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In the last decade, scientific advances have made it possible to diagnose and treat a rapidly growing number of diseases—especially various types of cancer—much earlier and with greater precision than ever before. These developments have vastly expanded doctors' power to customize therapy, maximizing the effectiveness of drug treatments and minimizing their side effects. That's the good news. The bad news is that progress in realizing the promise of personalized medicine has been slow and uneven in the United States and the rest of the world. Although science is always ahead of practice in the medical field, the gap today in the area of personalized medicine is inexcusably large.

Today, most U.S. physicians continue to practice traditional trial-and-error medicine. A patient presents with symptoms, and the doctor makes a "most likely" diagnosis that is consistent with those symptoms, then prescribes a drug and, possibly, other treatment such as surgery. The drug dosage is typically based on the patient's weight. If the drug

doesn't work or has significant side effects, the doctor may change the dosage or try another drug if one is available. Alternatively, the doctor may abandon the original diagnosis in favor of another and write a new prescription. This cycle is repeated until the correct, or a more precise, diagnosis and treatment plan are discovered.

In contrast, personalized medicine uses much more refined diagnostic testing to identify the exact disease at the outset. Then, to select the best treatment and determine the right dosage, doctors who use the personalized medicine approach take into account the patient's unique physiology; the physiology, if applicable, of the tumor, virus, or bacteria; and the patient's ability to metabolize particular drugs.

To be sure, there is no alternative to trial-and-error medicine for scores of diseases because of profound gaps in knowledge about their causes, about the biological markers of their presence or stage, and about the factors that influence the effectiveness of possible

remedies. What is alarming, though, is the degree to which the trial-and-error approach persists even when this knowledge does exist.

Four barriers are hindering the transition from trial-and-error medicine to personalized medicine in the U.S. and, to varying degrees, the rest of the world. First is the pharmaceutical industry's historically successful *blockbuster model*, which focuses on developing and marketing drugs for as broad a patient group as possible and discourages the development of therapies aimed at smaller subpopulations and the diagnostic tests that can identify them. Next is a *regulatory environment* that causes too many resources to be devoted to phase-three clinical trials (the "final exams" of a new drug's efficacy and safety) and too few to monitoring and assessment after the U.S. Food and Drug Administration has approved a drug. Third are the perverse economics of a *dysfunctional payment system*, which rewards physicians for activity (completing procedures and prescribing drugs) rather than for early diagnosis and prevention. The final barrier is *physician behavior* that is deeply rooted in trial-and-error medicine. In this article, we explore how these obstacles are impeding progress and suggest ways to overcome them. Our focus is the United States, but many of the solutions we recommend could also be applied in other countries.

### The Stakes

Accelerating the adoption of personalized medicine is enormously important in terms of saving both lives and dollars.

**Saving lives.** People with acute diseases don't have the luxury of extra time that trial-and-error diagnosis and treatment often require (see the exhibit "Quick-Killing Cancers"). Lung cancer is a good example. Only 43% of all patients with cancer of the lung or bronchus and 15% with advanced non-small-cell lung cancer (NSCLC) survive one year after diagnosis. The standard first-line treatment for NSCLC is chemotherapy. However, there is mounting evidence that drugs called tyrosine kinase inhibitors (TKIs) are more effective than chemotherapy in treating advanced NSCLC patients who have a mutation in a gene known as EGFR. TKIs include Tarceva, a Genentech drug approved by the FDA in 2004, and Iressa, an AstraZeneca drug avail-

able in Japan since 2002 and in Australia since 2003. Although the FDA approved Tarceva in 2004 only as a second-line therapy for all NSCLC patients, there is growing evidence that TKIs, as a class, are effective first-line treatment for those with the EGFR mutation. A small study presented at the American Society of Clinical Oncology's June 2007 meeting showed that 31 patients with the mutation who all received Iressa as first-line therapy had a median survival rate of 21 months. After 12 months, 73% of the patients were alive, compared with 15% of those who followed the traditional chemotherapy protocol. When Iressa treatment is delayed and is given as second-line therapy, the median survival rate does not differ materially from that of patients who get chemotherapy alone, according to a study from 2004 involving 1,000 patients.

The case is even stronger that Herceptin, a Genentech monoclonal antibody, should be used with chemotherapy as a first-line treatment for women with an aggressive form of breast cancer whose tumors have an overabundance of HER2, a protein that promotes cell growth. In 1998, the FDA approved this use of Herceptin for HER2-positive patients with metastatic cancer (cancer that has spread to other parts of the body) after surgery, and in November 2006, OK'd the same application for HER2-positive patients with early-stage, nonmetastatic breast cancer. In the case of the latter, Herceptin reduced the likelihood of cancer metastasizing to other parts of the body by a remarkable 53% compared with traditional therapy alone, according to a 2005 study. Barriers to personalized medicine, which we will discuss later in this article, are slowing the use of Herceptin and TKIs to treat patients with the relevant genetic profiles.

**Saving dollars.** Through the early identification and initiation of optimal treatments, personalized medicine has the potential to lower the overall cost of health care dramatically. Indeed, the cost of diagnostic tests—under \$1,000 for the vast majority—pales in comparison with the potential benefits. Consider Herceptin. The test to detect whether a breast cancer patient has an overabundance of the HER2 protein costs about \$400. There remain quality control issues about how laboratories conduct the test and questions about whether Herceptin might also help women with lower HER2 levels. Nonetheless, it's clear that

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identifying which patients should—and which patients should not—be treated with Herceptin can save tens of thousands of dollars per person: in the case of HER2-positive patients, by preventing their cancer from metastasizing; in the case of HER2-negative patients, by not treating them with a drug that won't help them.

The problem of giving drugs to people who don't benefit from them is huge. Multiple studies have shown that most drugs prescribed in the U.S. today are effective in fewer than 60% of treated patients (see the exhibit "The Limitations of Standard Drug Treatment"), costing the health care system billions of unnecessary dollars. Consider the percentages of patients for whom the following widely prescribed classes of drugs are, according to a recent study, either "ineffective" or "not completely effective": at least 70% of patients who take the cardiovascular drugs known as ACE inhibitors and beta-blockers; nearly 40% of the people prescribed antidepressants; and at least 30% of both the patients given statins for high cholesterol and those given beta<sub>2</sub>-agonists for asthma. Diagnostic tests don't yet exist to distinguish who does and who does not respond to these medications, but these statistics show the great need for such tests.

**Transition to a New Era**

The rise of personalized medicine is the result of several scientific advances. The sequencing

of the human genome has helped researchers link a growing number of diseases to specific genes. In addition, scientists have been making great strides in mapping the molecular pathways by which a change or mutation in a gene actually manifests itself as a disease. These advances have enabled drug researchers to develop diagnostic tools that can distinguish the subtypes of what had been considered a single disease, as well as chemical agents that target each. As a result, many once-deadly cancers can now be managed as chronic conditions by attacking them early.

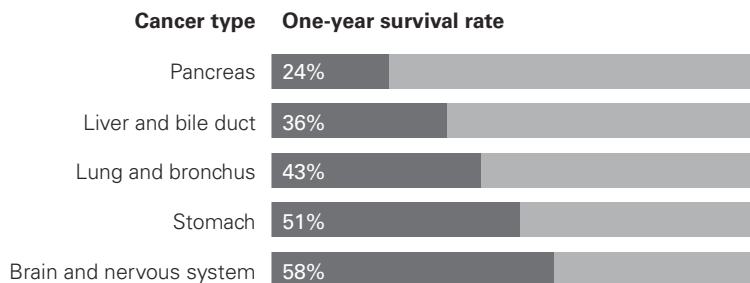
Take blood cancers. In the 1920s, the only available diagnoses for a patient presenting with bruising, fatigue, and night sweats were leukemia and lymphoma. Over the next 20 years, three forms of leukemia and two kinds of lymphoma were identified. Today, we know of 38 types of leukemia and 51 types of lymphoma. These diagnostic advances have aided drug companies in identifying targeted treatments for several of these cancer subtypes.

For example, we now know that an abnormal gene called BCR-ABL causes chronic myeloid leukemia (CML), a disease that strikes an estimated 4,500 people in the U.S. each year. When a diagnostic test determines that a patient has the abnormal BCR-ABL gene, the Novartis drug Gleevec can be prescribed to bind to and deactivate it. More than 95% of patients with this type of leukemia respond positively to initial Gleevec treatment. The five-year survival rate of CML patients receiving Gleevec is 89%; before the drug was approved in 2001, five-year survival for CML patients was only 69%. Such breakthroughs explain why cancer deaths fell in both 2003 and 2004, the most recent years for which data are available, and why survival rates for several cancers have been improving for more than a decade.

Advances in the knowledge of how individuals metabolize drugs are also key to personalized medicine. They are yielding a much more precise understanding of why people respond differently to the same medication. About 30 different enzymes, each made by a different gene or set of genes, control how humans metabolize drugs. A variation in, or the presence or absence of, any of these genes can affect both the minimum dosage that will be effective and the maximum dosage that an

**Quick-Killing Cancers**

For patients with various types of cancer, the survival rate one year after diagnosis is very low. These patients do not have the time to spare that trial-and-error medicine often requires to identify the right diagnoses and optimal therapies.



Source: National Cancer Institute (2003 data).

individual can tolerate without suffering an adverse reaction. Today, tests are available to spot many of the genetic differences, allowing drug dosages to be customized. Unfortunately, these tests are underused, thereby resulting in unnecessary adverse drug reactions and billions of dollars in avoidable costs. One illustrative example is warfarin, a widely prescribed anticoagulant. Members of the FDA estimate that if diagnostic tests to detect certain gene variations were routinely administered to patients who need warfarin, the resulting reduction in serious bleeding events and strokes caused by under- and overdosing of the drug could save the U.S. health care system as much as \$1.1 billion annually. (See the sidebar “An Underutilized Breakthrough.”)

Personalized medicine is not just about identifying optimal drugs and dosages. For some cancers, diagnostic tests can help a doc-

tor determine the aggressiveness of the tumor and, ultimately, decide whether to perform surgery or use less invasive treatments. For example, clinical studies have now shown that if a prostate cancer lacks genes that cause an aggressive form of the cancer, it may remain stable within the prostate gland for decades, obviating the need for radical surgical resection, radiation, and chemotherapy.

The number of diseases that can be precisely diagnosed and then treated with a highly specific therapy is certain to increase dramatically within the decade. In the past five years, oncology drugs for patients with specific genetic characteristics have soared from about 10% to more than 40% of those in clinical trials (phases one, two, and three). Although cancer diagnosis and therapy are at the forefront of progress in this area, similar developments are occurring in other medical subspecialties. For example, because the HIV virus can mutate rapidly, standard HIV care now involves regular testing to determine the current genetic makeup of a patient’s virus and then tailoring drug therapy accordingly. Down the road, one particularly promising area is cardiovascular disease. Researchers are making strides toward identifying genetic variants in patients who do not respond to certain drugs for treating high blood pressure and heart failure (ACE inhibitors, beta-blockers, calcium channel blockers, and diuretics).

Of course, after a link between a gene and a disease is identified, developing a diagnostic test for the gene takes time. Even when such tests are commercially available, routine use is not a given. To get there, four barriers to personalized medicine must be overcome.

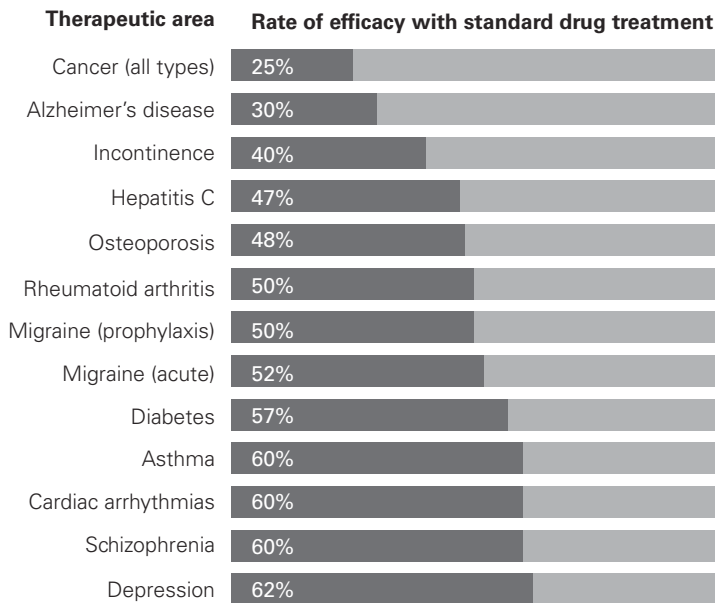
**Understanding the Barriers**

As often happens with the emergence of any new paradigm, strong and powerful entrenched forces are working against the adoption of personalized medicine in the United States.

**The pharmaceutical industry.** Developed over the past 50 years, the blockbuster-drug business model has been highly successful. When things go right, it produces an effective therapy for millions and a highly profitable product. Indeed, the financial performance of the pharmaceutical industry has historically been among the highest of all industries, not only in the U.S. but worldwide.

**The Limitations of Standard Drug Treatment**

For each of these therapeutic areas, standard drug treatment provides a therapeutic benefit only to a limited percentage of patients who receive it. Giving more patients targeted therapy that is guided by diagnostic testing has the potential to increase those numbers.



For depression, the data apply specifically to the drug class known as selective serotonin reuptake inhibitors.

Source: Brian B. Spear, Margo Heath-Chiozzi, and Jeffrey Huff, “Clinical Application of Pharmacogenetics,” *Trends in Molecular Medicine* (May 2001).

Many indicators suggest, however, that the blockbuster model's days are numbered. First, identifying and developing new blockbuster treatments is becoming more difficult: Even though total R&D spending by the drug industry and the federal government has tripled (in real terms) since 1990, the number of new molecular entities, or NMEs, approved by the FDA to be used as drugs has declined from an average of 33 per year during 1993–1997 to 26 during 1998–2003. What's more, an increasing number of NMEs are targeted in their action, meaning that they are effective in treating only subpopulations of people with a given disease.

As a result, the major pharmaceutical companies have not been able to create enough new drugs to offset the declining sales of blockbusters coming off patent, let alone meet Wall Street expectations for continuous growth. This shortfall has triggered a wave of industry consolidation, as companies have

resorted to acquisitions to fill their product lines and boost profits by achieving greater economies of scale. However, the vast majority of the traditional pharmaceutical giants have been reluctant to abandon the blockbuster model and focus on developing a larger number of drugs with much more limited market potential. Indeed, they often choose *not* to develop targeted therapies.

In addition, the large pharmaceutical companies have tended to take a dim view of drugs that are linked to diagnostics, fearing that the diagnostic component would complicate marketing to physicians and slow the identification of treatment-worthy patients by adding another step to the diagnosis process. As a result, few pharmaceutical companies have adopted diagnostics as a critical component of their discovery, clinical trial, and commercialization efforts. Even when diagnostics have been part of R&D, most pharmaceutical companies have not wanted the FDA to urge

## An Underutilized Breakthrough

New genetic tests that can be used to help ascertain the appropriate dosage of warfarin, a widely prescribed anticoagulant, show the great potential of personalized medicine to improve the safety and effectiveness of therapy and to lower costs. Marketed under several brand names, including Coumadin, Jantoven, and Marevan, warfarin is used to treat and prevent blood clots. Approximately 2 million people in the United States are prescribed the drug for the first time each year. Figuring out the appropriate dosage, however, has been a major challenge because the range of possible dosages is very large (the highest is more than 20 times the lowest). Getting the dosage right is extremely important because too much warfarin can cause serious bleeding, and too little won't prevent dangerous clots.

For decades, determining the dosage of warfarin to give a patient was largely guesswork. While doctors understood that a host of clinical factors (weight, age, race, body surface area, vitamin K intake, and so on) were involved, these collectively accounted for only 10% to 27% of the variability in how patients respond.

Then, in the last 15 years, scientists determined that variations in two genes (CYP2C9 and VKORC1) account for roughly 45% of the variability in patient response to warfarin. Diagnostic tests to detect the gene variations were developed in the past five years or so. Such companies as Clinical Data, Kimball Genetics, and PGxL Laboratories began to roll them out in 2006. According to initial reports, the tests may make it possible to reduce the time typically required to determine with reasonable accuracy the proper warfarin dosage for a patient—from at least five to seven days to just one or two.

In a paper published by the American Enterprise Institute–Brookings Joint Center for Regulatory Studies in November 2006 and updated in April 2007, three members of the Food and Drug Administration's Office of Policy and Planning estimated that routine use of the genetic tests, which each cost about \$350, would reduce the number of serious warfarin-associated bleeding events that occur annually in the U.S. by between 32,000 and 81,000 and the number of strokes by between 1,700 and 17,000. At the low end of the ranges, routine performance of the test

would cost the health care system an estimated \$160 million annually; at the high end, it would save the system \$1.1 billion.

Today, the test is administered to fewer than 5% of patients who start warfarin therapy. The big question now is how long will it take for the genetic testing to become routine? On the basis of studies conducted before the test was commercialized, an advisory subcommittee of the FDA decided in November 2005 that there was sufficient evidence to warrant taking genetic variation into account when prescribing warfarin. In August 2007, the FDA acted: It required the label to explain that genetic variations may influence how patients respond to the drug. However, it stopped short of mandating the genetic tests, noting that their availability and reliability vary from lab to lab and that more clinical studies are needed to pinpoint how the genetic information should affect dosing decisions. Still, the label revision should increase pressure on physician associations to change their warfarin guidelines and to spread the word among doctors. Ideally, before too long, prescribing warfarin will no longer be a dangerous game of trial and error.

or require doctors to perform the diagnostic tests before they prescribe the drug.

**The FDA.** This agency has been requiring pharmaceutical companies to conduct increasingly large and detailed clinical trials to prove the safety and efficacy of new drugs. These big clinical trials add enormously to drug-development costs.

Consider a new drug that would be safe and effective for 25% of the population with a particular disease but ineffective or potentially harmful to the other 75%. A large-scale clinical trial to test the drug for the entire disease population would not only be expensive but also yield results unlikely to win FDA approval of the drug. However, a much smaller trial aimed at just the 25%, which uses a genetic test to identify the appropriate participants, would generate strong positive results.

Although the FDA has voiced support for personalized medicine in principle, its actions have lagged behind its words. Even in cases where a specific diagnostic test was used as a criterion for enrolling drug-trial participants, the agency has only infrequently required doctors to perform the test before prescribing the drug. A good example is Roche's Vesanoid, which is effective in treating acute promyelocytic leukemia (APL), a disease defined by a particular genetic marker. The FDA-approved label states that Vesanoid has been studied in patients with the marker and that doctors should consider alternative treatment for patients who lack it. However, this wording is only informational. The FDA does not require the available biomarker test even though roughly 25% of Vesanoid users can suffer a potentially fatal syndrome characterized by fever, acute respiratory distress, and multiple-organ failure. It seems absurd to subject people who don't stand to benefit from the drug to this risk.

Making matters worse, the FDA lacks a system for rigorously tracking and learning about the impact of off-label prescribing. Such a system would not only stop potentially dangerous off-label uses but also help more quickly identify beneficial off-label applications—for example, using tyrosine kinase inhibitors in treating patients with non-small-cell lung cancer that have the EGFR gene mutation, which we discussed earlier.

**Reimbursement.** Eighty percent of all U.S. health care bills are paid by Medicare, Medic-

aid, or employer-provided insurance. Sadly, the reimbursement system controlled by these institutions pays for—and thus encourages—the performance of procedures rather than accurate diagnosis.

Today's pay-for-procedure approach is rooted in a current procedural terminology (CPT) code system, which the American Medical Association developed for the Centers for Medicare & Medicaid Services (CMS) in 1966. The CPT-approval process is controlled by an AMA committee and its advisory boards of more than 90 physicians nominated by national medical specialty societies. The diagnostics industry is not represented on the committee or its boards. Since the priority of physicians on the committee and boards is the level of reimbursement for treatment in their specialties and because the process for adding, deleting, or changing codes is long and laborious, the CPT codes and fees associated with diagnostic testing are rarely updated. Pricing has been increased for inflation only twice in the past 15 years, but that's hardly the biggest problem. If a new technique that reduces the number of needed laboratory activities from, say, eight to six is developed, the payment is cut accordingly. When a new diagnostic test requires a new lab activity for which no CPT code exists, the lab performing the test has three unattractive choices: accept no reimbursement for the activity, try to make a case for why the new activity should be reimbursed according to an existing code that doesn't match the activity, or start the long process of creating a new code. Even if the lab succeeds in obtaining a new CPT code, that's no guarantee that the CMS will pay for the test.

The bottom line: Companies have little incentive to develop new diagnostic tests or to improve the efficiency and efficacy of existing ones.

**Physicians' habits.** Several phenomena are preventing even the most well-intentioned physicians from embracing personalized medicine. The just-discussed reimbursement system is one. It rewards physicians for procedures and undercompensates them for the time and effort needed to make an accurate diagnosis. Unless a diagnosis can be reached in a single visit, the time required outpaces the compensation. Furthermore, unless a diagnostic test can be performed in a doctor's office,

the physician has no financial incentive to order it. Yet, virtually all tests involved in personalized medicine are complex and must (at least today) be conducted outside the physician's office.

The bulk of the 700,000 practicing U.S. physicians also lack an understanding of issues in personalized medicine. Most received their medical education before the genomics revolution. The challenge of educating a critical mass of such a large and fragmented community in the new paradigm is huge. In addition, most medical schools have yet to fully incorporate genetics and genomics into their curricula.

Finally, physician organizations historically have been reluctant to take strong, proactive stands in recommending new standards of care. Given the number of standards that doctors already have to comply with, professional organizations have been concerned about unnecessarily adding to physicians' burdens, overly constraining their freedom to decide what's best for patients, and making them more vulnerable to malpractice suits.

Such problems help explain why it takes so long for new tests and treatments for subpopulations to be widely used. Consider the previously discussed HER2 protein test for breast cancer. Even though the rate at which doctors have been adopting it has been relatively high, plenty of doctors still don't use it as part of the initial diagnosis.

### Overcoming the Barriers

There are specific, practical ways to overcome each of the barriers personalized medicine faces, some relatively simple and others extremely complex.

**Transforming pharmaceutical giants.** Big pharmaceutical companies can take three steps to speed the introduction of personalized medicine: abandon the blockbuster business model, forge alliances with diagnostic companies, and step up efforts to communicate the safety and efficacy advantages of targeted therapies.

It's hard to exaggerate the challenge of changing the business model of the pharmaceutical giants from blockbuster to tailored therapies. It would mean moving from a grand-slam mentality (creating a handful of drugs that can generate annual sales of \$1 billion or more each) to one that empha-

sizes singles, doubles, and occasional triples (creating a larger portfolio of \$200 million- to \$500 million-a-year sellers).

A move to the targeted model would probably reduce sales and profits in the short term as companies start biomarker, diagnostic, and other discovery programs. In the intermediate and long terms, however, the targeted-drug business model would increase sales and profits for several reasons:

*A subpopulation may turn out not to be so small.* Once a highly effective therapy for a disease is available, more of the affected patients see their physicians, who are then aware of and willing to provide the treatment. Also, some studies and anecdotal evidence suggest that knowledge of the greater effectiveness of a targeted therapy makes patients more likely to adhere to their drug regimens.

*Payers are beginning to recognize the real and increasing cost of administering ineffective drugs and treating side effects.* As a result, if a pharmaceutical company can demonstrate that its drug lowers the overall cost of treating a subpopulation with a disease, private and government insurers will become increasingly willing to pay for the relevant diagnostic test and to pay a higher price for the drug treatment.

*Focusing clinical trials on targeted subpopulations would slash their size, duration, and cost.* Since clinical trials now consume more than half the money spent on drug development, this change would improve the profitability of drugs.

To achieve these benefits, however, large pharmaceutical companies must embrace a business model that includes diagnostics in drug development, trial design, and ultimately patient treatment. Those that do will not only improve their financial performance in the long run but also earn the goodwill of patients and society as a whole. Given the trends, large pharmaceutical companies have little choice but to change. Those that stick with the blockbuster model face a frustrating future of declining sales and profits.

**Overhauling regulation.** In the past three years, the FDA has begun to support the principles of personalized medicine. The agency has made the creation of guidelines for codeveloping diagnostic tests and drugs an element of its "critical path initiative." In addition, it is working with drug and diagnostic companies to create a formal process for

*Large pharmaceutical companies have little choice but to change. Those that stick with the blockbuster model face a frustrating future of declining sales and profits.*



validating biomarker tests. How long it takes these efforts to bear fruit remains to be seen. In the meantime, more must be done in the U.S. and elsewhere. (For example, European agencies are at about the same place as the FDA. They also are exploring how to incorporate biomarker and other diagnostic tests into drug regulations but have not yet adopted formal policies.)

The FDA should give pharmaceutical companies incentives to develop diagnostics and targeted drugs in tandem. One straightforward inducement would be to fast-track the review of all new drugs that include a diagnostic test as part of the patient-selection process. The quicker the drug and test are approved, the sooner the treatment will get to patients and the sooner the financial benefits will accrue to manufacturers.

Even more important, when a drug and a diagnostic test are developed and go through clinical trials together, the FDA should uniformly require that the test be conducted and its results reviewed before the treatment is prescribed. These tests should include those that determine how patients metabolize particular drugs. As many as 10% of drug labels today contain information on how genetic variations affect individuals' responses to drugs. However, very few mention the tests that can be used to obtain and interpret those data for individual patients, let alone require that the tests be conducted to help determine the optimal drug dosages.

Finally, it is critical that the FDA craft appropriate standards to ensure the accuracy and integrity of diagnostic tests. The agency needs to implement practical regulations that continue to encourage industry innovation but maintain high standards of quality. Done well, such regulations will increase the confidence of both doctors and patients in personalized medicine.

**Paying for performance.** The most influential of all payers in the United States is the Centers for Medicare & Medicaid Services, which directly reimburses 34% of all health care and whose framework most other U.S. payers emulate. Historically, the FDA and the CMS have operated independently. However, by working together, these agencies could do much to advance personalized medicine. An immediate opportunity is the new pay-for-performance standards that the CMS is in

the process of creating. The FDA should, with physician societies, develop standards for appropriate use of diagnostic tests, and the CMS should reimburse providers according to how well they adhere to those standards. In this way, the CMS would reward excellence in diagnosis, not just treatment. Unfortunately, the initial drafts of pay-for-performance guidelines do not include provisions for diagnostic tests.

In addition, the FDA and the CMS should coordinate their efforts to evaluate the effectiveness of a drug after it is approved and marketed. Today, the FDA evaluates a drug's safety and efficacy, and the CMS separately assesses the drug's cost-effectiveness. As a result, the two agencies have overlapping and inconsistent policies, slowing the pace of change. Here's a change that would go a long way: The CMS has already shown that it will pay for targeted drug therapies at a relatively high rate only if their effectiveness in the market is fully tracked and reviewed. To give this policy a backbone, the FDA should consistently include on the drug labels the requirement that diagnostics, when available, be used to select appropriate patients for the treatment. Then it would be reasonable for the CMS to make proof of testing a prerequisite for drug reimbursement.

Finally, the CPT-code reimbursement system for diagnostics must be reformed. Under the model that we envision, diagnosis and treatment would share in the financial reward. Physicians would be compensated for using appropriate state-of-the-art diagnostic tests. Laboratories that perform the tests would be paid according to the tests' value in helping doctors make the best diagnoses, allowing the labs to earn a fair return and support ongoing research and training. Pharmaceutical companies would be allowed to charge what might otherwise appear to be high prices for extremely effective, targeted drugs. These radical reforms will not be easy or quick to institute, but they are critical steps toward the full adoption of personalized medicine.

**Changing physicians' habits.** The changes proposed above will remove many of the economic disincentives that dissuade physicians from ordering all necessary diagnostic tests. Then, altering physicians' habits will largely be a matter of education. Fortunately, most doctors are already required to attend 12

to 50 hours of continuing medical education (CME) courses per year to maintain their licenses. However, very few states stipulate the specific content of these courses. To get physicians up to speed on personalized medicine, states should mandate that a certain portion of required CME credits focus on genomics, diagnostic testing, and targeted therapies. This change alone will play a critical role in moving personalized medicine into mainstream practice.

It should be easier to educate future generations of doctors. For this to happen, though, medical schools must take several steps. They need to focus more on the importance of accurate diagnosis and the science of diagnostics. They must better incorporate genetics and genomics into their curricula so that students understand the underlying science and its application to diagnostic and therapeutic tools. Finally, the schools need to provide more fellowships in genomic medicine, which would help to establish the field as a subspecialty.

Physician organizations, which have been largely silent in many of the recent debates about the expanded use of diagnostics and personalized medicine, need to become committed advocates. They should actively engage in developing new standards of care that integrate new therapeutics, diagnostics, and quality standards for testing. Such standards are essential for speeding physicians' adop-

tion of personalized medicine as well as for reforming the reimbursement system.

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U.S. employers can help accelerate the pace of change in several practical ways. They can push insurers to cover targeted therapies, including diagnostics, and insist that providers routinely offer them to their employees. They can demand that insurers, in their drive to control costs, focus on the overall expense of treatment during the entire course of a disease, not just the cost of the initial procedures.

Yes, the slow progress of personalized medicine in the past decade has been frustrating, but it's hardly surprising given the complexity of the health care system with all of its vested interests. Paradigm change rarely happens quickly. Consider the Toyota Production System, which was a similar revolutionary movement to "get it right the first time." It took 30 years for manufacturers outside Japan to recognize the superiority of this approach. Given the higher stakes involved in personalized medicine—people's lives and the viability of health care systems—it would be unconscionable to allow the widespread adoption of personalized medicine to take as long.

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