*Cambridge Prisms: Precision Medicine*

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# Cardiovascular precision medicine – A pharmacogenomic perspective

Sandosh Padmanabhan, Clea du Toit and Anna F. Dominiczak

BHF Glasgow Cardiovascular Research Centre, School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow, UK

**Review**

**Cite this article:** Padmanabhan S, du Toit C and Dominiczak AF (2023). Cardiovascular precision medicine – A pharmacogenomic perspective. *Cambridge Prisms: Precision Medicine*, **1**, e28, 1–14
https://doi.org/10.1017/pcm.2023.17

Received: 06 March 2023
Revised: 24 May 2023
Accepted: 12 June 2023

**Keywords:**
pharmacogenomics; cardiovascular; warfarin; clopidogrel; cytochrome-P-450

**Corresponding author:**
Anna F. Dominiczak;
Email: Anna.Dominiczak@glasgow.ac.uk

## Abstract

Precision medicine envisages the integration of an individual's clinical and biological features obtained from laboratory tests, imaging, high-throughput omics and health records, to drive a personalised approach to diagnosis and treatment with a higher chance of success. As only up to half of patients respond to medication prescribed following the current one-size-fits-all treatment strategy, the need for a more personalised approach is evident. One of the routes to transforming healthcare through precision medicine is pharmacogenomics (PGx). Around 95% of the population is estimated to carry one or more actionable pharmacogenetic variants and over 75% of adults over 50 years old are on a prescription with a known PGx association. Whilst there are compelling examples of pharmacogenomic implementation in clinical practice, the case for cardiovascular PGx is still evolving. In this review, we shall summarise the current status of PGx in cardiovascular diseases and look at the key enablers and barriers to PGx implementation in clinical practice.

## Impact statement

Pharmacogenomics, the study of the effect of inherited or acquired genetic variation on differences in drug response or adverse effects. Around 95% of the population carry one or more actionable pharmacogenetic variants and over 75% of adults over 50 years old are on a prescription with a known PGx association. Pharmacogenomic evidence for cardiovascular drugs is growing along with emerging evidence for efficacy and cost-effectiveness. Successful pharmacogenomic implementation in healthcare requires strong scientific evidence, comprehensive and updated clinical guidelines, clinician champions and stakeholder engagement.

## Introduction

An average one-size-fits-all approach is the foundation of the existing general healthcare paradigm of therapeutic, and preventative interventions. Whilst this is a very practical and effective strategy, only 40–50% of patients respond to treatment in this all-comers approach prescribed as per current practice, indicating a large proportion of the population may be facing a deficit in addressing their medical needs (Collins and Varmus, 2015). This requirement for a transformation in the current paradigm of healthcare has motivated the emergence of precision medicine as a more targeted approach to treatment (Goldberger and Buxton, 2013; Schork, 2015). Precision medicine envisages an integration of an individual's clinical and biological features obtained from laboratory tests, imaging, high-throughput omics and health records, to drive a personalised approach to diagnosis and treatment with a higher chance of success (Collins and Varmus, 2015). The anticipated benefits of the precision medicine approach for patients are quicker diagnosis and targeted treatment leading to higher treatment success with minimal to no adverse drug reactions (ADRs), with wider benefits in terms of decreased healthcare costs and increased economic productivity.

One of the routes to precision medicine is pharmacogenomics (PGx), the study of the effect of inherited or acquired genetic variation on drug absorption, distribution, metabolism and excretion (pharmacokinetics) or modification of drug target or biological pathways (pharmacodynamics) resulting in variations in drug response or adverse effects. Around 95% of the population carry one or more actionable pharmacogenetic variants and over 75% of adults over 50 years old are on a prescription with a known PGx association (Chanfreau-Coffinier et al., 2019; Heise et al., 2020; Zhou and Lauschke, 2022; Zhou et al., 2023). The U.S. Food and Drug Administration (FDA) lists around 499 drugs which have PGx biomarkers in the labelling, with around a 100 of them linked to data supporting PGx-guided therapeutic recommendations (FDA, 2023a, 2023b). PharmGKB (PharmGKB, 2023a, 2023b) and the Clinical Pharmacogenetics Implementation Consortium (CPIC) (Relling et al., 2020) publish evidence-based, peer-

reviewed guidelines on applying PGx test results into actionable prescribing decisions. PharmGKB Level 1 genes or gene–drug combinations are considered pharmacogenomically significant and are linked to specific prescribing guidance. Similarly, CPIC Levels A and B indicate that genetic information should be considered before prescribing.

CPIC currently reports around 480 gene–drug interactions, including 93 gene–drug pairs (24 genes with 75 drugs) that are annotated with Level A evidence and prescription guidelines (Crews et al., 2014; Ramsey et al., 2014; Hicks et al., 2015; Bell et al., 2017; Johnson et al., 2017; Amstutz et al., 2018; Relling et al., 2019; CPIC, 2022). Although integration of PGx into routine clinical practice is not widespread, the recent PREPARE trial demonstrated both efficacy and feasibility of implementation of a 12 gene pharmacogenomic panel across diverse European healthcare system organisations and settings (Swen et al., 2023) even if only limited to current CPIC Level A drugs (Chanfreau-Coffinier et al., 2019; Heise et al., 2020; Relling et al., 2020; Hicks et al., 2021; Pritchard et al., 2022). Only a small subset of the roughly 15% of medications that cite PGx information on their labels have actionable pharmacogenes (Ehmann et al., 2015; Mehta et al., 2020). Of the approximately 20,000 human genes, only 34 of them are considered clinically actionable with PGx (PharmGKB level 1) (PharmGKB, 2023a, 2023b). The majority of PGx-labelled agents are cancer therapies targeted for somatic mutations, rather than germline variants. Actionable germline PGx variants are present for around 7% of medications with CPIC Level A or B recommendations directing prescribing changes based on genotype (Relling et al., 2020).

## Pharmacogenomics

The broad clinical relevance of PGx is evident across the medical spectrum from improving treatment efficacy to avoiding ADRs. *CYP2D6* genotype guided optimisation of opioid analgesia resulted in a 30% reduction in pain intensity among 24% of patients (Smith et al., 2019). Antidepressant prescribing guided by PGx variants across eight genes (*CYP1A2, CYP2C9, CYP2C19, CYP3A4, CYP2B6, CYP2D6, HTR2A, SLC6A4*) in the Genomics Used to Improve DEpression Decisions (GUIDED) trial (Greden et al., 2019) showed improved response and remission rates in difficult-to-treat depression, but no difference between the study arms for symptom improvement (primary outcome). A trial in a predominantly white human immunodeficiency virus type 1 infected population showed 100% elimination of immunologically confirmed abacavir hypersensitivity syndrome in those randomised to pre-emptive HLA-B*57:01-guided abacavir initiation (Mallal et al., 2008). Similarly, pre-emptive *DPYD* genotype guided dosing reduced from 73% to 28% the risk of fluoropyrimidine toxicity and completely abolished fluoropyrimidine-related mortality (Deenen et al., 2016). Whilst these examples are compelling, the case for cardiovascular PGx is still evolving. In this review, we shall summarise the current status of PGx in cardiovascular diseases (CVDs) and look at the key enablers and barriers to PGx implementation in clinical practice.

## Warfarin

The coumarin derivatives (warfarin, acenocoumarol and phenprocoumon) are a mainstay of CVD therapy due to their crucial role in preventing or treating thromboembolism.

Coumarins inhibit vitamin K epoxide reductase complex subunit 1 (VKORC1) and thence clotting factors II, VII, IX and X to yield its pharmacological anticoagulant effect (Verhoef et al., 2014). Coumarins are racemic mixtures with one dominant pharmacological enantiomer. For warfarin, S-warfarin is 3–5 times more potent than R-warfarin and is preferentially metabolised by CYP2C9 (Kaminsky and Zhang, 1997). Warfarin is unique in that, unlike most other drugs, its dose titration is based on coagulation levels in response to treatment. Warfarin has a narrow therapeutic index and exceeding optimal anticoagulation (measured by the international normalised ratio, INR) increases the risk of bleeding, necessitating frequent monitoring and dose titration (Landefeld and Beyth, 1993). One study found hospitalisation due to bleeding and supra-therapeutic INRs was seen in 6–7% of patients prescribed warfarin (Hylek et al., 2007; Lau et al., 2017), while conversely, decreased time in the therapeutic INR range (TTR) was associated with increased ischaemic stroke, other thromboembolic events and mortality (Jones et al., 2005; Cancino et al., 2014).

There is substantial interpatient variability in warfarin response, with warfarin doses necessary to attain target INR ranging from <1 mg/day to >10 mg/day (stable dosing after loading dose) (Pokorney et al., 2015). Genetic variation accounts for 55–60% of this dose variability: *VKORC1* (∼25%), *CYP2C9* (∼15%), *CYP4F2**3 (∼1–7%) (Zhou et al., 2023). Non-genetic factors collectively account for <20%: age, body mass index (BMI), smoking and drug interactions (Rost et al., 2004; Wadelius et al., 2009; Verhoef et al., 2014; Bourgeois et al., 2016).

The *CYP2C9**2, *3, *5, *6, *8 and *11 alleles reduce clearance of the more active S-warfarin, thus decreasing dose requirements by 5–7 mg/week in those carrying *2, *8 and *11 alleles, and 14 mg/week reported for the *3 and *5 alleles. Consequently, these variants are also associated with increased risk of over-anticoagulation. The *2 and *3 alleles are common among Europeans, while the *5, *6, *8 and *11 alleles occur almost exclusively in African ancestry populations (Johnson et al., 2017; Zhou et al., 2023).

*VKORC1* regulatory variant c.−1639G>A (rs9923231) is associated with reduced *VKORC1* expression and lower warfarin dose requirements, with the −1,639 AA (high sensitivity) genotype more common among Asians and the −1,639 GG (reduced sensitivity) genotype more common among Africans (Limdi et al., 2010; Johnson et al., 2017; Zhou and Lauschke, 2022). Consequently, warfarin dose requirements are, respectively, lower and higher in Asian and African ancestry patients, respectively, as compared to Europeans (Limdi et al., 2010).

The CYP4F2 enzyme contributes to the variation in warfarin dose requirements not by metabolising warfarin, but rather by metabolising 75–90% of all vitamin K consumed by humans. Vitamin $K_1$ reduction to vitamin K hydroquinone is critical to clotting factor activation. The *3 allele (rs2108622) is associated with reduced CYP4F2 activity resulting in higher concentrations of vitamin K1 and, consequently, higher warfarin dose requirements compared to the *1 allele, but this affects only European and Asian populations, with no impact on African ancestry individuals (Danese et al., 2019; Zhou and Lauschke, 2022).

While *VKORC1* and *CYP2C9* variants have emerged as the main genetic contributors to warfarin dose requirements in European and Asian ancestry populations (Cooper et al., 2008), the associations in African ancestry populations include single nucleotide polymorphisms (SNPs) in the chromosome 10 CYP2C cluster and in chromosome 6 upstream of *EPHA7* (Perera et al., 2013; De et al., 2018; Zhou and Lauschke, 2022).

### Validation of PGx-based warfarin dosing

The complexity of estimating initial warfarin dosing has been significantly diminished by the development of dosing algorithms, which take into account not only an individual's clinical features (e.g., age, BMI and use of CYP2C9 inhibiting drugs), but also their genotype (*VKORC1* −1639G>A, *CYP2C9**2 and *CYP2C9**3 alleles) (Gage et al., 2008; International Warfarin Pharmacogenetics et al., 2009). However, *CYP2C9**5, *6, *8, *11 and rs12777823 are not represented in the algorithms significantly reducing their utility in patients of African ancestry. The Gage algorithm incorporates *CYP2C9**5, *6 and *CYP4F2**3 allele (Gage et al., 2008; International Warfarin Pharmacogenetics et al., 2009).

Three large multi-site RCTs (EU-PACT, COAG and GIFT) have evaluated the efficacy of genotype-guided warfarin dosing (Kimmel et al., 2013; Pirmohamed et al., 2013; Gage et al., 2017) incorporating *VKORC1* −1639G>A and *CYP2C9**2 and *3 variants in a PGx algorithm, with *CYP4F2* additionally included in the GIFT trial (Gage et al., 2017). The primary endpoint was TTR for the EU-PACT and COAG trials (Kimmel et al., 2013; Pirmohamed et al., 2013) and clinical outcomes for the GIFT trial (Gage et al., 2017). PGx-guided dosing showed significant improvement in the primary endpoints for EU-PACT and GIFT, but not COAG trials. EU-PACT (Pirmohamed et al., 2013) compared genotype-guided warfarin dosing on days 1–5 followed by routine practice to routine practice. At 12 weeks, TTR was 7% higher in the genotype-guided arm (67.4% vs. 60.3%, $P < 0.001$). Conversely, TTR was similar in both the genotype-guided and clinically guided dosing arms of the COAG trial (4-week TTR 45.2% vs. 45.4%) (Kimmel et al., 2013). In the GIFT trial (Gage et al., 2017), the primary composite endpoint (INR ≥ 4, 30-day major bleeding, 30-day mortality death, 60-day incident venous thromboembolism) was lower in the genotype-guided group (10.8% vs. 14.7%, $P = 0.02$). Participants included in both the EU-PACT and GIFT trials were predominantly European. Although 27% of the COAG trial participants were African American, only the *CYP2C9* alleles common in Caucasians (*2 and *3) were genotyped. Thus, all the three trials were blind to African ancestry-specific variants, and failure to account for these variants resulted in substantial warfarin overdosing in African American participants in the genotype-guided arm of COAG (Kimmel et al., 2013). The reason is that *CYP2C9**5, *6, *8 or *11 allele (present in ~15% of patients of African ancestry) or rs12777823 A allele (>40% of patients) may be misclassified as normal metabolisers (e.g., *1/*1) and dosed accordingly (Drozda et al., 2015).

Patients with two or more *CYP2C9* or *VKORC1* variants are more prone to rapid INR surges and supratherapeutic anticoagulation at warfarin initiation. This may explain the differences between EU-PACT which used a loading dose and COAG which did not (Arwood et al., 2017).

### Clinical implementation of warfarin PGx

*CYP2C9**2, *3, *5, *6, *8, *11, and *VKORC1* −1639G>A alleles (Pratt et al., 2020) are the minimum set of panel variants supported by cost-effectiveness data on the implementation of multigene genotype-guided warfarin dosing (Zhu et al., 2020). Both the FDA and Dutch Pharmacogenetics Working Group (DPWG) genotype-guided dosing recommendations are limited to just *VKORC1* −1639G>A and *CYP2C9**2 and *3 alleles. CPIC, in contrast, provides African and non-African specific guidance, with the former requiring *CYP2C9**5, *6, *8 and *11 genotypes, and the latter requiring on *CYP2C9**2 and *3 and *VKORC1* genotypes (Johnson et al., 2017). Presence of *CYP4F2**3 allele in non-African individuals results in a 5–10% dose increase. For those of African ancestry, rs12777823 variant, if available, results in an additional 15–30% dose reduction (Johnson et al., 2017).

## Clopidogrel

Antiplatelet therapy is a cornerstone of atherosclerotic CVD management involving aspirin or a $P2Y_{12}$ receptor antagonist (clopidogrel, prasugrel and ticagrelor), either as single agent therapy for secondary prevention or dual agents after percutaneous coronary intervention (PCI) (Roffi et al., 2016; Ibanez et al., 2018). Prasugrel and ticagrelor are more potent $P2Y_{12}$ receptor antagonists with an increased bleeding risk but are preferred over clopidogrel in high-risk cases (Wallentin et al., 2009). Genetic variation is partly responsible for the observed variability in effectiveness of antiplatelet therapy (Angiolillo et al., 2017). Assessment of platelet function status is time-consuming, lacks standard reference values and is hence not clinically feasible for tailoring antiplatelet therapy. The prospect of a genotype profile providing a measure of antiplatelet efficacy and thus predicting adverse cardiovascular outcomes makes a compelling case for the use of PGx to personalise treatment.

Clopidogrel, the most commonly prescribed antiplatelet drug, is a prodrug that undergoes a two-step transformation to its active metabolite which irreversibly inhibits platelet activation (Kazui et al., 2010). CYP2C19 is involved in both activation steps, and thus, plays a crucial role in the bioactivation process of clopidogrel (Sangkuhl et al., 2010). *CYP2C19* is highly polymorphic with alleles representing a range of metaboliser phenotypes (summarised in Table 1; Kazui et al., 2010; Sangkuhl et al., 2010; Scott et al., 2013; Pratt et al., 2018; Zhou and Lauschke, 2022; Zhou et al., 2023).

The CYP2C19 poor metaboliser (PM) and intermediate metaboliser (IM) phenotypes have higher on-treatment platelet reactivity and an increased risk of ischaemic events compared to the normal metaboliser (NM) phenotype (*1/*1 genotype) (Varenhorst et al., 2009; Mega et al., 2009a). The equivalent of a 75 mg dose of clopidogrel in NMs is 225 mg in IMs, but 300 mg is insufficient in PMs (Mega et al., 2011; Price et al., 2012; Carreras et al., 2016).

**Table 1.** *CYP2C19* allele dependent enzyme activity

| *CYP2C19* allele | Enzyme activity | Homozygous | Heterozygous (with *1 or *17) |
|---|---|---|---|
| *1 | Normal | EM | UM |
| *2 | None | PM | IM |
| *3 | None | PM | IM |
| *4 | None | PM | IM |
| *5 | None | PM | IM |
| *6 | None | PM | IM |
| *7 | None | PM | IM |
| *8 | None | PM | IM |
| *9 | Decreased | PM | IM |
| *10 | Decreased | PM | IM |
| *17 | Increased | UM | UM |

Abbreviations: EM, extensive metaboliser; IM, intermediate metaboliser; PM, poor metaboliser; UM, ultrarapid metaboliser.

The antiplatelet drugs prasugrel and ticagrelor are not affected by the *CYP2C19* genotype, offering the option for switching IMs and PMs to these drugs in preference to clopidogrel dose escalation in the absence of contraindications (Varenhorst et al., 2009; Mega et al., 2009b; Wallentin et al., 2010).

Several real-world studies showed a significantly higher risk of major adverse cardiovascular events (MACE) in CYP2C19 PMs and IMs compared to NMs (Hulot et al., 2010; Mega et al., 2010; Holmes et al., 2011; Zabalza et al., 2012; Sorich et al., 2014; Cavallari et al., 2018; Kheiri et al., 2020). However, the higher risk of MACE in clopidogrel-treated PMs and IMs was less evident in lower-risk populations, such as atrial fibrillation or medically managed acute coronary syndrome (ACS) cases (Bauer et al., 2011; Holmes et al., 2011). Two prospective trials, POPular Genetics (Claassens et al., 2019) and TAILOR-PCI (Pereira et al., 2020) trials stratified IMs and PMs to prasugrel or ticagrelor while NMs received clopidogrel. The *CYP2C19*-guided approach reduced bleeding risk and was non-inferior to treatment with prasugrel or ticagrelor in preventing atherothrombotic events in the POPular Genetics study that enrolled post ST-segment elevation MI patients undergoing PCI (Claassens et al., 2019). In the TAILOR-PCI trial (Pereira et al., 2020), patients with either stable coronary disease or ACS undergoing PCI showed lower rates of the composite cardiovascular primary endpoint in the genotype-guided group compared to the non-genotype-guided cohort at 1-year follow-up, but this did not reach statistical significance (HR 0.66; 95% CI 0.43–1.02; $P = 0.06$) (Pereira et al., 2020). A post hoc analysis indicated benefit in the genotype-directed group during the first 3 months after PCI (HR 0.21; 95% CI 0.08–0.54; $P = 0.001$) (Pereira et al., 2020). Other indications for clopidogrel include stroke prevention and peripheral arterial disease. PMs and IMs show reduced rates of stent patency after endovascular treatment for peripheral arterial disease (Guo et al., 2014; Diaz-Villamarin et al., 2016). For stroke, a large randomised controlled trial (RCT) showed that absence of the *CYP2C19* no-function allele in patients with a minor ischaemic stroke or transient ischaemic attack (TIA) predicted better effectiveness of clopidogrel plus aspirin over aspirin alone (Wang et al., 2016). A meta-analysis including nearly 5,000 clopidogrel-treated patients with ischaemic stroke or TIA confirmed higher risk of new stroke in PMs and IMs (Pan et al., 2017).

### *Clinical implementation of clopidogrel PGx*

Since 2010, the FDA, European Medicine Agency (EMA) and other regulatory bodies recommend alternative $P2Y_{12}$ inhibitors to clopidogrel in PMs (but not IMs) in their labels (Holmes et al., 2010). The FDA table of gene–drug pairs includes therapeutic management recommendations for IMs and PMs (FDA, 2023a, 2023b), which is echoed by CPIC guidelines citing 'strong' evidence for IMs and PMs with ACS or undergoing PCI, and 'moderate' evidence PMs for all indications. In all of the above cases, alternative antiplatelet agents are recommended (Lee et al., 2022).

Joint PCI guidelines from 2016 by the American College of Cardiology (ACC) and the American Heart Association (AHA) recommend against routine genotyping for all patients undergoing PCI, but to consider testing high-risk patients and use either prasugrel or ticagrelor for patients with the no-function allele. The 2020 European Society of Cardiology (ESC) guidelines were influenced by the POPular Genetics trial to recommend genotype-guided de-escalation for post-PCI patients deemed to be at high bleeding risk (Claassens and Sibbing, 2020; Collet et al., 2021).

*CYP2C19*-guided antiplatelet therapy after PCI is one of the most common PGx tests in clinical practice (Empey et al., 2018) conducted either for patients at high risk of MACE in line with ACC/AHA guidelines or for all-comers (Empey et al., 2018). If point-of-care genotyping is not available, a de-escalation approach is proposed where patients are commenced on prasugrel or ticagrelor initially pending genotype results and then switched to clopidogrel if the genotype results indicate the NM phenotype. This approach maximises benefit given the high risk of atherothrombotic events early after ACS and PCI, while reducing the high risk of bleeding with prasugrel and ticagrelor during long-term therapy (Becker et al., 2011; Rollini et al., 2016; Angiolillo et al., 2017). The case for implementing pre-emptive *CYP2C19* genotyping (Peterson et al., 2016) is evident due to the impact of *CYP2C19* genotype on other drugs in addition to clopidogrel, such as proton pump inhibitors (Lima et al., 2021) and selective serotonin reuptake inhibitors (SSRIs) (Hicks et al., 2015).

## Direct-acting oral anti-coagulants

Apixaban, dabigatran, edoxaban and rivaroxaban are direct-acting oral anticoagulants (DOACs) with several advantages compared to warfarin – wider therapeutic index, regular monitoring not required, lower risk of intracranial haemorrhage, stroke or systemic embolic events (Proietti et al., 2018). Despite the favourable profile of DOACs, their higher cost, lower adherence rates, limited indications, and the high cost of reversal agents has limited uptake of DOAC compared to warfarin (Zhu et al., 2018; Ho et al., 2020). Pharmacokinetic variation related to genetic variation is indicated but there is no data on clinical outcomes yet.

In a sub-study of the ENGAGE AF TIMI-48 trial (which compared warfarin and edoxaban in atrial fibrillation patients; Mega et al., 2015) warfarin-treated participants with a sensitive or highly sensitive genotype (e.g., *VKORC1* −1639AA or *CYP2C9**1/*3) spent a greater proportion of time within the supratherapeutic INR range (i.e., INR >4) and had higher rates of bleeding in the initial 90 days of treatment, as compared to those with non-sensitive genotypes. In a genetic sub-study of the RE-LY trial (dabigatran versus warfarin in atrial fibrillation), carriers of the *CES1* rs2244613 minor allele had a reduced risk of bleeding with dabigatran than with warfarin (Shi et al., 2016).

## Statins

Lipid lowering treatment by statins (HMG-CoA reductase inhibitors) are used in the prevention of CVD (Catapano et al., 2016). Statin-associated muscle symptoms (SAMS) (range from mild myalgia without an elevation in creatine kinase to life-threatening rhabdomyolysis or autoimmune-necrotizing myositis) are the commonest reasons for treatment discontinuation (Alfirevic et al., 2014). A number of enzymes and transporters are responsible for intracellular skeletal myocyte entry that underlie disruption of muscle function leading to SAMS (Turner and Pirmohamed, 2019). Hepatic uptake and elimination of statins are mainly carried out by the solute carrier anion transporter family 1B1 gene (*SLCO1B1*) encoding the organic anion transporting polypeptide 1B1 (OATP1B1) (Shitara, 2011). The rs4149056 SNP in the *SLCO1B1* gene (*SLCO1B1**5) is linked to OATP1B1 function (Tirona et al., 2001) with the C allele being associated with decreased OATP1B1 transporter function with greatest reduction in homozygous patients resulting in significantly increased plasma concentrations

of all statins, except fluvastatin (Tirona et al., 2001). Additionally, the risk of myopathy increases by 2.6 and 4.3 per copy of SLCO1B1*5 in patients, respectively, on simvastatin 40 mg and 80 mg daily (Tirona et al., 2001). The mechanism of *SLCO1B1**5 variant causing statin-related myopathy is through the accumulation of circulating simvastatin acid (the active form of simvastatin) reflecting liver transport (Choi et al., 2015). This effect is most prominent for simvastatin followed by pitavastatin, lovastatin and atorvastatin (Ramsey et al., 2014). Each copy of the C allele of rs4149056 increases the risk of statin-induced myopathy threefold in genome-wide association studies (GWAS) (Carr et al., 2019). Atorvastatin is partially metabolised by the CYP3A and UDP-glucuronosyltransferase 1A1 (UGT1A) enzyme families. One study showed the SNP rs45446698 just upstream of *CYP3A7* and another, rs887829, located in multiple overlapping *UGT1A* genes, to be associated with atorvastatin-to-metabolite ratios in patients with ACS (Turner et al., 2020). Inconsistent associations with SAMS have been reported for polymorphisms in *CYP3A4*, *ABCB1*, *COQ2* (involved in coenzyme Q10 synthesis) and *GATM* (involved in creatine synthesis) (Fiegenbaum et al., 2005; Hoenig et al., 2011; Mangravite et al., 2013; Carr et al., 2019).

### Validation of PGx-based statin dosing

The pragmatic *SLCO1B1* genotype-informed statin therapy (GIST) trial randomised patients who had discontinued any statins due to myalgia to *SLCO1B1* genotype guided therapy (rosuvastatin, pravastatin, or fluvastatin for *SLCO1B1**5 carriers and any statin for non-carriers) or standard care (Peyser et al., 2018). At the end of 8-month follow-up, increased statin re-initiation, reduced LDL-C levels, and no change in self-reported medication adherence were seen in those randomised to genotype guided (Peyser et al., 2018). Whilst these results are interesting, the inclusion of patients who developed myopathy from any statins in the trial limits the translational potential of the results. This is because the impact of *SLCO1B1* variation is highest for simvastatin and variable for other statins, hence the results of the trial do not present a clear case for genotype-guided simvastatin therapy.

### Clinical implementation of statin PGx

The *SLCO1B1**5 variant (rs4149056) shows wide population differences (1%, 8% and 16% in African, Asian and European populations, respectively). CPIC recommends not exceeding a dose of simvastatin 20 mg/day or, prescribing another statin (rosuvastatin or pravastatin) in patients who carry at least one rs4149056 C allele (Voora et al., 2009; Danik et al., 2013; Ramsey et al., 2014; Lamoureux et al., 2017). The French National Network of Pharmacogenetics recommends commencing statins in patients with risk factors for myopathy only after rs4149056 genotyping (Lamoureux et al., 2017). The DPWG recommends that homozygotes avoid simvastatin entirely and individuals with other clinical risk factors for SAMS avoid atorvastatin (de Keyser et al., 2014; Bank et al., 2019; Linskey et al., 2020; Turner et al., 2020).

## Beta blockers

β-Adrenergic receptor antagonists, or beta blockers, are indicated for treatment of heart failure, hypertension, and secondary prevention of myocardial infarction. CYP2D6 is responsible for biotransformation of 70–80% of an oral dose of metoprolol and has negligible effects on other beta blockers (Ingelman-Sundberg et al., 2007; Baudhuin et al., 2010; Blake et al., 2013; Zisaki et al., 2015; Vieira et al., 2018). There is only weak evidence for PGx-guided prescribing of beta blockers (PharmGKB level 2–3, CPIC level B/C). Compared to EMs, IMs and PMs are associated with a decreased heart rate (Bijl et al., 2009; Batty et al., 2014; Anstensrud et al., 2020) and lower diastolic BP (Bijl et al., 2009; Batty et al., 2014; Hamadeh et al., 2014; Anstensrud et al., 2020). These studies have not studied the entire spectrum of major variations in *CYP2D6* and have not been independently validated.

Three other genes (*ADRB1*, *ADRB2* and *GRK5*) have been associated with the beta blocker pharmacodynamics rather than pharmacokinetics, but there is no evidence of clinical utility for using these variants to guide prescribing (White et al., 2003; Pacanowski et al., 2008; Magvanjav et al., 2017; Huang et al., 2018).

FDA and DPWG have slightly different recommendations on metoprolol dosing. The FDA recommends caution with co-administration of strong CYP2D6 inhibitors (SSRIs, antipsychotics) or substrates. The DPWG recommend cautious dose titration and reduced maximal doses in CYP2D6 IMs and PMs supramaximal metoprolol dose or an alternative beta blocker in UMs (Brouwer et al., 2022).

## Hydralazine

Hydralazine is a direct vasodilator seldom used in the treatment of hypertension (Whelton et al., 2018). Hydralazine is metabolised primarily by hepatic *N*-acetyltransferase type 2 (NAT2) acetylation. The common *NAT2**4 genetic variant defines a 'rapid acetylator' phenotype with decreased hydralazine levels after drug administration (Gonzalez-Fierro et al., 2011; Han et al., 2019). Homozygous *NAT2**5, *6, and *7 indicate a 'slow acetylator' phenotype, while heterozygous individuals (e.g., *4/*5) are 'intermediate acetylators'. One study of resistant hypertension patients demonstrated that only those with the slow acetylator phenotype showed notable blood pressure reductions in response to hydralazine (Spinasse et al., 2014).

One of the rare side effects of hydralazine is the occurrence of lupus-like symptoms, with indirect evidence suggesting slow acetylators are more prone to developing this ADR (Weber and Hein, 1985; Mazari et al., 2007; Schoonen et al., 2010). However, clinical utility and cost-effectiveness data are lacking.

## Antiarrhythmic drugs

Inhibition of the rapid component of the delayed rectifier potassium current, $I_{kr}$, encoded by *KCNH2* is the commonest cause of drug induced long QT syndrome (LQTS) and torsades des pointes (TdP; ventricular tachycardia (Roden and Viswanathan, 2005; Wada et al., 2022).

Similar to beta blockers, the class 1 antiarrhythmic drugs flecainide and propafenone are metabolised by CYP2D6 (PharmGKB level 2A, CPIC level B/C; Doki et al., 2015; Rouini and Afshar, 2017) with *CYP2D6* genotype-related differences in QTc interval (Lim et al., 2010). The FDA recommends caution in the use of propafenone in patients with CYP2D6 deficiency when combined with CYP3A4 inhibition. The DPWG recommends a dose reduction of 50% and 30%, respectively, for flecainide and propafenone in CYP2D6 PMs.

Quinidine- or dofetilide-induced QT prolongation and drug-induced TdP was significantly associated with a polygenic risk score

constructed from 61 SNPs excluding the *CYP2D6* locus (Arking et al., 2014; Strauss et al., 2017). Though not validated, this highlights the potential for using polygenic risk scores in predicting drug-induced arrhythmias.

## PGx implementation

Successful pharmacogenomic implementation in healthcare require strong scientific evidence, comprehensive and updated clinical guidelines, clinician champions and stakeholder engagement (Manolio et al., 2013).

### *Laboratory*

Characterisation of pharmacogenomic variants in patients requires a certified molecular pathology laboratory to ensure analytical accuracy, precision, sensitivity and specificity of the results (Tayeh et al., 2022). Most clinical PGx tests based on selected panel of clinically relevant variants (single gene or multigene) are more cost-effective than sequencing panels. It is likely that the decreasing cost of sequencing will make sequencing cost-competitive over multi-gene panels in the future (Figure 1).

### *Guidelines and clinical decision support systems*

Effective pharmacogenomic guided prescribing requires evidence from multiple sources to be distilled into guidelines and made available through clinical decision support systems (CDSS) that distil information on drug–gene interactions from published guidelines or prescribing labels. Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Groups (DPWG) have published guidelines covering 66 medications across several drug classes. However, the major PGx guideline and recommendation sources are not completely concordant in terms of their advice. A recent study found inconsistencies in clinical PGx recommendations (48.1%) and in 93.3% of recommendations from CPIC, FDA and clinical practice guidelines (Shugg et al., 2020). These inconsistencies were spread across a range of domains – recommendation category (29.8%), the patient group (35.4%) and routine screening (15.2%), suggesting a potential barrier to rapid PGx implementation until this is resolved.

CDSS is an effective tool to guide clinicians with limited PGx knowledge (van der Wouden et al., 2017). In pre-emptive PGx, patient-specific CDSS alerts prompt and guide clinicians to use genetic information when prescribing drugs with known genetically-determined ADRs (Overby et al., 2014; Dunnenberger et al., 2015).

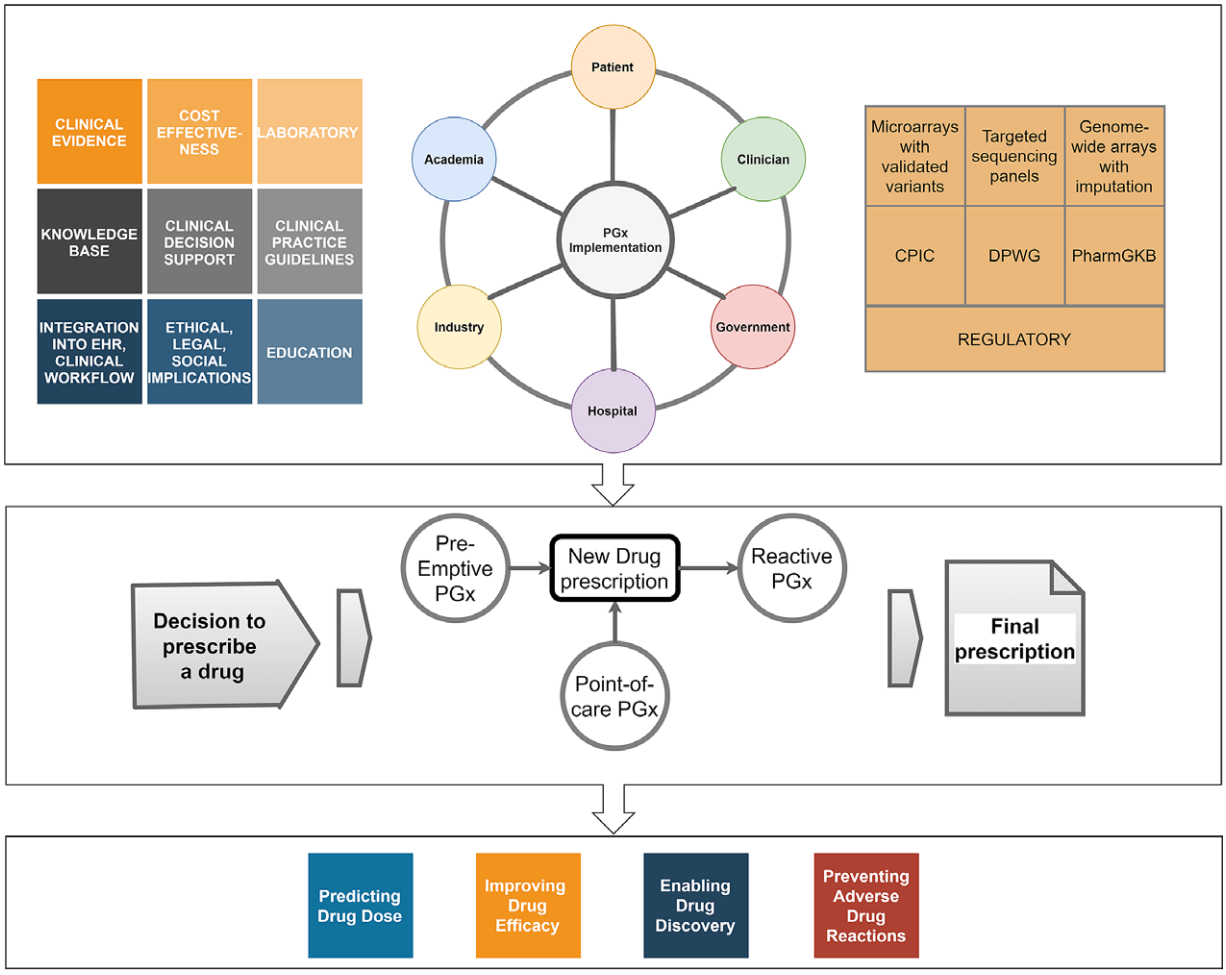


**Figure 1.** Pharmacogenomic implementation. The top panel shows the range of stakeholders, technology, knowledge and evidence that need to be harnessed to realise the value of PGx. The middle panel depicts the uses of PGx in the clinical prescribing pathway. The bottom panel presents the applications of PGx. CPIC, the Clinical Pharmacogenetics Implementation Consortium; DPWG, Dutch Pharmacogenetics Working Groups; PharmGKB, the Pharmacogenomics Knowledge Base.

PGx may be implemented either reactively on a gene-by-gene basis at the time of prescribing a drug, or pre-emptively where a single sample is assessed for several pharmacogenes simultaneously with the results stored for future prescribing encounters. Reactive implementation is expensive and has a slow turnaround time and is unsuitable in situations where rapid drug initiation is required. In contrast, pre-emptive screening of multiple pharmacogenes is likely to be more cost-effective and provides the patient with a lifetime's worth of test results readily available whenever a drug is prescribed, especially when integrated into electronic health records (EHRs) and drug prescription systems (Relling and Evans, 2015). This further underlines the importance of efficient interoperability between different healthcare systems. A patient may be screened for *CYP2C19* prior to being prescribed clopidogrel. These results could inform the prescription of an SSRI or proton pump inhibitor in the future – but only if the results have been stored in an EHR in an accessible format and trigger a CDSS alert at the point of prescription.

### Health informatics

PGx implementation in healthcare can be developed in-house if there is availability of capabilities in laboratory and informatics infrastructure and expertise or outsourced to commercial partners. Due to the considerable diversity in commercial PGx products, it is essential to ensure the clinical, IT integration and interoperability requirements along with robust and continuous updating of evidence are rigorously assessed before deciding on the PGx service provider. The significant costs associated with the use of PGx in clinical practice are now in the domain of decision support, IT integration and interoperability, rather than in laboratory genetic testing (Dunnenberger et al., 2015; Relling and Evans, 2015; van der Wouden et al., 2017). Informatics builds within the EHR are easier for a single gene–drug pair as opposed to the multiple pairs and networks that form as drug interactions and clinical factors are also considered. However, the cost-effectiveness data on the pre-emptive panel approach must be assessed, particularly when considering implementation early in life.

### Patient and provider acceptability

Patient and healthcare professional acceptability is critical for effective and successful PGx implementation. This requires early and continuous engagement with both clinicians and patients, preferably with champions who are committed (Dressler et al., 2018; McDermott et al., 2022). The main barriers to be tackled in the route to implementation are demonstrating that the system will not overburden the physicians, seamlessly integrate into hospital cornerstone systems, provide sufficient support for the users of the system to navigate the pharmacogenetic evidence base through education and decision support systems, demonstrate utility and cost-effectiveness (Stanek et al., 2012; Just et al., 2019; Bagautdinova et al., 2022; Scheuner et al., 2023).

Pharmacists are crucial in the PGx service for evaluating appropriate patient eligibility, providing informative post-test counselling, or leading a PGx consult service (Crews et al., 2011; Brown et al., 2021; Bagautdinova et al., 2022; Krause and Dowd, 2022).

### Health economics

Implementation of PGx in clinical practice requires demonstration of its value and cost-effectiveness to key decision makers and a lack of RCTs that compare genotype-guided prescribing with conventional therapy has not helped. Conducting RCTs for each single drug–gene pair across different ethnicities is not a viable option. Big data analysis of EHRs has the advantage of being able to study diverse populations, limiting concerns about external validity of data and health equality (as is exemplified by the warfarin dosing algorithms that fail to serve patients of African descent). There is limited data on cost-effectiveness multiplexed pre-emptive strategies which are likely to be the preferred solution and the majority of existing cost-effectiveness PGx data are from single gene–drug pair studies (Roden et al., 2018). Most of the cost-effectiveness studies have been conducted separate from implementation initiatives and they indicate that PGx testing results in a reduction in per-patient treatment cost (Winner et al., 2015; Deenen et al., 2016), lower cost-per-QALY (Mitropoulou et al., 2015) and cost savings in long-term care (Saldivar et al., 2016). A recent systematic appraisal of economic evaluations of PGx testing to prevent ADRs found a number of deficiencies in the quality of data used in cost-effectiveness and cost-utility analyses (Turongkaravee et al., 2021). Of the 14 economic evaluation studies of *CYP2C9* and *VKORC1* testing, 10 studies showed that *CYP2C9* and *VKORC1* testing would be a variably cost-effective and four studies suggested otherwise (Turongkaravee et al., 2021). In contrast, all nine economic evaluation studies of *CYP2C19* testing before prescription of clopidogrel ACS patients undergoing PCI showed that *CYP2C19* testing would be a potentially cost-effective treatment strategy for avoiding MACE.

The clopidogrel–*CYP2C19* implementation successes need to be contrasted with the difficulties faced in the implementation of warfarin–*CYP2C9/CYP4F2/VKORC1* PGx. The key enablers for clopidogrel–*CYP2C19* implementation include a discrete patient population (post-PCI), single-gene testing, a high frequency of actionable results, clinically well-established alternative therapies, and a focused group of providers (interventional cardiologists) (Crisamore et al., 2019).

### Implementation in diverse health care systems

Whilst the above discussion related to healthcare systems in high-income countries, the specific challenges in implementing PGx low- and middle-income countries need to be recognised – lack of clinical efficacy and effectiveness data, under-resourced clinical settings, socio-cultural issues and the identification of population specific pharmacogenomic markers (Tata et al., 2020; Magavern et al., 2022; Sukri et al., 2022). The lack of consistent and widely accepted definitions of race, ethnicity and ancestry in genomics and clinical research has resulted in erroneous, inconclusive or absent data on non-European ancestry populations (Popejoy et al., 2020). Initiatives such as Human Heredity and Health in Africa (H3Africa) Consortium and the African Pharmacogenomics Research Consortium attempt to increase the representativeness of pharmacogenomic panels (Matimba et al., 2016). It is imperative that progress in pharmacogenomic research and implementation occurs at pace in diverse populations so that health disparities are not amplified when PGx becomes more mainstream in clinical practice.

#### Author contribution

S.P., C.T. and A.F.D. made substantial contributions to the conception drafting, and revision of the manuscript, it critically for important intellectual content. S.P., C.T. and A.F.D. provided final approval of the version to be published.

**Abbreviations**

| | |
|---|---|
| ABCB1 | ATP-binding cassette sub-family B member 1 |
| ACC | American College of Cardiology |
| ACS | acute coronary syndrome |
| ADR | adverse drug reaction |
| ADRB1 | β1-adrenergic receptor |
| ADRB2 | β2-adrenergic receptor |
| AHA | American Heart Association |
| BMI | body mass index |
| CDSS | clinical decision support systems |
| CES1 | liver carboxylesterase 1 |
| CPIC | the Clinical Pharmacogenetics Implementation Consortium |
| CVD | cardiovascular disease |
| CYP | cytochrome P450 |
| DOAC | direct-acting oral anticoagulants |
| DPYD | dihydropyrimidine dehydrogenase |
| DPWG | Dutch Pharmacogenetics Working Groups |
| EHR | electronic health records |
| EMA | European Medicines Agency |
| EPHA7 | ephrin type A receptor 7 |
| ESC | European Society of Cardiology |
| FDA | U.S. Food and Drug Administration |
| GATM | Glycine amidinotransferase, mitochondrial |
| GIST | genotype-informed statin therapy |
| GRK5 | G protein-coupled receptor kinase 5 |
| GWAS | genome-wide association studies |
| HLA-B | human leukocyte antigen B |
| IM | intermediate metaboliser |
| INR | international normalised ratio |
| KCNH2/ hERG | human Ether-à-go-go-related gene |
| LQTS | long QT syndrome |
| MACE | major adverse cardiovascular event |
| NAT2 | *N*-acetyltransferase 2 |
| NM | normal metaboliser |
| OATP1B1 | organic anion transporting polypeptide 1B1 |
| PCI | percutaneous coronary intervention |
| PM | poor metaboliser |
| PGx | pharmacogenomics |
| QALY | quality-adjusted life year |
| RCT | randomised controlled trial |
| SAMS | statin-associated muscle symptoms |
| SLCO1A2 | organic anion transporter family member 1A2 |
| SLCO1B1 | solute carrier anion transporter family 1B1 |
| SNP | single nucleotide polymorphism |
| SSRI | selective serotonin reuptake inhibitors |
| STEMI | ST-segment elevation myocardial infarction |
| TdP | torsades des pointes |
| TIA | transient ischaemic attack |
| TTR | time in the therapeutic INR range |
| UGT1A | UDP-glucuronosyltransferase 1A1 |
| UM | ultrarapid metaboliser |
| VKORC1 | vitamin K epoxide reductase complex subunit 1 |

**Open peer review.** To view the open peer review materials for this article, please visit http://doi.org/10.1017/pcm.2023.17.

**Financial support.** S.P. and A.F.D. are supported by the British Heart Foundation Centre of Excellence Award (RE/18/6/34217) and the UKRI Strength in Places Fund (SIPF00007/1).

**Competing interest.** The authors have no competing interest to disclose.

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