Published in final edited form as:

Mayo Clin Proc. 2015 June ; 90(6): 716–729. doi:10.1016/j.mayocp.2015.03.016.

Evidence for Clinical Implementation of Pharmacogenomics in Cardiac Drugs

Amy L. Kaufman, B.S.[1], **Jared Spitz, B.S.**[2], **Michael Jacobs, B.S.**[2], **Matthew Sorrentino, M.D.**[3], **Shennin Yuen, M.A.**[2], **Keith Danahey, M.S.**[4], **Donald Saner, M.S.**[4], **Teri E. Klein, Ph.D.**[5], **Russ B. Altman, M.D., Ph.D.**[5,6], **Mark J. Ratain, M.D.**[2,3,7], and **Peter H. O'Donnell, M.D.**[2,3,7]

[1]The University of Chicago, Pritzker School of Medicine, Chicago, IL

[2]Center for Personalized Therapeutics, The University of Chicago, Chicago, IL

[3]Department of Medicine, The University of Chicago, Chicago, IL

[4]Center for Research Informatics, The University of Chicago, Chicago, IL

[5]Department of Genetics, Stanford University, Palo Alto, CA

[6]Departments of Bioengineering and Medicine, Stanford University, Palo Alto, CA

[7]Committee on Clinical Pharmacology and Pharmacogenomics, The University of Chicago, Chicago, IL

Abstract

Objective—To comprehensively assess the pharmacogenomic evidence of routinely-used drugs for clinical utility.

Methods—From January 2, 2011 to May 31, 2013, we assessed 71 drugs by identifying all drug/genetic variant combinations with published clinical pharmacogenomic evidence. Literature supporting each drug/variant pair was assessed for study design and methodology, outcomes, statistical significance, and clinical relevance. Proposed clinical summaries were formally scored using a modified AGREE (Appraisal of Guidelines for Research and Evaluation) II instrument, including recommendation for or against guideline implementation.

Results—Positive pharmacogenomic findings were identified for 51 of 71 cardiovascular drugs (71.8%) representing 884 unique drug/variant pairs from 597 publications. After analysis for quality and clinical relevance, 92 drug/variant pairs were proposed for translation into clinical

Corresponding author: Peter H. O'Donnell, MD, Center for Personalized Therapeutics, Department of Medicine, The University of Chicago, Chicago, IL 60637, USA, podonnel@medicine.bsd.uchicago.edu, Phone: (773) 702-7564; Fax: (773) 702-3163.

[a]Pharmacogenomic information (PGx)

Disclosure:

- MJR is a coinventor holding patents related to pharmacogenetic diagnostics and receives royalties related to *UGT1A1* genotyping.
- RBA is a founder of, stockholder of, and consultant to Personalis, Inc.

summaries, encompassing 23 drugs (32.4% of drugs reviewed). All were found recommended for clinical implementation using AGREE, with average overall quality scores of 5.18 (out of 7.0; range 3.67 to 7.0; SD 0.91). Drug guidelines had highest scores in AGREE domain 1 (Scope) (average 91.9 out of 100; SD 6.1), and moderate but still robust scores in domain 3 (Rigour) (average 73.1; SD 11.1), domain 4 (Clarity) (average 67.8; SD 12.5), and domain 5 (Applicability) (average 65.8; SD 10). The drugs clopidogrel (*CYP2C19)*, metoprolol (*CYP2D6)*, simvastatin (rs4149056), dabigatran (rs2244613), hydralazine (rs1799983, rs1799998), and warfarin (*CYP2C9/VKORC1*) were distinguished by the highest scores. Eight of the 10 most commonly-prescribed drugs warranted translation guidelines summarizing clinical pharmacogenomic information.

Conclusions—Considerable clinically actionable pharmacogenomic information for cardiovascular drugs exists, supporting the idea that consideration of such information when prescribing is warranted.

Introduction

Each year, over 2 million patients experience adverse drug reactions (ADRs), the fifth leading cause of death in the United States[1]. In particular, cardiovascular drugs are a common cause of ADRs[2,3]. It is estimated that 53,457 individuals of all ages are treated annually in emergency rooms for adverse reactions to cardiovascular agents[2]. In adults over age 65, cardiovascular drugs are implicated in a sizeable fraction of hospitalizations for ADRs, most notably warfarin (33.3%) and antiplatelet agents (13.3%), among others[3].

In addition to the harm caused by drug-related toxicities, the healthcare system wastes resources when medications are ineffective. Intolerance and suboptimal response rates to cardiovascular drugs have been widely reported[4–7]. For example, the response rate to any given hypertension medication is approximately 50%, regardless of the class of medication[4,8]. In general, drugs are developed based on their effectiveness in large, carefully selected populations; a drug's performance in that setting is less informative when treating individual patients[5,9]. Thus, there is a need to better identify therapies that are both more likely to be beneficial and less likely to cause harm to individual patients, who show remarkable variability in their response to medications[10,11].

Pharmacogenomics, the study of genetic variation in drug response, has enabled the identification of genetic variants that impact response or toxicity to several prominent cardiovascular drugs[5,9,12–16]. While the effective clinical translation of this information has the potential to guide the selection and dosing of medications[4,17] few cardiovascular drug pharmacogenomic findings have been translated into clinical practice[18,19]. This gap in translation exists for numerous reasons, including lack of knowledge and cost-effectiveness concerns[19]. Foremost among these, however, is the need to establish clinical utility[16,20]. Yet, as exemplified by the cases of clopidogrel and warfarin, even when a Food and Drug Administration (FDA) label is changed in recognition of the potential clinical impact of pharmacogenomic evidence, controversy concerning the implementation of this information persists[16,18,21–29]. In light of these challenges, there is considerable disagreement

concerning the overall strength of pharmacogenomic evidence, with some[30,31] arguing the evidence is considerable and others[32,33] refuting its overall usefulness.

Since cardiovascular drugs are widely prescribed[34], our study aimed to rigorously assess the state of potential clinical utility for the pharmacogenomic evidence surrounding cardiovascular drugs—a necessary foundation for clinical implementation. We systematically assessed the quality and quantity of pharmacogenomic data to permit and inform clinical implementation projects that will ultimately determine utility on clinical outcomes. We sought to critically appraise the pharmacogenomic literature and propose translation-enabling clinical summaries on a drug-by-drug basis. We hypothesized that the composite amount of clinically relevant pharmacogenomic information for cardiovascular drugs would provide considerable evidence for a major contribution to drug prescribing decisions.

Methods

Data collection

From publicly available sources, including all FDA-approved drugs and the Pharmacogenomics Knowledge Database (PharmGKB)[35], a list of commonly prescribed cardiovascular drugs was selected (Supplementary Material, Appendix A). For each drug, a manual literature search of PubMed was performed. The formal search began in January 2011, but inclusion of papers was not restricted to this interval; rather, any publication from any month and year until May 2013 that met search criteria was included for subsequent review. The search criteria used was “[Drug name] polymorphism.” Only articles that assessed a link between a germline genetic variant and a pharmacologic or clinical outcome were included. Non-English language articles, articles concerning *in vitro* studies, pediatric studies, manuscripts simply describing literature searches, and reviews were excluded. All articles meeting these inclusion and exclusion criteria were then formally reviewed using the below process. The complete date range of the study was January 2, 2011 to May 31, 2013.

Data assessment

The unit of study, the drug/variant pair, refers to a specific drug and genetic variant (e.g., hydrochlorothiazide and rs1799752). The drug/variant pairs reported within each article were cataloged with supporting PMID(s) in a database built to support a larger clinical pharmacogenomics implementation project, The 1200 Patients Project[36]. This database catalogs a list of pharmacogenomic publications and reported drug/variant pairs for over 650 drugs[36]. The publication concerning each pair in the database is classified as “Positive PGx” if the authors reported a positive genotype-phenotype association, or “Negative PGx” if the association was not reported as significant; these designations were verified during literature review and were corrected if necessary after reviewing the paper. Drug/variant pairs were then first stratified regarding their supporting evidence using four criteria: (1) a drug/variant pair with three or more positive supporting publications in The 1200 Patients Project database, (“3+ Studies”); (2) a drug/variant pair independently clinically annotated (publicly available pharmacogenomic “Clinical Annotation” on the PharmGKB webpage[35]) by PharmGKB, (“PharmGKB”); (3) both of (1) and (2), (“3+ Studies & PharmGKB”); or (4)

none of the above (1) through (3) (“Other”). The PharmGKB data used for these analyses was captured between January 2012 and May 2013.

Each positive publication supporting a cardiovascular drug/variant pair was then comprehensively assessed. Pharmacogenomic associations were assessed for study cohort size, whether statistical significance was reported using a correction for multiple testing, consideration of Hardy-Weinberg equilibrium, and, importantly, the clinical relevance of the phenotypes being reported. If, for each drug/variant pair, the data was determined by two independent members of the research team to provide clinically relevant evidence that could influence a physician’s drug prescribing decision, a clinical translation summary was proposed and written. For each proposed clinical summary, a level of evidence was assigned:

- Level 1: from a well-performed large study including replication, or replicated by two or more large, well-performed studies; published dosing guidelines or FDA label information likely exists; or
- Level 2: from at least one well-performed study of at least 100 patients; or from several small or moderately-sized studies which show consistent results; or
- Level 3: from a relatively small single study (<100 patients); or several similarly executed contradictory studies exist.

Finally, each proposed summary was formally assessed using a modified AGREE II scoring instrument to determine whether each clinical summary warranted clinical implementation[37]. After the writing of each draft summary, three independent appraisers applied a modified AGREE II scoring system to the summaries for each drug/variant pair. The modified AGREE II scoring system encompassed all domains of AGREE II with the exceptions of domain 2 (Stakeholder Involvement) and domain 6 (Editorial Independence), which were removed from our modified instrument since these domains were not applicable to any of the accumulated drug/variant evidence summaries in our project. The resulting modified AGREE II instrument included the specific AGREE II instrument items encompassing the domains of Scope and Purpose, Rigor of Development, Clarity of Presentation, and Applicability, as shown in full in Appendix B. The AGREE instrument has been previously validated as a tool for guideline assessment, and the items comprising the tool have been found to be useful, easy-to-use, and transparent[38–41].

In addition to applying the modified AGREE II instrument to obtain scores across the AGREE domains for the proposed summaries from our evidence assessment, each summary was given an overall score and was rated as to whether it deserved standing as a clinical guideline. Domain scores were calculated as per the methods outlined in the AGREE II user manual[37] and the overall guideline score was obtained by averaging scores from the three appraisers. The AGREE appraisal of whether to recommend or not was used as the final determination of worthiness for implementation.

Results

Drugs with High-Level Pharmacogenomic Evidence

Among the included 71 cardiovascular drugs, 51 (71.8%) had positive pharmacogenomic ("Positive PGx") findings reported in the literature (Table 1). The literature supporting these 51 drugs encompassed 597 unique publications, 611 unique genetic variants, and 884 unique drug/variant pairs (some drugs were associated with the same genetic variants) (Supplementary Material, Appendix C).

The 884 unique drug/variant pairs were divided into four categories (Table 1). The first category, "3+ Studies & PharmGKB," comprised 33 drug/variant pairs that were supported by 3 or more studies and had a publicly available clinical annotation in the external PharmGKB database. Per our inclusion criteria, 25 (75.8%) of the pairs in this group warranted proposed clinical summaries, of which 4 were rated as Level 1 evidence, and 6 were Level 2 evidence (Table 1). The second category, pairs with only a pharmacogenomic clinical annotation ("PharmGKB only"), consisted of 43 drug/variant pairs annotated by PharmGKB, but which, in our comprehensive search, did not have at least 3 identified, published studies. Of these, 10 pairs (23.3%) warranted proposed clinical summaries, of which 5 had Level 2 evidence ratings and 5 had Level 3 (Table 1). The third category, "3+ Studies only," comprised 37 drug/variant pairs supported by 3 or more published studies but for which no public annotation was found. Of these, 9 (24.3%) warranted proposed clinical summaries, of which 4 had Level 2 evidence ratings and 5 had Level 3 (Table 1). The final category, "Other," consisted of the 771 drug/variant pairs that did not have 3 or more studies nor a public annotation. Of these, 48 (6.2%) warranted proposed clinical summaries, the majority of which 32 pairs had Level 2 evidence ratings while 16 had Level 3 (Table 1).

In total, 92 (10.4%) of the 884 drug/variant pairs warranted proposed clinical implementation summaries, of which 25 were supported by both 3 or more publications and a PharmGKB annotation and 9 were supported by 3 or more positive publications alone (Table 2). A few key genes, *CYP2C9*, *CYP2C19*, and *VKORC1*, comprise half (17 of 34) of the summaries supported by three or more positive publications (Table 2). In sum, 23 of the 71 cardiovascular drugs (32.4%) warranted at least one proposed clinical summary (Table 3).

AGREE Assessment of Clinical Translation Summaries for Clinical Implementation

The clinical summaries were assessed in the four domains (Scope & Purpose, Rigour of Development, Clarity of Presentation, and Applicability) and given an overall score (on a scale of 1 to 7) (Table 3). For the overall guideline assessment, all proposed clinical summaries were recommended for implementation. The average overall quality score was 5.18, with a standard deviation (SD) of 0.91 and range of 3.67 to 7 (Table 3). For domain 1 (Scope & Purpose) scores averaged 91.9, with a SD of 6.1 and range of 74.1 to 100. For domain 3 (Rigor of Development), scores averaged 73.1, with a SD of 11.1 and range of 51.9 to 100. For domain 4 (Clarity of Presentation), scores averaged 67.8, with a SD of 12.5 and range of 44.4 to 100. For domain 5 (Applicability), scores averaged 65.8, with a SD of 10 and range of 50 to 97.2. Per the AGREE scores, the summaries for clopidogrel

(*CYP2C19*), metoprolol (*CYP2D6*), warfarin (*CYP2C9/VKORC1*), simvastatin (rs4149056), dabigatran (rs2244613), and hydralazine (rs1799983 and rs1799998) performed the highest, with average quality scores greater than 6 on a 7-point scale (Table 3).

The AGREE-rated summaries that were appraised as worthy of clinical implementation are currently being delivered to physicians through a pharmacogenomic results delivery interface in an institutional pharmacogenomic clinical implementation project[36]. These clinical summaries provide key information about the implications of a pharmacogenomic genotype result on clinical outcomes (such as adverse drug reactions, response to treatment, or drug vs. drug comparisons) and represent a synthesis of the key published studies including information on effect size and statistical significance, with an emphasis on replication whenever possible. The clinical summaries for two different cardiovascular drugs are shown in Figure 1.

External Comparison of Implementation Guidelines with FDA Labels

Using data from the FDA's published Table of Pharmacogenomic Biomarkers in Drug Labeling, three drugs have key pharmacogenetic information incorporated into their FDA labels concerning the same genetic variants that we report on (warfarin, clopidogrel, and metoprolol)[42]. We agree with the labeling for clopidogrel and *CYP2C19*, metoprolol and *CYP2D6*, and warfarin and *CYP2C9* and *VKORC1*. However, our analyses for these drugs also contain additional information on variants beyond those listed on FDA labels (Tables 2 and 3).

Additional drugs, including atorvastatin, pravastatin, and carvedilol also have pharmacogenomic relationships incorporated into their FDA labels, but our findings cover different subgroups, variants, and clinical phenotypes than those on the label[42]. The remaining drugs we report on do not presently contain pharmacogenomic markers within their labeling.

Special Considerations

The AGREE instrument identified four very high scoring drug/variant pairs that have received particular attention in multiple prior publications, and therefore we consider those drugs specially here.

Clopidogrel—We identified 30 drug/variant pairs with positive pharmacogenomic associations for the antiplatelet agent clopidogrel, of which 10 pairs warranted proposed clinical summaries. Of the 10 clinical summaries, 3 were designated as Level 1 evidence. All 3 of these variants are located in the gene *CYP2C19*: rs12248560, rs4244285, and rs4986893. The clopidogrel/*CYP2C19* pair was among the highest AGREE scoring summaries in both overall quality score and by domain scores. Scores for clopidogrel across almost all items in the modified instrument were considerably above published cut-point values for "high quality"[40].

Metoprolol—Metoprolol and *CYP2D6* was determined to warrant clinical implementation as a drug/gene pair with a very high AGREE score. The metoprolol/*CYP2D6* pair received

an average overall quality score of 7 with domain 1, 3, 4, and 5 scores of 100, 100, 98.1, and 97.2 respectively (Table 3). Similar to clopidogrel and *CYP2C19*, scores for almost all individual items assessing the metoprolol/*CYP2D6* pair were above published cut-points defining "high quality."

Simvastatin—For simvastatin, 2 of the 61 identified drug/variant pairs with positive pharmacogenomic information were determined to warrant clinical summaries (Table 3). Of these, one variant (rs4149056) in the gene *SLCO1B1* concerning myopathy risk was assigned Level 1 evidence and was among the highest scoring pairs when the modified AGREE instrument was applied (Figure 1B, Table 3). This pair was identified by a GWAS and had an average overall quality score of 6.33, with domain 1, 3, and 4 scores of 98.1, 92.6, and 92.6 respectively. Additionally, almost all item scores in the modified AGREE evaluation of this pair were well above published values for "high quality".

Warfarin—The proposed warfarin clinical summary is unique in that it provides a recommended starting dose based on several factors, including genetic variants. According to the modified AGREE instrument, the warfarin summary was among the highest performing; it had an average overall quality score of 7 and domain scores over 90 in all four scored domains. The average scores for the items comprising domains 1, 3, and 4 are all above published values for "high quality." Despite these high scores on AGREE assessment, the level of evidence designation for this summary in our strata is only Level 3. This is because, subsequent to the primary literature capture period, the level of evidence designation for warfarin was lowered to reflect the data from several high impact studies that were published during data analysis that brought into question the clinical value of genomically-guided warfarin dosing compared to simply dosing based on patient-specific clinical factors[24,28,29].

Blockbuster Drugs

Finally, we examined the published pharmacogenomic evidence for the 10 most commonly prescribed cardiovascular drugs in the United States in 2011[34] (Table 4). Of these 10 blockbuster drugs, 8 warranted at least one clinical pharmacogenomic summary per assessment by the modified AGREE instrument. The average overall quality score for these 8 drugs was 5.03, with a SD of 0.94. For these 8 drugs, the domain 1 scores averaged 89.9 (SD 6.3), the domain 3 scores averaged 72.4 (SD 11.4), the domain 4 scores averaged 65.8 (SD 14.3), and the domain 5 scores averaged 65.0 (SD 11.7).

Among these blockbuster drugs, the potential for clinical impact is large. As one consideration, three of the drugs—simvastatin, atorvastatin and atenolol—have two different clinical outcomes that can be considered pharmacogenomically: treatment response and adverse effect. Additionally, for some drugs, the potential impact could touch millions of patients: simvastatin (and the genetic variant for myopathy risk) is illustrative here, as our analysis identified that the evidence base is large (encompassing data from over 17,000 patients) but the pool of patients potentially impacted by this information is even orders of magnitude larger (as simvastatin is the most commonly prescribed cardiovascular drug with 96.8 million annual prescriptions). Some drugs have clinical outcomes of very high interest:

for atorvastatin (with 43.3 million annual prescriptions), we identified 4 studies representing 8,078 patients that show an approximate 10% reduction in the risk of myocardial infarction or major cardiovascular event for patients with a favorable genotype. In total, for these top 10 cardiovascular blockbuster drugs alone, pharmacogenomic information having a published clinical impact on outcomes has been gathered from studies including over 83,575 total patients and is available to inform potentially 390 million current prescriptions per year.

Discussion

In this study, we comprehensively assessed the literature concerning the pharmacogenomics of cardiovascular drugs for clinical relevance, leading to the creation of pharmacogenomic composite summaries that could impact drug prescribing as part of pharmacogenomic clinical implementation efforts. We identified 51 cardiovascular drugs with positive published pharmacogenomic evidence, including 23 higher-evidence drugs warranting clinical summaries worthy of consideration for clinical implementation. These data, and the development of these clinical translation summaries for each of the highest drug/gene pairs, impact 8 of the 10 most commonly prescribed cardiovascular agents in the United States.

Given these results, our key finding is that the breadth and depth of clinically relevant pharmacogenomic information for cardiovascular therapeutics is both considerable and potentially meaningful. Several projects utilizing summarized pharmacogenomic information for clinical implementation are already underway[36,43–48], including use of the above developed summaries for clinical delivery at our institution. Aggregate, longer-term outcomes research from these and other projects will be necessary to ultimately evaluate clinical utility.

The determination of clinical relevance always depends on the specific patient in question being cared for by an individual physician, who may have his or her own interpretation of the data. We assigned relevance by assessing which clinical outcomes would be potentially important to clinical decision-making in two domains: treatment response and adverse events. For treatment response, we assessed studies that examined a drug's ability to achieve its desired clinical outcome based on its indication for use and we focused on results that physicians commonly measure as evidence of treatment response. Conversely, for genetic variants that govern risk of adverse reactions, our requirement was that the adverse effect be clinically important and have a clinically important effect size. In doing so, we tried to focus on those adverse effects a physician would factor into a decision to stop or change a medication. Whenever possible, published guidelines or dosing algorithms were referenced, and summaries were compared with such publicly available sources.

We applied Level of Evidence designations in addition to evaluating the strength of our summaries based on a modified AGREE II instrument. Our criteria for Level 1 designations were rigorous, and accordingly, only the best-studied drug/variant pairs were classified as such. Our stratified designations were consistent with Level of Evidence stratification systems developed similarly by PharmGKB[49], though small differences exist. Use of this system revealed that those drug/variant pairs not meeting either classifying criterion

("Other") yielded the lowest percent of pairs translated to summaries, as expected. Yet, this category still produced 48 summaries, highlighting the importance of a broad examination.

When applying the AGREE instrument, the average overall quality scores suggested very good quality to our summaries (Table 3). Our clinical summaries perform best in domain 1 (Scope & Purpose), averaging 91.9 out of 100, suggesting that our clinical summaries are clear in their objective, health question, and target population. The summaries perform relatively less well in the other domains, with the lowest scores in domain 5 (Applicability) with an average of 65.8. This is likely due to the fact that our guideline summaries were not initially designed to describe facilitators and barriers to application (the specific focus of domain 5 item 18) and only a few drug guidelines have strong enough evidence for specific tools for implementation (domain 5 item 19). Scores in domains 3 (Rigor of Development) and 4 (Clarity of Presentation), while still robust, are likely lower than those of domain 1 due to the difficulty in making unambiguous and specific recommendations when supporting studies are contradictory and/or small.

The field of pharmacogenomics suffers from a relative lack of large trials[50] and replicated findings which are required for the highest quality guidelines. As highlighted in Table 3, it is notable that most of the high-evidence variants were identified through candidate gene studies. Indeed, data from prospective, randomized controlled trials is not available for most pharmacogenomic drug/variant pairs. It has been argued that the lack of these studies presents a strong barrier to wider clinical implementation of pharmacogenomics. However, high quality drug/variant associations from other types of trials, many of which are reproduced across multiple studies and/or have strong supporting pharmacokinetic or pharmacodynamic evidence, can provide valuable and worthy information. We would argue that our formal analysis here has in fact shown that. Therefore, we posit that implementation of pharmacogenomic evidence can occur even in the absence of a randomized trial, if high quality data standards are met, and especially for situations of prescribing equipoise. For example, the clinical summaries recommended in our manuscript highlight the range of information that can be provided to clinicians, from predicting the chance a patient will respond clinically in terms of cholesterol lowering (Supplemental Figure 1A) or heart failure improvement (Supplemental Figure 1B), to providing a drug vs. drug comparison (Supplemental Figure 1C). Likewise, the clinical summaries of atenolol and verapamil (Supplemental Figure 1D–E) inform the physician about mortality in coronary artery disease patients and specifically provide a treatment recommendation choice between these two drugs for an individual patient.

The real life clinical decision of which drug to prescribe is multi-faceted. Yet, if a physician is faced with the choice of which beta-blocker among several to prescribe, this information may provide additional, additive dimensions to the clinical calculus, while invoking little to no additional risk of harm[19,30,36]. It may be the case that in situations of clinical equipoise, guidelines with lower AGREE scores may still influence the decision, whereas in other scenarios, only the highest AGREE scoring pairs or only through an assessment of absolute risk could a clinician justify changing a prescribing decision. Additionally, a physician may require a different level of confidence or certainty in the findings to alter his recommendation based on the patient population or the drug itself. In this way, the role of

pharmacogenomics in informing therapeutic decisions will necessarily depend on consideration of a number of clinical, environmental, and potentially even economic factors to achieve the most beneficial choice. Genetic relationships are just one of many factors that influence treatment response and will likely be best incorporated in the larger context of individualizing care.

There are limitations to this study. This work focused on a subset of all FDAapproved drugs indicated for the treatment of cardiovascular diseases, so other cardiovascular pharmacogenomic information could exist for drugs that were not included in the analysis. Also, by focusing on individual drugs, our analysis does not consider potential drug class effects (e.g., a specific variant for all statins).

Considering the hundreds of millions of annual cardiovascular drug prescriptions[34], frequency of adverse drug events[2,3], and variable levels of drug response[6,7,11], the impact of this knowledge for improving patient care is potentially prodigious[17,51]. Key to facilitating clinical implementation appears to be the production of guidelines[46], such as the work done by the Clinical Pharmacogenetics Implementation Consortium (CPIC)[52] and PharmGKB[35], which synthesize basic and clinical science research into tools for clinical use. Our work has attempted to do this as a comprehensive effort for cardiovascular drugs, with the output being clinically usable translations of genomic information into their practice meaning. The establishment of such clinical translations for routine use is essential to—and will permit—subsequent, necessary, larger, and potentially prospective, randomized and/or pragmatic clinical outcomes analyses.

Conclusion

There is substantial pharmacogenomic information on cardiovascular drugs that could potentially be applied to patient care. Given the burden of cardiovascular disease and the potential of personalized medicine, this information merits being made available for clinical implementation in a research context to determine if it impacts physician decision-making and patient outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial support

- Supported by The University of Chicago Pritzker Summer Research Program (ALK), NIH K12 CA139160 and K23 GM100288-01A1 (PHO), NIH/NHLBI 5 U01 HL105198-09 (MJR and PHO), The Conquer Cancer Foundation of the American Society for Clinical Oncology (MJR), and The William F. O'Connor Foundation (MJR).

List of Abbreviations

ADR	adverse drug reaction

CPIC	Clinical Pharmacogenetics Implementation Consortium
FDA	Food and Drug Administration
PharmGKB	Pharmacogenomics Knowledge Database
PGx	pharmacogenomic information
PMID	PubMed identifier

References

1. Meyer UA. Pharmacogenetics and adverse drug reactions. Lancet. Nov 11; 2000 356(9242):1667–1671. [PubMed: 11089838]
2. Budnitz DS, Pollock DA, Weidenbach KN, Mendelsohn AB, Schroeder TJ, Annest JL. National surveillance of emergency department visits for outpatient adverse drug events. JAMA. Oct 18; 2006 296(15):1858–1866. [PubMed: 17047216]
3. Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older Americans. N Engl J Med. Nov 24; 2011 365(21):2002–2012. [PubMed: 22111719]
4. Johnson JA. Advancing management of hypertension through pharmacogenomics. Ann Med. Jun; 2012 44(Suppl 1):S17–22. [PubMed: 22713143]
5. Myburgh R, Hochfeld WE, Dodgen TM, Ker J, Pepper MS. Cardiovascular pharmacogenetics. Pharmacol Ther. Mar; 2012 133(3):280–290. [PubMed: 22123178]
6. Postmus I, Verschuren JJ, de Craen AJ, et al. Pharmacogenetics of statins: achievements, whole-genome analyses and future perspectives. Pharmacogenomics. May; 2012 13(7):831–840. [PubMed: 22594514]
7. Mangravite LM, Thorn CF, Krauss RM. Clinical implications of pharmacogenomics of statin treatment. Pharmacogenomics J. Nov-Dec;2006 6(6):360–374. [PubMed: 16550210]
8. Materson BJ, Reda DJ, Cushman WC, et al. Single-drug therapy for hypertension in men. A comparison of six antihypertensive agents with placebo. The Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. N Engl J Med. Apr 1; 1993 328(13):914–921. [PubMed: 8446138]
9. Wilffert B, Swen J, Mulder H, Touw D, Maitland-Van der Zee AH, Deneer V. From evidence based medicine to mechanism based medicine. Reviewing the role of pharmacogenetics. Int J Clin Pharm. Feb; 2011 33(1):3–9. [PubMed: 21365387]
10. Zineh I, Johnson JA. Pharmacogenetics of chronic cardiovascular drugs: applications and implications. Expert Opin Pharmacother. Aug; 2006 7(11):1417–1427. [PubMed: 16859425]
11. Roden DM, Johnson JA, Kimmel SE, et al. Cardiovascular pharmacogenomics. Circ Res. Sep 16; 2011 109(7):807–820. [PubMed: 21921273]
12. Klein TE, Altman RB, Eriksson N, et al. Estimation of the warfarin dose with clinical and pharmacogenetic data. N Engl J Med. Feb 19; 2009 360(8):753–764. [PubMed: 19228618]
13. Link E, Parish S, Armitage J, et al. SLCO1B1 variants and statin-induced myopathy--a genomewide study. N Engl J Med. Aug 21; 2008 359(8):789–799. [PubMed: 18650507]
14. Mega JL, Close SL, Wiviott SD, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. N Engl J Med. Jan 22; 2009 360(4):354–362. [PubMed: 19106084]
15. Mirnezami R, Nicholson J, Darzi A. Preparing for precision medicine. N Engl J Med. Feb 9; 2012 366(6):489–491. [PubMed: 22256780]
16. Wang L, McLeod HL, Weinshilboum RM. Genomics and drug response. N Engl J Med. Mar 24; 2011 364(12):1144–1153. [PubMed: 21428770]
17. Katsios CS, Ziogas DE, Roukos DH. Pharmacogenomics for tailoring cardiovascular and anticancer drugs: from genotyping to whole-genome sequencing. Pharmacogenomics. Aug; 2011 12(8):1081–1085. [PubMed: 21843060]

18. Pirmohamed M. Pharmacogenetics: past, present and future. Drug Discov Today. Oct; 2011 16(19–20):852–861. [PubMed: 21884816]
19. Mrazek DA, Lerman C. Facilitating clinical implementation of pharmacogenomics. JAMA. Jul 20; 2011 306(3):304–305. [PubMed: 21771991]
20. Lesko LJ, Zineh I, Huang SM. What is clinical utility and why should we care? Clin Pharmacol Ther. Dec; 2010 88(6):729–733. [PubMed: 21081937]
21. Anderson JL, Horne BD, Stevens SM, et al. A randomized and clinical effectiveness trial comparing two pharmacogenetic algorithms and standard care for individualizing warfarin dosing (CoumaGen-II). Circulation. Apr 24; 2012 125(16):1997–2005. [PubMed: 22431865]
22. Castelan-Martinez OD, Hoyo-Vadillo C, Sandoval-Garcia E, et al. Allele frequency distribution of CYP2C9 2 and CYP2C9 3 polymorphisms in six Mexican populations. Gene. Jul 10; 2013 523(2): 167–172. [PubMed: 23587916]
23. Fang MC, Go AS, Hylek EM, et al. Age and the risk of warfarin-associated hemorrhage: the anticoagulation and risk factors in atrial fibrillation study. J Am Geriatr Soc. Aug; 2006 54(8): 1231–1236. [PubMed: 16913990]
24. Kimmel SE, French B, Kasner SE, et al. A pharmacogenetic versus a clinical algorithm for warfarin dosing. N Engl J Med. Dec 12; 2013 369(24):2283–2293. [PubMed: 24251361]
25. Lane S, Al-Zubiedi S, Hatch E, et al. The population pharmacokinetics of R- and S-warfarin: effect of genetic and clinical factors. Br J Clin Pharmacol. Jan; 2012 73(1):66–76. [PubMed: 21692828]
26. Mahtani KR, Heneghan CJ, Nunan D, et al. Optimal loading dose of warfarin for the initiation of oral anticoagulation. Cochrane Database Syst Rev. 2012; 12:CD008685. [PubMed: 23235665]
27. Penning-van Beest FJ, Koerselman J, Herings RM. Risk of major bleeding during concomitant use of antibiotic drugs and coumarin anticoagulants. J Thromb Haemost. Feb; 2008 6(2):284–290. [PubMed: 18031295]
28. Pirmohamed M, Burnside G, Eriksson N, et al. A randomized trial of genotype-guided dosing of warfarin. N Engl J Med. Dec 12; 2013 369(24):2294–2303. [PubMed: 24251363]
29. Verhoef TI, Ragia G, de Boer A, et al. A randomized trial of genotype-guided dosing of acenocoumarol and phenprocoumon. N Engl J Med. Dec 12; 2013 369(24):2304–2312. [PubMed: 24251360]
30. Altman RB. Pharmacogenomics: “noninferiority” is sufficient for initial implementation. Clin Pharmacol Ther. Mar; 2011 89(3):348–350. [PubMed: 21326263]
31. Ashley EA, Butte AJ, Wheeler MT, et al. Clinical assessment incorporating a personal genome. Lancet. May 1; 2010 375(9725):1525–1535. [PubMed: 20435227]
32. Swen JJ, Nijenhuis M, de Boer A, et al. Pharmacogenetics: from bench to byte-- an update of guidelines. Clin Pharmacol Ther. May; 2011 89(5):662–673. [PubMed: 21412232]
33. Kitsios GD, Kent DM. Personalised medicine: not just in our genes. BMJ. 2012; 344:e2161. [PubMed: 22491484]
34. The Use of Medicines in the United States: Review of 2011. IMS Institute for Healthcare Informatics; 2012.
35. PharmGKB. [Accessed 5/17/2013] The Pharmacogenomics Knowledgebase. 2013. http://www.pharmgkb.org
36. O’Donnell PH, Bush A, Spitz J, et al. The 1200 patients project: creating a new medical model system for clinical implementation of pharmacogenomics. Clin Pharmacol Ther. Oct; 2012 92(4): 446–449. [PubMed: 22929923]
37. Brouwers MC, Kho ME, Browman GP, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. CMAJ. Dec 14; 2010 182(18):E839–842. [PubMed: 20603348]
38. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. Qual Saf Health Care. Feb; 2003 12(1):18–23. [PubMed: 12571340]
39. Brouwers MC, Kho ME, Browman GP, et al. Development of the AGREE II, part 1: performance, usefulness and areas for improvement. CMAJ. Jul 13; 2010 182(10):1045–1052. [PubMed: 20513780]

40. Brouwers MC, Kho ME, Browman GP, et al. Development of the AGREE II, part 2: assessment of validity of items and tools to support application. CMAJ. Jul 13; 2010 182(10):E472–478. [PubMed: 20513779]
41. Vlayen J, Aertgeerts B, Hannes K, Sermeus W, Ramaekers D. A systematic review of appraisal tools for clinical practice guidelines: multiple similarities and one common deficit. Int J Qual Health Care. Jun; 2005 17(3):235–242. [PubMed: 15743883]
42. FDA. Table of Pharmacogenomic Biomarkers in Drug Labeling. http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm
43. Bielinski SJ, Olson JE, Pathak J, et al. Preemptive genotyping for personalized medicine: design of the right drug, right dose, right time-using genomic data to individualize treatment protocol. Mayo Clin Proc. Jan; 2014 89(1):25–33. [PubMed: 24388019]
44. Hall-Flavin DK, Winner JG, Allen JD, et al. Utility of integrated pharmacogenomic testing to support the treatment of major depressive disorder in a psychiatric outpatient setting. Pharmacogenet Genomics. Oct; 2013 23(10):535–548. [PubMed: 24018772]
45. Hoffman JM, Haidar CE, Wilkinson MR, et al. PG4KDS: a model for the clinical implementation of pre-emptive pharmacogenetics. Am J Med Genet C Semin Med Genet. Mar; 2014 166C(1):45–55. [PubMed: 24619595]
46. Shuldiner AR, Relling MV, Peterson JF, et al. The Pharmacogenomics Research Network Translational Pharmacogenetics Program: overcoming challenges of real-world implementation. Clin Pharmacol Ther. Aug; 2013 94(2):207–210. [PubMed: 23588301]
47. Van Driest SL, Shi Y, Bowton EA, et al. Clinically actionable genotypes among 10,000 patients with preemptive pharmacogenomic testing. Clin Pharmacol Ther. Apr; 2014 95(4):423–431. [PubMed: 24253661]
48. Weitzel KW, Elsey AR, Langaee TY, et al. Clinical pharmacogenetics implementation: approaches, successes, and challenges. Am J Med Genet C Semin Med Genet. Mar; 2014 166C(1):56–67. [PubMed: 24616371]
49. Whirl-Carrillo M, McDonagh EM, Hebert JM, et al. Pharmacogenomics knowledge for personalized medicine. Clin Pharmacol Ther. Oct; 2012 92(4):414–417. [PubMed: 22992668]
50. Holmes MV, Shah T, Vickery C, Smeeth L, Hingorani AD, Casas JP. Fulfilling the promise of personalized medicine? Systematic review and field synopsis of pharmacogenetic studies. PloS One. 2009; 4(12):e7960. [PubMed: 19956635]
51. Shin J, Kayser SR, Langaee TY. Pharmacogenetics: from discovery to patient care. Am J Health Syst Pharm. Apr 1; 2009 66(7):625–637. [PubMed: 19299369]
52. Relling MV, Klein TE. CPIC: Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network. Clin Pharmacol Ther. Mar; 2011 89(3):464–467. [PubMed: 21270786]

Genomic Prescribing System™ [GPS]

Patient Name :
Sex :
DOB :

Print Page

Patient Home/Current Medications | Search Drugs/Diseases | Search Results

Drug Search Results for : Clopidogrel

Your patient carries a gene associated with poor metabolizer function for the enzyme CYP2C19 required to activate clopidogrel. Individuals with this genotype have severely reduced platelet inhibition, increased residual platelet aggregation, and dramatically increased risk for adverse cardiovascular events. The FDA label for clopidogrel contains a "black box" warning for patients in this group and recommends consideration of an alternative treatment.

This recommendation is based on numerous studies. Among 1,535 patients with acute myocardial infarction who underwent percutaneous coronary intervention (PCI) and received clopidogrel, patients with the poor metabolizer status (like your patient) had a 3.58-fold (95% CI: 1.71 to 7.51) higher adjusted risk of death, recurrent myocardial infarction, or stroke than those not carrying the loss-of-function allele ($p<0.005$). In another study of 2,208 patients with acute coronary syndrome (ACS), the rate of adverse cardiovascular events at 1 year was 21.5% in poor metabolizers (like your patient), compared to 13.3% in those without a risk genotype. A meta-analysis including this study with 31 others found the same relationship--higher risk of CV events in patients with your patient's genotype.

Of note, the most definitive studies showing this pharmacogenomic association have predominantly been conducted in acute coronary syndrome patients, almost all of whom underwent percutaneous coronary intervention. Therefore, this recommendation may not apply to other clinical situations in which clopidogrel is being considered.

Guidelines from the Clinical Pharmacogenetics Implementation Consortium strongly recommend use of prasugrel or ticagrelor, instead of clopidogrel, if there are no contraindications. Guidelines from the Royal Dutch Pharmacists Association - Pharmacogenetics Working Group also note that individuals with a genotype identical to your patient have an increased risk for reduced response to clopidogrel. This group has published guidelines recommending use of an alternative drug.

Note that prasugrel and ticagrelor are associated with increased bleeding risk compared to clopidogrel. Prasugrel is NOT recommended for patients with active bleeding or a history of TIA or stroke. Ticagrelor is NOT recommended for patients with active bleeding or a history of intracranial hemorrhage.

Evidence
Level 1

Primary Literature Sources
N Engl J Med (2009)
JAMA (2010)
JAMA (2011)
Clin Pharmacol Ther (2011)
Clin Pharmacol Ther (2013)

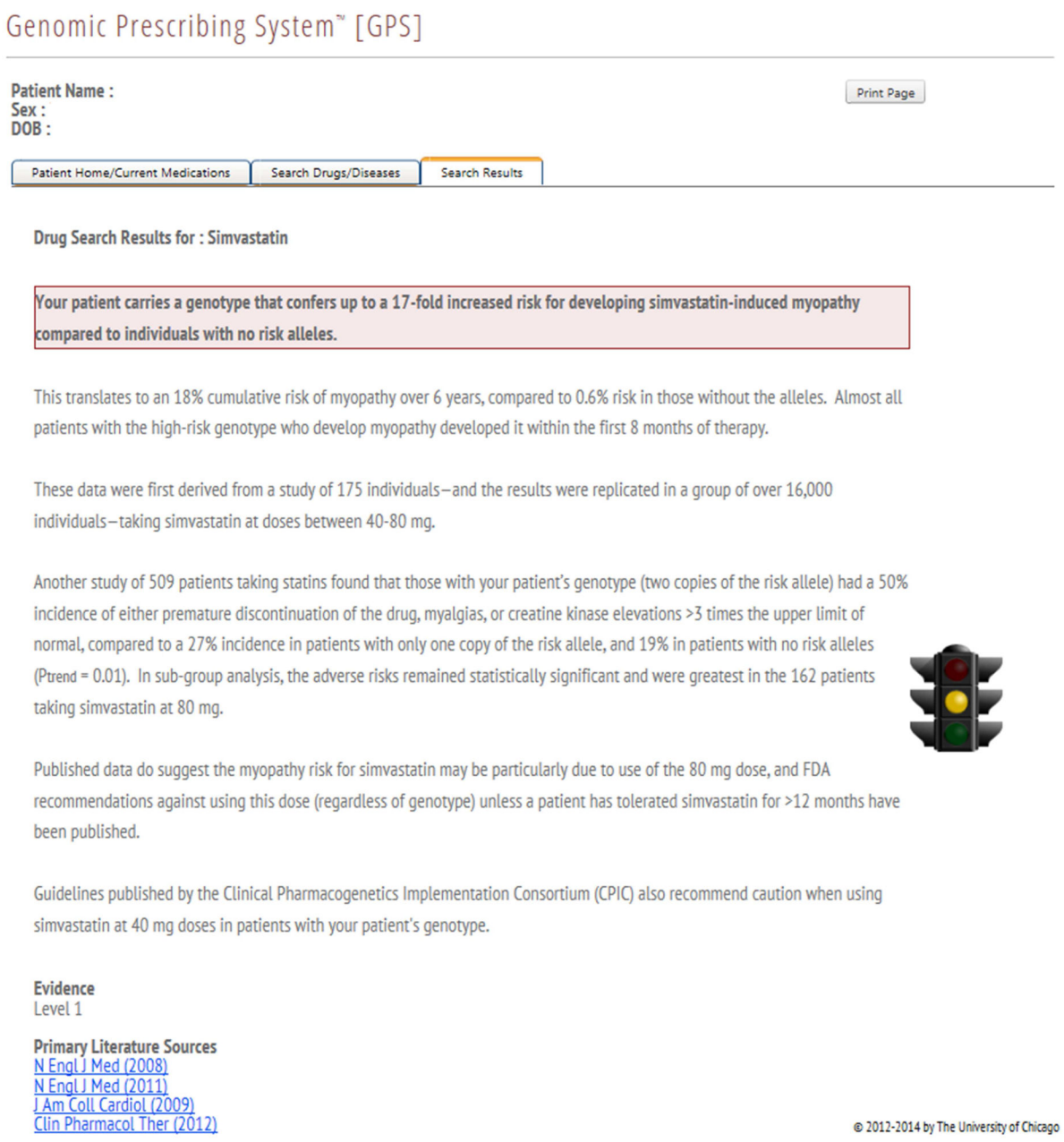

Figure 1.

Clinical implementation summaries / clinical decision supports for given genotypes of (A) clopidogrel and (B) simvastatin.

The creation of a clinical implementation summary (genotype-specific pharmacogenomic result with clinical decision support), which informs physicians of important pharmacogenomic information, was our measure of the ultimate clinical applicability of a specific drug/variant pair. Each summary contains an interpretation of the evidence, the assigned Level of Evidence rating, and hyperlinks to the primary literature evidence forming the basis for the summary.

Table 1

Comprehensive evaluation of the scope, depth, and quality of pharmacogenomic evidence for cardiovascular drugs.

Cardiovascular drugs, N=71					
Positive PGxa	51 (71.8%)				
Clinical summary warranted	23 (32.4%)				
Drug/variant pairs, N=884					
Classification		Clinical summaries warranted			
	N	N	Level 1	Level 2	Level 3
3+ Studies & PharmGKB	33	25 (75.8%)	4	6	15
PharmGKB only	43	10 (23.3%)	0	5	5
3+ Studies only	37	9 (24.3%)	0	4	5
Other (None of above)	771	48 (6.2%)	0	32	16
	884	92 (10.4%)	4	47	41

71 cardiovascular drugs with pharmacogenomic information were identified and critically reviewed, encompassing analysis of 884 unique drug/variant pairs; of the 71 drugs, 51 had positive pharmacogenomic findings in the literature (“Positive PGx”). The existence of 3 or more positive supporting publications for any given drug/variant pair (“3+ Studies”) and/or existence of a PharmGKB clinical annotation (“PharmGKB”) were the criteria used to stratify drug/variant pairs into one of four groups.

Table 2

Drug/variant pairs with 3 or more positive publications warranting a proposed clinical summary

A.

Drug	Variant	Gene	Positive PMIDs N	PharmGKB Clinical Annotation
Warfarin	rs1057910	*CYP2C9*	75	Yes
Warfarin	rs1799853	*CYP2C9*	57	Yes
Clopidogrel	rs4244285	*CYP2C19*	42	Yes
Warfarin	rs9923231	*VKORC1*	42	Yes
Warfarin	rs9934438	*VKORC1*	27	Yes
Clopidogrel	rs4986893	*CYP2C19*	15	Yes
Warfarin	rs7294	*VKORC1*	12	Yes
Warfarin	rs2359612	*VKORC1*	10	Yes
Warfarin	rs28371686	*CYP2C9*	10	Yes
Warfarin	rs8050894	*VKORC1*	9	Yes
Metoprolol	rs1801253	*ADRB1*	8	Yes
Pravastatin	rs4149056	*SLCO1B1*	8	Yes
Warfarin	rs2108622	*CYP4F2*	6	Yes
Warfarin	rs28371685	*CYP2C9*	6	Yes
Warfarin	rs2884737	*VKORC1*	6	No
Carvedilol	rs1042714	*ADRB2*	5	Yes
Clopidogrel	rs12248560	*CYP2C19*	5	Yes
Rosuvastatin	rs2231142	*ABCG2*	5	Yes
Clopidogrel	rs1045642	*ABCB1*	4	Yes
Hydrochlorothiazide	rs4961	*ADD1*	4	No
Simvastatin	rs2032582	*ABCB1*	4	Yes
Warfarin	rs56165452	*CYP2C9*	4	No
Warfarin	rs9332131	*CYP2C9*	4	Yes
Aspirin	rs730012	*LTC4S*	3	Yes
Atorvastatin	rs4149056	*SLCO1B1*	3	Yes
Atorvastatin	rs20455	*KIF6*	3	No
Benazepril	rs1801133	*MTHFR*	3	No
Carvedilol	rs1801253	*ADRB1*	3	Yes
Clopidogrel	rs28399504	*CYP2C19*	3	No
Metoprolol	rs1065852	*CYP2D6*	3	No
Perindopril	rs1799752	*ACE*	3	No
Pravastatin	rs17238540	*HMGCR*	3	Yes
Simvastatin	rs4149056	*SLCO1B1*	3	Yes
Warfarin	rs17880887	*VKORC1*	3	No

B.

Drug	Variants	Gene	Positive PMIDs N	Clinical summary warranted Y/N
Warfarin	All	*CYP2C9*	183	Y
Warfarin	All	*VKORC1*	130	Y

B.

Drug	Variants	Gene	Positive PMIDs N	Clinical summary warranted Y/N
Clopidogrel	All	*CYP2C19*	73	Y
Metoprolol	All	*CYP2D6*	20	Y
Aspirin	All	*FSIP1*	20	N
Digoxin	All	*ABCB1*	16	N
Pravastatin	All	*SLCO1B1*	16	Y
Atorvastatin	All	*APOE*	13	N
Metoprolol	All	*ADRB1*	12	Y
Losartan	All	*CYP2C9*	12	N
Phenprocoumon	All	*CYP2C9*	12	N
Lovastatin	All	*LPL*	12	N
Simvastatin	All	*ABCB1*	11	Y
Aspirin	All	*GPIIIa*	10	N

Part A. The associated drug, variant, and corresponding gene are shown for the 34 drug/variant pairs with 3 or more positive pharmacogenomic publications that warranted a proposed clinical summary. Of these, 25 had a publicly available Clinical Annotation in PharmGKB at the close of data capture.

Part B. Results are displayed at the level of drug/gene pairs, encompassing all positivelyassociated variants within the corresponding gene, for each of the drug/gene pairs with 10 or more positive publications. For each drug, yes (“Y”) or no (“N”) indicates whether at least one variant warranted a proposed clinical summary.

Table 3

Drugs warranting clinical summaries for implementation per modified AGREE guideline assessment

Drug	Variant	Method of identification[1]	Modified AGREE II Scores[2]					
			Domain 1 Scope	Domain 3 Rigour	Domain 4 Clarity	Domain 5 Applicability	Overall Quality Score, Averaged	Recommended for Implementation
Amlodipine	rs2238032	Candidate gene	90.7	64.8	72.2	61.1	5.33	Yes
	rs2239050	Candidate gene	90.7	64.8	72.2	61.1	5.33	Yes
	rs2239128	Candidate gene	90.7	63.0	66.7	61.1	5.33	Yes
	rs2246709	Candidate gene	85.2	70.4	50.0	50.0	4.33	Yes
Aspirin	rs730012	Candidate gene	87.0	74.1	57.4	61.1	5.33	Yes
Atenolol	rs688	Candidate gene	74.1	66.7	57.4	63.9	3.67	Yes
	rs699	Candidate gene	87.0	72.2	63.0	63.9	4.33	Yes
	rs5051	Candidate gene	87.0	72.2	63.0	63.9	4.33	Yes
	rs5443	Candidate gene	85.2	70.4	63.0	63.9	5.33	Yes
	rs1801252/rs1801253	Candidate gene	88.9	68.5	70.4	61.1	5.33	Yes
	rs2301339	Candidate gene	85.2	70.4	63.0	63.9	5.33	Yes
	rs11064426	Candidate gene	85.2	70.4	63.0	63.9	5.33	Yes
Atorvastatin	rs5443	Candidate gene	88.9	66.7	51.9	52.8	4.67	Yes
	rs20455	Candidate gene	98.1	74.1	79.6	69.4	6.00	Yes
	rs4149056	Candidate gene	87.0	63.0	44.4	58.3	3.67	Yes
Benazepril	rs7079	Candidate gene	87.0	66.7	63.0	58.3	5.00	Yes
	rs1799752	Candidate gene	94.4	81.5	68.5	63.9	5.33	Yes
	rs1799998	Candidate gene	88.9	70.4	63.0	61.1	5.00	Yes
	rs1801133	Candidate gene	85.2	51.9	46.3	50.0	3.67	Yes
Candesartan	rs1799998	Candidate gene	87.0	59.3	55.6	63.9	4.00	Yes
Carvedilol	rs1042714	Candidate gene	98.1	81.5	70.4	63.9	6.00	Yes
	rs1801253	Candidate gene	92.6	77.8	74.1	66.7	5.67	Yes
Clopidogrel	*CYP2C19*	GWAS + Candidate gene	100	96.3	100	91.7	7.00	Yes
	rs1045642	Candidate gene	98.1	87.0	79.6	72.2	6.00	Yes

Drug	Variant	Method of identification[1]	Modified AGREE II Scores[2]					
			Domain 1 Scope	Domain 3 Rigour	Domain 4 Clarity	Domain 5 Applicability	Overall Quality Score, Averaged	Recommended for Implementation
Dabigatran	rs2244613	GWAS	98.1	98.1	85.2	83.3	6.33	Yes
Felodipine	rs2238032	Candidate gene	90.7	64.8	72.2	61.1	5.33	Yes
	rs2239050	Candidate gene	90.7	64.8	66.7	61.1	5.33	Yes
	rs2239128	Candidate gene	90.7	64.8	66.7	61.1	5.33	Yes
Fenofibrate	rs320	Candidate gene	92.6	57.4	63.0	55.6	4.00	Yes
	rs676210	Candidate gene	92.6	72.2	66.7	61.1	5.33	Yes
	rs2727786	Candidate gene	90.7	53.7	59.3	58.3	3.67	Yes
Fluvastatin	rs1799752	Candidate gene	96.3	66.7	63.0	58.3	5.33	Yes
	rs11045819	Candidate gene	96.3	72.2	72.2	66.7	5.33	Yes
Hydralazine	rs1799983	Candidate gene	100	79.6	85.2	80.6	6.33	Yes
	rs1799998	Candidate gene	100	79.6	85.2	80.6	6.33	Yes
HCTZ	rs4961	Candidate gene	96.3	72.2	57.4	58.3	4.67	Yes
	rs11240688	Candidate gene	96.3	75.9	63.0	61.1	4.67	Yes
Irbsartan	rs1367117	Candidate gene	74.1	66.7	57.4	63.9	3.67	Yes
	rs1799752	Candidate gene	90.7	72.2	64.8	63.9	4.33	Yes
Metoprolol	*CYP2D6*	Candidate gene	100	100	98.1	97.2	7.00	Yes
	rs1024323	Candidate gene	92.6	75.9	57.4	61.1	4.33	Yes
	rs1801253	Candidate gene	83.3	55.6	53.7	58.3	4.33	Yes
Nifedipine	rs2238032	Candidate gene	92.6	64.8	66.7	61.1	5.33	Yes
Perindopril	rs1799752	Candidate gene	96.3	77.8	70.4	66.7	5.00	Yes
Pravastatin	rs4149056	Candidate gene	96.3	74.1	51.9	61.1	4.00	Yes
	rs17238540	Candidate gene	96.3	81.5	74.1	72.2	6.00	Yes
	rs17244841	Candidate gene	96.3	81.5	68.5	72.2	5.67	Yes
	rs4986790	Candidate gene	96.3	83.3	74.1	72.2	6.00	Yes
Rosuvastatin	rs2231142	Candidate gene	98.1	77.8	74.1	69.4	6.00	Yes
Simvastatin	rs2032582	Candidate gene	88.0	63.0	51.9	61.1	4.00	Yes

Drug	Variant	Method of identification[1]	Modified AGREE II Scores[2]					
			Domain 1 Scope	Domain 3 Rigour	Domain 4 Clarity	Domain 5 Applicability	Overall Quality Score, Averaged	Recommended for Implementation
	rs4149056	GWAS	98.1	92.6	92.6	77.8	6.33	Yes
Verapamil	rs1801252/rs1801253	Candidate gene	98.1	81.5	81.5	72.2	6.00	Yes
Warfarin	All variants	GWAS + Candidate gene	100	100	92.6	97.2	7.00	Yes
		Average	91.9	73.1	67.8	65.8	5.18	
		SD	6.1	11.1	12.5	10.0	0.91	
		Range	74.1–100	51.9–100	44.4–100	50.0–97.2	3.67–7.00	

[1] Genome-wide association study (GWAS), Candidate gene

[2] Brouwers M, et al. AGREE II: Advancing guideline development, reporting and evaluation in healthcare. *Can Med Assoc J*. 2010.

Mayo Clin Proc. Author manuscript; available in PMC 2016 June 01.

Table 4

Considerable pharmacogenomic evidence exists for the Top 10 most commonly prescribed cardiovascular drugs in the U.S.

Drug	Modified AGREE Overall Guideline Assessment		Number of Positive Publications	Number of Subjects Studied	Clinical Outcome(s) Studied	Reported Effect Size	Annual U.S. Prescriptions, in millions[34]
	Decision to Recommend	Average Quality Score					
Simvastatin (toxicity)	Y	6.33	3	17,323	Myopathy	Odds ratio of myopathy up to 4.5× greater for carrying 1 risk allele, and 17× greater for carrying 2 risk alleles	96.8
Simvastatin (response)	Y	4.0	4	2,943	Cholesterol lowering	Approximately 6% greater total cholesterol lowering in patients with favorable allele	96.8
Lisinopril	Not proposed	N/A	5	17,472	N/A	N/A	88.8
Metoprolol[i]	Y	4.33 – 7.0	12	916	Blood pressure lowering	Odds ratio of reaching target MAP[ii] ~2× higher with favorable allele	72.3
Amlodipine	Y	5.33	2	263	Blood pressure lowering	Patients with favorable allele are 2× as likely to reach target MAP	62.5
Hydrochlorothiazide	Y	4.67	5	530	Blood pressure lowering	1.5× greater SBP[iii] decline and 2× greater MAP decline with favorable allele	48.1
Atorvastatin (toxicity)	Y	3.67	3	500	Myopathy	Risk of adverse event 1.4× higher with 1 risk allele and 2.5× higher with 2 risk alleles	43.3
Atorvastatin (response)	Y	4.67 – 6.0	4	8,078	Risk of MI[iv] or major cardiovascular event	~10% reduction in risk with favorable alleles	43.3
Furosemide	Not proposed	N/A	2	192	N/A	N/A	42.3
Warfarin	Y	7.0	87	28,050	Prediction of required warfarin dose	Identifies the required stable dose in approximately 16% of patients not accurately predicted by a clinical algorithm who needed extreme warfarin doses[v]	33.9
Atenolol (blood pressure response)	Y	3.67 – 5.33	3	1,413	Blood pressure lowering	~4× greater SBP decline and 1.75× greater DBP[vi] decline with two favorable alleles	33.4
Atenolol (risk of death)	Y	5.33	1	5,895	Mortality risk	Differential risk of all-cause mortality depending on haplotype makeup; hazard	33.4

Drug	Modified AGREE Overall Guideline Assessment		Number of Positive Publications	Number of Subjects Studied	Clinical Outcome(s) Studied	Reported Effect Size	Annual U.S. Prescriptions, in millions[34]
	Decision to Recommend	Average Quality Score					
						ratio of 8.58 for certain genotypes ratio of 8.58 for certain genotypes	

[i] Includes metoprolol succinate and metoprolol tartrate

[ii] Mean arterial pressure (MAP)

[iii] Systolic blood pressure (SBP)

[iv] Myocardial infarction (MI)

[v] Prospective randomized trials examining attainment of therapeutic INRs showed no improvement of pharmacogenomic-guided algorithm dosing except when compared to an empiric dosing strategy. Therefore, in our clinical implementation project, the warfarin summary is supplied as a Level 3 dosing algorithm that includes clinical factors along with pharmacogenomic factors with the understanding that an algorithm containing such clinical information will promote among providers the use of the algorithm-based approach rather than an empiric dosing strategy.

[vi] Diastolic blood pressure (DBP)