Personalized medicine promises to increase the quality of clinical care and, in some cases, to decrease health care costs. The biggest hurdles are economic, not scientific.

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Diagnostics is the key to personalized medicine, a tailored approach to treatment based on the molecular analysis of genes, proteins, and metabolites. Yet although this approach has generated much excitement, few personalized-medicine tests have achieved high levels of clinical adoption. To understand better the challenges to the development and acceptance of personalized medicine—and how to overcome them—we interviewed more than 60 leading experts in this and related fields and conducted microeconomic analyses of various stakeholder issues.

We focus here on the US market, but the challenges are also relevant elsewhere. Our proposals for overcoming them could significantly accelerate the adoption of personalized medicine.

Stakeholder incentives and challenges

Our investigation highlighted three main obstacles to the advancement of personalized medicine: scientific challenges (a poor understanding of molecular mechanisms or a lack of molecular markers associated with some diseases, for example), economic challenges (poorly aligned incentives), and operational issues. Although scientific difficulties remain, the economic challenges and operational questions now seem to be the biggest hurdle. Operational issues can often be largely resolved within a particular stakeholder group, but correcting the incentive structure and modifying the relationships between stakeholders could be more complex.

Payers

Investors and analysts have suggested that personalized medicine can dramatically reduce health care costs and help payers market products to the most attractive customers. Yet most payers have been slow to invest in personalized medicine. Leaders in payer organizations say that several factors could explain this reluctance. First, it is hard to identify which tests truly save costs. Second, the belief that it is difficult to track much earlier-stage and experimental testing leads to fears that although individual tests may not be very expensive, the overall eventual costs could be unjustifiably high. A third concern is the difficulty of enforcing standard protocols to ensure that physicians follow through with appropriate patient care based on test results. Fourth, test information could be misused—particularly in the early stages of investigation and development—which could harm patients. Finally, there is no longitudinal accounting, which would enable payers to capture long-term cost savings from near-term testing.

To understand which tests avert costs, we analyzed various types of tests. Two primary factors determine a test's cost effectiveness from a payer's perspective: per patient savings (the difference between the cost of treating a disease and the cost of the intervention indicated by the test) and the likelihood that a test suggests an intervention for any

Our interview subjects included payers, providers, regulatory experts, executives of pharmaceutical and biotechnology companies, academic opinion leaders, and executives of diagnostics and clinical-laboratory companies.
particular patient (Exhibit 1). Tests that help avoid the use of expensive therapies (for example, cancer therapies such as trastuzumab or imatinib), minimize costly adverse events (such as the warfarin dosing test), or delay expensive procedures can be extremely cost effective for payers. Although such tests cost $100 to $3,000 each, they save $600 to $28,000 per patient. Tests that save a small amount per patient or have a low probability of identifying patients requiring intervention are not cost effective. BRCA1 testing to predict the risk of breast cancer can save around $25,000 per patient identified, for example. But mutations are so rare in the general population that this test, which costs up to $3,000 per patient, is cost effective only when performed on a patient with a family history of breast cancer.

The payers’ adoption of personalized-medicine tests is further complicated by the high customer turnover of many commercial payers in the United States. This makes it less economically attractive for payers to reimburse prophylactic tests that minimize the likelihood of conditions occurring much later in life: the costs accrue to the payer that screens the patient and performs the intervention, the benefits to the payer covering the patient when the disease actually arises. The pharmacoeconomics for the BRCA1 test illustrate the point (Exhibit 2). This longitudinal-accounting issue is particularly acute for diseases with a late or delayed onset: insurers for the elderly—for example, the US Centers for Medicare and Medicaid Services (CMS)—get the benefit of interventions paid for years earlier by commercial payers. Notably, payer systems that have low patient turnover, such as integrated systems like Kaiser Permanente in the United States or single-payer systems in Europe, are less exposed to this incentive challenge.

### Exhibit 1
**Testing for savings**

<table>
<thead>
<tr>
<th>Companion diagnostics</th>
<th>Genomic markers</th>
<th>Procedure-focused diagnostics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Her2</td>
<td>BRCA1</td>
<td>AlloMap</td>
</tr>
<tr>
<td>BCR-ABL</td>
<td>BRCA1-F</td>
<td>KIF6 (statin)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Savings from changed decision, $ thousand</th>
<th>$28</th>
<th>$4</th>
<th>$0.7</th>
<th>$3.1</th>
<th>$0.5</th>
<th>$5</th>
<th>&lt;0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability that diagnostic changes treatment decision, %</td>
<td>70</td>
<td>5</td>
<td>35</td>
<td>75</td>
<td>2</td>
<td>20</td>
<td>50</td>
</tr>
<tr>
<td>Savings per test, $ thousand</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost of test, $ thousand</td>
<td>$0.1</td>
<td>$1</td>
<td>$0.3</td>
<td>$3</td>
<td>$2–3</td>
<td>$2–3</td>
<td>N/A</td>
</tr>
<tr>
<td>Cost savings for payers $1</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

1. Estimated savings per test is product of savings from single changed treatment decision and probability that any given patient will have a positive test (such that treatment decision is changed).
2. Human epidermal growth factor receptor 2.
4. BRCA1 screening in an individual with a family history of breast cancer.
Because the actual cost savings of personalized-medicine tests may not be known until a test has been on the market for some time, it will remain in the interests of payers to delay adopting such diagnostics until they can differentiate between cost-saving and cost-creating ones. The winning strategy for diagnostics companies may therefore be to collaborate with stakeholders whose economics are more aligned with theirs (for example, Kaiser Permanente, large self-insured employers, and the US Veterans Affairs system, which have relatively low membership turnover). Generating high-quality health economic evidence will provide the confidence that enables payers more rapidly to adopt tests and will align physicians’ incentives with patient care and outcomes rather than procedures. Such developments could create a source of competitive advantage for payers that are better at identifying and implementing policies to promote cost-saving diagnostics.

Providers
Today’s procedure-based reimbursement system for providers also presents a challenge: provider economics create incentives for some personalized-medicine tests but discourage others. Physicians could be more likely to embrace tests that increase the number of procedures performed than tests that diminish procedure volume. A test that identifies three times more patients at high risk of colon cancer than current approaches do would align well with the interests of gastroenterologists, for example, since a patient’s lifetime value related to such a molecular diagnostic is around $2,000. Other tests may be cost neutral or have microeconomic disincentives. Oncotype DX, a gene-based breast cancer
diagnostic test used to assess the likelihood of benefit from chemotherapy, for example, reduces the number of patients that physicians treat with it and thus the revenue those patients generate. Yet Onco
type DX has been widely adopted because of its clinical merit.

**Pharmaceutical and biotechnology companies**

Biomarkers (an indicator of a biological state) are now helping pharmaceutical and biotechnology companies to aid R&D. In some cases, companies will develop these markers as companion diagnostics—tests to identify a patient’s likelihood of responding to a drug or experiencing side effects. R&D executives at 16 of the top 20 biopharmaceutical companies interviewed in a 2007 McKinsey survey indicated that, on average, 30 to 50 percent of drugs in development have an associated biomarker program and suggested that this number would probably increase. By contrast, the same executives also suggested that less than 10 percent of drugs that now have biomarker programs would be launched with a companion diagnostic over the next five to ten years (this is highly dependent on the disease area).

In theory, companion diagnostics can improve R&D productivity by decreasing trial sizes, reducing attrition, or increasing speed to market, as well as enhance commercial performance by boosting market share or supporting higher drug prices. Many companies, however, are moving slowly to use biomarkers and companion diagnostics: while the most aggressive players have biomarker programs for 100 percent and companion diagnostics for 30 percent or more of their compounds, the average company has far fewer (30 to 50 percent and less than 10 percent, respectively). Moreover, many experts we interviewed said that their companies hadn’t prioritized companion diagnostics and were taking a cautious approach to investments. Scientific and clinical factors place some limits on the pace of development. In certain disease areas, understanding of molecular mechanisms is insufficient to select biomarkers at early stages of development. In others, there is no big clinical need for companion diagnostics. In many disease areas, however, companies are moving slowly despite scientific advances.

Our research suggests that the potential to generate greater value after marketing, through increasing prices and market share, is vastly more important for the economics of pharmaceutical and biotechnology companies than making development more productive (Exhibit 3). Indeed, companion diagnostics may do little to improve development productivity. Often, they might actually increase overall costs and delay development. Experts suggested that Phase II clinical trials must frequently be larger when companion diagnostics are employed. Trials often need to be designed with several potential candidate biomarkers in Phase II (and sometimes Phase III), as it is unclear which markers will be predictive. In addition, the US Food and Drug Administration (FDA) is likely to require that marker-negative patients be included in Phase III trials, given concerns that drugs could be used off-label by these patients. This is likely to eliminate the widely cited upside
from smaller trials. Other commonly cited applications of personalized medicine during drug development also seem unlikely to improve drug-development productivity much.

Nonetheless, companion diagnostics could create significant potential commercial benefits from increased market share and pricing power. Yet there are also significant risks, as companion diagnostics divide the treatable patient population into subsegments and can reduce market share. They are therefore most likely to create value for later-to-market entrants in crowded markets characterized by significant pricing flexibility.

If two drugs are already on the market and relatively undifferentiated, for example, the third drug on the market is likely to capture a relatively small share—say, 5 to 20 percent. A companion diagnostic that identifies a segment of patients who will respond especially well to a drug or will find it less toxic, and thereby enables higher pricing, could generate value. A key determinant is the payers’ price scrutiny and sensitivity, which varies dramatically by disease area, particularly in the United States. For instance, BiDil, a fixed-dose combination of two generic cardiovascular drugs (hydralazine hydrochloride and isosorbide dinitrate), has been approved by the FDA specifically for African Americans with heart failure. Attempts to charge a price premium faced aggressive differential copay tiering by payers, which contributed to lower-than-expected sales. In therapeutic classes where payers scrutinize prices less intensely (oncology drugs, for example), companies would be more likely to charge a premium and maintain coverage.

These companies are rightly considering investing in personalized medicine in certain disease areas. To highlight those where near-term investment in companion diagnostics is most likely to occur, we segmented drug classes according to their scientific and commercial potential (Exhibit 4). This segmentation reflects not only quantitative factors...
but also qualitative factors from interviews. Our analysis indicates that companies are most likely to invest in diagnostics in areas such as oncology, immunology, and infectious disease. The segmentation also reveals disease areas where incentives are not aligned to drive investment, despite technical feasibility and clinical need. These areas, such as anticoagulants, antipsychotics, and antidepressants, are ripe for development by other organizations, such as diagnostics companies.

Companies should also realize that the payer environment is evolving rapidly and that personalized-medicine tools will increasingly be required to preserve value. Although pharmaceutical and biotechnology companies must be aware of areas where diagnostics can destroy value by subsegmenting existing markets, it will be equally important to prepare for the day when regulatory bodies will demand greater proof of patient outcomes to justify approval, reimbursement, and prices. Companies should thus act quickly to build the required capabilities and experience.

Diagnostics companies
Companies that develop diagnostics and life science tools enable a wide variety of test types, including companion diagnostics (often in collaboration with a biotechnology or pharmaceutical company), early-stage diagnostics, disease recurrence and monitoring tests, adverse-drug-events tests, and genotypic-risk-marker analyses. However, diagnostics developers have faced difficulty capturing the full value they generate.
Diagnostic tests are estimated to influence 60 to 70 percent of all treatment decisions, for example, yet account for only 5 percent of hospital costs and 2 percent of Medicare expenditures. Molecular diagnostics are often cited as a more attractive market segment than typical diagnostics, given the potential for higher prices ($100 to $3,000 per test, compared with $20 to $50 for a typical diagnostic test) and higher gross margins (50 to 70 percent for a sample molecular diagnostic, compared with 30 to 50 percent for most diagnostics of typical large laboratory companies). Indeed, a number of emerging companies, including Celera, Genomic Health, Myriad, Monogram Biosciences, and XDx, have successfully raised funding and developed innovative molecular-diagnostic tests.

Unfortunately, the molecular-diagnostics business case still holds significant risk (Exhibit 5) as a result of factors such as development costs, the timing of development and approval, time-to-payer coverage, rates of provider adoption, and peak sales prices. To understand these factors’ relative importance, we modeled the economics of a hypothetical start-up and then performed a sensitivity analysis using upside and downside scenarios for each variable.

Our model, intended to test the importance of risk factors, was based on benchmarks from a few molecular-diagnostics businesses. It doesn’t represent a specific company, and the economics of companies with products now on the market vary significantly. This model suggests that the expected ten-year net present value (NPV) of an average diagnostic test

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**Exhibit 5**

**The business risks of molecular diagnostics**

Sensitivity analysis for factors affecting the commercial potential of a company developing a molecular diagnostic

<table>
<thead>
<tr>
<th>Sensitivity assumptions</th>
<th>Sensitivity assumptions</th>
<th>Impact of 10-year NPV of EBITDA, $ million</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Worst case</td>
<td>Today</td>
</tr>
<tr>
<td>1 Cost to develop test, $ million</td>
<td>50</td>
<td>45</td>
</tr>
<tr>
<td>2 Timing of test approval and adoption</td>
<td>Timing of development and approval, years</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Time to payer coverage, years</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Time to physician adoption, years</td>
<td>8</td>
</tr>
<tr>
<td>3 Peak sales price, $</td>
<td>2,500</td>
<td>3,000</td>
</tr>
</tbody>
</table>

**Best case 10-year NPV = 14.8**

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1. A representative profit-and-loss (P&L) model for a start-up molecular-diagnostics company was created from a number of sources. The aim of this model was not to define the P&L statement for all such molecular-diagnostics companies but to create a model that would allow us systematically to explore the factors affecting profitability. The cost of test development (including investments in start-up infrastructure) was based on interviews with venture-capital groups and start-ups as well as actual data on seed funding for relevant companies. To assess the impact of various factors, we used estimates from expert interviews as well as historical data.

2. NPV = net present value; EBITDA = earnings before interest, taxes, depreciation, and amortization.
is around $15 million. The most important factors influencing profitability are the time to approval and the rate of payer adoption. If the time to approval is delayed by a year, the ten-year NPV becomes negative, at around –$10 million. This finding is relevant, since it remains unclear how the FDA will regulate in vitro diagnostic multivariate index assays (IVDMIAs)—tests like Oncotype DX for breast cancer recurrence, which is already on the market.

At the time of writing, the FDA had suggested that a 510(k) approval process for diagnostics may be sufficient for tests that are prognostic indicators, but premarket approval from the FDA will probably be required if a test directly influences therapy decisions. A pre-market-approval review is likely to increase time to market by at least a year. Nonetheless, good communication between the Center for Drug Evaluation and Research and the Office of In Vitro Diagnostic Device Evaluation and Safety may partially mitigate this problem through priority reviews. Approval timelines for other systems remain unclear. The European Medicines Agency and Japan’s Pharmaceuticals and Medical Devices Agency also have yet to establish clear guidelines for approving personalized-medicine tests.

The case of Oncotype DX demonstrates the challenge of slow coverage by payers. Although the test was launched in 2004, analysts and company estimates suggest it will be 2010 before all payers routinely cover it. Coverage stands at about 85 percent, contrasting starkly with typical adoption rates for new drugs, which are generally reimbursed immediately at launch or within the year in the United States. In Europe, drug coverage may take slightly longer, depending on the extent of the review, but is unlikely to take more than four years—the adoption timeline of Oncotype DX.

Start-up diagnostics companies therefore face challenging economics. However, as more tests become available and payers, regulators, and molecular-diagnostic companies gain experience, development and adoption times are likely to shorten. Likewise, as the regulatory process becomes clearer—but potentially longer—the adoption rates of payers may also increase. Given their unease with personalized-medicine testing, it will therefore be advantageous for leading diagnostics companies to help shape the development of rigorous but efficient regulatory and approval standards.

Potential catalysts for personalized medicine

Conversations and analyses conducted during the course of our investigation revealed four main catalysts that could significantly affect the adoption of personalized medicine in the near term.

Regulatory environment

First, regulatory bodies such as the FDA must improve the clarity and efficiency of regulatory-approval processes, both for stand-alone and companion diagnostics. These
clarifications are critical to help diagnostics companies plan ahead and design trials. Our conversations with more than 60 experts indicate that the key questions regulatory bodies ought to address include the following:

• Should marker-negative patients be required for Phase III trials?

• Will the use of retrospective analyses on archived samples be permitted for approving companion diagnostics (and if so, under what circumstances)?

• What regulatory standards and oversight should be required to let personalized-medicine tests, especially laboratory-developed ones, be used in therapy decisions?

For regulations under consideration, the authorities must weigh short-term costs against long-term benefits. Current plans include basing the classification of tests as Class I, II, or III on the level of risk of the intended use. As a result of higher approval standards, IVDMA changes promoting more rigorous evaluation of safety and effectiveness may have long-term benefits, encouraging faster adoption by payers and physicians. However, the near-term consequences may harm short-term market investments.

For diagnostics companies, the approval process can actually be an opportunity to justify higher pricing by showing a willingness to set appropriately stringent standards and by shaping regulatory guidelines to bolster the industry and protect patients. The FDA should work to minimize approval delays resulting from higher standards and help mitigate any negative impact on investment in development. Leading pharmaceutical, biotechnology, and diagnostics companies should seek opportunities to help shape the development of these guidelines and standards.

To drive changes in market incentives, regulators could decide not to require the collection of clinical data on marker-negative patients, thus lowering development costs. Concerns about the use of therapeutics in this population could be reduced through parallel moves by payers and regulatory bodies to increase barriers to off-label use. Furthermore, regulators could increase the flexibility of trial designs and even allow the approval of companion diagnostics on the basis of retrospective tests of the DX marker (that is, performed on archived samples). Finally, governments and regulators could directly reward the development of companion diagnostics by increasing the patent life for drugs developed with them, providing tax-based incentives, and continuing to award grants for R&D.

Payer coverage
In the United States, approval and reimbursement-coverage decisions are discrete processes with minimal coordination between the FDA and CMS. Uncertainty remains about how this coordination will work elsewhere in the world. Processes have not been
established—for example, at the time of writing, the United Kingdom’s National Institute for Health and Clinical Excellence (NICE) does not have any guidance on reviewing molecular-diagnostics tests. State payers, private payers, and diagnostics companies can help fuel growth in the personalized-medicine market by making coordinated efforts to improve the pace and process of coverage decisions.

One step could be for CMS to take a lead in aligning the reimbursement process with the regulatory-approval process. Presubmission meetings to delineate data requirements for regulatory and coverage approval and ongoing joint reviews can facilitate interagency collaboration. Optimal alignment across the two agencies implies that if suitably stringent guidelines were set, CMS would provide coverage and adequately reimburse companies that meet the hurdles. Additional health economic data or regulatory approval for clinical claims, for instance, may be reasonable prerequisites for coverage and could thus help ensure adequate reimbursement, pricing, and value for diagnostics players.

The development of formal guidelines could make decisions on coverage more transparent and efficient. CMS now typically makes coverage decisions for molecular diagnostics at the regional rather than national level. Decisions are thus made many times, based on different guidelines and processes and often with different outcomes. Private payers also lack clear guidelines for these decisions. Both CMS and private payers have an important role to play in shaping coverage and payment decisions. Private payers we interviewed are waiting to understand (and potentially follow) CMS coverage policies, as often occurs with therapeutics.

One way to improve coverage guidelines in both systems and processes would be to establish an agency to assess the clinical and cost effectiveness of tests. This agency—which could take the form of a third-party nonprofit agency, a consortium, or a new government agency—could be a coordinated effort by payers, CMS, pharmaceutical and biotechnology companies, and diagnostics players. The formation of new oversight agencies (for example, an FDA center for diagnostics) could also help. Notably, single-payer systems, such as those that predominate in Europe, have two advantages in adopting personalized medicine: they are not as susceptible to longitudinal-accounting issues, and coverage decisions can be less complex and involve fewer decision makers.

Physician incentives
Aligning physicians’ incentives could further hasten adoption. In many countries, physicians get disproportionately higher rates for procedure-oriented services than for evaluation and management. They therefore often have a real financial disincentive to perform tests that might make further treatment unnecessary.

Efforts are under way to shift toward a more outcome-based approach to reimbursement, so that physicians will have incentives to use and act on appropriate personalized-
medicines yet diagnostics. Yet to encourage adoption, payers should also work to develop a system ensuring that physicians are reimbursed for the test itself. Moreover, in the United States, personalized-medicine tests are now billed by a nonscalable approach called “CPT² code stacking,” which can encourage laboratories to game the system. Eventually, individual codes that are commensurate with a test’s cost and value and that provide appropriate reimbursement to physicians will have to be developed for each molecular diagnostic.

**Investment by pharmaceutical and biotechnology companies**

Pharmaceutical and biotechnology companies should take a long-term–investment view. Some already do: of the leaders we interviewed, those who have invested most heavily in personalized medicine suggested that they are renewing the focus on outcomes and clinical value in the process of drug discovery. They realize that the drugs their companies develop today will be entering markets with more competitors, more pricing pressure, and a higher bar for differentiated clinical outcomes.

An aggressive move toward value- or outcomes-based pricing by CMS or private payers could greatly increase the financial value of personalized medicine and so the incentive to invest in it. One possibility might be innovative risk-sharing models for drug and diagnostic coverage. Payers could, for instance, follow the examples in Europe of bortezomib (Velcade) for multiple myeloma and the interferon-beta drugs for multiple sclerosis: reimbursement is contingent upon patient outcomes. Payers could also create innovative risk-sharing agreements with diagnostics companies. A test could, say, receive conditional, partial reimbursement for a number of years until its clinical effectiveness was definitively demonstrated, when the diagnostics company would be paid in full. The payer would limit cost exposure by covering part of the costs for a limited time; diagnostics companies would benefit from early coverage decisions.

Over the next few decades, the development of “omics” sciences (such as genomics) and supporting technologies will enable the creation of more and more personalized-medicine tests. Yet poorly aligned incentives for stakeholders could hamper their use. All stakeholders should therefore work together to reshape these incentives and so reap the benefits of personalized medicine.

²Current procedural terminology.