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THEMED ISSUE REVIEW

Implementation of pre-emptive testing of a pharmacogenomic panel in clinical practice: Where do we stand?

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Abstract

Adverse drug reactions (ADRs) account for a large proportion of hospitalizations among adults and are more common in multimorbid patients, worsening clinical outcomes and burdening healthcare resources. Over the past decade, pharmacogenomics has been developed as a practical tool for optimizing treatment outcomes by mitigating the risk of ADRs. Some single-gene reactive tests are already used in clinical practice, including the *DPYD* test for fluoropyrimidines, which demonstrates how integrating pharmacogenomic data into routine care can improve patient safety in a cost-effective manner. The evolution from reactive single-gene testing to comprehensive pre-emptive genotyping panels holds great potential for refining drug prescribing practices. Several implementation projects have been conducted to test the feasibility of applying different genetic panels in clinical practice. Recently, the results of a large prospective randomized trial in Europe (the PREPARE study by Ubiquitous Pharmacogenomics consortium) have provided the first evidence that prospective application of a pre-emptive pharmacogenomic test panel in clinical practice, in seven European healthcare systems, is feasible and yielded a 30% reduction in the risk of developing clinically relevant toxicities. Nevertheless, some important questions remain unanswered and will hopefully be addressed by future dedicated studies. These issues include the cost-effectiveness of applying a pre-emptive genotyping panel, the role of multiple co-medications, the transferability of currently tested pharmacogenetic guidelines among patients of non-European origin and the impact of rare pharmacogenetic variants that are not detected by currently used genotyping approaches.

KEYWORDS
adverse drug reactions, pharmacogenomics, pre-emptive, PREPARE trial

1 | INTRODUCTION

Adverse drug reactions (ADRs) reportedly account for 5-15% of all hospitalizations among adults, and for over 15% among patients with multimorbidities, with detrimental impacts on clinical outcomes and burdening healthcare resources.[1–4] A 1-year survey of hospital admissions at 11 Massachusetts hospitals revealed that about 24% of patients developed an adverse event during hospitalization, and 39% of

these events were related to medication use.[5] The economic burden is large, with ADRs costing US healthcare systems approximately $136 billion annually,[6] and the annual cost of ADR admissions to NHS England estimated as £2.21 billion using patient-level cost data.[3] Notably, Osanlou et al monitored hospital admissions due to ADRs in a UK hospital and found that about 40% of ADRs are considered avoidable or potentially preventable by making more detailed reviews of patients' clinical and pharmacological profiles.[3] In this context, some preliminary trials have attempted to address the issues of patient polypharmacy and comorbidities and how more intensive pharmacological monitoring could help reduce the ADR rate in clinical practice.[7,8]

Stratifying patients according to ADR risk could certainly be improved by accurate evaluation of personal information, such as comorbidities, personal characteristics, concomitant medications and previous drug sensitivity.[3] However, it is also important to understand the mechanistic basis for variability in drug safety and response, which may be related to both pharmacokinetic and pharmacodynamic factors. The patient's genetic background is one factor underlying this interindividual variability. Much progress has been made towards identifying the roles of genetic factors, particularly in terms of drug pharmacokinetic profiles (absorption, distribution, metabolism and excretion [ADME]) but also in pharmacodynamic aspects.[9]

Pharmacogenetics (PGx) is the study of how genes and genetic variants may affect the way a person responds to drugs. The potential impact of PGx on global health is impressive. According to currently available pharmacogenetic guidelines (Pharmacogenomics Knowledgebase, www.pharmgkb.org), across different ethnicities, over 90% of the general population harbours at least one high-risk actionable pharmacogenetic variant, that is, a genetic variant likely to affect drug response. Since a single pharmacogene can affect multiple drugs, it is estimated that approximately two-thirds of the general patient population will be prescribed at least one drug with pharmacogenetic association, especially when considering high-risk categories, such as elderly patients.[10,11]

A number of germline polymorphisms reduce or abolish the activity of enzymes involved in the metabolism of specific drugs and thus strongly influence the likelihood of developing ADRs. Representative examples include *CYP2C9* for **warfarin**,[12] *TPMT* and *NUDT15* for thiopurines,[13] *DPYD* for fluoropyrimidines[14,15] and *UGT1A1* for **irinotecan**.[16–18] The initial data on this subject were derived only from small observational studies. Subsequently, many consortia were formed, including the International Warfarin Pharmacogenetics Consortium,[19] Metformin Genetics[20] and the International Clopidogrel Pharmacogenomics Consortium,[21] with the goal of increasing the number and quality of association studies.

In addition to these research consortia, over the past 15 years, several scientific consortia have been established with the aim of developing pharmacogenetic guidelines for application in clinical practice, for example the Clinical Pharmacogenetics Implementation Consortium (CPIC),[22] the Pharmacogenomics Knowledge Base,[23] the Canadian Pharmacogenomics Network for Drug Safety[24] and the Dutch Pharmacogenetics Working Group (DPWG).[25] Pharmacogenetic guidelines and clinical annotations have been developed to facilitate clinical decision-making based on genetic laboratory test results and to personalize a wide range of therapies. There are currently guidelines and clinical annotations on over 90 gene-drug interactions, which provide recommended actions for prescribing. Moreover, drug regulatory agencies, such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), have included PGx information and test recommendations on drug labels, which constitute a strong incentive for clinical implementation.[26] A total of 58 gene-drug interaction guidelines have been developed by the CPIC and DPWG. For 26% of these guidelines, no relevant pharmacogenetic information is included on the EMA and FDA labels, and for 27% of these gene-drug interactions, regulatory agencies have provided pharmacogenetic information without specific recommendations. Compared with the FDA, the EMA provides more dose recommendations based on pharmacogenetics (24% *vs* 16%).[27]

Despite the high level of scientific evidence and recognized clinical benefits of PGx application to improve drug therapy outcomes and enhance treatment safety, promoting adoption by prescribing physicians remains challenging. The major barriers to implementing PGx in clinical practice include low knowledge of the potential of PGx and lack of familiarity with PGx data.[28,29] Several surveys have been conducted in Europe and the United States regarding the perceptions of PGx application in routine practice and have shown that physicians are very interested in the potential benefits of PGx information but do not feel adequately prepared to use it.[30–33] Education and training programmes could increase physicians' confidence in requesting PGx testing, thereby supporting PGx implementation, as well as direct participation in PGx-based clinical trials.[29,34] Notably, a recent global survey of PGx education in medical and pharmacy programmes found that only 10% of participants considered PGx a required course.[35]

In parallel with educational activities, clinical decision support (CDS) tools that translate genetic information into practical therapeutic recommendations could also help physicians in their routine clinical practice, thus favouring the implementation of pharmacogenetic guidelines. CDS systems can provide automated recommendations for dose modification or drug selection before a physician prescribes high-risk medications, thereby increasing PGx adoption and the usefulness of comprehensive PGx data.[28]

2 | SINGLE GENE-DRUG INTERACTIONS ALREADY TRANSPLANTED TO CLINICAL PRACTICE: THE CASE OF *DPYD* AND FLUOROPYRIMIDINES

Implementation of pharmacogenetics in the clinical setting is already at a well-advanced stage for some specific gene-drug interactions, notably including the *DPYD* test for prescription of fluoropyrimidines (FPs). **Dihydropyrimidine dehydrogenase** (DPD) (encoded by the *DPYD* gene) is the main enzyme responsible for the catabolism of FPs (ie, **fluorouracil**, **capecitabine** and **tegafur**) in patients undergoing cancer treatment. A defect in DPD functionality can lead to severe, or even lethal, toxicity during the first phase of treatment due to accumulation of FP active metabolites. DPD deficiency has been described in 3-8%

of the European population, which is partly explained by inherited genetic variants.[36] *DPYD**2A is the most studied genetic defect in FP catabolism, exhibits a minor allele frequency of approximately 1.5% in European patients and has been associated with increased risk of severe FP-related toxicity.[14,15] Other genetic variants in *DPYD*, eg, *DPYD*13* (rs55886062), *DPYD c.2846A>T* (rs67376798) and *DPYD c.1236G>A* (rs56038477, tagging *DPYD-HapB3*), have been successively identified in meta-analyses and prospective studies as being significantly associated with toxicity risk, indicating that genotype-guided FP dose individualization improves the safety profile of FPs.[14,15,37–40]

International authoritative consortia, such as CPIC and DPWG, have developed clinical PGx guidelines for clinical use of FPs based on the *DPYD* genotype.[41–45] Both guidelines highlight the importance of adjusting FP dosage according to the four above-mentioned *DPYD* variants, and the pre-treatment testing approach has been prospectively validated by large prospective studies in Europe.[14] It has been thoroughly demonstrated that pre-treatment *DPYD* testing with FP can prevent several toxic and even lethal drug-related adverse reactions, as well as save economic resources. Importantly, the cost of treating drug-related toxicity is significantly higher among carriers of any of the four *DPYD* variants compared with wild-type patients,[46,47] and thus it is cost-effective to reduce dosing according to genotype.[46,48]

A large prospective clinical trial conducted in the Netherlands[14,46] reported compelling clinical and economic evidence supporting the utility of *DPYD* testing in clinical practice. In May 2020, this prompted the European regulatory agency to publish its own pharmacogenetic recommendations to improve the appropriate use of FPs.[49] The EMA recommended a reduced starting dose of FPs in patients with DPD deficiency, as determined either by phenotyping (ie, measuring plasma uracil concentration) or by genotyping for the four-variant *DPYD* panel.[49] Recently, a large survey was conducted in many European countries that provided an overview of the state of the art of DPD testing implementation in Europe and the impact of the 2020 EMA recommendation. The findings demonstrated that the EMA recommendation was the pivotal event leading to a change of reimbursement strategies in different European countries and the introduction of country-specific guidelines.[50] An important change was made in the clinical guidelines for cancer treatment in Europe, resulting in an increase of FP prescriptions based on *DPYD* test results.[34] However, the clinical relevance of *DPYD* testing remains poorly understood by prescribing physicians, which hinders the implementation in clinical practice.[50] All stakeholders should be continuously trained and motivated to use PGx in their routine activities.[30,51–53] Although *DPYD* testing has become routine in some European countries, implementation in other parts of the world remains limited.[54] In the United States, the FDA has been reluctant to change the labelling of fluoropyrimidines to include the recommendation of *DPYD* testing for several reasons, most importantly because of concerns about reduced treatment efficacy due to dose reduction.[55] However, a recently published paper reports, for the first time, that prospective fluoropyrimidine dose reduction based on *DPYD* testing has a nonsignificant effect on cancer patient survival, further supporting the introduction of this practice in the clinic.[56]

The *DPYD* example shows that reactive testing (ie, testing ordered only after the decision has been made to prescribe a drug) of a single drug-gene interaction (DGI) with clinical value in routine care is currently feasible and promotes increased patient safety and reduced use of economic resources.[34,57,58]

3 | MOVING FROM A SINGLE REACTIVE DGI TEST TO A PRE-EMPTIVE EXPANDED PANEL APPROACH

3.1 | Characteristics of pharmacogenetic genotyping approaches

As described for the case of *DPYD*-fluoropyrimidine interaction, the reactive testing strategy is often performed for only a single gene. This type of test is certainly more accessible, less time-consuming and easier to perform and interpret. In addition, the immediate clinical benefits from improved clinical decision-making have been shown to outweigh the costs of performing a single genetic analysis, making the test cost-effective.

On the other hand, a multigene panel pre-emptive testing strategy requires analysis of a larger panel of variants, which is associated with additional technical and economic challenges. However, the test results can guide the future prescription and dosing of several drugs, with a potentially larger long-term clinical benefit.[59] Hypothetically, this could increase the cost-effectiveness of the test when considering the potential future benefit of applying PGx at a genotyping cost that is roughly comparable to the cost of a single-gene test.[60,61] However, further investigations are needed, additionally considering the specific healthcare system in which the studies are conducted.

CDS support is strongly desirable when using a multigene panel approach, since the large amount of data generated can make interpretation more difficult for physicians. In addition, dedicated information technology (IT) tools would be helpful for storing the acquired data in the electronic health record (EHR) support. This could help make the PGx information available in the event that a patient should receive a prescription with a risk of DGI long after the time of genotyping. Although a broad panel includes multiple variants, only the variants associated with the prescription can be included in the EHR, or the reported results could be limited to clinically validated variants; however, there is not yet a common consensus on this (Figure 1).[60–62]

Limited data are presently available regarding the potential of pre-emptive testing of an entire pharmacogenetic panel. Different pharmacogenetic consortia and networks have sought to provide evidence for the pre-emptive approach of genotyping based on a complete pharmacogenetic panel. A pioneer in this field was the Pharmacogenomics Global Research Network, which collaborated with the Electronic Medical Records and Genomics Network (eMERGE) to form the eMERGE Network, involving many US sites, as well as the Implementing Genomics Practice (IGNITE) network.[60,63] The eMERGE Network promoted a multicentre study that enabled the sequencing of 82 pharmacogenes among nearly 5700 patients and the integration of established clinically validated PGx genotypes into the EHR with associated CDS.[64] Additionally, the IGNITE

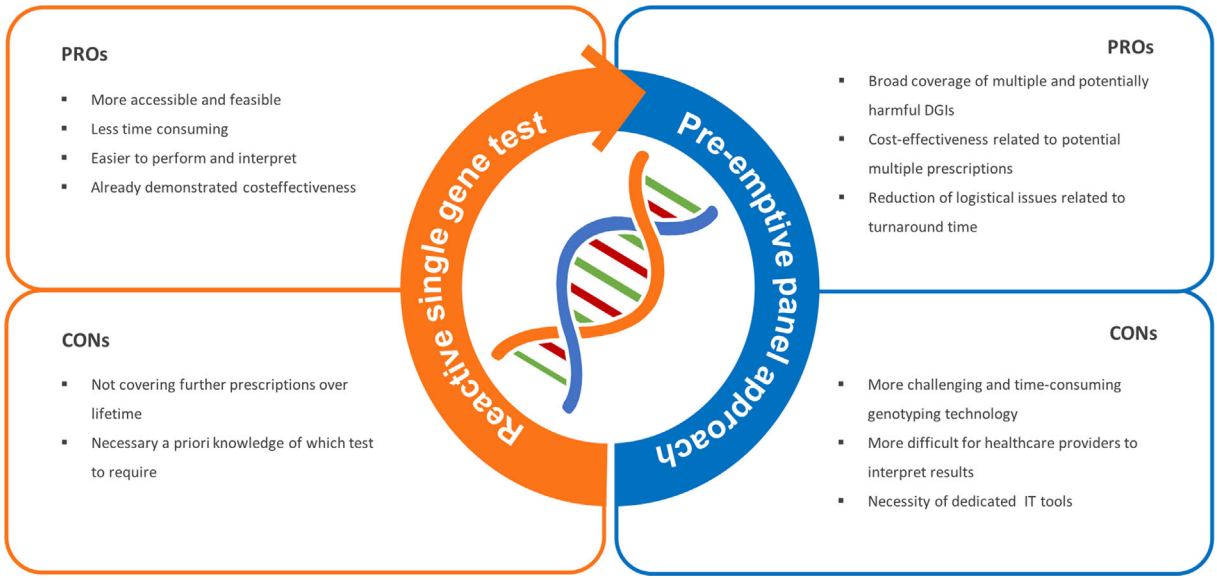

FIGURE 1 Advantages and disadvantages of applying a pre-emptive pharmacogenetic panel approach compared to a reactive single gene-drug approach.

network, comprising five sites and 17 affiliates, was established to assess the feasibility of integrating PGx data into clinical practice.[65]

Over the last 15 years, other projects have been established to address the issue of the prospective clinical implementation of genotyping panels in various healthcare contexts (Table 1). In 2011, PG4KDS was founded at St Jude Children's Research Hospital to establish processes for using PGx tests in the EHR to pre-emptively guide prescribing in paediatric cancer patients.[67] The Pharmacogenomic Resource for Enhanced Decisions in Care and Treatment (PREDICT) was another programme in the field, proposed by Vanderbilt University Medical Center. Thanks to a dedicated infrastructure and framework, PGx data derived from over 10 000 patients were included in the EHR to be available to physicians at the time of prescription.[72] Another relevant programme was approved by the CLIPMERGE PGx Mount Sinai Institutional review board (HS no. 12-00501, GCO no. 12-0931), which was founded with the aim of creating an infrastructure that implements genomic information into real-time clinical decision support provided via the EHR.[73]

All of the projects reported in Table 1 adopted a pre-emptive panel genotyping strategy with high-throughput technology, which were integrated with dedicated IT tools including a CDS system. Among these projects, the Ubiquitous Pharmacogenomics Consortium (U-PGx) recently published the results of the Preemptive Pharmacogenomic Testing for Preventing Adverse Drug Reactions (PREPARE) clinical study, which will be presented in detail below.[69]

4 | UBIQUITOUS PHARMACOGENOMICS PROJECT AND THE PREPARE CLINICAL TRIAL

In 2015, the U-PGx Consortium was funded under Leiden University's coordination to promote PGx implementation in Europe. The consortium included 15 research centres in 10 European countries and was supported by a European Horizon 2020 grant (Grant Agreement No. 668 353)[74] to test the clinical validity and utility of pre-emptively testing a panel of pharmacogenetic variants and prescribing pharmacological treatment according to DPWG guidelines.[75]

The 36-month PREPARE clinical trial (**ClinicalTrials.gov** identifier: NCT03093818) embedded in the U-PGx project was a prospective, open-label, multicentre, controlled, cluster-randomized trial that enrolled 6944 participants and was conducted at several clinical sites in seven European countries. The overall study period was divided into two time blocks. First, for 19 months, countries were randomized to initially enrol either patients receiving PGx-guided prescriptions (study arm) or patients receiving standard care (control arm). After this period, for an additional 19 months, a new group of patients was recruited using the opposite strategy.[76] The primary aim of the study was to demonstrate whether patients treated according to PGx exhibited a reduction in the overall number of clinically relevant ADRs. The secondary endpoints of this study included evaluation of additional clinical outcomes, testing of cost-effectiveness and assessing various quantitative and qualitative parameters of the implementation strategies.

The study tested a panel of 50 polymorphisms, covering 12 genes, having an actionable impact on 42 routinely prescribed drugs with different therapeutic uses, selected among drugs for which DPWG guidelines were available. The main eligibility criterion was receiving a first prescription for a drug from this list, referred to as an 'index drug'. Any adult patient receiving one or more listed medications was eligible to participate in the study. If the patient was enrolled in the control arm, they were treated according to the standard of care and received a PGx report with their complete genetic profile only at the end of the study. Conversely, patients in the study arm received the PGx report before starting therapy, and their clinical practitioners were provided with advice for tailoring the drug dosage based on DPWG recommendations.[25,76,77] To emphasize the patient's active

TABLE 1 Description of some relevant projects/studies implementing PGx with a pre-emptive panel genotyping approach.

Study	Promoter	Study design	Main findings
1200-patient project[66]	University of Chicago Center for Personalized Therapeutics, Illinois, USA	Pre-emptive testing using a commercial ADME pharmacogenomics panel from Sequenom applied on patients from the clinical practice	Ongoing project with the primary aim to demonstrate the feasibility of incorporating pharmacogenomic testing into routine medical care
PG4KDS: Pharmacogenetics for Kids[67]	St Jude Children's Research Hospital, Tennessee, USA	Over 1000 paediatric patients were genotyped for 230 genes using the Affymetrix Drug Metabolizing Enzymes and Transporters Plus array	Demonstrated the feasibility, clinical utility and scalability of their approach to pre-emptive clinical pharmacogenetic tests
PREDICT: Pharmacogenomics Resource for Enhanced Decisions in Care and Treatment[68]	Vanderbilt University Medical Center, Tennessee, USA	More than 10 000 patients were genotyped using the VeraCode ADME Core panel of 184 variants in 34 genes	Cost reductions of 60% for pre-emptive testing compared to reactive genotypin were observed
PREPARE: Preemptive Pharmacogenomic Testing for Preventing Adverse Drug Reactions[69]	Ubiquitous Pharmacogenomics Consortium in Europe, the Netherlands, the UK, Germany, Sweden, Austria, France, Italy, Spain, Greece and Slovenia	Randomized prospective study where patients in the study arm were pre-emptively genotyped compared to control arm In total 6944 patients were genotyped for 50 polymorphisms in 12 genes	Demonstrated a decrease of risk by 30% of clinically relevant ADRs in patients treated according to PGx and the feasibility of applying this approach across seven diverse European healthcare system organizations
RIGHT: Right Drug, Right Dose, Right Time[70]	Mayo Clinic, Minnesota, USA	Approximately 10 000 long-term patients of the Mayo Clinic were genotyped for 77 pharmacogenes through target-enriched capture sequencing	Demonstrated the clinical utility of a pre-emptive sequence-based PGx panel and that about 79% of volunteers carried at least three actionable variants
ChinaMAP: China Metabolic Analytics Project[71]	China	Retrospective analysis of the genotyping outcomes on 22 918 individuals pre-emptively genotyped for a 52-gene targeted next-generation sequencing PGx panel	More than 99% of subjects carried at least one actionable genotyping according to CPIC guidelines, with high heterogeneity among the 20 China provinces involved in the study

Abbreviations: ADME, absorption, distribution, metabolism, and excretion; ADR, adverse drug reaction; CPIC, Clinical Pharmacogenetics Implementation Consortium; PGx, pharmacogenetics.

role in the PGx implementation process, patients in the study arm were provided with a 'Safety-Code' card incorporating their PGx results in a digital format accessible by QR code scan. This mobile-based CDS system was intended to use patient empowerment to maximize the accessibility and sharing of PGx results within different healthcare settings, regardless of the national healthcare existing IT infrastructures.[78] A post hoc survey was administered regarding the uptake of this tool across the different countries participating in the PREPARE study. The results demonstrated that use of the tool was mostly related to the IT advancement among the general population in the countries examined, with higher use of the tool among patients from north European countries compared to Mediterranean countries.[78] Notably, clinicians were not in any way forced to apply PGx indication in their decision process, and it was up to the individual prescriber to decide whether to tailor the treatment based on PGx information.

A common genotyping platform with a related genotyping panel kit was installed and used across the seven coordinating clinical centres: Austria (Medical University of Vienna), Greece (University of Patras), Italy (Centro di Riferimento Oncologico of Aviano), the Netherlands (Leiden University Medical Centre), Slovenia (University of Ljubljana), Spain (San Cecilio University Hospital, Granada) and the UK (Royal Liverpool University Hospital). This enabled reproducible genotyping of patients for the entire panel within a maximum turn-around time of 7 days, as specified by the protocol to guarantee prompt transfer of the data at the patient's bed site. The platform's analytical performance was externally verified by the adherence to a dedicated proficiency testing programme.[79] Consistent with data from the literature, the genotyping results showed that 92.5% of the patients were carriers of at least one actionable genotype for at least one of the drugs included in DPWG pharmacogenetic guidelines.

After enrolment, patients were followed up for at least 12 weeks to collect information regarding the development of adverse side effects, as well as related costs and quality of life. To evaluate the study's primary aim, only clinically relevant ADRs were considered, achieved by filtering events according to severity (based on

NCI-CTCAE version 4.0) and assumption of causal relationship with the index drug (based on the Liverpool Causality Assessment Tool[80]). Overall, a total of 12 470 ADRs were registered, with an average of 1.8 events per patient. The number of ADRs per patient substantially varied according to country, with a minimum of 0.42 event per patient in Spain, to a maximum of 5.05 events per patient in Slovenia. This reflects the different types of patients enrolled in each country. The different countries were characterized by specific focus on, for example, cardiology, oncology, psychiatry, transplant patients, etc, with a related differential risk of ADRs according to specific treatments. However, when focusing only on clinically relevant and genotype-related ADRs according to the study protocol, the overall number of evaluable ADRs was 667.

When considering how those events were distributed between the study and control arm, a significant difference was identified. Patients who received PGx-based personalized drug treatment had an overall 30% lower risk of clinically relevant ADRs. When considering the cohort of patients having an actionable test result for the index drug ($n = 1558$), clinically relevant ADRs were observed in 152 (21.0%) of 725 patients in the study arm, compared to 231 (27.7%) of 833 patients in the control arm (odds ratio [OR] 0.70, 95% confidence interval [CI] 0.54-0.91; $P = 0.0075$). When considering the entire cohort, clinically relevant toxicity developed in 628 (21.5%) of 2923 patients in the study arm and 934 (28.6%) of 3270 patients in the control arm (OR 0.70, 95% CI 0.61-0.79, $P < 0.0001$).[69] It was expected that this effect would be diluted when comparing the risk of ADRs in the whole population *vs* only actionable patients, but this change was not noted. The real-world study design of the PREPARE trial allowed individual centres to enrol patients treated with different drugs in the control and study arms, generating a so-called case-mix effect due to the possibility of having an imbalance of drugs with a different burden of ADRs in the two arms. When the analysis was corrected for case-mix, the effect size in the entire study population decreased from 0.30 to 0.13, and the effect was no longer statistically significant. In contrast, the effect size among patients with an actionable genotype increased from 0.30 to 0.39.[69]

The PREPARE study is the first example of the prospective large-scale implementation of a panel-based approach to PGx testing in clinical practice, moving away from the mainstream drug-gene pair approach. The U-PGx study provides the first real-world evidence of the clinical benefit and feasibility of creating a standardized, validated and harmonized workflow for pharmacogenetic testing in heterogeneous European healthcare settings.[69] Moreover, it demonstrated how systematic application of an educational programme improved general knowledge and awareness of the drug safety benefits of pharmacogenetics, and increased the number of test prescriptions after participation in the study, as reported in some centres.[34]

Indeed, despite the demonstration that PGx application reduced ADRs in clinical practice, U-PGx leaves us with some unanswered questions that should be addressed by future dedicated analyses. Notably, it remains uncertain whether it is cost-effective to apply a PGx panel approach for different drug treatments in clinical practice. Additionally, it is presumed that multiple co-medications should be considered when applying pre-emptive pharmacogenetic panels to guide drug prescriptions, but it is unclear how this should be done. Furthermore, one might wonder how transferable the results of the U-PGx/PREPARE study are outside Europe, considering that almost all of the enrolled patients were of self-declared European origin. Finally, the impacts of rarer pharmacogenetic variants not detected by the U-PGx/PREPARE panel are probably relevant in defining patients at risk of toxicity, but there is presently no method to account for this.

Some of the information retrieved from U-PGx could be helpful for answering some of these questions. The following sections include a brief discussion of how we may move forward.

4.1 | Economic considerations related to a pre-emptive genotyping panel approach

One cornerstone of this discussion is the thorough evaluation of the cost-effectiveness of single gene-drug pairs. The implementation of PGx testing for specific drugs (such as FP with the *DPYD* gene) has shown clinical benefits and has also sparked inquiries regarding the economic viability of such targeted approaches. Rigorous studies, including the works by Deenen et al[37] and Toffoli et al,[47] have examined the economic feasibility of analysing these gene-drug interactions, providing insights into the potential returns on investment by PGx implementation.

Delving deeper, a parallel emerges between the costs associated with reactive and pre-emptive testing methodologies. The expenses linked to a single reactive DGI test (encompassing aspects such as blood collection, patient-related expenditures, DNA extraction and genetic testing) appear to closely align with those associated with a pre-emptive panel genotyping test.[81] Beyond the targeted DGIs, 'incidental findings' that emerge from a comprehensive and pre-emptive genotyping panel hold the promise of providing valuable genetic insights regarding a range of drugs that may be prescribed in the future. The availability of additional variants could potentially increase the cost-effectiveness of panel testing, although prospective testing is required to clarify the relationship between additional testing and increased patient benefit.[82,83] Although there is not yet any conclusive evidence about the cost-effectiveness of a panel genetic profiling strategy, pilot data support this practice. Being a carrier of pharmacogenetic polymorphisms, according to a panel of ADME genes, has been linked to frequent hospitalizations among elderly individuals in polypharmacy, supporting its role as an independent risk factor.[84] The integration of pharmacogenetic profiling, in conjunction with CDS systems and medication management tools, has been linked to discernible reductions of hospitalizations and emergency admissions, augmentation of clinical decision-making processes and potential reductions of healthcare costs, especially within the elderly population subjected to complex medication regimens.[85,86]

Within the U-PGx study, 21.9% of patients exhibited at least one actionable genotype for the index drug they were prescribed. Moreover, within the 18-month follow-up period, 13.7% of patients received a second prescription and 1.1% of patients a third

prescription for drugs associated with known DGIs that were covered by the initially tested panel. These subsequent prescription patterns underscore the clinical relevance of pre-emptive panel genotyping. The possibility that implementing a pre-emptive genotyping panel approach in clinical practice could have increasing clinical utility over time may suggest the increased economic viability of PGx and sets the stage for a significant paradigm shift in patient care.

As we await pharmacoeconomic evaluation of the whole cohort of the PREPARE study, insightful analyses are starting to arise from each implementation site.[87] The global economic assessment of the study will measure the cost-utility and effectiveness of the preventive implementation of a panel of clinically relevant PGx markers in the clinical practice of seven European institutions. Information from individual countries can provide valuable insights into how pre-emptive panel genotyping may impact specific disease categories. In addition, it will be interesting to consider how different healthcare systems may influence the allocation of healthcare resources and budgets in different therapeutic areas.

Single-gene tests, priced between $100 and $500 depending on the testing company and platform, are in competition with more complex multigene panel tests, which could potentially be twice as expensive. The available evidence supports the economic viability of both single-gene and panel-based approaches.[9] However, multigene panel testing, while promising, remains relatively underexplored, suggesting the need for additional research in this area.[88–90]

Elucidating economic aspects of implementing a pre-emptive panel genotyping approach in clinical practice may be useful for improving patient care and optimizing drug treatment over time, and could potentially reshape healthcare landscapes and drive precision medicine forward.

4.2 | Drug-drug interactions and phenoconversion in pharmacotherapy

The increasing ageing of the population, due to improvements in living conditions and medical care, contributes to the accumulation of chronic health conditions (multimorbidity) and polypharmacy. Previously published surveys show that multimorbidity affects more than 70% of people over 65 years of age. Additionally, in the United States, it has been reported that more than two-thirds of people over 65 years of age are on polypharmacy treatment.[91,92] Polypharmacy is defined as the concurrent use of multiple medications to treat multiple comorbidities, with the most common definition based on five or more medications taken simultaneously and regularly.[93] Concurrent use of more medications is associated with higher risks of drug-drug interactions (DDIs), ADRs, lack of adherence and medical errors, and increased risk of morbidity and mortality due to associated ADRs. Furthermore, the prescription of multiple medications is often inappropriate in older adults with multimorbidity, which has an even greater impact on the risk of ADRs, and constitutes a major clinical burden.[3,94]

Drug-drug-gene interactions (DDGIs) represent a complex interplay between multiple factors that can significantly impact a patient's response to medications. These interactions involve both the administered drugs and the genetic makeup of the individual receiving the treatment. The potential effects of DDGIs extend beyond the simple additive effects of DDIs and DGIs, and can lead to profound changes of both the direction and magnitude of a therapeutic response, thereby influencing clinical outcomes. Bruckmueller and Cascorbi emphasized that DDGIs can result in clinically relevant consequences and unexpected therapeutic outcomes, potentially enhancing or inhibiting the treatment efficacy and altering the risk profile of adverse effects.[95] An important implication of DDGIs is that they add another layer of complexity to personalized medicine. To tailor a treatment approach based on an individual's genetic profile, it becomes crucial to understand and predict how different drugs will interact within a specific patient's body. Healthcare providers must consider not only potential DDIs, but also the genetic factors that can modulate these interactions.

The concept of phenoconversion adds another layer of complexity to the intricate landscape of DDGIs. Phenoconversion refers to the phenomenon in which an individual's genotype (genetic makeup) initially appears to suggest a certain drug response, but this response is altered because the presence of another drug or environmental factor causes the individual to exhibit a different phenotype (observable characteristics or traits).[96]

Within the PREPARE trial, it was calculated that each patient received an average of 7.88 co-medications.[69] Thus, it is likely that the enrolled patients' clinical outcomes were profoundly impacted by DDGIs, although with similar effects in the two study arms. The current guidelines do not consider either the phenomenon of phenoconversion or DDGIs. Powerful computational tools will be needed to effectively extract insights from extensive databases, facilitating the development of finely tailored guidelines within the context of specific DDGIs. Several exploratory works have been performed in this context. For example, physiologically based pharmacokinetic modelling has been used to comprehensively assess complex drug interactions involving genetic, drug-drug and drug-gene factors, presenting a novel approach for optimizing dosing precision and understanding exposure effects across diverse scenarios.[97–99]

The application of systems pharmacology approaches has emerged as a formidable tool for dissecting the intricate effects of DDGIs. This innovative approach leverages a holistic understanding of the interconnected biological pathways, molecular networks and genetic factors that govern drug responses within the complex human system. By integrating computational modelling, bioinformatics and high-throughput data analysis, pharmacology systems unravel the synergistic or antagonistic effects of multiple drugs and their interplay with genetic variations. This enables researchers and clinicians to delve beyond the traditional one-drug-at-a-time paradigm and explore the intricate web of interactions that underlie pharmacological outcomes. With the ability to predict potential DDGIs, elucidate underlying mechanisms and optimize drug combinations based on an individual's genetic profile, systems pharmacology opens new vistas for personalized medicine and therapeutic interventions, ushering in a paradigm shift regarding how to approach drug interactions in a comprehensive and context-rich manner.[98]

4.3 | The role of ethnicity in pharmacogenomics implementation

Although the PREPARE study design included patients of any ethnicity, nearly 98% of the patients enrolled were of European, Mediterranean or Middle Eastern ethnicity, therefore there remains a need to demonstrate the validity and utility of the proposed approach among patients of different ethnicities. Moreover, the genetic panel tested within U-PGx is based on DPWG pharmacogenetic guidelines, which were developed in patients of European countries.

Genetic variants in clinically relevant drug-related genes have exhibited variable frequencies among different populations,[100] such that optimal treatment regimens and susceptibility to ADRs may differ according to a patient's ethnicity.[101–103] A recent study reported that about 10% of the new molecular entities approved between 2014 and 2019 showed substantial differences in exposure and/or response according to ethnicity or pharmacogenetic factors that vary in frequency across populations.[104] The vast majority of genomic studies have been conducted in people of European ancestry,[105] as have most of the PGx studies. Ethnic-specific profiling of genetic variability is therefore an important aspect that should be considered in the development of PGx guidelines.[106]

The literature includes multiple examples of relevant gene-drug interactions that are affected by patients' ethnicity. Considering the case of *DPYD*, about 7% of Europeans are carriers of at least one of the variants included in the international guidelines, that is, *DPYD**2A (rs3918290), *DPYD**13 (rs55886062), c.2846A>T (rs67376798) and c.1129-5923C>G (rs75017182).[42] On the other hand, these variants are very rare in populations of African origin,[107,108] where additional variants might play a relevant role. For example, the African-specific missense variant rs115232898-C (c.557A>G; Tyr186Cys) appears with an average frequency of 3% and has been correlated with reduced DPD activity (activity score of 0.5) and linked to cases of severe FP-related toxicity.[107,108] The rs115232898 variant has already been proposed as an additional marker in populations of admixed ethnicity.[109] Other polymorphisms specific for African populations, such as rs61622928-T and rs2297595-C, require additional functional characterization to enable conclusive interpretations.[107,108]

Another relevant ADME gene with an ethnicity-based impact is *CYP2C9*, the activity of which is associated with the safety of many clinically important medications, including the oral anticoagulant warfarin.[110] Although warfarin has now been largely replaced by direct oral anticoagulants for most of its clinical indications, it still represents a good example of the importance of considering ethnicity when personalizing a drug's starting dose. The warfarin dosing algorithm includes a variant associated with reduced activity, *CYP2C9**2 (rs1799853, Arg144Cys), which is highly prevalent in European and admixed American populations, as well as the non-functional variant *CYP2C9**3 (rs1057910, Ile359Leu), which is most prevalent in Asian populations.[102] On the other hand, the loss-of-function alleles *CYP2C9*5* (rs28371686, Asp360Glu), *CYP2C9*6* (rs9332131, 10601delA), *CYP2C9*8* (rs7900194, Arg150His) and *CYP2C9*11* (rs28371685, Arg335Trp) are rarer among individuals of European ancestry but common in Africans.[111] Warfarin pharmacogenetic dosing algorithms must account for ethnically specific variants to avoid underperformance due to inter-ethnic differences in *CYP2C9* genotype frequency.[110–113]

The highly polymorphic gene *CYP2D6* is relevant to a number of drugs commonly used as antipsychotics (ie, **atomoxetine**), **5-hydroxytryptamine** type 3 receptor antagonists (ie, **ondansetron**/**tropisetron**), anticancer treatments (i.e. **tamoxifen**) and opioids.[114] The distribution of *CYP2D6* variants significantly varies according to ethnicity. The null function *CYP2D6**4 allele is more frequent in Europe, while the decreased function *CYP2D6**10 allele is more common in Asia and East Asians. Compared to other ethnic groups, *CYP2D6**41 and duplication/multiplication of active alleles are more common in Middle Eastern populations, and *CYP2D6**17 and *CYP2D6**29 are more frequent in African and Black populations. Globally, poor metabolisers are more frequent among European populations, and ultrarapid metabolizers among Middle Eastern and Ethiopian populations.[115,116] These differences must be considered when **CYP2D6** substrate drug are administered as opioids.[117] Interestingly, patients with a CYP2D6 UM phenotype showed an increased risk of hospital presentations over a 10-year period, compared to other phenotype groups.[118]

The examples above are only a few of many instances in the literature where pharmacogenetic markers have ethnic-specific effects,[102,106,119] therefore current pharmacogenetic guidelines may not be applicable to all populations, and further research efforts are needed to create a specific map for population-specific pharmacogenetic biomarkers. This may have the potential to directly influence and promote clinical implementation of PGx in very specific and unrepresented populations. Future pharmacogenetic research should be expanded to the population level to unravel relevant variants with a more realistic understanding of the distribution of actionable variants across and between populations. Several such programmes have already been initiated worldwide.[9]

4.4 | Rare genetic variants to refine drug outcome prediction

Currently used pharmacogenetic guidelines, including the DPWG guidelines that are the basis of the U-PGx project, are derived from studies of common polymorphisms (minor allele frequency [MAF] >1%) in candidate genes. However, over recent years, a growing body of published data has shown that rare (MAF < 1%) and novel variants may also have significant clinical value for personalized medicine.[120–124]

A series of studies have investigated the genetic variability of clinically relevant genes involved in drug pharmacokinetics and pharmacodynamics by integrating data from large publicly available population datasets of genetic variation (ie, 1000 Genomes Project, Exome Sequencing Projects and ExAC dataset).[101,103,125] Kozyra et al characterized 146 pharmacogenes (including transporters, phase I and II enzymes and nuclear receptors) and showed that about 30-40% of the overall functional variability was caused by rare variants that were not commonly captured by the targeted genotyping approach.[103]

Similarly, Ingelman-Sundberg et al mapped the variability of 208 clinically relevant genes and estimated that rare variants contributed to the inter-individual variability in warfarin pharmacokinetics and irinotecan toxicity. Specifically, rare variants accounted for 18.4% of deleterious *CYP2C9* alleles and >40% of the variability in irinotecan transport, whereas they were less important for modulation of **simvastatin**, voriconazole and **olanzapine** metabolism.[125] Analysis of a breast cancer patient cohort from The Cancer Genome Atlas dataset demonstrated that the vast majority (98.4%) of genetic variations in the major chemotherapy resistance transporters (ie, *ABCB1*, *ABCC1* and *ABCG2*) were rare, and a high burden of germline variants in the transporter gene *ABCC1* (encoding **MRP1**) was associated with shorter disease-specific survival after therapy with the MRP1 substrates **cyclophosphamide** and **doxorubicin**.[122]

More recent publications describe interesting examples of the translation of this evidence into the clinical setting. For example, Gray et al recently demonstrated that the burden of rare non-synonymous genetic variants in phase I cytochrome genes was associated with the risk of cardiac adverse events (ie, acquired long QT syndrome) among pharmacologically treated patients.[123] In a study of cancer patients treated with irinotecan, Karas et al reported that the germline rare variant burden in the **epidermal growth factor** gene contributed to modulating the clearance of SN-38, the active metabolite of irinotecan.[126] Another previous study focused on the transporter OATP1B1 (*SLCO1B1*) and revealed that a rare damaging variant affected the **methotrexate** clearance in children with acute lymphoblastic leukaemia, supporting that rare variants can have important effects on pharmacogenetic phenotype.[124]

Only scarce data are available regarding the possibility of tailoring patients' treatment and dosing based on the presence of rare or not previously reported genetic variants in pharmacogenes. However, a potential effective workflow has been proposed, involving the prospective application of targeted next-generation sequencing (NGS) technology, coupled with powerful in silico algorithms that can return a reliable functional prediction about the deleteriousness of highlighted variants.[127] We recently published the results of a retrospective analysis including about 200 cancer patients treated with FP-based therapy, which shows that the carriers of at least one rare missense *DPYD* variant exhibited a 16-fold increased risk of developing a severe toxic event in the first cycle and an 11-fold increased risk throughout the course of chemotherapy.[120] Moreover, patients at a higher risk of toxicity can be identified using the combination of a NGS approach and variants analysis, with the optimized ADME-optimized prediction framework algorithm used to infer the deleteriousness of missense variants.[128] These results may pave the way for the potential prospective validation of results and future formulations of new pharmacogenetic guidelines to be implemented in clinical practice.

5 | CONCLUSION

In conclusion, the field of PGx holds substantial promise for enhancing patient care by mitigating ADRs and the potential for overall optimization of medication outcomes. Existing research highlights the high prevalence of ADRs among hospitalized adults, particularly in patients with multimorbidity treated with polypharmacy. The economic burden of ADRs underscores the urgency of effective interventions. PGx testing has emerged as a potential strategy to personalize drug therapy, and initiatives like the PREPARE clinical trial exemplify efforts to implement such an approach. The case of *DPYD* testing for FPs demonstrates the clinical utility and feasibility of incorporating PGx information into routine care, yielding improved patient safety and cost-effectiveness. Transitioning from single DGI tests to pre-emptive expanded panel approaches holds promise for optimizing drug prescribing practices. However, challenges remain, including the complex landscape of DDGIs, the need for comprehensive and diverse population representation and the integration of rare genetic variants into clinical decision-making. Overcoming barriers to physician education and promoting familiarity with PGx data will be pivotal for achieving successful clinical implementation. As research continues to uncover the intricate interplay between genetics and drug responses, the integration of PGx into routine practice will be an important tool for advancing personalized medicine and enhancing patient outcomes.

5.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[129]

AUTHOR CONTRIBUTIONS

Erika Cecchin was responsible for the conception and design of the manuscript. Erika Cecchin, Elena Peruzzi, Elena De Mattia, Alessia Bignucolo and Rossana Roncato contributed to the drafting of the manuscript. Giuseppe Toffoli, Jesse J. Swen and Henk-Jan Guchelaar critically revised the review. All authors approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable – no new data generated.

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