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Abstract

Pharmacogenetics (PGx) aims to optimize drug treatment outcomes by using a patient's genetic profile for individualized drug and dose selection. Currently, reactive and pretherapeutic single-gene PGx tests are increasingly applied in clinical practice in several countries and institutions. With over 95% of the population carrying at least one actionable PGx variant, and with drugs impacted by these genetic variants being in common use, pretherapeutic or preemptive PGx panel testing appears to be an attractive option for better-informed drug prescribing. Here, we discuss the current state of PGx panel testing and explore the potential for clinical implementation. We conclude that available evidence supports the implementation of pretherapeutic PGx panel testing for drugs covered in the PGx guidelines, yet identification of specific patient populations that benefit most and cost-effectiveness data are necessary to support large-scale implementation.

INTRODUCTION

Drug response is highly variable. While one person may show a favorable response to the normal dose, others experience nonresponse or adverse drug reactions (ADRs). It has been repeatedly shown that 6–7% of hospitalizations can be attributed to ADRs, and related costs are estimated to be as high as $30–135 billion annually in the United States, clearly indicating the need for improvement (1–5). The interindividual variability in drug response is partially caused by genetic variations, which account for 20–95% of variability in drug disposition and drug effects depending on the drug and gene (6, 7). Pharmacogenetics (PGx) utilizes a patient's genetic profile to select the most safe and efficient drug and dose (8, 9). In the last decade, the use of PGx has shifted from reactive single-gene testing, which is the diagnostic use of a single-gene PGx test to explain the occurrence of toxicity or lack of efficacy in an individual patient, toward single-gene pretherapeutic testing following a new drug prescription, for example, *DPYD* testing for fluoropyrimidines. Ultimately, preemptive PGx panel testing, which is testing for a panel that includes all relevant PGx genes, without a prescription or ADR, could become an integrated part of standard health care.

To aid health-care providers with the application of PGx in clinical practice, the Dutch Pharmacogenetics Working Group (DPWG) and the Clinical Pharmacogenetics Implementation Consortium (CPIC) have published guidelines. In these guidelines, CPIC provides guidance on how to utilize available genetic test results in clinical decision making, rather than indicating whether genetic testing should be performed. DPWG similarly provides recommendations for patients with available genetic test results as well as recommendations for when a PGx test should be performed. For the latter, a clinical implication score was developed (10–12). To date, CPIC has published 26 guidelines containing recommendations for 106 drug-gene pairs, which are readily available on their website (**https://cpicpgx.org**). The DPWG has issued guidelines for 108 drug-gene pairs, of which 63 include recommendations that are actionable drug-gene interactions. In the Netherlands, these guidelines are available at the point of care for prescribers in hospitals, general practitioners, and pharmacists. In addition, both sets of guidelines have been published in peer reviewed journals (10, 13) and can be found on PharmGKB (**https://www.pharmgkb.org/**) and KNMP (**https://www.knmp.nl/dossiers/farmacogenetica**). More recently, other groups and consortia such as the Canadian Pharmacogenomics Network for Drug Safety and the French National network (Réseau) of Pharmacogenetics have also published PGx guidelines (10, 11, 14, 15).

In this review, we provide an overview of the evidence for, and current practice of, PGx panel testing. We present and discuss examples of pretherapeutic single-gene and panel-based PGx testing and compare studies and approaches to identify barriers for the implementation of panel-based PGx testing. Finally, we provide a perspective for the future development of panel-based PGx testing.

PRETHERAPEUTIC SINGLE GENE

PGx testing for single drug-gene pairs either following ADRs (reactive) or following a first prescription (pretherapeutic) was introduced in clinical practice for specific drug-gene pairs approximately two decades ago (**Table 1**). Typically, these drug-gene pairs are supported by a high level of clinical evidence (16–21). To date, this type of single drug-gene testing remains the most frequently applied example of PGx testing in clinical practice (22).

A classic example of a pretherapeutic single-gene PGx test is *DPYD* testing for fluoropyrimidines (23). While effective, fluoropyrimidines cause severe toxicity in up to 28% of patients, and it is estimated the treatment is fatal in 0.5–1% of the patients (16, 23–26). An early prospective

Table 1 Examples of highly evidenced single drug-gene pairs and the adverse drug reactions resulting from interaction between the gene and the drug

Drug	Gene	Design, sample size, outcome	Adverse drug reaction	CPIC	DPWG	Reference(s)
Abacavir	*HLA-B*5701*	Randomized, double-blind, prospective study in 1,956 patients with HIV type 1 who had not yet received abacavir The intervention group was prospectively screened for *HLA-B*5701*; 5.6% of patients were carriers of *HLA-B*5701* After 6 weeks, the hypersensitivity reaction was observed significantly less in the intervention group (3.4% versus 7.8%, $P < 0.001$)	Hypersensitivity reaction	Level 1A	Essential	20
Acenocoumarol Phenprocoumon	*VKORC1*	Single-blind, multicenter, randomized trial to compare PGx-guided dosing for *CYP2C9* and *VKORC1* in 548 patients with atrial fibrillation or venous thromboembolism who initiated acenocoumarol or phenprocoumon treatment After the 12-week follow-up, no significant difference in the percentage of time in the therapeutic INR range was observed, but the time in the therapeutic range was improved for the genotype-guided group (52.8% versus 47.5% in the control group, $P = 0.02$)	Increased risk of bleeding, stroke, or thromboembolism	Level 1A	Beneficial	102
Azathioprine 6-MP	*TPMT*	Prospective study in 30 Dutch hospitals (378 patients) where the intervention group was screened for *TPMT* variants and received the appropriate dose adjustment; the control group received standard care Similar proportion of patients (7.4% in the intervention versus 7.9% in the control group) developed a hematologic ADR during the 20-week follow-up Of the *TPMT*-variant carriers, the intervention showed significantly fewer hematologic ADRs compared to the control (2.6% versus 22.9%)	Hematologic ADRs	Level 1A	Essential	19
Clopidogrel	*CYP2C19*	Randomized, open-label, assessor-blinded trial with 2,488 patients that underwent primary PCI with stent implantation The intervention group was genotyped for *CYP2C19* and received tailored treatment; the control group received standard treatment The follow-up at 12 months showed no significantly lower risk of myocardial infarction, definite stent thrombosis, stroke, or major bleeding; however, a significantly lower risk of bleeding was observed in clopidogrel users in the genotype-guided group	Thrombotic events	Level 1A	Essential	21
Fluoropyrimidines	*DPYD*	Retrospective screening of databases and patient files to evaluate the value of prospective *DPYD* screening as part of routine care 540 patients were included; 14 of 275 patients (5.1%) carried a *DPYD* variant and were recommended a 25–50% dose reduction, where no toxicity was observed anymore	Gastrointestinal adverse events, neutropenia, hand-foot syndrome	Level 1A	Essential	23, 27, 29

(*Continued*)

Table 1 (*Continued*)

Drug	Gene	Design, sample size, outcome	Adverse drug reaction	CPIC	DPWG	Reference(s)
Irinotecan	*UGT1A1*	Prospective, multicenter, nonrandomized study in 350 patients that were pretherapeutically genotyped for *UGT1A1*28* and *UGT1A1*93* Homozygous variant carriers received a 30% dose reduction The adjustment reduced the incidence of febrile neutropenia significantly (6.5% compared to 24% in a historical control, $P = 0.04$)	Febrile neutropenia	Level 1A	Essential	103
Warfarin	*VKORC1*	Multicenter, randomized controlled trial with 455 enrolled patients with atrial fibrillation or venous thromboembolism Intervention group was genotyped for *VKORC1* and *CYP2C9* Significantly fewer cases of excessive anticoagulation and significantly fewer days to reach INR ($P < 0.001$) in the intervention group were observed after the 12-week follow-up	% of time in therapeutic INR, bleeding	Level 1A	Not yet evaluated	17, 104

Abbreviations: 6-MP, 6-mercaptopurine; ADR, adverse drug reaction; CPIC, Clinical Pharmacogenetics Implementation Consortium; DPWG, Dutch Pharmacogenetics Working Group; HIV, human immunodeficiency virus; INR, international normalized ratio; PCI, percutaneous coronary intervention; PGx, pharmacogenetics.

study investigating a 50% dose reduction in *DPYD*2A* carriers showed a significant reduction of grade 3 or higher toxicity in *DPYD*2A* carriers from 73% in historical controls to 28% in study subjects carrying the *DPYD*2A* variant (23). In a subsequent study, the panel was expanded to include four variants: *DPYD*2A*, c.2846A>T, c.1679T>G, and c.1236G>A. This study showed that a dose reduction of 25% (c.2846A>T and c.1236G>A) or 50% (*DPYD*2A* and c.1679T>G) in heterozygous *DPYD* variant allele carriers leads to a lower relative risk (RR) for severe toxicity compared to the historical controls (RR 1.31 versus 2.87 for *DPYD*2A* carriers, 2.00 versus 3.11 for c.2846A>T carriers, and 1.69 versus 1.72 for c.1236G>A carriers) (27). Though not a formal cost utility analysis, an analysis of the economic impact indicates that *DPYD* testing is slightly cost reducing, with €2,599 per patient for screening versus €2,650 per patient for nonscreening (28). Results from a recent survival analysis show that overall, there was no difference in progression-free survival (PFS) or overall survival (OS). However, in a subgroup analysis, a shorter PFS [hazard ratio (HR) 1.43, $P = 0.007$] but not OS (HR 1.17, $P = 0.385$) was observed in c.1236G>A carriers receiving a dose reduction of 25% (29). Together, these data suggest that pretherapeutic *DPYD* testing can be effective, cost-efficient, and beneficial for patient safety. Combined with the European Medicines Agency recommendation regarding pretherapeutic *DPYD* testing released in 2020, these results have contributed to the broad adoption of pretherapeutic testing of *DPYD* within the European Union (16, 30). However, in the United States, pretherapeutic *DPYD* testing remains controversial and part of an increasingly public debate despite a label change for fluorouracil and capecitabine by the FDA in March 2024 (31–33).

A second example of a pretherapeutic single-gene PGx test is *CYP2C19* and clopidogrel. In contrast to the pragmatic studies of PGx-informed fluoropyrimidine dosing, results are available from two randomized controlled clinical trials assessing the effect of *CYP2C19*-guided clopidogrel treatment on ischemic outcomes in cardiology. First, the POPular Genetics trial, a randomized, open-label, assessor-blinded noninferiority trial, enrolled 2,488 patients who underwent primary percutaneous coronary intervention (PCI) with stent implantation and were followed for 12 months. Patients were randomized between *CYP2C19*-guided treatment or standard of care. In

the genotype-guided group, patients without a *CYP2C19* variant received clopidogrel (step down). All other patients in the study and control group received standard treatment with ticagrelor or prasugrel. Results show that the PGx-guided strategy was noninferior to standard treatment, with 5.1% thrombotic events in the PGx-guided group and 5.9% in the standard-treatment group ($P > 0.001$ for noninferiority). In the PGx-guided group, the major bleeding incidence was 9.8%, compared to 12.5% in the standard-treatment group ($P = 0.04$) (21).

Secondly, the Tailored Antiplatelet Initiation to Lessen Outcomes Due to Decreased Clopidogrel Response After Percutaneous Coronary Intervention (TAILOR-PCI) trial enrolled 5,302 patients at 40 centers in the United States, Canada, South Korea, and Mexico, all of whom underwent PCI. Patients were randomized between *CYP2C19*-guided treatment or standard of care. In the genotype-guided group, patients with a *CYP2C19* variant received alternative treatment with ticagrelor (step up). No statistically significant difference regarding ischemic outcomes was observed after 12 months (HR 0.66, $P = 0.06$). The study was powered to detect a 50% reduction in ischemic outcomes; however, only a 35% reduction in ischemic outcomes was observed. While this limits the clinical impact, the results of a post hoc analysis showed a significantly lower HR for ischemic events in the *CYP2C19* loss-of-function intervention group in the first 3 months (0.21, $P = 0.001$) (34).

Additionally, five other randomized controlled trials and four observational studies were reported, including a meta-analysis. Results of the meta-analysis show that the superior effectiveness of ticagrelor and prasugrel compared to clopidogrel is indeed primarily based on the *CYP2C19* loss-of-function carrier status, with a significant reduction in ischemic events, but not a significant effect on bleeding events in patients with ticagrelor and prasugrel compared to clopidogrel [RR 0.70, 95% confidence interval (CI) 0.59–0.83] (35). These findings therefore support the use of PGx testing prior to prescribing P2Y12 inhibitor therapy and underline the results of the POPular Genetics and the TAILOR-PCI trials.

These examples are part of a larger group of drugs, including abacavir, irinotecan, warfarin, and coumarins (**Table 1**), for which a substantial body of evidence exists supporting pretherapeutic single-gene PGx testing.

PANEL-BASED APPROACHES IN PHARMACOGENETICS

The body of evidence and guidelines for many single drug-gene pairs, combined with the technological developments and associated price drops for PGx panel tests, raises the question of whether PGx panel testing offers an improvement compared to testing for single drug-gene pairs (36).

The first argument supporting PGx panel testing is that studies repeatedly show that more than 95% of the population harbors at least one actionable PGx variant (10, 37–39). A second argument is that the drugs that are covered in the available CPIC and DPWG guidelines are commonly used (40, 41). US data indicate that out of patients 40 years of age or older, approximately half received at least one PGx drug during a 4-year period, and 25–30% received two or more (42). Other data show that approximately 65% of adults are prescribed at least one drug with a PGx recommendation over a period of 5 years (43). This number increases with age due to polypharmacy, with 90% of the patients over 70 years expected to use at least one drug with a PGx recommendation (8). The high frequency of PGx variants and prescription of drugs with a PGx recommendation results in a considerable risk for a relevant drug-gene interaction and holds the potential to significantly impact health care for those who start a prescription for a drug with an actionable PGx recommendation (10, 37). Indeed, for the Netherlands it was estimated that in 2016, if a PGx profile would have been available for all Dutch citizens, 5.4% of all first prescriptions would have been changed according to the DPWG guidelines. In the subgroup of patients that received

a first prescription for one of the 45 drugs with an actionable recommendation in the DPWG guidelines, this number of adjusted prescriptions increases to 23.6% (37). For the United States, a retrospective analysis in adults over 65 years of age with polypharmacy showed that, based on the CPIC guidelines, 14.3% of participants would have been recommended a dose adjustment or drug switch. Additionally, this retrospective study indicates a positive shift in health-care resource usage toward more sustainable and cost-effective options, with 1.6% fewer outpatient events, 6.8% fewer emergency department events, and 14.9% fewer inpatient events, resulting in $37 million in savings in direct medical charges in the first 32 months after the implementation of PGx testing (44).

Two main types of panel-based testing can be distinguished. The first approach is pragmatic and disease oriented. In these types of panels, genes that are relevant for a set of drugs that are commonly used for a particular disease area are combined. Examples of this approach are *DPYD* and *UGT1A1* in colorectal cancer; *NUDT15* and *TPMT* in inflammatory bowel disorders; *CYP2D6*, *CYP2C19*, and *CYP3A4* in mood disorders; and *CYP2C9* and *VKORC1* for anticoagulation (14, 17, 45, 46). Based on the 21 actionable genes in CPIC and DPWG guidelines, approximately five to ten of such panels can be defined (see **Table 2** for examples). A recent study investigating PGx testing practice in primary care showed that in 2021, 66% of all general practitioner–requested tests were such a small PGx panel (47). There are several ongoing studies using this disease-oriented approach, including the Pharmacogenomics in Depression (PRESIDE) trial (ACTRN12621000181808), which is a double-blind, randomized, controlled trial in depressed patients. Participants are randomized between *CYP2C19*- and *CYP2D6*-guided prescribing versus standard of care. Patients are monitored for 12 weeks to assess the efficacy and cost-effectiveness of PGx-guided antidepressant prescribing (48). A second example is the PhOCus trial (NCT04541381), which aims to assess the effect of *UGT1A1*- and *DPYD*-guided dosing on the proportion of patients that receive dose adjustments in the first treatment cycle and grade 3 or higher treatment-related ADRs by genotyping patients in the intervention arm and adjusting their therapy accordingly. The control arm will receive standard treatment (48, 49). However, it can be argued that this disease-based approach is not truly PGx panel testing and may be considered an intermediary step, as the panels contain only a small number of genes, bringing little added value compared to pretherapeutic single-gene testing. A *UGT1A1* and *DPYD* panel,

Table 2 Examples of possible disease-based PGx panels based on current DPWG and CPIC guidelines

Disease-based PGx panel	Genes
Cardiovascular	*CYP2C19*, *CYP2C9*, *VKORC1*, *SLCO1B1*, *CYP2D6*, *CYP3A4*, *CYP3A5*
Pain management	*CYP2C19*, *CYP2D6*, *CYP2C9*, *CYP3A4*, *CYP3A5*, *CYP2B6*, *HLA-B*, *ABCG2*
Cancer and immunosuppressive	*CYP2C9*, *CYP2D6*, *CYP3A4*, *CYP3A5*, *NUDT15*, *TPMT*, *DPYD*, *UGT1A1*
Neurological and psychiatric	*CYP2C19*, *CYP2D6*, *CYP2C9*, *CYP3A4*, *CYP3A5*, *CYP2B6*, *HLA-B*1502*, *COMT*, *HLA-A31:01*
Infectious disease	*HLA-B*5701*, *CYP2C19*, *CYP2B6*, *CYP3A4*
Gastrointestinal	*CYP2D6*, *CYP2C19*, *CYP2C9*
Endocrine and metabolic	*CYP2D6*, *MTHFR*, *CYP2C9*, *CYP3A4*, *CYP3A5*

Abbreviations: CPIC, Clinical Pharmacogenetics Implementation Consortium; DPWG, Dutch Pharmacogenetics Working Group; PGx, pharmacogenetics.

for example, covers only six drugs (*UGT1A1* for irinotecan and atazanavir; *DPYD* for tegafur, fluorouracil, flucytosine, and capecitabine) (50–54).

A second approach is broad pretherapeutic PGx panel testing. This type of PGx panel testing ultimately includes a panel covering all genotypes and variants from clinically actionable guidelines (55). Several early exploratory studies utilizing this approach are available. One such study, focusing on preventing rehospitalizations and emergency department visits, enrolled 110 patients over 50 years of age receiving or initiating treatment with drugs with actionable drug-gene interactions based on the CPIC guidelines. The intervention group ($n = 57$) was genotyped for a five-gene panel consisting of *CYP2C19*, *CYP2C9*, *CYP2D6*, *CYP3A4*, and *CYP3A5*. Test results were used in combination with CPIC guidelines to provide recommendations to involved clinicians. The control group ($n = 53$) received standard treatment. Findings indicated significantly reduced rehospitalizations and emergency department visits (0.33 mean visits in intervention group versus 0.70 in control group, $P = 0.007$) at 60 days (56). A second example is a study involving 342 polypharmacy patients (six or more drugs) eligible for medication therapy management (MTM, a service to optimize the therapeutic outcomes for individual patients) who were randomly assigned to three arms: standard MTM ($n = 104$), MTM incorporating a clinical decision support tool ($n = 180$), and MTM with the clinical decision support tool enhanced with PGx ($n = 58$). Patients in the MTM plus PGx group were genotyped for a panel consisting of *CYP2D6*, *CYP2C19*, *CYP2C9*, *CYP3A4*, *CYP3A5*, and *VKORC1*. At 1-year follow-up, no significant increase in the number of identified ADRs or drug-drug interactions was observed for the genotyped group. However, PGx testing and the decision support tool helped to identify more serious problems, causing pharmacist-provided recommendations to be more readily accepted by prescribers (57, 58). A third example is a study performed in patients 65 years of age or older with polypharmacy (five or more drugs) who were frequently hospitalized (three or more times per two years). Cases were matched by age, gender, race, ethnicity, and chronic disease score to rarely hospitalized (fewer than three times per two years) controls. Both groups were genotyped for a panel consisting of *CYP2C19*, *CYP2C9*, *VCORC1*, *CYP2D6*, *CYP3A4*, and *CYP3A5*. In the cases, the mean number of drug-gene interactions was 2.8 ± 2.2, while the controls had none, highlighting the PGx profile as an independent risk factor for hospitalization frequency in older polypharmacy patients (59).

While these studies show promising results in favor of broad pretherapeutic PGx panel testing, their small sample size, retrospective design (in the case of case-control studies), and involvement of commercial testing in companies in multiple studies limit the clinical impact. Results were recently published from two prospective clinical implementation studies that aimed to investigate the clinical utility of preemptive PGx panel testing (**Table 3**). Both studies enrolled patients diagnosed with a broad range of diseases using a range of different drugs for which a PGx recommendation was available from CPIC or the DPWG. In both cases, the occurrence of ADRs was used as a primary end point.

The Preemptive Pharmacogenomic Testing for Prevention of Adverse Drug Reactions (PREPARE) study (NCT03093818) was an open-label, multicenter, controlled, cluster-randomized, crossover implementation study involving a 12-gene PGx panel combined with the DPWG recommendations. It was conducted in 18 hospitals, 9 community health centers, and 28 community pharmacies across 7 European countries. Patients were eligible when they received a first prescription for a drug with an actionable recommendation from the DPWG guidelines as part of routine care. In total, 6,944 patients were enrolled in the study and followed for at least 12 weeks. The PGx panel consisted of 50 single-nucleotide variants (SNVs) in 12 genes—*CYP2B6*, *CYP2C9*, *CYP2C19*, *CYP2D6*, *CYP3A5*, *DPYD*, *F5*, *HLA-B*, *SLCO1B1*, *TPMT*, *UGT1A1*, and *VKORC1*—for which actionable DPWG guidelines were available at the time of the study (60, 61). The primary outcome was the incidence of clinically relevant, patient-reported ADRs within

Table 3 Comparison of the PREPARE study and INGENIOUS trial

	PREPARE	INGENIOUS
Study design	Open-label, multicenter, cluster-randomized crossover implementation study	Open-label, single-center, propensity-matched cohort study
Sample size	6,944 patients	2,612 patients
Main inclusion criteria	Start with actionable drug in DPWG guidelines ($n = 39$)	Start with index drug, targeted by a CLIA-certified panel; all are actionable according to DPWG and CPIC guidelines ($n = 26$)
Objective	Determine the effect of a genotype-guided drug-prescribing approach using a preemptive PGx panel across different health-care systems	Identify and overcome barriers to implement PGx in the clinic by determining whether a PGx panel for 26 drug-gene pairs helps to avoid ADRs and reduce health-care costs
Primary outcome	Primary end point: incidence of causal and clinically relevant ADRs for the index drug within the 12-week follow-up ADR definition: CTCAE grade 2 or higher, except for patients receiving 5-fluorouracil, capecitabine, tegafur, or irinotecan; in these cases, grade 3 and higher was included in the end point Secondary end points: PROMs to study differences between patient-reported ADRs and ADRs collected by the research team, drug continuation rate in intervention versus control arm, and cost-effectiveness Intention to treat analysis	Primary end point: occurrence of ADRs in one-year follow-up period ADR definition: CTCAE grade 3 or higher Secondary end point: cost analysis of preemptive PGx panel testing Intention to treat analysis
Reporting of PGx results	To physician and pharmacist and to patients with medication safety code card	EHR message in case of genotype-guided prescribing recommendation
Follow-up and data collection	18 months Questionnaires at baseline, week 4, week 12, and end of follow-up Self-reported survey at weeks 2 and 8	12 months Outcome data extracted from EHR
Panel test	50 variants *CYP2B6*, *CYP2C9*, *CYP2C19*, *CYP2D6*, *CYP3A5*, *DPYD*, *F5*, *HLA-B*, *SLCO1B1*, *TPMT*, *UGT1A1*, and *VKORC1*	43 variants *CYP2B6*, *CYP2C19*, *CYP2C9*, *CYP2D6*, *CYP3A4*, *CYP3A5*, *CYP4F2*, *DPYD*, *G6PD*, *ITPA*, *SLCO1B1*, *TPMT*, and *VKORC1*
Main study results	25.2% of patients had an actionable genotype 30% reduction in risk of ADRs	34.7% of patients had an actionable genotype No significant difference in ADR risk Subgroup analyses showed a reduction of ADRs in the PGx-guided group for subjects receiving aripiprazole, serotonin, or serotonin-norepinephrine reuptake inhibitors (OR 0.34, 95% CI 0.12–0.85)
Limitations	Not blinded End point definition based on patient-reported ADRs Limited external validity due to selection of patients with particular drugs; effect cannot be extrapolated to all drugs Underpowered for conclusions on individual drugs Possible start of PGx drug before PGx test results were available Potentially underestimated net effect of intervention because 70% of DPWG recommendations are adopted	Not blinded End point definition based on EHR data extraction with ICD9 and ICD10 codes Did not meet planned sample size, resulting in lack of power to detect signals Limited external validity due to selection of patients with particular drugs; effect cannot be extrapolated to all drugs Underpowered for conclusions on individual drugs Possible start of PGx drug before PGx test results were available

Abbreviations: ADR, adverse drug reaction; CI, confidence interval; CLIA, Clinical Laboratory Improvement Amendments of 1988; CPIC, Clinical Pharmacogenetics Implementation Consortium; CTCAE, Common Terminology Criteria for Adverse Events; DPWG, Dutch Pharmacogenetics Working Group; HER, electronic health record; ICD, International Classification of Diseases; INGENIOUS, Indiana Genomics Implementation: An Opportunity for the Underserved; OR, odds ratio; PGx, pharmacogenetics; PREPARE, Preemptive Pharmacogenomic Testing for Prevention of Adverse Drug Reactions; PROM, patient-reported outcome measure.

the 12-week follow-up period. PGx test results were returned to physicians, pharmacists, and the patients. The latter received a medication safety code (MSC) card, including a quick response (QR) code that led to a website that provided the relevant DPWG recommendations. Adherence to the guidelines was not mandatory and was left to the judgement of the treating physician and/or pharmacists. The control group was genotyped after completion of the follow-up. ADRs were filtered for severity using the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) (grade 2 or higher, with the exception of patients with cancer receiving 5-fluorouracil, capecitabine, tegafur, or irinotecan; in these cases grade 3 and higher was included in the end point) and causality (Liverpool Causality Assessment Tool score of possible or higher) (60, 61). Out of the 6,944 patients, 1,558 (22%) had an actionable test result for the index drug. ADRs occurred in 152 (21%) out of 725 patients with an actionable test result for the index drug in the study group and 231 (28%) of 833 patients in the control group [odds ratio (OR) 0.70, $P = 0.0075$]. Surprisingly, a similar result was observed when comparing all patients in the study and control groups (OR 0.70, $P < 0.0001$). However, after performing a post hoc exploratory analysis corrected for confounding factors, the effect in all patients decreased from 30% to 13% and was no longer statistically significant (60, 62, 63). Interestingly, the effect size in patients with an actionable genotype increased from 30% to 39% and remained statistically significant (64–66).

The Indiana Genomics Implementation: An Opportunity For The Underserved (INGENIOUS) trial (NCT02297126) was conducted by the Implementing Genomics in Practice (IGNITE) network (67). This was a pragmatic prospective randomized controlled trial powered to assess the impact of prospective PGx on health-care costs for 1-year follow-up. The trial recruited 2,612 patients within the Eskenazi Health System. Patients were eligible when they received a new prescription for one or more of 26 PGx-actionable drugs based on the CPIC and DPWG guidelines. The PGx panel test consisted of 43 SNVs in 13 genes—*CYP2B6*, *CYP2C19*, *CYP2C9*, *CYP2D6*, *CYP3A4*, *CYP3A5*, *CYP4F2*, *DPYD*, *G6PD*, *ITPA*, *SLCO1B1*, *TPMT*, and *VKORC1*—based on actionable recommendations provided by CPIC and DPWG (67–69). The main outcome was the occurrence of ADRs during the follow-up period of 1 year. ADRs were extracted from the electronic health record (EHR) using International Classification of Diseases (ICD)9 and ICD10 codes. Severity was determined according to CTCAE criteria. In the intervention group, PGx test results were reported to the prescribing physician through an EHR message whenever a genotype-guided prescribing recommendation was present (69, 70). The results indicate a statistically nonsignificant decrease in risk for a serious ADR (CTCAE grade 3 or higher) in the genotype arm (OR 0.91, $P = 0.74$) (69). Currently, the IGNITE network is running several other studies. A Depression and Opioid Pragmatic Trial in Pharmacogenetics (ADOPT-PGx) is a multicenter trial (NCT05966155, NCT05966142, NCT05966129) that comprises three studies focusing on different medical conditions, including acute pain, chronic pain, and depression. This trial aims to assess the impact of genotype-guided therapy in a real-world setting.

One difference between the INGENIOUS trial and the PREPARE study is that INGENIOUS extracted data on the occurrence of ADRs from the EHR, while PREPARE used patient-reported ADRs (60, 61, 64–69). Another difference is the method used to report the PGx results. PREPARE included a MSC card carried by the patient, while INGENOUS reported results as a clinical decision support alert in the EHR (60, 61, 66, 69, 70). Both studies had some limitations. Both were implementation studies and therefore applied an unblinded design that introduced the risk of a type of Hawthorne effect where patients over- or underreport ADRs based on their knowledge of study arm assignment (65, 66). In addition, PREPARE used patient-reported ADRs, omitting ADRs that cannot be detected by the patient such as a high international normalized ratio or low leukocyte counts (71). In the INGENIOUS trial, ADR information was extracted from the EHR

using ICD9 and ICD10 codes. It is well recognized that these codes are not suitable to attain the full range of potential ADRs, and therefore ADRs have been potentially missed (65, 69, 70). These differences in ADR source may have impacted ADR rates. Indeed, PREPARE reported ADRs in 25.2% of the participants, while INGENIOUS reported ADRs in 16.1% of the participants. However, this may also be caused by the different ADR definition (CTCAE grade 2 or higher in PREPARE versus CTCAE grade 3 or higher in INGENIOUS) (60, 61, 64–69). Moreover, the INGENIOUS trial enrolled only 2,612 of the planned 6,000 patients, causing the study to be underpowered to draw conclusions regarding the effect of PGx panel testing on the occurrence of ADRs (69).

Both the INGENIOUS trial and PREPARE study allowed patients to start drug treatment before the PGx results were available. This could potentially lead to an underestimation of the effect of the PGx intervention as ADRs might have already occurred before PGx results were available and treatment could have been adjusted accordingly (60, 61, 69, 70). Moreover, in the PREPARE study, adoption of DPWG recommendations was 70%, which might have resulted in an underestimation of the effect of the PGx-guided strategy (60). This may have also happened for the INGENIOUS trial, but unfortunately no data on adoption rates are available for this study. It is important to note that both INGENIOUS and PREPARE were not designed to assess the impact of PGx panel testing in the general population. Both studies enrolled a selected set of patients starting treatment with a drug covered in the CPIC and/or DPWG guidelines, and both studies enrolled mostly Caucasian individuals. In addition, capping was applied for a number of drugs in the PREPARE study, meaning that the maximum percentage of patients enrolled with a certain drug was limited to 10% of all patients, further limiting generalizability to the general population (60, 61).

Despite these differences and limitations, these studies indicate a favorable effect of pretherapeutic PGx panel testing. Though this finding only reaches statistical significance in PREPARE, they both support the clinical implementation of pretherapeutic PGx panel testing for patients receiving a first prescription for a drug with an actionable recommendation in the CPIC and/or DPWG guidelines.

CHALLENGES AND OPPORTUNITIES FOR IMPLEMENTATION OF PRETHERAPEUTIC PGx PANEL TESTING IN THE CLINIC

Challenges for PGx Panel Testing

Despite the available body of evidence in favor of pretherapeutic PGx panel testing, challenges remain for its implementation into clinical practice. These barriers for panel PGx implementation overlap with the barriers known to hamper PGx testing in general. Examples of these overlapping barriers are harmonization between the different guidelines, registration of PGx results in the EHR and decision support system, and lack of education on PGx for health-care providers and patients (72). The remaining challenges specific to pretherapeutic PGx panel testing can be divided into (*a*) technical, (*b*) timing, and (*c*) lack of genetic diversity in current studies (see **Figure 1**). We outline these barriers and discuss specific challenges of different implementation routes.

Technical Barriers

One of the technical barriers specific to the implementation of PGx panel testing in the clinic is a lack of standardization in applied panels. Selection of genes ranges from a very narrow selection of genes relevant to the population of the specific medical center to an almost genome-wide approach. To address this lack of standardization, the US-based Association of Molecular Pathology has issued guidelines defining which genetic variants are crucial in PGx (45, 73–76).

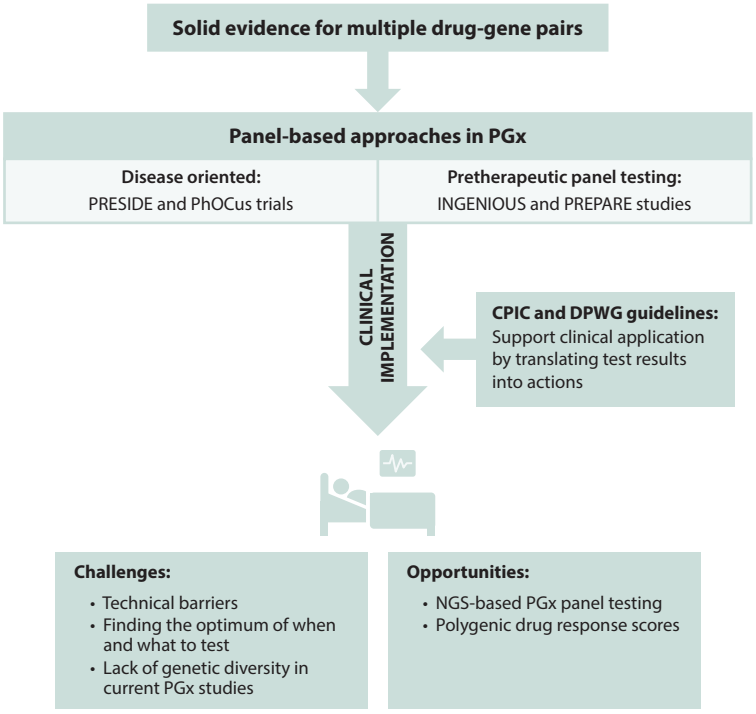

Figure 1

Outline of the development from the first evidence of single gene-drug pairs to challenges in and opportunities for the implementation of pretherapeutic PGx panel tests in the clinic. Abbreviations: CPIC, Clinical Pharmacogenetics Implementation Consortium; DPWG, Dutch Pharmacogenetics Working Group; INGENIOUS, Indiana Genomics Implementation: An Opportunity for the Underserved; NGS, next-generation sequencing; PGx, pharmacogenetics; PhOCus, Implementation of Pharmacogenomic Testing in Oncology Care; PREPARE, Pre-emptive Pharmacogenomic Testing for Preventing Adverse Drug Reactions; PRESIDE, Pharmacogenomics in Depression.

Moreover, efforts to standardize the recommendations and phenotype assignments between CPIC and DPWG guidelines are currently ongoing, for example, by the Clinical Genome Resource (ClinGen) Pharmacogenomics Working Group, which aims to establish a structure of tiered standard terminology and definitions to classify PGx genes and variants (77, 78).

A second technical barrier is the translation of identified variants with unknown effects, variants of unknown significance (VUS), into clinically relevant alleles and phenotypes. This barrier becomes particularly relevant when a PGx panel test is performed with a large array or sequencing-based approaches, such as whole-exome sequencing (WES). Currently, in the PGx field, the star (*) nomenclature system is most commonly used to classify haplotypes. Each star allele represents a combination of variants that is curated and assigned an activity impact, as is documented by the Pharmacogene Variation (PharmVar) Consortium. This consortium facilitates a central repository for PGx variation focusing on haplotype structure and allelic variation (**https://www.pharmvar.org/**). Based on these star alleles, predicted phenotypes are assigned. However, with the growing number of clinically relevant variants and star alleles, these translations become more challenging. Moreover, with the increasing amount of next-generation sequencing (NGS) studies, the proportion of rare variants and VUS detected in pharmacogenes increases. Including these variants in clinical reports is challenging as their function and relevance are often

not validated. It is, however, believed that these rare variants play an important role in the drug response, causing these VUS to have a major impact on drug response at an individual level (79–83). Possible solutions to overcome the translation of VUS include artificial intelligence, such as machine learning and deep learning, together with in vitro assays to provide training data to feed the algorithms. Follow-up experiments can aid in the validation of the predicted functions as well as in understanding the link between the genetic variant and functional effects (84). An example of these computational approaches to predict VUS effects is the application of algorithms trained for the identification of unknown variants in sequence variation data. After analyzing the sequencing data of 38 CYP genes from 141,456 individuals, 107 variants not included in commonly available databases like gnomAD were identified. Of these, 31 (29%) were estimated to impact CYP enzyme function. However, further biochemical characterization of these variants is necessary to draw conclusions about the value of the software predictions (85).

Finding the Optimum of What and When to Test

As mentioned above, reactive, pretherapeutic, and preemptive PGx testing strategies can all be applied. While CPIC and DPWG guidelines are evidence based and support PGx testing, it remains to be elucidated what is the best moment in a patient's journey to perform PGx panel testing and realize maximal cost-effectiveness (12). The DPWG provides some guidance to select patients eligible for testing with the Clinical Implication Score (CIS). This score system uses four criteria to indicate for which drugs pretherapeutic PGx testing should be performed (12). However, the CIS still considers pretherapeutic testing. Because pharmacogenes do not change during one's life, implementing population-wide preemptive PGx panel testing might be an interesting strategy. One approach for population-wide PGx screening could be to integrate a PGx panel into the heel prick that is part of newborn screening programs. This idea becomes particularly feasible when these programs implement NGS-based diagnostic approaches. Studies are currently ongoing to facilitate this implementation (86). Dried blood spot samples, which are typically used in these types of screenings, have already proven to be an accurate resource for genetic analyses (87).

Lack of Genetic Diversity

Ample evidence supporting the implementation of PGx in the clinic is available for individuals of Caucasian descent. However, frequencies of PGx variants show considerable variation between different genetic backgrounds. It was reported that African Americans have the highest median number of genomic variants per person while European Americans have the lowest (38). Therefore, the impact of PGx on pharmacological response can differ depending on the studied population. For example, there is a higher incidence of drug hypersensitivity reactions related to HLA-B in Han Chinese (77–100%) and Southeast Asian (67–100%) patients as compared to other populations, for example, 0–50% in Caucasians (88). While these numbers apply to carbamazepine and not to all hypersensitivity reactions, they indicate that there is an urgent need for more worldwide initiatives to study PGx variant diversity between different ethnic groups, and for multiethnic studies that include diverse populations (8). An example of variant diversity is *CYP3A4*20*, a rare variant of *CYP3A4* that occurs in 1.2% of the Spanish population compared to 0.2% of the Portuguese and has no carriers in other countries. This loss-of-function allele was discovered in a patient of Latin American descent during a clinical pharmacokinetic trial in Switzerland. As this patient lives in both Latin America and Switzerland, the rare variant unexpectedly presented itself in the Swiss population (89, 90). This case highlights the importance of considering intraindividual variability in the expression of pharmacogenes. Several initiatives focusing on investigating the diversity in PGx variants in minorities are currently ongoing. An example of this is the H3Africa Consortium, which aims to initiate PGx research in sub-Saharan

Africa (91–94). In the future, real-world data from EHRs or biobanks could also be a valuable source to detect low-frequency PGx variants. As biobanks often contain an abundance of clinical information regarding diagnosis, ADRs, and sometimes drug efficacy, this could be linked to the broad genetic data to pinpoint new associations and detect these variants.

IMPROVING PANEL-BASED PGx TESTING

Next-Generation-Sequencing-Based PGx Panel Testing

Due to its ability to cover the whole exome or genome, NGS is a promising technique to improve PGx panel testing. Targeted NGS approaches specifically designed for PGx proved to be 91% to 99% in accordance with conventional PGx strategies. In addition, WES and whole-genome sequencing (WGS) are increasingly applied in the diagnostic setting. These WES and WGS data can be potentially repurposed to extract most common variants that are well known and used in clinical PGx (95). While WES has shown valuable results, by design it lacks coverage of intronic PGx variants (81, 96, 97). WGS is rapidly decreasing in cost, making it a highly competitive approach; hence, there is an increase in research projects applying WGS for PGx (98). Nonetheless, the complexities of pharmacogenes can complicate the application of short-read WGS due to the presence of structural variants and high sequence homology. Examples of complex loci are the *CYP2D6* locus, which is characterized by high sequence homology with *CYP2D7* and the occurrence of common structural variants (gene deletions, duplications, or *CYP2D6-CYP2D7* hybrids), and the *UGT1A1* gene, which contains a clinically relevant tandem repeat that can be difficult to characterize. Despite these inherent difficulties, it is possible to characterize these complex loci. One study showed that a short-read WGS-based diagnostic pipeline for rare Mendelian disorders, which is suitable for both diagnostics and PGx profiling, was able to characterize the complex *CYP2D6* locus (98). While currently too expensive for routine clinical application, long-read sequencing has proven superior to resolve complex genetic regions. This is exemplified by a proof-of-concept study that showed high-quality variant calls in clinically relevant DPWG-based pharmacogenes, including *CYP2D6* and *CYP2D7* (99).

Polygenic Drug Response Scores

Similar to polygenic risk scores (PRSs), data from large PGx panels can be used to derive polygenic drug response scores (PDRSs). PRSs predict disease risk by aggregating the small effects of numerous genetic variants identified in large genome-wide association studies (84). The strongest evidence for using a PDRS approach to predict treatment response is available for statins. Studies showed that the RR reduction of statin treatment to prevent a first coronary event is higher in patients with a higher PRS for cardiovascular disease (100). Another example of the use of PRSs in combination with the prediction of drug responses is the PRS for atherosclerotic cardiovascular disease (ASCVD) and PCSK9 inhibitors, where a higher risk score for ASCVD correlates with a higher risk reduction of major vascular events (HR 0.96, 95% CI 0.55–0.86) as compared to patients with low and intermediate genetic risk [HR 0.92 (95% CI 0.72–1.18) and 0.91 (95% CI 0.79–1.03), respectively] (101). A major challenge for the development of PDRSs is the large sample size required, typically 100,000–500,000 individuals, which is considerably larger than for common PGx studies. To this end, biobanks may prove to be a promising solution.

CONCLUSIONS

The available evidence supports implementation of pretherapeutic PGx panel testing for drugs covered in the PGx guidelines, yet the identification of specific patient populations

that benefit most and collection of cost-effectiveness data are necessary to support large-scale implementation.

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