Received: 21 October 2020 | Revised: 4 December 2020 | Accepted: 7 December 2020

DOI: 10.1111/bcp.14704

ORIGINAL ARTICLE

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

Essra Youssef[1] | Charlotte L. Kirkdale[2] | David J. Wright[1] | Henk-Jan Guchelaar[3] | Tracey Thornley[2,4]

[1]School of Pharmacy, University of East Anglia, Norwich, UK

[2]Boots UK, Thane Road, Nottingham, UK

[3]Department of Clinical Pharmacy & Toxicology, Leiden University Medical Center, Leiden, The Netherlands

[4]School of Pharmacy, University of Nottingham, Nottingham, UK

Correspondence
Essra Youssef, School of Pharmacy, University of East Anglia, Norwich Research Park, Norwich, NR4 7TJ, UK.
Email: e.youssef@uea.ac.uk

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

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,

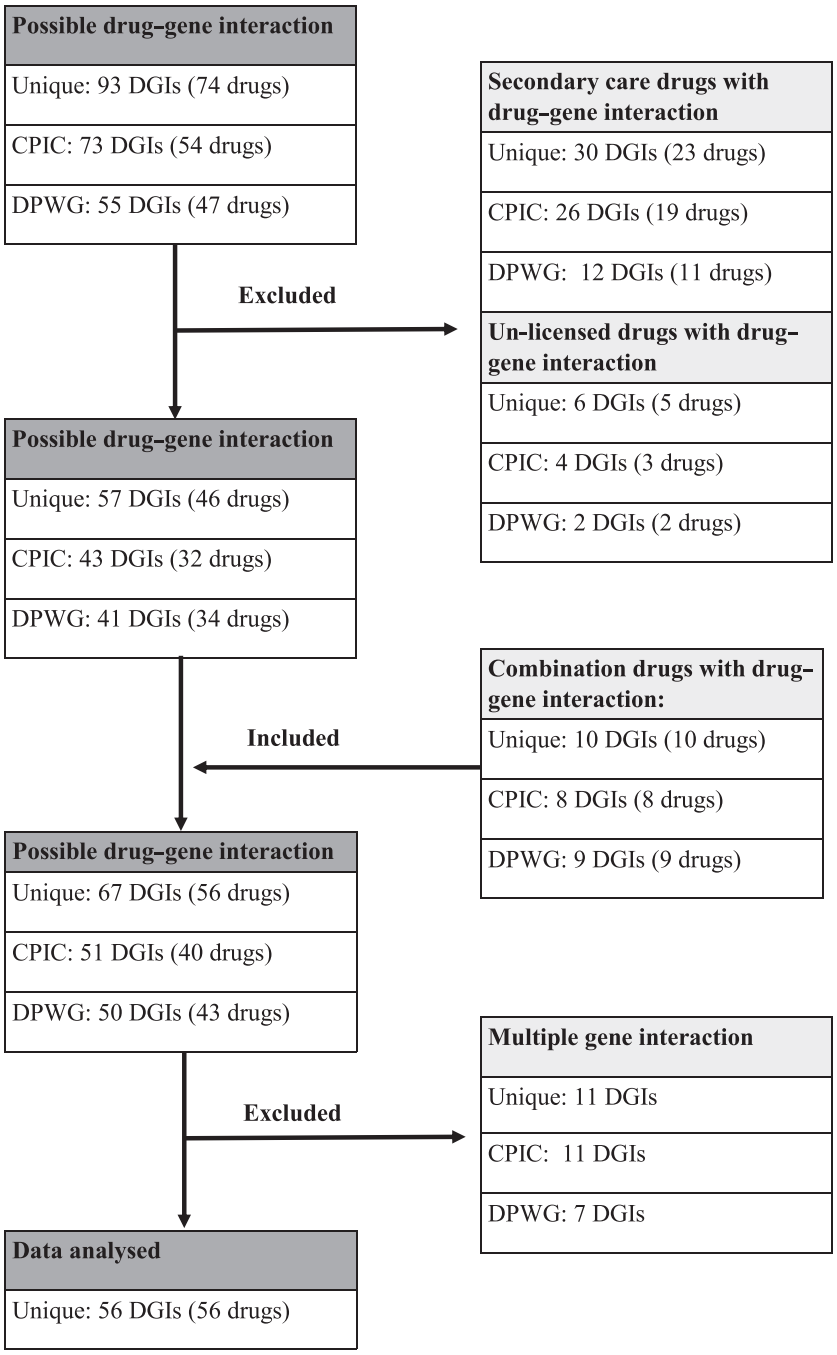

FIGURE 1 Drug–gene interactions (DGIs) included in study. Flowchart of DGIs and drugs selection process using Clinical Pharmacogenetics Implementation Consortium (CPIC) and Dutch Pharmacogenetics Working Group (DPWG) guidelines

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.

ORCID

Essra Youssef https://orcid.org/0000-0002-2332-1064
David J. Wright https://orcid.org/0000-0003-3690-9593
Henk-Jan Guchelaar https://orcid.org/0000-0002-7085-1383
Tracey Thornley https://orcid.org/0000-0002-9276-052X

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.

How to cite this article: Youssef E, Kirkdale CL, Wright DJ, Guchelaar H-J, Thornley T. Estimating the potential impact of implementing pre-emptive pharmacogenetic testing in primary care across the UK. *Br J Clin Pharmacol*. 2021;87:2907–2925. https://doi.org/10.1111/bcp.14704