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Patients Dispensed Medications with Actionable Pharmacogenomic Biomarkers: Rates and Characteristics

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Abstract

Purpose.—Pharmacogenomic biomarkers are increasingly listed on medication labels and authoritative guidelines but pharmacogenomic-guided prescribing is not yet common. Our objective was to assess the potential for incorporating knowledge of patients' genomic characteristics into prescribing practices.

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Author Contributions

Conceptualization: K.D.M.; Methodology D.L., K.L.O.: Data curation: S.F.M., D.L., K.L.O.; Formal Analysis: D.L., K.L.O.; Writing: D.L., K.L.O., S.F.M., K.D.M.

[*]These two authors contributed equally.

Ethics Declaration

Boston Children's Hospital Institutional Review Board approved waiving consent for this study. Risks were determined to be minimal with no potential for direct benefit. Aetna gave approval for the manuscript submission, confirming that no beneficiaries were identifiable.

Data Availability

Raw data for this study were pharmacy claims and membership and enrollment information from a private insurer. The Data Use Agreement does not allow the investigators to share these beneficiary level data. The supplementary materials contain counts derived from the raw data files. In particular, Supplementary Table 2 has counts of the number of enrollees who were dispensed each Medication with an Actionable Pharmacogenomic Biomarker (MAPB) by age group and for the whole cohort.

Conflict of Interest Statement

Dianbo Liu – None.

Shannon F. Manzi – Scientific Advisory Board member at Global Gene, Inc.

Karen L. Olson – None.

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Methods.—We performed a retrospective analysis of claims data for 2,096,971 beneficiaries with pharmacy coverage from a national, commercial health insurance plan between January 2017 and December 2019. Children between 0 and 17 years comprised 21% of the cohort. Adults were age 18 to 64. Medications with actionable pharmacogenomic biomarkers (MAPB) were identified using public information from the FDA, CPIC, and PharmGKB.

Results.—MAPBs were dispensed to 63% of the adults and 29% of the children in the cohort. Most frequently dispensed were ibuprofen, ondansetron, codeine, and oxycodone. Most common were medications with CYP2D6, G6PD, or CYPC19 pharmacogenomic biomarkers. Ten percent of the cohort were co-dispensed more than one MAPB for at least 30 days.

Conclusion.—The number of people who might benefit from pharmacogenomic-guided prescribing is substantial. Future work should address obstacles to integrating genomic data into prescriber workflows, complex factors contributing to the magnitude of benefit, and the clinical availability of reliable on-demand or preemptive pharmacogenomic testing.

Keywords

Pharmacogenomics; Prescribing; Medication Safety; Pediatrics; Adverse Drug Reactions

INTRODUCTION

The lowest hanging fruit for introducing genomics into routine care may be use of a patient's pharmacogenomic variants to influence prescribing.[1] Genetic variants are linked to inter-individual differences in efficacy and toxicity of many medications and are involved in drug metabolism, drug transport, and target binding. Hundreds of genes affecting medication metabolism have been reported and availability of genomic data is leading to discovery of new interactions. Actionable pharmacogenomic biomarkers are increasingly listed on United States (US) Food and Drug Administration (FDA) labels, and the Clinical Pharmacogenomics Implementation Consortium (CPIC) has published 25 peer-reviewed consensus guidelines for pharmacogenomic-guided therapy. We characterize use of medications with an actionable pharmacogenomic biomarker (MAPB) among beneficiaries from a national-scale, privately insured health plan, and estimate the opportunity for pharmacogenomic-guided prescribing.

MATERIALS AND METHODS

Subjects.

Claims data from a national commercial health insurance plan were used to select beneficiaries with continuous pharmacy coverage from January 1, 2017 to December 31, 2019. Individuals 0 to 64 years old were included even if they had no pharmacy claims (14.5%) but were known to have pharmacy coverage. The final cohort (n= 2,096,971) included 1,067,875 females (50.9%), 1,029,065 males (49.1%), and 31 with sex unknown. Children (n= 439,828, 21%) were defined as those who remained 0 to 17 years old throughout the study period. Adults were similarly defined as age 18 to 64 years. Individuals who would change age groups during the study were excluded.

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Medications with an actionable pharmacogenomic biomarkers (MAPB).

Actionability was defined for medications with recommended variant-based dose modification, drug choice modification, frequency modification, increased therapeutic drug monitoring recommendations or enhanced screening for adverse reactions. This is in keeping with a CPIC description of actionable variants as those that would alter standard prescribing practices if the data were present.[2] Our initial search list was compiled from three publicly available sources: CPIC, FDA, and the Pharmacogenomics Knowledgebase (PharmGKB).[3] Drugs included were listed on the FDA Table of Pharmacogenetic Associations (https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations), had a CPIC guideline (https://cpicpgx.org/guidelines/), were listed as Level A or B on the CPIC Table of Genes-Drugs (https://cpicpgx.org/genes-drugs/), or were on the FDA Table of Biomarkers (https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling) and labeled 'Actionable,' 'Testing recommended' or 'Testing required' in the FDA column of the PharmGKB Drug Label Annotations (https://www.pharmgkb.org/labelAnnotations).

Topical preparations were excluded except for mafenide.[4] We included all drug-gene pairs with evidence suggesting a possibility for adverse events. Our list contained 253 MAPBs. Other studies have focused on high level associations such as CPIC Level A drug-gene pairs only[4,5] or Dutch Pharmacogenetics Working Group clinical relevance classes C to F.[4] The FDA Table of Pharmacogenomic Biomarkers in drug labeling was used to assign a therapeutic area to each MAPB. Those not listed in this table were assigned a therapeutic area by author SFM.

Dispensed medications with pharmacogenomic biomarkers.

To find patients exposed to MAPBs, drug names were used to select a set of drug identification codes from the Cerner Multum™ VantageRx™ database (https://www.cerner.com/solutions/drug-database). These were converted to 11-digit US National Drug Codes and used to filter pharmacy claims.

Simultaneous Dispensing of MAPBs.

MAPBs were considered co-dispensed when they had at least 30 consecutive overlapping dispensed days. Days summed for total days dispensed did not all have to be consecutive.

Analysis.

Counts and percentages for medications reflect the number of distinct individuals, not the number of pharmacy dispenses. A 2-sided t-test was used to compare means.

RESULTS

There were 206 MAPBs in the claim database (see Supplementary Table 1), dispensed in the form of 270 unique single or combination drugs. 1,176,011 beneficiaries (56% of the total population) were dispensed a mean of 2.6 (SD=2.0) MAPBs. Among adults, 63% (1,049,939) were dispensed at least one MAPB, and among children, this figure was 29% (126,072). Among those with claims for MAPBs, adults were dispensed more (mean 2.7, st dev 2.0) medications than children (mean 1.5, st dev 1.0, p<.001).

The ten most frequently dispensed MAPBs for each age group are shown in Table 1. The two lists have five MAPBs in common, although in different proportions for each age group. Most frequent for children was ondansetron (9.3%), which was #4 for adults (10%). Most frequent for adults was ibuprofen (17%), which was #5 for children (2.9%), although this is likely an under-representation given the ubiquitous availability of ibuprofen without a prescription. Age group differences for all the MAPBs are presented in Supplementary Table 2. For children, 4 MAPBs from the top 10 were dispensed for more than 180 days, on average (methylphenidate, amphetamine, sertraline, escitalopram). For adults, only one drug in the top 10 was dispensed for an average of 180 days or more (omeprazole), which is unsurprising given these drugs are primarily indicated for short-term use. The total days supply for each MAPB is presented in Supplementary Table 3, reflecting the longer duration of use expected for most drugs prescribed for chronic conditions.

The most common biomarker, CYP2D6, was associated with 51 medications dispensed to 98,907 (22%) children, and 63 medications to 731,753 (44%) adults. G6PD was the next most frequent, associated with 26 medications dispensed to 26,312 (6%) children, and 34 dispensed to 435,956 (26%) adults. The next 5 top genes (CYP2C9, CYP2C19, Nonspecific NAT, NAT2, SLC6A4) are common to both age groups, although in a different rank order after the first two. Supplementary Table 4 contains the complete list of biomarkers.

In terms of therapeutic area, 15 MAPBs for gastroenterology were dispensed to 45,159 (10.3%) children, 29 for psychiatry to 33,412 (7.6%), and 13 for neurology for 32,044 (7.3%). These same areas ranked #3, #4, and #5 for adults. 9 MAPBs for anesthesiology were dispensed to 619,233 (37.4%) adults, 29 for infectious diseases to 370,602 (22.4%), and 14 for gastroenterology to 356,077 (21.5%). The first 2 adult therapeutic areas were #4 and #5 for children. Supplementary Table 5 contains the complete list.

Two or more MAPBs were co-dispensed for at least 30 consecutive days to 6,869 children (1.6%) and 204,748 adults (12.4%). This is 10% of the full population or 18% of those dispensed any MAPB. Table 2 lists the ten most common pairs for each age group as well as descriptive statistics regarding the total number of days the pair was dispensed. Adults were dispensed 5,624 different pairs of MAPBs, and 23% (1,277) of them were unique to single individuals. Children were dispensed 913 different pairs, and 42% (385) were dispensed to single individuals. The MAPBs in the most common pairs differed for adults and children. The most frequent for children were methylphenidate-sertraline (n=1,130, 0.26%), amphetamine-sertraline (n=569, 0.13%), and escitalopram-methylphenidate (n=469, 0.11 %). The top 10 pairs for children were also observed in adults, but with different percentages

and lower rank orders. For adults, the most frequent pairs were metoprolol-rosuvastatin (n=7,045, 0.43%), metoprolol-pantoprazole (n=5,666, 0.34%), and clopidogrel-metoprolol (n=5,252, 0.32%). Of the top 10 pairs for adults, 5 were not observed in children, 4 were only dispensed to one child, and 1 (meloxicam-omeprazole) was dispensed to 12 children. All pairs are listed in Supplementary Tables 6 and 7.

DISCUSSION

We find substantial opportunity for pharmacogenomic-guided medication prescribing. MAPBs were dispensed to 56% of a cohort of child and adult beneficiaries of a national health plan over a three-year period. Further, 18% of those prescribed MAPBs are co-prescribed an additional MAPB for at least 30 days, potentially increasing risk of toxicity and adverse events, particularly when the metabolic pathway is shared. Adverse drug events are responsible for 4 out of 1000 US emergency department visits, with 27.3% resulting in hospitalization.[6] Anticoagulants, antibiotics, and diabetic agents are responsible for 47% of these visits, several of which have clinically relevant MAPBs.

A previous study of 10 years of administrative claims from 3 sources for over 73 million patients with private insurance (from multiple employers/payers across the US), public insurance (Medicaid from multiple US states), or public/private insurance (employer-paid Medicare supplemental for US retirees) focused on incident use of 61 MAPBs during a four-year period.[4] Two genetic testing strategies were evaluated: pre-emptive (at the start of the four-year period, before any MAPBs were dispensed), and a mixed strategy where testing would occur at the time the first MAPB was used. Incident use for younger patients (age 0 to 13) was quite low (11–14% depending on data source) and few received 2 drugs (1–2%) in the pre-emptive group. Older age groups had higher incidence, up to 55% for the public insurance group (age 40 to 64) and 51% for those age 65 and older who were covered by both government and supplemental private insurance. Incident use of a second drug was 33% and 27%, respectively for these 2 adult age groups.

A recent study projected prevalence of genes associated with CPIC Level A drugs using sequencing data from the 1000 Genomes Project.[7] They estimated that almost all 7.7 million veterans who used the US Veterans Health Administration pharmacy could potentially benefit from pharmacogenetic guided prescribing because they had a gene with actionable medication recommendations.[5] In fact, 55% were dispensed a Level A drug.

A recent pilot study offered clinical pharmacogenomic testing to 667 patients in 5 cardiology and 4 perioperative clinics.[8] The 41-gene panel contained 12 genes with CPIC guidelines. Both CPIC drugs and FDA labels were used to identify actionable gene-drug pairs. MAPBs were prescribed to 46% of the 600 patients with medication data. Depending on source of information (FDA, CPIC), 88% or 99% of the patients had an actionable test result, with 5% or 16% currently prescribed an associated medication. One lesson learned from this pilot study was that additional expertise, perhaps from automated clinical decision support systems consultants, might help providers better utilize pharmacogenomic recommendations.

We were able to assess prevalence of MAPB use in two distinct age groups covered by the same national insurer. Our finding that 29% of children age 0 to 17 and 63% of adults age 18 to 64 had MAPBs dispensed, is in keeping with prior studies, given that our expanded drug list included medications with any evidence of actionability as described in the methods. In addition, 10% of the people in the cohort were dispensed more than one MAPBs simultaneously, which further complicates potential clinical decisions.

This study has limitations. The cohort is restricted to a single, though large, private insurer with formulary restrictions. Patients 65 and older were not assessed. A general limitation of pharmacy claims for measuring medication use is that not all dispensed medications are necessarily taken by the patient as prescribed, and some medications may be purchased without exercising a pharmacy benefit. Further, though we measured total exposure of the cohort to MAPBs, we did not estimate the magnitude of benefit from pharmacogenomic guided prescribing. Of course, genotype does not universally correspond to phenotype, so a predicted drug metabolism response may be inaccurate. Medication metabolism involves factors beyond genetics, including drug-drug interactions, organ function, and diet.

In contrast to *diagnostic* genomic testing—which risks incidental findings, can implicate unconsented genetically-related family members, and can identify of risks of unknown significance—pharmacogenomic testing poses few medical, ethical, or legal dilemmas. Yet unresolved obstacles prevent widespread real-time use of pharmacogenomic variants, including difficulties integrating large sets of retrievable genomic data into electronic health records and scaling clinician decision support.[9] However, the near ubiquitous use of electronic health records and emerging standards for point of care integration of external data sets and applications may soon make decision support at scale possible.[10–14]

Profiling an individual patient's response to medications is a rapidly maturing capability. Most pharmacogenomic testing is performed reactively after development of toxicity or non-response.[15] Preemptive screening[16] will likely increase as microarray-based genetic testing and next generation sequencing become more affordable. Effectiveness of on-demand as well as preemptive pharmacogenomic testing should be both modeled and measured.[17] Advancing clinical practice requires thorough evaluation of diagnostic testing strategies and expansion of the limited number of pharmacogenomic–based prescribing guidelines.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Top 10 Medications with Actionable Pharmacogenomic Biomarkers

MAPB	Number of enrollees	Percent of enrollees	Biomarker	has CPIC Guideline	CPIC Level	FDA Table[a]	PharmGKB: FDA column
Age 0–17 (N 439,828)							
ondansetron	40,814	9.28	CYP2D6	Yes	A		Informative PGx
dextromethorphan	28,314	6.44	CYP2D6		B		
sulfamethoxazole-trimethoprim	20,764	4.72	G6PD		B		Actionable PGx
			NAT2				Actionable PGx
			Nonspecific (NAT)			2	
methylphenidate	17,378	3.95	CYP2D6		B/C		
ibuprofen	12,872	2.93	CYP2C9	Yes	A		
amphetamine	8,795	2.00	CYP2D6			1	Informative PGx
sertraline	7,528	1.71	CYP2C19	Yes	B		
			CYP2D6		B		
codeine	7,435	1.69	CYP2D6	Yes	A	1	Actionable PGx
oxycodone	6,481	1.47	CYP2D6		A		
escitalopram	4,070	0.93	CYP2C19	Yes	A	3	Actionable PGx
			CYP2D6				Actionable PGx
			SLC6A4		B/C		
Age 18–64 (N 1,657,143)							
ibuprofen	282,044	17.02	CYP2C9	Yes	A		
codeine	189,095	11.41	CYP2D6	Yes	A	1	Actionable PGx
oxycodone	177,937	10.74	CYP2D6		A		
ondansetron	164,895	9.95	CYP2D6	Yes	A		Informative PGx
sulfamethoxazole-trimethoprim	145,620	8.79	G6PD		B		Actionable PGx
			NAT2				Actionable PGx
			Nonspecific (NAT)			2	
ciprofloxacin	138,625	8.37	G6PD		B		
meloxicam	120,738	7.29	CYP2C9	Yes	A		Actionable PGx
tramadol	110,170	6.65	CYP2D6		A	1	Actionable PGx
nitrofurantoin	103,093	6.22	G6PD		B		Actionable PGx
omeprazole	93,566	5.65	CYP2C19		B	3	Actionable PGx

Abbreviations: MAPB= Medication with an Actionable Pharmacogenomic Biomarker, N= total number enrolled in the healthcare plans with continuous pharmacy coverage, CPIC= Clinical Pharmacogenomics Implementation Consortium, FDA= United States Food and Drug Administration, PharmGKB= Pharmacogenomics Knowledgebase, PGx=pharmacogenomic.

[a]FDA Table of Pharmacogenetic Associations: 1 = Data support therapeutic management recommendations, 2 = Data indicate potential impact on safety or response, 3 = Data demonstrate potential impact on pharmacokinetic properties.

Table 2.

Top 10 overlapping pairs of Medications with Actionable Pharmacogenomic Biomarkers

MAPB1	Biomarker1	MAPB2	Biomarker2	Number of enrollees	Percent of enrollees
Age 0–17 (N 439,828)					
methylphenidate	CYP2D6	sertraline	CYP2C19, CYP2D6	1,130	0.26
amphetamine	CYP2D6	sertraline	CYP2C19, CYP2D6	569	0.13
escitalopram	CYP2C19, CYP2D6, SLCC6A4	methylphenidate	CYP2D6	469	0.11
aripiprazole	CYP2D6	sertraline	CYP2C19, CYP2D6	411	0.09
aripiprazole	CYP2D6	methylphenidate	CYP2D6	394	0.09
methylphenidate	CYP2D6	risperidone	CYP2D6	297	0.07
aripiprazole	CYP2D6	escitalopram	CYP2C19, CYP2D6, SLCC6A4	274	0.06
atomoxetine	CYP2D6	methylphenidate	CYP2D6	265	0.06
amphetamine	CYP2D6	escitalopram	CYP2C19, CYP2D6, SLCC6A4	256	0.06
amphetamine	CYP2D6	methylphenidate	CYP2D6	241	0.05
Age 18–64 (N 1,657,143)					
metoprolol	CYP2D6	rosuvastatin	ABCG2, SLCO1B1	7,045	0.43
metoprolol	CYP2D6	pantoprazole	CYP2C19	5,666	0.34
clopidogrel	CYP2C19	metoprolol	CYP2D6	5,252	0.32
metoprolol	CYP2D6	simvastatin	SLCO1B1	5,142	0.31
metoprolol	CYP2D6	omeprazole	CYP2C19	5,104	0.31
meloxicam	CYP2C9	omeprazole	CYP2C19	3,624	0.22
omeprazole	CYP2C19	simvastatin	SLCO1B1	3,534	0.21
pantoprazole	CYP2C19	rosuvastatin	ABCG2, SLCO1B1	3,515	0.21
meloxicam	CYP2C9	metoprolol	CYP2D6	3,495	0.21
omeprazole	CYP2C19	rosuvastatin	ABCG2, SLCO1B1	3,391	0.20

Abbreviations. MAPB= Medications with an Actionable Pharmacogenomic Biomarker, N= total number enrolled in the healthcare plans with continuous pharmacy coverage.

Patients are included in the number of enrollees if they were dispensed the same pair of drugs for a time period of at least 30 consecutive days.