PERSPECTIVES

OUTLOOK

The microeconomics of personalized medicine: today's challenge and tomorrow's promise

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Abstract | 'Personalized medicine' promises to increase the quality of clinical care and, in some cases, decrease health-care costs. Despite this, only a handful of diagnostic tests have made it to market, with mixed success. Historically, the challenges in this field were scientific. However, as discussed in this article, with the maturation of the '-omics' sciences, it now seems that the major barriers are increasingly related to economics. Overcoming the poor microeconomic alignment of incentives among key stakeholders is therefore crucial to catalysing the further development and adoption of personalized medicine, and we propose several actions that could help achieve this goal.

'Personalized medicine' — defined here as a tailored approach to patient treatment, based on the molecular analysis of genes, proteins and metabolites — has generated much excitement, but few personalized medicine tests have been widely adopted in the clinic so far. With this in mind, we have investigated the key challenges to the development and acceptance of personalized medicine in order to identify the actions required to overcome them. In this article, we present our perspective on these issues based on interviews with more than 60 leading payers, providers, regulatory experts, pharmaceutical and biotechnology companies, academic opinion leaders, and diagnostics and clinical laboratory companies, as well as microeconomic analyses of different stakeholders (see BOX 1 and Supplementary information S1 (box) for an explanation of the methodology).

Our investigation highlighted three major obstacles that have held back the advancement of personalized medicine: first, scientific challenges (for example, poor understanding of molecular mechanisms or a lack of molecular markers associated with some diseases); second, economic challenges (that is, incentives that are poorly aligned between stakeholders); and third, operational issues (for example, electronic tracking of diagnostic information, privacy concerns, reimbursement coding issues and provider and patient education). Although scientific challenges remain, it now seems that the economic challenges and operational issues present the most significant obstacles to the further development of personalized medicine. In many cases, operational issues can largely be resolved within a particular stakeholder group. However, correcting the incentive structure and modifying the relationships between stakeholders could be significantly more complex.

In this article, we first discuss the economic challenges related to personalized medicine from the perspective of four key stakeholders: payers, providers, pharmaceutical and biotechnology companies, and diagnostics companies. These perspectives are focused on the US market in particular, but many are also relevant elsewhere. We then present our proposals for actions that could help overcome these market failures and significantly accelerate the adoption of personalized medicine.

Stakeholder incentives and challenges

Payers. Investors and analysts have suggested that personalized medicine can dramatically reduce health-care costs and help payers provide products to the most attractive customers. Despite this, most payers have been slow to invest in personalized medicine. Leaders in payer organizations have identified several concerns that could explain this reluctance. The first is an inability to easily identify which tests truly reduce costs. Second, there is apprehension that it is difficult to track the use of molecular diagnostic tests, leading to fears that, although individual tests may not be expensive, the overall eventual costs could be unjustifiably high. A third concern is the difficulty of enforcing standard protocols to ensure physicians follow through with appropriate patient care based on test results. Fourth, there is potential for misuse of test information, particularly in early stages of test investigation and development, which could harm the patient. Fifth, there is a lack of longitudinal accounting that would allow payers to make long-term cost savings from near-term testing.

To understand which tests actually cut cost, we analysed various types of tests (BOX 2, note 1). Two primary factors determine the cost-effectiveness of a test from a payer perspective: first, per patient savings (that is, the difference between the cost of treating the disease and the cost of the treatment intervention indicated by the test); and second, the likelihood that a test suggests an intervention for any particular patient (FIG. 1). Tests that help to avoid the use of expensive therapies (for example, the anticancer drugs trastuzumab (Herceptin; Genentech/Roche) or imatinib (Gleevec; Novartis)), minimize costly adverse events (such as the warfarin dosing test to reduce the risk of serious bleeding), or delay expensive procedures can be extremely cost-effective for payers. Although such tests cost from US$100–3,000 per test, they save $600–28,000 per patient.

By contrast, tests that save a small amount per patient or that have a low probability of identifying patients requiring intervention are not cost-effective. For example, although screening for *BRCA1* variants to predict the

Box 1 | **Basis of analysis**

To gather stakeholder perspectives on personalized medicine, we performed 60 interviews in the first half of 2008 with executives and key opinion leaders from leading private payer organizations, academic research institutions, health-care provider organizations (for example, academic medical centres and hospitals), regulatory bodies, biopharmaceutical companies, molecular diagnostics and clinical laboratory companies, and venture capital funds. These interviewees were:

- Eight payer executives, including individuals from private payer companies (for example, Blue Cross/Blue Shield and Health Net) and the Centers for Medicare and Medicaid Services. The expertise of these individuals spanned coverage decisions and health technology assessment.
- 20 biopharmaceutical executives at positions ranging from vice president to chief executive officer. Expertise among these individuals spanned business strategy and operations, research and development, regulatory affairs and reimbursement.
- 13 diagnostic company executives from large clinical laboratory companies as well as small and mid-sized molecular diagnostics firms. All interviewees were senior executives with several years' experience of working in the diagnostics industry.
- Six researchers from leading academic institutions in the United States and the United Kingdom recognized as experts in molecular genetics, pharmacogenomics, bioinformatics and molecular and protein diagnostics.
- Three venture capitalists from leading firms that focus on molecular diagnostics investments.
- Two attorneys with legal expertise spanning intellectual property, US Food and Drug Administration (FDA) regulation and health-care law.
- Eight regulatory experts from the Department of Health and Human Services, the FDA, and the National Institute for Health and Clinical Excellence.

The interview process entailed an open-ended discussion of the challenges and opportunities in personalized medicine across all stakeholders and a more detailed discussion about the practical use of personalized medicine in their field of expertise, both currently and over the next 5 years.

The targeted quantitative analysis and financial modelling we conducted to better understand specific stakeholder issues is highlighted in FIGS 1–5 and described in detail in Supplementary information S1 (box).

risk of breast cancer can save ~$25,000 per patient identified, variants are so rare in the general population (1–3%) that this test, which costs ~$3,000 per patient, is only cost-effective when performed on a patient with a family history of breast cancer. Some tests might also create costs on a per patient basis. As an illustrative example, variants in *KIF6* have been linked to a 50% increase in the risk of myocardial infarction, but this risk can be reduced to normal levels through treatment with statins[1–3]. Widespread use of a hypothetical test based on these markers could actually result in higher costs: treating the identified patients with statins would cost more money than would be saved by avoiding cases of myocardial infarction (FIG. 1).

Payer adoption of personalized medicine tests is further complicated by the high customer turnover experienced by many commercial payers in the United States. This high turnover makes it less economically attractive for payers to reimburse prophylactic tests that minimize the likelihood of conditions that will occur much later in life: costs accrue to the payer that screens the patient and performs the intervention, but the benefit accrues to the payer covering the patient when the disease would have arisen (perhaps 10 years later). The pharmacoeconomics of the *BRCA1* test illustrate the point well (FIG. 2). This longitudinal accounting issue is particularly acute for diseases with a late or delayed onset: the insurer for the elderly (for example, the Centers for Medicare and Medicaid Services (CMS) in the United States) accrues the benefit of interventions that were 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.

As described above, personalized medicine tests can range from cost-effective to cost-creating. Because the ultimate cost effects may not be known until the test has been on the market for some time, it will remain in payers' best interests to delay adopting personalized medicine tests until they can differentiate between those that are cost-saving and those that are cost-creating. The best strategy for diagnostics companies may therefore be to collaborate with payers whose economics may be well aligned (for example, Kaiser Permanente, large self-insured employers and the Veterans Affairs system in the United States, which have lower membership turnover and so are more likely to accrue the financial benefits of testing) to establish a health economic rationale for testing. Generating high-quality health economic evidence will provide reimbursement confidence that will allow payers to more rapidly adopt tests and align physician incentives with patient care and outcomes, rather than procedures. This could create a source of competitive advantage for payers who are more successful in identifying and implementing policies to promote cost-saving diagnostics.

Providers. The current procedure-based reimbursement system for providers also poses a challenge to the adoption of personalized medicine. In this system, provider economics will create incentives for the use of some personalized medicine tests, but might discourage the use of others (see Supplementary information S2 (figure)). Physicians could be more likely to embrace tests that increase the number of procedures performed. For example, a test that identifies patients at a high risk of colon cancer such that they require colonoscopies at three times the normal frequency would align well from an economic incentive perspective with gastroenterologists, given the lifetime value of ~$2,000 per patient related to the use of such a molecular diagnostic test.

Other tests may be cost-neutral or may have negative microeconomic incentives for their use. For example, Oncotype Dx, a gene-based diagnostic test for breast cancer patients that can be used to assess the likelihood of benefit from chemotherapy, ultimately decreases the number of patients that physicians treat with such chemotherapy, and thus the revenue that those patients generate. Although Oncotype Dx has nevertheless had high adoption owing to clinical merit, this example illustrates the challenges that such tests can pose to provider economics.

Pharmaceutical and biotechnology companies. Pharmaceutical and biotechnology companies are now using biomarkers to aid in the research and development (R&D) process, and in some cases will develop these markers as companion diagnostics (tests to identify a patient's likelihood of responding to a drug or experiencing adverse events). R&D executives at 16 of the top 20 biopharmaceutical companies interviewed in a survey by McKinsey in mid 2007 indicated that, on average, 30–50% of drugs in development

Box 2 | **Additional notes**

Note 1. Some payers noted that recent thyroid cancer diagnostics have led to a dramatic increase in thyroid cancer incidence (250% increase from 1973 to 2002) but no improvements in mortality[5]. One explanation for the findings is that most of the incremental detection was for papillary cancers, which have a good prognosis.

Note 2. Experts we spoke with indicated that 2–6 markers are typically chosen for a drug's companion-diagnostic programme. These markers are typically chosen before Phase II, developed in parallel with the Phase II clinical trial and then tested retrospectively on Phase II participants.

Note 3. A widely cited example in this respect is the Phase III trial for the anticancer drug trastuzumab (Herceptin; Genentech/Roche), a monoclonal antibody that targets HER2 (human epidermal growth factor receptor 2). The trial included only 470 breast cancer patients and only a marker-negative arm. The expected size of the trial without a companion diagnostic based on HER2 expression levels has been estimated at 2,200 patients (based on a presentation from Arthur Levinson, chief executive officer of Genentech, in October of 2003).

Note 4. This figure is derived from an analysis by McKinsey and IMS Health sales data; the estimated range is based on 5% average share for third-to-market drugs at ~1–3 years post-launch and 20% average market share of second-to-market drugs ~1–3 years post-launch.

Note 5. Bidil was priced at a premium. In interviews with four different insurance companies, payers indicated that they placed Bidil on a higher co-pay tier (requiring a patient to pay more out of pocket) because they did not think the clinical benefit justified the cost.

Note 6. These figures are based on an analysis by McKinsey of selected molecular diagnostics and traditional diagnostics.

Note 7. Section 510(k) of the US Food, Drug and Cosmetics Act requires device manufacturers to notify the FDA of their device at least 90 days in advance of marketing. The review process for this Premarket Notification is more straightforward than Premarket Approval and typically takes less than 90 days.

Note 8. These figures are based on historical approval times, and include non-direct review time and direct review time. Pre-market approval typically takes ~18 months, whereas registration takes ~6 months[6].

Note 9. The Centers for Medicare and Medicaid Services (CMS) may make national coverage determinations for certain molecular technologies, whereas coverage for most laboratory tests is determined locally by CMS. A local coverage determination is based on a review of current medical practices and clinical data, and procedures for coverage decision are not uniform across localities.

Note 10. Reimbursement and billing for molecular diagnostics is performed using current procedural terminology (CPT) codes. Most molecular diagnostics do not have a single unique code assigned. Billing for multivariate tests involves 'stacking' multiple codes that describe individual components of the assay. For example, billing for a single Myriad's BRCA panel can involve employing five different codes and 171 separate CPT units.

have an associated biomarker programme, and suggested that this number is likely to increase over time. By contrast, the same executives also suggested that fewer than 10% of drugs with current biomarker programmes will be launched with a companion diagnostic over the next 5–10 years (and such launches are highly dependent on the disease area).

In theory, companion diagnostics can improve R&D productivity by decreasing trial size, reducing attrition rates and/or increasing speed to market, and can improve commercial performance by improving market share and/or supporting higher drug prices. However, many pharmaceutical and biotechnology companies are only slowly moving towards the application of biomarkers and companion diagnostics. This is indicated by the fact that the most aggressive companies in this respect have biomarker programmes for 100% of their compounds and companion diagnostics for at least 30% of them, whereas the average company has much lower proportions (30–50% and <10%, respectively). Moreover, many of the experts we interviewed explicitly stated that their corporations had not prioritized companion diagnostics and were taking a "cautious approach" to investments.

Scientific and clinical factors place some limitations on the pace of development. In some disease areas, an understanding of molecular mechanisms is insufficient to rationally select biomarkers at early stages of development. In other areas, there is not a large clinical need for companion diagnostics. However, in many disease areas, pharmaceutical and biotechnology companies are not yet embracing companion-diagnostic strategies, despite scientific advances.

Our research suggests that, from an economic perspective, the potential to generate greater value after marketing by increasing price and market share is vastly more important for pharmaceutical and biotechnology companies than improving development productivity. Indeed, it seems that companion diagnostics may do little to improve development productivity, and in many cases companion diagnostics could actually increase overall cost and delay development timelines. With respect to clinical trials, experts suggested that Phase II trials often have to be larger when companion diagnostics are used. In practice, trials often need to be designed with several potential biomarkers in Phase II (and sometimes Phase III), as it is unclear which markers will be predictive (BOX 2, note 2). In addition, the US Food and Drug Administration (FDA) is likely to require that 'marker-negative' patients be included in Phase III trials, based on concerns that the drug could be used off-label in these patients. This practice is likely to eliminate the upside from smaller trials that has been widely cited in recent years (BOX 2, note 3). Apart from trial size, other commonly cited applications of personalized medicine during drug development also seem unlikely to substantially improve drug development productivity (FIG. 3).

Although increasing development productivity might not provide sufficient incentives for pharmaceutical and biotechnology companies to pursue companion diagnostics, there are potential commercial benefits from increased market share and pricing power (FIG. 3). At the same time, there is also significant risk, as companion diagnostics divide the treatable patient population into subsegments and can decrease market share in some cases. Given this, companion diagnostics are most likely to be value-creating for later-to-market entrants into crowded markets, which are characterized by significant pricing flexibility. For example, if two drugs are already on the market and are relatively undifferentiated, the third drug on the market is likely to capture a relatively small share (for example, 5–20% (BOX 2, note 4)). A companion diagnostic that identifies a segment of the patient population that will respond especially well to a drug or experience lower toxicity, and that thereby enables higher pricing, could generate value.

A key determinant of pricing diversity is payer price scrutiny and sensitivity, which varies dramatically by disease area, particularly in the United States. This can be illustrated using the example of Bidil — a fixed-dose combination of two generic

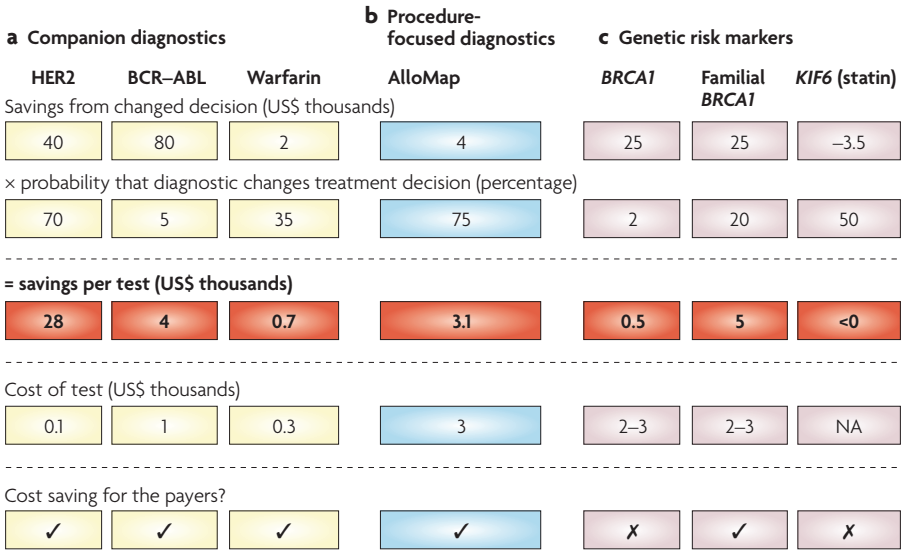

Figure 1 | **Not all diagnostic tests are cost-cutting for payers.** We estimated savings per test as the product of savings from a single changed treatment decision and the probability that any given patient will have a 'positive' test (such that treatment decision is changed), for three types of test: companion diagnostics (**a**); procedure-focused diagnostics (**b**) and genetic risk markers (**c**). For details of the underlying analysis, see Supplementary information S1 (box). BCR–ABL, breakpoint cluster region–abelson tyrosine kinase; HER2, human epidermal growth factor receptor 2.

cardiovascular drugs, hydralazine and isosorbite dinitrate, that has been approved by the FDA specifically for African Americans with heart failure. In this case, attempts to charge a price premium were met with aggressive differential co-pay tiering by payers, which contributed to lower sales than expected (BOX 2, note 5). In therapeutic classes with less payer scrutiny on price (for example, oncology drugs), pharmaceutical and biotechnology companies would be more likely to charge a premium and maintain coverage.

Pharmaceutical and biotechnology companies should be, and are, considering whether to invest in personalized medicine depending on the disease area. To highlight disease areas where near-term investment in companion diagnostics is most likely to occur, we divided drug classes based on scientific potential and commercial potential (FIG. 4). As described in Supplementary information S1 (box), this division is based on quantitative factors as well as qualitative factors from interviews, and the results should be taken in this light. Our analysis indicates that pharmaceutical and biotechnology companies are most likely to invest in diagnostics for disease areas such as oncology, immunology and infection. The division also reveals disease areas in which technical feasibility and clinical need exist but incentives are not aligned to drive investment by pharmaceutical and biotechnology companies. These areas, such as anticoagulants, antipsychotics and antidepressants, are ripe for development by other organizations, such as diagnostics companies.

However, pharmaceutical and biotechnology companies should also realize that, compared with drug discovery timelines, the payer environment is evolving rapidly and application of personalized medicine tools will increasingly be required to preserve value. Although pharmaceutical and biotechnology companies need to be aware of areas where diagnostics can destroy value by subdividing their existing markets, it will be equally important to prepare for an environment in which regulatory bodies will demand greater proof of positive patient outcomes to justify approval, reimbursement and price. With this long-term view in mind, pharmaceutical and biotechnology companies should act today, given the time that it takes to build the capabilities and experience to succeed in this anticipated future environment.

Diagnostics companies. Diagnostics and life science tools companies produce a wide variety of test types, including companion diagnostics (often in collaboration with a biotechnology and pharmaceutical company), early-stage diagnostics, disease recurrence and monitoring tests, adverse drug events tests and genotypic risk marker analyses. However, diagnostic-test developers have faced difficulty capturing the full value that the tests can generate, as exemplified by the fact that diagnostic tests are estimated to influence 60–70% of all treatment decisions, yet account for only 5% of hospital costs and 2% of Medicare expenditures[4]. Molecular diagnostics are often cited as a more attractive market segment than typical diagnostics, given the potential for higher prices ($100–3,000 per test compared with ~$20–50 for a typical diagnostic test) and higher gross margins (~50–70% for a sample molecular diagnostic compared with 30–50% for most typical large laboratory companies today; BOX 2, note 6). Indeed, a number of emerging companies, including Genomic Health, Myriad, Celera, Monogram and Xdx, have had some success in raising funding and developing innovative molecular diagnostic tests.

Unfortunately, the molecular diagnostics business case still holds significant risk (FIG. 5). A number of factors contribute to this risk, including development costs, timing of development and approval, time to payer coverage, rate of provider adoption and peak sales price. To understand the relative importance of these factors, we modelled the economics of a hypothetical start-up diagnostics company and then performed a sensitivity analysis using upside and downside scenarios for each variable (see Supplementary information S1 (box) for details). It should be noted that this model was based on benchmarks from a few molecular diagnostics businesses with the aim of testing the importance of risk factors. The model does not represent a specific company, and the economics for companies with products currently on the market vary significantly. Based on this model, the expected 10-year net present value of cash flows for an average diagnostic test is ~$15 million, and the most important factors affecting profitability are the time to approval and rate of payer adoption. If the time to approval is delayed by 1 year, the 10-year net present value becomes ~–$10 million.

This finding is relevant given that it remains unclear how the FDA will regulate *in vitro* diagnostic multivariate index assays (IVD-MIAs). At the time of writing, the FDA has suggested that a 510k (BOX 2, note 7) may be sufficient for tests that are prognostic indicators, but a pre-market approval (PMA) from the FDA is likely to be required if the test directly influences therapy decisions. PMA review is likely to increase the time to market by at least a year (BOX 2, note 8). Nevertheless, good communication

between the Center for Drug Evaluation and Research and the Office of In Vitro Diagnostic and Device Evaluation and Safety may partially mitigate this for priority reviews. It remains unclear what the approval timelines for other systems will be; for example, the European Medicines Agency (EMEA) and the Pharmaceuticals and Medical Devices Agency in Japan also have yet to establish clear guidelines for the approval of personalized medicine tests.

With respect to payer adoption, the case of Oncotype Dx illustrates well the challenge of slow coverage. Although this test launched in 2004, analysts' and company estimates suggest it will take until 2009–2010 for all payers to routinely cover it (coverage at present is approximately 85%). This rate of payer coverage contrasts starkly with typical adoption of a new drug. In the United States, new drugs are usually reimbursed immediately at launch or within the year. In Europe, drug coverage may take slightly longer, depending on the extensiveness of the review, but it is unlikely to take more than 4 years, as exemplified by Oncotype Dx uptake.

Start-up diagnostics companies therefore face challenging economics at present. However, development and adoption times are likely to shorten as more tests become available and payers, regulators and molecular diagnostics companies gain experience. Similarly, as the regulatory process becomes more clear (but potentially longer), payer adoption rates may also increase. Given payer trepidation about personalized medicine testing, it will therefore be advantageous for leading diagnostics companies to help develop rigorous but efficient regulatory and approval standards.

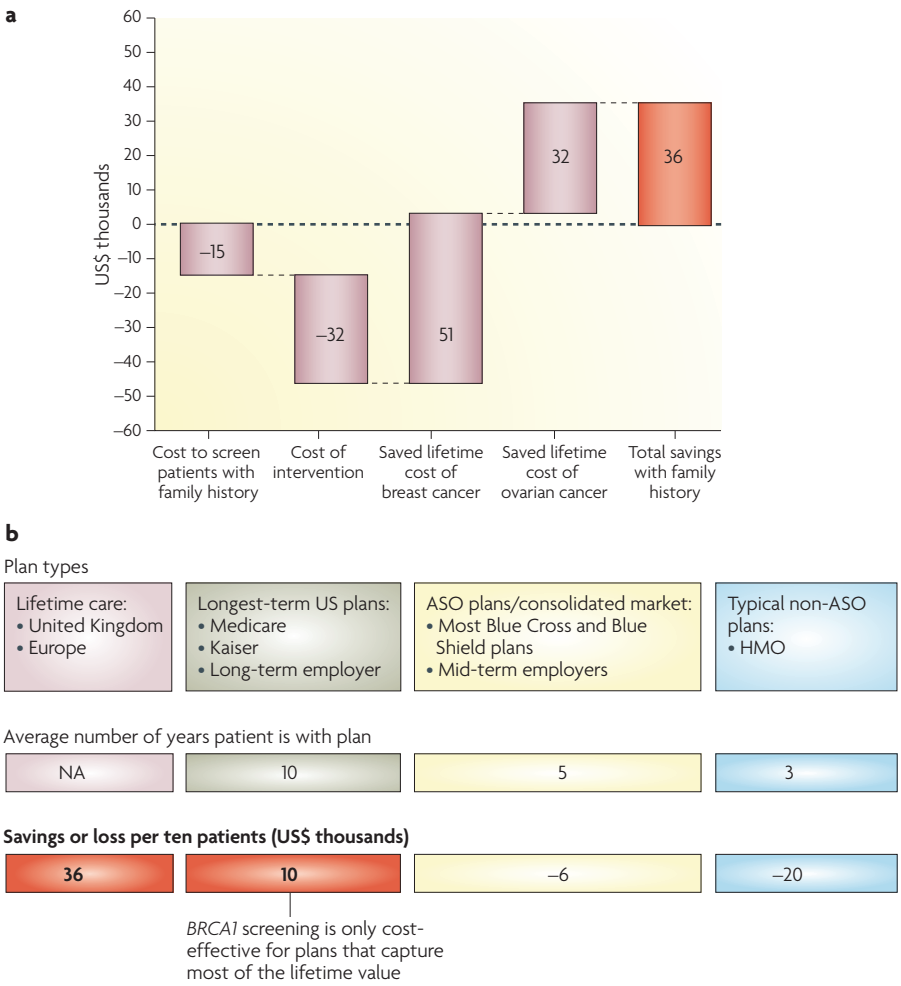

Figure 2 | **Markers for disease prevention are least cost-effective for programmes with a high patient turnover. a** | We estimated the lifetime cost savings for ten female patients with a family history of breast cancer who are screened for *BRCA1* variants associated with high risk of breast cancer. Costs included intervention from a prophylactic mastectomy and salpingoophorectomy with an estimated cost to the health plan of ~US$16,000 based on data from Health Grades. **b** | Savings estimates are based on lifetime cost estimates of breast cancer and ovarian cancer from various agencies (for example, see California Breast Cancer Research Program homepage). Lifetime savings figures were then applied to payers with different member turnover rates to calculate actual costs and savings accrued by payers. Approximate turnover rates are based on expert interviews as well as an analysis of internal data from commercial payers. ASO, Administrative Services Only; HMO, Health Maintenance Organization; NA, not applicable.

Catalysts for personalized medicine

We have described how current market failures limit the speed of adoption of personalized medicine from multiple stakeholder perspectives, and solutions to these economic challenges represent opportunities to accelerate market development. On the basis of conversations and analyses conducted during the course of this investigation, we see four major catalysts that could significantly affect the adoption of personalized medicine in the near-term: maximizing the transparency and efficiency of the regulatory approval process; increasing the pace and predictability of payer coverage for appropriate tests; aligning reimbursement practices to encourage appropriate diagnostic use by physicians; and encouraging pharmaceutical and biotechnology companies to take a long-term investment view.

Regulatory environment. Regulatory bodies such as the FDA must improve the clarity and efficiency of the test regulatory approval processes, both for stand-alone and companion diagnostics. These clarifications are crucial to diagnostics companies' ability to plan ahead and design trials. Based on our conversations with over 60 experts (see Supplementary information S1 (box)), the key questions that regulatory bodies such as the FDA and EMEA need to address include: will marker-negative patients be required for Phase III trials? Will use of archived samples and 'flexible' trial designs be permitted for the approval of companion diagnostics and, if so, under what circumstances? What regulatory standards and oversight will be required for personalized medicine tests, especially laboratory-developed tests to be used in therapy decisions?

For the new regulations under consideration, authorities need to balance short-term costs with long-term benefits. Current plans include classifying tests as Class I, II or III, based on the level of risk associated with the intended use. IVD-MIA changes that promote more rigorous evaluation of safety and effectiveness may have long-term benefits by encouraging faster

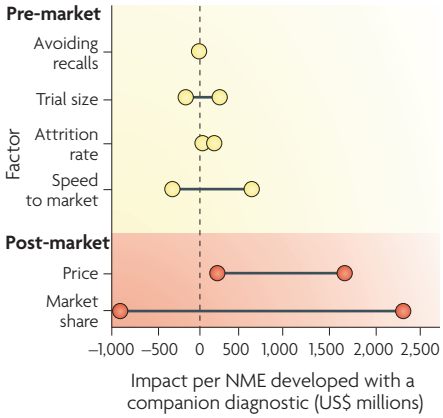

Figure 3 | **Impact of companion diagnostics on development and commercial value for pharmaceuticals.** We developed a model for the average spending per new molecular entity (NME) across the drug development life cycle (see Supplementary information S1 (box) for details). High-end and low-end estimates for the impact of a companion diagnostics programme were based on case examples and expert interviews (see Supplementary information S1 (box)). This analysis indicates that the post-market factors of pricing and market share could generate the greatest commercial benefit (and the most risk).

payer and physician adoption due to the higher approval standards, but the near-term consequences may be harmful to short-term market investment.

Diagnostics companies can use the approval process as an opportunity to justify higher pricing, by being willing to set appropriately stringent standards and by shaping regulatory guidelines to bolster the industry and protect patients. For its part, the FDA should work to minimize approval delays that will result from these higher standards, and help mitigate any negative impact on investment in development. Leading pharmaceutical and biotechnology companies and diagnostics companies should look for opportunities to help shape the development of these guidelines and standards.

To drive dramatic changes in market incentives, the regulatory bodies (for example, the FDA and EMEA) could decide not to require collection of clinical data on marker-negative patients, thus decreasing development costs. Concerns about the use of therapeutics in the marker-negative population could be reduced by parallel moves by payer organizations (for example, CMS) and regulatory bodies (for example, the FDA) to increase barriers to off-label use. Furthermore, regulatory bodies could increase the flexibility of trial design and even allow for the approval of companion diagnostics on the basis of prospectively designed tests of the marker that are performed on archived samples. Finally, governments and regulatory bodies could reward companion-diagnostic development directly by increasing the patent life for drugs developed with companion diagnostics, providing tax-based incentives and continuing to give grants for R&D.

Payer coverage. Currently, in the United States, approval and reimbursement coverage decisions for diagnostics represent two discrete processes, with minimal coordination between the FDA and CMS. Uncertainty remains about how this coordination will work in other parts of the world, and processes have not been established (for example, at the time of writing, the UK's National Institute for Health and Clinical Excellence has not reviewed a molecular diagnostics test). State payers (for example, CMS), private payers and diagnostics companies can help fuel growth of 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. Pre-submission meetings to delineate data requirements for regulatory and coverage approval and ongoing joint reviews can facilitate interagency collaboration. Optimal alignment across the two agencies would imply that, if appropriately stringent guidelines are set, CMS would provide coverage and adequately reimburse those interventions that satisfied the regulatory and cost-effectiveness requirements. For example, the requirement of additional health economic data and/or regulatory approval for clinical claims may be reasonable prerequisites for coverage, and could thus help ensure adequate reimbursement, pricing and value for diagnostic players.

Development of formal guidelines can potentially improve the transparency and efficiency of the coverage decision-making process. Today, CMS typically makes coverage decisions for molecular diagnostics at the regional level rather than at national level. As a consequence, a given decision is made several times for the same diagnostic based on different guidelines and processes and often with differing outcomes (BOX 2, note 9). Similarly, private payers do not have clear guidelines for molecular diagnostics coverage decisions. Both CMS and private payers have an important part to play in shaping coverage and payment decisions. The private payers we interviewed are waiting for clarification of CMS coverage policies on diagnostics (as often occurs with therapeutics).

One potential mechanism to improve coverage guidelines in both systems and processes is to establish an agency to assess

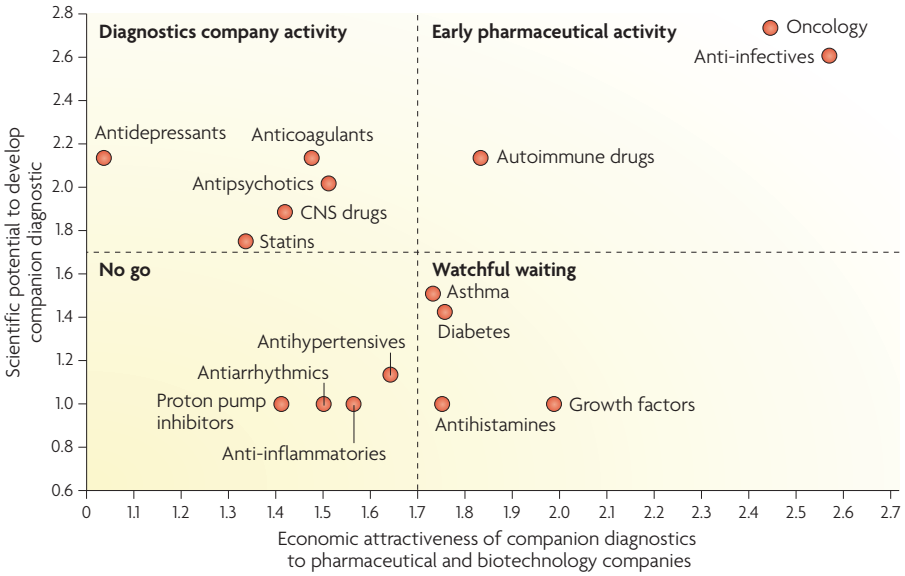

Figure 4 | **Scientific potential and economic attractiveness for companion diagnostics development across therapeutic areas.** We developed rank-order estimates for the scientific potential and economic attractiveness of the development of companion diagnostics in various therapeutic areas based on both qualitative factors (such as expert interviews) and quantitative factors (such as data on price premiums for drugs launched in the same therapeutic class). Results should be taken as directional only; for details of ranking process, see Supplementary information S1 (box). CNS, central nervous system.

the clinical- and cost-effectiveness of tests. This agency could be a coordinated effort by payers, CMS, interested pharmaceutical and biotechnology companies and diagnostics players, and could take the form of a third-party non-profit agency, a consortium or a new government agency. The formation of new overseeing agencies (for example, an FDA centre for diagnostics) could also help in this regard.

Notably, single-payer systems, such as those that predominate in Europe, have two advantages over multiple-payer systems when it comes to the adoption of personalized medicine. First, such systems are not as susceptible to longitudinal accounting issues. Second, coverage decisions can be less complex and involve fewer decision makers.

Physician incentives. In addition to improvements associated with regulatory approval and formal coverage, aligning physician incentives for the use of personalized medicine tests could further hasten adoption. Physician reimbursement schemes in many countries largely remain entrenched in a paradigm of 'activity-based' coding and billing: physicians receive professional fees for services they provide to patients, and procedure-oriented care receives rates that are not in proportion to evaluation and management activities. As such, there is little financial incentive for physicians to perform tests that might prevent downstream activity; in fact, there may be a very real financial disincentive.

This reimbursement system has unintended consequences (in terms of health and cost) that extend well beyond the sphere of personalized medicine; efforts are underway to shift towards a more 'outcome-based' approach to reimbursement. In such a system, opportunities will emerge to provide incentives for physicians to use and act on appropriate personalized medicine diagnostics. In addition to the movement towards outcome-based reimbursement, payers must work to develop a coding system that ensures physician reimbursement for the test itself, as this will help encourage adoption. Moreover, personalized medicine tests today are billed in the United States by 'CPT code stacking', in which a multivariate assay is billed by adding multiple, generic codes — for example, for a diagnostic based on a single gene (BOX 2, note 10). This approach is not scalable and can lead to billing practices in which laboratories exploit the system. Eventually, individual codes will need to be developed for each molecular diagnostic that are commensurate with the cost and value of the test and provide appropriate reimbursement to physicians.

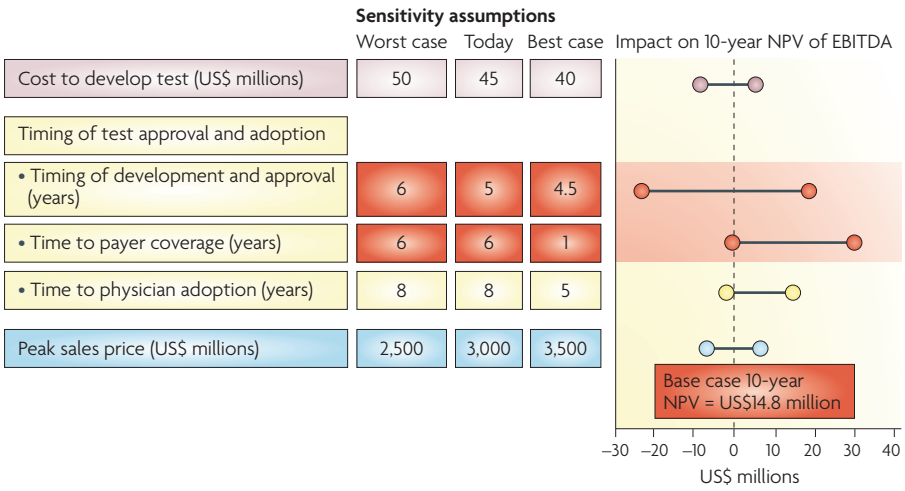

Figure 5 | **Sensitivity analysis for factors affecting the commercial potential of a company developing a molecular diagnostic.** A representative 'profit and loss' model for a start-up molecular diagnostics company was created through a number of sources (see Supplementary information S1 (box) for details). The model was not created to define the profit and loss statement for all such molecular diagnostics companies, as they are reported to vary considerably, but to allow us to systematically explore the factors that affect the 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 (see Supplementary information S1 (box)). Based on this model, the expected 10-year net present value (NPV) of cash flows for an average diagnostic test is ~US$15 million, and the most important factors affecting profitability are the time to approval and rate of payer adoption. EBITDA, earnings before interest, taxes, depreciation and amortization.

Investment by biotechnology and pharmaceutical companies. In our opinion, biotechnology and pharmaceutical companies should take a long-term investment view. Fortunately, a number of such companies are already doing this; the leaders we interviewed who have invested most heavily in personalized medicine suggested that they are renewing their focus on "outcomes" and "clinical value" in the drug discovery process. They realize that the drugs they are developing today will be entering future markets with more competitors, more pricing pressure and a higher bar for differentiated clinical outcomes. Not surprisingly, these same pharmaceutical and biotechnology companies are investing heavily in personalized medicine.

An aggressive move towards value- (or outcomes-) based pricing by CMS or private payers could dramatically change the incentives for investment by biotechnology and pharmaceutical companies, by greatly increasing the financial value of personalized medicine. A potential step in this direction could be to use innovative risk-sharing models for drug and diagnostic coverage. That is, payers could follow the examples of bortezomib (Velcade) for multiple myeloma and the interferon-β drugs for multiple sclerosis in Europe, where the level of reimbursement is contingent on patient outcomes.

Similarly, payers could create innovative risk-sharing agreements with diagnostics companies. For example, a test could receive conditional, partial reimbursement for a number of years until the clinical effectiveness can be definitively shown (at which point the diagnostics company would be paid in full). The payer limits cost exposure by covering part of the costs for a limited time while diagnostics companies benefit from early coverage decisions.

Outlook

Over the next few decades, the development of -omics sciences and supporting technologies will enable the creation of more personalized medicine tests across disease areas. We have argued that, even as scientific and technological advancements accelerate the development of these tests, the impact of these tests on the health-care system continues to be hampered by poor alignment of economic incentives among stakeholders.

All stakeholders must be willing to work together to help reshape these incentive structures. Only with this type of cooperation will all stakeholders reap the benefits that personalized medicine has to offer.

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DATABASES

Entrez Gene:
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene
BRCA1 | *KIF6*

FURTHER INFORMATION

California Breast Cancer Research Program:
http://www.cbcrp.org/

SUPPLEMENTARY INFORMATION

See online article: S1 (box) | S2 (figure)

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