frequency for some genes in certain populations is much higher than in the target population (UK) and was an integral part of the cost-utility estimation of single-gene testing as described in section 2.5.1 (Probability of allele x).

An example of this is the association between the Han Chinese and Thai population and *HLA-B*15:02*, where the frequencies of this allele are 5.9% and 8.5% respectively - compared with a European frequency of 0.0657% (allelefrequencies.net).

Using gene frequencies within a European population was an important indication of the likelihood of single-gene testing cost-effectiveness and was essential to estimate this from a UK NHS perspective. Populations of higher gene frequency may indicate the increased incidence of ADRs, which has the capacity to increase the need for testing and influence cost-effectiveness.

2.5.6 Choosing a relevant comparator drug economic analysis

For the comparator drug to be valid, it required use for the same indication as the drug relating to the ADR and should be considered as a genuine alternative. Another essential characteristic of the comparator was no known risk of genetic predisposition correlated with a severe ADR. Full search teams attached in appendix 5.

2.5.7 Monitoring or excluding a drug

Previous work has assessed the cost-effectiveness of treatment management of allele positive patients by costing the monitoring of a patient's response to the drug, or excluding the drug associated with an ADR and offering an alternative. To decide on excluding or monitoring a drug, methodology suggested in a recent publication on genomics of adverse drug reactions should be followed (Alfirevic and Pirmohamed, 2017).

This paper describes criteria for a drug to be excluded from a patient's treatment regime, i) there must be other available drugs with a similar pharmacological effect, ii) a high NPV, iii) similar efficacy and iv) no risk of a severe ADR. In the instance there is no available alternative treatment, the dosage (of drug associated with the ADR) must be altered and the patient must be closely monitored. This allows for the drug to produce therapeutic benefits whilst the patient is more closely monitored for symptoms of toxicity.

Sometimes the decision to monitor a drug will be based on the strength of evidence for the genetic association to the ADR, but may also be on the balance of risk when considering efficacy (or lack of efficacy) of other available treatments. Where an alternative drug is available offering similar efficacy for the same indication and no risk of severe ADR, this meant the drug in question could be excluded from a patient's regime and the alternative drug used.

This study assumed that in all cases the purpose of testing is to exclude the drug associated with the ADR. This was because of the extensive assumptions involved in calculating cost-effectiveness of drug monitoring following an allele positive test. For example, assumptions would have to be made on how effective monitoring is at reducing the ADR, how many patients would change treatment as a result of monitoring and how frequent monitoring may occur in a patient cohort. Further than this, the costs and health utility capacities involved with this method.

2.5.8 Costs and utility extraction

To estimate the cost-utility of pharmacogenetic testing to avoid ADRs, all costs were reported in GBP (£) and inflated to 2015/16 values using the hospital and community services index (Unit Costs of Health and Social Care, 2016). This study takes the perspective of the UK NHS therefore searches were conducted to find the cost of the ADR and incremental costs within studies and published figures using this perspective. Only studies using GBP sterling were included as treatment approach and costing may differ in other countries – this is also affected by the use of a National Health Service and not an insurance or personal finance situation as seen in European countries, America and Asia.

The cost of a single-gene test used in the calculation was estimated at £30 this was informed by the price of a single loci HLA type to the NHS of MC Diagnostics and other genotyping tests costing around £30 such a CYP2D6 (Fleeman et al., 2011) and TMPT testing estimated at around £20 to £30 (Thompson et al., 2014).

The incremental cost of the alternative was taken from an economic analysis comparing the cost-effectiveness of the drug associated with ADR and a comparator drug used for the same indication without the risk of ADR. Similarly, the incremental QALY for the alternative was taken from this study to assess the difference in utility of the comparator. These values contributed to the cost-utility estimate calculation on the pharmacogenetic testing side of the equation (equation A and C, section 2.5.1), which describes effects on cost and QALY of avoiding the ADR and treating with an alternative therapy - in that an ADR would be avoided.

The cost of treating each ADR was required for each estimation. Costing ADRs is a challenging process as not all measurements of outcomes are straight forward, as the cost of the ADR is dependent on the individual as severity and the care needed for each ADR can be very different between patients. Costs are only readily available for a minority of inputs and consequences, therefore the impact on the healthcare system is difficult to estimate as there is a lack of accessible patient data and findings must be extrapolated from research rather than datasets from the NHS. Published estimates of ADR cost were extracted from existing economic evaluations, and where this was not possible, assumptions were made based on comparable diseases, and costed using the National Schedule of Reference Costs (Reference costs | NHS Improvement, 2018).

It is assumed that adverse drug reactions are associated with a temporary or permanent reduction in a patients' quality of life. For input into cost-utility estimates health state utilities for the ADR (QALYs) were extracted directly from previous economic analysis which assessed the effect of the ADR on patient health state. The quality of life metric which is recommended by NICE is the QALY, therefore this metric was most applicable to use. For the single-gene cost-utility estimate, the ADR utility was inputted as utility decrement (ADR). If the health state of patients without an ADR were not published the UK average QALY score sufficed, 0.86 (Kind, Hardman & Macran, 1999).

2.6 MULTI-GENE PANEL TEST SCENARIO ANALYSIS

Using data extracted from evidence from the Plumpton et al (2016) systematic review, the updated systematic review (section 2.3) and the single-gene test cost-utility estimates (2.5) different panel scenarios could be built and assessed for cost-effectiveness considering different panel configurations (and therefore a different range of incidental findings). The scenario analysis also helped to identify the cost-effectiveness of a fully inclusive panel of genes with different genes as the prospective test (i.e. with the cost of test applied to the incremental cost of single-gene testing), applying the multi-gene panel test to the different disease groups and analysing cost-effectiveness.

With the overlapping of genetic polymorphisms on different panel scenarios, an incremental analysis should be performed on every combination of the panel test if each panel is mutually exclusive (Drummond,1997). However, as the panel scenarios are not necessarily mutually exclusive, due to the there being different possible prospective tests and incidental finding out comes of every scenario, an incremental analysis was not necessary in this study as the panels have different outcomes on each subgroup of different areas of disease receiving the prospective test.

2.6.1 THE BASE CASE SCENARIO

The base case was the scenario which would be most plausible to the NHS for cost-effectiveness of implementation. This was set at the £20,000 cost-effectiveness threshold, at a £30 per multi-gene panel test. The price of the panel test was informed by the cost of manufacturing to MC Diagnostics (the product developers) which needed to be competitive with other methods to genotype such as next generation sequencing. MC Diagnostics currently sell single-gene tests to the NHS and therefore suggested a price which reflects the extra information obtained by a panel. Other cost per tests and thresholds were explored in a range of sensitivity and scenario analysis to assess the robustness of this price on cost-effectiveness estimates.

Tests which were above the £20,000 threshold were not cost-effective to test prospectively, however, these are still included in the model to analyse their cost-effectiveness as incidental findings (i.e. with the cost of test removed). This was to explore cost-effectiveness of incidental findings, whereby treating by genotype may be cost-effective when the information is already

known, and the cost of test is covered by the primary test. To enable the test to calculate cost-effectiveness of returning incidental findings of the panel test to avoid ADRs pre-emptively, the cost of a panel test was included only once when incorporated into the model.

To calculate the base case ICER for each gene used prospectively, the incremental cost without the cost of the single-gene test (δ cost) was added to the cost of a panel test, assumed in the base case as £30 (δ cost+ panel test cost = Δ cost), and then weighted by disease incidence (δ cost of each single gene test in the incidental findings, and divided by the incremental QALY (Δ QALY) for the single gene test combined with the weighted QALY of each single gene test in the incidental findings.

$$ICER = (cost\ (test) + \delta\ cost + cost(incidental\ findings))/\ (\Delta\ QALY + QALY(incidental\ findings))$$

The model reflects the overall cost-effectiveness of multiple-gene testing, as well as the cost-effectiveness of multiple-gene testing by initial condition. Tests which would be included as an initial test to commission the multiple gene test and also the tests which be included as they were cost-effective within the incidental findings.

2.6.2 Sensitivity analysis

Sensitivity analysis is a useful way to test parameter uncertainty and measure its impact on the model results. As there were many inputs (direct costs, indirect, QALYs etc.) that coiuld vary (due to currency conversions and different healthcare systems with varying costs), the use of confidence intervals to assess robustness was very important within this model. Sensitivity analysis was also important to quantitatively assess robustness of the results in relation to the different assumptions necessary to populate the model.

As there is uncertainty around the data inputs, the sensitivity analysis of the panel test combinations had a similar level of uncertainty regarding estimates for incremental costs and QALY gain and simulations were conducted to explore the robustness of the findings. This parameter uncertainty was tested by simultaneously varying both point estimates of incremental costs and QALYs for all tests within their 95% confidence interval (CI). Cost and QALY confidence intervals and mean values were used to compute the SD. Where confidence

intervals were not published, a plausible range was used (± 20%), as used in the Verhoef et al (2016) study of warfarin pharmacogenetics cost-effectiveness. This allowed for uncertainty to be assessed by producing SD, which expresses by how much the costs and QALYs differ from the mean value.

The sensitivity analysis was conducted using 10,000 Monte Carlo simulations which produces a distribution of possible outcomes. This was performed for every multi-gene panel combination but was specifically explored for the base-case. The sensitivity analysis of the base-case scenario allowed for the different genetic tests to be assessed for the probability they would be cost-effective as the prospective test, or cost-effective when returned as incidental findings.

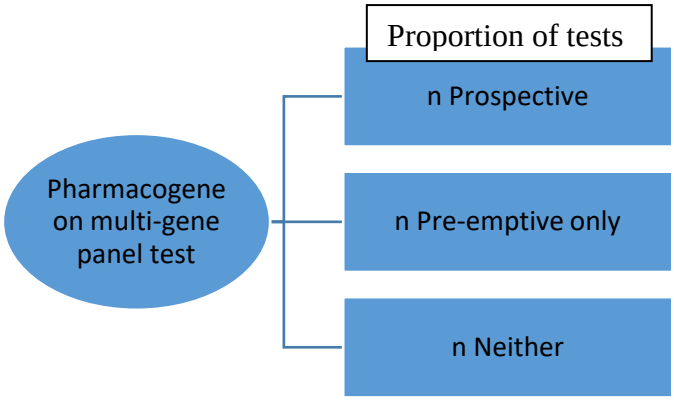

Figure 7: Base-case scenario sensitivity analysis example, Monte Carlo simulation (10,000 replications). Each pharmacogene on the panel tested for its cost-effectiveness when panel-testing is initiated, and single-gene result is used prospectively, results are returned as incidental findings or neither. This was done as a panel configuration of all pharmacogenes included in the study.

The difference in cost and utility was calculated for each replication, analysing the number of times the gene was prospective, pre-emptive or neither when placing uncertainty on the mean using SD. This allowed for valuation of which inputs had the biggest effect on the results and determined the probability of how likely each outcome is to occur. These simulations create

varying ICERs plotted on the cost-effectiveness plane to show visual interpretation of the sensitivity.

Statistical analysis was not appropriate to test robustness of the ICERS, as it is not possible to generate 95% confidence intervals because the 2 distributions does not necessarily have a finite mean or therefore finite variance (Barber and Thompson, 2000).

2.6.3 FURTHER SCENARIO ANALYSES

There were several scenarios of different plausible configurations of the panel test to answer various policy questions which were included in the scenario analysis (Table 2).

Table 2: Inclusion criteria of each panel scenario tested for cost-effectiveness

	Inclusion criteria (pharmacogenes)
Scenario 1	Drugs which require pharmacogenetic testing prior to prescription
Scenario 2	Drugs which require or recommended pharmacogenetic testing prior to prescription
Scenario 3	Drugs which require or recommended pharmacogenetic testing or have actionable information on pharmacogenetic testing
Scenario 4	Pharmacogenes associated with common drugs (prescriptions >100,000 (thousands) items),
Scenario 5	Pharmacogenes with high UK gene prevalence (>1%)
Scenario 6	Pharmacogenes with high South East Asian prevalence.

To prioritise the most economically viable gene combinations, the single-gene ICER without the test cost was calculated for all associations. This indicates the cost-effectiveness of pre-emptively testing for the single-gene, therefore implying a likelihood of cost-effectiveness when incorporated into the multi-gene test. For single-gene tests which had a negative effect on health (reduction in QALYs), the cost-effectiveness of pre-emptive testing was not likely plausible and therefore they were left out of the model.

A principal aim of the project is to determine the value-based price test of a panel. Scenario analysis was also conducted to explore the variability in costs and QALYs, this range represents a plausible set of test costs to start with (£10, £20, £30, £50). By varying the test cost the value-based price of the gene panel could be analysed against the ICER threshold, as this product is not yet developed it was important to assess the most applicable test cost to coordinate the value-based price to the NHS. A range of cost-effectiveness thresholds were also used to conduct scenario analysis (£20,000, £30,000, no threshold).

2.6.4 Resource use costs and utilities for input into the economic model

For input into the economic model of the panel, the primary source of data was extracted from previous economic evaluations found in the Plumpton et al (2016) systematic review and the updated search (section 2.3) and from estimating single-gene cost-effectiveness (section 2.5). Data extracted from these studies included the incremental QALY, incremental cost, cost year, cost of test, cost and QALY standard deviations or confidence intervals (CI).

The total incremental costs of economic analyses previously conducted included pharmaceutical costs, genotype testing cost, hospitalisations, investigations and appointments with healthcare professionals. Each study will have included different costs etc. the pragmatic approach is to assume that all units included were the same in each study. This was similar for the incremental QALY, it was assumed the health utility was recorded at the same point in time and stage of the ADR however this cannot be fully established.

The incremental cost extracted from the economic analysis of testing included the cost for the single-gene test. With the production of a multi-gene panel that is cost-effective to the NHS as the concluding outcome of this study, the test cost of a single-gene was removed due to the

development of a product which will encompass many single-genes within one test, with one test cost. Therefore, the marginal cost of the incidental results is zero. The test cost could then be varied as part of a sensitivity analysis within the model to produce the most viable ICER and value-based price to the NHS.

Within the model, patients accumulate one-off costs associated with the increment or decrement associated with genetic testing to avoid ADR and provide alternative therapy. Every panel-test performed has a one-off cost, covering the cost of testing for genes as incidental findings. This enables the genes which are cost-effective to screen prospectively to be separated from genes which are not.

Standard deviations (SD) for incremental costs and QALYs was reported in a few of the economic analyses of testing. For studies with 95% confidence intervals (CI) the SD could be calculated using the equation below. Where published confidence intervals were not available, upper and lower boundaries were assumed using +/-20% (mean) and therefore SD could be estimated using the calculation below (Verhoef et al., 2016).

$$SD = (Upper\ limit\ CI - Mean)/1.96$$

As the present study takes the perspective of the UK NHS, all costs were reported in GBP (£) and inflated to 2015/16 using the hospital and community services index (Unit Costs of Health and Social Care, 2016).

2.6.5 Disease incidence

The proportion of patients diagnosed with each disease was determined by annual UK incidence data. The incidence rates were resultant of published data from several sources including published studies and Office for National Statistics (ONS) derived. The most recent papers which published on incidence of disease were used where available and only UK populations were used to provide relatable incidence. The UK population was set at 65,600,000 taken from the Office for National Statistics mid-2016 figures and was used to apply the disease incidence (new prescriptions) and weight the model (ONS, 2017).

2.6.6 Discounting

With the costs and QALYs being directly taken from published resources, discounting was assumed to have been previously applied to the data and therefore data did not need further discounting. Considering the timeframes were appropriate to the specific disease group of data used to populate the meta-model, discounting would have been appropriate for the specific study therefore applying a lifetime discount to the panel would not have been appropriate.

3. RESULTS

3.1 Identification of pharmacogenes and prioritisation based on PharmGKB recommendations

Out of 488 drug labels containing pharmacogenetic information approved by FDA, EMA, PMDA and HCSC, 125 were found to contain information relating to ADRs. Drug-gene associations which aided in diagnostics or efficacy alone were not included in this study. However, this was not always characteristically defined and there was some cross-over between toxicity and efficacy. This was particularly prevalent for informative level pharmacogenetic information where evidence was limited. Guidance from medicine agencies is not homogenous for associations and pharmacogenetic clinical implementation reflects this. An example of the disparity in guidance can be seen with Factor V Leiden (*FVL*) testing in patients with familial thrombosis prior to oral contraceptive prescription. This association is required by the EMA but merely actionable elsewhere.

As this study focused on the required, recommended and actionable pharmacogenetic information (as per PharmGKB), many of the 125 were not included in this study (n=111) due to several factors, with lack of gene-ADR association data being the foremost reason for exclusion. The list of 125 genes which has the reason for exclusion for each relevant pharmacogene is in the appendices of this thesis. (appendix 3).

There were 15 genetic associations where the label implied pharmacogenetic testing as a requirement, or testing was recommended or actionable, which were included in the analysis with the available data sufficient for the model criteria. As there were many associations that had actionable pharmacogenetic information contained within the label, inclusion of actionable pharmacogenetic testing was restricted to associations with a previously published economic analysis of testing (Table 2).

The associations were checked for licensing within the UK of which a handful had obtained an EU license but were however not yet approved by NICE. An example of this being the tyrosine kinase inhibitor drug, lapatinib - used in the treatment of advanced or metastatic breast HER2+ cancer. This drug has been denied approval by NICE several times for first-line therapy due to lapatinib failing to fulfil criterion for life-extending end-of-life treatment (NICE, 2015). Although the criteria were not met for the NHS to approve this drug, it is available for women

currently receiving lapatinib. This drug is also used in other European countries therefore the associated pharmacogenes were considered for inclusion in the gene panel.

Gene frequency and ADR prevalence was obtained for calculating cost-effectiveness estimates (Table 2). From the literature, *TPMT* had the highest frequency with 30% of the UK population with a genetic polymorphism causing *TPMT* deficiency (Thompson et al., 2014). The very low gene frequency in the UK of *HLA-B*15:02* (0.0657%) was a result which, when weighted in the cost-effectiveness had the possibility of deeming testing not cost-effective in this population.

On the SPC the ADR statistics were displayed in proportions of patients who will develop the ADR e.g. 1/1000. For this to be used within the PPV calculation, it was converted into a frequency between 0 and 1 (Table 2). For warfarin the risk of bleeding events was stated on the SPC as 'not known', therefore frequency of ADR was taken from the ROCKET AF trial, a report into the management of major bleeding events from the use of warfarin (Patel et al.,2011). ADR prevalence was highest in patients receiving thiopurine drugs, with 1/10 patients suffering from myelotoxicity. Chemotherapeutic drug irinotecan also presents a high risk of neutropenia (0.1%).

Disease incidence findings were abundant for common diseases however this factor was more challenging to identify with drug interactions causing ADR, particularly with HIV patients routinely treated with antiretroviral drugs - atazanavir or ritonavir. HIV patients with severe fungal infections are limited as to the drug treatment options available. Voriconazole is often prescribed, but interactions with antiretroviral therapies can cause drug-induced liver injury (DILI). In a study estimating the burden of invasive and serious fungal disease in the UK, it was estimated that between 0.6-4% of the HIV population will suffer from severe fungal infection each year (Pegorie, Denning, Welfare, 2016) (appendix 6).

The UK incidence of fungal infection in HIV patients was deduced from the fungal disease incidence in HIV patients multiplied by the UK HIV population, 0.023 x 101,500 = 2334.5 (Aghaizu et al., 2016). This was then calculated in relation to the UK population (Table 2). Other disease incidence estimates were taken from the literature and the Office for National Statistics (ONS) (Appendix 7).

Table 3: Pharmacogenes associated with ADR extracted from PharmGKB along with testing annotation, ADR prevalence and UK gene frequency.

Drug/Marker	**Pharmacogenetic testing**	**ADR**	**ADR prevalence**	**Gene frequency**	**Reference**
Drug: Ethinyl estradiol/Noralgestromin (Oral contraceptive) Marker: *FVL*	Required	Deep vein thrombosis	0.0002	0.05	Smith et al., 2008
Drug: Carbamazepine Marker: *HLA-B*15:02*	Required	SJS/TEN	0.0001	0.000657	Allelefrequencies.net, 2017
Drug: Lapatinib Marker: *HLA-DRB1*07:01*	Required	Hepatotoxicity	0.02	0.12337	Allelefrequencies.net, 2017
Drug: Lapatinib Marker: *HLA-DQA1*02:01*	Required	Hepatotoxicity	0.02	0.128803	Allelefrequencies.net, 2017
Drug: Abacavir Marker: *HLA-B*57:01*	Required	Hypersensitivity	0.02	0.033039	Allelefrequencies.net, 2017
Drug: Azathioprine Marker: *TPMT*	Recommended	Myelosuppression	0.1	0.3	Thompson et al., 2014
Drug: Mercaptopurine Marker: *TPMT*	Recommended	Myelosuppression	0.1	0.3	Thompson et al., 2014

Drug/Marker	**Pharmacogenetic testing**	**ADR**	**ADR prevalence**	**Gene frequency**	**Reference**
Drug: Oxcarbazepine Marker: *HLA-B*15:02*	Recommended	SJS/TEN	0.0001	0.000657	Allelefrequencies.net, 2017
Drug: Phenytoin Marker: *HLA-B*15:02*	Recommended	SJS/TEN	0.0001	0.000657	Allelefrequencies.net, 2017
Drug: Carbamazepine Marker: *HLA-A*31:01*	Recommended	SJS/TEN	0.0001	0.026195	Allelefrequencies.net, 2017
Drug: Voriconazole and Atazanavir/Ritonavir Marker: *CYP2C19*	Recommended	Hepatotoxicity	0.002	0.022	Bhatt et al., 2012
Drug: Clopidogrel Marker: *CYP2C19*	Actionable	Cardiovascular events	0.0001	0.022	Bhatt et al., 2012
Drug: Warfarin Marker: *CYP2C9*	Actionable	Bleeding events	0.0352	0.126	Kurose, Sugiyama, & Saito, 2012
Drug: Irinotecan Marker: *UGT1A1*	Actionable	Neutropenia	0.1	0.271	Kurose, Sugiyama, & Saito, 2012

Drug/Marker	**Pharmacogenetic testing**	**ADR**	**ADR prevalence**	**Gene frequency**	**Reference**
Drug: Allopurinol Marker: *HLA-B*58:01*	Actionable	SJS/TEN	0.0002	0.019	http://www.allelefrequencies.net/

Pharmacogenetic testing recommendation as per SPC annotation (PharmGKB.org, 2017)

ADR prevalence extracted from European Medicines Consortium (Medicines.org.uk, 2017)

ADR= Adverse drug reaction, SJS/TEN= Steven Johnsons Syndrome/Toxic Epidermal Necrolysis

3.2 LITERATURE REVIEW AND UPDATE OF SYSTEMATIC REVIEW OF SINGLE-GENE TESTING ECONOMIC ANALYSES

3.2.1 SEARCH RESULTS

A total of 89 articles were identified from PubMed from June 2015 to November 2017, 15 full articles were retrieved of which 6 met the inclusion criteria for review. Reasons for exclusion are presented in Figure 8. The Plumpton et al (2016) systematic review identified 852 articles of which met the inclusion criteria.

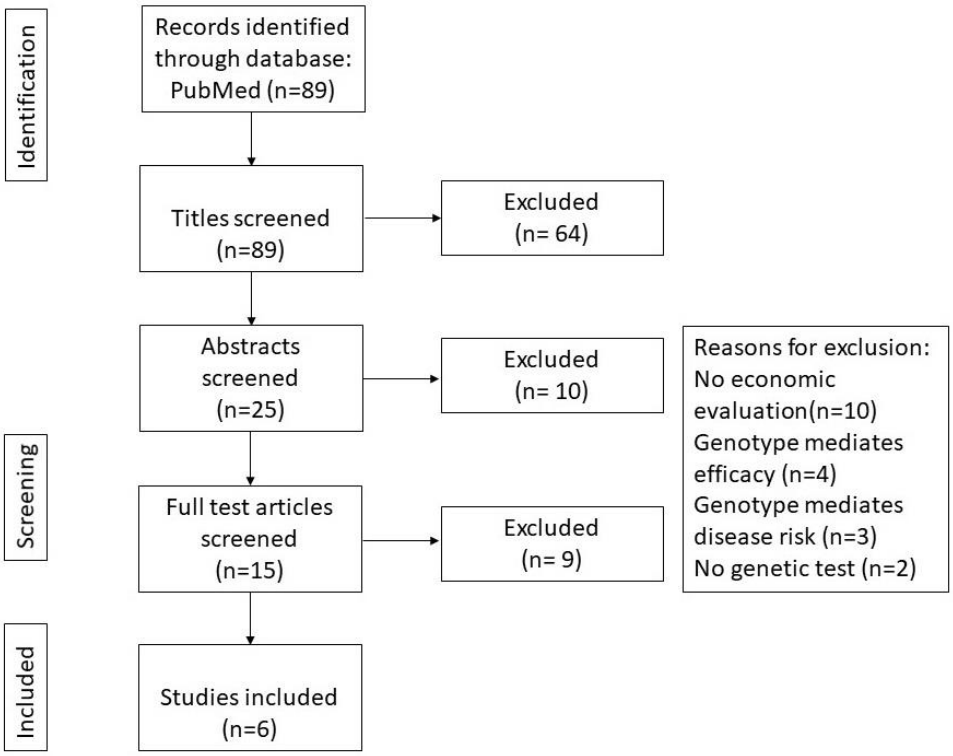

Figure 8: PRISMA flow chart.

3.2.2 STUDY CHARACTERISTICS

The study characteristics are described in Table 3 with data extracted from chosen studies. Data was also extracted from the single-gene cost-effectiveness studies chosen from the Plumpton et al (2016) systematic review for inclusion in the economic modelling of a multi-gene panel (Table 4).

The most common allele evaluated for cost-effectiveness since the Plumpton et al., (2015) systematic was *HLA-B*58:01* (n=3) (Ke et al., 2017; Plumpton, Alfirevic, Pirmohamed & Hughes, 2017; Dong, Tan-Koi, Teng, Finkelstein & Sung, 2015). This allele is associated with

a risk of hypersensitivity reactions, SJS/TEN, in patients receiving allopurinol for the treatment of gout. Other studies evaluated the cost-effectiveness of genotyping *HLA-B*15:02* for carbamazepine therapy in epilepsy (n=1) (Chen, Liew and Kwan, 2015), *UGT1A1* for the chemotherapeutic drug irinotecan (n=1) (Butzke et al., 2015) and VKORC1/*CYP2C9* guided warfarin therapy (n=1) (Verhoef et al., 2016).

All economic evaluations were cost-utility analyses with the majority (n=5) based on economic models and the remaining conducted to coordinate with a randomized controlled trial (n=1) (Verhoef et al., 2016). One study was conducted in the UK (Plumpton et al., 2017) and two in Europe (Verhoef et al., 2016, Butzke et al., 2015), the remainder were conducted in Taiwan (Ke et al., 2017), Singapore (Dong et al., 2015) and Hong Kong (Chen, Liew and Kwan, 2015).

3.2.3 Reported results

The literature search conducted to update the Plumpton et al (2016) systematic review of pharmacogenetic economic evaluations in the prevention of ADRs, presented evidence for the cost-effectiveness on several associations. *HLA-B*58:01* is associated with increased risk of SJS and TEN in patients receiving allopurinol for the treatment of gout. There were multiple economic analyses published after 2015 reporting on this genetic association (n=3), all of which gave reasoning against clinical implication of routine testing for allopurinol. Plumpton, Alfirevic, Pirmohamed & Hughes (2017) reported small QALY gains with increased costs and suggested that *HLA-B*58:01* testing is unlikely to be cost-effective. This study reported that the probability that genotyping is cost effective at a threshold of £30,000 per QALY is 25%. This was a particularly important finding as this is reflective of the UK population and uses costs applicable to the NHS – giving a more relatable input to the meta-model on costs and utilities. The EMA does not currently implement pharmacogenetic guidance for allopurinol and this study is concurrent with this guidance.

Dong et al (2015) reported on cost-effectiveness of genotyping for *HLA-B*58:01* in Singapore to avoid allopurinol in carriers. This yielded lower QALYs and higher costs and was therefore dominated by a monitoring program. Both genetic guided uric lowering therapy and genetic testing to exclude allopurinol strategies had ICERs above the US threshold ($50,000). Low PPV (1.52%) and the limited choices of drugs for chronic gout treatment were thought to drive the result. However, the Taiwan based study found *HLA-B*58:01* testing to be very cost-

effective with an ICER of $7508, much lower than the suggested threshold ($50,000/QALY) (Ke et al., 2017). This shows the disparity between different healthcare systems and ethnic backgrounds on cost-effectiveness.

The suggestion of routine *UGT1A1* testing prior to irinotecan prescription in the Plumpton et al (2016) systematic review was confirmed in this update, in the model synthesis by Butzke et al (2015). Adverse reactions associated with this allele include neutropenia, febrile neutropenia and myelosuppression. This study found testing for *UGT1A1* to dominate non-personalised colon cancer care, under a statutory German health insurance perspective, resulting in a marginal QALY increase (0.0002) and a cost saving of €580 per patient. The testing recommendation for irinotecan and *UGT1A1* remains the same - listed as an actionable by regulatory authorities.

Another particularly important finding for data extrapolation within the present study was the highly likely cost-effectiveness of genotype guided warfarin therapy in the UK in an analysis of the EU-PACT trial (Pirmohamed et al., 2013). This analysis found pharmacogenetic testing to be cost-effective in both the UK and Sweden, with 93% of simulations using UK data having an ICER lower than the £20,000 willingness-to-pay threshold (Verhoef et al., 2016). The current guidance contained within the label suggests testing for *CYP2C9* as actionable, this study provides evidence for the adoption of testing into clinical practice.

Carbamazepine is an anti-epileptic drug which has a pharmacogenetic association *HLA-B*15:02* to the severe cutaneous adverse drug reactions SJS and TEN. The current testing policy for *HLA-B*15:02* was assessed for cost effectiveness in the Chen, Liew and Kwan (2016) study. This strategy was reported as not cost-effective in practice in Hong Kong and returned an ICER of $85,697 which is above the US $50,000/QALY threshold.

From the updated systematic review, studies most reflective of a European population with comparable costing to the NHS were the most appropriate for use within the model due to the commercial availability of the gene-panel being focused in the UK and Europe. This minimised the cost and QALY variability between different areas of the world as healthcare costs and the systems of which these are applied differ greatly. Four of the studies within the systematic review met this criterion, a cost-utility analysis of prospective testing for *HLA-B*58:01* prior to allopurinol treatment in sufferers of gout (Plumpton et al.,2017), *HLA-A*31:01* prior to

carbamazepine therapy in epileptics (Plumpton et al., 2015), *TPMT* for genotype guided azathioprine treatment (Thompson et al., 2014) and the Verhoef et al cost-utility analysis of pharmacogenetic-guided warfarin therapy (2016).

Table 4: Systematic review update, data extracted for incorporation into model.

Drug/marker/ADR	**References**	**Year of value, currency**	**Cost of genetic test (£, 2016)**	**Incremental cost (£, 2016)**	**Incremental QALY**	**Study characteristics**
Drug: Allopurinol Marker: *HLA-B*58:01* ADR: SJS/TEN	Ke et al., 2017	2015, NT$	2648	2620	0.0112	Decision-analytic model Location: Taiwan Quality: High
Drug: Allopurinol* Marker: *HLA-B*58:01* ADR: SJS/TEN	Plumpton, Alfirevic, Pirmohamed & Hughes, 2017	2014, GBP	55	103	0.0023	Decision-analytic and Markov model Location: UK Quality: High
Drug: Allopurinol Marker: *HLA-B*58:01* ADR: SJS/TEN	Dong, Tan-Koi, Teng, Finkelstein & Sung, 2015	2014, US$	270	572	-0.0423	Decision-analytic model Location: Singapore Quality: High
Drug: Phenytoin Marker: *HLA-B*15:02* ADR: SJS/TEN	Chen, Liew & Kwan, 2016	NR, US$	192	41	0.0005	Decision tree model Location: Hong Kong Quality: High
Drug: Carbamazepine Marker: *HLA-B*15:02* ADR: SJS/TEN	Chen, Liew & Kwan, 2016	NR, US$	192	199	0.0019	Decision tree model Location: Hong Kong Quality: High

Drug/marker/ADR	**References**	**Year of value, currency**	**Cost of genetic test (£, 2016)**	**Incremental cost (£, 2016)**	**Incremental QALY**	**Study characteristics**
Drug: Warfarin Marker: *CYP2C9*/VKORC1 ADR: Bleeding events	Verhoef et al., 2016	2014, GBP	35	26	0.0004	Markov model Location: UK Quality: High

*Allopurinol study used in the model was by Plumpton et al., 2017 using NHS perspective.
NT$ = New Taiwan Dollar, GBP = Great British Pound, US $ = United States Dollar, NR= Not recorded.

Table 5: Studies selected, and data extracted from previous systematic review by Plumpton et al (2016) for use in economic model.

Drug/marker/ADR	**References**	**Year of value, currency**	**Cost of test (£, 2016)**	**Incremental cost (£, 2016)**	**Incremental QALY**	**Study characteristics**
Drug: Irinotecan Marker: *UGT1A1* ADR: Neutropenia	Butzke et al., 2015	2013, EUR	70	-580	0.0002	Decision-analytic Markov model Location: Germany Quality:
Drug: Abacavir Marker: *HLA-B*57:01* ADR: SJS/TEN	Kauf et al., 2010	2007, US$	88	-5058	0.0180	Decision-analytic model Location: US Quality: High
Drug: Azathioprine Marker: *TPMT* ADR: Myelosuppression	Thompson et al., 2014	2009/10, GBP	20	-421	-0.0080	UK NHS RCT Location: UK Quality: High
Drug: Carbamazepine Marker: *HLA-A*31:01* ADR: SJS/TEN	Plumpton at al., 2015	2010/11, GBP	90	300	0.0234	Decision-analytic model Location: Europe Quality: Hugh
Drug: Clopidogrel Marker: *CYP2C19* ADR: CV events	Panattoni et al., 2012	2009, NZ$	175	475	0.0190	Decision-analytic model Location: New Zealand Quality: High

GBP = Great British Pound, US $ = United States Dollar, EUR = Euro, NZ$ = New Zealand Dollar.

3.3 Single gene cost-utility estimates

There were total of 15 pharmacogenes associated with ADRs extracted from the PharmGKB database, 7 of which had previously conducted economic analyses. In an economic analysis of *TPMT* testing for azathioprine prescription, the incremental QALY reported a negative effect on health which would not have been cost-effective, therefore this was removed from the analysis (Thompson et al., 2014). For the remaining 6 drug-gene associations; mercaptopurine (*TPMT*), oxcarbazepine (*HLA-B*15:02*), oral contraceptive (*FVL*), atazanavir/ritonavir (*CYP2C19*), lapatinib (*HLA-DQA1*02:01*, *HLA-DRB1*07:01*), cost-effectiveness of single-gene testing was estimated using the calculation described in section 2.5.

3.3.1 ADR-association data extraction

From reviewing the literature to confirm genetic associations with ADRs, data could then be extracted to calculate the sensitivity, specificity, PPV and NPV (Table 5) to calculate a cost-utility estimate. PPV in the context of ADRs is the risk of having the ADR if you are positive for the allele. A low PPV can relates to a low risk of having the ADR with the allele, occasionally alleles are protective, so you are at lower risk of ADR when you have the allele. All alleles included within this study are associated with causing an ADR.

One of the lowest PPVs was *HLA-B*15:02* and carbamazepine, out of patients which carry this HLA variant and are placed on carbamazepine therapy, 0.08% will suffer from the hypersensitivity reaction. The PPV is much higher for other associations such as 30% of patients with the *UGT1A1* polymorphism will suffer from neutropenia when placed on irinotecan therapy, a chemotherapeutic drug.

Conversely, many of these associations have a high NPV which suggests being allele negative is a likely predictor of no adverse drug reaction. Both the PPV and NPV are weighted in the calculation by the ADR prevalence taken from the EMC. Because of the low incidence of some ADRs (e.g. CBZ- induced SJS/TEN is 0.01 in Europeans), many pharmacogenetic tests used for testing have high NPVs but low PPVs (Yip, Alfirevic & Pirmohamed, 2014)

Table 6: Parameters to evaluate genetic association to ADR, for incorporation into estimates cost-utility analysis of single-gene testing.

Drug/Marker	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Study**
Drug: Ethinyl estradiol/ Noralgestromin (Oral Contraceptive) Marker: *FVL*	0.27	0.98	0.0027	0.9998	(Wu et al., 2005)
Drug: Carbamazepine Marker: *HLA-B*15:02*	0.87	0.9	0.0009	0.9998	(Tangamornsuksan, 2013)
Drug: Lapatinib Marker: *HLA-DRB1*07:01*	0.78	0.8	0.0737	0.9648	(Schaid et al., 2014)
Drug: Lapatinib Marker: *HLA-DQA1*02:01*	0.78	0.79	0.0705	0.9648	(Schaid et al., 2014)
Drug: Abacavir Marker: *HLA-B*57:01*	0.4	0.98	0.2900	0.9724	(Sousa-Pinto et al., 2015)
Drug: Azathioprine Marker: *TPMT*	0.1	0.92	0.1220	0.900	(Liu et al., 2015)
Drug: Mercaptopurine Marker: *TPMT*	0.29	0.94	0.3494	0.881	(Liu et al., 2015)
Drug: Oxcarbazepine Marker: *HLA-B*15:02*	0.76	0.92	0.0010	0.9998	(Chen et al., 2017)
Drug: Phenytoin Marker: *HLA-B*15:02*	0.43	0.86	0.0003	0.9999	(Li et al., 2015)
Drug: Carbamazepine Marker: *HLA-A*31:01*	0.22	0.97	0.0007	0.9999	(Genin et al., 2013)
Drug: Voriconazole and Atazanavir/Ritonavir Marker: *CYP2C19*	0.125	0	0.0003	0.000	Zhu et al., 2017

Drug/Marker	Sensitivity	Specificity	PPV	NPV	Study
Drug: Clopidogrel Marker: *CYP2C19*	0.34	0.68	0.0001	0.9999	(Mao et al., 2013)
Drug: Warfarin Marker: *CYP2C9*	0.34	0.78	0.0534	0.9541	(Yang et al., 2013)
Drug: Irinotecan Marker: *UGT1A1*	0.4	0.92	0.3571	0.8700	(Liu, Cheng, Kuang, Liu & Xu, 2013)
Drug: Allopurinol Marker: *HLA-B*58:01*	0.64	0.96	0.0032	0.9997	(Gonacalo, 2013)

3.3.2 Comparator drug economic analysis data extraction, ADR costs and QALYs

The literature was searched for data on the incremental cost and QALYs of comparator drugs (appendix 7). The comparator drugs used were; depot medroxyprogesterone acetate (DMPA) as an alternative to ethinyl estradiol (oral contraceptive) (Mavranezouli, 2008), meslamine as an alternative to mercaptopurine (Doherty, Miksad, Cheifetz, & Moss, 2012), fluconazole as an alternative to voriconazole (Mauskopf et al., 2013), lamotrigine as an alternative to oxcarbazepine (Marson et al., 2007), and trastuzumab as an alternative to lapatinib (Squires, Stevenson, Simpson, Harvey & Stevens, 2016). The ADR costs and QALY data was also required to populate the calculation, details of these are in appendix 8.

3.3.3 Single-gene testing cost-utility estimates

For prioritisation purposes the single-gene cost effectiveness ICERs were calculated based on test costs of £10, £20, £30 and £50 (Table 7). Reporting the single-gene ICERs was important to inform further stages of the study, as the incremental cost and QALY of the single-genes would be used in the economic model of panel testing. Most associations had an ICER below the threshold maximum £30,000 threshold with a test cost of £10 or £20. At a test cost of £30 – the single-gene ICER for *HLA-B*58:01* genotyping prior to allopurinol therapy was £33992/QALY, which would suggest prospective genotyping for warfarin would not be commissioned. The results of the incidental findings allow for the primary genotype to cover this test cost and therefore the ICER decreases below the £20,000 threshold (not including test cost). Genotypes which were not cost-effective at a test cost of £10 had this same result throughout cost-variants and thresholds; *FVL*, *HLA-B*15:02* (oxcarbazepine and carbamazepine) and *CYP2C19*.

All other genes on were considered cost-effective to prospectively test for. At a threshold of £20,000/QALY, *HLA-B*58:01* for Allopurinol, *HLA-DRB1*07:01* for Lapatinib and *HLA-DQA1*02:01* for Lapatinib, the ICER was above this threshold at the minimum test cost of £10. ICERs were £25296/QALY, £22201/QALY and £22306/QALY, respectively and were resultantly not considered cost-effective of a single-gene basis.

For *HLA-B*15:02*, oxcarbazepine the ICER was dominated presenting a negative ICER caused by an incremental cost of £0.78 and decremental QALY. For *FVL* testing in contraceptive users and *CYP2C19* for atazanavir/ritonavir co-administration with voriconazole, the incremental costs were -£71.44 and -£20.87, respectively. Both the QALYs were found to reduce with genetic testing, atazanavir/ritonavir co-administration had a reduction in QALYs of -0.0011 and *FVL* testing reduced QALYs by -0.0004. As both testing estimates had decreased costs but also decreased QALYs – they are therefore not cost-effective compared with the current practice of no testing.

Single-gene ICERs were also calculated excluding a test cost to provide evidence of pre-emptive genotyping cost-effectiveness. This related to the incidental findings of a panel test. At a £30,000 ICER threshold, the single-gene ICERs above the threshold were again; *FVL*, oral contraceptives; *HLA-B*15:02*, oxcarbazepine, carbamazepine and *CYP2C19*, atazanavir/ritonavir co-administration with voriconazole.

3.3.4. SINGLE GENE COST-UTILITY TREND

From reviewing the published literature and estimating cost-utility of single-gene testing, generally rare alleles are less likely to be cost-effective to prospectively test for. The drug-gene associations of more severe ADRs are more likely to be cost-effective to test for, particularly where there is high frequency of the ADR - as seen with abacavir hypersensitivity (2%). The common ADRs do not seem to follow a trend as previous work suggests *TPMT* is not cost-effective however the cost-utility estimate for this genetic polymorphism (for an alternative drug conformation) suggests testing is cost-effective.

Table 7: Single-gene test ICERs of genetic testing to avoid ADRs.

				Single-gene test ICERs			
Genotype, Drug	**δ Cost**	**Δ QALY**	**δ Cost/Δ QALY**	**£10**	**£20**	**£30**	**£50**
*HLA-A*31:01*, Carbamazepine	264.19	0.0234	11290.17	11717.52	12144.87	12572.22	13426.92
*HLA-B*57:01*, Abacavir	-2,931.73	0.0180	dominant	dominant	dominant	dominant	dominant
*HLA-B*15:02*, Phenytoin	-98.35	0.0005	dominant	dominant	dominant	dominant	dominant
CYP2C19, Atazanavir/Ritonavir & Voriconazole	-20.87	-0.0011	18988.75	9891.97	795.20	-8301.58	-26495.14
TPMT, Mercaptopurine	-449.33	0.0172	dominant	dominant	dominant	dominant	dominant
*HLA-B*15:02*, Oxcarbazepine	0.78	-0.0000	dominated	dominated	dominated	dominated	dominated
FVL, Oral contraceptive	-71.44	-0.0004	163504.36	140616.39	117728.42	94840.45	49064.50
CYP2C19, Clopidogrel	131.93	0.0190	6943.87	7470.19	7996.50	8522.82	9575.45
UGT1A1, Irinotecan	-423.49	0.0002	dominant	dominant	dominant	dominant	dominant
CYP2C9, Warfarin	-9.12	0.0039	dominant	225.70	2789.81	5353.91	10482.11
*HLA-B*58:01*, Allopurinol	48.18	0.0023	20949.00	25296.83	29644.65	33992.48	42688.13
*HLA-DRB1*07:01*, Lapatinib	401.73	0.0185	21662.11	22201.33	22740.55	23279.78	24358.23
*HLA-DQA1*02:01*, Lapatinib	420.57	0.0193	21788.02	22306.07	22824.13	23342.18	24378.29
*HLA-B*15:02*, Carbamazepine	199.16	0.0019	104822.85	110086.01	115349.17	120612.32	131138.64

δ = incremental cost (no test cost)

Δ Cost = incremental cost (including cost of test)

Δ QALY = incremental QALY

All costs expressed in 2016 GBP (£).

3.4 Modelling the cost-utility of a multi-gene panel

3.4.1 The base-case scenario

The base-case analysis reported the cost-effectiveness of multi-gene panel for all genes (n=14) (Table 8), with a complete panel test cost of £30 and a cost-effectiveness threshold of £20,000. The data for this panel was informed by the single-gene economic evidence and cost-utility estimates (Table 7). The result of this analysis was 7 genes contained within the panel returned as cost-effective to prospectively test; carbamazepine (*HLA-A*31:01*), abacavir (*HLA-B*57:01*), mercaptopurine (*TPMT*), Clopidogrel (*CYP2C19*), warfarin (*CYP2C9*), phenytoin (*HLA-B*15:02*) and irinotecan (*UGT1A1*). This suggests that prospectively testing (and using this result immediately) for these genes is cost-effective in the respective disease groups when delivering incidental findings of the panel test to be used pre-emptively.

The following drug-gene associations were found to be not cost-effective to use a panel to test prospectively using point estimates for incremental cost and QALY; lapatinib (*HLA-DRB1*07:01*, *DQA1*01:02*), atazanavir when co-administered with ritonavir (*CYP2C19*), oral-contraceptive (*FVL*), allopurinol (*HLA-B*58:01*), carbamazepine (*HLA-B*15:02*) and oxcarbazepine (*HLA-B*15:02*).

This outcome was reflected in the genes which were cost-effective to test for pre-emptively as part of the panel test. The same 7 drug-gene associations were pre-emptively cost-effective to test for and return incidental findings; carbamazepine (*HLA-A*31:01*), abacavir (*HLA-B*57:01*), mercaptopurine (*TPMT*), Clopidogrel (*CYP2C19*), warfarin (*CYP2C9*), phenytoin (*HLA-B*15:02*).

The corresponding mean incremental cost and QALYs were -£35 (95% central range, -£88.41, £14.12) and 0.0077 (95% central range, 0.0051, 0.0116), respectively. The ICER for this panel was dominant and would reflect a cost-effective strategy for decision makers and encourage implementation. The value-based price for this panel test was £3292 with an ICER of £20,000, before the ICER became dominated.

Table 8: Pharmacogenetic associations included in the base-case analysis.

Allele	**Drug**	**Indication**
*HLA-B*57:01*	Abacavir	HIV
CYP2C19	Atazanavir/Ritonavir and voriconazole co-administration	Fungal infection in HIV patients (aspergillosis)
TPMT	Mercaptopurine	Acute lymphoblastic leukaemia
*HLA-B*15:02*	Oxcarbazepine	Epilepsy
FVL	Ethinyl estradiol	Contraceptive
CYP2C19	Clopidogrel	Cardiovascular disease
UGT1A1	Irinotecan	Cancer
CYP2C9	Warfarin	Atrial fibrillation
*HLA-B*15:02*	Phenytoin	Epilepsy
*HLA-B*58:01*	Allopurinol	Gout
*HLA-DRB1*07:01*	Lapatinib	HER2+ breast cancer
*HLA-DQA1*02:01*	Lapatinib	HER2+ breast cancer
*HLA-B*15:02*	Carbamazepine	Epilepsy
*HLA-A*31:01*	Carbamazepine	Epilepsy

3.4.2 SENSITIVITY ANALYSIS

The sensitivity analysis (table 9) shows the proportion of times each allele was prospective, pre-emptive or neither in the context of the multi-gene panel (methods described in section 2.6.2). This used the SD of incremental costs and QALYs to evaluate the range around point estimates. Replications with ICERs less than £20,000/QALY showed which genes were cost-effective use as the prospective test (i.e. including the test cost). ICERs less than £20,000/QALY with cost of test removed showed the genes on the base-case scenario panel which were cost-effective pre-emptively (reported as incidental findings).

In 100% of the 10,000 replications, testing prospectively for genotypes using the panel test (n=7 genes) prior to treatment was cost-effective for abacavir, phenytoin, irinotecan, warfarin, mercaptopurine, carbamazepine (*HLA-A*31:01*) and iriotecan. Testing for *CYP2C19* prior to treatment with clopidogrel for heart related disease, was found to be cost-effective to test prospectively in 99% of replications and pre-emptive only in 1%. The majority of replications of *HLA-B*15:02* testing prior to carbamazepine therapy were cost-effective with 3% cost-effective to return genotype as part of incidental findings; 28% of replications indicated that acting on results of *HLA-B*15:02* was not cost effective even when returned as incidental findings.

Allopurinol related ADR testing by *HLA-B*58:01* as the prospective test was found to be cost-effective in 17% of replications, with over 50% of replications appearing neither prospectively or pre-emptively. A similar pattern is seen with lapatinib associated genotypes (>70% not prospective or pre-emptive).

Table 9: Base-case sensitivity analysis to show proportion of tests which were cost-effective prospectively, pre-emptively only or neither.

	Test proportion		
Genotype, Drug	**Prospective**	**Pre-emptive only**	**Neither**
*HLA-B*15:02*, Carbamazepine	0.69	0.03	0.28
*HLA-B*57:01*, Abacavir	1.00	0.00	0.00
*HLA-B*15:02*, Phenytoin	1.00	0.00	0.00
CYP2C19, Atazanavir/Ritonavir & Voriconazole	0.00	0.00	1.00
TPMT, Mercaptopurine	1.00	0.00	0.00
*HLA-B*15:02*, Oxcarbazepine	0.00	0.00	1.00
FVL, Oral contraceptive	0.00	0.00	1.00
CYP2C19, Clopidogrel	0.99	0.01	0.00
UGT1A1, Irinotecan	1.00	0.00	0.00
CYP2C9, Warfarin	1.00	0.00	0.00
*HLA-B*58:01*, Allopurinol	0.18	0.30	0.53
*HLA-DRB1*07:01*, Lapatinib	0.14	0.15	0.71
*HLA-DQA1*02:01*, Lapatinib	0.14	0.14	0.72
*HLA-A*31:01*, Carbamazepine	1.00	0.00	0.00

3.4.3 COST-EFFECTIVENESS PLANE

The cost-effectiveness plane highlights the effect of uncertainty around incremental costs and incremental QALYs – displaying them as ICERs produced by the Monte Carlo simulations (10,000 replications) of multi-gene panel prospective testing including incidental findings.

Using the base-case scenario (section 3.4.1), figure 9 illustrates the distribution of 10,000 replications of the panel ICER on the cost-effectiveness plane, where each individual spot represents a possible ICER when the incremental costs and/or QALYs deviate from the mean.

Notably, all results were distributed between the north-east quadrant (increased cost, QALY gain) and the south-east quadrant (reduced cost, QALY gain), the latter referred to as an economically dominant strategy. Most replications were found to increase the cost with a gain in QALYs. The mean ICER was positioned as a dominant test (x), as it is estimated to save costs and increase utility.

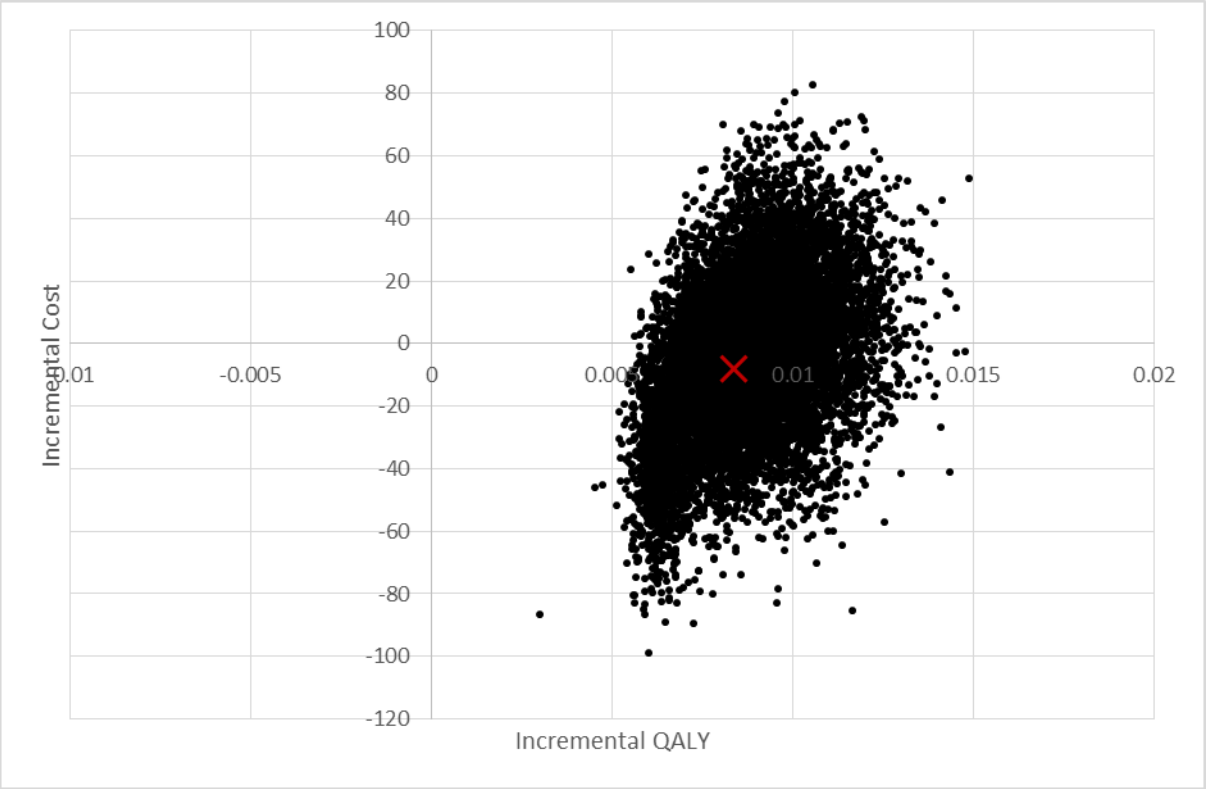

Figure 9: Cost-effectiveness plane, 10,000 Monte Carlo simulations to analyse uncertainty around incremental cost and QALY mean. Plotted centrally is the mean estimated ICER for the base-case scenario (test cost £30, ICER threshold <£20,000/QALY, drug-gene associations n=7 (section 3.4.1), around calculated ICERs using 10,000 Monte Carlo simulations.

3.4.5 Scenario analysis

There were 6 different gene-panel scenarios, each panel scenario was simulated at an ICER of £20,000 and £30,000/QALY with 4 varied test costs (£10, £20, £30, £40) each of which were tested using 10,000 Monte Carlo simulation sensitivity analysis. Each scenario has the value-based price of the panel detailed in the results table (VBP).

Scenario 1: testing required annotation on PharmGKB

The cost-utility analysis of the gene panel containing only required pharmacogenes (n=5) (Table 10) produced negative ICERs which were particularly cost saving at the £20,000/QALY threshold (Table 11). The panel incremental QALY was also the highest of all combinations, 0.0180. At this threshold, only *HLA-B*57:01* for abacavir was cost-effective to screen for prospectively and pre-emptively. The value-based price of this test at £20,000/QALY was £3291.

This panel would therefore not be commissioned as a multi-gene panel test, as a panel would be considered when containing 2 or more genes. *FVL* testing in OC had a negative incremental QALY and was therefore not incorporated into the gene-panel, the remaining genes had ICERs above the £20,000/QALY threshold either prospectively, or when returned as incidental findings.

With the upper cost-effectiveness threshold applied (£30,000/QALY), 3 genes became cost-effective to screen for prospectively, or within incidental findings; *HLA-B*57:01*, *HLA-DRB1*07:01* and *HLA-DQA1*02:01*. When the threshold was removed entirely the panel was largely cost-saving, with minimal QALY gains.

Table 10: Scenario 1, Genes which have a testing required annotation on PharmGKB as per their SPC (n=5).

Allele	**Drug**	**Indication**
*HLA-B*57:01*	Abacavir	HIV
*HLA-DRB1*07:01*	Lapatinib	HER2+ breast cancer
*HLA-DQA1*02:01*	Lapatinib	HER2+ breast cancer
FVL	Ethinyl estradiol	Contraceptive
*HLA-B*15:02*	Carbamazepine	Epilepsy

Table 11: Results for multi-gene panel testing cost-utility at varied ICER/QALY thresholds and test costs. Number of genes cost-effective to test for prospectively and pre-emptively – required pharmacogenetic testing (scenario 1).

Threshold	**Test cost**	**Δ Cost (CI), (£)**	**Δ QALY (CI)**	**ICER (£)**	**Prospective (n)**	**Pre-emptive (n)**
£20,000	£10	-2921.73 (-3441.70, -1522.61)	0.0180 (0.0148, 0.0925)	-162277 (dominant)	1	1
	£20	-2911 (-3445.25, -1651.88)	0.0180 (0.0147, 0.0890)	-161763 (dominant)	1	1
	£30	-2901.73 (-3448.90, -1729.47)	0.0180 (0.0147, 0.0628)	-161207 (dominant)	1	1
	£50	-246.75 (-341.42, -78.09)	0.0180 (0.0146, 0.0602)	-14262 (dominant)	1	1
	£3291 (VBP)	359.27 (-480.59, -174.97)	0.0180 (0.0116, 0.0210)	20000	1	1
£30,000	£10	-307.11 (-480.59, -174.97)	0.0187 (0.0116, 0.0210)	-16398 (dominant)	3	3
	£20	-297.11 (-486.60, -165.74)	0.0187 (0.0112, 0.0210)	-15864 (dominant)	3	3
	£30	-287.11 (-492.87, 156.90)	0.0187 (0.0110, 0.0210)	-15330 (dominant)	3	3
	£50	-267.11 (-513.09, -140.84)	0.0187 (0.0106, 0.0210)	-14262 (dominant)	3	3
No threshold	£10	-58.26 (-72.97, -43.82)	0.0007 (0.0006, 0.0008)	-82931 (dominant)	5	5
	£20	-48.26 (-62.98, -33.80)	0.0007 (0.0006, 0.0008)	-68585 (dominant)	5	5
	£30	-38.26 (-52.96, -23.78)	0.0007 (0.0006, 0.0008)	-54240 (dominant)	5	5
	£50	-18.26 (-32.95, -3.74)	0.0007 (0.0006, 0.0008)	-25548 (dominant)	5	5

SCENARIO 2: REQUIRED AND RECOMMENDED RECOMMENDATIONS ON PHARMGKB

When the required and recommended pharmacogenes (n=10) (Table 12) were compiled into the model for analysis of multi-gene panel cost-effectiveness, including only tests where the ICER was below the £20,000/QALY threshold resulted in a particularly cost-saving panel – with testing being dominant. The incremental QALY for this panel combination was 0.125 at every test cost and threshold (Table 13).

At the lower threshold (£20,000/QALY) there were 4 genes which were cost effective to screen for prospectively and pre-emptively (*HLA-B*57:01, HLA-A*31:01, HLA-B*15:02, TPMT*). At the upper threshold (£30,000/QALY) the number of genes cost effective to prospectively and pre-emptively screen increased to 6 (*HLA-B*57:01, HLA-DRB1*07:01, HLA-DQA1*02:01, HLA-A*31:01, TPMT, HLA-B*15:02*), as both lapatinib associated pharmacogenes (*HLA-DRB1*07:01, HLA-DQA1*02:01*) had ICERs below the £30,000/QALY threshold. The incremental QALY increased to 0.014 as the number of genetic associations on the panel increased, compared with an incremental QALY of 0.0125 with a £20,000/QALY threshold. When the test was run with no threshold/QALY, again a dominant ICER was the result with a reduced gain in QALYs (0.0018). Results for all genes are assumed to be implemented both prospectively and pre-emptively (n=10).

The value-based price for this panel test was £3291 at the £20,000/QALY threshold, prospective genes (n=1), pre-emptive (n=4). Using a panel test (and returning incidental findings) was cost-effective for patients eligible for abacavir, at £3291 per test. The maximum price for the panel test (ICER = <£20,000) to be viable to all disease groups prospectively (n=4) was £105 with an ICER of -£5647.

Table 12: Scenario 2, genes which have a testing required and recommended recommendation on PharmGKB as per their SPC (n=10).

Allele	**Drug**	**Indication**
*HLA-B*57:01*	Abacavir	HIV
*HLA-DRB1*07:01*	Lapatinib	HER2+ breast cancer
*HLA-DQA1*02:01*	Lapatinib	HER2+ breast cancer
FVL	Ethinyl estradiol	Contraceptive
*HLA-B*15:02*	Carbamazepine	Epilepsy
*HLA-A*31:01*	Carbamazepine	Epilepsy
*HLA-B*15:02*	Phenytoin	Epilepsy
CYP2C19	Atazanavir/Ritonavir and voriconazole	Fungal infection in HIV patients (aspergillosis)
TPMT	Mercaptopurine	Acute lymphoblastic leukaemia
*HLA-B*15:02*	Oxcarbazepine	Epilepsy

Table 13: Results for multi-gene panel testing cost-utility at varied ICER/QALY thresholds and test costs. Number of genes cost-effective to test for prospectively and pre-emptively – required and recommended pharmacogenetic testing (scenario 2).

Threshold	**Test cost**	**Δ Cost (CI), (£)**	**Δ QALY (CI)**	**ICER (£)**	**Prospective (n)**	**Pre-emptive (n)**
£20,000	£10	-165.71(-317.71, -42.58)	0.0125 (0.0017, 0.0302)	-13236 (dominant)	4	4
	£20	-155.71 (-315.12, -40.04)	0.0125 (0.0017, 0.0297)	-12437 (dominant)	4	4
	£30	-145.71 (-311.52, -38.82)	0.0125 (0.0017, 0.0296)	-11638 (dominant)	4	4
	£50	-125.71 (-303.73, -32.76)	0.0125 (0.0017, 0.0290)	-10041 (dominant)	4	4
	£3291 (VBP)	360.25 (-154.72, 27.50)	0.0180 (0.0116, 0.0210)	20000	1	4
£30,000	£10	-29.71 (-154.72, 27.50)	0.0140 (0.0054, 0.0262)	-2122 (dominant)	6	6
	£20	-19.74 (-150.21, 36.83)	0.0140 (0.0054, 0.0262)	-1409 (dominant)	6	6
	£30	-9.74 (-146.43, 46.12)	0.0140 (0.0053, 0.0262)	-695 (dominant)	6	6
	£50	10.26 (-143.70, 64.61)	0.0140 (0.0039, 0.0261)	-732 (dominant)	6	6
No threshold	£10	-39.26 (-53.48, -24.86)	0.0018 (0.0000, 0.0036)	-21458 (dominant)	10	10
	£20	-29.26 (-43.48, -14.86)	0.0018 (0.0000, 0.0036)	-15993 (dominant)	10	10
	£30	-19.26 (-33.49, -4.87)	0.0018 (0.0000, 0.0036)	-10528 (dominant)	10	10
	£50	0.74 (-13.50, 15.13)	0.0018 (0.0000, 0.0036)	403	10	10

SCENARIO 3: REQUIRED, RECOMMENDED AND ACTIONABLE ANNOTATIONS OF PHARMGKB

Required, recommended and actionable genes (n=14) (Table 14) returned another highly cost-effective combination (Table 15). This combination has the potential to return more incidental findings – with an increased number of genes within the multi-gene test which are cost-effective when the cost of test is removed. At £20,000/QALY threshold, the number of genes cost-effective prospectively and pre-emptively stayed continuous (n=7) throughout the test cost variables.

At the upper threshold, there were 10 genes cost-effective to test for pre-emptively throughout all of which were cost effective to test for prospectively at a test cost of £10 and £20. When the test cost increased, one association - HLA B*58:01 related SJS/TEN in allopurinol treatment of gout, rose above the threshold and became only cost-effective to test on a pre-emptive basis. As the test cost-increased the number of genes included in the panel prospectively decreased (n=9), whilst the pre-emptive tests remain the same (n=10).

The value-based price for this panel test was £3292 at the £20,000/QALY threshold, prospective genes (n=1), pre-emptive (n=7). Using a panel test (and returning incidental findings) was cost-effective for Abacavir patients only at £3292 per test. The maximum price for the panel test (ICER = <£20,000) to be viable to all disease groups prospectively (n=7) was £115 with an ICER of £9215.

Table 14: Scenario 3, genes which have a testing required and recommended and actionable annotation on PharmGKB as per their SPC (n=14).

Allele	**Drug**	**Indication**
*HLA-B*57:01*	Abacavir	HIV
CYP2C19	Atazanavir/Ritonavir and voriconazole	Fungal infection in HIV patients (aspergillosis)
TPMT	Mercaptopurine	Acute lymphoblastic leukaemia
*HLA-B*15:02*	Oxcarbazepine	Epilepsy
FVL	Ethinyl estradiol	Contraceptive
CYP2C19	Clopidogrel	Cardiovascular disease
UGT1A1	Irinotecan	Cancer
CYP2C9	Warfarin	Atrial fibrillation
*HLA-B*15:02*	Phenytoin	Epilepsy
*HLA-B*58:01*	Allopurinol	Gout
*HLA-DRB1*07:01*	Lapatinib	HER2+ breast cancer
*HLA-DQA1*02:01*	Lapatinib	HER2+ breast cancer
*HLA-B*15:02*	Carbamazepine	Epilepsy
*HLA-A*31:01*	Carbamazepine	Epilepsy

Table 15: Results for multi-gene panel testing cost-utility at varied ICER/QALY thresholds and test costs. Number of genes cost-effective to test for prospectively and pre-emptively – required, recommended and actionable pharmacogenetic testing (scenario 3).

Threshold	**Test cost**	**Δ Cost (CI), (£)**	**Δ QALY (CI)**	**ICER (£)**	**Prospective (n)**	**Pre-emptive (n)**
£20,000	£10	-33.76 (-78.41, 17.37)	0.0077 (0.0053, 0.0120)	-7114 (dominant)	7	7
	£20	-44.91 (-95.51, 7.84)	0.0077 (0.0052, 0.0118)	-5819 (dominant)	7	7
	£30	-34.91 (-88.41, 14.12)	0.0077 (0.0051, 0.0116)	-4553 (dominant)	7	7
	£50	14.91(-73.58, 28.44)	0.0077 (0.0050, 0.0113)	-1932	7	7
	£3292 (VBP)	360.38 (-40.63, 64.39)	0.0180 (0.0050, 0.0113)	20000	1	7
£30,000	£10	-8.47 (-55.25, 17.51)	0.0070 (0.0048, 0.0094)	-1210 (dominant)	10	10
	£20	1.53 (-48.80, 26.45)	0.0070 (0.0047, 0.0094)	219	10	10
	£30	-7.95 (-55.06, 44.70)	0.0084 (0.0060, 0.0121)	-950 (dominant)	9	10
	£50	12.05 (-40.63, 64.39)	0.0084 (0.0059, 0.0119)	1442	9	10
No threshold	£10	-25.64 (-41.90, -9.25)	0.0032 (0.0021, 0.0044)	-7959 (dominant)	14	14
	£20	-15.64 (-15.64, 0.73)	0.0032 (0.0021, 0.0044)	-4854 (dominant)	14	14
	£30	-5.64 (-21.90, 10.72)	0.0032 (0.0021, 0.0044)	-1750 (dominant)	14	14
	£50	14.36 (-1.90, 30.73)	0.0032 (0.0021, 0.0044)	4459	14	14

SCENARIO 4: COMMONLY PRESCRIBED DRUGS

UK prescription data was also used to prioritise pharmacogenes for cost-effectiveness –producing a 'common disease' panel (n=6) (Table 16). Prescriptions with >10,000 (thousands) items prescribed annually were included; carbamazepine, allopurinol, warfarin, phenytoin and clopidogrel. This again produced ICERs below both £20,000/QALY and £30,000/QALY thresholds which were again cost-saving (Table 17). Allopurinol testing was not cost-effective prospectively or pre-emptively at the base-case threshold (£20,000/QALY), however was cost-effective prospectively and pre-emptively at £30,000/QALY at test costs £10 and £20 and pre-emptive only thereafter.

With the threshold removed, all tests had ICERs below the base case threshold, but did incur small costs (£61-101) compared to normal procedure. QALY increments were minimal throughout thresholds and test costs. This allele combination produced the highest ICER when weighted by the threshold throughout simulations and also incurred the highest incremental cost.

The value-based price for this panel test was £248 at the £20,000/QALY threshold, prospective genes (n=1), pre-emptive (n=4). Using a panel test (and returning incidental findings) was cost-effective for patients eligible for phenytoin only, at £248 per test. The maximum price for the panel test (ICER = <£20,000) to be viable to all disease groups prospectively (n=4) was £21 with an ICER of £8,888.

Table 16: Scenario 4, drugs which have a prescription >10,000 (thousands) items prescribed annually (common disease), as per prescription cost analysis (2016) (n=6).

Allele	**Drug**	**Indication**
CYP2C19	Clopidogrel	CVD
CYP2C9	Warfarin	AF
*HLA-B*15:02*	Phenytoin	Epilepsy
*HLA-B*58:01*	Allopurinol	Gout
*HLA-B*15:02*	Carbamazepine	Epilepsy
*HLA-A*31:01*	Carbamazepine	Epilepsy

Table 17: Results for multi-gene panel testing cost-utility at varied ICER/QALY thresholds and test costs. Number of genes cost-effective to test for prospectively and pre-emptively – common disease panel (scenario 4).

Threshold	**Test cost**	**Δ Cost (CI), (£)**	**Δ QALY (CI)**	**ICER (£)**	**Prospective (n)**	**Pre-emptive (n)**
£20,000	£10	46.71 (-2.79, 91.66)	0.0084 (0.0055, 0.0130)	5529	4	4
	£20	56.71 (4.03, 100.50)	0.0084 (0.0055, 0.0129)	6713	4	4
	£30	66.71 (11.35, 109.52)	0.0084 (0.0054, 0.0127)	7897	4	4
	£50	86.71 (26.65, 122.75)	0.0084 (0.0053, 0.0124)	10264	4	4
	£248 (VBP)	360.63 (-47.06, 32.56)	0.0180 (0.0050, 0.0224)	20000	1	4
£30,000	£10	49.83 (3.20, 72.69)	0.0068 (0.0043, 0.0097)	7281	5	5
	£20	59.83 (8.93, 81.21)	0.0068 (0.0043, 0.0097)	8742	5	5
	£30	66.79 (19.93, 122.26)	0.0085 (0.0043, 0.0097)	7903	4	5
	£50	86.79 (35.21, 143.64)	0.0085 (0.0056, 0.0129)	10270	4	5
No threshold	£10	61.69 (30.89, 92.52)	0.0074 (0.0043, 0.0105)	8366	6	6
	£20	71.69 (40.88, 102.52)	0.0074 (0.0043, 0.0105)	9722	6	6
	£30	81.59 (60.86, 112.53)	0.0074 (0.0043, 0.0105)	11078	6	6
	£50	101.69 (70.84, 132.50)	0.0074 (0.0043, 0.0105)	13790	6	6

SCENARIO 5: HIGH GENE FREQUENCY - UK

The panel which prioritised for cost-effectiveness by UK gene frequency >1% (n=11) (Table 17), returned dominant ICERs for most cost variations (Table 18). *FVL* and *CYP2C19* were excluded due to previous studies finding a negative effect on QALYs. All genotypes included in the model (n=9) were cost-effective pre-emptively at the maximum threshold - this was similar prospectively with the allopurinol genotype (*HLA-B*58:01*) the only exception with a test cost of £30 and £50. The base case threshold returned 6 genes cost-effective prospectively, HLA- B*57:01, A*31:01, *TPMT*, CYPC19, *UGT1A1*, and *CYP2C9* - all of which were pre-emptive at this threshold. When the model was run without a cost-effectiveness threshold, all genes initially included (n=11) could be considered cost-effective prospectively and pre-emptively if all the genes were included regardless of their single-gene ICER.

The value-based price for this panel test was £2392 at the £20,000/QALY threshold, prospective genes (n=1), pre-emptive (n=6). Using a panel test (and returning incidental findings) was cost-effective for patients eligible for abacavir only, at £2392 per test. The maximum price for the panel test (ICER = <£20,000) to be viable to all disease groups prospectively (n=6) was £27 with an ICER of £1231.

Table 18: Scenario 5, genes which have a frequency in the UK >1% (n=11).

Allele	**Drug**	**Indication**
*HLA-B*57:01*	Abacavir	HIV
CYP2C19	Atazanavir/Ritonavir and voriconazole	Fungal infection in HIV patients (aspergillosis)
TPMT	Mercaptopurine	ALL
FVL	Ethinyl estradiol	Contraceptive
CYP2C19	Clopidogrel	CVD
UGT1A1	Irinotecan	Cancer
CYP2C9	Warfarin	AF
*HLA-B*58:01*	Allopurinol	Gout
*HLA-DRB1*07:01*	Lapatinib	HER2+ BC
*HLA-DQA1*02:01*	Lapatinib	HER2+ BC
*HLA-A*31:01*	Carbamazepine	Epilepsy

Table 19: Results for multi-gene panel testing cost-utility at varied ICER/QALY thresholds and test costs. Number of genes cost-effective to test for prospectively and pre-emptively – UK gene prevalence >1% (scenario 5).

Threshold	**Test cost**	**Δ Cost (CI), (£)**	**Δ QALY (CI)**	**ICER (£)**	**Prospective (n)**	**Pre-emptive (n)**
£20,000	£10	-51.54 (-103.41, 8.54)	0.0084 (0.0057, 0.0132)	-6118 (dominant)	6	6
	£20	-41.54 (-97.08, 15.26)	0.0084 (0.0056, 0.0130)	-4931 (dominant)	6	6
	£30	-31.54 (-91.09, 22.35)	0.0084 (0.0056, 0.0127)	-3744 (dominant)	6	6
	£50	-11.54 (-76.21, 34.80)	0.0084 (0.0054, 0.0123)	-1370 (dominant)	1	6
	£2392	360.63 (-47.06, 32.56)	0.0180 (0.0054, 0.0224)	20000		
£30,000	£10	-2.83 (-53.12, 24.24)	0.0074 (0.0050, 0.0100)	-379 (dominant)	9	9
	£20	7.17(-47.06, 32.56)	0.0074 (0.0050, 0.0100)	963	9	9
	£30	-2.31 (-53.89, 54.13)	0.0091 (0.0065, 0.0131)	-255 (dominant)	8	9
	£50	17.69 (-39.20, 75.04)	0.0091 (0.0064, 0.0130)	1948	8	9
No threshold	£10	-32.80 (-50.80, -15.22)	0.0035 (0.0022, 0.0048)	-9462 (dominant)	11	11
	£20	-22.80 (-40.81, -5.23)	0.0035 (0.0022, 0.0048)	-6577 (dominant)	11	11
	£30	-12.80 (-30.81, 4.77)	0.0035 (0.0022, 0.0048)	-3692 (dominant)	11	11
	£50	7.20 (-10.79, 24.76)	0.0035 (0.0022, 0.0048)	2078	11	11

SCENARIO 6: TESTING SPECIFIED FOR SOUTH-EAST ASIAN POPULATIONS

The multi-gene panel which focused on testing for the UK south-east Asian sub-population for genes which have specific population testing requirements within the drug label (carbamazepine, oxcarbazepine, allopurinol and phenytoin) (Table 20), returned an ICERs below the base-case and maximum threshold (Table 21). Oxcarbazepine had a negative QALY therefore was excluded in the simulations restricted by a threshold, leaving 3 associations to be trialled within this panel. Two of the associations were the same genotype (*HLA-B*15:02*). Using a panel test for patients eligible for carbamazepine therapy was found to be not cost-effective. For patients eligible for Phenytoin and Allopurinol, all the cost variants were cost-effective to screen prospectively and pre-emptively.

The value-based price for this panel test was £224 at the £20,000/QALY threshold, prospective genes (n=1), pre-emptive (n=2). Using a panel test (and returning incidental findings) was cost-effective for patients eligible for phenytoin only, at £224 per test. The maximum price for the panel test (ICER = <£20,000) to be viable to all disease groups prospectively (n=2) was £105 with an ICER of £9,350.

Table 20: Scenario 6, genetic associations for which testing is advised for south-east Asian populations (n=4)

Table 21: Results for multi-gene panel testing cost-utility at varied ICER/QALY thresholds and test costs. Number of genes cost effective to test for prospectively and pre-emptively in the Han Chinese sub-population– scenario 6.

Threshold	**Test cost (£)**	**Δ Cost (CI), (£)**	**Δ QALY (CI)**	**ICER (£)**	**Prospective (n)**	**Pre-emptive (n)**
£20,000	£10	-12.61 (-17.10, -8.19)	0.088 (0.0071, 0.0106)	-1432 (dominant)	2	2
	£20	-2.61 (-7.09, 1.80)	0.088 (0.0071, 0.0106)	-297 (dominant)	2	2
	£30	7.39 (2.93, 11.80)	0.088 (0.0071, 0.0106)	838	2	2
	£50	27.39 (22.95, 31.79)	0.088 (0.0071, 0.0106)	3108	2	2
	£224 (VBP)	223.21 (22.95, 31.79)	0.0112 (0.0054, 0.0245)	20000	1	2
£30,000	£10	-12.61 (-17.10, -8.19)	0.088 (0.0071, 0.0106)	-1432 (dominant)	2	2
	£20	-2.61 (-7.09, 1.80)	0.088 (0.0071, 0.0106)	-297 (dominant)	2	2
	£30	7.39 (2.93, 11.80)	0.088 (0.0071, 0.0106)	838	2	2
	£50	27.39 (22.95, 31.79)	0.088 (0.0071, 0.0106)	3108	2	2
No threshold	£10	52.70 (44.05, 61.44)	0.0047 (0.0035, 0.0060)	11173	4	4
	£20	62.70 (54.05, 71.44)	0.0047 (0.0035, 0.0060)	13292	4	4
	£30	72.71 (64.05, 81.45)	0.0047 (0.0035, 0.0060)	15412	4	4
	£50	92.71 (84.04, 101.46)	0.0047 (0.0035, 0.0060)	19651	4	4

3.4.7 SUMMARY OF RESULTS

Table 22: summary of all simulations with the base-case inputs, ICER/QALY threshold (£30,000) and a cost test of £30

Scenario	**Required**		**Required, recommended**		**Required, recommended, actionable**		**Common diseases**		**Gene prevalence >1%**		**Han-Chinese**	
Genotype, Drug	Prospective	Pre-emptive	Prospective	Pre-emptive	Prospective	Pre-emptive	Prospective	Pre-emptive	Prospective	Pre-emptive	Prospective	Pre-emptive
*HLA-A*31:01*, Carbamazepine	N/A	N/A	✓	✓	✓	✓	✓	✓	✓	✓	N/A	N/A
*HLA-B*57:01*, Abacavir	✓	✓	✓	✓	✓	✓	N/A	N/A	✓	✓	N/A	N/A
*HLA-B*15:02*, Phenytoin	N/A	N/A	✓	✓	✓	✓	✓	✓	N/A	N/A	✓	✓
CYP2C19, Atazanavir/Ritonavir & Voriconazole	N/A	N/A	x	x	x	x	N/A	N/A	x	x	N/A	N/A

Scenario	**Required**		**Required, recommended**		**Required, recommended, actionable**		**Common diseases**		**Gene prevalence >1%**		**Han-Chinese**	
Genotype, Drug	Prospective	Pre-emptive	Prospective	Pre-emptive	Prospective	Pre-emptive	Prospective	Pre-emptive	Prospective	Pre-emptive	Prospective	Pre-emptive
*HLA-B*15:02*, Oxcarbazepine	N/A	N/A	x	x	x	x	N/A	N/A	N/A	N/A	x	x
FVL, Oral contraceptive	x	x	x	x	x	x	N/A	N/A	x	x	N/A	N/A
CYP2C19, Clopidogrel	N/A	N/A	N/A	N/A	✓	✓	✓	✓	✓	✓	N/A	N/A
UGT1A1, Irinotecan	N/A	N/A	N/A	N/A	✓	✓	N/A	N/A	✓	✓	N/A	N/A
CYP2C9, Warfarin	N/A	N/A	N/A	N/A	✓	✓	✓	✓	✓	✓	N/A	N/A
*HLA-B*58:01*, Allopurinol	N/A	N/A	N/A	N/A	x	x	x	x	x	x	✓	✓
*HLA-DRB1*07:01*, Lapatinib	x	x	x	x	x	x	N/A	N/A	x	x	N/A	N/A
*HLA-DQA1*02:01*, Lapatinib	x	x	x	x	x	x	N/A	N/A	x	x	N/A	N/A

Scenario	**Required**		**Required, recommended**		**Required, recommended, actionable**		**Common diseases**		**Gene prevalence >1%**		**Han-Chinese**	
Genotype, Drug	Prospective	Pre-emptive	Prospective	Pre-emptive	Prospective	Pre-emptive	Prospective	Pre-emptive	Prospective	Pre-emptive	Prospective	Pre-emptive
TPMT, Mercaptopurine	N/A	N/A	✓	✓	✓	✓	N/A	N/A	✓	✓	N/A	N/A
*HLA-B*15:02*, Carbamazepine	x	x	x	x	x	x	x	x	N/A	N/A	x	x

The base case scenario consisted of the widest range of genes whilst remaining cost-effective (n=10), with a test cost of £30 and a cost-effectiveness threshold of £20,000/QALY. There were a handful of associations which were cost-effective both pre-emptively and prospectively throughout the simulations (Table 24) - *HLA-B*57:01*, abacavir; *HLA-B*15:02*, Phenytoin; *HLA-B*15:02*, carbamazepine; *TPMT*, mercaptopurine; CYPC19, clopidogrel; *UGT1A1*, irinotecan and *HLA-A*31:01*, carbamazepine.

The common trend throughout simulations containing *HLA-B*58:01* allopurinol prior to therapy was the cost-effectiveness of pre-emptively testing despite prospectively testing not being cost-effective at the base-case scenario. Both lapatinib associated genotypes and *HLA-B*58:01* for allopurinol, were neither prospectively or pre-emptively cost-effective.

Genotypes associated with ADR in oral contraceptive, oxcarbazepine and atazanavir/voriconazole were never cost-effective due to the negative QALY, eliminating them from model input. Both HLA genotypes for carbamazepine, *HLA-B*57:01* associated with abacavir hypersensitivity and *HLA-B*15:02* associated with phenytoin were the most frequent, appearing in 6 of the simulations.

For the value-based price of each panel test scenario, at a £20,000/QALY threshold, using the panel test was only cost-effective for patients eligible for abacavir (scenarios 1, 2, 3, 5) or phenytoin (scenarios 4 and 6). It becomes apparent that increasing the price per test dramatically reduces the cost-effectiveness of the using a panel test to the wider disease population (who would be eligible for a genetic test to avoid ADRs). This was explored by calculating the maximum price per test for the panel to be cost-effective to every disease eligible for the particular panel test, where maximum prices varied from £21 to £115 before some of the genes on the panel became not cost-effective to test for prospectively.

4. DISCUSSION

4.1 Major results interpretation and explanation.

This study assessed the cost-effectiveness of a multi-gene panel when used as a genetic testing tool to prevent severe adverse drug-reactions. The use of genetic panels for ADRs is not currently implemented within the UK healthcare service and little is known on the quality of life and cost implications. However, single-gene tests for several associations are required, recommended or actionable (as per PharmGKB). The purpose of this study was to assess the addition of incidental findings of a primary genetic test contained within a multi-gene panel for ADRs.

A list of 14 genes which contain pharmacogenetic information within the drug label were included in several economic model simulations to understand the cost and QALY characteristics of panels with a variety of gene combinations.In the base-case scenario (ICER/QALY <£20,000, cost of test £30) a panel which included 14 drug-gene associations was found to be cost-effective for patients eligible for carbamazepine (*HLA-A*31:01*), abacavir (*HLA-B*57:01*), mercaptopurine (*TPMT*), Clopidogrel (*CYP2C19*), warfarin (*CYP2C9*), phenytoin (*HLA-B*15:02*) and irinotecan (*UGT1A1*). This panel resulted in a cost-saving of £35 and a QALY gain of 0.0077.

This evidence suggests that prospectively testing using a panel test of genes within and beyond the HLA family (and returning the incidental findings for pre-emptive use) is a cost-effective method to avoid adverse drug reactions in the relevant disease groups.

4.1.1 Review and categorization of pharmacogenetic information containing summary of product characteristics (SPC) from PharmGKB.

There were 125 associations retrieved from the PharmGKB database with an annotation referencing genetic testing to avoid adverse drug reactions. However, the separation of genetic testing to avoid toxicity (ADR) or to guide drug efficacy was not always clear on the SPC as this is not always characteristically defined and there is some cross-over between toxicity and efficacy testing guidance. This may be due to the pharmacological complexity of the association not being fully understood, therefore the genetic association could be useful but perhaps not for a defined purpose (as yet). This led to the genetic associations with explicit advice on toxicity to be included in the study only.

Study results show there is a vast amount of pharmacogenetic information contained within the SPC, however there are factors which affect the annotations becoming implemented as a requirement or recommendation. Out of the 125 associations, only 8 of these are a requirement prior to prescription; *G6PD* and pegloticase, *G6PD* and rasburicase, *POLG* and divalproex, *FVL* and ethinyl estradiol/noralgestromin, *HLA-B*15:02* and carbamazepine, *HLA-DRB1*07:01* and lapatinib, *HLA-DQA1*02:01* and lapatinib, *HLA-B*57:01* and abacavir. Some of these associations were excluded from this study due to a lack of evidence on the link between genetics and ADR risk, or the fact that the drug is not relevant or licensed for use in the UK.

There were few associations where genetic testing is recommended and many which were optional under an actionable annotation in the SPC. The bulk of the ADR associations have an actionable annotation, which perhaps is a consequence of the slow progress associated with precision medicine implementation. Although precision medicine is of interest clinically and the ways in which healthcare can be improved by this, is valued, the commendation is challenged. Full understanding of the features may lead to highly personalized treatment opportunities and accumulated cost-savings from the return of genetic information (Roberto et al., 2017).

There was also some disparity in guidance retained in the PharmGKB database from medicine/ agencies, as guidance is not always homogenous for associations and pharmacogenetic clinical implementation reflects this. Therefore, there were some associations which had a requirement within one medicine agency which did not concur with other medicine agencies recommendations. This may be due to several conflicting factors including gene frequency, disease incidence, prescription number, pharmaceutical licensing and social factors (e.g. obesity, country affluence etc.).

4.1.2 Literature review and update of systematic review of single-gene testing economic analyses

Updating the Plumpton et al (2016) systematic review of economic evaluations of pharmacogenetic testing for prevention of adverse drug reactions, returned evidence of cost effectiveness for genotyping in patients eligible for warfarin, irinotecan and carbamazepine. The economic analysis of *HLA-B*58:01* testing prior to allopurinol therapy in the treatment of gout by Plumpton et al (2017) took this perspective. This study found that genetic testing for the risk allele was unlikely to be cost-effective for the NHS to implement prospectively when considering the

NICE cost-effectiveness threshold. This result was paralleled in by Dong et al., (2015) but differed from the Taiwan study (Ke et al., 2017).

The opposing outcome of testing cost-effectiveness within Plumpton et al (2017) may be a result of the lower allele prevalence in the UK population. Within the UK *HLA-B*58:01* can be found with 1.9% of the population, it also has a low PPV derived from the association study by Gonacalo et al (2013) which assessed the relative consequence of the *HLA-B*58:01* genotype on drug reaction with eosinophilia and systemic symptoms (0.003) and the PPV value within the Plumpton study (2017) relating to SJS/TEN (0.0048).

The Dong et al., (2017) study was an outlier of the east-Asian population studies, as the gene prevalence estimates within Singapore are relatively high 22%, 7.5% and 3.5% in Singaporean Chinese, Malays and Indians – which displays some of the highest frequencies within the Asian population. Regardless of this high allele prevalence, this study found prospective testing to not be cost-effective. This outcome related to the limited treatment options of patients commencing ULT therapy for the treatment of gout, which consequently cause a worsened treatment outcome and thus a loss of QALYs (-0.0423), the low PPV (1.52%) associated with the *HLA-B*58:01* genotype and SJS/TEN also corresponds to this finding.

Verhoef et al (2016) found single-gene testing of *CYP2C9* prior to warfarin therapy in the UK to be cost-effective with an ICER of £6702/QALY gained. Previous studies collated in the Plumpton et al (2016) systematic review reported mixed results, six studies suggested genotyping is either dominant or cost effective and four high-quality studies reported genetic testing as not cost effective. The results from the present study concur with the majority from the previous work in that genetic testing of *CYP2C9* is not only cost-effective but dominant suggesting cost savings and health gain. This was also the second study using an NHS health perspective which found testing to be cost-effective, the Pink et al (2014) study was the first which calculated an ICER for genetic testing to guide warfarin therapy at £13,226/QALY.

4.1.3 Estimating single-gene testing cost-utility

For many of the associations there were no UK economic evaluations of single-gene testing to reduce ADRs. This may be due to several limiting factors such as insufficient evidence of the association, low gene frequency or high costing drugs with suitable cheaper comparators.

From the calculated testing cost-effectiveness estimates there were several important findings which have the possibility of endorsing clinical implementation. Testing for *HLA-B*15:02* to prevent hypersensitivity reactions for the antiepileptic drug oxcarbazepine was found to have a small negative QALY (-0.000047) and incurred an incremental cost of £0.78. In the base-case scenario (£20,000/QALY threshold, £30 test cost) and using UK gene prevalence data, testing was dominated by standard practice; which was treatment by lamotrigine. This ICER was placed in the south-west quadrant (increased costs, decreased in QALYs) on the cost-effectiveness plane. The calculation of cost-effectiveness used the QALY decrement between oxcarbazepine and lamotrigine from the SANAD study which reported lamotrigine to be more clinically beneficial yet more expensive (Marson et al., 2007). The cost-effectiveness of testing for this pharmacogene within a panel was not sustainable due to the limited (or no) probability of cost-effectiveness.

This finding may be explained by the UK allele prevalence of *HLA-B*15:02* which is very low in the UK population (0.000657) and when incorporated into the calculation this prevalence weights the calculation of both incremental cost and QALY (allelefrequencies.net). The PPV may have also influenced the ICER (which suggested increased cost and decreased QALYs), as the Chen et al (2017) PPV result use in the cost-utility estimation calculation (section 2.5) found that only 0.095% of patients treated with oxcarbazepine with this allele, will suffer from the ADR.

Within the decision-analytic meta-model, inputs from single-gene testing economic evidence which reported a reduction in QALYs were automatically excluded from the panel test. Testing for *HLA-B*15:02* in patients eligible for oxcarbazepine was therefore found to be cost-effective within a panel test on this estimation, genetic testing would not be of benefit and would not likely be commissioned by NICE for either the general population or the south-east Asian population.

This was similar for *FVL* testing prior to oral contraceptives, the ICER was above both £20,000/QALY and £30,000/ QALY thresholds which reflects the decrement in QALYs related with to test. Previous testing cost-effectiveness studies have looked specifically at female relatives of patients with a previous VTE. Smith et al., (2007) concluded testing and counselling female relatives of known *FVL* carriers prior to prescribing oral contraceptives was economically favourable with an ICER of $390/QALY and a QALY gain of 0.0078. The 2005 UK study of *FVL* genotyping cost-effectiveness in high-risk populations described testing prior to oral contraceptive prescription as the least cost-effective strategy, with an ICER of £202,402/QALY (Wu et al.,

2005). This was concordant with the estimated cost-effectiveness calculation within present study. For the base-case analysis the test cost of £30 and threshold of £30,000/QALY produced an ICER of £94840/QALY.

TPMT genotyping prior to mercaptopurine (6-MP) therapy was estimated to be cost-effective throughout variable test cost analysis and at both the £20,000 and £30,000/QALY cost-effectiveness thresholds. The thiopurine metabolising enzyme *TPMT*, has intermediate and poor metabolising polymorphisms prevalent in 30% of the UK population and has been connected with the high incidence ADR myelosuppression with 10% of patients on thiopurine therapy suffering from this ADR. Currently the EMA suggests *TPMT* genotyping can be requested as confirmation of the phenotype (enzyme level) which is monitored haematologically, however the genotype test is not currently implemented as the primary testing method. Although a UK clinical trial showed the use of correlating genotypes and phenotypes (Newman, Payne & Tricker et al., 2012), a 2014 cost-utility analysis following up this clinical trial which evaluating the cost-effectiveness of *TPMT* testing prior to azathioprine therapy found genotyping to have a small negative effect on QALYs (Thompson et al., 2014). The present study assessed *TPMT* testing with the associate thiopurine drug, mercaptopurine, compared with alternative treatment (mesalamine). The cost-effectiveness estimate provided evidence of increased QALYs and decreased costs with a base-case ICER of -£24375/QALY. The combinations which contained this gene had *TPMT* pre-emptively and prospectively cost-effective throughout. This result contrasts with the Thompson et al study (2014) where TMPT testing was compared with phenotyping, which may suggest reason for discrepancies between the studies.

The co-administration of antiretroviral pharmaceuticals atazanavir or ritonavir and the anti-fungal drug voriconazole has an annotation for testing of *CYP2C19* by the EMA, due to increased risk of hepatoxicity (Zhu et al., 2017). This study was the first to estimate the cost-effectiveness of testing CYPC19 and found that testing was dominated by standard practice due to the negative effect on health gain (-0.0011 QALYs). This does not concur with the current EMA guidance, although the inputs for this calculation were problematic. As the association data was limited and had a small sample size of CYP1C19 poor metabolisers (n=8), assumptions on population data were also pragmatic and perhaps do not truly represent the invasive fungal infection incidence in the HIV population. The estimation of testing cost-utility for this scenario found a negative effect on QALYs retrieved from the comparison of voriconazole and fluconazole. This meant that the test was never cost-effective pre-emptively or prospectively.

The small QALY gain seen for many of the pharmacogenetic test panels (Table 16-23) to prevent ADRs is expected in pharmacogenetic testing due to the low allele prevalence in the population, the rarity of the adverse event leading to a low PPV and the risk-benefit trade-offs between testing and usual care (Veenstra, 2015).

Since mid-2015, the publication of cost-utility analyses for genetic testing to avoid adverse drug reactions has been limited with only 5 journals found in the search conducted to update the Plumpton et al (2016) systematic review and only 3 conducted within the UK. This highlighted the fact that there is still limited evidence to support precision medicine as standard practice for some avoidable ADRs.

4.1.4 Modelling the cost-utility of a multi-gene panel

The multiple gene test combinations assessed for cost-effectiveness were all found to have ICERs below both the thresholds suggested by NICE (£20000/QALY, £30000/QALY). The purpose of this study was assess different panel configurations for their cost-effectiveness and estimate the value-based price of the panel configurations to the NHS. The likely cost-effective panel configurations would return ICERs <£20,000/QALY.

The overall finding of the economic model to explore multi-gene panel cost-utility was that testing using a panel is very cost-effective, with every ICER being below the £20,000/QALY threshold. Costs which could be avoided using a multi-gene panel include; SJS/TEN, reportedly costing around £31,220 (Oster et al., 2009), hepatotoxicity more than £2700 (NHS reference costs, 2009) and abacavir hypersensitivity € 2,235 (Wolf et al., 2010). Further than this, this result suggests that panel (and returning incidental findings for possible future use) testing as an alternative to single-gene testing is a cost-effective method.

Panel configurations containing *HLA-B*57:01* for abacavir hypersensitivity were particularly cost-saving (scenario 1,2,3 & 5 as in section 3.4.5). As genetic testing for *HLA-B*57:01* is highly cost-effective prior to abacavir treatment due to the massive costs associated with the ADR, this resulted in favourable panel ICERs for cost-effectiveness. This cost saving from testing *HLA-B*57:01* is indicated in the single gene ICER (table 7) taken from Kauf et al (2010) and many other studies are concordant with this , with evidence of testing cost-effectiveness (Hughes et al., 2004; Shackman et al., 2008; Caltravaa et al., 2010; Wolf et al., 2010).

There are several explanations for the extreme cost savings of abacavir testing which may be due to the population reflected in the Kauf et al study (2010), which assessed the value of testing from the US healthcare system perspective. The US gene prevalence was 5.66%, HSR incidence 6% and costs of clinically diagnosed HSR were between $131.72 and $1739.12. When participating in a gene panel, the huge cost savings associated with testing and the QALY gain cause a negative ICER (cost saving and increased QALYs) to impact each panel (favourably) to encourage cost effectiveness.

The cost-utility analysis of abacavir pharmacogenetic testing in the present study found the test for *HLA-B*57:01* in abacavir therapy, at a test cost of £10, to be the most cost effective ICER of -£166,277/QALY dominating abacavir treatment without genotyping (scenario 1, section 3.4.5). This was a cost-effective test, however as this only included the *HLA-B*57:01* gene, this did not answer the policy question around panel testing but does suggest that using a panel for abacavir is still cost-effective (e.g. scenarios 2,3 & 5) but a single-gene test would incur less costs. This would therefore suggest that a panel test for patients eligible for abacavir might not be implemented as the single-gene test alone is highly cost-effective, however this would mean patients who may require further testing to avoid ADRs will incur further costs (which may be avoided using a panel test).

In scenario 1, using a panel test to prospectively test was cost-effective for a single association at the £20,000/QALY threshold (*HLA-B*57:01)*, which increased to three at £30,000/QALY and had the highest QALY gains of 0.0180 and 0.0187 respectively (*HLA-B*57:01, HLA-DRB1*07:01* & *HLA-DQA1*02:01)*. The high incremental QALY corresponds to the clinical benefit when testing for these genes and preventing the ADR and provides evidence of improved health using the current clinical implementation guidelines (genetic testing required). This is also reflected in the PPV of most of these genes which were amongst the highest throughout the associations; *HLA-B*57:01* = 0.29, *HLA-DRB1*07:01* = 0.07 *HLA-DQA1*02:01* = 0.07. The incremental QALY for this panel is higher than the QALY increase of single-gene economic analysis for testing of *HLA-B*57:01* prior to abacavir as documented in the Plumpton, Roberts, Pirmohamed and Hughes systematic review (2015) – where testing produced QALY increments of 0.0067 (Shackman et al., 2011), 0.017 (Kauf et al., 2010) in the US studies and reduced risk of ADR by 1.8% in the only UK study (Hughes et al., 2004).

The second scenario; required and recommended genes at a test cost of £10 and £20,000/QALY threshold was again, cost-effective. This panel was inclusive of 4 genes which were found to all be cost-effective to test prospectively using a panel; *TPMT* (Mercaptopurine), *HLA-B*15:02* (Phenytoin), *HLA-A*31:01* (Carbamazepine), *HLA-B*57:01* (Abacavir). The ICER for this panel was dominant and was relatively unaffected by a change in test cost suggesting the panel would be still cost-saving to the NHS at a higher price, maximising economic benefit for the product developers.

The largest ICER for a multi-gene panel (with an ICER/QALY threshold applied) was £10,270/QALY resultant of scenario 4 – common diseases. This panel included 4 genes which were found to be cost-effective to test prospectively (using a panel) and 5 genes were cost effective as incidental findings (to be used pre-emptively), at a test cost of £50 and threshold of £30,000/QALY. This showed the cost-effectiveness of pre-emptively testing for *HLA-B*58:01* in the treatment of gout with allopurinol and was concurrent with the Plumpton et al study (2017) however, this study identified that using a panel test to prospectively test is not cost-effective for this disease group.

This was also reflected in other panels which incorporated *HLA-B*58:01* for SJS/TEN from allopurinol therapy in the treatment of gout. At the higher threshold allopurinol was not cost effective to test prospectively above a test cost of £20, although it remained cost-effective to test for pre-emptively. Using the base case scenario, testing was only cost-effective prospectively in 18%, and pre-emptively in 30% of simulations. This is an example of where the test would not be commissioned as a prospective test but may be included as an incidental finding and would be cost-effective if the information was returned in this way.

Testing for the carbamazepine pharmacogene, *HLA-B*15:02*, was not cost-effective prospectively or pre-emptively throughout panel scenarios which reflects the finding of Chen, Liew and Kwan (2015) study. Although this may be a result of a lower PPV in the Chinese population of Chen, Liew and Kwan used as PPV in other populations has been higher, 1.92% in Thailand (Tassaneeyakul et al., 2010) and 5.6% in Singapore (Dong et al., 2012). This provides evidence that *HLA-B*15:02* is not cost-effective, even when returned as incidental findings.

When the threshold was removed to evaluate the cost-effectiveness of the excluded genes (genes with a negative QALY), QALYs were decreased in each of the simulations. This displays the

reduction in health associated with testing for some genetic associations (i.e. the previously excluded). The multi-gene panel containing genes where testing is currently required prior to prescription (scenario 1) the QALY decrement at no threshold was 0.0007. This combination at £20,000 and £30,000/QALY had the highest QALYs out of the different panel combinations. The reduction in QALY can be explained by the negative incremental QALY estimated for *FVL* testing prior to oral contraceptive use (-0.0004), which may counteract the increase in QALYs of the other alleles. This reduction in QALYs was identified in all of the multi-gene panels with the threshold removed.

4.2 Study limitations

Although this model incorporates evidence from high quality resources, there were a number of assumptions which had to be made inevitably creating limitations in this analysis.

Firstly, as this study collated data from cost-utility analyses conducted globally, there may be varied interpretation of health by different populations (by health-state utility measurements) which may result in under/overestimated QALYs in studies compared with that of the UK population. The value of a QALY will vary on how a population values life and the willingness to pay for healthcare (Whitehead & Ali, 2010). This is also affected by the vast difference in cost-effectiveness threshold adopted by each country, a factor which may influence the multi-gene panel ICERs – using QALYs which are possibly inconsistent between population groups.

The economic inputs used within the cost-effectiveness inputs of this study have several limitations, however due to the scope of this study these were justified. Only some of the studies used actual clinical data within their research, therefore the model was based on extrapolation of assumptions and estimates which may not reflect the actuality of cost and QALY effects. In the calculated cost-effectiveness estimates, ADR costs and QALYs were derived from published resources including NHS publications and laboratory studies. This may not be an accurate assumption due to the difficulty in calculating the effect of an ADR on these parameters due to the wide-range of effects on each individual.

Precise costs and utilities within healthcare can be difficult to identify due to the amount of input associated with patient care and the wide range of variability between each individual case. Definitions of costs are different between research studies therefore the SD was used to

acknowledge variation via sensitivity analysis. With economic analyses outside the UK, the costs and QALYs extracted have another issue with variation due to the healthcare system of the country involved. Some of the comparator drug economic analyses were US based where a health insurance system is used, and this can cause inconsistency when comparing with a tax payer funded healthcare system such as the NHS.

The economic model pragmatically extrapolates short-term cost-effectiveness estimates to lifetime. This was necessary to reduce bias in the economic model. Pharmacogenetic testing may impact differently on survival for each of the drug-gene combinations and therefore can accrue costs and QALYs beyond the time horizon of each study. Although the QALYs were calculated from EQ-5D questionnaires, the time period at which they were taken may differ and some patients may have been at different stages of ADR onset. This is a limitation of combining data from multiple resources – the time horizons of costs and QALYs are not necessarily the same. This can be a limitation as the outcome of a multi-gene panel is an informed prediction and there is no guarantee the actual cost and QALY outcomes would be reflected over a lifetime. However, most of the studies included were extrapolated over a lifetime.

Another limitation of testing for genetic associations to ADRs using a multi-gene panel and the economic model within this study, may be the incidental findings. Whilst a patient may be screened initially for the therapy they are receiving for a current condition, it may be problematic to provide them with information about incidental findings. It may be difficult for the patient to interpret if they do not understand the relevance of the incidental findings, causing distress over a potential risk which at the time of testing may not be relevant to the patients' current health and healthcare strategy. This could also have a downstream effect on costs and QALYs which cannot be completely considered within the model. The possibility of healthcare staff spending excess time explaining the results and also the patients wish to know, may all accrue costs which were not accounted for in this model, which could possibly bias the ICER result.

An issue which was not considered in this study but may impact panel testing cost-effectiveness (particularly health utility), is a patients' right to their own genetic information. The Subject Access Request an element of the Data Protection Act (1998), replaced by the GDPR in 2016 for implementation in 2018 allows a patient access to their medical records. With developments in genomic science occurring rapidly, there is an issue of ethics involved with retaining information on a patients' genetic information. This may be particularly powerful if a new disease linkage was made with a genotype they have been tested for.

In the model each disease is independent, and proportions are calculated in the model as individual populations, which is not the case for multiple drugs used for the same condition (most frequently, epilepsy) or as with Lapatinib and Carbamazepine, which both have multiple genetic associations relating to an ADR, which crucially means they are not independent of each other.

Although age of genetic testing was not considered within this study, this is a factor assessed within similar work. This may possibly affect the cost-effectiveness outcome of the model due to theorising that the earlier in life the multi-gene panel is requested, the more beneficial (and possibly cost-effective) a panel test is. Alogaz, Durham and Kasirajan found ICERs for one-time genetic testing to be cost-effective at ages 40, 50, 65, 70 and 75 although the ICERs did increase with age and the most cost effective was the base-case of 40-years old. Bennette, Gallego, Burke, Jarvik & Veenstra, (2014) explored different ages for the cost-effectiveness of returning incidental findings. The present study did not apply age ranges as the returning incidental findings are potentially applicable at any age and applying a variety of ages to this economic model was beyond the scope of the study. However, applying age would have possibly affected panel ICERs as panel combinations may contain drug-gene associations which may have differing age of onsets. With the possibility of receiving less genetic information from incidental findings, this may have reduced the incremental QALYs associated with the panel test.

For the purpose of this study, it was assumed that all drugs were to be excluded from a patient's regime if they are found to have the risk allele for the drug-gene association. This is a limitation to this study as with some patients and drugs, it is very much a case-by-case decision depending on the availability of other treatment and often the risk of giving a drug over and monitoring the patient's response closely will offer more benefit than completely excluding the drug. If monitoring was incorporated into the model this would involve a lot more assumptions in the initial data input and would also have an effect on the incremental costs associated with this test, as monitoring a patient's drug response may possibly be costlier than excluding the drug.

The estimates of single-gene cost utility also included PPV values of which were extracted from single studies and not meta-analyses. With single-study cohort size being small in comparison to that of a meta-analysis, this may have biased the results of these estimates as a smaller cohort may not truly reflect the actual sensitivity and specificity of the allele (to the ADR) in the wider population.

There are also some downstream costs associated with discouraging the use of certain drugs e.g. oral contraceptives following genetic testing of *FVL;* there may be associated incremental costs in mutation carriers. An example being the reduced uptake of contraceptives which could increase risk of unplanned pregnancy which is also associated with thromboembolic events. And, although the testing of *FVL* was not found to be cost-effective this would not have been relevant (as an incidental finding to be used pre-emptively) to the male population using a panel because of its relevance towards oral contraceptives which are currently a therapy indicated for females of child bearing age. Which is a similar argument for post-menopausal women.

4.3 Reporting incidental findings and implementation of multi-gene panel testing

Incidental findings of pharmacogenetic testing has been a particular debate on ethics and cost-effectiveness. Ethically, withholding valuable information regarding a patient's genome which could possibly enhance the healthcare of a patient and improve QALYs can be seen as immoral. Acting on each of the probabilities may be associated with prescription of less effective medicines and increased downstream costs of the personalisation of medicine associated with the presence of genes, which also have the probability of not causing harm. However, this can be greatly beneficial when improving health and saving costs.

Using a multi-gene panel rather than whole genome sequencing addresses this problem by only testing for genes of known association to an ADR, genetic information beyond this is not exposed and therefore is not actionable. This is an approach suggested by Clarke (2014) to minimize the ethical difficulty associated with incidental findings.

With other sequencing techniques having the possibility of actionable incidental findings, as previously mentioned in section 1.5.4.2, Bennette, Gallego, Burke, Jarvik & Veenstra, (2014) assessed the cost-effectiveness of returning incidental findings from NGS. This returned an ICER of $44,800 per QALY for cardiomyopathy patients. This study projected that testing of generally healthy individuals is not likely to be cost-effective unless the price of NGS falls below $500 and even with the announcement by Illumina of $1000 whole genome sequencing, this is still above what would be efficient in achieving cost-effectiveness (McDermott, 2015). Which demonstrates the expensive application of genetic testing that is NGS, especially when applied to the obtaining the possible presence of just 14 genes - which would not be likely cost-effective using this technique. Also, to implement this as a diagnostic technique for ADR associated genotypes would

be difficult as it can take 5 days sequence and process patient samples, conduct analyses and produce results (Yin et al., 2016).

The multi-gene panel within this study allows for rapid results with the assay taking less than 3 hours. This means that pharmaceutical therapy can begin almost immediately, which is important for high risk diseases such as epilepsy and doesn't have much of an impact on normal procedure with regards to time. The price of the panel is minimal (£30, base-case panel) for the impact on cost-effectiveness by actually saving costs and improving health gain (QALYs). This test price to return the NHS is important in comparison to other methods genotyping single-genes, the multi-gene panel method is competitive and returns further genetic information at a minimal cost without the need for time and budget exhaustive sequencing methods.

4.4 Conclusions

Adverse drug reactions are an important effect of pharmaceutical therapy and can have huge implications on patient morbidity and mortality and costs to the NHS. Many of these ADRs are likely avoidable with genetic testing, which has been acknowledged by worldwide medicine agencies and implemented for a handful of drugs. By creating technology which can incorporate a panel of pharmacogenes at the same or cheaper cost of a single-gene test, the return on incidental findings may have the ability to limit lifetime adverse drug reactions – saving on cost accumulation and improving patient health.

This study assessed the cost-effectiveness of multi-gene panel testing to prevent ADRs and was inclusive of HLA genotypes and other genetic polymorphisms associated with an increased risk of suffer from an ADR. This was a significant piece of research to contribute to a credible presentation of this product for health technology assessment by the product developers. Throughout the scenarios, multi-gene panel testing was found to be cost-effective at the £20,000/QALY threshold, which provides supporting evidence for implementation. This evidence also offers an insight into the investment of returning additional genetic information from one test. Importantly, for the product developers – the ICERs were not extremely sensitive to the test cost and most panel tests were cost-effective when tested with minimum to maximum test costs.

The caveat to this result is the effectiveness of returning incidental findings of a panel might not be as optimistic as suggested by this research. This is due to the extrapolation of costs and QALYs

by economic modelling and the assumptions involved in this study, although scenarios were tested by sensitivity analysis - actual panel cost-effectiveness may be different. The impact of the multi-gene test information on incidental findings is still an unknown subject particularly in the NHS and there is uncertainty as to how incidental findings would be used and how the information will be fed back to the patient.

Integrating the information of a multi-gene panel into a healthcare system however may be a challenge. Although the benefits are possibly vast on both costs and QALYs, using the information provided from a multi-gene panel is only cost-effective if the incidental findings are utilised upon future pharmaceutical requirement and the test is not requested again.

This study was important to analyse the cost-effectiveness of testing for a panel of pharmacogenes to provide a profile of a patient's genes relating to ADRs and concluded that multi-gene panel testing is likely to be cost-effective for a wide variety of panel configurations and also is cost-effective in genes which extend beyond the HLA gene family.

The policy implications of this therefore suggest that multi-gene panel testing to avoid ADRs could be a cost-effective method for certain genes and in certain disease groups. However, further research would be useful to assess the clinical effectiveness of multi-gene panel testing and would be interesting to view in a cohort of patients eligible for each of the drugs with a genetic association on the panel test. This would identify the long-term impact of multi-gene panel testing on costs and QALYs and would conclude whether this method of pharmacogenetic testing is cost-effective to the NHS for each of the eligible disease groups.

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6. APPENDICES

APPENDIX 1 – STUDY TIMEFRAMES

Study		Timeframe
Drug: Irinotecan Marker: *UGT1A1* ADR: Neutropenia	Butzke et al., 2015	6-months (Decision analytic markov)
Drug: Abacavir Marker: *HLA-B*57:01* ADR: SJS/TEN	Kauf et al., 2010	Lifetime (Discrete-event simulation model)
Drug: Azathioprine Marker: *TPMT* ADR: Myelosuppression	Thompson et al., 2014	4 months (generalized linear model)
Drug: Carbamazepine Marker: *HLA-A*31:01* ADR: SJS/TEN	Plumpton at al., 2015	Lifetime (Markov model)
Drug: Clopidogrel Marker: *CYP2C19* ADR: CV events	Panattoni et al., 2012	Lifetime (Decision-tree)
Drug: Allopurinol Marker: *HLA-B*58:01* ADR: SJS/TEN	Plumpton, Alfirevic, Pirmohamed & Hughes, 2017	Lifetime (Markov model)
Drug: Phenytoin Marker: *HLA-B*15:02* ADR: SJS/TEN	Chen, Liew & Kwan, 2016	Lifetime (Decision tree)
Drug: Carbamazepine Marker: *HLA-B*15:02* ADR: SJS/TEN	Chen, Liew & Kwan, 2016	Lifetime (Decision tree)
Drug: Warfarin Marker: *CYP2C9*/VKORC1 ADR: Bleeding events	Verhoef et al., 2016	Lifetime (markov model)

APPENDIX 2 - SEARCH STRATEGY ECONOMIC EVIDENCE SYSTEMATIC REVIEW (PLUMPTON, ROBERTS, PIRMOHAMED & HUGHES, 2016)

1 (Pharmacogenomic* or pharmacogenetic* or genomic* or genotype* or genetic* or single nucleotide polymorphism* or SNP)

2 (Cost?effective* or cost?utility or cost?benefit or cost?minimization or economic* or pharmacoeconomic*)

3 (Adverse or side?effect* or harm* or ADR? or toxic*)

4 (Drug* or medicine* or medication* or pharmaceutical*)

5 All drug names from appendix 4 separated by * or

6 (1 AND 2 AND 3 AND 4 AND 5)

APPENDIX 3 – PHARMGKB LIST OF ADR RELATED PHARMACOGENES, REASON FOR EXCLUSION

EE= Economic Evaluation

Pharmacogene	Drug	PGx Screening	Category	Mandated by	Reason for exclusion
G6PD	Pegloticase	Required	ADR	EMA	Not licensed
G6PD	Rasburicase	Required	ADR	FDA	Not licensed
POLG	Divalproex	Required	ADR	FDA/HCSC	No association studies
F5	Ethinyl estradiol/Noralgestromin	Required	ADR	EMA	Included
*HLA-B*15:02*	Carbamazepine	Required	ADR	FDA/HCSC/PMDA	Included
*HLA-DRB1*07:01*	Lapatinib	Required	ADR	EMA/HCSC/PMDA	Included
*HLA-DQA1*02:01*	Lapatinib	Required	ADR	EMA/HCSC/PMDA	Included
*HLA-B*57:01*	Abacavir	Required	ADR	EMA/FDA/HCSC/PMDA	Included
CYP2D6	Dextromethorphan/Quinidine	Recommended	ADR	FDA	No association studies
TPMT	Azathioprine	Recommended	ADR	FDA/HCSC/PMDA	Negative QALY
TPMT	Mercaptopurine	Recommended	ADR	EMA/FDA/HCSC	Included
*HLA-B*15:02*	Oxcarbazepine	Recommended	ADR	FDA	Included
*HLA-B*15:02*	Phenytoin	Recommended	ADR	HCSC	Included
*HLA-A*31:01*	Carbamazepine	Recommended	ADR	FDA/HCSC/PMDA	Included
CYP2C19	Atazanavir/Vorinacole and Ritonavir	Recommended	ADR	EMA/HCSC/PMDA	Included
CYP2D6	Dextromethorphan/ Quinidine	Recommended	ADR	FDA	No association studies
CYP2D6	Clozapine	Actionable	ADR	HCSC	No EE
CYP2C19	Clopidogrel	Actionable	ADR	HCSC	No EE
CYB5R1-4	Metoclopramide	Actionable	ADR	FDA	No EE
CYB5R1-4	Lidocaine/Prilocaine	Actionable	ADR	FDA	No EE
CYB5R1-4	Primaquine	Actionable	ADR	HCSC	No EE
CYP2B6	Tenofovir/Efavirenz	Actionable	ADR	EMA/PMDA/HCSC	No EE
CYP2C9	Warfarin	Actionable	ADR	FDA/HCSC	Included
DPYD	Fluorouracil	Actionable	ADR	FDA/HCSC/PMDA	No EE
G6PD	Erythromycin	Actionable	ADR	EMA/FDA/HCSC/PMDA	No EE
G6PD	Norfloxacin	Actionable	ADR	FDA/ HCSC	No EE
G6PD	Probenecid	Actionable	ADR	FDA/HCSC	No EE
G6PD	Sulfadiazine	Actionable	ADR	FDA/HCSC	No EE
G6PD	Sulfasalazine	Actionable	ADR	FDA/HCSC	No EE
G6PD	Sulfasalazine	Actionable	ADR	FDA/HCSC	No EE
G6PD	Methylene blue	Actionable	ADR	FDA/ EMA	No EE
G6PD	Chloroquine	Actionable	ADR	FDA/ HCSC	No EE
G6PD	Chlorpropamide	Actionable	ADR	FDA/ HCSC	No EE
G6PD	Dapsone	Actionable	ADR	FDA/ HCSC	No EE
G6PD	Glipalamide	Actionable	ADR	FDA/ HCSC	No EE
G6PD	Glimepiride	Actionable	ADR	FDA/ HCSC	No EE
G6PD	Glipizide	Actionable	ADR	FDA	No EE
G6PD	Lidocaine/ Prilocaine	Actionable	ADR	FDA	No EE
G6PD	Mafenide	Actionable	ADR	FDA	No EE
G6PD	Metoclopramide	Actionable	ADR	FDA	No EE
G6PD	Nalidixic acid	Actionable	ADR	FDA	No EE
G6PD	Nitrofurantoin	Actionable	ADR	FDA/HCSC	No EE
G6PD	Primaquine	Actionable	ADR	FDA/HCSC	No EE
G6PD	Quinine	Actionable	ADR	FDA/HCSC	No EE
G6PD	Sodium nitrate	Actionable	ADR	FDA/HCSC	No EE
G6PD	Sulfamethoxazole/ Trimethoprim	Actionable	ADR	FDA/HCSC	No EE
G6PD	Vitamin C	Actionable	ADR	FDA/HCSC	No EE
POLG	Valproic acid	Actionable	ADR	FDA/HCSC	No EE
PROC	Warfarin	Actionable	ADR	FDA	No EE
PROC	Ethinyl estradiol/ Drospirenone/ Norelgestromin	Actionable	ADR	HCSC	No EE
PROS1	Warfarin	Actionable	ADR	FDA	No EE
PROS1	Ethinyl estradiol/ Drospirenone/ Norelgestromin	Actionable	ADR	HCSC	No EE
RYR1	Desflurane	Actionable	ADR	FDA/HCSC	No EE
RYR1	isoflurane	Actionable	ADR	FDA/HCSC	No EE
RYR1	Sevoflurane	Actionable	ADR	FDA/HCSC	No EE
RYR1	Succinylcholine	Actionable	ADR	FDA	No EE
VKORC1	Warfarin	Actionable	ADR	FDA/HCSC	No EE
CACNA1S	Desflurane	Actionable	ADR	FDA/HCSC	No EE
CACNA1S	Isoflurane	Actionable	ADR	FDA/HCSC	No EE
CACNA1S	Sevoflurane	Actionable	ADR	FDA/HCSC	No EE
CACNA1S	Succinylcholine	Actionable	ADR	FDA	No EE
F5	Eltrombopag	Actionable	ADR	EMA/FDA/HCSC	No EE
F5	Tamoxifen	Actionable	ADR	FDA	No EE
F5	Ethinyl estradiol/Noralgestromin/ Drospirenone	Actionable	ADR	HCSC	No EE
F2	Tamoxifen	Actionable	ADR	FDA	No EE
F2	Ethinyl estradiol/Noralgestromin	Actionable	ADR	HCSC	No EE
SERPINC1	Eltrombopag	Actionable	ADR	EMA/FDA/HCSC	No EE

SERPINC1	Ethinyl estradiol/Noralgestromin	Actionable	ADR	HCSC	No EE
*HLA-B*58:01*	Allopurinol	Actionable	ADR	PMDA	Included
CYP2C19	Citalopram	Actionable	ADR	FDA/HCSC	No EE
CYP2C19	Filbanserin	Actionable	ADR	FDA	No EE
CYP2D6	Ranolazine	Actionable	ADR	EMA	No EE
CYP2D6	Codeine	Actionable	ADR	FDA/HCSC/PMDA	No EE
DPYD	Capecitabine	Actionable	ADR	EMA/FDA/HCSC/PMDA	No EE
UGT1A1	Pazopanib	Actionable	ADR	FDA/EMA	No EE
CYP2D6	Atomoxetine	Actionable	ADR	FDA/HCSC/PMDA	No EE
CYP2D6	Propafenone	Actionable	ADR	FDA/HCSC	No EE
TPMT	Thioguanine	Actionable	ADR	FDA/HCSC	No EE
UGT1A1	Belinostat	Actionable	ADR	FDA	No EE
OTC/CPS1	Valproic acid	Actionable	ADR	FDA/HCSC/PMDA	No EE
UGT1A1	Irinotecan	Actionable	ADR	FDA/HCSC/PMDA	Included
CYP2C9	Celecoxib	Actionable	Efficacy/ADR	FDA/PMDA/HCSC	No EE
CYP2C19	Flibanserin	Actionable	Efficacy/ADR	FDA	No EE
CYP2C9	Lesinurad	Actionable	Efficacy/ADR	FDA	No EE
CYP2C9/C19	Phenytoin	Actionable	Efficacy/ADR	FDA	No EE
CYP2C19	Carisoprodol	Actionable	Efficacy/ADR	FDA	No EE
CYP2C19	Clobazam	Actionable	Efficacy/ADR	FDA	No EE
CYP2C19	Dexlansoprazole	Actionable	Efficacy/ADR	FDA/HCSC	No EE
CYP2C19	Diazepam	Actionable	Efficacy/ADR	FDA/HCSC	No EE
CYP2C19	Doxepin	Actionable	Efficacy/ADR	FDA	No EE
CYP2C19	Escitalopram	Actionable	Efficacy/ADR	FDA/PMDA	No EE
CYP2C19	Esomeprazole	Actionable	Efficacy/ADR	EMA/FDA/HCSC	No EE
CYP2C19	Pantoprazole	Actionable	Efficacy/ADR	FDA	No EE
CYP2C19	Phenytoin	Actionable	Efficacy/ADR	FDA	No EE
CYP2C19	Rabeprazole	Actionable	Efficacy/ADR	FDA/HCSC/PMDA	No EE
CYP2C19	Voriconazole	Actionable	Efficacy/ADR	EMA/FDA/HCSC/PMDA	No EE
CYP2D6	Trimipramine	Actionable	Efficacy/ADR	FDA	No EE
CYP2D6	Vortioxetine	Actionable	Efficacy/ADR	EMA/FDA/HCSC	No EE
CYP2D6	Aripiprazole	Actionable	Efficacy/ADR	EMA/FDA/HCSC	No EE
CYP2D6	Darifenacin	Actionable	Efficacy/ADR	EMA/FDA/HCSC	No EE
CYP2D6	Fesoterodine	Actionable	Efficacy/ADR	EMA/FDA/HCSC/PMDA	No EE
CYP2D6	Vortioxetine	Actionable	Efficacy/ADR	EMA/FDA/HCSC	No EE
CYP2D6	Atomoxetine	Actionable	Efficacy/ADR	FDA/HCSC/PMDA	No EE
CYP2D6	Escitalopram	Actionable	Efficacy/ADR	FDA/PMDA	No EE
CYP2D6	Fesoterodine	Actionable	Efficacy/ADR	EMA/FDA/HCSC/PMDA	No EE
CYP2D6	Perphenazin	Actionable	Efficacy/ADR	FDA/PMDA	No EE
CYP2D6	Aripiprazole	Actionable	Efficacy/ADR	EMA/FDA/HCSC	No EE
CYP2D6	Carvedilol	Actionable	Efficacy/ADR	FDA/HCSC	No EE
CYP2D6	Nortriptyline	Actionable	Efficacy/ADR	FDA/HCSC	No EE
CYP2D6	Acetaminophen/ Tramadol	Actionable	Efficacy/ADR	FDA/PMDA	No EE
CYP3A4	Aripiprazole	Actionable	Efficacy/ADR	EMA	No EE
NAGS	Valproic acid	Actionable	Efficacy/ADR	FDA	No EE
UGT1A1	Dolutegravir	Actionable	Efficacy/ADR	FDA	No EE
SLCO1B1	Rosuvastatin	Actionable	Efficacy/ADR	-	No EE
NAT2	Isoniazid	Informative	ADR	FDA/PMDA	N/A
NAT2	Hydralazine, Isosorbide dinitrate	Informative	ADR	FDA	N/A
TPMT	Cisplatin	Informative	ADR	FDA	N/A
CYP3A4	Indinavir/ when co-administered with CYP2A4 inhibitors	Informative	ADR	EMA	N/A
UGT1A1	Regorafenib	Informative	ADR	EMA	N/A
CYP2C9	Prasugrel	Informative	Efficacy/ADR	FDA	N/A
CYP2C9	Flurbiprofen	Informative	Efficacy/ADR	FDA	N/A
CYP1A2	Olanzapine	Informative	Efficacy/ADR	EMA	N/A
CYP2B6	Prasugrel	Informative	Efficacy/ADR	FDA	N/A
CYB5R1-4	Rasburicase	Informative	ADR	FDA	N/A

APPENDIX 4 - GENETIC ASSOCIATION SEARCH STRATEGY

1 (Pharmacogenomic* or pharmacogenetic* or genomic* or genotype* or genetic* or single nucleotide polymorphism* or SNP)

2 (Adverse or side?effect* or harm* or ADR? or toxic*)

3 (Drug* or medicine* or medication* or pharmaceutical*)

4 (Pegloticase* or rasburicase* or divalproex* or ethinyl estradiol* or noralgestromin * or carbamazepine* or lapatinib* or abacavir* or azathioprine* or dextromethorphan* or mercaptopurine* or oxcarbazepine* or phenytoin* or atazanavir* or ritonavir * or voriconazole* or clozapine* or clopidogrel * warfarin* or fluorouracil* or irinotecan)

5 (1 AND 2 AND 3 AND 4)

APPENDIX 5 – COMPARATOR DRUG ECONOMIC ANALYSIS SEARCH STRATEGY

1 (Cost?effective* or cost?utility or cost?benefit or cost?minimization or economic* or pharmacoeconomic*)

2 (Drug* or medicine* or medication* or pharmaceutical*)

3 (ethinyl estradiol* or noralgestromin * lapatinib* or mercaptopurine* or oxcarbazepine* or atazanavir* or ritonavir * or voriconazole* or fluorouracil*)

3 (1 AND 2 AND 3)

APPENDIX 6– UK DISEASE (DRUG INDICATION) INCIDENCE

Drug	Indication	Disease incidence UK	Source
Ethinyl estradiol/Noralgestromin	Contraception	0.001	ONS, 2014
Carbamazepine	Epilepsy	0.001	Epilepsy council, 2011
Lapatinib - not routinely recommended	Secondary HER2 Breast cancer	0.00017	ONS, 2014
Lapatinib - not routinely recommended	Secondary HER2 Breast cancer	0.00017	ONS, 2014
Abacavir	HIV	0.000094	Public Health England 2014/15
Azathioprine	Autoimmunity disease (Crohns)	0.005	Loftus, 2004
Mercaptopurine	Acute lymphoblastic leukemia	0.00001	ONS, 2014

Oxcarbazepine	Epilepsy	0.001	Epilepsy council, 2011
Phenytoin	Epilepsy	0.001	Epilepsy council, 2011
Carbamazepine	Epilepsy	0.001	Epilepsy council, 2011
Atazanavir/Ritonavir---voriconazole	HIV	0.6-4% (2.3%) of aids population (101,500*0.023)	Fungal infection in HIV patients, aspergillosis
		0.000036	Pegorie et al., 2016 (F), Aghaizu et al., 2016 (HIV)
Clopidogrel	CVD - MI	0.001	Smolina et al., 2012
Warfarin	Atrial Fibrillation	0.003	Martinex et al., 2015
Allopurinol	Gout	0.002	Kuo et al., 2015
Irinotecan	Colorectal cancer	0.001	ONS, 2016

APPENDIX 7– COMPARATOR DRUG COST-EFFECTIVENESS DATA EXTRACTION.

Pharmacogene	**Drug**	**Indication**	**Comparator drug**	**Utility decrement**	**Incremental cost (2016 GBP)**	**Source**
FVL	Ethinyl estradiol/Noralgestromin	Oral contraceptive	DMPA	-0.01	-1423.13	(Sonnenberg, 2004)
*HLA-DRB1*07:01*	Lapatinib	Breast cancer	Trastuzumab	0.32	3459.00	(Squires, Stevenson, Simpson, Harvey, & Stevens, 2016)
*HLA-DQA1*02:01*	Lapatinib	Breast cancer	Trastuzumab	0.32	3459.00	(Squires, Stevenson, Simpson, Harvey, & Stevens, 2016)
TPMT	Mercaptopurine	ALL	Mesalamine	0.01	-523.14	(Doherty, Miksad, Cheifetz, & Moss, 2012)
*HLA-B*15:02*	Oxcarbazepine	Epilepsy	Lamotrigine	-0.07	983.00	(Marson et al., 2007)
CYP2C19	Atazanavir/Ritonavir and voriconazole	HIV	Fluconazole	-0.05	-948.19	(Mauskopf et al., 2013)

APPENDIX 8 – ADR COST AND QALYS

ADR	**Cost (2016 GBP)**	**Source**	**Utility decrement**	**Source**
SJS/TEN	31,220.708	Plumpton et al., 2015 (Oster C., 2009)	(0.140)	Plumpton et al., 2015 (Oster C., 2009)
Bone marrow suppression	3,087.910	Department of Health. NHS Reference costs (2008-2009), 2009.	(0.750)	Elliot et al., 2008
Hepatotoxicity	2,749.753	Department of Health. NHS Reference costs (2008-2009), 2009.	(0.198)	Fontana et al 2015
DVT	2,083.401	NICE	(0.003)	Enden et al., 20