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ARTICLE

Primary Care Prescription Drug Use and Related Actionable Drug-Gene Interactions in the Danish Population

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Pharmacogenetics (PGx) aims to improve drug therapy using the individual patients' genetic make-up. Little is known about the potential impact of PGx on the population level, possibly hindering implementation of PGx in clinical care. Therefore, we investigated how many patients use actionable PGx drugs, have actionable genotypes or phenotypes and which patients could benefit the most of PGx testing. We included PGx recommendations from two international PGx consortia (Clinical Pharmacogenetics Implementation Consortium (CPIC) and Dutch Pharmacogenetics Working Group (DPWG)). Using data from publically accessible sales information drawn from the Danish Register of Medicinal Product Statistics (MEDSTAT), we identified the number of users of actionable prescription PGx drugs among the total Danish population in 2017. We estimated actionable genotypes or phenotypes based on reported frequencies from literature. We identified 49 drug-gene interactions related to 41 unique prescription drugs. The estimated median frequency of actionable genotypes or phenotypes among prescription drug users was 25% (interquartile range 7–26%). Six of 41 drugs were used more than twice as much in women. Actionable PGx drugs were most frequently used by 45–79 year old patients (62%), followed by 25–44 year old patients (18%). Almost half of the actionable PGx drugs (19/41) were psychotropics (i.e., antidepressants, antipsychotics, or psychostimulants). PGx testing can have a substantial impact on the population, as one in four prescription drug users has an actionable genotype or phenotype and could thus benefit from PGx testing. We advocate for prospective panel-based PGx testing at the time of the first PGx drug prescription ("as needed"), with PGx results ready prior to start of the first, and all future, therapies.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Little is known about the potential impact of pharmacogenetics (PGx) among outpatient prescription drug users. Two prior publications have investigated PGx on large scale levels, but could not include data of a whole population.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ What is the number of patients who use actionable PGx prescription drugs, how many of them have actionable genotypes or phenotypes, and who could benefit most of PGx testing?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ The study provides a real-world estimation of the number of people using prescription PGx drugs in the Danish population.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ This study will help understand the clinical impact of PGx on the population level, which benefits implementation of PGx in clinical care and improves current drug therapy.

Many commonly used drugs are affected by variability in drug metabolism and response, potentially contributing to treatment failure and increasing the risk of adverse events. Examples are antidepressants, proton-pump inhibitors, statins, and anticoagulants.[1–5] Many drugs are metabolized by cytochrome P450 enzymes, such as CYP2D6 and CYP2C19, which have great variability in activity.[6,7] Pharmacogenetics or pharmacogenomics (PGx) comprise the study of genetic variation leading to changes in, for example, enzymes, transporters, or receptors, potentially resulting in different drug responses. One of the aims of practicing PGx is to utilize genetic information to predict treatment response in the individual patient, thereby improving drug effectiveness and reducing the risk of adverse events. The generalized terms gene-drug interaction or drug-gene interaction (DGI) are used to describe the interaction between specific genes with specific drugs. Genes technically do not interact with drugs directly, but they are, for example, encoded to proteins, which, in turn, influence drug metabolism. Most of PGx research and guidelines

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comprise pharmacokinetics (PK; e.g., an altered drug metabolism). Yet, pharmacodynamics (PD; e.g., altered drug targets or receptors), are also studied in PGx.[8] As many of the gene-affected drugs are frequently used, PGx testing improving the treatment outcomes of the individual can have a major impact on the healthcare system at population level, with a potential to reduce costs caused by insufficient treatment response and adverse events. This ultimately improves patients' quality of life.

Literature on PGx has increased exponentially over the last 2 decades, with currently over 29,000 publications on PGx published, yet little is known about the current implementation of PGx on the population level and the potential impact of PGx (e.g., improved health care or reduced costs).[9–11]

Moreover, it is known that not all genetic variations will have clinical impact and thereby not all DGIs are actionable. Evidence for clinical benefit of a dose adjustment differs per DGI and has been derived from studies, ranging from prospective clinical data to *ex vivo* data. "Actionable PGx" refers to drugs or specific genotypes or phenotypes for which dosing recommendations in PGx guidelines are available. For nonactionable DGIs, dose adjustments are not expected to improve treatment response. Guidelines for dose adjustments are made available by international consortia (e.g., the Clinical Pharmacogenetics Implementation Consortium (CPIC) and Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Pharmacist's Association). These guidelines are built by systematic and peer-review of the available literature.[12–14] Previously, the DPWG and CPIC have each provided, largely overlapping, guidelines for 54 and 40 actionable DGIs, respectively.[12–15] Despite these guidelines, clinical implementation has not been optimized yet. Several barriers to the implementation of PGx testing have been identified, such as limited data on clinical validity and utility, limited data on (cost-) effectiveness or a low positive predictive value of the test.[16] In addition, the availability of non-PGx tests, such as therapeutic drug monitoring,[17] could be argued as an alternative and competing option for dose adjustments. Yet, the power of PGx lies in the prospective identification of patients at risk (i.e., prior to start of therapy), instead of a reactive way to identify genetic variants in patients who already were exposed to the risk of decreased drug effectiveness or increased toxicity. Pre-emptive PGx testing means to have PGx results ready at the point of prescribing a drug, whereas the term reactive testing is used to describe testing in anticipation of drug prescriptions ("as needed") or in response to unexplained adverse effects.[18–21]

Based on the limited available information within the field to date, it is still largely unknown what the impact of PGx could be on the population level. Therefore, we aimed to visualize the possible impact of PGx by answering how many patients use actionable PGx drugs, what is the estimated proportion of people with actionable genotypes or phenotypes, and who could benefit the most in terms of indications of use or sociodemographic characteristics with regard to potential sex and age differences. The latter may add information if PGx testing could best be applied at a specific age.

METHODS

Study population

We identified all users of actionable PGx prescription drugs among the total Danish population of 5,748,769 inhabitants in 2017.

Data sources

In this study, "actionable" PGx drugs refer to drugs or specific genotypes or phenotypes for which dosing recommendations according to CPIC or DPWG PGx guidelines are available, and, thus, imply a clinically relevant change from standard practice. Data of actionable PGx drugs were extracted from MEDSTAT (www.medstat.dk). MEDSTAT is a publicly accessible web-service based on data of the Register Medicinal Products Statistics. It was established in 1994 and includes information on redeemed prescription drugs at pharmacies, as well as aggregated data on drug sales to all hospitals in Denmark.[22–24] Because all data are aggregated, single person identification is not possible and no informed consent or ethical approval is required. The data can be searched by levels of the anatomic therapeutic chemical classification system or product names for each drug.[25] Aggregated (outcome) measures of drug consumption can be chosen as turnover, paid reimbursement, volume sold (per 1,000 inhabitants per day), and number of users (per 1,000 inhabitants). Due to the setup of the data, it is not possible to identify new users (incidence). Moreover, it is possible to stratify include or exclude these measures according to calendar year, sex, age groups, geographic regions of Denmark, and primary or hospital sector. For hospital sector data only turnover and volume sold were available, not linked to sex or age. We extracted number of users of actionable PGx drugs in the primary sector (as defined below) for the whole population of Denmark and stratified by sex and age groups 0–17, 18–24, 25–44, 45–64, 65–79, and 80 years or older. Users are defined as anyone having redeemed at least one prescription for the drugs of interest in 2017.

Actionable drug-gene interactions

The DGIs or drugs investigated in this study were searched using the PharmGKB website, where, among others, CPIC and DPWG recommendations are listed.[26,27] The PharmGKB website lists "clinical guideline annotations," which contain dosing guidelines, "drug label annotations," containing PGx information approved by organizations such as the US Food and Drug Administration (FDA), and "clinical or variant annotations," which summarize supportive evidence for DGIs. In this study, we only focused on clinical guideline annotations. Additionally, the original CPIC and DPWG guidelines were checked to assure correct and complete guidelines.[28,29] We identified 134 unique possible DGIs of 99 unique drugs. After exclusion of "no DGI" and "not actionable interaction," 87 actionable DGIs (68 unique drugs) remained and were searched in MEDSTAT. An overview of the drugs and genes from these actionable DGIs, together with relevant drug and disease clusters, is shown in **Figure 1**. There was no information on 27 of 68 searched drugs in MEDSTAT. Therefore, a

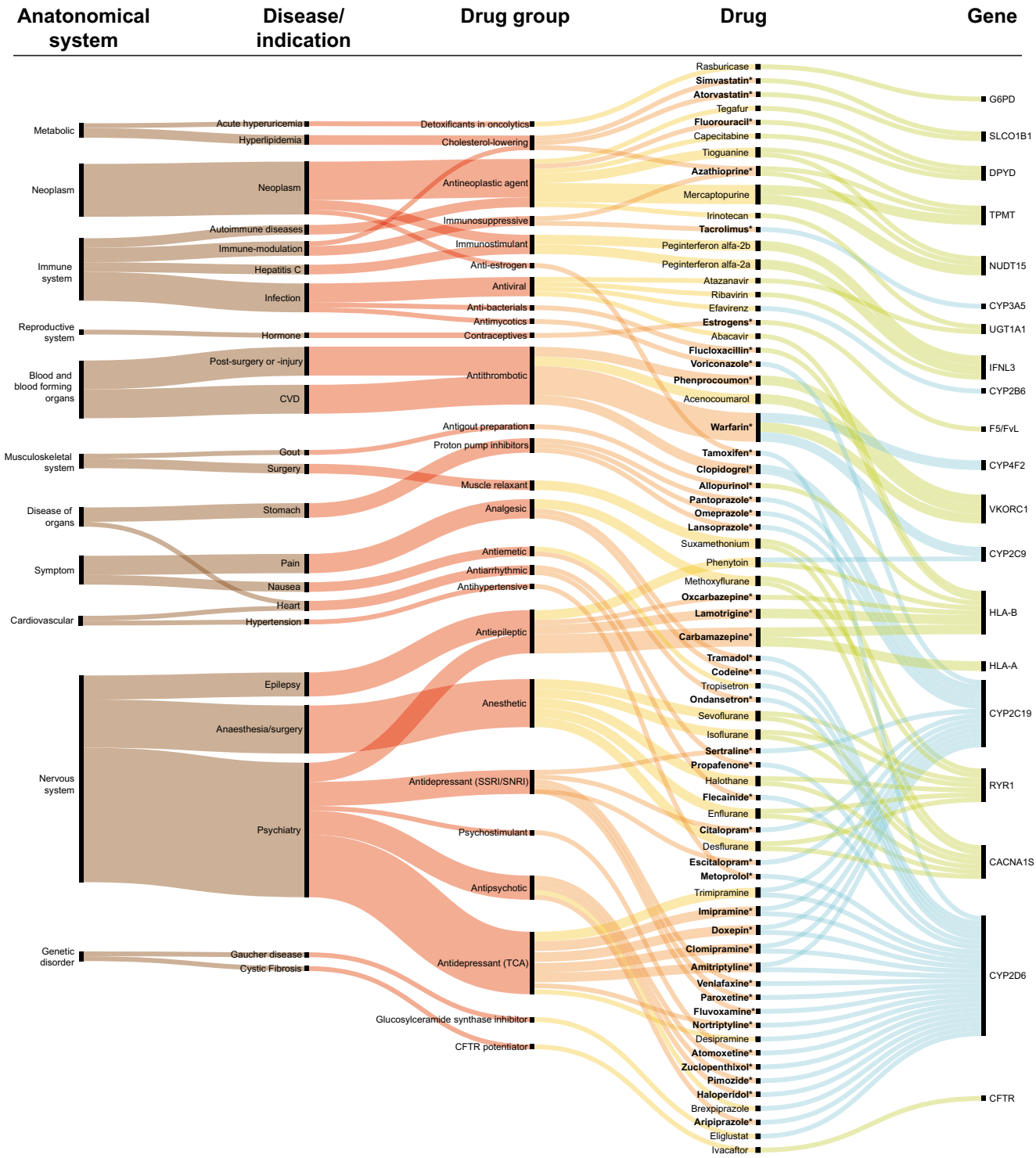

Figure 1 Overview of actionable drug-gene interactions (DGIs). Shown is a representation of all 87 actionable DGIs in pharmacogenetics (PGx; 68 unique drugs), including disease area and associated genes. In total, 49 actionable DGIs (41 unique drugs) were included in the actionable PGx drug list in this study. These drugs are shown in bold and marked with an * in the fourth text column (Drug). In addition, these drugs are color-coded in orange instead of yellow in the third colored waves column (between Drug group and Drug). All CYP genes are colored blue, and non-CYP genes are green with the intention to improve readability of the figure. The figure has no scale. CVD, cardiovascular disease.

total of 49 DGIs (41 drugs) were included in this study. An overview of the included and excluded DGIs is shown in **Figure 2**.

Defined genotype-phenotype frequencies

Genetic variation in PK-related PGx guidelines is often translated into a phenotype prediction (e.g., poor or extensive

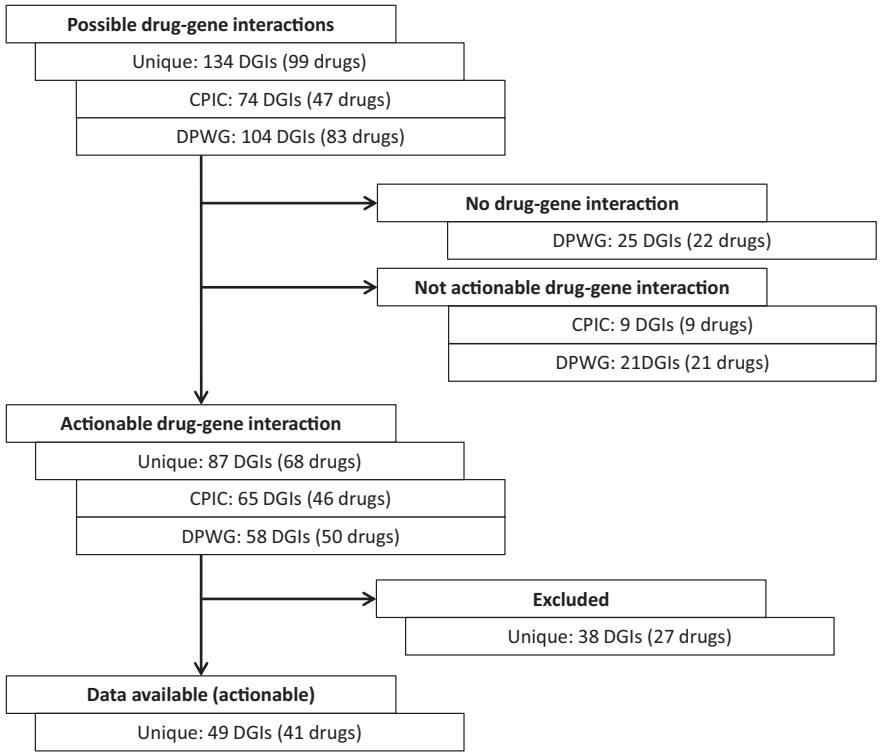

Figure 2 Drug-gene interactions (DGIs) in the study. Flowchart of DGIs and drugs identified using Clinical Pharmacogenetics Implementation Consortium (CPIC) and Dutch Pharmacogenetics Working Group (DPWG) guidelines. Some drugs were excluded because there was no information in MEDSTAT for these drugs, possibly due to no market authorization in Denmark, no sale, no data, or no calculation available. The figure was build using CPIC and DPWG guidelines and data from MEDSTAT.[12–14,24,29]

metabolizer) or into a gene activity score. These phenotype predictions are used to "quantify" any genetic variation, which includes, for example, single nucleotide polymorphisms or copy number variations. Frequencies of poor metabolizers, intermediate metabolizers, extensive metabolizers, and (ultra)rapid metabolizers (UM) of the enzymes included in this study were estimated using previously published studies.[9,10,29–33] SLCO1B1 phenotypes were described as poor, intermediate, or normal transporter activity, VKORC1 phenotypes as either high or normal sensitivity, HLA phenotypes as carrier or noncarriers per associated variant, and CYP3A5 phenotypes as nonexpressers, heterozygous expressers, and homozygous expressers. For each actionable DGI, the dosing guidelines were consulted to determine which phenotypes had to be included in the calculations of actionable or nonactionable phenotypes, because actionable phenotypes can differ per actionable DGI.[28,29] Phenotypes are mutually exclusive, and the summed frequencies of actionable phenotypes were used to calculate an expected number of users who require a treatment or dose adjustment. **Figure 3** and **Table S1** show which phenotypes are actionable according to DPWG or CPIC guidelines. In case of discrepancies between guidelines, we chose the most inclusive guideline, and did not prefer one consortium over the other.[15] The identified phenotypes were taken into account in the calculations for the number of drug users of actionable DGIs who would require a dose adjustment. The estimated frequencies of actionable and nonactionable phenotypes per enzyme are shown in **Table 1**. Due to the fact that the Danish population was investigated in this study with a majority of persons (92.3%) with European or Western ancestry,[34] frequencies of white patients from literature were applied in these calculations.[9,10,29–33,35]

Microsoft Excel 2010 (Redmond, WA) was used to list and calculate extracted numbers of users, frequencies, means, medians, interquartile ranges, and to create the heat-map colors. Graphics were created in Python (version 3.7.3, Python Software Foundation, Wilmington, DE) and package plotly (version 4.1.1, Python Software Foundation).

RESULTS

Actionable drug-gene interactions

All 87 identified actionable DGIs, including drug groups and indications of each drug, are presented in **Figure 1**. We identified all users of prescription drugs of 49 DGIs within the entire Danish population in 2017.[34] **Figure 4** displays for each DGI the (i) total number of drug users, (ii) total estimated number of users with an actionable genotype or phenotype, (iii) the estimated frequency of actionable genotype or phenotypes, (iv) sex ratio in favor of women, and (v) estimated number of users with an actionable genotype or phenotype per age group. Individuals can occur in more than one drug class or subcategory within drug classes. The total number of users in 2017 varied from 10 for tacrolimus to 341,395 for users of simvastatin. The median frequency of actionable genotypes or phenotypes was 25% (interquartile range 7–26%). Statins (simvastatin

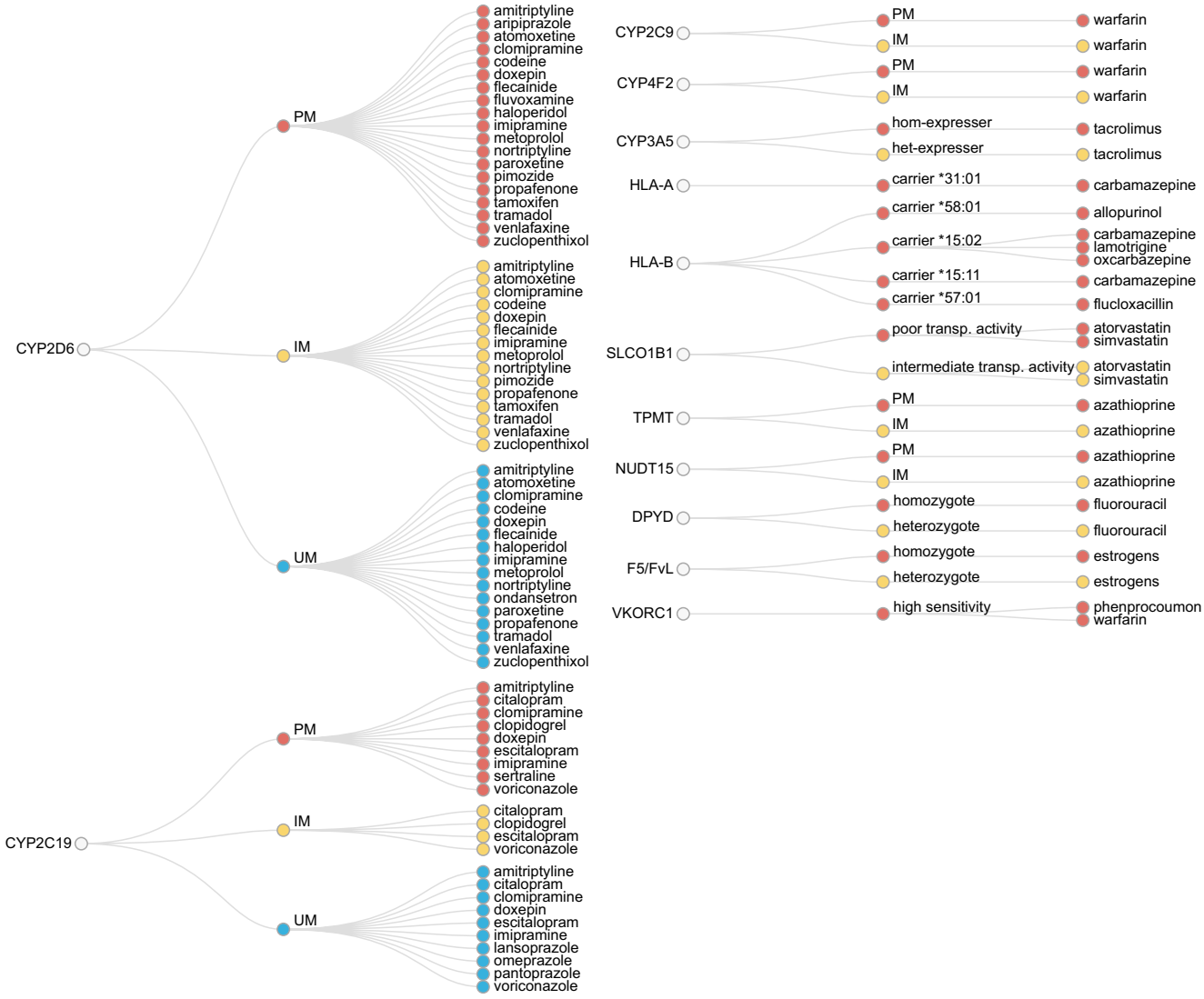

Figure 3 Actionable genotypes or phenotypes. The figure shows actionable genotypes or phenotypes (metabolizer status, transport activity, sensitivity, or genotype, expresser, or carrier status) of actionable drug-gene interactions. The figure was build using Clinical Pharmacogenetics Implementation Consortium (CPIC) and Dutch Pharmacogenetics Working Group (DPWG) guidelines.[12–14,29] Estrogens*: Contraceptives with estrogens (i.e.< progestogens and estrogens). het, heterozygous (yellow); hom, homozygous (red); IM, intermediate metabolizer (yellow); PM, poor metabolizer (red); transp., transporter (yellow); UM, (ultra)rapid metabolizers (blue).

(124,182) and atorvastatin (95,912)), metoprolol (73,531), tramadol (69,835), and pantoprazole (69,657) had the most estimated users with an actionable genotype or phenotype. Among psychotropics, (es-)citalopram, venlafaxine, and amitriptyline had the most estimated users with an actionable genotype or phenotype, varying from 8,766 users of amitriptyline to 50,152 users of citalopram.

Sex differences in actionable drug-gene interactions

An overview of sex ratio per DGI indicating sex differences is shown in **Figure 4**. Six of 41 drugs were used more than twice as much in women. The median sex ratio in favor of women was 1.7 over 25 drugs, and in favor of men 1.2 over 16 drugs. The most used actionable PGx drugs in women were progestogens and estrogens (contraceptives) with 325,251 users in 2017, followed by the proton-pump inhibitor pantoprazole (173,245) and simvastatin (164,605). In men, the three most frequently used drugs were the cholesterol-lowering drugs simvastatin (176,800) and atorvastatin (148,900), followed by pantoprazole (138,701). More specifically, beyond the expected sex differences in users of progestogens and estrogens and the anti-estrogen tamoxifen, the anti-emetic drug ondansetron and the antidepressant doxepin were used more than twice as much in women. The antigout drug allopurinol was more frequently used in men (3.5 times).

Age differences in actionable drug-gene interactions

Actionable PGx drugs were most frequently used by 45–64 year old patients (32%) and 65–79 year old patients (30%), followed by 25–44 year old patients (18%). Actionable drugs were only used by 4, 4, and 12% of the 0–17 year old

Table 1 Estimated white population frequencies of phenotypes

Genes/enzymes	PM	IM	EM	UM	References
CYP2C9	0.0707	0.294	0.635		9,10,29
CYP2C19	0.0270	0.251	0.499	0.223	9,10,2
CYP2D6	0.0547	0.179	0.707	0.03	9,10,29
DPYD	0.0076	0.038	0.954		9,10
TPMT	0.0037	0.116	0.879		9,29
CYP4F2	0	0.299	0.711		29
NUDT15	0.000015	0.008	0.986		29
fVL/F5		0.0094	0.105	0.916	30,31,35
Genes	**Carrier**	**Noncarrier**			**References**
HLA-A*31:01	0.028	0.972			29
HLA-B*15:02	0.00036	0.9996			29
HLA-B*57:01	0.032	0.968			29
HLA-B*58:01	0.013	0.987			29
HLA-B*15:11	0.003	0.997			33
Gene	**Poor TA**	**Intermediate TA**	**Normal TA**		**References**
SLCO1B1	0.139	0.225	0.734		9,10
Genes/enzymes	**High sensitivity**	**Normal sensitivity**			**References**
VKORC1	0.159	0.835			9,10
Genes/enzymes	**Non-expresser**	**Het-expresser**	**Hom-expresser**		**References**
CYP3A5	0.720	0.269	0.071		9,10,29,32

Estimated white population frequencies of phenotypes (EM, IM, PM, UM) were searched in literature and averages are shown in the table.
EM, extensive metabolizers; het, heterozygous; hom, homozygous; IM, intermediate metabolizers; PM, poor metabolizers; TA, transporter activity; UM, (ultra) rapid metabolizers.

patients, 18–24 year old patients, and 80+ year old patients, respectively. Individual drugs though show a different age pattern. For example, atomoxetine had 90% of users younger than 45 years, with 34% of users between 0 and 17 years old. In addition, 94% of progestogens and estrogens users were younger than 45 years. On the other hand, 95% of haloperidol users were 45 years or older, with 42% of the users being 80 + year old patients, followed by 34% of users being 65–79 year old patients. The top 10 most used drugs in children (0–17 year olds) were progestogens and estrogens, omeprazole, atomoxetine, pantoprazole, sertraline, lamotrigine, flucloxacillin, tramadol, codeine, and lansoprazole, respectively.

Actionable drug-gene interactions in psychotropics

Almost half of the actionable PGx drugs (19/41) in this study were psychotropics (i.e., antidepressants, antipsychotics, or psychostimulants). Of the 19 psychotropic drugs, sertraline and citalopram had the highest number of users. Psychotropic drugs were used more often by women (factor 1.7). Only atomoxetine and pimozide were used more frequently by men, by a factor 1.4 and 1.1, respectively (**Figure 4**).

DISCUSSION

Current knowledge on PGx originates mostly from small and selected patient cohorts, and little is known about the potential impact of PGx on population level, possibly hindering implementation of PGx in clinical care.[36] In this study, we visualized the possible impact of PGx in primary care in the population of Denmark by determining the number of prescription drug users of 49 actionable DGIs, stratified on age and sex in 2017.

It was stated previously that > 95% of patients carry at least one actionable PGx variant, yet the combination of carrying a variant and taking the associated drug is important for it to have clinical impact.[37,38] In this study, we identified an estimated median frequency of actionable genotypes or phenotypes within 49 DGIs (41 drugs) of 25%. Thus, one of four patients using one of these 41 PGx drugs would require intervention (e.g., a dose adjustment). The possible use of PGx in primary care was previously studied by Bank *et al*.[9] They investigated the number of new prescriptions of 45 PGx primary care drugs in The Netherlands, and estimated that 22.9% of these patients have actionable genotypes or phenotypes (5.4% of 23.6%).[9] Van der Wouden *et al.*[36] identified 24.2% actionable genotypes or phenotypes in a real-world impact study including 200 patients in primary care. Alshabeeb *et al.*[39] identified 24.1% of prescription drug exposures in a 7-year period in the Dutch population with European ancestry (85%) to have clinical significance (actionable). Some differences may exist between Denmark and The Netherlands in prescribing or marketing of certain drugs for which PGx guidelines are available, and, in the current study, the total Danish population and CPIC PGx guidelines were taken into account. Still, the results are similar. Possibly, the frequency of actionable genotypes or

Class	Drug	Gene/Enzyme	Total users	Total Act. Users	Freq. Act.	Sex ratio	0-17y Act.	18-24y Act.	25-44y Act.	45-64y Act.	65-79y Act.	≥80y Act.
A	Omeprazole	CYP2C19	130485	29137	22%	1.4	959	806	4333	10121	9548	3370
A	Pantoprazole	CYP2C19	311945	69657	22%	1.2	652	2196	10898	24187	22295	9429
A	Lansoprazole	CYP2C19	144590	32287	22%	1.3	246	794	4619	12092	10793	3744
A	Ondansetron	CYP2D6	11945	358	3%	3.0	16	24	90	88	91	49
B	Clopidogrel	CYP2C19	119735	33234	28%	0.8	3	21	670	8571	15788	8181
B	Warfarin	VKORC1	74170	11760	16%	0.6	18	41	372	2025	5737	3567
B	Warfarin	CYP2C9	74170	27070	36%	0.6	42	95	856	4661	13206	8210
B	Warfarin	CYP4F2	74170	22177	30%	0.6	34	78	701	3818	10819	6726
B	Phenprocoumon	VKORC1	1325	210	16%	0.6	0	1	9	52	93	55
C	Propafenone	CYP2D6	465	123	26%	0.9	0	0	1	37	69	16
C	Flecainide	CYP2D6	2975	784	26%	0.8	4	3	29	316	386	46
C	Metoprolol	CYP2D6	279055	73531	26%	1.3	108	307	2466	20391	34416	15843
C	Simvastatin	SLCO1B1	341395	124182	36%	0.9	2	45	3105	38228	62314	20488
C	Atorvastatin	SLCO1B1	263675	95912	36%	0.8	16	135	3790	37721	45360	8890
G	Estrogens[1]	F5/FvL	325310	37215	11%	6023.2	5158	15515	14994	1545	3	0
J	Flucloxacillin	HLA-B	17900	578	3%	0.9	42	36	115	168	144	74
J	Voriconazole	CYP2C19	35	18	50%	0.9	0	0	3	8	8	0
L	Fluorouracil	DPYD	1060	48	5%	0.8	0	0	0	7	28	13
L	Tamoxifen	CYP2D6	785	183	23%	22.0	0	6	138	13	9	18
L	Tacrolimus	CYP3A5	10	3	34%	/0	2	0	0	2	0	0
L	Azathioprine	TPMT	8315	996	12%	1.1	51	99	303	313	189	40
L	Azathioprine	NUDT15	8315	64	1%	1.1	3	6	19	20	12	3
M	Allopurinol	HLA-B	58225	766	1%	0.3	0	2	39	236	349	139
N	Codeine	CYP2D6	116315	30649	26%	1.9	299	834	5053	11237	9470	3756
N	Tramadol	CYP2D6	265030	69835	26%	1.3	323	1872	12830	25308	20362	9141
N	Carbamazepine	HLA-B	8320	28	0.3%	0.97	1	1	4	12	8	2
N	Carbamazepine	HLA-A	8320	236	3%	0.97	6	5	34	103	69	19
N	Oxcarbazepine	HLA-B	5300	2	0.04%	0.8	0	0	0	1	0	0
N	Lamotrigine	HLA-B	41875	15	0.04%	1.5	1	1	5	5	2	1
N	Haloperidol	CYP2D6	6285	532	8%	1.03	0	3	22	99	183	225
N	Zuclopenthixol	CYP2D6	4475	1179	26%	1.1	0	20	194	573	319	74
N	Pimozide	CYP2D6	620	145	23%	0.90	9	11	28	49	32	16
N	Aripiprazole	CYP2D6	11895	650	5%	1.2	44	89	249	195	55	17
N	Citalopram	CYP2C19	100130	50152	50%	1.9	75	1295	9371	17087	13937	8387
N	Paroxetine	CYP2D6	12935	1095	8%	1.9	1	26	238	494	272	64
N	Sertraline	CYP2C19	100920	2721	3%	1.7	64	259	883	820	464	232
N	Fluvoxamine	CYP2D6	180	10	5%	2.1	0	0	4	3	2	1
N	Escitalopram	CYP2C19	24015	12028	50%	1.7	25	516	2908	4360	2790	1430
N	Venlafaxine	CYP2D6	50155	13216	26%	1.9	11	520	3825	5519	2615	726
N	Atomoxetine	CYP2D6	9125	2404	26%	0.7	810	559	797	232	7	0
N	Imipramine	CYP2C19	4085	1022	25%	1.6	30	19	155	392	319	108
N	Imipramine	CYP2D6	4085	1076	26%	1.6	32	20	163	412	336	113
N	Clomipramine	CYP2D6	2780	733	26%	2.1	0	20	153	294	216	50
N	Clomipramine	CYP2C19	2780	696	25%	2.1	0	19	145	279	205	48
N	Amitriptyline	CYP2D6	35025	9229	26%	1.6	45	216	1714	3960	2455	839
N	Amitriptyline	CYP2C19	35025	8766	25%	1.6	43	205	1628	3762	2331	797
N	Nortriptyline	CYP2D6	14965	3943	26%	1.8	25	88	859	1706	951	314
N	Doxepin	CYP2D6	485	128	26%	2.4	0	0	7	29	62	30
N	Doxepin	CYP2C19	485	121	25%	2.4	0	0	6	28	59	29

Figure 4 Heat-map of number of users of actionable drug-gene interactions (DGIs). The figure shows a list of actionable pharmacogenetics drugs included in this study. Drugs are sorted on anatomic therapeutic chemical (ATC) code and shown per ATC drug class. For each DGI, the (i) total number of drug users, (ii) total estimated number of users with an actionable genotype or phenotype, (iii) the estimated ratio of actionable genotypes or phenotypes, (iv) sex ratio in favor of women, and (v) estimated number of users with an actionable genotype- or phenotype per age group are shown. Data originate from the population of Denmark in 2017 (MEDSTAT)[24] and is calculated using **Figure 3** and **Table 1** and **Table S1**. Age groups are 0–17, 18–24, 25–44, 45–64, 65–79 years, and 80 years or older. Drugs in dark blue are psychotropic drugs. [1]Contraceptives with estrogens (i.e., progestogens and estrogens). A, alimentary tract and metabolism; Act, actionables; B, blood and blood forming organs; C, cardiovascular system; Freq, frequency; G, genito urinary system and sex hormones; J, general anti-infectives for systemic use; L, antineoplastic and immunomodulating agents; M, musculo-skeletal system; N, nervous system; ND, not done, cannot divide by 0 users.

phenotypes might differ when other PGx guidelines are included, even though there is considerable overlap between available PGx guidelines.

In the stratified analyses by sex and age groups, we found a slightly higher prevalence in drug use in women compared with men. We note that women are not over-represented in the general Danish population (factor 1.01).[34] The higher use might possibly be explained by sex differences in disease prevalence or treatment of these diseases with the included drugs, or the fact that there are more elderly women, and the elderly often use more drugs.[34,40–42] The highest number of drug users was found in middle-aged patients, whom are not over-represented in the Danish population.[34] A possible reason could be the disease treatment indications of the drugs and the increasing number of long-term chronic diseases in middle-aged individuals.[43] Only 4% of the drug users were aged below 17 years. The top 10 drugs pattern differed between all age groups and children (0–17 year old patients) in four drugs; children used atomoxetine, sertraline, lamotrigine, and flucloxacillin more often. PGx dosing recommendations though do not comment on the drug users' age. Different dosages can be used when treating children

and PGx dose reductions may also be applied to children if the gene is expected to have the same functional impact in children and adults. This is probably the case for, as an example, CYP2D6 and CYP2C19, which are expressed in children on a similar level as adults.[44] However, for the majority of commonly used drugs which have a DGI, more data are required to support PGx implementation in children.[44]

The discussion regarding the methodology of PGx tests and the optimal timing (i.e., pre-emptive, "as needed," or reactive testing) is ongoing.[20,21,45] The data shown in our study would advocate for testing a panel of genes instead of a single-gene test, as many DGIs were identified and it is likely people will use more than one of these drugs in their lifetime. Together with improving sequencing techniques (both in quality and price) and a more favorable cost and benefit evaluation, testing a panel of genes would be the best choice for applying PGx.[21,45,46] A cost-benefit evaluation based on the presented data was outside of the scope of this work. Current PGx dosing recommendations mainly focus on drug metabolizing enzymes, and, thus, PK-related DGIs, which might extend to more recommendations involving transporters and receptors in the future. Testing a panel of genes would be even more beneficial with the expected increasing number of PGx guidelines. The data shown in our study suggest to test at the time of the first PGx drug prescription ("as needed"), with PGx results ready prior to start of therapy, instead of early execution of a PGx test prior to any first drug prescription (pre-emptive testing) or reactive PGx testing after start of therapy. Depending on the timing of the first prescription of a drug for which a DGI is known, some patients will need a PGx test quite early on in life and some might never need a PGx test in their lifetime; but most patients will first require it as an adult. Therefore, pre-emptive PGx testing cannot be suggested for everyone at one specific age (e.g., 18 years).

The impact of PGx on the public health is insufficiently investigated. Although it is the individual patient who is affected and would benefit from therapeutic recommendations, it is the population perspective that could really improve precision medicine.[47] The overall importance of this study was to better visualize the possible impact of PGx on public health, therefore, we identified all PGx prescription drug users of the total Danish population (n = 5,748,769). Previously, three larger studies were executed.[9,10,39] Because we used the data of the total Danish population, we eliminated the risk for selection bias of specific drug users. Samwald *et al.*[10] used a combination of selected sources (private insurance data, Medicaid, and Medicare data), which could introduce selection bias in their study population by lacking a population-representative sample. Bank *et al.*[9] were able to include data of 94.4% of the pharmacies in The Netherlands, and expect the missing data are likely originating from outpatient pharmacies, dispensing more specialized pharmacotherapy. Alshabeeb *et al.* focused on prescription drug users in The Netherlands with a European ancestry (85%) only. They used genotype data of 498 Dutch people to define frequencies of actionable variants, which may be too small a sample size and not be representative for the whole population.

Our study also has some limitations. First, data on the number of users were only available for primary sector data, thus investigated DGIs from drugs used outside of the hospital sector, whereas actionable DGIs also exist for drugs used in hospital care but could not be included in this study. Data were unavailable in MEDSTAT for 27 of 68 drugs (39.7%), some of these drugs are likely nonprimary care drugs, whereas others were not marketed or sold at all in Denmark in 2017. The estimated impact of PGx would likely increase if hospital care drugs were included, as it is known there are PGx dosing recommendations for hospital drugs as well. Second, only the total (aggregated) number of drug users was available, no individual drug data. This made it impossible to determine how many drug users filled prescriptions of more than one actionable drug, or to calculate incidence instead of prevalence. Third, there were no genetic data available for the drug users in this study, thus we relied on allele frequencies of genetic variants based on literature. Van Driest *et al.* showed that literature allele frequencies were concordant to frequencies identified in 9,589 genotyped patients in the United States.[48] In addition, we assume these estimated frequencies represent our study population, as the Danish population mostly consists of white people, as did the study samples in most of the used literature.[9,10,29–33,35] Fourth, we did not include data of nonactionable DGIs, and were, thus, unable to estimate the share of PGx drugs in the total drug industry. Finally, we only looked at the number of users of actionable DGIs and actionable genotypes or phenotypes. We did not calculate numbers based on the type of PGx advice on drug use outcomes, as the advice may differ between PGx consortia. In some cases, the PGx advice is to perform additional monitoring (e.g., flecainide CYP2D6 UM), sometimes a dose adjustment is advised (e.g., azathioprine thiopurine S-methyltransferase intermediate metabolizer) and, in some cases, an alternative drug is required (e.g., abacavir HLA-B*5701 carrier).[28] These differences are based on characteristics of the involved drug (e.g., therapeutic index), severity and type of side effects, and identified genotype or phenotype. Neglecting a PGx recommendation in case of expected lack of efficacy or a relatively mild side effect compared with a life-threatening adverse event can make a huge difference in the possible impact of PGx. An example is the difference between UGT1A1 poor metabolizers using a lower dose of the cytostatic irinotecan to prevent life-threatening myelosuppression compared with CYP2C19 UMs using the proton-pump inhibitor lansoprazole, which might not be effective with the standard dose.

CONCLUSION

This is the first study using an unselected national population to describe the number of users of prescription PGx drugs that have actionable DGIs. We found PGx testing can have a substantial impact on the population, with an estimated one of four drug users who could receive a PGx recommendation based on currently available PGx dosing guidelines. We advocate for prospective panel-based PGx testing at the time of the first PGx drug prescription ("as needed"), with PGx results ready prior to start of the first, and all future, therapies.

Supporting Information. Supplementary information accompanies this paper on the *Clinical and Translational Science* website (www.cts-journal.com).

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