Pharmacogenomics of Medically Important Adverse Drug Effects

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I certify that all material in this thesis which is not my own work has been identified and that any material that has previously been submitted and approved for the award of a degree by this or any other University has been acknowledged.

Publications

A Comparative Safety Analysis of Medicines Based on the UK Pharmacovigilance and General Practice Prescribing Data in England: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8931874/

Conferences

The European Society of Human Genetics Conference, June 10–13th, 2023, Glasgow, Scotland, UK. I orally presented and delivered a hybrid poster [Pharmacogenomic Variants Associated with Medically Important Adverse Events Related to Endocrine Therapy for Breast Cancer Can Not Be Replicated in 2,729 Participants of UK Biobank].

The 16th Annual Meeting of Korean Society of Medical Oncology & 2023 International Conference & 11th International FACO Conference, September 7th to 8th 2023, Seoul, Korea. I orally presented and delivered a hybrid poster [Pharmacogenetics of Endocrine Therapy Associated Toxicities in Breast Cancer: A Systematic Review and Meta-Analysis].

The 7th International Congress of the European Society for Pharmacogenomics and Personalised Therapy (ESPT 2023), October 25-27th, 2023, Copenhagen, Denmark. [Pharmacogenomic Variants of Medically Important Adverse Effects Related to High-Risk Medicines in General Practice Can Not Be Replicated in UK Biobank].

The Clinical Pharmacy Congress North 3-4 November 2023, Manchester, England. [A Novel Data Integration Approach Based on the Yellow Card Reporting Scheme and the English General Practice Prescription Data].

Abstract

Introduction Medicines with high toxicity profiles have a heightened risk of causing serious and fatal adverse drug effects (ADEs). General Practice (GP) is key in identifying and potentially preventing ADEs. While the use of genomic information has the potential to reduce ADEs, the robustness and reproducibility of genetic research findings are questionable. Hence, separating true positives from false positives and minimising the overabundance of false-positive signals is vital.

Aim To assess the current state of the art in pharmacogenomics (PGx) of adverse drug effects and analyse whether variants previously reported to be associated with medically important adverse effects (MIADEs) replicate in the UK Biobank (UKBB).

Methods and Materials Three separate systematic reviews of the literature were conducted to identify relevant studies. To identify high-risk medicines, data on serious and fatal ADEs from the UK pharmacovigilance was mapped onto GP prescription data in England. Previously described associations between variants and MIADEs related to high-risk medicines in GP and endocrine drugs for breast cancer were interrogated in UKBB.

Results I created a list of variants associated with ADEs and further generated a set of variant–drug pairs significantly associated with MIADEs. I identified medicines with high toxicity profiles in GP and created comparative safety charts to support evidence-based decision-making around formulary choices. No statistically significant genotype-treatment interactions were found for either baseline measurements or incident MIADEs in UKBB. This included MIADEs related to statins, NSAIDs, antipsychotics and endocrine therapy.

Conclusions

None of the PGx findings tested were replicated in UKBB. This included associations between variants and MIADEs related to high-risk medicines in GP and endocrine agents, in relation to neither baseline measurements nor incident MIADEs. These variants are not accurate at identifying those who are at risk of developing MIADEs in patients receiving these treatments and therefore should not be considered for personalised recommendations.

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Author's declaration

This work is my individual contribution. This degree was financially funded via the Sanctuary Scholarship Scheme by the University of Exeter.

List of Abbreviations

PG: Pharmacogenomic or pharmacogenetic

PGx: Pharmacogenomics or pharmacogenetics

ADEs: Adverse Drug Effects

ADRs: Adverse Drug Reactions

UKBB: UK Biobank

BC: Breast Cancer

PharmGKB: The Pharmacogenomics Knowledge Base

RCTs: Randomised controlled trials

MIADEs: Medically Important Adverse Drug Effects

HCPs: Health Care Professionals

SNV: Single nucleotide variant

SNP: Single nucleotide polymorphism

MAHs: Marketing Authorisation Holders

MHRA: Medicines and Healthcare Regulatory Agency

GP: General Practice

GPs: General Practitioners

BNF: British National Formulary

YCS: Yellow Card Scheme

iDAPs: Interactive Drug Analysis Profiles

START: Screening Tool Alert Doctors to Right Prescribing

STOPP: Screening Tool of Older Persons' Prescriptions

MAI: Medication Appropriateness Index

IPET: Inappropriate Prescribing in the Elderly Tool

VIP: Very Important Pharmacogenes

PGRN: Pharmacogenomics Research Network

emc: electronic medicines compendium

CTCAE: Common Terminology Criteria for Adverse Events

MS-ADEs: Musculoskeletal Adverse Drug Effects

VM-ADEs: Vasomotor Adverse Drug Effects

GWAS: genome-wide association studies

ICD-9: International Classification of Disease Version 9

ICD-10: International Classification of Disease Version 10

HES: Hospital Episode Statistics

EMA: European Medicines Agency

ICH: International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

DMEs: Designated Medical Events

EV-EWG: EudraVigilance Expert Working Group

IMEs: Important Medical Event

NHS: National Health Service

FDA: Food and Drug Administration

FAERS: Adverse Event Reporting System

WHO: World Health Organization

EU: European Union

DoPHER: Database of Promoting Health Effectiveness Reviews

CDSR: Cochrane Database of Systematic Reviews

NICE: National Institute for Health and Clinical Excellence

SIGN: Scottish Intercollegiate Guidelines Network

DPWG: Dutch Pharmacogenetics Working Group

FFPE: formalin-fixed, paraffin-embedded

PRESS: Peer Review of Electronic Search Strategies

GLMM: Generalised Linear Mixed-effects Model

BMI: Body Mass Index

CDA: Chlorproguanil-Dapsone-Artesunate

CPIC: Construction Project Information Committee

NSAIDs: non-steroidal anti-inflammatory drugs

CNS: Central Nervous System

HR+: hormone receptor-positive

OS: Overall Survival

DFS: Disease-Free Survival

PICO: Population, Intervention, Comparison, Outcome

HRQL: Health-Related Quality of Life

STREGA: STrengthening the REporting of Genetic Association Studies

STROBE: Strengthening the Reporting of OBservational Studies in Epidemiology

1 Chapter One. Introduction

1.1 Adverse drug effects can lead to significant morbidity and mortality

Adverse drug events are defined as untoward outcomes that occur throughout or following the use of a medicinal product but are not necessarily caused by it as they might occur as a result of human errors. The definition of “adverse drug events” by the international CIOMS ADR Working Group and the European Medicines Agency (EMA) are undesirable and unintended noxious responses to a medicinal product which might arise from using it either within or outside the marketing authorisation terms including the off-label use, abuse, misuse, overdose, medication errors or from occupational exposure (1, 2). While “drug side effects” refer to any unintended drug effects, whether they are beneficial or harmful, “adverse drug reactions or effects” are adverse drug events that occur at doses normally used for treatment, diagnosis or prophylaxis excluding intentional overdose, errors in drug administration, therapeutic failures and non-adherence (3). The terms adverse drug reactions (ADRs) and adverse drug effects (ADEs) are used interchangeably in this report to denote adverse drug events for which there is a reasonable possibility of a causal relationship between the drug and the unintended adverse event.

All medications carry a risk of causing ADEs, and the benefits of a medication must outweigh its potential adverse effects. ADEs represent a major concern contributing to a significant increase in both morbidity and mortality and imposing a huge burden on health services with enormous financial costs worldwide (3–10). ADEs are considered the fourth leading cause of death in the USA (3) with comparable figures for hospital deaths in Western countries (11–13). It was estimated that 200,000 deaths annually in the European Union (EU) are caused by ADEs (5). In addition to hospital admissions and prolongation of hospital stay (7, 8, 14, 15), ADEs can impact patients’ everyday activities (16–18) and lead to poor adherence as well as discontinuation of vital treatments. Furthermore, the ADEs-related burden on the National Health Service (NHS) is substantial with a considerable economic cost of around £2 billion per year (19).

While the identification and further quantification of ADEs is considered a core element in clinical trials before approval, clinical trials are considered less effective for ADE detection. Thus, data from clinical trials has limited utility in

extrapolating and drawing conclusions about risks related to medication in routine clinical practice (20–27). During clinical trials, ADEs often remain undetected due to both the relatively small sample size of participants studied (28–31), and the short duration of follow-up as well as the strict inclusion criteria, which generally exclude the participation of the frailest (32). In contrast to easily identifiable and well-known ADEs that are frequently detected in clinical trials during the various pre-marketing stages, late-onset, as well as rare ADEs, are usually not recognised or detected until the post-marketing drug safety surveillance phase (i.e, in the real world or everyday clinical practice). During the post-marketing phase, medications are being used by a larger as well as more diverse range of patient populations than initially studied and for longer periods (30, 33–36). The relatively short duration of clinical trials and the emphasis on main outcomes may also impede the capture of unpredictable (37–39) and less common ADEs (40) that are rarely considered to be the primary endpoints and thus may not be precisely diagnosed or recorded. The various stages of drug discovery and development are described in (Figure 1.1).

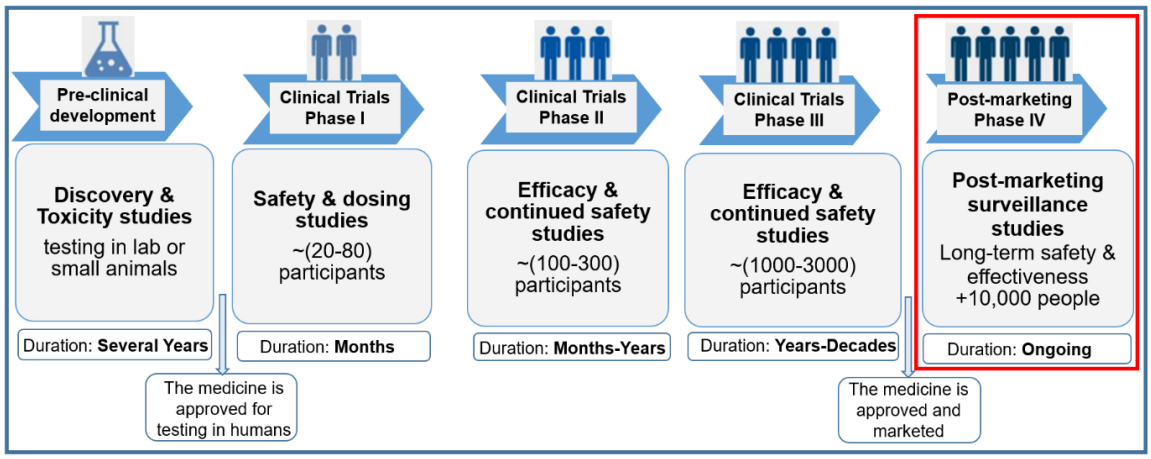


Figure 1.1 The process of drug discovery and development.

This diagram demonstrates various stages of the process of drug discovery and development including the pre-clinical, clinical trials and post-marketing surveillance phases.

The principal means of maintaining and assuring post-marketing drug safety is the spontaneous reporting of adverse events (referred to as pharmacovigilance). Pharmacovigilance is the key system for detecting and identifying drug safety signals (41, 42) and most of the medication-associated safety signals are flagged up via this pathway (36, 43). Examples include the FDA Adverse Event Reporting System (FAERS) database in the USA (44) and the MHRA Yellow Card Scheme (YCS), which is the established route for ADE reporting to the Medicines and

Healthcare Regulatory Agency (MHRA) in the UK (45). In this system, suspected ADEs are reported and submitted by both patients and healthcare professionals (HCPs) on a voluntary basis (46). The pharmaceutical industry has however a legal obligation to independently report ADEs relating to their medicinal products. While there is no encouragement to report relatively minor ADEs by regulators and policymakers (47), serious ADEs are usually well-reported even for established drugs. Hence, conducting analyses of reports related to serious ADEs contained in pharmacovigilance databases is potentially useful (48–50). While important findings have been published in the literature from analyses of ADE reports contained in pharmacovigilance databases (51), the utility of pharmacovigilance databases for pharmaco-epidemiological studies is limited, mainly because of the lack of an evidence-based approach. Without adjustment for confounding factors, including the period for which the medication has been in general use and the number of patients taking it, quantitative analyses and conclusions regarding the medication-related risks using data derived merely from ADE reports can be flawed (52, 53). To overcome the above-mentioned limitations (54), linking data derived from ADE reports to other observational data is therefore preferable (55, 56).

1.2 High-risk medicines have a heightened risk of causing serious and fatal adverse effects

Serious ADEs are associated with significant mortality and morbidity and usually impact the patient's functional capabilities. The most common definitions of seriousness are those developed by the CIOMS WORKING GROUP (1, 57) and the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (58, 59). The ICH introduced the following official definition of a serious adverse event: "Any untoward medical occurrence that at any dose results in death, is life-threatening, or results in persistent or significant disability or incapacity, or a congenital anomaly/birth defect or requires inpatient hospitalisation or prolongation of existing hospitalisation".

Examples of inherently serious ADEs include Designated Medical Events (DMEs) as per the European Medicines Agency (EMA) (60, 61), and Important Medical Events (IMEs) by EudraVigilance Expert Working Group (EV-EWG) based on the official ICH definition of seriousness (62). While some IMEs may not fulfil the

criteria for seriousness as per WHO in its administrative definition of pharmacovigilance activities (e.g., do not result in death or hospital admission), these "medically serious events" are still encoded as serious in most pharmacovigilance databases as they may jeopardise the patient's health or require treatment or intervention in the emergency department in order to prevent serious outcomes. Examples of grading scales of severity of ADEs include the Common Terminology Criteria for Adverse Events (CTCAE) (63), which are usually used in randomised controlled trials (RCTs). ADEs in the CTCAE standardised grading scale are considered mild or moderate (grade 1/2) or severe (grade 3/4).

The proportion of ADEs that are considered serious or life-threatening varies from 2.2% to 29.79% (64–66). This very broad range reflects the wide variation in the populations, study designs, endpoints and follow-up periods examined as well as measurement methods used. It has been estimated that 30%–70% of serious ADEs leading to hospitalisation are deemed predictable and therefore potentially preventable (64, 67–71).

Access to reliable information on the safety of medicines is key in the context of shared decision-making in patient-prescriber encounters. Both the General Pharmaceutical Council (72) and the UK General Medical Council (73) emphasise the importance of effective and safe prescribing. Hence, providing HCPs and patients with real-world data on drug safety is vital to facilitate evidence-based and informed decision-making. This is crucial in particular in ageing populations such as in the UK with a steady rise in multimorbidity and polypharmacy, which are more prone to serious ADEs and their associated adverse consequences (74–77).

Serious ADEs are more frequently linked to medications with a high-risk profile. This is particularly evident in critical therapies employed for prolonged periods in the management of significant diseases. Such vital treatments often pose additional challenges, as their associated toxicities contribute to suboptimal adherence and/or potential discontinuation. This, in turn, jeopardises treatment efficacy, resulting in a substantial increase in mortality rates. An illustrative key example is the extended use of endocrine therapy in the context of breast cancer (BC), spanning 10-15 years. The toxicities associated with this therapy are a significant factor in suboptimal treatment adherence, high recurrence and low

survival rates. Despite advancements in breast cancer treatment leading to a decline in mortality rates, BC remains the most common cause of cancer-related death in women, primarily due to recurrence and metastasis (78, 79). Previous research demonstrated that fewer than 50% of women successfully complete the 5-year endocrine therapy course, contributing significantly to a 20% rise in BC mortality (80–82).

In the context of medication safety, it is important to acknowledge that there often exist multiple similar medication options for a given indication and the limited availability of tools to objectively compare their safety profiles. Thus, the significance of safety tools for predicting the relative safety of medications within a therapeutic class cannot be overstated.

1.3 Primary care plays a key role in identifying and potentially preventing adverse drug effects

Most patient safety research has been conducted in hospital settings (83, 84), in which substantial progress has been achieved. However, most patient care is managed and coordinated in primary care, where most medicines are prescribed (85). Further, ADEs are very common in this less controlled environment with an estimated incidence ranging from 6% to 80% (86). Primary care settings are however still perceived as less risky compared to specialist care settings (87, 88). This is mainly due to the failure to differentiate between absolute and relative risks (89). Of note, approximately one-fifth of ADEs in primary care settings are considered preventable (90). Hence, primary care plays a gatekeeper role in identifying, monitoring and potentially preventing such ADEs.

1.4 Use of inherited genomic information has the potential to reduce adverse drug effects

In contrast to the homogeneous patient populations studied in clinical trials, individual patients in routine clinical practice respond to medications variably. While some individuals may not respond to treatment at typical doses, others may experience ADEs (Figure 1.2). Biologically plausible mechanisms by which ADEs are elicited are not yet fully explained. Inherited genetic variation can play a key role in susceptibility to ADEs, primarily via the changes in the pharmacodynamics or pharmacokinetics of medicines (91). Evidence from experimental studies and clinical trials indicates that particular genomic variants may predispose some to

the development of certain ADEs which can potentially be avoided through individualisation of drug therapies based on genetic information (92). Preemptive genetic testing has the potential to shift unpredictable ADEs, even those mechanistically undefined, to predictable ADEs therefore decreasing their incidence and severity (92–95). This is known as pharmacogenetics or pharmacogenomics (PGx).

The publicly available Pharmacogenomics Knowledge Base (PharmGKB), which is a worldwide resource of pharmacogenomic (PG) biomarkers, provides a descriptive summary of PGx associations to which a rating based on "Strength of Evidence" is assigned (96, 97). Yet, PharmGKB is not updated at regular intervals and does not cover the literature in its totality and there is more literature that supports or contradicts a PG association that is not included in PharmGKB (98). As essential as it is to report instances with positive outcomes, it is equally important to report and evaluate studies that document either negative or null findings. The non-appearance of unpublished studies in PharmGKB has the potential to overestimate the PG effects and can be a source of bias.

Hence, in the pursuit of investigating previously documented associations between genomic variants and ADEs, it is imperative to conduct a thorough and systematic review of the existing evidence of PGx pertaining to ADEs linked to the specific treatment modality under consideration. This rigorous review is essential for compiling a comprehensive list of variants that demonstrate significant associations with ADEs related to those medications. Additionally, synthesising evidence in a systematic and reproducible manner has the potential to provide the quality of evidence needed to improve evidence regarding PG testing of ADEs. Well-conducted systematic reviews in the context of clinical decision-making have become progressively the gold standard for evidence-based practice in medicine (99–101). By occupying the top in the hierarchy of evidence in health care research (Level 1a), systematic reviews of RCTs are likely to provide high-quality research and the strongest evidence (102–104). Further, combining multiple studies reliably via meta-analyses can minimise the probability of both false-positive and false-negative findings and increase the precision and power of estimates of PG effects (105).

Despite the increasing recognition of the potential value of widespread paradigm-shifting personal genomics in mitigating ADEs, its implementation in clinical

practice is progressing at a markedly slow pace (106). To date, only a very few germline variants have been introduced into prescribing decision-making in this context. Two notable examples are severe hypersensitivity caused by the anti-HIV/AIDS medication, Abacavir (94) and the anticonvulsant medication, Carbamazepine (95). The impact of PGx on inter-individual variability in response to pharmacotherapy is often overlooked by HCPs in prescribing, in which this variability is often addressed by adjusting the dose or using a trial-and-error approach, leading to rises in empiricism in pharmacotherapy selection (Figure 1.3).

In addition to the concerns raised about the methodological quality of PGx studies (107), false-positive results are very common and therefore the majority of associations require multiple steps of replication. The lack of clarity regarding the generalisability of the results and the contradictory findings of PGx studies of ADEs underscores the need for a comprehensive assessment of the pertinent evidence and replication of previously described associations at scale.

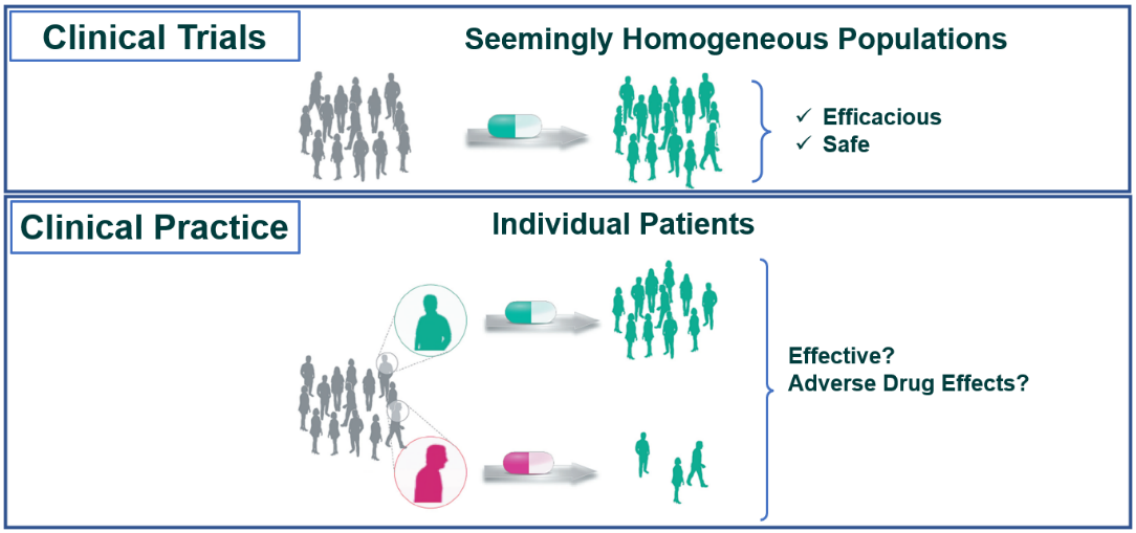


Figure 1.2 Inter-individual variability in response to pharmacotherapy in clinical practice.

This schematic diagram shows that in contrast to clinical trials, individual patients respond to medications variably in routine clinical practice. While some individuals may not respond to treatment at typical doses, others may experience ADEs.

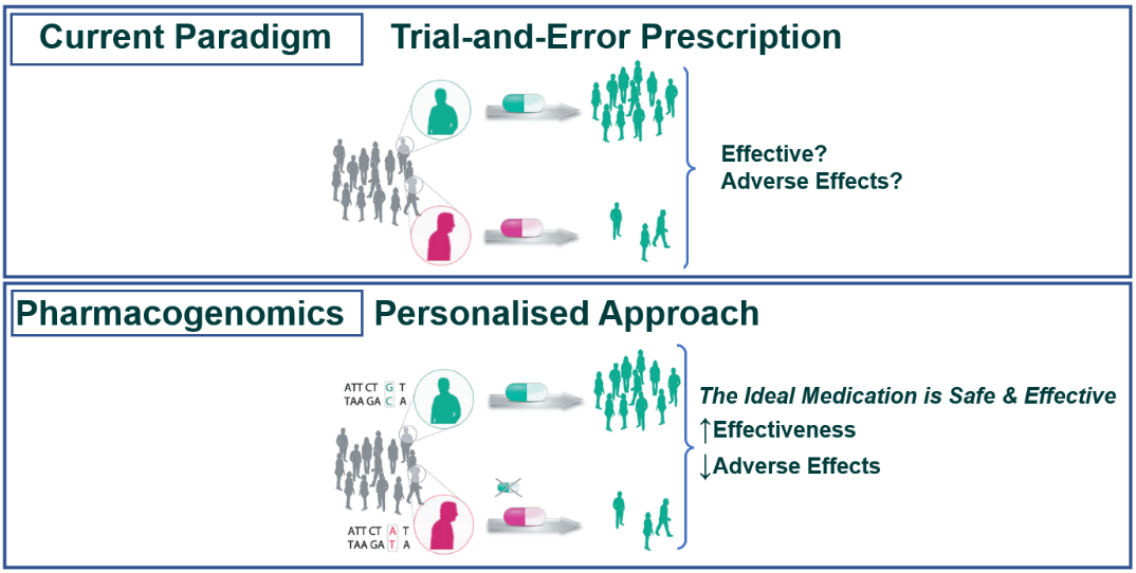


Figure 1.3 The current paradigm and PGx-based strategies to address the inter-individual variability in response to pharmacotherapy.

This schematic diagram illustrates the current trial-and-error approach in prescribing and the potential role of PGx in personalised medicine.

1.5 Reproducibility crisis of research findings in genetic studies

There has been more attention to initial discoveries of genetic association rather than reproducible research, on which scientific progress should be predicated (108). In addition to helping separate true positives from false positives and minimise the overabundance of false-positive signals, findings from replication studies are invaluable for researchers who may consider extending their analyses or attempting to conduct a follow-up replication study. It is evident that replicating genotype–phenotype associations in human genetics, particularly across different populations, is a challenge (108, 109). The overwhelming majority of previously reported human genetic associations including PGx have not been successfully replicated in independent samples at large scale (109–113). Most genetic associations do not stand the test of time (114, 115) and their effect estimates drop as follow-up replication studies are attempted (i.e. winner's curse) (116).

Published reports usually had an overall larger effect size compared to grey literature and the adverse impact of publication bias can be detrimental and misleading, particularly where there is no real effect (117, 118). This is of considerable importance, especially in safety outcome measures, for which reporting outcome bias is widespread and significant (119). Causes of spurious genetic associations include but are not limited to, small sample size, poor study

designs, imbalance between cases and controls, data dredging or “fishing”, reporting bias and failure to apply rigorous statistical significance thresholds (120). There are also a plethora of potential reasons for non-reproducibility. For example, replication has been more successful within populations than across populations due to environmental variation, genetic heterogeneity, population stratification or differences in allele frequencies among patients’ samples (115).

The identified negative findings of genetic research in the literature are only the tip of the iceberg as not all studies conducted have been written up and subsequently submitted for publication (121). Investigators’ reluctance to acknowledge non-significant findings and unwillingness to provide or share their negative findings is very common. Clearly, negative results usually complicate the authors’ interpretation and render drawing decisive conclusions in the context of previous positive results challenging (122). Refuting established or previously reported associations in the literature presents a challenge. In addition to a general enthusiasm for publishing positive reports, financial incentives for securing significant findings exist and may enhance this practice. The pharmaceutical industry may also encourage some researchers to exaggerate conclusions, particularly for pharmaceutically funded clinical trials or select a subset of the original outcome variables analysed and report the significant associations. This is very noticeable when the final publications are being compared to their original protocols (123, 124). While they are not exclusively responsible for publication bias, editorial policy and reviewers are always conscious of limited space in their journals and potentially thinking that negative results may distort the medical literature and are therefore not worthy of publication. Statistically significant findings are on average four times more likely to be accepted for publication and cited than reports of non-significant or null results (118, 125). This encourages some researchers to search for statistical significance by pursuing different tests or conducting analyses of several subgroups or endpoints without correction for multiple testing to prevent false positive results (126). Reporting outcome bias can arise due to the selective within-study reporting of outcome measures despite measuring a wider array of outcome variables or omitting key outcome measurements that are routinely collected and recorded based on the direction and nature of the results (127, 128).

1.6 Biobanks provide an unprecedented opportunity for pharmacogenomics research

Recent advances and fast progress of developments of genomic technologies as well as the rapid increase in both computational techniques and bioinformatics resources allowed for genotyping and analysing massively high-throughput data at low cost (129, 130). This provided opportunities to enhance our understanding of the underlying variations underpinning the risk of some complex diseases (131–133). The availability of bio-banking with both genetic and real-time clinical data has also progressed at a rapid pace in both scale as well as resolution. This enabled studying thousands of traits as well as both rare and common phenotypes simultaneously (133). Examples of large biobanks with genome-wide and phenome-wide combinatorial data include; The Electronic Medical Records and Genomics (eMERGE) Network which comprises nine geographically distinct groups (134), the UK Biobank (UKBB) which recruited around 500,000 people (135, 136) and deCODE Genetics (137).

With its large sample size and linking genetics to clinical data, the UKBB provides a unique opportunity to examine the risk of ADEs conferred by genetic variants at scale. This is expected to improve preventative and surveillance measures and potentially pave the way for a new era of “precision personalised medicine” (138, 139). Studies using data from the UKBB have already demonstrated its capacity to further our understanding and provide valuable insights into the field of PGx (139). Due to the restricted research funds and the existence of various guidelines established by various PGx working groups for many medicines, prioritising PGx analyses in such biobanks is essential.

1.7 Aim

To assess the current state of the art in PGx of ADEs in the literature and analyse whether previously described associations between variants and MIADEs replicate in the UKBB.

1.8 Objectives

I. To create a comprehensive list of variants associated with ADEs and further curate a set of those significantly associated with medically important ADEs (MIADEs).

II. To test previously reported associations between variants and MIADEs related to high-risk medicines in GP in the UKBB.

III. To systematically review and critically describe the current evidence of PGx of ADEs related to endocrine therapy in breast cancer (BC).

IV. To construct a list of variants significantly associated with MIADEs related to endocrine therapy in BC.

V. To examine associations between previously reported variants and MIADEs related to endocrine therapy in BC, in the UKBB.

VI. To create comparative safety visual tools for medications within the therapeutic class to support evidence-based decision-making around formulary choices.

2 Chapter Two. A Comprehensive Assembly of Genomic Variants Associated with Adverse Drug Effects: A Systematic Review and Pharmacogenomic Meta-analysis

2.1 Abstract

Background/Aim There is increasing evidence that ADEs can be predicted and potentially prevented through pretreatment PG testing. Previous systematic reviews investigated single drugs and a single genetic variation or gene and focused on a specific type of ADE or toxicity. A full list of variants associated with a risk of ADEs has however not been collated. I aimed to create a comprehensive list of variants associated with ADEs and further generate a set of variant–drug pairs significantly associated with MIADEs.

Materials and methods Two separate bibliographic searches of the literature were conducted to identify all PGx studies of RCTs, *post-hoc* analyses of RCTs, and meta-analyses. MEDLINE, Embase, Cochrane Library/Cochrane Register of Controlled Trials and Google Scholar databases were searched from inception to 27th May 2020. The list of variants associated with ADEs was further curated to generate a set of variant–drug pairs significantly associated with MIADEs with fully specified and interrogable genotypes and the International Classification of Disease (ICD-10) codes for indications of the related medicine(s).

Results A total of 254 RCTs and *post-hoc* analyses of RCTs, and 207 meta-analyses were included in the list of variants associated with ADEs. Chemotherapy-based regimens were the most common therapeutic modalities examined in the identified studies. A set of variant–drug pairs significantly associated with MIADEs with fully specified genotypes and ICD-10 codes was also synthesised.

Conclusions This is the first study that created a comprehensive list of variants associated with ADEs and generated a set of variant–drug pairs significantly associated with MIADEs with fully interrogable genotypes and ICD-10 codes. As this analysis yielded a large and broad array of articles with significant heterogeneity and mixed findings, further replication is essential.

2.2 Introduction

Evidence from experimental and clinical studies indicates that certain genomic variants may predispose some to the development of certain ADEs (92). Yet, a comprehensive and up-to-date list of PG variants associated with ADEs does not exist. While PharmGKB is a worldwide resource of PG biomarkers, it is not updated at regular intervals and does not cover the literature in its totality. There is more literature that supports or contradicts a PG association that is not included in PharmGKB (98). Besides, there have been concerns about the methodological quality and false positives in PGx studies (107). Thus, to provide robust evidence in the context of PGx of ADEs, it is vital to synthesise the current body of literature in a systematic and reproducible manner.

Well-conducted systematic reviews in the context of clinical decision-making have become progressively the gold standard for evidence-based practice in medicine (99–101). By occupying the top of the hierarchy pyramid of evidence (Level 1a) (140), systematic reviews of RCTs are likely to provide high-quality research and the strongest evidence (102–104). RCTs are inherently of higher quality with a lower likelihood for many biases compared to non-randomised studies, in which the PG effects are usually overestimated. Compared to other study designs, RCTs are better characterised and usually registered in advance with protocols in which the clinical endpoints are typically pre-defined. In addition to consideration of the favourable outcomes, almost all well-conducted RCTs are expected to consider and provide a detailed summary of the safety profile(s) of the intervention(s). Besides, patients' adherence to treatment is usually monitored throughout the study and ADEs are systematically collected and accurately graded (141). This makes it substantially more accurate to attribute observed ADEs to the therapy used in RCTs and ultimately helps minimise the risk of confounding factors, publication bias and selective reporting (142, 143). Further, combining multiple studies reliably via meta-analyses can minimise the probability of both false-positive and false-negative findings and increase the precision of the estimates of PG effects (105).

In certain situations, RCTs are not suitable or feasible to be performed due to ethical reasons (144, 145) and therefore other types of study designs can facilitate decision-making (146, 147). Additionally, many ADEs might not have been previously identified or pre-determined when the RCTs were designed.

Besides, the paucity of well-designed RCTs in the context of PGx of ADEs is particularly evident (148). Hence, both RCTs and *post-hoc* analyses of RCTs (i.e., PG associations which were performed in a retrospective manner) as well as meta-analyses were included in this analysis. This helps enrich the list of variants by encompassing both primary and secondary literature (149). As MIADEs are associated with significant mortality and morbidity, I aimed to further curate the list of variants associated with ADEs to generate a set of variant–drug pairs significantly associated with MIADEs.

2.3 Aims

I. To collate a list of variants associated with ADEs
II. To generate a set of variant–drug pairs significantly associated with MIADEs.

2.4 Objectives

I. To perform systematic reviews of the literature to identify RCTs, *post-hoc* analyses of RCTs and meta-analysis studies.
II. When appropriate, conduct meta-analyses of the identified RCTs and *post-hoc* analyses of RCTs.

2.5 Materials and Methods

2.5.1 Data sources and search strategy

To ensure there were no previous or ongoing systematic reviews addressing the same research question, I conducted scoping searches in various databases using general search terms. This included the Database of Abstracts of Reviews of Effects (DARE) which comprises critical appraisals of systematic reviews with regard to health interventions (150), the Cochrane Database of Systematic Reviews (CDSR) which includes regularly updated systematic reviews with respect to the effects of interventions in healthcare contexts conducted by the Cochrane Collaboration (151), and Database of Promoting Health Effectiveness Reviews (DoPHER) (152). Since most guidelines rely on systematic review evidence, I also searched the National Institute for Health and Clinical Excellence (NICE) (153) and the Scottish Intercollegiate Guidelines Network (SIGN) (154).

This systematic review was guided by a peer-reviewed protocol and followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)

statement (155). To identify variants conferring the risk of ADEs, I conducted bibliographic computerised searches using several different databases that catalogue published literature, namely MEDLINE and Embase via the Ovid interface and Cochrane CENTRAL/Cochrane Register of Controlled Trials databases. Searching more than two bibliographic databases as per the AMSTAR guidelines (156). This search was also supplemented with comprehensive searches in the non-traditional and more encompassing platform, namely the Google Scholar database. The searches in Google Scholar were carried out without any language or date restrictions via its “Advanced Search Portal” by applying highly articulated modes of execution and operation such as Boolean operators and scope qualifiers (Table 2.14 [Appendix]). This is expected to retrieve reports published in journals not indexed in the above-mentioned electronic databases.

In addition to the peer-reviewed articles in journals that are indexed in the above bibliographic databases, I attempted to include grey literature and unpublished studies to minimise the effect of publication bias (157, 158). This was achieved by searching for pertinent theses, dissertations, conference abstracts or reports from independent investigations (159). Besides, additional sources such as study registries and other grey literature sources were sought (160).

To retrieve RCTs and meta-analyses of PGx of ADEs, I devised search filters specific to each electronic database. To identify RCTs, I tested the reliability and performance of several pre-designed search filters as well as search filters which I customised for identifying relevant records in Embase and MEDLINE databases (see Table 2.6 [Appendix] for examples). Having treated the search filters as "diagnostic tests" for a segment of the literature represented by sentinel articles, I improved the search filter by determining the retrieval and the fractions of the records that failed to be detected by the different search filters. I ultimately used the sensitivity and precision maximising version of the Cochrane Highly Sensitive Search Strategy for identifying randomised trials suited for Ovid format (161). Having been validated and evaluated for their precision and sensitivity, these search filters are highly sensitive to retrieve relevant records without leading to low precision (162). To identify articles related to PGx of ADEs, I specified the corpus of key search terms and relevant constructs using a pool of pertinent

scholarly articles as well as the subheadings utilised to identify data on ADEs (163).

The search filters were constructed using automatic term explosion and mapping' features (164) using a combination of free text keywords, singular and plural, controlled vocabulary and delineated subject indexing related to the selected databases (e.g., Emtree and MeSH terms: Medical Subject Headings). To appropriately broaden or narrow the search results, spelling variations and synonyms of search terms as well as wildcards and truncations were used in the search string when applicable. The two clauses of these search terms were combined using Boolean operators including (AND, OR and NOT) among domains and within one domain (165, 166).

To reduce the risk of missing relevant articles and to ensure that adequate saturation had been achieved, the search was supplemented with retrospective reference harvesting by manual searching for any eligible studies among the references of highly salient studies and landmark chapters, as recommended (167–169). To ensure the inclusion of all extant evidence, the methodology used in individual studies was investigated in the full-text papers and by interrogating the original trial registers to enquire about studies that used initials, acronyms or unique identification codes in the ''title'' or ''abstract'' (see Table 2.7 [Appendix]). When appropriate, the original investigators were also contacted to obtain missing information, seek clarification to determine the eligibility of a study for inclusion and identify any subsequent unpublished papers.

In brief, I conducted two separate systematic reviews of the literature to identify variants conferring ADEs or toxicities from RCTs and *post-hoc* analyses of RCTs as well as meta-analysis articles. Studies were sought from MEDLINE (from 1946 to 27th May 2020), EMBASE (from 1974 to 27th May 2020), Cochrane Library/Cochrane Register of Controlled Trials databases (CENTRAL), and Google Scholar without date restrictions. The database-specific search strategies are shown in (Table 2.8 & Table 2.9 & Table 2.10 & Table 2.11 & Table 2.12 & Table 2.13 [Appendix]).

2.5.2 Eligibility criteria

2.5.2.1 The list of variants associated with ADEs

To create a list of variants associated with ADEs, eligibility criteria were defined *a priori* and using the PICO framework (Population, Intervention, Comparison, Outcome) (170, 171) (Table 2.1), which is endorsed by the Cochrane Collaboration (172). To be included in this review, articles must have met the inclusion criteria and none of the exclusion criteria (Table 2.2). Due to the significant difference in randomisation designs between the majority of RCTs and *post-hoc* analyses of RCT studies compared to prospective genotype-guided treatment trials and pretreatment PGx screening studies, the latter were excluded.

Table 2.1 The PICO four key components in this study

Population	Patients or participants of any age, gender, ethnicity, stage of disease, comorbidity
Intervention	Pharmacological interventions at any dose, frequency, timing, route of delivery or in any treatment settings
Comparison	Comparison to the intervention can be either placebo or active comparator
Outcome	Incidence of at least one toxicity outcome of any grade or type whether acute, chronic or late-onset, as either a primary or secondary outcome

Table 2.2 Eligibility criteria for inclusion in the systematic review

Inclusion Criteria	Exclusion Criteria
English-language publications	Non-human studies
Articles in journals, theses, dissertations	Editorial articles, case reports, study protocols, ongoing studies
Single or multi-centre RCTs of any design, length, follow-up period, setting	No access to full text, meeting abstracts, conference proceedings
post-hoc analyses of RCTs	Non-randomised trials, single-arm trials, case-control, cohort studies (unless nested in RCTs)
Meta-analyses	RCTs with concerns over the integrity of the trial design or the randomisation process
Any germline genomic variants	Systematic or narrative reviews without meta-analysis
Studies in which carriers of specific genotype(s) were only eligible or ineligible for enrolment	GWAS/Meta-analyses of GWAS
Metaboliser status, phenotypes or activity scores defined based on genotypes	Gene expression, pathogenic variants, somatic variants, bacterial or viral genome variants
Any length of intervention or follow-up	Metaboliser status or phenotypes determined by biochemical assays
Comparison to the intervention can be either placebo or active comparator	Treatment algorithms (studies examined the combined genetic with clinical moderator)
Toxicity outcome of any grade	Genotype-guided treatment or pretreatment PG screening studies
Toxicity-related death or discontinuation of therapy	Irrelevant investigations (e.g., recreational drugs)

Composite outcomes provided included at least one ADE as a clinical endpoint	Studies of radiation-induced toxicities or toxicity to organophosphate insecticides
	Radio-chemotherapy or chemo-radiation with radiotherapy not applied on both treatment arms analysed
	Drug-drug interactions
	Surrogate measurements or biomarker levels for toxicities as an endpoint using in vitro assays
	Pharmacokinetics/ pharmacodynamics studies
	Adverse events or mortality due to reduced response to treatment
	Studies of response, disease progression, prognosis, recurrence, survival, treatment resistance, treatment failure, disease-related death, all-cause mortality
	Adverse outcomes such as addiction or physical/psychological dependence
	Acute/chronic transplant rejection due to reduced efficacy
	Economic evaluation studies

2.5.2.2 The set of variants–drug pairs significantly associated with MIADEs

The list of variants associated with ADEs was further curated to generate a set of variant–drug pairs significantly associated with MIADEs. To achieve this, variants related to cancer chemotherapy were excluded, unless they overlapped with indications related to other therapeutic classes (e.g., Methotrexate). Criteria for the definition of MIADEs were customised to address my research questions.

MIADEs are defined as events contributed to seriousness and/or severity based on the investigators' statements, events considered serious as per WHO and CIOMS criteria (1, 57) or severe as graded by CTCAE (63), DMEs as per the EMA (60, 61) and IMEs as per EV-EWG based on the official ICH definition of seriousness (58, 62). Composite toxicity outcomes were included provided that at least one of the incorporated toxicity endpoints fulfilled the inclusion criteria for MIADEs. Undefined discontinuation of treatment and underspecified toxicity outcomes such as (e.g., overall toxicity or Grade (1-4) or Grade (≥2) or moderate/severe) were excluded. For ambiguous toxicity outcomes, clinical judgment was exercised.

The generated set of variant–drug pairs significantly associated with MIADEs were subsequently curated for possible future use by interpreting the haplotypes and star alleles into more specified and interrogable genotypes using allele nomenclature for Cytochrome P450 (173–175), nomenclature of HLA alleles (176), UGT1A and UGT2B haplotypes and SNVs (177). When available, I

reported rs IDs using dbSNP. To facilitate the potential use of these variant-drug pairs in future analyses in biobanks, I identified the related ICD-10 codes (178, 179) for the indications of the related medicine(s) (i.e., conditions for which the culprit medication(s) are indicated). Diagnoses and phenotypes are usually coded in the clinically relevant electronic healthcare records data in most biobanks using ICD-10 codes.

2.5.3 Study selection

The search results from different databases were extracted from Ovid and Cochrane platforms, listed, organised, exported to the Reference Manager namely Mendeley and subsequently merged (180). Duplicated citations were then removed manually rather than using the built-in auto-function identification of duplicates. Manual hand screening to remove duplicates effectively in reference management software is recommended (181).

Following the Cochrane guidance and best practice guidelines for systematic reviews (182), two reviewers (KM, LJ) working independently have performed title and abstract screening, and literature retrieval, assessed full-texts of all relevant studies and selected eligible articles by applying the pre-specified inclusion criteria. In line with the guidelines for Peer Review of Electronic Search Strategies (PRESS) for systematic reviews (183), disagreements and discrepancies identified between the two reviewers at stages of screening of abstracts/titles and full-text analysis were addressed jointly and resolved by discussion and/or consulting with the original study's author when necessary to achieve consensus.

After screening both titles and abstracts, irrelevant items were removed. To be over-inclusive at this point, articles deemed irrelevant were re-interrogated and further screened for any omitted eligible record by cross-checking for names of genes from sentinel reviews and Very Important Pharmacogenes (VIP) associated with toxicity (184) as well as using keywords that potentially confer toxicity or side effects (Table 2.15 [Appendix]).

The full texts of all relevant studies that merit subsequent scrutiny were then retrieved and further assessed by applying the pre-specified inclusion and exclusion criteria consistently. Decisions on which studies to include were made via general consensus and tangentially relevant records were excluded.

2.5.4 Data extraction

The key characteristics of the included studies were catalogued by extracting the relevant study-specific data into a spreadsheet for further analyses using Microsoft Office Professional Plus Excel® 2016 (185). To simplify the tables, the following data variables from the included studies were extracted and presented: treatment modality or therapeutic class, interventions(s) or culprit drug(s), toxicity outcomes, genomic variant(s) and reference (containing study's authors and year of publication). For meta-analysis, quantitative data was subsequently collected from eligible studies. The relevant drugs identified were classified using the classification in the British National Formulary (BNF) (47). The variants associated with ADEs were annotated using the following font colour; Black colour to denote a significantly increased risk of ADEs, green colour represents a significantly reduced risk of ADEs, and red colour denotes a non-significant association with ADEs.

2.5.5 Quality assessment

The methodological quality of the studies was systematically evaluated in terms of the PICO framework and the application of strict inclusion criteria. This review included RCTs and meta-analyses from systematic reviews and therefore high methodological quality of such study designs is expected. Besides, due to the paucity of RCT designs in PGx of ADEs (particularly large, well-designed and conducted trials), I included such study designs provided they passed my pre-specified criteria.

2.5.6 Quantitative data synthesis and statistical analysis

Quantitative data was extracted from studies eligible for quantitative synthesis and pooled where possible via a meta-analytical statistical approach. A meta-analysis was performed provided that there were at least studies that do not differ substantially in terms of comparator, design, outcome measures, method and timing of ADE outcome measurements or ascertainment were considered for exclusion. To minimise heterogeneity in the meta-analyses and avoid performing multiple separate statistical tests (126, 186), both clinical (i.e., clinically meaningful interpretation) and statistical aspects (i.e., sharing a common metric) were taken into consideration to decide the appropriateness of

conducting a meta-analysis. Only studies investigated the same variant and treatment and similar measures of conceptually-related toxicity outcomes were combined. Studies that combined different or tangentially related outcomes altogether or created a composite measure of substantively dissimilar toxicity endpoints were also considered inappropriate for a meta-analysis, as drawing a general conclusion from such meta-analyses can be misleading.

In case multiple studies used the same cohort, I included only the study with the largest analysis and/or longest follow-up period to eliminate over-representation of that particular patient data in the meta-analysis. For studies that provided individual patient data, I computed effect sizes for relevant outcomes using standard calculation procedures and converted them into a uniform metric before performing meta-analyses. Such individual patient data permitted pooling results from studies reporting different genetic models by re-computing the pertinent index of the PG effect. Studies without a common effect size metric but that used fundamentally different effect measures (continuous vs. dichotomous data) were not quantitatively synthesised. Correlations of change-from-baseline measures in longitudinal studies were not combined with correlations at a particular point in time in cross-sectional studies. If multiple dissimilar effect size indices were reported within one outcome analysis (e.g., risk ratios or odds ratios), I re-calculated or transformed all indices to the most common reported metric. I combined similar indices such as risk ratios and odds ratios as they are almost equivalent, provided that the toxicity outcome of interest was not common. For studies that expressed the association by reporting fundamentally different indices (e.g., odd ratio, hazard ratio), I considered synthesising these studies separately to avoid confusion; This was accomplished by performing a meta-analysis for studies that reported ORs and a meta-analysis for those reported a HR separately, followed by a qualitative assessment for these subgroups.

To visualise the overall pattern of the meta-analyses, forest plots were created and pooled estimates with their 95% confidence intervals were reported, consistent with best practice for reporting meta-analyses (187). To evaluate publication bias, I used funnel plots, which represent the effects estimated from individual studies against standard errors, a measure of study size. I used the *metabias* function in R software to test the regression for funnel-plot asymmetry

(i.e. there is no linear association between the effect estimate against its standard error) as recommended (188). Yet, funnel plots are only recommended to be performed when there were multiple studies in the meta-analysis (172). Thus, when the number of combined studies in a meta-analysis was <10, funnel plots and asymmetry tests were not used. This is because the power of the tests for funnel plot asymmetry would be too low to differentiate between real or chance asymmetry when few studies exist.

Due to the wide diversity of characteristics of studies that met my broad criteria for eligibility, significant heterogeneity was expected and thus the random-effects method was used to obtain more conservative estimates of statistical significance (189). It should be noted that when R software was used, both random-effects and fixed-effects statistical modes were reported by default. Having extracted and calculated the effect sizes for all relevant AE outcomes, pairwise random effects meta-analyses were performed (190) and data were pooled for outcome comparisons. The Mantel-Haenszel method and restricted maximum-likelihood estimator for tau^2 were used as a meta-analytical method. To measure the amount of variation in the reported effect sizes among the eligible studies in the meta-analysis, heterogeneity among the PG effects was tested and both I^2 and *p*-value for the *Q*-statistic were reported (186, 191).

To provide valid conclusions and minimise the likelihood that the meta-analyses are subject to multiplicity issues and their ramifications (126, 192, 193), the *p*-values were adjusted for multiple hypothesis testing by applying Bonferroni correction as follows: the new alpha level (Bonferroni corrected *p*-value)= α/k where k stands for number of independent tests or comparisons performed and α represents the predetermined nominal level (usually 0.05) (194)(195).

Analyses were performed and forest plots were created using Stata 16.0 (StataCorp, College Station, TX) and the 'meta' package in software R (v 4.1.1). Both I^2 and *p*-value for the *Q*-statistic were reported in the forest plots.

2.6 Results

2.6.1 I identified 254 RCTs and *post-hoc* analyses of RCTs and 207 meta-analyses of variants associated with ADEs

The original search yielded 33,459 and 15,737 records which are potentially RCTs and meta-analyses, respectively. In the final synthesis, 254 RCTs or *post-hoc* analyses of RCTs, and 207 meta-analyses were eventually included (Figure 2.1 & Figure 2.2). Of these, there were 93 (37%) and 52 (25%) studies that did not report any significant associations, respectively. The full lists of variants associated with ADEs and the studies included in this systematic review are shown in (Table 2.4 & Table 2.5).

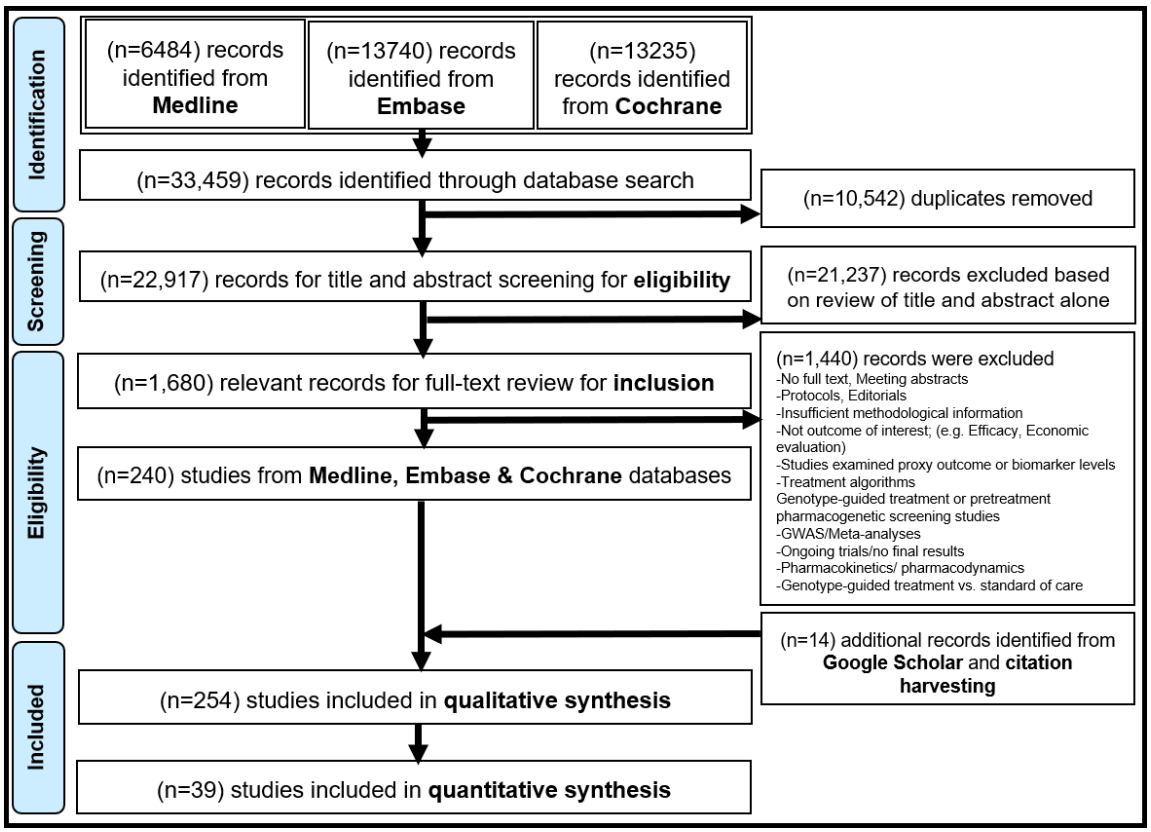


Figure 2.1 PRISMA flow chart of systematic literature search and selection process of RCTs and post-hoc studies of RCTs.

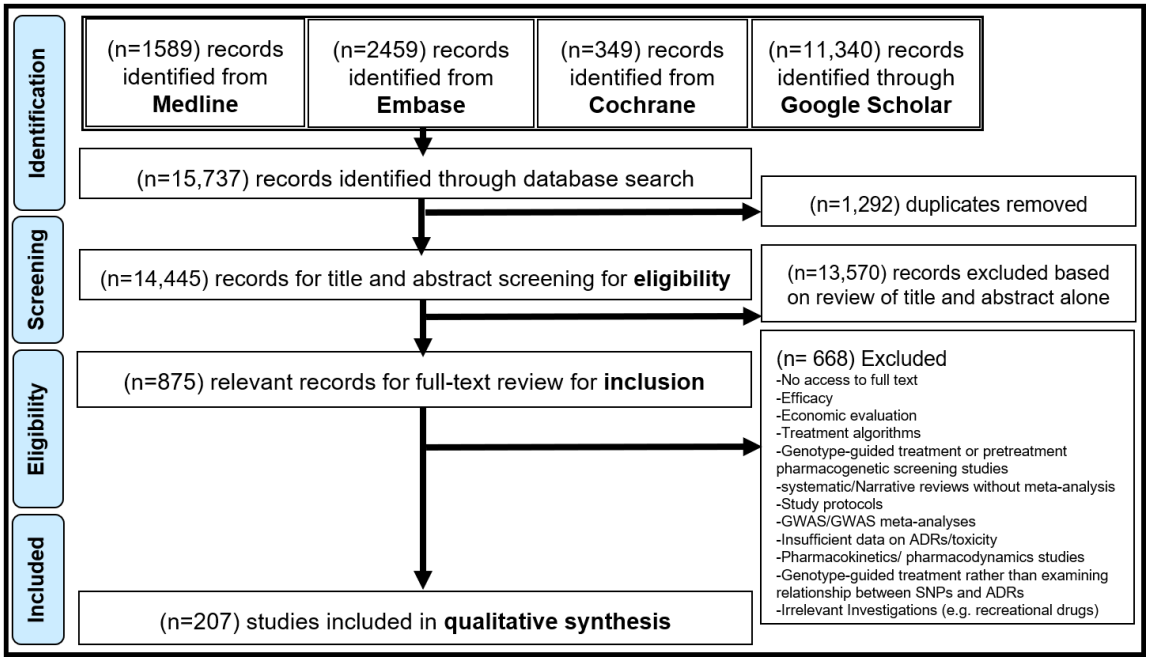


Figure 2.2 PRISMA flow chart of systematic literature search and selection process of meta-analyses studies.

2.6.2 Antineoplastic regimens were the most commonly investigated therapeutic modalities in the included studies

Chemotherapy-based cytotoxic regimens were the most common therapeutic modalities examined in PGx reports included in this systematic review. Antiplatelet drugs (mainly Clopidogrel), antipsychotic drugs and rheumatic disease suppressant drugs (primarily Methotrexate) were the second most frequent therapeutic classes investigated by authors of the included studies (Figure 2.3).

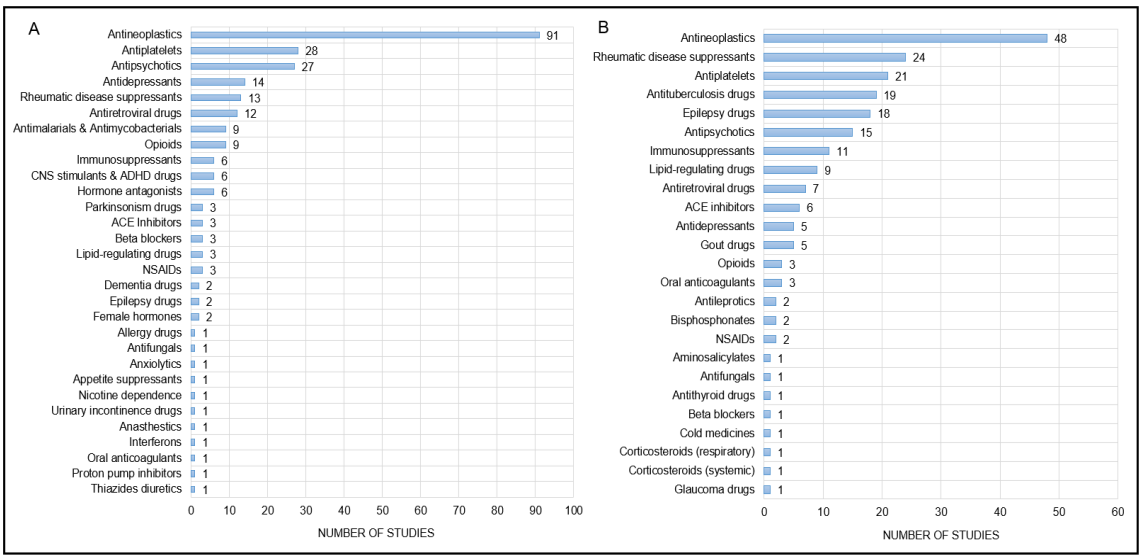


Figure 2.3 The therapeutic classes investigated in studies included in this systematic review.

(A) RCTs & post-hoc analyses of RCTs studies (B) Meta-Analyses studies. This bar chart shows that chemotherapy-based cytotoxic regimens are the most commonly examined therapeutic modalities in PGx reports included in this systematic review. Antiplatelet drugs were the second, antipsychotic drugs were the third most frequently therapeutic classes investigated whilst in meta-analyses rheumatic disease suppressant drugs were the second with antiplatelets ranking third.

2.6.3 Only one of the meta-analyses of RCTs performed was statistically significant

Of the RCTs and *post-hoc* analyses of RCTs identified, I performed 24 meta-analyses including a total of 39 studies. Each meta-analysis included a range of two to fourteen studies. This comprised associations between *CYP2C19* genotypes or metaboliser status with bleeding risk in Clopidogrel treated patients in eighteen studies (196, 197, 206–213, 198–205), *MTHFR* 677 C>T and the risk of hepatotoxicity and gastrointestinal toxicities in patients treated with methotrexate in five studies (214–218), *SLCO1B1* −521 T>C (rs4149056) and myopathy in patients taking statins in three studies (219–221), *CYP2B6* 516 G>T and CNS ADEs in patients taking efavirenz in two studies (222, 223), *G6PD* A− and severe anaemia in patients taking artemisinin-based combination therapy or Chlorproguanil-Dapsone-Artesunate (CDA) for malaria in seven studies (224–230). Also, HLA-DRB1*01, *MDR1* 3435 C>T, *MDR1* 2677 G>T*, CYP2B6* 516 G>T, *CYP2B6* 1459 C>T with the risk of hepatotoxicity in patients taking nevirapine were metanalysed in three studies (231–233).

The association between *G6PD* A− and severe anaemia in patients taking CDA or artemisinin-based combination therapy for malaria was the only meta-analysis with a statistically significant summary effect size OR [95% CIs]= 15 [10.27, 21.9], $p<0.0001$ (Figure 2.4). None of the pooled effect sizes in the remaining meta-analyses was significant after correction for multiple testing (corrected p-value =0.05/24=0.002). Results of all meta-analyses performed in this study are available in (Table 2.16 [Appendix]). I provided examples of the forest and funnel plots for the association of *CYP2C19* LOF polymorphisms and bleeding risk in clopidogrel-treated patients in (Figure 2.6 & Figure 2.7 [Appendix]).

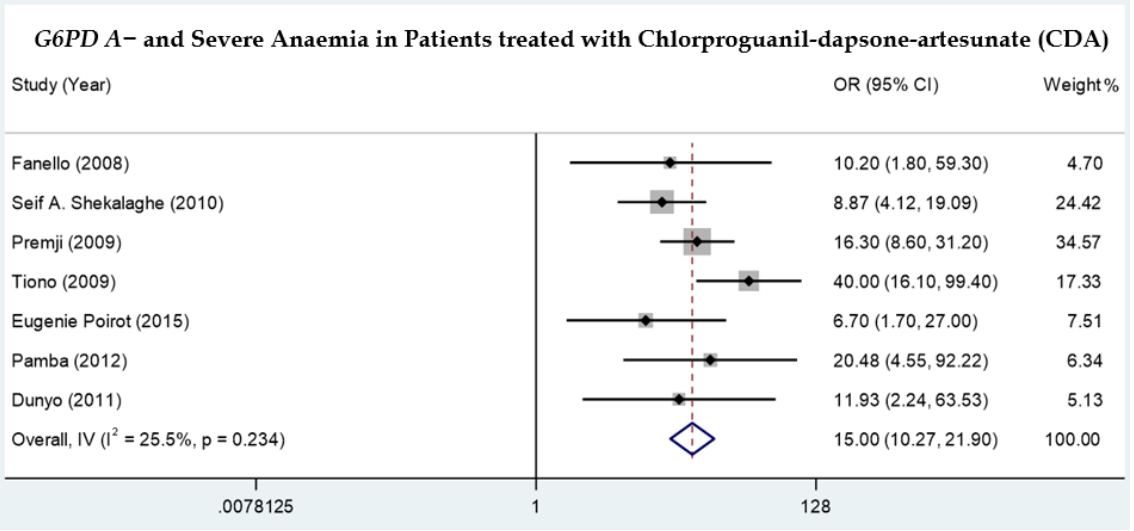


Figure 2.4 Meta-analysis of G6PD A− and severe anaemia in patients taking CDA or artemisinin-based combination therapy for malaria.

Meta-analysis of seven studies examined G6PD A− and severe anaemia in patients taking CDA or artemisinin-based combination therapy for malaria. Individual and pooled odds ratios from studies were reported in the forest plot. Squares represent study-specific effect estimates and the size of the square reflects the study-specific weight (i.e., the inverse of the variance). The diamond represents the summary effect estimate with a 95% confidence interval, and the horizontal lines indicate 95% confidence intervals. Odds ratios (OR) and 95% confidence intervals (CI).

2.6.4 I generated a set of variant-drug pairs significantly associated with MIADEs

Having excluded variants associated with ADEs related to cancer chemotherapy, I generated a set of variant-drug pairs significantly associated with MIADEs. This set of variant–drug pairs associated with MIADEs was identified from 34 RCTs & *post-hoc* analyses of RCTs and 86 meta-analyses, respectively (Figure 2.5). The set of variant–drug pairs associated with MIADEs is itemised in (Table 2.3). The complete set of variant–drug pairs with interrogable genotypes and the related ICD-10 codes for indications of the related medicine(s) are listed in the Supplementary Excel file S1 & S2.

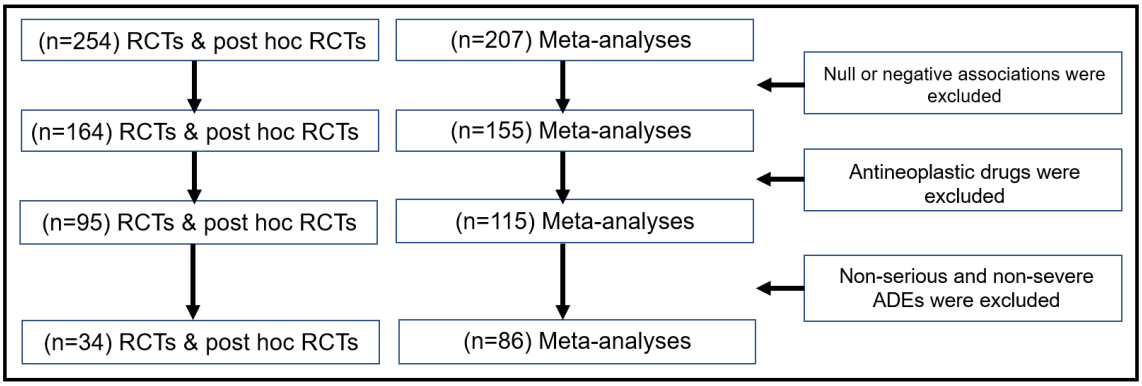


Figure 2.5 The process of synthesising the set of variant-drug pairs significantly associated with MIADEs.

Variants associated with ADEs related to cancer chemotherapy were excluded, and only variant-drug pairs significantly associated with MIADEs were included. The set of variant-drug pairs was identified from 34 RCTs & post-hoc analyses of RCTs and 86 meta-analyses.

Table 2.3 The set of variant-drug pairs significantly associated with MIADEs

Treatment or Drug(s)	Variant (s)
Abacavir	HLA-B*57:01
Antiretroviral Therapy (Nevirapine, Abacavir)	HLA-A*24, HLA-B*18, HLA-*35, HLA-B *39, HLA-B*51, HLA-B*81, HLA-C*04
Nevirapine	HLA-B*58:01, HLA-DRB1*01
Atazanavir	UGT1A1*1/*28, UGT1A1*28/*28
Efavirenz	ABCB1 3435C>T
Ribavirin	ITPA rs1127354 CC, ITPA rs7270101 AA, ITPA rs6051702 AA, Absent ITPase deficiency haplotype
Ritonavir-boosted Atazanavir	UGT1A1 rs887829 T/T, UGT1A1*28/*28
Antituberculous agents[1]	CYP2E1 RsaI/PstI polymorphism [RsaI is −1053C>T (rs2031920), PstI is −1293G>C (rs3813867)], CYP2E1 96-bp homozygous insertion allele (*1D/*1D), CYP2E1 homozygous (*1A/*1A), NAT2 481C>T (rs1799929), NAT2 590G>A (rs1799930), NAT2 857G>A (rs1799931), NAT2 282C-T (rs1041983), NAT2 slow acetylators or NAT2 ultra-slow acetylator [*5B/*6A, *5B/*7A, *6A/*6A, *6A/*7B, *7B/*7B], GSTT1 (null/null), GSTM1 null
CDA or Chlorproguanil-dapsone	G6PD A−
Dapsone	G6PD A−, HLA-B*1301
Antipsychotics	DRD3 Ser9Gly, Taq1A in DRD2 the A2 variant, CYP2D6*3, *4, *5, *6, *7, *12,*14, homozygotes for the *2 or *10 alleles
Aripiprazole	VNTR polymorphism in DAT1/SLC6A3 (rs28363170)
Trazodone	ABCB1 C3435T T/T
Atomoxetine	CYP2D6 PM [2 non-functioning alleles CYP2D6*3, *4, *5, *6, *7, *8]
Citalopram	GRIA3 rs4825476, GRIK2 rs2518224
Paroxetine	HTR2A -1438G/G
Aromatic antiepileptic drugs	HLA-A*24:02, HLA-B*15:02
Carbamazepine	HLA-B*15:02, HLA-B*1511, HLA-A*31:01, HLA-B*57:01
Lamotrigine	HLA-A*2402
Oxcarbazepine	HLA-A*3101, HLAB*1502
Phenytoin	HLA-B*13:01, HLA-B*15:02, HLA-B*51:01, CYP2C9*3
NSAIDs[2]	HLA-DRB1*11
NSAIDs[3]	CYP2C8*3 (rs11572080; rs10509681), CYP2C9*2 (rs1799853), CYP2C9*3 (rs1057910)
Celecoxib	ALOX15 (rs2255888), EP4 (rs4133101, rs13186505), GPX3 (rs8177406), PGES (rs2241271, rs2302821), CRP (rs1800947), SRC (rs6017996, rs6018256, rs6018257), CYP2C9*2 (R144C), CYP2C9*3 (I359L)
Oxycodone	ABCB1 G2677T/A
ACE inhibitors	MME rs989692, CRB1 rs2786098 T allele, ETV6 rs2724635 G allele
ACE inhibitors or ARBs	KCNMA1 rs2253202
Metoprolol	CYP2D6 PM
Statins[4]	LILRB5 (rs12975366: T > C: Asp247Gly), SLCO1B1 (rs4149056: c.521T>C: Val174Ala)
Clopidogrel	ABCB1 rs1045642 (c.3435C > T), CYP2C19*17 rs12248560 (4195C→T/A)
Warfarin	CYP2C9*2 (rs1799853), *3 (rs1057910)

Methotrexate	MTHFR C677T (rs1801133), MTHFR A1298C (rs1801131), ATIC 347C/G (rs2372536), ALDH2 rs671, SLC19A1 80G>A
Thiopurine-based drugs (Azathioprine or 6-mercaptopurine)	NUDT 15 c.415C>T, NUDT 15 c.52G>A, TPMT variants (*2,*3A,*3B,*3C,*3D,*4,*5,*6,*7,*8,*10,*12,*21,*37,*40), ITPA 94C>A (rs1127354), ITPA IVS2 + 21A>C (rs7270101), NUDT15 R139C, NUDT15 c.36_37ins/delGGAGTC, NUDT15 rs116855232
Tacrolimus plus everolimus or mycophenolate	FKBP2 c.-2110GG
Sulfasalazine	NAT2 slow acetylators
Glucocorticoid[5]	PAI-1 –675 4G/5G (rs1799889), ABCB1 C3435T C allele
Glucocorticoids[6]	GSTM1 (null/null) (homozygous deletion)
Inhaled Corticosteroids ± Additional Corticosteroids[7]	PDGFD rs591118
Hormone Therapy[8]	GP6 13254 TC+CC genotypes, GP1BA −5TT genotype
Letrozole or Tamoxifen	CYP19A1 rs700518, ESR2 rs4986938
Tamoxifen	CYP19A1 rs10046
Exemestane	ESR1 rs9322336
Antithyroid drugs (Carbimazole/Methimazole)	HLA-B*27:05, HLA- B*38:02, HLA-DRB1*08:03
Bisphosphonates	CYP2C8 rs1934951, VEGF rs3025039
Allopurinol	HLA-B*58:01, HLA-A*33:03, HLA-C*03:02
Lansoprazole	CYP2C19 PMs [CYP2C19*2, *3, *8, or *9]

Abbreviations
ACEIs: Angiotensin-converting enzyme inhibitors, ARBs: angiotensin receptor blockers, CDA: Chlorproguanil-dapsone-artesunate, NSAIDs: Non-steroidal anti-inflammatory drugs
Antituberculosis agents[1]: [Isoniazid, rifampicin, pyrazinamide, ethambutol, streptomycin]
NSAIDs[2]: [Dipyrone, Propyphenazone, acetic derivatives such as Diclofenac, Indomethacin, ASA]
NSAIDs[3]: [Indomethacin, Celecoxib, Flurbiprofen, Ibuprofen, Meloxicam, Piroxicam, Tenoxicam, Naproxen, Aceclofenac, Diclofenac, Ketorolac, Dexketoprofen]
Statins[4] (Simvastatin, Rosuvastatin, Cerivastatin, Simvastatin, Atorvastatin)
Glucocorticoids[5]: [Prednisone, Dexamethasone, Methylprednisolone]
Glucocorticoids[6]: [Prednisone +/- Dexamethasone]
Additional Corticosteroids[7]: [Prednisone, Dexamethasone]
Hormone Therapy[8]: [oral conjugated equine oestrogen plus medroxyprogesterone acetate]

2.7 Discussion

2.7.1 This study created a comprehensive list of variants associated with adverse effects

This systematic review identified genomic variants associated with ADEs via extensive reviews of the literature on RCTs, *post-hoc* analyses of RCTs and meta-analyses. Although PharmGKB collates this type of PGx data, this list of PG variants is more comprehensive and better annotated. This all-inclusive list provides a reliable source of up-to-date information with potential utility for regulatory agencies, researchers and HCPs.

2.7.2 This study synthesised a novel set of variant-drug pairs associated with MIADEs

Due to their significant clinical impact on mortality and morbidity, this review created a novel set of variant-drug pairs associated with MIADEs. The seriousness and clinical importance of ADEs are the most influential factors to weigh in the implementation of the tests at scale (234). While PharmGKB includes similar PGx data, this set of variant-drug pairs related to MIADEs is more inclusive, better annotated and focused purely on MIADEs. Further, this set of variant-drug pairs encompasses fully defined and interrogable genotypes as well as ICD-10 codes and therefore is readily available for potential future use in biobanks. Focused analyses in this context can be especially invaluable.

2.7.3 No statistically significant meta-analyses of RCTs of currently used medicines

Apart from the association between *G6PD* A− and severe anaemia in patients taking CDA or artemisinin-based combination therapy for malaria, none of the meta-analyses of RCTs and *post-hoc* analyses of RCTs were significant. However, the development of CDA combination for malaria was a previously promising therapy that was terminated prematurely and withdrawn from the market due to toxicity concerns related to severe haemolytic anaemia in G6PD-deficient patients (235). My meta-analysis of *CYP2C19* genotypes and bleeding risk in clopidogrel-treated patients is consistent with the most recent genotype-guided RCTs in which neither the risk of major bleeding (236) nor even any bleeding event (237) were significantly different between the genotype-guided group and the standard-treatment group. This is also in agreement with the most recent meta-analysis which showed no significant differences in the risk of any bleeding event with the use of prasugrel or ticagrelor as compared to clopidogrel in either *CYP2C19* LOF carriers or non-carriers (238). Similarly, the most recent RCT which examined the effect of PG testing of the *SLCO1B1* genotype for statin myopathy risk suggested that the marginally higher rate of ADEs in the control group could not have been prevented using genotype-guided treatment (239). There were no genotype-guided RCTs for the rest of the variants included in the meta-analyses performed.

2.7.4 Significant heterogeneity and mixed findings exist among studies identified

The vast majority of findings from individual studies were not statistically significant. The search strategy yielded a large and broad array of studies with substantial heterogeneity. This included randomisation designs, settings, interventions, length of intervention and follow-up, ADE outcomes reported, genomic variants investigated, statistical methods and covariates used as well as participants characteristics (e.g., sex, age, disease stage, comorbidities, co-interventions, demographics).

The lack of uniformity observed among the identified studies was particularly notable in the toxicity outcomes and diverse synonyms and variations of toxicity terms used synonymously by authors to describe ADEs. Many studies investigated composite outcomes of ADEs or used underspecified terms to refer to toxicities or used laboratory or immunological assays rather than clinical endpoints of ADEs. Besides, inconsistent definitions and designation of ADEs for seriousness and severity were observed. Notably, the terms “serious” and “severe” were used synonymously and interchangeably and at times loosely in some studies. This underscores the need for more precise definitions of ADEs to reduce the risk of erroneous designation of seriousness or severity (240). Internationally agreed scales particularly for designation of seriousness are therefore indispensable.

The scarcity of RCTs of PGx studies of ADEs was noteworthy. Indeed, the vast majority of included studies were *post-hoc* analyses of RCTs rather than RCTs. Remarkably, almost all *post-hoc* analyses of RCTs had the randomisation status of the initial RCTs not being explicitly stated neither in the title or abstract but rather used initials or acronyms or unique identification codes to refer to the initial RCTs. To facilitate identifying these studies in the literature, better reporting of randomisation status in such retrospective analyses of PGx studies is therefore vital.

Further, reports included in this study showed considerably mixed results. Around a quarter to one-third of included studies did not report any significant associations with a notable lack of replication in other populations. To improve the evidence base for the clinical utility of germline PG testing in the context of

ADEs, associations from such studies with mixed findings merit further replication in larger cohorts with longer follow-up periods.

2.7.5 Adverse drug effects were not consistently indexed or reported in the literature

The vast majority of ADEs in RCTs were secondary endpoints, which are often assessed with less rigour than the main outcomes or endpoints (241). ADEs which reported as secondary endpoints were poorly reported and indexed in the titles and abstracts. Of note, "adverse effect" or "drug toxicity" were indexed in the databases and mentioned in the title or abstract provided that the authors of those studies dedicated substantive components of discussion to the ADEs. This usually occurs when the authors consider the examined ADEs to be serious or clinically significant (242). As MIADEs are more likely to be transparently and adequately reported, my novel set of variant–drug pairs significantly associated with MIADEs is expected to be inclusive. There is a need for a higher degree of scrutiny to be applied with regard to the transparency and reporting of ADEs as well as using standardised ADE terms in RCTs.

2.7.6 Strengths and limitations

This systematic review is the first study of PGx of ADEs with no restrictions on patients' characteristics, pharmacological interventions, length of intervention or follow-up, toxicity outcomes or type of genomic variants investigated. Instead of employing such a comprehensive approach that provides wider coverage, all previous reviews investigated single drugs and a single genetic variation or gene and focused on a specific type of ADE. This study thereafter generated a set of variant-drug pairs significantly associated with MIADEs. MIADEs are associated with significant mortality and morbidity, and the seriousness of ADEs is the most influential factor to weigh in the implementation of the PG tests at scale. These comprehensive searches in major databases and other resources were inclusive of both published and peer-reviewed articles in journals, theses and dissertations and grey literature. By identifying primary and secondary studies (i.e., RCTs, *post-hoc* analyses of RCTs and meta-analyses) reporting both significant and non-significant findings, this comprehensive systematic review provides up-to-date evidence with regard to PGx of ADEs with minimised publication bias against negative findings.

This study however has a few limitations. First, this systematic review was performed based on a literature search on 27th May 2020 and any study published after this has not been included. The pertinent research published since this systematic review was performed is however not expected to significantly change my conclusions. Second, I restricted my search to include English-only publications and therefore language bias is anticipated. While excluding non-English language studies may introduce bias, language delimitations are very common search parameters due to the difficulty in translating publications (243). Although some pertinent non-English publications were potentially overlooked, the vast majority of RCTs are published in English. Compared to clinical trials published in English, trials published in non-English languages are also of lower methodological quality (244). Third, studies that examined chemotherapy-based regimens were excluded when I generated the set of variant–drug pairs significantly associated with MIADEs. This was inevitable due to the complexity of their combination regimens and designs (e.g., sequential use and treatment arms) as well as concerns regarding drug-drug interactions (usually $\geqslant$3 medicines) with the development of complex toxicities associated with these multicomponent chemotherapy-based treatments.

2.8 Conclusions

To date, this is the most comprehensive systematic identification of PG variants associated with ADEs. This study also curated a novel set of variant–drug pairs significantly associated with MIADEs in a rigorous and reproducible manner. Meta-analyses of the RCTs showed no statistical significance for the currently used medicines. The observed heterogeneity and mixed findings among the studies suggest that further replication is necessitated. Finally, better indexing of ADEs and standardised definitions of seriousness and/or severity in the literature are required.

*Table 2.4 The full list of variants associated with ADEs identified from randomised controlled trials**

Therapeutic Class/Treatment Modality	Culprit Drug(s)	Toxicities or Adverse Drug Effect(s)	Variants(s)/ Genotype(s)	Reference
Amphetamine Derivatives	Sibutramine	Pulse Rate Changes	CYP2B6*6, CYP3A5*3	(245)
Anaesthetics, General › NMDA Receptor Antagonists	Ketamine (subanaesthetic)	Cardiovascular ADEs (maximal systolic blood pressure)	NET rs28386840 T homozygous vs. A	(246)
Analgesics › Non-Steroidal Anti-inflammatory Drugs	NSAIDs	Anaphylactoid reaction	HLA-DRB1*11	(247)
	NSAIDs	Anaphylactoid reaction	HLA-DQ alleles	
Analgesics › Non-Steroidal Anti-inflammatory Drugs	Celecoxib	Gastrointestinal toxicity	ALOX15 (rs2255888), EP4 (rs4133101, rs13186505), GPX3 (rs8177406), PGES (rs2241271, rs2302821), CRP (rs1800947), SRC (rs6017996, rs6018256, rs6018257)	(248)
	Celecoxib	Cardiovascular toxicity	IL23R (rs10789229, rs11465810, rs1884444), ALOX12 (rs11078659), FLAP (rs4293222)	
Analgesics › Non-Steroidal Anti-inflammatory Drugs	Celecoxib (High dose)	Cardiovascular & thrombotic events	CYP2C9*2 (R144C), CYP2C9*3 (I359L)	(249)
Analgesics › Opioids	Oxycodone	(Nausea/vomiting, tiredness/drowsiness, itching) & Total sum of ADEs	ABCB1 C3435T, ABCB1 G2677T/A, Combined ABCB1 genotype 3435CC-2677GG	(250)
	Oxycodone	Dizziness and reduced ability to keep focus	ABCB1 C3435T	
	Oxycodone	Total sum of ADEs	OPRM1 A118G	
	Oxycodone	Reduced ability to keep focus	OPRM1 A118G	
	Oxycodone	Urine retention, headaches	ABCB1 G2677T/A	
	Oxycodone	Tiredness/drowsiness and reduced ability to keep focus	ABCB1 G2677T/A	
	Oxycodone	Other ADEs	Combined ABCB1 genotype 3435CC-2677GG	
	Oxycodone	Reduced ability to keep focus	Combined ABCB1 genotype 3435CC-2677GG	
Analgesics › Opioids	Codeine, Tramadol	ADEs	*10/*10, *2/*1, *4/*4, *4/*1, *5/*4, *5/*5, *6/*6, *6/*1, *9/*9	(251)
Analgesics › Opioids	Codeine	All side effects	Extensive metabolisers: CYP2D6*1/CYP2D6*5, CYP2D6*1/CYP2D6*2, CYP2D6*1/CYP2D6*2, CYP2D6*1/CYP2D6*10, CYP2D6*1/CYP9D6*1, CYP2D6*3/CYP2D6*2, CYP2D6*1/CYP2D6*2, CYP2D6*1/CYP2D6*1, CYP2D6*1/CYP2D6*2 Poor metabolisers: CYP2D6*4/CYP2D6*4, CYP2D6*4/CYP2D6*4, CYP2D6*3/CYP2D6*5, CYP2D6*4/CYP2D6*4, CYP2D6*4/CYP2D6*4, CYP2D6*4/CYP2D6*4, CYP2D6*4/CYP2D6*5, CYP2D6*4/CYP9D6*4, CYP2D6*4/CYP2D6*5	(252)
Analgesics › Opioids	Fentanyl	Reduced Systolic Blood Pressure	ADRB 2 C523A A	(253)
	Fentanyl	Somnolence	OPRM1 A118G, COMT G472A	
	Fentanyl	Safety Profile	CYP3A5*3, ABCB1 C3435T, ABCB1 G2677T/A	
Analgesics › Opioids	Morphine	Side effect of “Feeling in Control”	COMT rs4633, rs4680	(254)
	Butorphanol	Side effect of “Feeling in Control”	COMT rs4633, rs4680	
Analgesics › Opioids	Morphine A (IV)	Nausea/Vomiting/Itching/dizziness/Lethargy	OPRM1 118A>G	(255)
Analgesics › Opioids	Oxycodone & Sufentanil	ADEs	OPRM1 A118G, CYP3A5*3, CYP2D6*10	(256)
	Oxycodone & Sufentanil	Respiratory depression	CYP3A4*1G AA vs. GG and GA	
	Oxycodone	ADEs	CYP3A4*1G	
	Sufentanil	ADEs	CYP3A4*1G	
	Sufentanil	Respiratory depression	CYP3A4*1G AA vs. GG and GA	

	Sufentanil	Other adverse reactions (apart from respiratory depression)	CYP3A4*1G AA vs. GG and GA	
Analgesics › Opioids	Remifentanil	Postoperative Nausea and Vomiting	OPRM1 A118G GG vs. AA and AG (in all anaesthetic techniques), OPRM1 A118G AA and AG types only at T1, T2, and T3, compared with I group	(257)
Analgesics › Opioids	Tramadol	Drug Related Symptoms (e.g., faint and vomiting)	ABCB1 G1199A, ABCB1 C1236T, ABCB1 G2677T/A, ABCB1 C3435T	(258)
Antiallergic Drugs	Tranilast	Hyperbilirubinemia	TA repeat polymorphism in UGT1A1 $(TA)_7/(TA)_7$ genotype	(259)
	Tranilast	Hyperbilirubinemia	UGT1A1 GLY71Arg	
Anticholinesterases › Centrally Acting	Galantamine	Weight Loss	APOE epsilon4 allele	(260)
Anticholinesterases › Centrally Acting	Rivastigmine vs. Donepezil	Gastrointestinal events, particularly vomiting Psychiatric ADEs	BuChE K-variant	(261)
	Rivastigmine or Donepezil	Discontinuation rate due to ADEs	BuChE K-variant	
Antidepressants	Antidepressants	Serotonergic side effects	HTR2C rs6644093 or other variants in the HTR2C gene	(262)
Antidepressants	Antidepressants	Sleep-related side effects	ABCB1 rs2032583	(263)
Antidepressants › Selective Serotonin Reuptake Inhibitors & Antipsychotics › Second Generation	Citalopram	Early ADEs	5-HTTLPR S*S*/S*La genotypes	(264)
	Risperidone	Early ADEs	5-HTTLPR S*S*/S*La genotypes	
Antidepressants › Selective Serotonin Reuptake Inhibitors & CNS Stimulants › Centrally Acting Sympathomimetics	Sertraline, Atomoxetine	Cardiovascular measures or vital signs	5-HTTLPR (S/S, S/L, L/L)	(265)
	Sertraline+Placebo Vs. Sertraline+Atomoxetine	Greater increase in sitting pulse, body temperature, cardiac PR interval	5-HTTLPR S/S	
Antidepressants › Selective Serotonin Reuptake Inhibitors & Serotonin and Noradrenaline Reuptake Inhibitors	Escitalopram, Sertraline	Side effects	ABCB1 rs10245483 homozygotes	(266)
	Escitalopram, Sertraline, Venlafaxine	Impaired cognition	ABCB1 rs10245483 homozygotes	
Antidepressants › Selective Serotonin Reuptake Inhibitors & Tetracyclic Antidepressants	Paroxetine	Discontinuation due to side effects	HTR2A 102 T/C C/C vs. T/C and T/T	(267)
	Paroxetine, Mirtazapine	Baseline body weight, baseline cognition	HTR2A 102 T/C C/C vs. T/C and T/T	
	Paroxetine, Mirtazapine	ADEs or the frequency of discontinuations	11 CYP2D6 alleles and 33 genotypes	
	Mirtazapine	ADEs, final daily dose, dosing compliance, plasma levels, early discontinuations or dropouts due to ADEs	HTR2A 102 T/C	
Antidepressants › Selective Serotonin Reuptake Inhibitors & Tetracyclic Antidepressants	Mirtazapine	Discontinuations due to ADEs, severe ADEs	5HTTLPR (S allele)	(268)
	Paroxetine	Severe ADEs	5HTTLPR (S allele)	
Antidepressants › Selective Serotonin Reuptake Inhibitors & Tricyclic Antidepressants	Fluoxetine or Nortriptyline	ADEs	CYP2D6 PMs and EMs	(269)
Antidepressants › Selective Serotonin Reuptake Inhibitors & Tricyclic Antidepressants	Escitalopram and Nortriptyline	Sexual dysfunction	5-HTTLPR (s/s vs. s/l vs. l/l)	(270)

Antidepressants › Selective Serotonin Reuptake Inhibitors	Citalopram	Tolerance	ABCB1 gene (C1236T, G2677T, C3435T), CYP3A5*3C, CYP2C19 variants (*2, *3, *17), CYP3A4* 1B, CYP2D6 alleles (*3, *4, *6, *7, *8, *9), CYP2D6*5 deletion Status	(271)
	Citalopram	Tolerance or ability to remain in the trial	CYP2D6 or CYP2C19 metabolizer status (PM vs. EM)	
Antidepressants › Selective Serotonin Reuptake Inhibitors	Citalopram	Reaction time reduction	Tri-allelic 5-HTTLPR and rs25532 (LAC/LAC=LL) vs. homozygous S allele carriers (SS), 5-HTTLPR LL group	(272)
	Citalopram	Reaction time increase	5-HTTLPR SS group	
	Citalopram	Significant decrease in N2 amplitudes	group LL	
	Citalopram	N2 amplitudes	group SS	
	Citalopram	P3a increase	group LL	
	Citalopram	P3a increase	group SS	
	Citalopram	P3b decrease in LL, increase in group SS	LL group, SS group	
Antidepressants › Selective Serotonin Reuptake Inhibitors	Escitalopram	Increased duration of sleep, dry mouth, diarrhoea, and diminished sexual desire	HTR1A (C-1019G) rs6295: High-Expressing Genotype CC, HTR2A (G-1438A) rs6311: High-Expressing Genotype AA, 5-HTTLPR [L/S + rs25531]: High-Expressing Genotype L+A	(273)
	Escitalopram	Dry mouth	(Low-expressing) genotype LA−, 5-HTTLPR triallelic haplotype LA	
	Escitalopram	Diarrhoea	CC (low-expressing) genotype at the 1A receptor compared to the GG/GC (high-expressing) genotype, HTR1A rs6295 CC (low), HTR1A rs6295 GG/CG (high)	
	Escitalopram	Diminished Sexual Desire	HTR1A rs6295 GG/CG (high), HTR1A rs6295 CC (low), HTR2A rs6311 GG (low), HTR2A rs6311 AA/AG (high), 5-HTTLPR triallelic haplotype LA, GG/CG (high-expressing) compared to the low-expressing genotype, AA/AG (high-expressing) genotype at the 2A receptor, High expressing serotonin transporter genotype LA+	
Antidepressants › Selective Serotonin Reuptake Inhibitors	SSRIs	Severe gastrointestinal ADEs, total gastrointestinal ADEs or total ADEs	TPH1 218 A/C	(274)
Antidepressants › Selective Serotonin Reuptake Inhibitors	Citalopram	ADEs Burden	Long (L) and short (S) alleles of the triallelic HTTLPR locus, L(A) allele, L allele, S with LG vs LA alleles	(275)
	Citalopram	ADEs Burden in White non-Hispanics	L(A)L(A) genotype or L(A) allele	
	Citalopram	ADEs Burden in White non-Hispanics	LA and LG alleles combined, [SS, SL, LL], [S, L]	
Antidepressants › Selective Serotonin Reuptake Inhibitors	Citalopram	Suicidal Ideation	GRIA3 rs4825476, GRIK2 rs2518224	(276)
Antidepressants › Selective Serotonin Reuptake Inhibitors	Escitalopram	Reductions in attention	5-HTR2A rs6311, 5-HTR1B rs11568817	(277)
Antidepressants › Selective Serotonin Reuptake Inhibitors	Paroxetine, Fluvoxamine	ADEs	HTR2A –1438A/G, HTR3A 178C/T, HTR3B –100–102AAG ins/del, SERTPR (s/s and l carriers)	(278)
	Paroxetine	Severe nausea	HTR2A -1438G/G	
	SSRIs, Paroxetine, Fluvoxamine	Discontinuation due to ADEs, Severe nausea, Total of ADEs	HTR2A genotype, SERTPR l/l · l/s, s/s, HTR3A genotype, HTR3B ins/del	
Antidepressants › Selective Serotonin Reuptake Inhibitors	Sertraline	ADEs	CYP2B6 (G516T), CYP2C9 phenotypes [PM, IM, EM], CYP2C19 phenotypes [IM, EM, UM], CYP2D6 phenotypes [PM, IM, EM, UM], ABCB1 (C3435T), ABCB1 (C1236T), ABCB1 (G2677T/A), SLC6A4 (5-HTTLPR), SLC6A4 (VNTR), HTR2A (T102C), HTR2C (-759C/T)	(279)
Antidepressants › Serotonin and Noradrenaline Reuptake Inhibitors	Bupropion SR	Discontinuation due to ADEs	DRD2 (A1A1 or A1/A2 vs A2/A2)	(280)

Antidepressants › Serotonin Reuptake Inhibitors	Trazodone	Dizziness	CYP2D6 PM	(281)
	Trazodone	Paraesthesia	CYP2D6 PM	
	Trazodone	ADEs	ABCB1 T allele	
	Trazodone	QTc prolongation	ABCB1 T/T	
	Trazodone	Paraesthesia	CYP3A5*3/*3, ABCB1 T/C	
Antidepressants › Tricyclic Antidepressants	Nortriptyline	Postural hypotension	Homozygous ABCB1 3435C>T	(282)
	Nortriptyline	Postural hypotension	Heterozygous ABCB1 3435C>T	
	Fluoxetine	Postural hypotension	ABCB1 3435C>T genotypes	
Antiepileptics	Topiramate	Severity of side effects	GRIK1 (rs2832407)	(283)
Antiepileptics	Topiramate	Severity of ADEs	rs2832407*CC, rs2832407*A-allele	(284)
Antifungals › Triazole Antifungals & Echinocandin Antifungals	Voriconazole & Anidulafungin	Treatment-related hepatic ADEs	CYP2C19 genotype status	(285)
Antihypertensives › Beta-Adrenoceptor Blockers	Atenolol	Impaired fasting glucose (IFG)	69 SNPs in BCAT1 and 26 SNPs in PAH	(286)
	Atenolol	Impaired fasting glucose (IFG)	PAH (rs2245360) AA vs. AG and GG	
Antihypertensives › Beta-Adrenoceptor Blockers	Bisoprolol	Baseline heart rate or perioperative changes in heart rate or decrease in peak expiratory flow	ADRB1 Arg389Arg and Gly genotype	(287)
	Bisoprolol	Bradycardia	ADRB1 Ser49Gly-WT, ADRB1 Arg389Gly-WT, ADRB2 Gly16Arg-WT, ADRB2 Gln27Glu-WT	
	Bisoprolol	Hypotension	ADRB1 Ser49Gly-WT, ADRB1 Arg389Gly-WT, ADRB2 Gln27Glu-WT	
	Bisoprolol	Hypotension	ADRB2 Gly16Arg-WT	
Antihypertensives › Drugs Acting on The Renin-Angiotensin System › ACE Inhibitors	Cilazapril	Cough	ACE II vs. DD	(288)
Antihypertensives › Drugs Acting on The Renin-Angiotensin System › ACE Inhibitors	Lisinopril	Cough	ACE D/I: ACE D and I alleles, chymase A and B alleles (absence/presence of BstXI site), B2BKR +/-: for B2-bradykinin receptor + and – alleles (presence/absence of a 21 to 29 non-nucleotide sequence)	(289)
Antihypertensives › Drugs Acting on The Renin-Angiotensin System › ACE Inhibitors	ACE inhibitors	Angioedema	PRKCQ rs500766	(290)
	ACE inhibitors	Angioedema	ETV6 rs2724635 G allele, MME rs989692 T, CRB1 rs2786098 T	
Antimalarials & Antimycobacterials	CD	Severe anaemia	G6PD-deficient (G6PD A−) (202G→A)	(224)
Antimalarials & Antimycobacterials	CDA versus AL	Severe and clinically concerning haemoglobin decreases	G6PD-deficient (G6PD A−)	(225)
	CDA versus AL	Severe and clinically concerning haemoglobin decreases	G6PD-deficient (G6PD A−) heterozygous females	
Antimalarials & Antimycobacterials	CDA vs CPG–DDS	Haemoglobin drop or blood transfusion	G6PD-deficient (G6PD A−)	(226)
	CDA vs CPG–DDS	Haemoglobin drop or blood transfusion	Heterozygous G6PD-deficient (G6PD A−)	
Antimalarials & Antimycobacterial s	Dapsone	Haemolytic anaemia	G6PD A−	(227)
Antimalarials	Artesunate	ADEs (e.g., facial flushing and nausea)	Homozygous or heterozygous CYP2A6*1B	(291)
Antimalarials	CD vs. AL	Severe anaemia	G6PD-deficient (G6PD A−)	(228)
Antimalarials	CD	Haemolysis	G6PD-deficient (G6PD A−) homo-/hemizygous genotype vs. wild type	(229)
Antimalarials	DHAPP+SLDPQ vs. DHAPP alone	Acute haemolytic anaemia/ required a blood transfusion	G6PDd Viangchan vs. G6PDn	(292)
	DHAPP+SLDPQ	Mean nadir Hb (modest Hb declines)	G6PDd Viangchan vs. G6PDn	

Antimalarials	Artemisinin-based combination (Primaquine plus artemisinin)	Haemolysis/moderate anaemia	G6PD-deficient (G6PD A−) heterozygotes (G6PD A)	(230)
Antimuscarinics › Parkinson's Disease	Trihexyphenidyl	Increased mental slowing, Correlations with Memory	APOE-ε4 positive	(293)
	Trihexyphenidyl	Confusion, Mood Rating Scale Ratings of Sedation	APOE-ε4 positive	
Antimuscarinics › Parkinson's Disease	Trihexyphenidyl (1 or 2mg)	Impairments in delayed recall, Persistent Impairments in delayed recall	APOE-ε4 positive	(294)
	Trihexyphenidyl (1 or 2mg)	Psychomotor performance, Total Recall	APOE-ε4 positive	
	Trihexyphenidyl (2mg)	Reduction in delayed recall scores	APOE-ε4 positive	
Antimuscarinics › Urinary	Tolterodine	CNS side effects such as sleepiness [Rapid eye movement/sleep duration: as a percentage of total sleep time]	Patients carrying one or more deficient alleles CYP2D6 (IM + PM)	(295)
	Tolterodine	CNS side effects such as sleepiness [Rapid eye movement/sleep duration: as a percentage of total sleep time]	Two active alleles of CYP2D6 in the EM group	
Antineoplastic Drugs › Alkylating Agents & Antimetabolites	Fludarabine/cyclophosphamide	Lymphocytosis/lymphadenopathy	CYP2B6*6 [CYP2B6 c.516G>T and c.785A>G]	(296)
	Chlorambucil or fludarabine	Lymphocytosis/lymphadenopathy	CYP2B6*6 [CYP2B6 SNPs c.516G>T and c.785A>G]	
Antineoplastic Drugs › Alkylating Agents	Cyclophosphamide-based chemotherapy	Grade 3–4 neutropenia	SOD2 CC genotypes vs. TT genotypes (rs4880 or Val16Ala)	(297)
	Cyclophosphamide-based chemotherapy	Grade 3 and 4 leukopenia	SOD2 CC genotypes vs. TT genotypes (rs4880 or Val16Ala)	
Antineoplastic Drugs › Alkylating Agents	Cyclophosphamide-based chemotherapy	Grade 3 and 4 neutropenia	GSTP1 at least 1 GSTP1 rs1695 variant G allele compared with AA	(298)
	Cyclophosphamide-based chemotherapy	High-grade haematological toxicity	GSTP1 at least 1 GSTP1 rs1695 variant G allele compared with AA	
	Cyclophosphamide-based chemotherapy	Grade 3 and 4 leukopenia	GSTP1 at least 1 GSTP1 rs1695 variant G allele compared with AA	
	Cyclophosphamide-based chemotherapy	Grade 4 haematological toxicity	CYP2B6 rs3745274, CYP3A4 rs2740574, GSTA1 rs3957356	
	Cyclophosphamide-based chemotherapy	High grade neutropenia, high grade leukopenia	CYP2B6 rs3745274, CYP3A4 rs2740574, GSTA1 rs3957356	
Antineoplastic Drugs › Anthracyclines & Platinum Compounds & Antimetabolite	ECF	Grade 3 diarrhoea	DPYD2A IVS14+1G>A GA	(299)
	ECF	Diarrhoea, Stomatitis, Haematological	TYMS (TS) [2R/2R, 2R/3R, 3R/3R], TYMS (TS) [2R/2R, 2R/3R/3R/3R], GSTP1 rs1695 (A, AG, G), OPRT rs1801019 (C, GC, G), DPYD2A IVS14+1G>A (G, GA), DPYD rs1801159 (A, AG, G), ERCC1 rs11615 (C, CT, T, CT + T), ERCC1 rs3212986 (G, GT, T), ERCC2 rs13181 (G, GT, T). XRCC1 rs25487 (A, AG, G)	
Antineoplastic Drugs › Anthracyclines	Anthracycline-based chemotherapy	Congestive heart failure	rs28714259	(300)
Antineoplastic Drugs › Anthracyclines & Alkylating Agent & Vinca Alkaloids & Antimetabolites & Corticosteroids & Other	(Protocol IA+IB)	Grade III/IV gastrointestinal and neurological toxicities	ITPA rs1127354 homozygous	(301)
	(Protocol IA+IB)	Grade III/IV gastrointestinal and neurological toxicities	TPMT (rs1142345, rs1800460 and rs1800462)	
	(Protocol IA+IB)	Grade III/IV neurological toxicities	ABCC1 rs246240	
	(Protocol IA+IB)	Grade III/IV hepatic toxicities	ADORA2A rs2236624 homozygous	

Antineoplastic Drugs › Anthracyclines & Alkylating Agent & Vinca Alkaloids & Cytotoxic Antibiotics & Monoclonal Antibodies & Corticosteroids	R-CHOP	Diarrhoea, vomiting & mucositis	ABCB1 rs2229109	(302)
	R-CHOP	Febrile neutropenia	CBR1 rs20572, CBR1 rs9024	
	(R-CHOP or I-ACVBP	Grade 3–4 toxicities: high-grade diarrhoea & vomiting	ABCB1 rs2229109 (Ser400Asn), CBR1 (Ala209Ala and 3′-UTR): CBR1 rs20572, rs9024	
	I-ACVBP	Febrile neutropenia & vomiting	ABCB1 rs2229109	
	I-ACVBP	Febrile neutropenia	GSTP1 rs1695	
Antineoplastic Drugs › Anthracyclines & Alkylating Agent & Vinca Alkaloids & Monoclonal Antibodies & Corticosteroids	CHOP-14+/-rituximab	Cardiotoxicity	RAC2 rs13058338 TA/AA	(303)
	CHOP-14+/-rituximab	Cardiotoxicity	CYBA rs4673 CT/TT	
Antineoplastic Drugs › Anthracyclines & Alkylating Agents	Cyclophosphamide and doxorubicin	Grade 3 and 4 haematological toxicity	ALDH1A1 (rs8187996, rs3764435 and rs63319), ABCC1 (rs903880, rs16967126 and rs4148350)	(304)
	Cyclophosphamide and doxorubicin	Grade 3 and 4 haematological toxicity	A two-SNP haplotype consisting of the A allele of rs3764435 and a neighbouring SNP rs168351	
	Cyclophosphamide and doxorubicin	Haematological toxicity	SNPs in ABCB1	
	Cyclophosphamide and doxorubicin	Grade 3 gastrointestinal toxicity	ABCC1 (rs35596, rs4148354, rs2889517 and rs11861115), none of the SNPs in ABCB1 or ALDH1A1	
Antineoplastic Drugs › Anthracyclines & Podophyllotoxin Derivatives & Antimetabolites & Immunostimulants › Granulocyte-Colony Stimulating Factors	Chemotherapy induction regimens	Lung toxicity	XPD Lys751Gln heterozygotes	(305)
	Chemotherapy induction regimens	GU toxicity	XPD Asp312Asn AA genotype, XPD Asp312Asn heterozygotes	
	Chemotherapy induction regimens	Lung/metabolic toxicities	ERCC1 (rs3212961)	
	Chemotherapy induction regimens	Liver toxicity	XRCC3 241Met	
Antineoplastic Drugs › Anthracyclines & Vinca Alkaloids & Alkylating Agent & Cytotoxic Antibiotics & Other	ABVD, CEC, BEA	Grade 3-4 anaemia	GSTP1Ile105Val	(306)
		Alopecia grade >2	GSTM1 deletion	
Antineoplastic Drugs › Anti-Oestrogens & Hormone Antagonists and Related Agents › Aromatase Inhibitors	Letrozole (vs. Tamoxifen)	Bone ADEs	ESR1 rs2077647(T>C) CC, TC	(307)
	Tamoxifen	Bone ADEs	ESR1 rs2077647(T>C) CC, TC, ESR2 rs4986938(G>A) variants AA and AG	
	Letrozole (vs. Tamoxifen)	Bone adverse events	ESR2 rs4986938(G>A) variants AA and AG	
	Letrozole or Tamoxifen	Grade 3–4 osteoporosis or any grade bone fracture	ESR1 (rs9340799(XbaI), rs2234693(PvuII), rs11963577, rs2077647, rs9341070, rs746432), ESR2 (rs4986938, rs1256049)	
	Letrozole or Tamoxifen	Bone ADEs and early onset hot flushes or night sweats	ESR2 rs4986938 homozygous (AA) vs. (AG) or (GG)	
Antineoplastic Drugs › Anti-Oestrogens & Hormone Antagonists and Related Agents › Aromatase Inhibitors	Tamoxifen or Letrozole, alone or in sequence	Musculoskeletal and bone side effects	CYP19A1 rs700518(T>C) variants (CC or TC) vs. (TT)	(308)
	Tamoxifen or Letrozole, alone or in sequence	Musculoskeletal ADEs	Five SNPs	

	Tamoxifen or Letrozole, alone or in sequence	Bone ADEs	CYP19A1 genotypes: rs700519 (G>A) and rs28757184(G>A); rs700518(T>C); two SNPs in the 3′UTR, rs4646(C>A) and rs10046(C>T); and rs936308(C>G).	
	Tamoxifen	Bone ADEs	rs4646 (AA) or (CA)	
	Letrozole	Bone ADEs	rs4646 (AA) or (CA), minor allele I of rs10046	
	Tamoxifen	Bone ADEs	rs10046 I, rs936308 (GG) or (GC)	
	Letrozole	Bone ADEs	rs936308 (GG) or (GC)	
Antineoplastic Drugs › Anti-Oestrogens	Tamoxifen	Hot flashes in year 1	CYP2D6 genotypes/phenotypes, ESR1 genetic variants: ESR1 SNPs PvuII and XbaI, (CG, CA, TA haplotypes)	(309)
	Tamoxifen	Time to the occurrence of hot flashes during the complete time on tamoxifen	The ESR1 PvuII XbaI CG haplotype	
Hormone Antagonists and Related Agents › Aromatase Inhibitors	Exemestane	Musculoskeletal toxicity, discontinuation/musculoskeletal syndrome, discontinuation due to any toxicity	ESR1 (rs9322336)	(310)
	Letrozole	Increased risk of discontinuation of letrozole, therapy because of musculoskeletal syndrome	ESR1 (rs9322336)	
	Exemestane, Letrozole	Discontinuation of exemestane because of toxicity	(rs11849538 and rs2369049)	
	Exemestane, Letrozole	Musculoskeletal syndrome	At least one 8-repeat $TTTA_n$ allele in intron 4 of the aromatase gene (rs60271534)	
Hormone Antagonists and Related Agents › Aromatase Inhibitors	Exemestane	MS-ADEs and VM-ADEs	CYP19A1 rs934635 Homozygous AA	(311)
	Exemestane	VM-ADEs	CYP19A1 rs1694189 and rs7176005 homozygous variant genotypes (TT)	
	Exemestane	MS-ADEs	CYP19A1 rs1694189 and rs7176005 homozygous variant genotypes (TT)	
Hormone Antagonists and Related Agents › Aromatase Inhibitors	Exemestane	Grade ≥2 hot flashes/sweating	CYP19A1 rs10046 variant T/T	(312)
	Exemestane vs. Tamoxifen	Early-onset grade 2–3 hot flashes/sweating	CYP19A1 rs10046 TT vs CT/CC	
	Exemestane	Early-onset musculoskeletal side effects	CYP19A1 (rs4646 and rs10046), ESR1 (rs207764, rs2234693 and rs9340799)	
Antineoplastic Drugs › Antimetabolites & Anthracyclines & Alkylating Agents	5-fluorouracil, epirubicin, cyclophosphamide	Grade 3 or 4 neutropenia or leukopenia events	PIGB rs12050587	(313)
Antineoplastic Drugs › Antimetabolites & Corticosteroids	Corticosteroids & methotrexate	Bone toxicity, osteonecrosis and bone fracture	2R/2R TS genotype	(314)
Antineoplastic Drugs › Antimetabolites & Platinum Compound	FOLFOX-4 or XELOX	Grade ≥3 haematological toxicity	rs1801133, rs1799793	(315)
	FOLFOX-4 or XELOX	Grade ≥3 gastrointestinal toxicity	rs13181	
	FOLFOX-4 or XELOX	Grade ≥2 neurological toxicity	rs11615	
Antineoplastic Drugs › Antimetabolites & Platinum Compounds & Monoclonal Antibodies	FOLFIRI & Bevacizumab	Grade 2-3 hypertension	FIP200 rs1129660 G allele vs. A/A, ATG13 rs13448 C allele vs. homozygous T/T	(316)
	FOLFIRI & Bevacizumab	Grade 2–3 proteinuria	FIP200 rs17337252 G allele	
	FOLFIRI & Bevacizumab	Grade 3–4 venous thromboembolism	BECN1 rs11552192 A/A	
Antineoplastic Drugs › Antimetabolites & Platinum Compounds	Fluorouracil and leucovorin plus either oxaliplatin or cisplatin	Grade 3-4 neurotoxicity	GSTP1-105Ile/Ile vs. Ile/Val or Val/Val	(317)
	Fluorouracil and leucovorin plus either oxaliplatin or cisplatin	Nephrotoxicity	XPD-Asn312/751Gln haplotype	

	Fluorouracil and leucovorin plus either oxaliplatin or cisplatin	Haematological toxicities, grade 3-4 leukopenia	TS haplotype 3R/+6	
	Fluorouracil and leucovorin plus either oxaliplatin or cisplatin	Grade 3-4 neutropenia	MTR-2756AA and AG vs. GG, GSTP1-105Ile/Ile genotype	
	Fluorouracil and leucovorin plus either oxaliplatin or cisplatin	Grade 3-4 neutropenia	ERCC1-118T/8092C haplotype	
	Fluorouracil and leucovorin plus either oxaliplatin or cisplatin	Grade 3-4 anaemia or thrombocytopenia	All examined genotypes/haplotypes	
Antineoplastic Drugs › Antimetabolites & Platinum Compounds	FOLFOX-4 or XELOX	Grade ⩾ 3 ADEs	DPYD *6 rs1801160 A allele, DPYD *2A rs3918290 A allele, DPYD rs2297595 GG	(318)
	FOLFOX-4 or XELOX	Neutropenia	DPYD *6 rs1801160, DPYD *2A rs3918290	
Antineoplastic Drugs › Antimetabolites & Platinum Compounds	Oxaliplatin and fluoropyrimidine (FOLFOX-4 or XELOX)	Neutropenia & neurotoxicity	GST-T1/M1null/null genotype (presence of homozygous deletion in both genes) vs. wild-type genotype	(319)
	FOLFOX-4 or XELOX	Neurotoxicity	ABCC1 rs2074087	
	FOLFOX-4 or XELOX	Grade 3–4 leukopenia, time to leukopenia was shorter	ABCC2 (rs 4148386) GG vs. ABCC2AA	
	FOLFOX-4 or XELOX	Mucositis	TS 3′UTR L allele	
	FOLFOX-4 or XELOX	Vomiting	TS 5′UTR 2R2R genotype vs. TS 5′UTR 3R3R	
Antineoplastic Drugs › Antimetabolites & Platinum Compounds	Pemetrexed plus Carboplatin	Grade 3 and 4 toxicities	MTHFR C677T	(320)
Antineoplastic Drugs › Antimetabolites & Podophyllotoxin Derivatives & Anthracyclines & Corticosteroids	Chemotherapy: AML-87, AML-89 and AML-92 protocols	Early death after the initiation of chemotherapy (within 120 days), Toxicities (respiratory failure, cardiac arrhythmia)	GSTT1(-) null genotype	(321)
Antineoplastic Drugs › Antimetabolites & Taxanes	Gemcitabine plus paclitaxel	Neurotoxicity	RRM1 rs9937 AA genotype, RRM1 ATAA and ATGA haplotypes	(322)
Antineoplastic Drugs › Antimetabolites	5-FU chemotherapy	Toxicity	MTHFR C677T	(323)
	5-FU chemotherapy	Haematological toxicity	SLC19A1 G80A	
	5-FU chemotherapy	Esophagitis/stomatitis	TSER 2R/2R, 2R/3R, 3R/3R	
Antineoplastic Drugs › Antimetabolites	5-FU chemotherapy	Severe toxicity	DPYD c.1129-5923 C>G, hapB3 c.1236 C>G, hapB3 c.959-51 T>C	(324)
	5-FU chemotherapy	Grade≥3 5FU-AE neutropenia	c.483+18 G>A, c.680+139 G>A, c.1129-5923 C>G (Complete linkage was observed between c.1129-5923 C>G, c.1236 G>A, and c.959-51 T>C therefore only c.1129-5923 C>G is displayed)	
	5-FU chemotherapy	Grade≥3 5FU-AE Stomatitis / Mucositis	DPYD c.680+139 G>A	
	5-FU chemotherapy	Grade ≥3	DPYD c.1129-5923 C>G, DPYD c.483+18 G>A, DPYD c.680+139 G>A, hapB3 variants	
Antineoplastic Drugs › Antimetabolites	Capecitabine	Grade ≥ 3 global toxicity (diarrhoea, nausea and vomiting, mucositis/stomatitis, neutropenia, thrombocytopenia, and HFS)	TYMS 5′VNTR2R, TYMS 3′UTR6bp ins, DPYD 2846A	(325)
Antineoplastic Drugs › Antimetabolites	Capecitabine	Grade 3 to 4 diarrhoea, grade 3 to 4 toxicity, capecitabine-related death	DPYD IVS14+1G>A, 2846A>T, 1236G>A,	(326)
	Capecitabine	Grade 3 to 4 diarrhoea	DPYD HP3 (wild type at all SNP loci except heterozygous for 85T>C)	
	Capecitabine	Grade 3 to 4 diarrhoea	DPYD 1 rare variant haplotype allele (HP5) or 2 variant haplotype alleles (HP6)	
	Capecitabine	Grade 2 to 3 hand-foot syndrome grade 3 to 4 toxicities	Haplotype pairs: HP1 HP2 HP3 HP4 HP5 HP6	
Antineoplastic Drugs › Antimetabolites	Capecitabine	Grade 3-4 overall toxicity, febrile neutropenia or hand-foot syndrome.	MTHFR 1298A>C and 677C>T	(327)

	Capecitabine	Grade 3-4 diarrhoea	MTHFR 1298CC homozygotes	
Antineoplastic Drugs › Antimetabolites	Gemcitabine	Haematological toxicity	CDA Lys[27]Gln polymorphism (either the homozygote wild-type genotype (Lys/Lys) alone) or in combination with the heterozygote when compared with homozygote variant genotype (Gln/Gln)	(328)
Antineoplastic Drugs › Antimetabolites	Gemcitabine	High-grade neutropenia	CDA rs2072671 (A>C), AC and CC	(329)
	Gemcitabine	High-grade neutropenia	SLC28A1 rs3825876 (G>A), AA	
Antineoplastic Drugs › Antimetabolites	Methotrexate	ADEs	ATIC 347 G allele	(330)
	Methotrexate	ADEs	AMPD1 34C>T T allele, ATIC 347C>G CC or ITPA 94C>A CC, or combinations of these genotypes	
Antineoplastic Drugs › Antimetabolites_	Methotrexate	Toxicity	MTHFR 677 C→T	(214)
Antineoplastic Drugs › Antimetabolites	Methotrexate	Toxicity	CMYA5 rs12651804, rs1504582	(331)
Antineoplastic Drugs › Antimetabolites	Methotrexate	Toxicity	ALDH2 rs671	(332)
Antineoplastic Drugs › Antimetabolite	Methotrexate	Gastrointestinal complaints, skin and mucosa disorders and elevated liver enzymes	FPGS 1994A>G (A) and (G), FPGS 114G>A (G) and (A), GGH 16T>C (T) and (C), GGH 452C>T (C) and (T)	(333)
Antineoplastic Drugs › Antimetabolites	Methotrexate	ADEs/elevation of liver enzymes	MTHFR C677T	(215)
Antineoplastic Drugs › Antimetabolites	Methotrexate	Hepatotoxicity	SLC19A1 80G>A	(334)
	Methotrexate	Gastrointestinal toxicity	TYMS 6bp deletion	
Antineoplastic Drugs › Antimetabolites	Methotrexate	Mucositis and diarrhoea	MTHFR C677T	(216)
	Methotrexate	Gastrointestinal toxicities (mucositis, diarrhoea) and haematological toxicities (anaemia)	MTHFR A1298C vs. 1298AA	
	Methotrexate	Haematological toxicities and neurologic toxicities	MTHFR A1298C vs. 1298AA	
Antineoplastic Drugs › Antimetabolites	Methotrexate	grade 3 and 4 toxicity	TNF -308 (G->A), LT-a +252 (A->G)	(335)
Antineoplastic Drugs › Antimetabolites	Methotrexate	Hepatotoxicity or gastrointestinal toxicities	MTHFR 677 C>T	(218)
Antineoplastic Drugs › Antimetabolites	Methotrexate	Hepatotoxicity or gastrointestinal toxicities	MTHFR 677 C>T	(217)
Antineoplastic Drugs › Antimetabolites	Pemetrexed	Liver toxicity	ABCC2 rs2273697, SLCO1B1 rs4149056, SLCO1B1 rs11045879, SLCO1B1 GCC haplotype vs. reference ATT haplotype	(336)
	Pemetrexed	Gastrointestinal toxicity	ABCC2 rs717620	
	Pemetrexed	Gastrointestinal toxicity	ABCC2 CAG haplotype	
Antineoplastic Drugs › Antimetabolites	Pemetrexed	3-4 grade SGPT (ALT) elevation	FPGS IVS1 (28) G>A vs. GG	(337)
Antineoplastic Drugs › Antimetabolites	Thioguanine	Liver veno-occlusive disease	TPMT*3	(338)
Antineoplastic Drugs › Immunosuppressants › Thalidomides	Docetaxel and Thalidomide	Toxicities	CHST3 rs4148950, CHST3 rs1871450, CHST3 rs4148945, SPG7 rs2292954, SPG7 rs12960, CYP2D6*19 (2539–2542del), NAT2 rs1799931, ABCC6 rs2238472, ATP7A rs2227291, CYP4B1 rs4646487, SLC10A2 rs2301159	(339)
	Docetaxel and Thalidomide	Toxicities	CYP3A5*3C and other variants in CYP3A5 or CYP3A4)	
Antineoplastic Drugs › Immunosuppressants › Thalidomides	Lenalidomide	Haematological Toxicities	ABCB1 1199G>A (Ser400Asn, rs2229109), 1236C>T (silent, rs1128503), 2677G>T/A (Ala893Ser, rs2032582), 3435C>T (silent, rs1045642)	(340)
Antineoplastic Drugs › Immunosuppressants › Thalidomides_	Thalidomide	Peripheral neuropathy	ABCA1 (rs363717), ICAM1 (rs1799969), PPARD (rs2076169), SERPINB2 (rs6103), SLC12A6 (rs7164902	(341)
Antineoplastic Drugs › Immunosuppressants › Thalidomides	Thalidomide	Venous thrombotic events	rs7011 in CINP, rs289747 in CETP, rs610529 in ALDH1A1, rs3829963 in CDKN1A, rs2608555 in GAN, rs699947 in VEGF, rs168351 in ALDH1A	(342)

	Thalidomide	Venous thrombotic events	F2-455G/A (rs3136430) splice variant 20210G/A (rs3136431), SNPs MTRR, PLAUR, PPARD, PPARGC1A, PPARGC1B, THBS4, and WNK	
Antineoplastic Drugs › Microtubule-Stabilising Agents	Ixabepilone	Neutropenia and sensory neuropathy	ABCB1 rs2032582 (c.2677T/G/A, p.S893T/A), rs1128503 (c.1236T/C, p.G412G) and rs1045642 (c. 3435T/C, p.I1145I), CYP3A4 rs12721627 (c.20716C/G, p.T185S), CYP2C8 rs11572080 (c.7225G/A, p.R69K)	(343)
Antineoplastic Drugs › Monoclonal Antibodies & Anthracycline	Trastuzumab-based chemotherapy	Cardiotoxicity: decline in left ventricular ejection fraction (LVEF)	ERBB2 rs1136201 (I655V) rs1058808 P1170A, rs1136201 (I655V), rs1058808 P1170A	(344)
Antineoplastic Drugs › Monoclonal Antibodies	Bevacizumab	Grade 3-4 hypertension	SV2C (rs6453204)	(345)
Antineoplastic Drugs › Monoclonal Antibodies	Bevacizumab	Early grade 3+ hypertension	rs9381299, rs834576	(346)
	Bevacizumab	Early grade 3+ hypertension	rs6929249, rs3734704	
	Bevacizumab	Systolic blood pressure >180 mm Hg	rs9381299	
Antineoplastic Drugs › Monoclonal Antibodies	Cetuximab	Grades 2–3 skin toxicity	EGF c.61A > G (rs4444903), EGFR CA14–22 (CA-repeat polymorphism in intron 1 of the EGFR gene), CCND1 c.932G > A (rs9344; 870G > A), FCGR2A c.535A > G (rs1801274), FCGR3A c.818A > C (rs396991)	(347)
Antineoplastic Drugs › Monoclonal Antibodies	Cetuximab	Grade ≥2 skin rash (SR)	Asn283Lys in PIK3R3	(348)
	Cetuximab	Rash (SR)	rs602990, rs785467, rs16858808, rs41292521	
	Cetuximab	Lethargy	Val906Ile in MAP3K1	
	Cetuximab	Nausea/vomiting	His321Arg in RASAL1, Arg574Pro in MMP9	
	Cetuximab	Diarrhoea	Lys344Thr in RPS6KA1, Val906Ile in MAP3K1	
	Cetuximab	stomatitis	Arg298His in PTGES2, Met322Thr in TSC1, Phe212Val in FCGR3A, c.1-1671insA in MMP3	
	Cetuximab	HFS	c.1–382 A>G in EGF, Pro1170Ala in ERBB2, Cys141Phe in EREG, Asp806Asn in MAP3K1	
	Cetuximab	Hypomagnesaemia	Tyr187His in DUSP1	
	Cetuximab	Nail changes	Arg335Cys in IL8RA, Glu920Val in EGF, Lys220Arg in PLAUR	
Antineoplastic Drugs › Monoclonal Antibodies	CHOP	Grade 3 or 4 anaemia	FcγRIIa R/R	(349)
	CHOP	Grade 3 or 4 anaemia	FcγRIIa R/H, FcγRIIa H/H	
	CHOP	Grade 3 or 4 leukocytopenia and thrombocytopenia, grade 3 or 4 infections	FcγRIIa (rs1801274) and FcγRIIIa (rs396991) SNPs	
	CHOP	Therapy-associated deaths	FcγRIIa (rs1801274)	
Antineoplastic Drugs › Monoclonal Antibodies	Trastuzumab	Cardiotoxicity	Ala1170Pro homozygous ERBB2 (Ala/Ala) vs. Pro/Pro + Ala/Pro	(350)
	Trastuzumab	Cardiotoxicity	FcgR3A Val158Phe, FcgR2B Ile232Thr, FcgR2A His166Arg, HER2 Ile655Val, HER2 Ile654Val	
Antineoplastic Drugs › Monoclonal Antibodies	Trastuzumab	Cardiotoxicity	HER2-I655V	(351)
	Trastuzumab	Cardiotoxicity	FCGR2A–H131R, FCGR3A–V158F	
Antineoplastic Drugs › Platinum Compounds	Platinum-based chemotherapy	High-grade neutropenia	GSTP1 105Val allele, GSTP1*B allele	(352)
	Platinum-based chemotherapy	Grade 0 mucositis	GSTP1 105Val allele	
	Platinum-based chemotherapy	Non-haematological toxicity	GSTP1 114 allele	
	Platinum-based chemotherapy	Toxicity for haemoglobin level or total white cell count	GSTP1 105Val allele, GSTP1*B allele	
Antineoplastic Drugs › Platinum Compounds	Oxaliplatin	Overall grades 3–4 toxicity	GSTP1 codon 105 polymorphisms	(353)
	Oxaliplatin	Grades 3–4 vomiting	GSTP1 105 Val/Val	
	Oxaliplatin	Grades 3–4 neurotoxicity	GSTP1 codon 105 Ile/Ile	
Antineoplastic Drugs › Platinum Compounds	Oxaliplatin	Peripheral neuropathy	Pro379Ser or Glu875Gly in ERCC4, Asp425Ala, Gly446Asp, or Ser797Cys in ERCC6	(354)

	Oxaliplatin	Peripheral neuropathy	ERCC6 Gly399Asp, ERCC6 Arg1213Gly, ERCC6 Arg1230Pro, ERCC6 Gln1413Arg	
Antineoplastic Drugs › Platinum Compounds	Oxaliplatin	Toxicity	Homozygosity for (ATM) rs1801516 or (ERCC5) rs1047768	(355)
	Oxaliplatin	Grades 3–4 toxicity	ERCC2 (rs238406)	
	Oxaliplatin	Grades 3–4 toxicity	MGMT AGT, rs1803965 and rs12917, ligase I (LIG1, rs3730849)	
	Oxaliplatin	Grades 3–4 toxicity	ERCC2 rs238406	
Antineoplastic Drugs › Proteasome Inhibitors & Vinca Alkaloids	Bortezomib	Early-onset bortezomib-induced peripheral neuropathy	CASP9 rs4646091, ALOX12 rs1126667, rs434473, RDM1 rs2251660, LSM1 rs7823144	(356)
	Bortezomib	Early-onset bortezomib-induced peripheral neuropathy	IGF1R rs1879612, NEK4 rs1029871	
	Bortezomib	Late-onset bortezomib-induced peripheral neuropathy	PPARD rs2267668, ATM rs189037, rs664677, rs664982	
	Bortezomib	Late-onset bortezomib-induced peripheral neuropathy	ERCC4 rs1799800, rs1799801, ERCC3 rs2276583, MRE11A rs10501815	
	Vincristine	Grade 2–4 early-onset vincristine-induced peripheral neuropathy	GLI1 (rs2228224) and rs2242578	
	Vincristine	Grade 2–4 early-onset vincristine-induced peripheral neuropathy	SNPs (rs7739752, rs6901410, rs6902123, and rs6457816) in PPARD, (rs909253) and (rs1041981) in LTA, ABCC4 rs2274407, ABCC5 rs3749442, SLC10A2 rs3803258, ALDH1A1 rs2288087, rs1413239 in DPYD, rs3887412 in ABCC1	
Antineoplastic Drugs › Proteasome Inhibitors	Bortezomib	Peripheral Neuropathy	PKNOX1 rs2839629	(357)
Antineoplastic Drugs › Protein Kinase Inhibitors	Lapatinib	Liver Injury	HLA-DRB1*07:01, HLA-DQA1*02:01	(358)
Antineoplastic Drugs › Protein Kinase Inhibitors	Lapatinib (l in combination with trastuzumab and/or taxanes)	Liver Toxicity	HLA-DRB1*07:01	(359)
Antineoplastic Drugs › Protein Kinase Inhibitors	Pazopanib	reversible ALT elevation	rs2858996 and rs707889 in HFE gene	(360)
Antineoplastic Drugs › Protein Kinase Inhibitors	Sorafenib	Cytotoxicity	FLT4 rs307826 (A>G, T494A), VEGFA rs58159269 (T>C)	(361)
Antineoplastic Drugs › Taxanes & & Anthracyclines & Alkylating Agents	Anthracycline-based chemotherapy (docetaxel, doxorubicin, cyclophosphamide)	Febrile Neutropenia	388C>T in FGFR4 (rs351855) vs. CC	(362)
	Anthracycline-based chemotherapy (docetaxel, doxorubicin, cyclophosphamide)	Febrile Neutropenia	TP53 (rs1042522) 82G>C (CC genotype)	
Antineoplastic Drugs › Taxanes & Alkylating Agents & Anthracyclines	ddAC or TAC	Peripheral neuropathy	TECTA (TT, rs1829), GSTP1 (CT/TT, rs1138272)	(363)
	ddAC or TAC	Anaemia	FGFR4 (CC vs CT/TT), ABCB1 (TT/TC vs CC) and ABCC4 (GG vs GT/TT), no significant interaction between a clinical variable or SNP and treatment (ddAC vs TAC) for the risk of developing anaemia	
	ddAC or TAC	Febrile neutropenia	GSTP1 (AG rs1695 and CC rs1138272 vs other; rs1695 AA vs AG/GG), ABCB1 (TT vs TC/CC), ABCG2 (CC vs CA/AA), MDM2 (TT/TG vs GG), SLCO1B3 (AA vs AG/GG), ABCC4 (GG vs GT/TT), a haplotype of ABCB1 and CYP1B1 (rs1045642*rs1056836), ABCC2 (CC/CG vs GG), GSTP1 rs1695 AG and rs1138272 CC	

	ddAC or TAC	Peripheral neuropathy (PNP)	GSTP1 (105) Ile/ (105) Ile vs. GSTP1105Ile/105Val or 105Val/105Val, RWDD3 (rs2296308) (GG/GT vs TT)	
	TAC vs ddAC	Febrile neutropenia	FGFR4 (rs351855), GSTP1 rs1695 AG and rs1138272 CC	
Antineoplastic Drugs › Taxanes & Platinum Compounds	Carboplatin/Taxane	Grade III/IV GI toxicity	rs1061472, ATP7B, A→G, risk genotype: AA), (rs1801249 ATP7B A→G, AA), (rs3594 GSR A→G, CC), (rs6900017 VEGFA A→G, AA), (rs879825 VEGFA A→G, GG), (rs9369421 VEGFA A→G, GG), (rs9825762 SCN10A A→G, AA)	(364)
Antineoplastic Drugs › Taxanes & Platinum Compounds	Docetaxel/Cisplatin	Haematological toxicities/grade 3–4 neutropenia	CYP3A5 A6986G *3/*3 (GG) vs. AG or AA	(365)
	Docetaxel/Cisplatin	Haematological toxicities	[CYP3A4 (-A392G): *1A/*1A (AA), *1A/*1B (AG), *1B/*1B (GG)], [ABCB1 (C3435T): C/C, C/T, T/T], [ABCB1 (G2677T/A): G/G, G/T(A), T(A)/T(A)]	
Antineoplastic Drugs › Taxanes & Platinum Compounds	Paclitaxel plus Carboplatin	Grade 4 neutropenia	ABCB1 3425C->T, Com v Het/Var (CC v CT/TT), CYP2C8 R139K, Com v Het/Var (GG v GA/AA), CYP3A4*1B, Com v Het/Var (AA v AG/GG), CYP3A5*3C, Com/Het v Var (AA/AG v GG), ERCC1, TT v TC/CC, ERCC2 K751Q, Com v Het/Var (AA v AC/CC), nr1I2-206 del, Com v Het/Var 206 deletion	(366)
Antineoplastic Drugs › Taxanes & Platinum Compounds	Paclitaxel/Carboplatin	Neutropenia, Sensory Neuropathy	CYP2C8*3 [CYP2C8 rs10509681, A1196G (*3)], ABCB1 rs1128503 C1236T, ABCB1 rs2032582 G2677T/A, ABCB1 rs1045642 C3435T	(367)
Antineoplastic Drugs › Taxanes & Platinum Compounds	Paclitaxel/Carboplatin (Arm B: Taxol IV infusion and carboplatin)	Myelosuppression	ABCB1 1236TT, 2677TT and 3435TT in All and Arm B	(368)
	Paclitaxel/Carboplatin (Arm A Paclical IV infusion and carboplatin)	Neutrophil toxicity	ABCB1 3435C>T	
Antineoplastic Drugs › Taxanes & Platinum Compounds	Taxanes and platinum	Grade 3-4 GI toxicity	ABCB1 1236C>T, ABCB1 2677G>T/A, ABCB1 3435C>T, ABCC1 S1334S, ABCC1 IVS18-30C>G, ABCC2–24C>T, ABCC2 IVS12+148A>G, ABCC2 V417I, ABCG2 Q141K, CDKN1A 10971C>T, CYP1B1*3, CYP2C8 M264I, CYP2C8 R139K, CYP2C8 K399R, CYP3A4*1B, CYP3A5*3C, ERCC1 17677G>T, ERCC1 8092C>A, ERCC1 N118N, ERCC2 K751Q, GSTP1 A114V, GSTP1 I105V, MAPT P587P, MPO -463G>A, TP53 R72P, XRCC1 R399Q, combined CYP1B1*3 and CDKN1A10971C	(369)
Antineoplastic Drugs › Taxanes	Docetaxel, prednisone and bevacizumab	Neuropathy	FGD4 (rs10771973), EPHA4 (rs17348202), EPHA5 (rs7349683), intergenic (rs3125923), FCAMR (rs1856746, GSTP1 Ala114Val (rs1138272), ABCB1 1236C>T (rs1128503), ABCB1 (rs4148738), ABCB1 3435C>T (rs1045642)	(370)
Antineoplastic Drugs › Taxanes	Docetaxel [doxorubicin–docetaxel arm (arm A) and doxorubicin–cyclophosphamide arm (arm B)]	Febrile neutropenia	SLCO1A2 rs4762699 and rs2857468 Haplotype T–T	(371)
	Doxorubicin–docetaxel	Febrile neutropenia	CYP1B1 (rs10916, rs2855658, rs1056837, rs1056836, rs162549, rs1056827, rs4646429, rs10012, rs162556, rs1800440, rs2551188), CYP3A4 (rs4646437, rs2242480, rs12333983, rs2740574, rs2246709), CYP3A5 (rs4646450, rs776746), SLCO1B3 (rs11045586, rs11045595, rs1515766, rs7970514, rs1356148, rs2117032, rs10770757, rs1017385, rs10841661), ABCB1 (rs17064, rs2235015, rs2235023, rs1045642, rs12720067, rs7787082, rs10248420, rs4148740, rs10280101, rs2032583,rs11983225, rs2235040, rs1128503, rs868755, rs3842, rs2235013, rs2235033), ABCC2	

			(rs2002042, rs2756109, rs2273697, rs11190291, rs4148398, rs3740065, rs3740066, rs2756112, rs17222723, rs1137968, rs8187707, rs717620, rs2756103), ABCG2 (rs2725252, rs2622610, rs13120400, rs2231148, rs2231164, rs2725270, rs2622604, rs1564481, rs9999111, rs1481012, rs12505410, rs2622621, rs6857600, rs2622626)	
Antineoplastic Drugs › Taxanes	Taxanes [cyclophosphamide I, doxorubicin (A) and paclitaxel (T)]	Grade 3-4 neurotoxicity	(rs7637888, rs6786638, rs6442150, rs7648104), FANCD2 haplotypes: rs7648104-rs7637888 (A-G haplotype), rs3846177-rs9849434 A-T-A-G-A-A-G-G-G-G-A, rs1552244-rs12152512 G-A-C-G-A-G-G-A	(372)
	Taxanes [cyclophosphamide I, doxorubicin (A) and paclitaxel (T)]	Neuropathy	(FANCD2: rs3846177 A/C, rs9881859 T/A, rs9875081 A/G, rs9879080 A/G, rs3895942 G/C, rs6805869 G/A, rs9849434 A/G, rs6807485 C/G, rs1552244 G/A, rs7610821 A/G, rs2272125 C/A, rs2272124 G/A, rs2272123 A/G, rs7647987 G/A, rs3172417 A/G, rs12152512 A/G) (BRCA1: rs8176305, rs8070179, rs8176257, rs8176242, rs8176237, rs3737559, rs8176161, rs8176160, rs16942, rs4986850, rs1799950, rs799923, rs8176109, rs8176098)	
Antineoplastic Drugs › Taxanes	Paclitaxel	Clinician-reported neuropathy or patient-reported neuropathy	(MAPT; rs242557 and rs1052553), (GSK3B; rs6438552 and rs3755557), CEP72 rs924607, (TUBB2; rs909961)	(373)
	Paclitaxel	Patient-reported neuropathy	MAPT additive SNPs (rs1052553 and rs242557)	
	Paclitaxel	Clinician reported neuropathy	GSK3B additive SNPs (rs3755557 + rs6438552)	
Antineoplastic Drugs › Taxanes	Paclitaxel	Neuropathy	EPHA5-rs7349683, EPHA6-rs301927, EPHA8-rs209709	(374)
Antineoplastic Drugs › Taxanes	Paclitaxel	Peripheral Neuropathy	CYP2C8*3 variant (c.416G>A)	(375)
	Paclitaxel	Peripheral Neuropathy	FGD4 c.2044-236 A-allele	
Antineoplastic Drugs › Taxanes	Paclitaxel	Sensory Peripheral Neuropathy	FGD4 rs10771973	(376)
Antineoplastic Drugs › Taxanes	Taxanes	Peripheral neuropathy Grade 3-4, peripheral neuropathy Grade 2-4	rs3125923, rs9862208	(377)
Antineoplastic Drugs › Topoisomerase I Inhibitors & Antimetabolites & Platinum Compounds & Monoclonal Antibodies	FOLFIRI or FOLFOXIRI plus bevacizuma	Haematological ADEs and stomatitis	DPYD c.1905+1G/A and c.2846A/T, UGT1A1*28	(378)
	FOLFIRI or FOLFOXIRI plus bevacizumab	Stomatitis	DPYD c.1905+1G>A, DPYD c.2846A>T, DPYD c.1905+1G>A and DPYD c.2846A>T	
	FOLFIRI or FOLFOXIRI plus bevacizumab	Neutropenia, Overall toxicity, Gastrointestinal ADEs Overall	DPYD c.1905+1G>A and DPYD c.2846A>T	
	FOLFIRI or FOLFOXIRI plus bevacizumab	Thrombocytopenia, Anaemia	DPYD c.1905+1G>A	
Antineoplastic Drugs › Topoisomerase I Inhibitors & Antimetabolites & Platinum Compounds	IROX	Grade 4 neutropenia	Homozygous UGT1A1*28 allele	(379)
	FOLFOX	Grade 4 neutropenia	GSTM1*0 (Deletion in GSTM1)	
	IFL	Severe neutropenia	GSTM1*0 (Deletion in GSTM1)	
	FOLFOX	Discontinue FOLFOX because of neurotoxicity	GSTP1 I105V genotype of T/T	
	IROX	Grade 3 neurotoxicity	GSTP1 I105V genotype of T/T	
	FOLFOX	Grade ≥ 3 neurotoxicity	GSTP1 I105V genotype of T/T	
	IROX	Grade 3 vomiting	UGT1A1 −3156 C>T [or UGT1A1*93 (A/A)]	
		Neurotoxicity	ABCB1 1236 C>T, ABCB1 3435 C>T, ABCB1 2677 G>T, ABCC1 IVS18-30 C>G, ABCC1 4002 G>A, ABCC2 −24 C>T, ABCC2 4544 G>A, ABCC2 1058 G>A, ABCC2 1249 G>A,	

			ABCC2 3972 G>A, ABCG2 421 C>A, CYP3A4 −329 A>G (*1B), CYP3A4 1334 T>C (*3), CYP3A5 6986 A>G (*3C), CYP3A5 14690 G>A (*6), DPYD IVS14 + 1 G>A (*2A), DPYD 1627 A>G (*5), DPYD 2194 G>A (*6), DPYD 85 T>C (*9A), ERCC1 354 C>T, ERCC2 −1989 A>G, ERCC2 2133 C>T, ERCC2 2251 A>G, GSTM1 *0, GSTP1 2293 C>T, GSTP1 1578 A>G, MTHFR 677 C>T, MTHFR 1298 A>C, MTHFR 1793 G>A, TYMS 1494del, TYMS TSER, UGT1A1 −3156 G>A (*93), UGT1A1 (TA)nTAA (*28), XRCC1 1196 G>A	
Antineoplastic Drugs › Topoisomerase I Inhibitors & Antimetabolites & Platinum Compounds	FOLFOX [FU+leucov (LV5FU2) #(FOLFOX)#(FOLFIRI)]	Grade 3 or 4 haematological toxicity	ERCC2-K751QC allele	(380)
	FOLFIRI	Severe haematological or GI toxicity	UGT1A1 (UGT1A1*28 and UGT-3156G>A)	
	LV5FU2	Toxicity, whether haematological or GI	No statistically significant association was found between any genotype	
	LV5FU2 or FOLFOX or FOLFIRI	Severe (grade 3-4) haematological toxicity	No statistically significant association was found between any genotype	
	LV5FU2 or FOLFOX or FOLFIRI	Severe (grade 3-4) GI toxicity	No statistically significant association was found between any genotype	
	FOLFOX	Severe GI or severe (≥ grade 2) oxaliplatin-induced peripheral neuropathy	No statistically significant association was found between any genotype	
Antineoplastic Drugs › Topoisomerase I Inhibitors & Antimetabolites & Platinum Compounds	IrFU or OxFU versus FU alone	Toxicity	(DPYD) IVS14+1G>A (DPYD*2A); (TYMS-ER) 28 base pair (28-bp) repeat; (TYMS-1494) 6-bp insertion; (MTHFR) C667T; (MLH1) −93G>A; (UGT1A1*28); (ABCB1) 3435C>T; (XRCC1) R399Q; (GSTP1) Ile105Val; (ERCC2) K751Q	(381)
	Irinotecan-containing treatment	Toxicity	XRCC1 R399Q G/G, G/A, and A/A, XRCC1 genotype	
	Irinotecan or IrFU over FU	Toxicity	ERCC2, XRCC1, and GSTP1	
	Irinotecan-containing treatment	Toxicity/≥ 3 neutropenia and diarrhoea	UGT1A1*28 7/7 (vt) or 6/7 (ht)	
Antineoplastic Drugs › Topoisomerase I Inhibitors & Antimetabolites	5-fluorouracil/leucovorin/irinotecan	Grade III-IV neutropenia	UGT1A*28	(382)
	FOLFIRI	Grade III–IV neutropenia	UGT1A*28 [UGT1A1 7/7]	
	LV/5FU	Grade III–IV neutropenia	UGT1A*28 [UGT1A1 7/7]	
	FOLFIRI	Neutropenia grade III–IV	UGT1A*28 [UGT1A1 7/7]	
	Both arms	Diarrhoea grade III or more	UGT1A*28 [UGT1A1 7/7]	
	FOLFIRI arm	Total serious ADEs	UGT1A*28 [UGT1A1 7/7]	
Antineoplastic Drugs › Topoisomerase I Inhibitors & Antimetabolites	Irinotecan and 5-fluorouracil	Clinically relevant early toxicity	ABCB1 3435 T/T genotype, UGT1A1(*)28/(*)28 genotype, homozygous for the ABCB1 1236T–2677T–3435T haplotype, MTHFR 677 heterozygotes compared with C/C and T/T, heterozygous for TYMS*2/*3	(383)
	Irinotecan and 5-fluorouracil	Clinically relevant early toxicity	MTHFR 677–1298 haplotypes	
	Irinotecan and 5-fluorouracil	Neutropenia and diarrhoea	UGT1A1(*)28/ (*)28	
	Irinotecan and 5-fluorouracil	Overall toxicity: any grade 3–4 toxicity except alopecia	[UGT1A1 (TA)n wt/*28, *28/*28], [UGT1A1 −3279 *60/*60, wt/*60], [ABCB1 1236 C/T, T/T], [ABCB1 2677 T/T, G/T, G/A + T/A], [ABCB1 3435 T/T, C/T], [TYMS 28 bp repeat *3/*3, *2/*3], [MTHFR 677 T/T, C/T], [MTHFR 1298 C/C, A/C]	
Antineoplastic Drugs › Topoisomerase I Inhibitors & Antimetabolites	Irinotecan and fluorouracil	Haematological toxicity	UGT1A1*28/*28	(384)
		Neutropenia	UGT1A1*28/*28	
		Neutropenia together with diarrhoea	UGT1A1*28/*28	

		Non-haematological toxicity	UGT1A9*1/*1, Haplotype VII	
Antineoplastic Drugs › Topoisomerase I Inhibitors & Platinum Compounds	Irinotecan plus cisplatin	Grade 3 or worse diarrhoea	ABCB1 (C3435T) T/T compared with C/C and C/T	(385)
	Irinotecan plus cisplatin	Grade 3 or worse neutropenia	UGT1A1 (G-3156A) A/A	
	Irinotecan plus cisplatin	Grade ≥ 3 neutropenia and diarrhoea	ABCB1 (C3435) T/T, UGT1A1 (G-3156A) A/A	
Antineoplastic Drugs › Topoisomerase I Inhibitors & Platinum Compounds	irinotecan/cisplatin	Grade 1-4 late-onset diarrhoea	UGT1A1*28 allele	(386)
	irinotecan/cisplatin	Grade 1-4 late-onset diarrhoea	UGT1A1*6 allele	
Antineoplastic Drugs › Topoisomerase I Inhibitors	Capecitabine single agent or plus irinotecan	Grades 3–4/ Diarrhoea, grades 3–4/ febrile neutropenia	GSTP1 Ile105Val	(387)
Antineoplastic Drugs › Topoisomerase I Inhibitors	Fluoropyrimidine-based chemotherapy	Toxicity	DPYD (Cys29Arg and Val732Ile)	(388)
	Fluoropyrimidine-based chemotherapy	Neutropenia, nausea and vomiting, diarrhoea and infection	Asp949Val	
	Fluoropyrimidine-based chemotherapy	Diarrhoea, stomatitis, hand-foot syndrome and infection	IVS14+1G>A	
	Fluoropyrimidine-based chemotherapy	Peripheral neuropathy	DCLRE1A Asp317His	
	Xelox compared with OxMdG	infection	Asp949Val	
	Fluoropyrimidine-based chemotherapy	lethargy, diarrhoea, stomatitis, HFS and infection	IVS14+1G>A	
Antineoplastic Drugs › Topoisomerase I Inhibitors	Fluoropyrimidine-based chemotherapy (5-FU)	Grade ≥3 overall ADEs	DPYD*2A, D949V	(389)
	Fluoropyrimidine-based chemotherapy (5-FU)	Neutropenia, specific ADEs nausea/vomiting and neutropenia, or ADEs nausea/vomiting	DPYD*2A	
	Fluoropyrimidine-based chemotherapy (5-FU)	5FU-ADEs or overall grade ≥3 ADEs	DPYD I560S	
	Fluoropyrimidine-based chemotherapy (5-FU)	DFS	None of the DPYD variants	
	Fluoropyrimidine-based chemotherapy (5-FU)	Dehydration, diarrhoea, leukopenia, neutropenia, thrombocytopenia	D949V	
Antineoplastic Drugs › Topoisomerase I Inhibitors	Fluoropyrimidine-based chemotherapy (5-FU)	Grade 3 or greater fluorouracil ADEs	D949V and V732I (DPYD*6)	(390)
	Fluoropyrimidine-based chemotherapy (5-FU)	Grade 3 or greater overall haematological ADEs, grade 3 or greater fluorouracil ADEs and overall haematological ADEs, grade 3 or greater neutropenia	V732I	
	Fluoropyrimidine-based chemotherapy (5-FU)	Grade 3 or greater overall haematological ADEs	D949V	
Antineoplastic Drugs › Topoisomerase I Inhibitors	Irinotecan	Grade 3 diarrhoea	rs1517114 (C8orf34), rs1661167 (FLJ41856), rs2745761 (PLCB1)	(391)
	Irinotecan	Grade 4 neutropenia	rs11128347 (PDZRN3), rs11979430 (SEMAC3), rs7779029 (SEMAC3)	
	Irinotecan	irinotecan related G3D and G4N	SLCO1B1 521T>C, UGT1A9*22, ABCC2 3972C>T, ABCG2 34G>A	
Antineoplastic Drugs › Topoisomerase I Inhibitors	Irinotecan	Severe haematological toxicity in arm A	3435C>T for ABCB1, 6986A>G for CYP3A5, UGT1A1*28	(392)
	Irinotecan	Toxicity	6986A>G (CYP3A5),3435C>T (ABCB1)	

	Irinotecan	Severe haematological toxicity	Homozygous for the mutant allele of −3156G>A UGT1A1 compared with homozygous for the wild-type allele	
	Irinotecan	Severe gastrointestinal toxicity (grade 3 or more diarrhoea, nausea, vomiting, or mucositis)	UGT1A1 promoter TA indel, UGT1A1 −3156G>A, CYP3A5 6986A>G, ABCB1 3435C>T	
Antineoplastic Drugs › Topoisomerase I Inhibitors	Irinotecan-containing regimens	Grade 4 neutropenia	homozygous or heterozygous for UGT1A1*6 and UGT1A1*27	(393)
	Irinotecan-containing regimens	Grade 4 neutropenia	UGT1A1*28, UGT1A1*60, UGT1A7, UGT1A9*22	
	irinotecan-containing regimens	Toxicity	UGT1A1*28	
	Irinotecan-containing regimens	Grade 3 diarrhoea	UGT1A1*6, UGT1A1*27, UGT1A1*28, UGT1A1*60, UGT1A7, UGT1A9*22	
Antineoplastic Drugs › Topoisomerase I Inhibitors	Irinotecan	Neutropenia	UGT1A1 genotype 7/7	(394)
Antineoplastic Drugs › Topoisomerase I Inhibitors	Irinotecan (given as semisolid matrix capsules)	Severe toxicity	UGT1A1*28	(395)
Antineoplastic Drugs › Topoisomerase I Inhibitors	Irinotecan	Severity, and duration of delayed-type diarrhoea	UGT1A1*28	(396)
	Irinotecan	Grade 2–3 diarrhoea	At least one UGT1A1*28 allele	
Antineoplastic Drugs › Vinca Alkaloids	Vincristine	severe neuropathy episodes (grades 3–4)	CEP72 rs924607 TT	(397)
Antiplatelet Drugs	Clopidogrel, Prasugrel	Major or minor bleeding not related to coronary artery bypass grafting	ABCB1 3435C→T (TT vs. CT/CC)	(398)
Antiplatelet Drugs	Clopidogrel-aspirin treatment	Bleeding [minor bleeding, moderate bleeding, severe bleeding, and any bleeding event]	CYP2C19 LOF carriers compared with non-carriers	(399)
Antiplatelet Drugs	Clopidogrel or Prasugrel	Major, minor, and clinically relevant bleeding All bleeding events	EM or IM+PM	(196)
Antiplatelet Drugs	Clopidogrel or Prasugrel	Major or minor bleeding	CYP2C19 EM, CYP2C19 RM	(197)
Antiplatelet Drugs	Clopidogrel	Bleeding	CYP2C19 loss-of-function allele (ie, *2 or *3): *1/*2, *1/*3, *2/*2, *2/*3, *3/*3, or CYP2C19 *2/*17, *3/*17 or CYP2C19*2(681G>A), CYP2C19*3(636G>A), CYP2C19*17(-806C>T)	(198)
Antiplatelet Drugs	Clopidogrel	Major or minor bleeding	CYP2C19 genotypes	(199)
Antiplatelet Drugs	Clopidogrel	Bleeding	CYP2C19: Metabolizer phenotype, loss-of-function carrier status, or gain-of-function carrier status	(200)
Antiplatelet Drugs	Clopidogrel	Major bleeding/ Minor bleeding	Rapid and slow metabolizer phenotype CYP2C19	(400)
Antiplatelet Drugs	Clopidogrel	Major bleeding at 12 months	CYP2C19 extensive metabolizers (EM), intermediate metabolizers (IM), poor metabolizers (PM)	(201)
	Clopidogrel	Bleeding	CYP2C19: LOF allele	(202)
	Clopidogrel	Bleeding	CYP2C19: LOF allele	(203)
	Clopidogrel	Bleeding	CYP2C19: LOF allele	(204)
	Clopidogrel	Bleeding	CYP2C19: LOF allele	(205)
	Clopidogrel	Bleeding	CYP2C19: LOF allele	(206)
	Clopidogrel	Bleeding	CYP2C19: LOF allele	(207)
	Clopidogrel	Bleeding	CYP2C19: LOF allele	(208)
Antiplatelet Drugs	Clopidogrel	Major bleeding	PON1 Q192R	(401)
Antiplatelet Drugs	Prasugrel	Major or Minor Bleeding	[CYP2C19 *1A, *2A, *3, *4, *5A, *6, *7, *8, *9, *10, *12, *13, *14, *17a], [CYP2C9 *1A, *2A, *3A, *4, *5, *6, *8, *9, *10, *11A, *12], [CYP2B6 *1A, *1C, *6, *8, *9, *11, *12, *13, *14, *15],	(402)

			[CYP3A5 *1A, *3A, *3B, *3D, *3F, *6, *8, *9, *10], [CYP3A4 *1A, *17, *18], [CYP1A2 *1A, *1C, *1D, *1E, *1K, *1L, *7]	
	Prasugrel/Ticagrelor	Bleeding	CYP2C19: LOF allele	(209)
	Prasugrel/Ticagrelor	Bleeding	CYP2C19: LOF allele	(210)
	Prasugrel/Ticagrelor	Bleeding	CYP2C19: LOF allele	(211)
	Prasugrel/Ticagrelor	Bleeding	CYP2C19: LOF allele	(212)
Antiplatelet Drugs	Clopidogrel	Major bleeding related to non-coronary artery bypass graft (CABG)	CYP2C19 any gain-of-function allele	(213)
	Ticagrelor	Major bleeding related to non-coronary artery bypass graft (CABG)	ABCB1 3435C→T	
Antiplatelet Drugs › GPIIB-IIIA Antagonists	Orbofiban	Bleeding	COL3A1-3 Carriers of allele 3 (versus noncarriers)	(403)
Antiplatelet Drugs › GPIIB-IIIA Antagonists	Orbofiban	Bleeding	−5C or the VNTR polymorphisms, Polymorphisms in the platelet receptor glycoprotein (GP) Ibα	(404)
Antiplatelet Drugs › GPIIB-IIIA Antagonists	Orbofiban	Bleeding	Glycoprotein IIIa (GPIIIa) PI(A) polymorphism	(405)
Antiplatelet Drugs › GPIIB-IIIA Antagonists	Orbofiban	Bleeding	GNB3 (825C>T)	(406)
Antiplatelet Drugs › GPIIB-IIIA Antagonists	Orbofiban	Bleeding events (severe, major, minor and recurrent)	GPIIb/IIIa PLA2, GPIbα −5C, MMP9 −1562T	(407)
Antiprotozoals & Analgesics › Non-Steroidal Anti-inflammatory Drugs	Eflornithine and Sulindac	Ototoxicity	ODC1 AA	(408)
Antipsychotics	Antipsychotic Medications	Tardive Dyskinesia	2,580 SNPs in 118 candidate genes: No single marker or haplotype, the strongest association was for SLC18A2/rs2015586	(409)
Antipsychotics	Antipsychotic Medications (Olanzapine, Perphenazine, Quetiapine, Risperidone or Ziprasidone)	Excessive weight gain as >7% weight gain	[FTO rs17819033, rs7188300, rs11861870, rs12932373], [LEPR rs6690625, rs3828039, rs4655555], [PCSK1 rs1498928], [CHD7 rs11997122, rs11990117]	(410)
Antipsychotics	Antipsychotic Medications (haloperidol, olanzapine, risperidone, ziprasidone, aripiprazole, or quetiapine)	Weight gain during the first year of antipsychotic treatment	FTO rs9939609 AA, AT, TT, SH2B1 rs7498665, LEP rs7799039 (j2548 G9A), LEPR rs1137101 (Q223R)	(411)
Antipsychotics	Second-generation antipsychotic and mood stabilisers and their combinations	Weight gain	rs9997787 TBC1D1 T/T, rs2911927 TBC1D1 C/C, rs6127676 MC3R T/T, rs2111112 FTO G/G, rs17497040 TBC1D1 T/C, rs13353739 TBC1D1 A/A, rs602618 ADRA2A C/C, rs4911874 HTR2C T/A, rs17700926 MC4R C/T, rs1133398 MTHFR A/A, rs242728 GHRL A/G, rs1560214 LEP A/A, rs617156 HRH1 A/A, rs9932411 FTO C/T, rs4728108 LEP A/A, rs2562730 LEP A/A, rs17424192 TBC1D1 G/G, rs3928987 FTO C/C, rs5946197 HTR2C C/T, rs2665272 FTO T/T, rs9930506 FTO T/T, rs4145870 HTR2C A/G, rs4731454 LEP C/C, rs1121980 FTO T/C, rs1943226 MC4R C/C, rs10860847 PMCH T/T, rs12935710 FTO G/G, rs5946229 HTR2C A/G, rs6644132 HTR2C T/C, rs9940128 FTO T/C, rs9939973 FTO T/C	(412)
Antipsychotics › First-Generation & Second Generation	Antipsychotic medications (olanzapine, quetiapine, risperidone, ziprasidone and perphenazine)	Overall tolerability, or tardive dyskinesia	CYP1A2*1F C(-163)A, CYP2D6*2 C2850T, CYP2D6*3 A2549del, CYP2D6*4 C100T G1846A, CYP2D6*5 CYP2D6 deleted, CYP2D6*6 T1707del, CYP2D6*9 AGA2613del, CYP2D6*10 C100T, CYP2D6*17 C1023T C2850T, CYP2D6*29 G3183A, CYP2D6*41 G2988A, CYP2C19*2 G681A, CYP2C8*2 A805T, CYP2C8*3 G416A A1196G, CYP2C9*2 C3608T, CYP2C9*3 A42614C, CYP3A4*1B A(-392)G, CYP3A5*3 A6986G, CYP3A5*6 G14690A, ABCB1 Ile1145 C3435T, ABCB1 Ala893Ser G2677T, FMO3	(413)

			Glu308Gly A21443G, FMO3 Glu158Lys G15167A, UGT1A4 Pro24Thr C70A, UGT1A4 Val48Leu T142G	
Antipsychotics › First-Generation & Second Generation	Antipsychotic medications (perazine, olanzapine or ziprasidone)	Body weight changes, Extrapyramidal ADEs	Several gene polymorphisms: COMT, MAOA, GRIK3, 5HT2A, DAT, SERT, DRD2 ins/del, DRD2 Taq1A, DRD2 exon 8	(414)
Antipsychotics › First-Generation	perphenazine	Prolactin elevation	DRD2 Taq1A A1/A1 genotype	(415)
	Perphenazine	Prolactin elevation	DRD2 Ser311Cys	
	perphenazine	Prolactin elevation	DRD2-141C ins/ins	
Antipsychotics › First-Generation Selective Dopamine D2 Antagonists	Antipsychotics (bromperidol and nemonapride)	Extrapyramidal ADEs	Taq1 A (one or two A1 alleles)	(416)
Antipsychotics › First-Generation Selective Dopamine D2 Antagonists	Antipsychotics (bromperidol and nemonapride)	Extrapyramidal ADEs	DRD2 -141C Ins/Del	(417)
Antipsychotics › Second Generation	Clozapine or Olanzapine	Weight gain	HCRTR2 rs3134701, HCRTR2 rs12662510	(418)
Antipsychotics › Second Generation	Aripiprazole	Akathisia	DRD2 rs2514218 C/C homozygotes	(419)
	Risperidone	Akathisia	DRD2 rs2514218 C/C homozygotes	
	Risperidone	Prolactin elevations	DRD2 rs2514218 T allele	
Antipsychotics › Second Generation	Aripiprazole	Severe insomnia	DAT1 VNTR: (VNTR) polymorphism in DAT1/SLC6A3 = 40 bp variable number tandem repeat (VNTR) polymorphism (rs28363170) in the 3′-untranslated region of the DAT gene (DAT1/SLC6A3)	(420)
	Aripiprazole	Somnolence, irritability, trouble concentrating, nausea/vomiting, dizziness, fatigue, blurry vision, and difficulty reaching orgasm	DAT1 VNTR: (VNTR) polymorphism in DAT1/SLC6A3 = 40 bp variable number tandem repeat (VNTR) polymorphism (rs28363170) in the 3′-untranslated region of the DAT gene (DAT1/SLC6A3)	
Antipsychotics › Second Generation	Iloperidone	Long QT interval syndrome	CYP2D6*4 (G1846A), CYP2D6*10 (C100T), KCNQ1 (position 79764 of contig AJ006345.1)	(421)
Antipsychotics › Second Generation	Iloperidone	Weight gain	HTR2C -759C/T polymorphism	(422)
Antipsychotics › Second Generation	Olanzapine	Fatigue	TPMT *1/*3A, *1/*3C *a, UGT1A1 *1/*1 ***a, MDR1 C/C *	(423)
	Olanzapine	Hypotension	CYP2C9 *3 *a, ADD1 Trp/Trp *	
	Olanzapine	Dizziness	TPMT *1/*3A, *1/*3C *, BCHE (Asp/Gly)	
	Olanzapine	Dry mouth	5-HTR2A His/Tyr *a, CYP3A4 *1/*1B, *1B/*1B *	
	Olanzapine	Syncope	GSTP1 A/A**, BCHE Ala/Thr, Thr/Thr *	
	Olanzapine	Irritability	MDR1 T/T	
	Olanzapine	QT prolongation	CYP1A2*1/*1, CYP2B6 T/T	
	Olanzapine	Vomiting	AGTR1 C/C, BCHE Asp/Gly, TNFα G/A	
Antipsychotics › Second Generation	Olanzapine	Prolactin increase	In women only: DRD2/ANKK1 region negative strand minor alleles: rs2734842I, rs6275(T), rs6279I	(424)
	Olanzapine	Change in prolactin	rs2734842, rs6279, rs6275, rs2734841, rs1124493	
	Olanzapine	Prolactin increase	rs6278, rs6276, rs1124491, rs1079594, rs6277	
	Olanzapine	Overall TEAEs, TEAEs in men, TEAEs in women, sexual dysfunction TEAEs, non-sexual dysfunction TEAEs	All DRD2 genotypes	
Antipsychotics › Second Generation	Olanzapine	Weight gain	DRD2: rs2440390(A/G), rs1079598(T/C), rs1079596(G/A), rs1125394(A/G), rs1125393(G/A), rs7103679(G/A), rs4648319(C/T), rs12364283, rs1800497 (Taq1A). Three HTR2C SNPs in strong linkage disequilibrium: rs6318, rs2497538, and rs1414334	(425)
	Olanzapine	Weight gain	HTR2C SNPs (−997G/A, −759C/T, or −697G/C), -759C/T (rs3813929), -697G/C (rs518147), C-C-C haplotype in HTR2C, [HTR2C haplotype C (-759C, -697C, and 23Ser)]	

Antipsychotics › Second Generation	Risperidone	Decrease in blood pressure, a mild increase in QTc and a quick increase in prolactin. Somnolence	PMs, IMs, UMs	(426)
Antipsychotics › Second Generation	Risperidone	Headache	CYP2C9: *1/*1, *1/*2, *1/*3 + *3/*3, NAT2: EM, IM, PM, AGTR1 A/A, A/C, C/C	(427)
	Risperidone	Neurological effects	CYP2C19: *1/*1, *1/*2, *2/*2 + *2/*4	
	Risperidone	Tiredness	[BDKRB2 C/C, C/T], [MTHFR C/C, C/T]	
	Risperidone	Hypotension	[VKORC1 G/G, G/A]	
	Risperidone	Dizziness	DRD2 Taq1A A1+A2/A2	
	Risperidone	Psychiatric ADEs	CYP2C9 *1/*1, *1/*2, *1/*3 + *3/*3], [HTR2A His/His, His/Tyr]	
	Risperidone	General ADEs	CYP3A5 *1/*3, *3/*3 + *3/*6], [GSTM1 Present, Absent], [MTHFR C/C, C/T]	
	Risperidone	Cardiovascular ADEs	UGT1A1 *1/*28, *28/*28	
	Risperidone	Gastrointestinal ADEs	SLC6A4 Ins/Ins, Ins/Del, Del/Del	
	Risperidone	Genitourinary ADEs	[ADRB1 Gly/Gly, Gly/Arg], [GRIN2B C/C, C/T]	
Antipsychotics › Second Generation	Risperidone	Increases in prolactin	DRD2 alleles (Taq1A, -141C Ins/Del, C957T)	(428)
Antipsychotics › Second Generation	Risperidone	Weight gain	CNR1 rs806378, CNR1 rs1049353, LEP rs7799039	(429)
	Risperidone	Weight gain	[MC4R variants: rs8087522, rs11872992, rs8093815, rs489693, [FTO: rs1421085, rs6499640, rs1121980, rs17817449a, rs8050136a, rs9939609a], [LEP rs12706832, rs2071045], [CNR1 rs806377, rs806368], [FAAH rs324420]	
Antipsychotics › Second Generation	Atypical Antipsychotics	Serum triglyceride levels	MnlI polymorphisms, DdeI polymorphism, 3'UTR region in the SNAP-25 gene (TaiI T/C, DdeI T/C, MnlI T/G)	(430)
	Atypical Antipsychotics	Weight gain	MnlI polymorphisms	
	Atypical Antipsychotics	Weight gain	DdeI polymorphism	
Antithrombotic Drugs › Thrombin Inhibitors, Direct	Dabigatran	Any bleeding	rs4148738* (ABCB1), rs8192935* (CES1)	(431)
	Dabigatran	Any bleeding	rs2244613* (CES1)	
	Dabigatran	Major bleeding	rs4148738* (ABCB1), rs8192935* (CES1), rs2244613* (CES1), rs4148738* (ABCB1), rs8192935* (CES1)	
	Dabigatran	Minor bleeding	rs2244613* (CES1)	
Antivirals › Non-Nucleoside Reverse Transcriptase Inhibitors	Abacavir	Clinical HSR	HLA-B*5701 and other HLA-B*57 alleles: B*5701, B*5702, B*5703 As well as other alleles: 07, 08, 13, 14,15, 18, 27, 35, 37, 38, 39, 40, 41, 42, 44, 45, 47, 49, 50, 51, 52, 53, 56, 57, 58, 81, 82	(432)
Antivirals › Non-Nucleoside Reverse Transcriptase Inhibitors	Efavirenz	CNS-related ADEs	CYP2B6 983TC/CC	(223)
	Efavirenz	CNS-related ADEs	CYP2B6 15582CT/TT, ABCB1 3435TT	
Antivirals › Non-Nucleoside Reverse Transcriptase Inhibitors	Efavirenz	Toxicity-related failure (any severe or life-threatening toxic side effect that could not be managed by dose reductions, temporary drug discontinuation, or within-class substitution)	ABCB1 2677G>T	(433)
	Efavirenz	Toxicity related failure	ABCB1 3435C>T	
Antivirals › Non-Nucleoside Reverse Transcriptase Inhibitors	Efavirenz	Central nervous system side effects at 1 week	CYP2B6 G516T	(434)
	Efavirenz	Central nervous system side effects at 24 weeks	CYP2B6 G516T	

	Efavirenz	Vestibular symptoms, altered dreams, or difficulty sleeping. Tolerability over 24 weeks	CYP2B6 (G516T), CYP2B6 (C1459T), CYP3A4 (A-392G), CYP3A5 (A6986G), MDR1 (G2677TA), ATMDR1 (C3435T)	
Antivirals › Non-Nucleoside Reverse Transcriptase Inhibitors	Efavirenz	CNS ADEs (grade 2 or greater CNS ADEs by week 48)	CYP2B6 516G→T, CYP2B6 983T→C, CYP2B6 15582C→T, CYP2A6 -48T→G	(435)
	Efavirenz	Grade 2 or greater CNS adverse events within 48 weeks	SNPS of (SLC6A2, SLC6A3, NR3C3, HTR2A, HTR2B, HTR2C, HTR6, NR3C4)	
Antivirals › Non-Nucleoside Reverse Transcriptase Inhibitors	Efavirenz	CNS symptoms	CYP2B6 516 T	(222)
	Efavirenz	CNS symptoms	CYP2B6 516 G/G genotype vs. CYP2B6 516 T	
Antivirals › Non-Nucleoside Reverse Transcriptase Inhibitors	Nevirapine	Hepatotoxicity	MDR1 3435C→T	(231)
	Nevirapine	Hepatotoxicity	CYP3A5 6986A→G, CYP3A5 713G→A, CYP3A4 _392A→G, MDR1 2677G→T, CYP2B6 1459C→T, CYP2B6 516G→T	
Antivirals › Non-Nucleoside Reverse Transcriptase Inhibitors	Nevirapine	Early or global toxicity	CYP2B6 516G>T and 1459C>T, ABCB1 2677G>T/A or 3435C>T, Expressors of CYP3A5 (wild-type homozygous *1/*1 and heterozygous *1/*3) and non-expressors (mutant homozygous *3/*3), carriers and non-carriers of the 516G>T, 785A>G or 1459C>T CYP2B6, MDR1 diplotype (wild-type homozygous for both loci (2677 and 3435) versus all the others combinations)	(232)
	Nevirapine	Hepatotoxicity or hypersensitivity	HLA-DRB1*0101	
Antivirals › Non-Nucleoside Reverse Transcriptase Inhibitors	Nevirapine	Hepatotoxicity	HLA-DRB1*0101	(233)
Antivirals › Nucleoside & Non-Nucleoside Reverse Transcriptase Inhibitors & Protease Inhibitors	Didanosine (ddI), stavudine (d4T)	Peripheral neuropathy	HFE C282Y heterozygotes	(436)
Antivirals › Nucleoside & Non-Nucleoside Reverse Transcriptase Inhibitors & Protease Inhibitors	Antiretroviral therapy	Symptomatic peripheral neuropathy (⩾ grade 1)	MTND2*LHON4917G, MTND1*LHON4216C	(437)
Antivirals › Protease Inhibitors	Ritonavir-Boosted Atazanavir	Bilirubin-related discontinuation	UGT1A1 rs887829 T/T	(438)
Antivirals › Protease Inhibitors	Ritonavir-Boosted Atazanavir	Grade 4 elevations in bilirubin level	Homozygous for UGT1A1*28/*28	(439)
Chemoradiation_Antimetabolite	Arm 1	More haematological toxicities	EGF +61A>G polymorphism (rs4444903)	(440)
	Arm 3	Experienced less PUGIT mucositis	EGF +61A>G polymorphism (rs4444903)	
	Arm 1	Experienced less gastrointestinal toxicities	COX2 +8743 C/C genotype (rs5275)	
	Arm 1	Higher risk of grade 3–5 proximal upper gastrointestinal tract (PUGIT) mucositis	EGFR +497G>A A/A genotype (rs2227983)	
	Arm 2	Higher risk of grade 3–5 proximal upper gastrointestinal tract (PUGIT) mucositis	VEGFR2 H472Q Q/Q (rs1870377)	
	Arm 2	Lower risk of any grade 3-5 toxicities	IL8-251A/A compared to A/T or T/T genotypes	
	Arm 1	Lower risk of PUGIT mucositis	VEGFR2 H472Q Q/Q genotype (rs1870377)	
	Arms 1 and 3	Overall toxicity in the two arms with bolus 5-FU-based CRT	None of the evaluated polymorphisms	
CNS Stimulants › Centrally Acting Sympathomimetics	Atomoxetine	Treatment-emergent ADEs	Extensive/ultrarapid and intermediate metabolizers	(441)
	Atomoxetine	Increases in diastolic blood pressure and pulse	Extensive/ultrarapid and intermediate metabolizers compared with CYP2D6 non-PMs, PMs	
	Atomoxetine	Decrease in BMI	Extensive/ultrarapid and intermediate metabolizers compared with CYP2D6 non-PMs, PMs	

	Atomoxetine	Dry mouth, erectile dysfunction, hyperhidrosis, insomnia, and urinary retention	Poor metabolizers	
	Atomoxetine	Dry mouth and sleep disorder	IMs compared with EMs/UMs	
CNS Stimulants › Centrally Acting Sympathomimetics	Atomoxetine	ADEs	CYP2D6*10/*10	(442)
CNS Stimulants › Centrally Acting Sympathomimetics	Methylphenidate	Cardiovascular or spontaneously reported ADEs	DAT1 VNTR	(443)
CNS Stimulants › Centrally Acting Sympathomimetics	Methylphenidate	Irritability	SNAP25 T1065G	(444)
	Methylphenidate	Motor tics, buccal-lingual (oral) movements picking/biting	SNAP25 T1069C	
	Methylphenidate	Picking	DRD4-VNTR 4-repeat allele	
	Methylphenidate	Social withdrawal	DRD4-VNTR 7-repeat allele	
	Methylphenidate	Any Side effects	DRD4-VNTR-repeat allele, 10-repeat, 9-repeat	
Corticosteroids	Glucocorticoids	Severe infection (grade 3 or 4 infections), moderate infection (grade 1 or 2 infections)	GST-M1 (null vs. normal) (homozygous deletion)	(445)
	Glucocorticoids	Several side effects (enhanced appetite, weight gain, or both. Cushingoid appearance was also extremely common, as well as neuropsychiatric signs; indeed, depression, anxiety, cefalea, and emotional lability were observed in most patients. Asthenia, neuromuscular weakness, and muscular pain)	[ABCB1 G2677T, C3435T], NR3C1 BclI, IL-10 A-1082G, GST-P1 A2627G, GST-M1 (null vs. normal), GST-T1 (null vs. normal)	
Diuretics › Thiazides and Related Diuretics	Hydrochlorothiazide	Elevation of serum urate concentration	rs1002976 near VEGFC, rs950569 near BRINP3, rs508362 in RREB1 in men, rs2477134 near PADI4	(446)
	Hydrochlorothiazide	Elevation of serum urate concentration	rs1418243	
Dopaminergic Drugs › Catechol-O methyltransferase Inhibitors	Tolcapone	Severe diarrhoea	COMT HH high/high	(447)
Glaucoma and Ocular Hypertension › Beta-Adrenoceptor Blockers	Ophthalmic Timolol	Systemic effects: heart rate	CYP2D6 PMs vs IMs and Ums	(448)
	Ophthalmic Timolol	Systemic effects: systolic and diastolic arterial pressure	ADRB1 Ser49 homozygotes	
	Ophthalmic Timolol	Systemic effects: diastolic arterial pressure	GNAS1 T393C homozygotes	
Hypnotics, Sedatives and Anxiolytics › Benzodiazepines	Lorazepam	Persistent deficit in memory/ poor performance	APOE ε4-positive	(449)
Immunostimulants › Interferons	Interferon Therapy	Autoimmunity	CTLA-4 (AG 49, CT 318, CT 60, JO 27, JO30 and JO 31)	(450)
Immunosuppressants › Antimetabolites	Azathioprine	Drop-outs attributable to AZA related side effects	ITPA 94C>A	(451)

	Azathioprine	Drop-outs attributable to AZA related side effects	TPMT *2 or *3	
Immunosuppressants › Antimetabolites	Thiopurines	leukopenia	TPMT*3C	(452)
Immunosuppressants › Calcineurin Inhibitors and Related Drugs & Purine Synthesis Inhibitors & Antineoplastic Drugs › Protein Kinase Inhibitors	Tacrolimus plus everolimus or mycophenolate	Leukopenia	FKBP2 c.-2110GG	(453)
	Tacrolimus plus everolimus or mycophenolate	Constipation	FKBP1A n.259+24936C allele	
	Tacrolimus plus everolimus or mycophenolate	Gastrointestinal disorders	FOXP3 c.-22-902A or c.-23+2882A allele	
Immunosuppressants › Calcineurin Inhibitors and Related Drugs	Tacrolimus	Incidence of new-onset diabetes mellitus/ opportunistic infections, including cytomegalovirus infection	CYP3A5*1/*1 (i.e., expressors) vs. CY3A5*3/*3 (i.e., nonexpressors)	(454)
Immunosuppressants › Non-Calcineurin Inhibitors	Sirolimus	Decrease in haemoglobin levels	AGAAA (rs1770345/rs2300095/rs2076655/rs1883965/rs12732063) m-TOR haplotype	(455)
	Sirolimus	Total cholesterol (tCHL), triglyceride (TRG) low-density-lipoprotein plasma-cholesterol (LDL-C), infections, cutaneous ADEs and oedema	m-TOR, p70S6K or Raptor polymorphisms (p70S6K rs2526354, rs180535, rs8067568 and m-TOR rs12732063 SNPs were studied using a dominant genetic model. Raptor rs2289759 and rs7211818 were studied using a recessive genetic model)	
Immunosuppressants › Purine Synthesis Inhibitors	Mycophenolic Acid	Diarrhoea, Leukopenia	UGT2B7-840G>A	(456)
Lipid Modifying Drugs › Statins	Simvastatin	Myopathy	SLCO1B1 rs4149056 (Val174Ala)	(219)
Lipid Modifying Drugs › Statins	Atorvastatin, Simvastatin, Pravastatin	Composite adverse event (CAE)	SLCO1B1 rs4149056 (Val174Ala)	(220)
Lipid Modifying Drugs › Statins	Rosuvastatin	Clinical myalgia	rs4363657C or rs4149056C in SLCO1B1	(221)
Nicotinic Receptor Agonists › Nicotine & Antidepressants › Serotonin and Noradrenaline Reuptake Inhibitors	Smoking cessation medications (bupropion and nicotine replacement therapy)	Gastrointestinal ADEs	rs12899425 Near IREB2, rs4243083 PSMA4, rs2869546 CHRNA3, rs1878399 CHRNA3	(457)
	Smoking cessation medications	Gastrointestinal ADEs	rs684513 CHRNA5, rs6495309 Between CHRNA3-B4, rs4887072 CHRNB4, CHRNA5-CHRNA3-CHRNB4 region rs578776, CHRNA5-CHRNA3-CHRNB4 region rs12443170	
Oestrogens & Progestogens	Hormone Therapy (estradiol, progesterone, drospirenone)	Anthropometric and metabolic variables/ lipid accumulation product index	Homozygous AA genotype of rs9939609	(458)
	Hormone Therapy (oestradiol, progesterone, drospirenone)	Lipid accumulation product index	rs9939609 and haplotype AAAA	
Oestrogens & Progestogens	Hormone Therapy	CHD events	GP1BA −5TT genotype, GP1BA −5TT plus GP6 13254TC+CC genotypes	(459)
	Hormone Therapy	CHD events	GP1BA −5TC or CC, GP6 13254 TC+CC genotypes	
Proton Pump Inhibitors	Lansoprazole	Upper respiratory infections/sore throat	CYP2C19 PMs	(460)

*The list of variants associated with ADEs was annotated using the following font colour; Black colour for significantly increased risk of ADEs, green colour represents significantly reduced risk of ADEs, and red colour denotes non-significant association with ADEs. For toxicities and adverse drug effects, the comma "," was used when these adverse drug effect(s) were analysed and

reported separately, and “or” was used when these were analysed and reported jointly in the study (i.e., patients who developed ADE1, ADE2 or ADE3 etc were combined in the analysis). This also applies to the culprit drugs and variants/genotypes. For variants and genotypes, the word “combined” was used when these variants occurred simultaneously in the same individual.

Abbreviations

Anthracycline-based chemotherapy: daunorubicin, doxorubicin, mitoxantrone. Protocol (IA+IB): prednisone or dexamethasone then: cytarabine; cyclophosphamide; daunorubicin; L-asparaginase; 6-mercaptopurine; methotrexate; vincristine. IFL: irinotecan [CPT-11, Camptosar] with bolus 5-FU plus leucovorin. LV: leucovorin. CPT-11: Campto'l", irinotecan. FOLFOX: 5-fluorouracil, folinic acid and oxaliplatin. FOLFIRI: infusional 5-fluorouracil, leucovorin, and irinotecan. LV5FU2: fluorouracil, leucovorin. FOLFOXIRI: infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan. CEC: cyclophosphamide. BEA: bleomycin, etoposide, doxorubicin. ECF: Epirubicin + Cisplatin + 5-Flurouracil. TAC: docetaxel, doxorubicin, cyclophosphamide. ddAC: doxorubicin-cyclophosphamide. IROX: irinotecan plus oxaliplatin. ABVD: doxorubicin, bleomycin, vinblastine and dacarbazine. CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone with or without rituximab. R-CHOP: cyclophosphamide, doxorubicin, vincristine prednisolone, and rituximab. ACVBP: doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone. I-ACVBP: intensified immunochemotherapy with ACVBP. FU or 5-FU: Fluorouracil. Ox: Oxaliplatin. Ir: Irinotecan. Xelox: Oxaliplatin and capecitabine. OxMdG: Oxaliplatin de Gramont (=FOLFOX). DHAPP: Dihydroartemisinin-piperaquine and primaquine. SLDPQ: single low dose primaquine. CDA: Chlorproguanil-dapsone-artesunate. CPG–DDS: chlorproguanil–dapsone. AL: artemether-Lumefantrine. NSAIDs: Nonsteroidal Anti-Inflammatory Drugs. ADEs: Adverse Drug Effects. HSR: hypersensitivity reaction. TEAE: Treatment-emergent adverse events. CNS: Central Nervous System. HIV: human immunodeficiency virus. LoF: loss-of-function. MS-ADEs: Musculoskeletal ADEs. VM-ADEs: vasomotor ADEs. EM: Extensive metaboliser. IM: Intermediate metaboliser. PM: Poor metaboliser. UM: Ultrarapid metaboliser. NMDA: N-methyl-D-aspartate. CNS: Central Nervous System.

*Table 2.5 The full list of variants associated with ADEs identified from Meta-analyses**

Therapeutic Class/Treatment Modality	Culprit Drug(S)	Toxicities or Adverse Drug Effect(s)	Variants(s)/ Genotype(s)	Reference
Lipid Modifying Drugs › Statins	Statins	Myopathy	LILRB5 (rs12975366: T > C: Asp247Gly)	(461)
Lipid Modifying Drugs › Statins	Statins	Myotoxicity	GATM rs1719247	(462)
	Statins	Myotoxicity	rs1346268 Chr15: 43,460,321	
Lipid Modifying Drugs › Statins	Atorvastatin	Myopathy	SLCO 1B1 c.521T>C (rs4149056)	(463)
Lipid Modifying Drugs › Statins	Statins, Simvastatin, Atorvastatin	ADEs	SLCO1B1 −521T>C	(464)
	Statins	ADEs	SLCO1B1 −388A>G	
Lipid Modifying Drugs › Statins	Statins	Myotoxicity	SLCO1B1 T521C	(465)
Lipid Modifying Drugs › Statins	Statins	Myopathy	SLCO1B1 T521C	(466)
Lipid Modifying Drugs › Statins	Statins, Simvastatin, Rosuvastatin, Cerivastatin	Myopathy	SLCO1B1 T521C	(467)
Lipid Modifying Drugs › Statins	Statins	Myopathy	SLCO1B1 c.521C>T	(468)
Lipid Modifying Drugs › Statins	Statins	Myopathy	ABCB1 C3435T	(469)
Antiplatelet Drugs	Clopidogrel	Major Bleeding	CYP2C19*2, ABCB1 C3435T	(470)
Antiplatelet Drugs	Clopidogrel	Bleeding	ABCB1 C3435T	(471)
Antiplatelet Drugs	Clopidogrel	Bleeding	Reduced function CYP2C19 allele non-carriers vs. carriers. Among IMs, PMs and EMs	(472)
Antiplatelet Drugs	Clopidogrel	Bleeding	P2Y12 C34T	(473)
Antiplatelet Drugs	Clopidogrel	Bleeding	CYP2C19*17	(474)
Antiplatelet Drugs	Clopidogrel	Bleeding	CYP3A5 A6986G (rs776746) (GG vs. AA + AG)	(475)
Antiplatelet Drugs	Clopidogrel	Bleeding	P2RY12 alleles carriers: rs2046934 T > C, rs6785930 C > T, rs6809699 G > T	(476)
Antiplatelet Drugs	Clopidogrel	Bleeding	ABCB1 C3435T	(477)
Antiplatelet Drugs	Clopidogrel	Bleeding	ABCB1 C3435T	(478)
Antiplatelet Drugs	Clopidogrel	Bleeding	loss-of-function (CYP2C19) alleles (*2, *3, *4, *5, *6, *7, or *8)	(479)
Antiplatelet Drugs	Clopidogrel	Bleeding	CYP2C19 loss-of-function (LOF) alleles: (*1/*2, *1/*3)	(480)
Antiplatelet Drugs	Clopidogrel	Bleeding	Carriage of one or two CYP2C19 loss-of-function (LoF) alleles versus no CYP2C19 LoF alleles	(481)
Antiplatelet Drugs	Clopidogrel	Bleeding, Severe bleeding	CYP2C19 Genotype (Any Copy of *2 Through *8 vs *1 or *17)	(482)
	Clopidogrel	Major Bleeding Events	CYP2C19 ∗2 or ∗3, CYP2C19∗1 or ∗17	
Antiplatelet Drugs	Clopidogrel	Bleeding	CYP2C19*2-*8	(483)
Antiplatelet Drugs	Clopidogrel	Bleeding events, major bleeding	CYP2C19*17	(484)
Antiplatelet Drugs	Clopidogrel	Bleeding	CYP2C19 *2 or *3 to wild-type (*1) or *17 (reference)	(485)
Antiplatelet Drugs	Clopidogrel	Major bleeding	rs12248560 (*17: 4195C→T/A)	(486)
Antiplatelet Drugs	Clopidogrel	Major Bleeding, major or minor bleeding	Carriers and noncarriers of the CYP2C19 LOF allele	(487)
Antiplatelet Drugs	Aspirin	Bleeding	GUCY1A3 (rs7692387)	(488)
Antiplatelet Drugs	Aspirin	Asthma	TBXA2R +795C/T (C vs T)	(489)
Antiplatelet Drugs	Aspirin	Asthma	LTC4S Gene −444A/C (CC + AC vs. AA)	(490)
Antithrombotic Drugs › Vitamin K Antagonists	Warfarin	Bleeding	CYP2C9 *2 or *3	(491)
Antithrombotic Drugs › Vitamin K Antagonists	Warfarin	Bleeding	CYP2C9*2, CYP2C9*3, CYP2C9*2 and *3 combined, VKORC1 rs9934438	(492)
Antithrombotic Drugs › Vitamin K Antagonists	Warfarin	Haemorrhagic Complications	CYP2C9*2 and *3	(493)
	Warfarin	Haemorrhagic Complications	CYP2C9 *1/*1, *3/*3, 1 copy of CYP2C9*3, *1/*3, *3/*3	
	Warfarin	Haemorrhagic Complications	CYP2C9*1/*2, *2/*2, *2/*3	
	Warfarin	Haemorrhagic Complications	VKORC1 c. −1639G>A (rs 9923231), GA and AA	

Analgesics › Non-Steroidal Anti-inflammatory Drugs	NSAIDs	Gastrointestinal Bleeding	PM CYP2C9, CYP2C9*3	(494)
Analgesics › Non-Steroidal Anti-inflammatory Drugs	NSAIDs	Gastrointestinal Bleeding	CYP2C9*2 and CYP2C9*3 variant alleles	(495)
Analgesics › Opioids	Opioid Analgesics	Side effects (including nausea and vomiting)	(OPRM1) 118G allele variant	(496)
	Opioid Analgesics	Side effects mainly postoperative nausea/vomiting	CYP3A4*1G, ABCB1 3435T	
Analgesics › Opioids	Opioid	Less Nausea/Vomiting	OPRM1 118A>G	(497)
Analgesics › Opioids	Opioid	Nausea	OPRM1 118A > G	(498)
	Opioid	Vomiting	OPRM1 118A > G	
Antimycobacterials	Anti-Tuberculosis (Most Studies Used INH, RMP, PZA And EMB For TB Treatment)	Liver Injury	Null GSTM1 genotypes	(499)
	Anti-Tuberculosis (Most Studies Used INH, RMP, PZA And EMB For TB Treatment)	Liver Injury	GSTP1 Ile105 Val GG + AG vs AA	
Antimycobacterials	Anti-Tuberculosis Drugs (Most Studies Had an Anti-Tuberculosis Regimen Containing INH, RMP, PZA And EMB)	Liver Injury	CYP2E1 RsaI/PstI polymorphism (rs2031920)	(500)
Antimycobacterials	Anti-Tuberculosis Drugs	Hepatotoxicity	CYP2E1 RsaI polymorphism (TT or CT vs. CC)	(501)
	Anti-Tuberculosis Drugs	Hepatotoxicity	CYP2E1 RsaI, CYP2E1 DraI polymorphism (AA or TA vs. TT), CYP2E1 PstI (CC or GC vs. GG)	
	Anti-Tuberculosis Drugs	Hepatotoxicity	CYP2E1 96-bp deletion-insertion SNP: homozygous mutant-type	
	Anti-Tuberculosis Drugs	Maculopapular Eruption	CYP2C9 rs9332096, CYP2C19 rs4986893, homozygous mutant-type or heterozygous genotype vs. homozygous wild-type	
	Anti-Tuberculosis Drugs	Maculopapular Eruption	CYP2E1 (RsaI, rs2070672, rs2070673), CYP2C9 (rs4918758, rs1057910), CYP2C19 (-1418 C-T)	
Antimycobacterials	Anti-Tuberculosis Drugs (either monotherapy with INH or RIF or a combination therapy including a four-drug regimen of INH, RIF, PZA and EMB)	Liver Injury	CYP2E1 RsaI/PstI c1/c1, NAT2 (slow vs. intermediate and fast acetylators), GSTM1 null	(502)
	Anti-tuberculosis drugs (either monotherapy with INH or RIF or a combination therapy including a four-drug regimen of INH, RIF, PZA and EMB)	Liver Injury	CYP2E1 DraI, GSTT1 null, GSTM1/GSTT1 (dual-null vs one-null or non-null), SLCO1B1 388A>G, SLCO1B1 521T>C	
Antimycobacterials	Anti-Tuberculosis Drugs INH+RMP+PZA+EMB, or+SM	Hepatotoxicity	GSTM1 null genotypes	(503)
	Anti-Tuberculosis Drugs INH+RMP+PZA+EMB, or+SM	Hepatotoxicity	GSTT1 polymorphism	
Antimycobacterials	Anti-Tuberculosis Drug	Hepatotoxicity	GSTM1 present genotype	(504)
Antimycobacterials	Anti-tuberculosis drugs (most studies used INH, RMP and PZA)	Liver Injury	GSTM1 null genotype	(505)
	Anti-Tuberculosis Drugs (Most Studies Used INH, RMP and PZA)	Liver Injury	GSTT1 polymorphism	
Antimycobacterials	Anti-Tuberculosis Drugs (INH, RFP, PZA, EMB)	Hepatotoxicity	PstI/RsaI polymorphism CYP2E1 c1/c1, CYP2E1 c1/c1 genotype combined with NAT2 slow acetylator status versus that with the rapid plus intermediate acetylator status	(506)
	Anti-Tuberculosis Drugs (INH, RFP, PZA, EMB)	Hepatotoxicity	CYP2E1-DraI polymorphism	
Antimycobacterials	Antituberculosis drugs	Liver Injury	GSTM1 present genotype	(507)

Antimycobacterials	Anti-Tuberculosis Drugs INH+RMP+PZA+EMB, or+SM	Hepatotoxicity	CYP 2E1 Rsa I/Pst I (C1/C1 vs. C1/C2 + C2/C2)	(508)
	Anti-Tuberculosis Drugs INH+RMP+PZA+EMB, or+SM	Hepatotoxicity	Dra I polymorphism (DD vs. DC+CC)	
Antimycobacterials	Anti-Tuberculosis Drugs	Liver Injury	NAT2 slow and ultra-slow acetylator genotypes, NAT2*6A/*6A,*6A/*7B	(509)
	Anti-Tuberculosis Drugs	Liver Injury	Ultra-slow acetylator, NAT2*5B/*5B	
Antimycobacterials	Anti-Tuberculosis Drugs (at least one of INH, RMP, PZA Or EMB)	Hepatotoxicity, hepatotoxicity outcomes ADEs (defined as at least one of the following: gastric, joint, neuromuscular or skin reactions, hepatotoxicity)	Slow acetylators vs. rapid acetylators, slow acetylators vs. rapid/intermediate acetylators	(510)
	Anti-tuberculosis drugs (at least one of INH, RMP, PZA or EMB)	Peripheral Neuropathy, Skin Rash and Eosinophilia	Acetylator status	
	Anti-tuberculosis drugs (at least one of INH, RMP, PZA or EMB)	Maculopapular Eruption	SNPs investigated by Kim et al.	
Antimycobacterials	Anti-Tuberculosis Drugs (INH+RMP+PZA+EMB or INH or INH+RMP)	Liver Injury	NAT2 slow acetylators, NAT2 intermediate acetylators	(511)
Antimycobacterials	Anti-TB Treatment	Liver Injury	NAT2 slow acetylators, NAT2*6/*7	(512)
Antimycobacterials	Antituberculosis Drugs (when standard dose of isoniazid was administered)	Liver Injury	NAT2 slow acetylators	(513)
Antimycobacterials	Anti-Tuberculosis Drugs (most studies RMP and PZA)	Hepatotoxicity	NAT2 slow acetylators	(514)
Antimycobacterials	Anti-Tuberculosis Drugs	Liver Injury	GSTT1 polymorphism	(515)
	Anti-Tuberculosis Drugs	Liver Injury	NAT2 slow acetylator (without wild-type NAT2*4 allele), CYP2E1 c1/c1, GSTM1 null, GSTM1 null and GSTT1 null combined	
Antimycobacterials	Anti-Tuberculosis Drugs	Liver Injury	CYP2E1c1/c1 genotypes, CYP2E1 homozygous wild genotype (*1A/*1A), GSTM1 null, GSTM1 homozygous null genotype (null/null), GSTT1 homozygous null genotype (null/null), NAT2 homozygous variant genotype (mt/mt), NAT2 homozygous variant (mt/mt) and the combined genotype (w/w + w/mt)	(516)
	Anti-Tuberculosis Drugs	Liver Injury	NAT2*4 allele might be a protective gene	
Antimalarials & Antimycobacterials	Dapsone	CADRS, DHS, SJS/TEN, DRESS	HLA-B*1301	(517)
Antimycobacterials › Other	Isoniazid	Hepatotoxicity	NAT2 481C>T (rs1799929), NAT2 590G>A (rs1799930), NAT2 857G>A (rs1799931)	(518)
Immunosuppressants › Antimetabolites	Azathioprine or other thiopurine-based drugs	Leukopenia, Thrombocytopenia, Hepatitis or elevated hepatic transaminases	Heterozygous for TPMT mutations (TPMT*2, *3A, *3B, *3C)	(519)
	Azathioprine or other thiopurine-based drugs	Infection, withdrawal due to ADEs, myelotoxicity, anaemia, pancreatitis	Heterozygous for TPMT mutations (TPMT*2, *3A, *3B, *3C)	
Immunosuppressants › Antimetabolites	Thiopurine	Leukopenia	NUDT 15: c.415C > T, c.52G > A, 36_37insGGAGTC	(520)
Immunosuppressants › Antimetabolites	Thiopurines	Myelotoxicity, Intolerance	NUDT15 rs116855232	(521)
Immunosuppressants › Antimetabolites	Thiopurine	Leukopenia	TPMT variants (*2, *3A, *3B, *3C, *3D, *6, *8, *12, *21, *37 and *40), NUDT15 R139C and G52A and 36_37ins/delGGAGTC, NUDT15 R139C, NUDT15 c.36_37ins/delGGAGTC, NUDT15 c.52G > A	(522)
	Thiopurine	Leukopenia	ITPA rs1127354 or rs7270101	
	Thiopurine	Severe early leukopenia	NUDT15 R139C	
Immunosuppressants › Antimetabolites	Azathioprine	Overall ADEs, Bone Marrow Toxicity, Gastric Intolerance	TPMT*3 family (including TPMT*3A, TPMT *3B and TPMT *3C)	(523)
	Azathioprine	Hepatotoxicity	TPMT*3 family (including TPMT*3A, TPMT *3B and TPMT *3C)	

Immunosuppressants › Antimetabolites	Thiopurine (e.g., 6-MP or AZA)	Bone Marrow Toxicity, Hepatotoxicity, Pancreatitis	ITPA 94C→A	(524)
Immunosuppressants › Antimetabolites	Thiopurines	Leukopenia, withdrawals due to ADEs	At least TPMT*2, TPMT*3A, TPMT*3B, TPMT*3C	(525)
Immunosuppressants › Antimetabolites	6-MP or AZA	Overall ADEs, Bone Marrow Toxicity, Hepatotoxicity, Pancreatitis	TPMT*3A and TPMT*3C	(526)
Immunosuppressants › Antimetabolites	Thiopurine	Overall ADEs, Other ADEs (Gastric Intolerance, Flu-Like Symptoms and Skin Reactions), BMI, Hepatotoxicity, Pancreatitis	TPMT*2, *3A, *3B, *3C, *3D, *4, *5, *6, *7, *8, *10 alleles	(527)
Antineoplastic Drugs › Antimetabolites	Methotrexate	Toxicity	ATIC 347 C/G	(528)
Antineoplastic Drugs › Antimetabolites	Methotrexate	All-grade (grade 1–4) and severe (grade 3–4) hepatic and all-grade and severe gastrointestinal toxicities, all-grade and severe mucositis and all-grade and severe hepatic and all-grade and severe haematological toxicity	MTHFR C677T	(529)
Antineoplastic Drugs › Antimetabolites	Methotrexate	Overall ADEs and Toxicity	MTHFR C677T (rs1801133)	(530)
Antineoplastic Drugs › Antimetabolites	Methotrexate	Toxicity, Leukopenia, Thrombocytopenia, Myelosuppression, Mucositis, Hepatotoxicity, Neurotoxicity	RFC1 G80A	(531)
Antineoplastic Drugs › Antimetabolites	Methotrexate	Oral Mucositis (Grade ≥2), Oral Mucositis (Grade ≥ 3)	(TYMS) rs34743033 (2R3R)	(532)
Antineoplastic Drugs › Antimetabolites	Methotrexate	Toxicity	(TYMS) 2R/3R, TYMS 2R/3R 3R vs. 2R Overall and Caucasian and Non-Caucasians, 3R3R vs. 3R2R + 2R2R (Recessive) Overall and Caucasian and Non-Caucasians, 3R3R + 3R2R vs. 2R2R (Dominant) Overall and Caucasian and Non-Caucasians, 3R2R vs.3R3R + 2R2R (Co-dominant) Overall and Caucasian and Non-Caucasians, 3R3R vs. 2R2R Overall and Caucasian and Non-Caucasians, TYMS 6 bp I/D polymorphism, TYMS 6 bp I/D D vs. I Overall and Caucasian and Asian, DD vs. DI + II (Recessive) Overall and Caucasian and Asian, DD + DI vs. II (Dominant) Overall and Caucasian and Asian, DI vs. DD + II (Co-dominant) Overall and Caucasian and Asian, DD vs. II Overall and Caucasian and Asian	(533)
Antineoplastic Drugs › Antimetabolites	Methotrexate	Overall ADEs	TYMS 1494 del6 and FPGS rs10106 were correlated to absenting overall ADEs in recessive and dominant models	(534)
	Methotrexate	Overall ADEs	MTHFR C677T	
	Methotrexate	Overall ADEs	MS A2756G, ABCB1/MDR-1 C1236T, AMPD1 34C>T, GGH 401C/T, GGH 452C>T, GGH -354 G>T, ITPA 94C/A, MTHFR A1298C, MTHFD1 1958 G/A, MTRR 66 A>G, MTR A2756G, SHMT1 1420C/T and SLC19A1/RFC-1 80G/A	
	Methotrexate	Gastrointestinal ADEs	ATIC 347C>G	
	Methotrexate	Dermatological ADEs	RFC1 80 G/A	
Antineoplastic Drugs › Antimetabolites	Methotrexate	Toxicity	3 MTHFR 677C>T (rs1801133) alleles, MTHFR 677C>T (rs1801133) 3 allele, MTHFR 1298A>C (rs1801131) 3 allele, ATIC 347C>G (rs2372536), MTR 2756A>G (rs1805087), MTRR 66A>G (rs1801394), RFC −1 80G>A (rs1051266), ABCB1 3435C>T (rs1045642)	(535)
Antineoplastic Drugs › Antimetabolites	Methotrexate	Mucositis, Hepatic Toxicity, Neutropenia, Thrombocytopenia, Anaemia, Leukopenia	MTHFR C677T	(536)

	Methotrexate	Leukopenia	MTHFR A1298C	
	Methotrexate	Myelosuppression, Thrombocytopenia, Hepatic Toxicity, Anaemia	MTHFR A1298C	
Antineoplastic Drugs › Antimetabolites	Methotrexate	Toxicity	(MTHFR) 677C>T(rs1801133), (ATIC) 347C>G (rs2372536), (RFC-1) 80G>A (rs1051266), (ABCB1) 3435C>T(rs1045642)	(537)
Antineoplastic Drugs › Antimetabolites	Methotrexate	Overall ADEs and Toxicity	MTHFR C677T	(538)
Antineoplastic Drugs › Antimetabolites	Methotrexate	Overall Toxicity	MTHFR C677T	(539)
	Methotrexate	Overall Toxicity	MTHFR A1298C	
	Methotrexate	Overall Toxicity	MTHFR 1298CC	
Antineoplastic Drugs › Antimetabolites	Methotrexate	Toxicity	C677T MTHFR, MTHFR A1298C	(540)
Antineoplastic Drugs › Antimetabolites	Methotrexate	Hepatotoxicity (Grade ⩾2), Haematological Toxicity (Grade 3–4), Mucositis (Grade ⩾3)	MTHFR C677T	(541)
	Methotrexate	Hepatotoxicity (Grade ⩾2), haematological toxicities or mucositis	MTHFR A1298C	
Antineoplastic Drugs › Antimetabolites	Methotrexate	Haematological Toxicity, Neurotoxicity, Neutropenia	MTHFR C677T	(542)
	Methotrexate	Liver Toxicity, Myelosuppression, Oral Mucositis, Gastrointestinal Toxicity, Haematological Toxicity, Neurotoxicity, or Neutropenia	MTHFR A1298C	
	Methotrexate	Skin Toxicity/ Leukopenia	MTHFR A1298C	
Antineoplastic Drugs › Antimetabolites	Methotrexate	Toxicity	MTHFR A1298C	(543)
	Methotrexate	Toxicity in Latin American Population	MTHFR A1298C	
Antineoplastic Drugs › Antimetabolites	Methotrexate	Toxicity	MTHFR C677T	(544)
Antineoplastic Drugs › Antimetabolites	Methotrexate	Overall toxicity: more than two ADEs, hepatotoxicity and haematological toxicity, gastrointestinal toxicity, neurotoxicity	MTHFR C677T	(545)
	Methotrexate	Overall toxicity: more than one ADE	MTHFR C677T	
	Methotrexate	Overall toxicity: more than one ADE	MTHFR A1298C	
	Methotrexate	Overall toxicity: more than two ADEs	MTHFR A1298C	
Antineoplastic Drugs › Antimetabolites	Methotrexate	Toxicity	MTHFR C677T, MTHFR A1298C	(546)
Antineoplastic Drugs › Antimetabolites	Methotrexate	Toxicity	MTHFR C677T (CC vs. CT + TT), MTHFR A1298C (AA vs. AC + CC)	(547)
Antineoplastic Drugs › Antimetabolites	Methotrexate	Liver Toxicity/ Hepatotoxicity	The 677C>T variant (rs1801133)	(548)
Antineoplastic Drugs › Antimetabolites	Methotrexate	Toxicity	RFC1 80G>A	(549)
Antineoplastic Drugs › Antimetabolites	Methotrexate	Toxicity	RFC1 80G/A	(550)
Antineoplastic Drugs › Antimetabolites	Methotrexate	Overall Toxicity	ABCB1 C3435T T allele (T vs. C alleles), (Over-dominant), TC vs.TT + CC (Over-dominant), TT + TC vs. CC (Dominant), TT + TC vs. CC (Dominant), TT vs. TC + CC (Recessive)	(551)
Antiepileptics	Antiepileptic Drug	Cutaneous ADRs	HLA-A*24:02	(552)
Antiepileptics	Antiepileptic Drugs (Pht- or Ltg-)	SJS/TEN	HLA -B *15:02	(553)
Antiepileptics	Aromatic Antiepileptic Drugs (CBZ, PHT, PB & Non-Aromatic Antiepileptic Drugs: Dapsone & Salazosulfapyridine]	CADRS	HLA-B*13:01	(554)
Antiepileptics	Phenytoin, Lamotrigine	SJS/TEN	HLA-B*1502	(555)
Antiepileptics	Phenytoin	SJS/TEN	CYP2C9*3	(556)

Antiepileptics	Phenytoin	Severe CADRS, SJS-TEN, DRESS, (SJS-TEN and DRESS)	CYP2C9*3	(557)
Antiepileptics	Phenytoin	Hypersensitivity	CYP2C9*3 /HLA-B*13:01 /HLA-B*15:02 /HLA-B*51:01	(558)
Antiepileptics	Carbamazepine	Serious Cutaneous ADRs	HLA-B*15:02	(559)
Antiepileptics	Carbamazepine	SJS/TEN	HLA-B*1511	(560)
	Carbamazepine	SJS/TEN	HLA-B*5801 in Southeast Asian population	
Antiepileptics	Carbamazepine	Hypersensitivity	HLA-A*3101, HLA-B*1511	(561)
	Carbamazepine	Hypersensitivity	HLA-B*1502, HLA-B*4001, HLA-A*2402	
Antiepileptics	Carbamazepine	SJS/TEN	HLA-B*1502	(562)
	Carbamazepine	Hypersensitivity	HLA-A*3101	
Antiepileptics	Carbamazepine	DRESS, SJS/TEN	HLA-A*31:01	(563)
Antiepileptics	Carbamazepine	SJS/TEN	HLA-B*15:02	(564)
Antiepileptics	Carbamazepine	SJS/TEN	HLA-B*1502	(565)
Antiepileptics	Carbamazepine	SCAR, DILI	HLA-A*31:01	(566)
	Carbamazepine	SJS/TEN	HLA-B*57:01	
Antiepileptics	Oxcarbazepine	CADRS, SCAR	HLA-B∗15:02	(567)
Antiepileptics	Oxcarbazepine	SJS, MPE	HLA-B*1502	(568)
	Oxcarbazepine	CADRS (i.e., MPE, SJS, DRESS)	HLA-A*3101, HLA-A*3201, HLA-B*1501, HLA-B*1502, HLA-B*1511, HLA-DQBI*0501, HLA-DQBI*0503, HLA-DRBI*0403, HLA-DRBI*0406, HLADRBI*	
	Oxcarbazepine	MPE	HLAA* 3101	
Antiepileptics	Lamotrigine	SJS/TEN	HLA-B*1502	(569)
Antiepileptics	Lamotrigine	CADRS	HLA-B*1502, HLA-A*2402	(570)
	Lamotrigine	MPE	HLA-B*3303	
	Lamotrigine	MPE	HLA-B*5801	
	Lamotrigine	SJS/TEN	HLA-B*1502	
Xanthine Oxidase Inhibitors	Allopurinol	Severe Hypersensitivity Syndrome	HLA-B*5801	(571)
Xanthine Oxidase Inhibitors	Allopurinol	SJS/TEN	HLA-B*58:01	(572)
Xanthine Oxidase Inhibitors	Allopurinol	SJS/TEN	HLA-A*33:03, HLA-C*03:02	(573)
Xanthine Oxidase Inhibitors	Allopurinol	CADRS	HLA-B*58:01	(574)
Xanthine Oxidase Inhibitors	Allopurinol	SJS/TEN	HLA-B*5801	(575)
Antidepressants	Antidepressants	Mania	SLC6A4 promoter polymorphism (S allele of 5-HTTLPR) (genotypes ss/sl versus ll)	(576)
Antidepressants	Antidepressants	Mania	SLC6A4 promoter polymorphism (S allele of 5-HTTLPR)	(577)
Antidepressants	Antidepressants	Mania	SLC6A4 (S allele of 5-HTTLPR)	(578)
Antidepressants	Antidepressant	Side Effects	(5-HTTLPR) I, HTR2A −1438G/G	(579)
Antidepressants › Selective Serotonin Reuptake Inhibitors	SSRIS	Side Effects	HTR2A −1438G/G	
Antidepressants › Selective Serotonin Reuptake Inhibitors	SSRIS	Side Effects/Gastrointestinal Side Effects	(5-HTTLPR) I	
Antidepressants	Antidepressants	Side effects: gastro-intestinal (dry mouth, diarrhoea, constipation, nausea or vomiting), cardiovascular (palpitations, dizziness or feeling light-headed on standing), central nervous system (headache, tremors, feeling like the room is spinning), sleep (insomnia, drowsiness or oversleeping) and sexual (loss of desire, trouble achieving orgasm, trouble with erection)	PMs, at weeks 2–4	(580)

	Antidepressants	Sexual Side Effects	PMs, At week 6	
Antipsychotics	Antipsychotics	Tardive Dyskinesia	COMT val158met (rs4680) using Val–Val homozygotes as reference category (a protective effect for Val–Met heterozygotes)	(581)
	Antipsychotics	Tardive Dyskinesia	COMT val158met (rs4680)	
	Antipsychotics	Tardive Dyskinesia	Taq1A in DRD2 (using the A1 variant as reference category)	
	Antipsychotics	Tardive Dyskinesia	Taq1A in DRD2 A2–A2 homozygotes (using A1–A1 as reference category)	
	Antipsychotics	Tardive Dyskinesia	MnSOD Ala–9Val, using Ala–Ala homozygotes as reference category	
Antipsychotics	Antipsychotics	Tardive Dyskinesia	DRD3 Ser9Gly	(582)
Antipsychotics	Antipsychotics	Tardive Dyskinesia	DRD3 Ser9Gly	(583)
Antipsychotics	Antipsychotics (Olanzapine, Risperidone, and Clozapine)	Weight Gain	ADRA2A rs1800544 −1291C/G, BDNF rs6265 Val66Met (G/A), DRD2, rs1799732 −141C Ins/Del, HTR2C HTR2C rs3813929 −759C/T, HTR2C HTR2C rs6318 Cys23Ser, HTR2C HTR2C rs518147 −697G/C, MC4R rs489693	(584)
Antipsychotics	Antipsychotics	Tardive Dyskinesia	COMT Val158Met	(585)
Antipsychotics	Antipsychotics	Hyperprolactinaemia	CYP2D6 PMs vs EMs, IMs vs EMs, Combined PMs/IMs vs combined EMs/UMs	(586)
Antipsychotics	Antipsychotics	Tardive Dyskinesia	CYP2D6 genotype mut/mut vs wt/wt, wt/mut vs wt/wt, mut/mut+wt/mut vs wt/wt, mut/mut vs wt/wt+wt/mut, mut/mut vs wt/wt (prospective studies only)	(587)
	Antipsychotics	Tardive Dyskinesia	CYP2D6 wt/mut vs wt/wt (prospective studies only), mut/mut+wt/mut vs. wt/wt (prospective studies only)	
	Antipsychotics	Abnormal Involuntary Movement Scale Score (AIMS)	CYP2D6 mut/mut vs wt/wt, wt/mut vs wt/wt, mut/mut vs wt/mut	
	Antipsychotics	Parkinsonism	CYP2D6 mut/mut or wt/mut	
Antipsychotics	Antipsychotics	Tardive Dyskinesia	CYP2D6 loss of function alleles, the *2 allele and the *10 allele	(588)
	Antipsychotics	Tardive Dyskinesia	CYP2D6 homozygotes for loss of function alleles (poor metabolizers), CYP2D6 *2, CYP2D6 *10	
Antipsychotics	Antipsychotic (first-generation antipsychotics (bromperidol and nemonapride), mixed first- and second-generation antipsychotics, olanzapine in one study, and olanzapine and fluoxetine combination)	Prolactin Levels	DRD2 Taq1A (rs1800497) (when comparing A2 carriers and A2 non-carriers), DRD2 -141C Ins/Del, 141C Ins/Del (rs1799732)	(589)
	Antipsychotics	Prolactin Levels (in patients with schizophrenia)	DRD2 Taq1A carriers and A1 non-carriers	
Antipsychotics	Antipsychotic (mixed antipsychotics, Olanzapine, Clozapine)	Weight Gain	GNB3 C825T	(590)
		BMI	GNB3 C825T	
Antipsychotics	Antipsychotics (Clozapine or Olanzapine)	Weight Gain	HTR2C C-759T polymorphism C allele: C-759T (CC/C versus CT or TT/T)	(591)
Antipsychotics	Antipsychotics	Weight Gain	HTR2C gene –759C/T promoter polymorphism (rs3813929)	(592)
Antipsychotics	Antipsychotic	Weight Gain	Leptin gene -2548G/A	(593)
Antipsychotics › Second Generation	Clozapine	Metabolic Outcomes (increases in BMI and metabolic syndrome)	rs381328 in HTR2C	(594)
Antipsychotics	Olanzapine	Weight Gain	HTR2C -759C/T (rs3813829)	(595)
	Olanzapine/Clozapine/Risperidone	Metabolic Syndrome	HTR2C -759C/T (rs3813829)	
	Olanzapine/Clozapine/Risperidone	Metabolic Syndrome	HTR2C intragenic rs1414334:C> G polymorphism, HTR2C -697 G/C polymorphism	

Antifungals › Triazole Antifungals	Voriconazole	Overall ADEs	CYP2C19 HEM versus EM, PM versus EM, HEM versus PM, Non-PM versus PM	(596)
	Voriconazole	Hepatotoxicity	HEM versus EM, PM versus EM, HEM versus PM, Non-PM versus PM, HEM versus EM, PM versus EM, HEM versus PM, Non-PM versus PM	
Antiretroviral Drugs	Antiretroviral Therapy (Nevirapine, Abacavir)	Hypersensitivity	HLA-A *24, HLA-C *04, HLA-B *35, *39, *51, *81, *18	(597)
	Antiretroviral Therapy (Nevirapine, Abacavir)	Hypersensitivity	HLA-B *15, HLA-C *02, *03, *07, HLA-DRB1 *05	
	Antiretroviral Therapy (Nevirapine, Abacavir)	Hypersensitivity	HLA-B *05, *07, *08, *13, *14, *17, *27, *37, *38, *40, *41, *42, *44, *45, *46, *47, *49, *50, *52, *53, *57, *58, and *82. HLA-DRB1 *03, *04, *07, *08, *09, *10, *11, *12, *13, *14, *15 and *16	
Antivirals › Non-Nucleoside Reverse Transcriptase Inhibitors	Efavirenz	Central Nervous System Side Effects	CYP2B6-516G>T	(598)
Antivirals › Nucleoside Analogues	Ribavirin	Haemolytic Anaemia	ITPA rs1127354 CC, ITPA rs7270101 AA, ITPA rs6051702 AA	(599)
	Ribavirin	Haemoglobin Decline	Absent (−) ITPase deficiency haplotype, mild (+) ITPase deficiency haplotype, moderate (++) ITPase deficiency	
	Ribavirin	Severe Anaemia, Stop Treatment	ITPA rs1127354 CC	
Antivirals › Non-Nucleoside Reverse Transcriptase Inhibitors	Nevirapine	HSR and hepatotoxicity	HLA-allelotype	(600)
	Nevirapine	CADRS	HLA-B*35	
	Nevirapine	Hepatotoxicity	HLA-B*58:01	
	Nevirapine	HSR	HLA-C*04, HLA-DRB1*01	
Antivirals › Non-Nucleoside Reverse Transcriptase Inhibitors	Abacavir	HSR	HLA-B*57:01	(601)
Antivirals › Non-Nucleoside Reverse Transcriptase Inhibitors	Abacavir	HSR (clinical manifestation), Using confirmed immunologic test as their diagnostic criteria	HLA-B*5701	(602)
Antivirals › Protease Inhibitors, HIV	Atazanavir	Hyperbilirubinemia	UGT1A1*1/*28 or UGT1A1*28/*28	(603)
Antihypertensives › Drugs Acting on The Renin-Angiotensin System › Ace Inhibitors	ACE Inhibitors	Cough	ACE I/D polymorphism	(604)
Antihypertensives › Drugs Acting on The Renin-Angiotensin System › Ace Inhibitors	ACE Inhibitors (Mainly: Benazepril, Enalapril)	Cough	ACE I/D I carriers	(605)
	ACE Inhibitors (Mainly: Benazepril, Enalapril)	Cough	BDKRB2-58T/C polymorphism (rs1799722)	
Antihypertensives › Drugs Acting on The Renin-Angiotensin System › Ace Inhibitors	Angiotensin-Converting Enzyme Inhibitors	Cough	ACE insertion/deletion polymorphism (rs4646994)	(606)
Antihypertensives › Drugs Acting on The Renin-Angiotensin System › Ace Inhibitors	ACE Inhibitors	Cough	Deletion/insertion (ACE D/I)	(607)
	ACE Inhibitors	Cough	Bradykinin B2 receptor -58T/C	
Antihypertensives › Drugs Acting on The Renin-Angiotensin System › Ace Inhibitors	ACE Inhibitors	ADEs (Intolerance)	rs2061538 (RBFOX3)	(608)
Antihypertensives › Drugs Acting on The Renin-Angiotensin System › Ace Inhibitors	ACE Inhibitors and Angiotensin Receptor Blockers	Angioedema	KCNMA1 rs2253202	(609)

Antihypertensives › Beta-Adrenoceptor Blockers	Metoprolol	All-Cause ADEs	PM or non-PM	(610)
	Metoprolol	Bradycardia	PM vs. non-PM	
Bisphosphonates	Bisphosphonates	Osteonecrosis of the jaw	CYP2C8 rs1934951, PPARG rs1152003	(611)
	Bisphosphonates	Osteonecrosis of the jaw	CYP2C8 rs1934951, VEGF rs3025039	
Bisphosphonates	Bisphosphonate	Osteonecrosis of the jaw	SIRT1 rs7896005, HERC4 rs3758392	(612)
Antithyroid Drugs	Antithyroid Drugs (Carbimazole, Methimazole, Propylthiouracil), Carbimazole/Methimazole (after excluding Propylthiouracil)	Agranulocytosis	HLA-B*27:05, HLA-B*38:02, HLA-DRB1*08:03	(613)
Corticosteroids (Inhaled) ± Corticosteroids (Systemic)	Inhaled Corticosteroids ± Additional Corticosteroids	Adrenal Suppression (peak cortisol <350 Nmol/L)	PDGFD rs591118	(614)
Corticosteroids (Systemic)	Glucocorticoid	Osteonecrosis	- 675 4G/5G (rs1799889), PAI-1 4G allele vs. 5G allele (4G vs. 5G), PAI-1 for (4G/4G vs. 5G/5G), PAI-1 (4G/4G vs. 5G/5G), PAI-1 (4G/4G vs. 4G/5G + 5G/5G), PAI-1 (4G/4G + 4G/5G vs. 5G/5G), PAI-1 4G/4G + 4G/5G vs. 5G/5G, PAI-1 4G/4G vs. 4G/5G + 5G/5G, ABCB1 C3435T C vs. T, ABCB1 C3435T CC + CT vs. TT, ABCB1 C3435T CC vs. TT	(615)
	Glucocorticoid	Osteonecrosis	ABCB1 C3435T CC vs. CT + TT, MTHFR C677T CC vs.TT, C vs.T, CC vs. CT + TT CC + CT vs. TT	
Immunosuppressants › Calcineurin Inhibitors and Related Drugs	Tacrolimus	Nephrotoxicity	CYP3A5 6986 A>G	(616)
	Tacrolimus	Acute nephrotoxicity, chronic nephrotoxicity	CYP3A5*1 (CYP3A5*1/*1 or CYP3A5 *1/*3, CYP3A5 expressor)	
Immunosuppressants › Calcineurin Inhibitors	Calcineurin Inhibitors	Nephrotoxicity	CYP3A5*3/*3	(617)
Aminosalicylates	Sulfasalazine	Overall ADEs (Primary Outcome), Number of patients who discontinued the drug due to overall ADEs	NAT2 slow acetylators	(618)
Glaucoma › Carbonic Anhydrase Inhibitors	Methazolamide	SJS/TEN	HLA-B*5901, HLA-Cw*0102, HLA-B*5901-Cw*0102 haplotype	(619)
Antineoplastic Drugs › Protein Kinase Inhibitors	TKI (lapatinib, pazopanib)	Liver Injury	HLA-DQA1*02:01, HLA-DQB1*02:02, HLA-DRB1*07:01	(620)
Antineoplastic Drugs › Protein Kinase Inhibitors	Gefitinib	Overall Toxicity	ABCG2 G34A	(621)
	Gefitinib	Diarrhoea, skin toxicity, hepatotoxicity, interstitial pneumonia	ABCG2 C421A	
Chemotherapy NSCLC	Chemotherapy (Erlotinib, Gefitinib, Platinum, Cisplatin, Irinotecan)	Diarrhoea, Skin Rash	MDR1 C3435T	(622)
Chemotherapy (Non-Anthracycline Antineoplastics)	Non-Anthracycline Antineoplastics Trastuzumab	Cardiotoxicity	(HER2) rs1136201	(623)
Antineoplastic Drugs › Monoclonal Antibodies	Bevacizumab	Hypertension	Heterozygous and homozygous: VEGF (rs699947, rs833061, rs1570360, rs2101963, rs3025039)	
Antineoplastic Drugs › Monoclonal Antibodies	Bevacizumab	Decreased LVEF	(HER2) variant 655A > G rs1136201	
	Bevacizumab	Heart Failure	rs1058808	
	Bevacizumab	Cardioprotection	FCGR2A rs1801274	
Antineoplastic Drugs › Platinum Compounds	Oxaliplatin-Based Chemotherapy	Toxicity	ERCC1 C118T	(624)

Antineoplastic Drugs › Monoclonal Antibodies	Trastuzumab	Cardiotoxicity	HER2 655 A>G (rs1136201)	(625)
Antineoplastic Drugs › Platinum Compounds	Cisplatin	Ototoxicity	ACYP2 rs1872328, LRP2 rs4668123, TPMT (rs12201199, rs1142345, rs1800460), COMT rs9332377	(626)
	Cisplatin	Ototoxicity	(EPXH1) rs2234922, rs6721961 of NFE2L2, rs10950831 of ABCB5, GSTM3*B (rs1799735), SLC22A2 rs316019, rs1051640 of ABCC3, COMT rs4646316	
Antineoplastic Drugs › Platinum Compounds	Cisplatin	Hearing Loss	rs4646316 in COMT	(627)
	Cisplatin	Hearing Loss	COMT (rs9332377), TPMT (rs12201199, TPMT (rs1800460), TPMT (rs1142345)	
Antineoplastic Drugs › Platinum Compounds	Cisplatin	Ototoxicity	ACYP2 rs1872328, SLC22A2 rs316019	(628)
Antineoplastic Drugs › Platinum Compounds	Cisplatin	Nephrotoxicity	GSTT1 gene deletion, GSTT1-null	(629)
Antineoplastic Drugs › Platinum Compounds	Oxaliplatin	Neuropathy	GSTP1 Ile105Val	(630)
Antineoplastic Drugs › Platinum Compounds	Platinum-Based Chemotherapy	GI Toxicity	MTHFR rs1801131AA, MDM2 rs1690924TC/CC	(631)
	Platinum-Based Chemotherapy	Haematological Toxicity	MTHFR rs1801133 CT/TT genotype	
	Platinum-Based Chemotherapy	Grade 3–4 Haematological Toxicity	P53 Arg72Pro, ABCB1 G2677T/A, ABCB2 −24C>T, GSTP1 A313G, XPD A2251C and G934A, MDM2 rs1470383, rs2279744, and rs1690924	
	Platinum-Based Chemotherapy	Grade 3–4 Overall, Haematological, and GI Toxicities	ABCB1 G2677T/A, BAX rs4645878, BCL2 rs2279115, MTHFR A1298C and C677T, ERCC1 C118T and C8092A, XRCC1 G1196A	
Antineoplastic Drugs › Platinum Compounds	Platinum (Oxaliplatin)	NCI CTC grade 3–4, grade 2–4, any grade	GSTP1 Ile105Val)	(632)
Antineoplastic Drugs › Platinum Compounds	Platinum (Oxaliplatin)	NCI CTC grade 3-4, grade 2-4 neuropathy	GSTM1 deletion, GSTT1 deletion	
Antineoplastic Drugs › Platinum Compounds	Platinum (Oxaliplatin)	NCI CTC grade 3–4, grade 2–4	ERCC1 C118T, XRCC1 Arg399Gln, ERCC1 C809A, ERCC2 Lys751Gln,	
Antineoplastic Drugs › Platinum Compounds	Platinum (Oxaliplatin)	NCI CTC grade 2-4	ERCC2 C156A, AGXT I340M	
Antineoplastic Drugs › Taxanes	Taxanes (Paclitaxel)	NCI CTC grade 3–4, grade 2–4, any grade	CYP3A4*22	
Antineoplastic Drugs › Taxanes	Taxanes (Paclitaxel)	NCI CTC grade 3-4	CYP2C8*3	
Antineoplastic Drugs › Taxanes	Taxanes (Paclitaxel)	Neuropathy	rs7349683 in EPHA5, rs4737264 in XKR4	
Antineoplastic Drugs › Platinum Compounds	Platinum-Based Drugs	Myelosuppression, Thrombocytopenia, Granulocytopenia	GSTP1 rs1695	(633)
Antineoplastic Drugs › Platinum Compounds › Topoisomerase I Inhibitors	Fluoropyrimidine and platinum-based triplet combinations	Hand-Foot Syndrome	DPYD 2846A4T	(634)
	Fluoropyrimidine and platinum-based triplet combinations	Gastrointestinal Toxicity	CYP3A4*22, ENOSF1 rs2612091	
Antineoplastic Drugs › Topoisomerase I Inhibitors & Antimetabolites & Platinum Compounds & Taxanes	Chemotherapy (FOLFOX4/FOLFOX7/FOLFOX9/GEMOX/ TOMOX, 5-FU/CPT-11/LV, fluorouracil/cisplatin, taxane + cisplatin as first-line, oxaliplatin, irinotecan, and	Overall toxicity, neurotoxicity, neutropenia, or gastrointestinal toxicity	Null genotypes of GSTM1 and GSTT1	(635)

	capecitabine, irinotecan/oxaliplatin-based treatment)			
Chemotherapy (5-FU Monotherapy or Combination Therapy)	5-FU Monotherapy or Combination Therapy	Severe toxicity (≥grade 2 or grades 3 and 4) [stomatitis (3,4), diarrhoea (3,4), neutropenia (3,4), bone marrow (3.4), haematology (>2), gastroenterology (>2), arrhythmias (2), nausea (2)]	DPYD variants. *5B/*5B, 1737T>C, 1*/*5B, *1/*5A,1525-1G>A, 1525-9A>G, 1129-15T>C, *5B/*9A, 1896T>C, 496A>G, 1774C>T, 1*/*1, 2194G>A, 85T>C, 464T>A, 1627A>G, 2194G>A, 496A>G, 274T>A, 74A>G, 85T>C, 1627A>G, 812 del T, 1714C>G, 1896T>C, 1627A>G, 967G>A, 1774C>T, 14+G>A, 1011A>T, 1236G>A, 1896T>C	(636)
Antineoplastic Drugs › Topoisomerase I Inhibitors	5-Fu Based Chemotherapy	Severe Haematological Toxicity	MTHFR polymorphism C677T	(637)
	5-Fu Based Chemotherapy	Serious Global Toxicity	MTHFR polymorphism C677T	
Antineoplastic Drugs › Topoisomerase I Inhibitors	5-FU Based Chemotherapy	Grade 3-4 ADRs	MTHFR rs1801133 C>T CT+TT and CC groups, recessive model TT vs CT+CC	(638)
Antineoplastic Drugs › Topoisomerase I Inhibitors	5-FU Chemotherapy	Toxicities	DPYD Genetic Polymorphisms (including IVS14+1G>A, 85T>C, 464T>A, 2194G>A, 496A>G, 1896T>C, 1627A>G)	(639)
	5-FU Chemotherapy	Marrow Suppression, Gastrointestinal Reaction	DPYD IVS14+1G>A, 464T>A, and 2194G>A polymorphisms	
Antineoplastic Drugs › Topoisomerase I Inhibitors	Fluoropyrimidines	Severe Toxicity	DPYD c.1679T>G, DPYD*2A and c.2846A>T	(640)
	Fluoropyrimidines	Severe Toxicity	DPYD c.1601G>A	
	Fluoropyrimidines	Gastrointestinal Toxicity, Haematological Toxicity	DPYD c.1679T>G and DPYD c.1236G>A/HapB3	
Antineoplastic Drugs › Topoisomerase I Inhibitors	Fluoropyrimidines	Severe Toxicity	Rs895819 in MIR27A	(641)
	Fluoropyrimidines	Severe Toxicity	rs11671784 and DPYD variants: DPYD c.2846A>T, c.1679T>G, c.1129-5923C>G and c.1601G>A	
Antineoplastic Drugs › Topoisomerase I Inhibitors	Fluoropyrimidines	Toxicities	ENOSF1 c.742-227G>A (rs2612091), TYMS 5'VNTR 28bp-repeat (rs45445694) and 3'UTR 6bp-indel (rs11280056)	(642)
	Fluoropyrimidines	Severe HFS	ENOSF1 c.742-227G>A and the TYMS 28bp-repeat	
Antineoplastic Drugs › Topoisomerase I Inhibitors	Fluoropyrimidines	Overall grade ≥3 toxicity, haematological toxicity, mucositis and diarrhoea	DPYD IVS14+1G>A	(643)
	Fluoropyrimidines	Overall grade ≥3 toxicity or grade ≥3 diarrhoea	DPYD 2846T allele	
Antineoplastic Drugs › Antimetabolites & Topoisomerase I Inhibitors	Capecitabine, Tegafur or 5-FU (as monotherapies or in combination with other agents)	ADEs	TYMS 5′ UTR repeat polymorphism, (rs45445694)	(644)
	Capecitabine, Tegafur or 5-FU (as monotherapies or in combination with other agents)	ADEs	MTHFR 677 C> T, (rs1801133)	
Chemotherapy Regimens	Folfox4/Folfox7/Folfox9/Gemox/Tomox, 5-Fu/Irinotecan/Oxaliplatin, 5-FU/Cisplatin/Fa Taxane + Cisplatin, (Oxaliplatin, Irinotecan and Capecitabine), (Docetaxel, Cisplatin, And T-Fluorouracil)	Overall toxicity, neutropenia	GSTP1 Ile105Val	(645)
		Neurotoxicity	GSTP1 Ile105Val	
Chemotherapy Regimens	(Cyclophosphamide alone or as part of a combination chemotherapy regimen in combination with an anthracycline, platinum-based chemotherapy alone or as	Acute Vomiting	HTR3C C1214G	(646)

	part of a combination chemotherapy regimen, cytarabine)			
	(Cyclophosphamide alone or as part of a combination chemotherapy regimen in combination with an anthracycline, platinum-based chemotherapy alone or as part of a combination chemotherapy regimen, cytarabine)	Nausea/Vomiting (CINV)	ABCB1 C3435T	
Antineoplastic Drugs › Antimetabolites	Capecitabine Monotherapy	Global G3+ Toxicity	TYMS5′VNTR2R (TYMS5′VNTR2R/3R 2-repeat allele), TYMS3′UTR6bp ins (TYMS3′UTR6bpins-del (6bp-insertion allele)	(647)
Antineoplastic Drugs › Antimetabolites	Infusional FU Monotherapy	Global G3+ Toxicity	TYMS 5′VNTR2R	
Antineoplastic Drugs › Antimetabolites	Bolus FU Monotherapy	Global G3+ Toxicity	TYMS3′UTR6bp ins	
Antineoplastic Drugs › Antimetabolites	Bolus FU Monotherapy	Neutropenia	DPYD*2A exon skipping allele (A)	
Antineoplastic Drugs › Antimetabolites & Platinum Compounds & Topoisomerase I Inhibitors	Fluorouracil combination therapy regimens (FOLFOX; CAPOX; FOLFIRI and fluorouracil [IFL or FLIRI]	Global G3+ Toxicity	TYMS 5'VNTR 2–repeat allele, TYMS 3'UTR 6bp–ins allele	
Antineoplastic Drugs › Antimetabolites	Gemcitabine	Severe Anaemia	CDA A79C (AA and AC)	(648)
	Gemcitabine	Severe Neutropenia	AA versus the AC+CC, AA/AC genotypes with the CC	
	Gemcitabine	Severe Thrombocytopenia	AA genotype was compared to the AC/CC, AA/AC genotypes	
Antineoplastic Drugs › Antimetabolites	Gemcitabine-Based Chemotherapy	Grade ≥ 3 leukopenia, severe neutropenia	CDA 79C	(649)
Antineoplastic Drugs › Anthracyclines	Anthracyclines	Cardiotoxicity	NADPH oxidase polymorphisms: ABCC2_rs8187694, ABCC2_rs8187710, ABCC1_rs45511401, NCF4_rs1883112, RAC2_rs13058338, CYBA_rs4673	(650)
Antineoplastic Drugs › Anthracyclines	Anthracyclines	Cardiotoxicity	ABCC2 rs8187710, CYBA rs4673, RAC2 rs13058338	(651)
Antineoplastic Drugs › Anthracyclines & Taxanes	Neoadjuvant chemotherapy (docetaxel, anthracycline-based regimen)	Grade 2–4 Toxicity	ABCB1 1236C>T, ABCB1 2677G>T/A, ABCB1 3435C>T	(652)
Antineoplastic Drugs › Vinca Alkaloids	Vincristine	Peripheral Neuropathies (VIPN)	CEP72 rs924607-TT, TTPA rs10504361	(653)
Antineoplastic Drugs › Topoisomerase I Inhibitors	Irinotecan-Based Chemotherapy	Grade 3/4 Toxicity	MTHFR (677 C>T and 1298 A>C)	(654)
Antineoplastic Drugs › Topoisomerase I Inhibitors	Irinotecan	Toxicity	UGT1A1*6	(655)
	Irinotecan	Severe Toxicity	UGT1A1*6, UGT1A1*28, UGT1A1*28, UGT1A1*6 and UGT1A1*28	
Antineoplastic Drugs › Topoisomerase I Inhibitors	Irinotecan	Neutropenia	ABCC2 3972T>T	(656)
	Irinotecan	Neutropenia	ABCB1 2677G>T/G	
	Irinotecan	Non-haemolytic ADEs (diarrhoea)	ABCG2 34G>A	
	Irinotecan	Haemolytic ADEs (Neutropenia and thrombocytopenia)	ABCC2 -24T>T, ABCC2 1249G>A	
	Irinotecan	Haemolytic ADEs (Neutropenia and thrombocytopenia)	ABCC2 3972T>T	
	Irinotecan	Non-haemolytic ADEs (diarrhoea)	ABCC2 -24T>T, ABCC2 1249G>A	
	Irinotecan	Non-Haemolytic ADEs (Diarrhoea)	ABCC2 3972T>T	
Antineoplastic Drugs › Topoisomerase I Inhibitors	Irinotecan	Neutropenia	SLCO1B1 521T>C, SLCO1B1 -11187G>A	(657)
	Irinotecan	Diarrhoea	SLCO1B1 521T>C, SLCO1B1 -11187G>A	
	Irinotecan	Neutropenia	SLCO1B1 388G>G	
	Irinotecan	Diarrhoea	SLCO1B1 388A>G	

Antineoplastic Drugs › Topoisomerase I Inhibitors	Irinotecan	Diarrhoea	UGT1A1∗28/∗28, UGT1A1∗1/∗28	(658)
	Irinotecan	Severe Diarrhoea	UGT1A1∗28/∗28 versus UGT1A1∗1/∗1 or UGT1A1∗1/∗28	
	Irinotecan	Severe Diarrhoea	UGT1A1∗1/∗28 versus UGT1A1∗1/∗1	
Antineoplastic Drugs › Topoisomerase I Inhibitors	Irinotecan	Severe Neutropenia	UGT1A1*28/*28 vs UGT1A1*1/*1, UGT1A1*1/*28 vs UGT1A1*1/*1	(659)
	Irinotecan	Severe Diarrhoea	UGT1A1*1/*28 vs UGT1A1*1/*1, UGT1A1*28/*28 vs UGT1A1*1/*28 or UGT1A1*1/*1	
Antineoplastic Drugs › Topoisomerase I Inhibitors	Irinotecan	Neutropenia	[UGT1A1*6 (*6/*6 vs. *1/*6 or *1/*1) (*6/*6 or *1/*6 vs. *1/*1)], [UGT1A1*6/*28 (*6/*6 or *28/*28 or *6/*28 vs. *1/*6 or *1/*28 or *1/*1)]	(660)
Antineoplastic Drugs › Topoisomerase I Inhibitors	Irinotecan	Severe Toxicity	UGT1A1*6 GA versus GG, UGT1A1*6 AA versus GG	(661)
Antineoplastic Drugs › Topoisomerase I Inhibitors	Irinotecan	Haematological Toxicities (Grade III–IV)	UGT1A1*28/*28	(662)
	Irinotecan	Haematological Toxicities (Grade III–IV)	UGT1A1*28/*28 (at low irinotecan doses)	
Antineoplastic Drugs › Topoisomerase I Inhibitors	Irinotecan	Neutropenia	UGT1A1*28 versus UGT1A1*1	(663)
Antineoplastic Drugs › Topoisomerase I Inhibitors	Irinotecan-Based Chemotherapy	Diarrhoea and neutropenia	UGT1A1*28 TA6/7 and TA7/7 genotypes	(664)
	Irinotecan-Based Chemotherapy	Severe Diarrhoea	UGT1A1*28	
	Irinotecan-Based Chemotherapy	Severe Neutropenia	UGT1A1*28	
Antineoplastic Drugs › Topoisomerase I Inhibitors	Irinotecan	Neutropenia and diarrhoea, late-onset diarrhoea, Severe neutropenia	UGT1A1*6	(665)
	Irinotecan	Severe neutropenia, Severe late-onset diarrhoea, Diarrhoea	UGT1A1*28	
Antineoplastic Drugs › Topoisomerase I Inhibitors	Irinotecan	Neutropenia, Severe Neutropenia	UGT1A1*6	(666)
Antineoplastic Drugs › Topoisomerase I Inhibitors	Irinotecan	Neutropenia	UGT1A1*6	(667)

*The list of variants associated with ADEs was annotated using the following font colour; Black colour for significantly increased risk of ADEs, Green colour represents significantly reduced risk of ADEs, and red colour denotes non-significant association with ADEs. For toxicities and adverse drug effects, the comma "," was used when these adverse drug effect(s) were analysed and reported separately, and "or" was used when these were analysed and reported jointly in the study (i.e., patients who developed ADE1, ADE2 or ADE3 etc were combined in the analysis). This also applies to the culprit drugs and variants/genotypes. For variants and genotypes, the word "combined" was used when these variants occurred simultaneously in the same individual.

Abbreviations

Anthracycline-based chemotherapy: daunorubicin, doxorubicin, mitoxantrone. IFL: irinotecan [CPT-11, Camptosar] with bolus 5-FU plus leucovorin. FLIRI: 5-FU, folinic acid, irinotecan. CAPOX: capecitabine and oxaliplatin. FOLFOX: 5-fluorouracil, folinic acid and oxaliplatin. FOLFIRI: infusional 5-fluorouracil, leucovorin, and irinotecan. GEMOX: Gemcitabine/oxaliplatin. TOMOX: Raltitrexed plus oxaliplatin. CPT-11: Campto'l", irinotecan. LV: leucovorin. FU or 5-FU: Fluorouracil. NSAIDs: Nonsteroidal Anti-Inflammatory Drugs. ADEs: Adverse Drug Effects. HSR: hypersensitivity reaction. TEAE Treatment-emergent adverse events. ADRs: Adverse Drug Reactions. INH: Isoniazid. RMP or RFP: Rifampicin. PZA: Pyrazinamide. EMB: Ethambutol. SM: Streptomycin. CADRS: Cutaneous Adverse Drug Reactions. DHS: Dapsone-Induced Hypersensitivity Syndrome. SJS: Stevens-Johnson Syndrome. TEN: Toxic Epidermal Necrolysis. DRESS: drug rash with eosinophilia and systemic symptoms. 6-MP: Mercaptopurine. AZA: Azathioprine. CBZ: Carbamazepine. PHT: Phenytoin. PB: Phenobarbital. SCAR: Severe Cutaneous Adverse Drug Reactions. DILI: Drug-induced liver injury. MPE: Maculopapular Eruption. HIV: human immunodeficiency virus. LoF: loss-of-function. BMI: Body Mass Index. EM: Extensive metaboliser. HEM: Heterozygous extensive metaboliser. IM: Intermediate metaboliser. PM: Poor metaboliser. UM: Ultrarapid metaboliser.

2.9 Appendix

Table 2.6 Examples of the search filters tested to identify RCTs and meta-analyses.

Resource of the Filter Tested	URL
Ovid built-in generic filters	-
Health Information Research Unit (HiRU) at McMaster University	(668, 669)
Cochrane sensitivity- and precision-maximising version	(161)
CADTH Search Filters	(670)

Table 2.7 The main clinical trial registries used to enquire about potential RCTs.

Clinical trial registry	URL link
Clinical Trials	https://clinicaltrials.gov/ct2/home
International Clinical Trials Registry Platform (ICTRP)	https://www.who.int/ictrp/en/
The ISRCTN registry	http://www.isrctn.com/
The European Union Clinical Trials Register	https://www.clinicaltrialsregister.eu/ctr-search/search
Chinese Clinical Trial Registry	http://www.chictr.org.cn/searchprojen.aspx
The Institute of Cancer Research	https://www.icr.ac.uk/
ICH GCP Clinical Trials Registry	https://ichgcp.net/clinical-trials-registry/
University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR)	https://www.umin.ac.jp/ctr/index.htm

Table 2.8 The search filter used to identify RCTs of PGx of ADEs in Embase.

1. crossover procedure.sh.
2. double-blind procedure.sh.
3. single-blind procedure.sh.
4. (crossover$ or cross over$).tw.
5. placebo$.tw.
6. (doubl$ adj blind$).tw.
7. allocat$.tw.
8. trial.ti.
9. randomized controlled trial.sh.
10. random$.tw.
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. exp animal/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
13. human/ or normal human/
14. 12 and 13
15. 12 not 14
16. 11 not 15
17. exp pharmacogenetics/
18. exp genetic polymorphism/
19. genetic variability/
20. (pharmacogenomic* or pharmacogenetic* or toxicogenetic* or polymorphism* or "gen* varia*" or mutation* or snp or genotype* or allele* or haplotype*).ab,ti.
21. 17 or 18 or 19 or 20
22. exp drug hypersensitivity/pc [Prevention]
23. exp drug toxicity/pc [Prevention]
24. ((adverse or undesirable or harms* or serious or toxic) adj3 (effect* or reaction* or event* or outcome*)).ab,ti.
25. ("adverse effect*" or "adverse reaction*" or "adverse drug reaction*" or "adverse event*" or "side effect*" or toxicit* or poisonin* or pharmacotox* or "drug hypersensitiv*" or "hypersensitiv* reaction*" or anaphyla* or "drug induced*" or "drug related" or "drug reaction*" or neurotoxic* or nephrotoxic* or hepatotoxic* or cardiotoxic* or immunotoxic* or immunocytotoxic* or cytotoxic* or myotoxic* or tolera* or intolera* or noxious or death* or fatal*).ab,ti.
26. 22 or 23 or 24 or 25
27. 16 and 21 and 26
28. limit 27 to english language

Table 2.9 The search filter used to identify RCTs of PGx of ADEs in Medline.

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. clinical trials as topic.sh.

6. randomly.ab.
7. trial.ti.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp animals/ not humans.sh.
10. 8 not 9
11. exp Pharmacogenetics/
12. exp Polymorphism, Genetic/
13. exp Genetic Variation/
14. (pharmacogenomic* or pharmacogenetic* or toxicogenetic* or polymorphism* or "gen* varia*" or mutation* or snp or genotype* or allele* or haplotype*).ab,ti.
15. 11 or 12 or 13 or 14
16. exp Drug Toxicity/ge, pc [Genetics, Prevention & Control]
17. exp Drug Hypersensitivity/ge, pc [Genetics, Prevention & Control]
18. ((adverse or undesirable or harms* or serious or toxic) adj3 (effect* or reaction* or event* or outcome*)).ab,ti.
19. ("adverse effect*" or "adverse reaction*" or "adverse drug reaction*" or "adverse event*" or "side effect*" or toxicit* or poisonin* or pharmacotox* or "drug hypersensitiv*" or "hypersensitiv* reaction*" or anaphyla* or "drug induced*" or "drug related" or "drug reaction*" or neurotoxic* or nephrotoxic* or hepatotoxic* or cardiotoxic* or immunotoxic* or immunocytotoxic* or cytotoxic* or myotoxic* or tolera* or intolera* or noxious or death* or fatal*).ab,ti.
20. 16 or 17 or 18 or 19
21. 10 and 15 and 20
22. limit 21 to english language

Table 2.10 The search filter used to identify RCTs of PGx of ADEs in Cochrane.

#1	MeSH descriptor: [Pharmacogenetics] explode all trees
#2	MeSH descriptor: [Polymorphism, Genetic] explode all trees
#3	MeSH descriptor: [Genetic Variation] explode all trees
#4	(pharmacogenomic* or pharmacogenetic* or toxicogenetic* or polymorphism* or "gen* varia*" or mutation* or snp or genotype* or allele* or haplotype*):ab,ti
#5	#1 or #2 or #3 or #4
#6	MeSH descriptor: [Drug-Related Side Effects and Adverse Reactions] explode all trees
#7	MeSH descriptor: [Drug Hypersensitivity] explode all trees
#8	("adverse effect*" or "adverse reaction*" or "adverse drug reaction*" or "adverse event*" or "side effect*" or toxicit* or poisonin* or pharmacotox* or "drug hypersensitiv*" or "hypersensitiv* reaction*" or anaphyla* or "drug induced*" or "drug related" or "drug reaction*" or neurotoxic* or nephrotoxic* or hepatotoxic* or cardiotoxic* or immunotoxic* or immunocytotoxic* or cytotoxic* or myotoxic* or tolera* or intolera* or noxious or death* or fatal*):ab,ti
#9	#6 or #7 or #8
#10	#5 and #9

Table 2.11 The search filter used to identify meta-analyses of PGx of ADEs in Embase.

1. exp animal/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
2. human/ or normal human/
3. 1 and 2
4. 1 not 3
5. exp pharmacogenetics/
6. exp genetic polymorphism/
7. genetic variability/
8. (pharmacogenomic* or pharmacogenetic* or toxicogenetic* or polymorphism* or "gen* varia*" or mutation* or snp or genotype* or allele* or haplotype*).ab,ti.
9. 5 or 6 or 7 or 8
10. exp drug hypersensitivity/pc [Prevention]
11. exp drug toxicity/pc [Prevention]
12. ((adverse or undesirable or harms* or serious or toxic) adj3 (effect* or reaction* or event* or outcome*)).ab,ti.
13. ("adverse effect*" or "adverse reaction*" or "adverse drug reaction*" or "adverse event*" or "side effect*" or toxicit* or poisonin* or pharmacotox* or "drug hypersensitiv*" or "hypersensitiv* reaction*" or anaphyla* or "drug induced*" or "drug related" or "drug reaction*" or neurotoxic* or nephrotoxic* or hepatotoxic* or cardiotoxic* or immunotoxic* or immunocytotoxic* or cytotoxic* or myotoxic* or tolera* or intolera* or noxious or death* or fatal*).ab,ti.
14. 10 or 11 or 12 or 13
15. meta-analysis as topic/ or Meta-Analysis.pt. or (meta-analy* or metaanaly*).ti,ab.
16. 15 not 4
17. 9 and 14 and 16
18. limit 17 to english language
19. limit 18 to dc=19740101-20200527

Table 2.12 The search filter used for identification of meta-analyses of PGx of ADEs in Medline.

1. exp animals/ not humans.sh.
2. exp Pharmacogenetics/
3. exp Polymorphism, Genetic/

4. exp Genetic Variation/
5. (pharmacogenomic* or pharmacogenetic* or toxicogenetic* or polymorphism* or "gen* varia*" or mutation* or snp or genotype* or allele* or haplotype*).ab,ti.
6. 2 or 3 or 4 or 5
7. exp Drug Toxicity/ge, pc [Genetics, Prevention & Control]
8. exp Drug Hypersensitivity/ge, pc [Genetics, Prevention & Control]
9. ((adverse or undesirable or harms* or serious or toxic) adj3 (effect* or reaction* or event* or outcome*)).ab,ti.
10. ("adverse effect*" or "adverse reaction*" or "adverse drug reaction*" or "adverse event*" or "side effect*" or toxicit* or poisonin* or pharmacotox* or "drug hypersensitiv*" or "hypersensitiv* reaction*" or anaphyla* or "drug induced*" or "drug related" or "drug reaction*" or neurotoxic* or nephrotoxic* or hepatotoxic* or cardiotoxic* or immunotoxic* or immunocytotoxic* or cytotoxic* or myotoxic* or tolera* or intolera* or noxious or death* or fatal*).ab,ti.
11. 7 or 8 or 9 or 10
12. meta-analysis as topic/ or Meta-Analysis.pt. or (meta-analy* or metaanaly*).ti,ab.
13. 12 not 1
14. 6 and 11 and 13
15. limit 14 to english language
16. limit 15 to dt=19460101-20200527 [January 1st, 1946 to May 27th, 2020]

Table 2.13 The search filter used to identify meta-analyses of PGx of ADEs in Cochrane.

#1	MeSH descriptor: [Pharmacogenetics] explode all trees
#2	MeSH descriptor: [Polymorphism, Genetic] explode all trees
#3	MeSH descriptor: [Genetic Variation] explode all trees
#4	(pharmacogenomic* or pharmacogenetic* or toxicogenetic* or polymorphism* or "gen* varia*" or mutation* or snp or genotype* or allele* or haplotype*):ab,ti
#5	#1 or #2 or #3 or #4
#6	MeSH descriptor: [Drug-Related Side Effects and Adverse Reactions] explode all trees
#7	MeSH descriptor: [Drug Hypersensitivity] explode all trees
#8	("adverse effect*" or "adverse reaction*" or "adverse drug reaction*" or "adverse event*" or "side effect*" or toxicit* or poisonin* or pharmacotox* or "drug hypersensitiv*" or "hypersensitiv* reaction*" or anaphyla* or "drug induced*" or "drug related" or "drug reaction*" or neurotoxic* or nephrotoxic* or hepatotoxic* or cardiotoxic* or immunotoxic* or immunocytotoxic* or cytotoxic* or myotoxic* or tolera* or intolera* or noxious or death* or fatal*):ab,ti
#9	#6 or #7 or #8
#10	MeSH descriptor: [Meta-Analysis as Topic] explode all trees
#11	MeSH descriptor: [Network Meta-Analysis] explode all trees
#12	(meta-analy* or metaanaly*):ti,ab
#13	{or #10-#12}
#14	#5 and #9 and #13

Table 2.14 The search strategy to identify meta-analyses of PGx of ADEs in Google Scholar.

The following searches using scope qualifiers and sorted by relevance were executed. The top 1000 records were assessed.

“Any time” "anywhere in the article": ‘’meta-analysis’’ AND [pharmacogenetic OR pharmacogenomic OR pharmacogenetics OR pharmacogenomics]
“Any time” "anywhere in the article": ‘’systematic review’’ AND [pharmacogenetic OR pharmacogenomic OR pharmacogenetics OR pharmacogenomics]
“Since 2020” "anywhere in the article": ‘’meta-analysis’’ AND [pharmacogenetic OR pharmacogenomic OR pharmacogenetics OR pharmacogenomics]
“Since 2020” "anywhere in the article": ‘’systematic review’’ AND [pharmacogenetic OR pharmacogenomic OR pharmacogenetics OR pharmacogenomics]
Since 2011: intitle:pharmacogenetics AND intitle:("systematic review" | meta-analysis)
Since 2008: intitle:pharmacogenomics AND intitle:("systematic review" | meta-analysis)
“Any time”: intitle:pharmacogenetic(s) AND intitle:("umbrella review" | "overview of reviews" |"review of reviews" |"summary of systematic reviews" |"synthesis of reviews")
“Any time” "anywhere in the article":pharmacogenetic(s) AND intitle:("umbrella review" | "overview of reviews" |"review of reviews" |"summary of systematic reviews" |"synthesis of reviews")
“Any time”: intitle:pharmacogenomic(s) AND intitle:("umbrella review" | "overview of reviews" |"review of reviews" |"summary of systematic reviews" |"synthesis of reviews")
“Any time” "anywhere in the article":pharmacogenomic(s) AND intitle:("umbrella review" | "overview of reviews" |"review of reviews" |"summary of systematic reviews" |"synthesis of reviews")
Since 2016: polymorphism variant genotype drug toxicity serious severe adverse drug reactions systematic review meta-analysis
Since 2016: allintitle: "pharmacogenetics"
Since 2016: allintitle: "pharmacogenetic"
Since 2016: allintitle: "pharmacogenomics"= 1,260 results (Top 1000 were selected)
Since 2016: allintitle: "pharmacogenomic"= 634 results

Table 2.15 Gene names used to re-interrogate the irrelevant records.

Source	Genes

Sentinel meta-analyses and systematic reviews	*Xpd, IL-28B, GPIIIa, CFH, MRP2, WT1, BDNF, GNB3, OPRM1, ADRB1 2, PON1, TNF-α, GGCX, OCT1, FSHR, LHR, LHCGR*
Very Important Pharmacogenes associated with toxicity from PharmGKB	*NAT2, UMPS, PARD3B, TPMT, MTHFR, HLA, HLA-A, HLA-B, HLA-C, COMT, CES1, CES1P1, ABCB1, ABCC (1, 2, 3, 4, 5), ABCG2, ABCA1, TYMS, HTR2A, XPO1, NRP2, GRIN2B, CAPG, MDR1, GATM, ACE, CYP2D6, CYP2C8, CYP1A2, CYP2C9, CYP2C19, CYP3A4, CYP3A5, CYP19A1, CYP2E1, CYP2E1, CYP4F2, SLC6A4, SLC22A7, SLC31A1, SLCO1B1, SLC6A4, SLCO1B1, SLC19A1, UGT1, UGT1A1, GSTM1, GSTT1, GSTs, SHOX, ERCC1, DHFR, DPYD, HapB3, XRCC1, RFC1, DRD(1, 2, 3), MnSOD, HTR2C, 5-HTTLPR, STin2, VKORC1*
Genes potentially confer Adverse events, Drug Hypersensitivity and Severe cutaneous adverse reactions	*HLA-B, HLA-C, NOTCH4, HLA-DRB1, HLA-DQB1, CYCSP5, POU5F1, PSORS1C1, PSORS1C3, SLC22A1, HLA-A, COMT, ARRB2, CACNA1C, NR1I2, ERCC2, LST1, LTA, LTB, TNF, LGALS3, VEGFA, ITGAV, WWOX, FLT4*

Table 2.16 Meta-analyses of variants associated with ADEs identified in RCTs.

Drug(s)	Genomic variant	Toxicity outcomes	Pooled effect estimate OR or RR (95% Conf. Interval)	Studies (N)	Ref.
Clopidogrel	*CYP2C19* LOF	Bleeding	1.1210 [0.8547; 1.4702], 0.4091	14	(196, 197, 206–213, 198–205)
	CYP2C19 LOF	Major bleeding	1.4204 [0.9765; 2.0660], 0.0664	5	
	*CYP2C19*17*	Major bleeding	1.1410 [0.9283; 1.4024], 0.2102	4	
	UM vs. PM/IM	Major bleeding	0.9156 [0.6602; 1.2698], 0.5971	4	
	PM/IM vs. EM	Major bleeding	1.1746 [0.9710; 1.4208], 0.0974	4	
Clopidogrel in PCI patients	*CYP2C19* LOF	Bleeding	0.9429 [0.7199; 1.2349], 0.6692	3	
Clopidogrel in non-PCI patients	*CYP2C19* LOF	Bleeding	1.2083 [0.6513; 2.2419], 0.5485	3	
	UM vs. PM/IM	Major bleeding	0.7585 [0.4024; 1.4295], 0.3926	3	
Clopidogrel in ACS patients	UM vs. PM/IM	Major bleeding	1.0855 [0.8676; 1.3581], 0.4730	2	
Ticagrelor or Prasugrel vs. Clopidogrel	*CYP2C19* LOF	Minor bleeding	1.1607 [0.5335; 2.5251], 0.7071	5	
	CYP2C19 LOF	Major bleeding	1.0254 [0.8269; 1.2715], 0.8192	3	
Ticagrelor or Prasugrel vs. Clopidogrel in ACS patients	*CYP2C19* LOF	Clinically significant bleeding	1.0119 [0.7942; 1.2893], 0.9236	3	
Methotrexate	*MTHFR* 677 CC vs. CT+TT	Hepatotoxicity	0.6417 [0.3545; 1.1615], 0.1428	2	(214–218)
	MTHFR 677 TT vs. CT+CC	Mucositis or gastrointestinal toxicity	1.47 [1.02; 2.13], 0.0348	3	
Statins	*SLCO1B1* −521 CT vs. TT	Myopathy	1.109 [0.913, 1.347], 0.299	3	(219–221)
Efavirenz	*CYP2B6* 516 GG+GT vs. TT	CNS Adverse Effects	0.504 [0.268, 0.947], 0.033	2	(222, 223)
Nevirapine	HLA-DRB1*01	Hepatotoxicity or Hypersensitivity	1.912 [0.776, 4.710], 0.159.	2	(231–233)
	MDR1 3435 C>T	Hepatotoxicity	0.621 [0.289, 1.332], 0.221	2	
	MDR1 2677 G>T	Hepatotoxicity	0.715 [0.526, 0.972], 0.032	2	
	CYP2B6 516 G>T	Hepatotoxicity	1.049 [0.484, 2.275], 0.903	2	
	CYP2B6 1459 C>T	Hepatotoxicity	0.980 [0.543, 1.767], 0.946	2	
CDA and artemisinin-based combination therapy	*G6PD* A−	Severe anaemia	**15 [10.27, 21.9], *p*<0.0001***	7	(224–230)

***Statistically significant associations are in bold.**
Abbreviations: PCI= Percutaneous Coronary Intervention. ACS= Acute Coronary Syndrome. CNS= Central Nervous System. CDA= Chlorproguanil-Dapsone-Artesunate. *CYP2C19* LoF polymorphisms= *CYP2C19* 2* or 3*.

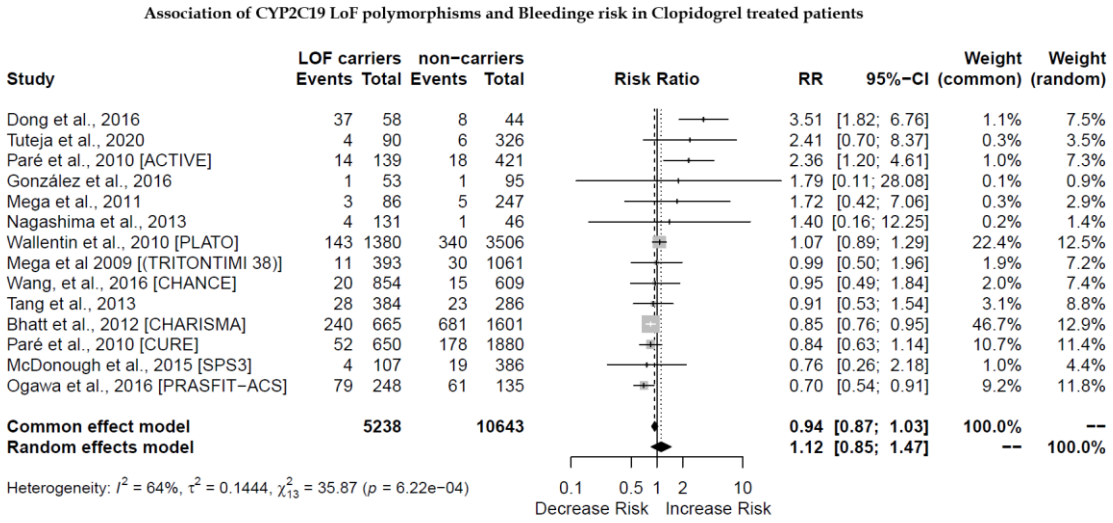


Figure 2.6 Association of CYP2C19 LOF polymorphisms and bleeding risk in clopidogrel-treated patients.

Meta-analysis of the risk ratios (RR) and 95% confidence intervals (CI) of 14 studies examined the association of CYP2C19 LOF polymorphisms and bleeding risk in clopidogrel-treated patients. Individual and pooled risk ratios from studies were reported in the forest plot. Squares represent study-specific effect estimates and the size of the square reflects the study-specific weight (i.e., the inverse of the variance). The diamond represents the summary effect estimate with a 95% confidence interval, and the horizontal lines indicate a 95% confidence interval.

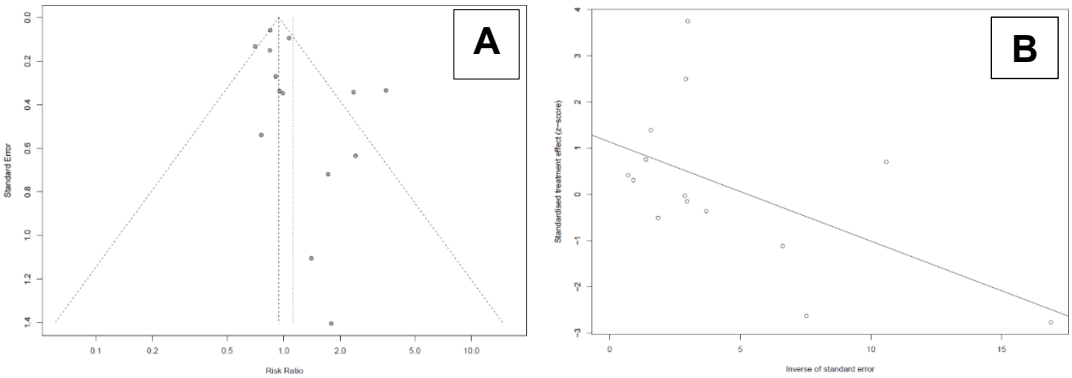


Figure 2.7 Publication bias for association of CYP2C19 LOF polymorphisms and bleeding risk in clopidogrel-treated patients.

(A) Publication bias funnel plot (B) Metabias using Egger's method for publication bias. Funnel plot asymmetry indicated that no small studies (with SE>0.6) reporting a negative association exist in the literature

3 Chapter Three. Pharmacogenomic Variants of Medically Important Adverse Effects Related to High-Risk Medicines in General Practice Can Not Be Replicated in UK Biobank

3.1 Abstract

Background/Aim MIADEs represent a major concern leading to significant increases in both morbidity and mortality worldwide. While variants can modulate the risk for such MIADEs, this requires multiple steps of replication and validation at scale using real-world data. Thus, I sought to examine and determine the robustness of previously described associations between variants associated with MIADEs related to high-risk medicines in general practice (GP).

Materials and methods In the UKBB participants, I examined associations between previously reported variants and MIADEs related to high-risk medicines in GP, using a statistical model including both the main effects and interaction terms. The variants were obtained from the clinical annotations in PharmGKB. The high-risk medicines were identified by mapping data on serious and fatal ADEs from the UK pharmacovigilance database, namely the Yellow Card system, onto GP prescription data in England.

Results A total of 56 clinical annotations with either moderate or high levels of evidence for the risk of MIADEs were identified in PharmGKB. By mapping data on serious and fatal ADEs onto GP prescription data, I identified 78 high-risk medicines (i.e., medicines with a high toxicity profile). Having cross-examined the high-risk medicines and variants identified in PharmGKB, there were eight single nucleotide variants that have been previously reported to modulate the risk of MIADEs related to three high-risk therapeutic classes. No statistically significant genotype-treatment interactions were found for either baseline measurements or incident MIADEs in the UKBB.

Conclusions This large study found that previously reported associations between PG variants and MIADEs related to high-risk medicines in GP including statins, NSAIDS and antipsychotics were not replicated in the UKBB. Hence, these variants are not accurate at identifying those who are at risk of developing MIADEs in patients receiving these treatments and therefore should not be considered for personalised recommendations in clinical practice.

3.2 Introduction

3.2.1 Pharmacogenomics has the potential to predict ADEs and individualise treatment in primary care

Using genomic data to determine whether a patient may develop ADEs in order to individualise treatment in primary care has been suggested. Endeavours to incorporate PGx data in GP have been progressing in the direction of implementation. The nature of long-term patient care provided for chronic conditions which often require multiple medicines and the necessitated long-term adherence to medication render in GP optimal for such wide-scale implementation. The prevalence of PG variants influencing response to medicines in the general population is considerably high and more than a third of patients seen in primary care carry one or more PG variants (671–674), each of which may modulate the effects of multiple medicines for several conditions. For example, an analysis of 14 pharmacogenes in the UKBB reported that over 99% of the participants have a predicted atypical response to at least one medicine (675). Another study of prescribing trends in primary care settings over 20 years reported that exposure to medicines with PG variants with dosing guidelines in PharmGKB was remarkably high, with over 80% of patients being exposed to at least one medicine (676). Nevertheless, the incorporation of such PG variants into the prescribing pipeline to support decision-making in primary care and translating that into clinically actionable advice has been challenging. The validity and clinical utility of PG variants remain the main obstacles and therefore further efforts need to be considerably devoted to replication research, particularly in independent large datasets.

3.3 Aim

I. In the UKBB, this study aims to determine the robustness of previously described associations between variants associated with MIADEs related to high-risk medicines in GP.

3.4 Objectives

II. To identify high-risk medicines or medicines with or high-toxicity profile in GP.

III. To identify variants associated with MIADEs in PharmGKB

IV. To assess associations between previously reported variants and MIADEs related to high-risk medicines in GP.

V. To generate quantitative comparative safety charts for medicines pertaining to the same therapeutic class.

3.5 Materials and Methods

3.5.1 Identification of high-risk medicines in general practice

Data on serious and fatal ADE reports from the Yellow Card database was mapped onto GP prescription data in England during the period (Jan-2016 Jan-2021). All fatal and serious ADE reports received in the UK by the MHRA were retrieved for all available medications from the Interactive Drug Analysis Profiles (iDAPs) in the MHRA's Yellow Card database (45). As MHRA regularly checks for duplicate ADE reports at the data entry stage, de-duplication was not necessary prior to this analysis. GP prescribing data was extracted from the OpenPrescribing platform (677). This includes English prescriptions from General Practitioners (GPs) as well as non-medical prescribers connected to GPs which are dispensed everywhere in the United Kingdom. One prescription item represents the single supply of a particular medication prescribed which is dispensed in the United Kingdom. Medications listed in the MHRA's Yellow Card database were linked to English prescribing data using the following approach:

For medications with ADE reports submitted within the specified period, I calculated the number of reports regarding fatal and serious ADEs for those with available prescribing data for the period specified. If prescription data were available for a specific time frame where no ADE reports existed, I assumed that no ADE reports had been submitted during this period. Prescription data were assessed at the same time and the number of prescribed items for the longest period was computed. Medications with available ADE reports but lacking prescribing data for a particular time frame were not included.

Medications were thereafter categorised according to therapeutic classes, sections and chapters as per the British National Formulary (BNF). Medications which belong to multiple categories were re-classified according to the frequency of their prescribing. Clinical judgment was applied for medications which could not be classified unequivocally based on the frequency of their prescribing. The extent of the analyses was then reduced by only including medications which are

prescribed most frequently during the given time frame.

Medications were analysed within their therapeutic categories and relative safety was thus determined. Safety profiles were analysed by the total number of fatal and serious ADE reports per 1,000,000 items dispensed. The comparative medication safety profiles were presented using forest plots. This allows any two medications within a particular therapeutic category to be directly compared by seeing whether their confidence intervals overlap, potentially facilitating informed and evidence-based prescribing decisions.

In this analysis, I only included medicines that are licensed in the UK and initiated or continued in GP and excluded multiple constituent medicines and medicines administered via other inappropriate routes of administration. For example, ADE reports that are considered to have derived from the medication use via means not deemed suitable for GP (e.g., parenteral formulations) were excluded. In addition to this analysis, sensitivity analyses were performed to assess the robustness of the results and relative ranking of medicines by applying different exclusion and inclusion criteria. This comprised two distinct sensitivity analyses: i) aggregated analysis, and ii) analysis by inclusion. In the aggregated analysis, I included all single and multiple constituent medicines administered via all different routes of administration in both reporting and prescribing databases. In the analysis by inclusion, I included both prescriptions and ADE reports solely for medicines administered via means deemed suitable for GP (e.g., oral or SC formulations). This was crucial as the count of ADE reports available on iDAPs for a multiple constituent medication comprises the total number for both its combination and single formulations.

Top-ranked medications (i.e., high-risk medicines) were thereafter identified. This was achieved by identifying the top-ranked medicine for which confidence intervals do not overlap with other medicines within each therapeutic class. If the confidence intervals for the top-ranked overlapped with other medicines within a therapeutic class, I selected the medicine with the narrowest confidence intervals. If the *p*-value of the *Q*-statistic for a therapeutic class was >0.05, no medicines were included from that class. Similarly, if confidence intervals for most medicines in a therapeutic class were overlapping, no medicines were included from that class. The notion of ‘high-risk medicines’ or ‘medicines with high toxicity profile’ was utilised as an alternative to top-ranked medicines.

As providing HCPs and patients with real-world data on drug safety is imperative to facilitate informed decision-making, comparative safety charts were produced for clinically meaningful medicines by excluding medicines with <220,000 items dispensed in the specified period. For this purpose, I also excluded medicines with substantially dissimilar mechanisms of action or administered via fundamentally dissimilar routes to the other related medicines and those prescribed for indications substantially different to other related medicines within the therapeutic class. Combination medicines, highly specialised as well as pharmacies and supermarkets medicines were excluded.

3.5.2 Systematic identification of variants associated with MIADEs in PharmGKB

To create a list of variants associated with the risk of MIADEs to be interrogated in the UKBB, I systematically searched for PG variants associated with the risk of ADEs or toxicities mapped by PharmGKB up to 22nd July 2020. Criteria for the definition of MIADEs are detailed in 2.5.2.2. Only clinical annotations and phenotypes related to ADEs or toxicities with moderate or high-level evidence by PharmGKB (1A, 1B, 2A and 2B) were considered (Appendix

Table 3.5 [Appendix]). This includes variants annotated in medical society-endorsed PGx guidelines including Construction Project Information Committee (CPIC), variants implemented by the Pharmacogenomics Research Network (PGRN), used in multiple clinics or replicated in more than a single cohort with a strong effect size and significant p-values. Annotations based on a non-significant study or single case report or a single significant association but not further replicated were excluded. Annotations from functional, molecular or in vitro assays were also excluded. Further exclusions include clinical annotations of adverse events due to the ineffectiveness of treatment and annotations related to Cmax and AUC, response, resistance, dose requirement, metabolism and bioavailability. Since the purpose of my analyses was to quantify the risk in the UK population, medicines which do not longer exist on the market or are not listed in either BNF or electronic medicines compendium (emc) were removed. I only included medicines administered orally or parenterally, and therefore medicines predominantly used via ophthalmic and dermatological routes were excluded. Further, I excluded annotations related to cancer chemotherapy agents and anaesthetic medications unless their indications overlapped with other

therapeutic classes. The pertinent literature related to the eligible clinical annotations and phenotypes was further scrutinised by screening the abstracts, reviewing the methods when necessary and applying the inclusion and exclusion criteria.

The generated list of variants was subsequently curated for possible future use by interpreting the haplotypes and star alleles into more specific genotypes when possible and reporting the ICD-10 diagnostic codes used in healthcare records data in most biobanks (Please see 2.5.2.2 for more details). Further, I curated and constructed a set of variant-drug pairs associated with MIADEs.

3.5.3 UK Biobank analyses

3.5.3.1 Description of the study population

Briefly, the UKBB is a population-based cohort with over 500,000 community-based participants who visited one of the assessment centres located in England, Scotland or Wales between 2006-2010 (136). In addition to the wide-ranging health-related information and clinical examinations recorded at baseline assessment, blood samples were collected for genomic and biomarker analyses. Participants are continuously followed up and their health records data is periodically updated including self-reported questionnaires or survey information with updated Hospital Episode Statistics (HES) and linkage to both death and cancer registries (136). To minimise confounding and control for population stratification or substructure that usually occurs in genetic association studies when groups of distinct ethnicities are analysed together, I restricted my analyses to 389,805 unrelated individuals with genetically determined European Ancestry (~80% of UKBB participants with genotype data) and incorporated principal components of ancestry in my analyses (678, 679).

Patients who self-reported at the baseline assessment receiving treatments of interest were included. Key characteristics of study participants (e.g., age, BMI) were described. I consulted with the BNF (47), emc (680) and DrugBank database (681) to identify all brand names of single or multiple constituent formulations that contain the medicine of interest. In the UKBB, treatment/medication Field ID 20003 and medication codes used are listed in (Table 3.6 [Appendix]).

3.5.3.2 Ascertainment of biomarkers, adverse drug effects and other phenotypes

Both baseline measurements and data from follow-up visits and updated HES were utilised. To create variables for incident phenotypic endpoints of interest (i.e. MIADEs), self-reported and International Classification of Diseases 9th and 10th revision codes (ICD-9, ICD-10) were used (Table 3.7 [Appendix]). The self-reported questionnaire codes ICD-9, and ICD-10 codes with Data Field IDs used in this study are itemised in (Table 3.8 [Appendix]). HES data was available up to fourteen years follow-up from the baseline assessment (data from England and Scotland up to 2020, data from Wales up to 2018).

3.5.3.3 Variants selection and genotyping

Having identified the high-risk medicines in GP and variants conferring a risk of MIADEs as per PharmGKB, I cross-examined these to identify variants conferring a risk of MIADEs and related to the high-risk medicines in GP to be interrogated in the UKBB. When an annotation in PharmGKB was related to a whole therapeutic class, all medicines that fall under that class were included in the UKBB analyses.

I used microarray data generated in the UKBB in two platforms; the Affymetrix Axiom UK Biobank array for approximately 438,000 participants and the UK BiLEVE array for around 50,000 (682). The genotyping dataset underwent stringent quality control (683) and the variants I extracted from the imputed data (682) were all imputed with high confidence >99.7%.

3.5.4 Methods of statistical analysis

3.5.4.1 Statistical analyses of comparative safety data

The extracted data from both pharmacovigilance and prescribing databases was loaded onto a Microsoft Office Professional Plus Excel® 2016 (185). Statistical analyses were conducted using the ‘meta’ package in software R (v4.1.1) (684). Since the outcomes of interest are rate data that follow a Poisson distribution, a model of random intercept Poisson regression was fitted (685). To perform analyses of the rates of fatal and serious ADE reports per item dispensed, I used the function *metarate* with the generalised linear mixed-effects model argument "GLMM“, as described previously (686). For the GLMM, I utilised the maximum-

likelihood estimator (687) to compute the between-medications variance τ^2. Heterogeneity among the medications studied was calculated utilising the I^2 statistic (191), which denotes the percentage of variance among the medications within a therapeutic category that is here explained by the between-medication heterogeneity (based on *Q*) (186). Forest plots were created using the 'meta' package in software R (v4.1.1) to provide visual tools for all the medications analysed. Both τ^2 and I^2, as well as *the p*-value for the *Q*-statistic, were reported in the forest plots.

3.5.4.2 Statistical analyses of UK Biobank data

In an attempt at replication, regression analyses were performed to test the associations between variants and MIADEs as per how they were annotated in PharmGKB or stated by the initial papers. Thus, I fitted a main effects model for the risk of MIADEs (i.e., comparing the risk of MIADEs for those with a specific genotype to that for those without) into the multivariate regression models.

In addition, I conducted the statistical analyses by fitting interaction terms into the multivariate regression models to test the interaction between treatment and genotypes (i.e., whether the variant modifies the association of treatment with the risk of developing MIADEs). Dissimilar to the linear and additive effects of variant on the risk of developing MIADEs in the main effects regression modelling of the total population, treatment-specific regression modelling tests for interaction between treatment and genotype by adding the interaction variable to the model (treatment multiplied by variant), indicating a non-additive effect. Interaction effects, which represent a multiplicative or synergistic effect, actually exist when a third variable (e.g., genotype) modifies the relationship between an independent or predictor variable (e.g., treatment) and a dependent variable (e.g., toxicity outcome). A statistically significant interaction effects test indicates an interactive relationship between independent and dependent variables that change depending on the value of a third variable (i.e., the relationship between the treatment and the development of toxicity depending on the genomic variant). Failure to include the interaction effects in the model and making decisions based solely on the outcome of the main effects may result in erroneous conclusions. In instances where interactions were not possible, a main effects model for the risk of MIADEs was used instead.

Variants were analysed for dominant, recessive or additive statistical genetic models according to PharmGKB annotations or as stated in the initial studies. In addition to adjusting for potential confounders in the multivariable regression models, all statistical analyses were adjusted for assessment locations and the first five genetic principal components of ancestry to control for population stratification and minimise bias (679).

Since I tested multiple variants and phenotypes and to minimise the probability of obtaining false positives (688), I corrected for multiple testing by applying the Bonferroni correction to limit Type I error rates (115). The formula used for the corrected critical value is explained in 2.5.6.

For the continuous baseline measurements of interest, outcomes were dichotomised. Weight gain was considered severe if BMI >= 41.66 (defined as 3 standard deviations over the average BMI of unrelated Europeans in the UKBB). As per the British Heart Foundation and HEART UK experts (689, 690), hypertriglyceridemia was defined as having non-fasting triglycerides higher than 2.3 mmol/L. This dichotomisation provides easily interpretable summary statistics and makes findings useful for HCPs. Logistic regression models were used to test associations between variants and binary outcomes using the *logistic* command. I further conducted secondary analyses by examining individual medicines or relaxing the definition of some of the toxicity phenotypes analysed. The analyses were two-tailed, and STATA (version 16.0) was utilised for data management and performing the statistical analyses.

3.5.5 Ethical approval

Both the GP prescribing as well as the Yellow Card databases contain anonymised and non-identifiable datasets, ethical approval was not required.

Access to the UKBB data was approved under Application Numbers (49847 and 9072). All study participants were given written informed consent to enrol; the UKBB is approved by the UKBB Research Ethics Committee.

3.6 Results

3.6.1 The comparative safety analyses identified 78 high-risk medicines

There were 2,331 medicinal products on the iDAPs platform, and 2,317 chemicals on the OpenPrescribing database. Having linked the data on serious and fatal ADEs from the Yellow Card database onto GP prescription data in England, there existed 2,317 medications pertaining to 406 therapeutic categories. Having applied further exclusion criteria, there remained 365 medications pertaining to 71 therapeutic classes in the final analysis dataset.

Based upon the *p*-value for *Q*-statistic and I^2 statistic, the quantitative comparative safety analyses showed significant differences within most therapeutic classes with respect to the rate of fatal and serious ADE reports per dispensed unit (Figure 3.5 [Appendix]). The sensitivity analyses showed that the overall relative rankings of medicines within therapeutic classes in the aggregated analysis and analyses by exclusion and inclusions were largely consistent.

Having exhaustively examined the quantitative comparative safety analyses for 71 therapeutic classes (as detailed above in 3.5.1), I identified 78 high-risk medicines (Figure 3.1).

This study also generated comparative safety charts for clinically meaningful medicines belonging to 26 therapeutic categories (Figure 3.6 [Appendix]). The linkage for clinically meaningful medicines also revealed significant differences with respect to the rate of fatal and serious ADE reports per million items dispensed among medications belonging to 23 classes out of the 26 therapeutic categories studied. There were only three therapeutic classes that demonstrated no significant differences among the medications examined, namely: 1) potassium-sparing diuretics and aldosterone antagonists, 2) angiotensin-converting-enzyme inhibitors, and 3) medications used for erectile dysfunction. The comparative safety charts for the clinically meaningful medicines are shown in (Figure 3.7 [Appendix]).

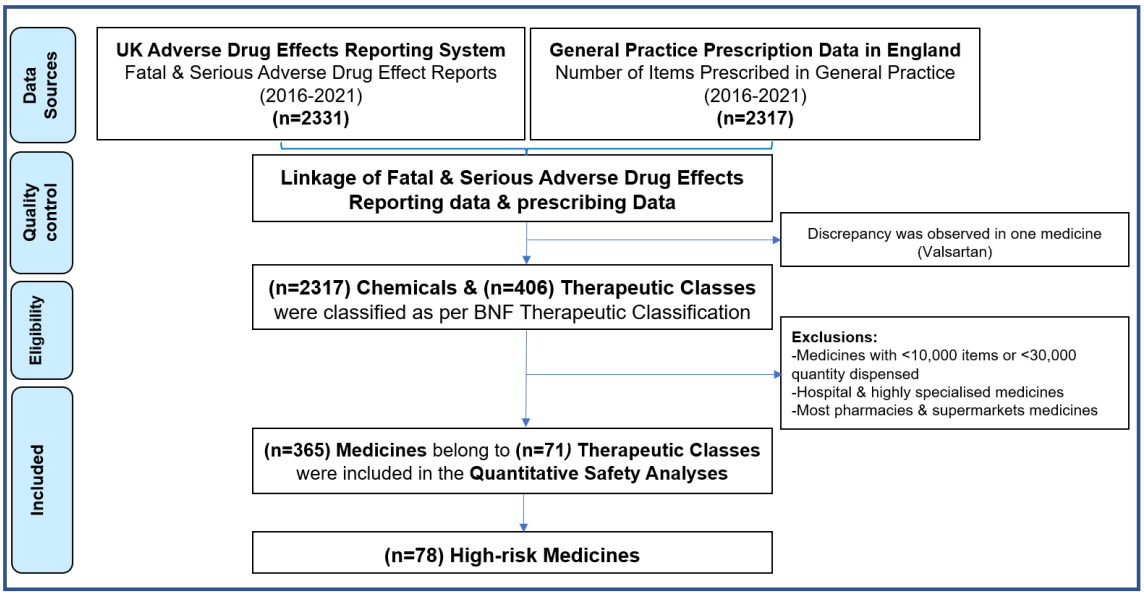


Figure 3.1 The process of mapping data on adverse drug effects onto general practice prescription data.

A flowchart demonstrates the method utilised to identify high-risk medicines. Data on serious and fatal ADEs from the Yellow Card database was linked to GP prescription data in England. Exclusion criteria were further applied to identify top-ranked medicines (i.e., high-risk medicines).

3.6.2 I identified 56 clinical annotations related to MIADEs in PharmGKB

Of 11,951 phenotypes in PharmGKB, there were 3,057 records of significant associations related to ADEs or toxicity. However, almost all of these were supported by a single publication with a low level of evidence, so they were removed. Of 4,564 clinical annotations, a total of 183 records related to ADRs/toxicity for 106 drugs or therapeutic classes with either moderate or high-level evidence were identified. Having further excluded annotations for cancer chemotherapy agents and anaesthetic medications (n=81), this resulted in a total of 102 clinical annotations for the risk of developing ADEs. Further curation based on the contribution of variants to seriousness, severity or medical importance criteria (i.e., MIADEs) yielded 56 clinical annotations related to the risk of developing MIADEs (Figure 3.2). I further constructed a set of variant-drug pairs associated with MIADEs by PharmGKB (Table 3.1). The full list of variant-drug pairs associated with MIADEs with fully specified genotypes and ICD-10 codes is catalogued in (supplementary Excel file S3).

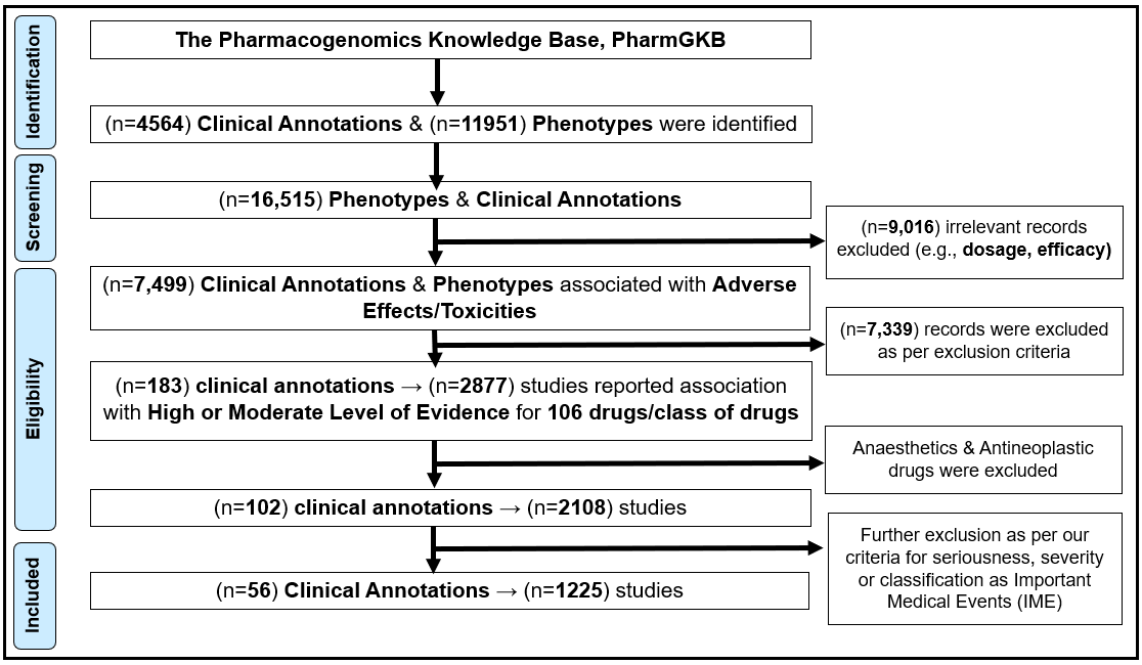


Figure 3.2 A flowchart illustrates the identification procedure of variant-drug pairs for MIADEs in PharmGKB.

Table 3.1 The set of variant-drug pairs associated with MIADEs in PharmGKB.

Treatment or Drug(s)	Variant
Abacavir	HLA-B*57:01:01
Nevirapine	rs1045642, rs28399499, HLA-B *35:05:01, HLA-B*35:01:01:01, HLA-DRB1*01:01:01, HLA-C*04:01:01:01
Atazanavir	rs887829
Ritonavir-boosted Atazanavir	UGT1A1*1, UGT1A1*28
Efavirenz	rs3745274
Peginterferon alfa-2b; Ribavirin	rs7270101, rs1127354
Antituberculosis agents[1]	rs1799930, rs1041983
Antituberculosis agents; Isoniazid	NAT2*12, NAT2*13, NAT2*14, NAT2*4, NAT2*5, NAT2*6, NAT2*7
CDA	rs1050828
Dapsone	HLA-B*13:01:01
Aminoglycoside Antibacterials[2]	rs267606617, rs267606619, rs267606618
Antipsychotics	rs6977820
Antipsychotics[3]	rs1800497
Antipsychotics[4]	rs489693
Atomoxetine	CYP2D6*1, CYP2D6*10, CYP2D6*2, CYP2D6*3, CYP2D6*4, CYP2D6*5
Nortriptyline	CYP2D6*1, CYP2D6*10, CYP2D6*1xN, CYP2D6*2, CYP2D6*2xN, CYP2D6*3, CYP2D6*4, CYP2D6*5, CYP2D6*6
Citalopram	CYP2C19*1, CYP2C19*17, CYP2C19*2, CYP2C19*3, CYP2C19*4
Carbamazepine	HLA-B*15:11:01, HLA-B*15:02:01, HLA-A*31:01:02
Oxcarbazepine	HLA-B*15:02:01
Phenytoin	HLA-B*15:02:01, CYP2C9*1, CYP2C9*2, CYP2C9*3
NSAIDs[5]	rs1057910
Aspirin	rs730012
Codeine	CYP2D6*1, CYP2D6*10, CYP2D6*17, CYP2D6*1xN, CYP2D6*2, CYP2D6*2xN, CYP2D6*3, CYP2D6*4, CYP2D6*40, CYP2D6*41, CYP2D6*5, CYP2D6*6

Statins[6]	rs1346268, rs1719247, rs4149056
Statins[7]	rs4693075
Acenocoumarol, Phenprocoumon, Warfarin	rs9923231
Acenocoumarol, Warfarin	rs1799853 [T], rs1057910 [C]
Warfarin	VKORC1 (−1639G>A) rs992323, CYP2C9*1, CYP2C9*11, CYP2C9*2, CYP2C9*3, CYP2C9*5, CYP2C9*6
Clopidogrel	rs12248560
Azathioprine	ITPA rs7270101
Azathioprine, Mercaptopurine	rs116855232, NUDT15 *1/*2, *1/*3, *1/*4,*1/*6,*3/*3
Mercaptopurine	NUDT15*1, NUDT15*2, NUDT15*3, NUDT15*4, NUDT15*5, NUDT15*6
Azathioprine, Mercaptopurine, Purine Analogues, Thioguanine	TPMT*2,*3A,*3B,*3C
Methotrexate	rs1045642, rs1801133
Carbimazole, Methimazole, Propylthiouracil	HLA-B*38:02:01
Hormonal contraceptives for systemic use	rs6025
Allopurinol	HLA-A*33:03, HLA-B*58:01, HLA-C*03:02

Abbreviations
CDA: Chlorproguanil-dapsone-artesunate, NSAIDs: Non-steroidal anti-inflammatory drugs
Antituberculosis agents[1]: Ethambutol, Isoniazid, Pyrazinamide, Rifampin
Aminoglycoside Antibacterials[2]: Amikacin, Gentamicin, Kanamycin, Neomycin, Streptomycin, Tobramycin
Antipsychotics[3]: Clozapine, Olanzapine, Risperidone
Antipsychotics[4]: Amisulpride, Aripiprazole, Clozapine, Haloperidol, Olanzapine, Paliperidone, Quetiapine, Risperidone, Ziprasidone
NSAIDs[5]: Celecoxib, Diclofenac
Statins[6]: hmg coa reductase inhibitors including Simvastatin.
Statins[7]: hmg coa reductase inhibitors including Atorvastatin, rosuvastatin.

3.6.3 Cross-examination of high-risk medicines and clinical annotations yielded three therapeutic classes

Having identified 78 high-risk medicines in GP and 56 clinical annotations related to the risk of MIADEs as per PharmGKB, I cross-examined these to identify variants conferring a risk of MIADEs and related to the high-risk medicines in GP to be interrogated in the UKBB. This yielded seven high-risk medicines with clinical annotations related to the risk of MIADEs. These annotations were pertinent to three therapeutic classes including all medicines classified underneath, namely statins, non-steroidal anti-inflammatory drugs (NSAIDs) and antipsychotics. A cohort flowchart of the UKBB participants with sufficient genomic and treatment data eligible for inclusion, in the final analysis, is demonstrated in (Figure 3.3). The summary statistics for the key characteristics of the UKBB are shown in (Table 3.2). Details on the included variants and their prevalence in the UKBB are summarised in (Table 3.3).

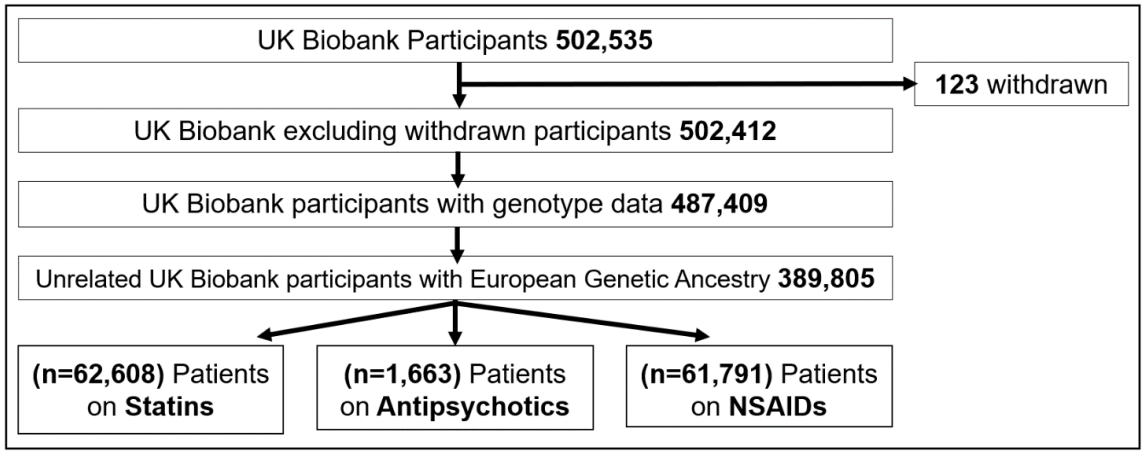


Figure 3.3 UK Biobank participants with European genetic ancestry eligible for the analysis.

A cohort flowchart of the UKBB participants with sufficient genomic and treatment data eligible for inclusion in the final analysis.

Table 3.2 Key characteristics and summary statistics for the UKBB participants included in the analysis.

Main characteristics & Toxicity measures	Statins (n=62,608)	Rest of UKBB Participants (n=439,928)
Age (years) Mean (SD)	62 (6)	56.3 (8)
BMI (kg/m2) Mean (SD)	29.4 (5)	27 (4.6)
Myopathy, Rhabdomyolysis, Muscular Diseases (n)	(n=408)	(n=1819)
Main characteristics & Toxicity measures	Anti-psychotics [Group 1] (n=1,125)	Rest of UKBB Participants (n=501,411)
Age (years) Mean (SD)	54.6 (8)	57.2 (8)
BMI (kg/m2) Mean (SD)	29.6 (6.1)	27.4 (4.8)
Hypertriglyceridemia (High vs. low) (n)	(n=478)	(n=209,966)
Severe weight gain [>= 41.66] (n)	(n=57)	(n=118,826)
Main characteristics & Toxicity measures	Anti-psychotics [Group 2] (n=1,663)	Rest of UKBB Participants (n=500,873)
Age (years) Mean (SD)	55.7 (8)	57.2 (8)
BMI (kg/m2) Mean (SD)	29.4 (6)	27.4 (4.8)
Hyperprolactinemia (n)	(n=6)	(n=35)
Tardive dyskinesia (n)	(n=2)	(n=24)
Severe weight gain [>= 41.66] (n)	(n=78)	(n=118,805)
Main characteristics & Toxicity measures	NSAIDs (n=61,791)	Rest of UKBB Participants (n=440,745)
Age (years) Mean (SD)	55.9 (8.1)	57.5 (8)
BMI (kg/m2) Mean (SD)	28.1 (5.1)	27.2 (4.7)
Gastrointestinal bleeding (n)	(n=2,398)	(n=16,672)

Table 3.3 The genomic variants included in the analysis and their prevalence in the UK Biobank.

Gene	Variant ID	Directly genotyped or Imputed	Imputation Score R2*	Chromosome number	Position	Allele 1	Allele 2	Minor Allele UKBB	MAF UKBB (Unrelated Europeans)
NAT2	rs1041983	Imputed	0.999	chr8	18257795	C	T	T	0.33
NAT2	rs1799930	Genotyped	N/A	chr8	18258103	G	A	A	0.30
DPP6	rs6977820	Genotyped	N/A	chr7	154072020	T	C	T	0.28
COQ2	rs4693075	Genotyped	N/A	chr4	84192168	G	C	G	0.38

MC4R	rs489693	Genotyped	N/A	chr18	57882787	C	A	A	0.33
GATM	rs1346268	Imputed	1	chr15	45673029	T	C	C	0.26
GATM	rs1719247	Imputed	0.995	chr15	45620985	C	T	T	0.26
SLCO1B1	rs4149056	Genotyped	N/A	chr12	21331549	T	C	C	0.15
ANKK1	rs1800497	Genotyped	N/A	chr11	113270828	G	A	A	0.21
CYP2C9	rs1057910	Genotyped	N/A	chr10	96741053	A	C	C	0.06

*R2 is the squared correlation between input genotypes and imputed dosages (i.e., true and inferred genotypes).

3.6.4 No statistically significant genotype-treatment interactions were found

The analysis in the UKBB included eight variants; Four variants were reported to be associated with statin-related myopathy, one variant was reported to increase the risk of NSAIDs-induced acute gastrointestinal bleeding and three variants were reported to modulate the risk of antipsychotics-related tardive dyskinesia, hyperprolactinaemia, hypertriglyceridaemia or severe weight gain (Figure 3.4).

In the primary analysis, participants taking antipsychotic medications who carry *MC4R* rs489693 (in the recessive mode of inheritance AA) were more likely to develop severe weight gain in the main effects model [OR=1.23 (1.14, 1.33), *p*=8.32 E-08]. This was an attempt at replication of these genetic associations as per how they were annotated in the PharmGKB or stated by the initial papers. Yet, this variant was not statistically significant in the interaction terms model. Similarly, no statistically significant interactions between treatment and mutation status for the risk of MIADEs for the other variants analysed were found (i.e., the confidence intervals for the point estimates for each genotype group in those receiving treatment overlapped substantially). The corrected critical *p*-value for the primary analyses was 0.05/28= 1.79E-03 (Table 3.4).

In the secondary analyses, I excluded Ibuprofen from NSAIDS, and further analysed individual statins and in men and women separately to determine if and how the effect is related to individual statins and sex. I also relaxed some of the definitions of some toxicity phenotypes by investigating extremely high triglycerides levels (>=5.6) for antipsychotics-related hypertriglyceridemia and incorporating chronic ulcers with haemorrhage and/or perforation in NSAIDs-related acute gastrointestinal bleeding. Still, no statistically significant associations between the SNVs analysed and MIADEs were found either in the main effects or interaction terms models. The corrected critical *p*-value for the secondary analyses was 0.05/130= 3.85E-04.

The results of the primary and secondary analyses including both the main effects and interaction terms statistical models are presented in (Table 3.9 [Appendix]).

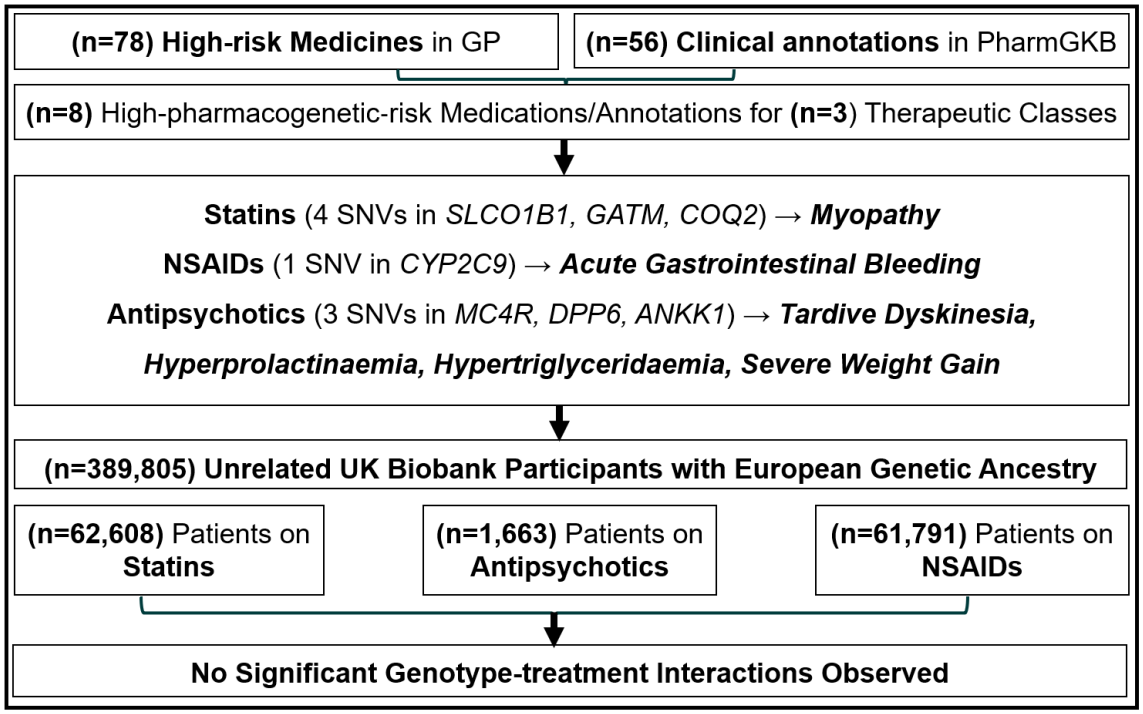


Figure 3.4 The UK Biobank analyses.

This figure demonstrates the analysis performed in UKBB. This included eight variants; four were reported to be associated with statin-related myopathy, one variant was reported to increase the risk of NSAIDs-induced acute gastrointestinal bleeding and three were reported to modulate the risk of antipsychotics-related tardive dyskinesia, hyperprolactinaemia, hypertriglyceridaemia or severe weight gain.

Table 3.4 The main results and the change in the Level of Evidence in PharmGKB

Treatment(s)	Adverse Drug Effect	Variant	Genetic model	UKBB Study	Level of Evidence in PharmGKB	
				OR (low 95%, high 95%), *p*-value [Interaction terms] *	**[2020]**	**[2022]**
Statins	Myopathy, Muscular Diseases	rs1719247 [C]	[Recessive CC vs. CT or TT]	1.12 (0.89, 1.40), 3.38E-01	2B	Level 3
		rs4149056 [C]	[Dominant: CC+CT vs. TT]	1.03 (0.80, 1.32), 8.31E-01	1A, 2A	1A, 2A
		rs1346268 [T]	[Recessive TT vs. CC or CT]	1.14 (0.91, 1.43), 2.57E-01	2B	Level 3
			[Dominant CT+TT vs. CC]	0.92 (0.60, 1.41), 6.91E-01	2B	Level 3
		rs4693075 [G]	[Dominant GG or CG vs. CC]	1.02 (0.81, 1.28), 8.90E-01	2B	Level 3
Anti-psychotics [Group 1]	Hypertriglyceridemia	rs489693 [A]	[Recessive AA vs. AC or CC]	1.17 (0.78, 1.77), 4.52E-01	2B	Level 3
	Severe weight gain	rs489693 [A]	[Recessive AA vs. AC or CC]	1.59 (0.78, 3.26), 2.03E-01	2B	Level 3
		rs1800497 [A]	[Dominant AA+AG vs. GG]	1.12 (0.65, 1.93), 6.92E-01	2B	Level 3
Anti-psychotics [Group 2]	Hyperprolactinemia	rs1800497 [A]	[Dominant AA+AG vs. GG]	9.04 (0.91, 89.96), 6.03E-02	2B	Level 3
	Severe weight gain	rs489693 [A]	[Recessive AA vs. AC or CC]	1.53 (0.82, 2.86), 1.79E-01	2B	Level 3
		rs1800497 [A]	[Dominant AA+AG vs. GG]	1.12 (0.70, 1.78), 6.45E-01	2B	Level 3
	Tardive dyskinesia	rs1800497 [G]	[Additive G]	0.61 (0.29, 1.27), 1.85E-01 [Main effects]	2B	Level 3
		rs6977820 [T]	[Dominant CT+TT vs. CC]	1.01 (0.39, 2.62), 9.83E-01 [Main effects]	2B	Level 3
NSAIDs	Acute gastrointestinal bleeding	rs1057910 [C]	[Additive C]	0.99 (0.87, 1.13), 9.06E-01	2A	Level 3

* **Interaction terms model** unless annotated otherwise (e.g., main effects)

3.7 Discussion

3.7.1 No statistically significant genotype-treatment interactions were observed

Primary care and GP settings with their readily well-developed infrastructure are optimally placed to implement PG testing. Genomic variants relevant to primary care patients conferring a risk of occurrence of ADEs have been previously described and many were optimistic about their role in optimising prescribing to help improve safety (691, 692). This large investigation aimed to replicate previously described associations between variants with moderate or high levels of evidence associated with MIADEs related to high-risk medicines in GP. However, I observed no statistically significant genotype-treatment interactions in the UKBB, either in the primary or secondary analyses.

Findings from this study showed that none of the variants analysed should be incorporated in clinical decision support systems in primary care contexts, corroborating the lack of consensus regarding whether PGx should be implemented within primary care settings (693–696). The differences between my results and findings from initial studies were noticeable and much larger than can be explained by random variation or residual stratification. If these associations were robust, they are expected to hold when examined in a subtly dissimilar population for slightly different phenotype definitions.

While I identified the variants associated with a risk of ADEs mapped by PharmGKB up to 22nd July 2020, a change in the level of evidence assigned to these variants was made later by PharmGKB. With the exception of the association between *SLCO1B1* rs4149056 and statins-related muscular toxicity, my findings are entirely consistent with the low level of evidence (Level 3) assigned to these variants by PharmGKB in May 2022 (Table 3.4). Yet, findings from my study are supported by results from the meta-analysis of RCTs and *post-hoc* analyses of RCTs I previously performed which showed no significant association between rs4149056 and myopathy in statin-treated patients: OR [95% CIs] =1.109 [0.913, 1.347], p=0.299 (Please see 2.6.3 for further details). Thus, results from my meta-analysis and this investigation in the UKBB still contest the current high level of evidence assigned to *SLCO1B1* rs4149056 and statin-musculoskeletal toxicity by PharmGKB, which is largely debatable (697).

Several previous reports did not find a significant association between rs4149056 and statin-related muscular toxicity (698, 699, 708, 709, 700–707). Multiple studies reported significant associations in subjects receiving a specific statin but not in those receiving other statins when stratified by statin type (220, 704, 717, 707, 710–716). Other reports did not show consistent results when using different genetic models (716). Further, the case of the very high dose of simvastatin in the literature cited to assign this high level of evidence by PharmGKB is a source of concern (718, 719). Also, most of the studies cited to produce the high-level of evidence assigned to this association by PharmGKB examined the effect rs4149056 genotypes on the pharmacokinetic variability or plasma concentration of statins (698, 720, 729–738, 721, 739–748, 722, 749–756, 723–728), a small but significant proportion of which did not report on the significance of this association (698, 730–733, 740, 757) or reported results opposite to what is expected or seen previously (728, 751). Prior reports showed that statin-related musculoskeletal toxicity occurred in subjects with plasma concentrations of statins at an acceptable normal range, suggesting that effects of rs4149056 on statin-related musculoskeletal toxicity are unrelated to high plasma exposure of neither statins nor their metabolites (758, 759).

Although the rs4149056 may play a role in inter-subject variability in the disposition of some statins within specific ethnic groups and potentially modulate the risk of musculoskeletal toxicity, it does not seem to explain the differences observed in pharmacokinetic variability or musculoskeletal toxicity between carriers and non-carriers. Most statin-related ADEs were found to be nocebo as well as extremely difficult to identify (760), and therefore using patient-reported data of ADEs in the clinical trials cited to assign this high level of evidence was also a concern (761). The conflicting evidence and contradictory findings observed highlight the presence of other genetic and non-genetic risk factors associated with PG variability of statins and subsequent development of musculoskeletal toxicity that evidently cannot be solely ascribed to rs4149056.

To assess the pre-emptive genotyping approach to prevent ADEs, the PREemptive Pharmacogenomic testing for Preventing Adverse drug REactions (PREPARE) study initiated the implementation of preemptive PG testing in clinical sites for 6944 patients included in the study (762). The authors stated that genotype-guided treatment had significantly decreased the incidence of clinically

relevant ADEs by 30%. However, this finding deserves rigorous and detailed scrutiny. There was a loss of around 10% of patients in the follow-up, which disproportionately affected the intervention group more than the control group. The impact of differential attrition on the effect of intervention on the prevalence of ADEs, which is anticipated (763), was not explored by the authors. Further, the trial was unblinded which could impact the reporting of ADEs (764). There was a decrease in ADEs even among those with no actionable results and therefore the decrease in ADEs was irrespective of having an actionable result (765). This indicates that patients were potentially reluctant to report ADEs if they were aware that the PG test was carried out for them. The observed heterogeneity in the effect of the PG intervention among the different EU countries was an additional concern, casting doubt on the feasibility of wide-scale implementation of PG testing and its extension to other populations. Further, while PG testing can result in lower drug doses and is subsequently associated with inferior efficacy outcomes of therapy in patients tested, this has not been assessed by the investigators. Besides, the medicines were very heterogeneous and multiple medicines were taken by very small numbers of patients, particularly for high-risk medicines. The assigned actionability for the drug-variants combination in the DPWG guideline used by the investigators of (PREPARE) study is questionable with serious doubts having been cast on this designation (697). Finally, aggregate analysis of all these medicines and subsequently drawing an overall conclusion that genotype-guided treatment significantly decreased the incidence of ADEs is futile.

3.7.2 Reviewing the pertinent literature relating to PharmGKB annotations is vital

Of note, out of the clinical annotations identified in PharmGKB, around one-fifth, were originally annotated with general terms to refer to ADEs. These were re-classified as MIADEs when the abstracts and/or method sections in the original papers were reviewed. Hence, examining the literature that underpins the clinical annotations or is used to produce the evidence in PharmGKB is vital.

3.7.3 I created comparative medication safety charts to support evidence-based decision-making around formulary choices

To provide HCPs and patients with real-world data on drug safety and facilitate

informed and evidence-based decision-making, this study produced comparative safety charts for clinically meaningful medicines. Access to such evidence-based safety information is key in the context of shared decision-making in patient-prescriber encounters. Besides, this study demonstrated that using aggregate data in both prescribing and ADE reporting databases is adequately robust. The sensitivity analyses showed that the relative ranking of medicines in the aggregated analysis compared to analyses by exclusion and inclusions (i.e., when applying different exclusion and inclusion criteria) were largely consistent, suggesting that the aggregated analysis of these databases is sufficiently robust to draw conclusions with regard to the safety analyses.

There exists an earlier analysis of ADE reports and prescriptions written in the United Kingdom's primary care settings between 2008-2012 (766). Nevertheless, that analysis examined the total number of prescriptions instead of individual medications. Also, the main objective of that report was to compare the proportion of reported ADEs for particular age ranges with what is projected based on the proportion of prescriptions in primary care settings. Moreover, the analysis was limited by the utilisation of the IMS Disease Analyzer to project up the number of prescriptions issued in primary care in the UK. The IMS Disease Analyzer reflects only 1.7 per cent of the general UK population, and therefore all the number of prescriptions therein were merely projected to reflect the entire UK population. A systematic review of the literature has endeavoured to identify medications associated with fatal and serious adverse drug events (767). However, that review predominantly focused on medication errors instead of ADEs occurring in routine clinical practice within the licence pertaining to those medications. A more recent systematic literature review examined ADEs within primary care settings (90), yet its main focus was to determine the prevalence as well as the proportion of ADEs deemed preventable rather than to identify high-risk medications.

Many studies and various organisations have endeavoured to identify high-alert or high-risk medications (767–771). Nevertheless, the lists of high-risk medications catalogued by those studies were generated with a particular emphasis on reports of medication errors instead of ADEs (769). Notably, those lists of high-risk medications were predominantly based on specific clinical contexts such as in-patient, acute, long-term or ambulatory care settings (770, 772, 773) and so, may differ significantly for other settings (774). Examples

include tools devised to identify high-risk medicines such as Inappropriate Prescribing in the Elderly Tool (IPET) (775), Medication Appropriateness Index (MAI) (776, 777), Screening Tool of Older Persons' Prescriptions (STOPP) (778), GerontoNet (779), Screening Tool Alert Doctors to Right Treatment (START) (780) and Beers criteria. However, such tools were mainly created to identify potentially inappropriate prescribing of medications (781). Additionally, the majority of these tools were constructed with a focus on in-patient settings and in the elderly, such as IPET in patients older than 70 years in hospital settings, and STOPP and Beers criteria in patients older than 65 years (782, 783). As a result, these tools may not apply to everyday clinical practice throughout dissimilar age ranges and populations. Moreover, tools like STOPP/START were mainly constructed to standardise the medication review process (784) based on expert consensus instead of data derived from real-world or clinical practice (785). To date, no robust evidence exists to demonstrate that these tools can mitigate the incidence of deaths or hospital admissions (786). Taken together, none of the above-mentioned reviews and tools was designed to provide HCPs and patients with comparative safety data for fatal or serious ADEs within a therapeutic category.

3.7.4 The existent inherent imitations in prescribing and ADE reporting databases require attention

Caution should be exercised when interpreting the results from the comparative medication safety analyses considering the inherent limitations pertaining to the nature of prescription data as well as ADE reporting data utilised.

First, the prescription data utilised were derived solely from prescriptions issued in England. Yet, England contains approximately 85 % of the United Kingdom population and therefore the English prescription data represents the majority of the prescriptions issued in GP in the United Kingdom. Second, medicines less frequently prescribed in GP were not included to narrow the dataset to a more manageable level. This could have resulted in some under-representation of a number of clinically significant GP medications with substantial ADE rates. Third, the prescribing data used denotes the total number of times a particular medication has been prescribed but lacks information on either the length of therapy or the precise quantity of medication prescribed. Yet, UK GPs are urged

to prescribe only for one month at a time and therefore this is not expected to be a concern. Fourth, prescription data do not inevitably imply patient exposure to medications. Yet, I used dispensing data which is likely to better represent exposure than prescribing data alone. Estimates show that only around 87 to 95 per cent of prescriptions originating from primary care settings are dispensed thereafter (787, 788). Fifth, reporting of ADEs is completely voluntary apart from Marketing Authorisation Holders (MAHs) who are legally obliged to submit ADE reports related to their medications (789–791). Nevertheless, fatal and serious ADEs are reasonably more likely to be identified and reported as patients with serious or life-threatening ADEs are usually admitted to hospital or treated under hospital supervision. Yet, the majority of the above-mentioned limitations are expected to affect all medications similarly, and therefore the relative rankings that reflect the rates of ADEs per dispensed unit are not likely to be affected.

3.7.5 Implications for research and practice

The variants analysed in this study should not serve as predictors of risk of developing MIADEs in patients receiving these treatments and therefore PG testing in this context should not be considered in clinical practice for personalised treatment. These findings can inform stakeholders and policymakers considering implementing PG tests in GP or primary care. Based on NHS England recent policies regarding the adoption of PG testing preemptively for variants with robust evidence (792), this study demonstrated that the evidence base for these variants is insufficient to justify the integration in clinical practice prescribing support tools.

3.8 Conclusions

This is the first study that used real-world recent data derived from GP-specific prescribing data and national incident ADE reporting data in PG analyses. None of the previously reported PG associations between variants and MIADEs related to high-risk medicines and therapeutic classes in GP were replicated in the UKBB. This included statins, NSAIDs and antipsychotics. Hence, PG testing in these contexts should therefore not be implemented in clinical practice.

This study employed a novel data integration approach to map the Yellow Card system onto the English GP prescription data. The generated comparative medication safety visuals have the potential to predict medication relative safety

and represent a benchmark against which outcomes from pharmaco-epidemiological investigations exploring high-risk medications are compared. Nevertheless, validating these comparative safety charts and evaluating their suitability and usefulness in routine clinical practice is required.

3.9 Appendix

Table 3.5 Phenotype categories in PharmGKB which are systematically searched to identify variants associated with the risk of ADEs.

Phenotype Categories
Toxicity
Toxicity/ADR
Toxicity/ADR; other
Dosage; Toxicity/ADR
Toxicity/ADR; Metabolism/PK
Efficacy; Toxicity/ADR
Dosage; Efficacy/ADR
Efficacy; Toxicity/ADR; Metabolism/PK
Others

Table 3.6 High-risk medicines in GP and medications codes examined in the UK Biobank.

Treatment modality	Generic name	Other Brand Names investigated	Codes*
Statins	Simvastatin	Zocor, zocor heart-pro, INEGY, Cholib, FloLipid, Simcor, Vytorin	1140861958, 1140881748, 1141200040
	Pravastatin	Lipostat, Elisor, Mevalotin, Pravaselect, Selipran	1140888648, 1140861970
	Rosuvastatin	Crestor	1141192410, 1141192414
	Fluvastatin	Dorisin, Lescol, Nandovar, Canef, Cranoc	1140888594, 1140864592
	Atorvastatin	Lipitor, Caduet	1141146234, 1141146138
Anti-psychotics	Amisulpride	Solian, Deniban, Barhemsys	1141153490, 1141184742
	Aripiprazole	Abilify, Abilify Maintena, Abilitat	1141195974, 1141202024
	Clozapine	Clozaril, Denzapine, Zaponex, Fazaclo, Versacloz	1140867420, 1140882320, 1141200458, 1141201792
	Haloperidol	Halkid, Haldol, Haldol Decanoate	1140867168, 1140867184
	Olanzapine	Zalasta, Zyprexa, Zypadhera, Lybalvi, Olazax, Symbyax	1140928916, 1141167976
	Quetiapine	Seroquel, Atrolak, Biquelle, Brancico, Mintreleq, Sondate, Zaluron, Alaquet	1141152848, 1141152860
	Risperidone	Risperdal Consta, Perseris	1140867444, 1141177762
	Perphenazine	Decentan, Emesinal, Fentazin, Perphenan, Trilafon,Trilifan	1140867208, 1140867948, 1140867210
	Chlorpromazine	Largactil	1140879658, 1140910358, 1140863416
	Zuclopenthixol	Clopixol, Ciatyl-Z	1140882100, 1140867342
	Flupentixol	Fluanxol, Depixol, Psytixol	1140909800, 1140867952, 1140867152
	Promazine	Combelen, Prazine, Sparine, Talofen	1140879746, 1140867288
	Pericyazine	Neuleptil	1140867134
	Levomepromazine	Nozinan	1140909802, 1140867122
	Trifluoperazine	Eskazine / Eskazinyl / Jatroneural / Modalina / Stelazine / Terfluzine / Trifluoperaz / Triftazin	1140868120, 1140867944, 1140867244
	Sulpiride	Bosnyl / Dogmatil / Dogmatyl / Dolmatil / Eglonyl / Espiride / Meresa / Modal	1140867304, 1140867306
NSAIDs	Aceclofenac	Preservex, Cincofen / Clanza / Hifenac	1140925808, 1140925806
	Sulindac	Clinoril	1140871606, 1140871604
	Naproxen	Naprosyn, Stirlescent, Boots Period Pain Relief, Aleve, Aleve PM, Aleve-D, Anaprox, EC-Naprosyn, Naprelan, Sallus, Sudafed Sinus & Pain, Treximet, Vimovo	1140871472, 1140871462, 1140881612
	Mefenamic Acid	Ponstan, Ponstel	1140871546, 1140871542
	Etodolac	Etolyn, Etopan, Lodine	1140871196, 1140871188
	Celecoxib	Celebrex, Consensi, Elyxyb	1141176668, 1141176670, 1141176662
	Diclofenac	Voltarol, Diclo-SR, DICLOZIP, diclotard, Dicloflex Retard, diclovol, diclomol, Enstar	1140871168, 1140871174, 1140917394, 1140921828, 1141146404, 1141157112,

		XL, Diclomax SR, Diclomax Retard, Motifene, Akis, Econac, Misofen, Arthrotec	1140871260, 1140909354, 1141176878, 1141191028, 1140871266, 1140927086, 1140884488, 1140878036
	Indomethacin	Indocid, Indocin, Tivorbex	1140871354, 1140871336, 1141157452
	Flurbiprofen	Froben	1140871238, 1140871236
	Ketorolac	Ketorolac Trometamol	1140884558
	Piroxicam	Feldene, Feldene Melt	1140871672, 1140871666, 1141169526, 1141182754
	Dexketoprofen	Keral, Skudexa	1141164750, 1141164746
	Ibuprofen	Sudafed Sinus Pain Relief , Soleve, Pedea, Nuromol Dual Action Pain Relief, Flarin, Fenpaed Ibuprofen, Cuprofen, Care Cold & Flu Relief, anadin ibuprofen, Anadin Joint Pain, Boots Rapid Ibuprofen lysine, Feminax Express, Ibucalm, Ibular, Nurofen, Nurofen Express, Nurofen Joint & Back Pain Relief, Nurofen Migraine Pain, Brufen, Cuprofen Maximum Strength, Numark Max Strength Pharmacy Ibuprofen, Nurofen Meltlets, Brufen Retard, Anadin Ultra, Galpharm Migraine Relief, Calprofen	1141153134, 1141191742, 1141190952, 1140871388, 1141182868, 1141187776, 1141157412, 1140871310, 1141184546, 1141194296, 1140878030, 1140910496

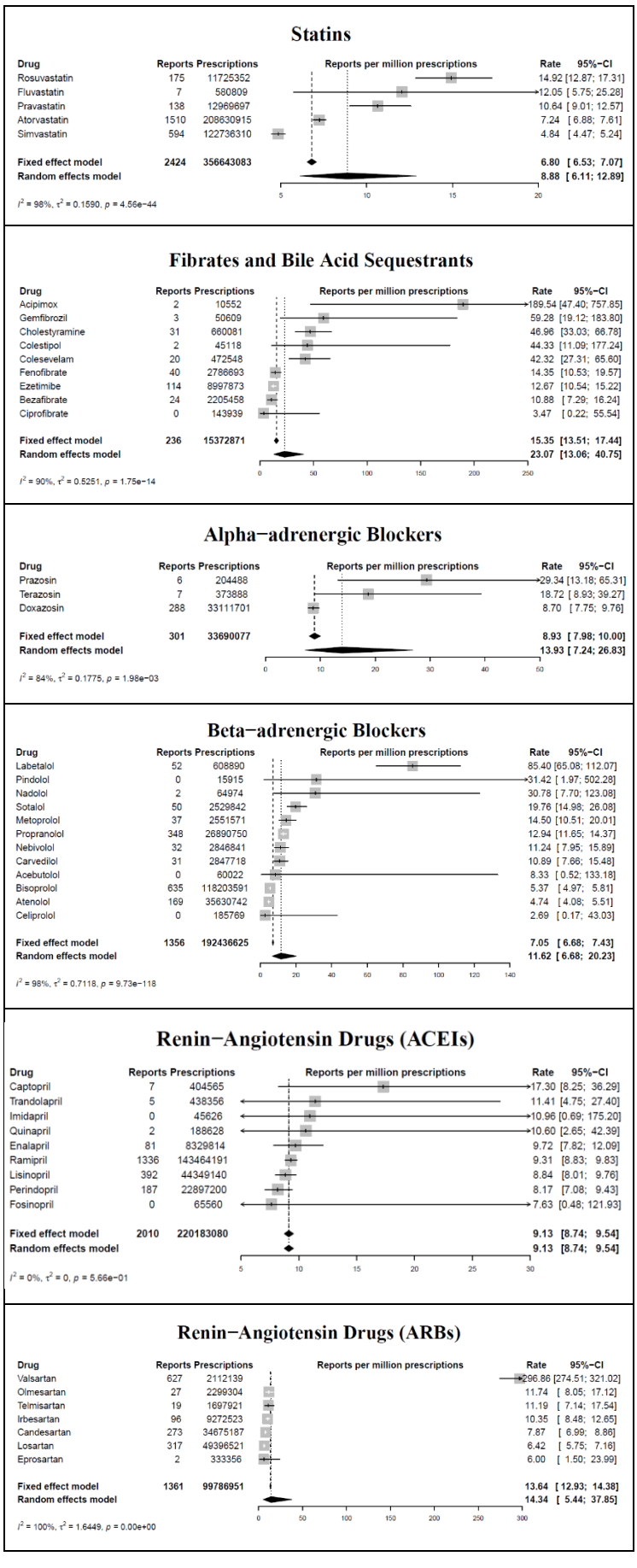
*Treatments and medication codes (including those used as used as covariates) were obtained from:
https://biobank.ctsu.ox.ac.uk/crystal/coding.cgi?id=4&nl=1
https://biobank.ndph.ox.ac.uk/showcase/field.cgi?id=20003

Table 3.7 Ascertainment of adverse drug effects, diagnoses and other phenotypes in the UK Biobank.

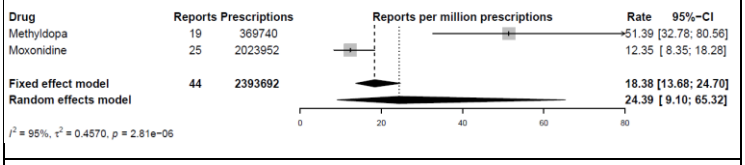
Item of data	URL
Diagnoses - ICD10 (to level 4)	https://biobank.ndph.ox.ac.uk/showcase/field.cgi?id=41270
ICD-10 codes	https://biobank.ndph.ox.ac.uk/showcase/coding.cgi?id=19 or https://icd.who.int/browse10/2010/en
ICD-9 main and secondary codes	https://biobank.ndph.ox.ac.uk/showcase/coding.cgi?id=87&nl=1
Non-cancer illnesses self-reported codes	https://biobank.ndph.ox.ac.uk/showcase/coding.cgi?id=6
For cancer codes, self-reported:	https://biobank.ndph.ox.ac.uk/showcase/coding.cgi?id=3

Table 3.8 Adverse drug effects and codes related to high-risk medicines examined in the UK Biobank.

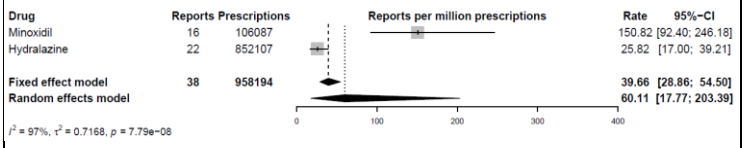
Phenotype	ICD-10	ICD-9	Self-report code from n_20002_* variable
Myopathy, Muscular Diseases *[including myalgia, Rhabdomyolysis]*	G720 G728 G729 M608 M609 M791 M628	3599 7291 7283 72888 3598	1322 1297
Tardive dyskinesia	G240		
Acute gastrointestinal bleeding	K922 K290 K250 K252 K260 K262 K270 K272 K280 K282 K290 K922 K625	5310 5312 5320 5322 5330 5332 5340 5342 5693 578 5789	1191
Gastrointestinal bleeding *[including chronic ulcer with haemorrhage and/or perforation]*	K922 K290 K921 K250 K251 K252 K254 K255 K256 K260 K261 K262 K264 K265 K266 K270 K271 K272 K274 K275 K276 K280 K281 K282 K284 K285 K286 K290 K922 K625 K228	5310 5311 5312 5314 5315 5316 5320 5321 5322 5324 5325 5326 5330 5331 5332 5334 5335 5336 5340 5341 5342 5344 5345 5346 5693 578 5781 5789	1191
Hyperprolactinemia	E221	2531	1431


Statins
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Rosuvastatin 175 11725352 14.92 [12.87; 17.31]
Fluvastatin 7 580809 12.05 [5.75; 25.28]
Pravastatin 138 12969697 10.64 [9.01; 12.57]
Atorvastatin 1510 208630915 7.24 [6.88; 7.61]
Simvastatin 594 122736310 4.84 [4.47; 5.24]
Fixed effect model 2424 356643083 6.80 [6.53; 7.07]
Random effects model 8.88 [6.11; 12.89]
5 10 15 20
I^2 = 98%, τ^2 = 0.1590, p = 4.56e−44
Fibrates and Bile Acid Sequestrants
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Acipimox 2 10552 189.54 [47.40; 757.85]
Gemfibrozil 3 50609 59.28 [19.12; 183.80]
Cholestyramine 31 660081 46.96 [33.03; 66.78]
Colestipol 2 45118 44.33 [11.09; 177.24]
Colesevelam 20 472548 42.32 [27.31; 65.60]
Fenofibrate 40 2786693 14.35 [10.53; 19.57]
Ezetimibe 114 8997873 12.67 [10.54; 15.22]
Bezafibrate 24 2205458 10.88 [7.29; 16.24]
Ciprofibrate 0 143939 3.47 [0.22; 55.54]
Fixed effect model 236 15372871 15.35 [13.51; 17.44]
Random effects model 23.07 [13.06; 40.75]
0 50 100 150 200 250
I^2 = 90%, τ^2 = 0.5251, p = 1.75e−14
Alpha−adrenergic Blockers
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Prazosin 6 204488 29.34 [13.18; 65.31]
Terazosin 7 373888 18.72 [8.93; 39.27]
Doxazosin 288 33111701 8.70 [7.75; 9.76]
Fixed effect model 301 33690077 8.93 [7.98; 10.00]
Random effects model 13.93 [7.24; 26.83]
0 10 20 30 40 50
I^2 = 84%, τ^2 = 0.1775, p = 1.98e−03
Beta−adrenergic Blockers
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Labetalol 52 608890 85.40 [65.08; 112.07]
Pindolol 0 15915 31.42 [1.97; 502.28]
Nadolol 2 64974 30.78 [7.70; 123.08]
Sotalol 50 2529842 19.76 [14.98; 26.08]
Metoprolol 37 2551571 14.50 [10.51; 20.01]
Propranolol 348 26890750 12.94 [11.65; 14.37]
Nebivolol 32 2846841 11.24 [7.95; 15.89]
Carvedilol 31 2847718 10.89 [7.66; 15.48]
Acebutolol 0 60022 8.33 [0.52; 133.18]
Bisoprolol 635 118203591 5.37 [4.97; 5.81]
Atenolol 169 35630742 4.74 [4.08; 5.51]
Celiprolol 0 185769 2.69 [0.17; 43.03]
Fixed effect model 1356 192436625 7.05 [6.68; 7.43]
Random effects model 11.62 [6.68; 20.23]
0 20 40 60 80 100 120 140
I^2 = 98%, τ^2 = 0.7118, p = 9.73e−118
Renin−Angiotensin Drugs (ACEIs)
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Captopril 7 404565 17.30 [8.25; 36.29]
Trandolapril 5 438356 11.41 [4.75; 27.40]
Imidapril 0 45626 10.96 [0.69; 175.20]
Quinapril 2 188628 10.60 [2.65; 42.39]
Enalapril 81 8329814 9.72 [7.82; 12.09]
Ramipril 1336 143464191 9.31 [8.83; 9.83]
Lisinopril 392 44349140 8.84 [8.01; 9.76]
Perindopril 187 22897200 8.17 [7.08; 9.43]
Fosinopril 0 65560 7.63 [0.48; 121.93]
Fixed effect model 2010 220183080 9.13 [8.74; 9.54]
Random effects model 9.13 [8.74; 9.54]
5 10 15 20 25 30
I^2 = 0%, τ^2 = 0, p = 5.66e−01
Renin−Angiotensin Drugs (ARBs)
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Valsartan 627 2112139 296.86 [274.51; 321.02]
Olmesartan 27 2299304 11.74 [8.05; 17.12]
Telmisartan 19 1697921 11.19 [7.14; 17.54]
Irbesartan 96 9272523 10.35 [8.48; 12.65]
Candesartan 273 34675187 7.87 [6.99; 8.86]
Losartan 317 49396521 6.42 [5.75; 7.16]
Eprosartan 2 333356 6.00 [1.50; 23.99]
Fixed effect model 1361 99786951 13.64 [12.93; 14.38]
Random effects model 14.34 [5.44; 37.85]
0 50 100 150 200 250 300
I^2 = 100%, τ^2 = 1.6449, p = 0.00e+00

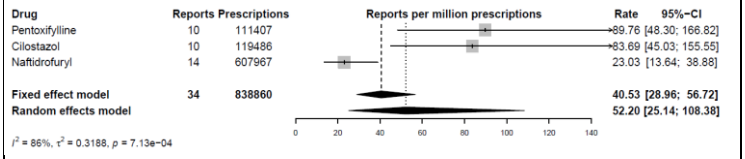
Centrally−acting Antihypertensives



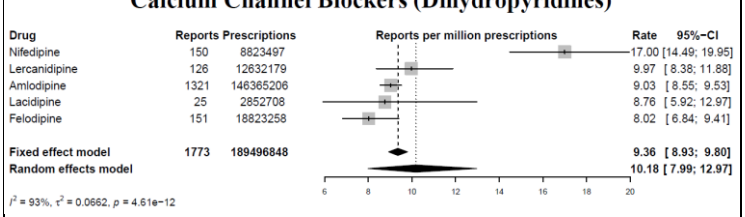
Vasodilator Antihypertensives



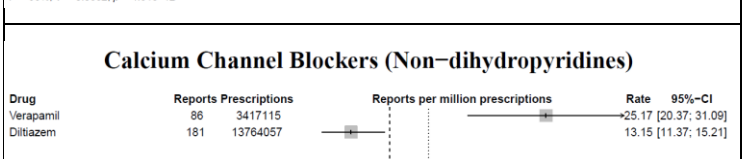
Peripheral Vasodilators



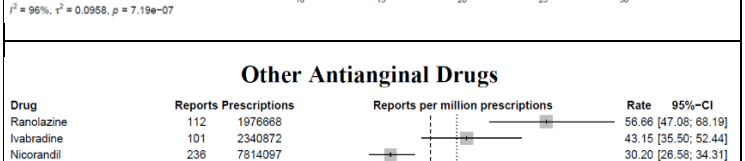
Calcium Channel Blockers (Dihydropyridines)



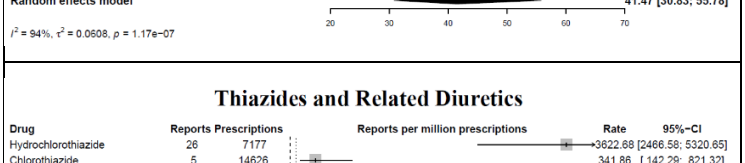
Calcium Channel Blockers (Non−dihydropyridines)



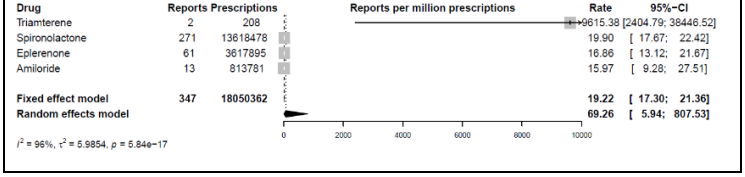
Other Antianginal Drugs



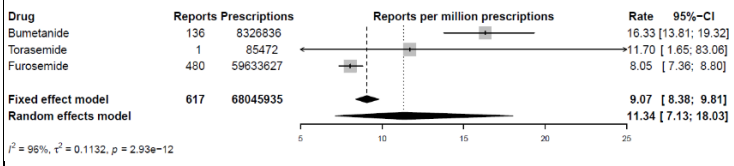
Thiazides and Related Diuretics



Potassium−sparing Diuretics and Aldosterone Antagonists

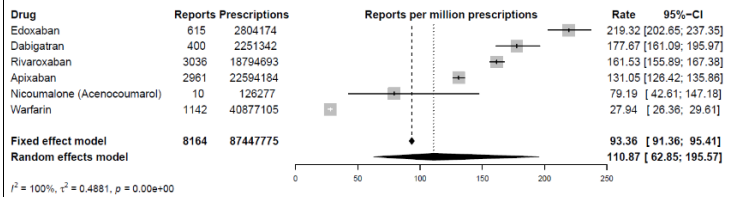


Loop Diuretics



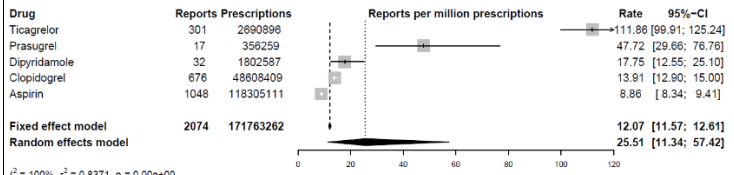
I^2 = 96%, τ^2 = 0.1132, p = 2.93e−12

Oral Anticoagulants



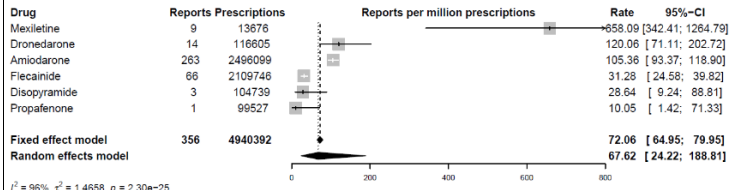
I^2 = 100%, τ^2 = 0.4881, p = 0.00e+00

Antiplatelet Drugs



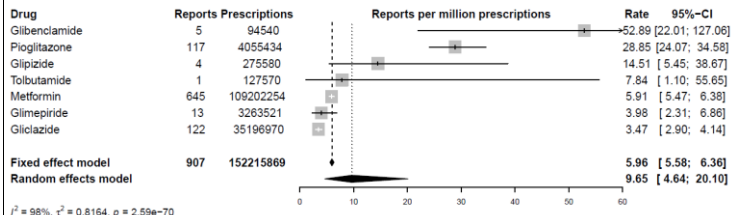
I^2 = 100%, τ^2 = 0.8371, p = 0.00e+00

Drugs for Arrhythmias



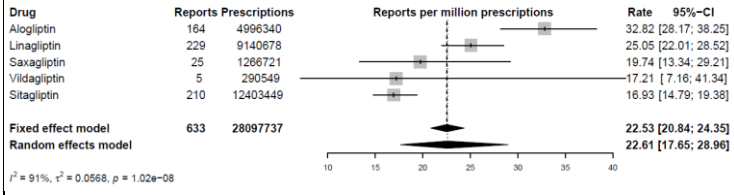
I^2 = 96%, τ^2 = 1.4658, p = 2.30e−25

Antidiabetic Drugs (Biguanides, Sulfonylureas & Thiazolidinediones)



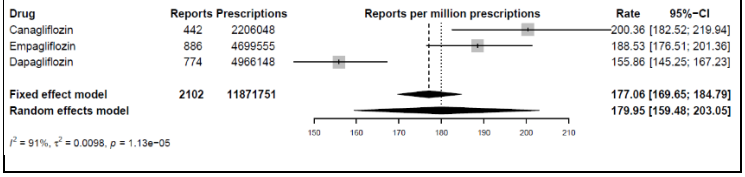
I^2 = 98%, τ^2 = 0.8164, p = 2.59e−70

Antidiabetic Drugs (DPP−4 inhibitors)

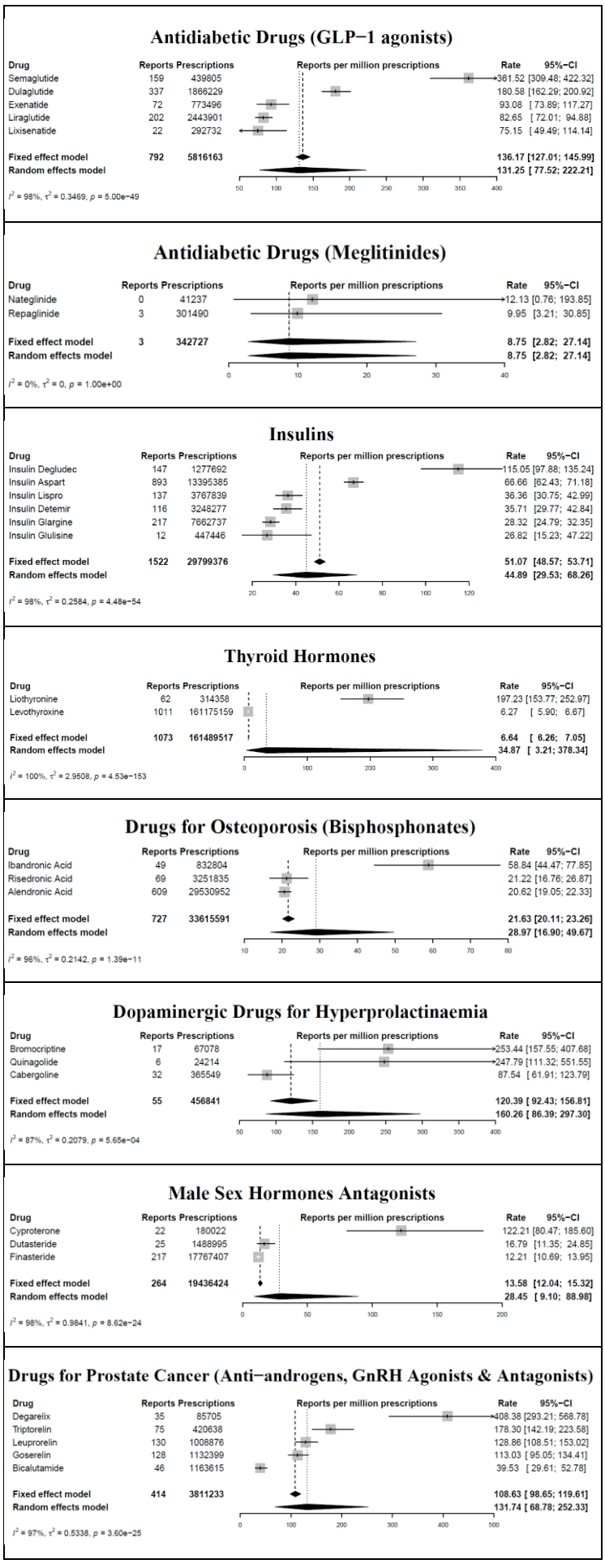


I^2 = 91%, τ^2 = 0.0568, p = 1.02e−08

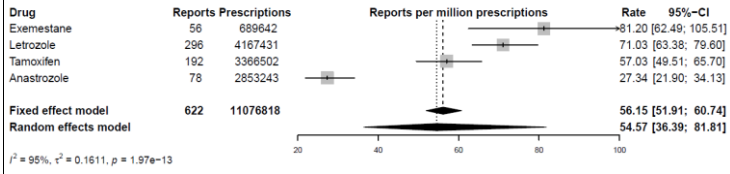
Antidiabetic Drugs (SGLT−2 inhibitors)



I^2 = 91%, τ^2 = 0.0098, p = 1.13e−05

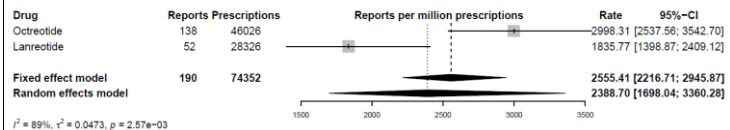

Antidiabetic Drugs (GLP−1 agonists)
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Semaglutide 159 439805 361.52 [309.48; 422.32]
Dulaglutide 337 1866229 180.58 [162.29; 200.92]
Exenatide 72 773496 93.08 [73.89; 117.27]
Liraglutide 202 2443901 82.65 [72.01; 94.88]
Lixisenatide 22 292732 75.15 [49.49; 114.14]
Fixed effect model 792 5816163 136.17 [127.01; 145.99]
Random effects model 131.25 [77.52; 222.21]
50 100 150 200 250 300 350 400
I^2 = 98%, τ^2 = 0.3469, p = 5.00e−49
Antidiabetic Drugs (Meglitinides)
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Nateglinide 0 41237 12.13 [0.76; 193.85]
Repaglinide 3 301490 9.95 [3.21; 30.85]
Fixed effect model 3 342727 8.75 [2.82; 27.14]
Random effects model 8.75 [2.82; 27.14]
0 10 20 30 40
I^2 = 0%, τ^2 = 0, p = 1.00e+00
Insulins
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Insulin Degludec 147 1277692 115.05 [97.88; 135.24]
Insulin Aspart 893 13395385 66.66 [62.43; 71.18]
Insulin Lispro 137 3767839 36.36 [30.75; 42.99]
Insulin Detemir 116 3248277 35.71 [29.77; 42.84]
Insulin Glargine 217 7662737 28.32 [24.79; 32.35]
Insulin Glulisine 12 447446 26.82 [15.23; 47.22]
Fixed effect model 1522 29799376 51.07 [48.57; 53.71]
Random effects model 44.89 [29.53; 68.26]
20 40 60 80 100 120
I^2 = 98%, τ^2 = 0.2584, p = 4.48e−54
Thyroid Hormones
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Liothyronine 62 314358 197.23 [153.77; 252.97]
Levothyroxine 1011 161175159 6.27 [5.90; 6.67]
Fixed effect model 1073 161489517 6.64 [6.26; 7.05]
Random effects model 34.87 [3.21; 378.34]
0 100 200 300 400
I^2 = 100%, τ^2 = 2.9508, p = 4.53e−153
Drugs for Osteoporosis (Bisphosphonates)
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Ibandronic Acid 49 832804 58.84 [44.47; 77.85]
Risedronic Acid 69 3251835 21.22 [16.76; 26.87]
Alendronic Acid 609 29530952 20.62 [19.05; 22.33]
Fixed effect model 727 33615591 21.63 [20.11; 23.26]
Random effects model 28.97 [16.90; 49.67]
10 20 30 40 50 60 70 80
I^2 = 96%, τ^2 = 0.2142, p = 1.39e−11
Dopaminergic Drugs for Hyperprolactinaemia
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Bromocriptine 17 67078 253.44 [157.55; 407.68]
Quinagolide 6 24214 247.79 [111.32; 551.55]
Cabergoline 32 365549 87.54 [61.91; 123.79]
Fixed effect model 55 456841 120.39 [92.43; 156.81]
Random effects model 160.26 [86.39; 297.30]
50 100 150 200 250 300 350 400
I^2 = 87%, τ^2 = 0.2079, p = 5.65e−04
Male Sex Hormones Antagonists
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Cyproterone 22 180022 122.21 [80.47; 185.60]
Dutasteride 25 1488995 16.79 [11.35; 24.85]
Finasteride 217 17767407 12.21 [10.69; 13.95]
Fixed effect model 264 19436424 13.58 [12.04; 15.32]
Random effects model 28.45 [9.10; 88.98]
0 50 100 150 200
I^2 = 98%, τ^2 = 0.9841, p = 8.62e−24
Drugs for Prostate Cancer (Anti−androgens, GnRH Agonists & Antagonists)
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Degarelix 35 85705 408.38 [293.21; 568.78]
Triptorelin 75 420638 178.30 [142.19; 223.58]
Leuprorelin 130 1008876 128.86 [108.51; 153.02]
Goserelin 128 1132399 113.03 [95.05; 134.41]
Bicalutamide 46 1163615 39.53 [29.61; 52.78]
Fixed effect model 414 3811233 108.63 [98.65; 119.61]
Random effects model 131.74 [68.78; 252.33]
0 100 200 300 400 500
I^2 = 97%, τ^2 = 0.5338, p = 3.60e−25

Drugs for Breast Cancer (Anti−oestrogens & Aromatase Inhibitors)



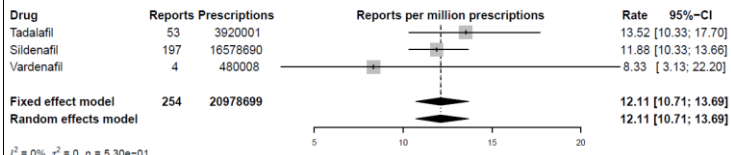
I^2 = 95%, τ^2 = 0.1611, p = 1.97e−13

Drugs for Neuroendocrine Cancers and Acromegaly (Somatostatin Analogues)



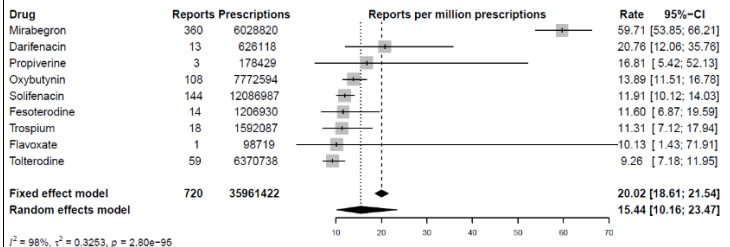
I^2 = 89%, τ^2 = 0.0473, p = 2.57e−03

Drugs for Erectile Dysfunction



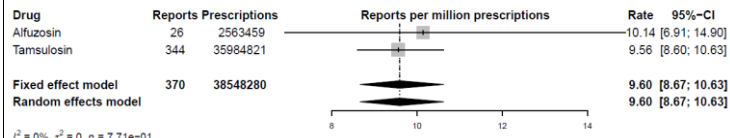
I^2 = 0%, τ^2 = 0, p = 5.30e−01

Drugs for Urinary Incontinence



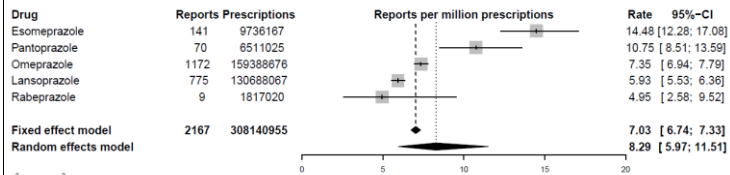
I^2 = 98%, τ^2 = 0.3253, p = 2.80e−95

Drugs for Urinary Retention



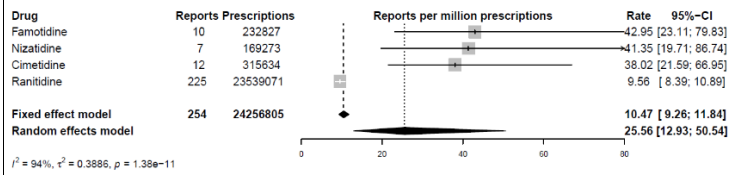
I^2 = 0%, τ^2 = 0, p = 7.71e−01

Proton Pump Inhibitors



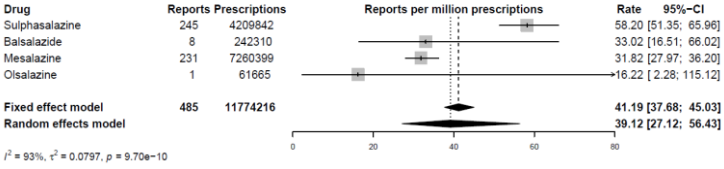
I^2 = 96%, τ^2 = 0.1228, p = 4.32e−23

H2−receptor Antagonists



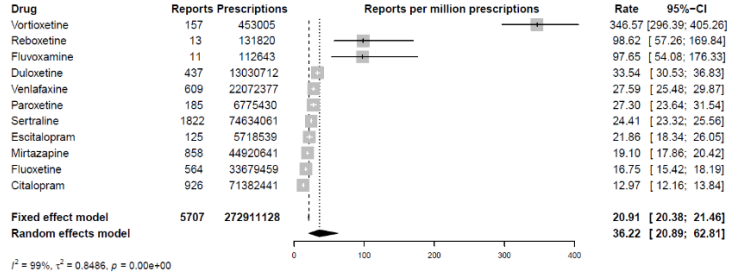
I^2 = 94%, τ^2 = 0.3886, p = 1.38e−11

Drugs for Inflammatory Bowel Disease (Aminosalicylates)



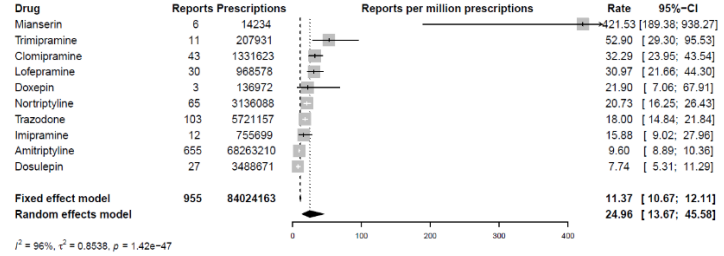
I^2 = 93%, τ^2 = 0.0797, p = 9.70e−10

SSRIs and Related Antidepressants



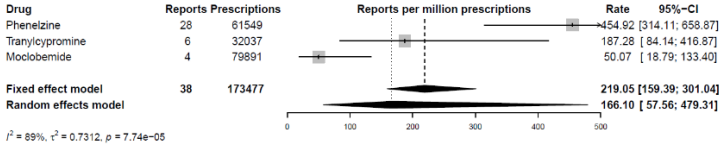
I^2 = 99%, τ^2 = 0.8486, p = 0.00e+00

Tricyclic and Related Antidepressants



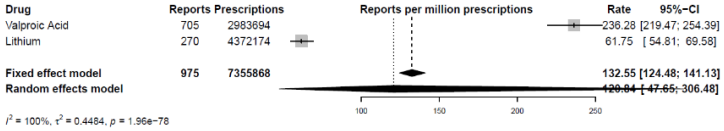
I^2 = 96%, τ^2 = 0.8538, p = 1.42e−47

Monoamine Oxidase Inhibitors



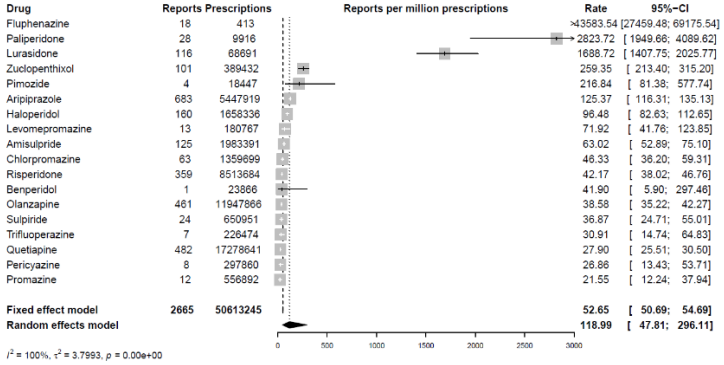
I^2 = 89%, τ^2 = 0.7312, p = 7.74e−05

Drugs for Mania and Hypomania



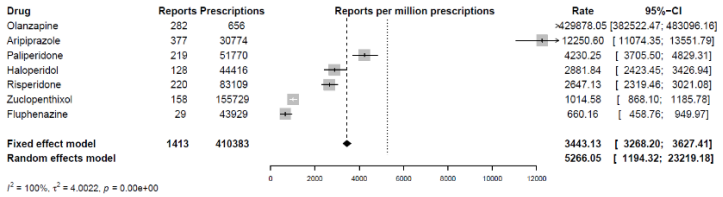
I^2 = 100%, τ^2 = 0.4484, p = 1.96e−78

Antipsychotic Drugs (Oral)



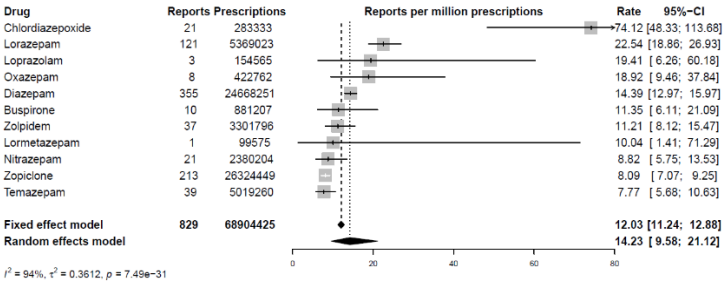
I^2 = 100%, τ^2 = 3.7993, p = 0.00e+00

Antipsychotic Drugs (Depot Injections)



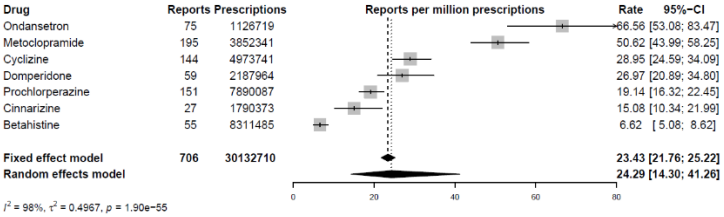
I^2 = 100%, τ^2 = 4.0022, p = 0.00e+00

Hypnotics and Anxiolytics



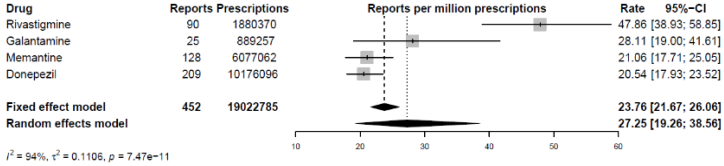
I^2 = 94%, τ^2 = 0.3612, p = 7.49e−31

Drugs for Nausea and Vertigo



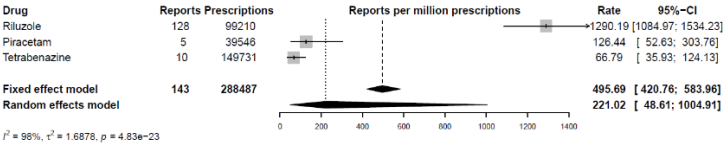
I^2 = 98%, τ^2 = 0.4967, p = 1.90e−55

Drugs for Dementia



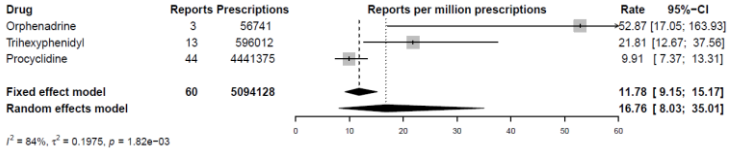
I^2 = 94%, τ^2 = 0.1106, p = 7.47e−11

Drugs for Essential Tremor and Related Disorders



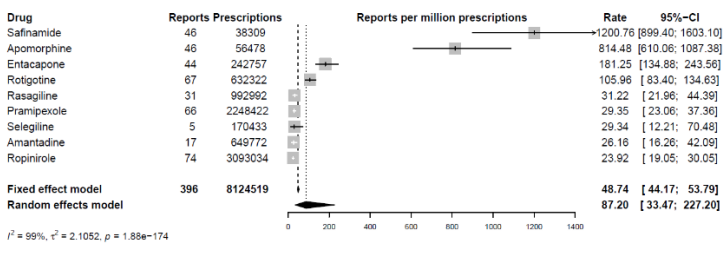
I^2 = 98%, τ^2 = 1.6878, p = 4.83e−23

Antimuscarinic Drugs for Parkinsonism

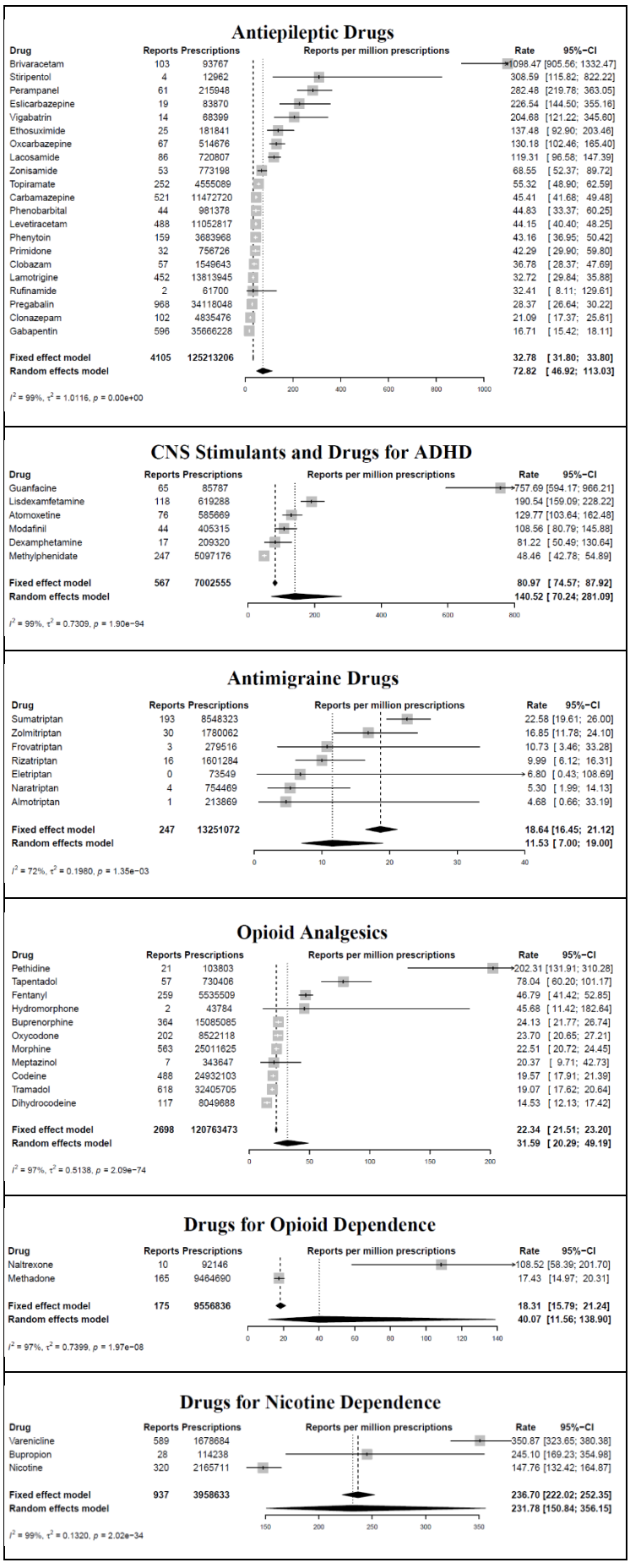


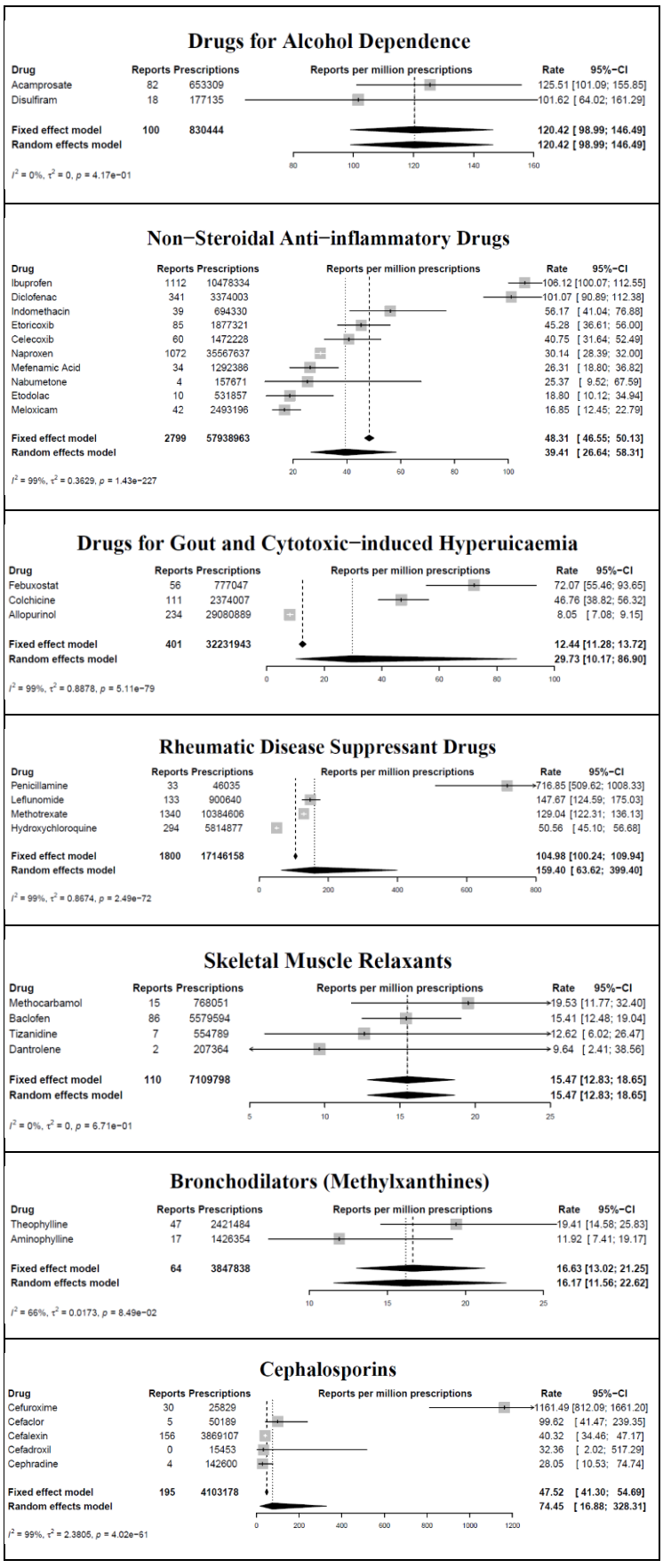
I^2 = 84%, τ^2 = 0.1975, p = 1.82e−03

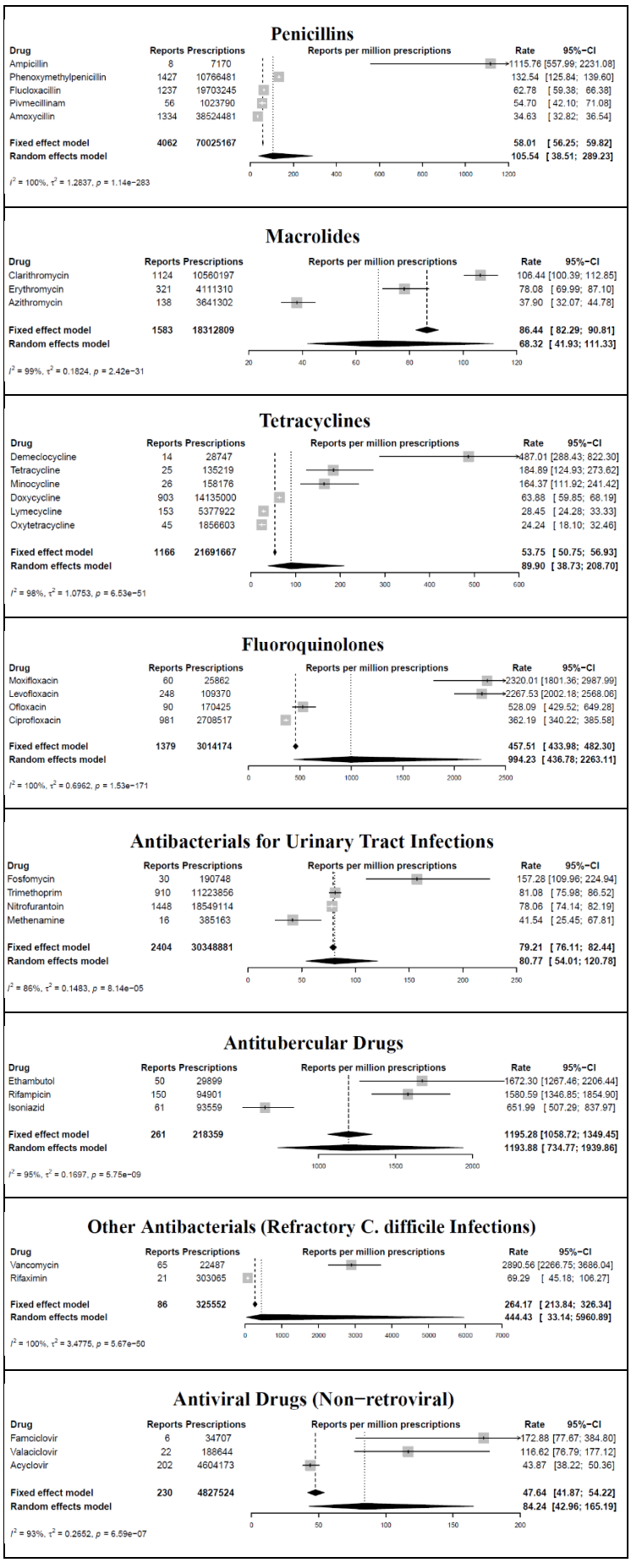
Dopaminergic Drugs for Parkinsonism



I^2 = 99%, τ^2 = 2.1052, p = 1.88e−174


Antiepileptic Drugs
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Brivaracetam 103 93767 1098.47 [905.56; 1332.47]
Stiripentol 4 12962 308.59 [115.82; 822.22]
Perampanel 61 215948 282.48 [219.78; 363.05]
Eslicarbazepine 19 83870 226.54 [144.50; 355.16]
Vigabatrin 14 68399 204.68 [121.22; 345.60]
Ethosuximide 25 181841 137.48 [92.90; 203.46]
Oxcarbazepine 67 514676 130.18 [102.46; 165.40]
Lacosamide 86 720807 119.31 [96.58; 147.39]
Zonisamide 53 773198 68.55 [52.37; 89.72]
Topiramate 252 4555089 55.32 [48.90; 62.59]
Carbamazepine 521 11472720 45.41 [41.68; 49.48]
Phenobarbital 44 981378 44.83 [33.37; 60.25]
Levetiracetam 488 11052817 44.15 [40.40; 48.25]
Phenytoin 159 3683968 43.16 [36.95; 50.42]
Primidone 32 756726 42.29 [29.90; 59.80]
Clobazam 57 1549643 36.78 [28.37; 47.69]
Lamotrigine 452 13813945 32.72 [29.84; 35.88]
Rufinamide 2 61700 32.41 [8.11; 129.61]
Pregabalin 968 34118048 28.37 [26.64; 30.22]
Clonazepam 102 4835476 21.09 [17.37; 25.61]
Gabapentin 596 35666228 16.71 [15.42; 18.11]
Fixed effect model 4105 125213206 32.78 [31.80; 33.80]
Random effects model 72.82 [46.92; 113.03]
0 200 400 600 800 1000
I^2 = 99%, τ^2 = 1.0116, p = 0.00e+00
CNS Stimulants and Drugs for ADHD
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Guanfacine 65 85787 757.69 [594.17; 966.21]
Lisdexamfetamine 118 619288 190.54 [159.09; 228.22]
Atomoxetine 76 585669 129.77 [103.64; 162.48]
Modafinil 44 405315 108.56 [80.79; 145.88]
Dexamphetamine 17 209320 81.22 [50.49; 130.64]
Methylphenidate 247 5097176 48.46 [42.78; 54.89]
Fixed effect model 567 7002555 80.97 [74.57; 87.92]
Random effects model 140.52 [70.24; 281.09]
0 200 400 600 800
I^2 = 99%, τ^2 = 0.7309, p = 1.90e−94
Antimigraine Drugs
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Sumatriptan 193 8548323 22.58 [19.61; 26.00]
Zolmitriptan 30 1780062 16.85 [11.78; 24.10]
Frovatriptan 3 279516 10.73 [3.46; 33.28]
Rizatriptan 16 1601284 9.99 [6.12; 16.31]
Eletriptan 0 73549 6.80 [0.43; 108.69]
Naratriptan 4 754469 5.30 [1.99; 14.13]
Almotriptan 1 213869 4.68 [0.66; 33.19]
Fixed effect model 247 13251072 18.64 [16.45; 21.12]
Random effects model 11.53 [7.00; 19.00]
0 10 20 30 40
I^2 = 72%, τ^2 = 0.1980, p = 1.35e−03
Opioid Analgesics
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Pethidine 21 103803 202.31 [131.91; 310.28]
Tapentadol 57 730406 78.04 [60.20; 101.17]
Fentanyl 259 5535509 46.79 [41.42; 52.85]
Hydromorphone 2 43784 45.68 [11.42; 182.64]
Buprenorphine 364 15085085 24.13 [21.77; 26.74]
Oxycodone 202 8522118 23.70 [20.65; 27.21]
Morphine 563 25011625 22.51 [20.72; 24.45]
Meptazinol 7 343647 20.37 [9.71; 42.73]
Codeine 488 24932103 19.57 [17.91; 21.39]
Tramadol 618 32405705 19.07 [17.62; 20.64]
Dihydrocodeine 117 8049688 14.53 [12.13; 17.42]
Fixed effect model 2698 120763473 22.34 [21.51; 23.20]
Random effects model 31.59 [20.29; 49.19]
0 50 100 150 200
I^2 = 97%, τ^2 = 0.5138, p = 2.09e−74
Drugs for Opioid Dependence
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Naltrexone 10 92146 108.52 [58.39; 201.70]
Methadone 165 9464690 17.43 [14.97; 20.31]
Fixed effect model 175 9556836 18.31 [15.79; 21.24]
Random effects model 40.07 [11.56; 138.90]
0 20 40 60 80 100 120 140
I^2 = 97%, τ^2 = 0.7399, p = 1.97e−08
Drugs for Nicotine Dependence
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Varenicline 589 1678684 350.87 [323.65; 380.38]
Bupropion 28 114238 245.10 [169.23; 354.98]
Nicotine 320 2165711 147.76 [132.42; 164.87]
Fixed effect model 937 3958633 236.70 [222.02; 252.35]
Random effects model 231.78 [150.84; 356.15]
150 200 250 300 350
I^2 = 99%, τ^2 = 0.1320, p = 2.02e−34


Drugs for Alcohol Dependence
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Acamprosate 82 653309 125.51 [101.09; 155.85]
Disulfiram 18 177135 101.62 [64.02; 161.29]
Fixed effect model 100 830444 120.42 [98.99; 146.49]
Random effects model 120.42 [98.99; 146.49]
80 100 120 140 160
I^2 = 0%, τ^2 = 0, p = 4.17e−01
Non−Steroidal Anti−inflammatory Drugs
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Ibuprofen 1112 10478334 106.12 [100.07; 112.55]
Diclofenac 341 3374003 101.07 [90.89; 112.38]
Indomethacin 39 694330 56.17 [41.04; 76.88]
Etoricoxib 85 1877321 45.28 [36.61; 56.00]
Celecoxib 60 1472228 40.75 [31.64; 52.49]
Naproxen 1072 35567637 30.14 [28.39; 32.00]
Mefenamic Acid 34 1292386 26.31 [18.80; 36.82]
Nabumetone 4 157671 25.37 [9.52; 67.59]
Etodolac 10 531857 18.80 [10.12; 34.94]
Meloxicam 42 2493196 16.85 [12.45; 22.79]
Fixed effect model 2799 57938963 48.31 [46.55; 50.13]
Random effects model 39.41 [26.64; 58.31]
20 40 60 80 100
I^2 = 99%, τ^2 = 0.3629, p = 1.43e−227
Drugs for Gout and Cytotoxic−induced Hyperuricaemia
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Febuxostat 56 777047 72.07 [55.46; 93.65]
Colchicine 111 2374007 46.76 [38.82; 56.32]
Allopurinol 234 29080889 8.05 [7.08; 9.15]
Fixed effect model 401 32231943 12.44 [11.28; 13.72]
Random effects model 29.73 [10.17; 86.90]
0 20 40 60 80 100
I^2 = 99%, τ^2 = 0.8878, p = 5.11e−79
Rheumatic Disease Suppressant Drugs
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Penicillamine 33 46035 716.85 [509.62; 1008.33]
Leflunomide 133 900640 147.67 [124.59; 175.03]
Methotrexate 1340 10384606 129.04 [122.31; 136.13]
Hydroxychloroquine 294 5814877 50.56 [45.10; 56.68]
Fixed effect model 1800 17146158 104.98 [100.24; 109.94]
Random effects model 159.40 [63.62; 399.40]
0 200 400 600 800
I^2 = 99%, τ^2 = 0.8674, p = 2.49e−72
Skeletal Muscle Relaxants
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Methocarbamol 15 768051 19.53 [11.77; 32.40]
Baclofen 86 5579594 15.41 [12.48; 19.04]
Tizanidine 7 554789 12.62 [6.02; 26.47]
Dantrolene 2 207364 9.64 [2.41; 38.56]
Fixed effect model 110 7109798 15.47 [12.83; 18.65]
Random effects model 15.47 [12.83; 18.65]
5 10 15 20 25
I^2 = 0%, τ^2 = 0, p = 6.71e−01
Bronchodilators (Methylxanthines)
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Theophylline 47 2421484 19.41 [14.58; 25.83]
Aminophylline 17 1426354 11.92 [7.41; 19.17]
Fixed effect model 64 3847838 16.63 [13.02; 21.25]
Random effects model 16.17 [11.56; 22.62]
10 15 20 25
I^2 = 66%, τ^2 = 0.0173, p = 8.49e−02
Cephalosporins
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Cefuroxime 30 25829 1161.49 [812.09; 1661.20]
Cefaclor 5 50189 99.62 [41.47; 239.35]
Cefalexin 156 3869107 40.32 [34.46; 47.17]
Cefadroxil 0 15453 32.36 [2.02; 517.29]
Cephradine 4 142600 28.05 [10.53; 74.74]
Fixed effect model 195 4103178 47.52 [41.30; 54.69]
Random effects model 74.45 [16.88; 328.31]
0 200 400 600 800 1000 1200
I^2 = 99%, τ^2 = 2.3805, p = 4.02e−61


Penicillins
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Ampicillin 8 7170 1115.76 [557.99; 2231.08]
Phenoxymethylpenicillin 1427 10766481 132.54 [125.84; 139.60]
Flucloxacillin 1237 19703245 62.78 [59.38; 66.38]
Pivmecillinam 56 1023790 54.70 [42.10; 71.08]
Amoxycillin 1334 38524481 34.63 [32.82; 36.54]
Fixed effect model 4062 70025167 58.01 [56.25; 59.82]
Random effects model 105.54 [38.51; 289.23]
0 200 400 600 800 1000 1200
I^2 = 100%, τ^2 = 1.2837, p = 1.14e−283
Macrolides
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Clarithromycin 1124 10560197 106.44 [100.39; 112.85]
Erythromycin 321 4111310 78.08 [69.99; 87.10]
Azithromycin 138 3641302 37.90 [32.07; 44.78]
Fixed effect model 1583 18312809 86.44 [82.29; 90.81]
Random effects model 68.32 [41.93; 111.33]
20 40 60 80 100 120
I^2 = 99%, τ^2 = 0.1824, p = 2.42e−31
Tetracyclines
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Demeclocycline 14 28747 487.01 [288.43; 822.30]
Tetracycline 25 135219 184.89 [124.93; 273.62]
Minocycline 26 158176 164.37 [111.92; 241.42]
Doxycycline 903 14135000 63.88 [59.85; 68.19]
Lymecycline 153 5377922 28.45 [24.28; 33.33]
Oxytetracycline 45 1856603 24.24 [18.10; 32.46]
Fixed effect model 1166 21691667 53.75 [50.75; 56.93]
Random effects model 89.90 [38.73; 208.70]
0 100 200 300 400 500 600
I^2 = 98%, τ^2 = 1.0753, p = 6.53e−51
Fluoroquinolones
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Moxifloxacin 60 25862 2320.01 [1801.36; 2987.99]
Levofloxacin 248 109370 2267.53 [2002.18; 2568.06]
Ofloxacin 90 170425 528.09 [429.52; 649.28]
Ciprofloxacin 981 2708517 362.19 [340.22; 385.58]
Fixed effect model 1379 3014174 457.51 [433.98; 482.30]
Random effects model 994.23 [436.78; 2263.11]
0 500 1000 1500 2000 2500
I^2 = 100%, τ^2 = 0.6962, p = 1.53e−171
Antibacterials for Urinary Tract Infections
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Fosfomycin 30 190748 157.28 [109.96; 224.94]
Trimethoprim 910 11223856 81.08 [75.98; 86.52]
Nitrofurantoin 1448 18549114 78.06 [74.14; 82.19]
Methenamine 16 385163 41.54 [25.45; 67.81]
Fixed effect model 2404 30348881 79.21 [76.11; 82.44]
Random effects model 80.77 [54.01; 120.78]
0 50 100 150 200 250
I^2 = 86%, τ^2 = 0.1483, p = 8.14e−05
Antitubercular Drugs
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Ethambutol 50 29899 1672.30 [1267.46; 2206.44]
Rifampicin 150 94901 1580.59 [1346.85; 1854.90]
Isoniazid 61 93559 651.99 [507.29; 837.97]
Fixed effect model 261 218359 1195.28 [1058.72; 1349.45]
Random effects model 1193.88 [734.77; 1939.86]
1000 1500 2000
I^2 = 95%, τ^2 = 0.1697, p = 5.75e−09
Other Antibacterials (Refractory C. difficile Infections)
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Vancomycin 65 22487 2890.56 [2266.75; 3686.04]
Rifaximin 21 303065 69.29 [45.18; 106.27]
Fixed effect model 86 325552 264.17 [213.84; 326.34]
Random effects model 444.43 [33.14; 5960.89]
0 1000 2000 3000 4000 5000 6000 7000
I^2 = 100%, τ^2 = 3.4775, p = 5.67e−50
Antiviral Drugs (Non−retroviral)
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Famciclovir 6 34707 172.88 [77.67; 384.80]
Valaciclovir 22 188644 116.62 [76.79; 177.12]
Acyclovir 202 4604173 43.87 [38.22; 50.36]
Fixed effect model 230 4827524 47.64 [41.87; 54.22]
Random effects model 84.24 [42.96; 165.19]
0 50 100 150 200
I^2 = 93%, τ^2 = 0.2652, p = 6.59e−07

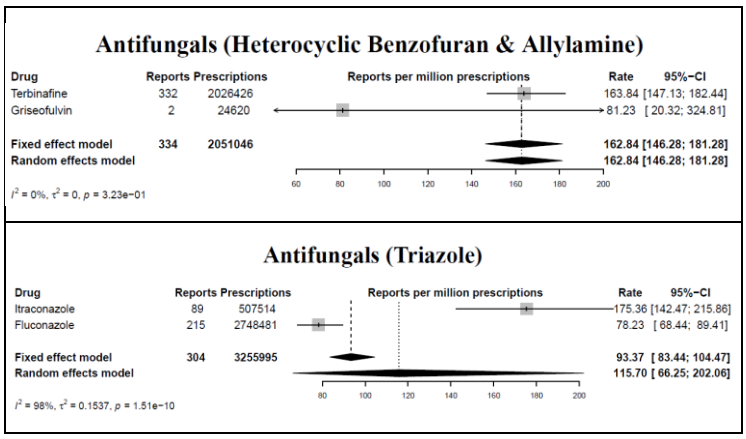


Figure 3.5 Comparative safety charts for 365 medicines belonging to 71 therapeutic classes.

Data on serious and fatal ADE reports from the Yellow Card database in the UK was mapped onto GP prescription data in England. Based upon the p-value for Q-statistic and I^2 statistic, these quantitative comparative safety analyses showed significant differences within most therapeutic classes and sections with respect to the rate of fatal and serious ADE reports per prescribing unit.

Table 3.9 Associations between previously reported variants and MIADEs related to high-risk medicines in GP tested in the UK Biobank.

A. Primary analyses

Drug(s)	Adverse Event	Variant [Risk Allele]	Main Effects vs. Interaction Model	Genetic model	OR	low 95%	high 95%	*p*_value
Anti-psychotics [Group 1]	Hypertriglyceridemia	rs489693 [A]	[Main effects]	[Recessive AA vs. AC or CC]	1.01	0.98	1.03	6.75E-01
		rs489693 [A]	[Interaction]	[Recessive AA vs. AC or CC]	1.17	0.78	1.77	4.52E-01
	Severe weight gain	**rs489693 [A]**	**[Main effects]**	**[Recessive AA vs. AC or CC]**	**1.23**	**1.14**	**1.33**	**8.70E-08**
		rs489693 [A]	[Interaction]	[Recessive AA vs. AC or CC]	1.59	0.78	3.26	2.03E-01
		rs1800497 [A]	[Main effects]	[Dominant AA+AG vs. GG]	1.00	0.95	1.05	9.42E-01
		rs1800497 [A]	[Interaction]	[Dominant AA+AG vs. GG]	1.12	0.65	1.93	6.92E-01
Anti-psychotics [Group 2]	Hyperprolactinemia	rs1800497 [A]	[Main effects]	[Dominant AA+AG vs. GG]	1.34	0.67	2.69	4.14E-01
		rs1800497 [A]	[Interaction]	[Dominant AA+AG vs. GG]	9.04	0.91	89.96	6.03E-02
	Severe weight gain	**rs489693 [A]**	**[Main effects]**	**[Recessive AA vs. AC or CC]**	**1.23**	**1.14**	**1.33**	**8.32E-08**
		rs489693 [A]	[Interaction]	[Recessive AA vs. AC or CC]	1.53	0.82	2.86	1.79E-01
		rs1800497 [A]	[Main effects]	[Dominant AA+AG vs. GG]	1.00	0.95	1.05	9.44E-01
		rs1800497 [A]	[Interaction]	[Dominant AA+AG vs. GG]	1.12	0.70	1.78	6.45E-01
	Tardive dyskinesia	rs1800497 [G]	[Main effects]	[Additive G]	0.61	0.29	1.27	1.85E-01
		rs6977820 [T]	[Main effects]	[Dominant CT+TT vs. CC]	1.01	0.39	2.62	9.83E-01
NSAIDs	Acute gastrointestinal bleeding	rs1057910 [C]	[Main effects]	[Additive C]	0.98	0.93	1.03	3.97E-01
		rs1057910 [C]	[Interaction]	[Additive C]	0.99	0.87	1.13	9.06E-01
Statins	Myopathy, Muscular Diseases	rs1719247 [C]	[Main effects]	[Recessive CC vs. CT or TT]	0.93	0.84	1.02	1.39E-01
		rs1719247 [C]	[Interaction]	[Recessive CC vs. CT or TT]	1.12	0.89	1.40	3.38E-01
		rs4149056 [C]	[Main effects]	[Dominant: CC+CT vs. TT]	1.08	0.97	1.20	1.65E-01
		rs4149056 [C]	[Interaction]	[Dominant: CC+CT vs. TT]	1.03	0.80	1.32	8.31E-01
		rs1346268 [T]	[Main effects]	[Recessive TT vs. CC or CT]	0.94	0.85	1.03	1.89E-01
		rs1346268 [T]	[Interaction]	[Recessive TT vs. CC or CT]	1.14	0.91	1.43	2.57E-01
		rs1346268 [T]	[Main effects]	[Dominant CT+TT vs. CC]	0.89	0.74	1.07	2.22E-01
		rs1346268 [T]	[Interaction]	[Dominant CT+TT vs. CC]	0.92	0.60	1.41	6.91E-01
		rs4693075 [G]	[Main effects]	[Dominant GG or CG vs. CC]	0.98	0.89	1.09	7.49E-01
		rs4693075 [G]	[Interaction]	[Dominant GG or CG vs. CC]	1.02	0.81	1.28	8.90E-01

***Significant associations are in bold (*p*-value < 1.79E-03)**

B. Secondary analyses

Drug(s)	Adverse Drug Event or Parameter	Variant [Risk Allele] [Main effects vs. Interaction Model]	Genetic model	OR	low 95%	high 95%	p_value
	Severe weight gain	**rs489693 [A] [Main effects]**	**[Recessive AA vs. AC or CC]**	**1.23**	**1.14**	**1.33**	**8.70E-08**
		rs489693 [A] [Interaction]	[Recessive AA vs. AC or CC]	1.59	0.78	3.26	2.03E-01
		rs1800497 [A] [Interaction]	[Dominant AA+AG vs. GG]	1.12	0.65	1.93	6.92E-01

Anti-psychotics [Group 1]		rs1800497 [A] [Main effects]	[Dominant AA+AG vs. GG]	1.00	0.95	1.05	9.42E-01
	Tardive dyskinesia	rs1800497 [G] [Main effects]	[Additive G]	0.60	0.29	1.27	1.81E-01
		rs6977820 [T] [Main effects]	[Dominant CT+TT vs. CC]	1.01	0.39	2.61	9.91E-01
	Hyperprolactinemia	rs1800497 [A] [Main effects]	[Dominant AA+AG vs. GG]	1.34	0.67	2.70	4.07E-01
	Triglycerides [High]	rs489693 [A] [Interaction]	[Recessive AA vs. AC or CC]	1.17	0.78	1.77	4.52E-01
		rs489693 [A] [Main effects]	[Recessive AA vs. AC or CC]	1.01	0.98	1.03	6.75E-01
	Triglycerides [Extremely high]	rs489693 [A] [Main effects]	[Recessive AA vs. AC or CC]	0.99	0.95	1.04	7.72E-01
		rs489693 [A] [Interaction]	[Recessive AA vs. AC or CC]	0.96	0.47	1.96	9.02E-01
Anti-psychotics [Group 2]	Severe weight gain	**rs489693 [A] [Main effects]**	**[Recessive AA vs. AC or CC]**	**1.23**	**1.14**	**1.33**	**8.32E-08**
		rs489693 [A] [Interaction]	[Recessive AA vs. AC or CC]	1.53	0.82	2.86	1.79E-01
		rs1800497 [A] [Interaction]	[Dominant AA+AG vs. GG]	1.12	0.70	1.78	6.45E-01
		rs1800497 [A] [Main effects]	[Dominant AA+AG vs. GG]	1.00	0.95	1.05	9.44E-01
	Hyperprolactinemia	rs1800497 [A] [Interaction]	[Dominant AA+AG vs. GG]	9.04	0.91	89.96	6.03E-02
	Tardive dyskinesia	rs6977820 [T] [Main effects]	[Dominant CT+TT vs. CC]	1.01	0.39	2.62	9.83E-01
		rs1800497 [G] [Main effects]	[Additive G]	0.61	0.29	1.27	1.85E-01
	Triglycerides [High]	rs489693 [A] [Interaction]	[Recessive AA vs. AC or CC]	1.21	0.86	1.71	2.71E-01
		rs489693 [A] [Main effects]	[Recessive AA vs. AC or CC]	1.01	0.98	1.03	6.73E-01
	Hyperprolactinemia	rs1800497 [A] [Main effects]	[Dominant AA+AG vs. GG]	1.34	0.67	2.69	4.14E-01
	Triglycerides [Extremely high]	rs489693 [A] [Interaction]	[Recessive AA vs. AC or CC]	0.91	0.48	1.73	7.71E-01
		rs489693 [A] [Main effects]	[Recessive AA vs. AC or CC]	0.99	0.95	1.04	7.72E-01
Atorvastatin	Myopathy, Muscular Diseases [Definition1]	rs1346268 [T] [Interaction]	[Recessive TT vs. CC or CT]	4.03	1.13	14.41	3.18E-02
	Myopathy, Muscular Diseases [Definition1]	rs1719247 [C] [Interaction]	[Recessive CC vs. CT or TT]	3.96	1.11	14.14	3.42E-02
	Myopathy, Muscular Diseases [Definition2]	rs1346268 [T] [Interaction]	[Recessive TT vs. CC or CT]	1.49	0.99	2.25	5.57E-02
	Myopathy, Muscular Diseases [Definition2]	rs1719247 [C] [Interaction]	[Recessive CC vs. CT or TT]	1.42	0.94	2.14	9.51E-02
	Myopathy, Muscular Diseases [Definition2]	rs1719247 [C] [Main effects]	[Recessive CC vs. CT or TT]	0.93	0.84	1.02	1.40E-01
	Myopathy, Muscular Diseases [Definition2]	rs4149056 [C] [Main effects]	[Dominant: CC+CT vs. TT]	1.08	0.97	1.20	1.70E-01
	Myopathy, Muscular Diseases [Definition1]	rs4693075 [G] [Interaction]	[Dominant GG or CG vs. CC]	2.23	0.70	7.03	1.73E-01
	Myopathy, Muscular Diseases [Definition2]	rs1346268 [T] [Main effects]	[Recessive TT vs. CC or CT]	0.94	0.85	1.03	1.91E-01
	Myopathy, Muscular Diseases [Definition1]	rs4149056 [C] [Main effects]	[Dominant: CC+CT vs. TT]	1.18	0.91	1.54	2.09E-01
	Myopathy, Muscular Diseases [Definition2]	rs1346268 [T] [Main effects]	[Dominant CT+TT vs. CC]	0.89	0.74	1.07	2.23E-01
	Myopathy, Muscular Diseases [Definition2]	rs4693075 [G] [Interaction]	[Dominant GG or CG vs. CC]	1.24	0.81	1.89	3.14E-01
	Myopathy, Muscular Diseases [Definition1]	rs4149056 [C] [Interaction]	[Dominant: CC+CT vs. TT]	0.65	0.21	2.07	4.69E-01
	Myopathy, Muscular Diseases [Definition1]	rs1346268 [T] [Main effects]	[Dominant CT+TT vs. CC]	1.21	0.71	2.07	4.88E-01
	Myopathy, Muscular Diseases [Definition1]	rs4693075 [G] [Main effects]	[Dominant GG or CG vs. CC]	0.93	0.73	1.20	5.90E-01
	Myopathy, Muscular Diseases [Definition2]	rs4693075 [G] [Main effects]	[Dominant GG or CG vs. CC]	0.98	0.89	1.09	7.40E-01
	Myopathy, Muscular Diseases [Definition1]	rs1346268 [T] [Main effects]	[Recessive TT vs. CC or CT]	1.03	0.80	1.31	8.42E-01
	Myopathy, Muscular Diseases [Definition2]	rs4149056 [C] [Interaction]	[Dominant: CC+CT vs. TT]	0.97	0.63	1.51	8.99E-01
	Myopathy, Muscular Diseases [Definition2]	rs1346268 [T] [Interaction]	[Dominant CT+TT vs. CC]	0.96	0.45	2.02	9.05E-01
	Myopathy, Muscular Diseases [Definition1]	rs1719247 [C] [Main effects]	[Recessive CC vs. CT or TT]	0.99	0.77	1.26	9.11E-01
	Myopathy, Muscular Diseases [Definition1]	rs1346268 [T] [Interaction]	[Dominant CT+TT vs. CC]	0.95	0.12	7.72	9.60E-01
	Myopathy, Muscular Diseases [Definition2]	rs1719247 [C] [Main effects]	[Recessive CC vs. CT or TT]	0.93	0.84	1.02	1.38E-01
	Myopathy, Muscular Diseases [Definition2]	rs4149056 [C] [Main effects]	[Dominant: CC+CT vs. TT]	1.08	0.97	1.20	1.71E-01

Fluvastatin	Myopathy, Muscular Diseases [Definition2]	rs1346268 [T] [Main effects]	[Recessive TT vs. CC or CT]	0.94	0.85	1.03	1.89E-01
	Myopathy, Muscular Diseases [Definition1]	rs4149056 [C] [Main effects]	[Dominant: CC+CT vs. TT]	1.18	0.91	1.54	2.09E-01
	Myopathy, Muscular Diseases [Definition2]	rs1346268 [T] [Main effects]	[Dominant CT+TT vs. CC]	0.89	0.74	1.07	2.22E-01
	Myopathy, Muscular Diseases [Definition1]	rs1346268 [T] [Main effects]	[Dominant CT+TT vs. CC]	1.21	0.71	2.07	4.89E-01
	Myopathy, Muscular Diseases [Definition1]	rs4693075 [G] [Main effects]	[Dominant GG or CG vs. CC]	0.93	0.73	1.20	5.93E-01
	Myopathy, Muscular Diseases [Definition2]	rs4693075 [G] [Main effects]	[Dominant GG or CG vs. CC]	0.98	0.89	1.09	7.48E-01
	Myopathy, Muscular Diseases [Definition1]	rs1346268 [T] [Main effects]	[Recessive TT vs. CC or CT]	1.03	0.80	1.31	8.43E-01
	Myopathy, Muscular Diseases [Definition1]	rs1719247 [C] [Main effects]	[Recessive CC vs. CT or TT]	0.99	0.77	1.26	9.10E-01
Pravastatin	Myopathy, Muscular Diseases [Definition1]	rs1346268 [T] [Interaction]	[Dominant CT+TT vs. CC]	0.12	0.01	1.41	9.15E-02
	Myopathy, Muscular Diseases [Definition2]	rs1719247 [C] [Main effects]	[Recessive CC vs. CT or TT]	0.93	0.84	1.02	1.38E-01
	Myopathy, Muscular Diseases [Definition2]	rs4149056 [C] [Main effects]	[Dominant: CC+CT vs. TT]	1.08	0.97	1.20	1.70E-01
	Myopathy, Muscular Diseases [Definition2]	rs1346268 [T] [Main effects]	[Recessive TT vs. CC or CT]	0.94	0.85	1.03	1.89E-01
	Myopathy, Muscular Diseases [Definition1]	rs4149056 [C] [Main effects]	[Dominant: CC+CT vs. TT]	1.18	0.91	1.54	2.08E-01
	Myopathy, Muscular Diseases [Definition2]	rs1346268 [T] [Main effects]	[Dominant CT+TT vs. CC]	0.89	0.74	1.07	2.22E-01
	Myopathy, Muscular Diseases [Definition2]	rs1346268 [T] [Interaction]	[Dominant CT+TT vs. CC]	0.47	0.10	2.19	3.38E-01
	Myopathy, Muscular Diseases [Definition2]	rs4149056 [C] [Interaction]	[Dominant: CC+CT vs. TT]	1.65	0.54	5.11	3.81E-01
	Myopathy, Muscular Diseases [Definition1]	rs1346268 [T] [Main effects]	[Dominant CT+TT vs. CC]	1.21	0.71	2.07	4.88E-01
	Myopathy, Muscular Diseases [Definition1]	rs4693075 [G] [Main effects]	[Dominant GG or CG vs. CC]	0.93	0.73	1.20	5.91E-01
	Myopathy, Muscular Diseases [Definition2]	rs1719247 [C] [Interaction]	[Recessive CC vs. CT or TT]	1.33	0.43	4.09	6.22E-01
	Myopathy, Muscular Diseases [Definition1]	rs1346268 [T] [Interaction]	[Recessive TT vs. CC or CT]	1.61	0.14	18.07	6.98E-01
	Myopathy, Muscular Diseases [Definition1]	rs1719247 [C] [Interaction]	[Recessive CC vs. CT or TT]	1.60	0.14	17.90	7.03E-01
	Myopathy, Muscular Diseases [Definition2]	rs4693075 [G] [Main effects]	[Dominant GG or CG vs. CC]	0.98	0.89	1.09	7.45E-01
	Myopathy, Muscular Diseases [Definition1]	rs1346268 [T] [Main effects]	[Recessive TT vs. CC or CT]	1.03	0.80	1.31	8.44E-01
	Myopathy, Muscular Diseases [Definition1]	rs4149056 [C] [Interaction]	[Dominant: CC+CT vs. TT]	1.20	0.11	13.45	8.83E-01
	Myopathy, Muscular Diseases [Definition1]	rs1719247 [C] [Main effects]	[Recessive CC vs. CT or TT]	0.99	0.77	1.26	9.10E-01
	Myopathy, Muscular Diseases [Definition2]	rs4693075 [G] [Interaction]	[Dominant GG or CG vs. CC]	0.98	0.32	3.01	9.67E-01
	Myopathy, Muscular Diseases [Definition2]	rs1346268 [T] [Interaction]	[Recessive TT vs. CC or CT]	1.00	0.33	3.01	9.97E-01
Rosuvastatin	Myopathy, Muscular Diseases [Definition2]	rs4693075 [G] [Interaction]	[Dominant GG or CG vs. CC]	0.38	0.14	1.06	6.55E-02
	Myopathy, Muscular Diseases [Definition2]	rs4149056 [C] [Interaction]	[Dominant: CC+CT vs. TT]	0.15	0.02	1.15	6.86E-02
	Myopathy, Muscular Diseases [Definition2]	rs1719247 [C] [Main effects]	[Recessive CC vs. CT or TT]	0.93	0.84	1.02	1.38E-01
	Myopathy, Muscular Diseases [Definition2]	rs4149056 [C] [Main effects]	[Dominant: CC+CT vs. TT]	1.08	0.97	1.20	1.71E-01
	Myopathy, Muscular Diseases [Definition2]	rs1346268 [T] [Main effects]	[Recessive TT vs. CC or CT]	0.94	0.85	1.03	1.88E-01
	Myopathy, Muscular Diseases [Definition1]	rs4149056 [C] [Main effects]	[Dominant: CC+CT vs. TT]	1.18	0.91	1.54	2.08E-01
	Myopathy, Muscular Diseases [Definition2]	rs1346268 [T] [Main effects]	[Dominant CT+TT vs. CC]	0.89	0.74	1.07	2.21E-01
	Myopathy, Muscular Diseases [Definition2]	rs1346268 [T] [Interaction]	[Recessive TT vs. CC or CT]	1.89	0.65	5.48	2.41E-01
	Myopathy, Muscular Diseases [Definition2]	rs1719247 [C] [Interaction]	[Recessive CC vs. CT or TT]	1.82	0.63	5.27	2.71E-01
	Myopathy, Muscular Diseases [Definition1]	rs1346268 [T] [Main effects]	[Dominant CT+TT vs. CC]	1.21	0.71	2.07	4.88E-01
	Myopathy, Muscular Diseases [Definition1]	rs4693075 [G] [Main effects]	[Dominant GG or CG vs. CC]	0.93	0.73	1.20	5.92E-01
	Myopathy, Muscular Diseases [Definition2]	rs4693075 [G] [Main effects]	[Dominant GG or CG vs. CC]	0.98	0.89	1.09	7.47E-01
	Myopathy, Muscular Diseases [Definition1]	rs1346268 [T] [Main effects]	[Recessive TT vs. CC or CT]	1.03	0.80	1.31	8.44E-01
	Myopathy, Muscular Diseases [Definition1]	rs1719247 [C] [Main effects]	[Recessive CC vs. CT or TT]	0.99	0.77	1.26	9.09E-01
	Myopathy, Muscular Diseases [Definition2]	rs1719247 [C] [Main effects]	[Recessive CC vs. CT or TT]	0.93	0.84	1.02	1.38E-01

Simvastatin	Myopathy, Muscular Diseases [Definition2]	rs4149056 [C] [Main effects]	[Dominant: CC+CT vs. TT]	1.08	0.97	1.20	1.67E-01
	Myopathy, Muscular Diseases [Definition2]	rs1346268 [T] [Main effects]	[Recessive TT vs. CC or CT]	0.94	0.85	1.03	1.88E-01
	Myopathy, Muscular Diseases [Definition1]	rs4149056 [C] [Main effects]	[Dominant: CC+CT vs. TT]	1.18	0.91	1.54	2.07E-01
	Myopathy, Muscular Diseases [Definition2]	rs1346268 [T] [Main effects]	[Dominant CT+TT vs. CC]	0.89	0.74	1.07	2.21E-01
	Myopathy, Muscular Diseases [Definition2]	rs4149056 [C] [Interaction]	[Dominant: CC+CT vs. TT]	1.11	0.83	1.47	4.88E-01
	Myopathy, Muscular Diseases [Definition1]	rs1346268 [T] [Main effects]	[Dominant CT+TT vs. CC]	1.21	0.71	2.07	4.90E-01
	Myopathy, Muscular Diseases [Definition1]	rs4693075 [G] [Main effects]	[Dominant GG or CG vs. CC]	0.93	0.73	1.20	5.95E-01
	Myopathy, Muscular Diseases [Definition2]	rs1346268 [T] [Interaction]	[Dominant CT+TT vs. CC]	0.90	0.55	1.48	6.89E-01
	Myopathy, Muscular Diseases [Definition2]	rs1719247 [C] [Interaction]	[Recessive CC vs. CT or TT]	0.95	0.73	1.23	6.96E-01
	Myopathy, Muscular Diseases [Definition2]	rs4693075 [G] [Main effects]	[Dominant GG or CG vs. CC]	0.98	0.89	1.09	7.52E-01
	Myopathy, Muscular Diseases [Definition1]	rs1719247 [C] [Interaction]	[Recessive CC vs. CT or TT]	1.10	0.58	2.08	7.71E-01
	Myopathy, Muscular Diseases [Definition1]	rs1346268 [T] [Interaction]	[Dominant CT+TT vs. CC]	0.83	0.22	3.10	7.81E-01
	Myopathy, Muscular Diseases [Definition2]	rs1346268 [T] [Interaction]	[Recessive TT vs. CC or CT]	0.97	0.74	1.26	8.02E-01
	Myopathy, Muscular Diseases [Definition1]	rs4693075 [G] [Interaction]	[Dominant GG or CG vs. CC]	0.93	0.49	1.77	8.32E-01
	Myopathy, Muscular Diseases [Definition1]	rs1346268 [T] [Main effects]	[Recessive TT vs. CC or CT]	1.02	0.80	1.31	8.46E-01
	Myopathy, Muscular Diseases [Definition1]	rs1719247 [C] [Main effects]	[Recessive CC vs. CT or TT]	0.99	0.77	1.26	9.08E-01
	Myopathy, Muscular Diseases [Definition1]	rs1346268 [T] [Interaction]	[Recessive TT vs. CC or CT]	1.01	0.54	1.90	9.82E-01
	Myopathy, Muscular Diseases [Definition1]	rs4149056 [C] [Interaction]	[Dominant: CC+CT vs. TT]	1.01	0.51	1.98	9.88E-01
	Myopathy, Muscular Diseases [Definition2]	rs4693075 [G] [Interaction]	[Dominant GG or CG vs. CC]	1.00	0.77	1.31	9.95E-01
Statins	Myopathy, Muscular Diseases [Definition1]	rs1719247 [C] [Interaction]	[Recessive CC vs. CT or TT]	1.60	0.90	2.85	1.07E-01
	Myopathy, Muscular Diseases [Definition2]	rs1719247 [C] [Main effects]	[Recessive CC vs. CT or TT]	0.93	0.84	1.02	1.39E-01
	Myopathy, Muscular Diseases [Definition1]	rs1346268 [T] [Interaction]	[Recessive TT vs. CC or CT]	1.50	0.85	2.66	1.61E-01
	Myopathy, Muscular Diseases [Definition2]	rs4149056 [C] [Main effects]	[Dominant: CC+CT vs. TT]	1.08	0.97	1.20	1.65E-01
	Myopathy, Muscular Diseases [Definition2]	rs1346268 [T] [Main effects]	[Recessive TT vs. CC or CT]	0.94	0.85	1.03	1.89E-01
	Myopathy, Muscular Diseases [Definition1]	rs4149056 [C] [Main effects]	[Dominant: CC+CT vs. TT]	1.19	0.91	1.54	2.06E-01
	Myopathy, Muscular Diseases [Definition2]	rs1346268 [T] [Main effects]	[Dominant CT+TT vs. CC]	0.89	0.74	1.07	2.22E-01
	Myopathy, Muscular Diseases [Definition2]	rs1346268 [T] [Interaction]	[Recessive TT vs. CC or CT]	1.14	0.91	1.43	2.57E-01
	Myopathy, Muscular Diseases [Definition2]	rs1719247 [C] [Interaction]	[Recessive CC vs. CT or TT]	1.12	0.89	1.40	3.38E-01
	Myopathy, Muscular Diseases [Definition1]	rs1346268 [T] [Interaction]	[Dominant CT+TT vs. CC]	0.63	0.20	1.96	4.27E-01
	Myopathy, Muscular Diseases [Definition1]	rs1346268 [T] [Main effects]	[Dominant CT+TT vs. CC]	1.21	0.71	2.07	4.89E-01
	Myopathy, Muscular Diseases [Definition1]	rs4693075 [G] [Main effects]	[Dominant GG or CG vs. CC]	0.93	0.73	1.20	5.92E-01
	Myopathy, Muscular Diseases [Definition2]	rs1346268 [T] [Interaction]	[Dominant CT+TT vs. CC]	0.92	0.60	1.41	6.91E-01
	Myopathy, Muscular Diseases [Definition1]	rs4149056 [C] [Interaction]	[Dominant: CC+CT vs. TT]	0.89	0.49	1.63	7.06E-01
	Myopathy, Muscular Diseases [Definition2]	rs4693075 [G] [Main effects]	[Dominant GG or CG vs. CC]	0.98	0.89	1.09	7.49E-01
	Myopathy, Muscular Diseases [Definition2]	rs4149056 [C] [Interaction]	[Dominant: CC+CT vs. TT]	1.03	0.80	1.32	8.31E-01
	Myopathy, Muscular Diseases [Definition1]	rs1346268 [T] [Main effects]	[Recessive TT vs. CC or CT]	1.03	0.80	1.31	8.44E-01
	Myopathy, Muscular Diseases [Definition2]	rs4693075 [G] [Interaction]	[Dominant GG or CG vs. CC]	1.02	0.81	1.28	8.90E-01
	Myopathy, Muscular Diseases [Definition1]	rs1719247 [C] [Main effects]	[Recessive CC vs. CT or TT]	0.99	0.77	1.26	9.10E-01
	Myopathy, Muscular Diseases [Definition1]	rs4693075 [G] [Interaction]	[Dominant GG or CG vs. CC]	1.02	0.58	1.80	9.42E-01
NSAIDs	Acute gastrointestinal bleeding [Definition1]	rs1057910 [C] [Main effects]	[Additive C]	0.98	0.93	1.03	3.97E-01
		rs1057910 [C] [Interaction]	[Additive C]	0.99	0.87	1.13	9.06E-01
	Acute gastrointestinal bleeding	rs1057910 [C] [Interaction]	[Additive C]	0.98	0.87	1.10	6.89E-01

	[Definition2]	rs1057910 [C] [Main effects]	[Additive C]	0.99	0.95	1.04	8.23E-01

***Significant associations are in bold (*p*-value < 3.85E-04)**

Definitions:
- Anti-psychotics [Group 1] = Amisulpride, aripiprazole, clozapine, haloperidol, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone
- Anti-psychotics [Group 2] =All antipsychotics in the treatment codes above.
-**Myopathy, Muscular Diseases [Definition1 & Definition2]**:
Definition 1 codes only for Myopathy, Muscular Diseases
Definition 2 codes= for Myopathy, Muscular Diseases including myalgia and Rhabdomyolysis
-**Acute gastrointestinal bleeding [Definition1 & Definition2]:**
Definition 1 codes only for acute gastrointestinal bleeding.
Definition 2 codes for acute gastrointestinal bleeding including chronic ulcer with haemorrhage and/or perforation.
- **Triglycerides:**
Triglycerides [High] >= 2.3mmol/L
Triglycerides [Extremely high] >= 5.6 mmol/L

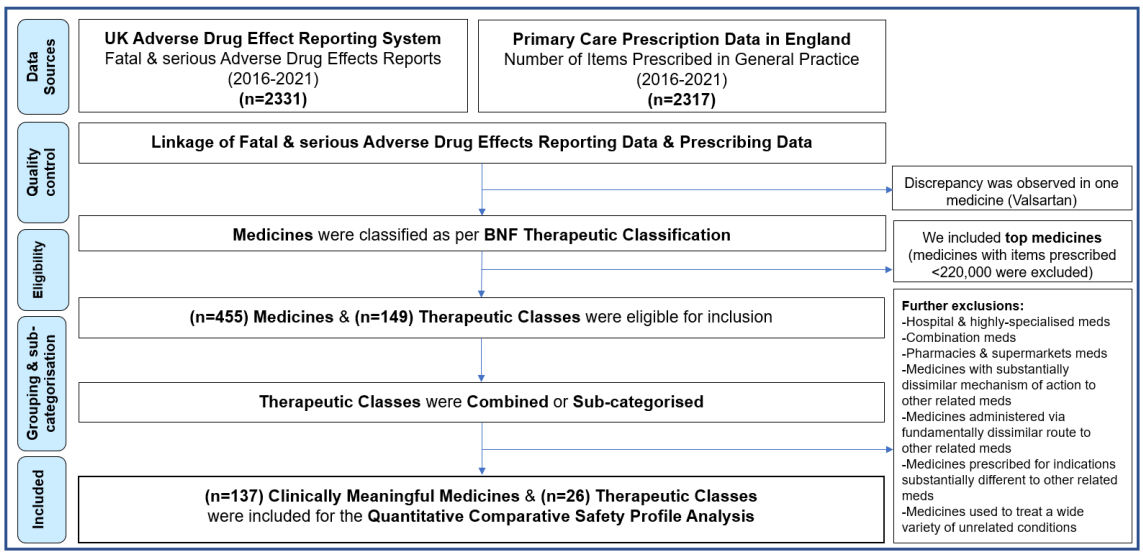
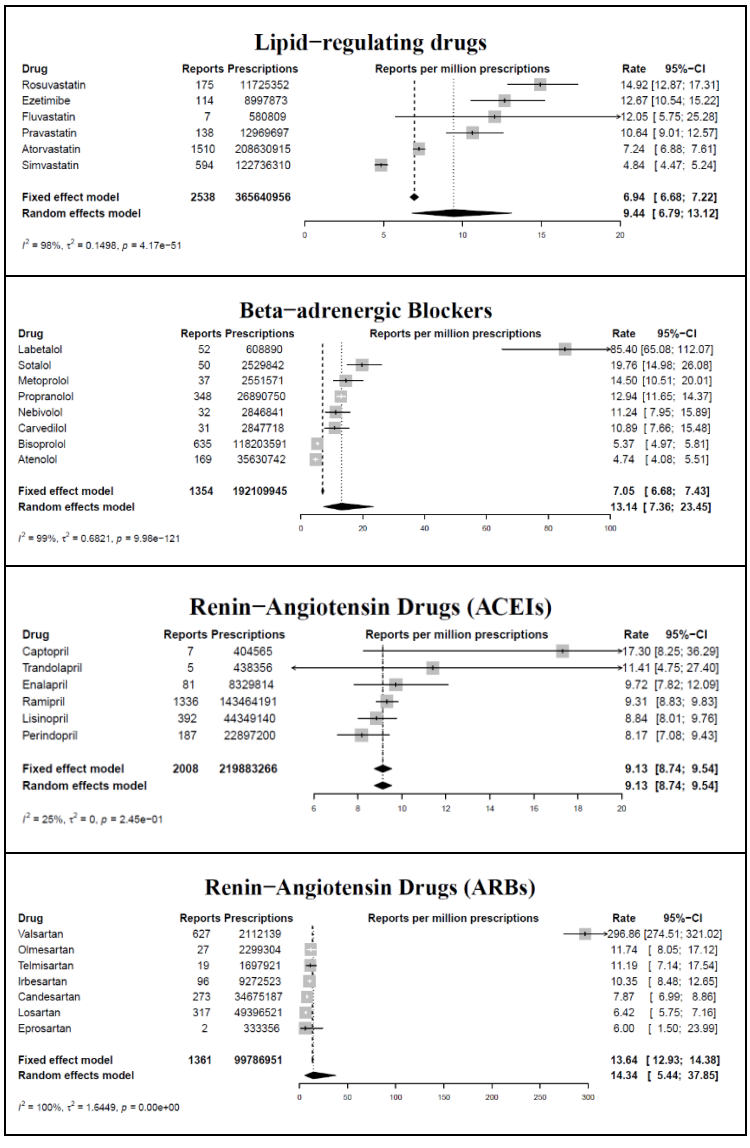
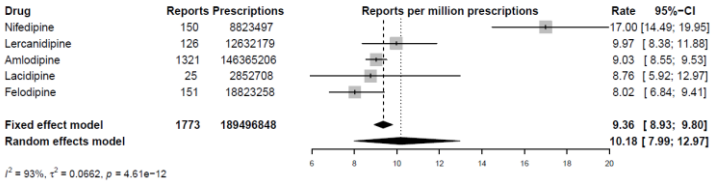


Figure 3.6 Methodology used to create comparative safety charts for clinically meaningful medicines in general practice.

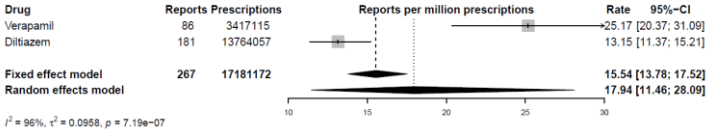


Calcium Channel Blockers (Dihydropyridines)



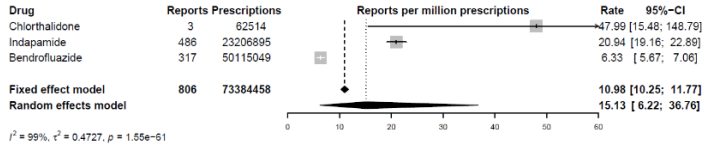
I^2 = 93%, τ^2 = 0.0662, p = 4.61e−12

Calcium Channel Blockers (Non−dihydropyridines)



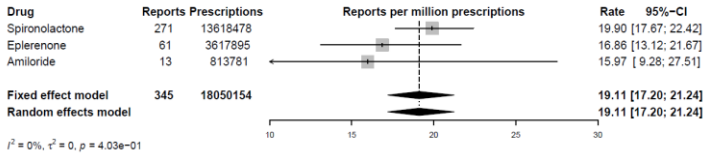
I^2 = 96%, τ^2 = 0.0958, p = 7.19e−07

Thiazides and Related Diuretics



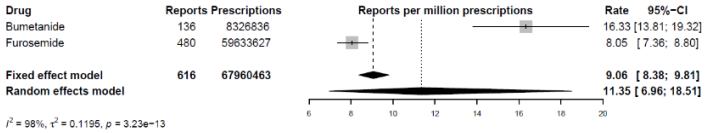
I^2 = 99%, τ^2 = 0.4727, p = 1.55e−61

Potassium−sparing Diuretics and Aldosterone Antagonists



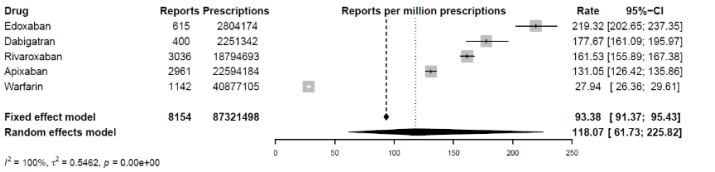
I^2 = 0%, τ^2 = 0, p = 4.03e−01

Loop Diuretics



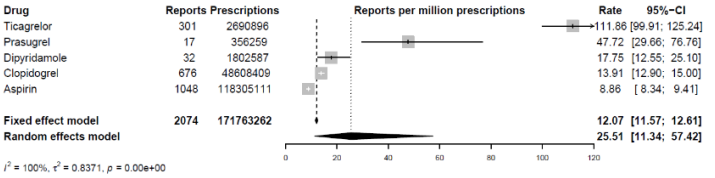
I^2 = 98%, τ^2 = 0.1195, p = 3.23e−13

Oral Anticoagulants



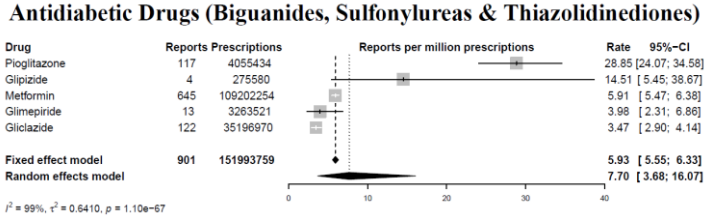
I^2 = 100%, τ^2 = 0.5462, p = 0.00e+00

Antiplatelet Drugs

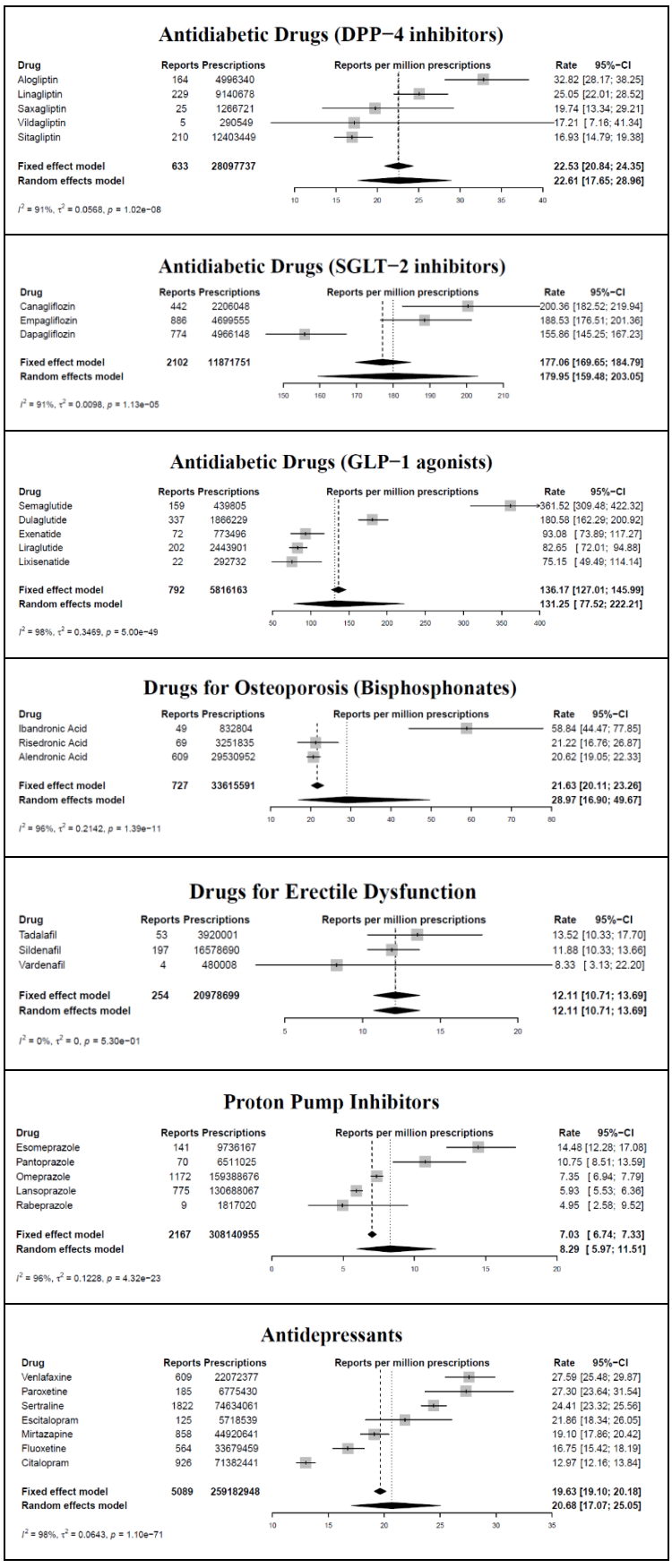


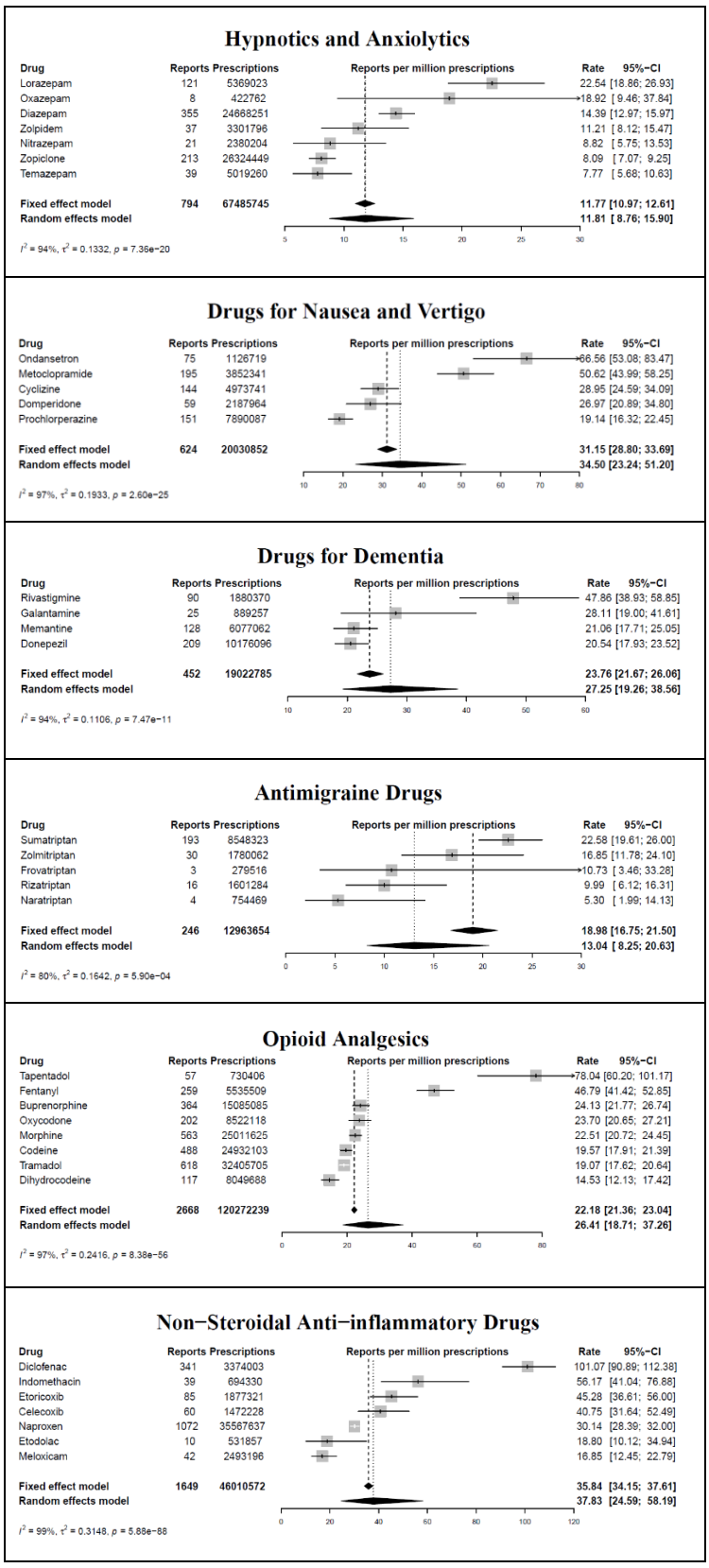
I^2 = 100%, τ^2 = 0.8371, p = 0.00e+00

Antidiabetic Drugs (Biguanides, Sulfonylureas & Thiazolidinediones)



I^2 = 99%, τ^2 = 0.6410, p = 1.10e−67


Antidiabetic Drugs (DPP−4 inhibitors)
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Alogliptin 164 4996340 32.82 [28.17; 38.25]
Linagliptin 229 9140678 25.05 [22.01; 28.52]
Saxagliptin 25 1266721 19.74 [13.34; 29.21]
Vildagliptin 5 290549 17.21 [7.16; 41.34]
Sitagliptin 210 12403449 16.93 [14.79; 19.38]
Fixed effect model 633 28097737 22.53 [20.84; 24.35]
Random effects model 22.61 [17.65; 28.96]
10 15 20 25 30 35 40
I^2 = 91%, τ^2 = 0.0568, p = 1.02e−08
Antidiabetic Drugs (SGLT−2 inhibitors)
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Canagliflozin 442 2206048 200.36 [182.52; 219.94]
Empagliflozin 886 4699555 188.53 [176.51; 201.36]
Dapagliflozin 774 4966148 155.86 [145.25; 167.23]
Fixed effect model 2102 11871751 177.06 [169.65; 184.79]
Random effects model 179.95 [159.48; 203.05]
150 160 170 180 190 200 210
I^2 = 91%, τ^2 = 0.0098, p = 1.13e−05
Antidiabetic Drugs (GLP−1 agonists)
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Semaglutide 159 439805 361.52 [309.48; 422.32]
Dulaglutide 337 1866229 180.58 [162.29; 200.92]
Exenatide 72 773496 93.08 [73.89; 117.27]
Liraglutide 202 2443901 82.65 [72.01; 94.88]
Lixisenatide 22 292732 75.15 [49.49; 114.14]
Fixed effect model 792 5816163 136.17 [127.01; 145.99]
Random effects model 131.25 [77.52; 222.21]
50 100 150 200 250 300 350 400
I^2 = 98%, τ^2 = 0.3469, p = 5.00e−49
Drugs for Osteoporosis (Bisphosphonates)
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Ibandronic Acid 49 832804 58.84 [44.47; 77.85]
Risedronic Acid 69 3251835 21.22 [16.76; 26.87]
Alendronic Acid 609 29530952 20.62 [19.05; 22.33]
Fixed effect model 727 33615591 21.63 [20.11; 23.26]
Random effects model 28.97 [16.90; 49.67]
10 20 30 40 50 60 70 80
I^2 = 96%, τ^2 = 0.2142, p = 1.39e−11
Drugs for Erectile Dysfunction
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Tadalafil 53 3920001 13.52 [10.33; 17.70]
Sildenafil 197 16578690 11.88 [10.33; 13.66]
Vardenafil 4 480008 8.33 [3.13; 22.20]
Fixed effect model 254 20978699 12.11 [10.71; 13.69]
Random effects model 12.11 [10.71; 13.69]
5 10 15 20
I^2 = 0%, τ^2 = 0, p = 5.30e−01
Proton Pump Inhibitors
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Esomeprazole 141 9736167 14.48 [12.28; 17.08]
Pantoprazole 70 6511025 10.75 [8.51; 13.59]
Omeprazole 1172 159388676 7.35 [6.94; 7.79]
Lansoprazole 775 130688067 5.93 [5.53; 6.36]
Rabeprazole 9 1817020 4.95 [2.58; 9.52]
Fixed effect model 2167 308140955 7.03 [6.74; 7.33]
Random effects model 8.29 [5.97; 11.51]
0 5 10 15 20
I^2 = 96%, τ^2 = 0.1228, p = 4.32e−23
Antidepressants
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Venlafaxine 609 22072377 27.59 [25.48; 29.87]
Paroxetine 185 6775430 27.30 [23.64; 31.54]
Sertraline 1822 74634061 24.41 [23.32; 25.56]
Escitalopram 125 5718539 21.86 [18.34; 26.05]
Mirtazapine 858 44920641 19.10 [17.86; 20.42]
Fluoxetine 564 33679459 16.75 [15.42; 18.19]
Citalopram 926 71382441 12.97 [12.16; 13.84]
Fixed effect model 5089 259182948 19.63 [19.10; 20.18]
Random effects model 20.68 [17.07; 25.05]
10 15 20 25 30 35
I^2 = 98%, τ^2 = 0.0643, p = 1.10e−71


Hypnotics and Anxiolytics
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Lorazepam 121 5369023 22.54 [18.86; 26.93]
Oxazepam 8 422762 18.92 [9.46; 37.84]
Diazepam 355 24668251 14.39 [12.97; 15.97]
Zolpidem 37 3301796 11.21 [8.12; 15.47]
Nitrazepam 21 2380204 8.82 [5.75; 13.53]
Zopiclone 213 26324449 8.09 [7.07; 9.25]
Temazepam 39 5019260 7.77 [5.68; 10.63]
Fixed effect model 794 67485745 11.77 [10.97; 12.61]
Random effects model 11.81 [8.76; 15.90]
I^2 = 94%, τ^2 = 0.1332, p = 7.36e−20
5 10 15 20 25 30
Drugs for Nausea and Vertigo
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Ondansetron 75 1126719 66.56 [53.08; 83.47]
Metoclopramide 195 3852341 50.62 [43.99; 58.25]
Cyclizine 144 4973741 28.95 [24.59; 34.09]
Domperidone 59 2187964 26.97 [20.89; 34.80]
Prochlorperazine 151 7890087 19.14 [16.32; 22.45]
Fixed effect model 624 20030852 31.15 [28.80; 33.69]
Random effects model 34.50 [23.24; 51.20]
I^2 = 97%, τ^2 = 0.1933, p = 2.60e−25
10 20 30 40 50 60 70 80
Drugs for Dementia
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Rivastigmine 90 1880370 47.86 [38.93; 58.85]
Galantamine 25 889257 28.11 [19.00; 41.61]
Memantine 128 6077062 21.06 [17.71; 25.05]
Donepezil 209 10176096 20.54 [17.93; 23.52]
Fixed effect model 452 19022785 23.76 [21.67; 26.06]
Random effects model 27.25 [19.26; 38.56]
I^2 = 94%, τ^2 = 0.1106, p = 7.47e−11
10 20 30 40 50 60
Antimigraine Drugs
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Sumatriptan 193 8548323 22.58 [19.61; 26.00]
Zolmitriptan 30 1780062 16.85 [11.78; 24.10]
Frovatriptan 3 279516 10.73 [3.46; 33.28]
Rizatriptan 16 1601284 9.99 [6.12; 16.31]
Naratriptan 4 754469 5.30 [1.99; 14.13]
Fixed effect model 246 12963654 18.98 [16.75; 21.50]
Random effects model 13.04 [8.25; 20.63]
I^2 = 80%, τ^2 = 0.1642, p = 5.90e−04
0 5 10 15 20 25 30
Opioid Analgesics
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Tapentadol 57 730406 78.04 [60.20; 101.17]
Fentanyl 259 5535509 46.79 [41.42; 52.85]
Buprenorphine 364 15085085 24.13 [21.77; 26.74]
Oxycodone 202 8522118 23.70 [20.65; 27.21]
Morphine 563 25011625 22.51 [20.72; 24.45]
Codeine 488 24932103 19.57 [17.91; 21.39]
Tramadol 618 32405705 19.07 [17.62; 20.64]
Dihydrocodeine 117 8049688 14.53 [12.13; 17.42]
Fixed effect model 2668 120272239 22.18 [21.36; 23.04]
Random effects model 26.41 [18.71; 37.26]
I^2 = 97%, τ^2 = 0.2416, p = 8.38e−56
0 20 40 60 80
Non−Steroidal Anti−inflammatory Drugs
Drug Reports Prescriptions Reports per million prescriptions Rate 95%−CI
Diclofenac 341 3374003 101.07 [90.89; 112.38]
Indomethacin 39 694330 56.17 [41.04; 76.88]
Etoricoxib 85 1877321 45.28 [36.61; 56.00]
Celecoxib 60 1472228 40.75 [31.64; 52.49]
Naproxen 1072 35567637 30.14 [28.39; 32.00]
Etodolac 10 531857 18.80 [10.12; 34.94]
Meloxicam 42 2493196 16.85 [12.45; 22.79]
Fixed effect model 1649 46010572 35.84 [34.15; 37.61]
Random effects model 37.83 [24.59; 58.19]
I^2 = 99%, τ^2 = 0.3148, p = 5.88e−88
0 20 40 60 80 100 120

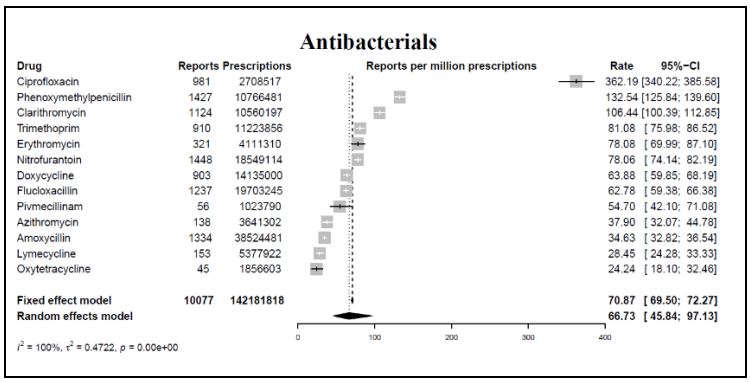


Figure 3.7 Comparative safety charts for clinically meaningful medicines in general practice.

Data on serious and fatal ADE reports from the Yellow Card database in the UK was mapped onto GP prescription data in England. This study created these comparative safety charts for clinically meaningful medicines belonging to 26 therapeutic categories by excluding medicines with <220,000 items prescribed in the defined period. Presenting safety profiles for medications using forest plots allows any two medications within a particular therapeutic category to be directly compared by seeing whether their confidence intervals lap over.

4 Chapter Four. Pharmacogenomics of Endocrine Therapy Associated Toxicities in Breast Cancer: A Systematic Review and Meta-Analysis

4.1 Abstract

Background/Aim Endocrine therapy is the standard of care for hormone receptor-positive (HR+) breast cancers. Endocrine therapy is however associated with toxicities leading to poor adherence to treatment, high recurrence and low survival rates. While PG predictors of endocrine therapy-related ADEs have the potential to inform personalised treatment decisions, data on whether such PG variants provide meaningful information regarding toxicity risk is inconsistent. As all published reviews on this topic were mainly narrative and focused on a particular gene or certain toxicities for a specific endocrine agent, this study aimed to critically describe both the current landscape and characteristics of the relevant literature.

Materials and methods Medline, Embase, the Cochrane CENTRAL library, Google Scholar and PharmGKB databases were systematically searched from inception to 22 March 2022. The PRISMA guidelines were followed and the methodological quality of the included studies was assessed using a checklist derived from STREGA, an extension of the STROBE Statement. If applicable, data from the independent studies were combined via meta-analyses.

Results Of 2,050 publications identified from the literature search and 4939 clinical annotations in PharmGKB, a total of 87 articles satisfied the predefined eligibility criteria and were therefore included in the qualitative synthesis. A substantial heterogeneity and considerable variation in PG effects across the included studies were observed. About half of the publications used data from the same clinical trials and the overwhelming majority of associations (87%) were investigated in Caucasians and predominantly (90%) in postmenopausal women. I conducted 44 meta-analyses, including 30 studies. Meta-analyses showed that Factor V Leiden mutation is a predictive maker of thromboembolic events in tamoxifen-treated breast cancer women OR=3.47 (1.95,6.17), p<0.0001, and rs2234693 and rs7984870 were potential predictors of musculoskeletal toxicities in postmenopausal women taking third-generation aromatase inhibitors OR=1.64 (1.25,2.14), p<0.0001 and OR=1.45 (1.18,1.79), p<0.0001, respectively.

Conclusions: The current evidence regarding the potential role of PG variants in endocrine therapy-related toxicity in breast cancer is inconsistent and its clinical usefulness is still unclear. In addition to heterogeneity in definitions of toxicity outcomes, limitations related to methodologies of individual studies such as failure to correct for multiple testing or accounting for genotype-treatment interactions are causes of concern. More studies in non-Caucasian populations and premenopausal women, which are high-risk populations, are warranted. Confirming and validating the predictive value of the variants reported to significantly modulate endocrine therapy-related toxicities in larger and well-designed studies is required.

4.2 Introduction

4.2.1 Endocrine treatment is the standard of care in hormone receptor-positive breast cancer

Female breast cancer (BC) is the most commonly diagnosed malignancy of global cancer with an estimated 2.3 million new cases annually, surpassing lung cancer (79). BC accounts for approximately 30% of female cancers and is still the leading cause of cancer-related death in women (78, 79). It is estimated that 70-80% of breast cancers are hormone receptor-positive (HR+), for which endocrine therapy is usually the mainstay for treatment and prevention of recurrence, for both primary and metastatic tumours. The most widely available endocrine treatments are I) Tamoxifen, a selective oestrogen receptor modulator, and II) third-generation aromatase inhibitors (AIs for brevity), which decrease oestrogen production by inhibiting the aromatase enzyme (793). In the past five years (12/2017-11/2022), Letrozole was the most commonly prescribed endocrine agent in GP in England, followed by Tamoxifen, Anastrozole and Exemestane (677) (Figure 4.7 [Appendix]).

4.2.2 Endocrine therapy use for 5–10 years reduces recurrence and increases survival rates in breast cancer

In both adjuvant and neoadjuvant settings, studies have demonstrated that endocrine therapy reduces recurrence and increases both overall survival (OS) and disease-free survival (DFS) rates in HR+ early BC when administered for a 5–10-year period (794–797). In HR+ early BC, treatment with tamoxifen for five years decreases relapse rates by about half and approximately one-third in the

following five years, as well as decreases BC mortality by nearly one-third during the first fifteen years (794). When treatment with tamoxifen is extended to ten years, further reductions in BC mortality are achieved (796).

AIs are recommended as first-line endocrine therapy in postmenopausal women with HR+ early BC (798) and in both pre- and postmenopausal women with HR+ and HER2-negative metastatic BC. AIs are also recommended in patients with unknown advanced BC and can be used in HR+ early or advanced BC in postmenopausal women whose disease has progressed despite having previously been treated with tamoxifen (799–802). Compared with five years of treatment with tamoxifen alone, AIs yield significantly greater reductions in relapse rate (797) as well as further reductions in BC mortality (803).

4.2.3 Endocrine therapy-induced adverse effects can result in high recurrence risk and low survival rates

Despite the declines in BC mortality due to advances in BC treatment (78), BC is still the most common cause of cancer-related death due to recurrence and metastasis (78, 79). Studies have demonstrated that <50% of women complete their full 5-year endocrine therapy, resulting in a 20% rise in BC mortality. This might explain the reduced OS benefit from endocrine therapy (80–82).

Since endocrine therapy is recommended for 5-10 years in adjuvant settings, one considerable concern for BC patients is the widespread occurrence and severity of related ADEs during treatment, which may result in treatment discontinuation (804–806). The incidence, cumulative toxicity and severity of endocrine therapy-associated ADEs were identified as the main predictors for suboptimal adherence and persistence (805, 806), affecting 30%-80% of these patients in the “real world”. This results in the lack of OS benefits and rises in both advanced-stage disease and mortality (80–82). The time trends for the number of reports of serious and fatal ADEs for endocrine agents submitted to the MHRA yellow card scheme (from inception till Nov-2022) are shown in (Figure 4.8 [Appendix]).

4.2.4 Determined approaches to manage endocrine therapy-associated toxicities are required

To improve BC survivorship, interventions designed to help prevent ADEs related to endocrine therapy were proposed (807). Tumour characteristics such as

pathologic stage and prognostication aids such as genomic prediction tools (808, 809) were validated to predict survival rate and identify those at heightened risk of disease recurrence. However, there are no currently validated biomarkers available to reliably identify those potentially at high risk of endocrine-related toxicities. Yet, the existing literature suggests that certain genomic variants are associated with clinical toxicity outcomes among BC patients who are treated with endocrine therapy.

4.2.5 Systematic evaluation of current evidence regarding PGx of endocrine therapy toxicity risk is warranted

Almost all previously published reviews of PGx of endocrine therapy-associated toxicities were mainly narrative and focused on a particular gene or certain toxicities for a specific endocrine agent. Yet, identifying variant(s) that confer a risk of a wider range of toxicity outcomes for more than one endocrine drug would be more clinically useful as these patients would have greater choice and thus could switch endocrine agents (810). Thus, a comprehensive systematic evaluation of PGx of endocrine therapy-associated toxicities is vital to enhance researchers' and clinicians' understanding of the current evidence base.

4.3 Aim

I. To critically describe the current landscape and identify any gaps in the literature of PGx of endocrine therapy-related toxicities in BC.

4.4 Objectives

I. To systematically review PGx studies of endocrine therapy-related toxicities in BC.
II. To critically evaluate the methodological quality of both the design and execution of identified studies.
III. When appropriate, perform meta-analyses of included studies.

4.5 Materials and Methods

4.5.1 Data sources and search strategy

The data sources used and the search strategy employed in this study are described in 2.5.1. This systematic review was not registered with a protocol. The searches were conducted from inception to 22nd Mar 2022. I ensured that

synonyms and both the generic and brand names of endocrine drugs were included by consulting with the BNF (47), the electronic medicines compendium (emc) (680) and the DrugBank database (681). The database-specific search strategies are presented in (Table 4.4 & Table 4.5 & Table 4.6 [Appendix]). To achieve comprehensiveness, I also systematically identified variants associated with endocrine therapy-related toxicities mapped by PharmGKB (96) by searching clinical annotations and phenotypes related to endocrine-related toxicity.

4.5.2 Eligibility criteria

Eligibility criteria were defined *a priori* and were based on the PICO four key components (Population, Intervention, Comparison, Outcome) (170, 171), which is endorsed by the Cochrane Collaboration (172). Both inclusion and exclusion criteria are detailed in (Table 4.1).

Table 4.1 The inclusion and exclusion criteria in this study

Inclusion Criteria	Exclusion Criteria
English-language publications	Non-human studies
Articles in journals	Case reports
Theses and dissertations	Editorials
Toxicity outcome of any grade	Publications without full texts
Toxicity-related biomarker changes	Abstracts only/conference proceedings
Toxicity-related quality of life (HRQL)	non-cancerous disease
Toxicity-related discontinuation	Adverse events due to reduced effectiveness
Female patients	Studies of overall response, recurrence, survival
Breast cancer disease	
Endocrine agents: Tamoxifen, Anastrozole, Letrozole or Exemestane	
Genomic variants (e.g., SNVs, frame-shift mutations, repeats, deletions, duplications, diplotypes, haplotypes)	
Phenotypes or activity scores derived from genotypes	

4.5.3 Study selection

The study selection process is summarised in 2.5.3.

4.5.4 Data extraction

The data extraction component of this systematic review is described in 2.5.4. The following data variables from the included studies were extracted and presented in table format: study's authors, year of publication, sample size, population description, study design, interventions(s), gene, genomic variant(s),

toxicity outcomes, covariates used for adjustment and menopausal status.

4.5.5 Quality assessment

The methodological quality of the included studies was critically evaluated (105). I applied a 15-item validated quality assessment checklist tailored to incorporate crucial methodological aspects that are vital to genetic studies including the risk of bias (811). This checklist was derived from the STREGA (STrengthening the REporting of Genetic Association Studies), an Extension of the STROBE Statement (Strengthening the Reporting of OBservational Studies in Epidemiology) (812). Summary scores were calculated for the final dataset of studies included in this review.

4.5.6 Quantitative data synthesis and statistical analysis

Quantitative data synthesis via meta-analysis was carried out as per 2.5.6. When applicable, I excluded the discovery GWA study published from the meta-analyses to avoid over-estimation of the effect size. Due to the significant heterogeneity in their definitions, I did not meta-analyse studies that investigated associations between *CYP2D6* genotype-predicted metaboliser phenotypes or activity scores and ADEs. Rather, findings from these publications were qualitatively synthesised and narratively discussed as recommended (813). All meta-analyses were performed and forest plots were created using Stata 16.0 (StataCorp, College Station, TX).

4.6 Results

4.6.1 Eighty-seven studies fulfilled the inclusion criteria

The search strategy identified a total of 2,050 publications retrieved from MEDLINE, Embase and Cochrane Library databases. Of these, 63 fulfilled the inclusion criteria. Having reviewed 4939 potentially relevant clinical annotations in PharmGKB and performed searches in Google Scholar, 32 additional records concerning endocrine therapy-related toxicities were found to be eligible for inclusion. Having contacted the authors of the identified abstracts and conference proceedings, eight abstracts were removed due to insufficient data. This resulted in the inclusion of 87 studies (307, 308, 819–828, 309, 829–838, 310, 839–848, 312, 849–858, 814, 859–868, 815, 869–878, 816, 879–888, 817, 889–895, 818)

including 45,630 patients. The study sample sizes ranged from 24 to 4580 (mean 524, median 218).

Most studies included in this analysis were relatively small. While, there were only ten publications with sample sizes of more than 1,000 participants (307, 308, 312, 839, 851, 866, 878, 882, 883, 885), three publications of these (307, 308, 839) used DNA samples extracted from formalin-fixed, paraffin-embedded (FFPE) BC tissue derived from the same clinical trial, and two publications (866, 878) used the cohort from the same clinical trial and investigated endocrine therapy associated decline in health-related quality of life.

The PRISMA flow chart of the systematic literature search and selection process of studies is presented in (Figure 4.1). PRISMA checklist is provided in (Table 4.7 [Appendix]).

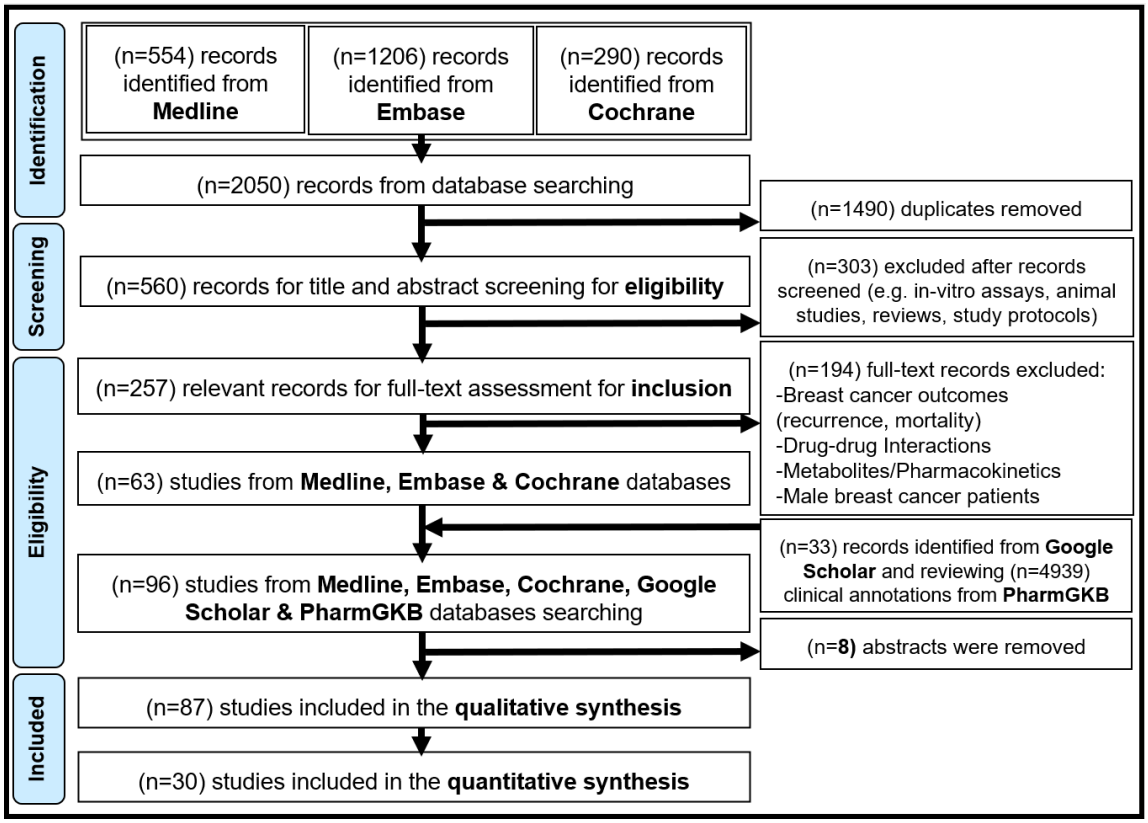


Figure 4.1 The PRISMA flow chart of systematic literature search and selection process.

Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram demonstrating the screening and selection stages of PGx studies of ADEs related to endocrine therapy in breast cancer.

4.6.2 The included studies had overall high-quality scores

Studies included in this systematic review had an average score of 88.24%. The descriptive statistics for each criterion of the STREGA and STROBE checklists

are provided in (Table 4.8 [Appendix]). There were 4 theses included in this review (866, 867, 874, 878) with an average quality score of 96.43%.

Remarkably, all included studies fully fulfilled the requirements for stating the study design and setting, clear eligibility criteria for study participants in the methods section, and reporting numbers of participants at each stage of the study. The overwhelming majority of studies (83 to 86 of the studies) satisfied the requirements for stating a clear statement of rationale, including objectives and hypotheses in the introduction, a clear definition of all variables and the outcome, data sources measurement and replicability of statistical methods in the methods section, and sufficient descriptive demographic data in the results section. Notably, only 56 studies fulfilled all the requirements for bias, and only 47 studies reported Hardy-Weinberg equilibrium. I observed inconsistency in ethnic and race classification in some studies. Of the 45 studies in which mixed ethnicities should have been addressed statistically, only 21 fulfilled the requirement for this.

4.6.3 The vast majority of identified associations were not statistically significant

Across the 87 studies, there were numerous toxicity outcomes, genomic variants, and genetic models as well as multiple associations and effect sizes within the same study. In total, 4,423 associations were reported, the majority of which (94.3%) were non-significant. There were 32 studies did not report any significant results (814, 816, 831, 832, 835–837, 843, 845, 849, 851, 864, 817, 866, 868, 873, 874, 876, 879–881, 887, 889, 818, 892, 894, 819, 820, 824, 826, 828, 830) (Figure 4.9 [Appendix]). A summary table describing the key characteristics of the included studies with statistically significant results was provided in (Table 4.2). A spreadsheet detailing the characteristics at the individual level associations for all studies included is provided in the Supplementary Excel file S4. The associations were annotated using the following font colour; Black colour to denote significantly increased risk of ADEs, green colour represents significantly reduced risk of ADEs, and red colour denotes a non-significant association with ADEs.

Table 4.2 Characteristics of studies reported statistically significant findings

Study (author, year of publication)	Drug(s)	Gene	Genomic Variant(s)	Toxicity outcomes	Study size	Demographics/ Population description	Menopausal status	Study type	Ref.
Al-Mamun 2017	Tam	*CYP2D6, UGT2B7, SULT1A1*	CYP2D6*10, UGT2B7*2, SULT1A1*2	Decreased libido, Depression, Vaginal dryness, HF	388	Bangladesh	Pre-, Peri-, Post-	Cohort	(867)
Basmadjian 2019	Exe	*UGT2B17*	*UGT2B17* deletion	Decline in physical HRQL	3345	Canada, USA, Spain, France	Post-	Post-hoc analysis of RCT	(878)
Argalacsova 2017	Tam	*ABCB1*	rs1045642, rs2032582	Time to ADEs, EH, Endometrial cancer, HF	258	Czech Republic	Pre-, Post-	Cohort	(870)
Baatjes 2020	Anas; Exe; Letr	*CYP19A1*	rs10046	BMD [LS, hip]	72	South Africa	Post-	Prospective cohort	(886)
Baxter 2014	Tam	*CYP2D6, CYP3A4*	CYP2D6 IM vs. EM, CYP3A4*22	HF severity	132	Canada	Pre-, Post-	Prospective cohort	(854)
Borrie 2020	Anas; Letr	*ESR1, CYP19A1*	rs2234693, rs4775936, rs9322336, rs9340799	Arthralgia, Arthralgia-related treatment discontinuation	196	Canada	Post-,	Prospective cohort	(888)
Chu 2007	Tam	*CYP3A4*	CYP3A4*1B	Endometrial cancer	63 cases/63 controls	Canada	Pre-, Post-	Case/control	(821)
Dempsey 2018	Exe; Letr	*RANKL*	rs7984870	Time to MS-ADEs discontinuation	500	(89%) Caucasian, remaining African or Asian	Post-	Prospective cohort	(877)
Dezentje 2014	Tam	*ESR1*	XbaI/PvuII diplotype (rs9340799/rs2234693)	HF	742	Netherlands	Post-	Post-hoc cohort of randomised trial	(309)
Dieudonné 2014	Tam	*CYP2D6*	rs1800716	ET	184	Belgium	Post-	Retrospective cohort	(853)
Fontein 2014	Exe	*CYP19A1*	rs16964189, rs7176005, rs934635	VM-ADEs, MS-ADEs	737	Netherlands	Post-	Post-hoc of randomised open-label trial	(852)

Garber 2010	Tam	*F5*	Factor V Leiden mutation	Thromboembolic events	124 cases/248 controls	USA	Pre-, Peri-, Post- [Most were Post-]	Case/control	(829)
Garcia-Giralt 2013	Anas; Exe; Letr	*CYP17A1, VDR*	rs10786712, rs11568820, rs3781287, rs4775936 rs4919683, rs4919687, rs6163, rs743572	Arthralgia	343	Spain	Post-	Prospective observational cohort	(846)
Gervasini 2017	Anas	*CYP19A1, ABCB1*	rs1008805, rs1045642	Arthralgia	110	Spain	Post-	Retrospective cohort	(869)
Günaldı 2014	Tam	*CYP2D6*	*CYP2D6* UM EM IM PM groups	TC, TG, ET	92	Turkey	Pre-, Post- [Most were Pre-]	Cohort	(850)
Hartmaier 2012	Tam	*NCOA1*	rs1804645	BMD [LS]	111	USA	Pre-, Post-	Cohort from prospective observational study	(840)
He 2020	Tam	*CYP2D6*	*CYP2D6* UM vs. NM	Treatment discontinuation	1309	Sweden	Pre-, Post-	Data from case-only cohort and cohort studies	(882)
Henry 2009	Tamo	*CYP2D6*	CYP2D6 IMs vs. EMs or PMs	HF	297	USA	Pre-, Peri, Post-	Prospective cohort	(827)
Henry 2013	Exe	*ESR1*	rs9322336	MS-ADEs discontinuation	432	USA	Post-	Data from prospective randomised trial	(310)
Hertz 2016	Tam	*CYP2D6*	CYP2D6 UM, EM, IM, PM	Distractedness, Irritability, Mood swings, Vomiting, Night sweats, HF, Breast tenderness, Vaginal problems, Dyspareunia, incontinence, Arm Problems	480 [353 were available for follow-up analysis]	USA	Pre-, Peri-, Post-	Secondary analysis of prospective genotype-guided study	(863)

Hertz 2021	Anas; Exe; Letr	*OPG*	rs2073618	MS-ADEs	143	USA	Post-	Secondary analysis of prospective observational cohort	(891)
Hertz 2022	Exe; Letr	*TCL1A, ESR1, SUPT20H, CCDC148, RANKL, PPP1R14C*	rs11849538, rs1324052, rs2347868, rs2369049, rs74418677, rs79048288, rs7984879, rs912571, rs9322336	MS-ADEs discontinuation	400	USA	Post-	GWAS of prospective, open-label study	(893)
Ho 2020	Exe	*UGT2B17*	*UGT2B17* deletion	Severe fatigue	1752	Canada, USA, Spain, France	Post-	Post-hoc of RCT	(883)
Jin 2008	Tam	*ESR2*	ESR2–02 (rs4986938)	HF	297	USA	Pre-, Peri-, Post-	Open-label prospective observational trial	(823)
Johansson 2016	Exe; Tam	*CYP19A1*	rs10046	HF, Sweating	1967	International	Pre- (+OFS)	Retrospective analysis of RCT	(312)
Kiyotani 2012	Tam	*CYP2D6*	CYP2D6 [*10,*41] or [*5,*21,*36-*36] vs. *1/*1	Hyperhidrosis	98	Japan	Pre-, Post-	Cohort	(838)
Koukouras 2012	Anas; Exe; Letr	*ESR1*	PuvII (rs2234693), XbaI (rs9340799)	LDL, TG, ET	87 cases/80 control	Greece	Post-	Prospective case-control study	(841)
Kovac 2015	Tam	*F5*	Factor V Leiden and Factor II mutations	VTE	150	Serbia	Pre-, Post-	Prospective case-control study	(855)
Leyland-Jones 2015 [1]	Tam; Letr	*CYP19A1*	rs10046, rs700518, rs936308, rs4646	Fractures, Osteoporosis, MS-ADEs	4580	Denmark, France, Switzerland	Post-	Substudy of RCT	(308)

Leyland-Jones 2015 [2]	Tam; Letr	*ESR2, ESR1*	ESR2–02 (rs4986938), XbaI (rs9340799), rs2077647	HF, Night sweats, Fractures, Osteoporosis	3401	Denmark, France, Switzerland	Post-	Sub-study of RCT	(307)
Lintermans 2016	Anas; Exe; Letr	*OPG*	rs2073618	MS-ADEs	159	Belgium	Post-	Analysis of prospective observational cohort study	(861)
Mao 2011	Anas; Exe; Letr	*CYP19A1*	rs60271534 (TTTAn) At least one 8-repeats	Arthralgia, MS-ADEs	390	USA	Post-	Cross-sectional study	(834)
Mazzuca 2016	Anas; Letr	*CYP19A1*	rs4646	Bone loss [osteoporosis]	45	Italy	Post-	A retrospective cohort	(865)
Miranda 2021	Tam	*ESR1 CYP3A5 SULT1A1*	rs121913044, CYP3A5*3, SULT1A1*2	Vaginal bleeding, EH	162	Chile	Pre-, Post-	Retrospective case-control study	(890)
Napoli 2013	Anas; Exe; Letr	*CYP19A1*	rs700518	BMD [LS]	97	USA	Post-	Longitudinal prospective observational study	(844)
Napoli 2015	Anas; Exe; Letr	*CYP19A1*	rs700518	Truncal fat and fat-free mass indexes	82	USA	Post-	Longitudinal prospective study	(860)
Niravath 2018	Anas; Exe	*VDR*	rs2228570	Arthralgia	72 cases/144 controls	USA, Canada	Post-	Nested case-control study	(875)
Ntukidem 2008	Tam	*ESR2, ESR1*	ESR2–02 (rs4986938), XbaI (rs9340799)	TG, HDL, TC	134	USA	Post-	Cohort from a prospective observational open-label clinical study	(822)
Oesterreich 2015	Anas; Exe; Letr	*ESR2, ESR1,*	rs10140457, rs2813543, rs3742278,	BMD and T score [LS, hip], Bone loss [urinary NTx, serum BAP]	503	USA	Post-	PGx analysis of randomised study	(857)

		HTR2A, CYP19A1	rs4870061, rs6493497, rs9322335						
Ohnishi 2005	Tam	*CYP17A1*	rs743572	Hepatic steatosis	180	Japan	Pre-, Post-	Cohort	(815)
Onitilo 2009	Tam	*ESR1*	XbaI/PvuII diplotype, rs9340799 (XbaI)	VTE [PE or DVT]	219	USA	Pre-, Peri-, Post-	Population-based cohort study	(825)
Park 2011	Letr	*CYP19A1*	Haplotype M_5_3	Arthralgia, HF	109	Korea	Pre-, Post-	Cohort	(833)
Pineda-Moncusi 2017	Anas; Exe; Letr	*CYP11A1*	D15S520 [pentanucleotide [TTTTA] n repeat, Haplotypes: GATGAAA 17.3; GATGACA 17.4; CAT 11.2	BMD [FN], Arthralgia	391	Spain	Post-	Cohort	(871)
Regan 2012	Tam	*CYP2D6*	CYP2D6 IM vs EM, CYP2D6 PM vs EM	HF, Night sweats	4393	Denmark, France, Switzerland	Post-	Post-hoc of randomised, phase III double-blind study	(839)
Rodríguez-Sanz 2015	Anas; Exe; Letr	*CYP11A1*	SNPs and haplotypes for (rs11632698, rs4077581, rs900798)	BMD [FN]	391	Spain	Post-	Prospective, observational, clinical cohort study	(858)
Rolla 2012	Tam	*CYP2D6*	CYP2D6 UM vs EM-IM-PM	ADEs [HF, headache, muscle cramps, weight gain, depression, vaginal symptoms, ET]	61	Italy	Pre-, Post-	Cohort	(842)
Romero 2020	Anas; Exe; Letr	*HSD17B2*	rs11648233	Arthralgia	1049	USA (White)	Post-	Cross-sectional study	(885)
Santa-Maria 2016	Letr	*CYP19A1*	rs1062033, rs749292, rs10046, rs1008805, rs2289105, rs3759811, rs4646, rs4775936	HDL, TG	303	USA	Post-	Subset analysis of prospective	(862)

			rs700518					randomised open-label trial	
Servitja 2015	Anas; Exe; Letr	*CYP27B1, CYP17A1*	rs4646536, rs6163	MS-ADEs	687	Spain	Post-	Cohort	(856)
Umamaheswaran 2020	Letr	*CYP19A1*	rs10459592, rs4775936, rs700518, rs700519. Haplotypes: H11; H5; H6; H10; H3	MS-ADEs, VM-ADEs	198	India	Post-	Cohort	(884)
Wang 2013	Anas; Letr	*ESR1*	rs2234693 and rs9340799	MS-ADEs	206 cases/230 controls	China [East Asian]	Post-	Case/control study	(848)
Wang 2015	Anas; Letr	*RANKL, OPG*	SNPs and haplotypes for rs7984870, rs2073618	MS-ADEs, Bone turnover [CTX, PINP], BMD and T-score [LS]	208 cases/212 controls	China [East Asian]	Post-	Case/control study	(859)
Weng 2013	Tam	*PTCSC2, E2F7, SLC22A23, PLEKHA5*	rs10983920, rs10983932, rs10984098, rs310786, rs4959825, rs9862879	BMD [hip, LS], HF	245	USA	Pre-, Peri-, Post-	Sub-study of open-label, prospective observational trial	(847)
Wickramage 2017	Tam	*CYP2D6*	CYP2D6*41	Fatty liver	24	Sri Lanka	Pre-, Post-	Retrospective cohort	(872)
Zhou 2022	Tam	*CYP2D6*	CYP2D6 EM	GGT, Liver dysfunction, DET, Gynaecological ADEs, Dyslipidemia events (TG, abnormality in LP(a), TC)	192	China	Pre-, Post-	Propensity-score matched cohort study	(895)

Abbreviations

LS=Lumbar Spine; NTx=type I cross-linked N telopeptides; BAP=Bone Alkaline Phosphatase; OFS=Ovarian Function Suppression; AIs=Aromatase Inhibitors; RCT=Randomised Control Trial; HF=Hot Flushes; TC=Total Cholesterol; TG=Triglycerides; HDL=High-Density Lipoprotein; ADEs=Adverse Drug Effects; EH=Endometrial Hyperplasia; VTE=Venous Thromboembolic Events; PE=Pulmonary Embolism; DVT=Deep Vein Thrombosis; MS-ADEs=Musculoskeletal Adverse Effects [Muscle pain or Arthralgia]; VM-ADEs=Vasomotor Adverse Effects; FFPE=Formalin-Fixed Paraffin-Embedded Tumour; HRQL=Physical Health-Related Quality of Life; CTX=Carboxy Terminal Telopeptide; PINP=Procollagen type I N-terminal Propeptide; GGT=Gamma-Glutamyl Transferase; ET=Endometrial Thickness; DET=Double Endometrial Thickness; EH=Endometrial Hyperplasia; FM=Femoral Neck; LP(a)=Lysophosphatidic acid; BMD=Bone Mineral Density; EM=Extensive metaboliser; IM=Intermediate metaboliser; PM=Poor metaboliser; UM=Ultrarapid metaboliser; Tam=tamoxifen; Anas=Anastrozole; Exe=Exemestane; Letr=Letrozole; Pre-=premenopausal; Peri-=peri-menopausal; Post-=postmenopausal.

4.6.4 There were only three meta-analyses with a statistically significant summary effect size

I conducted 44 meta-analyses including a total of 30 studies. The number of studies within a meta-analysis ranged from two to five studies. There were only 3 meta-analyses that had a statistically significant summary effect size which are presented in (Table 4.3). The forest plots are shown in (Figure 4.2, Figure 4.3, Figure 4.4, Figure 4.5). FVL mutation was found to increase the risk of thromboembolic events in tamoxifen-treated women in four studies (814, 819, 829, 855) OR=3.47 (1.95, 6.17), p<0.0001 with no evidence for heterogeneity (I^2 %=3.0%). However, one of the four studies used a broad definition for thromboembolic events (829) while the other three studies examined specific and more serious ADE outcomes (814, 819, 855), namely venous thromboembolism including deep vein thrombosis and pulmonary thromboembolism. On removal of this study from the meta-analysis, the association of FVL mutation and venous thromboembolism also persisted OR=2.55 (1.13, 5.75), p=0.024 with no evidence of heterogeneity (I^2=0%). Also, *ESR1* PuvII (rs2234693) and *RANKL* rs7984870 were significantly associated with MS-ADEs in postmenopausal women treated with AIs OR=1.64 (1.25, 2.14), p<0.0001 and OR=1.45 (1.18, 1.79), p<0.0001, respectively. No other genomic variants were found to be significantly associated with ADEs. Pooled estimates for all meta-analyses performed in this study are shown in (Table 4.9 [Appendix]).

Studies which reported different effect size measures were meta-analysed separately. Three variants were described to be associated with MS-ADEs in postmenopausal women treated with AIs with both HR and OR being reported. This included eight studies examined rs10046 (308, 310, 312, 833, 834, 861, 884, 891), five studies investigated rs4646 (308, 310, 833, 845, 884) and five studies for rs700518 (308, 310, 833, 861, 884). Overall, no indication of significant associations between any of these variants and MS-ADEs in postmenopausal women treated with AIs.

Since the number of combined studies in a meta-analysis was <10, funnel plots were not created and asymmetry tests were not performed. This is because the

power of the tests for funnel plot asymmetry is too low to differentiate between real or chance asymmetry when few studies were included.

Table 4.3 Meta-analyses with a statistically significant summary effect size

Toxicity outcomes	Drug(s)	Genomic variant	Risk Allele	Pooled effect estimate (95% CI)	I^2 (%), *p*-value (Cochran's Q)	Ref.
Thromboembolic Events	Tam	*Factor V Leiden* (rs6025)	A	OR=3.474 (1.955, 6.174), *p*<0.0001	(3.0%), 0.378	(814, 819, 829, 855)
MS-ADEs	Anas; Exe; Letr	*PuvII* (rs2234693)	C	OR=1.636 (1.250, 2.141), *p*<0.0001	(43.1%), 0.153	(859, 861, 888, 891)
MS-ADEs	Anas; Exe; Letr	rs7984870	C	OR=1.455 (1.184, 1.786), *p*<0.0001	(60.5%), 0.079	(859, 888, 891)

Tam=tamoxifen; Anas=Anastrozole; Exe=Exemestane; Letr=Letrozole

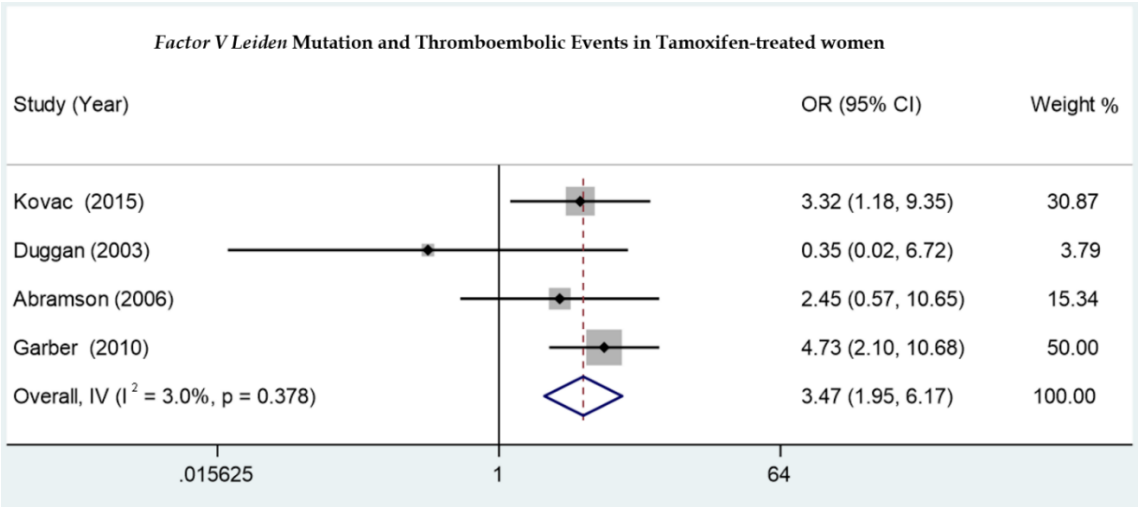


Figure 4.2 Meta-analysis of Factor V Leiden mutation and thromboembolic events in Tamoxifen-treated patients.

Meta-analysis of the odds ratios (OR) and 95% confidence intervals (CI) of four studies examined Factor V Leiden mutation (rs6025) and thromboembolic events in patients taking Tamoxifen. Individual and pooled odds ratios from studies were reported in the Forest plot. Squares represent study-specific effect estimates and the size of the square reflects the study-specific weight (i.e., the inverse of the variance). The diamond represents the summary effect estimate with a 95% confidence interval, and the horizontal lines indicate a 95% confidence interval.

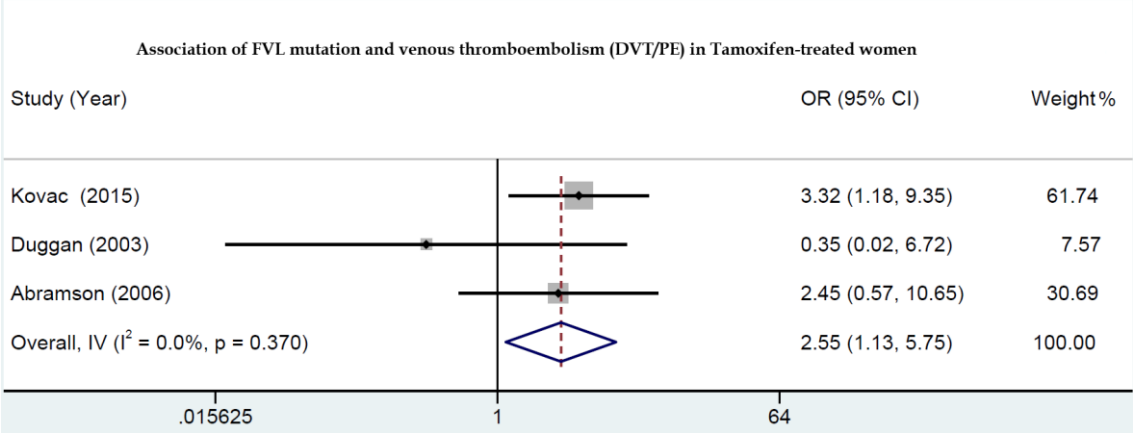


Figure 4.3 Meta-analysis of Factor V Leiden mutation and venous thromboembolism in Tamoxifen-treated patients.

Meta-analysis of the odds ratios (OR) and 95% confidence intervals (CI) of three studies examined Factor V Leiden mutation (rs6025) and venous thromboembolism in patients taking Tamoxifen. Individual and pooled odds ratios from studies were reported in the Forest plot. Squares represent study-specific effect estimates and the size of the square reflects the study-specific weight (i.e., the inverse of the variance). The diamond represents the summary effect estimate with a 95% confidence interval, and the horizontal lines indicate a 95% confidence interval.

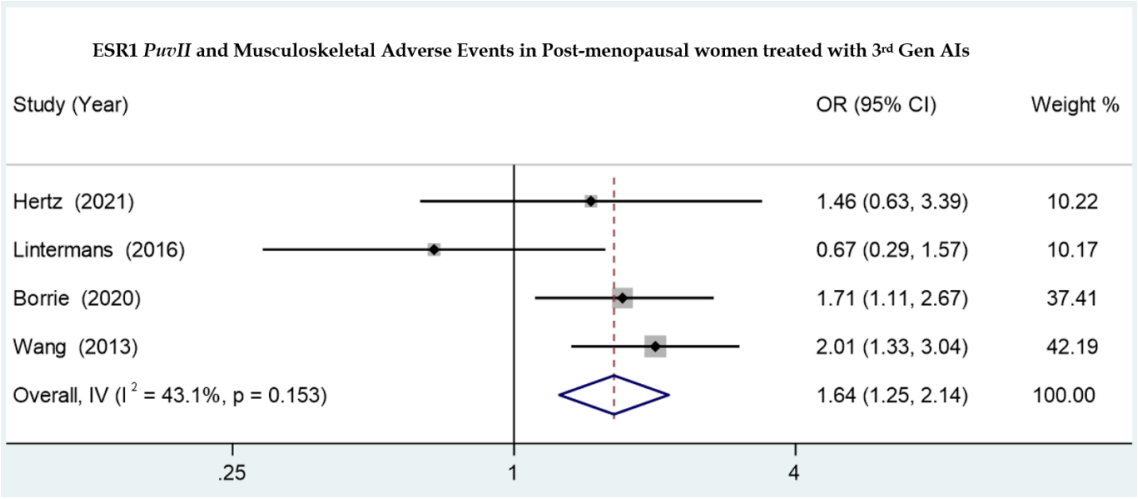


Figure 4.4 Meta-analysis of ESR1 PuvII and musculoskeletal adverse effects in postmenopausal women treated with third-generation aromatase inhibitors.

Meta-analysis of the odds ratios (OR) and 95% confidence intervals (CI) of three studies examined ESR1 PuvII (rs2234693) and musculoskeletal adverse effects in postmenopausal women taking third-generation aromatase inhibitors. Individual and pooled odds ratios from studies were reported in the Forest plot. Squares represent study-specific effect estimates and the size of the square reflects the study-specific weight (i.e., the inverse of the variance). The diamond represents the summary effect estimate with a 95% confidence interval, and the horizontal lines indicate 95% confidence intervals.

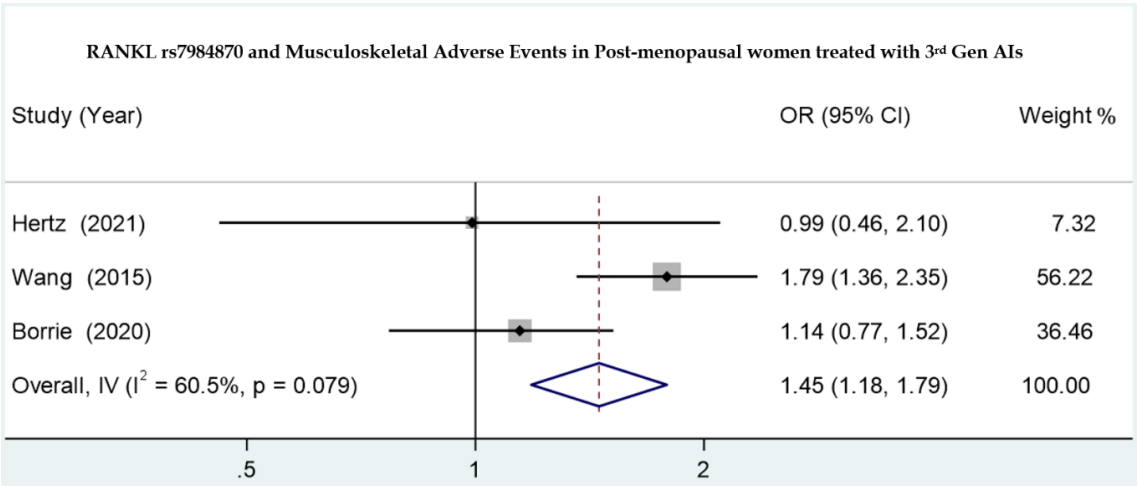


Figure 4.5 Meta-analysis of RANKL rs7984870 and musculoskeletal adverse effects in postmenopausal women treated with third-generation aromatase inhibitors.

Meta-analysis of the odds ratios (OR) and 95% confidence intervals (CI) of three studies examined RANKL rs7984870 and musculoskeletal adverse effects in postmenopausal women taking third-generation aromatase inhibitors. Individual and pooled odds ratios from studies were reported in the Forest plot. Squares represent study-specific effect estimates and the size of the square reflects the study-specific weight (i.e., the inverse of the variance). The diamond represents the summary effect estimate with a 95% confidence interval, and the horizontal lines indicate 95% confidence intervals.

4.6.5 Third generation of aromatase inhibitors were the most investigated treatment modality

While some studies grouped more than two endocrine agents in their analyses, most studies investigated individual endocrine agents, or two medications belonging to the AIs class. Among the individual endocrine agents analysed, more significant associations were reported for tamoxifen (43%) (Figure 4.10 [Appendix]). Yet, AIs collectively had more significant associations (55.5%) compared to SERM analysed (i.e. tamoxifen). AIs were also the most investigated treatment modality (87% of total associations) (Figure 4.11 [Appendix]).

4.6.6 Musculoskeletal and vasomotor adverse effects were the most explored toxicities

Musculoskeletal and vasomotor ADEs (MS-ADEs and VM-ADEs) were the most examined ADEs. Of 87 included studies, 47 explored MS-ADEs (307, 308, 840–842, 844–848, 850, 851, 310, 852, 856–859, 861, 863, 865, 869, 871, 312, 873–875, 877, 879–881, 883–885, 826, 886–888, 891–894, 828, 830, 832–834) and 32 investigated VM-ADEs (309, 814, 832, 833, 835, 837, 838, 842, 843, 847, 849, 854, 816, 855, 861, 863, 864, 867, 868, 870, 872, 876, 879, 817, 883, 889, 819, 820, 823, 825, 827, 829) (Figure 4.12 [Appendix]). Of the total number of associations, MS-ADEs were also the most investigated ADEs (48.4% of associations), followed by overall toxicities being the second most examined by ten studies (34.4% of total associations) (Figure 4.13 [Appendix]).

4.6.7 Less than 1% of associations were analysed in premenopausal women

Of the total associations, 89% were analysed in postmenopausal women and only 0.9% were tested in premenopausal women (Figure 4.6). While BC stages ranged from early stage to advanced or metastatic BC in the included studies, early-stage BC was the most studied malignancy. Yet, several studies did not state the BC stage and only a few studies examined data derived from patients with advanced or metastatic BC (824, 845, 889).

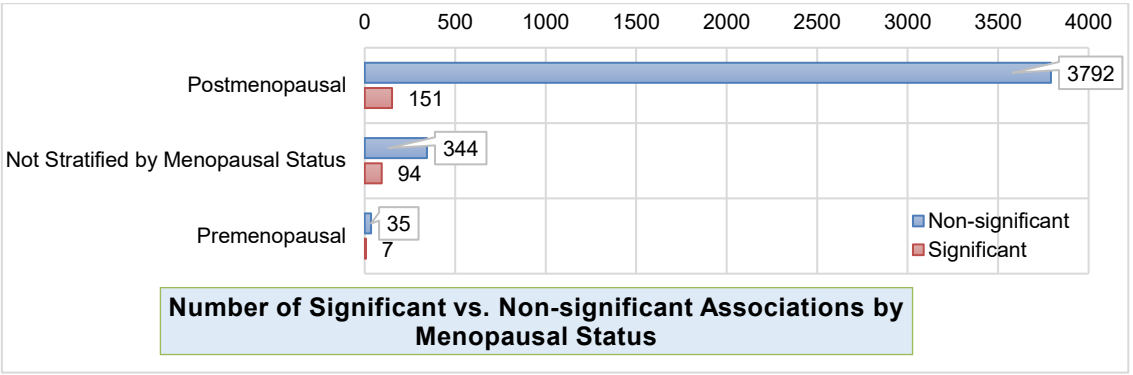


Figure 4.6 The number of associations analysed as per menopausal status.

The bar chart shows that less than 1% of associations analysed were in premenopausal women.

4.6.8 Most studies were performed in high-income countries and within predominantly caucasian cohorts

While studies included in this review were published in different countries, they were conducted largely in the USA and Europe. The overwhelming majority of associations (86.6%) were performed within cohorts which were predominantly Caucasian or recruited from countries primarily identified as white populations (Figure 4.14 [Appendix]).

4.6.9 Majority of reports were candidate gene studies and there were only three GWAS

The majority of retrieved studies were candidate gene studies and there was only one randomised genotype–guided tamoxifen dosing study (889). There were three genome-wide association studies (GWAS) (830, 851, 893) all explored AIs-associated MS-ADEs, two of which (830, 851) obtained their cases and controls from the same trial, namely MA.27

The included studies reported variants belonging to 58 genes, of which *ESR1* and *CYP19A1* were the most investigated, with 23% and 19% of total associations, respectively (Figure 4.15 [Appendix]). The overwhelming majority of studies examined single nucleotide variants (SNVs) and genotype-predicted metaboliser phenotypes. Eight studies analysed diplotypes or haplotypes (309, 825, 833, 848, 858, 859, 871, 884). Apart from CYP2D6 metaboliser phenotypes predicted based on deletion(s), five studies examined deletions, namely *UGT2B17* deletion (866, 874, 878, 881, 883).

Whilst the majority of studies used germline DNA, seven studies used DNA samples extracted from FFPE BC tissues (307–309, 816, 824, 839, 852), and four studies (825, 856, 877) did not explicitly state where their DNA samples were extracted from.

4.6.10 Duplicated data existed across studies

The significant overlap of studies' subjects existed and 37 publications (42.5%) used overlapping data derived from the same trial(s). These studies produced multiple estimates based on data derived from the same participant sample. For example, six studies used data from ELPh trial (310, 857, 862, 877, 881, 893), six studies used data from patients enrolled in TAM trial (822, 823, 827, 828, 840, 847), four studies used data derived from participants in MAP.3 trial (866, 874, 878, 883), three studies analysed patients recruited from BIG 1–98 trial (307, 308, 839), three studies included patients enrolled in MA.27 study (830, 851, 875), three studies used data from the same B-ABLE cohort (846, 858, 871), two studies included patients from TEAM trial (309, 852), two studies included participants enrolled in the (IBIS-I) trial (814, 837), two publications included participants from the same longitudinal study (844, 860), two studies recruited patients from the same cohort (884, 892), one study (863) was an expansion on a previous pilot study (832) to achieve statistical power.

4.6.11 Heterogeneity in definitions and measures of toxicity outcomes.

There was substantial variation in defining toxicity outcomes. Some studies have not used standardised symptom measurement for the seriousness and severity of toxicities. Toxicity outcomes varied from a specific toxicity endpoint of particular severity (e.g., severe hot flushes ≥grade 3) to unspecified toxicity outcomes of any grade (e.g., any ADEs, general aches or pains). Toxicity outcome measurement included toxicity-related changes in the mean of biomarkers (e.g., lipid profile, bone mineral density BMD), time to appearance of toxicity endpoints (e.g., presence of hepatic steatosis) or toxicity-related discontinuation of treatment. Many studies used global assessments or combined two or more side effects as a single composite outcome (e.g., gynaecological ADEs). Some studies investigated toxicity-related discontinuation of treatment or incorporated it in their outcome definitions (310, 834, 846, 866, 877, 882, 885, 888, 893). Few studies examined quality-of-life measures or toxicity-associated worsened

health-related quality of life and/or its impact on treatment discontinuation (832, 863, 866, 878).

4.7 Discussion

4.7.1 This analysis adopted a holistic approach to synthesise the available body of evidence

To date, this is the most comprehensive systematic review of the PGx of endocrine therapy-related toxicities using a comprehensive and well-explicated search strategy in several bibliographic and PG databases. The relevant landscape was critically described and the body of evidence available was meticulously evaluated and synthesised. Distinct from previous reviews, data from individual studies have been extracted, collated and analysed at the level of individual associations. Further, large-scale meta-analyses were performed to minimise the probability of both false-positive and false-negative findings.

In addition to identifying existent gaps and what remains to be investigated, this analysis provides a holistic understanding of the current level of PGx of endocrine therapy-related toxicity, keeping clinicians and researchers abreast of the extant evidence base. As BC and endocrine therapy are well-studied areas with RCTs and large cohorts as well as long follow-ups, this study has the potential to advance overall development in the field of PGx. To an extent, conclusions derived from this systematic review can be extrapolated to the PGx of other therapeutic classes as there is no reason to assume that the landscape of PGx of other fields would significantly differ from the PGx of endocrine therapy in BC.

4.7.2 Substantial heterogeneity and variability in pharmacogenomic effects were observed

The wide diversity of characteristics of articles that met the eligibility criteria resulted in substantial clinical and methodological heterogeneity. This was compounded by the conflicting results and notably considerable variation in PG effects across the studies. Sources of heterogeneity comprise types of genomic variants, enrollment criteria, BC stages, patient populations under study, geography, treatment settings (e.g., adjuvant and neoadjuvant settings), study designs, outcome definitions and ascertainment. This analysis adopted an approach by grouping the retrieved studies as per their key characteristics such

as interventions, outcomes, populations, menopausal status and study designs. This informative grouping helped draw reliable conclusions and identify potential modifiers and areas in which the evidence is more consistent and robust compared to other groupings. However, multiple researchers addressed the same research question using different approaches. This added a further layer of complexity in terms of synthesising collective evidence, drawing definitive conclusions or providing valid practical implications.

4.7.3 Meta-analyses identified variants that can serve as predictive markers of endocrine therapy in BC

While the overwhelming majority of findings from individual studies were not statistically significant, there were three meta-analyses with statistically significant summary effect sizes among the meta-analyses performed in this study. Meta-analyses showed that Factor V Leiden mutation can serve as a predictive marker of thromboembolic events in tamoxifen-treated BC patients, who can be switched to other endocrine agents or targeted for monitoring strategies to improve adherence and overall survival.

Moreover, MS-ADEs were significantly associated with *PuvII* (rs2234693) in postmenopausal women treated with AIs. However, in other studies, no significant associations were observed between *PuvII* and either MS-ADEs-related discontinuation in Exemestane and/or Letrozole under any genetic model (310) or with MS-ADEs in patients taking endocrine agents (312). Meta-analyses also demonstrated that postmenopausal women treated with AIs and carrying *RANKL* rs7984870 have an increased risk of MS-ADEs. This was to some extent supported by another study reporting that patients homozygous for rs7984870 allele (G) treated with Exemestane or Letrozole had significantly a reduced risk of MS-ADE-related treatment discontinuation (877). However, the authors did not find significant changes in MS-ADE symptom clusters. These meta-analyses also included a small number of studies with a limited number of patients and therefore heterogeneity among the studies cannot be eliminated. Also, the patients were derived from a specific population or particular geographic region, and there is no evidence to support the rs2234693 and rs7984870 increase risk with respect to MS-ADEs in patient populations different from those included in the meta-analyses. The evidence is therefore inconsistent and larger studies are needed

to provide more robust findings regarding rs2234693 and rs7984870 and MS-ADEs.

4.7.4 Almost all of included studies were retrospective

The overwhelming majority of PGx studies included in this systematic review were observational studies, mainly cohorts and retrospective PG analyses of RCTs. Even though some studies used data derived from RCTs, ADEs were mostly not the primary endpoints or outcomes, and ascertainment of toxicity outcomes was largely based upon retrospective identification of potential cases. The retrospective nature of this identification of cases is prone to overestimation of the PG effect and false positives.

Compared to observation studies, RCTs are usually inherently of higher quality with a lower likelihood bias. There was a lack of randomised genotype–guided endocrine therapy studies among the reports identified. Only one randomised genotype–guided tamoxifen dosing study of 184 patients has been carried out (889). Yet, the study focused on common tamoxifen-related ADEs and safety was not the primary endpoint. Moreover, the researchers of the study concluded that there was no statistically significant difference in the incidence of ADEs between the arm employing genotype-guided escalated dosage and those using a standard dosage.

4.7.5 Studies in non-Caucasian ethnicities should be conducted to facilitate the external validity of findings

The overwhelming studies were performed in high-income countries or within cohorts which were predominantly Caucasians or primarily identified as white populations. As certain genomic variants might dominate in specific ethnic groups (189), findings from these studies might not be generalisable to under-represented populations that are not adequately represented such as African, Asian, Indian or Chinese populations.

BC is still the most common cause of cancer-related death due to recurrence and metastasis, particularly in middle and low-income countries. Compared to Caucasian or white women, black females have 4% lower BC incidence yet have 40% increased BC-related mortality. Black women are less likely to be diagnosed with BC yet have the highest BC-related death rate and lower adherence to

endocrine therapy. Compared to well-studied European populations, African genomes comprise more variation and African genetic variability can be associated with transport and/or metabolic pathways of endocrine agents which may lead to reduced adherence due to the associated toxicity. To reduce racial disparities and health inequalities, studies in larger cohorts or using biobanks with more diverse populations are required particularly in ethnic populations in which racial disparity in BC-related mortality has stagnated for decades (78).

4.7.6 More studies in premenopausal breast cancer patients are required

There were very few studies, less than 1% of associations, analysed premenopausal women. Yet, premenopausal women with ER-positive, early-stage BC are more likely to report endocrine therapy-related ADEs due to the abrupt reduction in oestrogen concentrations associated with systemic endocrine treatment (896). Premenopausal women with ER-positive were found to be less likely to complete their endocrine therapy regimen (897). Additionally, dense breast tissue in premenopausal women makes it difficult for clinicians to identify issues on mammograms and therefore BC in premenopausal women is typically diagnosed at later stages (898). Premenopausal women with BC usually present with more aggressive and complex manifestations and therefore need multimodality therapy. Besides, premenopausal women with BC often have lower survival rates compared with their postmenopausal counterparts (896). Hence, future efforts should be made to conduct more PGx studies of ADEs related to endocrine therapy in premenopausal subjects.

4.7.7 No consistent definitions of ADE outcomes, follow-up periods or timing of outcome measurements

It has been noted that most studies in this review had relatively small sample sizes, which therefore may theoretically lack sufficient statistical power to detect some toxicity outcomes. Studies need to be sufficiently large and followed up enough to observe a particular outcome.

In addition to the wide range and considerable heterogeneity in toxicity outcomes analysed in individual studies, there were no consistent definitions of ADE outcomes. Even when the same toxicity outcome was explored, studies varied in the endpoints assessed and measurement instruments used. The limited use of validated toxicity-related symptom measures, particularly for mild and moderate

toxicity outcomes, was also a matter of concern. There also existed substantial variability in both follow-up periods and the timing at which the toxicity outcome was measured.

Further, some studies analysed a combination of heterogeneous ADEs by grouping very diverse and dissimilar ADEs with varying degrees of seriousness and severity. While grouping ADEs may increase the statistical power, this alerts to the potential of outcome reporting bias.

This analysis underscores the need for using specific toxicity endpoints, more accurate phenotype delineation and standardised toxicity outcome measures to maintain a precise level of granularity.

4.7.8 Selective reporting of findings and potential outcome reporting bias

This study identified incomplete and selective outcome reporting by authors of some studies. At times, investigators stated the existence of non-significant results without citing adequate details on effect sizes (822, 828). Other studies reported their non-significant results in bulk without describing which genomic variants or outcomes had been analysed (862, 885). Authors of around 10% of studies reported solely positive results and did not report any non-significant results. As the majority of reported associations identified in this study were non-significant, authors who solely reported positive results have potentially opted to publish the findings based on their results. This indicates that statistically non-significant results might have been selectively under-reported (i.e., the potential existence of selection and reporting biases) (127).

Further, selective within-study reporting of outcome variables based on the direction and nature of the results was observed. For instance, authors of some studies did not report key outcomes that are routinely measured and reported by most analogous studies, leading to a form of reporting bias, namely publication bias (127, 128). There exists evidence of 'file drawer issue' or publication bias as none of the eight eligible abstracts with unremarkable findings presented at conferences was subsequently published in full-text or had their data shared despite thoroughly contacting the authors. More efforts should be taken with regard to dissemination of data and transparency as well as complete reporting of data among investigators to facilitate further statistical analyses (899).

Moreover, while the overwhelming majority of studies adjusted their analyses for patient risk factors, some investigators were not clear if their statistical analyses were adjusted for any covariates (Figure 4.16 [Appendix]). There was also some inconsistency among researchers as to which covariates needed to be adjusted for situations in which the toxicity outcome assessed was the same.

4.7.9 Duplicated data can induce biases and over-estimate pharmacogenomic effects

In-depth analysis showed considerable overlap among samples analysed across studies (i.e. multiple publications used data derived from a single study), particularly studies with positive findings. Around half of the included studies used cohorts from the same clinical trial or research centre over the same period. This can result in over-estimation of PG effects and induce bias in many ways (900).

Dependence can occur whether the same participant samples were utilised in individual studies to estimate multiple effect sizes for the same or interrelated toxicity outcomes resulting in dependent sampling errors, or for dissimilar toxicity outcomes assuming independent sampling errors. Dependence might arise in both the former (i.e. correlated effects) and latter (i.e. hierarchical effects) scenarios (193).

Overlapping studies usually fail to cross-reference each other (901) and publications using data derived from the same patient cohort may not share a common investigator (900, 902). Thus, it is difficult to identify duplicate publications of results or decide whether publications are duplicates of a single study or separate articles. As interpreting meta-analyses of such statistically-dependent effect sizes can be misleading (903–909), I included only the study with the largest analysis and/or longest follow-up period in such instances.

4.7.10 Authors should adhere to multiplicity corrections procedures

The majority of studies included in this review have conducted many independent analyses and provided several effect sizes by investigating numerous variants and multiple indicators of toxicity outcomes. Yet, few authors have corrected for multiple testing or addressed the multiplicity issue in their analyses. This was sufficiently concerning to warrant caution of the results.

In this analysis, the ramifications of the meta-analysis multiplicity were considered (126). Thus, I decided *a priori* to correct for all statistical tests to provide a fair balance between the elimination of false positives and false negatives (910, 911). Authors of high-quality meta-analyses must adhere to the same correction for multiple testing procedures applied in primary studies.

4.7.11 Failure to incorporate interaction terms can lead to misinterpretation of pharmacogenomic effects

Potential interactions in regression analyses have not been adequately explored by the authors of the overwhelming majority of studies. Of the 87 studies included in this review, only 13 studies used genotype-treatment interactions in their analyses. The significant adverse implications of disregarding effect modifications or interaction effects in statistical analyses performed in epidemiological studies are well-documented (912). Best practice guidelines recommend the incorporation of statistical interactions in the regression models (913, 914). As the failure to investigate potential interactions in regression analyses has significant implications, caution should be exercised in the interpretation of findings from associations reported across the studies that have not used interaction terms. This analysis suggests and advocates the incorporation of interaction terms as an item in the checklist derived from the STREGA/STROBE statement.

4.7.12 More GWAS studies with larger sample sizes are needed

There were only three GWAS studies (830, 851, 893) that all explored AI-related MS-ADEs with a relatively small sample size. One study has a sample size of 400 (893), and the remaining two obtained their cases and controls from the same trial (830, 851). Such sample sizes are considered far smaller than the typical sample sizes of GWAS disease studies of polygenic traits that usually include a far larger number of participants (915–917). To identify new candidate genes, future efforts should include large-scale GWAS discovery studies investigating other endocrine agents with more diverse ADEs. This hypothesis-free approach has the potential to identify associations for rare variants or those with smaller effect sizes or variants in particular enriched pathways (918).

Yet, time-lag bias and the winner's curse are very common in genetics studies (919). The first published or discovery study usually has a greater overall effect

than subsequent studies (159, 920). To minimise over-estimation of the effect size estimates, I excluded the first published GWA study of the discovery phase from the meta-analysis. Further, studies with significant or striking findings, particularly those with high accrual of participants, are published earlier than studies with non-significant results (921, 922). Subsequent confirmatory studies that examined a specific association are thought to be driven largely by the study that first reported the association and expected to have diminishing effect sizes which may ultimately lead to rejecting the initial association as a false positive (923). This emphasises the requirement for successful replication of discovery-phase PG associations with a similar trend of effect in multiple independent non-overlapping samples (924).

4.7.13 Study limitations

A few limitations of this systematic review need to be considered. First, despite the comprehensive searches, systematic reviews are subject to bias due to their retrospective nature and are largely limited to published data. Second, I restricted my search to include English-only publications and therefore language bias is anticipated. Third, this systematic review included four theses and dissertations (866, 867, 874, 878), which can be a cause for concern. This is due to the assumed variable design quality of theses and dissertations compared with articles published in journals, as the former do not typically undergo the comparable rigorous peer-review procedure (925). Yet, dissertations and theses can have a higher quality compared to published studies (926). Besides, with a comparable level of expertise and scrutiny required to assess manuscripts as peer reviewers, I appraised and further analysed the included theses and dissertations, which scored high-quality ratings in STREGA and STROBE quality assessment criteria. Further, the inclusion of such non-traditional sources of research studies helps minimise the effect of publication bias and reduce the under-representation of relevant research, which is especially more prevalent in nascent and rapidly evolving fields such as PGx (157, 158).

4.8 Conclusions

The existing evidence regarding the potential role of PGx in endocrine therapy-related toxicity in BC is largely inconsistent. To develop a more robust body of evidence, successful replication of previously reported genomic markers in larger

cohorts with independent samples using well-designed methods is warranted. PGx of endocrine therapy-related toxicities in BC must move beyond small studies and *post-hoc* analyses of trials originally conducted to assess efficacy endpoints, which contain limited information on toxicity outcomes. This in-depth interrogation identified methodological caveats in individual studies and raised crucial issues that need to be considered when designing PGx studies. Future research efforts should aim to implement more hypothesis-free methods and expand approaches to other candidate variants. Further, more focus on premenopausal women and the formation of larger African and Asian cohorts in future investigations is warranted to facilitate generalisability in this topic.

4.9 Appendix

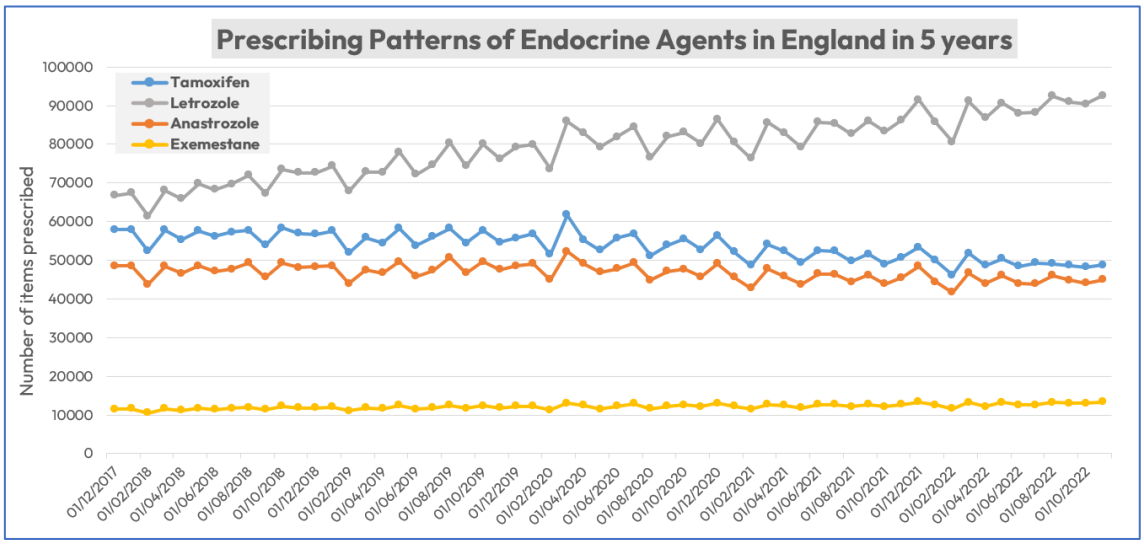


Figure 4.7 Prescribing patterns of endocrine agents in England between (12/2017- 11/2022)

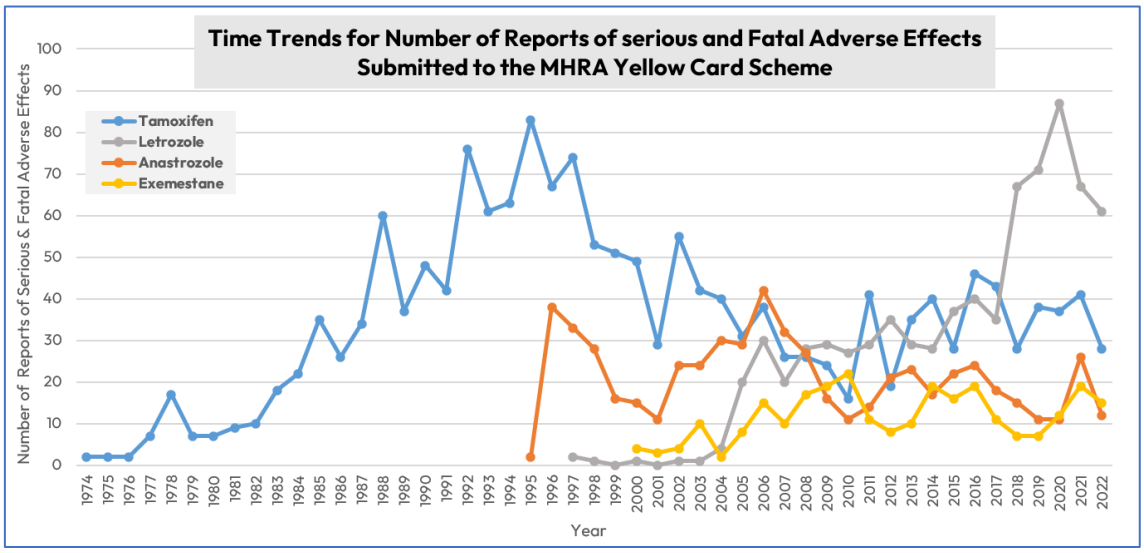


Figure 4.8 Time trends for the number of reports of serious and fatal ADEs for endocrine agents submitted to the Yellow card scheme.

Table 4.4 The search filter used to identify PGx studies of ADEs related to endocrine therapy in Embase.

1. (tamoxifen).ab,ti.
2. (letrozole).ab,ti.
3. (anastrozole).ab,ti.
4. (exemestane).ab,ti.
5. (nolvadex).ab,ti.
6. (femara).ab,ti.
7. (arimidex).ab,ti.
8. (aromasin).ab,ti.
9. ("aromatase inhibitor*").ab,ti.
10. (adjuvant).ab,ti.
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. exp animal/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
13. human/ or normal human/
14. 12 and 13
15. 12 not 14
16. 11 not 15
17. exp pharmacogenetics/

18. exp genetic polymorphism/
19. genetic variability/
20. (pharmacogenomic* or pharmacogenetic* or toxicogenetic* or polymorphism* or ''gen* varia*'' or mutation* or snp or genotype* or allele* or haplotype*).ab,ti.
21. 17 or 18 or 19 or 20
22. exp drug hypersensitivity
23. exp drug toxicity
24. ((adverse or undesirable or harms* or serious or toxic) adj3 (effect* or reaction* or event* or outcome*)).ab,ti.
25. ("adverse effect*" or "adverse reaction*" or "adverse drug reaction*" or "adverse event*" or "side effect*" or toxicit* or poisonin* or pharmacotox* or "drug hypersensitiv*" or "hypersensitiv* reaction*" or anaphyla* or "drug induced*" or "drug related" or "drug reaction*" or neurotoxic* or nephrotoxic* or hepatotoxic* or cardiotoxic* or immunotoxic* or immunocytotoxic* or cytotoxic* or myotoxic* or tolera* or intolera* or noxious or death* or fatal*).ab,ti.
26. 22 or 23 or 24 or 25
27. (breast).ab,ti.
28. (Mammary).ab,ti.
29. 27 or 28
30. 16 and 21 and 26 and 29
31. limit 30 to english language

Table 4.5 The search filter used for identification of PGx studies of ADEs related to endocrine therapy in Medline.

1. (tamoxifen).ab,ti.
2. (letrozole).ab,ti.
3. (anastrozole).ab,ti.
4. (exemestane).ab,ti.
5. (nolvadex).ab,ti.
6. (femara).ab,ti.
7. (arimidex).ab,ti.
8. (aromasin).ab,ti.
9. ("aromatase inhibitor*").ab,ti.
10. (adjuvant).ab,ti.
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. exp animals/ not humans.sh.
13. 11 not 12
14. exp Pharmacogenetics/
15. exp Polymorphism, Genetic/
16. exp Genetic Variation/
17. (pharmacogenomic* or pharmacogenetic* or toxicogenetic* or polymorphism* or "gen* varia*" or mutation* or snp or genotype* or allele* or haplotype*).ab,ti.
18. 14 or 15 or 16 or 17
19. exp Drug Toxicity/ge, pc [Genetics, Prevention & Control]
20. exp Drug Hypersensitivity/ge, pc [Genetics, Prevention & Control]
21. ((adverse or undesirable or harms* or serious or toxic) adj3 (effect* or reaction* or event* or outcome*)).ab,ti.
22. ("adverse effect*" or "adverse reaction*" or "adverse drug reaction*" or "adverse event*" or "side effect*" or toxicit* or poisonin* or pharmacotox* or "drug hypersensitiv*" or "hypersensitiv* reaction*" or anaphyla* or "drug induced*" or "drug related" or "drug reaction*" or neurotoxic* or nephrotoxic* or hepatotoxic* or cardiotoxic* or immunotoxic* or immunocytotoxic* or cytotoxic* or myotoxic* or tolera* or intolera* or noxious or death* or fatal*).ab,ti.
23. 19 or 20 or 21 or 22
24. (breast).ab,ti.
25. (Mammary).ab,ti.
26. 24 or 25
27. 13 and 18 and 23 and 26
28. limit 27 to english language

Table 4.6 The search filter used to identify PGx studies of ADEs related to endocrine therapy in Cochrane.

Date Run:	**22/03/2022 16:27:07**
ID	Search
#1	MeSH descriptor: [Pharmacogenetics] explode all trees
#2	MeSH descriptor: [Polymorphism, Genetic] explode all trees
#3	MeSH descriptor: [Genetic Variation] explode all trees
#4	(pharmacogenomic* or pharmacogenetic* or toxicogenetic* or polymorphism* or "gen* varia*" or mutation* or snp or genotype* or allele* or haplotype*):ab,ti
#5	#1 or #2 or #3 or #4 62546
#6	MeSH descriptor: [Drug-Related Side Effects and Adverse Reactions] explode all trees
#7	MeSH descriptor: [Drug Hypersensitivity] explode all trees

#8	("adverse effect*" or "adverse reaction*" or "adverse drug reaction*" or "adverse event*" or "side effect*" or toxicit* or poisonin* or pharmacotox* or "drug hypersensitiv*" or "hypersensitiv* reaction*" or anaphyla* or "drug induced*" or "drug related" or "drug reaction*" or neurotoxic* or nephrotoxic* or hepatotoxic* or cardiotoxic* or immunotoxic* or immunocytotoxic* or cytotoxic* or myotoxic* or tolera* or intolera* or noxious or death* or fatal*):ab,ti
#9	#6 or #7 or #8
#10	(tamoxifen):ab,ti
#11	(letrozole):ab,ti
#12	12 (anastrozole):ab,ti
#13	(exemestane):ab,ti
#14	(nolvadex):ab,ti
#15	(femara):ab,ti
#16	(arimidex):ab,ti
#17	(aromasin):ab,ti
#18	("aromatase inhibitor*"):ab,ti
#19	(adjuvant):ab,ti
#20	#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19
#21	(breast):ab,ti
#22	(Mammary):ab,ti
#23	#21 or #22
#24	#5 and #9 and #20 and #23

Table 4.7 PRISMA Checklist for the systematic review of PGx studies of ADEs related to endocrine therapy in breast cancer.

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Location is available here
ABSTRACT			
Abstract	2	the PRISMA 2020 for Abstracts checklist	Location is available here
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Location is available here
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Location is available here
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Location is available here
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Location is available here
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Location is available here
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Location is available here
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Location is available here
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Location is available here
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Location is available here
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Location is available here
Effect measures	12	Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.	Location is available here
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Location is available here
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Location is available here
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Location is available here
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Location is available here
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression).	Location is available here
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	N/A

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Location is available here
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Location is available here
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Location is available here
Study characteristics	17	Cite each included study and present its characteristics.	Location is available here
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Location is available here
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots.	Location is available here
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Location is available here
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Location is available here
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Location is available here 1, 2
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Location is available here
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Location is available here
	23b	Discuss any limitations of the evidence included in the review.	Location is available here
	23c	Discuss any limitations of the review processes used.	Location is available here
	23d	Discuss implications of the results for practice, policy, and future research.	Locations are available here 1, 2, 3, 4, 5, 6, 7
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Location is available here
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Location is available here
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Location is available here
Competing interests	26	Declare any competing interests of review authors.	Location is available here
Availability of data, code and other	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from	N/A

Section and Topic	Item #	Checklist item	Location where item is reported
materials		included studies; data used for all analyses; analytic code; any other materials used in the review.	

Table 4.8 The descriptive statistics for each criterion of the STREGA and STROBE checklists for PGx studies of ADEs related to endocrine therapy in breast cancer.

Study [Author_Year]	Title & abstract	Introduction	Methods								Results			Discussion		Total score %	Interaction effects used appropriately
	Study's design & summary of method and results	Clear statement of rationale, objectives, and hypothesis	Study design & setting	Clear eligibility criteria for study participants	Clear definition of all variables and the outcome	Data sources measurement	Bias	Replicability of statistical methods	Reported Hardy-Weinberg equilibrium	If applicable, mixed ethnicities addressed statistically	Number of participants at each stage of the study	Sufficient descriptive demographic data	Statement of genotype frequencies and outcome data	Limitations	Generalisability & Consideration of population		
Al-Mamun 2017	+	+	+	+	+	+	-	+	-	N/A	+	+	+	+	+	85.71	-
Bai 2018	+	+	+	+	+	+	+	+	+	N/A	+	+	+	+	+	100	+
Basmadjian 2019	+	+	+	+	+	+	+	+	+	N/A	+	+	+	+	+	100	+
Knight 2017	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100	+
Abed 2022	+	+	+	+	+	+	-	+	-	N/A	+	+	+	-	-	71.43	-
Abramson 2006	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	93.33	+
Abubakar 2019	+	+	+	+	+	+	+	+	-	N/A	+	-	-	+	+	78.57	-
Argalacsova 2017	+	+	+	+	+	+	-	+	+	N/A	+	+	+	+	-	85.71	-
Baatjes 2020	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	86.67	-
Baxter 2014	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	93.33	-
Bojanic 2020	+	+	+	+	+	+	-	+	+	N/A	+	+	+	+	+	92.86	-
Bonanni 2006	-	+	+	+	-	+	-	+	-	N/A	+	-	+	-	+	57.14	-
Borrie 2018	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	93.33	-
Borrie 2020	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	93.33	-
Cajal 2010	+	+	+	+	+	+	-	+	-	N/A	+	+	+	+	+	85.71	-
Chu 2007	+	+	+	+	+	+	+	+	-	+	+	-	+	+	-	80	-
Colomer 2008	+	+	+	+	-	+	-	+	-	N/A	+	+	+	+	+	78.57	-
Damodaran 2012	+	+	+	+	+	+	+	+	+	N/A	+	+	-	+	+	92.86	-
Dempsey 2018	-	+	+	+	+	-	-	+	+	+	+	+	+	+	+	80	-
Dezentje 2014	+	+	+	+	+	+	+	+	+	N/A	+	+	+	+	+	100	-
Dieudonné 2014	+	+	+	+	+	+	-	+	+	N/A	+	+	+	+	+	92.86	-
Duggan 2003	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	86.67	-
Fontein 2014	+	+	+	+	+	+	+	+	+	N/A	+	+	+	+	+	100	-
Fox 2016	+	+	+	+	+	+	-	+	+	-	+	+	-	-	-	66.67	-
Garber 2010	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	86.67	-
Garcia-Giralt 2013	+	+	+	+	+	+	+	+	+	N/A	+	+	+	+	-	92.86	-
Georgopoulos 2006	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	86.67	-

Gervasini 2017	+	+	+	+	+	+	-	+	-	N/A	+	+	+	+	+	85.71	-
Goetz 2005	+	+	+	+	+	+	-	+	-	-	+	+	+	+	+	80.00	-
Günaldı 2014	+	+	+	+	-	+	-	+	-	N/A	+	+	+	-	+	71.43	-
Hartmaier 2012	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	86.67	-
He 2020	+	+	+	+	+	+	+	+	+	N/A	+	+	+	+	+	100	-
Henry 2009	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	86.67	-
Henry 2010	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	86.67	-
Henry 2013	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	86.67	-
Hertz 2016	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	86.67	-
Hertz 2021	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100	-
Hertz 2022	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	93.33	+
Ho 2020	+	+	+	+	+	+	-	+	-	-	+	+	+	+	+	80	-
Ingle 2010	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100	-
Irvin, Jr. 2011	-	+	+	+	+	+	-	+	-	+	+	+	+	+	+	80	-
Jager 2013	+	+	+	+	+	+	+	+	-	N/A	+	+	+	+	+	92.86	-
Jansen 2018	+	+	+	+	+	+	+	+	-	-	+	+	+	-	-	73.33	-
Jin 2008	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	86.67	+
Johansson 2016	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	86.67	+
Kamdem 2019	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100	-
Kiyotani 2012	+	+	+	+	+	+	-	+	-	N/A	+	+	+	+	-	78.57	-
Koukouras 2012	+	+	+	+	+	+	-	+	+	N/A	+	+	-	+	+	85.71	-
Kovac 2015	+	+	+	+	+	+	+	+	-	N/A	+	+	+	+	-	85.71	-
Leyland-Jones 2015 (1)	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100	+
Leyland-Jones 2015 (2)	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100	+
Lintermans 2016	+	+	+	+	+	+	+	+	+	N/A	+	+	+	+	+	100	-
Liu 2013	-	-	+	+	+	+	+	+	+	N/A	+	+	-	+	-	71.43	-
Liu 2014	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	86.67	-
Lorizio 2012	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	86.67	-
Mao 2011	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100	-
Mazzuca 2016	+	+	+	+	+	+	+	+	-	-	+	+	+	+	-	80	-
Miranda 2021	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100	-
Napoli 2013	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	86.67	-
Napoli 2015	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	93.33	-
Niravath 2018	+	+	+	+	+	+	+	+	-	N/A	+	+	+	+	+	92.86	-
Ntukidem 2008	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100	-
Oesterreich 2015	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	86.67	-
Ohnishi 2005	+	+	+	+	+	+	-	+	-	N/A	+	+	+	+	+	85.71	-
Okishiro 2009	+	+	+	+	+	+	+	-	-	N/A	+	+	-	+	+	78.57	-
Onitilo 2009	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	86.67	-
Park 2011	+	+	+	+	+	+	+	+	+	N/A	+	+	+	-	-	85.71	-
Pineda-Moncusi 2017	+	+	+	+	+	+	+	+	-	N/A	+	+	+	+	-	85.71	-
Rangel-Méndez 2019	+	+	+	+	+	+	-	+	+	N/A	+	+	+	+	+	92.86	-

Regan 2012	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	93.33	+
Rodríguez-Sanz 2015	+	+	+	+	+	+	+	+	+	N/A	+	+	+	+	+	100	-
Rolla 2012	+	+	+	+	+	+	-	+	-	N/A	+	-	+	+	+	78.57	-
Romero 2020	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100	-
Ruddy 2013	+	+	+	+	+	+	-	+	-	-	+	+	+	+	+	80	-
Santa-Maria 2016	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100	+
Servitja 2015	-	+	+	+	+	-	-	-	-	N/A	+	+	+	+	-	57.14	-
Sestak 2012	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	86.67	-
Tamura 2020	-	+	+	+	+	+	+	+	-	N/A	+	+	+	+	-	78.57	-
Tucker 2005	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100	-
Umamaheswaran 2020	+	+	+	+	+	+	-	+	+	N/A	+	+	+	+	+	92.86	+
Umamaheswaran 2021	+	+	+	+	+	+	+	+	+	N/A	+	+	+	+	+	100	-
Wang 2013	+	+	+	+	+	+	+	+	-	N/A	+	+	+	+	+	92.86	-
Wang 2015	+	+	+	+	+	+	+	+	-	N/A	+	+	+	+	+	92.86	-
Weng 2013	+	+	+	+	+	+	+	+	-	N/A	+	+	-	+	+	85.71	-
Wickramage 2017	+	+	+	+	+	+	-	+	-	N/A	+	+	+	+	+	85.71	-
Zembutsu 2017	+	+	+	+	+	+	-	+	+	N/A	+	+	+	+	-	85.71	-
Zhou 2022	+	+	+	+	+	+	+	+	-	N/A	+	+	+	+	+	92.86	+

Table 4.9 Meta-analyses of PGx studies of ADEs related to endocrine therapy in breast cancer.

System Organ Class	Toxicity outcomes	Drug(s)	Genomic variant	Allele	Pooled effect estimate (95% Conf. Interval)	I² (%), p-value (Cochran's Q)	Studies (N)	Ref.
Vascular Disorders	VTE	Tam	*Factor II* (or rs1799963)	A	OR=1.603 (0.500, 5.134), *p*=0.427	(0.0%), 0.533	3	(814, 819, 855)
	VTE	Tam	*Factor V Leiden* (or rs6025)	A	OR=2.552 (1.132, 5.755), *p*=0.024	(0.0%), 0.370	3	(814, 819, 855)
	Thromboembolic Events	Tam	*Factor V Leiden* (or rs6025)	A	**OR=3.474 (1.955, 6.174), *p*<0.0001***	(3.0%), 0.378	4	(814, 819, 829, 855)
	MS-ADEs	Anas; Exe; Letr	rs10046	T	OR=0.844 (0.676, 1.054), *p*=0.134	(0.0%), 0.422	5	(312, 834, 861, 884, 891)
	MS-ADEs	Letr	rs10046	C	HR=0.993 (0.852, 1.157), *p*=0.927	(0.0%), 0.928	2	(308, 310)
	MS-ADEs	Anas; Exe; Letr	rs10459592	G	OR=0.817 (0.498, 1.340), *p*=0.422	(85.1%), 0.010	2	(861, 884)
	MS-ADEs	Letr; Exe	rs1062033	G	OR=0.879 (0.560, 1.381), *p*=0.577	(0.0%), 0.568	2	(852, 884)
	MS-ADEs	Anas; Exe; Letr	rs11849538	G	OR=0.993 (0.695, 1.420), *p*=0.970	(0.0%), 0.665	4	(869, 888, 891, 892)
	MS-ADEs	Anas; Exe; Letr	rs16964189	T	OR=0.808 (0.441, 1.478), *p*=0.488	(0.0%), 0.379	2	(852, 891)
	MS-ADEs	Anas; Exe; Letr	rs2073618	G	OR=1.045 (0.790, 1.384), *p*=0.757	(88.0%), <0.0001	4	(859, 861, 888, 891)
	MS-ADEs	Anas; Exe; Letr	*PuvII* (or rs2234693)	C	**OR=1.636 (1.250, 2.141), *p*<0.0001***	(43.1%), 0.153	4	(859, 861, 888, 891)
	MS-ADEs	Anas; Letr	rs2369049	G	OR=0.916 (0.545, 1.538), *p*=0.740	(0.0%), 0.925	2	(869, 892)
	MS-ADEs or related discontinuation	Letr	rs28757184	A	HR=0.747 (0.427, 1.308), *p*=0.308	(0.0%), 0.648	2	(308, 310)
	MS-ADEs	Anas; Letr	rs4646	T	OR=1.007 (0.674, 1.505), *p*=0.974	(61.0%), 0.109	2	(845, 884)

Musculoskeletal & Connective Tissue Disorders	MS-ADEs	Letr	rs4646	A	HR=0.933 (0.789, 1.103), *p*=0.417	(80.0%), 0.025	2	(308, 310)
	MS-ADEs	Anas; Exe; Letr	rs4775936	T	OR=1.319 (1.046, 1.664), *p*=0.019	(84.7%), <0.0001	4	(846, 861, 884, 888)
	MS-ADEs or related discontinuation	Anas; Letr	rs4775936	T	HR=1.355 (1.009, 1.819), *p*=0.043	(7.5%), 0.299	2	(310, 888)
	MS-ADEs	Letr; Exe	rs6493497	A	OR=1.218 (0.646, 2.296), *p*=0.541	(0.0%), 0.638	2	(852, 884)
	MS-ADEs	Anas; Exe; Letr	rs700518	G	**OR=0.419 (0.247, 0.710), *p*=0.001***	(90.8%), 0.001	2	(861, 884)
	MS-ADEs	Letr	rs700518	C	HR=1.058 (0.853, 1.312), *p*=0.606	(0.0%), 0.909	2	(308, 310)
	MS-ADEs	Letr; Anas	rs7158782	G	OR=0.934 (0.585, 1.490), *p*=0.774	(0.0%), 0.893	2	(869, 892)
	MS-ADEs	Letr; Anas	rs7159713	G	OR=0.921 (0.546, 1.554), *p*=0.759	(0.0%), 0.942	2	(869, 892)
	MS-ADEs	Anas; Exe; Letr	rs7176005	T	OR=0.947 (0.565, 1.588), *p*=0.837	(0.0%), 0.964	3	(852, 884, 891)
	MS-ADEs	Anas; Exe; Letr	rs727479	G	OR=0.909 (0.565, 1.463), *p*=0.694	(0.0%), 0.867	4	(834, 861, 869, 884)
	MS-ADEs	Anas; Exe; Letr	rs749292	A	OR=1.051 (0.706, 1.567), *p*=0.806	(0.0%), 0.619	4	(834, 861, 869, 884)
	MS-ADEs	Anas; Exe; Letr	rs6163	A	OR=1.678 (1.040, 2.707), *p*=0.034	(41.3%), 0.182	3	(856, 861, 891)
	MS-ADEs	Anas; Exe; Letr	rs9322336	C	OR=0.654 (0.429, 0.995), *p*=0.047	(40.7%), 0.194	2	(888, 891)
	MS-ADEs	Anas; Exe; Letr	*XbaI* (rs9340799)	G	OR=0.807 (0.626, 1.039), *p*=0.097	(85.7%), 0.001	3	(848, 888, 891)
	MS-ADEs	Anas; Exe; Letr	rs7984870	C	**OR=1.455 (1.184, 1.786), *p*<0.0001***	(60.5%), 0.079	3	(859, 888, 891)
	MS-ADEs	Anas; Exe; Letr	rs934635	A	OR=2.218 (1.166, 4.219), *p*=0.015	(75.0%), 0.046	2	(852, 891)
	MS-ADEs	Letr	rs936308	G	HR=1.082 (0.836, 1.399), *p*=0.551	(0.0%), 0.845	2	(308, 310)
Vascular and/or Skin & Subcutaneous Tissue Disorders	VM-ADEs	Letr; Exe	rs10046	T	OR=0.641 (0.484, 0.848), *p*=0.002	(0.0%), 0.830	2	(312, 884)
	VM-ADEs	Letr; Exe	rs1062033	G	OR=1.198 (0.748, 1.918), *p*=0.453	(0.0%), 0.375	2	(852, 884)
	VM-ADEs	Tam	*PuvII* (or rs2234693)	C	HR=0.966 (0.867, 1.076), *p*=0.527	(67.8%), 0.078	2	(307, 309)
	VM-ADEs	Tam	*ESR2–02* (or rs4986938)	A	HR=0.969 (0.826, 1.138), *p*=0.704	(87.7%), 0.004	2	(307, 823)
	VM-ADEs	Letr; Exe	rs6493497	A	OR= 1.512 (0.786, 2.909), *p*=0.216	(0.0%), 0.519	2	(852, 884)
	VM-ADEs	Letr; Exe	rs7176005	T	OR=1.499 (0.740, 3.038), *p*=0.261	(63.6%), 0.098	2	(852, 884)
	HF	Tam	*CYP3A5*3* (or rs776746)	G	OR=0.734 (0.341, 1.583), *p*=0.431	(11.2%), 0.324	3	(816, 817, 867)
	HF	Tam	*XbaI* (rs9340799)	G	HR=1.150 (0.940, 1.406), *p*=0.174	(84.9%), 0.010	2	(307, 309)
	Severe HF or Worsened Vasomotor HRQL	Exe	*UGT2B17*2*	Gene deletion	RR=1.037 (0.964, 1.114), *p*=0.327	(69.7%), 0.069	2	(866, 883)
Reproductive System & Breast Disorders	Vaginal Dryness	Tam	*CYP3A5*3* (or rs776746)	G	OR=1.310 (0.630, 2.727), *p*=0.470	(66.2%), 0.085	2	(817, 867)
	Vaginal Dryness or Bleeding	Tam	*SULT1A1*2* (or rs9282861)	A	OR=0.717 (0.336, 1.531), *p*=0.390	(48.8%), 0.162	2	(867, 890)
Psychiatric Disorders	Depression	Tam	*CYP3A5*3* (or rs776746)	G	OR=0.511 (0.272, 0.962), *p*=0.037	(0.0%), 0.752	2	(817, 867)
General Disorders	Severe Fatigue or Decline in Physical HRQL	Exe	*UGT2B17*2*	Gene deletion	RR=1.376 (1.087, 1.743), *p*=0.008	(59.7%), 0.115	2	(878, 883)

*__Significant associations after multiple testing corrections__. __Abbreviations__: HF=Hot Flushes; VTE=Venous Thromboembolic Events; MS-ADEs=Musculoskeletal ADEs [Muscle pain or Arthralgia]; VM-ADEs=Vasomotor ADEs [Hot Flushes/Night Sweats]; HRQL=Physical Health-Related Quality of Life; Tam=tamoxifen; Anas=Anastrozole; Exe=Exemestane; Letr=Letrozole.

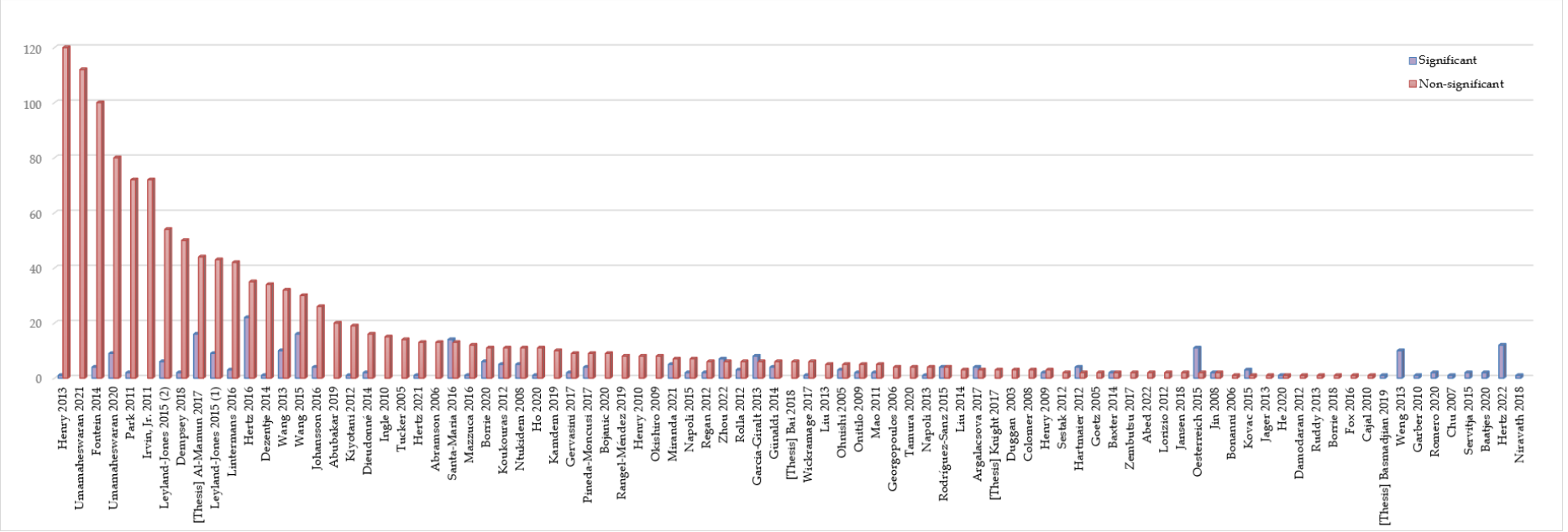


Figure 4.9 Number of associations in PGx studies of ADEs related to endocrine therapy in breast cancer.

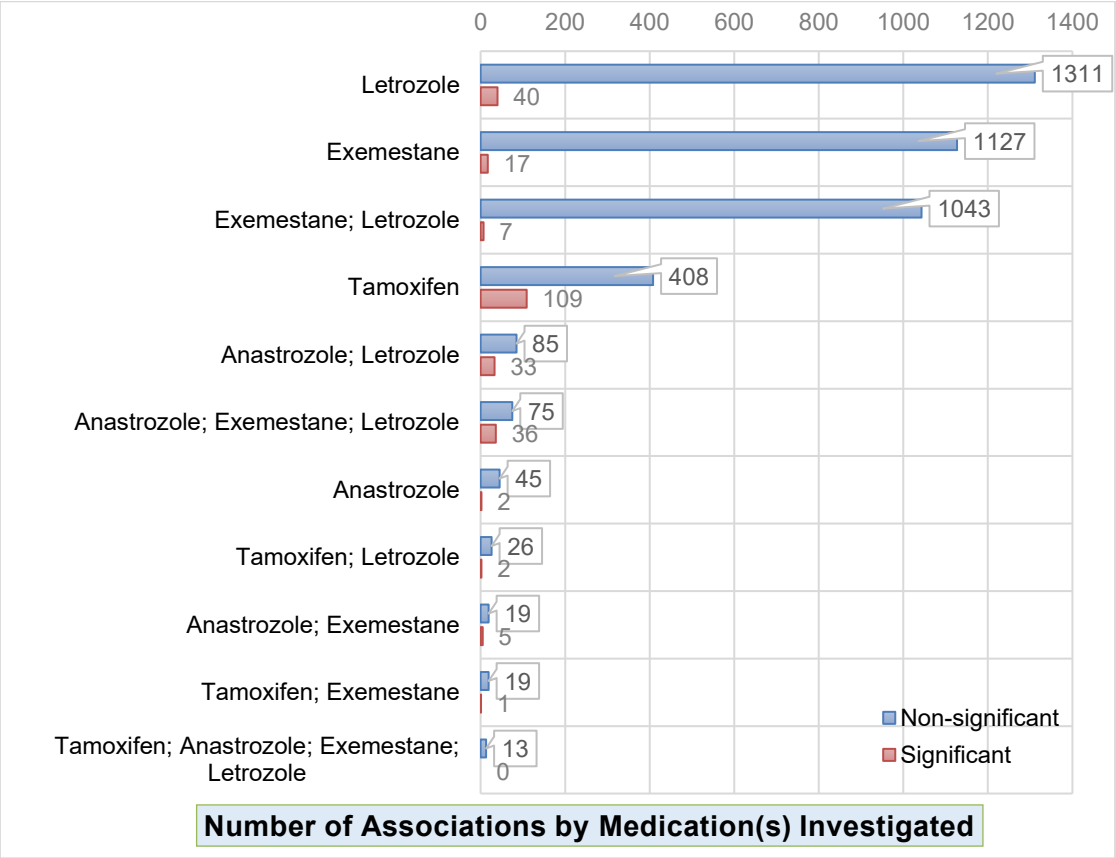


Figure 4.10 Number of associations in PGx studies of ADEs related to endocrine therapy in breast cancer by medication(s) investigated.

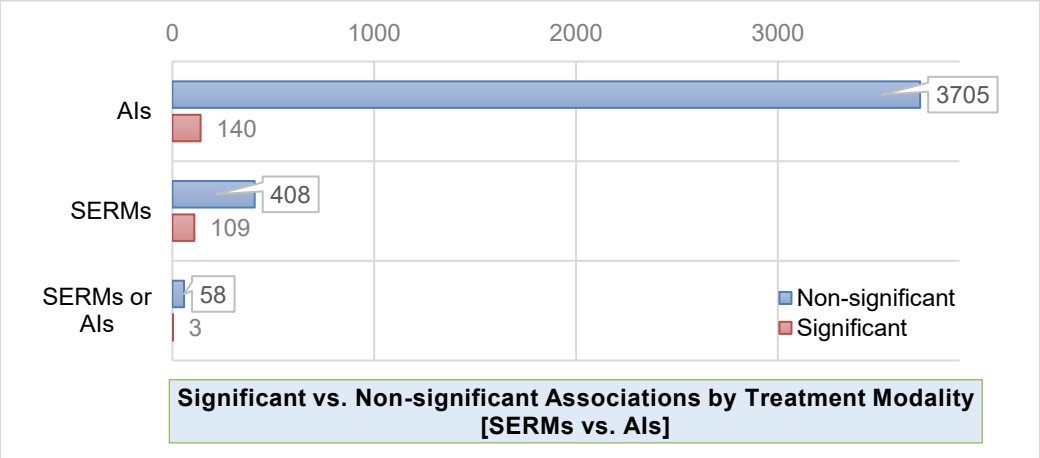


Figure 4.11 Number of associations in PGx studies of ADEs related to endocrine therapy in breast cancer by treatment modality

**Selective Estrogen Receptor Modulators (SERMs) included [Tamoxifen], Aromatase Inhibitors (AIs) included [Anastrozole; Exemestane; Letrozole]*

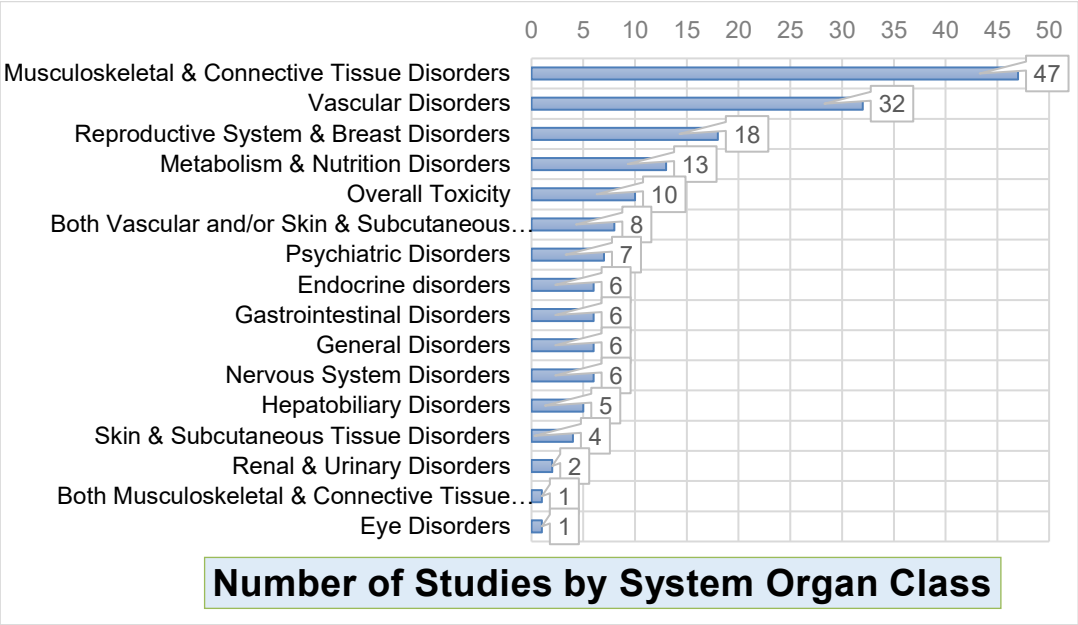


Figure 4.12 Number of studies included in the systematic review of PGx studies of ADEs related to endocrine therapy in breast cancer by system organ class.

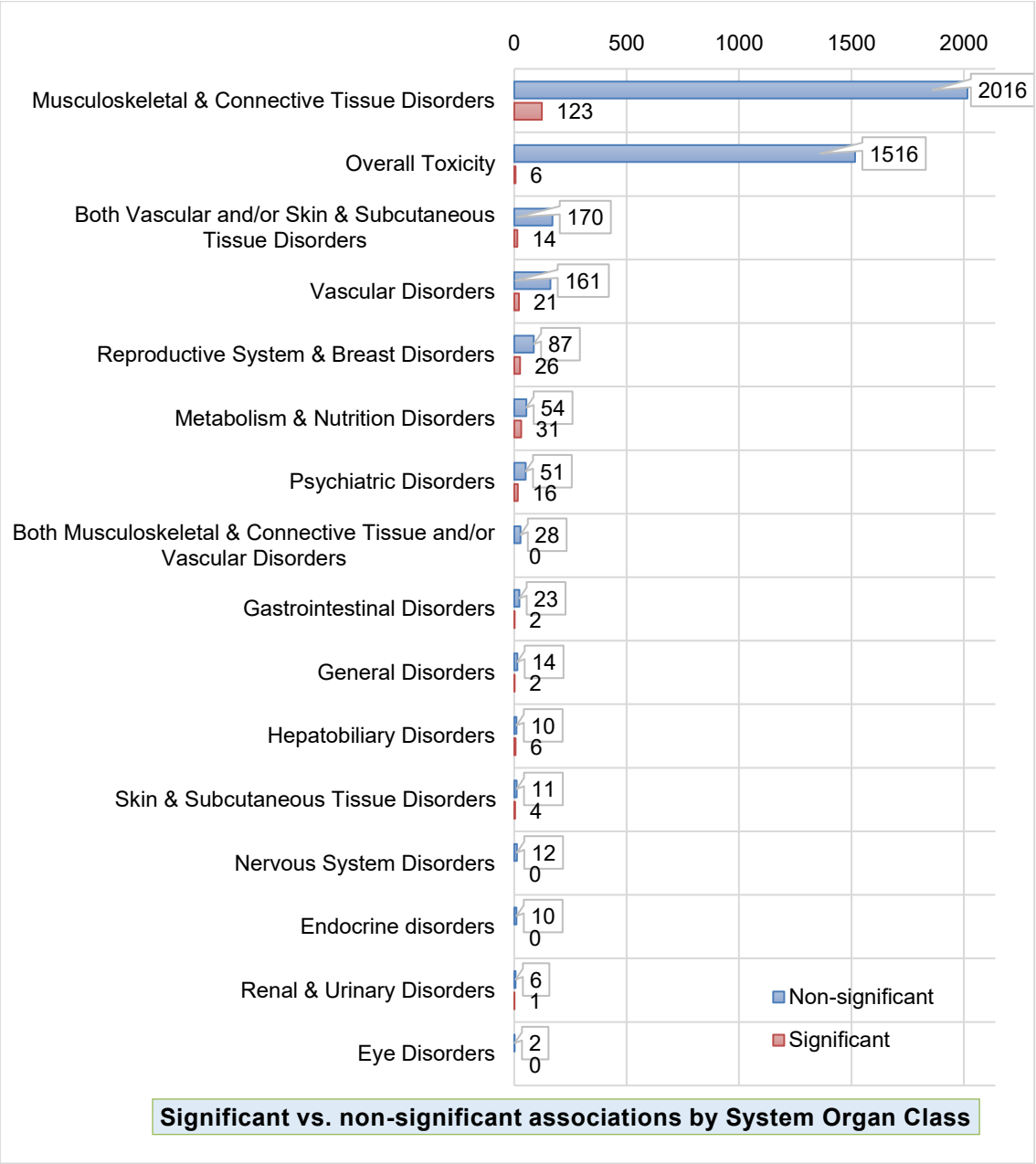


Figure 4.13 Number of associations in PGx studies of ADEs related to endocrine therapy in breast cancer by system organ class.

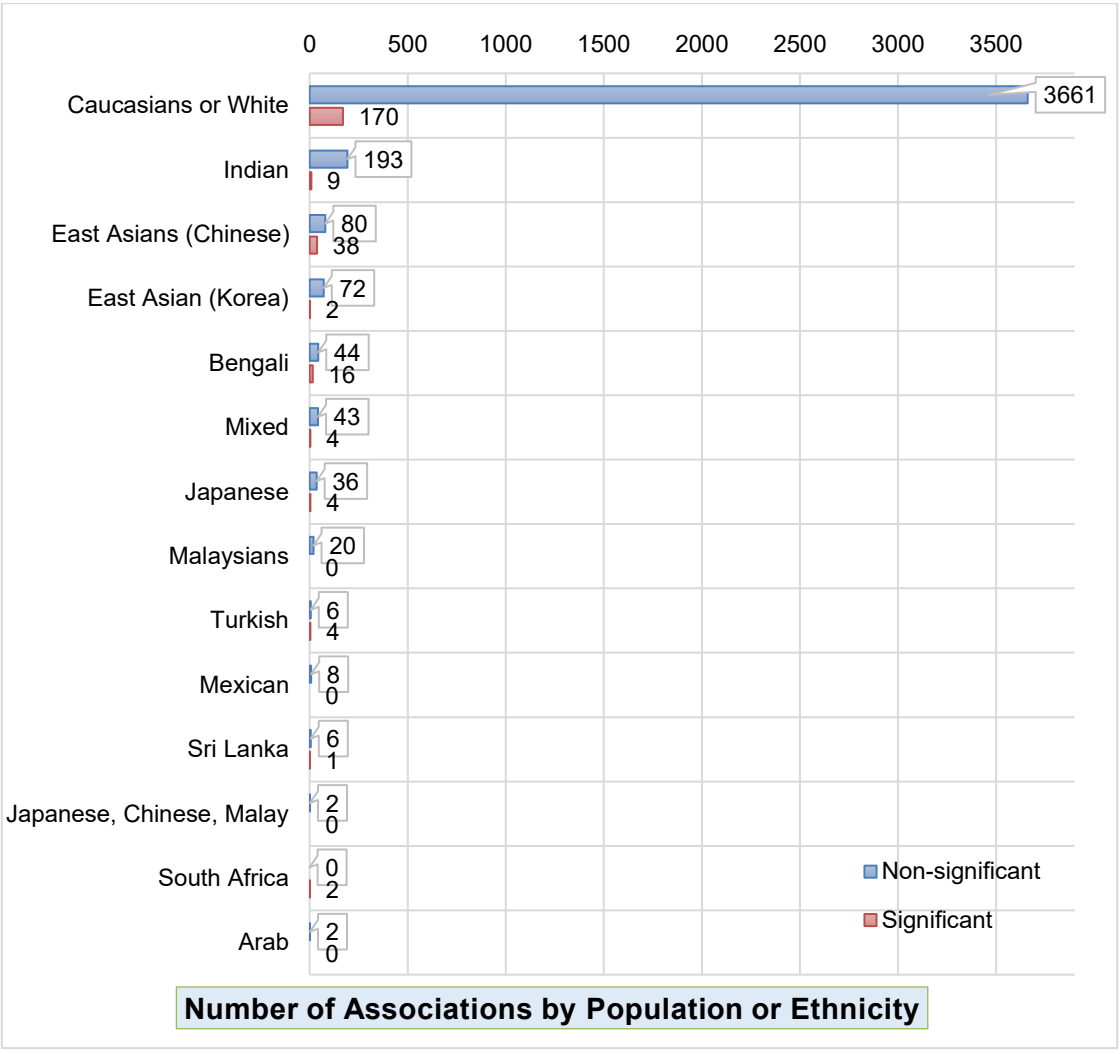


Figure 4.14 Number of associations in PGx studies of ADEs related to endocrine therapy in breast cancer by country or ethnicity.

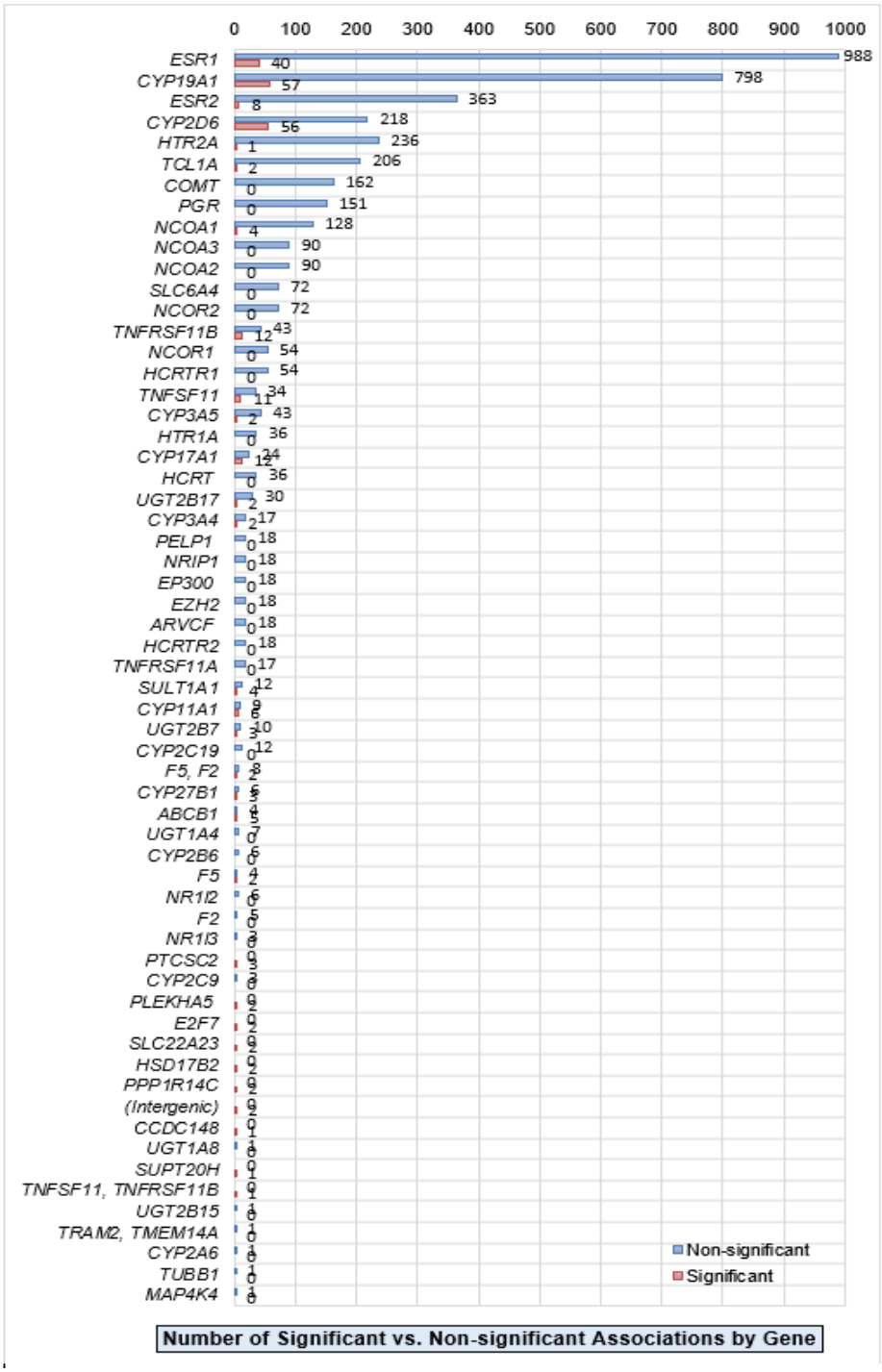


Figure 4.15 Number of associations in PGx studies of ADEs related to endocrine therapy in breast cancer by gene.

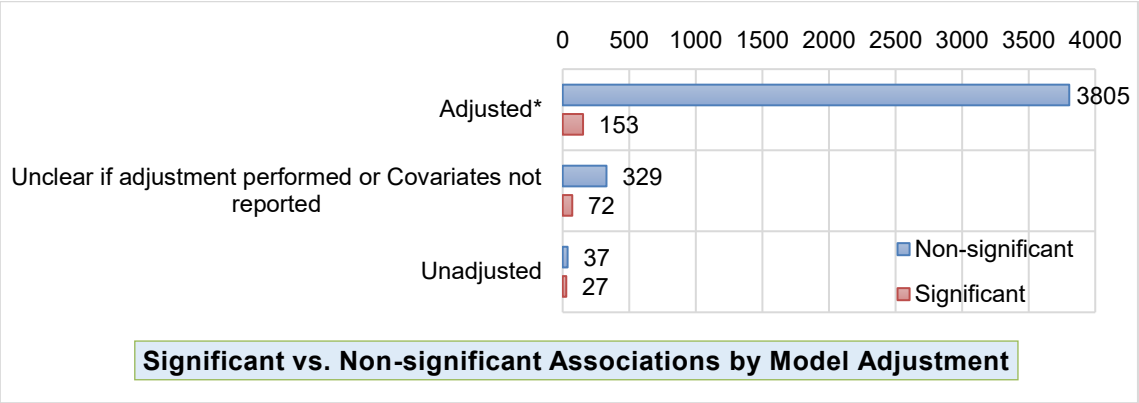


Figure 4.16 Number of associations by adjustment status for covariates for PGx of ADEs related to endocrine therapy in breast cancer.

**Adjusted or selected matched controls or there were no significant differences between the two groups in their clinical variables or none of the clinical variables were significantly associated with phenotype of interest.*

5 Chapter Five. No evidence of Associations of Pharmacogenomic Variants with Medically Important Adverse Effects Related to Endocrine Therapy in Breast Cancer in UK Biobank

5.1 Abstract

Background/Aim Previous PGx studies showed that patients carrying specific genomic variants are at a higher risk of ADEs associated with endocrine therapy. However, associations from these studies need to be replicated and validated to develop a more robust body of evidence regarding their potential clinical utility. This study sought to assess previously reported associations between variants and MIADEs among UKBB patients treated with endocrine agents.

Materials and methods I assessed previously published associations between SNVs and MIADEs related to endocrine therapy in the UKBB female participants who reported taking endocrine agents. This was achieved by fitting both a main effects model and interaction terms in the regression models.

Results: There were 2,729 female participants of European ancestry reported taking endocrine agents in the UKBB. No significant interactions were found between 41 variants and endocrine treatment in relation to either continuous measurements or incident MIADEs in women taking endocrine agents in the UKBB.

Conclusion: This data does not support the previously reported PG associations of endocrine therapy-induced MIADEs in BC. Based on the current level of evidence, PG testing in this context should not be considered for personalised recommendations in clinical practice.

5.2 Introduction

5.2.1 Successful replication of pharmacogenetic markers may facilitate implementation of personalised treatment in BC

Prior PGx studies investigating the association between genomic variants and endocrine therapy-related ADEs in BC patients have exhibited mixed results. Further, previous findings have been subjected to substantial heterogeneity and

limited by small sample size and sub-optimal methodological rigour. Also, most of these studies were cohorts of BC patients with specific BC stages or comorbidities. Hence, it is essential to determine the robustness and successfully replicate these findings in independent and well-performed large cohorts. Here, I conducted an association study for MIADEs associated with endocrine therapy in female participants in the UKBB (682). This replication attempt is a step forward on whether or not these associations may be considered in clinical settings as a means of preventing endocrine therapy-related MIADEs.

5.3 Aims

I. To assess whether previously reported associations between SNVs and biochemical markers or MIADEs replicate in the UKBB patients treated with endocrine agents.

5.4 Objectives

I. To construct a list of variants significantly associated with MIADEs related to endocrine therapy in BC.
II. To evaluate and determine the robustness of previously reported positive findings between SNVs and MIADEs related to endocrine therapy in BC.

5.5 Materials and Methods

5.5.1 Description of Study Population

The description of the study population and treatment/medication Field ID used are detailed in 3.5.3.1. Women who self-reported taking endocrine therapy at the baseline assessment for BC treatment or prevention were included. Endocrine agents included tamoxifen and 3rd generation AIs (Anastrozole, Exemestane, Letrozole). Treatments and medication codes used in this study are listed in (Appendix

Table *5.5* [Appendix]). The key characteristics of study participants (e.g., age, BMI, menopausal status) were described.

5.5.2 Ascertainment of biomarkers, adverse drug effects and other phenotypes

Having reviewed the literature and extracted relevant information from previously published studies, every effort was made to examine MIADEs comparable to those reported in the initial papers. This analysis is restricted to MIADEs, which are defined as per 2.5.2.2. I performed two distinctive analyses to examine the MIADEs, the first using baseline measurement data alone and the second utilising data from baseline assessment along with that from follow-up visits and/or updated HES.

Details about the ascertainment of ADEs, diagnoses and other phenotypes are available in 3.5.3.2. Data Field IDs and codes used for the biomarkers, incident phenotypic endpoints of interest (i.e. MIADEs after initiation of endocrine therapy) and other phenotypes used as covariates are detailed in (Table 5.6 & Table 5.7 [Appendix]).

Menopausal status at the baseline UKBB visit was determined based on self-reported mode of menopause and menstrual history. Women who self-reported to have regular menses were defined as premenopausal and those who had natural menopause or induced menopause due to surgery (i.e. hysterectomy or bilateral oophorectomy) were defined as postmenopausal. This resulted in three categories: premenopausal women, postmenopausal women and those with undefined mode of menopause.

5.5.3 SNVs selection and genotyping

SNVs previously described and reported to be significantly associated with MIADEs related to endocrine therapy were selected to be subsequently interrogated in the UKBB. I utilised microarray data produced in the UKBB (682). The direct genotyping dataset underwent stringent quality control (683) and the SNVs I extracted from the imputed data (682) were all imputed with high confidence >99%.

5.5.4 Statistical methods and data analysis

In an attempt at replication, regression analyses were performed to test the associations between variants and MIADEs as per how they were reported in the

initial papers. I fitted a main effects model for the risk of MIADEs into the multivariate regression models. In addition, I conducted the statistical analyses by fitting interaction terms into the multivariate regression models to test the interaction between endocrine treatment and genotypes. Associations between SNVs and the relevant biochemical markers (continuous variables) and incident MIADEs (discrete variables) were analysed using multivariate linear and logistic regression models, respectively. More details about the statistical methods employed are available at 3.5.4.2. The *regress* and *logistic* commands were used to conduct the linear and logistic regression analyses, respectively. If applicable, analyses were stratified by menopausal status as per the initial studies.

5.5.5 Ethical approval

Information on the ethical approval for this study can be found at 3.5.5.

5.6 Results

5.6.1 I identified twenty-four previously published studies

Having reviewed the literature, I identified 24 previously published studies (307, 308, 847, 848, 853, 855, 857–859, 862, 865, 867, 815, 870, 872, 886, 890, 821, 822, 825, 829, 840, 841, 844) which had investigated the PGx of endocrine therapy related MIADEs (Table 5.1). Studies included in this analysis were grouped by system organ class, treatment modality, number of SNVs and related MIADEs (Table 5.2). Musculoskeletal and reproductive MIADEs were the most analysed outcomes being investigated by 42% and 21% of studies, respectively (Figure 5.3 [Appendix]).

Table 5.1 Main characteristics of the studies included in this analysis

Study first Author & Reference	Year	Drug(s)	Genes	SNV ID or Alternate names	Adverse Drug Event or Parameter	Menopausal status	Sample	Study size/ Ethnicity or Country	Study type
Al-Mamun (867)	2017	Tamoxifen	*UGT2B7* *CYP2D6*	UGT2B7*2 CYP2D6*4 CYP2D6*10	Depression	Pre-, peri- and postmenopausal	Blood	(N=388), Bangladesh	Cohort
Argalacsova (870)	2017	Tamoxifen	*ABCB1*	rs1045642	Endometrial hyperplasia or cancer	Pre- and postmenopausal	Blood	(N=258), Czech Republic	Cohort
Baatjes (886)	2020	Anastrozole; Exemestane; Letrozole	*CYP19A1*	rs10046	Bone loss (bone mineral density) at total hip, lumbar spine	Postmenopausal	Blood	(N=72), South Africa	Nested study within a prospective cohort
Chu (821)	2007	Tamoxifen	*CYP3A4*	CYP3A4*1B	Endometrial cancer	Pre- and postmenopausal	Blood	(N=126) (cases=63; controls=63), European	Case/control
Dieudonné (853)	2014	Tamoxifen	*CYP2D6*	rs3892097	Double endometrial thickness/Hyperplasia	Postmenopausal	Blood	(N=184), Belgium	Cohort
Garber (829)	2010	Tamoxifen	*F5*	rs6025	Thromboembolic events	Pre-, peri- and postmenopausal	Blood	(N=412) (cases=141; controls=271), United States (mixed)	Case/control
Hartmaier (840)	2012	Tamoxifen	*NCOA1*	rs1804645	Bone loss (bone mineral density) at lumbar spine	Pre-, peri- and postmenopausal	Blood	(N=111), Mostly Caucasian	Substudy of prospective observational cohort
Koukouras (841)	2012	Anastrozole; Exemestane; Letrozole	*ESR1*	XbaI (rs9340799)	Endometrial thickness	Postmenopausal	Blood	(cases=87; controls=80)	Prospective case-control study
		Anastrozole; Exemestane; Letrozole	*ESR1*	XbaI (rs9340799) PvuII (rs2234693)	LDL serum levels, Triglycerides serum levels				

Kovac (855)	2015	Tamoxifen	*F5*	rs6025	Venous thromboembolism	Pre- and postmenopausal	Blood	(N=150) (cases=50; controls=100), Serbia	Prospective case-control study
Leyland-Jones [2] (307)	2015	Letrozole	*ESR1* *ESR2*	rs2077647 rs4986938	Grade 3-4 osteoporosis or bone fractures	Postmenopausal	FFPE primary breast cancer tissue #	(N=1940) [Predominantly European Caucasian population]	Post-hoc of randomised, double-blind phase III trial
Leyland-Jones [1] (308)	2015	Tamoxifen	*CYP19A1*	rs4646	Grade 3-4 osteoporosis or bone fractures	Postmenopausal	FFPE primary breast cancer tissue #	(N=4580) patients on tamoxifen and/or letrozole [Predominantly European Caucasian population]	Post-hoc of randomised, double-blind trial
		Letrozole	*CYP19A1*	rs936308					
Mazzuca (865)	2016	Anastrozole; Letrozole	*CYP19A1*	rs4646	Osteoporosis (bone mineral density) at lumbar spine and proximal femur	Postmenopausal	Blood	(N=45), Italy	Retrospective cohort
Miranda (890)	2021	Tamoxifen	*CYP3A5* *CYP3A5*	CYP3A5*3	Endometrial hyperplasia	Pre- and postmenopausal	Blood	(N=162), Chilean	Retrospective case-control study
Napoli (844)	2013	Anastrozole; Exemestane; Letrozole	*CYP19A1*	rs700518	Bone loss (bone mineral density) at spine, hip and femur	Postmenopausal	Blood	(N=97), United States	Longitudinal prospective observational study
Ntukidem (822)	2008	Tamoxifen	*ESR1* *ESR2*	XbaI (rs9340799) ER-β (rs4986938)	Total cholesterol, Triglycerides, HDL-cholesterol, LDL-cholesterol	Postmenopausal	Blood	(N=134), 92% Caucasians	Substudy of prospective observational cohort
Oesterreich (857)	2015	Letrozole; Exemestane	*CYP19A1* *ESR1* *ESR2*	rs6493497 rs4870061 rs9322335 rs10140457	Bone loss [T score at the spine or hip]	Postmenopausal	Blood	(N=123 on letrozole; N=101 on exemestane), United States	

			HTR2A	rs3742278 rs2813543					Post-hoc of prospective randomised trial
Ohnishi (815)	2005	Tamoxifen	*CYP17*	rs743572	Hepatic steatosis	Pre- and postmenopausal	Blood	(N=180), Japan	Cohort
Onitilo (825)	2009	Tamoxifen	*ESR1*	XbaI (rs9340799)	Venous thromboembolism [DVT/PE]	N/R	Blood	(N=219), white females, United States	Population-based cohort study
Rodríguez-Sanz (858)	2015	Anastrozole; Exemestane; Letrozole	*CYP11A1*	rs4077581 rs11632698 rs900798	Bone loss (bone mineral density) at femoral neck	Postmenopausal	Blood	(N= 307), Spain	Prospective, observational, clinical cohort study
Santa-Maria (862)	2016	Letrozole	*CYP19A1*	rs1062033 rs1008805 rs10046 rs2289105 rs3759811 rs700518 rs4775936 rs749292 rs4646 rs1008805	HDL, Triglycerides	Postmenopausal	Blood	(N=303), United States	Sub-analysis of a prospective multicenter randomised observational open-label trial
Wang (848)	2013	Anastrozole; Letrozole	*ESR1*	rs2234693 rs9340799	Grade ≥2 MS-ADEs	Postmenopausal	Blood	(N=436) (cases=206; controls=230), East Asian	Case/control
Wang (859)	2015	Anastrozole; Letrozole	*OPG* *RANKL*	rs2073618 rs7984870	Lumbar spine T-score or bone loss (bone mineral density) at lumbar spine	Postmenopausal	Blood	(cases=208; controls= 212), East Asian	Case/control
		Anastrozole; Letrozole	*OPG* *RANKL*	rs2073618 rs7984870	Grade ≥3 MS-ADEs	Postmenopausal	Blood	(cases=208; controls= 212), East Asian	Case/control
Weng (847)	2013	Tamoxifen	*E2F7* *PTCSC2*	rs310786 rs10983920 rs9862879	Bone loss (bone mineral density) at spine and hip	Pre-, peri- and postmenopausal	Blood	(N=245) European/Caucasian	Post-hoc of open-label,

			POLQ *SLC22A23*	rs4959825					prospective observational trial
Wickramage (872)	2017	Tamoxifen	*CYP2D6*	CYP2D6*41	Fatty liver	Pre- and postmenopausal	Blood	(N=24), Sri Lanka	Retrospective cohort

FFPE: Formalin-fixed, paraffin-embedded

Table 5.2 Studies included in this analysis grouped by system organ class, treatment modality, number of SNVs and related MIADEs

System Organ Class	Endocrine agent & SNVs (n)	Adverse Effects	Studies (n)	Reference.
Musculoskeletal Disorders	Tamoxifen (n=7), Aromatase Inhibitors (n=18)	BMD*, T-score*, Bone fractures, Osteoporosis*, MS-ADEs	(n=10)	(308, 840, 844, 847, 848, 857–859, 865, 886)
Metabolism Disorders	Tamoxifen (n=2), Aromatase Inhibitors (n=11)	Hypercholesterolaemia*, Hypertriglyceridaemia*	(n=3)	(822, 841, 862)
Hepatobiliary Disorders	Tamoxifen (n=4)	Hepatosteatosis	(n=2)	(815, 872)
Vascular Disorders	Tamoxifen (n=3)	Thromboembolic events (incl. DVT, PE)	(n=3)	(825, 829, 855)
Reproductive System Disorders	Tamoxifen (n=4), Aromatase Inhibitors (n=1)	Endometrial cancer, Endometrial Hyperplasia	(n=5)	(821, 841, 853, 870, 890)
Psychiatric Disorders	Tamoxifen (n=3)	Depression	(n=1)	(867)

* **Continuous measurements** or **binary outcomes** derived from baseline measurements.

5.6.2 I examined 41 previously reported variants

A total of 41 SNVs in 19 genes were analysed. Of these variants, 44% (n=18) were directly genotyped and 56% (n=23) were imputed. Minor allele frequency (MAF) ranged from (0.01-0.49) (Table 5.3). The SNVs in *CYP19A1* and *ESR1* were the most analysed variants (Figure 5.4 [Appendix]).

Table 5.3 The genomic variants analysed including frequencies of reference and minor alleles.

Gene	SNV ID	Variant type/Consequence	Directly genotyped or Imputed	Imputation Score R2*	Chromosome number	Position	allele 1	allele 2	Minor Allele UKBB	MAF UKBB (Unrelated Europeans)
CYP19A1	rs10046	3 Prime UTR	Genotyped	N/A	15	51502986	G	A	G	0.47
	rs1008805	Intronic	Imputed	0.990	15	51549599	G	A	G	0.42
	rs1062033	Intronic	Imputed	0.991	15	51547938	C	G	G	0.46
	rs3759811	Intronic	Imputed	1	15	51529265	T	C	T	0.49
	rs4646	3 Prime UTR	Genotyped	N/A	15	51502844	A	C	A	0.26
	rs4775936	Intronic	Imputed	0.996	15	51536022	C	T	T	0.48
	rs2289105	Intronic	Imputed	0.997	15	51507508	T	C	T	0.47
	rs6493497	Upstream	Genotyped	N/A	15	51630835	G	A	A	0.12
	rs700518	Synonymous	Genotyped	N/A	15	51529112	T	C	T	0.49
	rs936308	Intronic	Imputed	0.994	15	51581074	C	G	G	0.14
	rs749292	Intronic	Imputed	0.997	15	51558731	G	A	A	0.45
CYP11A1	rs4077581	Promoter	Imputed	1	15	74665514	C	T	C	0.30
	rs11632698	Intronic	Imputed	0.998	15	74637867	A	G	A	0.38
	rs900798	3 Prime UTR	Imputed	0.995	15	74629070	T	G	T	0.31
CYP2D6	rs1065852	Missense	Imputed	0.994	22	42526694	G	A	A	0.22
	rs1080985	Upstream	Imputed	0.991	22	42528382	C	G	C	0.23
	rs16947	Missense	Imputed	0.997	22	42523943	A	G	A	0.33
	rs3892097	Splice Acceptor	Imputed	0.992	22	42524947	C	T	T	0.21
	rs28371725	Intronic	Imputed	0.989	22	42523805	C	T	T	0.10
ESR1	rs9322335	Intronic	Imputed	0.977	6	152200129	T	C	T	0.26
	rs9340799 (XbaI)	Intronic	Genotyped	N/A	6	152163381	A	G	G	0.35
	rs2077647	Synonymous	Genotyped	N/A	6	152129077	T	C	C	0.48
	rs2234693 *(PvuII)*	Intronic	Genotyped	N/A	6	152163335	T	C	C	0.46
	rs2813543	Intronic	Imputed	0.957	6	152424478	A	G	A	0.23
	rs4870061	Intronic	Imputed	0.997	6	152237468	T	C	T	0.25
	rs10140457	Intronic	Imputed	0.994	14	64716693	A	C	C	0.02

ESR2	rs4986938	Non-coding	Genotyped	N/A	14	64699816	C	T	T	0.38
F2	rs1799963 *(F2 FII G20210A)*	3 Prime UTR	Imputed	0.950	11	46761055	G	A	A	0.01
F5	rs6025 *(FVL)*	Missense	Genotyped	N/A	1	169519049	T	C	T	0.02
CYP17A1	rs743572	5 Prime UTR	Genotyped	N/A	10	104597152	A	G	G	0.38
CYP3A4	rs2740574	Upstream	Genotyped	N/A	7	99382096	C	T	C	0.03
CYP3A5	rs776746	Splice Acceptor	Genotyped	N/A	7	99270539	C	T	T	0.07
TNFRSF11B	rs2073618	Missense	Genotyped	N/A	8	119964052	G	C	C	0.45
TNFSF11	rs7984870	Intronic	Imputed	0.997	13	43146482	G	C	C	0.45
PTCSC2	rs10983920	Intronic	Imputed	0.997	9	100602613	C	A	A	0.12
NCOA1	rs1804645	Missense	Genotyped	N/A	2	24974958	C	T	T	0.03
E2F7	rs310786	Intronic	Genotyped	N/A	12	77436148	C	T	C	0.14
ABCB1	rs1045642	Missense	Genotyped	N/A	7	87138645	A	G	G	0.46
SLC22A23	rs4959825	Intronic	Imputed	0.988	6	3412240	T	C	T	0.31
UGT2B7	rs7439366	Missense	Genotyped	N/A	4	69964338	T	C	C	0.46
POLQ	rs9862879	Downstream	Genotyped	N/A	3	121149009	C	T	T	0.12

*R2 is the squared correlation between input genotypes and imputed dosages (i.e., true and inferred genotypes).

5.6.3 There were 2,729 female participants taking endocrine therapy

Two thousand seven hundred and twenty-nine female participants of European ancestry in the UKBB were taking endocrine agents considered for analysis (mean age=59.2 years; SD=7; 95%CI: 40.2 to 70.8 years). Of these, 1,195 were taking Tamoxifen and 1,544 were receiving AIs (Figure 5.1). The key characteristics of the UKBB female participants on endocrine therapy included in this analysis are summarised in (Table 5.4).

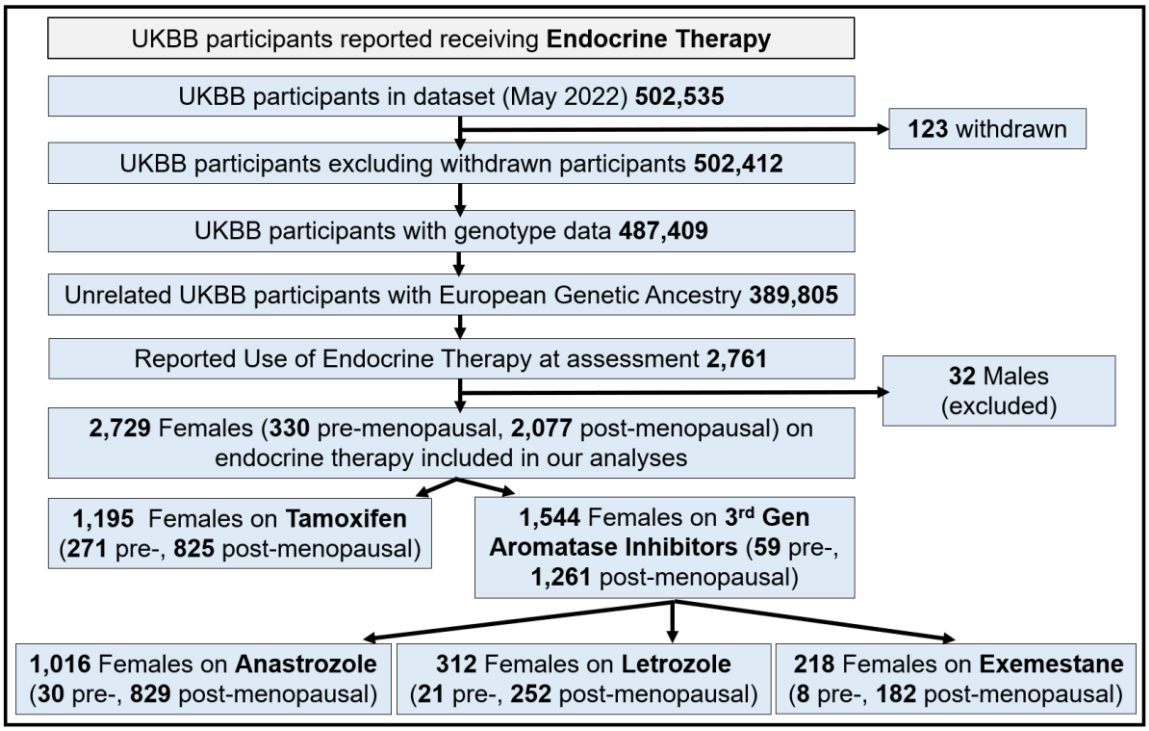


Figure 5.1 The UK Biobank cohort who reported taking endocrine agents.

A flow chart demonstrating the number of UKBB female participants with sufficient genomic and treatment data included in the analyses.

Table 5.4 Characteristics of the UK Biobank female participants taking endocrine agents.

	Treatment	Endocrine therapy				Rest of UKBB female Participants			
Main characteristics	Menopausal Status	Premenopausal (n=330)	Postmenopausal (n=2,077)	Other (n=322)	Total (n=2,729)	Premenopausal (n=55,819)	Postmenopausal (n=132,736)	Other (n=19,164)	Total (n=207,719)
	Age (years) Mean (SD)	49.6 (5.1)	60.2 (6.2)	62.7 (5.1)	59.2 (7)	47.4 (4.5)	60.2 (5.7)	62.6 (5.2)	57 (7.9)
	BMI (kg/m2) Mean (SD)	25.7 (4.4)	27.4 (4.9)	27.7 (5.1)	27.2 (4.9)	26.4 (5.3)	27.1 (5)	27.6 (5.2)	27 (5.1)
Continuous outcomes	Bone Mineral Density (g/cm2) Mean (SD)	0.51 (0.11)	0.49 (0.11)	0.48 (0.1)	0.49 (0.11)	0.55 (0.12)	0.5 (0.12)	0.5 (0.12)	0.52 (0.12)
	T-score Mean (SD)	-0.58 (0.97)	-0.83 (1.02)	-0.96 (0.88)	-0.82 (1)	-0.24 (1.04)	-0.68 (1.06)	-0.73 (1.06)	-0.57 (1.07)
	Total cholesterol [mmol/L] Mean (SD)	5.3(1.03)	5.81 (1.12)	5.89 (1.19)	5.76 (1.13)	5.45 (0.97)	6.07 (1.13)	6 (1.17)	5.9 (1.12)
	Triglycerides [mmol/L] Mean (SD)	1.53 (0.92)	1.77 (0.97)	1.84 (1.02)	1.75 (0.98)	1.3 (0.74)	1.64 (0.87)	1.7 (0.88)	1.55 (0.85)
	LDL [mmol/L] Mean (SD)	3.13 (0.79)	3.57 (0.87)	3.61 (0.92)	3.52 (0.88)	3.33 (0.76)	3.76 (0.87)	3.71 (0.91)	3.64 (0.87)
	HDL [mmol/L] Mean (SD)	1.59 (0.39)	1.57 (0.37)	1.55 (0.39)	1.57 (0.38)	1.56 (0.36)	1.62 (0.38)	1.59 (0.39)	1.6 (0.38)
Binary outcomes	Osteoporosis [n (%)]	4 (1.31)	56 (3.03)	2 (0.7)	62 (2.54)	177 (0.36)	2,452 (2.06)	442 (2.58)	3,071 (1.65)
	Bone fractures [n (%)]	31 (9.84)	138 (7.04)	34 (11.22)	203 (7.88)	1,935 (3.59)	8,727 (6.92)	1,577 (8.71)	12,239 (6.17)
	MS-ADEs [n (%)]	0 (0)	2 (0.1)	1 (0.31)	3 (0.11)	21 (0.04)	115 (0.09)	17 (0.09)	153 (0.07)
	Hepatosteatosis [n (%)]	4 (1.21)	49 (2.37)	5 (1.56)	58 (2.13)	542 (0.97)	2,113 (1.6)	390 (2.04)	3,045 (1.47)
	Thromboembolic events [n (%)]	7 (2.16)	70 (3.54)	22 (7.33)	99 (3.8)	502 (0.91)	2,871 (2.24)	528 (2.86)	3,901 (1.93)
	Venous thromboembolism (DVT/PE) [n (%)]	6 (1.85)	48 (2.42)	12 (3.99)	66 (2.53)	311 (0.57)	1,706 (1.33)	288 (1.55)	2,305 (1.14)
	Endometrial cancer [n (%)]	4 (1.21)	27 (1.3)	4 (1.25)	35 (1.29)	183 (0.33)	784 (0.59)	109 (0.57)	1,076 (0.52)
	Endometrial hyperplasia [n (%)]	10 (3.05)	8 (0.39)	1 (0.31)	19 (0.7)	203 (0.36)	241 (0.18)	45 (0.24)	489 (0.24)
	Depression [n (%)]	14 (4.62)	84 (4.41)	19 (6.83)	117 (4.7)	1,934 (3.78)	4,808 (3.91)	1,003 (5.77)	7,745 (4.04)

*Values are presented as Mean (SD) [Range Min-max] or [Number of cases (%)]

5.6.4 No significant genotype-treatment interactions either for continuous outcomes or incident ADEs were found

I performed 97 regression analyses including 46 and 51 for continuous and binary outcomes, respectively. This was achieved by fitting a main effects model including both adjusted and unadjusted models in pre-, post- or peri-menopausal women as per how they were reported in the initial papers. Similar numbers of regression analyses were performed by fitting interaction terms into the multivariate regression models to test the interaction between endocrine treatment and genotypes (Figure 5.2). The corrected critical *p*-value is 5.15E-4.

For the continuous outcomes, the genetic association analysis using the main effects model showed that postmenopausal women taking AIs and carrying *CYP19A1* rs700518 may have reduced BMD under recessive mode of inheritance (β coefficient, 95%CI, *P*: -0.003 (-0.005, -0.002), 4.54E-06). No other statistically significant associations between the SNVs analysed and continuous outcomes were observed in the main effects model. However, this association between and *CYP19A1* rs700518 and reduced BMD in postmenopausal women taking AIs was not statistically significant in the interaction model (*P*=5.5E-01). No statistically significant interactions between endocrine treatment and mutation status in relation to the continuous outcomes were found.

For the binary outcomes, the genetic association analysis using the main effects model showed that only five (10%) out of 51 regression analyses were statistically significant. Notably, for all of these five associations, the estimates in the initial studies reporting the associations were markedly overestimated and inflated compared to the estimates observed in this replication attempt. This observation was entirely consistent with the “winner's curse” phenomenon. None of the interactions between treatment and mutation status in relation to the binary outcomes was statistically significant.

All association analyses for both continuous and discrete outcomes analysed in this study including both the main effects and interaction terms models are shown in the Supplementary Excel file S5 & S6.

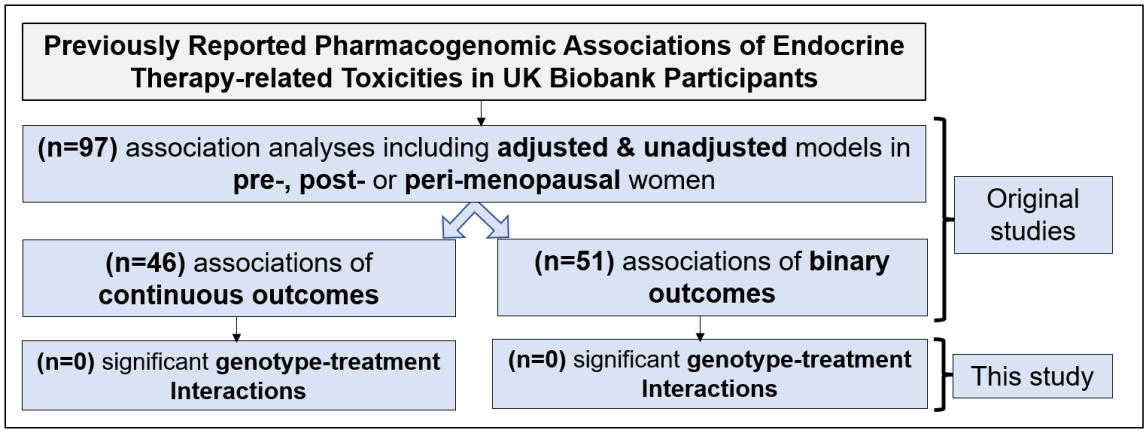


Figure 5.2 The main results from the UK Biobank analysis of PGx of endocrine therapy-related MIADEs.

Associations between previously reported SNVs and MIADEs related to endocrine therapy were tested in the UKBB participants. No statistically significant interactions between treatment and mutation status for the risk of MIADEs for any of the variants analysed were observed.

5.7 Discussion

5.7.1 No significant genotype-treatment interactions either for continuous measurements or incident MIADEs were observed

Previous studies have reported associations between various SNVs and endocrine therapy-related toxicities in BC patients. Replication or refutation of these associations in independent populations helps establish their credibility and usefulness for personalised recommendations in BC. However, none of the previously reported associations between SNVs and endocrine therapy-induced MIADEs were replicated in this large investigation neither for continuous measurements nor for incident MIADEs. Hence, the current evidence regarding the potential use of PGx for endocrine therapy-related MIADEs in BC is inconsistent at best and their clinical usefulness is lacking. Whilst additional evaluation in other datasets may be suggested, such further research is very unlikely to have an important impact on the confidence in the parameter estimates observed in this study.

5.7.2 These results are in line with the level of evidence in PharmGKB

While findings from this study are at variance with the initial studies, they are in agreement with the PharmGKB level of evidence (Level 3) assigned to the clinical annotations related to these SNVs in Feb 2022 (927). Of 4,939 clinical annotations in PharmGKB relating to the toxicity phenotype category, only 26 were related to endocrine therapy-associated toxicities, all had level 3 of

supporting evidence (Figure 5.5 [Appendix]). This low level of evidence indicates that none of these associations have been successfully and consistently replicated across studies. In line with this investigation, numerous studies did not observe any significant associations between SNVs and various ADEs in BC patients receiving endocrine therapy (814, 816, 831, 832, 835–837, 843, 845, 849, 851, 864, 817, 866, 868, 873, 874, 876, 879–881, 887, 889, 818, 892, 894, 819, 820, 824, 826, 828, 830). Likewise, several studies did not observe any significant associations between SNVs and various ADEs in BC patients receiving endocrine therapy despite examining multiple SNVs and various ADEs (817, 819, 830, 832, 880, 881, 892), or found only a few significant associations despite the large number of tests conducted (307, 309, 883, 884, 891, 310, 833, 838, 852, 853, 861, 865, 877).

This study, combined with the discrepant results from the above-cited PG reports, does not support previously reported PG associations in this context, suggesting potential false positive findings. It seems certain that fewer studies with statistically non-significant or inconclusive results are published compared to reports with positive findings or studies with interventions of a profitable or commercial value (123, 124).

5.7.3 The majority of included studies did not account for genotype-treatment interaction effects

The differences between results from this investigation and findings from the initial studies were noticeable and much larger than can be explained by random variation or residual stratification, which are unlikely to affect the replication of individual associations in this study. Unlike this investigation, authors of the overwhelming majority of the initial studies failed to account for interaction effects between the genotypes and treatment. Having assessed the frequency of the failure to consider potential interaction effects in the analyses performed by authors of initial studies, only three of the initial studies (12.5%) used interaction effects models appropriately (Table 5.8 [Appendix]). This is comparable to what I found in the systematic review of PGx of endocrine therapy-related toxicities, in which only 15% of studies used genotype-treatment interactions in their analyses. This study demonstrated that the majority of published literature on PGx of endocrine therapy-related toxicities that utilised multivariable regression models have not mentioned anything related to testing for statistical interactions, effect

modification, or heterogeneity of effect. Interaction effects are usually tested via multivariable regression models, but they can be also performed with a likelihood ratio test or the Wald chi-squared test. Caution should be exercised in the interpretation of results from associations reported by researchers who have not accounted for such interactions (912).

Interaction effects help reduce bias in estimated regression coefficients and improve the inferences for the coefficient estimates, provided that the effects are synergic or interactive. To minimise bias and misinterpretation of findings and avoid erroneous clinical interventions with potentially adverse consequences, incorporation of interaction terms is therefore essential. Following best practices, which recommend the incorporation of interactions in statistical models (913, 914), an interaction between the genotypes and endocrine treatment was fitted in the regression models performed in this analysis.

5.7.4 Most included studies did not adjust for relevant covariates or correct for multiplicity

This study endeavoured to replicate previously reported associations and adjust for covariates as per the initial studies, if applicable. Yet, many authors of the initial studies failed to adjust for well-documented patient risk covariates or were not clear if their analyses were adjusted for any covariates. There was also some inconsistency among researchers as for which covariates needed to be adjusted, even when the toxicity outcomes were the same.

Further, many of the included studies did not correct for multiplicity despite the considerable number of statistical comparisons conducted in their analyses, which increases the likelihood of false positive findings. Failure to apply multiplicity corrections can amplify the probability of falsely rejecting a true null hypothesis yielding spurious conclusions (928). Multiple endpoints can also adversely impact publication bias and that failure to use multiplicity corrections can enhance publication bias. Thus, investigators should pay serious attention to this phenomenon in their research. Having considered the ramifications of the multiplicity issue (126), I decided *a priori* to adjust the *P*-value using the Bonferroni correction procedure as recommended in statistical practice (195). This provides a reasonable balance between the control of false positives (i.e., a higher threshold) and false negatives (i.e., a lower threshold) (910, 911).

5.7.5 There was a notable non-significant association that warrants further investigation

Although not significant, this study found an indicative association between FVL and venous thromboembolism. FVL genetic variant was associated with an increased likelihood of both venous thromboembolism and thromboembolic events in tamoxifen-treated patients. This association persisted even after including relevant patient-related risk factors in the multivariable regression model and in pre-, postmenopausal and the whole cohort of tamoxifen-treated women in both adjusted and unadjusted models. Thus, FVL mutation may warrant further investigation regarding venous thromboembolism in tamoxifen-treated patients.

5.7.6 Strengths and limitations

This study has many strengths. First, the population-based nature of the UKBB makes the sample of female participants receiving endocrine treatment more representative of the whole female population and helps minimise selection bias risk, which is intrinsically inherent in data derived from clinical trials. Second, this study used longitudinal data including follow-up visits and HES data that is significantly longer than the initial studies. The relatively short follow-up periods observed in many of the studies included can additionally hamper the observation of some MIADEs in such small studies. Third, this study is the largest population-based study of PGx of endocrine therapy-related toxicities using germline DNA. All previous investigations were smaller than this study, except a large analysis that performed genotyping on FFPE tumour tissue rather than germline DNA (308). Unlike germline DNA, using FFPE tumour tissue to determine germline genotype or detect low-frequency alleles, particularly in some genomic regions (e.g., *CYP2D6* gene), may result in inaccuracies as a result of somatic chromosomal abnormalities that exist in tumour tissue samples (929). The large sample size in my study made it possible to capture specific MIADE outcomes, particularly in those who carry a genetic variant in a recessive mode of inheritance. The small sample size, which is observed in many of the initial studies, can diminish the statistical power to analyse some toxicity outcomes conferred by variants with MAF of <5% and is a possible source of false-positive findings. Fourth, this study investigated MIADEs which are considered medically

serious events and may result in hospital admission or need intervention or treatment in an emergency room to prevent serious outcomes. MIADEs are expected to be very well recorded particularly in HES data or reported during subsequent visits to the UKBB centres. This helps minimise the underestimation of ADE outcomes observed in population-based studies due to the absence of or omissions in individual patient data.

There are, however, a few points that should be considered. First, this analysis is performed in the UKBB participants with genetically determined European Ancestry and findings from this study may therefore not be generalisable to other non-Caucasian populations. Second, since the UKBB cohort is considered healthier than the general population (930), individuals in the UKBB who carry risk variants might be healthier on average than the carriers in the general population or other cohorts, which may mitigate the expected PG effects. Nonetheless, genetic variants are inherited at birth and the UKBB participants were not informed whether they carry particular genetic variants therefore my findings are less confounded compared to results from conventional clinical trials (931). Third, some genomic variants occur almost exclusively in a particular population and therefore some relatively rare outcome measures were not adequately detected due to the small number of patients on endocrine agents and carrying such variants with low MAF frequencies in the UKBB. Fourth, while including primary care prescribing data in the UKBB can be useful, this data was only available for a proportion of the UKBB participants at the time I performed the analyses.

5.7.7 Potential implications for practice and research

This large investigation demonstrated that the evidence base surrounding the potential use of PGx in the context of MIADEs induced by endocrine therapy in BC is lacking or tenuous at best. None of the previously reported SNVs was robustly replicated to be considered for personalised recommendations in clinical practice as they may simply be false positive findings. This is crucial as many of the SNVs analysed in this study are included in PGx databases or reported individually in the literature as potential genetic markers of endocrine therapy-related MIADEs in BC, which may subsequently be used by HCPs in treatment decision-making processes. To manage endocrine therapy-related MIADEs in

BC and mitigate the potential toxicity-related non-adherence, other interventions may therefore need to be considered.

The non-replication observed in this study has the potential to inform policymakers about decisions they might make with regard to what research programmes should be prioritised for funding. Since BC and endocrine therapy are well-studied fields, my results have the potential to improve the overall research and development of the PGx field. Besides, this evidence supports the rationale of robust replication of previously published PG variants in cohorts with large sample sizes before any consideration or attempt to translate these variants into clinical practice (932).

Further, this study underscores the importance of adherence to best methodological practices including multiplicity correction procedures and the use of reliable statistical models such as the inclusion of interaction terms in PGx studies to minimise bias in coefficient estimates and avoid erroneous interpretations of PG effects.

5.8 Conclusions

This is the largest cohort study aimed at replicating multiple associations between SNVs previously reported to be significantly associated with endocrine therapy-induced MIADEs in BC. This investigation showed that none of the SNVs analysed were replicated and the current level of evidence regarding their predictive value and usefulness is therefore lacking. Hence, PG tests in this context should not be considered for personalised recommendations in clinical practice. An urgent need exists for genetic or non-genetic safety biomarkers that facilitate the prediction of endocrine therapy-induced MIADEs. Comprehensive approaches such as GWA studies using data from large clinical studies with sufficient follow-up periods and diverse populations have the potential to identify novel associations.

5.9 Appendix

Table 5.5 Endocrine agents and other medications codes used in the UK Biobank analysis.

Treatment modality	Generic name	Brand names	Codes
Endocrine Therapy	Tamoxifen	TAMOXIFEN, EMBLON, NOLTAM, NOLVADEX, Soltamox, tamofen	1140870164, 1140870182, 1140858348, 1140870170, 1140870176, 1141170264
	Letrozole	LETROZOLE, FEMARA	1141145896, 1141145900
	Anastrozole	ANASTROZOLE, ARIMIDEX	1140923018, 1140923022
	Exemestane	EXEMESTANE, AROMASIN	1141171100, 1141171104
Bone Antiresorptive Therapy	Alendronate sodium	Fosamax, Binosto, Fosavance, Bentexo	1140922174, 1141176570
	Ibandronic acid	Bondronat, Iasibon, Bonviva, Quodixor	1141180314, 1141190534
	Pamidronate disodium		1140868784
	Risedronate sodium	Actonel	1141175684, 1141175690
	Zoledronic acid	Zometa, Aclasta, Zerlinda	1141173814
	Teriparatide	Forsteo, Movymia, Terrosa	1141188794, 1141188798
	Raloxifene	Evista	1141168574, 1141168578
	Denosumab	Prolia, Xgeva	N/A
	Romosozumab	Evenity	N/A
Lipid-lowering Therapy	Lipid-lowering drug (generic)		1140861922
	Simvastatin	Zocor, zocor heart-pro, INEGY	1140861958, 1140881748, 1141200040
	Pravastatin	Lipostat	1140888648, 1140861970
	Rosuvastatin	Crestor	1141192410, 1141192414
	Fluvastatin	Lescol	1140888594, 1140864592
	Atorvastatin	Lipitor	1141146234, 1141146138
	Ezetimibe	Ezetrol	1141192736, 1141192740
	Acipimox	Olbetam	1140861892, 1140861894
	Bezafibrate/Bezafibrate product	Bezalip, Fibrazate	1140861924, 1141157260, 1141201306, 1140861926, 1140861928
	Ciprofibrate		1140862026
	Fenofibrate	Supralip, Lipantil	1140861954, 1141172214, 1141162544
	Gemfibrozil/Gemfibrozil product	Lopid	1140861856, 1141157262, 1140861858
	Colestipol	Colestid	1140888590, 1140861848
	Cholestyramine/Cholestyramine product	Questran	1140909780, 1141180722, 1141180734, 1140861936
	Clofibrate		1140861944

Table 5.6 Ascertainment of biomarkers and other phenotypes.

Biomarkers at the baseline

Description	Data-Field	Items of Data/Participants	Units of measurement	Measurement method
Cholesterol	30690	487,377/470,756	mmol/L	Measured by CHO-POD analysis on a Beckman Coulter AU5800
HDL cholesterol	30760	429,793/429,793	mmol/L	Measured by enzyme immunoinhibition analysis on a Beckman Coulter AU5800
Triglycerides	30870	486,969/470,386	mmol/L	Measured by GPO-POD analysis on a Beckman Coulter AU5800
LDL direct	30780	486,454/469,918	mmol/L	Measured by enzymatic protective selection analysis on a Beckman Coulter AU5800

Oestradiol	30800	78,509/77,688	pmol/L	Measured by two-step competitive analysis on a Beckman Coulter Unicel Dxl 800

Definitions and other variables:
Bone Mineral Density (BMD) g/cm2. The Heel bone mineral density (BMD):
https://biobank.ndph.ox.ac.uk/ukb/field.cgi?id=3148
Method: Heel ultrasound method (left). Bone-densitometry of heel:
https://biobank.ndph.ox.ac.uk/ukb/field.cgi?id=4092
This uses BMD and if it is missing, we used Heel bone mineral density (BMD), manual entry:
https://biobank.ndph.ox.ac.uk/ukb/field.cgi?id=3084
And if this was missing, we used Heel bone mineral density (BMD) (left) or Heel bone mineral density (BMD) (right):
https://biobank.ndph.ox.ac.uk/ukb/field.cgi?id=4105
https://biobank.ndph.ox.ac.uk/ukb/field.cgi?id=4124

The following data Field IDs were used for **BMD**:
3148 Heel bone mineral density (BMD)
4105 Heel bone mineral density (BMD) (left)
4124 Heel bone mineral density (BMD) (right)
3084 Heel bone mineral density (BMD), manual entry

T-score (number of SD BMD above or below standard) was computed from **Heel bone mineral density (BMD) T-score, automated** (bone-densitometry of heel). The following data Field IDs were used:
78 Heel bone mineral density (BMD) T-score, automated
4125 Heel bone mineral density (BMD) T-score, automated (right)
4106 Heel bone mineral density (BMD) T-score, automated (left)
4138 Heel bone mineral density (BMD) T-score, manual entry (left)
4143 Heel bone mineral density (BMD) T-score, manual entry (right)

Osteoporosis and Osteopenia were calculated based on **Heel bone mineral density (BMD) T-score** as follows:
Osteopenia: T score less than or equal to -1 but greater than -2.5
Osteoporosis: T score less than or equal to -2.5

Table 5.7 Ascertainment of phenotypic endpoints of adverse drug effects and other phenotypes.

Phenotype	ICD10	ICD9	Self-report code from n_20002_* variable
Scoliosis (including Kyphoscoliosis)	M41 M965 Q763 Q675	7373 75420	1535
Osteoporosis	M80 M81 M82	7330	1309
Fractures	M484 M840 M841 M842 M843 M844 S02 S12 S220 S222 S223 S224 S228 S229 S32 S42 S52 S62 S72 S82 S92 T02 T08 T10 T12 T14 M800 M801 M804 M805 M808 M809	80 81 82 7331 E8879	1626 1627 1628 1629 1630 1631 1632 1633 1634 1635 1636 1637 1638 1639 1640 1644 1645 1646 1647 1648 1649 1650 1651 1652 1653 1654 1655 1656
Severe musculoskeletal adverse events (e.g., myopathy, myositis)	G720 G728 G729 M608 M609 M814	3599	1322
Thromboembolic events	I82 I26 I801 I802 I803 I808 I809 I81 I82 I630 I631 I633 I634 I74 K550 I82 I513 I676 I636 I240	453 4151 4341 444 59381 3259 4340 4376 4511 4512 4518 4519 4529 59382	1094 1093 1088 1068
Venous thromboembolism (DVT/PE)	I82 I26 I513 I676 I636 I240	453 4151 3259 4340 4376 4511 4512 4518 4519 4529 59382	1094 1093 1068
Hepatosteatosis	K76 K760 K758	5715 5716 5718 5719	
Gynaecological events [endometrial thickening, uterine fibroids, ovarian cysts, adenomyosis and cervical canal cysts]	N850 N851 D25 N830 N832 N800 Q516	6213 2191 2360 218 6200 6201 6202	1351 1349
Gynaecological events [endometrial hyperplasia or endometrial cancer]	N850 N851 C541	6213 2191 2360 182	1040
Endometrial hyperplasia or Double endometrial thickness	N850 N851	6213 2191 2360	
Depression	F33 F32 F412 F341	3004 311	1286
Varicose veins	I83 I86	454 456	1494
Endometrial cancer	C541	182	1040
Prosthetic limb by prosthesis	Z441 Z971	V437 V520	
Chemotherapy	Z082 Z511 Z542 Z926	V581 V662 V6621 V6622 V6629 V672	
Radiotherapy	Z081 Z091 Z510	V580 V661 V6611 V6612 V6619 V671	
Family history of ischaemic heart disease	Z824	V173	
Family history of stroke	Z823	V171	
Family history of musculoskeletal diseases or arthritis	Z826	V177 V178	
Family history of malignant neoplasm of genital organs	Z804	V164	
Family history of genital disease	Z804 Z842	V187 V164	
Family history of psychiatric and other mental and behavioural disorders	Z818	V170	

Family history of blood disease	Z832	V183	

Definitions and other variables:

Family history of cancer, depression or stroke, I used data field IDs and codes for relevant illnesses of father/mother/siblings

Field ID for illnesses of father/mother/siblings:
20107 Illnesses of father
20110 Illnesses of mother
20111 Illnesses of siblings

Coding for illnesses of father/mother/siblings:
2 Stroke
3 Lung cancer
4 Bowel cancer
5 Breast cancer
13 Prostate cancer
12 Severe depression

Menopausal status was determined at the baseline UKBB visit:
0=premenopausal
1=postmenopausal due to natural menopause
2=postmenopausal due to surgery i.e., hysterectomy or oophorectomy
3=postmenopausal but can't tell what type of menopause or age at menopause as taking HRT over age at menopause
4=premenopausal but taking HRT so can't be sure
9=missing data for one or more variables so can't define this.

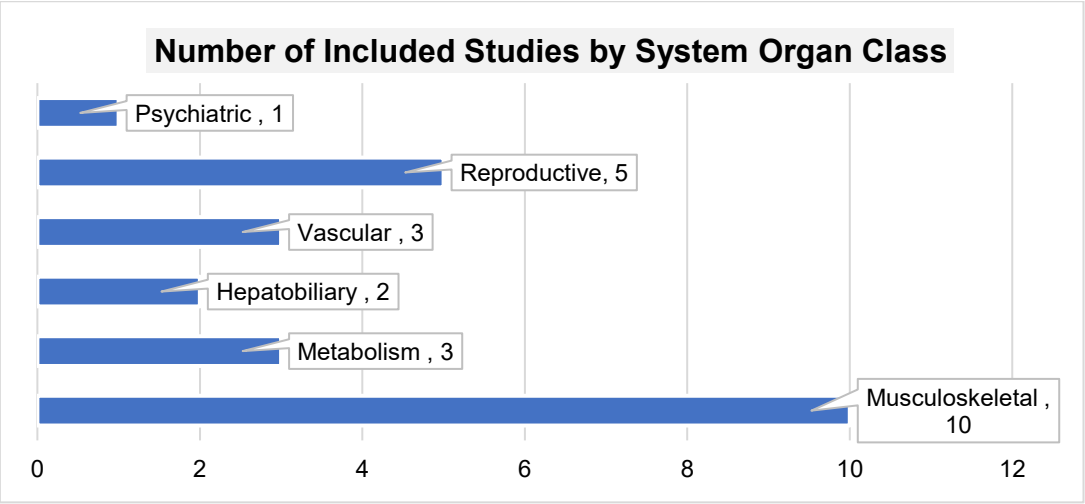


Figure 5.3 Number of identified PGx studies of MIADEs related to endocrine therapy by system organ class.

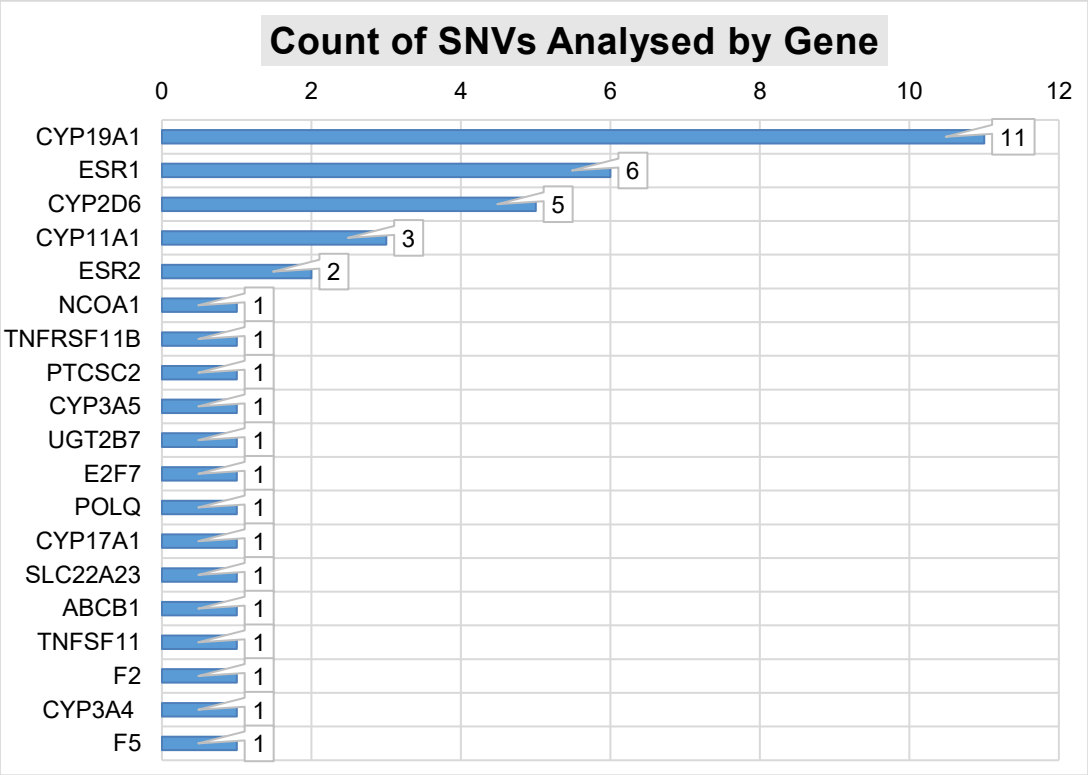


Figure 5.4 Count of SNVs analysed in the UK Biobank per gene regarding PGx studies of MIADEs related to endocrine therapy.

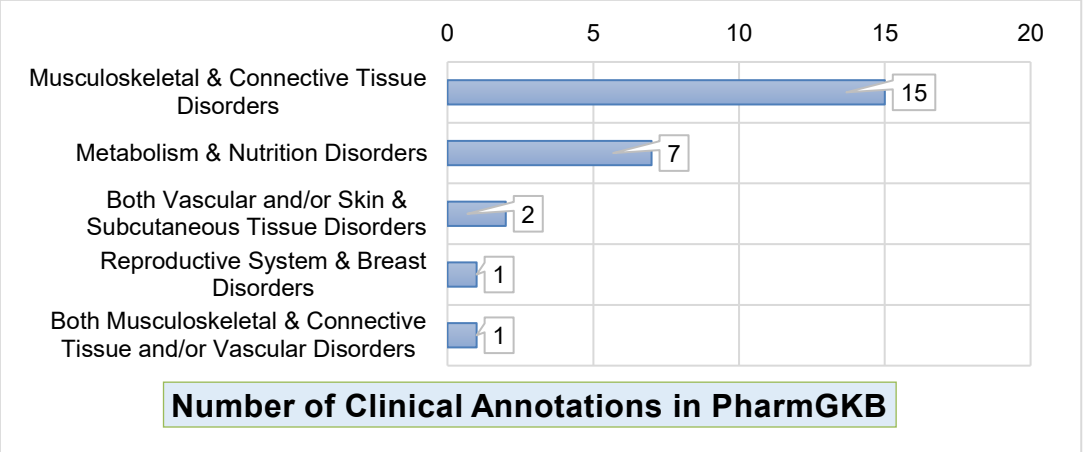


Figure 5.5 Number of clinical annotations PGx of ADEs related to endocrine therapy in PharmGKB grouped by organ system.

Table 5.8 Status of inclusion of interaction effects in analytical models performed by authors of PGx studies of MIADEs related to endocrine therapy.

The frequency of the failure to consider potential interaction effects in the analyses was assessed using the following search terms: moderator, heterogeneity of effect, magnifier, qualifier, synergy, buffering effect, statistical interactions, effect modification, effect modifier, multiplicative or synergistic.

Study [Author, Year]	The interaction effects model was used appropriately
Al-Mamun 2017	No
Argalacsova 2017	No
Baatjes 2020	No
Chu 2007	No
Dieudonné 2014	No
Garber 2010	No
Hartmaier 2012	No
Koukouras 2012	No
Kovac 2015	No
Leyland-Jones 2015 (1)	Yes
Leyland-Jones 2015 (2)	Yes
Mazzuca 2016	No
Miranda 2021	No
Napoli 2013	No
Ntukidem 2008	No
Oesterreich 2015	No
Ohnishi 2005	No
Onitilo 2009	No
Rodríguez-Sanz 2015	No
Santa-Maria 2016	Yes
Wang 2013	No
Wang 2015	No
Weng 2013	No
Wickramage 2017	No

6 Chapter Six. Discussion

6.1 This study created novel lists of variants associated with adverse drug effects

This is the first study that has created two comprehensive lists of variants associated with ADEs, derived from both primary and secondary studies using systematic reviews of the literature and PGx databases. These were further curated and a novel set of genotype–drug pairs significantly associated with MIADEs with an overall high level of evidence was created. The primary and secondary studies encompassed RCTs and *post-hoc* analyses of RCTs, meta-analyses, and the PGx database included PharmGKB.

This study also generated a catalogue of variants associated with the risk of endocrine therapy-related toxicities in BC by comprehensively and systematically reviewing the literature and PharmGKB. Unlike the above systematic reviews, these systematic searches were conducted with no restriction on study design and thus the PG associations had variable levels of evidence. This catalogue was further curated and a list of variants significantly associated with MIADEs was generated.

6.2 Pharmacovigilance data was mapped onto prescription data and subsequently used in pharmacogenomic analysis

This is the first study that has established the feasibility of linking real-world real-time data derived from pharmacovigilance and prescribing databases to be subsequently utilised in PG analyses. While these databases were formerly used in epidemiological studies, this database linkage helped identify high-risk medicines in GP which were further used in PG analyses in the UKBB. This work is already being incorporated into the discussions and evidence evaluation of the Yellow Card Biobank initiative (933). Despite the acknowledged inherent limitations of data derived from pharmacovigilance and prescribing databases, this study demonstrated that using aggregate data derived from these databases is robust enough to draw reasoned conclusions with regard to the safety analyses.

6.3 None of the pharmacogenomic findings tested in this large investigation were reproduced

The observed heterogeneity and mixed findings among the PGx studies in the literature indicated that more focused analyses and further replication, for those that merit follow-up replication, are necessary. This study found none of the associations between PG variants and MIADEs related to high-risk medicines in GP (including statins, NSAIDs and antipsychotics) was statistically significant in the UKBB, failing to replicate the findings from the initial studies in relation to neither baseline measurements nor incident MIADEs. Findings from this study were independently corroborated by the updated low level of evidence assigned to these genotype–drug pairs in PharmGKB in 2022. Similarly, none of the genotype–drug pairs reported to be significantly associated with MIADEs related to endocrine therapy in BC were replicated in the UKBB, in relation to neither baseline measurements nor incident MIADEs. This was in agreement with the low level of evidence assigned by PGx guidelines and PharmGKB to these genotype–drug pairs.

The genotype-drug pairs for MIADEs related to high-risk medicines in GP examined here were assigned with a moderate or high level of evidence by PharmGKB at the time of my analyses. Thus, a large effect size of genotype-treatment interactions was expected, particularly as this large analysis used longitudinal data including follow-up visits and hospital medical records data that is significantly longer than the initial studies.

Findings from this study provide extremely convincing evidence that previous associations were false positive results. While the sources of discordance remain uncertain, the discrepancies between the results from this investigation and the findings from initial studies are much larger than can be explained by random variation, an imbalance between cases and controls (e.g., significant differences in environmental factors exposure), genetic heterogeneity or residual population stratification. These factors are insufficient to explain the widely discrepant findings, suggesting that the initial findings are false positives. A combination of sub-optimal methods, lenient statistical criteria and thresholds, data dredging (120), reporting bias as well as small sample sizes in most of the initial studies, might have led to the observed increased rate of their false positive signals. The substantial variation observed in the PG effect estimates in the small studies

means that only significant effect estimates of the numerous initially analysed outcomes may be selected to be reported.

These findings are corroborated by the observed heterogeneity and mixed findings as well as considerable variation in PG effects among studies identified in my systematic reviews. These systematic reviews also showed that the vast majority of findings were not statistically significant with a notable lack of stringent replication across different populations. For instance, 95% of associations reported by authors of PGx studies of endocrine therapy-related toxicities in BC were non-significant in my systematic review.

6.4 Adverse drug effects are not consistently defined, indexed or reported in pharmacogenomic studies

This lack of uniformity observed among the identified studies was particularly notable in the toxicity outcomes and terms used synonymously by authors to describe ADEs. There were no consistent definitions of ADE outcomes, the timing of outcome measurements and ascertainment, with many studies having investigated composite outcomes of ADEs or used underspecified terms to refer to toxicities. This pointed to another fundamental issue, which is the potential presence of reporting bias. The inconsistent assignment of risk category (e.g., seriousness, severity) and the use of the terms “serious” and “severe” interchangeably and loosely by many authors were also matters of concern. This study showed that reviewing the relevant literature relating to PharmGKB annotations was vital for the correct designation of the risk category of ADEs. These inconsistent definitions add to the substantial heterogeneity and mixed findings, making synthesis of evidence and drawing reasoned conclusions or providing valid practical implications from these studies difficult. Hence, this study constructed a toxicity outcome of MIADEs using unambiguously clear criteria for definition.

6.5 Outcome reporting bias and duplicated data represent major challenges in pharmacogenomics

This study found some evidence of incomplete reporting and selective outcome reporting of significant or positive findings among the authors of PGx studies of ADEs. The selective reporting of outcomes based on the direction and nature of the results (i.e., data 'dredging') but not key outcomes that are routinely measured

by most investigators are major problems. In addition to concerns around the dissemination of data, this increases reporting bias (120) and combining results from such reports via meta-analysis can result in both distortion and overestimation of the PG effects.

Notably, substantial overlap existed among the samples analysed by the investigators across identified studies, particularly positive studies. For example, 43% of PGx studies of endocrine therapy-related toxicities in BC used overlapping data derived from the same trials. Such significant overlap and over-estimation of the overall sample size can induce biases and lead to the overestimation of PG effects.

6.6 Stringent statistical measures are fundamental

Despite the considerable number of statistical tests performed in many studies included in the systematic reviews, most did not correct for multiple testing or address the multiplicity issue. This was sufficiently significant to warrant caution regarding the validity of findings from these studies. Not only does this boost the probability of false positive findings and result in erroneous conclusions, but this can also increase publication bias. The ramifications of multiple comparisons were considered in this study to minimise the overabundance of false-positive signals and artefactual results. Thus, multiplicity corrections for all statistical tests including meta-analyses were applied. This provided a fair balance between the elimination of false positives and false negatives.

Besides, genotype-treatment interactions have not been adequately explored or included in the statistical analyses performed by authors of the majority of the identified studies. For instance, only 15% of studies of PGx of endocrine therapy-related toxicities in BC used genotype-treatment interactions appropriately. Such failure to incorporate interaction effects in the model and relying solely on the main effects can result in a significant bias in coefficient estimates, leading to misinterpretation of PG effects. Hence, caution should be exercised in the interpretation of findings from these reported associations. Having been aware of the significant adverse implications of disregarding statistical interaction effects, genotype-treatment interactions were consistently tested in this study to help reduce bias and improve the inferences from estimated regression coefficients.

6.7 Study limitations

First, this study included only UKBB participants of European ancestry and thus extrapolation of the findings to other populations may not be applicable. Second, the performed systematic reviews are largely limited to published data. As the overwhelming majority of RCTs are published in English, the searches were limited to include English-only publications and therefore language bias is anticipated. Third, studies which examined chemotherapy-based regimens were excluded from the list of genotype–drug pairs associated with MIADEs. This was due to concerns regarding the complexity of their combination regimens and designs as well as drug-drug interactions. Fourth, caution should be exercised when using the comparative medication safety charts by HCPs and patients, considering the inherent shortcomings of pharmacovigilance and prescribing data used. However, these limitations are expected to affect all medicines similarly, and therefore the relative rates of ADEs are unlikely to be affected.

6.8 Implication for research and practice

This PG analysis in the UKBB showed that the evidence regarding the potential use of PGx for MIADEs related to statins, NSAIDs, antipsychotics and BC endocrine therapy is tenuous at best. These are among the most frequently prescribed medicines in the UK and this robust refutation of the initial findings has practical implications. These drug-variant pairs are reported in the literature with many incorporated into PGx guidelines or FDA drug labels as potential PG markers of related toxicities. Yet, the designated actionability for these drug-variant combinations in such guidelines is inexpedient and questionable (697). At the time of writing this report, the overall updated level of evidence assigned to these genotype–drug pairs in PharmGKB is low, supporting my findings.

This study added further evidence for the rationale of replication of previously reported variants at scale with a large sample size by applying robust and stringent statistical methods and criteria before any consideration or attempt to translate these genotype–drug pairs into clinical practice (932). Despite the promising perspectives and enthusiasm in the literature to translate some of this genotype–drug pairs into routine clinical practice, these claims are inadequately substantiated to support such translation (934). There is not a single RCT that convincingly supports a clinically meaningful effect of PG intervention for any of

these genotype-drug pairs. Compared with the initial studies, this study in the UKBB was significantly larger and longer and utilised longitudinal data relating to both follow-up visits and hospital medical records data. Yet, this study did not find a single association that had been stringently replicated or shown significant statistical association to be considered for clinical utility or used as a source for HCPs regarding treatment decision-making. Whilst my findings did not replicate previous studies, there is no implication that these studies were deliberately misleading or undertaken in bad faith.

The prescribing decision-making process for a patient, particularly one with multiple disorders and taking other medicines concomitantly, is already complex given the scarcity of differential management options, and sizable information needs to be reviewed. Despite the understandably continuous enthusiasm among precision medicine advocates, patient management in these contexts therefore needs to shift to more evidence-based decision-making practices using validated biomarkers instead of unsubstantiated PGx associations. To support evidence-based and informed decision-making in practice, this study generated quantitative comparative safety charts for medicines pertaining to the same therapeutic class, providing both HCPs and patients with real-world data on drug safety. These novel safety visual tools could assist in the context of shared decision-making in patient-prescriber encounters.

The created list of variants associated with ADEs provides a reliable source of up-to-date information which can be useful to regulatory agencies, researchers and HCPs. Furthermore, the curated set of variant–drug pairs significantly associated with MIADEs contains fully specified interrogable genotypes and ICD-10 codes for potential use in biobanks. Customisable PGx analyses in the UKBB by prioritising genotype-drug pairs pertinent to a specific disease or commonly prescribed medicines can be especially invaluable.

6.9 Recommendations and future research

The notable lack of uniformity and transparency observed in the toxicity outcomes reported and terms used by investigators underscores the importance of using clearly defined and internationally agreed toxicity outcomes, definitions, measurements and ascertainment. The different official definitions used by various regulators and the numerous terms used to describe ADEs by

researchers and HCPs make centralising information in worldwide databases practically unachievable (58, 935). Likewise, consensus and standardised scales for the categorisation of ADEs with regard to seriousness and severity are of paramount importance for the correct designation of ADEs. Furthermore, selective reporting of toxicity outcomes and covariates accentuates the concerns around data dissemination in order to facilitate yielding unbiased conclusions of PG effects. More efforts should be made with regard to transparent and complete reporting as well as sharing data among investigators to allow reproducibility and independent replication of, or expansion on, the reported findings. There needs to be more acceptance of inconclusiveness and contradictory data in the same way as confirmatory data and positive findings. Both authors and publishers of PGx studies should be under an obligation to publish carefully designed studies fully, including those with findings which contradict previously published reports (936). This is of paramount importance, particularly in the field of PGx (899). Further, to reduce bias in estimated regression coefficients and minimise the impact of type I errors on the validity of findings, authors should use the most reliable methods in examining associations of variants and toxicities outcomes, rigorous statistical methodology and stringent statistical significance thresholds.

The vast majority of ADEs in the identified RCTs and *post-hoc* analyses of RCTs were secondary outcomes, which were poorly reported and indexed in the titles and abstracts. This stresses the need for a higher degree of scrutiny to be applied with regard to the transparency and reporting of ADEs in RCTs. Almost all *post-hoc* analyses of RCTs had the randomisation status of the original RCTs not being explicitly stated, either in the title or abstract. Hence, better reporting of randomisation status is vital to facilitate identifying these studies in the literature. The observed scarcity of RCTs of PGx studies in the context of ADEs, particularly genotype–guided therapy trials, underscores the need for RCTs with a large number of patients. This is crucial to demonstrate a reduction in rare ADEs and validate PGx clinical utility. Yet, the debate over the level of evidence needed to establish clinical utility (937) indicates that clear and internationally agreed criteria for this are necessary to facilitate standardised translation of PGx variant-drug pairs into everyday clinical practice.

This study only considered UKBB participants of European ancestry, and the overwhelming majority of studies identified in the literature were performed in high-income countries or within cohorts consisting predominantly of Caucasians. This can limit the external validity of the findings across global populations and increase racial disparities and health inequalities. Hence, more studies are needed in other under-represented populations, particularly in middle and low-income countries.

This was not a follow-up study and therefore future studies using the UKBB-linked primary care records allow examination of prescriptions and has the potential to complement these findings. At the time I performed the analyses, primary care prescription records and clinical data were only available for a proportion of participants.

Further, as PG variants can have subtle or small effects when assessed individually, further research and replication of prognostic discrimination of PGx polygenic scores that incorporate multiple genetic markers is warranted (139, 938).

In summary, this large investigation found none of the PG findings tested were replicated in the UKBB. This included associations between genomic variants and MIADEs related to high-risk medicines in GP comprising statins, NSAIDs, antipsychotics, and endocrine therapy in BC, in relation to neither baseline measurements nor incident MIADEs.

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