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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 growing 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.

Sections

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Introduction

Inter-individual variability in response to foods and medicines has been recognized for millennia – Pythagoras (570 BC to 495 BC) described the occurrence of red blood cell haemolysis after ingestion of fava beans by some individuals. 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 worldwide[1].

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 drug[2]. 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 optimization of drug dose and choice in individual patients to maximize efficacy and minimize toxicity (Fig. 1a).

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 response[5]. 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 articles[6–9].

In terms of drug safety, adverse drug reactions (ADRs) account for about 6.5% of hospital admissions in adults[10], increasing to >15% when focusing on people with multimorbidity[11]. Furthermore, ADRs affect about 15% of people in hospital[12]. Although these are UK figures, similar frequencies have been reported in other countries[13,14].

Variation in drug efficacy or safety 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 of the 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 personalized choice and dose of drug that is relevant for the individual patient's needs.

Although pharmacogenomics has largely been a focus for academic research over the past few decades, policy makers are now increasingly interested in the role of pharmacogenomics in improving patient outcomes, which might enable implementation into clinical practice. In addition, growing evidence from the pharmaceutical industry of the value of genomically defined targets in improving success rates in drug development will further increase interest and research in this area.

In this Review, 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.

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[15–23] (Table 1). In addition, drugs whose response is affected by pharmacogenomic variation are frequently used in clinical practice. For example, ~50% of prescriptions in the USA are affected by actionable germline pharmacogenes[24]. In the UK, over 1 year, 58% of patients were prescribed at least one drug affected by polymorphisms in actionable pharmacogenes[25]. Furthermore, as individuals age, they are prone to more diseases that require drug therapy; therefore, almost 90% of patients older than 70 years of age will be exposed to at least one drug with pharmacogenomic guidance[25].

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 annotations[26,27]. PharmVar, a centralized data repository, provides high-quality data on pharmacogene variation[28]. The FDA has a list of 517 gene–drug associations that have been included in drug labels[29], and its table of pharmacogenomic associations lists 121 drug–gene interactions[30]. However, harmonization in pharmacogenomic drug labelling between different regulatory agencies is lacking (Fig. 1b) 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 provide guidance on 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 for tamoxifen[31], 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. As a result, approximately 1 in 10 women who are homozygous for non-functional *CYP2D6* alleles[32], and are thus poor metabolizers, might potentially receive reduced benefit from tamoxifen.

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 interactions[33], reflecting our greater knowledge of drug pharmacokinetics than of 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 – absorption, distribution, metabolism and excretion – and how these determine inter-individual variability in drug handling. Such advances have also shown that genetic factors have an important role in determining drug pharmacokinetics. For example, studies of monozygotic and dizygotic twin pairs have shown the heritability of metoprolol and torsemide pharmacokinetics to be 91% and 86%, respectively[34].

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 are largely derived from observational studies that vary in size and quality, with many small studies claiming large effect sizes that have not been replicated in subsequent
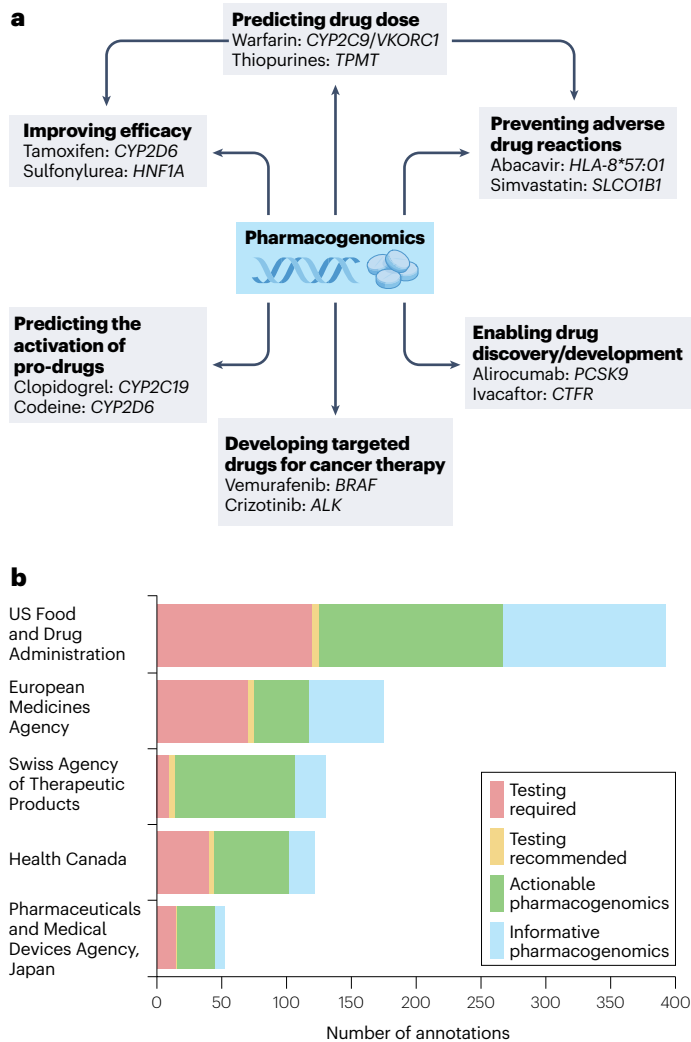
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Fig. 1 | The pharmacogenomics landscape. a, Pharmacogenomics is important for predicting drug dose (for example, predicting the dose of thiopurines such as 6-mercaptopurine based on variation in the thiopurine methyltransferase (*TPMT*) gene), improving drug efficacy (for example, the use of sulfonylureas in patients with rare *HNF1A* mutations; also see Table 3), predicting the 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, genotyping *SLCO1B1* before the use of simvastatin). Pharmacogenomics is also important for drug discovery and development through evaluation of both germline (Box 2) and somatic (Supplementary Table 1) genomes. **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 'testing required' and 'testing recommended' categories refer to situations where a test 'should be performed' or 'should be considered', respectively. 'Actionable pharmacogenomics' means that the label provides information on a drug–gene interaction but does not require or recommend testing. 'Informative pharmacogenomics' refers to drugs for which a drug–gene interaction has been ruled out or is not clinically significant, or for which the label appears on the FDA biomarker list but does not fit into the above categories. Annotation counts were taken from the Pharmacogenomics Knowledge Base (PharmGKB) in 2022 (https://www.pharmgkb.org/labelAnnotations; please note, data for US Food and Drug Administration, European Medicines Agency and Health Canada are continually updated. Data from the Swiss Agency of Therapeutic Products are from 2019. Data from Pharmaceuticals and Medical Devices Agency (Japan) are from 2016). Part **b** adapted with permission from PharmGKB.

larger studies. 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. Randomized 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 trial[35]. The role of RCTs in determining the clinical utility of gene–drug associations is covered later in the article.

Genome-wide association studies (GWAS) represent a fairly cost-effective and unbiased method for identifying gene–drug interactions and might be particularly important for identifying pharmacodynamic drug–gene interactions[36,37] and providing novel insights into mechanisms of action or toxicity. However, <10% of the studies in the GWAS catalogue have so far investigated drug response[38]. Furthermore, over the years, the sample size for drug response GWAS has not increased, unlike the increase in numbers seen in complex-disease GWAS[38]. 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, pharmacogenomic-predisposing loci have been identified in GWAS because of the larger effect sizes than those found for complex diseases[39].

Dose

The dose determines both the efficacy and the 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 metabolizing warfarin) and *VKORC1* (which encodes the enzyme inhibited by warfarin) determine the 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 overexposure, to achieve therapeutic anticoagulation[40]. The importance of germline polymorphisms in determining the dose of anticancer drugs has also been shown with *TPMT* and *NUDT15* polymorphisms and thiopurines[41], *DPYD* polymorphisms and fluoropyrimidines[42], and *UGT1A1* polymorphisms and irinotecan[43]. In all of these instances, a polymorphism that either reduces or abolishes the activity of the relevant enzyme is associated with reduced metabolism of the anticancer drug, resulting in systemic overexposure and dose-dependent toxicity, typically causing bone marrow suppression and/or severe diarrhoea.

Drug safety

ADRs can be divided into type A and type B reactions[44], 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 ADR[44]. The examples given in the previous section on dose are illustrations of type A ADRs.

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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	Ref.
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]
USA	9,589	6	91.4%	[22]
USA	1,013	5	99.0%	[23]

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 ADR[44]. 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 reactions[45] (Table 2). Indeed, some of the associations are akin to Mendelian diseases with genome-wide significant results, such as associations with flucloxacillin hepatitis[46] and carbamazepine hypersensitivity[47] being discovered in just 51 and 23 affected patients, respectively.

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 RCT[48,49]. Drug labels worldwide include a recommendation to genotype individuals before starting abacavir: implementation of HLA genotyping before abacavir administration has led to the virtual disappearance of abacavir hypersensitivity, which was seen in 5% of patients with HIV treated with the drug before genotyping was implemented[48,49].

Advances in HLA pharmacogenomics have generated extensive research to understand the mechanisms of immune-mediated ADRs (for example, with abacavir hypersensitivity[50]). 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 injury[51,52].

Drug efficacy

It has been estimated that only 15% of drugs will have genetic predictors of efficacy with a large enough effect size[53]. 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 benefit[6–9]; lack of accounting for the placebo effect[54]; the effect of non-adherence to medications[55]; inadequate assessment of variation in disease phenotypes between different participants[56]; and inadequate statistical power[57], 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, metabolized 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*[58]. Patients harbouring these polymorphisms have high on-treatment platelet reactivity and an increased risk of ischaemic events[59]. Although there has been a lot of debate and controversy about implementing *CYP2C19* genotyping before 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%[60]. In patients with stroke or transient ischaemic attack, the risk of recurrent ischaemic events is increased in patients with *CYP2C19* loss-of-function variants[61]. Indeed, the use of ticagrelor instead of clopidogrel in such patients reduced the risk of stroke at 90 days by 23%[62].

The opiate analgesic codeine is a pro-drug that is metabolized to morphine by CYP2D6. *CYP2D6*, which is the most widely studied pharmacogene, is highly polymorphic, with approximately 133 *CYP2D6* allelic variants listed in the PharmVar data repository[63]. Individuals can be segregated into poor, intermediate, normal and ultra-rapid metabolizers. Given that the majority of the analgesic activity of this drug is due to morphine rather than codeine, poor metabolizers who lack the CYP2D6 enzyme will have a reduced analgesic effect[64]. The frequencies of the loss-of-function polymorphisms vary in different ethnic groups, from 0% in West Africa to 12% in the UK[32]. By contrast, about 2% of the UK population are ultra-rapid metabolizers, rising to 39.5% in Algeria[32]. Ultra-rapid metabolizers 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 metabolizers, whereas the use of a standard dose can lead to toxicity. For example, increased conversion of codeine to morphine can lead to respiratory depression[65]. Some children, for example those with obstructive sleep apnoea, might be at increased risk of respiratory depression with codeine if they are ultra-rapid metabolizers[66]. 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 younger than 18 years of age) and for the treatment of cough in those younger than 12 years of age.

Implementation into clinical practice

Implementation of pharmacogenomics into clinical practice has been slow, and pharmacogenomic testing has been restricted to certain specialist centres[67]. 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 issues[68]. 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,

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but not when the variation is due to a genetic variant that has the same effect on drug exposure[69].

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 hierarchy[70,71]. Although RCTs will be needed for some drug–gene pairs, and in fact many have been undertaken using different designs[72], conducting trials for many gene–drug pairs would be difficult for several reasons. First, RCTs are costly[73] and, given that in many cases the drug involved is generic and off-patent, funding may not be available. Second, there is lack of generalizability of many trials given the strict inclusion and exclusion criteria. Third, ethical issues might arise in dosing participants with known functional variants[71]. 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 because of both cost and difficulties in recruitment.

To enable clinical implementation, all types of evidence should be taken into account and evaluated[74]. Furthermore, implementation should be accompanied by continuous monitoring in real-world practice so that the process of implementation is continually refined to optimize 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 recommendations[75]; a set of recommendations adapted to make them relevant for any health-care system is presented in Box 1.

An emerging consensus is that implementation needs to embrace a pre-emptive genotyping strategy[76]. 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 in the electronic health record for future use if and when 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 Hospital[77], Vanderbilt University Medical Center[22] and the Mayo Clinic[78].

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 care[79]. The pharmacogenomics panel utilized in the trial tested for 44 variants in 12 genes relevant for 42 drugs[80]. 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 randomized evidence of the utility of pharmacogenomic panel-based testing[81].

To bridge the knowledge gap in pharmacogenomics, several organizations 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, a number likely to increase over the years, and guidelines are updated as new evidence emerges[82]. 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 under which health services operate, evidence of cost-effectiveness of pharmacogenomic testing is important. Fortunately, evidence of the cost-effectiveness of individual pharmacogenomic tests is increasing[83], including a panel-based approach[84]. The cost-effectiveness of genotyping is often dependent on the frequency of the variant allele(s) of interest; 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%)[85]. 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 country[86].

Drug discovery and drug safety

Drug discovery and development is a risky and costly business. The overall failure rate is >96%[87], and the estimated cost of bringing one drug to market is ~$1.3 billion[88]. Use of genomics data has been shown to increase success rates. For example, the selection of genetically

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*[129]	NA
	Carbamazepine	*HLA-A*31:01*[47,130] *HLA-B*15:02*[131] *B*15:21*[132] *B*57:01*[133]	NA
	Dapsone	*HLA-B*13:01*[134,135]	NA
	Nevirapine	*HLA-C*04:01*[136,137]	NA
	Phenytoin	*HLA-B*15:02*[138]	NA
DRESS	Abacavir	*HLA-B*57:01*[139]	NA
	Vancomycin	*HLA-A*32:01*[140]	NA
DILI	Amoxicillin-Clavulanate	*HLA-A*02:01*[141]	*HLA-DRB1*15:01-DRB5*01:01-DQB1*06:02* haplotype[142,143]
	Flucloxacillin	*HLA-B*57:01*[46]	NA
	Ticlopidine	*HLA-A*33:03*[144,145]	NA
Agranulocytosis	Clozapine	*HLA-B*38* *HLA-B*39* *HLA-B*67*[146] *HLA-Cw7-B18* *HLA-Cw7-B39* haplotype[147]	*HLA-DRB5*02:01*[147]
Type I hypersensitivity reaction	β-Lactam antibiotics	NA	*HLA-DRB1*10:01*[102] *HLA-DRA* rs7192[148]

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

Table 3 | Examples of drugs with alterations in efficacy due to variation in specific genes[a]

Drug	Indication	Gene	Efficacy trait	Clinical action[b]
Clopidogrel	Primary percutaneous coronary intervention, transient ischaemic attacks and strokes	CYP2C19	Risk of major adverse cardiovascular events[149] and cerebral ischaemic events[61]	Use other anti-platelet agents in CYP2C19 PMs
Codeine	Pain relief	CYP2D6	Analgesic effect[54]	Use other analgesic agents in CYP2D6 PMs
Eculizumab	Paroxysmal nocturnal haemoglobinuria	C5	Red blood cell haemolysis[150]	Consider alternative therapies in patients with C5 mutations
Lansoprazole, omeprazole, pantoprazole	Gastric acid suppression	CYP2C19	Ulcer healing, eradication of Helicobacter pylori[151]	Change dose according to metabolizer status
Metformin	Type 2 diabetes mellitus	ATM, SLC2A2	Improvement in HbA1c[152,153]	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 cancers[154]	Use in patients with BRCA1/2- mutated cancers
Sulfonylurea	Maturity-onset diabetes of the young	HNF1A	Fasting plasma glucose reduction[155]	Change treatment from insulin to low-dose sulfonylurea
Sulfonylurea	Neonatal diabetes	KCNJ11, ABCC8	Diabetes control[156]	Change from insulin to high-dose sulfonylurea
Tamoxifen	Breast cancer	CYP2D6	Breast cancer recurrence and survival[157,158]	Use alternative therapeutic approaches in CYP2D6 PMs
Voriconazole	Fungal infections	CYP2C19	Resolution of fungal infection[159]	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 INR[114]	Alter dose based on genotype and clinical factors

[a]Alteration in efficacy due to variation in genes involved in either the pharmacokinetic or pharmacodynamic actions of the drug. [b]The clinical actions suggested are based on the original articles describing these efficacy traits and/or guidelines. INR, international normalized ratio; PM, poor metabolizer; URM, ultra-rapid metabolizer.

supported targets doubled the success rate in clinical development[89]. Further analysis has shown that genetically supported targets are more likely to be successful in phase II and III trials[90]. Notably, two-thirds of FDA-approved drugs in 2021, mostly in the oncology area, had supportive human genetic evidence[91]. Open Targets is a useful open-access database that provides a resource for identifying and prioritizing genomically supported targets. Three examples of how 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 (Supplementary Table 1), with an improvement in prognosis[92]. 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, such as imatinib, which targets the BCR–ABL1 fusion gene in chronic myeloid leukaemia (CML)[93]. 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 population[94]. Furthermore, some patients with durable molecular responses can discontinue the tyrosine kinase inhibitor[95]. 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 initially[96], 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 participants[97], 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 descent[98]. Previous knowledge of the phenotype associated with DGAT1 mutations might 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)[99]. 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)[100], 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 cataracts[100].

Future perspectives
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, larger sample sizes might be possible with biobank-based studies, which is likely to make them 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 the median cost per year per participant being about 5 times higher for the traditional study[101].

However, biobank studies have some disadvantages: many have been set up for billing, so 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 locus[102]. However, another study conducted in the UK, Estonian and BioVu biobanks, with replication using 23andMe samples, showed an association of *HLA-B*55:01* (OR 1.41, 95% CI 1.33–1.41) with the phenotype of self-reported penicillin allergy[103]. Self-reporting of penicillin allergy has been shown to be incorrect in >90% of cases[104]. 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 contextualizing 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.

Rare variants
Most of the heritability in drug response phenotypes is unknown, with a study providing estimates ranging from 0.05 to 0.59[105]. 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 variants[106]. 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%[107]. With decreasing costs and increasing availability of human genome sequencing, a challenge for pharmacogenomics will be to assess the effects of rare variants on the drug response phenotype and, subsequently, to incorporate this information into clinical implementation programmes[108]. 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 needed[5,72]. Another key issue with rare variants is their functionality, with most of them being categorized as variants of uncertain significance. In silico methods to predict functionality, including methods that use artificial intelligence for pharmacogenomic variants, have been developed[109]. 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 method[110]. Functional genomic evaluation will also be required in some cases using high-throughput methods such as massively parallel reporter assays[111] and deep mutational scanning[112].

Polygenic scores
Interest in using polygenic scores (also known as polygenic risk scores) for disease risk prediction, disease stratification, prognostication and screening is growing[113]. Polygenic scores also have potential applications in pharmacogenomics; indeed, the warfarin dosing algorithm

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Box 1

Recommendations for the implementation of pharmacogenomics in clinical practice[75]

- 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 that the service does not exacerbate health inequalities.
- 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 minimize errors and maximize cost efficiency.
- The pharmacogenomic service should undergo continuous audit and evaluation, leading to the development of a learning health system that maximizes 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.

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 *Phe508del*, reduced the exacerbation rate by 63%. Further information can be found in Tewkesbury et al.[160].

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, reduce levels of LDL-C and have been associated with reduced risk of cardiovascular disease. Alirocumab and evolocumab, fully humanized 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 Wierzbicki[161].

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. Although homozygotes are severely affected with skull abnormalities, syndactyly and central nervous system complications, heterozygotes have increased bone mass but without complications 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 post-menopausal 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.[162] and Bovjin et al.[163].

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represents an early example of a polygenic score with RCT evidence of utility[114]. Polygenic scores have also been reported for clopidogrel in preventing ischaemic cardiac events[115], β-blockers in treating heart failure[116] and drug-induced liver injury[117], 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 alone[118]. However, whether this approach is cost-effective will depend on the health-care setting, the predictive accuracy of the polygenic score and genotyping costs[119]. Implementation of polygenic scores into clinical practice is further away than conventional pharmacogenomic markers because of the need to

demonstrate clinical utility and the inherent complexity of integrating polygenic scores into clinical pathways. In fact, polygenic scores will face many of the same issues highlighted above for the implementation of pharmacogenomics.

Diversity

Genomic studies are increasingly recognized 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 were of European ancestry with only 2.2% Asian, 0.02% African and 0.02% African American or Afro-Caribbean ancestry[120]. Polygenic scores, which have largely been developed from European ancestries, are also problematic because of low portability across global populations[121].

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 populations[122]. Studies that have evaluated the role of *CYP2C9* polymorphisms that are more prevalent in African populations are scant[123,124]. Lack of consideration of ethnic diversity is also seen in drug labels.

For example, the drug label for siponimod[125], a drug used for multiple sclerosis, instructs prescribers to genotype for *CYP2C9* before prescribing the drug, reduce the dose by 50% for those in whom CYP2C9 activity is partially reduced (*CYP2C9*2*3, CYP2C9*1*3*) and avoid it altogether when 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 in European populations)[126]. 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 populations[42], and many non-European patients might be at risk of potentially preventable fluoropyrimidine toxicity.

To improve the diversity of genomics data, numerous programmes have been launched worldwide, for example H3Africa, Qatar Genome Programme, GenomeAsia 100K Project[127] and the China Kadoorie Biobank, to name a few. In the Trans-Omic for Precision Medicine (TOPMed) programme, 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 in the USA is recruiting 1 million participants from community settings, with a focus on ensuring diversity in the recruitment processes. In the UK, Our Future Health, which aims to recruit 5 million individuals, will ensure that 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 populations[128]. 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 optimize drug development and use for all global populations are required. Another key issue is the need

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Box 3

Research priorities for pharmacogenomics in the future

- Research to identify new drug–gene associations is still needed, but lessons need to be learned 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 for medicine optimization but also for de-prescribing (that is, stopping certain drugs to reduce the medicine burden).
- Methodologies need to be developed to incorporate rare variants (alongside common variants) to determine their contribution to pharmacogenomic phenotypes.
- Multimodal 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, 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, therapeutic drug monitoring and pharmacogenomics) enhances utility.
- A wide variety of study designs should be utilized 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.
- Implementation of pharmacogenomics into clinical practice needs to be actively pursued. This will require multidisciplinary 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 realized in all global populations and do not exacerbate 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.
- Multicentre, international collaborations with standardized 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-target 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.

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to increase capacity and capability within different countries, without which it will be impossible to overcome these inequalities.

Conclusions

Research in pharmacogenomics has increased since the completion of the Human Genome Project, spanning the full spectrum from drug discovery to clinical implementation. 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.

Pharmacogenomics is just one component of the drive towards personalized or precision medicine. Multimodal algorithms that incorporate both clinical (for example, age, sex and body weight) and genetic factors (Supplementary Fig. 1), 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. Advancing 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 is likely to lead to many opportunities to improve human health (Box 3).

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