will result in meaningful reform of the U.S. health care system? One of the Shattuck Lecture panelists, Charles Baker, voiced skepticism, calling the candidates’ plans “political bromide” that serves only to show the voters that they have plans and arguing that these plans are not certain to bring needed changes to a health care system in crisis. In his Perspective article, Oberlander notes that “the McCain and Obama health plans are best viewed as sketches rather than finished portraits.”

The last time that legislation successfully produced a seismic shift in the U.S. health care system was in 1965, when the Medicare bill was signed into law by President Lyndon Johnson. Since then, change has been incremental and has failed to keep pace with the mounting problems confronting American health care. In 1994, a major health care reform bill produced under the aegis of President Bill Clinton and Hillary Clinton was essentially dead on arrival in Congress.

There is some reason to be pessimistic that we will see meaningful health care reform in the next administration. Given the divergent views of the two major parties on health care, it is uncertain that — unless the new President’s party has substantial majorities in both branches of Congress — a health care bill will achieve sufficient political consensus for passage. Much, too, will depend on presidential leadership.

We believe, however, that it would be a mistake to rely on government alone to solve the crisis. Meaningful health care reform will require a concerted effort by all the major stakeholders in our health care system, as represented by the panelists in the Shattuck Lecture. As was pointed out by panelist Reed Tuckson, reform will also require a willingness to compromise. We offer a challenge to these stakeholders: create together a system that

Pharmacogenomics and Drug Toxicity

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In the United States alone, it is estimated that adverse drug reactions affect nearly 2 million patients and kill about 100,000 people each year. Adverse drug reactions are often classified into two groups. The first group can be explained by the mode of action of the therapeutic drug. Examples of adverse drug reactions in this group include hypoglycemia induced by diabetic drugs, leukopenia induced by cytotoxic anticancer drugs, and bleeding induced by warfarin, an oral anticoagulant. The phenotypes of the second group are not explained by the mode of action of the
drug. Examples in this group are toxic epidermal necrolysis and injury to the liver caused by various drugs.

Among many potential causes of adverse drug reactions, genetic variants that cause susceptibility to a drug reaction loom large. The identification of such variants is expected to improve the management of patient care by determining which patients should avoid a specific drug and which patients should take a modified dose of the drug. This strategy could potentially reduce medical costs and improve the process of drug development.

Genes that are currently known to be associated with adverse drug reactions can be classified mainly into three categories: drug-metabolizing enzymes, drug transporters, and HLAs. Genes in the first two categories influence the pharmacokinetics and pharmacodynamics of drugs. Poor clearance of drugs from the body can increase the concentration of the drug to a toxic level and thus result in adverse drug reactions; for example, genetic variants in the genes encoding thiopurine-S-methyltransferase and uridine diphosphoglucuronosyltransferase 1A1 are known to increase the risk of myelotoxicity associated with treatment with azathioprine and irinotecan, respectively. The HLAs have been implicated in different types of adverse drug reactions. The HLA-B1502 allele is associated with serious dermatologic reactions — such as toxic epidermal necrolysis and the Stevens–Johnson syndrome — to the drug carbamazepine. These three drugs are listed in the “Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels” by the Food and Drug Administration, which recommends that the relevant genetic tests be performed before the drug is prescribed. Although the mechanism by which HLA molecules drive dermatologic adverse drug reactions is unclear, it is suspected that an interaction between a certain HLA molecule and a drug (or its metabolite) may trigger the cellular immune response.

Although the usefulness of identifying those people who have a high risk of adverse drug reactions in response to certain drugs is not in dispute and pharmacogenetic testing is slowly making its way into the clinic, the comprehensiveness of most studies has been less than robust for two reasons: the number of genetic loci typically screened is limited, and the number of patients with specific types of adverse drug reactions is very small. The result is that many studies have lacked sufficient statistical power. The problem of screening only a limited number of genetic loci is now principally addressed by combining our knowledge of the human genome with very-high-throughput technologies to screen hundreds of thousands of genetic variations throughout the genome in a single experiment. Although some scientists argue that sequencing the entire genome is necessary for the comprehensive detection of a genetic variation that causes susceptibility to adverse drug reactions, knowing which polymorphic markers predict (even though they do not actually cause) adverse drug reactions can benefit medical management.

A study reported by the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group in this issue of the Journal demonstrates the power of the genomewide association study. With the use of this method, the SEARCH Collaborative Group identified a genetic risk factor for myopathy in patients who were being treated with simvastatin, a drug that reduces low-density lipoprotein cholesterol levels and prevents cardiovascular disease. The authors studied two sets of patient and control groups from large trials involving approximately 12,000 and 20,000 participants who were treated with 80 mg and 40 mg of simvastatin per day, respectively. By screening about half a million genetic markers in each patient with myopathy who was taking 80 mg of simvastatin per day and comparing the prevalence of these markers with the prevalence among patients who were taking the same dose of the drug but who did not have myopathy, the authors observed a strong association between myopathy and two tightly linked variants in the SLC01B1 gene, which encodes an organic anion transporter. They went on to confirm this association in patients in the second trial, who were randomly assigned to 40 mg of simvastatin per day.

Polymorphisms in some solute transporter genes have been associated with altered hepatic uptake of pravastatin, another statin, and some data indicate that genetic variations in SLC01B1 might affect the variability of outcomes in patients treated with statins. A variant of SLC01B1 was found in a patient with pravastatin-induced myopathy. These studies have led some to spec-
ulate that SLCO1B1 variants cause a susceptibility to statin-induced myopathy, but the study by the SEARCH Collaborative Group shows an unequivocal association. Since approximately 60% of the cases of simvastatin-induced myopathy were attributed to variant SLCO1B1, avoiding the administration of high-dose simvastatin to those who are homozygous or heterozygous for the variant allele (about 30% of the population analyzed by the SEARCH group) could reduce the incidence of myopathy by nearly 60%. Alternatively, one might choose to avoid prescribing simvastatin only to those who are homozygous for the risk allele (nearly 2% of the population analyzed by the SEARCH group), which could reduce the incidence of myopathy by 25%, and prescribe a relatively low dose of the drug to patients who are heterozygous for the risk allele. Further investigation is required to identify the optimal therapeutic approach.

The degree of myopathy that occurred in these two trials was mild and reversible, in stark contrast to a form of statin-induced rhabdomyolysis that involves severe muscle damage accompanied by toxic effects in other organs such as the kidney. SLCO1B1 variants must be tested for an association with this adverse drug reaction as soon as possible. However, severe adverse drug reactions are very rare, and the incidence of statin-induced rhabdomyolysis is reported to be as low as 0.000044 event per person per year. Hence, a global network for the collection of data on patients with severe adverse drug reactions would benefit the field of pharmacogenetics enormously and encourage the development of new technologies.

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Preeclampsia — A Glimpse into the Future?
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Preeclampsia, a disorder of pregnancy characterized by elevated blood pressure and proteinuria, complicates approximately 5% of pregnancies. Although several risk factors for this condition are well recognized, including nulliparity, extremes of maternal age, obesity, and preexisting diabetes or hypertension, the causes of preeclampsia remain uncertain; recent studies have suggested that circulating angiogenic factors, alterations in the renin–angiotensin system, and insulin resistance may be involved in pathogenesis. Despite several trials examining various interventions, no strat-