Published in final edited form as:
Clin Pharmacol Ther. 2012 August ; 92(2): 235–242. doi:10.1038/clpt.2012.66.

Optimizing drug outcomes through pharmacogenetics: A case for preemptive genotyping

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Abstract

Routine integration of genotype data into drug decision-making could improve patient safety, particularly if many relevant genetic variants can be assayed simultaneously before target drug prescribing. The frequency of pharmacogenetic prescribing opportunities and the potential adverse events (AE) mitigated are unknown. We examined the frequency with which 56 medications with known outcomes influenced by variant alleles were prescribed in a cohort of 52,942 medical home patients at Vanderbilt University Medical Center. Within a five-year window, we estimated that 64.8% (95% CI: 64.4%-65.2%) of individuals were exposed to at least one medication with an established pharmacogenetic association. Using previously published results for six medications with well-characterized, severe genetically-linked AEs, we estimated that 398 events (95% CI, 225 - 583) could have been prevented with an effective preemptive genotyping program. Our results suggest that multiplexed, preemptive genotyping may represent an efficient alternative approach to current single use ("reactive") methods and may improve safety.

Introduction

Pharmacogenetics encompasses an increasing body of knowledge that links genetic variation to clinically important drug responses.(1,2) Although the US Food and Drug Administration (FDA) began incorporating this information into drug labels in 2007, including the listing of some as "black box warnings,"(3,4) a clear path towards applying pharmacogenetics to routine healthcare practice remains unknown.(5) Currently, pharmacogenetic testing is typically ordered at the point of care when initiating a treatment regimen. This one-at-a-time, reactive approach has several drawbacks. For example, the correct test must be ordered, retrieved, and interpreted by the physician, after which the patient must be

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Conflicts of interest
The authors have no conflicts of interest to disclose.

recontacted if changes are needed. Such an approach is especially problematic when treatment cannot be deferred. A delay in obtaining genetic results to guide drug selection or dosing may render the information obsolete as interim decisions are required and providers may not effectively respond to genetic results returned beyond the typical time frame of a clinical encounter. Further, single tests of individual genes are likely to be expensive relative to the potential benefit for guiding a single therapeutic decision.(6,7)

An alternate vision is to prospectively collect and embed data on multiple pharmacogenetic variants into the electronic health record (EHR).(5,8) The routine application of genotyping to drug decision making is enabled by a rapid decrease in per genotype cost and the development of EHR systems with advanced point of care decision support capabilities. In this paradigm, generation of a prescription would automatically trigger a search for genetic variant information in the patient's EHR; if variants that affect the drug are identified, the system guides the practitioner to the most appropriate individualized therapy. An especially appealing feature of this preemptive approach is that testing can be multiplexed, assaying hundreds to thousands of relevant genetic variants in a single genotyping assay. In this way, the genetic testing results can be reused as multiple drugs linked to different genetic variants are prescribed over time and as the knowledge base of variant effects grows.

We present an analysis of drug therapies with known pharmacogenetic effects in a population receiving primary care at Vanderbilt University Medical Center (VUMC). We combined medication exposure information from VUMC with variant allele frequencies, overall adverse event (AE) rates, and excess risk estimates from published data, to estimate the number of AEs (including both drug toxicities and efficacy failures) that might have been prevented using an effective, preemptive pharmacogenetic genotyping strategy for six well-characterized medications with severe AEs. Our findings support the development and further evaluation of incorporating preemptive genotyping into standard care.

Results

Pharmacogenetic medication exposure

We identified 52,942 medical home individuals eligible for inclusion in our study from the Synthetic Derivative (SD), a de-identified version of the Vanderbilt EHR. Table 1 shows demographic characteristics and clinical experiences during the time they were observed from January 2005 to June 2010. The gender distribution was 58% female, and the ancestry distribution was 73% European American (EA), 13% African American (AA), 3% other, and 11% unspecified ancestries. We have found that those of unspecified ancestries tend to distribute proportionately into the EA, AA, and other ancestry groups.(9) We therefore estimate the medical home population is composed of 82% EA, 14% AA, and 4% other ancestries. The median age of all individuals was 54 years at the medical home date [interdecile (10th-90th percentile) range (IDR): 31-75]. The median follow-up time was 3.1 years (IDR: 0.6-5.4). Over the course of follow-up, 64.7% of individuals were prescribed at least one of the 56 medications with drug labels indicating known pharmacogenetic variation in response, and 12.0% of individuals were prescribed four or more of them.

Figure 1 shows the cumulative incidence of medication exposures over five years following the medical home date. According to the upper left panel, 54.0% (95% CI: 53.5%-54.4%), 62.3% (61.8%-62.7%), and 64.8% (64.4%-65.2%) of individuals were exposed to at least one PG medication within one, three, and five years, respectively. The exposure rate to at least two, three, four and five medications by the end of year five was 40.0% (39.6%-40.4%), 22.9% (22.5%- 23.3%), 11.9% (11.6%-12.1%), and 5.9% (5.7%-6.1%), respectively. In the medical home population, this corresponds to 3123 (3018 – 3229)

patients exposed to at least five PG medications. Figure 1 also shows the cumulative incidence of exposure to the twelve most commonly prescribed medications in our list.

Table 2 shows five-year exposure rates (per 1000 individuals) to the 25 most commonly prescribed PG medications included in our list. The estimated exposure probability was more than 10% for each of the top six most commonly prescribed medications (simvastatin, metoprolol, esomeprazole, warfarin, atorvastatin, clopidogrel), and was more than 5% for each of the top twelve. The five-year exposure rates for the less commonly prescribed PG medications are shown in the Appendix (see Table A1).

Estimated preventable adverse events

Table 3 shows the results of the number of possible AEs prevented assuming a highly effective intervention based on available genotypic data for a select group of medications. Details regarding the specific calculations and the data used from each study are provided in the Methods section and in the online Supplementary Material. As an example of how this table should be interpreted, consider the tamoxifen row. The probability of a recurrence within nine years that was estimated from a prior study (10) was 0.186. Using this event probability, the probabilities of being an extensive, intermediate and poor metabolizer of CYP2D6 (i.e. 0.62, 0.33, and 0.05, respectively), the hazard ratio of breast cancer recurrence for each genotype, and the number of expected exposures to tamoxifen in the VUMC sample $(N_{tamoxifen}=540)$, we calculated that with an effective mitigation strategy we might have the opportunity to prevent 11 (95% CI: 1-22) breast cancer recurrences among intermediate metabolizers and 4 (0-9) recurrences among poor metabolizers. We estimated prevention of 172 (34-316) and 93 (8-193) *CYP2C9**2 and *CYP2C9**3 attributable bleeds for those on warfarin, respectively. It should be noted that both tamoxifen and warfarin have relatively narrow therapeutic indices. However, even with simvastatin, a drug with a very wide therapeutic index and a correspondingly low event rate, assuming patients receive 40 mg doses, (11) we estimated the potential prevention of 19 (8-30) cases of true myopathy (>10-fold elevation in creatine kinase level) attributable to the *SLC01B1* C allele. It should be noted that the number of preventable AEs is directly proportional to and therefore highly influenced by the assumed event probabilities. In the Appendix, we report a sensitivity analysis that calculates numbers of preventable AEs over a range of event probabilities (see Table A2).

Across the medication-AE combinations studied here, we estimated that an effective preemptive, multiplexed genotyping program could have prevented a total of 398 (225-583) adverse events among 52,942 individuals, while only considering six severe adverse drug events. We refer readers to a web application (http://data.vanderbilt.edu/rapache/Case4PG) that calculates the number of preventable AEs from user defined data inputs and to the Appendix that provides a contour plot of the number of preventable AEs for a broad range of population features (variant allele frequencies and odds ratios of AEs associated with variant alleles).

Discussion

To our knowledge we report the first assessment of the potential benefits of prospective measurement of pharmacogenetic variants across multiple genes simultaneously to guide future drug therapy. Our analysis suggests that a significant portion of a large, real-world medical home population is exposed to PG medications, with 65% of VUMC individuals expected to receive at least one and more than ten percent expected to receive at least four PG medications within five years from the established medical home date. Each of these exposures represents an additional opportunity to utilize preemptively captured genetic data to guide therapy. Assuming adverse drug outcomes (including side effects and therapeutic

failure) attributable to genetic variation are averted, we estimated that the effective use of pharmacogenetic information potentially could have prevented 398 (95%CI: 225-583) serious adverse events in this population. Thus, we believe that our results suggest that the use of prospective collection of genotype data might present an efficient alternative approach to current methods.

In estimating the number of AEs prevented, we have only included six AEs that are clinically serious, and only those genetic variants for which reliable outcome data have been reported. Indeed, other variants such as *VKORC1* are likely to have important effects on the incidence of warfarin-related bleeding.(12) A preemptive genotyping program could also lead to the prevention of less serious and more common adverse events and more efficient dosing and selection of medications. For example, the number of patients needed to genotype to prevent a 20% over or under dosing of warfarin was estimated to be approximately 13.3.(12) Thus, we could have improved warfarin dosing on approximately 500 individuals in the medical home population. For less severe cases of simvastatin-induced muscle toxicity, that may occur in approximately 3% of patients, we estimated that we might have been able to prevent approximately 190 cases. Genotyping technology that enables the simultaneous capture of information about multiple variants in multiple genes makes a preemptive genotyping program feasible.

It is beyond the scope of this study to conduct a full-scale economic analysis; however, we believe that with effective mitigation strategies, and relative to the likely program costs, the savings to a health care system are potentially large. For example, some estimated costs (in 2010 US$, including professional and institution services) include: warfarin-related bleeding, $11,542;(13) breast cancer recurrence, $24,400-56,521 (in the first year); (14) and abacavir hypersensitivities, $121-$36,850, depending on severity.(15) According to these analyses, the utilization of prospective genotype data might have prevented 265 warfarin related bleeds due to two common *CYP2C9* variants alone. With the plummeting costs of genomic testing, which could soon reach $100 for sets of common PG variants, such a program could prove to be highly cost-effective in addition to benefiting patients.

The potential utility of this approach is underscored by the recent Patient Protection and Affordable Care Act of 2010, through which federal legislators have established an aggressive timeline to encourage widespread implementation of EHRs, and to provide incentives if the application is determined to fulfill pre-specified “meaningful use” objectives. The implementation of clinical decision support rules related to high priority conditions like preventable AEs may typify “meaningful use.” Growth in EHR adoption provides the foundation to rapidly implement decision support rules for genetic prescribing across many healthcare systems nationally.

While the results of this research point towards a beneficial impact of preemptive, multiplexed genotyping, it is important to recognize several limitations. First, only medication exposures that were observed at VUMC were recorded, and so medications obtained elsewhere were not included in our calculations. Second, since the medical home date occurred at a single point in time, our estimates of medication exposure rates are only directly applicable at that time-point and may not be applicable to all patients, dynamically over time. Third, the medical home requirement (i.e., three clinic visits in two years occurring after January 1, 2005) may lead to a sample that differs from the general population of adults due to selecting patients who are seeking healthcare multiple times. Likely they would be older and sicker than the general population. We do not believe the population is fundamentally different than that seen in other medical home populations, though application of these results to other populations minimally would require careful consider consideration and likely will require further research. Fourth, for calculating AEs

prevented, we used AE rates derived from research cohorts; we expect real-world rates are likely to be similar or higher given compliance issues and other barriers to optimal care, as has been demonstrated recently with major cardiovascular events during clopidogrel therapy.(16) Future studies could use carefully defined EMR algorithms based on natural language processing (such as developed previously) (17) or patient observation to determine actual AE rates. Fifth, the overall impact of a preemptive genotyping program would vary depending on the demographic and ancestral makeup of the population to which it is applied. Sixth, in our calculation of number of AEs prevented, we did not incorporate all sources of uncertainty. For example, we assumed genotype probabilities and overall adverse event rates were known quantities. Lastly, in many cases, we do not know how well a PG-based intervention, if used, would perform for those in the high-risk genetic strata and how it would alter adverse event risk profiles. In this manuscript, we assumed a highly effective mitigation strategy that reduced the higher risk genetic strata to the baseline risk. We point the reader to a web application that performs calculations for individual AEs and that features inputs such as mitigation strategy effectiveness (see http://data.vanderbilt.edu/rapache/Case4PG). Ideally, future studies will seek to examine pharmacogenetic effects in the presence of alternative strategies as was done in one study,(18) that examined the interaction between *CYP2C19* polymorphisms and clopidogrel versus prasugrel treatment. Factors such as the cost and efficacy of alternative therapies, compliance with medication regimens, delivery of complex PG-based decision support to providers, and insurance coverage would each impact PG-based mitigation strategies.

In summary, we present a study of a medical home population for possible exposures to medications with FDA-listed pharmacogenetic variants. The widespread exposure of this population supports the development of systems that incorporate prospective genotyping and that thus will allow examination of the extent of applicability to other populations, and evaluation of the logistics, patient understanding, costs, and outcomes of this approach.

Methods

Identifying individuals using VUMC as their Medical Home

To identify individuals followed by physicians at VUMC, we selected the subset that had completed three outpatient visits in a two-year time frame within primary care, nephrology, cardiology, or diabetes clinics. These individuals were considered to have their primary "medical home" at VUMC. To be included, individuals had to meet the medical home definition after January 1, 2005, the date after which the current EHR system at VUMC was used uniformly throughout all inpatient and outpatient facilities.

Measurement of drug exposure

Once the medical home date was established, we obtained prescription records from that date through June 30, 2010 by combining all inpatient and outpatient electronic prescription records with medication records extracted from clinical documentation using a validated natural language processing (NLP) tool.(19) Records scanned included outpatient medication lists and all electronic clinical documentation, such as clinic notes, discharge summaries, and provider-staff communication. This approach has been shown to produce drug-exposure records with high specificity.(20,21) All NLP references to medication prescriptions were dated, and we required mention of a tablet strength, medication dose, route, or frequency. From these data, we calculated the rates at which individuals were prescribed each of the target medications. We used the SD, a de-identified copy of the EHR, for this study.(22) Race and ethnicity were derived from patient registration within the SD; we have previously observed that this ethnicity and race designation agrees closely with

genetic ancestry determined by ancestry informative markers for individuals of European and African descent.(23)

Generation of a set of study medications

We generated a list of medications for which existing studies indicate that genetic variation modulates response; we refer to these as PG medications. We considered only germline variants (excluding somatic mutations such *EGFR* with cetuximab) in this analysis, and we included all medications listed as having pharmacogenetic biomarkers by the FDA (http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm) or were found in searches of FDA package inserts using DailyMed (http://dailymed.nlm.nih.gov/dailymed/about.cfm) as of January 2011. We also included simvastatin because of the association of myotoxicity with *SLC01B1* variants,(11) that has been the subject of new guidance from the FDA.(24)

Ascertainment of Effect Sizes and Allele Frequencies

We searched PubMed to obtain estimates of effect sizes and allele frequencies for PG medications. The search included articles written in English published through December 31, 2010. For each medication-AE combination, meta-analyses that included recent, relevant literature were selected, if available. If not available, a single, high quality article was selected. When more than one article was available, the following criteria were applied to select a single study (in order of application): cohort size, date of study, and journal impact factor. Three authors (E.B., J.D., J.S.) extracted and reviewed data from studies retained for review. We focused on medications shown to have an effect in patients of European or African ancestries, the two predominant ancestry groups seen at VUMC. The articles reviewed and the results used for the present analysis are described in the Supplementary Material.

Medication Exposure Estimation

To calculate the rates at which individuals at VUMC were exposed to individual and multiple target medications, we used the Kaplan-Meier product limit estimator of cumulative incidence (25) beginning with the medical home date while remaining agnostic to prior exposure. This allowed us to estimate the probability of medication exposure within a fixed time period from the medical home date, and we focused on a five-year time horizon. By multiplying initial risk set sample size (N) by the five year medication *med* exposure probability [pr(*med*)], we estimated the expected number of *med* exposures, i.e., $N_{med}=N \bullet pr(med)$. For medications with glucose-6-phosphate dehydrogenase (*G6PD*) deficiency indications, we considered only the medication exposures occurring in African Americans, given the very low incidence of *G6PD* deficiency in European Americans. (26-28)

Adverse Events Prevented Calculations

We selected six medications with well-established AEs influenced by pharmacogenetic variants; they included abacavir skin/mucosal hypersensitivity, azathioprine myelosuppression, clopidogrel lack of efficacy to prevent major cardiovascular events (myocardial infarction, stroke, or death), simvastatin myopathy, tamoxifen and breast cancer recurrence, and warfarin-related bleeding. We combined the number of medication exposures N_{med} with literature based estimates of 1) PG effects (e.g., odds ratio, risk ratio, risk difference), 2) overall AE prevalences associated with medications, and 3) prevalences of genetic risk strata (e.g., homozygote or heterozygote for a given variant), to estimate the number of AEs that might have been prevented had an effective genotyping and mitigation

strategy program been in place. Detailed descriptions of the calculations are provided in the Appendix, and a brief summary is provided here.

Let G=g(g=0, 1, or 2)) denote the genetic risk stratum where $g=0$ denotes the common allele (usually lower risk) stratum and $g=1$ and 2 denote variant allele strata (usually higher risk). This assumes the lower frequency variants confer higher risk. While often the case, such an assumption may not hold across all race/ancestry groups. This structure permits three risk stratum models (0, 1, and 2 copies of risk alleles), although many studies report two stratum models (e.g., with allelic tests of association) in which case there is no $G=2$ stratum. Let $\mathrm{pr}(G=g|med)$ and pr(AE|G=g, *med*) denote the stratum g prevalence and the AE probability (i.e., risk)) in stratum g for those receiving medication *med*, respectively. Then, if we assume we are able to lower the AE risk in the high risk strata $100 \bullet p$ percent of the way towards the common allele stratum (e.g., with a $100 \bullet p$ percent effective mitigation strategy, $0 \leq p \leq 1$), the number of AEs prevented ($NP_{med,g,p}$) for those in stratum $G=g$ on medication *med* is given by,

$$NP_{med,g,p}=N_{med} \bullet pr(G=g|med) \bullet p \bullet ARD_{med,g,}$$

where $ARD_{med,g}$=pr(AE|G=g, *med*))-pr(AE|G=0, *med*)) is the absolute risk difference of experiencing an AE between risk stratum $G=g$ and $G=0$. For the sake of this research, we will assume that $p=1$ (and report $NP_{med,g,1}$) indicating the ideal situation of a highly effective mitigation strategy. We note that such an assumption is strong since p is often unknown; however, for a $100 \bullet p$ percent mitigation strategy, $NP_{med,g,p}=p \bullet NP_{med,g,1}$, and so calculations for less effective mitigation strategies from the results we report are straightforward. Since many pharmacogenetic studies are retrospective, case-control studies, they report relative effect measures such as the odds ratio (OR) or the relative risk (RR). The calculation of $ARD_{med,g}$, from ORs and RRs is detailed in the Appendix.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This research was supported in part by National Institutes of Health grants RC2 GM092618, U19 HL065962 of the Pharmacogenomics Research Network (PGRN), and Vanderbilt CTSA Grant 1 UL1 RR024975 from the National Center for Research Resources. We thank two referees and the associate editor for their feedback that improved the manuscript.

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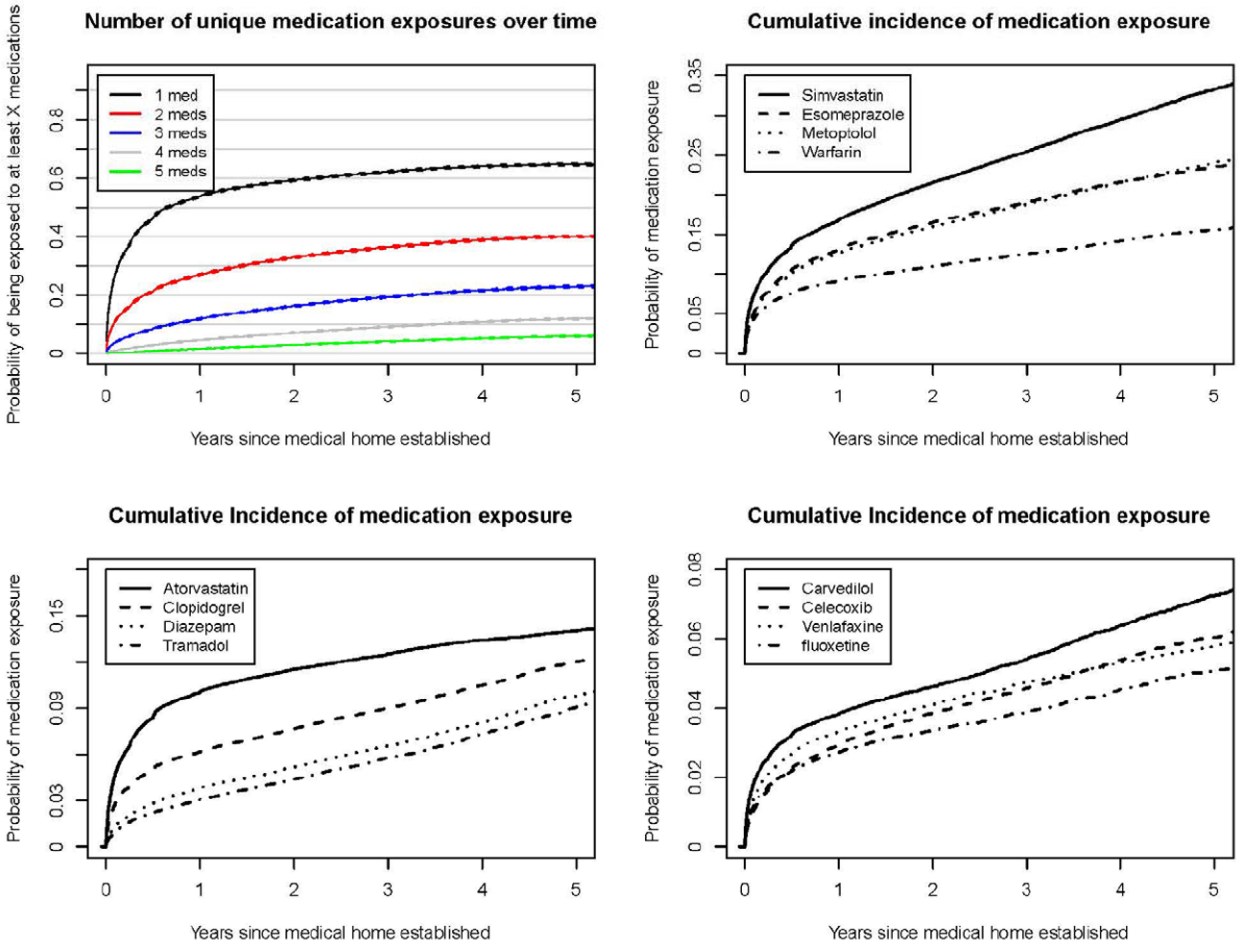

Figure 1.
Cumulative incidence of medication exposures as a function of time since medical home was established.

Table 1

Characteristics of the medical home population.

	Overall	Female	Male	European American	African American	Other ancestries	Unspecified ancestry
N	52942	30568	22374	38619	6685	1761	5877
Female	0.577	-	-	0.561	0.672	0.599	0.574
Race							
European American	0.729	0.708	0.759				
African American	0.126	0.147	0.098	-	-	-	-
Other	0.033	0.035	0.032	-	-	-	-
Unspecified	0.111	0.11	0.112	-	-	-	-
Age (years)	31,54,75	30,52,75	33,55,75	32,55,76	29,50,72	28,43,67	30,51,72
Follow-up time	0.6,3.1,5.4	0.6,3.1,5.4	0.6,3.0,5.4	0.7,3.3,5.4	0.8,3.6,5.6	0.6,2.9,5.2	0.1,1.6,4.2
Number of Pharmacogenetic Medications *							
0	0.353	0.372	0.327	0.325	0.293	0.514	0.557
1	0.246	0.249	0.241	0.246	0.24	0.241	0.252
2	0.17	0.164	0.179	0.179	0.174	0.128	0.121
3	0.11	0.104	0.12	0.119	0.13	0.062	0.049
4	0.061	0.055	0.068	0.067	0.072	0.032	0.016
5	0.031	0.03	0.034	0.034	0.044	0.012	0.004
6	0.016	0.014	0.018	0.018	0.022	0.007	0.001
≥7	0.012	0.013	0.012	0.013	0.026	0.003	0.000

Continuous variables are summarized with the 10^{th}, 50^{th}, 90^{th} percentiles, and categorical variables are summarized with proportions.

* The top 25 most commonly prescribed pharmacogenetic medications are listed in Table 2. A total of 56 medications were included in the search; see Appendix for the less commonly prescribed medications.

Clin Pharmacol Ther. Author manuscript; available in PMC 2013 September 27.

Table 2

Cumulative number of medication exposures per 1000 individuals within five years of establishing medical home.

	Overall		Female		Male		European American		African American		Other Ancestries		Unspecified Ancestry	
Med	**Rank**	**per 1000**	**Rank**	**per 1000**	**Rank**	**per 1000**	**Rank**	**per 1000**	**Rank**	**per 1000**	**Rank**	**per 1000**	**Rank**	**per 1000**
simvastatin	1	333 (327, 339)	1	285 (278, 292)	1	399 (390, 408)	1	337 (330, 343)	1	367 (352, 381)	1	243 (216, 268)	1	273 (248, 296)
metoprolol	2	241 (236, 246)	3	208 (201, 214)	2	287 (279, 295)	2	253 (248, 259)	2	265 (252, 278)	3	138 (118, 158)	4	112 (100, 124)
esomeprazole	3	236 (231, 241)	2	239 (232, 245)	3	232 (225, 239)	3	246 (241, 251)	3	249 (237, 262)	2	194 (169, 218)	2	127 (113, 141)
warfarin	4	156 (152, 160)	4	130 (125, 135)	4	192 (185, 198)	4	172 (168, 177)	4	142 (132, 153)	8	55 (41, 68)	5	71 (57, 86)
atorvastatin	5	140 (137, 144)	5	115 (111, 119)	5	175 (169, 181)	5	148 (144, 153)	6	121 (112, 130)	4	109 (91, 127)	3	116 (99, 133)
clopidogrel	6	120 (116, 124)	8	90 (86, 94)	6	162 (155, 168)	6	129 (125, 133)	7	112 (103, 122)	5	78 (61, 95)	6	58 (48, 68)
diazepam	7	98 (94, 101)	7	102 (97, 106)	8	93 (88, 98)	7	105 (101, 109)	9	100 (91, 110)	7	55 (39, 70)	12	28 (20, 35)
tramadol	8	91 (87, 94)	6	107 (102, 112)	9	69 (64, 74)	8	91 (87, 95)	8	112 (101, 122)	6	72 (52, 91)	8	46 (35, 57)
carvedilol	9	72 (70, 75)	12	55 (52, 58)	7	96 (91, 101)	9	74 (70, 77)	10	86 (78, 95)	10	36 (25, 47)	7	48 (39, 56)
celecoxib	10	60 (58, 63)	10	68 (64, 72)	10	50 (46, 54)	11	64 (61, 67)	13	51 (44, 58)	9	47 (34, 61)	11	38 (31, 45)
venlafaxine	11	58 (55, 60)	9	75 (72, 79)	13	34 (31, 37)	10	65 (62, 68)	15	37 (32, 43)	12	27 (17, 36)	9	39 (31, 47)
fluoxetine	12	51 (48, 53)	11	66 (63, 70)	14	29 (27, 32)	12	56 (53, 59)	16	35 (29, 40)	14	18 (11, 24)	10	38 (31, 45)
tiotropium_bromide	13	38 (36, 40)	14	34 (31, 37)	11	43 (40, 47)	13	42 (39, 45)	19	28 (23, 33)	21	10 (1, 18)	13	22 (17, 27)
terbinafine	14	29 (27, 31)	18	24 (21, 26)	12	36 (32, 39)	15	28 (26, 30)	17	34 (28, 39)	11	36 (22, 49)	14	21 (14, 29)
tolterodine	15	26 (25, 28)	13	35 (32, 37)	19	15 (13, 17)	14	29 (27, 31)	22	23 (19, 27)	20	12 (5, 20)	16	12 (7, 16)
codeine	16	24 (22, 26)	15	29 (26, 31)	16	18 (16, 21)	16	26 (24, 28)	21	25 (20, 30)	16	15 (7, 23)	21	7 (4, 11)
rabeprazole	17	20 (19, 22)	17	24 (22, 26)	18	16 (14, 17)	17	22 (20, 23)	25	16 (13, 20)	17	15 (6, 24)	15	20 (13, 27)
co-trimoxazole *	18	20 (18, 22)	16	25 (22, 27)	22	13 (11, 15)	-	-	5	142 (131, 153)	-	-	-	-
risperidone	19	19 (17, 20)	20	20 (18, 22)	17	17 (14, 19)	18	17 (16, 19)	18	33 (28, 38)	22	9 (4, 14)	19	8 (3, 14)
timolol_maleate	20	19 (17, 20)	23	18 (16, 20)	15	20 (17, 22)	21	16 (14, 18)	14	38 (33, 44)	13	19 (9, 29)	17	11 (4, 17)
azathioprine	21	17 (15, 18)	21	19 (17, 21)	21	13 (12, 15)	20	16 (15, 18)	23	22 (18, 26)	18	14 (7, 21)	18	10 (7, 14)
doxepin	22	15 (14, 17)	22	18 (16, 20)	24	12 (10, 14)	19	17 (15, 18)	29	13 (10, 17)	15	16 (6, 27)	23	6 (2, 11)
propanolol	23	15 (13, 16)	25	17 (15, 19)	25	11 (9, 12)	23	15 (14, 17)	26	14 (11, 18)	24	7 (2, 12)	20	8 (5, 10)
aripiprazole	24	14 (13, 16)	24	17 (15, 19)	26	11 (9, 12)	22	16 (14, 18)	27	14 (10, 17)	23	7 (2, 12)	29	3 (1, 5)
tamoxifen	25	12 (11, 13)	19	21 (19, 23)	47	0 (0, 1)	24	14 (13, 15)	32	7 (5, 9)	19	13 (8, 19)	25	6 (3, 8)

Columns display the rank of the 25 most prescribed (of 56) PG medications and the expected count (95% CI) for groups defined by gender and ancestry. For calculations involving *G6PD* medications (e.g., co-trimoxazole), exposure to the medication in EA individuals were ignored given the low incidence of *G6PD*. Thus, co-trimoxazole exposure to susceptible individuals occurs at a rate of 20 per 1000 overall, but at a rate of 142 per 1000 in the AA race.

* *G6PD* medication

Table 3

Number of preventable adverse events for the VUMC sample with an effective preemptive genotyping and mitigation strategy program.

Medication	Adverse Event	Gene	Ancestry	Risk Strata (G=0, G=1, G=2)	Risk stratum prevalence [pr(G=0), pr(G=1), pr(G=2)]	N_{med}	Overall Event Probability*	$NP_{med,g,1}$ (number of events prevented)		
								G=1	G=2	Total (G=1+G=2)
Abacavir (29)	Reaction within first 6 weeks of treatment	*HLA-B**5701 allele	All	(Absent, Present,--)	[0.944, 0.056, --]	87	--	3 (3, 3)	--	3 (3, 3)
Azathioprine (30)	Myelosuppression (leukopenia) after at least 3 months	*TPMT* activity	All	(CA, 1 VA,--)	[0.898, 0.102, --]	878	0.098	17 (13, 21)	--	17 (13, 21)
Clopidogrel (31)	Myocardial infarction, death, or stroke	*CYP2C19**2 or *3 or *4 or *5	All	(CA, 1 VA, 2 VA)	[0.715, 0.263, 0.022]	6361	0.089	71 (13, 131)	8 (3, 16)	79 (23, 139)
Simvastatin (11)	Myopathy during follow-up (average of 6 years)	*SLCO1B1* rs4149056	All	(TT, CT, CC)	[0.7225, 0.255, 0.0225]	17631	0.003	14 (4, 25)	5 (1, 14)	19 (8, 30)
Tamoxifen (10)	Breast cancer recurrence at 9 years of follow-up	*CYP2D6* (IM or PM)	EA	(EM, IM, PM)	[0.62, 0.33, 0.05]	540	0.186	11 (1, 22)	4 (0, 9)	15 (4, 26)
Warfarin (32)	All bleeding events	carrier of *CYP2C9**2	EA	(CA, ≥1 VA, --)	[0.729, 0.271, --]	6651	0.13	172 (34, 316)	--	172 (34, 316)
Warfarin (32)	All bleeding events	carrier of *CYP2C9**3	EA	(CA, ≥1 VA, --)	[0.851, 0.149, --]	6651	0.13	93 (8, 193)	--	93 (8, 193)
Total										398 (225, 583)

CA=common allele; VA=variant allele; EM=extensive metabolizer; IM=intermediate metabolizer; PM=poor metabolizer.

N_{med} represents the number of individuals exposed to the medication within five years of the medical home date.

*Assumed probability of the adverse event across all individuals receiving the medication. This value was not required for $NP_{med,g,1}$ calculations when examining abacavir because event rates reported(26) within genetic risk strata were used directly. We refer readers to the appendix for a sensitivity analysis that examines the number of preventable adverse events for varying assumed adverse event rates.