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

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Running head: *'Impact of PGx testing in UK primary care'*

1. 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.

2. 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 eleven 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.

Abstract

Background: 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 9 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 January 1-December 31, 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: Between 19.1 and 21.1% (n=5,233,353 - 5,780,595) of all new prescriptions for56 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 to 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.

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 fourteen 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 1993-2017, 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 more than or equal to two PGx drugs over a 20-year period. A limitation of this study was the inclusion of drugs which 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, Banks 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 nineteen 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 ten 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 Banks 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.

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:

- Identification and selection of DGI relevant to UK primary care
- Classifying therapeutic recommendations and defining the concept 'actionable'
- Estimating number of new medicines with DGI initiated in UK primary care
- Estimating frequency of actionable phenotypes for relevant medicines initiated in UK primary care
- 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 31.03.2020 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 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 was 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 seen in Table 1.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 01.01.2019 and 31.12.2019 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 01.01.2018 and 31.12.2018 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 01.01.2019 and 31.12.2019 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 6 genes (CYP2C9, CYP2C19, CYP2D6, SLCO1B1, TPMT, and VKORC1) and 3 genetic variants (HLA-B*57:01, HLA-B*15:02, and factor V Leiden) were obtained from 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. 2019.[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.

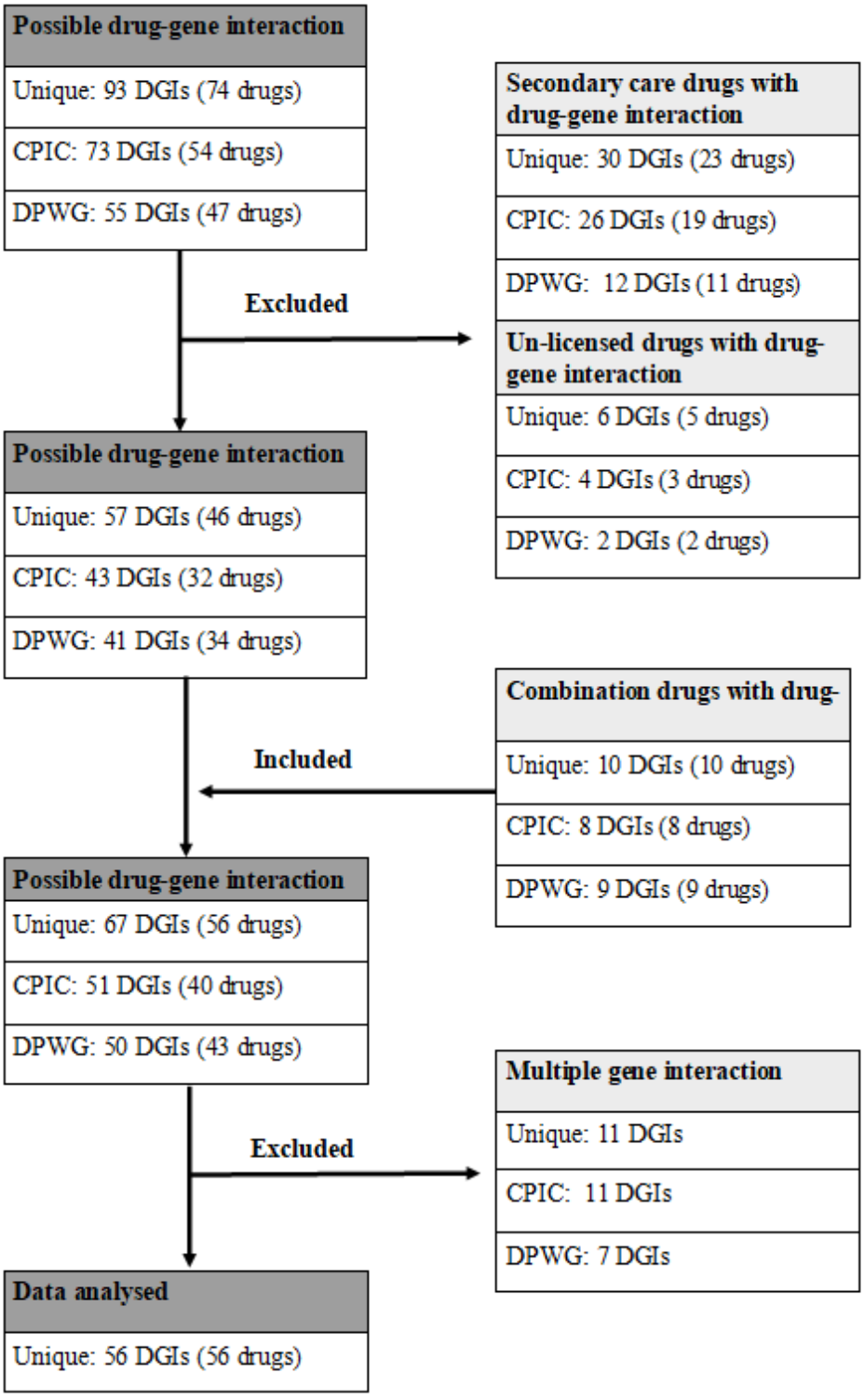
2.8 Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in https:/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.



194

195 *Figure 1. Drug-gene interactions (DGIs) included in study. Flowchart of DGIs and drugs*

196 *selection process using Clinical Pharmacogenetics Implementation Consortium (CPIC) and*

197 *Dutch Pharmacogenetics Working Group (DPWG) guidelines.*

198 **3.2 Overall UK results**

199 There were 27,411,287 estimated new prescriptions for 56 PGx drugs in 2019. (England:
200 22,264,390 items, Scotland 2,416,941 items, Wales 1,753,062 items, Northern Ireland
201 976,894 items). Table 2 shows the overall estimated newly initiated prescription volumes for
202 56 PGx drugs dispensed by community pharmacies in 2019. Table 3 shows the breakdown of
203 drug volumes per actionable phenotype. It is estimated that between 5,233,353 to 5,780,595
204 of these prescriptions had an actionable therapeutic recommendation according to CPIC
205 and/or DPWG guidelines. Table 4 shows a breakdown of the estimated volume ranges of
206 prescriptions dispensed in UK primary care in 2019.

207

208 Based on the data presented in this study, between one in four to one in five new
209 prescriptions for one of these 56 PGx drugs newly initiated in the community requires a
210 therapeutic intervention. Should all patients in the UK with a new prescription for this
211 selection of drugs have been pre-emptively genotyped for 9 genes (CYP2C19, CYP2C9,
212 CYP2D6, F5,HLA-A, HLA-B, SLCO1B1, TPMT, VKORC1), then one in every eleven new
213 prescriptions could be adjusted based on the genetic result. This frequency is the same across
214 England, Northern Ireland, Scotland and Wales.

215 **3.3 Frequency of exposure to PGx drugs by therapeutic group**

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

220 For those medicines with a therapeutic recommendation requiring ‘direct action’
221 (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

Table 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, 25.0% (n=624,298) were CYP2C19 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 19-59. In those 0-18 years exposure to an anti-infective PGx drug was most common (34.4%), whilst those aged between 19-49 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 6 genes from 879 patients and the estimated actionable phenotypes for 3 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% to 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 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 patients and 4,133,126 patients annually in primary care would benefit for 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 a 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 of time. They found that 3 genes (CYP2C19, CYP2D6 and SCLO1B1) accounted for >95% of the common PGx drugs dispensed. Our analysis when restricted to PGx drugs associated with 'direct action' 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 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 impact of PGx testing using UK phenotype frequency data. A comparison of a 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 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 only account for 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 safe guarding 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 ten 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

368 economic modelling, by identifying drug-gene pairs for implementation prioritisation in
369 primary care.

370 **COMPETING INTERESTS**

371 The authors have no competing interests to declare.

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

374 **CONTRIBUTORS**

375 Tracey Thornley had the original idea for the study and all authors contributed to the study
376 design. Essra Youssef led the data analysis with Tracey Thornley and Charlotte Kirkdale
377 contributing to the interpretation of the data. Essra Youssef wrote the first draft of the
378 manuscript. All authors contributed to the revision of the manuscript related to its intellectual
379 content. All authors approved the final version submitted for publication.

380 **DATA AVAILABILITYS**

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

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	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	

Table 1. Therapeutic recommendations assigned 'direct action', 'indirect action' and 'no action'.

	Estimate of volumes of PGx medicines newly initiated in primary care (2019)				
Drug	England	Scotland	Wales	Northern Ireland	UK (total)
Acenocoumarol	1,107	26	27	5	1,165
Allopurinol	280,391	22,658	24,466	7,190	334,705
Amitriptylline	1,456,603	136,070	113,825	55,169	1,761,667
Ampicillin_flucloxacillin	4,663	243	64	94	5,064
Aripiprazole	90,819	5,680	7,215	2,643	106,357
Atomoxetine	12,830	1,417	968	829	16,044
Atorvastatin with concomitant CYP inhibitors	102,695	5,070	6,248	2,897	116,910
Azathioprine	43,786	5,547	2,939	1,801	54,073
Carbamazepine	93,188	8,277	6,371	3,252	111,088
Celecoxib	41,410	7,904	2,087	3,957	55,358
Citalopram	1,306,405	101,452	120,505	49,224	1,577,586
Clomipramine	14,210	2,139	1,193	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	2,991	385	259	4,365
Codeine_paracetamol_caffeine	490	0	31	2	523

Doxepin	1,056	220	70	50	1,396
Escitalopram	154,094	9,115	4,773	11,362	179,344
Estrogen_contraceptives	1,316,077	132,871	64,667	57,844	1,571,459
Flecainide	25,056	1,522	1,772	380	28,730
Flucloxacillin	2,842,764	323,869	198,383	96,471	3,461,487
Flurbiprofen	0	70	45	38	153
Fluvoxamine	1,571	128	92	54	1,845
Haloperidol	56,980	4,523	3,727	2,326	67,556
Ibuprofen	584,337	169,678	78,355	41,800	874,170
Ibuprofen_paracetamol	110	0	1	1	112
Imipramine	12,530	2,046	618	285	15,479
Lamotrigine	120,310	11,409	7,847	4,726	144,292
Lansoprazole	2,130,638	126,705	136,903	57,234	2,451,480
Meloxicam	69,546	9,345	4,278	4,425	87,594
Mercaptopurine	4,776	813	331	190	6,110
Metoprolol	17,253	1,532	830	461	20,076
Nortriptylline	80,164	9,632	3,288	1,955	95,039
Omeprazole	3,211,202	364,505	260,405	128,861	3,964,973
Ondansetron	81,088	10,221	4,616	10,181	106,106
Oxcarbazepine	5,005	342	225	88	5,660
Pantoprazole	99,827	4,468	4,922	9,217	118,434
Paroxetine	74,841	6,949	7,348	2,400	91,538
Phenytoin	13,801	1,088	831	262	15,982
Piroxicam	1,758	201	93	244	2,296

Sertraline	2,094,199	170,666	173,404	93,388	2,531,657
Simvastatin	508,662	52,615	42,996	13,184	617,457
Simvastatin_ezetimibe	555	21	18	38	632
Simvastatin_fenofibrate	16	5	0	6	27
Tamoxifen	42,740	4,213	2,784	1,321	51,058
Tenoxicam	28	8	2	2	40
Tramadol	666,669	100,900	43,281	40,733	851,583
Tramadol_paracetamol	6,208	325	678	1,193	8,404
Trimipramine	887	61	59	25	1,032
Venlafaxine	289,694	30,099	22,516	24,245	366,554
Voriconazole	137	54	28	2	221
Warfarin	132,250	11,423	12,554	3,194	159,421
Zuclopenthixol	7,387	577	377	246	8,587
Total	**22,264,390**	**2,416,941**	**1,753,062**	**976,894**	**27,411,287**

399 *Table 2. Estimate of annual volume of PGx drugs newly initiated in UK primary care.*

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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	2,889	3,431	1,402	44,920	Lower dose required at start therapy	CPIC*
	UM	65,469	5,084	6,039	2,467	79,059	Switch to alternate drug at start therapy	CPIC*
Clopidogrel	EM	304,202	26,439	20,027	7,678	358,346	No action	Both

	IM	121,575	10,567	8,004	3,069	143,215	Switch to alternate drug at start therapy	Both
	PM	13,158	1,144	866	332	15,500	Switch to alternate drug at start therapy	Both
	UM	23,157	2,013	1,525	584	27,279	No action	Both
Escitalopram	EM	101,442	6,000	3,142	7,480	118,064	No action	Both
	IM	40,542	2,398	1,256	2,989	47,185	Guard maximum daily dose	DPWG*
	PM	4,388	260	136	324	5,108	Lower dose required at start therapy	CPIC*
	UM	7,722	457	239	569	8,987	Switch to alternate drug at start therapy	Both

Lansoprazole	EM	1,402,630	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	3,608	3,898	1,630	69,803	No action	DPWG
	UM	106,775	6,350	6,861	2,868	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	7,415	3,669	112,898	No action	DPWG
	UM	160,926	18,267	13,050	6,458	198,701	Higher dose required at start therapy	DPWG
Pantoprazole	EM	65,718	2,941	3,240	6,068	77,967	No action	DPWG
	IM	26,264	1,176	1,295	2,425	31,160	No action	DPWG
	PM	2,842	127	140	262	3,371	No action	DPWG

	UM	5,003	224	247	462	5,936	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	4,860	4,937	2,659	72,086	Guard maximum daily dose	DPWG
	UM	104,948	8,553	8,690	4,680	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
	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	5,200	1,373	2,604	36,423	No action	CPIC

	IM (AS=1.5)	8,329	1,590	420	796	11,135	No action	CPIC
	IM (AS=1.0)	4,941	943	249	472	6,605	Optional lower dose required at start therapy	CPIC
	PM	894	171	45	85	1,195	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	8,408	175,827	No action	CPIC
	IM (AS=1.0)	69,722	20,246	9,349	4,988	104,305	Optional lower dose required at start therapy	CPIC
	PM	12,616	3,664	1,692	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	6,148	2,816	2,911	57,633	No action	CPIC
	IM (AS=1.5)	13,988	1,880	860	890	17,618	No action	CPIC
	IM (AS=1.0)	8,298	1,115	510	528	10,451	Lower dose required start therapy	CPIC
	PM	1,502	202	92	96	1,892	Switch to alternate drug at start therapy	CPIC

Phenytoin	EM	9,080	716	547	172	10,515	No action	CPIC
	IM (AS=1.5)	2,776	219	167	53	3,215	Lower dose required at start therapy	CPIC
	IM (AS=1.0)	1,647	130	99	31	1,907	Lower dose required at start therapy	CPIC
	PM	298	23	18	6	345	Lower dose required at start therapy	CPIC
Piroxicam	EM	1,156	133	61	161	1,511	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	8,195	6,855	3,323	106,100	Switch to alternate drug at start therapy	CPIC

	UM	24,828	2,319	1,940	940	30,027	Switch to alternate drug at start therapy	CPIC
CYP2D6								
Aripiprazole	EM	46,441	2,904	3,689	1,352	54,386	No action	DPWG
	IM	37,360	2,337	2,968	1,087	43,752	No action	DPWG
	PM	5,470	342	435	159	6,406	Guard maximum daily dose	DPWG
	UM	1,548	97	123	45	1,813	No action	DPWG
Atomoxetine	EM	6,560	725	495	424	8,204	No action	Both
	IM	5,278	583	398	341	6,600	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	7,267	1,094	610	248	9,219	No action	Both
	IM	5,845	880	491	199	7,415	Lower dose at start therapy	DPWG*
	PM	856	129	72	29	1,086	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	8,721	644,582	No action	Both
	IM	472,044	20,585	18,887	7,015	518,531	Observe status of patient carefully	Both
	PM	69,111	3,014	2,765	1,027	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
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	7,926	5,238	3,612	60,260	Switch to alternate drug at start therapy	Both
Codeine_paracetamol_	EM	374	1,530	197	132	2,233	No action	Both

buclizine	IM	300	1,230	158	107	1,795	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	1,509	92	107	23	1,731	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
Haloperidol	EM	29,137	2,313	1,906	1,189	34,545	No action	DPWG
	IM	23,440	1,861	1,533	957	27,791	No action	DPWG

	PM	3,432	272	224	140	4,068	Lower dose required at start therapy	DPWG
	UM	971	77	64	40	1,152	Observe status of patient carefully	DPWG
Imipramine	EM	6,407	1,046	316	146	7,915	No action	DPWG
	IM	5,154	842	254	117	6,367	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	8,823	784	425	235	10,267	No action	DPWG

	IM	7,097	630	341	190	8,258	Guard maximum daily dose	DPWG
	PM	1,039	92	50	28	1,209	Guard maximum daily dose	DPWG
	UM	294	26	14	8	342	Observe status patient carefully	DPWG
Nortriptyline	EM	40,993	4,926	1,681	1,000	48,600	No action	Both
	IM	32,977	3,962	1,353	804	39,096	Lower dose required at start therapy	Both
	PM	4,828	580	198	118	5,724	Switch to alternate drug at start therapy	CPIC
	UM	1,366	164	56	33	1,619	Switch to alternate drug at start therapy	CPIC

Ondansetron	EM	41,465	5,226	2,360	5,206	54,257	No action	CPIC
	IM	33,357	4,205	1,899	4,188	43,649	No action	CPIC
	PM	4,884	616	278	613	6,391	No action	CPIC
	UM	1,382	174	79	174	1,809	Switch to alternate drug at start therapy	CPIC
Paroxetine	EM	38,271	3,553	3,757	1,227	46,808	No action	Both
	IM	30,787	2,859	3,023	987	37,656	No action	Both
	PM	4,507	419	443	145	5,514	Optional switch to alternate drug at start therapy	CPIC
	UM	1,276	118	125	41	1,560	Switch to alternate drug at start therapy	Both
Tamoxifen	EM	21,855	2,154	1,424	675	26,108	No action	Both

	IM	17,582	1,733	1,145	543	21,003	Switch to alternate drug at start therapy	Both
	PM	2,574	254	168	80	3,076	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	6,077	2,607	2,453	51,289	Observe status of patient carefully	DPWG
	UM	11,364	1,720	738	694	14,516	Switch to alternative	DPWG
Tramadol_paracetamol	EM	3,174	165	346	610	4,295	No action	DPWG

	IM	2,554	134	279	491	3,458	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	9,262	9,974	150,788	Switch to alternate drug at start therapy	DPWG
	PM	17,447	1,813	1,356	1,460	22,076	Switch to alternate drug at start therapy	DPWG
	UM	4,938	513	384	413	6,248	Observe status of patient carefully	DPWG
Zuclopenthixol	EM	3,777	295	193	126	4,391	No action	DPWG

	IM	3,039	237	155	101	3,532	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	5,417	2,636	2,358	64,068	Switch to alternate drug at start therapy	DPWG
HLA-A								

Carbamazepine	HLA-A*31:01 Negative	90,744	8,060	6,204	3,167	108,175	No action	CPIC
	HLA-A*31:01 Positive	2,444	217	167	85	2,913	Switch to alternate drug at start therapy	CPIC
HLA-B								
Allopurinol	HLA-B*58:01 Negative	275,944	22,299	24,078	7,076	329,397	No action	CPIC
	HLA-B*58:01 Positive	4,447	359	388	114	5,308	Switch to alternate drug at start therapy	CPIC
Ampicillin_flucloxacillin	HLA-B*57:01	4,372	228	60	88	4,748	No action	DPWG

	Negative							
	HLA-B*57:01 Positive	291	15	4	6	316	Observe status of patient carefully	DPWG
Flucloxacillin	HLA-B*57:01 Negative	2,665,289	303,650	185,998	90,448	3,245,385	No action	DPWG
	HLA-B*57:01 Positive	177,475	20,219	12,385	6,023	216,102	Observe status of patient carefully	DPWG
Lamotrigine	HLA-B*15:02 Negative	119,931	11,373	7,822	4,711	143,837	No action	DPWG
	HLA-B*15:02 Positive	379	36	25	15	455	Switch to alternate drug at start therapy	DPWG (not live)

Oxcarbazepine	HLA-B*15:02 Negative	4,989	341	224	88	5,642	No action	CPIC
	HLA-B*15:02 Positive	16	1	1	0	18	Switch to alternate drug at start therapy	CPIC
SLCO1B1								
Atorvastatin with concomitant CYP inhibitor	NT (521TT)	73,569	3,632	4,476	2,076	83,753	No action	DPWG
	PT (521TC)	27,269	1,346	1,659	769	31,043	Switch to alternate drug at start therapy	DPWG
	PT (521CC)	1,857	92	113	52	2,114	Switch to alternate drug at start therapy	DPWG
Simvastatin	NT (521TT)	364,398	37,693	30,802	9,445	442,338	No action	CPIC

	PT (521TC)	135,068	13,971	11,417	3,501	163,957	Switch to alternative	CPIC
	PT (521CC)	9,196	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	5,037	2,669	1,635	49,101	No action	Both
	IM	3,976	504	267	164	4,911	Lower dose required at start therapy	Both
	PM	50	6	3	2	61	Switch to alternate drug at start therapy	Both
Mercaptopurine	EM	4,337	738	301	173	5,549	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
VK0RC1								

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	4,670	5,132	1,306	65,176	No action	Both
	NS (1173CT/- 1639GA)	62,456	5,395	5,929	1,508	75,288	No action	Both

	HS (1173TT/-1639AA)	15,726	1,358	1,493	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 3. Overview of the inferred drug-gene interactions among 56 PGx drugs with CPIC and/or DPWG guidelines, relevant to UK primary care.

	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	5,595	1,697

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

Therapeutic Class	**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**	
	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	5,660,907	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%	9,809	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%	1,809	0.0%	1,809	0.1%
Proton pump inhibitor	6,534,887	23.8%	327,491	5.7%	327,491	13.1%
Immunosuppression	**60,183**	**0.2%**	**5,533**	**0.1%**	**5,533**	**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%	8,853	0.2%	8,853	0.4%
Antipsychotic	182,500	0.7%	15,822	0.3%	8,118	0.3%
Atomoxetine	16,044	0.1%	7,840	0.1%	0	0.0%
Other	**334,705**	**1.2%**	**5,308**	**0.1%**	**5,308**	**0.2%**
Gout	334,705	1.2%	5,308	0.1%	5,308	0.2%
Total	**27,411,287**	**100.0%**	**5,780,595**	**100.0%**	**2,500,283**	**100.0%**

Table 5 Distribution of newly initiated PGx drugs dispensed in the UK in 2019 by therapeutic group.

	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%	5,554	2.7%	2,637	1.6%	1,737	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%	5,417	2.6%	2,636	1.6%	2,358	2.7%	64,068	2.6%
HLA-A	2,444	0.1%	217	0.1%	167	0.1%	85	0.1%	2,913	0.1%
HLA-B	4,842	0.2%	396	0.2%	414	0.3%	129	0.1%	5,781	0.2%
SLCO1B1	173,551	8.5%	16,367	7.9%	13,971	8.7%	4,573	5.3%	208,462	8.3%
TPMT	4,465	0.2%	585	0.3%	300	0.2%	183	0.2%	5,533	0.2%
VKORC1	15,858	0.8%	1,361	0.7%	1,496	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%**

Table 6. Estimated volumes of medicines dispensed in 2019 with a CPIC and/or DPWG therapeutic guidelines recommending 'direct action'.

	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%	7,202	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%	2,358	1.0%	5,417	1.0%	2,636	0.7%	64,068	1.1%
HLA-A	2,444	0.1%	85	0.0%	217	0.0%	167	0.0%	2,913	0.1%
HLA-B	182,608	4.0%	6,158	2.6%	20,630	3.8%	12,803	3.3%	222,199	3.8%
SLCO1B1	173,551	3.8%	4,573	2.0%	16,367	3.0%	13,971	3.6%	208,462	3.6%
TPMT	4,465	0.1%	183	0.1%	585	0.1%	300	0.1%	5,533	0.1%

VKORC1	15,858	0.3%	381	0.2%	1,361	0.2%	1,496	0.4%	19,096	0.3%
Total	**4,612,625**	**100.0%**	**232,428**	**100.0%**	**547,094**	**100.0%**	**388,448**	**100.0%**	**5,780,595**	**100.0%**

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

	Therapeutic class											
Age (years)	**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

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.

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