The Institute of Medicine has estimated that approximately 1.5 million preventable adverse drug reactions occur in United States every year. Although these drug reactions have diverse origins and present in patients in a multitude of locations, in-hospital adverse drug reactions alone account for an estimated $3.5 billion in additional health care costs. Inheritance or genetics play an important role in patients’ predisposition to experience adverse drug reactions or therapeutic failure. For example, 5% to 10% of the general population are poor metabolizers of CYP2D6, and 1% to 10% are ultrarapid metabolizers (both being inherited traits). As such, these individuals are prone to drug toxicity and inefficacy, respectively, with the use of standard doses of antidepressants. Therefore, the timely delivery of pharmacogenomic information (or drug-gene interaction warnings based on genomic and other information) to ensure delivery of the right drug to the right patient at the right dose and thus maximize efficacy and minimize adverse events could be a cornerstone of President Obama’s 2015 State of the Union Address promise to deliver precision medicine “to keep ourselves and our families healthier.”

The cost of genotyping and genetic sequencing has dramatically decreased over the past decade, and breaking this cost barrier has led to a proliferation of drug-gene association studies. For example, as of February 20, 2015, 2111 genome-wide association studies have been published. Differentiating true associations from false-positives has therefore become an important step in establishing the clinical validity of the findings. This concept of validation is especially timely because a National Cancer Institute—National Human Genome Research Institute working group recently recommended that replication of sentinel drug-gene association study findings should be an essential component of assessing their nature and importance.

In this issue of Mayo Clinic Proceedings, Kaufman et al take another step toward routine clinical implementation of drug-gene rules by comprehensively and carefully assessing the clinical utility of cardiovascular pharmacogenomics. The authors began by reviewing the validity of the association of 884 drug/genetic variant pairs described in 597 publications, which collectively studied 51 cardiovascular drugs. The authors identified potential drug/genetic variant pairs by PubMed search and cross-referenced their findings with pharmacogenetic variant data in the Pharmacogenomics Knowledge Database, an online resource that “collects, curates, and disseminates knowledge about the impact of human genetic variation on drug responses.” The authors determined from the retrieved data that clinically relevant evidence of sufficient quality to justify clinical alerts was available for 92 (10.4% of the total) drug/genetic variant pairs involving 23 drugs. The strength of the pharmacogenomic association was based on (1) the number of patients enrolled in the study that found an association, (2) replication of the drug/genetic variant association, and (3) whether this association resulted in dosing guidelines and US Food and Drug Administration (FDA) labeling information. Of the 23 drugs for which clinical summaries of drug/genetic variant pairs were considered appropriate, there were 4 drugs (clopidogrel, simvastatin, dabigatran, and warfarin) for which significant variants were identified by genome-wide association; the rest were identified by candidate gene studies. Using this methodology, there were only 4 drug/genetic
variant associations of the 884 (3 on the CYP2C19 gene for clopidogrel and 1 in the SLC01B1 gene for simvastatin) that met stringent criteria for level 1 evidence, ie, high-quality and adequately powered studies that replicated findings or drug/genome pairs for which dosing guidelines or FDA label information exists.

The genetic variants associated with clopidogrel, simvastatin, and warfarin responses appear to meet these criteria, but multiple barriers to clinical implementation remain, including (1) evidence of clinical utility and incremental value beyond current testing, (2) objective practice guidelines, (3) availability of genotyping performed in a Clinical Laboratory Improvements Amendments–approved environment, (4) incorporation of genotype data in electronic medical records, (5) user-friendly decision support software and tools, (6) insurance coverage of pharmacogenetic testing, and (7) physician and patient perceptions.

Another variable is that although genetic variation can alter drug metabolism, it is not always associated with the predicted drug response. An example is the association of azathioprine, an immunosuppressant drug used to prevent rejection in heart transplant, and thiopurine S-methyltransferase (TPMT), an enzyme that metabolizes azathioprine. Loss-of-function genetic variation in TPMT results in higher levels of active azathioprine metabolite, and theoretically, carriers should be at a lower risk for rejection. Conversely, we have reported that heart transplant recipients who have such TPMT genetic variants are at a higher risk of rejection as compared with patients with TPMT wild-type.

The only cardiovascular drugs that have genomics-based “clinically actionable” drug label recommendations provided by the FDA are warfarin (dose adjustments based on CYP2C9 and VKORC1 genetic variants) and clopidogrel (use of alternative antiplatelet drug therapy in poor metabolizers of CYP2C19). Wang et al used a different approach to determine the importance and applicability of the various drug/genetic variants in clinical practice. They evaluated the clinical validity (defined as the capacity of the genetic variant to predict drug response) and clinical utility (defined as improvement of clinical outcomes by altering therapy based on genotype) for the various drug/genetic variant pairs identified by the FDA in drug labels. The warfarin-CYP2C9/VKORC1 and clopidogrel-CYP2C19 drug-gene pairs had clinical validity but did not fulfill criteria for clinical utility. The criteria for clinical utility were the performance of “a systematic review or meta-analysis of randomized clinical trials (RCTs) showing consistency in results or at least one large RCT.”

Cardiovascular clinical practice in the United States is perhaps most influenced by guidelines issued by the American College of Cardiology/American Heart Association (ACC/AHA). Clinicians are provided guidance by the “Class of Recommendation,” which describes the magnitude of benefit, as compared with risk and “Level of Evidence,” which is based on the certainty, precision, type, and quality of the evidence. The strongest recommendations and the highest level of evidence are primarily based on information provided by RCTs. The adherence to ACC/AHA class I recommendations has resulted in improvement in patient outcomes (reflecting the quality of these guidelines) and is in keeping with the Institute of Medicine’s recommendations that clinical practice guidelines should optimize patient care by being based on high-quality evidence. Therefore, despite an FDA issued black box warning advising practitioners to “consider alternative treatment in patients identified as CYP2C19 poor metabolizers” and that these patients can be identified by genotyping, routine genotyping to identify CYP2C19 genetic variants in patients treated with clopidogrel is not recommended in the latest guidelines established by the ACC/AHA. This omission is due to the lack of RCTs documenting that such patients with CYP2C19 genetic variants would benefit from alternative therapy.

The importance of RCTs in determining the level of evidence for drug/genetic variant pairs is highlighted in the example of warfarin-CYP2C9/ VKORC1. These drug/genetic variant pairs received high AGREE (Appraisal of Guidelines for Research and Evaluation) II scores (ie, a metric that successfully differentiates high- and low-quality guidelines and serves as a good predictor of successful implementation of guidelines) but the lowest level of evidence (ie, a level 3) because of the existence of “several similarly executed contradictory studies.” There were 2 RCTs, the European Pharmacogenetics of Anticoagulant Therapy and the Clarification of Optimal Anticoagulation Through Genetics.
trials, that examined the role of pharmacogenetics in maintaining patients within a therapeutic international normalized ratio, both completed in 2013. The European Pharmacogenetics of Anticoagulant Therapy trial indicated that a pharmacogenetic-based dosing strategy might be more desirable than fixed warfarin dosing, whereas the Clarification of Optimal Anticoagulation Through Genetics study did not find a difference in patients who received either genotyping-guided dosing or dosing guided on the basis of clinical variables only.\(^{14,15}\)

The widespread adoption of pharmacogenetics in cardiovascular clinical practice will require clinical evidence supported by well-conducted RCTs that document that utilizing such drug/genetic variant pairs to guide drug prescription will result in improved patient care and outcomes. There are currently several cardiovascular genotype-based RCTs that are being conducted, such as the Tailored Antiplatelet Therapy Following PCI (TAILOR-PCI) study (clinicaltrials.gov Identifier: NCT01742117) examining the role of CYP2C19 genetic testing to guide antiplatelet therapy after percutaneous coronary intervention and the Genetically Targeted Therapy for the Prevention of Symptomatic Atrial Fibrillation in Patients With Heart Failure (GENETIC-AF) trial (clinicaltrials.gov Identifier: NCT01970501) that compares bucindolol vs metoprolol in \(\beta\)-adrenergic receptor genetic variant (\(\beta_1\) 389 Arg/Arg) carriers who have atrial fibrillation. More recently, due to multiple ethical, legal, and practical issues of conducting genotype-based RCTs\(^{16}\) and in an attempt to reduce costs, studies are being performed using electronic medical records linked to preemptively obtained genetic data with decision support modules being provided to clinicians.\(^{17}\) As described in the article by Kaufman et al., the University of Chicago has implemented such a program called the “1200 Patients Project.” The Mayo Clinic Center for Individualized Medicine has also implemented 25 pharmacogenetic tests, 23 being indication specific and 2 being preemptive multigene panels, with 32,145 diplootypes reported thus far for 8 commonly used drugs, including clopidogrel, simvastatin, and warfarin. The prescribing practices based on the pharmacogenetic information provided by these practice modules and ensuing patient outcomes are being tracked to assess whether a change in drug therapy based on the genetic information provided will improve clinical outcomes. Whether such observational studies result in a change in clinical practice remains to be seen.

In summary, the study by Kaufman et al.\(^7\) in the current issue of the Proceedings describes the large number of studies performed in cardiovascular pharmacogenomics and reflects the potentially important role of genetic variation in cardiovascular drug response. However, the vast majority of these drug/genetic variant pairs do not yet meet the stringent level of evidence required for clinical implementation, which highlights the importance of performing RCTs or well-designed observational studies to move the field forward to bedside applications. Several large academic medical centers around the country, including Mayo Clinic, have organized these multidisciplinary efforts under the mantle of Centers for Individualized Medicine and, in partnership with the National Institutes of Health, are seeking to make precision medicine a reality for patients.

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