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ORIGINAL ARTICLE

# Estimating the potential impact of implementing pre-emptive pharmacogenetic testing in primary care across the UK

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**Aims:** Pharmacogenetics (PGx) in the UK is currently implemented in secondary care for a small group of high-risk medicines. However, most prescribing takes place in primary care, with a large group of medicines influenced by commonly occurring genetic variations. The goal of this study is to quantitatively estimate the volumes of medicines impacted by implementation of a population-level, pre-emptive pharmacogenetic screening programme for nine genes related to medicines frequently dispensed in primary care in 2019.

**Methods:** A large community pharmacy database was analysed to estimate the national incidence of first prescriptions for 56 PGx drugs used in the UK for the period 1 January–31 December 2019. These estimated prescription volumes were combined with phenotype frequency data to estimate the occurrence of actionable drug–gene interactions (DGI) in daily practice in community pharmacies.

**Results:** In between 19.1 and 21.1% ($n$ = 5 233 353–5 780 595) of all new prescriptions for 56 drugs ($n$ = 27 411 288 new prescriptions/year), an actionable drug–gene interaction (DGI) was present according to the guidelines of the Dutch Pharmacogenetics Working Group and/or the Clinical Pharmacogenetics Implementation Consortium. In these cases, the DGI would result in either increased monitoring, guarding against a maximum ceiling dose or an optional or immediate drug/dose change. An immediate dose adjustment or change in drug regimen accounted for 8.6–9.1% ($n$ = 2 354 058–2 500 283) of these prescriptions.

**Conclusions:** Actionable drug–gene interactions frequently occur in UK primary care, with a large opportunity to optimise prescribing.

KEYWORDS
community pharmacy, medicines optimisation, pharmacogenetics, pharmacogenomics

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## 1 | BACKGROUND

Pharmacogenetics (PGx) describes the relationship of how variations in an individual's DNA sequence affect drug metabolism, transport and response.[1] Application of these drug–gene interactions (DGI) can help support prescribing that is personalised to the individual. This is important for both drug safety and effectiveness.

The rate at which aberrant phenotypes occur in the general population is high. Most groups estimate over 95% of the population carry a genetic variant affecting the prescribing of at least one drug.[2–5] A recent study analysing the phenotype frequencies for 14 pharmacogenes in 487 409 participants in the UK biobank found 99.5% of individuals have a predicted atypical response to at least one drug.[6] Clinical guidelines advising management of these DGI are key to implementation. The international Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetic Working Group (DPWG) in the Netherlands have independently reviewed over 100 DGI and published therapeutic recommendations for 86 DGI.[7] Of these recommendations, a high proportion pertain to medicines initiated in primary care.

Recently, Kimpton and colleagues analysed prescribing patterns between 1993 and 2017, in a sample of 648 141 English primary care patients.[8] They found exposure to PGx drugs was high, with over 80% of patients being exposed to at least one PGx drug, and 58% exposed to two or more PGx drugs over a 20-year period. A limitation of this study was the inclusion of drugs that do not carry a published therapeutic recommendation, which means whilst the study shows exposure is high in primary care, it is unclear what the impact would be on prescribing.[8] In the Netherlands, Bank and colleagues analysed dispensing data for initiated medicines in primary care with a DPWG therapeutic recommendation.[9] They combined this information with population incidence of aberrant phenotypes to estimate the impact of pre-emptively PGx testing the entire Dutch population. The authors found that nearly one in four new prescriptions for 45 PGx drugs had an actionable DGI, with one in 19 new prescriptions requiring a dose adjustment or alternative drug choice.[9]

In the UK, implementation of PGx testing in the NHS has become a source of great interest to policymakers, clinicians and pharmacists. NHS Improvement and Genomics England have recently announced plans for a pre-emptive pharmacogenomic testing approach to be implemented by NHS England within the next 10 years.[10] PGx test results will be recorded in the patients' medical records, supporting clinicians and pharmacists in all sectors to make therapeutic decisions. As shown by Bank and colleagues in the Netherlands, accessing PGx results in primary care is likely to have a large impact on prescribing.[9] The aim of this paper was therefore to estimate the impact of PGx testing annually on primary care within a UK context. To do this, quantitative estimates of the volumes of medicines dispensed annually with a CPIC and/or DPWG therapeutic recommendation and affected by aberrant phenotypes were calculated. Furthermore, estimates for the volumes of medicines requiring a dose or drug change, increased monitoring, or change in long-term management were calculated.

### What is already known about the subject?

- Pharmacogenomic information at the point of prescribing can help improve safety and efficiency of prescribing.
- NHS England plan to embed pharmacogenomics in practice by 2025.
- Primary care prescribing of pharmacogenomic drugs is common but impact on prescribing is unknown.

### What this study adds?

- Within the UK, approximately 5 780 595 prescriptions for medicines dispensed annually in primary care have an actionable drug–gene interaction according to international guidelines.
- Four pharmacogenes (CYP2C19, CYP2D6, SLCO1B1, HLA-B) are responsible for >95% of all drug–gene interactions observed.
- One in 11 new prescriptions for pharmacogenomic medicines dispensed annually in UK primary care require a direct dose or drug change according to international guidelines.
- These findings could inform policy makers looking to implement pharmacogenetic testing in UK primary care.

## 2 | METHODS

### 2.1 | Overview

The process consisted of five stages relating to those medicines for which therapeutic recommendations published by DPWG and/or CPIC are available:

1. Identification and selection of DGI relevant to UK primary care.
2. Classifying therapeutic recommendations and defining the concept “actionable”.
3. Estimating number of new medicines with DGI initiated in UK primary care.
4. Estimating frequency of actionable phenotypes for relevant medicines initiated in UK primary care.
5. Applying frequency of actionable phenotypes to number of new medicines to estimate the frequency at which a change in prescribing or monitoring of medicine is required according to DPWG and/or CPIC guidelines.

## 2.2 | Approval

The study was confirmed as a service evaluation by the University of East Anglia Faculty of Medicine and Health Sciences Research Ethics Committee (Reference: 2019/20-080).

## 2.3 | Identification and selection of drugs and DGI relevant to UK primary care

Medicines included in the analysis were those with PGx drug/dosing guidelines published by the DPWG and/or CPIC. Guidelines published up to 31 March 2020 were identified through PharmGKB, which provides an up-to-date repository of gene–drug interactions and therapeutic recommendations published by DPWG, CPIC and other organisations.[11]

Medicines were screened against a set of inclusion/exclusion criteria using the following UK-based medicine resources: British National Formulary (BNF),[12] Martindale: the complete drug reference[13] and Openprescribing.net.[14]

Inclusion criteria:

- Licensed in the UK
- Initiated or continued in primary care

Exclusion criteria:

- Specialist medicines requiring long-term monitoring by secondary care prescribers.

For each drug selected, only a single gene interaction was included for analysis. Population frequency data for multiple concurrent aberrant phenotypes were unavailable, and thus to avoid overestimating the effect of PGx testing for a single drug, the phenotype frequency data was applied for the most impactful single gene. This was either the gene associated with phenotypes that led to more "actionable" therapeutic recommendations, e.g. choosing the gene with recommendations for "direct action" over the gene with "indirect action", or choosing the gene with the most frequently occurring aberrant phenotypes in the UK population. For example, the **VKORC1** gene was selected over **CYP2C9** and **CYP4F2** genes when analysing the impact of PGx testing on **warfarin**, because VKORC1 gene aberrant variants account for a higher percentage of variation in warfarin dosing (30% *vs* 18% and 11% respectively)[15] and occur more frequently in European populations compared to CYP2C9 and CYP4F2.[16]

## 2.4 | Classifying "actionability" of therapeutic recommendations

CPIC and DPWG guidelines were reviewed for each selected DGI and therapeutic recommendations were labelled in a standard format as shown in Table S1. Where differences between CPIC and DPWG therapeutic recommendations occurred,[17] both recommendations were considered and estimates for the overall impact were recorded as a range to reflect this. Additionally, both sets of guidelines were checked to see whether the therapeutic recommendations were dependent on specific patient factors, or concomitant medications.

## 2.5 | Estimating number of new medicines with DGI initiated in UK primary care

Total volumes of prescriptions for PGx drugs dispensed in primary care between 01 January 2019 and 31 December 2019 were extracted from national databases.[18–21] Dispensing patterns in a large UK pharmacy chain database were then analysed to estimate the proportion of medicines newly initiated as part of the total annual dispensing volumes for medicines relevant to UK primary care (Supplementary file 1). To calculate rates, total and newly dispensed volumes for all relevant PGx drugs between 01 January 2018 and 31 December 2018 were extracted from the dispensing database. Newly dispensed drug volumes were defined as drugs which were dispensed for the first time in 12 months to the patient.

To obtain national estimates of new prescriptions for the 56 drugs, these proportions were applied to total primary care dispensing volumes between 01 January 2019 and 31 December 2019 for England, Scotland, Northern Ireland and Wales.

## 2.6 | Estimating frequency of actionable phenotypes for relevant medicines initiated in UK primary care

Phenotypic frequency data for six genes (CYP2C9, **CYP2C19**, **CYP2D6**, **SLCO1B1**, TPMT and VKORC1) and three genetic variants (HLA-B*57:01, HLA-B*15:02 and factor V Leiden) were obtained from

**TABLE 1** Therapeutic recommendations assigned "direct action", "indirect action" and "no action"

| | Direct action | Indirect action | No action |
|---|---|---|---|
| Therapeutic recommendation | Lower dose required at start therapy | Observe status of patient carefully | |
| | Higher dose required at start therapy | Optional lower dose required at start therapy | |
| | Switch to alternate drug at start therapy | Optional higher dose required at start therapy | |
| | | Optional switch at start therapy | |
| | | Guard against maximum dose | |

an anonymised pool of 879 patients at the University of Liverpool, UK, as part of the "**Pre**emptive Pharmacogenomic Testing for **P**reventing **A**dverse Drug **R**eactions" (PREPARE) study (Clinical trial.gov identifier: NCT03093818). The genetic test results for CYP2D6, CYP2C19, SCLO1B1, TPMT and VKORC1 were translated to actionable phenotypes (intermediate, poor or ultra-rapid metaboliser) using DPWG guidelines.[22] For the gene CYP2C19, haplotype was translated to phenotype (intermediate [activity score 1], intermediate [activity score 1.5], poor metaboliser), using CPIC guidelines to support application of therapeutic recommendation for non-steroidal anti-inflammatories[23] (see Supplementary File 1). Phenotype frequencies for HLA-A*31:01, HLA-B*15:02 and HLA-B*58:01 were calculated using ethnicity incidence frequency tables[24] matched to UK census data 2011 similar to the methodology described by Fan and Bousman.[25] (Supplementary File 2 contains estimates for UK phenotype incidence used in this study.)

### 2.7 | Estimating impact

To estimate the potential impact of PGx testing on drugs newly initiated in the UK, the estimated newly initiated prescription volumes of relevant PGx drugs were multiplied by the percentage incidence of different actionable phenotypes to obtain estimates for prescription volumes of PGx drugs dispensed nationally that require a change in prescribing or monitoring.

### 2.8 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[26]

## 3 | RESULTS

### 3.1 | Identification of relevant PGx drugs to UK primary care

A total of 56 drugs with 56 unique DGIs were included in the study. Figure 1 is a flowchart representing the selection process for medicines included in the study.

### 3.2 | Overall UK results

There were 27 411 287 estimated new prescriptions for 56 PGx drugs in 2019 (England: 22264390 items, Scotland 2 416 941 items, Wales 1 753 062 items, Northern Ireland 976 894 items). Table 2 shows the overall estimated newly initiated prescription volumes for 56 PGx drugs dispensed by community pharmacies in 2019. Table 3 shows the breakdown of drug volumes per actionable phenotype. It is estimated that between 5 233 353 and 5 780 595 of these prescriptions had an actionable therapeutic recommendation according to CPIC and/or DPWG guidelines. Table 4 shows a breakdown of the estimated volume ranges of prescriptions dispensed in UK primary care in 2019.

Based on the data presented in this study, between one in four to one in five new prescriptions for one of these 56 PGx drugs newly initiated in the community requires a therapeutic intervention. Should all patients in the UK with a new prescription for this selection of drugs have been pre-emptively genotyped for nine genes (CYP2C19, CYP2C9, CYP2D6, F5, HLA-A, HLA-B, SLCO1B1, TPMT, VKORC1), then one in every 11 new prescriptions could be adjusted based on the genetic result. This frequency is the same across England, Northern Ireland, Scotland and Wales.

### 3.3 | Frequency of exposure to PGx drugs by therapeutic group

Table 5 shows the distribution of newly initiated PGx drugs dispensed in the UK in 2019 by therapeutic group. The PGx drugs with therapeutic recommendations ($n$ = 5 780 595) dispensed to UK patients in the largest volumes were for weak opioids (47.9%, $n$ = 2 766 128), antidepressants (30.9%, $n$ = 1 783 362) and proton pump inhibitors (5.7%, $n$ = 329 300).

For those medicines with a therapeutic recommendation requiring "direct action" ($n$ = 2 500 283), the top three drug classes were the same but in a different order; antidepressant (49.5%, $n$ = 1 236 804), weak opioid (15.4%, $n$ = 385 638), proton pump inhibitors (13.1%, $n$ = 327 491).

### 3.4 | Frequency of exposure to PGx drugs by gene

Tables 6 and 7 shows the distribution of newly initiated PGx drugs dispensed in the UK in 2019 by gene. Of the estimated 5 780 595 medicines with a therapeutic recommendation, four genes accounted for 95.8% of all DGI: 68.3% CYP2D6 ($n$ = 3 950 129), 20.1% CYP2C19 ($n$ = 1 159 040), 3.8% HLA-B ($n$ = 222 199) and 3.6% SLCO1B1 ($n$ = 208 462).

Of the estimated 2 500 283 prescription items dispensed in the UK with a recommendation for "direct action", 61.3% ($n$ = 1 531 923) were affected by the CYP2D6 gene, 25.0% ($n$ = 624 298) were CYP2C19 gene and 8.3% ($n$ = 208 462) were affected by the SLCO1B1 gene.

### 3.5 | Frequency of exposure to PGx drugs by age

Table 8 shows the age distribution of patients exposed to a PGx drug in 2018. Of the 4 439 352 patients in the community pharmacy database newly dispensed one of 56 PGx drugs, 61.9% ($n$ = 2 746 113) were between the ages 19 and 59. In those 0–18 years,

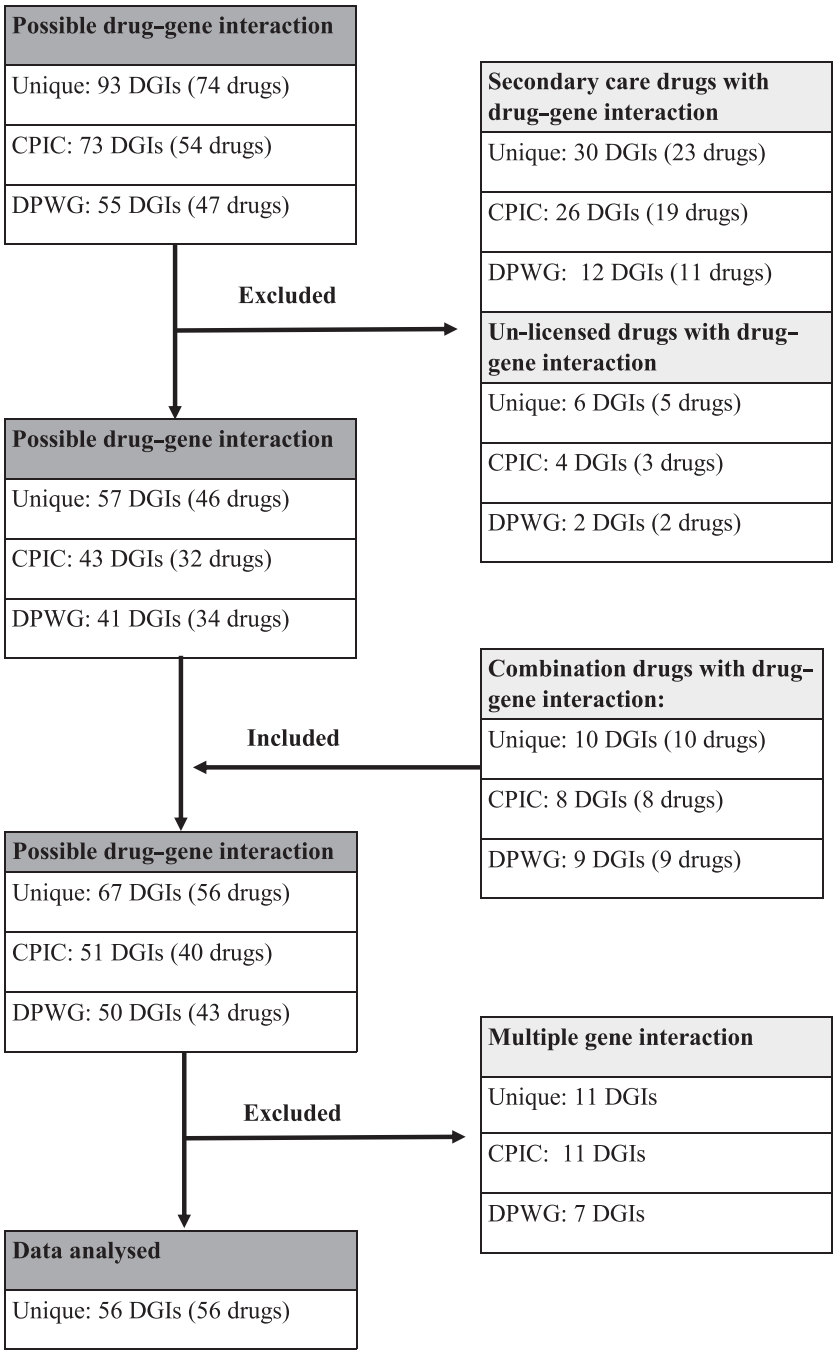


**FIGURE 1** Drug–gene interactions (DGIs) included in study. Flowchart of DGIs and drugs selection process using Clinical Pharmacogenetics Implementation Consortium (CPIC) and Dutch Pharmacogenetics Working Group (DPWG) guidelines

exposure to an anti-infective PGx drug was most common (34.4%), whilst those aged between 19 and 49 years were more likely to be exposed to antidepressants with a DGI. In age groups 50–115 years, exposure to proton pump inhibitors and analgesia were the most common sources for PGx exposure.

## 4 | DISCUSSION

### 4.1 | Main findings

Our findings demonstrate the high impact PGx testing could have on medicines prescribed across primary care in the UK. Based on the frequencies of actionable phenotypes for six genes from 879 patients and the estimated actionable phenotypes for three genetic variants from ethnicity census data, we inferred that between 19.1% and 21.1% of the first prescriptions for these 56 PGx drugs would have an actionable DGI requiring direct or indirect intervention. If the UK population were pre-emptively tested for this panel of genes, then an estimated 8.6–9.2% of the first prescriptions for these 56 PGx drugs would require a direct intervention as per CPIC and/or DPWG guidelines.

The most common newly initiated PGx drugs with an actionable DGI were for weak opioids like codeine and tramadol, antidepressants and proton pump inhibitors. Four genes (CYP2D6, CYP2C19, HLA-B and SCLO1B1) accounted for 95.8% of all drugs initiated with an actionable DGI. Age demographics within a community pharmacy database

**TABLE 2** Estimate of annual volume of PGx drugs newly initiated in UK primary care

| | Estimate of volumes of PGx medicines newly initiated in primary care (2019) | | | | |
|---|---|---|---|---|---|
| Drug | England | Scotland | Wales | Northern Ireland | UK (total) |
| Acenocoumarol | 1107 | 26 | 27 | 5 | 1165 |
| Allopurinol | 280 391 | 22 658 | 24 466 | 7190 | 334 705 |
| Amitriptylline | 1 456 603 | 136 070 | 113 825 | 55 169 | 1 761 667 |
| Ampicillin_flucloxacillin | 4663 | 243 | 64 | 94 | 5064 |
| Aripiprazole | 90 819 | 5680 | 7215 | 2643 | 106 357 |
| Atomoxetine | 12 830 | 1417 | 968 | 829 | 16 044 |
| Atorvastatin with concomitant CYP inhibitors | 102 695 | 5070 | 6248 | 2897 | 116 910 |
| Azathioprine | 43 786 | 5547 | 2939 | 1801 | 54 073 |
| Carbamazepine | 93 188 | 8277 | 6371 | 3252 | 111 088 |
| Celecoxib | 41 410 | 7904 | 2087 | 3957 | 55 358 |
| Citalopram | 1 306 405 | 101 452 | 120 505 | 49 224 | 1 577 586 |
| Clomipramine | 14 210 | 2139 | 1193 | 484 | 18 026 |
| Clopidogrel | 462 092 | 40 163 | 30 422 | 11 663 | 544 340 |
| Codeine | 1 147 510 | 50 040 | 45 913 | 17 054 | 1 260 517 |
| Codeine_aspirin | 72 | 9 | 5 | 2 | 88 |
| Codeine_paracetamol | 2 551 074 | 465 019 | 307 277 | 211 929 | 3 535 299 |
| Codeine_ibuprofen | 99 | 17 | 4 | 8 | 128 |
| Codeine_paracetamol_buclizine | 730 | 2991 | 385 | 259 | 4365 |
| Codeine_paracetamol_caffeine | 490 | 0 | 31 | 2 | 523 |
| Doxepin | 1056 | 220 | 70 | 50 | 1396 |
| Escitalopram | 154 094 | 9115 | 4773 | 11 362 | 179 344 |
| Estrogen_contraceptives | 1 316 077 | 132 871 | 64 667 | 57 844 | 1 571 459 |
| Flecainide | 25 056 | 1522 | 1772 | 380 | 28 730 |
| Flucloxacillin | 2 842 764 | 323 869 | 198 383 | 96 471 | 3 461 487 |
| Flurbiprofen | 0 | 70 | 45 | 38 | 153 |
| Fluvoxamine | 1571 | 128 | 92 | 54 | 1845 |
| Haloperidol | 56 980 | 4523 | 3727 | 2326 | 67 556 |
| Ibuprofen | 584 337 | 169 678 | 78 355 | 41 800 | 874 170 |
| Ibuprofen_paracetamol | 110 | 0 | 1 | 1 | 112 |
| Imipramine | 12 530 | 2046 | 618 | 285 | 15 479 |
| Lamotrigine | 120 310 | 11 409 | 7847 | 4726 | 144 292 |
| Lansoprazole | 2 130 638 | 126 705 | 136 903 | 57 234 | 2 451 480 |
| Meloxicam | 69 546 | 9345 | 4278 | 4425 | 87 594 |
| Mercaptopurine | 4776 | 813 | 331 | 190 | 6110 |
| Metoprolol | 17 253 | 1532 | 830 | 461 | 20 076 |
| Nortriptylline | 80 164 | 9632 | 3288 | 1955 | 95 039 |
| Omeprazole | 3 211 202 | 364 505 | 260 405 | 128 861 | 3 964 973 |
| Ondansetron | 81 088 | 10 221 | 4616 | 10 181 | 106 106 |
| Oxcarbazepine | 5005 | 342 | 225 | 88 | 5660 |
| Pantoprazole | 99 827 | 4468 | 4922 | 9217 | 118 434 |
| Paroxetine | 74 841 | 6949 | 7348 | 2400 | 91 538 |
| Phenytoin | 13 801 | 1088 | 831 | 262 | 15 982 |
| Piroxicam | 1758 | 201 | 93 | 244 | 2296 |
| Sertraline | 2 094 199 | 170 666 | 173 404 | 93 388 | 2 531 657 |
| Simvastatin | 508 662 | 52 615 | 42 996 | 13 184 | 617 457 |

(Continues)

**TABLE 2** (Continued)

| Drug | Estimate of volumes of PGx medicines newly initiated in primary care (2019) | | | | |
|---|---|---|---|---|---|
| | England | Scotland | Wales | Northern Ireland | UK (total) |
| Simvastatin_ezetimibe | 555 | 21 | 18 | 38 | 632 |
| Simvastatin_fenofibrate | 16 | 5 | 0 | 6 | 27 |
| Tamoxifen | 42 740 | 4213 | 2784 | 1321 | 51 058 |
| Tenoxicam | 28 | 8 | 2 | 2 | 40 |
| Tramadol | 666 669 | 100 900 | 43 281 | 40 733 | 851 583 |
| Tramadol_paracetamol | 6208 | 325 | 678 | 1193 | 8404 |
| Trimipramine | 887 | 61 | 59 | 25 | 1032 |
| Venlafaxine | 289 694 | 30 099 | 22 516 | 24 245 | 366 554 |
| Voriconazole | 137 | 54 | 28 | 2 | 221 |
| Warfarin | 132 250 | 11 423 | 12 554 | 3194 | 159 421 |
| Zuclopenthixol | 7387 | 577 | 377 | 246 | 8587 |
| **Total** | **22 264 390** | **2 416 941** | **1 753 062** | **976 894** | **27 411 287** |

suggest type of PGx drug exposure changes with age. Patients under 50 years were more likely to be exposed to antidepressants and anti-infectives with DGIs. In the over 50s, PGx exposure was more frequently attributed to gastrointestinal and analgesic medicines.

Using the community pharmacy database as reference [Supplementary File 1], we identified the number of unique patients newly dispensed at least one of the 56 PGx drugs selected in one year. We then extrapolated this to the national prescription volumes to estimate between 3 741 848 and 4 133 126 patients annually in primary care would benefit from PGx testing.

## 4.2 | Comparison with other studies

Our findings that UK patients are frequently exposed to pharmacogenomic drugs in primary care is supported by recent studies from England and the Netherlands. Bank and colleagues in the Netherlands[9] investigated the prescribing of 45 drugs with DPWG guidelines in primary care. They found that 23.6% of all new prescriptions of these drugs had an actionable DGI, with 5.4% requiring direct intervention in the form of drug/dose adjustment.

Our analysis showed similar results, but with a higher frequency of DGI occurrence requiring direct intervention (9.2% *vs* 5.4%). This is likely due to differences in methodology. Our analysis included more PGx drugs, 56 drugs versus 45 drugs, due to the inclusion of both CPIC and DPWG therapeutic recommendations. Currently, the UK has no organisation responsible for publishing PGx prescribing guidelines. As a result, inclusion of both CPIC and DPWG therapeutic recommendations provides the broadest interpretation of potential impact on UK prescribing patterns.

Kimpton and colleagues[8] investigated the exposure of 648 141 English primary care patients to 63 drugs over a 25-year period. They found that three genes (CYP2C19, CYP2D6 and SCLO1B1) accounted for >95% of the common PGx drugs dispensed. When restricted to PGx drugs associated with "direct action", our analysis showed similar results with the same three genes accounting for 94.6% of PGx drug dispensing. A broader analysis of our results of all DGI with any actionable recommendation shows 95.8% DGI are affected by four genes (CYP2C19, CYP2D6, SLCO1B1, HLA-B). A strength of our study was the inclusion of phenotype frequency data; therefore our analysis supports the assertion that testing for CYP2C19, CYP2D6, SCLO1B1 and HLA-B provides the biggest opportunity to optimise medicines dispensed in primary care due to the high incidence of actionable DGI for these genes occurring in the population.

## 4.3 | Implementation of PGx testing in the UK

NHS England have recently announced plans to adopt a pre-emptive PGx testing strategy for drug–gene pairs with the most evidence of clinical and cost-effectiveness.[27] The aim is for patients in the next ten years to be tested for a panel of genes and genetic variants, and to have these results recorded in their medical records, for healthcare professionals to access across primary and secondary care.[27]

Our study demonstrates that population-level PGx testing has a large impact on the prescribing of medicines in UK primary care, with approximately 5 780 595 prescriptions for medicines dispensed annually having an actionable DGI according to CPIC and/or DPWG guidelines. Of these affected medicines, more than 95% of DGIs were due to variants in CYP2C19, CYP2D6, SCL01B1 and HLA-B genes. To date, little has been published on which genes will be tested by the NHS England pre-emptive PGx testing panel. A pharmacogenomics working group has been set up by NHS Improvement and Genomics England to review evidence and design a panel accordingly.[28] Results from the ongoing PREPARE study, a multi-centre European randomised controlled trial investigating if panel PGx testing reduces the incidence of adverse events and healthcare expenditure,[29] will likely influence gene selection for panel design. The gene panel for the PREPARE study consists of

**TABLE 3** Overview of the inferred drug–gene interactions among 56 PGx drugs with CPIC and/or DPWG guidelines, relevant to UK primary care

| Drug | Phenotype | Estimated number of drugs dispensed in 2019 | | | | | Recommendation | Ref guideline |
|---|---|---|---|---|---|---|---|---|
| | | England | Scotland | Wales | Northern Ireland | UK total | | |
| *CYP2C19* | | | | | | | | |
| Citalopram | EM | 860 026 | 66 787 | 79 330 | 32 404 | 1 038 547 | No action | Both |
| | IM | 343 712 | 26 692 | 31 705 | 12 951 | 415 060 | Guard maximum daily dose | DPWG* |
| | PM | 37 198 | 2889 | 3431 | 1402 | 44 920 | Lower dose required at start therapy | CPIC* |
| | UM | 65 469 | 5084 | 6039 | 2467 | 79 059 | Switch to alternate drug at start therapy | CPIC* |
| Clopidogrel | EM | 304 202 | 26 439 | 20 027 | 7678 | 358 346 | No action | Both |
| | IM | 121 575 | 10 567 | 8004 | 3069 | 143 215 | Switch to alternate drug at start therapy | Both |
| | PM | 13 158 | 1144 | 866 | 332 | 15 500 | Switch to alternate drug at start therapy | Both |
| | UM | 23 157 | 2013 | 1525 | 584 | 27 279 | No action | Both |
| Escitalopram | EM | 101 442 | 6000 | 3142 | 7480 | 118 064 | No action | Both |
| | IM | 40 542 | 2398 | 1256 | 2989 | 47 185 | Guard maximum daily dose | DPWG* |
| | PM | 4388 | 260 | 136 | 324 | 5108 | Lower dose required at start therapy | CPIC* |
| | UM | 7722 | 457 | 239 | 569 | 8987 | Switch to alternate drug at start therapy | Both |
| Lansoprazole | EM | 1402,630 | 83 411 | 90 125 | 37 678 | 1 613 844 | No action | DPWG |
| | IM | 560 566 | 33 336 | 36 019 | 15 058 | 644 979 | No action | DPWG |
| | PM | 60 667 | 3608 | 3898 | 1630 | 69 803 | No action | DPWG |
| | UM | 106 775 | 6350 | 6861 | 2868 | 122 854 | Higher dose required at start therapy | DPWG |
| Omeprazole | EM | 2 113 980 | 239 958 | 171 428 | 84 831 | 2 610 197 | No action | DPWG |
| | IM | 844 861 | 95 901 | 68 512 | 33 903 | 1 043 177 | No action | DPWG |
| | PM | 91 435 | 10 379 | 7415 | 3669 | 112 898 | No action | DPWG |
| | UM | 160 926 | 18 267 | 13 050 | 6458 | 198 701 | Higher dose required at start therapy | DPWG |
| Pantoprazole | EM | 65 718 | 2941 | 3240 | 6068 | 77 967 | No action | DPWG |
| | IM | 26 264 | 1176 | 1295 | 2425 | 31 160 | No action | DPWG |
| | PM | 2842 | 127 | 140 | 262 | 3371 | No action | DPWG |
| | UM | 5003 | 224 | 247 | 462 | 5936 | Higher dose required at start therapy | DPWG |
| Sertraline | EM | 1 378 642 | 112 351 | 114 155 | 61 479 | 1 666 627 | No action | Both |
| | IM | 550 979 | 44 902 | 45 622 | 24 570 | 666 073 | No action | Both |
| | PM | 59 630 | 4860 | 4937 | 2659 | 72 086 | Guard maximum daily dose | DPWG |
| | UM | 104 948 | 8553 | 8690 | 4680 | 126 871 | No action | Both |
| Trimipramine | EM | 585 | 40 | 38 | 16 | 679 | No action | CPIC |
| | IM | 233 | 16 | 16 | 7 | 272 | Optional lower dose required at start therapy | CPIC |

(Continues)

**TABLE 3** (Continued)

| Drug | Phenotype | Estimated number of drugs dispensed in 2019 | | | | | Recommendation | Ref guideline |
|---|---|---|---|---|---|---|---|---|
| | | England | Scotland | Wales | Northern Ireland | UK total | | |
| | UM | 44 | 3 | 3 | 1 | 51 | Optional switch to alternate drug at start therapy | CPIC |
| | PM | 25 | 2 | 2 | 1 | 30 | Optional switch to alternate drug at start therapy | CPIC |
| Voriconazole | EM | 90 | 35 | 19 | 1 | 145 | No action | Both |
| | IM | 36 | 14 | 7 | 1 | 58 | Observe status of patient carefully | DPWG* |
| | PM | 4 | 2 | 1 | 0 | 7 | Switch to alternate drug at start therapy | CPIC |
| | UM | 7 | 3 | 1 | 0 | 11 | Switch to alternate drug at start therapy | CPIC |
| *CYP2C9* | | | | | | | | |
| Celecoxib | EM | 27 246 | 5200 | 1373 | 2604 | 36 423 | No action | CPIC |
| | IM (AS = 1.5) | 8329 | 1590 | 420 | 796 | 11 135 | No action | CPIC |
| | IM (AS = 1.0) | 4941 | 943 | 249 | 472 | 6605 | Optional lower dose required at start therapy | CPIC |
| | PM | 894 | 171 | 45 | 85 | 1195 | Lower dose required at start therapy | CPIC |
| Flurbiprofen | EM | 0 | 46 | 30 | 24 | 100 | No action | CPIC |
| | IM (AS = 1.5) | 0 | 14 | 9 | 8 | 31 | No action | CPIC |
| | IM (AS = 1.0) | 0 | 8 | 5 | 5 | 18 | Optional lower dose required at start therapy | CPIC |
| | PM | 0 | 2 | 1 | 1 | 4 | Lower dose required at start therapy | CPIC |
| Ibuprofen | EM | 384 468 | 111 640 | 51 554 | 27 501 | 575 163 | No action | CPIC |
| | IM (AS = 1.5) | 117 531 | 34 128 | 15 760 | 8408 | 175 827 | No action | CPIC |
| | IM (AS = 1.0) | 69 722 | 20 246 | 9349 | 4988 | 104 305 | Optional lower dose required at start therapy | CPIC |
| | PM | 12 616 | 3664 | 1692 | 903 | 18 875 | Lower dose required at start therapy | CPIC |
| Ibuprofen_paracetamol | EM | 73 | 0 | 1 | 1 | 75 | No action | CPIC |
| | IM (AS = 1.5) | 22 | 0 | 0 | 0 | 22 | No action | CPIC |
| | IM (AS = 1.0) | 13 | 0 | 0 | 0 | 13 | Optional lower dose required at start therapy | CPIC |
| | PM | 2 | 0 | 0 | 0 | 2 | Lower dose required at start therapy | CPIC |
| Meloxicam | EM | 45 758 | 6148 | 2816 | 2911 | 57 633 | No action | CPIC |
| | IM (AS = 1.5) | 13 988 | 1880 | 860 | 890 | 17 618 | No action | CPIC |
| | IM (AS = 1.0) | 8298 | 1115 | 510 | 528 | 10 451 | Lower dose required start therapy | CPIC |
| | PM | 1502 | 202 | 92 | 96 | 1892 | Switch to alternate drug at start therapy | CPIC |
| Phenytoin | EM | 9080 | 716 | 547 | 172 | 10 515 | No action | CPIC |

(Continues)

**TABLE 3** (Continued)

| Drug | Phenotype | Estimated number of drugs dispensed in 2019 | | | | | Recommendation | Ref guideline |
|---|---|---|---|---|---|---|---|---|
| | | England | Scotland | Wales | Northern Ireland | UK total | | |
| | IM (AS = 1.5) | 2776 | 219 | 167 | 53 | 3215 | Lower dose required at start therapy | CPIC |
| | IM (AS = 1.0) | 1647 | 130 | 99 | 31 | 1907 | Lower dose required at start therapy | CPIC |
| | PM | 298 | 23 | 18 | 6 | 345 | Lower dose required at start therapy | CPIC |
| Piroxicam | EM | 1156 | 133 | 61 | 161 | 1511 | No action | CPIC |
| | IM (AS = 1.5) | 354 | 40 | 19 | 49 | 462 | No action | CPIC |
| | IM (AS = 1.0) | 210 | 24 | 11 | 29 | 274 | Switch to alternate drug at start therapy | CPIC |
| | PM | 38 | 4 | 2 | 5 | 49 | Switch to alternate drug at start therapy | CPIC |
| Tenoxicam | EM | 18 | 5 | 2 | 2 | 27 | No action | CPIC |
| | IM (AS = 1.5) | 6 | 2 | 0 | 0 | 8 | No action | CPIC |
| | IM (AS = 1.0) | 3 | 1 | 0 | 0 | 4 | Optional switch at start therapy | CPIC |
| | PM | 1 | 0 | 0 | 0 | 1 | Optional switch at start therapy | CPIC |
| Amitriptylline | EM | 744 854 | 69 582 | 58 207 | 28 211 | 900 854 | No action | Both |
| | IM | 599 194 | 55 974 | 46 823 | 22 695 | 724 686 | Lower dose at start therapy | Both |
| | PM | 87 727 | 8195 | 6855 | 3323 | 106 100 | Switch to alternate drug at start therapy | CPIC |
| | UM | 24 828 | 2319 | 1940 | 940 | 30 027 | Switch to alternate drug at start therapy | CPIC |
| *CYP2D6* | | | | | | | | |
| Aripiprazole | EM | 46 441 | 2904 | 3689 | 1352 | 54 386 | No action | DPWG |
| | IM | 37 360 | 2337 | 2968 | 1087 | 43 752 | No action | DPWG |
| | PM | 5470 | 342 | 435 | 159 | 6406 | Guard maximum daily dose | DPWG |
| | UM | 1548 | 97 | 123 | 45 | 1813 | No action | DPWG |
| Atomoxetine | EM | 6560 | 725 | 495 | 424 | 8204 | No action | Both |
| | IM | 5278 | 583 | 398 | 341 | 6600 | Observe status of patient carefully | Both |
| | PM | 773 | 85 | 58 | 50 | 966 | Observe status of patient carefully | Both |
| | UM | 219 | 24 | 17 | 14 | 274 | Observe status of patient carefully | Both |
| Clomipramine | EM | 7267 | 1094 | 610 | 248 | 9219 | No action | Both |
| | IM | 5845 | 880 | 491 | 199 | 7415 | Lower dose at start therapy | DPWG* |
| | PM | 856 | 129 | 72 | 29 | 1086 | Lower dose at start therapy | DPWG* |
| | UM | 242 | 36 | 20 | 8 | 306 | Higher dose required at start therapy | DPWG* |
| Codeine | EM | 586 795 | 25 588 | 23 478 | 8721 | 644 582 | No action | Both |
| | IM | 472 044 | 20 585 | 18 887 | 7015 | 518 531 | Observe status of patient carefully | Both |
| | PM | 69 111 | 3014 | 2765 | 1027 | 75 917 | Switch to alternate drug at start therapy | Both |
| | UM | 19 560 | 853 | 783 | 291 | 21 487 | Switch to alternate drug at start therapy | Both |

(Continues)

**TABLE 3** (Continued)

| Drug | Phenotype | Estimated number of drugs dispensed in 2019 | | | | | Recommendation | Ref guideline |
|---|---|---|---|---|---|---|---|---|
| | | England | Scotland | Wales | Northern Ireland | UK total | | |
| Codeine_aspirin | EM | 37 | 4 | 3 | 1 | 45 | No action | Both |
| | IM | 30 | 4 | 2 | 1 | 37 | Observe status of patient carefully | Both |
| | PM | 4 | 1 | 0 | 0 | 5 | Switch to alternate drug at start therapy | Both |
| | UM | 1 | 0 | 0 | 0 | 1 | Switch to alternate drug at start therapy | CPIC* |
| Codeine_ibuprofen | EM | 50 | 9 | 2 | 5 | 66 | No action | Both |
| | IM | 41 | 7 | 2 | 3 | 53 | Observe status of patient carefully | Both |
| | PM | 6 | 1 | 0 | 0 | 7 | Switch to alternate drug at start therapy | Both |
| | UM | 2 | 0 | 0 | 0 | 2 | Switch to alternate drug at start therapy | Both |
| Codeine_paracetamol | EM | 1 304 527 | 237 794 | 157 130 | 108 373 | 1 807 824 | No action | Both |
| | IM | 1 049 419 | 191 292 | 126 403 | 87 180 | 1 454 294 | Observe status of patient carefully | Both |
| | PM | 153 644 | 28 007 | 18 506 | 12 764 | 212 921 | Switch to alternate drug at start therapy | Both |
| | UM | 43 484 | 7926 | 5238 | 3612 | 60 260 | Switch to alternate drug at start therapy | Both |
| Codeine_paracetamol_buclizine | EM | 374 | 1530 | 197 | 132 | 2233 | No action | Both |
| | IM | 300 | 1230 | 158 | 107 | 1795 | Observe status of patient carefully | Both |
| | PM | 44 | 180 | 23 | 16 | 263 | Switch to alternate drug at start therapy | Both |
| | UM | 12 | 51 | 7 | 4 | 74 | Switch to alternate drug at start therapy | CPIC* |
| Codeine_paracetamol_caffeine | EM | 250 | 0 | 15 | 1 | 266 | No action | Both |
| | IM | 202 | 0 | 13 | 1 | 216 | Observe status of patient carefully | Both |
| | PM | 30 | 0 | 2 | 0 | 32 | Switch to alternate drug at start therapy | Both |
| | UM | 8 | 0 | 1 | 0 | 9 | Switch to alternate drug at start therapy | CPIC* |
| Doxepin | EM | 540 | 112 | 36 | 25 | 713 | No action | Both |
| | IM | 434 | 91 | 29 | 21 | 575 | Lower dose required at start therapy | DPWG* |
| | PM | 64 | 13 | 4 | 3 | 84 | Lower dose required at start therapy | DPWG* |
| | UM | 18 | 4 | 1 | 1 | 24 | Higher dose required at start therapy | DPWG* |
| Flecainide | EM | 12 813 | 778 | 906 | 195 | 14 692 | No action | DPWG |
| | IM | 10 307 | 626 | 729 | 156 | 11 818 | Lower dose required at start therapy | DPWG |
| | PM | 1509 | 92 | 107 | 23 | 1731 | Lower dose required at start therapy | DPWG |
| | UM | 427 | 26 | 30 | 6 | 489 | Observe status of patient carefully | DPWG |
| Fluvoxamine | EM | 803 | 65 | 46 | 28 | 942 | No action | |
| | IM | 646 | 53 | 38 | 22 | 759 | No action | Both |
| | PM | 95 | 8 | 6 | 3 | 112 | Optional lower dose required at start therapy | CPIC |
| | UM | 27 | 2 | 2 | 1 | 32 | No action | Both |

(Continues)

**TABLE 3** (Continued)

| Drug | Phenotype | Estimated number of drugs dispensed in 2019 | | | | | Recommendation | Ref guideline |
|---|---|---|---|---|---|---|---|---|
| | | England | Scotland | Wales | Northern Ireland | UK total | | |
| Haloperidol | EM | 29 137 | 2313 | 1906 | 1189 | 34 545 | No action | DPWG |
| | IM | 23 440 | 1861 | 1533 | 957 | 27 791 | No action | DPWG |
| | PM | 3432 | 272 | 224 | 140 | 4068 | Lower dose required at start therapy | DPWG |
| | UM | 971 | 77 | 64 | 40 | 1152 | Observe status of patient carefully | DPWG |
| Imipramine | EM | 6407 | 1046 | 316 | 146 | 7915 | No action | DPWG |
| | IM | 5154 | 842 | 254 | 117 | 6367 | Lower dose required at start therapy | DPWG |
| | PM | 755 | 123 | 37 | 17 | 932 | Lower dose required at start therapy | DPWG |
| | UM | 214 | 35 | 11 | 5 | 265 | Higher dose required at start therapy | DPWG |
| Metoprolol | EM | 8823 | 784 | 425 | 235 | 10 267 | No action | DPWG |
| | IM | 7097 | 630 | 341 | 190 | 8258 | Guard maximum daily dose | DPWG |
| | PM | 1039 | 92 | 50 | 28 | 1209 | Guard maximum daily dose | DPWG |
| | UM | 294 | 26 | 14 | 8 | 342 | Observe status patient carefully | DPWG |
| Nortriptyline | EM | 40 993 | 4926 | 1681 | 1000 | 48 600 | No action | Both |
| | IM | 32 977 | 3962 | 1353 | 804 | 39 096 | Lower dose required at start therapy | Both |
| | PM | 4828 | 580 | 198 | 118 | 5724 | Switch to alternate drug at start therapy | CPIC |
| | UM | 1366 | 164 | 56 | 33 | 1619 | Switch to alternate drug at start therapy | CPIC |
| Ondansetron | EM | 41 465 | 5226 | 2360 | 5206 | 54 257 | No action | CPIC |
| | IM | 33 357 | 4205 | 1899 | 4188 | 43 649 | No action | CPIC |
| | PM | 4884 | 616 | 278 | 613 | 6391 | No action | CPIC |
| | UM | 1382 | 174 | 79 | 174 | 1809 | Switch to alternate drug at start therapy | CPIC |
| Paroxetine | EM | 38 271 | 3553 | 3757 | 1227 | 46 808 | No action | Both |
| | IM | 30 787 | 2859 | 3023 | 987 | 37 656 | No action | Both |
| | PM | 4507 | 419 | 443 | 145 | 5514 | Optional switch to alternate drug at start therapy | CPIC |
| | UM | 1276 | 118 | 125 | 41 | 1560 | Switch to alternate drug at start therapy | Both |
| Tamoxifen | EM | 21 855 | 2154 | 1424 | 675 | 26 108 | No action | Both |
| | IM | 17 582 | 1733 | 1145 | 543 | 21 003 | Switch to alternate drug at start therapy | Both |
| | PM | 2574 | 254 | 168 | 80 | 3076 | Switch to alternate drug at start therapy | Both |
| | UM | 729 | 72 | 47 | 23 | 871 | No action | Both |
| Tramadol | EM | 340 910 | 51 596 | 22 132 | 20 830 | 435 468 | No action | DPWG |
| | IM | 274 243 | 41 507 | 17 804 | 16 756 | 350 310 | Observe status of patient carefully | DPWG |
| | PM | 40 152 | 6077 | 2607 | 2453 | 51 289 | Observe status of patient carefully | DPWG |
| | UM | 11 364 | 1720 | 738 | 694 | 14 516 | Switch to alternative | DPWG |

(Continues)

**TABLE 3** (Continued)

| Drug | Phenotype | Estimated number of drugs dispensed in 2019 | | | | | Recommendation | Ref guideline |
|---|---|---|---|---|---|---|---|---|
| | | England | Scotland | Wales | Northern Ireland | UK total | | |
| Tramadol_paracetamol | EM | 3174 | 165 | 346 | 610 | 4295 | No action | DPWG |
| | IM | 2554 | 134 | 279 | 491 | 3458 | Observe status of patient carefully | DPWG |
| | PM | 374 | 20 | 41 | 72 | 507 | Observe status of patient carefully | DPWG |
| | UM | 106 | 6 | 12 | 20 | 144 | Switch to alternative | DPWG |
| Venlafaxine | EM | 148 139 | 15 391 | 11 514 | 12 398 | 187 442 | No action | DPWG |
| | IM | 119 170 | 12 382 | 9262 | 9974 | 150 788 | Switch to alternate drug at start therapy | DPWG |
| | PM | 17 447 | 1813 | 1356 | 1460 | 22 076 | Switch to alternate drug at start therapy | DPWG |
| | UM | 4938 | 513 | 384 | 413 | 6248 | Observe status of patient carefully | DPWG |
| Zuclopenthixol | EM | 3777 | 295 | 193 | 126 | 4391 | No action | DPWG |
| | IM | 3039 | 237 | 155 | 101 | 3532 | Lower dose required at start therapy | DPWG |
| | PM | 445 | 35 | 23 | 15 | 518 | Lower dose required at start therapy | DPWG |
| | UM | 126 | 10 | 6 | 4 | 146 | Observe status of patient carefully | DPWG |
| *Factor V Leiden* | | | | | | | | |
| Estrogen_contraceptives | Negative | 1 262 420 | 127 454 | 62 031 | 55 486 | 1 507 391 | No action | DPWG |
| | Positive | 53 657 | 5417 | 2636 | 2358 | 64 068 | Switch to alternate drug at start therapy | DPWG |
| *HLA-A* | | | | | | | | |
| Carbamazepine | HLA-A*31:01Negative | 90 744 | 8060 | 6204 | 3167 | 108 175 | No action | CPIC |
| | HLA-A*31:01Positive | 2444 | 217 | 167 | 85 | 2913 | Switch to alternate drug at start therapy | CPIC |
| *HLA-B* | | | | | | | | |
| Allopurinol | HLA-B*58:01Negative | 275 944 | 22 299 | 24 078 | 7076 | 329 397 | No action | CPIC |
| | HLA-B*58:01Positive | 4447 | 359 | 388 | 114 | 5308 | Switch to alternate drug at start therapy | CPIC |
| Ampicillin_flucloxacillin | HLA-B*57:01Negative | 4372 | 228 | 60 | 88 | 4748 | No action | DPWG |
| | HLA-B*57:01Positive | 291 | 15 | 4 | 6 | 316 | Observe status of patient carefully | DPWG |
| Flucloxacillin | HLA-B*57:01Negative | 2 665 289 | 303 650 | 185 998 | 90 448 | 3 245 385 | No action | DPWG |
| | HLA-B*57:01Positive | 177 475 | 20 219 | 12 385 | 6023 | 216 102 | Observe status of patient carefully | DPWG |
| Lamotrigine | HLA-B*15:02Negative | 119 931 | 11 373 | 7822 | 4711 | 143 837 | No action | DPWG |
| | HLA-B*15:02Positive | 379 | 36 | 25 | 15 | 455 | Switch to alternate drug at start therapy | DPWG (not live) |
| Oxcarbazepine | HLA-B*15:02Negative | 4989 | 341 | 224 | 88 | 5642 | No action | CPIC |
| | HLA-B*15:02Positive | 16 | 1 | 1 | 0 | 18 | Switch to alternate drug at start therapy | CPIC |
| *SLCO1B1* | | | | | | | | |
| Atorvastatin with concomitant CYP inhibitor | NT (521TT) | 73 569 | 3632 | 4476 | 2076 | 83 753 | No action | DPWG |
| | PT (521TC) | 27 269 | 1346 | 1659 | 769 | 31 043 | Switch to alternate drug at start therapy | DPWG |

(Continues)

**TABLE 3** (Continued)

| Drug | Phenotype | Estimated number of drugs dispensed in 2019 | | | | | Recommendation | Ref guideline |
|---|---|---|---|---|---|---|---|---|
| | | England | Scotland | Wales | Northern Ireland | UK total | | |
| | PT (521CC) | 1857 | 92 | 113 | 52 | 2114 | Switch to alternate drug at start therapy | DPWG |
| Simvastatin | NT (521TT) | 364 398 | 37 693 | 30 802 | 9445 | 442 338 | No action | CPIC |
| | PT (521TC) | 135 068 | 13 971 | 11 417 | 3501 | 163 957 | Switch to alternative | CPIC |
| | PT (521CC) | 9196 | 951 | 777 | 238 | 11 162 | Switch to alternative | CPIC |
| Simvastatin_ezetimibe | NT (521TT) | 398 | 15 | 13 | 27 | 453 | No action | CPIC |
| | PT (521TC) | 147 | 6 | 5 | 10 | 168 | Switch to alternative | CPIC |
| | PT (521CC) | 10 | 0 | 0 | 1 | 11 | Switch to alternative | CPIC |
| Simvastatin_fenofibrate | NT (521TT) | 12 | 4 | 0 | 4 | 20 | No action | CPIC |
| | PT (521TC) | 4 | 1 | 0 | 2 | 7 | Switch to alternative | CPIC |
| | PT (521CC) | 0 | 0 | 0 | 0 | 0 | Switch to alternative | CPIC |
| *TPMT* | | | | | | | | |
| Azathioprine | EM | 39 760 | 5037 | 2669 | 1635 | 49 101 | No action | Both |
| | IM | 3976 | 504 | 267 | 164 | 4911 | Lower dose required at start therapy | Both |
| | PM | 50 | 6 | 3 | 2 | 61 | Switch to alternate drug at start therapy | Both |
| Mercaptopurine | EM | 4337 | 738 | 301 | 173 | 5549 | No action | Both |
| | IM | 434 | 74 | 30 | 17 | 555 | Lower dose required at start therapy | Both |
| | PM | 5 | 1 | 0 | 0 | 6 | Switch to alternate drug at start therapy | Both |
| *VKORC1* | | | | | | | | |
| Acenocoumarol | NS(1173CC/1639GG) | 452 | 11 | 11 | 2 | 476 | No action | DPWG |
| | NS(1173CT/-1639GA) | 523 | 12 | 13 | 2 | 550 | No action | DPWG |
| | HS (1173TT/-1639AA) | 132 | 3 | 3 | 1 | 139 | Lower dose required at start therapy | DPWG |
| Warfarin | NS(1173CC/1639GG) | 54 068 | 4670 | 5132 | 1306 | 65 176 | No action | Both |
| | NS(1173CT/-1639GA) | 62 456 | 5395 | 5929 | 1508 | 75 288 | No action | Both |
| | HS (1173TT/-1639AA) | 15 726 | 1358 | 1493 | 380 | 18 957 | Lower dose required at start therapy | Both |

*Gene–drug interactions with difference in the actionability of recommendations between CPIC and DPWG. EM = extensive/normal metaboliser, IM = intermediate metaboliser, PM = poor metaboliser, UM = ultra-rapid metaboliser, NT = normal transport activity, PT = poor transport activity, NS = normal sensitivity, HS = high sensitivity, AS = activity score.

**TABLE 4** Estimation for prescription volumes of primary care medicines in 2019 with CPIC and/or DPWG therapeutic recommendations

| | Volume of prescriptions with CPIC and/or DPWG guidelines dispensed in UK primary care 2019 | |
|---|---|---|
| | **Highest estimation** | **Lowest estimation** |
| **Direct action** | 2 500 283 | 2 354 058 |
| Higher dose required at start therapy | 328 086 | 327 491 |
| Lower dose required at start therapy | 912 492 | 846 005 |
| Switch to alternate drug at start therapy | 1 259 705 | 1 180 562 |
| **Indirect action** | 3 280 166 | 2 879 465 |
| Guard maximum daily dose | 550 204 | 137 987 |
| Observe status of patient carefully | 2 613 125 | 2 613 037 |
| Optional lower dose required at start therapy | 119 241 | 111 325 |
| Optional switch drug at start therapy | 5595 | 1697 |

**TABLE 5** Distribution of newly initiated PGx drugs dispensed in the UK in 2019 by therapeutic group

| | Total volume of PGx drugs newly dispensed in UK | | Total volume of PGx drugs with an "actionable" therapeutic recommendation dispensed in UK | | Total volume of PGx drugs with direct action therapeutic recommendation dispensed in UK | |
|---|---|---|---|---|---|---|
| **Therapeutic class** | ***n*** | **%** | ***n*** | **%** | ***n*** | **%** |
| **Analgesic** | **6 680 630** | **24.4%** | **2 909 816** | **50.3%** | **418 380** | **16.7%** |
| NSAIDs | 1 019 723 | 3.7% | 143 688 | 2.5% | 32 742 | 1.3% |
| Weak opioids | 5660,907 | 20.7% | 2 766 128 | 47.9% | 385 638 | 15.4% |
| **Cardiovascular** | **1 488 758** | **5.4%** | **410 120** | **7.1%** | **399 822** | **16.0%** |
| Antiarrhythmic | 28 730 | 0.1% | 14 038 | 0.2% | 13 549 | 0.5% |
| Anticoagulant | 160 586 | 0.6% | 19 096 | 0.3% | 19 096 | 0.8% |
| Antiplatelet | 544 340 | 2.0% | 158 715 | 2.7% | 158 715 | 6.3% |
| Beta blocker | 20 076 | 0.1% | 9809 | 0.2% | 0 | 0.0% |
| Statin | 735 026 | 2.7% | 208 462 | 3.6% | 208 462 | 8.3% |
| **Endocrinology** | **1 571 459** | **5.7%** | **64 068** | **1.1%** | **64 068** | **2.6%** |
| Estrogenic contraceptive | 1 571 459 | 5.7% | 64 068 | 1.1% | 64 068 | 2.6% |
| **Gastrointestinal** | **6 640 993** | **24.2%** | **329 300** | **5.7%** | **329 300** | **13.2%** |
| Antiemetic | 106 106 | 0.4% | 1809 | 0.0% | 1809 | 0.1% |
| Proton pump inhibitor | 6 534 887 | 23.8% | 327 491 | 5.7% | 327 491 | 13.1% |
| **Immunosuppression** | **60 183** | **0.2%** | **5533** | **0.1%** | **5533** | **0.2%** |
| **Infections** | **3 466 772** | **12.6%** | **216 494** | **3.7%** | **18** | **0.0%** |
| Antibiotic | 3 466 551 | 12.6% | 216 418 | 3.7% | 0 | 0.0% |
| Antifungal | 221 | 0.0% | 76 | 0.0% | 18 | 0.0% |
| **Oncology** | 51 058 | 0.2% | **24 079** | **0.4%** | **24 079** | **1.0%** |
| **Psychiatry/neurology** | **7 116 729** | **26.0%** | **1 815 877** | **31.4%** | **1 253 775** | **50.1%** |
| Antidepressant | 6 641 163 | 24.2% | 1 783 362 | 30.9% | 1 236 804 | 49.5% |
| Antiepileptic | 277 022 | 1.0% | 8853 | 0.2% | 8853 | 0.4% |
| Antipsychotic | 182 500 | 0.7% | 15 822 | 0.3% | 8118 | 0.3% |
| Atomoxetine | 16 044 | 0.1% | 7840 | 0.1% | 0 | 0.0% |
| **Other** | **334 705** | **1.2%** | **5308** | **0.1%** | **5308** | **0.2%** |
| Gout | 334 705 | 1.2% | 5308 | 0.1% | 5308 | 0.2% |
| **Total** | **27 411 287** | **100.0%** | **5 780 595** | **100.0%** | **2 500 283** | **100.0%** |

**TABLE 6** Estimated volumes of medicines dispensed in 2019 with a CPIC and/or DPWG therapeutic guidelines recommending "direct action"

| | England | | Scotland | | Wales | | Northern Ireland | | UK (Total) | |
|---|---|---|---|---|---|---|---|---|---|---|
| Gene | Drug Volume | (%) | Drug Volume | (%) | Drug Volume | (%) | Drug Volume | (%) | Drug Volume | (%) |
| CYP2C19 | 522 225 | 25.5% | 45 247 | 21.8% | 38 875 | 24.3% | 17 951 | 20.7% | 624 298 | 25.0% |
| CYP2C9 | 28 281 | 1.4% | 5554 | 2.7% | 2637 | 1.6% | 1737 | 2.0% | 38 209 | 1.5% |
| CYP2D6 | 1 240 041 | 60.6% | 132 842 | 63.9% | 99 592 | 62.2% | 59 448 | 68.5% | 1 531 923 | 61.3% |
| F5 | 53 657 | 2.6% | 5417 | 2.6% | 2636 | 1.6% | 2358 | 2.7% | 64 068 | 2.6% |
| HLA-A | 2444 | 0.1% | 217 | 0.1% | 167 | 0.1% | 85 | 0.1% | 2913 | 0.1% |
| HLA-B | 4842 | 0.2% | 396 | 0.2% | 414 | 0.3% | 129 | 0.1% | 5781 | 0.2% |
| SLCO1B1 | 173 551 | 8.5% | 16 367 | 7.9% | 13 971 | 8.7% | 4573 | 5.3% | 208 462 | 8.3% |
| TPMT | 4465 | 0.2% | 585 | 0.3% | 300 | 0.2% | 183 | 0.2% | 5533 | 0.2% |
| VKORC1 | 15 858 | 0.8% | 1361 | 0.7% | 1496 | 0.9% | 381 | 0.4% | 19 096 | 0.8% |
| **Total** | **2 045 364** | **100.0%** | **207 986** | **100.0%** | **160 088** | **100.0%** | **86 845** | **100.0%** | **2 500 283** | **100.0%** |

13 genes, covering medicine used both in primary and secondary care.[30] If a similar panel of genes is adopted by NHS England, then PGx testing will have a significant effect on prescribing in primary care even if testing is initiated in other settings. It is key, therefore, that PGx test results are recorded in patients' medical records, so they are accessible to all relevant healthcare professionals across healthcare settings. Our study shows pharmacists and GPs will encounter actionable DGI frequently in UK primary care. It is therefore essential that education and training is provided to these professions so that PGx can be used to optimise medicines and reduce adverse drug reactions for primary care patients.

## 4.4 | Study strengths and limitations

This study addresses a key gap in the existing evidence base for the potential impact of multi-drug pharmacogenomic testing by estimating quantitatively the volume of prescriptions for medicines dispensed in UK primary care where prescribing could be optimised by PGx testing. These findings could help support a nationwide multi-drug pharmacogenomic testing programme in primary care by highlighting the annual exposure of patients to the PGx drugs.

A strength of this study is the inclusion of PGx medicines with CPIC and/or DPWG evidence-based published prescribing guidelines. Since there are no UK-based PGx prescribing guidelines, this approach allowed capture of the widest possible outcomes of PGx testing. Where differences occurred between "actionability" of recommendation, e.g. one body recommended direct action whilst the other recommended non-direct action or no action, both scenarios were included in the analysis to produce a range of volumes for drugs affected by particular phenotypes, minimising bias.[17] Additionally, inclusion of DGIs with published therapeutic recommendations allowed for a more granular analysis of the quantitative impact on prescribing nationally. Our study is the first to estimate the impact of PGx testing using UK phenotype frequency data. A comparison of a

**TABLE 7** Estimated volumes of medicines dispensed in 2019 with a CPIC and/or DPWG therapeutic recommendation

| | England | | Northern Ireland | | Scotland | | Wales | | UK (Total) | |
|---|---|---|---|---|---|---|---|---|---|---|
| Gene | Drug Volume | (%) | Drug Volume | (%) | Drug Volume | (%) | Drug Volume | (%) | Drug Volume | (%) |
| CYP2C19 | 966 447 | 21.0% | 36 560 | 15.7% | 79 232 | 14.5% | 76 801 | 19.8% | 1 159 040 | 20.1% |
| CYP2C9 | 102 961 | 2.2% | 7202 | 3.1% | 26 752 | 4.9% | 12 240 | 3.2% | 149 155 | 2.6% |
| CYP2D6 | 3 110 634 | 67.4% | 174 928 | 75.3% | 396 533 | 72.5% | 268 034 | 69.0% | 3 950 129 | 68.3% |
| F5 | 53 657 | 1.2% | 2358 | 1.0% | 5417 | 1.0% | 2636 | 0.7% | 64 068 | 1.1% |
| HLA-A | 2444 | 0.1% | 85 | 0.0% | 217 | 0.0% | 167 | 0.0% | 2913 | 0.1% |
| HLA-B | 182 608 | 4.0% | 6158 | 2.6% | 20 630 | 3.8% | 12 803 | 3.3% | 222 199 | 3.8% |
| SLCO1B1 | 173 551 | 3.8% | 4573 | 2.0% | 16 367 | 3.0% | 13 971 | 3.6% | 208 462 | 3.6% |
| TPMT | 4465 | 0.1% | 183 | 0.1% | 585 | 0.1% | 300 | 0.1% | 5533 | 0.1% |
| VKORC1 | 15 858 | 0.3% | 381 | 0.2% | 1361 | 0.2% | 1496 | 0.4% | 19 096 | 0.3% |
| **Total** | **2 045 364** | **100.0%** | **207 986** | **100.0%** | **160 088** | **100.0%** | **86 845** | **100.0%** | **2 500 283** | **100.0%** |

**TABLE 8** Age distribution of 4 439 352 patients in the community pharmacy database newly dispensed one or more of the selected 56 PGx drugs in 2018

| Age (years) | Therapeutic class | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Analgesia | Anti-infective | Cardiovascular | Antidepressant | Antipsychotic | Epilepsy | CNS-other | Contraceptive | Gastro-intestinal | Other | Total | Most common PGx drug group exposure |
| **<18** | 25.3% | 34.4% | 0.1% | 9.5% | 0.6% | 0.6% | 0.8% | 18.7% | 9.8% | 0.2% | 100.0% | Anti-infective |
| **19–29** | 13.5% | 12.0% | 0.2% | 31.3% | 0.6% | 0.9% | 0.1% | 26.9% | 13.0% | 1.5% | 100.0% | Antidepressant |
| **30–39** | 20.5% | 12.1% | 0.7% | 29.8% | 0.6% | 0.8% | 0.1% | 12.6% | 19.4% | 3.3% | 100.0% | Antidepressant |
| **40–49** | 24.5% | 10.9% | 2.5% | 28.8% | 0.6% | 0.7% | 0.0% | 2.7% | 24.6% | 4.7% | 100.0% | Antidepressant |
| **50–59** | 25.7% | 10.2% | 5.7% | 24.1% | 0.4% | 0.5% | 0.0% | 0.1% | 27.8% | 5.4% | 100.0% | Gastrointestinal |
| **60–69** | 27.5% | 10.2% | 9.9% | 17.0% | 0.4% | 0.4% | 0.0% | 0.0% | 28.8% | 5.7% | 100.0% | Gastrointestinal |
| **70–79** | 27.9% | 11.4% | 13.5% | 13.9% | 0.5% | 0.4% | 0.0% | 0.0% | 26.8% | 5.5% | 100.0% | Analgesia |
| **80–89** | 27.7% | 13.5% | 15.4% | 12.8% | 1.0% | 0.4% | 0.0% | 0.0% | 24.5% | 4.7% | 100.0% | Analgesia |
| **90–99** | 24.7% | 16.8% | 15.4% | 12.2% | 2.2% | 0.3% | 0.0% | 0.0% | 24.9% | 3.4% | 100.0% | Gastrointestinal |
| **100–115** | 24.2% | 20.7% | 10.5% | 10.5% | 5.6% | 0.3% | 0.1% | 0.4% | 25.9% | 1.8% | 100.0% | Gastrointestinal |

recent study analysing frequency of actionable PGx phenotypes of 487 409 participants in the UK biobank showed similar incidence of phenotypes for CYP2D6, CYP2C19, SCLO1B1, TPMT and VKORC1 as used in our study.[6] The frequencies for F5 and HLA-B*57:01 used in our study are also comparable to other published studies.[31,32]

For HLA-A*31:01, HLA-B*15:02, HLA-B*58:01, frequency was calculated based on ethnicity data taken from the UK census and published phenotype incidence per ethnicity provided by PharmGKB. There are several limitations to this approach. Firstly, UK census ethnicity categories differ from CPIC biogeographical groups. Secondly, the most recently reported UK census data is from 2011 and is based on self-reported ethnicity. As a result, this approach may lead to over- or underestimation of the incidence of these genetic variants in the UK population. However, collectively these three genetic variants account for only four of the 56 PGx drugs included in the study.

Our model to estimate the volumes of PGx drugs newly initiated in primary care has some limitations. Due to the structure of how dispensing data in the UK are reported by individual countries, data on annual volumes of medicines dispensed which are newly initiated is absent. To overcome this challenge, a large community pharmacy dispensing database was analysed to calculate what percentage of total medicines dispensed were newly initiated. To do this, we assumed medicines first dispensed within a one-year time frame in the community pharmacy database were newly initiated in primary care. This may be an overestimation as a patient's newly dispensed medicine could have been dispensed earlier by another pharmacy. However, targeting only medicines which have been newly initiated also has its limitations, since there are opportunities to optimise medicines even when they have already been started through PGx testing; for example, earlier identification of side effects or safeguarding against maximum dosing.

Additional sources of limitations to consider include the lack of patient clinical data in our dispensing data sets. For several drugs, there may an overestimation of effect as therapeutic recommendations are based on the combination of both genetic results and patient clinical factors. PGx drugs included in our analysis affected by these conditions include **clopidogrel**, **omeprazole**, **lansoprazole**, **pantoprazole**, and oral hormonal contraceptives.

Furthermore, our analysis included a single gene interaction for each drug. For 10 of the 56 PGx drugs (**amitriptyline**, **azathioprine**, **carbamazepine**, **clomipramine**, **doxepin**, **imipramine**, **mercaptopurine**, **phenytoin**, **trimipramine** and warfarin) included in our analysis, additional DGIs were excluded. Our methodology therefore gives a conservative estimate of the impact of PGx testing for these drugs and may underestimate the overall impact of PGx testing in UK primary care.

## 5 | CONCLUSION

In conclusion, this study demonstrates a high incidence of actionable DGI occurring in UK primary care. A small number of genes account for the majority of PGx drugs issued annually with an actionable prescribing recommendation. These findings could support health economic modelling, by identifying drug–gene pairs for implementation prioritisation in primary care.

## COMPETING INTERESTS

The authors have no competing interests to declare.

This study did not perform interventions with or administer substances to human subjects/patients and so did not have a Principal Investigator.

## CONTRIBUTORS

T.T. had the original idea for the study and all authors contributed to the study design. E.Y. led the data analysis with T.T. and C.K. contributing to the interpretation of the data. E.Y. wrote the first draft of the manuscript. All authors contributed to the revision of the manuscript related to its intellectual content. All authors approved the final version submitted for publication.

## DATA AVAILABILITY STATEMENT

The study is based on data from national prescribing databases which are freely available online. Anonymised genetic data was provided by patients and collected by the research team as part of the PREPARE study. Anonymised prescribing data on first prescriptions was identified by Boots UK. The interpretation and conclusions contained in this report are those of the authors alone.

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## REFERENCES

1. Roden DM, Altman RB, Benowitz NL, et al. Pharmacogenomics: challenges and opportunities. *Ann Intern Med*. 2006;145(10):749-757.
2. Mostafa S, Kirkpatrick CMJ, Byron K, Sheffield L. An analysis of allele, genotype and phenotype frequencies, actionable pharmacogenomic (PGx) variants and phenoconversion in 5408 Australian patients genotyped for CYP2D6, CYP2C19, CYP2C9 and VKORC1 genes. *J Neural Transm (Vienna)*. 2019;126(1):5-18.
3. Van Driest SL, Shi Y, Bowton EA, et al. Clinically actionable genotypes among 10,000 patients with preemptive pharmacogenomic testing. *Clin Pharmacol Ther*. 2014;95(4):423-431.
4. Bush WS, Crosslin DR, Owusu-Obeng A, et al. Genetic variation among 82 pharmacogenes: the PGRNseq data from the eMERGE network. *Clin Pharmacol Ther*. 2016;100(2):160-169.
5. Ji Y, Skierka JM, Blommel JH, et al. Preemptive pharmacogenomic testing for precision medicine: a comprehensive analysis of five actionable pharmacogenomic genes using next-generation DNA sequencing and a customized CYP2D6 genotyping cascade. *J Mol Diagn*. 2016;18(3):438-445.
6. McInnes G, Lavertu A, Sangkuhl K, Klein TE, Whirl-Carrillo M, Altman RB. Pharmacogenetics at scale: an analysis of the UK biobank. *Clin Pharmacol Ther*. 2020. https://doi.org/10.1002/cpt.2122
7. PharmGKB. PharmGKB FAQs. https://www.pharmgkb.org/guidelineAnnotations. Accessed 31 March 2020.

8. Kimpton JE, Carey IM, Threapleton CJD, et al. Longitudinal exposure of English primary care patients to pharmacogenomic drugs: an analysis to inform design of pre-emptive pharmacogenomic testing. *Br J Clin Pharmacol*. 2019;85(12):2734-2746.
9. Bank PCD, Swen JJ, Guchelaar HJ. Estimated nationwide impact of implementing a preemptive pharmacogenetic panel approach to guide drug prescribing in primary care in The Netherlands. *BMC Med*. 2019;17(1):110.
10. Department of Health and Social Care. Genome UK: the future of healthcare. 2020; https://www.gov.uk/government/publications/genome-uk-the-future-of-healthcare. Accessed 20 December 2020.
11. Barbarino JM, Whirl-Carrillo M, Altman RB, Klein TE. PharmGKB: a worldwide resource for pharmacogenomic information. *Wiley Interdiscip Rev Syst Biol Med*. 2018;10(4):e1417.
12. Joint Formulary Committee. British National Formulary. 2020; http://www.medicinescomplete.com. Accessed 10 September 2020.
13. Brayfield A. Martindale: The Complete Drug Reference (online). 2020; https://about.medicinescomplete.com. Accessed 10 September 2020.
14. OpenPrescribing.net. EBM DataLab. 2017; https://openprescribing.net/. Accessed 31 March 2020.
15. Johnson JA, Caudle KE, Gong L, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for pharmacogenetics-guided warfarin dosing: 2017 update. *Clin Pharmacol Ther*. 2017;102(3):397-404.
16. Shendre A, Dillon C, Limdi NA. Pharmacogenetics of warfarin dosing in patients of African and European ancestry. *Pharmacogenomics*. 2018;19(17):1357-1371.
17. Bank PCD, Caudle KE, Swen JJ, et al. Comparison of the guidelines of the Clinical Pharmacogenetics Implementation Consortium and the Dutch Pharmacogenetics Working Group. *Clin Pharmacol Ther*. 2018;103(4):599-618.
18. HSC Business Services Organisation. Prescription cost analysis 2019 at Northern Ireland level. 2020; http://www.hscbusiness.hscni.net/services/3125.htm. Accessed 31 March 2020.
19. NHS Wales. Prescription Cost Analysis. 2020; https://nwssp.nhs.wales/ourservices/primary-care-services/general-information/data-and-publications/prescription-cost-analysis/. Accessed 31 March 2020.
20. Public Health Scotland. Prescriptions in the Community. 2020; https://www.opendata.nhs.scot/dataset/prescriptions-in-the-community. Accessed 31 March 2020.
21. EBM DataLab. University of Oxford; 2020.
22. van der Wouden CH, Cambon-Thomsen A, Cecchin E, et al. Implementing pharmacogenomics in Europe: design and implementation strategy of the Ubiquitous Pharmacogenomics Consortium. *Clin Pharmacol Ther*. 2017;101(3):341-358.
23. Theken KN, Lee CR, Gong L, et al. Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for CYP2C9 and nonsteroidal anti-inflammatory drugs. *Clin Pharmacol Ther*. 2020;108(2):191-200.
24. CPIC. CPIC Guidelines. 2020; https://cpicpgx.org/guidelines/. Accessed 10 September 2020.
25. Fan M, Bousman CA. Estimating the potential impact of CYP2C19 and CYP2D6 genetic testing on protocol-based care for depression in Canada and the United States. *Mol Neuropsychiatry*. 2020;5(Suppl 1):27-33.
26. Alexander SPH, Fabbro D, Kelly E, et al. The Concise Guide to PHARMACOLOGY 2019/20: Enzymes. *Br J Pharmacol*. 2019;176(S1):S297-S396.
27. NHS Health Education England. Genomics 101: Genomics in Healthcare. 2020; https://www.genomicseducation.hee.nhs.uk/education/online-courses/genomics-101-genomics-in-healthcare/. Accessed 20 June 2020.
28. Health Education England. Pharmacogenomics: a new normal for the NHS? 2019; https://www.genomicseducation.hee.nhs.uk/blog/pharmacogenomics-a-new-normal-for-the-nhs Accessed 30 January 2020.
29. Blagec K, Koopmann R, Crommentuijn-van Rhenen M, et al. Implementing pharmacogenomics decision support across seven European countries: the Ubiquitous Pharmacogenomics (U-PGx) project. *J Am Med Inform Assoc*. 2018;25(7):893-898.
30. van der Wouden CH, van Rhenen MH, Jama WOM, et al. Development of the PGx-passport: a panel of actionable germline genetic variants for pre-emptive pharmacogenetic testing. *Clin Pharmacol Ther*. 2019;106(4):866-873.
31. Pherwani AD, Winter PC, McNamee PT, et al. Is screening for factor V Leiden and prothrombin G20210A mutations in renal transplantation worthwhile? Results of a large single-center UK study. *Transplantation*. 2003;76(3):603-605.
32. Martin MA, Hoffman JM, Freimuth RR, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for HLA-B genotype and abacavir dosing: 2014 update. *Clin Pharmacol Ther*. 2014;95(5):499-500.

## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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