


OUTLOOK — BIOMARKERS

Stratified medicine: strategic and economic implications of combining drugs and clinical biomarkers

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Abstract | The potential to use biomarkers for identifying patients that are more likely to benefit or experience an adverse reaction in response to a given therapy, and thereby better match patients with therapies, is anticipated to have a major effect on both clinical practice and the development of new drugs and diagnostics. In this article, we consider current and emerging examples in which therapies are matched with specific patient population characteristics using clinical biomarkers — which we call stratified medicine — and discuss the implications of this approach to future product development strategies and market structures.

Most medicines are currently prescribed empirically. Some work for almost all relevant patients, such as non-steroidal anti-inflammatory drugs (NSAIDs) for pain relief, the proton-pump inhibitors (PPIs) for gastroesophageal reflux disorder or the newly approved Gardasil vaccine (Merck) to prevent human papilloma virus infections. For other therapeutic classes, such as the antidepressant selective serotonin-reuptake inhibitors (SSRIs), although responses are variable, there is at present no way to identify patients who are likely to respond well to a particular agent. In such cases, a number of agents might need to be tried until a satisfactory response is attained.

However, advances in understanding the mechanisms underlying diseases, as well as drug response, are increasingly creating opportunities to match patients with therapies that are more likely to be effective and safe. At the extreme of patient matching are ‘individualized’ medicines, which vary inherently for each patient. The cancer vaccine Oncophage, which is currently in development, provides an example of an individualized medicine. To produce this vaccine, tumour cells are taken from a patient during surgery¹. A heat-shock protein and its associated peptides, which represent a unique ‘signature’ of that patient’s cancer, are then isolated from the tumour cells and formulated into a vaccine for administration when the patient has recovered from surgery. This vaccine, which is only suitable for the patient from whom it is derived, stimulates an immune response that attacks tumour

cells remaining in the body after surgery. Stem-cell-based therapies could also potentially increase the role of individualized medicine in the future.

Less extreme examples of patient matching to a medicine include therapies for which some form of marker is available to indicate that a given patient is likely to show a response to the therapy. Some call this approach of proactively testing and selecting populations for specific treatments ‘personalized’ medicine, but we believe a more useful description is ‘stratified’ medicine. In stratified medicine, a patient can be found to be similar to a cohort that has historically exhibited a differential therapeutic response using a biomarker that has been correlated to that differential response.

Here, we call this special class of biomarkers that links patient subpopulations to treatments clinical biomarkers. An example of a clinical biomarker that is linked to drug efficacy is the BCR-ABL-positive tyrosine kinase genotype, which is used to identify patients with chronic myeloid leukaemia who are likely to respond to imatinib mesylate (Gleevec; Novartis), an inhibitor of this kinase². An example of a clinical biomarker that is linked to drug toxicity is a genetic variant of the UDP-glucuronosyltransferase 1A1 enzyme UGT1A1, which can be used to identify patients that are likely to experience serious toxicity in response to the anticancer drug irinotecan (Camptosar; Pfizer); the rate of metabolism of the active metabolite of irinotecan by UGT1A1 is reduced in these patients³. Beyond genotypes, clinical

biomarkers include any diagnostic test or clinical observation that indicates a preferred treatment for a patient subpopulation. Clinical biomarkers can be based on gene-expression patterns, individual proteins, proteomic patterns, metabolomics, histology, imaging, physicians’ clinical observations and even self-reported patient surveys. A clinical biomarker is not defined by its technology or biological basis, but rather by its reliable, predictive correlation to differential patient responses.

In summary, we believe that individualized medicine represents one end of a continuum of patient therapy, with empirical medicine at the other end of this continuum, and that in between lies the field of stratified medicine (FIG. 1). The ability of stratified medicine to match a therapy with specific patient population characteristics through clinical biomarkers has important implications for:

- Defining the field for which a drug is used.
- Determining the economic value of the field.
- Establishing the economic barriers to defend the field.
- Allocating the value between the gatekeeper clinical biomarkers and the therapy.

In this article, we highlight selected examples of stratified medicine, and discuss the strategic and economic significance of the points above to the discovery and development of new drugs and associated diagnostics.

Stratified medicine and clinical decisions

Stratified medicine adds a step to traditional clinical practice (FIG. 2). After the differential diagnosis is made on the basis of patient history and physical assessment, and following diagnosis confirmation from laboratory tests and clinical observation, stratified medicine adds a clinical biomarker-assessment step to associate a patient with a specific therapy. Individualized medicines take this process a step further by custom producing the therapeutic — often using the patient’s own fluid, cells or tissue to ‘seed’ production.

Stratified medicine is already practiced in several contexts, albeit often after first-line empirical treatment proves unsatisfactory because of poor efficacy or intolerable toxicity. Antibiotics are matched to specific resistant infections, HIV therapies are tailored to the viral variant present and oncology treatment regimens prioritize agents based on molecular tests. Accelerating clinical biomarker development by both drug developers and diagnostic companies will correspondingly expand the clinical opportunities for stratified medicine.

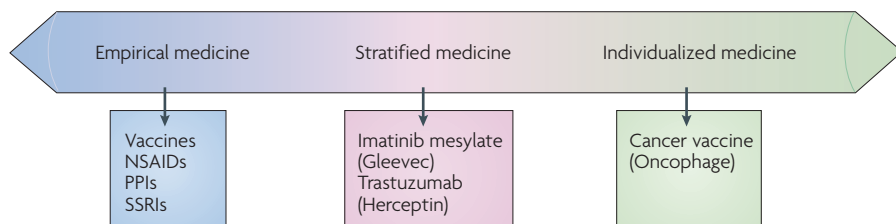


Figure 1 | The patient therapeutic continuum. Individualized medicines, such as cancer vaccines that are based on a particular patient’s tumour, represent one end of a continuum of patient therapy. Empirical medicine is at the other end of this continuum: some agents work for almost all relevant patients, such as non-steroidal anti-inflammatory drugs (NSAIDs), whereas others may only work for a subset of patients but no method is available to identify these patients, such as with antidepressants. In between lies the field of stratified medicine, in which a patient can be found to be similar to a cohort that has historically showed a differential therapeutic response to a particular therapy using a clinical biomarker that has been correlated to that differential response. For example, the anticancer drug trastuzumab (Herceptin) shows superior efficacy in breast cancer patients with HER2/*neu*-positive cancer. PPIs, proton-pump inhibitors; SSRIs, selective serotonin-reuptake inhibitors.

The border between stratified and empirical medicine is not rigid. Empirical therapy can progress to stratified therapy as biomarkers are identified that can be used to link patient subsets with greater positive therapeutic effects or side effects of a drug. This differential response sometimes serves to identify subtypes of the major disease. For example, in breast cancer, patients’ level of expression of the receptor tyrosine kinase **HER2/*neu*** characterizes their cancer type and their suitability for receiving trastuzumab (Herceptin; Genentech) as an adjuvant therapy⁴. Alternatively, a stratified medicine patient subpopulation might emerge as a clinically distinct syndrome treated empirically.

Why do only some markets stratify?

Today, some therapeutic areas include stratified medicines and others do not. If the absence of validated clinical biomarkers were the only factor responsible, then as scientific knowledge progressed, therapeutic areas would evolve from empirical to stratified medicine, and perhaps on to individualized medicine.

Alternatively, we believe that several key factors are necessary for the emergence of a clinically relevant patient subclass and, consequently, stratified medicine (FIG. 3). At least one of the following biological characteristics with the potential to differentiate patients must exist:

- Underlying disease variability reflecting multifactorial aetiology, or currently indistinguishable clinical presentations for biologically distinct conditions.
- Multiple relevant targets for medical intervention.
- Differential ADME (absorption, distribution, metabolism and excretion) characteristics,

toxicity or tolerability of the therapeutic regimen(s).

- Adaptiveness of the disease leading to treatment resistance.

In addition, both of the following conditions must be met:

- Multiple treatment options with heterogeneous responses for the disease.
- A logistically and medically acceptable clinical biomarker.

A well-known example in which these conditions have been fulfilled is provided by the anticancer drug trastuzumab, which has achieved blockbuster status although it is only efficacious for a population subset, in this case HER2/*neu*-positive cancers⁴. For patients with the appropriate genotype (clinical biomarker), the drug proves superior to alternative treatments, whereas for those without the genotype it is no better than standard therapy.

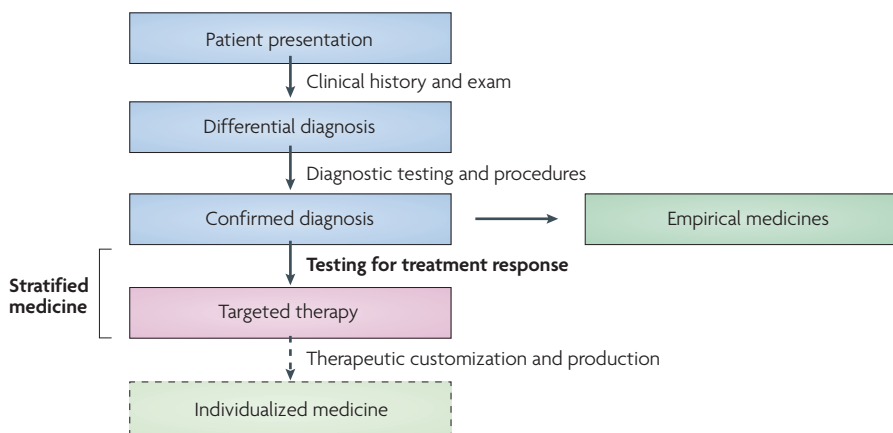


Figure 2 | Stratified medicine in the clinical context. In empirical medicine, a differential diagnosis is made on the basis of patient history and physical assessment, and following diagnosis confirmation from laboratory tests and clinical observation, a therapy is prescribed. Stratified medicine involves a further step in which a clinical biomarker is evaluated to associate a patient with a specific therapy. Extending this further, individualized medicine involves the customized production of the therapy (for example, using the patient’s own cells).

However, population variability in efficacy or safety is not by itself sufficient for a stratified medicine to emerge. The clinical variability must be sufficiently large to provide the incentive for the search for an optimal drug. Specifically, a viable stratified medicine must possess a sustainable, meaningful therapeutic benefit that exceeds the costs of identifying the appropriate patients. For example, lipid-modulating agents also exhibit variability in efficacy across the diagnosed population^{5,6}. Drugs such as simvastatin (Zocor; Merck) and atorvastatin (Lipitor; Pfizer) affect the various cholesterol and lipoprotein carriers by differing amounts and the level of effect (for example, degree of lowering of low-density lipoprotein (LDL) cholesterol) can be associated with distinct genetic profiles. Given the idiosyncratic responses, each patient theoretically has an optimal statin therapy, and so the hyperlipidaemia market might seem ripe for stratification into multiple targeted therapies. Nevertheless, statins remain traditional, empirical medicines, because although in principle an optimal therapy exists for subpopulations, most statins will lower an individual’s LDL cholesterol to a clinically satisfactory level. So, although Chasman *et al.* demonstrated in a >1,500-patient clinical trial that pravastatin (Pravachol; Bristol–Myers Squibb) is far less effective in patients with a particular genetic profile⁷, the impact on clinical practice and the use of genetic testing has been minimal because the added inconvenience and cost of finding the optimal statin have so far outweighed its incremental benefit over a randomly chosen statin. So, with regard to their efficacy at

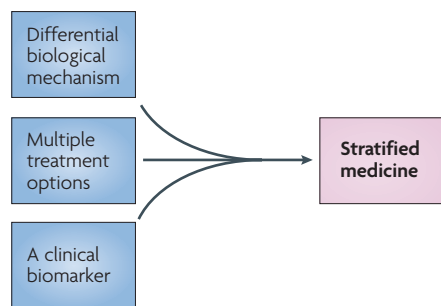


Figure 3 | Necessary conditions for stratified medicine. Three key factors are necessary for the emergence of a clinically relevant patient subclass and consequently stratified medicine: a biological characteristic with the potential to induce differential patient responses to a therapy; multiple therapeutic options that have sufficiently heterogeneous responses; and an appropriate clinical biomarker that can link therapies to a subset of patients that are more likely to show that different response.

lowering LDL cholesterol, statins will probably remain empirical medicines.

If no clinical biomarker exists, then stratified medicine will not emerge because a therapy and a patient subpopulation cannot be linked. For depression, the lack of biomarkers that are reflective of disease status or progression often results in patients receiving several different therapies in turn to identify one that leads to a satisfactory response; that is, at present, depression treatments remain empirical with regard to efficacy, although there might be the opportunity to stratify treatments on the basis of safety profiles. Genotypic and electroencephalogram (EEG) approaches are being pursued to develop efficacious clinical biomarkers⁸. Stratified medicine is also unlikely to emerge in therapeutic areas for which drugs with highly positive, uniform and readily ascertainable patient responses are available (that is, when most drugs have sufficient efficacy or those which do not are easily and rapidly detected).

Bearing in mind the above factors, additional markets that might be primed for stratification owing to scientific advances, patient impact and market value include arthritis and other autoimmune disorders, depression and related central nervous system conditions.

Large revenues from stratified medicines

Stratified medicines are demonstrating a new economic model for the biopharmaceutical industry. By charging a price premium for higher efficacy in a target

group, stratified medicines can generate high financial returns. The example of trastuzumab has already been mentioned. A further example, also an anticancer drug, is provided by imatinib: the peak annual revenues of this drug so far are nearly US\$2.5 billion (BOX 1, Note 1). At an estimated average US price of ~\$43,000 per patient year or treatment course, this corresponds to only about 55,000 patients receiving imatinib compared with more than 500,000 patients receiving tamoxifen (as a therapy for breast cancer), which generated \$630 million in peak annual revenues (BOX 1, Note 2). Higher pricing and adoption rates can overcome smaller population sizes for clearly superior stratified medicines — particularly in life-threatening conditions. FIGURE 4 shows three distinct \$1-billion product regions: classic blockbusters, high-value orphan drugs and the emerging targeted or stratified medicines (sometimes called ‘niche busters’).

Stratified medicine development criteria

Three criteria must be satisfied for the development of a stratified medicine to be viable: technical feasibility of identifying a patient subpopulation; attractive economics; and a sustainable franchise.

Criterion 1: Technical feasibility of identifying a patient subpopulation. The risks of developing stratified medicines would seem compounded compared with empirical medicines because of the additional need to identify a reliable clinical biomarker. However, clinical biomarkers assist by enriching patient populations in clinical trials with better responders, thereby reducing the size of the trial sample required to detect significant efficacy, and possibly shortening endpoint observation times when the clinical biomarker is an accepted surrogate for a longer-term endpoint such as survival. In addition, expanding the use of toxicity biomarkers to actively exclude patients could further reduce development risks.

Historically, stratification has occurred after drug approval, when the variation in a medicine’s clinical effects become better understood. For example, as mentioned above, irinotecan is severely toxic for patients with a specific variant of the UGT1A1 enzyme that detoxifies its active metabolite³, and patients can now be screened for this variant. Variations in efficacy also provide potential for stratification; for example, attempts to understand the basis of marked responses in a small subset of patients with non-small-cell lung

cancer to the kinase inhibitor gefitinib (Iressa; AstraZeneca) were made after it failed to show a survival benefit in an unselected patient population in post-approval Phase III trials⁹. A further example is provided by the impact of the emergence of HIV strains with specific mutations that confer resistance to protease inhibitors and nucleoside reverse transcriptase inhibitors that form the core of most HIV treatment regimens. This has affected surveillance methods, patient stratification and the continued search for therapies that can overcome resistance¹⁰. Whether intended to avoid toxicity or improve efficacy, clinical biomarkers for selecting appropriate patients for treatment in clinical trials will become increasingly prospective rather than retrospective.

Criterion 2: Attractive economics. For empirical medicines, a common rule of thumb in large pharmaceutical companies is that a drug must show potential for \$500-million peak annual sales to justify the costs of discovery, development and marketing.

Glossary

Biomarker

A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention.

Clinical biomarker

A biomarker that associates a treatment to a patient subpopulation that has historically showed a differential and substantial clinical response. These can be based on genotypes, proteins, metabolomic patterns, histology, imaging, physician clinical observations or even self-reported patient surveys.

Esoteric diagnostics

High-value molecular tests such as genotyping, gene expression or other ‘omics’-based tests.

Gedanken experiment

A mental exercise that examines the essence of a hypothetical situation. Often called ‘thought experiments’ to distinguish them from physical experiments.

Metabonomics

A systems-oriented approach involving the study of metabolic responses to drugs, diseases and environmental changes by surveying low-mass (< 1,000 atomic units) molecules.

Orphan drug

The Orphan Drug Act provides assistance and financial incentives for the development and approval of orphan drugs for diseases that affect patient populations of fewer than 200,000 people in the United States, including marketing exclusivity. Orphan drug exclusivity assures that no other sponsor will receive FDA marketing approval for the same drug for the same indication for 7 years after marketing approval of the innovator’s product.

Stratified medicines can violate the assumptions underlying this norm by changing the expected time and costs of development, revenues and product life, and sales and market adoption costs.

Development costs might be lower because population stratification and differential efficacy may dramatically reduce required clinical trial sizes, decrease the overall number of clinical trials and spur faster review cycles. For example, imatinib was approved by the FDA (Food and Drug Administration) in 3 months, with a total elapsed time from first human dose to FDA approval of under 4 years. However, development costs might increase from the need to validate a clinical biomarker for regulatory approval as a diagnostic. Moreover, with high exclusion rates due to the many patients who receive and fail the clinical biomarker assessment, and possibly the need for more investigator sites to compensate, clinical trial costs and total time to completion could increase.

Stratified medicine inherently restricts the potential number of patients, which correspondingly lowers potential revenue. However, in practice, actual revenues might increase because stratified medicines enjoy faster and wider adoption owing to their superior clinical performance, longer effective patent life arising from shortened development times as well as the possible revenues from the clinical biomarker. In addition, as with novel empirical medicines, a large efficacy or safety differential and/or a major improvement over the previous standard of care often generates a premium pricing capability. Numerous recent biologics, such as bevacizumab (Avastin; Genentech) for the treatment of colorectal cancer, breast cancer and lung cancer, demonstrate this potential (BOX 1, Note 3). With these various offsetting factors, the net effect on revenue will therefore differ according to the specific therapeutic.

The differential profile of a stratified medicine could allow more efficient marketing if it enables targeting of physicians and

timely inclusion into formularies. Offsetting these possible advantages is the need to educate providers with regards to the association of the therapeutic with the clinical biomarker.

In some but not all cases, these changes enable commercial success, as imatinib demonstrates. However, the low sales of antibiotics restricted to resistant infections illustrate that the different dynamics of stratified medicine do not guarantee high returns on investment. For example, the third-line antibiotic vancomycin posted only \$100 million in 2005 sales. Another example is provided by the antiseptic drug drotrecogin alpha (Xigris; Eli Lilly), which has not been a major commercial success owing to its narrow patient segment (patients with severe sepsis) and the complexities of diagnosing sepsis, physician education and reimbursement approval processes. So far, Xigris has only captured 25% of the \$1-billion potential market (BOX 1, Note 4).

Criterion 3: A sustainable franchise. For economic viability, a stratified medicine usually requires disproportionate adoption within its indicated population by successfully displacing current treatments and 'raising the bar' for the entry of potential competitors. In addition to inherent clinical benefits, factors contributing to a sustainable advantage include the following:

- Increased compliance due to patients perceiving better response directly or through positive feedback from ongoing clinical biomarker testing that confirms the drug's efficacy or safety, particularly for chronic conditions.
- Additional regulatory market protections due to small population size (orphan drug status).
- Stronger intellectual property position regarding the target or treatment modality (such as RNAi), which might impede potential follow-ons.

Stratified medicines face the same threats as empirical medicines, such as novel treatments that perform better; for example, the PPIs that improved on the H₂ receptor antagonists for the treatment of gastroesophageal reflux disorder. Second-generation products could severely affect stratified medicines because of smaller patient populations, but the smaller market might discourage their development.

Stratified medicine has so far emerged in specialized indications with highly differentiated products. If the stratified medicine development approach

Box 1 | Additional notes and financial sources

Note 1. Novartis's first-half 2006 earnings report stated US\$1.2 billion revenues for Gleevec (imatinib). Not all of these sales were for chronic myeloid leukaemia. Gleevec is also approved as a treatment for gastrointestinal stromal cancers that are associated with mutations in another kinase, c-KIT, which is also inhibited by the drug.

Note 2. Data from 2002 AstraZeneca Annual Review, p14. Universal Health Care Action Network of Ohio, Update, *UHCAN Ohio Newsletter* 2 August 2001. The Nolvadex/tamoxifen sales data for AstraZeneca were \$630 million in 2001 with retail US price of \$1,368. Assuming ~\$1,000 average world net price for AstraZeneca this results in more than 500,000 treated patients. 2001 was chosen as the comparative year as this was the last patent-protected year, with revenues dramatically declining in later years.

Note 3. A. Berenson: "A cancer drug shows promise, at a price that many can't pay," *New York Times*, 15 February 2006. "Genentech plans to charge for it [as a breast and lung cancer treatment] about \$100,000 a year. That price, about doubles the current price as a colon cancer treatment..."

Note 4. Wolters Kluwer Health, Source Pharmaceutical Audit Suite January–December 2005 based on Wholesale Acquisition Cost. Eli Lilly Q4, 2005 earnings press release and BioPortfolio/Datamonitor.

Note 5. In REF. 12, published in 2003, the Tufts Center for the Study of Drug Discovery and Development reported the cost of developing a new drug as ~\$800 million, and it has been estimated that this figure has probably grown to more than \$1 billion in current dollars.

Note 6. The Tufts Center for the Study of Drug Development recently estimated that a new biotechnology product costs \$1.2 billion (Tufts Center for the Study of Drug Development *Impact Report*, November/December 2006; see also [Tufts Center for the Study of Drug Development press release dated 9 November 2006](#)). The Tufts Center has further reported that the time required for clinical and approval phases increased by an average of 1.3 years to 8.5 years in the 2002–2004 period from the 7.2 years required in the 1999–2001 period. An assumed increase of 4 years for the time from initial drug discovery to market is plausible for the following reasons: a development time increase trend is already present before recent perceived issues with drug safety, which will further extend development and approval times; the same source reports that historic drug development times have been as long as 9.4 years (in the early 1990s); and a renewed industry emphasis on novel drugs in new chemical classes is occurring, which typically leads to greater testing requirements and correspondingly longer development time (Tufts Center for the Study of Drug Development, *Impact Report*, November/December 2005; see also [Tufts Center for the Study of Drug Development press release dated 1 November 2005](#)).

Note 7. Watson Pharmaceuticals Inc. First Quarter 2006 Form 10-Q 'Note 5-Operating Segments', p15.

Note 8. CMS press release, 22 March 2006. S.P. Westphal, 22 March 2006, pB1, *Wall Street Journal*.

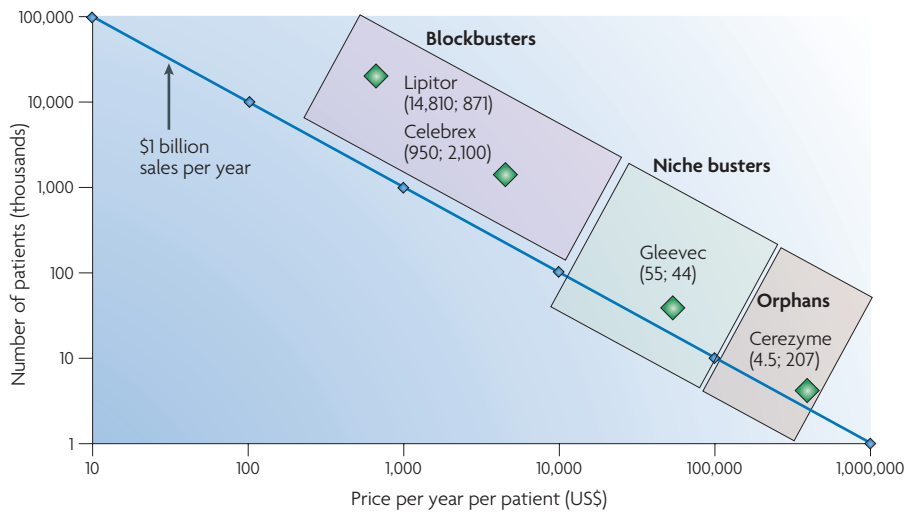


Figure 4 | **Different types of high-revenue medicines.** Classic blockbusters such as atorvastatin (Lipitor) are prescribed to large patient populations. Stratified medicines that can be demonstrated to be clearly superior to alternatives for a smaller patient population can also achieve high revenues resulting from higher pricing and adoption rates. At one extreme are orphan drugs, which often represent the only therapy for a small population with the disease in question, and which can therefore support even higher pricing if they are highly effective and the condition is sufficiently severe. In the figure, the numbers in brackets correspond to the number of patients (thousands) and the price per year per patient (US\$), respectively.

is applied to future products with lower differentiation — even in a subpopulation, the key economic benefits of premium pricing and rapid adoption for those products will also be correspondingly lower.

The diagnostic as gatekeeper

The link between the clinical biomarker and the therapy creates new opportunities for value creation, and barriers to the entry of other therapies. As a gatekeeper to patients, the diagnostic becomes a portal through which subsequent therapies must pass, and it can promote initial adoption of a particular therapy, potentially expanding the value of the market for the therapy.

For example, to encourage adoption of alendronate sodium (Fosamax; Merck) — a drug for reducing the risk of bone fractures associated with osteoporosis that is best prescribed early when the disease is asymptomatic — a complementary, cost-effective bone-density test was independently developed to identify women at risk who would benefit from the drug. This example demonstrates that combining a therapy and a diagnostic can reach under-diagnosed, under-treated patient populations. It also shows that using a diagnostic to monitor treatment progress can encourage long-term patient compliance, which further enhances revenues. A second example of a test promoting adoption of a treatment approach is provided by the use of breast cancer family

gene variants (*BRCA*) that are correlated with breast cancer occurrence, particularly in women with a family disease history. With the availability of a genetic test panel to identify those variants, ~50% of women with mutations have undergone prophylactic mastectomies¹¹. Before the existence of the test, such a treatment course was uncommon.

Gatekeeper value: is it better to market the drug, the diagnostic or both? If a company intends to market both drug and diagnostic, how should it partition the value between them? Although some decisions are straightforward because patent life or reimbursement differences clearly favour the drug, in other cases the issues will be more balanced or even favour the diagnostic.

For example, a company might find the diagnostic more profitable as the gatekeeper as it tests all patients with the diagnosis, whereas the drug is only taken by the fraction in the qualifying sub-segment. If the diagnostic also monitors treatment progression, or if a firm cannot build a barrier to exclude other follow-on drugs, the advantage of the diagnostic is enhanced. Esoteric diagnostics are increasingly receiving attractive reimbursement ranging from \$200–4,000 per test with substantial margins for both the clinical laboratory and test developer. The profit from a \$500 test given to all patients with a disease might generate more profit than a drug prescribed episodically

to the small fraction qualified by the diagnostic. However, high-priced tests could impede adoption of the stratified medicine. A time-phased approach that shifts value from drug to diagnostic can be envisioned, although historical payer resistance to diagnostic price increases probably makes this unfeasible.

The economic theory of double marginalization predicts that if a proprietary diagnostic and medicine are marketed by separate, uncoordinated entities, each will set the price of its product higher so that their sum is greater than the combined price in a more profitable ‘bundled’ approach in which volume increases more than offsets the price declines. Inefficiencies of managing distinct distribution channels and operations might offset any increased coordinated profit potential. If such inefficiencies can be avoided, marketing the diagnostic and stratified medicine jointly can enhance total profits at reduced prices.

A new equilibrium for stratified medicines

Given the numerous offsetting factors (FIG. 5), predicting whether a stratified medicine approach will enhance or reduce the economic value of a particular therapeutic requires careful analysis. Although the first step to the new equilibrium reduces patient populations because of diagnostic exclusion,

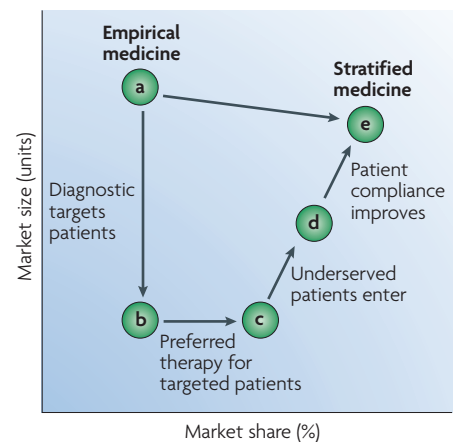


Figure 5 | **Potential effects of stratified medicine on the economic value of therapies.** Use of a diagnostic reduces the size of the treated patient population and thereby the potential market, but enhanced efficacy/safety increases market share as the therapy becomes the preferred treatment. Further market expansion occurs as underserved patients enter the market encouraged by the greater certainty of outcome should they qualify. Last, improved long-term compliance through diagnostic feedback and improved tolerability can further increase market size.

enhanced efficacy and safety increases market share as the therapy becomes the preferred treatment. Further market expansion occurs as underserved patients enter the market encouraged by the greater certainty of outcome should they qualify. Last, improved long-term compliance through diagnostic feedback and improved tolerability can further augment market size. When projecting the revenue potential of a stratified medicine, marketing assessments will need to account for these new dynamics and the opportunity for premium pricing.

Can stratified medicines sustain industry economics? A useful exercise strips a problem to its essential elements, then asks what one would observe if those key elements change — often with surprising results. Such ‘Gedanken experiments’ became famous through the work of physicists such as Einstein and Schrödinger. The following Gedanken experiment explores the industry economics of stratified medicine.

Essential components of such a Gedanken experiment for drug development are effective patent life, development cost, average yearly sales and gross margins. Proxy measures for the economic value of the drug are lifetime gross margin and the non-discounted payback ratio compared to development costs.

The first column in TABLE 1 describes the environment for recently approved medicines. In this environment, a reasonably successful drug with \$500 million yearly sales resulting from a \$1-billion development programme¹² (BOX 1, Note 5) having a 10-year effective patent life¹³ and receiving 80% gross margins¹⁴ yields a \$4-billion lifetime gross profit and a 4.0 payback ratio.

The ‘Current trend’ column in TABLE 1 demonstrates the impact of assuming continued increasing development costs to \$2 billion and development times to 14 years (BOX 1, Note 6). Pharmaceutical gross margins are also proposed to decline in this scenario to 50%, which remains above the 33% gross margin reported by a generic drug manufacturer (BOX 1, Note 7). With these changes to the Gedanken experiment, even if an average pharmaceutical product quadruples its annual peak sales to \$2 billion, the average payback ratio falls from today’s 4.0 to 3.0, with discounted values falling even further owing to later launches. The current trends scenario suggests a future of a declining industry able to pursue limited innovation for a very small number of very large new products.

By contrast, the ‘Bright future’ column suggests the potential impact of stratified

Table 1 | Potential drug development futures

Parameter	Today	Current trend	Bright future	Sustained future
Patent life*	20	20	20	20
Development time*	10	14	5	10
Development cost	\$1	\$2	\$0.25	\$0.5
Sales life*	10	6	15	10
Average yearly sales	\$0.5	\$2	\$0.2	\$0.33
Gross margin	80%	50%	80%	65%
Lifetime gross profit	\$4	\$6	\$2.4	\$2.15
Payback ratio [†]	4	3	9.6	4.3

*In years. †Gross margin divided by development costs.

medicine if innovators, regulators, clinicians and payers all adapt to newly emerging possibilities. If development times could be cut in half from 10 to 5 years through the better use of efficacy and safety biomarkers, costs might fall even further, by 75% owing to smaller clinical trial sizes and, most importantly, reduced failure rates as a result of stratification. Assuming also that superior drug performance maintains today’s reimbursement rates — as recent reimbursement successes of high-value biologics suggest might be possible — a stratified medicine with peak sales of just \$200 million more than doubles the payback ratio to nearly 10 from today’s 4.0. Diagnostic product profits from the clinical biomarker could further enhance the payback ratio.

Moderating the optimism of these ‘bright future’ results gives the still attractive ‘Sustained future’ scenario in the final column of TABLE 1, which assumes that the required discovery and development time is maintained at today’s 10-year length. It further suggests that development costs only fall by 50%, with most of that benefit coming from higher success rates. This scenario also surmises that gross margins decline to 65% from today’s 80%, recognizing that even superior stratified medicines would not fully resist the inexorable increase in government and managed care buying power. In this sustainable future, the Gedanken experiment suggests that the average peak sales for a successful product can decline from \$500 million to \$330 million resulting in a payback ratio that actually increases slightly to 4.3 even as lifetime gross profits decline by 50% to \$2 billion. Other futures could easily be imagined.

Although developers would clearly prefer the ‘bright future’, this Gedanken experiment suggests that even in a ‘sustained future’ environment, stratified medicines can achieve the economics of a vibrant, innovation-based industry that can attract investment, produce many more medicines per year than current rates and enjoy sustainable growth.

Regulatory, reimbursement and public policy implications of stratified medicine.

In today’s world of concentrated payers, any new medicine — empirical, stratified or individualized — must demonstrate superior performance (efficacy, safety or tolerability) to gain substantial market access. In this respect, stratified medicine approaches can aid drug developers in demonstrating differential response in subpopulations for some medicines. However, such approaches will pose challenges for developers and regulators as testing clinical biomarkers to select appropriate patients for treatment in clinical trials becomes increasingly prospective rather than retrospective. Joint clinical-trial designs for diagnostic and drug might require careful coordination among regulatory divisions to ensure a timely approval for both.

Stratified medicine also challenges current reimbursement approaches. For payers, the possible proliferation of stratified medicines for a given diagnosis raises questions about the validity of drug formularies that limit the therapeutic options for a disease and also creates issues associated with reimbursement for novel tests. A recent reimbursement decision by the Centers for Medicare and Medicaid Services (CMS) authorizing the reimbursement for a \$400 microvolt T-wave alternans (MTWA) test developed by Cambridge Heart provides an example of how all stakeholders can benefit. Currently only 10–15% of the 1.3 million US residents indicated receive an implantable cardioverter defibrillator (ICD). Counter-intuitively, the MTWA test, which shows that nearly 30% of those would not benefit and so reduces the theoretical US market by 450,000 patients, might actually increase near-term ICD sales as it gives physicians and patients confidence to proceed with the risky, costly procedure (BOX 1, Note 8). Patients, payers and innovators could all experience better results owing to this enlightened reimbursement decision.

Summary

Stratified medicine changes the incentives for innovation, alters the drug and diagnostic development process, complicates regulatory review, and further extends the fragile reimbursement structure. But if all players adapt, patients will reap the benefits of better clinical outcomes, payers will spend less on ineffective treatments and manufacturers will remain economically viable and continue to develop new products.

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doi:10.1038/nrd2251

Published online 23 March 2007

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Competing interests statement

The authors declare **competing financial interests**: see web version of details.

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