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ORIGINAL ARTICLE

Estimating the prevalence of potential and actionable drug-gene interactions in Irish primary care: A cross-sectional study

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Abstract

Aims: Pharmacogenetics (PGx) is increasingly recognized as a strategy for medicines optimisation and prevention of adverse drug reactions. According to guidelines produced by the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetic Working Group (DPWG), most medicines with drug-gene interactions (DGIs) are prescribed in primary care. This study aimed to estimate the prevalence of potential and actionable DGIs involving all medicines dispensed in Irish primary care.

Methods: Dispensings of 46 drugs to General Medical Services (GMS) patients in the Health Service Executive Primary Care Reimbursement Service Irish pharmacy claims database from 01 January 2021 to 31 December 2021 were analysed to estimate the national prevalence of total dispensings and incidence of first-time dispensings of drugs with potential DGIs according to the CPIC and/or DPWG guidelines. Phenotype frequency data from the UK Biobank and the CPIC were used to estimate the incidence of actionable DGIs.

Results: One in five dispensings (12 443 637 of 62 754 498, 19.8%) were medicines with potential DGIs, 1 878 255 of these dispensed for the first time. On application of phenotype frequencies and linked guideline based therapeutic recommendations, 2 349 055 potential DGIs (18.9%) required action, such as monitoring and guarding against maximum dose, drug or dose change. One in five (369 700, 19.7%) first-time dispensings required action, with 139 169 (7.4%) requiring a change in prescribing. Antidepressants, weak opioids and statins were most commonly identified as having actionable DGIs.

Conclusions: This study estimated a high prevalence of DGIs in primary care in Ireland, identifying the need and opportunity to optimize drug therapy through PGx testing.

KEYWORDS
pharmacogenomics, prescribing, primary care

1 | INTRODUCTION

Pharmacogenetics (PGx) is the study of the role of genetic variation in drug metabolism, transport and response.[1–3] PGx testing can help to identify patients at risk of treatment failure or adverse drug reactions (ADRs) through predicting drug response variability.[4,5] Using genomic data to individualize treatment has been identified as a strategy to enable the provision of the right drug, at the right dose, at the right time to individual patients.[1,6]

Estimates of 15-30% of individual drug response variability are attributed to genetic polymorphisms.[5] The prevalence of aberrant genotypes in the general population is high, with >95% of all individuals carrying at least one actionable genotype when tested for a panel of up to 12 genes.[7–9] The UK Biobank Project, a prospective cohort study that collected phenotypic frequencies for 14 genes in 487 409 individuals, found that 99.5% of individuals have a predicted atypical response to at least one drug.[10]

The Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG) were established to facilitate the clinical implementation of pharmacogenetics through the provision of evidence-based guidelines.[11,12] Both consortia have independently reviewed >200 drug-gene interactions (DGIs), and have produced linked therapeutic recommendations for 117 of these DGIs.[13] There are some differences in availability of these drugs throughout Europe, but most of the drugs with known DGIs are prescribed and dispensed in primary care.

Recent studies in the Netherlands and the UK have investigated the exposure of patients in primary care to DGIs.[14,15] In the Netherlands, Bank and colleagues estimated that nearly one in four of all new prescriptions for 45 drugs had an actionable DGI.[14] Youssef and colleagues estimated a similar degree of impact in the general UK population, with an actionable DGI being present in approximately one in five of all new prescriptions for 56 drugs.[15] The differences in the assessment of the number of drugs with DGIs in the study undertaken in the Netherlands (45) and the UK (56) highlights the differences in the availability of medicines between the UK and the Netherlands, and the need to tailor studies investigating the prescribing of drugs with DGIs to the availability of drugs in the country where the study is being undertaken. The Pre-emptive Pharmacogenomic Testing for Preventing Adverse Drug Reactions (PREPARE) study recently investigated the clinical utility of a pharmacogenetic-panel strategy across sites in seven European countries.[16] Patients who underwent pre-emptive PGx testing for a selection of 12 genes showed a 30% reduction in clinically relevant ADRs compared with patients who did not.

The PREPARE study considered a panel-based approach to PGx testing in which multiple genes with reported involvement in actionable DGIs are tested for simultaneously. Many of these genes have variants that affect the pharmacokinetic properties of a drug.[17] Only about a dozen CYP P450 enzymes are responsible for the metabolism of 70-80% of all drugs in clinical use.[18] Thus, simultaneous testing for genetic variants that affect CYP P450 drug metabolizing activity offers clinical relevance for many drugs.[17]

PGx is being increasingly recognized in healthcare delivery in many countries, with NHS England planning to embed pharmacogenomics into routine clinical practice by 2025.[19] PGx testing may be particularly impactful in primary care because of the wide range of illnesses encountered, the abundance of prescribing and dispensing that occurs, and the substantial volume of primary care drugs that are known to be impacted by PGx variants.[4,20] A recent systematic review further supported the benefits that PGx interventions could bring to patients with multimorbidity and polypharmacy,[6] and a recent questionnaire study conducted with Irish adults indicated that the public is strongly supportive of PGx testing. Authors reported that those with chronic disease were 2.17 times more likely to want pharmacogenomic service availability than participants without existing conditions.[21]

The aim of this study was to investigate the exposure of Irish patients in primary care to drugs listed in the CPIC and/or DPWG guidelines and estimate the volume of dispensings with actionable DGIs. Quantitative estimates of the volumes of dispensings of drugs with a CPIC and/or DPWG therapeutic recommendation to the Irish General Medical Services (GMS) population (representing >30% of the Irish population, further details below) in 2021 were calculated and the volumes of dispensings with DGIs requiring direct and indirect action were estimated.

What is already known about this subject

- Pharmacogenetic testing helps identify patients at risk of treatment failure and adverse drug reactions.
- Prescribing of medicines with a potential drug gene interaction (DGI) is common, but the incidence of actionable DGIs is unknown.
- A large proportion of Irish adults with chronic disease (83%) have expressed support for pharmacogenomic testing.

What this study adds

- Three genes are responsible for >95% of all actionable DGIs.
- One in five dispensings are medicines that carry the potential for a DGI; one in five of these require action.
- Antidepressants, weak opioids and statins were most commonly identified as having actionable DGIs.
- This study could inform the implementation of targeted and pre-emptive pharmacogenomics testing in Ireland.

2 | METHODS

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement was used to guide the reporting of this manuscript,[22] and the overall process is illustrated in Figure 1.

2.1 | Selection of DGIs and classification of therapeutic recommendations

The selection of drugs and genes for inclusion in this study was based on guidelines from the CPIC and DPWG.[11,12] All available guidelines were reviewed, and drugs with an actionable therapeutic recommendation for at least one phenotype were included, provided they were available as oral preparations in the Irish primary care setting. This resulted in the inclusion of 46 unique DGIs (involving 46 drugs and 10 genes). To harmonize recommendations between both the CPIC and DPWG organizations, therapeutic recommendations were classified in categories specified by Youssef and colleagues: direct action (lower dose required at the start of therapy, higher dose required at the start of therapy, switch to alternative drug at the start of therapy), indirect action (observe status of patient carefully, optional lower dose required at the start of therapy, optional switch at the start of therapy, guard against maximum dose) and no action.[15] Drugs with a narrow therapeutic index (eg, warfarin, carbamazepine) are more likely to have a recommendation involving a direct action, whereas those with a wide therapeutic index (eg, lansoprazole) are more likely to have an indirect action.

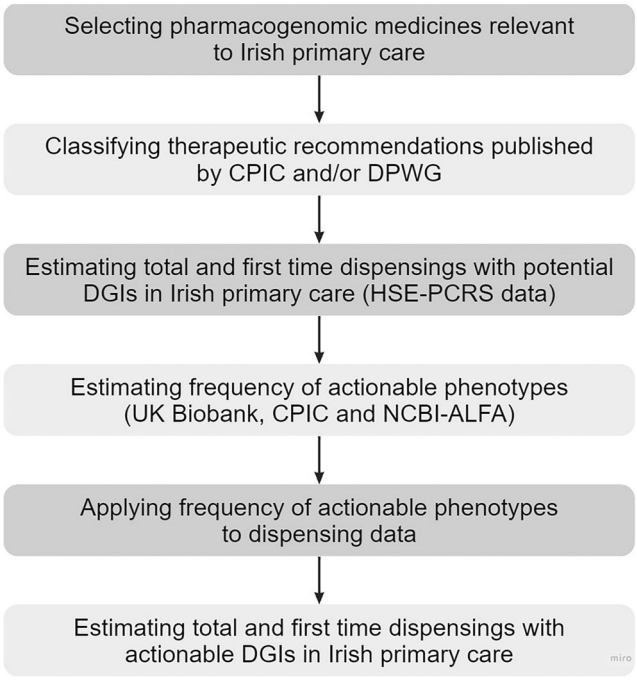

FIGURE 1 Overview of drug-gene interaction estimation process. CPIC; Clinical Pharmacogenetics Implementation Consortium; DGI, drug-gene interaction; DPWG, Dutch Pharmacogenetic Working Group; HSE-PCRS, Health Service Executive Primary Care Reimbursement Service; NCBI-ALFA, National Center for Biotechnology Information Allele Frequency Aggregator.

The most impactful single gene for each drug was selected due to the absence of population frequency data for multiple concurrent phenotypes. As described previously,[15] a gene was deemed most impactful if its aberrant phenotypes had the highest population frequency or if it was associated with more actionable recommendations. Where discrepancies arose between CPIC and DPWG recommendations, the most actionable recommendation was selected.

2.2 | Source of dispensing data

This cross-sectional study was undertaken using pharmacy claims data in the community setting in Ireland. Data were sourced from the GMS scheme pharmacy claims database via the Health Service Executive Primary Care Reimbursement Service (HSE-PCRS). The PCRS is a national service responsible for the reimbursement of medicines, and has been described in detail elsewhere.[23] The GMS scheme allows access to free or low-cost healthcare for patients whose household income falls below the eligibility threshold specification, with a higher income threshold applied for people ≥70 years.[24] The GMS database is the single largest pharmacy claims dataset in Ireland,[25] representing nearly one-third (30.8%) of the Irish population in 2021.[26] It contains basic demographic information and details on monthly dispensed medications coded using the World Health Organization's Anatomical Therapeutic Chemical classification system for all individuals within the scheme, and has been used previously to describe the quality of prescribing and prescribing trends for patients enlisted in the GMS.[25,27–29]

The volume of first-time and total dispensings of 46 drugs (61 medicines due to the inclusion of drug availability in combination products) between 1 January 2021 and 31 December 2021 were extracted from the GMS database. First-time dispensings were defined as the first dispensing of a medicine to a patient in the 12-month period, that is, the first observation of the medication being received by the patient in the study period.

2.3 | UK Biobank: Primary source of phenotypic frequency data for relevant genes

Of the 10 genes for inclusion in this study, phenotypic frequencies for CYP2C9, CYP2C19, CYP2D6, SLCO1B1, TPMT and VKORC1 were obtained from the UK Biobank,[10] a large-scale prospective cohort study with phenotypic and genomic data for approximately 500 000 participants in the UK.[10] This study involved analysis of pharmacogenetic haplotypes and phenotypes for 14 genes (CFTR, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A5, CYP4F2, DPYD, IFNL3, NUDT15, SLCO1B1, TPMT, UGT1A1 and VKORC1) across imputed, exome and integrated call sets. Population-aware diplotype concordance between imputed data and integrated data were calculated for the 49 790 participants with both exome and imputed data. The phenotypic frequencies for the Irish population were estimated using the

exome data of subjects with European genetic ancestry, which constitutes >90% (n = 45 322) of the total sample.[10]

2.4 | Other sources of phenotypic frequency data for relevant genes

Alternative sources were utilized for frequencies of specific phenotypes that were unavailable from the UK Biobank database (CYP2C19 intermediate [activity score 1], intermediate [activity score 1.5], CYP2D6 ultrarapid metaboliser, CYP3A4, HLA-B*57:01, HLA-B*58:01, HLA-B*15:02, HLA-A*31:01 and factor V Leiden). Where CPIC frequency tables were consulted, the European phenotypic frequency was used.

To estimate the CYP2D6 ultrarapid metaboliser phenotype frequency, the activity score of ≥2.5 was obtained for this phenotype from a CPIC publication on CYP2D6 and CYP2C19 genotypes.[30] The sum of the frequencies of phenotypes with an activity score ≥2.5 from CPIC CYP2D6 frequency tables was calculated.[31] CPIC guidelines were used to translate CYP2C19 haplotype to phenotype (intermediate [activity score 1], intermediate [activity score 1.5], poor metaboliser).[32] Phenotypic frequencies for CYP2C19 intermediate (activity score 1) and intermediate (activity score 1.5) and HLA-A*31:01 positive allele were obtained from CPIC frequency tables.[33,34] Frequencies for HLA-B*57:01 positive and HLA-B*58:01 positive alleles were obtained from frequency tables in the **Supporting Information** to a CPIC publication on HLA-B genotype and abacavir dosing[35] and to a CPIC publication on HLA-B genotype and allopurinol dosing,[36] respectively. The factor V Leiden allele of interest (rs6025 T) was identified through a DPWG guideline annotation published by the Pharmacogenomics Knowledge Base (PharmGKB).[37] Its frequency was obtained from data published on European participants (n = 135 734) by the National Center for Biotechnology Information Allele Frequency Aggregator,[38] accessed through PharmGKB.[39] Phenotypic frequency data for CYP3A4 was also obtained from PharmGKB.[40] Frequency data for HLA-B*15:02 was obtained from a US-based study that screened 28 897 US individuals for HLA-B*15:02.[41]

2.5 | Estimating the incidence of actionable DGIs annually in Irish primary care

The first-time and total dispensing volumes of relevant drugs were multiplied by the percentage frequency of actionable phenotypes for relevant genes to estimate the incidence of actionable DGIs, categorised according to actionability, as used by Youssef and colleagues.[15]

3 | RESULTS

3.1 | Volume of drugs dispensed with potential DGIs to the Irish GMS population in 2021

As noted above, 46 drugs (represented by 61 medicines due to the dispensing of combination products) were included in this study. Table 1 shows the volume of first-time and total dispensings of these drugs and their contribution to the overall total GMS dispensing for 2021. Of the total number of GMS items (62 754 498) dispensed, 12 443 637 (19.8%) were drugs with potential DGIs, of which 1 878 255 (3.0%) were first-time dispensings. Further details are provided in the supporting information.

3.2 | Frequency of actionable phenotypes for drugs with actionable DGIs in the Irish GMS population in 2021

Table 2 shows the breakdown of first-time and total dispensing volumes per actionable phenotype for each drug. Linked therapeutic recommendations are detailed in Table 3. Almost one in five first-time and total dispensings had an actionable therapeutic recommendation (369 700 [19.7%] and 2 349 055 [18.9%], respectively). Approximately one in 13 first-time and total dispensings had a directly actionable recommendation, requiring dose or drug change (139 169 [7.4%] and 971 114 [7.8%], respectively) (Table 3).

3.3 | Frequency of exposure to drugs with actionable DGIs by therapeutic class

Table 4 shows the distribution of first-time dispensing and total dispensing for the 46 drugs by therapeutic group. For first-time dispensings, the three therapeutic classes with the largest volume of actionable DGIs (n = 369 700) were weak opioids (42.7%, n = 157 823), antidepressants (26.4%, n = 97 542) and statins (12.5%, n = 46 200). Similarly, for total dispensings, antidepressants (33.0%, n = 774 145), weak opioids (26.3%, n = 618 375) and statins (25.1%, n = 588 702) accounted for the largest volume of actionable DGIs (n = 2 349 055). For first-time dispensings, a directly actionable recommendation (n = 139 169) applied most frequently to antidepressants (45.3%, n = 63 086), weak opioids (23.4%, n = 32 565) and proton pump inhibitors (PPIs) (10.5%, n = 14 634). Similarly, for total dispensings, antidepressants (50.3%, n = 488 914), weak opioids (13.1%, n = 127 595) and PPIs (10.9%, n = 105 973) accounted for the largest volume of directly actionable DGIs (n = 971 114).

3.4 | Frequency of exposure to drugs with actionable DGIs by gene

Figure 2 shows the proportion of actionability per gene based on the volume of total dispensings of drugs with actionable DGIs. Of the 2 349 055 total dispensed items with an actionable recommendation, three genes accounted for 95.7% of all actionable DGIs: CYP2D6 (49.4%, n = 1 159 900), SLCO1B1 (25.1%, n = 588 702) and CYP2C19 (21.2%, n = 497 399). The same three genes accounted for 94.1% of all directly actionable DGIs: CYP2D6 (61.9%, n = 601 492), CYP2C19 (24.6%, n = 238 887) and SLCO1B1 (7.6%, n = 73 523).

TABLE 1 Volume of dispensing of 46 drugs listed in the CPIC and/or DPWG guidelines, organized per Anatomical Therapeutic Chemical code category in the Irish GMS population in 2021.

Drug name	Volume of first-time dispensing	Total volume dispensed
Alimentary tract and metabolism		
Lansoprazole	111 010	882 621
Omeprazole	76 087	573 270
Ondansetron	17 777	28 439
Pantoprazole	137 542	895 009
Blood and blood-forming organs		
Clopidogrel	36 709	239 544
Warfarin	10 170	188 508
Cardiovascular system		
Atorvastatin	164 766	2 056 960
Atorvastatin, acetylsalicylic acid and ramipril	1463	10 616
Atorvastatin, amlodipine and perindopril	4	4
Atorvastatin and ezetimibe	3889	30 139
Atorvastatin and perindopril	185	185
Flecainide	2410	27 034
Fluvastatin	190	5799
Metoprolol	5833	66 372
Propafenone	608	4256
Rosuvastatin	74 657	983 588
Rosuvastatin and ezetimibe	5350	16 883
Simvastatin	13 370	216 555
Simvastatin and ezetimibe	5402	96 330
Genito urinary system and sex hormones		
Estrogens[a] (oral hormonal therapy)	94 594	405 301
Anti-infectives for systemic use		
Flucloxacillin	132 531	174 401
Antineoplastic and immunomodulating agents		
Azathioprine	2891	42 331
Mercaptopurine	566	5329
Tamoxifen	4192	39 500
Musculo-skeletal system		
Allopurinol	28 122	317 523
Celecoxib	12 803	32 602
Ibuprofen	99 983	183 386
Meloxicam	3863	12 194
Nervous system		
Amitriptyline	66 331	390 525
Aripiprazole	11775	85 027
Atomoxetine	1782	8196
Carbamazepine	5208	73 507
Citalopram	20 612	235 889
Clomipramine	456	7904
Codeine combinations excluding psycholeptics	234 201	931 680
Doxepin	345	1888
Escitalopram	92 013	693 047
Fluvoxamine	298	2035

(Continues)

TABLE 1 (Continued)

Drug name	Volume of first-time dispensing	Total volume dispensed
Haloperidol	3413	8783
Imipramine	137	1212
Lamotrigine	12 099	139 917
Nortriptyline	2159	10 059
Oxcarbazepine	767	6029
Paroxetine	5155	84 496
Phenytoin	1009	21 221
Quetiapine	80 333	471 480
Risperidone	17 538	135 016
Sertraline	111 916	629 069
Tramadol	53 651	223 800
Tramadol and dexketoprofen	1600	3162
Tramadol and paracetamol	53 296	184 299
Trimipramine	455	9144
Venlafaxine	53953	541 553
Zuclopenthixol	786	10 020
Total	1 878 255	12 443 637
Percentage (%) of total GMS items (n = 62 754 498)	3.0	19.8

Abbreviation: CPIC, Clinical Pharmacogenetics Implementation Consortium; DPWG, Dutch Pharmacogenetic Working Group; GMS, General Medical Services.

[a]Includes desogestrel and ethinylestradiol, dienogest and estradiol, drospirenone and ethinylestradiol, gestodene and ethinylestradiol, levonorgestrel and ethinylestradiol, nomegestrol and oestrogen, norelgestromin and ethinylestradiol and norgestimate and ethinylestradiol.

3.5 | The top 10 drugs with the largest volume of dispensings with actionable DGIs for first-time and total dispensings

Table 5 shows the ranking of the top 10 drugs with the largest volume of dispensings with actionable DGIs. For first-time dispensings, the drugs with the largest volume of dispensings with actionable DGIs were codeine (29.2%, n = 107 841), tramadol (13.5%, n = 49 982), atorvastatin (10.8%, n = 40 020), amitriptyline (8.3%, n = 30 543), escitalopram (8.2%, n = 30 473), venlafaxine (6.7%, n = 24 843), ibuprofen (4.3%, n = 15 897), clopidogrel (2.8%, n = 10 503), flucloxacillin (2.4%, n = 9012) and citalopram (1.8%, n = 6826). A similar selection of drugs was listed in the top 10 drugs for total dispensings: atorvastatin (21.0%, n = 492 976), codeine (18.3%, n = 429 004), venlafaxine (10.6%, n = 249 365), escitalopram (9.8%, n = 229 527), tramadol (8.1%, n = 189 371), amitriptyline (7.7%, n = 179 822), citalopram (3.3%, n = 78 123), simvastatin (3.1%, n = 73 523), clopidogrel (2.9%, n = 68 536) and pantoprazole (1.7%, n = 40 345).

3.6 | Discrepancies between CPIC and DPWG recommendations and chosen recommendations

Table 6 shows the discrepancies between CPIC and DPWG therapeutic recommendations for DGIs involving the 46 drugs and the classification of evidence by the CPIC and DPWG. Differences in the therapeutic recommendation in the CPIC and DPWG guidelines were identified for 22 unique DGIs, with six of these involving differences in action to take following DGI identification.

4 | DISCUSSION

This study provides insight into the occurrence of DGIs in primary care, based on Irish dispensing data and on phenotype frequencies obtained primarily from the UK Biobank. We found that nearly one-fifth (19.8%) of all medicines prescribed to patients enlisted in the GMS have a potential DGI. On application of phenotype frequencies, we estimate that nearly one in five dispensings of these drugs (18.9%) had a DGI requiring direct (eg, dose or drug change) or indirect action (eg, monitoring). One in 13 (7.4%) patients who received a medicine for the first time require an immediate change in drug regimen or dose adjustment, based on evidence-based guidelines.[11,12]

Antidepressants accounted for almost half (45.3%) of the identified DGIs with directly actionable recommendations for patients receiving their medicines for the first time, the greatest contributors being amitriptyline, venlafaxine and escitalopram (impacted by CYP2D6, CYP2D6 and CYP2C19, respectively). They were also the most commonly prescribed medicines with DGIs overall in 2021. The evidence-based recommended therapeutic action was to either switch to a different drug or to decrease the prescribed dose to avoid adverse effects associated with discontinuation and resultant

TABLE 2 Actionable DGI estimates for 46 drugs listed in the CPIC and/or DPWG guidelines in the Irish General Medical Services population in 2021.

Drug name	Phenotype	Volume (%) of first dispensing DGIs (n = 369 700)	Volume (%) of total dispensing DGIs (n = 2 349 055)	Recommendation	Ref guideline (DPWG/ CPIC)
CYP2C19					
Citalopram	IM	5398 (1.5)	61 775 (2.6)	Guard maximum daily dose	DPWG[g]
	PM	499 (0.1)	5715 (0.2)	Lower dose required at the start of therapy	CPIC[g]
	UM	929 (0.3)	10 633 (0.5)	Switch to alternative drug at the start of therapy	CPIC[g]
Clopidogrel	IM	9613 (2.6)	62 732 (2.7)	Switch to alternative drug at the start of therapy	Both
	PM	889 (0.2)	5803 (0.2)	Switch to alternative drug at the start of therapy	Both
Escitalopram	IM	24 097 (6.5)	181 496 (7.7.)	Guard maximum daily dose	DPWG[g]
	PM	2229 (0.6)	16 790 (0.7)	Lower dose required at the start of therapy	CPIC[g]
	UM	4148 (1.1)	31 241 (1.3)	Switch to alternative drug at the start of therapy	Both
Lansoprazole	UM	5004 (1.4)	39 786 (1.7)	Higher dose at the start of therapy	Both
Omeprazole	UM	3430 (0.9)	25 842 (1.1)	Higher dose at the start of therapy	Both
Pantoprazole	UM	6200 (1.7)	40 345 (1.7)	Higher dose at the start of therapy	Both
Sertraline	PM	2711 (0.7)	15 240 (0.6)	Guard maximum daily dose	DPWG[g]
CYP2C9					
Celecoxib	IM (AS = 1.0)	1754 (0.5)	4466 (0.2)	Optional lower dose at the start of therapy	CPIC
	PM	282(0,1)	717 (<0.1)	Lower dose required at the start of therapy	CPIC
Ibuprofen	IM (AS = 1.0)	13 698 (3.7)	25 124 (1.1)	Optional lower dose at the start of therapy	CPIC
	PM	2199 (0.6)	4034 (0.2)	Lower dose required at the start of therapy	CPIC
Meloxicam	IM (AS = 1.0)	529 (0.1)	1671 (0.1)	Lower dose required at the start of therapy	CPIC
	PM	85 (<0.1)	268 (<0.1)	Switch to alternative drug at the start of therapy	CPIC
Phenytoin	IM (AS = 1.5)	209 (0.1)	4393 (0.2)	Observe status of patient carefully	CPIC
	IM (AS = 1.0)	138 (0.04)	2907 (0.1)	Lower dose required at the start of therapy	Both
	PM	22 (<0.1)	467 (<0.1)	Lower dose required at the start of therapy	Both
CYP2D6					
Amitriptyline	IM	24 241 (6.6)	142 718 (6.1)	Lower dose required at the start of therapy	Both
	PM	4219 (1.1)	24 842 (1.1)	Lower dose required at the start of therapy	Both
	UM	2083 (0.6)	12 262 (0.5)	Switch to alternative drug at the start of therapy	Both
Aripiprazole	PM	749 (0.2)	5409 (0.2)	Guard maximum daily dose	DPWG

(Continues)

TABLE 2 (Continued)

Drug name	Phenotype	Volume (%) of first dispensing DGIs (n = 369 700)	Volume (%) of total dispensing DGIs (n = 2 349 055)	Recommendation	Ref guideline (DPWG/ CPIC)
Atomoxetine	IM	651 (0.2)	2995 (0.1)	Observe status of patient carefully	Both
	PM	113 (<0.1)	521 (<0.1)	Observe status of patient carefully	Both
	UM	56 (<0.1)	257 (<0.1)	Observe status of patient carefully	Both
Clomipramine	IM	167 (<0.1)	2889 (0.1)	Lower dose required at the start of therapy	DPWG[g]
	PM	29 (<0.1)	503 (<0.1)	Lower dose required at the start of therapy	DPWG[g]
	UM	14 (<0.1)	248 (<0.1)	Higher dose at the start of therapy	DPWG[g]
Codeine[a]	IM	85 589 (23.2)	340 484 (14.5)	Observe status of patient carefully	Both
	PM	14 898 (4.0)	59 266 (2.5)	Switch to alternative drug at the start of therapy	Both
	UM	7354 (2.0)	29 255 (1.2)	Switch to alternative drug at the start of therapy	CPIC
Doxepin	IM	126 (<0.1)	690 (<0.1)	Lower dose required at the start of therapy	DPWG[g]
	PM	22 (<0.1)	120 (<0.1)	Lower dose required at the start of therapy	DPWG[g]
	UM	11 (<0.1)	59 (<0.1)	Higher dose at the start of therapy	DPWG[g]
Flecainide	IM	881 (0.2)	9880 (0.4)	Lower dose required at the start of therapy	DPWG
	PM	153 (<0.1)	1720 (0.1)	Lower dose required at the start of therapy	DPWG
	UM	76 (<0.1)	849 (<0.1)	Observe status of patient carefully	DPWG
Fluvoxamine	PM	19 (<0.1)	129 (<0.1)	Optional lower dose at the start of therapy	CPIC[g]
Haloperidol	PM	217 (0.1)	559 (<0.1)	Lower dose required at the start of therapy	DPWG
	UM	107 (<0.1)	276 (<0.1)	Higher dose at the start of therapy	DPWG
Imipramine	IM	50 (<0.1)	443 (<0.1)	Lower dose required at the start of therapy	DPWG[g]
	PM	9 (<0.1)	77 (<0.1)	Lower dose required at the start of therapy	DPWG[g]
	UM	4 (<0.1)	38 (<0.1)	Higher dose at the start of therapy	DPWG[g]
Metoprolol	IM	2132 (0.5)	24 256 (1.0)	Guard maximum daily dose	DPWG
	PM	371 (0.1)	4222 (0.2)	Guard maximum daily dose	DPWG
	UM	183 (<0.1)	2084 (0.1)	Observe status of patient carefully	DPWG
Nortriptyline	IM	789 (0.2)	3676 (0.2)	Lower dose required at the start of therapy	Both
	PM	137 (<0.1)	640 (<0.1)	Lower dose required at the start of therapy	Both

TABLE 2 (Continued)

Drug name	Phenotype	Volume (%) of first dispensing DGIs (n = 369 700)	Volume (%) of total dispensing DGIs (n = 2 349 055)	Recommendation	Ref guideline (DPWG/ CPIC)
	UM	68 (<0.1)	316 (<0.1)	Switch to alternative drug at the start of therapy	Both
Ondansetron	UM	558 (0.2)	893 (<0.1)	Switch to alternative drug at the start of therapy	CPIC
Paroxetine	PM	328 (0.1)	5375 (0.2)	Optional switch to alternative drug at the start of therapy	CPIC[g]
	UM	162(<0.1)	2653 (0.1)	Switch to alternative drug at the start of therapy	Both
Propafenone	IM	222 (0.1)	1555 (0.1)	Switch to alternative drug at the start of therapy	DPWG
	PM	39 (<0.1)	271 (<0.1)	Lower dose required at the start of therapy	DPWG
	UM	19 (<0.1)	134 (<0.1)	Switch to alternative drug at the start of therapy	DPWG
Risperidone	PM	1116 (0.3)	8589 (0.4)	Lower dose at the start of therapy	DPWG
	UM	551 (0.1)	4240 (0.2)	Switch to alternative drug at the start of therapy	DPWG
Tamoxifen	IM	1532 (0.4)	14 435 (0.6)	Switch to alternative drug at the start of therapy	Both
	PM	267 (0.1)	2513 (0.1)	Switch to alternative drug at the start of therapy	Both
Tramadol[b]	IM	39 669 (10.7)	150 296 (6.4)	Observe status of patient carefully	Both
	PM	6905 (1.9)	26 161 (1.1)	Switch to alternative drug at the start of therapy	CPIC[g]
	UM	3408 (1.0)	12 914 (0.5)	Switch to alternative drug at the start of therapy	Both
Trimipramine	IM	166 (0.1)	3342 (0.1)	Optional lower dose at the start of therapy	CPIC
	PM	29 (<0.1)	582 (<0.1)	Optional switch at the start of therapy	CPIC
	UM	14 (<0.1)	287 (<0.1)	Optional switch at the start of therapy	CPIC
Venlafaxine	IM	19 717 (5.3)	197 911 (8.4)	Switch to alternative drug at the start of therapy	DPWG
	PM	3432 (0.9)	34 449 (1.5)	Switch to alternative drug at the start of therapy	DPWG
	UM	1694 (0.5)	17 005 (0.7)	Observe status of patient carefully	DPWG
Zuclopenthixol	IM	287 (0.1)	3662 (0.2)	Lower dose required at the start of therapy	DPWG
	PM	50 (<0.1)	637(<0.1)	Lower dose required at the start of therapy	DPWG
	UM	25 (<0.1)	315 (<0.1)	Observe status of patient carefully	DPWG
CYP3A4					
Quetiapine	PM	161 (<0.1)	943 (<0.1)		DPWG

(Continues)

TABLE 2 (Continued)

Drug name	Phenotype	Volume (%) of first dispensing DGIs (n = 369 700)	Volume (%) of total dispensing DGIs (n = 2 349 055)	Recommendation	Ref guideline (DPWG/ CPIC)
				Lower dose at the start of therapy	
Factor V Leiden					
Estrogens (oral hormonal therapy)	Positive (rs6025 T)	2403 (0.6)	10 295 (0.4)	Switch to alternative drug at the start of therapy	DPWG
HLA-A					
Carbamazepine	HLA-A*31:01Positive	138 (<0.1)	1944 (0.1)	Switch to alternative drug at the start of therapy	Both
HLA-B					
Allopurinol	HLA-B*58:01Positive	225 (0.1)	2540 (0.1)	Switch to alternative drug at the start of therapy	Both
Flucloxacillin	HLA-B*57:01Positive	9012 (2.4)	11 859 (0.5)	Observe status of patient carefully	DPWG
Lamotrigine	HLA-B*15:02Positive	12 (<0.1)	140 (<0.1)	Switch to alternative drug at the start of therapy	DPWG
Oxcarbazepine	HLA-B*15:02Positive	1 (<0.1)	6 (<0.1)	Switch to alternative drug at the start of therapy	Both
SLCO1B1					
Atorvastatin[d]	PF	3758 (1.0)	46 289 (2.0)	Guard maximum daily dose	CPIC[g]
	DF	36 247 (9.8)	446 502 (19.0)	Guard maximum daily dose	CPIC[g]
	PDF	15 (<0.1)	186 (<0.1)	Guard maximum daily dose	CPIC
Fluvastatin	PF	4 (<0.1)	128 (<0.1)	Guard maximum daily dose	CPIC[g]
Rosuvastatin[e]	PF	1765 (0.5)	22 075 (0.9)	Guard maximum daily dose	CPIC
Simvastatin[f]	PF	414 (0.1)	6904 (0.3)	Switch to alternative drug at the start of therapy	Both
	DF	3995 (1.1)	66 592 (2.8)	Switch to alternative drug at the start of therapy	Both
	PDF	1 (<0.1)	28 (<0.1)	Switch to alternative drug at the start of therapy	CPIC
TPMT					
Azathioprine	IM	283 (0.1)	4142 (0.2)	Lower dose required at the start of therapy	Both
	PM	8 (<0.1)	115 (<0.1)	Switch to alternative drug at the start of therapy	Both
Mercaptopurine	IM	55 (<0.1)	521 (<0.1)	Lower dose required at the start of therapy	Both
	PM	2 (<0.1)	14 (<0.1)	Switch to alternative drug at the start of therapy	Both
VKORC1					
Warfarin	HS (1173TT/ −1639AA)	1429 (0.4)	26 486 (1.1)	Lower dose required at the start of therapy	DPWG[g]
Total actionable DGIs		369 700	2 349 055		

Abbreviations: AS, activity score; CPIC, Clinical Pharmacogenetics Implementation Consortium; DF, decreased function; DPWG, Dutch Pharmacogenetic Working Group; DGI, drug-gene interaction; HS, high sensitivity; IM, intermediate metaboliser; NM, normal metaboliser; NS, normal sensitivity; PDF, possibly decreased function; PF, poor function; PM, poor metaboliser; UM, ultrarapid metaboliser.

[a]Includes combination products contain codeine, excluding psychedelics.

[b]Includes tramadol and combination products containing tramadol (tramadol, tramadol and dexketoprofen, tramadol and paracetamol).

[c]Includes desogestrel and ethinylestradiol, dienogest and estradiol, drospirenone and ethinylestradiol, gestodene and ethinylestradiol, levonorgestrel and ethinylestradiol, nomegestrol and oestrogen, norelgestromin and ethinylestradiol and norgestimate and ethinylestradiol.

[d]Includes atorvastatin and combination products containing atorvastatin (atorvastatin, atorvastatin and ezetimibe, atorvastatin, acetylsalicylic acid and ramipril, atorvastatin, amlodipine and perindopril, atorvastatin and perindopril).
[e]Includes rosuvastatin and combination products containing rosuvastatin (rosuvastatin, rosuvastatin and ezetimibe).
[f]Includes simvastatin and combination products containing simvastatin (simvastatin, simvastatin and ezetimibe).
[g]Drug-gene interactions with difference in actionable recommendations between CPIC and DPWG.

TABLE 3 Distribution of first-time and total dispensings for 46 drugs listed in the CPIC and/or DPWG guidelines in the Irish GMS population in 2021 by therapeutic recommendation.

	First-time dispensings (n = 369 700;%)	Total dispensings (n = 2 349 055;%)
Direct action		
Higher dose required at the start of therapy	14 770 (4.0)	106 593 (4.5)
Lower dose required at the start of therapy	36 140 (9.8)	241 467 (10.3)
Switch to alternate drug at the start of therapy	88 259 (23.9)	623 054 (26.5)
Subtotal	139 169 (37.6)	971 114 (41.3)
Indirect action		
Guard maximum daily dose	77 246 (20.9)	807 577 (34.4)
Observe status of patient carefully	137 277 (37.1)	531 058 (22.6)
Optional lower dose required at the start of therapy	15 637 (4.2)	33 062 (1.4)
Optional switch drug at the start of therapy	371 (0.1)	6244 (0.3)
Subtotal	230 531 (62.4)	1 377 941 (58.7)
Total	369 700	2 349 055
Percentage (%) of total GMS dispensing	0.6	3.7

Abbreviations: CPIC, Clinical Pharmacogenetics Implementation Consortium DPWG, Dutch Pharmacogenetic Working Group; GMS, General Medical Services.

treatment failure.[42,43] Recent systematic reviews have demonstrated that PGx-guided antidepressant prescribing is associated with achieving rapid target response and depressive symptom remission, and is found to be cost-effective.[44–46] Recent Irish studies have reported that antidepressant use has increased over the last number of years, a trend that is expected to continue.[29,47] Targeting the use of PGx for antidepressant prescribing in primary care could therefore lead to substantial patient benefit.

Weak opioids (codeine and tramadol) were also responsible for a large volume of actionable DGIs, both to patients receiving treatment for the first time (42.7%) and for the overall prescribing (26.4%) in 2021. Genetic variations in CYP2D6 affects opioid metabolism, specifically the conversion to morphine endogenously. This may result in ineffective pain relief for poor metabolisers and increased adverse effects for ultrarapid metabolisers. Alternative drug therapy is recommended in these scenarios. Opioid analgesics, including codeine and tramadol, have been previously identified as high-risk medicines and the need to implement measures to reduce associated ADRs has been emphasised.[48,49] Importantly, codeine-containing medicines are readily available for purchase from pharmacies without a prescription in Ireland.[50] The prevalence of DGIs with codeine is therefore underestimated.

The evidence base for prescribing of statins in the prevention of major cardiovascular events and mortality is well established.[51] Our

TABLE 4 Distribution of first-time and total dispensings of 46 drugs listed in the CPIC and/or DPWG guidelines in the Irish General Medical Services population in 2021 by therapeutic class.

	Volume of first-time dispensings				Volume of total dispensings			
Therapeutic class	Potential DGIs (n = 1 878 255) n (%)	Actionable DGIs (n = 369 700) n (%)	Direct action DGIs (n = 139 169) n (%)	Indirect action DGIs (n = 230 531) n (%)	Potential DGIs (n = 12 443 637) n (%)	Actionable DGIs (n = 2 349 055) n (%)	Direct action DGIs (n = 971 114) n (%)	Indirect action' DGIs (n = 1 377 941) n (%)
Alimentary tract and metabolism								
Proton pump inhibitors	324 639 (17.3)	14 634 (4.0)	14 634 (10.5)	0 (0.0)	2 350 900 (18.9)	105 973 (11.1)	105 973 (10.9)	0 (0.0)
Anti-emetics	17 777 (0.9)	558 (0.2)	558 (0.4)	0 (0.0)	28 439 (0.2)	893 (0.0)	893 (0.1)	0 (0.0)
Blood and blood-forming organs								
Anti-thrombotics	46 879 (2.5)	11 932 (3.2)	11 932 (8.6)	0 (0.0)	428 052 (3.4)	95 022 (4.0)	95 022 (9.8)	0
Cardiovascular system								
Anti-arrhythmics	3018 (0.2)	1390 (0.4)	1314 (0.9)	76 (0.0)	31 290 (0.3)	14 408 (0.6)	13 559 (1.4)	849 (0.1)
Beta-blockers	5833 (0.3)	2686 (0.7)	0 (0.0)	2686 (1.2)	66 372 (0.5)	30 562 (1.3)	0 (0.0)	30 562 (2.3)
Statins	269 276 (14.3)	46 200 (12.5)	4411 (3.2)	41 789 (18.1)	3 417 059 (27.5)	588 702 (25.1)	73 523 (7.6)	492 976 (36.4)
Genito urinary system and sex hormones								
Hormonal contraceptives	94 594 (5.0)	2403 (0.6)	2403 (1.7)	0 (0.0)	405 301 (3.3)	10 295 (0.4)	10 295 (1.1)	0 (0.0)
Anti-infectives for systemic use								
Antibacterials	132 531 (7.1)	9012 (2.4)	0 (0.0)	9012 (3.9)	174 401 (1.4)	11 859 (0.5)	0 (0.0)	11 859 (0.9)
Antineoplastic and immunomodulating agents								
Antineoplastic agents	566 (0.0)	57 (0.0)	57 (0.0)	0 (0.0)	5329 (0.0)	536 (0.0)	536 (0.1)	0 (0.0)
Endocrine therapy	4192 (0.2)	1799 (0.5)	1799 (1.3)	0 (0.0)	39 500 (0.3)	16 948 (0.7)	16 948 (1.7)	0 (0.0)
Immunosuppressants	2891 (0.2)	291 (0.1)	291 (0.2)	0 (0.0)	42 331 (0.3)	4257 (0.2)	4257 (0.4)	0 (0.0)
Musculo-skeletal system								
NSAIDs	116 649 (6.2)	18 547 (5.0)	3095 (2.2)	15 452 (6.7)	228 182 (1.8)	36 280 (1.5)	6690 (0.7)	29 590 (2.2)
Anti-gout preparations	28 122 (1.5)	225 (0.1)	225 (0.2)	0 (0.0)	317 523 (2.6)	2540 (0.1)	2540 (0.3)	0 (0.0)
Nervous system								
Weak opioids	342 748 (18.2)	157 823 (42.7)	32 565(23.4)	125 258 (54.3)	1 342 941 (10.8)	618 375 (26.3)	127 595 (13.1)	490 780 (36.2)
Antiepileptics	19 083 (1.0)	520 (0.1)	311 (0.2)	209 (0.1)	240 674 (1.9)	9856 (0.4)	5464 (0.6)	4393 (0.3)
Antipsychotics	113 845 (6.1)	3263 (0.9)	2489 (1.8)	774 (0.3)	710 326 (5.7)	24 629 (1.0)	18 906 (1.9)	5723 (0.4)
Antidepressants	353 830 (18.8)	97 542 (26.4)	63 086 (45.3)	34 456 (14.9)	2 606 821 (20.9)	774 145 (33.0)	488 914 (50.3)	285 231 (21.0)
Psychostimulants	1782 (0.1)	821 (0.2)	0 (0.0)	821 (0.4)	8196 (0.1)	3774 (0.2)	0 (0.0)	3774 (0.3)

Abbreviations: CPIC, Clinical Pharmacogenetics Implementation Consortium DPWG, Dutch Pharmacogenetic Working Group; NSAIDs, non-steroidal anti-inflammatory drugs.

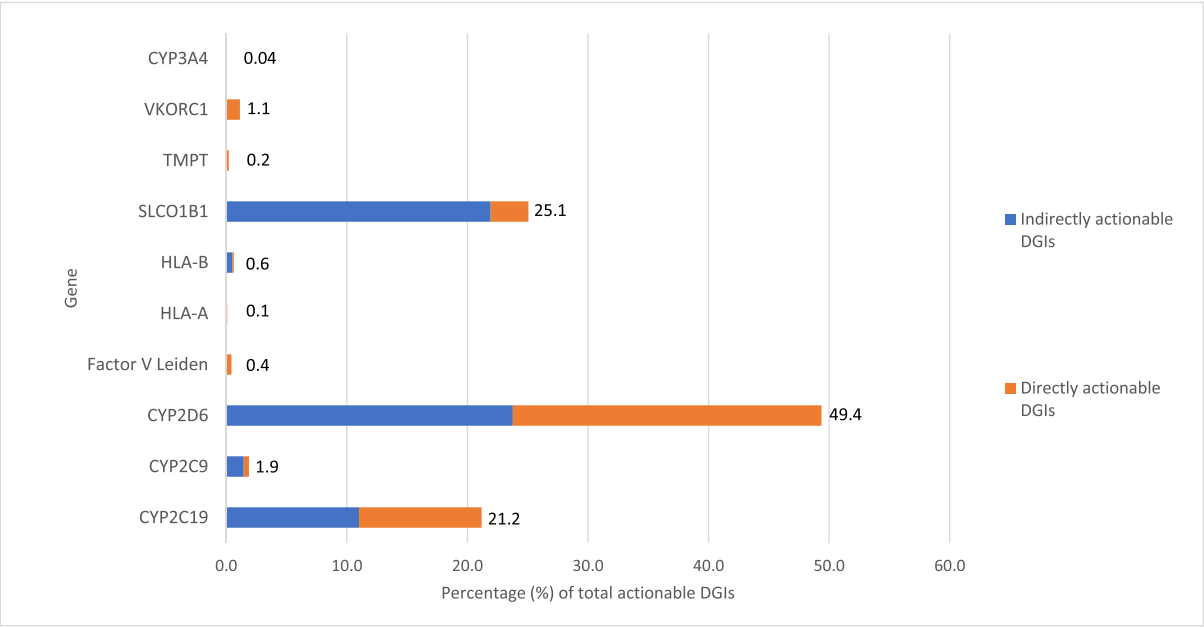

FIGURE 2 Proportion of actionability per gene. DGI, drug-gene interaction.

study demonstrates that 12.5% of first-time dispensing of medicines with actionable DGIs was for statins and 25.1% of all medicines with DGIs dispensed in 2021 were statins. Genetic variations in SLCO1B1 result in reduced transport of statins to the liver, increasing the plasma concentration of drug and thus the risk of side effects. For patients with "poor function" phenotype of SLC01B1, it is recommended to guard the maximum dose of atorvastatin, fluvastatin and rosuvastatin, and in the presence of additional risk factors of statin-induced myopathy, atorvastatin should be switched to an alternative drug immediately. Whilst not represented in this study due to the absence of concurrent phenotypic frequency data, a reduction in the starting dose of rosuvastatin is recommended for patients with concurrent "poor function" phenotypes of ABCG2 and SLCO1B1.[52] For patients prescribed simvastatin an immediate switch to an alternative drug is recommended regardless of risk factors or concurrent genetic variations The high rates of DGIs amongst statin users in Ireland highlights the need for personalizing and optimizing statin therapy to prevent side-effect and related poor adherence and treatment discontinuation.

The co-prescribing of medicines with DGIs at a patient level was not investigated as this is beyond the scope of the database used. Studies undertaken in Ireland and the UK have estimated that 20-30% of patients aged 65 years or older are dispensed five or more medications.[53,54] It is therefore probable that individual patients have ≥1 DGI, as many of the medicines with DGIs are commonly co-prescribed to patients with multimorbidity in primary care. Depression, for example, is commonly associated with an increased occurrence of cardiovascular and respiratory disease.[55] Integration of PGx into holistic, person-centred medication review may therefore confer significant benefit to individual patients. However, several barriers to the implementation of PGx testing, such as clinician knowledge, access to PGx tests, reimbursement, and storage and usage of PGx data within health records have been noted, which should be carefully considered and addressed prior to integration of PGx within healthcare systems.[4]

4.1 | Comparison with other studies

The findings of this study are supported by similar studies that have been conducted in the Netherlands and the UK. In the Netherlands, Bank and colleagues estimated that 23.6% of first-time dispensings of 45 drugs listed in DPWG guidelines had actionable DGIs, with 5.4% requiring a change to drug regimen or dose.[14] Youssef and colleagues' study in the UK estimated that 19.1-21.1% of first-time dispensings of 56 drugs listed in CPIC and/or DPWG guidelines had actionable DGIs, with actions required for 8.6-9.1% of first time dispensings.[15] The difference in the number of included drugs reflects the authorisation and availability of medicines in the respective countries.

Our analysis showed similar values for the frequency of actionable DGIs (19.7%) and directly actionable DGIs (7.4%) to these. The higher frequency of directly actionable DGIs observed in the UK study, compared to the Dutch study, is most possibly due to the inclusion of both CPIC and DPWG recommendations in the UK and Irish studies.

Our findings regarding gene actionability were generally consistent with the findings of previous studies. A study that explored the exposure of patients to 63 drugs in English primary care over 25 years showed that three genes (CYP2C19, CYP2D6 and SLCO1B1) accounted for >95% of commonly dispensed drugs with potential DGIs.[56] Youssef and colleagues found that the same three genes accounted for 94.6% of dispensings of drugs with directly actionable

TABLE 5 Ranking of the top 10 drugs with the largest volume of dispensings with actionable DGIs for first-time and total dispensings in the Irish General Medical Services population in 2021.

	Volume of first-time dispensings					Volume of total dispensings			
	Potential DGIs (n = 1 878 255)	Actionable DGIs (n = 369 700)	Direct action DGIs (n = 139 169)	Indirect action DGIs (n = 230 531)		Potential DGIs (n = 12 443 637)	Actionable DGIs (n = 2 349 055)	Direct action DGIs (n = 971 114)	Indirect action DGIs (n = 1 377 941)
Drug name	n (%)	n (%)	n (%)	n (%)	Drug name	n (%)	n (%)	n (%)	n (%)
Codeine[a]	234 201 (12.5)	107 841 (29.2)	22 252 (16.0)	85 589 (37.1)	Atorvastatin[c]	2 097 904 (16.9)	492 976 (21.0)	0 (0.0)	492 976 (35.8)
Tramadol[b]	108 547 (5.8)	49 982 (13.5)	10 313 (7.4)	39 669 (17.2)	Codeine[a]	931 680 (7.5)	429 004 (18.3)	88 520 (9.1)	340 484 (24.7)
Atorvastatin[c]	170 307 (9.1)	40 020 (10.8)	0 (0.0)	40 020 (17.4)	Venlafaxine	541 553 (4.4)	249 365 (10.6)	232 360 (23.9)	17 005 (1.2)
Amitriptyline	66 331 (3.5)	30 543 (8.3)	30 543 (21.9)	0 (0.0)	Escitalopram	693 047 (5.6)	229 527 (9.8)	48 031 (4.9)	181 496 (13.2)
Escitalopram	92 013 (4.9)	30 473 (8.2)	6377 (4.6)	24 096 (10.5)	Tramadol[b]	411 261 (3.3)	189 371 (8.1)	39 075 (4.0)	150 296 (10.9)
Venlafaxine	53 953 (2.9)	24 843 (6.7)	23 149 (16.6)	1694 (0.7)	Amitriptyline	390 525 (3.1)	179 822 (7.7)	179 822 (18.5)	0 (0.0)
Ibuprofen	99 983 (5.3)	15 897 (4.3)	2199 (1.6)	13 698 (5.9)	Citalopram	235 889 (1.9)	78 123 (3.3)	16 348 (1.7)	61 775 (4.5)
Clopidogrel	36 709 (2.0)	10 503 (2.8)	10 503 (7.5)	0 (0.0)	Simvastatin[d]	312 885 (2.5)	73 523 (3.1)	73 523 (7.6)	0 (0.0)
Flucloxacillin	132 531 (7.1)	9012 (2.4)	0 (0.0)	9012 (3.9)	Clopidogrel	239 544 (1.9)	68 536 (2.9)	68 536 (7.1)	0 (0.0)
Citalopram	20 612 (1.1)	6826 (1.8)	1428 (1.0)	5398 (2.3)	Pantoprazole	137 542 (1.1)	40 345 (1.7)	40 345 (4.2)	0 (0.0)

Abbreviation: DGI, drug-gene interaction.

[a]Includes combination products contain codeine, excluding psychedelics.

[b]Includes tramadol and combination products containing tramadol (tramadol, tramadol and dexketoprofen, tramadol and paracetamol).

[c]Includes atorvastatin and combination products containing atorvastatin (atorvastatin and ezetimibe, atorvastatin, acetylsalicylic acid and ramipril, atorvastatin, amlodipine and perindopril, atorvastatin and perindopril).

[d]Includes simvastatin and combination products containing simvastatin (simvastatin and ezetimibe).

TABLE 6 Discrepancies between CPIC and DPWG therapeutic recommendations for 46 drugs listed in the CPIC and/or DPWG guidelines and classification of evidence.

Drug	Gene	Phenotype	CPIC recommendation	Actionability	CPIC classification of evidence	DPWG recommendation	Actionability	DPWG classification of evidence
Atorvastatin[a]	SLCO1B1	PF	Guard maximum daily dose[b]	Indirect action	M	Observe status of patient carefully	Indirect action	3A
Atorvastatin[a]	SLCO1B1	DF	Guard maximum daily dose[b]	Indirect action	M	Observe status of patient carefully	Indirect action	3A
Citalopram	CYP2C19	IM	No action	No action	S	Guard maximum daily dose[b]	Indirect action	4A
Citalopram	CYP2C19	PM	Lower dose required at the start of therapy[b]	Direct action	M	Guard maximum daily dose	Indirect action	4A
Citalopram	CYP2C19	UM	Switch to alternativee drug at the start of therapy[b]	Direct action	M	No action	No action	3AA
Clomipramine	CYP2D6	IM	Optional lower dose at the start of therapy	Indirect action	O	Lower dose at the start of therapy[b]	Direct action	4C
Clomipramine	CYP2D6	PM	Optional switch to alternativee drug at the start of therapy or lower dose at the start of therapy	Indirect action	O	Lower dose at the start of therapy[b]	Direct action	4C
Clomipramine	CYP2D6	UM	Optional switch to alternativee drug at the start of therapy or higher dose at the start of therapy	Indirect action	O	Higher dose at the start of therapy[b]	Direct action	2C
Doxepin	CYP2D6	IM	Optional lower dose at the start of therapy	Indirect action	O	Lower dose at the start of therapy[b]	Direct action	3A
Doxepin	CYP2D6	PM	Optional switch to alternate drug at the start of therapy or lower dose at the start of therapy	Indirect action	O	Lower dose at the start of therapy[b]	Direct action	3F
Doxepin	CYP2D6	UM	Optional switch to alternative drug at the start of therapy or higher dose at the start of therapy	Indirect action	O	Higher dose at the start of therapy[b]	Direct action	3A
Escitalopram	CYP2C19	IM	No action	No action	S	Guard maximum daily dose[b]	Indirect action	4A
Escitalopram	CYP2C19	PM	Lower dose required at the start of therapy[b]	Direct action	M	Guard maximum daily dose	Indirect action	4A
Fluvastatin	SLCO1B1	PF	Guard maximum daily dose[b]	Indirect action	M	No action	No action	3AA
Fluvoxamine	CYP2D6	PM	Optional lower dose at the start of therapy[b]	Indirect action	O	No action	No action	3AA
Imipramine	CYP2D6	IM	Optional decrease dose	Indirect action	O	Lower dose at the start of therapy[b]	Direct action	4A
Imipramine	CYP2D6	PM	Optional switch at the start of therapy or optional lower dose at the start of therapy	Indirect action	O	Lower dose at the start of therapy*	Direct action	4C
Imipramine	CYP2D6	UM	Optional switch at the start of therapy or optional higher dose at the start of therapy	Indirect action	O	Higher dose at the start of therapy[b]	Direct action	4A

(Continues)

TABLE 6 (Continued)

Drug	Gene	Phenotype	CPIC recommendation	Actionability	CPIC classification of evidence	DPWG recommendation	Actionability	DPWG classification of evidence
Paroxetine	CYP2D6	PM	Optional switch to alternative drug at the start of therapy[b]	Indirect action	O	No action	No action	4A
Sertraline	CYP2C19	PM	Optional decrease dose	Indirect action	O	Guard maximum daily dose[b]	Indirect action	3C
Tramadol	CYP2D6	PM	Switch to alternative drug at the start of therapy[b]	Direct action	S	Observe status of patient carefully	Indirect action	4A
Warfarin	VKORC1	HS	Calculate dose based on validated published pharmacogenetic algorithm	Direct action	S	Lower dose required at the start of therapy	Direct action	4A

Abbreviations: A, minor clinical effect; AA, no statistically significant clinical or kinetic effect; AS, activity score; C, Clinical effect (S): long-standing discomfort (48-168 h) without permanent injury; CPIC, Clinical Pharmacogenetics Implementation Consortium; DF, decreased function; DPWG, Dutch Pharmacogenetic Working Group; F, death, arrhythmia, unexpected myelosuppression; HS, high sensitivity; IM, intermediate metaboliser, M, moderate; NM, normal metaboliser; O, optional; PF, poor function; PM, poor metaboliser; S, strong; UM, ultrarapid metaboliser; 2, well documented case reports with relevant pharmacokinetic or clinical end points/well documented case series; 3, published controlled studies of moderate quality; 4, published controlled studies of good quality.

[a]Includes atorvastatin and combination products containing atorvastatin (atorvastatin and ezetimibe, atorvastatin, acetylsalicylic acid and ramipril, atorvastatin, amlodipine and perindopril, atorvastatin and perindopril).

[b]Therapeutic recommendation selected for each DGI.

DGIs.[15] Our analysis showed that these three genes accounted for 95.7% of all dispensings with actionable DGIs, therefore including CYP2D6, CYP2C19 and SLCO1B1 in a panel approach to PGx testing provides the most potential to optimize medicines dispensed in primary care.

4.2 | Discrepancies between CPIC and DPWG guidelines

Whilst there is general consensus between CPIC and DPWG guidelines, some subtle differences in the phrasing of therapeutics recommendations following identification of a DGI exist.[57] For example, poor metabolisers of CYP2D6 prescribed escitalopram should have a lower dose at the start of therapy according to CPIC (a direct action) whereas if following the DPWG's guidelines, the maximum daily dose for the same patient would be guarded (indirect action). For poor metabolisers of CYP2D6 prescribed tramadol, an alternative drug would be prescribed if following CPIC recommendations (a direct action) or if following the DPGW's recommendations the patient would be observed carefully (indirect action). The clinical significance of these differences is not clear. One could argue that if a patient is being observed carefully, subsequent changes would be made to drugs with DGIs as appropriate. However, if PGx is to be embedded in routine clinical practice, harmonisation of recommendations from both CPIC and DPWG should be undertaken.

5 | STRENGTHS AND LIMITATIONS

This is the first study to quantitatively estimate the occurrence of DGIs in primary care in Ireland and provides details of key therapeutic areas to target to address DGIs. It also provided evidence to support the adoption of pre-emptive PGx testing and highlights the need for PGx testing for patients already prescribed therapy.

A strength of this study is the consideration of the evidence-based guidelines published by both the CPIC and DPWG. This added strength to recommendations where there was consistency between guidelines and facilitated documentation of discrepancies. This approach enabled us to provide a broad overview of the outcomes of PGx testing based on independent evaluations of the evidence base. Additionally, only DGIs with evidence deemed sufficient by CPIC and/or DPWG to make a therapeutic recommendation were included in this study.

Whilst estimates for phenotypic frequencies were used, they were based on robust data from the UK biobank and some CPIC guidelines. The UK Biobank, which includes a sample size of European participants (n = 45 322) and used principal component analysis alongside self-reporting to categorise ethnicity, was used to estimate phenotypic frequencies. The frequencies for all phenotypes were comparable to those published in the PREPARE study.[16]

This study had some limitations. Only drugs that are generally prescribed in Irish primary care were included in this study. This may

have resulted in an underestimation of the volume of dispensings with actionable DGIs, as drugs with potential DGIs that are dispensed in Irish primary care but initiated in secondary care, such as tacrolimus, were excluded. The inclusion of the most actionable recommendation in the case of discrepancies between consortia may result in overestimation of the volume of dispensings with actionable DGIs.

This study only includes data on drugs dispensed for the GMS population, as data from other national prescribing schemes were unavailable. The The GMS scheme tends to represent a more socially deprived population, with over-representation of older adults who are more likely to be prescribed more medicines than non-GMS patients.[23] This representation may limit the generalisability of the study findings. The data we had access to was limited and we were unable to examine the demographics of the population. Whilst the phenotypic frequencies were obtained from the European cohort within the UK biobank, it would have been preferrable to have had data from Irish participants.

We did not investigate the doses of drugs prescribed, the co-prescribing of more than one drug with DGIs or the co-prescribing of drugs with DGIs and CYP inhibitors at the patient level. For example, patients with a SLCO1B1 poor function or decreased function phenotype that are co-prescribed a CYP3A4 inhibitor with atorvastatin are advised to switch to rosuvastatin or pravastatin. Investigating co-prescribing was beyond the scope of the dataset. With regards to co-prescribing of drugs with DGIs and CYP inducers, neither CPIC nor DPWG guidelines include recommendations for dose or drug adjustments for a drug with a DGI co-prescribed with a CYP inducer.

Contrastingly, the volume of directly actionable DGIs involving atorvastatin may be underestimated as we did not have access to data on co-prescription of a CYP3A4 inhibitor. Furthermore, for nine drugs (amitriptyline, carbamazepine, clomipramine, doxepin, imipramine, phenytoin, rosuvastatin, trimipramine and warfarin), additional DGIs were excluded due to the absence of frequency data for multiple concurrent phenotypes. Thus, the volume of actionable DGIs for this selection of drugs may be underestimated.

The likelihood of patients experiencing an adverse effect from a DGI depends on the drug in question and also the time period over which the patient has been taking the drug. It is possible that patients receiving a DGI over a long period of time are tolerant of its effects and less likely to experience an adverse effect, therefore the actionability of DGIs may be overestimated for patients receiving DGIs long term.

6 | CONCLUSION

This study estimates that there is a high prevalence of actionable DGIs prescribed to the GMS population in Irish primary care. Three genes account for the majority of DGIs with actionable therapeutic recommendations. This study identifies therapeutic areas of primary care prescribing that could be targeted to prevent adverse drug reactions and therapeutic failures resulting from DGIs and demonstrates a potential role for pre-emptive testing and testing of patients already prescribed routine medicines. It highlights the need and potential opportunity that PGx could provide in optimizing drug therapy. Future research should investigate DGIs at an individual patient level as well as patient clinical outcomes following implementation of pharmacogenetic testing to evaluate its clinical utility and impact on patient care.

AUTHOR CONTRIBUTIONS

L. Johnson: Analysis; writing—original draft preparation; writing—review and editing. **E. Youssef**: Methodology; analysis; writing—review and editing. **J. O'Shea**: Methodology; analysis; writing—review and editing. **T. Thornley**: Methodology; writing—review and editing. **J. Gallagher**: Conceptualization; writing—review and editing. **M. Ledwidge**: Conceptualization; methodology; analysis; writing—review and editing. **C. Ryan**: Conceptualization; methodology; analysis; writing—original draft preparation; writing—review and editing; supervision.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The study is based on data from national prescribing databases which are available to request from the HSE-PCRS. Anonymised genetic data sourced from the UK Biobank were obtained from the appendix of the paper authored by G. McInnes et al, Pharmacogenetics at scale: an analysis of the UK Biobank.[10] Anonymised genetic data sourced from CPIC frequency tables are freely available online via the CPIC website.

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SUPPORTING INFORMATION

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

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