A 12-gene pharmacogenetic panel to prevent adverse drug reactions: an open-label, multicentre, controlled, cluster-randomised crossover implementation study

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Summary

Background The benefit of pharmacogenetic testing before starting drug therapy has been well documented for several single gene–drug combinations. However, the clinical utility of a pre-emptive genotyping strategy using a pharmacogenetic panel has not been rigorously assessed.

Methods We conducted an open-label, multicentre, controlled, cluster-randomised, crossover implementation study of a 12-gene pharmacogenetic panel in 18 hospitals, nine community health centres, and 28 community pharmacies in seven European countries (Austria, Greece, Italy, the Netherlands, Slovenia, Spain, and the UK). Patients aged 18 years or older receiving a first prescription for a drug clinically recommended in the guidelines of the Dutch Pharmacogenetics Working Group (ie, the index drug) as part of routine care were eligible for inclusion. Exclusion criteria included previous genetic testing for a gene relevant to the index drug, a planned duration of treatment of less than 7 consecutive days, and severe renal or liver insufficiency. All patients gave written informed consent before taking part in the study. Participants were genotyped for 50 germline variants in 12 genes, and those with an actionable variant (ie, a drug–gene interaction test result for which the Dutch Pharmacogenetics Working Group [DPWG] recommended a change to standard-of-care drug treatment) were treated according to DPWG recommendations. Patients in the control group received standard treatment. To prepare clinicians for pre-emptive pharmacogenetic testing, local teams were educated during a site-initiation visit and online educational material was made available. The primary outcome was the occurrence of clinically relevant adverse drug reactions within the 12-week follow-up period. Analyses were irrespective of patient adherence to the DPWG guidelines. The primary analysis was done using a gatekeeping analysis, in which outcomes in people with an actionable drug–gene interaction in the study group versus the control group were compared, and only if the difference was statistically significant was an analysis done that included all of the patients in the study. Outcomes were compared between the study and control groups, both for patients with an actionable drug–gene interaction test result (ie, a result for which the DPWG recommended a change to standard-of-care drug treatment) and for all patients who received at least one dose of index drug. The safety analysis included all participants who received at least one dose of a study drug. This study is registered with ClinicalTrials.gov, NCT03093818 and is closed to new participants.

Findings Between March 7, 2017, and June 30, 2020, 41 696 patients were assessed for eligibility and 6944 (51·4 % female, 48·6% male; 97·7% self-reported European, Mediterranean, or Middle Eastern ethnicity) were enrolled and assigned to receive genotype-guided drug treatment (n=3342) or standard care (n=3602). 99 patients (52 [1·6%] of the study group and 47 [1·3%] of the control group) withdrew consent after group assignment. 652 participants (367 [11·0%] in the study group and 285 [7·9%] in the control group) were lost to follow-up. In patients with an actionable test result for the index drug (n=1558), a clinically relevant adverse drug reaction occurred in 152 (21·0%) of 725 patients in the study group and 231 (27·7%) of 833 patients in the control group (odds ratio [OR] 0·70 [95% CI 0·54–0·91]; p=0·0075), whereas for all patients, the incidence was 628 (21·5%) of 2923 patients in the study group and 934 (28·6%) of 3270 patients in the control group (OR 0·70 [95% CI 0·61–0·79]; p <0·0001).

Interpretation Genotype-guided treatment using a 12-gene pharmacogenetic panel significantly reduced the incidence of clinically relevant adverse drug reactions and was feasible across diverse European health-care system organisations and settings. Large-scale implementation could help to make drug therapy increasingly safe.

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Research in context

Evidence before this study

The benefit of pharmacogenetic testing before starting drug treatment has been well documented for several single gene–drug pairs. However, the clinical utility of large-scale implementation of a pre-emptive genotyping strategy with a pharmacogenetic panel remains unclear. Several studies investigating the implementation of pharmacogenetics are available, many of which are US-based. These studies focused on implementing either single drug–gene pairs one at a time and were done in highly specialised care settings. On Aug 8, 2022, we searched PubMed for trials published in English from database inception and before July 1, 2022 that investigated the implementation of pre-emptive pharmacogenetic panel testing using the search terms "pharmacogenetics", "clinical utility", "implementation", "prospective", and "panel". There were no prospective studies that assessed the clinical utility of a pre-emptive genotyping strategy with a pharmacogenetic panel across multiple European countries and health-care settings.

Added value of this study

To our knowledge, our study is the first to investigate the benefits of a pharmacogenetic panel strategy combined with the Dutch Pharmacogenetics Working Group guidelines across a diversity of European health-system organisations and settings. Our results show that pharmacogenetics-guided prescribing results in a 30% reduction of clinically relevant adverse drug reactions. Furthermore, our results underpin the benefits of implementing a standardised, validated, and harmonised pharmacogenetic test system that supports pharmacogenetics-guided decision making at the point of care and show the value of an educational programme to ascertain a similar knowledge base on personalised medicine and pharmacogenetic testing at the beginning of a study.

Implications of all the available evidence

Together with the evidence from randomised clinical trials for various of single drug–gene combinations, our results support a personalised-medicine approach with pharmacogenetics-guided drug prescribing to reduce the incidence of clinically relevant adverse drug reactions.

Introduction

Variation in genes that encode drug-metabolising enzymes, drug transporters, and drug targets affects drug disposition and action, and therefore contributes to variability in drug response. Several studies, including randomised controlled trials, have shown that individualising drug therapy on the basis of pharmacogenetic testing leads to improved patient outcomes for specific drug–gene combinations.[1–5]

Consortia such as the Dutch Pharmacogenetics Working Group (DPWG) and the Clinical Pharmacogenetics Implementation Consortium have created guidelines,[6,7] based on evidence from the literature, which include more than 100 gene–drug pairs. Although the minor allele frequencies of specific variants in the genes are low and range from approximately 0·1–5·0%, testing for a panel that consists of multiple actionable variants in the 12 most important pharmacogenes identifies at least one actionable genotype in 90–95% of individuals across multiple populations.[8] Therefore, a panel-based pharmacogenetic testing strategy appears to be the most efficient approach. Indeed, a small number of pilot studies[9–11] that investigated the feasibility of a pharmacogenetic-panel test reported a decrease in hospitalisations, emergency department visits, and health-care costs, indicating a potential favourable outcome of this approach. However, although these results are encouraging, there is little convincing data for the clinical utility of genotype-guided drug therapy using a pharmacogenetic panel.[12] Therefore, the Ubiquitous Pharmacogenomics Consortium conducted the Pre-emptive Pharmacogenomic Testing for Preventing Adverse Drug Reactions (PREPARE) study. The PREPARE study is the first, large scale, prospective clinical study investigating the effect of a genotype-guided drug prescribing strategy using a pre-emptive 12-gene pharmacogenetic panel approach across different health-care setting in seven European countries.

Methods

Study design

The PREPARE study was an investigator-initiated, open-label, multicentre, cluster-randomised crossover implementation study conducted in seven European countries (Austria, Greece, Italy, the Netherlands, Slovenia, Spain, and the UK) that investigated the clinical utility of a pre-emptive genotyping strategy with a pharmacogenetic panel. The study design has been outlined in detail previously.[13] Countries as clusters were block randomised (block size 2) to start with either genotype-guided drug prescribing (study group) or standard clinical care (control group). After 19 months, countries crossed over to the other group. The study protocol was approved by the ethics committee of the Leiden University Medical Centre and the ethics committees of participating centres in each country. The trial was done in accordance with the principles of the Declaration of Helsinki.

Participants

Patients were recruited in Austria (Medical University of Vienna), Greece (Psychiatric Clinic, University of Patras General Hospital and 2nd Psychiatric Clinic, ATTIKON University General Hospital, Athens), Italy (three sites of

the Medical Oncology Department of the Centro di Riferimento Oncologico Aviano; Department of Medical Oncology, San Filippo Neri Hospital; and Department of Medical Oncology, Cà Foncello Hospital, Treviso), the Netherlands (28 community pharmacies and the neurology department of the Leiden University Medical Centre), Slovenia (six community health centres; five clinics and hospitals), Spain (San Cecilio University Hospital, Granada; Hospital Universitario Virgen de las Nieves, Granada; Zaidín South Primary Care centre, Granada; and Zaidín Speciality Centre, Granada), and the UK (The Royal Liverpool University Hospital; Vauxhall Primary Health Centre; and Fulwood Green Medical Centre, all in Liverpool; appendix pp 9–11). Patients were assessed for eligibility by the treating physician or pharmacist. Patients aged 18 years or older who were receiving a first prescription (defined as no prescription for the drug in the preceding 12 months) for a drug that had an actionable recommendation in the DPWG as part of routine care were eligible for inclusion. This drug we refer to as the index drug. Exclusion criteria included previous genetic testing (direct-to-consumer or clinical) for a gene relevant to the index drug, a planned duration of treatment less than 7 consecutive days, and severe renal or liver insufficiency. Detailed inclusion and exclusion criteria are provided in the appendix (p 12). All participants gave written informed consent before taking part in the study.

Procedures

During the preparatory phase of the study, germline-variant alleles were systematically selected as described previously.[14] In brief, five predefined criteria were used, including a minor allele population frequency (MAF) of 1% or higher, an established effect on protein functionality, and the availability of a DPWG guideline with an actionable therapeutic recommendation associated with the variant (for further details see appendix p 2). An actionable drug–gene interaction test result was defined as a result for which the DPWG recommended a change to standard-of-care drug treatment. A list of actionable variants is provided in the appendix (pp 3–5). The global MAF was defined as the mean frequency across all populations, using 1000 Genomes Project phase III allele frequencies. In addition, variant alleles that had a global MAF of less than 1%, but a MAF of 1% or higher among selected populations (ie, European, Asian, or African), were also included in the panel. Finally, variants with a MAF of less than 1% that had already been tested for during routine clinical practice at one or more of the Ubiquitous Pharmacogenomics Consortium sites (eg, *DPYD**13) were also added to the panel. As the DPWG continuously reviews literature and periodically updates guidelines, by design the panel was not static and changes to the variant panel were allowed during the study and several changes occurred to represent a real-world situation. The panel at the start of the study comprised 50 germline-variant alleles, located within 12 genes (*CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A5, DPYD, F5, HLA-B, SLCO1B1, TPMT, UGT1A1, VKORC1*), and was designated as the pharmacogenetic passport. Further details are in the appendix (pp 6–7).

Genotyping by use of the SNPline workflow (LGC Group Middlesex, UK) was done in the laboratory at each local site. To ensure the quality and consistency of the genotyping results, all laboratories participated in the quality assessment programme for pharmacogenetics that was set up as a distinct proficiency test by the European Molecular Genetics Quality Network.

The PREPARE study included all drugs for which an actionable drug–gene interaction was present in the DPWG recommendations, with the exceptions of abacavir, omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole, and drugs containing oestrogen (appendix pp 6–7). Abacavir was excluded because *HLA B*57:01* is already routinely tested for, in line with the mandatory testing requirements of the drug license. Proton-pump inhibitors were excluded because the DPWG recommendation focuses on increasing efficacy in *CYP2C19* ultrarapid metabolisers, and no proton-pump inhibitor adverse drug reactions are associated with any of the other *CYP2C19* genotype-predicted phenotypes. Drugs containing oestrogen were only considered as subsequent drugs during study follow-up. Owing to the implementation nature of this study, and as for the genetic variant panel, changes to the drug panel were allowed. Further details about the changes to the drug and gene panels during the study are given in appendix (p 8).

To prepare clinicians, other health-care professionals, and patients for pre-emptive pharmacogenetic testing, we did a systematic survey on current knowledge about pharmacogenetics.[15] Structured educational tools based on the outcomes of this survey were developed and provided to the study centres to assure equal knowledge and minimise inter-rater variability in the PREPARE trial. For the systematic education of the health-care professionals active in the implementation of pharmacogenetics during the study, an educational programme that included online modules was established, which included educational videos, brochures, and an interactive educational game.[16] In addition, local participants were educated during a site-initiation visit. A local study coordinator (GS in Austria, GP in Greece, GT in Italy, JJS in the Netherlands, VD in Slovenia, CLDF in Spain, and MP in the UK) was responsible for the execution of the study according to standard operating procedures provided by the Ubiquitous Pharmacogenomics Consortium.

At enrolment, a blood or saliva sample was obtained for DNA isolation. In the study group, pharmacogenetic test results and DPWG recommendations related to the index drug were returned to the treating health-care provider within 7 days of index drug initiation. Pharmacogenetic test results and DPWG recommendations for the other genes and drugs were returned to the health-care provider

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See **Online** for appendix

For more on the **European Molecular Genetics Quality Network** see https://www.emqn.org

For more on the **Medication Safety Code initiative** see https://safety-code.org/

as soon as they were available through a standardised pharmacogenetics decision support solution, which has been described in detail previously.[17] All patients received a Medication Safety Code card that included a quick response code (also known as a QR code) that stored the patient's encoded pharmacogenetic test results and led to a website that provided the relevant DPWG recommendations once the code was read with a standard smartphone or other device (see appendix p 13). The Medication Safety Code card could be used to guide dose and drug selection for the index drug or any subsequent prescribed drugs. Adherence to DPWG guidelines was not mandatory and was left to the discretion of the treating physicians and pharmacists. In the control group, patients received standard clinical care and a plastic card indicating their participation in the PREPARE study (in place of a Medication Safety Code card). Genotyping of patients in the control group was done after completion of follow-up, at which time the patients received their genetic test results. All patients were followed-up for at least 12 weeks and up to a maximum of 18 months. T=0 was defined as the day the patient initiated the index drug. Patients were contacted at baseline (t=0, plus or minus 1 week), 4 weeks (plus or minus 2 weeks), 12 weeks (plus or minus 3 weeks), and at the end of the time block (plus or minus 4 weeks) to go through a scripted questionnaire and to collect data on the occurrence and severity of adverse drug reactions. First, an open question regarding the occurrence of any adverse drug reactions was asked, followed by various specific questions related to the patient's answers. The full questionnaire can be found in the appendix (pp 14–15). In addition, patients were asked to complete a self-report online survey at 2 weeks and 8 weeks after initiation of the index drug. To ensure a balanced inclusion of drugs in the study, the inclusion of any individual index drug was capped at 10% of all drugs in both the intervention and control groups. All clinical data were recorded in an electronic case report form. Because of the nature of the study design, patients, and investigators were not masked to treatment.

Outcomes

The primary outcome was the incidence of causal (ie, assessed as a definite, probable, or possible cause by use of the Liverpool Causality Assessment Tool[18]) and clinically relevant (ie, grade 2–5 severity on the US National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] version 4.0 classification scale) adverse drug reactions reported for the index drug within the 12-week follow-up period. For patients with cancer receiving fluorouracil, capecitabine, tegafur, or irinotecan, only haematological toxicities of NCI-CTCAE grades 4–5 and non-haematological toxicities of NCI-CTCAE grades 3–5 were considered to be clinically relevant. All collected adverse drug reactions during the follow-up period were assessed by a trained physician or pharmacist from the local study team for severity and causality. If a patient reported multiple adverse drug reactions within the 12-week follow-up period, the most severe causal adverse drug reaction was used for the primary analysis. A random 10% sample generated using the Rand function of Office 365, Microsoft Excel (version 16.0) of severity and causality assessments was independently reassessed by trained assessors from Lareb (the Netherlands Pharmacovigilance Centre), who were masked to the patients' study group allocation. Agreement between study and Lareb was evaluated using Cohen's κ and indicated no significant differences between the two sets of assessments (appendix pp 16–18). Data on adherence to DPWG guidelines among physicians and pharmacists was systematically collected and recorded in the electronic case report form.

Statistical analysis

The study was designed to have 80% power to detect a 30% difference in incidence of clinically relevant adverse drug reactions within the 12-week follow-up period between the study groups.

Based on the European Medicines Agency frequency classification of adverse drug reactions in drug labels, the incidence of clinically relevant adverse drug reactions was estimated to range between 4% and 10% in patients with an actionable genotype (appendix pp 19–20). Data from a previous pilot study[19] among 200 patients indicated that approximately 30% of patients carried an actionable genotype for the index drug. With these assumptions, the sample size calculation led to a required sample size of 8100 patients. Because of a 2-month delayed start, a lower enrolment rate in the first time block, and a higher than expected number of reported adverse drug reactions, the protocol was amended to include a delayed crossover date (Oct 1, 2018). Owing to the COVID-19 pandemic, the second time block enrolment period was extended by 3 months, to June 30, 2020. Baseline characteristics between the treatment groups were compared by use of χ^2 and Wilcoxon tests. The primary outcome was analysed using mixed logistic regression with country as a factor. A random centre-level, centre-by-country interaction was included, as well as covariates that represented confounding factors (age, number of drug allergies, number of comedications, and global health score[20]). The global health score assesses an individual's physical, mental, and social health and consists of ten items, which represent five core domains. The score is the weighted sum of the ten individual items and ranges from 0·328 (lowest possible score) to 0·877 (highest possible score; see appendix pp 43–44).[20] The primary analysis was done using a gatekeeping analysis, in which outcomes in people with an actionable gene–drug interaction in the study group versus the control group were compared, and only when this difference was statistically significant was an analysis of all patients

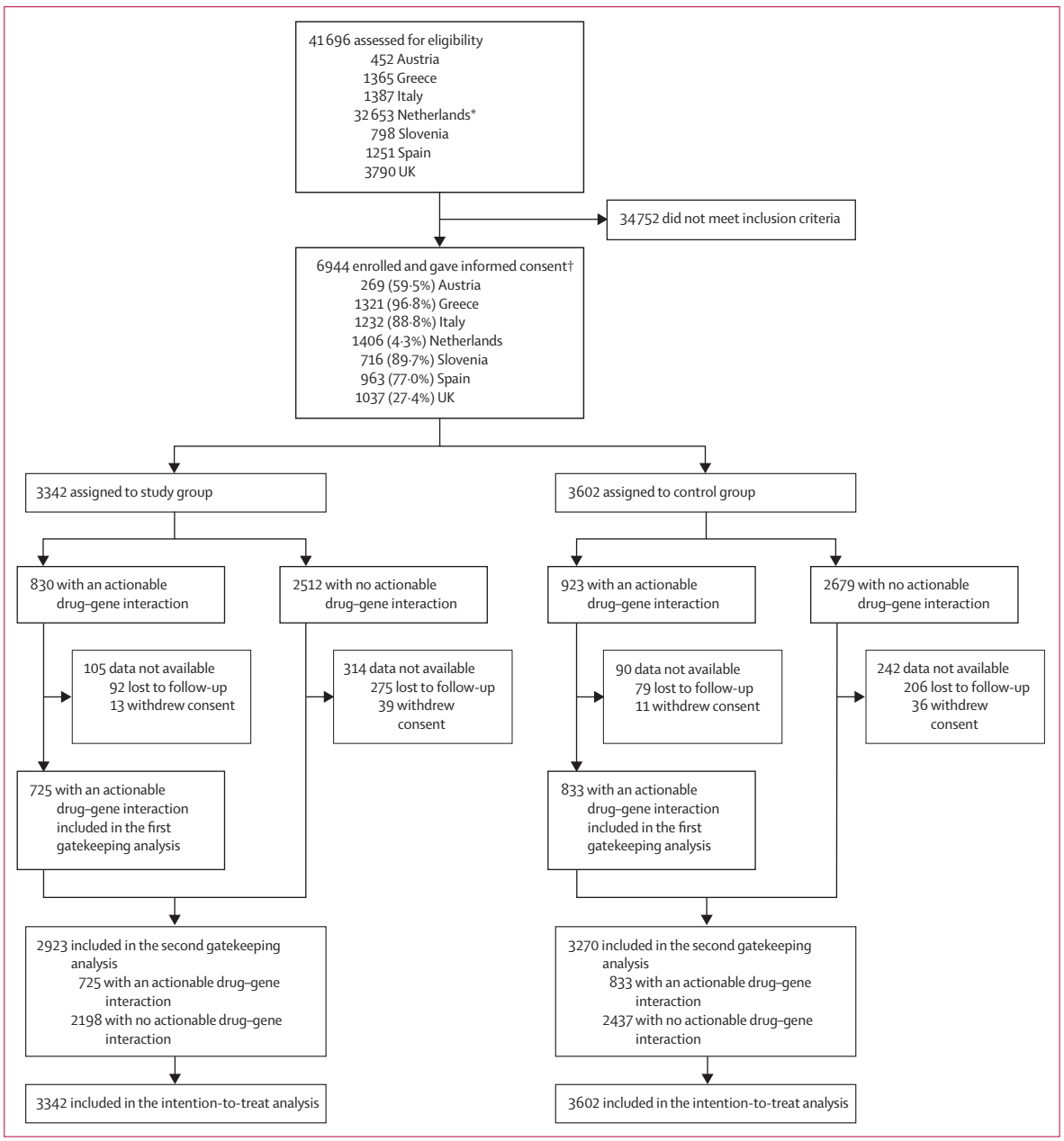

Figure 1: **Trial profile**
An actionable drug–gene interaction was defined as a pharmacogenetics-panel test result for which the Dutch Pharmacogenetics Working Group guidelines recommended a change to standard-of-care drug treatment. *In the Netherlands, community pharmacists used automated queries that used broad criteria to recruit potentially eligible patients,[19] which resulted in a higher number of potentially eligible patients, and a lower proportion enrolled, compared with other countries. †Percentages are of the total number of patients recruited from that country.

included in the study done. We used this approach to prevent dilution of the effect of the intervention owing to the frequency of people with an actionable drug–gene interaction.

A two-sided p value of 0·05 was considered to indicate statistical significance. All analyses included all participants who received at least one dose of the index drug and were done by use of R (version 4.1.1). The statistician was not unmasked to study group allocation until after data lock. The study was monitored by an independent monitor (Catalyst Clinical Research, Schiphol, the Netherlands). This study is registered with ClinicalTrials.gov, NCT03093818. The protocol and statistical analysis plan are available online (https://upgx.eu).

Role of the funding source

The funder had no influence on the design or conduct of the trial and was not involved in data collection, data

	All participants (n=6944)	Study group (n=3342)	Control group (n=3602)
Sex			
Male	3375 (48·6%)	1587 (47·5%)	1801 (50·0%)
Female	3569 (51·4%)	1755 (53·5%)	1801 (50·0%)
Self-reported race or ethnicity			
European, Mediterranean, or Middle Eastern	6753 (97·7%)	3244 (97·7%)	3509 (97·6%)
Other	162 (2·3%)	77 (2·3%)	85 (2·4%)
Median age	58·0 (47–69)	58·0 (47–69)	59·0 (47–69)
Mean global health score*	0·69 (0·1)	0·69 (0·1)	0·70 (0·1)
Mean number of allergies	0·38 (1·0)	0·36 (1·0)	0·40 (0·9)
Mean number of comedications	7·88 (6·6)	6·85 (5·8)	8·83 (7·1)
Country			
Austria	269 (3·9%)	145 (4·3%)	124 (3·4%)
Greece	1321 (19·0%)	684 (20·4%)	637 (17·7%)
Italy	1232 (17·8%)	622 (18·6%)	610 (16·9%)
Netherlands	1406 (20·2%)	643 (19·2%)	763 (21·2%)
Slovenia	716 (10·3%)	317 (9·5%)	399 (11·1%)
Spain	963 (13·9%)	489 (14·6%)	474 (13·1%)
UK	1037 (14·9%)	442 (13·2%)	595 (16·5%)

Data are n (%), median (IQR), or mean (SD). *The global health score is the weighted sum of the ten individual items that represent five core domains, and ranges from 0·328 (lowest possible score) to 0·877 (highest possible score).[20]

Table 1: **Baseline characteristics**

analysis, data interpretation, or in the writing of the manuscript.

Results

Between March 7, 2017, and June 30, 2020, 41 696 patients were assessed for eligibility and 6944 patients were enrolled, of whom 3342 (48·1%) were assigned to the genotype-guided treatment group and 3602 (51·9%) were assigned to the control group (figure 1). Spain, Greece, and Slovenia were randomly assigned to start with the genotype-guided treatment group, and Austria, Italy, the Netherlands, and the UK were assigned to start with standard care. On Oct 1, 2018, all sites crossed over to the other treatment. 3581 (52%) of 6944 patients were enrolled during the first time block (pre Oct 1, 2018) and 3363 (48%) patients were recruited during the second time block (Oct 1, 2018 onwards; appendix p 21). 52 (1·6%) of 3342 patients in the study group and 47 (1·3%) of 3602 patients in the control group withdrew consent. 419 (12·5%) patients in the study group and 332 (9·2%) patients in the control group were lost to follow-up.

The proportion of females was 1755 (53·5%) in the study group versus 1801 (50·0%) in the control group and the mean number of comedications was 6·85 (SD 5·8) in the study group versus 8·83 (7·1) in the control group. Age and mean number of drug allergies were similar between groups (table 1). Self-reported ethnicity was European, Mediterranean, or Middle Eastern for 97·7% of the patients. Small, but statistically significant, differences between study and control patients were observed in the global health score and number of comedications (table 1).

Of the 6944 patients enrolled, 6495 (93·5%) carried at least one actionable variant; 449 (6·5%) of carried no actionable variants, 1262 (18·2%) carried one, 2118 (30·5%) carried two, 1805 (26·0%) carried three, 928 (13·4%) carried four, 308 (4·4%) carried five, 62 (0·9%) carried six, and 12 (0·2%) carried seven actionable variants. The most common index drug was atorvastatin (n=716), followed by clopidogrel (n=619), and tacrolimus (n=472; appendix p 22). During the first time block, the drug capping threshold was reached for atorvastatin and clopidogrel in the study group, and for atorvastatin, capecitabine, codeine, flucloxacillin, and tacrolimus in the control group. In the second time block, the drug capping threshold was reached for atorvastatin and capecitabine in the study group, and for atorvastatin, clopidogrel, and tramadol in the control group. Overall, 1558 (25·2%) of 6193 patients carried an actionable variant for their index drug. *CYP2D6* resulted in the highest (3098 [44·6%] of 6944) and *HLA-B*57:01* resulted in the lowest (286 [4·1%] of 6944) proportion of patients with an actionable variant (appendix p 23). For the index drugs, the highest numbers of patients with an actionable variant were observed for atorvastatin (204 [28·5%] of 716), tramadol (183 [48·3%] of 379), and clopidogrel (172 [27·8%] of 619), and for drugs overall (taken by >25 patients and with actionability >20%), the highest extent of actionability was seen for venlafaxine, metoprolol, tamoxifen, codeine, oxycodone, amitriptyline, warfarin, simvastatin, sertraline, citalopram, and escitalopram (appendix p 24). These percentages are consistent with the known actionable allele frequencies in European, Mediterranean, or Middle Eastern populations (we retrieved percentages of actionability from the detailed background materials used by the DPWG to draft the guidelines, which are not published but the guidelines are available online (https://www.pharmgkb.org/search?query=dpwg).

Most patients completed the 12-week follow-up period, with the proportions ranging from 1038 (84·3%) of 1232 in Italy to 1213 (91·8%) of 1321 in Greece. The median turnaround time of genotype results varied per site and ranged from 1 day to 7 days (appendix p 25). As expected, the number of reported adverse drug reactions varied per country, ranging from 283 (1·1 per patient) in Austria to 4811 (3·9 per patient) in Italy (appendix p 26). The severity of adverse drug reactions also showed considerable variation between countries, in line with the types of medication prescribed (appendix p 26). The highest incidence of and most severe adverse drug reactions were reported in Italy, where patients were recruited from a

cancer clinic and mostly received cancer treatments at the maximum tolerated dose. By contrast, in the Netherlands, patients were recruited from primary care via community pharmacies and received substantially less toxic treatments. Adoption of the DPWG recommendations was high, and overall 69·9% of these recommendations were accepted by the physicians and pharmacists. All patients were included in the analysis, irrespective of adherence to the DPWG guidelines. The primary outcome was the occurrence of causal clinically relevant adverse drug reactions within the 12-week follow-up period. In total, 10718 events were reported by 3303 patients. After filtering for severity (NCI-CTCAE grade ≥2, with the exception of patients with cancer receiving 5-fluorouracil, capecitabine, tegafur, or irinotecan; see Methods) and causality (Liverpool Causality Assessment Tool[18] score of possible or higher), there were 3096 events reported by 1563 patients (appendix p 27).

In the first gatekeeping analysis, 195 (11·1%) of 1753 patients with actionable variants did not complete the 12-week follow-up, so 1558 patients with an actionable variant were available for analysis (figure 1). The incidence of the development of a causal clinically relevant adverse drug reaction in patients with an actionable test result was 152 (21%) of 725 in the study group and 231 (28%) of 833 in the control group. The study intervention significantly reduced adverse drug reaction risk by 30% (odds ratio [OR] 0·70 [95% CI 0·54–0·91]; p=0·0075). In the second gatekeeping analysis, which included all groups, the prevalence of the development of a causal clinically relevant adverse drug reaction was similar between groups, with 21% the study group and 29% in the control group, reducing the risk of an adverse drug reaction by 30% (OR 0·70 [95% CI 0·61–0·79]; p <0·0001; figure 2). Predefined covariates were also associated with the risk of adverse drug reaction. Patients with a better global health score or a higher age showed a decreased risk of an adverse drug reaction. By contrast, the incidence of adverse drug reactions increased with higher reported numbers of drug allergies and comedications (table 2).

The effect of the pharmacogenetic intervention varied by country (appendix p 37). A lower incidence of clinically relevant adverse drug reactions was observed in the study group than in the control group in Greece, Italy, the Netherlands, Spain, and the UK. No causal clinically relevant adverse drug reaction was reported by any of the patients allocated to the control group in Austria. Finally, in Slovenia, a higher incidence of adverse drug reactions was observed in patients allocated to receive genotype-guided drug treatment than the control.

In the study group, pharmacogenetic test results could also be used to guide treatment for any consecutive drugs that were prescribed or dispensed in addition to the index drug during the follow-up period. During follow up, 953 (13·7%) of 6944 patients received a second prescription with an actionable recommendation based upon their genotype, 79 (1·1%) received a third, six (<0·1%) received a fourth, and one (<0·1%) received a fifth. Accounting for these prescriptions slightly increased the effect of the pharmacogenetic intervention (OR 0·69 [95% CI 0·61–0·78]; p<0·0001).

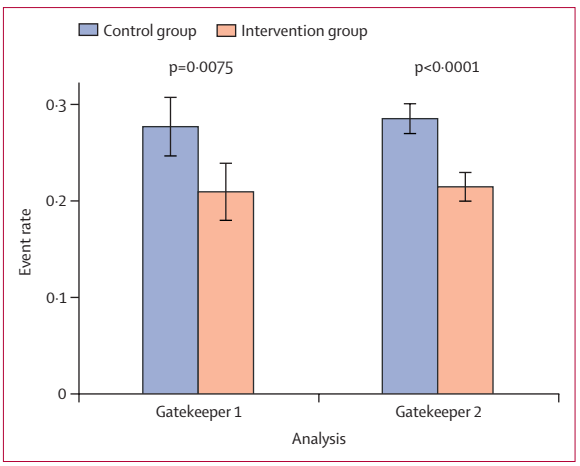

Figure 2: **Frequency of causal clinically relevant adverse drug reactions in patients with an actionable test result**
Error bars represent 95% CIs for event rates. p values for intergroup differences were based on the mixed-effects models used in the primary analysis. An actionable test result was defined as a drug–gene interaction for which the Dutch Pharmacogenetics Working Group guidelines recommended a change to standard-of-care drug treatment.

When the primary analysis was repeated with all 6944 included patients and all reported adverse drug reactions, without filtering for severity and causality, the effect of the pharmacogenetic intervention increased. Patients in the study group showed a lower occurrence of adverse drug reactions compared with patients in the control group (OR 0·55 [95% CI 0·49–0·62]; p<0·0001). The effect sizes of the other predefined covariates remained in the same order of magnitude as the primary analysis, except for the effect of country, for which a substantially increased number of adverse drug reactions was observed in Italy (appendix p 28).

Discussion

This prospective real-world implementation study in seven different European countries encompassing 6944 patients showed that genotype-guided prescribing using a 12-gene pharmacogenetic panel significantly reduced the incidence of clinically relevant adverse drug reactions. To our knowledge, our results are the first to show the feasibility and clinical use of the large-scale implementation of a panel-based pharmacogenetic-testing strategy and underpin the benefits of implementing a standardised, validated, and harmonised pharmacogenetic-test system that supports pharmacogenetics-guided decision making at the point of care.

Few studies investigating the clinical implementation of pharmacogenetics have been initiated, and are often US based.[8,13] These studies have addressed multiple

	All patients				Patients with an actionable variant*			
	Study group (n=2923)	Control group (n=3270)	OR (95% CI)	p value	Study group (n=725)	Control group (n=833)	OR (95% CI)	p value
Clinically relevant adverse drug reactions	628 (21·5%)	934 (29·0%)	0·70 (0·61–0·79)	<0·0001	152 (21·0%)	231 (27·7%)	0·70 (0·54–0·91)	0·0075
Age	58 (47–69)	59 (47–69)	0·98 (0·98–0·99)†	<0·0001	58 (47–68)	58 (48–68)	0·98 (0·97–0·99)†	<0·0001
Global health score	0·689 (0·108)	0·701 (0·105)	0·11 (0·06–0·21)†	<0·0001	0·682 (0·111)	0·699 (0·106)	0·056 (0·016–0·20)†	<0·0001
Number of drug allergies	0·350 (0·960)	0·389 (0·939)	1·09 (1·03–1·16)†	0·0062	0·353 (0·809)	0·444 (1·165)	1·15 (1·01–1·31)†	0·029
Number of comedications	7·03 (5·90)	8·90 (7·15)	1·04 (1·02–1·05)†	<0·0001	6·657 (5·661)	8·289 (6·914)	1·04 (1·02–1·07)†	0·0012
Country								
The Netherlands	552 (18·9%)	690 (21·1%)	1 (ref)	1 (ref)	158 (21·8%)	216 (25·9%)	1 (ref)	1 (ref)
Austria	133 (4·6%)	113 (3·5%)	0·38 (0·06–2·46)	0·31	17 (2·3%)	7 (0·8%)	0·39 (0·08–2·04)	0·27
Greece	652 (22·3%)	604 (18·5%)	0·18 (0·04–0·910	0·036	159 (21·9%)	142 (17·0%)	0·33 (0·08–1·28)	0·11
Italy	502 (17·2%)	553 (16·9%)	0·24 (0·06–1·01)	0·052	84 (11·6%)	96 (11·5%)	0·33 (0·09–1·21)	0·094
Slovenia	288 (9·9%)	364 (11·1%)	1·09 (0·29–4·06)	0·896	82 (11·3%)	108 (13·0%)	1·11 (0·37–3·35)	0·84
Spain	415 (14·2%)	420 (12·8%)	0·23 (0·04–1·46)	0·119	118 (16·3%)	110 (13·2%)	0·31 (0·08–1·25)	0·10
UK	381 (13·0%)	526 (16·1%)	0·46 (0·11–2·01)	0·304	107 (14·8%)	154 (18·5%)	0·56 (0·16–1·87)	0·34

Data are mean (SD), median (IQR), n (%), or OR (95% CI). The severity of adverse drug reactions was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 classification scale. Causality was assessed using the Liverpool Causality Assessment Tool.[18] p values were calculated using a Wald test for each regression coefficient for the null hypothesis of the regression coefficient being zero on the log-scale. OR=odds ratio. *Defined as a drug–gene interaction test result for which the Dutch Pharmacogenetics Working Group guidelines recommended a change to standard-of-care drug treatment. †OR per unit increase.

Table 2: **Mixed logistic regression analyses evaluating the effect of the 12-gene pharmacogenetic panel on the incidence of causal clinically relevant adverse drug reactions**

barriers in the implementation of pharmacogenetics and have focused on implementing either single drug–gene pairs one at a time or in the context of highly specialised care settings, rather than assessing the benefit of a pharmacogenetic testing strategy that focuses on a panel of pharmacogenes across various therapeutic areas and different health-care systems. The few available studies that focus on a panel-based approach were mostly done in patients aged 65 years or older with polypharmacy, and had little power to show the benefit of intervention owing to their observational study design or small sample size.[9–11] A large retrospective analysis of the economic effects of the clinical implementation of a 23-gene pharmacogenetics panel in 5288 patients aged 65 years or older compared with 22 357 controls showed a reduction of around US$7000 per patient in direct medical charges.[21] These results are in line with our results, and support further clinical implementation of pharmacogenetic-panel testing.

A major strength of our study is that it encompasses the diversity of national health system organisations in Europe and includes a broad range of different diseases and drug therapies. This real-world design introduced several challenges. The gene panel, list of eligible drugs, and recommendations were not static and changes that resulted from updates of the DPWG guidelines were allowed. During the study, this approach resulted in changes, including the removal of oxycodone because none of the genotype was considered actionable any more, and changes to the actionability of phenotypes for voriconazole, escitalopram, clomipramine, *CYP2B6*, and *DPYD* (appendix p 8).

We estimated that a truly pre-emptive study to investigate a genotyping strategy using a pharmacogenetic panel would require at least a 10–20 times larger sample size compared with our study, as many patients would not start an index drug within the timeframe of the study. Therefore, to increase efficiency, we enrolled patients who were receiving a first prescription for a drug with an actionable drug–gene interaction according to the DPWG guidelines. Pharmacogenetic test results and clinical recommendations were returned within 7 days, and the medication was adjusted if needed. Results for turnaround times showed that this timeline was feasible for all participating centres. As some of the adverse drug reactions that might have occurred within this maximum of 7 days could have been prevented if the pharmacogenetic testing had been fully pre-emptive, our reported effect might be an underestimation of the real effect size in patients with pre-emptive testing.

Our study had some limitations. We used patient-reported adverse drug reactions, collected during scheduled interviews with research nurses, that were not objectified by use of laboratory tests or physical examinations. However, we conducted causality analysis of the adverse drug reactions using a validated tool,[18] and this assessment was independently validated in a randomly selected 10% sample. We depended on patients recontacting the study team whenever a second drug was started during follow-up. On the basis of the available literature, we had expected at least one or two additional pharmacogenetically guided adjustments per patient for around 30% of the patients.[22] However, during our study, only 953 (13·7%) of 6944 patients reported the use of a secondary drug, indicating that our results might underestimate the true effect of our intervention. Importantly, the lower-than-expected number of patients with a secondary drug did not affect the primary endpoint of the study. Despite the considerable size of our study, for several drugs only very small numbers of patients were accrued, including for drugs with a high-toxicity profile, such as mercaptopurine, azathioprine, and thioguanine. These thiopurines are metabolised by thiopurine methyltransferase, for which highly penetrant variants are known and their absence in our study might therefore have resulted in an underestimation of the potential of a pharmacogenetic panel test. Of the included patients, 97·7% had self-declared European, Mediterranean, or Middle Eastern ancestry. Although our pharmacogenetic panel included specific variants with a MAF of 1% or higher in selected populations, such as in African or Asian people (appendix p 2), future studies will be required in patients of other racial groups to establish the global applicability of our findings.

The observed reduction of around 30% in clinically relevant adverse drug reactions when analysing all patients was similar to the effect size obtained in the patients with an actionable variant only. Both drug capping and the addition of recruiting centres during the study to ensure sufficient patient enrolment might have led to differences in type of medications prescribed with respect to crossover. For example, the addition of a centre that prescribes an increased amount of drugs with a high-toxicity profile (eg, capecitabine and tacrolimus) after crossover to the control group might result in an observed positive effect of the pharmacogenetic intervention in patients with a non-actionable test result when comparing the study group with the control group. Indeed, some heterogeneity in the effect of the pharmacogenetic intervention between countries is present in our data. Particularly in Slovenia, recruitment sites that prescribed different types of medications were added after the crossover, which might explain the increase in adverse drug reaction in the intervention group (appendix p 37). A post-hoc exploratory analysis that included index drug and index drug-by-country interactions in the statistical model indicated that changes in the case-mix were the main contributor to the observed comparable effect size in actionable patients versus all patients. We applied drug capping to prevent over-representation of a single drug–gene pair that would drive the effect simply as a result of prescribing patterns. A consequence of drug capping is that the distribution of index drugs does not fully represent natural prescribing patterns.

Patients with severe liver disease (defined as Child-Pugh class C[23]) and severely impaired kidney function (<15 mL/min per 1·73 m²) were excluded. Other factors such as drug–drug interactions and polypharmacy reflect the real-world context of our study. Obviously these factors might also have influenced drug response, but their influence on our primary endpoint is considered small, owing to the crossover design of our study.

Our study investigated only the effect of a pharmacogenetic panel test on the reduction of adverse drug reaction. Potentially, the effect of such a test could even be larger if drug efficacy is also taken into account. However, although it was possible to design a composite endpoint that captured diverse toxicities, it is difficult to define an efficacy endpoint for the 39 drugs used to treat the multiple diseases covered in the PREPARE study. To assess the effect of pharmacogenetic testing on drug efficacy, well designed prospective studies that focus on a specific drug and disease, such as the recently completed TAILOR-PCI[4] and Popular Genetics[24] trials remain essential. We did not investigate the potential beneficial effect of the pharmacogenetic-panel test for each of the specific drugs, settings, and patient groups involved, as our aim was to test prospectively a broad pharmacogenetics test panel, which covered a large number of drugs. A panel-based pre-emptive approach is likely to be the most cost-effective method for implementing pharmacogenetics. We are doing a cost–effect analysis of this study, which will be reported in a separate paper.

In conclusion, to our knowledge this is the first study to show the feasibility and benefits of a pharmacogenetic-panel strategy across a diversity of European health-care system organisations and settings, and provides evidence to support large-scale implementation of panel-based pharmacogenetics testing to make drug therapy increasingly safe.

Contributors

HJG was the scientific coordinator of the Ubiquitous Pharmacogenomics Consortium (U-PGx). HJG, JJS, MSa, MSc, and CM formed the executive board of U-PGx. JJS was the principal investigator of the PREPARE study. GSP, GPP, GT, VD, CLDF, and MP were principal investigators in the individual countries. HJG, JJS, MP, MSa, MSc, MIS, GP, and GT conceptualised the study design. JJS, SB, HJG, and LENM prepared the first draft of the manuscript. CHvdW and SB wrote the statistical analysis plan. SB was the lead statistician. All authors critically reviewed the report and approved the final version before submission. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. HJG, JJS, LENM, and SB accessed and verified the data.

Declaration of interests

MP received partnership funding from the UK Medical Research Council (MRC) Clinical Pharmacology Training Scheme (cofunded by MRC,

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Data sharing

Data from the PREPARE study are not publicly available but are planned to be made available after preplanned analyses have been completed. A complete deidentified dataset will be made accessible, together with a data dictionary, for a minimum of 5 years. Requests for access to the data can be made by sending an email together with a research plan to the corresponding author and will be evaluated by and require authorisation from the Ubiquitous Pharmacogenomics Consortium executive board. The criteria for data access (eg, who will be granted access, for what types of analyses, and by what mechanism) have yet to be determined; the procedure is under development by the consortium's executive board and will be published separately.

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