**Pharmacogenomics: current status and future perspectives**

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**Abstract**

Inter-individual variability in drug response, be it efficacy or safety, is common and likely to become an increasing problem globally given the increasingly elderly population requiring treatment. Reasons for this inter-individual variability include genomic factors, an area of study called pharmacogenomics. With genotyping technologies now widely available and decreasing in cost, implementing pharmacogenomics into clinical practice — widely regarded as one of the initial steps in mainstreaming genomic medicine — is currently a focus in many countries worldwide. However, major challenges of implementation lie at the point of delivery into health-care systems, including the modification of current clinical pathways coupled with a massive knowledge gap in pharmacogenomics in the health-care workforce. Pharmacogenomics can also be used in a broader sense for drug discovery and development, with increasing evidence suggesting that genomically defined targets have an increased success rate during clinical development.

**[H1] Introduction**

Inter-individual variability in response to foods and medicines has been recognised for millennia — Pythagoras (570 BC to 495 BC) described the occurrence of red blood cell haemolysis after ingestion of fava beans **[Au: Edit OK?]**. This haemolytic response is now known to be due to mutations in the *G6PD* gene leading to glucose-6-phosphate dehydrogenase deficiency, which is the most frequent human enzyme deficiency in the world, affecting ~400 million people worldwide1.

The term pharmacogenomics, which is often used interchangeably with its predecessor term pharmacogenetics, has conventionally been defined as the study of how a person’s genetic make-up affects their response (efficacy and/or safety) to a drug2. A broader definition of pharmacogenomics, which I favour, is the study of genomic technologies to enable the discovery and development of novel drugs, and the optimisation of drug dose and choice in individual patients to maximise efficacy and minimise toxicity.

Efficacy rates of different drugs have been reported to vary from 25% to 80%3. In 2003, Allen Roses famously said: “The vast majority of drugs — more than 90% — only work in 30 or 50 per cent of the people”4. A more recent analysis showed that for the ten highest grossing drugs in the USA, for every person helped, between 3 and 24 individuals failed to show a response5. These are very broad figures, and likely to be relatively imprecise when one considers individual drugs. Furthermore, the determination of whether a drug is efficacious (and whether this efficacy varies between individuals) is complex — it is beyond the scope of this article to elaborate on this idea further and readers are referred to other articles6-9.

In terms of drug safety, adverse drug reactions (ADRs) account for about 6.5% of hospital admissions in adults10, increasing to >15% when focusing on people with multimorbidity11. Furthermore, ADRs affect about 15% of people in hospital12. Although these are UK figures, similar frequencies have been reported in other countries13,14.

Variation in the efficacy or safety of drugs has detrimental effects on patient outcomes and leads to increased costs to resource-constrained health-care systems. Clearly, genetic factors do not account for all this variability, and the genetic contribution varies not only between individual drugs, but also between individual patients. From a clinical perspective, the aim of pharmacogenomics is to move away from our current ‘one drug fits all’ or ‘one dose fits all’ strategy to a more personalised choice and dose of drug that is relevant for the individual patient’s needs.

While pharmacogenomics has largely been a focus for academic research over the last few decades, there is now increasing interest from policy makers in the role of pharmacogenomics to improve patient outcomes, which may enable implementation into practice. Coupled with this is the growing evidence from the pharmaceutical industry of the value of genomically-defined targets in improving success rates in drug development, which will further increase interest and research in this area. In this Review, therefore, I provide an overview of the current state of the pharmacogenomics field using examples of clinically relevant drug–gene associations, before reviewing the steps needed for implementation of pharmacogenomics into clinical practice. I also consider the role of pharmacogenomics in drug discovery and development in keeping with the broader definition outlined earlier. I finish by looking at aspects likely to have an impact on pharmacogenomic studies in the future, including the use of biobanks, inclusion of rare variants and polygenic scores.

**[H1] Variation in pharmacogenes**

Genetic variation in the regulatory and coding regions of genes involved in determining drug response (that is, pharmacogenes) is common in the human population (**Table 1**). In addition, drugs whose response is affected by pharmacogenomic variation are frequently used in clinical practice. For example, 18% of out-patient prescriptions in the USA are affected by actionable germline pharmacogenes24. In the UK, over 1 year, 58% of patients were prescribed at least one drug affected by polymorphisms in actionable pharmacogenes25. Furthermore, as individuals age, they are prone to more diseases that require drug therapy; therefore, almost 90% of patients over the age of 70 years will be exposed to at least one drug with pharmacogenomic guidance25.

The Pharmacogenomics Knowledge Base (PharmGKB) is a comprehensive resource that provides up-to-date information on drug–gene pairs, including drug label annotations and clinical guideline annotations26,27. PharmVar, a centralized data repository, provides high quality data on pharmacogene variation28. The US Food and Drug Administration (FDA) has a list of 517 gene–drug associations that have been included in drug labels29, and its table of pharmacogenomic associations lists 121 drug–gene interactions30. However, harmonization in pharmacogenomic drug labelling between different regulatory agencies is lacking (**Fig. 1**) because of differing views on actionability, and differences in legal statutes and clinical practice. Much of the content in drug labels is for information only, rather than to undertake a change in drug dosage or choice, thus this information is probably largely ignored by prescribers. Moreover, although many drug labels advise prescribers to avoid drug–drug interactions, drug–gene interactions that can lead to the same effect as drug interactions are often not considered. For example, the drug label or summary of product characteristics (SmPC) for tamoxifen31, an oestrogen receptor modulator used for breast cancer, asks prescribers to avoid drugs that might interact with tamoxifen and reduce its effect, but a genetic polymorphism in *CYP2D6* that has the same effect as the drug interaction is given for information only without any instruction to genotype the patient before drug use, meaning that approximately 1 in 10 women who are homozygous for non-functional *CYP2D6* alleles32, and thus poor metabolisers, might potentially receive reduced benefit from tamoxifen.

**[H1] Basis of gene–drug associations**

Both pharmacokinetic (what the body does to the drug) and pharmacodynamic (what the drug does to the body) factors contribute to drug response. Undoubtedly we have greater knowledge of pharmacokinetically determined drug–gene interactions than of pharmacodynamic drug–gene interactions33, reflecting our greater knowledge of drug pharmacokinetics than the mode of action of drugs. Great advances have been made over the past 50 years in the *in vitro* and *in vivo* study of the four main processes involved in drug pharmacokinetics — that is absorption, distribution, metabolism and excretion — and how these determine inter-individual variability in drug handling. Such advances have also shown that genetic factors play an important role in determining drug pharmacokinetics, For example, studies in monozygotic and dizygotic twin pairs that have shown the heritability of metoprolol and torsemide pharmacokinetics to be 91% and 86%, respectively34.

Over the past few decades, advances in genotyping and sequencing technologies, statistical genetics analysis methods and clinical trial designs have driven the discovery of genetic variation associated with drug response*.* Pharmacogenomics data is largely derived from observational studies, which vary in size and quality, with many small studies claiming large effect sizes that have not been replicated in subsequent larger studies. In order to overcome this limitation, many consortia (such as the International Warfarin Pharmacogenetics Consortium [IWPC], Metformin Genetics [Met-Gen], and the International Clopidogrel Pharmacogenomics Consortium [ICPC]) have been formed to increase sample size, share data and undertake collaborative meta-analyses. Randomised controlled trials (RCTs) have been used to identify novel drug–gene associations, but this approach is uncommon and usually undertaken retrospectively after completion of the primary trial35. The role of RCTs in determining the clinical utility of gene–drug associations is covered later in the article.

GWAS now provide a fairly cost-effective and unbiased method to identify gene–drug interactions and might be particularly important for identifying pharmacodynamic drug–gene interactions36,37, which also provides novel insights into mechanisms of action or toxicity. However, <10% of the studies in the GWAS catalogue have so far investigated drug response38. Furthermore, over the years, the sample size for drug response GWAS has not increased unlike the increase in numbers seen in complex disease GWAS38. This factor is probably because of difficulties in defining an accurate phenotype for pharmacogenomic studies, recruiting adequate sample sizes, and replication of findings. Despite these issues **[Au: Edit OK?]**, pharmacogenomic-predisposing loci have been identified in GWAS because of the larger effect sizes than those found for complex diseases39.

***[H2] Dose***

The dose determines both the efficacy and safety of a drug, and genetic factors have a role in determining dose. The best example is warfarin, for which polymorphisms in *CYP2C9* (which encodes the enzyme responsible for metabolising warfarin) and *VKORC1* (which encodes the enzyme inhibited by warfarin) determine daily or weekly dose requirement. Loss-of-function polymorphisms in either or both of these genes are associated with reduced enzyme activity and hence the need for lower warfarin doses, which avoids over-exposure, to achieve therapeutic anticoagulation40. The importance of germline polymorphisms in determining the dose of anti-cancer drugs has also been shown with *TPMT* and *NUDT15* polymorphisms and thiopurines41, *DPYD* polymorphisms and fluoropyrimidines42, and *UGT1A1* polymorphisms and irinotecan43. In all these instances, a polymorphism that either reduces or abolishes the activity of the relevant enzyme is associated with reduced metabolism of the anti-cancer drug, with consequent systemic overexposure and dose-dependent toxicity, typically bone marrow suppression, but also severe diarrhoea.

***[H2] Drug safety***

ADRscan be divided into type A and type B reactions44, both of which can be affected by genetic factors. A great deal of progress has been made in identifying genetic predisposing factors for ADRs over the past 20 years. Type A ADRs are an augmentation of the pharmacological actions of a drug and show typical dose dependency, with a reduction in dose leading to improvement in the ADR44. The examples given in the previous section on dose are illustrations of type A ADRs.

Type B ADRs, sometimes called idiosyncratic reactions, cannot be easily explained based on the known pharmacology of the drug, do not exhibit clear dose dependency, and usually require drug discontinuation to ameliorate the ADR44. Many of these ADRs are immune-mediated. Substantial progress has been made particularly in relation to the role of HLA alleles in predisposing to these reactions45 (**Table 2**). Indeed, some of the associations are akin to Mendelian diseases with genome-wide significant results, such as associations with flucloxacillin hepatitis46 and carbamazepine hypersensitivity47, being discovered in just 51 and 23 affected patients, respectively **[Au: Edit OK? Is this what you meant?]**.

Abacavir hypersensitivity represents the poster child for translational pharmacogenomics. Abacavir, an anti-HIV drug, can lead to a severe and sometimes life-threating hypersensitivity reaction, which has been linked to *HLA-B\*57:01*. The association with *HLA-B\*57:01* has been replicated globally in observational studies, including prospective cohort studies, and in an RCT70,71. Drug labels worldwide include a recommendation to genotype individuals before starting abacavir, and implementation of HLA genotyping before abacavir administration has led to the virtual disappearance of abacavir hypersensitivity, which prior to genotyping was seen in 5% of patients with HIV treated with the drug70,71.

Advances in HLA pharmacogenomics have generated extensive research to understand the mechanisms of immune-mediated ADRs (for example, with abacavir hypersensitivity72). Novel findings suggest that drugs and their metabolites interact with specific HLA molecules and T-cell receptors leading to clonal T-cell proliferation and cytokine secretion resulting in tissue injury73,74.

***[H2] Drug efficacy***

It has been estimated that only 15% of drugs will have genetic predictors of efficacy with a large enough effect size75. This figure might be an underestimate given that identification of genetic factors for efficacy is difficult for the following reasons: inadequate study design leading to difficulties in defining treatment benefit6-9; lack of accounting for the placebo effect76; the effect of non-adherence to medications77; inadequate assessment of variation in disease phenotypes between different participants78; and inadequate statistical power79, particularly when efficacy is determined by multiple variants each contributing a small amount. Some examples of consistent evidence of germline variation determining drug efficacy are shown in **Table 3**. The association between olaparib and *BRCA1* and *BRCA2* mutations was detected before registration, whereas all the other examples have been identified post-marketing, two of which are discussed in more detail below.

Clopidogrel is an anti-platelet agent that is efficacious in patients with ischaemic heart disease and cerebrovascular disease. Clopidogrel is a pro-drug, metabolised to its active component by CYP2C19, with about one-third of patients having reduced enzyme activity owing to the loss-of-function variants *CYP2C19\*2* or *CYP2C19\*3*94. Patients harbouring these polymorphisms have high on-treatment platelet reactivity and an increased risk of ischaemic events95. Although there has been a lot of debate and controversy about implementing *CYP2C19* genotyping prior to the use of clopidogrel in coronary artery disease, consensus is now emerging in support of its use, particularly in patients undergoing percutaneous coronary intervention. A real-world evaluation from nine US medical centres of 3,342 patients showed that in patients with *CYP2C19* loss-of-function variants, the use of an anti-platelet agent other than clopidogrel reduced major atherothrombotic events by 44%96. In patients with stroke or transient ischaemic attack, the risk of recurrent ischaemic events is increased in patients with *CYP2C19* loss-of-function variants81. Indeed, the use of ticagrelor instead of clopidogrel in such patients reduced the risk of stroke at 90 days by 23%97.

The opiate analgesic codeine is a pro-drug that is metabolised to morphine by CYP2D6. *CYP2D6*, which is the most widely studied pharmacogene, is highly polymorphic, with approximately 133 *CYP2D6* allelic variants listed on the PharmVar data repository98. Individuals can be segregated into poor, intermediate, normal and ultra-rapid metabolisers. Given that the majority of the analgesic activity of this drug is due to morphine rather than codeine, poor metabolisers who lack the CYP2D6 enzyme will have a reduced analgesic effect82. The frequencies of the loss-of-function polymorphisms vary in different ethnic groups, from 0% in West Africa to 12% in the UK32. By contrast, about 2% of the UK population are ultra-rapid metabolisers, rising to 39.5% in Algeria32. Ultra-rapid metabolisers have two or more copies of the gene on the same chromosome, and typically require higher doses to achieve a therapeutic effect with active drugs.However, with pro-drugs, lower doses are needed to achieve a therapeutic effect in ultra-rapid metabolisers, while the use of a standard dose can lead to toxicity. For example, increased conversion of codeine to morphine can lead to respiratory depression99. Some children, for example those with obstructive sleep apnoea, might be at increased risk of respiratory depression with codeine if they are ultra-rapid metabolisers100. As *CYP2D6* genotyping is not routinely available in most countries, regulatory agencies have introduced a blanket contraindication to the use of codeine post tonsillectomy (in those under 18 years) and for the treatment of cough in those aged below 12 years.

**[H1] Implementation into clinical practice**

Implementation of pharmacogenomics into clinical practice has been slow, and pharmacogenomic testing has been restricted to certain specialist centres101. Reasons include a perceived lack of clinical utility, inability to access genotyping tests, lack of clarity on cost effectiveness, lack of knowledge on how to interpret pharmacogenomic tests and the actions to take when a patient has a variant allele, worries about disruption to the normal clinical pathway, and concerns over confidentiality issues102. Notably, a degree of genetic exceptionalism seems to exist in that regulators and clinicians accept the concept of dose modification in renal or hepatic failure based on pharmacokinetic modelling, but not when the variation is due to a genetic variant that has the same effect on drug exposure103.

Of course, evidence of clinical utility is needed before implementing a pharmacogenomic test. However, confirmation of utility cannot be achieved solely by waiting for RCTs, which are at the top of the evidence hierarchy104,105. Although RCTs will be needed for some drug–gene pairs, and in fact many have been undertaken using different designs106, conducting trials for many gene–drug pairs would be difficult for several reasons. First, RCTs are costly107, and given that in many cases the drug involved is generic and off-patent, funding may not be available. Second, there is lack of generalisability of many trials given the strict inclusion and exclusion criteria. Third, ethical issues might arise in dosing participants with known functional variants105. Fourth, trials that take into account polypharmacy (typically defined as ≥5 concomitant drugs) and multimorbidity, as well as multiple drug–gene associations in the elderly, are difficult to design. Finally, given that many genetic variants have low population allele frequencies, trials with large sample sizes would be needed, which might not be feasible not only because of cost but also because of difficulties in recruitment.

In order to enable clinical implementation, all types of evidence should be taken into account and evaluated108. Furthermore, implementation should be accompanied by continuous monitoring in real-world practice so that the process of implementation is continually refined to optimise patient outcomes. To facilitate implementation of pharmacogenomics into the UK National Health Service (NHS), the Royal College of Physicians and the British Pharmacological Society produced a report with some key recommendations109; an adapted set of recommendations to make them relevant for any health-care system are presented in **Box 1**.

An emerging consensus is that implementation needs to embrace a pre-emptive genotyping strategy110. Practically, this approach could mean that a patient requiring a pharmacogenetic test for a particular gene–drug pair would be genotyped using a pharmacogenomics panel containing a number of variants, with data being stored on the electronic health record for future use when, and if, a patient requires another drug for which response might be subject to pharmacogenomic variation. This strategy has been adopted at several US sites, including St Jude Children’s Research Hospital111, Vanderbilt University Medical Center22 and the Mayo Clinic112.

To provide high-quality evidence for the utility of pre-emptive genotyping for implementation, the European Ubiquitous Pharmacogenomics consortium has undertaken a prospective study in seven European centres with almost 7,000 patients randomly allocated to either standard care or genotype-guided care113. The pharmacogenomics panel utilised in the trial tested for 44 variants in 12 genes relevant for 42 drugs114. The primary outcome measure was the effect on ADR prevalence. The results of this innovative study showed that genotype-guided care reduced ADRs by 30%, providing the first randomised evidence of the utility of pharmacogenomic panel-based testing115.

To bridge the knowledge gap in pharmacogenomics, several organisations have developed guidelines, including the Clinical Pharmacogenetics Implementation Consortium (CPIC), the Canadian Pharmacogenomics Network for Drug Safety (CPNDS), the Dutch Pharmacogenetics Working Group (DPWG), and the French National Network (Réseau) of Pharmacogenetics (RNPGx); there are currently 26 [CPIC guidelines](https://cpicpgx.org/guidelines/), a number likely to increase over the years, and guidelines are updated as new evidence emerges116. However, it is important to note that the CPIC guidelines provide advice on what needs to be done when a patient already has pharmacogenomics data but do not advise on when patients should be tested. Therefore, implementation in any health-care system should also develop eligibility guidelines on who should be tested and when.

Given the constraints that health services operate under, evidence of cost-effectiveness of pharmacogenomic testing is important. Fortunately, evidence of the cost-effectiveness of individual pharmacogenomic tests is increasing117, including a panel-based approach118. Cost-effectiveness analyses are often dependent on the minor allele frequency of the polymorphism; for example, with allopurinol, a drug used for the treatment of gout, genotyping for *HLA-B\*58:01* to prevent serious cutaneous ADRs has been shown to be cost-effective in Asian populations (the variant allele is present in 15–18% of certain Asian populations) but not in European populations (the variant allele is present in 1–2%)119. However, of note, this approach has the potential to lead to inequalities within individual countries where some ethnic groups might be denied genotyping because the population frequency of the allele is lower than in other ethnic groups within the same country120.

**[H1] Drug discovery and drug safety**

Drug discovery and development is a risky and costly business. The overall failure rate is >96%121, and the estimated cost of bringing one drug to market is ~$1.3 billion122. Use of genomics data has been shown to increase success rates. For example, the selection of genetically supported targets doubled the success rate in clinical development123. Further analysis has shown that genetically supported targets are more likely to be successful in phase II and III trials124. It is also interesting to note that two-thirds of FDA-approved drugs in 2021 had supportive human genetic evidence, mostly in the oncology area125. [Open Targets](https://www.opentargets.org/) is a useful open access database that provides a resource for identifying and prioritising genomically supported targets. Three examples of where germline genetic data have been used to develop new drugs are provided in **Box 2**.

In oncology, sequencing technologies have enabled the identification of driver mutations within somatic cancer genomes, which has led to the development of drugs or drug combinations that target these mutations (Table S1), with an improvement in prognosis130. Vemurafenib which inhibits *BRAF* and crizotinib which inhibits *ALK* are two examples (**Fig 1**). Perhaps one of the most successful drug classes developed is the tyrosine kinase inhibitors (TKIs), such as imatinib, which targets the *BCR–ABL1* fusion gene in chronic myeloid leukaemia (CML)131. This drug has had a transformational effect on the prognosis of CML in most patients, whose life expectancy is now similar to age-matched individuals in the general population132. Furthermore, some patients with durable molecular responses can discontinue the TKI133. The effect of targeted agents in solid tumours has perhaps been less successful than in CML, but nevertheless can lead to dramatic responses at least initially134, with relapse being due to the development of new mutations. The challenge in solid cancers is now to identify the best combination of therapies targeting the aberrant pathway(s) to lead to durable progression-free and overall survival.

Evidence of genetic variation in the germline might also enable the prediction of drug toxicity, reducing the risk of failure during clinical development. An example is the inhibition of diacylglycerol acyltransferase 1 (DGAT1) as a potential treatment for type 2 diabetes mellitus and obesity. In a phase I trial, AZD7687, a reversible and selective DGAT1 inhibitor, led to severe diarrhoea, requiring drug discontinuation in >50% of participants135, making it unlikely that the drug would progress to the next phase of development. Consistent with this finding, *DGAT1* mutations have subsequently been identified as a cause of severe diarrhoea in a family of Ashkenazi Jewish descent136. Prior knowledge of the phenotype associated with *DGAT1* mutations may have modified, or prevented, the development of DGAT1 inhibitors.

Genetic evaluation might also help in determining causality even when a drug has been on the market for many years. For example, statins such as simvastatin have been reported to lead to cataracts, but causality remains uncertain. A systematic review and meta-analysis of 21 observational studies showed that statins were associated with an increased risk of cataracts (OR 1.11, 95% CI 1.02–1.21)137. However, a high degree of heterogeneity was found between the different studies included in the meta-analysis, and confounding could have accounted for the observed increased risk. An analysis of the UK biobank showed that low activity variants of the HMG-CoA reductase (*HMGCR*) gene, as a proxy for HMGCR inhibition by statins, increased the risk of cataracts (OR 1.14, 95% CI 1.00–1.29) and cataract surgery (OR 1.19, 95% CI 1.04–1.35)138, providing some evidence that statin use may be causally linked to cataract formation. Interestingly, low-activity variants of *PCSK9* and *NPC1L1*, proxies for PCSK9 inhibitors and NPC1L1 inhibition by ezetimibe, respectively, did not increase the risk of cataracts, providing the potential for alternative therapies for individuals who require lipid-lowering therapy but are at an increased risk of cataracts138.

**[H1] Future perspectives**

***[H2] Use of population biobanks***

The increasing availability of large population biobanks, with linked genomics data, provides an opportunity for future pharmacogenomics research. Compared with traditional studies, bigger sample sizes might be possible with biobank-based studies, which is likely to be more cost-effective. For instance, using BioVu as an example, a cost analysis showed that the median cost of a traditional study was >$1.3 million compared with ~$77,000 for a biobank study, with a median cost/year per participant being about 5 times higher for the traditional study139.

However, biobank studies have some disadvantages: many have been set up for billing, and therefore coding accuracy might be relatively poor, and even when the biobank has been set up for scientific research, the phenotype might be fairly superficial. For example, in a study evaluating type I hypersensitivity reactions (such as anaphylaxis) with penicillin antibiotics, a deep phenotyping approach identified *HLA-DRB1\*10:01* (OR 2.92, 95% CI 2.04–4.18) as the predisposing locus68. However, another study conducted in the UK, Estonian and BioVu biobanks, with replication using 23andMe samples, showed an association with *HLA-B\*55:01* (OR 1.41, 95% CI 1.33–1.41) with the phenotype of self-reported penicillin allergy140. Self-reporting of penicillin allergy has been shown to be incorrect in >90% of cases141. Although both loci are likely to be important in predisposing to different phenotypes of penicillin allergy, the different results highlight that phenotyping is crucial and needs to be considered in contextualising results.

Clearly the use of biobank data has huge advantages, and research in this area is likely to increase. Improving the phenotypes within biobanks would further strengthen the utility of biobanks for pharmacogenomic studies. However, traditional studies will still be needed for many phenotypes, and the two approaches should be regarded as being complementary rather than competitive. **[Au: Edit OK?]**

***[H2] Rare variants***

Most of the heritability in drug response phenotypes is unknown, with a study providing estimates ranging from 0.05 to 0.59142. As the majority of pharmacogenomic studies have focused on common variants, it is possible that a proportion of the missing heritability might be due to rare variants143. Evaluation of exome sequencing data from >60,000 individuals showed that rare variants are highly prevalent in pharmacogenes; of the 41 putatively functional variants being carried by each individual, rare variants accounted for 10.8%144. With decreasing costs and increasing availability of human genome sequencing, a challenge for pharmacogenomics will be how the effect of rare variants can be incorporated into assessing their contribution to a drug response phenotype and, consequently, incorporation into clinical implementation programmes145. It will be important to concentrate on well-known pharmacogenes, at least initially, but large sample sizes will be needed, and might only be achievable through the availability of large well-curated biobanks. Novel study designs including n-of-1 trials will also be needed5,106. Another key issue with rare variants is their functionality, with most of them being categorised as variants of uncertain significance. In silico methods to predict functionality, including methods that use artificial intelligence for pharmacogenomic variants, have been developed146. An analysis of long-read *CYP2D6* gene sequence data using neural network analysis showed that this model was able to explain 79% of inter-individual variability compared with 54% for the conventional method147. Functional genomic evaluation will also be required in some cases using high-throughput methods such as massively parallel reporter assays148 and deep mutational scanning149.

***[H2] Polygenic scores***

Interest in using polygenic scores (also known as polygenic risk scores) for disease risk prediction, disease stratification, prognostication and screening is growing150. Polygenic scores also have potential applications in pharmacogenomics; indeed, the warfarin dosing algorithm represents an early example of a polygenic score with RCT evidence of utility93. Polygenic scores have also been reported for clopidogrel in preventing ischaemic cardiac events151, β-blockers in heart failure152 and drug-induced liver injury153, but replication is needed. For most pharmacogenomic polygenic scores, a major issue will be the need for large sample sizes, which may only be possible using biobank data with good quality phenotypes.

Disease risk stratification using polygenic scores might also identify a subgroup of the population who would benefit from intervention earlier than would have been possible using clinical risk factors only. Analysis of UK biobank data on 306,654 individuals without a history of cardiovascular disease and not on lipid-lowering therapy showed that for those individuals at intermediate risk (5–10% cardiovascular risk), the use of a polygenic score, and starting statin therapy, could prevent one additional cardiovascular event for every 340 people screened, potentially preventing 7% more cardiovascular events than conventional risk prediction alone154. However, whether this approach is cost-effective will depend on the health-care setting, the predictive accuracy of the polygenic score and genotyping costs155. Implementation of polygenic scores into clinical practice is further away than conventional pharmacogenomic markers because there is still a need to demonstrate clinical utility and the inherent complexity of integrating of polygenic scores into clinical pathways. In fact, polygenic scores will face many of the same issues highlighted above for the implementation of pharmacogenomics.

***[H2] Diversity***

Genomic studies are increasingly realised to be highly Euro-centric and to lack ethnic diversity and therefore have the potential to exacerbate already existing health inequalities. Evaluation of existing GWAS data shows that 97% of the participants are of European ancestry with only 2.2% Asian, 0.02% African, and 0.02% African-American or Afro-Caribbean ancestry156. Polygenic scores, which have largely been developed from European ancestries, are also problematic because of low portability across global populations157.

Lack of diversity has also been observed in pharmacogenomic studies. For example, most warfarin dosing algorithms have been based on *CYP2C9\*2* and *CYP2C9\*3* polymorphisms, which are prevalent in European populations but largely absent in African ancestry populations158. Studies that have evaluated the role of *CYP2C9* polymorphisms that are more prevalent in African populations are scant159,160. Lack of consideration of ethnic diversity is also seen in drug labels. For example, the European label for siponimod161, a drug used for multiple sclerosis, instructs prescribers to genotype for *CYP2C9* prior to drug prescribing, with the dose being reduced by 50% in those in whom CYP2C9 activity is partially reduced (*CYP2C9\*2\*3, CYP2C9\*1\*3*), and avoid it altogether where activity is reduced to 10% of normal (*CYP2C9\*3\*3*). However, no mention is made of testing for African-specific alleles such as *CYP2C9\*5*, *CYP2C9\*6* and *CYP2C9\*11* that also reduce CYP2C9 activity (multiple sclerosis is just as common in African as it is in European populations)162. Another important example is *DPYD* genotyping to prevent toxicity from fluoropyrimidine anticancer agents. *DPYD* genotyping was implemented in most of Europe in late 2020; in the UK, currently about 38,000 genetic tests are undertaken per year. However, testing is only for four variants that have been identified in European ancestry populations42, and many non-European patients might be at risk of potentially preventable fluoropyrimidine toxicity.

In order to improve diversity of genomics data, numerous programmes have been launched worldwide, for example [H3Africa](https://h3africa.org/), [Qatar genome project](https://www.qatargenome.org.qa/about-qgp/qatar-genome/about-us), GenomeAsia 100K Project163 and the [China Kadoorie Biobank](https://www.ckbiobank.org/), to name a few. In the [Trans-Omic for Precision Medicine (TOPMed) program](https://topmed.nhlbi.nih.gov/), which aims to identify treatments tailored to individuals, 60% of the 180,000 sequenced participants are of non-European ancestry. The [All of Us Research Program](https://allofus.nih.gov/) in the US is recruiting 1 million participants from community settings, with a focus on ensuring diversity is represented in the recruitment processes. In the UK, [Our Future Health](https://ourfuturehealth.org.uk/), which aims to recruit 5 million individuals, will ensure that the recruitment is representative of the ethnic diversity in the UK. Furthermore, the global biobank meta-analysis initiative is a collaboration of 24 biobanks with >2.2 million patients with the aim of facilitating genetic discoveries in ancestrally diverse populations164. The progress is encouraging, but it is important to note that many of the biobanks lack the granular data needed to link ethnic-specific variants to pharmacogenomic phenotypes. Therefore, dedicated well-designed studies that can optimise drug development and use for all global populations are required. Another key issue is the need to increase capacity and capability within different countries, without which it will not be possible to overcome these inequalities.

**[H1] Conclusions**

Research in pharmacogenomics has increased since the completion of the Human Genome Project, spanning the full spectrum from drug discovery to clinical implementation **[Au: Edit OK?]**. Data on the utility of some pharmacogenomic associations are increasing, but implementing these into clinical practice has been frustratingly slow. Implementation of pharmacogenomics is likely to be a major driver for the mainstreaming of genomics into clinical practice. The increasing availability of human genomics data is also having a major impact on the drug discovery and development process and has already been shown to improve success rates. Genomics data will also help in safety determination in the early stages of drug development, identifying hazards which might not be detectable through preclinical toxicology studies. **[Au: Edit OK?]**

Pharmacogenomics is just one component of the drive towards personalised or precision medicine. Multimodal algorithms that incorporate both clinical (for example, age, sex, body weight etc) and genetic factors (**Fig. S1**), as well other -omic biomarkers, are needed. The development of such multimodal algorithms will undoubtedly be enhanced by the use of digital tools, developed by the burgeoning industry in digital therapeutics. Progressing the field of pharmacogenomics faces many challenges, as outlined in this article, but these challenges are not insurmountable, and overcoming them through concerted research efforts will likely lead to many opportunities to improve human health (**Box 3**).

**References**

 **[Au: Is there a doi for ref 113? The Lancet in press article]**

 **[Au: For references that are particularly worth reading (5-10% of the total), please provide a single bold sentence that indicates the significance of the work.]**

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**Peer review information**

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**Related links**

CPIC Guidelines

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China Kadoorie Biobank

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Our Future Health

<https://ourfuturehealth.org.uk/>

 **[Au: We usually include a maximum of 7 display items so I have suggested a couple of items to remove. Please see my comments below]**

**Table 1. Proportion of people who carry at least one actionable pharmacogenomic variant**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Country | Number studied | Number of genes evaluated | Proportion carrying at least one actionable genotype or diplotype | Reference |
| Australia | 5,408 | 4 | 95.9% | 15 |
| Canada | 98 | 19 | 96.9% | 16 |
| Estonia | 42,092 | 11 | 99.8% | 17 |
| Netherlands | 498 | 11 | 99.4% | 18 |
| Qatar | 6045 | 15 | 99.5% | 19 |
| UK | 487,409 | 14 | 99.5% | 20 |
| UK | 713 | 11 | 98.7% | 21 |
| US | 9,589 | 6 | 91.4% | 22 |
| US | 1,013 | 5 | 99.0% | 23 |

**Table 2. Examples of immune-mediated adverse reactions associated with HLA alleles**

|  |  |  |  |
| --- | --- | --- | --- |
| Reactions | Drug | HLA class I | HLA class II |
| SCAR | Allopurinol | *HLA-B\*58:01*48 | NA |
| Carbamazepine | *HLA-A\*31:01*47,49*HLA-B\*15:02*50*B\*15:21*51*B\*57:01*52 | NA |
| Dapsone | *HLA-B\*13:0153,54* | NA |
| Nevirapine | *HLA-C\*04:01*55,56 | NA |
| Phenytoin | *HLA-B\*15:02*57 | NA |
| DRESS | Abacavir | *HLA-B\*57:01*58 | NA |
| Vancomycin | *HLA-A\*32:0159*  | NA |
| DILI | Amoxicillin-Clavulanate | *HLA-A\*02:01*60  | *HLA-DRB1\*15:01-DRB5\*01:01-DQB1\*06:02* haplotype61,62  |
| Flucloxacillin | *HLA-B\*57:01*63,  | NA |
| Ticlopidine | *HLA-A\*33:03*64,65 | NA |
| Agranulocytosis | Clozapine | *HLA-B\*38HLA-B\*39HLA-B\*67*66HLA-Cw7-B18HLA-Cw7-B39 haplotype67 | *HLA-DRB5\*02:01*67 |
| Type I hypersensitivity reaction | Beta lactam antibiotics | NA | *HLA-DRB1\*10:01*68*HLA-DRA* rs719269 |

DILI, drug-induced liver injury; DRESS, drug reactions with eosinophilia and systemic symptoms; SCAR, Serious cutaneous adverse reactions (includes Stevens-Johnson syndrome and toxic epidermal necrolysis and DRESS), NA, not applicable.

**Table 3. Examples of drugs with known alterations in efficacy due to variation in genes involved in either the pharmacokinetic or pharmacodynamic actions of the drug.**

 **[Au: The germline variants are not actually listed in the table – please add them or change the table title to e.g. Examples of drugs with known alterations in efficacy due to germline variants]**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Drug | Indication | Gene | Efficacy trait | Clinical action\* |
| Clopidogrel | Primary percutaneous coronary intervention, Transient ischaemic attacks and strokes | *CYP2C19* | Major adverse cardiovascular events80, cerebral ischaemic events81 | Use other antiplatelet agents in *CYP2C19* PMs |
| Codeine | Pain relief | *CYP2D6* | Analgesic effect82 | Use other analgesic agents in *CYP2D6* PMs |
| Eculizumab | Paroxysmal nocturnal haemoglobinuria | *C5* | Red blood cell haemolysis83 | Consider alternative therapies in patients with C5 mutations |
| Lansoprazole, omeprazole, pantoprazole | Gastric acid suppression | *CYP2C19* | Ulcer healing, eradication of *H. pylori84* | Change dose according to metaboliser status |
| Metformin | Type 2 diabetes mellitus | *ATM, SLC2A2* | Improvement in HBA1c85,86 | Potential to change dose but unclear |
| Olaparib, niraparib, rucaparib | Cancers of the ovary, breast, pancreas or prostate | *BRCA1, BRCA2* | Progression-free survival of the different cancers87 | Use in patients with *BRCA1/2* mutated cancers |
| Sulfonylurea | Maturity onset diabetes of the young | *HNF-1α* | Fasting plasma glucose reduction88 | Change treatment from insulin to low-dose sulfonylurea |
| Sulfonylurea | Neonatal diabetes | *KCNJ11, ABCC8* | Diabetes control89 | Change from insulin to high dose sulfonylurea |
| Tamoxifen | Breast cancer | *CYP2D6* | Breast cancer recurrence and survival90,91 | Use alternative therapeutic approaches in *CYP2D6* PMs |
| Voriconazole | Fungal infections | *CYP2C19* | Resolution of fungal infection92 | Use alternative agent in URMs (lack of efficacy), and in PM (because of increased risk of toxicity) |
| Warfarin | Anticoagulation | *CYP2C9, VKORC1, CYP4F2* | Maintenance dose and time in therapeutic range for INR93 | Alter dose based on genotype and clinical factors |

**\***The clinical actions suggested are based on the original articles describing these efficacy traits and/or guidelines. PM: poor metaboliser, URM: ultra-rapid metaboliser, INR: international normalised ratio.

 **[Au: Table 4 doesn’t seem as strictly relevant to the main focus of the review as the other tables and, given our space restraints for display items, I would suggest that this table should be removed (it could be included as Supplementary Information instead if you wish).]**

**Box 1. Recommendations for the implementation of pharmacogenomics in clinical practice**

* Clinical implementation of pharmacogenomics should occur in all health-care settings and should focus on drugs that have actionable information. One model might be to start with a small number of drug–gene pairs and gradually increase to a comprehensive service.
* Appropriate funding is needed for implementing a pharmacogenomic clinical service; active efforts should be made from the beginning to ensure the service does not exacerbate health inequalities. **[Au: Edit OK, to keep it concise?]**
* The pharmacogenomic service should be adaptable — that is, able to modify and refine the available tests based on new evidence.
* A comprehensive education and training package that is relevant to all involved health-care professionals should accompany the implementation of a pharmacogenomic service.
* Support is needed for clinicians, including clinical decision support systems, to minimise errors and maximize cost efficiency.
* The pharmacogenomic service should undergo continuous audit and evaluation, leading to the development of a learning health system that maximises patient benefits.
* A pharmacogenomic service should be accompanied by funding for research; not only biomedical research, but also research into ethical, legal and social issues.
* Clear lines of communication should be established with health-care managers, patient representative bodies, the public and the media.

Footnote: Adapted from the Royal College of Physicians and the British Pharmacological Society109.

**Box 2. Successful drugs developed through a knowledge of human genetic mutations**

**CFTR MODULATORS FOR CYSTIC FIBROSIS**

Cystic fibrosis, an autosomal recessive condition, is caused by mutations in the *CFTR* gene, which codes for the cystic fibrosis transmembrane conductance regulator protein. The most common *CFTR* mutation *Phe508del* is observed in 70% of cases, although, to date, >2,000 mutations have been identified. High throughput screening has identified compounds able to modulate the function of the abnormal CFTR protein. These CFTR modulators have transformed the lives of patients and can be divided into potentiators (which increase chloride ion conductance) and correctors (which target abnormal protein folding and increase CFTR expression on the cell membrane). Ivacaftor, which was initially trialled in the 4% of patients carrying the *G551D* mutation, led to a 55% reduction in the pulmonary exacerbation rate, while the combination of elexacaftor, tezacaftor and ivacaftor, used in patients with at least one copy of the *Phe508del,* reduced exacerbation rate by 63%. Further information can be found in Tewkesbury *et al*126.

**PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 9 (PCSK9) INHIBITORS**

Gain-of-function mutations in the *PCSK9* gene lead to high LDL-C levels and premature cardiovascular disease through enhanced intracellular degradation of LDL receptors. Loss-of-function mutations increase LDL receptor function and reduce levels of LDL-C and have been associated with reduced risk of cardiovascular disease. Alirocumab and evolocumab, fully humanised anti-PCSK-9 antibodies, reduce LDL-C by 54% when given fortnightly. Cardiovascular outcome trials have shown that both antibodies reduce cardiovascular end-points, with the greatest absolute benefits seen in those at increased risk of disease. Further information can be found in Kim and Wierzbicki127.

**ANTI-SCLEROSTIN ANTIBODIES**

Sclerosteosis is a rare autosomal recessive disorder identified in the Afrikaner population caused by loss-of-function mutations in the *SOST* gene, which encodes sclerostin, a 231-amino acid protein that inhibits bone formation. While homozygotes are severely affected with skull abnormalities, syndactyly and CNS complications, heterozygotes have increased bone mass but without complications **[Au: ok to add]** and rarely get fractures. Non-clinical studies showed that anti-sclerostin antibodies increased bone mass with bone of good quality with the effect being anabolic rather than anti-resorptive. In clinical trials in patients with osteoporosis, romosozumab (an anti-sclerostin antibody) reduced vertebral fractures by 73%. Romosozumab has been approved for the treatment of severe osteoporosis in postmenopausal women with high fracture risk, but because it was associated with serious cardiovascular end-points in some studies, it is only recommended for use in patients without a history of myocardial infarction or stroke. In the UK biobank, SOST genetic variants (with the same effect as romosozumab) were associated with reduced risk of fracture and osteoporosis (commensurate with the therapeutic effect of romosozumab) and with a higher risk of myocardial infarction and/or coronary revascularization and major adverse cardiovascular events. Further information can be found in Fabre *et al*128 and Bovjin *et al*129.

**Box 3. Research priorities for pharmacogenomics in the future**

* Research to identify new drug–gene associations is still needed, but lessons need to be learnt from the past to increase the robustness and replicability of the findings.
* With the change in demographics in most countries, an important area for further study is the evaluation of the role of pharmacogenomics in elderly people living with multiple long-term conditions (multimorbidity), not only in terms of medicines optimisation, but also for de-prescribing (stopping certain drugs to reduce the medicines burden).
* Methodologies need to be developed to incorporate rare variants (alongside common variants) to determine their contribution to pharmacogenomic phenotypes.
* Multi-modal algorithms that incorporate host, environmental and clinical factors, in addition to genomic factors, need to be investigated to determine whether this approach can increase the predictability of drug response phenotypes. Combining such algorithms with digital tools might further enhance the dose and choice of drugs, as well as adherence to treatment.
* Therapeutic drug monitoring (TDM), which is available for many drugs, needs to be explored to identify novel drug–gene pair associations, as well as to determine whether a combined approach (that is, TDM and pharmacogenomics) enhances utility.
* A wide variety of study designs should be utilised for investigating the clinical utility of drug–gene pair associations, including novel designs such as n-of-1 trials, adaptive trials and basket trials, as appropriate, depending on the drug and phenotype being investigated.
* The use of real-world evidence in assessing drug–gene pair associations needs to encompass both the identification and replication of novel associations, and subsequent refinement and improvement through the development of learning health systems. **[Au: Edit OK?]**
* Implementation of pharmacogenomics into clinical practice needs to be actively pursued, and will require multi-disciplinary expertise including specialists in health economics, as well as ethical, legal and social expertise to ensure that inequalities are not exacerbated.
* An area that needs more work in terms of implementation is the interface with clinical systems and clinical pathways, which are rate-limiting factors to successful implementation. This step will require country-specific expertise in implementation science.
* Diversity of genomics data needs to be improved to ensure that the benefits of pharmacogenomics are realised in all global populations and are not a source of exacerbating racial inequalities.
* The phenotypes (clinical, pharmacological, imaging and laboratory) in large biobanks need to be improved to facilitate disease stratification, identify novel pharmacogenomic associations and facilitate implementation.
* Polygenic scores to enable choice of drug and dose need to be investigated for both efficacy and safety phenotypes, and pathways to implementation need to be developed, when appropriate. Polygenic scores that identify individuals at high risk of disease and therefore enable early drug treatment to improve prognosis need to be prospectively assessed using appropriate study designs. **[Au: Edit OK?]**
* Multicentre, international collaborations, with standardised drug-related phenotypes, need to be undertaken to improve study power, identify novel associations (including those with low effect sizes) and enhance diversity.
* Multi-omic approaches need to be investigated to determine the contribution of individual -omic technologies (and their combination) to drug response phenotypes.
* The use of genomics to identify targets for drug development, including for the assessment of on- and off-target effects that might lead to safety issues, should be supported not only by the pharmaceutical industry, but also through public–private partnerships.

**Figure 1. The pharmacogenomics landscape. A.** Pharmacogenomics is important for predicting drug dose (for example, predicting the dose of thiopurines such as 6-mercaptopurine based on variation in the thiopurine methyltransferase (*TPMT*) gene); improving drug efficacy (for example, the use of sulfonylureas in patients with rare *HNF-1α* mutations; also see table 3); activation of pro-drugs such as clopidogrel and codeine into active metabolites: and preventing adverse drug reactions by prospectively genotyping individuals for at-risk alleles, for example, *SLCO1B1* prior to the use of simvastatin. Pharmacogenomics is also important for drug discovery and development through evaluation of both germline (see box 2) and somatic (see table S1) genomes. **[Au: I think this figure provides a nice overview of the main applications of pharmacogenomics and could be developed a little further. Please do expand this figure legend here so that the figure and its legend can ‘stand alone’ from the main text. In addition, please could you make a mention of simvastatin, sulfonylurea, vemurafenib and crizotinib in the main article as these are not mentioned throughout. ]**

**B.** Pharmacogenomic information contained in drug labels from different regulatory agencies. The number of drugs with pharmacogenomic information, and the guidance provided in the drug labels, varies between different regulatory agencies. The guidance in the drug label falls into the following categories: Testing required (red); testing recommended (amber); actionable pharmacogenomics (green); and informative pharmacogenomics (blue). The testing required and testing recommended categories refer to situations where a test “should be” performed, or “should be considered”, respectively. Actionable pharmacogenomics provides information on a drug-gene interaction, but does not require or recommend testing. Informative pharmacogenomics refers to (a) drugs where a drug-gene interaction has been ruled out; (b) is not clinically significant; or (c) label appears on the FDA biomarker list but does not fit into the above categories. From the PharmGKB website (<https://www.pharmgkb.org/labelAnnotations>) with permission.

 **[Au: I suggest not including Figure 2. As mentioned above, we have a limit of 7 display items and as the information in this figure is not focused solely on pharmacogenomics I think it could be easily included in the main text of the article instead. OK?]**