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How Many Patients Could Benefit From Pre-emptive Pharmacogenomic Testing and Decision Support? A Retrospective Study Based on Nationwide Austrian Claims Data

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Abstract. Pre-emptive pharmacogenetic (PGx) testing combined with clinical decision support is a promising new strategy for making pharmacotherapy safer and more effective. To estimate the number of patients whose therapies could be guided by this approach, we analysed claims data for patients in Austria in the years 2006 and 2007. We calculated the number of patients receiving one or several drugs for with pharmacogenomic guidelines are available (PGx drugs). The cohort consisted of 6,761,034 patients and was split into four age groups. Patients in the age group >= 65 were prescribed the most PGx drugs, with 72% of the patients receiving at least one PGx drug. 39.1% of all people over 65 received at least one drug metabolized by the three most frequent cytochrome P450 enzymes. Our data indicate that a sizable fraction of elderly patients could profit from the implementation of pre-emptive PGx testing and decision support.

Keywords. pharmacogenomics, clinical decision support systems, clinical guidelines, drug safety, claims data, re-use of patient data

1. Introduction

Pharmacogenomic (PGx) testing of patients offers the potential of making drug therapy safer and more effective by adapting drug dosing to individual genetic profiles of patients.

Previous research shows that actionable genotypes are not uncommon in patient populations. For example, a study at the Vanderbilt University Medical Center conducted PGx tests in 9,589 patients receiving pharmacotherapy [1]. They found that the fraction of patients with an actionable genetic profile was 28.5% for clopidogrel, 25.7% for simvastatin, 69% for warfarin, 9.1% for thiopurines and 23% for tacrolimus [2].

Several organizations made it their priority to publish PGx guidelines for clinical use. The most established are the Clinical Pharmacogenetics Implementation Consortium (CPIC) in the United States and the Dutch Pharmacogenetics Working Group (DPWG) in Europe [3,4].

While PGx testing is now becoming available at very low cost, its widespread adoption is hindered by a lack of information on its cost-effectiveness and uncertainty about how to integrate pharmacogenomic testing most efficiently into existing clinical

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workflows. A promising approach for implementation is *pre-emptive* PGx testing. In pre-emptive testing, a genetic test yielding results for all important pharmacogenes is done once. With the assistance of clinical decision support software, the results can then be used to guide drug therapy with a wide variety of common medications in later patient care episodes. Several solutions for making PGx data and decision support tools are available, such as systems integrated into electronic health records or solutions based on mobile technologies [5].

The guidelines for specific combinations of genetic variants and pharmaceuticals are classified based on the clinical significance of potential adverse events. In guidelines from the DPWG, clinical significance is scored on a seven-point scale, with mild effects without clinical relevance classified as *AA* (lowest impact), and potentially lethal side-effect classified as *F* (highest impact) [4].

The aim of this study was to estimate the potential of pre-emptive PGx tests in Austria using drug claims data. Statistics on the usage of drugs for which PGx guidelines are available were analyzed for various age groups. These data can be used to estimate the potential reach of different PGx implementation scenarios in clinical settings.

2. Methods

2.1. Patient data source

We queried health claims data from the *General Approach for Patient-oriented Outpatient-based Diagnosis Related Groups* (GAP-DRG) database operated by the Main Association of Austrian Social Security Institutions. The database contains pseudonymized health claims data of patients who were enrolled in any public Austrian social insurance. Data are available for claims made in the years 2006 and 2007. The database was accessed through SQL queries. To access this database, a VPN connection secured with a password and single-use token was used to ensure data security.

2.2. Guidelines and data preparation

Our analysis was based on the guidelines from the DPWG [6]. Depending on the clinical relevance of outcomes for each drug-gene pair, two lists were generated.

The first list, named 'Highly significant', included all drug-gene pairs with a clinical significance rated C-F, while the other list, 'DPWG', included all drug-gene pairs irrespective of clinical significance of potential adverse outcomes. The study cohort was split up into four age groups (i.e. 0-13, 14-39, 40-64 and >= 65 years).

Table 1 lists all genes and the related drugs mentioned in the DPWG Guidelines and with a clinical relevance C-F (i.e., the 'Highly significant' list).

Since most drugs are metabolized by one of three cytochrome P450 enzymes (CYPs: CYP2D6, CYP2C9 and CYP2C19) and targeted genotyping for only these three genes might be easier to implement than for the entirety of PGx genes, we also calculated separate statistics for drugs metabolized by these specific genes only.

To identify claims referring to PGx medications within the GAP-DRG database, a document with all ATC codes for the drugs named in the guidelines was generated with the official ATC/DDD-Index 2007 [7]. 167 ATC codes were mapped to the related drugs. Table 2 shows an example with tramadol, metoprolol and clopidogrel.

Table 1. All drug-gene pairs in the DPWG guidelines which contain treatment recommendations of high clinical significance based on PGx test results

Gene	Substances in DPWG guideline ('highly-significant list')
CYP2D6	Amitriptyline, aripiprazole, clomipramine, codeine, doxepin, haloperidol, imipramine, metoprolol, nortriptyline, paroxetine, propafenone, risperidone, tamoxifen, tramadol, venlafaxine
CYP2C9	Acenocoumarol, glimepiride, phenprocoumon, phenytoin
CYP2C19	Clopidogrel, sertraline
UGT1A1	Irinotecan
TPMT	Azathioprine, mercaptopurine, thioguanine
HLA-B44	Ribavirine
HLA-B*5701	Abacavir
CYP3A5	Tacrolimus
VKORC1	Phenprocoumon
Factor V Leiden	Estrogen-containing OC
DPYD	Fluorouracil, capecitabine

Table 2. Examples of mappings between drugs and related ATC-Codes from the ATC-Index 2007

Drug	ATC-Codes
Tramadol	N02AX02, N02AX52
Metoprolol	C07AB02, C07AB52, C07FB02, C07CB02, C07BB02, C07BB52
Clopidogrel	B01AC04

Prodrugs were included, topical preparations of pharmaceuticals were excluded.

2.3. Statistics

The number of distinct drugs mentioned in PGx guidelines prescribed within the two-year period was calculated for each patient. Two hypothetical scenarios were considered:

First, a pre-emptive scenario, in which genetic testing is performed at the very beginning of the 2 years (of the available claims data) for all patients.

Second, a mixed 'reactive pre-emptive' scenario, in which a genetic test of all PGx genes is performed as soon as and exclusively for those patients who were first being prescribed a PGx drug within the timespan covered by the dataset. Each patient receiving a PGx test would also receive at least one PGx drug.

For both scenarios the number of patients receiving a multitude of different PGx drugs within the analyzed time period was calculated.

The data for this study has been extracted from GAP-DRG Database using SQL-Statements and was then transferred to a MS Excel Sheet for analyzing. For each age-group and PGx-druglist a separate Table was used.

3. Results

The database contained data on 6,831,128 patients in total. After exclusion of patients without a known date of birth, 6,761,034 patients (52% female) were included in our study cohort.

Table 3. Number of patients (absolute and percent of age group) with at least one PGx drug from the DPWG or "Highly significant" lists, grouped by age.

	0-13 y	14-39 y	40-64 y	>=65 y
DPWG-list	39,557 (4.6%)	547,441 (25.7%)	1,190,242 (51.1%)	1,037,127 (72.0%)
"Highly-significant"- list	33,483 (3.9%)	178,809 (8.4%)	599,811 (25.7%)	680,052 (47.2%)

3.1. DPWG list versus 'Highly significant' list

22.07% of the total included patients received at least one drug of the 'Highly significant' list and 41.63% received at least one drug of the 'DPWG' list (Table 3).

The most frequently prescribed drugs from the "DPWG"-List were proton pump inhibitors (i.e., pantoprazole, lansoprazole, omeprazole), while the most frequently prescribed drugs from the "Highly-significant"-list were tramadol, estrogen-containing drugs and metoprolol. Table 4 shows more details.

Table 4. Three most frequent prescribed drugs from DPWG and "Highly significant" lists and % of the included patients receiving each drug within the study period.

	DPWG	Highly-significant
Rank 1	Pantoprazole (15.1%)	Tramadol (6.1%)
Rank 2	Lansoprazole (8.6%)	Estrogen-containing drugs (5.9%)
Rank 3	Omeprazole (6.8%)	Metoprolol (4.1%)

In the pre-emptive simulation, 22.07% of all included patients received at least one PGx drug. In the cohort aged >= 65, even 47.24% received a PGx drug. 6.38% of the total population received at least two PGx drugs.

In the 'reactive pre-emptive' simulation, all of the 1,060,860 patients who received at least one drug are tested. With this selective inclusion to PGx testing, 22% receive two or more drugs, compared to 6% in the pre-emptive simulation.

3.2. Testing for CYP genes only

13.48% of the total included patients received at least one drug which is metabolized by the enzyme CYP2D6. Considering all three CYPs (CYP2D6, CYP2C9, CYP2C19) the number rose to 17.58%. In the >= 65 age group, 41.53% received at least one drug of these three CYPs. Table 5 illustrates these numbers with all age groups and only with the patients over 65.

Table 5. Percentage of total population in highly significant list in all age groups and only age group >= 65y

CYP-Enzymes	% of total population in highly-significant list all age groups	% of total population in highly-significant list with age group >= 65y
CYP2D6	13.5%	30.4%
CYP2C9	3.7%	12.8%
CYP2C19	3.5%	8.5%
All three CYPs	17.6%	41.5%

Table 6. Pre-emptive and 'reactive pre-emptive' simulations with the DPWG list and 'Highly significant' list with the percentage of the total study population who received PGx drugs. R-P: result for 'reactive pre-emptive' setting, P: result for pre-emptive setting.

	Pre-emptive simulation	**"Reactive pre-emptive" simulation**
At least one PGx drug	R-P: 41.2%, P: 22%	R-P: 100%, P: 100%
At least two PGx drugs	R-P: 19.5%, P: 6.4%	R-P: 48.4%, P: 28.9%
At least three PGx drugs	R-P: 9.9%, P: 1.7%	R-P: 23.9%, P: 7.9%

Pharmacogenetic testing for these 3 CYPs would already allow to optimize the prescriptions of about one third of the total population aged over 65.

Based on the DPWG list, a PGx test for the population over the age 65 for all three CYPs would include approximately 14.8% of the total study population and 69.59% of the study population over age 65.

3.3. Pre-emptive versus 'reactive pre-emptive' setting

In the pre-emptive setting, around 41% of the total included patients receives at least one drug from the DPWG guidelines and about 20% receives at least two drugs. In comparison to the reactive pre-emptive simulation, about 48% of all patients, who received at least one drug, are prescribed at least two drugs. Table 6 compares the two settings for both the DPWG and "Highly significant" lists.

4. Discussion

Patients who received two or more PGx drugs ranged between 6.38% in the 'Highly significant' list and 19.95% in the DPWG-list.

A pharmacogenetic test for patients aged 65 and over, including the three most frequent CYP-Enzymes (CYP2D6, CYP2C9, CYP2C19), covers about 39.1% of all patients in this cohort using the DPWG list.

If we take the amount of clinically actionable genotypes for clopidogrel CYP2C19 (28.5%) from the PREDICT study and put them into perspective with our results for all drugs in our test, about 20 % of all included patients aged 65 or older have at least one actionable result, for which the guidelines of DPWG recommends a different prescribing procedure [2]. The most frequently prescribed drugs are proton pump inhibitors (PPI), followed by the pain reliever tramadol. Using only the "Highly significant" list, the most frequently prescribed drugs are the analgesic tramadol followed by the cardiologic pharmaceutical metoprolol.

The main focus of this analysis was on the use of PGx drugs in the 'Highly-significant' list. About a quarter of the total study population and about the half of the patients over age 65 received drugs received drugs with already existing guidelines for avoiding adverse drug events by accounting for pharmacogenetic diversity.

This study has several limitation. The impact of pharmacogenomic testing varies depending on the demographic population and this study used Austrian data only. Also, the costs of genetic testing and the frequency of adverse drug events varies between regions. Finally, the scope of the dataset is limited to the two years covered by the GAP-DRG database. Future work could employ additional databases such as GAP-DRG2, which contains Austrian claims data from the years 2008-2011.

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