

A change in the market—investing in diagnostics

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Low margins, tricky reimbursement issues and the difficulty of market penetration have traditionally made diagnostics unattractive to investors. However, with changes to healthcare economics, regulation and the adoption of companion diagnostic tests that are predictive for drug response, that may be about to change.

Diagnostics have long been the ugly duckling of the healthcare market. Unlike the drug sector, there is no tradition of a 'blockbuster diagnostic' to provide investors with windfall returns. The US Medicare coding and payment mechanisms for diagnostics are fixed, time-consuming, lacking in transparency, inconsistently applied and outmoded. And the resulting low margins for *in vitro* diagnostics (IVDs) have created a crowded market that requires significant investment in technology development, clinical validation, marketing and product positioning if a diagnostic venture is to have a chance of succeeding with a new test. For molecular diagnostics, these problems are exacerbated by uncertainties about the validity and scope of gene patents and the licensing difficulties associated with negotiating patents on key technologies. Small wonder then that life-science investors have traditionally shied away from the diagnostic sector.

Investment diamonds are, however, increasingly likely to be found among the sector's coal. Innovative technology is already driving down the cost of biomarker discovery and companies that succeed both in enhancing the robustness and accuracy of tests and in marrying them with specific treatments to identify appropriate subpopulations of responders (or non-responders) will be in a good position to capitalize on the increasing enthusiasm of payers to move away from costly treatments in the hospital setting, but also on the greater use of



Dosing of warfarin, an antithrombotic drug with sales over \$500 million, is likely to be guided by CYP450 diagnostics in the future.

IVDs by physicians to enable more precise clinical decision making.

A different business proposition

There are some striking differences between the diagnostics and drugs businesses. According to healthcare consultants the Lewin Group (Falls Church, VA, USA), the worldwide market for diagnostics in 2005 was approximately \$29 billion. *Forbes* magazine has suggested

that the approximately \$11 billion portion of this market that is US based is growing by 4% annually, with the \$2.5-billion US molecular-diagnostic segment (DNA and RNA tests) expanding 15% annually. Approximately 80% of this market is in infectious disease, with the remainder made up of the 900 or more different assays related to genetic diseases, predictive testing, cancer and paternity testing.

Although encouraging, these figures contrast starkly with estimates for the drug sector. For example, IMS, the Fairfield, Connecticut-based consultants, put the global market for therapeutics in 2005 at around \$602 billion, with a 7% annual growth rate. Indeed, 2005 sales of a single blockbuster drug, Pfizer's (New York) atorvastatin (Lipitor), were \$8.2 billion and those of biotech's biggest seller, Amgen's (Thousand Oaks, CA, USA) and Ortho Biotech's (Bridgewater, NJ, USA) erythropoietin- α (Epogen/Procrit), totaled \$6.0 billion.

Although the potential returns for diagnostics are clearly less inviting to investors, this sector does offer several advantages. For example, there is no requirement in the development of diagnostics for the lengthy clinical trials process that a drug company must pursue to obtain marketing approval, and thus years are sliced off product time to market.

In addition, several different paths to commercialization are available for diagnostic manufacturers and their backers. Premarket regulatory clearance for a diagnostic product can be obtained through the US Food and Drug Administration (FDA; Rockville, MD, USA) 510(k) application—a cheaper and quicker route to approval for devices and diagnostics than clinical trials. Alternatively,

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manufacturers can forego FDA regulatory oversight completely by building their own laboratory—or working with an existing laboratory that is compliant with the Clinical Laboratory Improvement Amendments of 1988 (CLIA)—to market their diagnostic as a so-called ‘homebrew.’

Yet another route is to sell one or more of the components of their diagnostic to testing laboratories as analyte-specific reagents (ASRs), thus enabling early market penetration and enhancing early adoption of their technology. For diagnostics that have not yet established clinical utility, there are also opportunities to market them as kits for investigational-use only, as reagents for use by the research community or as products for use by drug companies in clinical studies.

A rough rule of thumb is that a market opportunity of \$10–50 million is required to generate a positive return on investment and to justify pursuing approval of FDA-cleared (class II) or approved (class III) diagnostic kits. As the market size for many molecular diagnostics—with the exception of tests for large patient populations, such as factor V Leiden or cystic fibrosis—is likely to be smaller than this, ASRs and homebrews have become an increasingly popular route for companies such as the suppliers Promega and Third Wave Technologies (both based in Madison, WI).

Thus, several commercialization paths are possible, enabling more investor dollars to be spent on marketing (which investors prefer), rather than development and approval. In addition, because of the lower regulatory hurdles, the time to market is also shorter. Faster development time means that diagnostic ventures require less investment, but can provide quicker outcomes than startups that aim to produce human therapeutics.

Perhaps most important of all, diagnostics have been central, and are poised to become increasingly critical, components of healthcare provision. Even in current hospital settings, they influence 60–70% of all critical decision making, including admittance, discharge and medication. However, as complex diseases, such as cancer and hypertension, are often revealed to be several (perhaps tens) molecular disorders masquerading as one set of symptoms, demand is likely to boom for diagnostic tests that can identify the condition and facilitate prescription of the right drug for a particular disease (or subtype of disease).

And superimposed on the heterogeneity of disease will be the ability to divide a particular clinical population into patients who are likely to respond or not respond to a particular therapy, enabling payers and physicians to avoid fruitless prescription of expensive

therapies and saving patients from needless side effects. Ultimately, the identification and mapping of predispositions to disease, which are predictive of disease in later life will necessitate the introduction of new diagnostics that can aid the population in maintaining wellness by taking cheaper, prophylactic therapeutics. Thus, the market growth for diagnostics as companions to treatments is likely to only increase.

Some investment caveats

This enthusiasm should be tempered, however, by several factors that have traditionally dampened investor interest in diagnostics. First, the amounts paid (reimbursement) by the US healthcare system for diagnostic tests have been significantly lower than the reimbursement for therapeutics. Reimbursement requires obtaining a Current Procedural Terminology code (CPT), having coverage (meeting the benefit plan policy and clinical conditions under which a third-party payer may pay for the insured benefit) and a payment level.

Although it might be expected that the payment level for a technology should reflect its value to patient care, current US coding and payment mechanisms for diagnostics often do not reflect this value¹. This problem is compounded by the fact that the Medicare clinical laboratory fee schedule has been updated for inflation in only two of the past 15 years and is not likely to be updated again until 2008.

Typically, a new diagnostic—even one using a different technology and demonstrating higher sensitivity and specificity or novel clinical insights—is assigned an existing CPT code. This new technology is then often compensated at the same dollar amount as, or in some cases less than, previous diagnostics sharing the same code. As a result, physicians and testing laboratories have little incentive to prescribe newer tests, which restricts patient access to cutting-edge technology.

Diagnostic companies also have to position themselves to be carried by the major laboratories in the same way a soft-drink maker fights for shelf space at a major grocery chain. It is a classic ‘chicken and egg’ scenario—the test must be used widely enough to get onto the big testing laboratories’ radar screens; the company finds it difficult to get the test widely known and used unless it is carried by a big laboratory. Few diagnostics companies have had the funding, or the skill set, to pursue creating a strong brand in the marketplace, although this situation is changing.

In addition, because of the shorter product development times, lower regulatory barriers and lower investment needed to enter the

business, existing diagnostics products are likely to be rapidly supplanted by new diagnostics, thus, the half-life of many diagnostics is shorter than that of therapeutics.

Notwithstanding all these challenges, we believe that ongoing changes in technology, regulation, adoption of companion diagnostics for drugs, reimbursement and marketing are all combining to make diagnostic companies much more interesting to investors.

Technology changes

Since the mapping of the human genome, as part of the Human Genome Program launched in the 1990s, the pace at which science is unlocking the molecular underpinnings of complex disease has accelerated at a remarkable rate. All the ‘omics’ (such as, genomics, proteomics, metabolomics), and an ever-expanding toolkit (DNA and protein chips, microarrays or microfluidics), are rapidly redefining the taxonomy of disease as biomarker-identified subgroups that can be addressed in novel ways. With this change comes a new vocabulary for diagnosis that must be mastered by physicians and patients, and a new way for patients to view themselves relative to disease (that is, the patient perspective is shifting from “I have got cancer” to “I am ‘such-and-such biomarker’-positive and thus must manage my health differently from others”). Importantly, the cost of identifying both the biomarkers and the appropriate subpopulations are being driven down, thereby making it economically feasible to make such subgrouping part of routine healthcare.

These advances have allowed the creation of new *in vitro* diagnostic tests that quantitatively measure response to therapy (e.g., α -fetoprotein assays in cancers of the liver, testes or ovaries.), can monitor disease progression (e.g., urine protein markers in chronic kidney disease) or predict recurrence (e.g., Oncotype Dx, a reverse transcription PCR-based test for determining the risk of recurrent breast cancer based on the expression of 16 genes²; Genomic Health, Redwood City, CA, USA). Results from these *in vitro* diagnostics, coupled with quantitative *in vivo* tests (e.g., functional magnetic resonance imaging), can now be efficiently collected, using electronic medical records, to allow validation of new biomarkers, monitor therapies and generate outcome data that can improve safety and efficacy of targeted therapies (and presymptomatic care) and provide cost justifications for payers.

Regulatory changes

In the United States, previous federal regulations related to Medicare, Medicaid and the

Center for Medicare and Medicaid Services (CMS) for determining payment and coding for new clinical diagnostic laboratory tests, have specifically limited reimbursements. For example, laboratory tests for screening purposes (that is, performed in the absence of signs, symptoms, complaints or personal history of disease or injury) are not covered by Medicare unless Congress authorizes specific coverage for screening applications: acts of Congress were required to provide Medicare coverage, and to change reimbursement rates, for mammograms and prostate cancer screening tests.

There are, however, indications that the situation may be about to change. The Advanced Laboratory Diagnostics Act of 2006, submitted to the US House of Representatives in May, is intended to “establish a demonstration project to evaluate a new payment system for molecular diagnostic tests designed to more appropriately reflect the value of these important technologies to patient care management.” The future of this particular bill is unclear, but there seems to be a desire in the US Congress to provide payment schedules that are in line with the clinical value of diagnostics. This would be a major change to the philosophy of reimbursement that is currently applied.

In addition, on January 23, CMS signed a Memorandum of Understanding between the FDA and the US National Cancer Institute (NCI) “to understand and develop the clinical utility of a new generation of biomarker technologies...whereas CMS is interested in the development of evidence to inform reimbursement decision making about existing or new treatment regimens.”

Acceptance and validation of companion diagnostics

Individualized treatment based on genomic testing has demonstrated value. For example, Genentech's (S. San Francisco, CA, USA) breast cancer therapy Herceptin (trastuzumab) has been shown to be effective for the subset of women whose breast cancer overexpresses the protein HER2/neu. Dako's (Glostrup, Denmark) HercepTest—an immunohistochemical test using primary rabbit polyclonal antibody to the HER-2/neu oncoprotein, horseradish peroxidase and goat anti-rabbit immunoglobulins, and diaminobenzidine as the chromogen—which was introduced to the market at the same time as Herceptin, is recommended for all patients with invasive breast cancer. Herceptin and HercepTest provide an example of a companion therapeutic and diagnostic. The FDA is expected to encourage more submissions of companion therapeutics and diagnostics.

Those who see personalized medicine coming have an opportunity to make strategic moves that will allow them to participate in the new healthcare future.

In this case, we see an interesting pattern: the diagnostic will be given to a much larger number of patients than the therapeutic drug. If reimbursements for both were similar, the revenues for the diagnostic would significantly exceed the revenues for the therapeutic drug. But as we have seen, diagnostic reimbursements are traditionally much lower than therapeutic reimbursements.

Reimbursement changes

The strategy of another diagnostics company is attempting to change this situation. Genomic Health's Oncotype Dx is a ‘clinically validated’ laboratory test, ordered by physicians, which predicts the likelihood of breast cancer recurrence in women with newly diagnosed, early-stage invasive breast cancer. In so doing, Oncotype Dx, it is claimed, also assesses the benefit of certain types of chemotherapy.

According to company documents, Genomic Health has been working to establish reimbursement coverage policies with third-party payers, several of which are supportive, including the National Heritage Insurance Company (NHIC; Chico, CA, USA), the local Medicare carrier for California, and regional payers, such as Harvard Pilgrim Health Care (Wellesley, MA, USA), Highmark Blue Cross (Pittsburgh, PA, USA) and Premera Blue Cross (Spokane, WA, USA).

A Genomic Health spokesperson was quoted in the press in January as saying that the company is getting reimbursement at a rate that is “very close” to its list price of \$3,460, although she declined to elaborate on the exact rate. This should be contrasted with the reimbursement price tag for more traditional diagnostic technology; for example, \$85 for a fluorescent *in situ* hybridization (FISH) assay.

If Genomic Health can blaze a path for genomic test reimbursement, they will set a precedent that will rapidly be followed by other companies. Genomic Health has been able to differentiate its diagnostic test from the rest of the field, and by doing, is obtaining reimbursements based on clinical value, rather than the cost of a few technician hours, which is garnering the company recognition in the industry.

Thus, we see a company with a widely used test and a company pursuing higher reimbursement for a genomic test. Combining these two models will offer significantly increased valuations for diagnostics companies.

Marketing changes

Another interesting opportunity for diagnostic companies to obtain revenue is to market directly to the consumer. Interleukin Genetics (Waltham, MA, USA) develops genetic tests to inform people about increased risk for disease and to develop preventive and therapeutic products to reduce the risk of those diseases based on the biology of interleukins. Among their products is the ‘Gensona’ Heart Health Genetic Test, which differentiates interleukin (IL)-1 alleles that are associated with inflammation and increased risk of cardiovascular disease.

In addition, Interleukin Genetics is currently in partnership with Alticor (Ada, MI, USA), which is also a significant shareholder, to market genetic tests that are linked to nutritional products directly to consumers. Nutrilite (Buena Park, CA, USA), the nutritional division of Alticor, is developing nutritional products that are matched to Interleukin Genetics’ genetic tests under the Gensona brand.

To complete the picture, Alticor is the parent company of Amway, a direct selling company. In a May 2006 press release, Amway announced that tens of thousands of its customers, most of whom sell products in Amway's Nutrilite division, will visit a company-owned center that will give them a “personalized, experiential and comprehensive health assessment...” It seems likely that the Interleukin Genetics’ test, and a line of supplements for those who test positive, will be part of this experience. The sales staff who learn from this experience will be more effective sales people for a combined test plus supplement. Amway, with its significant marketing channel, is now in the personalized medicine business.

Have investors noticed that these companies are different and the wave of the future? The answer is yes. As *Nature Biotechnology* went to press, Genomic Health's market cap was \$274 million and Interleukin Genetics' \$138 million. This indicates to us that the alignment of these events, so-called ‘personalized medicine,’ will be associated with a significant change in the attractiveness of diagnostic firms to the investment market.

The rise of companion diagnostics

We believe that major changes in the healthcare system are already beginning. Rather than simply additions to the toolsets of clinical and research practitioners, we will see

Box 1 Warfarin dosing—a new diagnostic model?

Warfarin—one of the most widely prescribed drugs in the world (available in generic form since 1997)—is intended to prevent and treat thromboembolism by modifying blood clotting following myocardial infarction, atrial fibrillation, stroke, venous thrombosis and various surgeries. It is difficult to determine an effective warfarin dose for a patient (e.g., there is a 20-fold variation in dose requirements for therapeutic clotting times) and the consequences of improper dosing are serious. Hemorrhage during warfarin therapy is a leading cause of death in Western countries and related adverse events account for 1 in 10 hospital admissions⁴. Getting initial dosing right is usually a labor-intensive and costly process.

Knowledge of a patient's genotype can significantly improve warfarin dosing and reduce warfarin-related adverse events. Variations in the cytochrome P450 genes, which are involved in the metabolism of warfarin, explain why certain people require a lower or higher dosage of warfarin to get its full benefits. Molecular diagnostic tests can determine an individual patient's genotype variation and are available from a variety of clinical laboratories (some via the web) at an estimated cost of \$300.

The FDA is actively reviewing a relabeling of warfarin to require pretherapy genetic diagnostic testing⁵. Moreover, at several recent FDA presentations related to this proposed relabeling, the FDA explicitly mentioned collaboration with the CMS on issues pertaining to reimbursement for warfarin diagnostics. If adopted, this relabeling would change the standard of care overnight for millions of patients and drive pharmacogenomics into the mainstream of healthcare. The potential economic impact is huge; warfarin is already widely used and will become even more so as the aging population grows.

The warfarin example illustrates the opportunities for applying increasing scientific knowledge to better target an existing therapy, thereby improving patient outcomes and lowering the cost of care. In addition, the interest on the part of the FDA in changing the standard of care around warfarin may presage similar interventions for other drugs in the generic space. CMS discussions with the FDA on warfarin lend optimism to the belief that reimbursement for this test (and other genomic diagnostics) will be robust. Thus, although the drug industry will not reap significant economic benefits from these developments, it seems likely that diagnostics firms will.

disruptive changes to the system that fall under the general rubric of personalized medicine. A combination of factors will increase the value of many new diagnostics and the companies making them.

The attentiveness of baby boomers to new information about scientific advances and their enthusiasm for learning about their state of health will fuel this market. There are some regulatory barriers; for example, at present not all states allow individuals to buy their own diagnostic tests directly. However, we believe that regulation will not be the driving force for what happens in personalized medicine. What the market wants, within reason, will drive regulation and there are 76 million worried baby boomers, who are internet informed, have disposable income and vote!

Growing perceptions of the value of diagnostics companies will cause competition among investors and company buyers. There are multiple ways in which interested parties will perceive value.

Firstly, efforts to achieve higher reimbursements through case-by-case negotiations and to seek new CPT codes will spur other firms with genomic tests to follow the same path. As other firms follow this model, they will break out of the low revenue situation in which the diagnostics sector has been mired for decades.

Secondly, large players in the consumer marketing sector are beginning to see the value of partnering with diagnostic companies. Companies with channels to consumers through which supplements, functional foods and/or nutraceuticals are sold, are recognizing

the value of providing diagnostic tests to consumers as part of their offerings. They want to allow the consumer to 'one-stop shop' for a presymptomatic disease predilection test, plus a product to take regularly, to help avoid the condition predicted by the test. Marketing this combination may create strong customer loyalty and 'stickiness' in a classic 'razor plus razor blade' annuity for the company.

Thirdly, pharma and biotech companies will need to acquire, or license, the intellectual property (IP) for diagnostics that will be the companions to drug therapies. In some cases, where competitive therapies are being developed on roughly the same timeline, competition for one or two key diagnostic tests could be intense. A buyer may well be interested in multiple diagnostics for several reasons: until a given therapy is close to the end of its development, it may not be known which diagnostic fits it best. In addition, locking up a range of diagnostics may provide a strategic competitive advantage by preventing competitors from finding quality diagnostic tests as companions for their therapies. What's more, identifying a robust diagnostic that allows the largest sales of a firm's therapy is important; if acquiring the rights to several diagnostics will result in higher sales over the life of the patent, investing in a portfolio of diagnostic options makes sense.

At the same time, diagnostics ventures will need to negotiate an increasingly complex IP environment. Although balkanization of IP among multiple parties, economic obstacles caused by patent 'stacking' (the need to execute multiple licenses and pay multiple royalties

to market a diagnostic) and the IP problems associated with addition of new, but patented, genes to existing diagnostic platforms are likely to complicate the diagnostic business, we contend that market and regulatory forces will make these problems secondary. Too much focus on the problems associated with IP will miss the significant commercial opportunities to come.

A fourth, and very important factor, in increasing valuations in the diagnostics sector will be the usefulness of diagnostics in health-care-cost reduction. New diagnostics will be able to dramatically increase the effective targeting of new and existing therapies (Box 1). Using diagnostics to target therapy will take time; sensitivities and specificities will have to be good—better than many diagnostics currently exhibit. Savings from diagnostics will also happen in inverse proportion to the seriousness of the disease. Many people are thinking about personalized medicine with a cancer focus, but there are other chronic, costly, non-life-threatening diseases that will be transformed by targeted medication. Individualized therapies in these categories can be guided by sensitivities and specificities lower than those required in oncology and as a result, real cost savings will be seen here soon.

Glimpsing the future

These factors will all lead to a future that few currently anticipate, but those who do see personalized medicine coming have an opportunity to make strategic moves that will allow them to participate in the new healthcare future. What will this future look like?

Healthcare costs will decrease. The overall cost of drug therapies will decrease because of better diagnostics to target them. In addition, the other costs in the system will go down because there will be fewer hospitalizations that currently occur because of adverse reactions to drugs, continuing acute illness because of lack of efficacy and inaccurate dosing. Adverse events currently cause more than 2 million hospitalizations and 100,000 deaths annually in the US alone, with a cost of \$100 billion to the healthcare system³.

Another factor in healthcare cost reduction is that a two-tiered system will emerge, in which concerned individuals will focus on their own wellness and prevention, and will personally assume the costs of buying presymptomatic diagnostics tests and making the lifestyle changes that these diagnostics suggest. Their out-of-pocket payment for prevention will reduce their morbidity and therefore reduce the costs to taxpayers and employers of serving them.

In this environment, the importance of therapies will decrease and the importance of diagnostics will increase. The costs of drugs for a course of therapy may increase, but target-

ing the medication more closely will reduce total drug revenues and dramatically increase efficacy per dollar for patients (and payers). Diagnostics will drive this future.

New diagnostic science will involve new players. New technologies are permitting improved quantification and repeatability, thus reducing interpretation by professionals and human error. Existing companies with platform technologies (in both the *in vitro* and the *in vivo* markets) capable of producing these results will do well, especially if they can approach the market strategically and can focus their sales forces on the promise of personalized medicine. With quantified diagnostic data, instead of interpretive data, the opportunities for using the large data sets that reside in a number of organizations increases.

Why is the analysis of large data sets important? Understanding long-term outcomes starting with presymptomatic individuals requires much larger numbers than clinical trials focused on a relatively small number of sick participants. Large data sets with analysis and information technology capability can provide participants in diagnostics with major strategic advantages.

Companies possessing rich longitudinal patient data sets, and/or the ability to analyze them, will be powerful partners for diagnostic companies. These assets exist within a number of large firms that have yet to announce their intention to take advantage of them. We believe that the ability to use these assets strategically will create differential responses from the market.

Thus, we see a future in which: diagnostic firms obtain increased investment; traditional healthcare payers are joined by individual purchasers in selected segments of the field; new players in new partnerships and merger/acquisition roles combine with diagnostic companies; healthcare costs decrease; and patients receive more individualized and targeted therapies and provide for their own wellness. And we believe it's coming sooner rather than later.

1. Forsman, R. *Clin. Chem.* **42**, 813–816 (1996).
2. Habel, L.A. *et al. Breast Cancer Res. [online]* **8**, R25 (2006) (doi:10.1186/bcr1412).
3. Lazrou, J., Pomeranz, B.H. & Corey, P.N. *J. Am. Med. Assoc.* **279**, 1200–1205 (1998).
4. Pirmohamed, M. *Br. Med. J.* **329**, 15–19 (2004).
5. <http://www.fda.gov/ohrms/dockets/ac/05/minutes/2005-4194M1.pdf>.