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Clinical applications of pharmacogenetics: Present and near future

“Change is the only constant.”
—Heraclitus (c 535–475 BCE)

WITH THE COST OF HEALTH CARE rising and money to pay for it shrinking, there has never been a greater need to reduce waste.

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Ineffective treatments and adverse drug effects account for much preventable morbidity and expense. New treatments, touted as more potent, are often introduced as replacements for traditional ones that are still effective in many patients, adding to costs and the potential for harm. For the pharmaceutical industry, the search for new “blockbuster” drugs seems to have hit a wall, at least in cardiovascular medicine.¹ Advances often come at the cost of adverse effects, such as bleeding with triple antiplatelet therapy and diabetes with potent statin drugs.

The path to maximizing benefit and reducing harm now appears to lie in stratifying populations and appreciating patient individuality in response to treatment. For many decades we have known that patients vary widely in their response to drugs, owing to personal factors such as body surface area, age, environment, and genetics. And indeed, we treat our patients as individuals, for example by tailoring aminoglycoside dose to weight and renal function.

However, clinical trials typically give us an idea of the benefits only to the average patient. While subgroup analyses identify groups that may benefit more or less from treatment, the additional information they provide is not easily integrated into the clinical model of prescribing, in which one size fits all.

THE PROMISE OF PHARMACOGENETICS

The emerging field of pharmacogenetics promises to give clinicians the tools to make informed treatment decisions based on predictive genetic testing. This genetic testing aims to match treatment to an individual’s genetic profile. This often involves analyzing single-nucleotide polymorphisms in genes for enzymes that metabolize drugs, such as the cytochrome P450 enzymes, to predict efficacy or an adverse event with treatment.

Pharmacogenetics is playing an increasing role in clinical trials, particularly in the early stages of drug development, by helping to reduce the number of patients needed, prove efficacy, and identify subgroups in which alternative treatment can be targeted. At another level, a molecular understanding of disease is leading to truly targeted treatments based on genomics.

Over recent years, genetic testing has been increasingly used in clinical practice, thanks to a convergence of factors such as rapid, low-cost tests, a growing evidence base, and emerging interest among doctors and payers.

An advantage to using genetic testing as opposed to other types of laboratory testing, such as measuring the concentration of

Pharmacogenetics will give clinicians the tools to make treatment decisions based on predictive genetic testing

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TABLE 1

FDA-approved drugs with pharmacogenomic information in the labeling

DRUG	THERAPEUTIC AREA	BIOMARKER	LABEL SECTIONS
Abacavir	Antiviral	<i>HLA-B*5701</i>	Warnings and precautions: Stevens-Johnson syndrome
Azathioprine	Rheumatology	TPMT	Warnings and precautions: bone marrow toxicity
Carbamazepine	Neurology	<i>HLA-B*1502</i>	Boxed warning: Stevens-Johnson syndrome
Citalopram	Psychiatry	<i>CYP2C19</i>	Poor metabolizers are less likely to tolerate treatment
Clopidogrel	Cardiovascular	<i>CYP2C19</i>	Poor metabolizers have a higher cardiovascular event rate; ultrametabolizers are at higher risk of bleeding
Ivacaftor	Pulmonary	<i>CFTR</i> (G551D)	Personalized treatment for cystic fibrosis
Trastuzumab	Oncology	HER2/neu	Personalized treatment for breast cancer
Vemurafenib	Oncology	<i>BRAF</i>	Personalized treatment for metastatic melanoma
Warfarin	Hematology	<i>CYP2C9, VKORC1</i>	Dosage predicted by genetic algorithm and risk of bleeding

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The cost of genotyping is falling inversely faster than Moore's law

the drug in the blood during treatment, is that genetic tests can predict the response to treatment before the treatment is started. Moreover, with therapeutic drug monitoring after treatment has begun, there are sometimes no detectable measures of toxicity. For example, both carbamazepine and the antiviral drug abacavir can—fortunately only rarely—cause Stevens-Johnson syndrome. But before genetic markers were discovered, there was no method of estimating this risk apart from taking a family history.^{2,3} Considering the numbers of people involved, it was not feasible until recently to suggest genetic screening for patients starting on these drugs. However, the cost of genotyping and gene sequencing has been falling at a rate inversely faster than Moore's law (an approximate annual doubling in computer power), and population genomics is becoming a reality.⁴

The US Food and Drug Administration (FDA) recognizes the current and future value of pharmacogenetics in drug safety and development. A number of approved pharmacogenetic biomarkers are listed on the FDA website (TABLE 1). Black box warnings have been mandated for a number of drugs on the basis of observational evidence.

The FDA also promotes rapid approval for

novel drugs with pharmacogenetic “companion diagnostics.” A recent example of this was the approval of ivacaftor for cystic fibrosis patients who have the G551D mutation.⁵ Here, a molecular understanding of the condition led to the development of a targeted treatment. Although the cost of developing this drug was high, the path is now paved for similar advances. Oncologists are familiar with these advances with the emergence of new molecularly targeted treatments, eg, BRAF inhibitors in metastatic melanoma, imatinib in chronic myeloid leukemia, and gefitinib in non-small-cell lung cancer.

■ PHARMACOGENETICS IN CARDIOVASCULAR MEDICINE

Cardiovascular medicine also stands to benefit from rapid advances in pharmacogenetics.

While no treatment has been developed that targets the molecular basis of cardiovascular disease, a number of genomic biomarkers have emerged that identify patients at risk of adverse reactions or treatment failure. These include genetic tests to predict the maintenance dose and risk of bleeding with warfarin,⁶ the likelihood of myopathy and myositis with simvastatin,⁷ and the risk of recurrent thrombotic events with clopidogrel.^{8–10}

Using pharmacogenetics in prescribing warfarin and its alternatives

The pharmacogenetics of warfarin has been extensively researched, but genotyping before prescribing this drug is not yet widely done.

In 2007, the FDA updated the labeling of warfarin to include information about the influence of two genes, *VKORC1* and *CYP2C9*, on a patient's response to this drug. In 2010 this was updated to add that testing for these genes could be used to predict the maintenance dose of the drug. Difficulties with algorithms used to integrate this into clinical practice have hindered adoption of this testing.

With the advent of new anticoagulants such as dabigatran, rivaroxaban, and apixaban, many have expected warfarin and its pharmacogenetics to become obsolete. However, the new agents cost considerably more. Further, they may not offer a very great advantage over warfarin: in the Randomized Evaluation of Long-term Anticoagulant Therapy (RE-LY) trial, the absolute risk reduction in intracranial hemorrhage with dabigatran vs warfarin was small.¹¹ Therefore, dabigatran is probably not cost-effective in populations at low risk of bleeding.¹² A cost-effectiveness analysis comparing warfarin with dabigatran in patients with uncomplicated atrial fibrillation has suggested that dabigatran is, however, cost-effective in patients at moderate risk.¹²

In the RE-LY trial, the international normalized ratios (INRs) of the patients in the warfarin group were in the therapeutic range only 64% of the time. The advantages of dabigatran over warfarin become less pronounced as warfarin control is tightened.¹³ Of note, pharmacogenetics and home monitoring of the INR have both been shown to lead to tighter control of the INR, with greater time within the therapeutic range.^{14,15}

Moreover, genetic testing can help us reduce the number of bleeding events in patients taking warfarin.¹⁶ Patients who carry the *CYP2C9**2 or *CYP2C9**3 polymorphism metabolize S-warfarin slower and therefore have a threefold higher risk of hemorrhage after starting warfarin.¹⁷ We could speculate that patients carrying these variants may be better served by the newer anticoagulants, though this has not been tested in any clinical trial.

It is also worth appreciating that the con-

ditions requiring anticoagulation, such as atrial fibrillation, also have a strong genetic basis. Variants in chromosomes 4q25, 1q21, and 16q22 have all been associated with atrial fibrillation.¹⁸ The risk of atrial fibrillation is five to six times higher in carriers of multiple variants within all of these loci.¹⁹ Genetic variants at 4q25 have been associated with the response to specific antiarrhythmic drug treatments,²⁰ response to pulmonary vein isolation,^{21,22} and direct-current cardioversion.²³ One can imagine a future in which patients with palpitations, carrying multiple gene risk variants, will choose prolonged monitoring at home to confirm a diagnosis. They would then be provided with a personalized best management strategy, using their personal preferences, clinical data, and genetic profile to make a treatment decision.

Using pharmacogenetics in prescribing clopidogrel and its alternatives

The pharmacogenetics of clopidogrel is of particular interest, as it has the potential of establishing a rational basis for using newer antiplatelet drugs such as ticagrelor and prasugrel, which are considerably more expensive than generic clopidogrel.

Most of the people who do not respond to clopidogrel carry the common cytochrome P450 2C19 variants *CYP2C19**2 or *CYP2C19**3.⁹ These variants are present in particularly high frequency in Asians and African Americans, who often do not feature in large randomized trials.

Newer antiplatelet agents have failed to demonstrate consistent superiority to clopidogrel without a tradeoff of more bleeding. However, in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis in Myocardial Infarction 39 (TRITON TIMI-38),^{24,25} patients with the *2 variant receiving prasugrel had lower cardiovascular event rates than *2 carriers receiving clopidogrel.

Similarly, the patients who benefit the most from ticagrelor are carriers of the 2C19 nonresponder variants. In a large study, clopidogrel responders who did not carry either 2C19 nonresponder genetic variants or *ABCB1* variants had cardiovascular outcomes similar to those of patients receiving ticagrelor.²⁶

Clopidogrel pharmacogenetic testing is recommended in selected patients according to ACC/AHA guidelines

Clinicians have been cautious in prescribing potent antiplatelet agents to all patients because of the risk of bleeding. One could assume that by reserving newer agents for clopidogrel nonresponders, the bleeding risk could be minimized and overall benefit could be preserved with this strategy.

Cost may also be contained. The cost-effectiveness of such an approach with prasugrel has been tested with computer modeling and appears favorable.²⁷ On the other hand, a similar yet limited analysis did not find genotype-driven use of ticagrelor to be cost-effective.²⁸ This was mostly due to fewer deaths in patients receiving ticagrelor. However, the cost estimate for genotype-guided therapy was overestimated, as heterozygotes in the model were treated with ticagrelor instead of a high dose of clopidogrel.

It now appears that heterozygotes, ie, patients with one copy of the nonresponder variant, can achieve similar platelet inhibition with clopidogrel 225 mg daily as noncarriers on 75 mg daily.²⁹ Since genotype-guided antiplatelet therapy has not been tested in a randomized outcomes trial, this tailored strategy has not been widely accepted.

THE FUTURE

The barriers to adoption of pharmacogenetics are considerable. Clinicians need to be educated about it, reimbursement needs to be worked out, and the pharmaceutical industry needs to get behind it. Nevertheless, the future of pharmacogenetics is extremely promising.

Research networks are forming to support the use of pharmacogenetics in clinical practice. The Pharmgkb (www.pharmgkb.org) database serves as a hub for educating clinicians and researchers as well as curating data for reference. Vanderbilt University is piloting the BioVu project, in which DNA and genotype data on patients are being stored and matched to the electronic clinical records.³⁰ These projects not only provide clinically useful information on the current state of the art of pharmacogenetics, they also aid in disseminating new information about genotype-phenotype relationships.

Analytical software that uses “natural language processing” is being applied to clinician-

generated notes to derive new observations and associations between genetic variants and clinical phenotypes. Integrating this information in real-time decision-support modules in the electronic health record provides a feedback loop for a rapid assimilation of new knowledge. Similar innovative decision-support modules are being established by Cleveland Clinic’s Center for Personalized Healthcare.³¹

The rise of ‘omic’ sciences

Pharmacogenetics and pharmacogenomics are part of a larger set of “omic” sciences. The suffix “-omics” implies a larger, more holistic view and is being applied to a number of fields—for example, the study of proteins (proteomics) and the study of metabolites (metabolomics). Profiling proteins and metabolites delivers a deluge of information on a patient that can be clustered, using pattern-recognition software, into population subgroups. Patterns of multiple proteins or metabolites are extracted from this spectral data to identify disease or response to treatment (pharmacometabolomics).

Metabolomics has been shown to predict the response to statins,³² diagnose myocardial infarction,³³ and reclassify cardiovascular risk status.³⁴ In addition, whereas traditional laboratory chemistry is reductionist, using single biomarkers for single-disease diagnosis, omic technologies hold the potential to reveal information on a number of possible health or disease states. The identification of “healthy” profiles using these technologies can potentially provide positive feedback to patients undertaking lifestyle changes and treatment.

The instrument costs for proteomic and metabolomic profiling are relatively high. However, the ongoing running costs are minimal, estimated at as low as less than \$13 per test, as there are no expensive reagents.³³ High-volume testing therefore becomes very cost-effective.

Although omic science appears futuristic, proteomics and metabolomics are already used in many clinical laboratories to rapidly identify bacteria. These methods have already revolutionized the way laboratories identify microbes, since they are automated, reduce workload, and give very fast results.

The ‘-omics’
suffix implies
a greater,
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The cost of genetic testing is falling

Critics of pharmacogenetics claim that the predictive value of genetic testing is poor, that evidence is lacking, and that the cost is too high. In all new technologies, the first iteration is coarse, but performance improves with use. The first major barrier is adoption. Projects like BioVu are establishing the infrastructure for a feedback loop to iteratively improve upon the status quo and provide the evidence base clinicians demand.

The cost of genetic testing is falling rapidly, with whole-genome sequencing and annotation now costing less than \$5,000. The cost of a pharmacogenetic test can be as low as \$100 using low-cost nanotechnology, and the test needs to be performed only once in a patient's lifetime.²⁷

As other related molecular technologies such as proteomics and metabolomics become available and are integrated with genomics, the predictive ability of this science will improve.

AWAY FROM ONE-SIZE-FITS-ALL MEDICINE

Over the last decade there has been a trend away from "one size fits all" to customized "markets of one" in everything from consumer products to education to medicine. Mass customizing, also known as personalization, has been embraced by the internet community as a means to increase efficiency and reduce cost. This occurs by eliminating waste in redundant work or production of ineffective products.

Personalization on the Internet has been enabled through the use of informatics, mathematics, and supercomputing. The same tools that have personalized the delivery of consumer products are also being applied to the field of pharmacogenetics. Applied in an evidence-based fashion, these new technologies should profoundly improve patient care now and in the future. ■

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