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The Importance of Gene-Drug-Drug-Interactions in Pharmacogenomics Decision Support: An Analysis Based on Austrian Claims Data

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Abstract. While pharmacogenomic testing combined with clinical decision support has the potential to increase the safety and efficacy of medical treatments, the intake of multiple prescription drugs can – if not sufficiently addressed by decision support solutions – impair the effectiveness of such interventions by modulating the capacity of precisely those enzymes whose function pharmacogenomic tests try to predict. We quantified the potential extent of such drug-mediated mismatches between genotype-derived phenotypes and real phenotypes, commonly called "phenoconversion", by screening claims data from 1,587,829 Austrian health insurance holders of the years 2006 and 2007 for concomitant prescriptions of drugs that can be dosed based on pharmacogenomics, and drugs that modulate enzyme activity. In total, 232,398 such prescription overlaps were detected, of which more than half (54.6%) could be attributed to co-prescriptions of *moderate* or *strong* modulators. Our results indicate that prescription drug-mediated phenoconversion is not uncommon, and should therefore be adequately reflected in decision support solutions by integrating algorithms to detect potential gene-drug-drug interactions.

Keywords. Pharmacogenomics, drug safety, claims data, re-use of patient data

1. Introduction

Pharmacogenomic (PGx) testing has—especially when combined with efficient clinical decision support (CDS)—the potential to improve the safety and efficacy of medical treatments by screening patients for genetic variants known to impact drug response and thereupon adjusting drug and dosage selection.

While there is sound evidence on the importance of PGx variants with regard to therapeutic response for a wide range of commonly used medications, it is equally well-known that these variants can oftentimes only explain a varying fraction of the actual individual differences in drug response [1-3]. Besides comorbidities, e.g. liver disease, renal impairment or inflammatory conditions, several other factors, such as smoking status, food or medication intake can modulate a patient's response to certain drugs [4,5].

Especially, both the intake of prescription and over-the-counter drugs can impact drug efficacy on the pharmacokinetic level, e.g. at the level of drug metabolizing enzymes or drug transporters, thereby amplifying or attenuating differences in drug

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response that are caused by pharmacogenetic variants [6]. The effects of these gene-drug-drug interactions (GDDI) are often subsumed under the term "phenoconversion" to account for a mismatch between the "phenotype" that was predicted merely based on a patient's PGx results and his real phenotype that may be influenced by many more factors.

If not sufficiently addressed by CDS algorithms, prescription-drug mediated phenoconversion has the potential to undermine the power of PGx CDS interventions in finding the right dosage for the individual patients. While these important limitations of PGx-guided prescribing are commonly acknowledged, the actual extent of prescription-drug mediated phenoconversion remains unclear. In this study, we aimed to assess the frequency of potential GDDIs in the Austrian population by screening claims data from four federal provinces for concomitant use of PGx drugs (i.e. drugs that can be dosed based on PGx guidelines) and drugs that are known to act as inhibitors or inducers of the affected enzyme or transporter.

2. Methods

2.1. Compiling the list of relevant drugs and genes

2.1.1. Drugs and genes relevant for pharmacogenomics-guided prescribing

A list of drug substances and genes for which actionable PGx-based therapeutic recommendations have been developed by two renowned consortia, the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG), served as a basis for this analysis. At the time of writing, such recommendations were available for 70 drugs across 14 genes [7,8]. Genes for which no relevant inducers and inhibitors could be determined based on the sources described in the next section were excluded. The final list comprised of 65 drug substances affected by one or more of following seven genes: CYP2D6, CYP2C19, CYP2C9, CYP3A5, TPMT, UGT1A1 and SLCO1B1.

2.1.2. Inducers and inhibitors

For each gene considered in this analysis, a comprehensive list of well-established inducers and inhibitors was compiled based on two sources: The Flockhart Cytochrome P450 Drug Interaction Table of the Indiana University and the compendium "The Top 100 Drug Interactions" by Hansten and Horn (2015 edition) [9,10].

The Flockhart Cytochrome P450 Drug Interaction Table assigns inhibitors and inducers to one of the following four categories based on the strength of their pharmacokinetic effect: *strong*, *moderate*, *weak* and *unclassified*. For example, a *strong* inhibitor is defined as one that causes a more than 5-fold increase in the plasma area under the curve value, or more than 80% decrease in clearance. The Hansten and Horn compendium differentiates only between *inhibitors* or *weak inhibitors*, and *inducers* or *weak inducers*.

For this study, the following consistent categorization scheme was used: For all substances covered by the Flockhart Cytochrome P450 Drug Interaction Table, the assignments to the categories *strong*, *moderate* and *weak* were adopted. Drug substances that were only listed in the Hansten and Horn compendium and were not marked by a "weak" label were subsumed under the "*moderate*" category. Drug substances classified as "*weak*" by Hansten and Horn were assigned to the "*weak*" category.

Table 1: Overview of the number of PGx drugs, inhibitors and inducers included in the analysis, broken down by gene.

Gene	PGx drug	Inhibitor	Inducer	Total
CYP3A5	1	64	30	95
CYP2D6	27	60	2	89
CYP2C9	8	37	16	61
CYP2C19	18	19	12	49
SLCO1B1	1	12	0	13
UGT1A1	1	5	2	8
TPMT	3	5	0	8

2.1.3. Compiling the list of corresponding ATC codes

In total, 55 distinct PGx drugs, 157 inhibitors and 36 inducers associated with one or more of seven different genes were included in the analysis. Several of these drugs could be assigned to more than one category (e.g. PGx drug *and* inhibitor), resulting in 4,440 distinct interaction pairs. Table 1 gives an overview of the number of PGx drugs, inhibitors and inducers, broken down by gene.

To identify claims referring to these drugs within the claims database, for each substance, corresponding ATC codes were extracted from the ATC/DDD Index 2016 of the WHO Collaborating Centre for Drug Statistics Methodology [11]. Topical preparations were excluded due to their limited systemic effects.

2.2. Quantifying the potential extent of prescription drug-mediated phenoconversion

2.2.1. Health claims data source

Statistics on the frequency of concomitant prescriptions of the 4,440 interaction pairs were queried 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. This database contains pseudonymized health claims data from insurance holders of Austrian public health insurances for the years 2006 and 2007.

2.2.2. Determining the frequency of concomitant prescriptions of PGx drugs and inhibitors or inducers

For all claims, the GAP-DRG database calculates and captures the hypothetical duration of drug intake based on the Defined Daily Dose (DDD) of the drug, the prescribed package size and the quantity of the active ingredient. DDD is a standardized measure defined by the World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology that captures the "*assumed average maintenance dose per day for a drug used for its main indication in adults*" [11].

For this study, prescriptions of PGx drugs and inhibitors / inducers were counted as *concomitant* prescriptions whenever an overlap of the hypothetical duration of intakes between these drugs was detected. This approach requires information on the exact date of prescription filling, which was not consistently available for all health insurance funds covered by the database. We therefore had to limit our analysis to four federal insurance funds for which these date specifications were captured.

Statistics on concomitant prescriptions of the interaction pairs of interest were queried from the GAP-DRG database via SQL statements and transferred to MS Excel for further analysis.

Table 2: Number of concomitant prescriptions of PGx drugs with inducers or inhibitors within the two-year observation period from 2006 to 2007, broken down by gene and level of inhibition or induction.

Gene	Strong	Moderate	Weak	Unclassified	Total
CYP2D6	16,620	34,963	37,356	53,737	**142,676**
CYP2C19	N/A	58,782	N/A	2,157	**60,939**
CYP2C9	317	8,117	5,934	5,537	**19,905**
SLCO1B1	N/A	7,377	N/A	N/A	**7,377**
TPMT	N/A	N/A	N/A	752	**752**
CYP3A5	61	663	17	8	**749**
UGT1A1	N/A	N/A	N/A	0	**0**
Total	**16,998**	**109,902**	**43,307**	**62,191**	**232,398**

3. Results

3.1. Study population

Our study population consisted of 1,587,829 Austrian insurance holders from four federal provinces and health insurance funds ("*Gebietskrankenkasse Niederösterreich*", "*Gebietskrankenkasse Kärnten*", "*Gebietskrankenkasse Salzburg*" and "*Betriebskrankenkasse Neusiedler*"). In total, 393,476,104 prescriptions issued in the years 2006 and 2007 were screened for overlapping prescriptions of PGx drugs and inhibitors or inducers of the respective enzyme or transporter. 928,309 patients (58.8% of the study population) received at least one PGx drug in the observed time frame.

3.2. Frequency of concomitant prescriptions of PGx drugs with inducers or inhibitors of the respective enzyme or transporter

For 1,124 out of the 4,440 included interaction pairs, our analysis revealed at least one case of a concomitant prescription of a PGx drug with an inhibitor or inducer in the observed time frame. In sum, our analysis detected a total of 232,398 such cases, implying that, on average, every fourth patient who was treated with a PGx drug was concomitantly prescribed an inhibitor or inducer of the respective enzyme or transporter.

More than half of those cases could be attributed to concomitant prescriptions of PGx drugs with *moderate* (47.3%) or *strong* (7.3%) inhibitors or inducers. Concomitant prescriptions of PGx drugs with *weak* or *unclassified* inhibitors or inducers accounted for 18.6% and 26.8% of all cases, respectively.

As can be seen from Table 2, interaction pairs associated with the CYP2D6 gene made up more than half of all detected cases, followed by CYP2C19 which accounted for more than a quarter of the overall number of cases.

3.3. Most prescribed interaction pairs and modulator drugs

Table 3 shows the ten most prescribed interaction pairs together with the affected gene and the level of inhibition or induction that is potentially caused by the agent. Antidepressants with moderate or weak inhibiting properties (i.e. citalopram, escitalopram, fluoxetine) were strongly represented among the most prescribed pairs.

Similarly, the ten most prescribed pairs of PGx drugs with *strong* inhibitors or inducers almost exclusively consisted of combinations of the antidepressants paroxetine and fluoxetine with other antidepressants or pain medication (see Table 4).

Table 3. Top 10 most prescribed pairs of PGx drugs and inducers or inhibitors

Inhibitor / Inducer	PGx drug	Degree of inhibition / induction	Gene	Number of concomitant prescriptions
Clarithromycin	Simvastatin	Moderate inhibition	SLCO1B1	5,483
Citalopram	Tramadol	Unclassified inhibition	CYP2D6	5,111
Dexamethasone	Tramadol	Unclassified induction	CYP2D6	4,423
Carvedilol	Tramadol	Moderate inhibition	CYP2D6	4,339
Omeprazole	Citalopram	Moderate inhibition	CYP2C19	4,253
Escitalopram	Mirtazapine	Weak inhibition	CYP2D6	3,783
Escitalopram	Tramadol	Weak inhibition	CYP2D6	3,647
Fluoxetine	Pantoprazole	Moderate inhibition	CYP2C19	3,639
Metoclopramide	Tramadol	Unclassified inhibition	CYP2D6	3,459
Citalopram	Mirtazapine	Unclassified inhibition	CYP2D6	3,101

An overview of the ten overall most co-prescribed drugs with inhibiting and/or inducing properties across all interaction pairs can be found in Table 5.

4. Discussion

While it is commonly acknowledged that the intake of multiple prescription drugs has the potential to weaken the significance of pharmacogenomic testing in predicting drug response, the actual extent of potential prescription-drug mediated phenoconversion remains unclear. This study aimed to address this gap by determining the frequency of concomitant prescription of drugs that can be subject to PGx-based dosing, and drugs that have the potential to modulate the activity of precisely those enzymes and transporters whose function PGx test results try to predict.

Our results indicate that, on average, every fourth person with a prescription of a PGx drug is concomitantly treated with an inhibitor or inducer of the respective enzyme or transporter, which—if not adequately addressed by decision support algorithms—has the potential to dilute the significance of PGx test results in finding the right dosage for the individual patient.

While both the development of clinical decision support solutions (CDS) for PGx testing and the optimization of CDS for drug-drug-interactions (DDI) have been major research focuses in the past years, far too little attention has been paid to the intersection between those two fields, i.e. gene-drug-drug interactions [12-16]. In light of the progressing efforts to integrate PGx in clinical routine, it will be essential to ensure that

Table 4. Top 10 most prescribed pairs of PGx drugs and *strong* inducers or inhibitors

Inhibitor / Inducer	PGx drug	Degree of inhibition / induction	Gene	Number of concomitant prescriptions
Paroxetine	Tramadol	Strong inhibition	CYP2D6	1,808
Paroxetine	Mirtazapine	Strong inhibition	CYP2D6	1,563
Fluoxetine	Tramadol	Strong inhibition	CYP2D6	1,528
Fluoxetine	Mirtazapine	Strong inhibition	CYP2D6	1,153
Paroxetine	Metoprolol	Strong inhibition	CYP2D6	1,121
Paroxetine	Carvedilol	Strong inhibition	CYP2D6	897
Fluoxetine	Metoprolol	Strong inhibition	CYP2D6	840
Paroxetine	Amitriptyline	Strong inhibition	CYP2D6	752
Paroxetine	Risperidone	Strong inhibition	CYP2D6	693
Fluoxetine	Carvedilol	Strong inhibition	CYP2D6	671
Fluoxetine	Amitriptyline	Strong inhibition	CYP2D6	648

Table 5. Top 5 most co-prescribed drugs with inhibiting and/or inducing properties

Drug	Number of concomitant prescriptions
Citalopram	8,212
Escitalopram	7,430
Clarithromycin	5,483
Dexamethasone	4,423
Carvedilol	4,339
Omeprazole	4,253
Fluoxetine	3,639
Metoclopramide	3,459
Amiodarone	3,081
Sertraline	3,033

important GDDI are adequately represented in clinical decision support solutions to call the healthcare provider's attention to their significance for PGx-based prescribing.

A limitation of our study lies in the fact that the duration of medication intake captured by GAP-DRG are inferred based on measures such as DDDs and package size, which do not necessarily reflect the real treatment duration. However, given that a sizeable fraction of the drugs considered in this analysis are primarily used for long-term treatment of chronic conditions, an overlap in the real intake duration can be assumed in the majority of cases.

Furthermore, the results we present here are based on a retrospective analysis of claims data from four Austrian federal provinces of the years 2006 and 2007. Prescribing practices may vary between different regions and countries, and change over time, which makes our findings less generalizable to other healthcare settings or later prescription periods. More recent claims data from the years 2008 to 2011 would have been available via the GAP-DRG2 database. However, using this dataset for our analysis would have yielded even more regionally restricted results since only the federal province of Lower Austria is covered.

This study emphasizes the importance of addressing GDDIs in PGx CDS systems by showing that co-prescriptions of PGx drugs with inhibitor and inducer drugs are not uncommon. For our analysis, we used a simple categorization scheme to grade the degree of inhibition or induction a drug potentially causes. While such schemes could, in a first step, be helpful in compiling a list of high priority GDDIs for use by PGx CDS systems to alert medical professionals to the risk of potential interactions, predicting the actual effects on a patient's drug response phenotype in the presence of pharmacogenetic variants will heavily rely on the availability of more detailed pharmacometric models which take into account the involved PGx variants, drug substances and inhibition/induction mechanisms.

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