Diagnosis or drug?

Will pharmaceutical companies or diagnostics manufacturers earn more from personalized medicine?

Pharmacogenomics and personalized medicine have become major buzzwords in public health and healthcare. They relate to technologies such as genomics, proteomics, microarrays and sophisticated immunoassays, which have the potential to deliver medicine tailored to an individual's biology or the specific pathology of their disease. The first products to help physicians base a treatment on the molecular profile of a patient are already on the market and, in addition to the potential improvements in healthcare, the possibility of a growing diagnostics industry in the wake of personalized medicine has captured the imagination of the biotechnology industry, investors and industry observers.

An increasing number of companies are offering molecular diagnostic tests to help

tailor medicine to an individual's biology. In 1998, the anti-cancer drug Herceptin®, developed by Genentech (San Francisco, CA, USA), was the first personalized treatment of breast cancer to reach the market. It is highly effective, but only in patients whose cancer cells express the HER2 receptor, for which molecular diagnostic tests are available. In 2003, Roche (Basel, Switzerland) introduced its AmpliChip® CYP450 product, which analyses variations in the CYP2D6 and CYP2C19 genes that are members of the cytochrome P450 oxidase system involved in metabolizing approximately 25% of all prescription drugs. On the basis of the test, which requires a PCR amplifier, a microfluidics station and scanning equipment, physicians can classify a patient as a poor,

intermediate, extensive or ultrarapid metabolizer, and thus prescribe the correct drug and dosage.

In 2004, Genomic Health (Redwood City, CA, USA) introduced its Oncotype DX™ assay, which analyses the expression levels of 21 genes in an effort to predict the probability of recurrence in early-stage invasive breast cancer. The information helps physicians to decide whether or not to prescribe chemotherapy. Similarly, the AlloMap® test, developed by XDx (Brisbane, CA, USA), analyses the expression levels of immune system genes to predict whether heart transplant patients will accept or reject a donor organ. Both tests are performed on tissue and blood samples, which the physician sends to the companies.

These and other tests are the vanguard for a new generation of diagnostics that are poised to help physicians make better-informed decisions. They also promise to overturn the traditional relationship between drugs and diagnostics because physicians will be able to use drugs more efficiently. This could shift the focus of the healthcare industry from therapeutics to diagnostics and, if that happens, the ‘poor stepchild’ of the medical industry—as Randy Scott, Chief Executive Officer of Genomic Health, refers to diagnostics—will reshape the economics of medicine. Mara Aspinall, President of Genzyme Genetics (Cambridge, MA, USA) agrees: “Diagnostics has been an overlooked, under-appreciated asset in the healthcare environment.”

Steve Burrill, who heads the venture capital firm Burrill & Company (San Francisco, CA, USA), has been predicting for some time that diagnostics and pharmaceuticals will swap price models. He thinks that the shift is already under way, pointing out that approximately 70% of the decisions made by physicians in the USA are based on the results of a diagnostic test, yet only 2% of the US\$2 trillion spent annually on healthcare goes into diagnostics. This suggests to Burrill that diagnostics should demand significantly higher profits. He also expects continued economic and consumer pressure to cause drug prices to fall, driven in part by the USA's Medicare prescription drug benefit, which gives private insurers more leverage to negotiate discounts on drugs. He explained that the concentration of buying power

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to a few buyers “changes the dynamic”—giving the buyers more power over the drug companies and forcing them to reduce their prices. Similarly, countries with national healthcare systems are also in a good position to negotiate lower prices and discounts with the pharmaceutical industry: “[Governments] will be powerful buyers that try to figure out how to allocate their spending dollars across more diseases,” Burrill said. US Food and Drug Administration (FDA, Rockville, MD, USA) advisory committees already consider the cost of a new drug and whether it is worth the additional benefit when they weigh up its effectiveness against existing drugs. “That’s not baked into the regulations,” Burrill said, “but it seems to be baked into the approval process [...] If you watch you’ll [see] it in the committee meetings all the time.”

However, some of the more sophisticated diagnostics do not come cheaply; Genomic Health charges around US\$3,500 for its Oncotype DX test, but is finding that physicians are increasingly using the product. Oncotype DX was launched in early 2004 and Genomic Health projects that around 24,000 tests will be performed in 2007, with more than 6,000 oncologists—around 80% of those who routinely work with breast cancer patients in the USA—using the test. “We’re really seeing this come into mainstream use,” Scott said.

The value of Oncotype DX lies in its ability to identify those breast cancer patients who would benefit from chemotherapy after surgery. Statistically, only 15% of stage-one breast cancers will recur and, of those patients, chemotherapy will benefit only a minority. However, because oncologists cannot identify which patients should and should not receive treatment, the gold standard is to prescribe chemotherapy for all patients to maximize their chances of survival. As treatment regimens cost between US\$15,000 and US\$30,000 per patient, and carry the risk of serious side effects, Oncotype DX helps physicians rule out patients who will

not benefit from chemotherapy. Insurance companies are therefore willing to pay a higher price for diagnostics because they potentially save on chemotherapy costs, and Scott estimates that about half of the people insured in the USA are eligible to be reimbursed for the test.

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The result of an Oncotype DX test is a score from 0 to 100, with higher scores indicating a higher probability that the cancer will recur. “It’s a continuous curve,” Scott commented. “We think that’s the best and most honest way to present it.” Patients with scores lower than 18 will not typically benefit from chemotherapy whereas “[f]or patients with a score of 31 or higher, there’s a substantial benefit to chemotherapy. It’s urgent that they know that and get treated,” Scott said. Part of Oncogene DX’s success is also due to the fact that extensive clinical trials have assured the reliability of the test. The company’s pre-launch market research revealed that health insurers insist that a decision to pay for a diagnostic test is based on its clinical utility, not its price. Genomic Health therefore knew that it would have to conduct clinical trials to conclusively show the utility of Oncotype DX. “We’re really applying a drug company model to diagnostics,” Scott said. Traditionally, diagnostics companies do not conduct clinical trials but rather rely on the accumulated experience of physicians to slowly build up a demand for their tests.

Other companies are pursuing similar marketing models and are investing in clinical research with the expectation of high returns once tests hit the market. Applied Genomics (Huntsville, AL, USA) launched its MammoStrat™ test this year after validation by three independent cohorts. MammoStrat is an antibody-based test performed on tissue samples to establish the likelihood of recurrence for oestrogen-receptor-expressing breast cancer. The cost is significantly lower than for Oncotype DX—around US\$1,250—in part because the test uses standard equipment. “Immunohistochemistry technology is performed in all pathology labs and reimbursed through established reimbursement codes,

and that makes it readily affordable,” said Doug Ross, Chief Scientific Officer and co-founder of Applied Genomics. Applied Genomics has licensed MammoStrat to the Molecular Profiling Institute—a reference laboratory in Phoenix, AZ, USA—to perform the remote analysis of tissue samples. The company plans to develop a kit that it can market directly to pathologists, although this will require approval by the FDA.

Yet, Ross is not sure whether diagnostics will ultimately command high prices. “Diagnostics are potentially bringing a higher value to therapeutics, therefore they deserve to capture that value. If we can save the healthcare system US\$30,000 per year on cancer patients, then [being paid for that] makes logical sense,” he commented. But, he is not convinced that diagnostic companies will have the leverage to demand high prices on a consistent basis. “Genomic Health has done an admirable job of that [securing a high price for their product], though they had to spend a considerable amount of money to penetrate the market. The rest of us owe them a debt of gratitude,” he said.

There are still various problems that are holding back diagnostics. One is the fact that the development of new drugs and analogous diagnostics often do not go hand-in-hand. Although many pharmaceutical companies have diagnostics divisions, diagnostic projects are usually only picked

up when a drug is in clinical testing. One exception to this is maraviroc (Selzentry™ or Celsentri®; Pfizer, New York, NY, USA), a new antiretroviral drug against HIV. It could become the first oral drug with a new mechanism of action approved in more than a decade, and an FDA advisory committee has already recommended it for approval.

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Maraviroc blocks the CCR₅ co-receptor, which so-called R5-tropic strains of HIV use to gain entry into immune cells. For maraviroc to succeed in clinical trials, Pfizer had to determine which patients were most likely to carry this strain, so they teamed up with Monogram Biosciences (San Francisco, CA, USA)—a company that had already developed a diagnostic test to determine the resistance profiles of HIV strains. At a cost of around US\$1,500 per Trofile (HIV Tropism Assay) test—which is much higher than traditional diagnostics—it had taken Monogram several years to penetrate the market. Alfred Merriweather, Chief Financial Officer of Monogram recalled, “We established the clinical utility

through a combination of scientific presentations and peer-reviewed publications.” The test allowed Pfizer to identify patients with this strain, and to target their trials accordingly.

If maraviroc is approved, Merriweather expects a surge in demand for Monogram’s Trofile tests because the drug will include a notice on its label indicating the need for such an R5-tropic HIV diagnosis. “The product labelling really is an opportunity to accomplish in one fell swoop what might otherwise take several years. It’s a shortcut. It’s an assertion of clinical utility through the FDA’s labelling,” Merriweather said.

In addition to cost, there are other barriers to developing effective and reliable diagnostic tests. Tests such as Oncotype DX do not give simple yes or no answers; instead, the interpretation of their results relies on years of clinical experience, specialist knowledge and patient data. “You generally have to have access to large databases of clinical information to draw inferences between the biomarkers and what’s happening to patients over time,” commented Dave Darling, Chief Executive Officer of Pacific Edge Biotechnology (Dunedin, NZ), which is developing and commercializing technology for cancer detection and management. “You need at least five years of clinical data in most instances.”

Ross agrees: “It is probably the largest barrier to progress,” he said, highlighting

the fact that clinical trial groups, which are a natural source of tissue samples, do not usually have the funding to collect samples and data. One exception to this was the National Surgical Adjuvant Breast and Bowel Foundation in Pittsburgh (PA, USA), which had the foresight to collect tissue samples from its trials and made its data available to Genomic Health. "The cooperative clinical trial groups, which are chronically under-funded for translational research, have the very difficult job of trying to use available samples in constructive ways," Ross noted. "The process of getting access to them is incredibly slow. Genomic Health's competitive advantage in the marketplace is derived in large part from the strength of the data from their published NSABP results."

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Companies that are unable to access clinical samples are usually forced to undertake prospective trials, which can take 5–10 years. Not surprisingly, there are increasing demands to improve access to clinical tissue samples, not only for biotechnology and pharmaceutical companies, but also for academic researchers. "As the power of molecular diagnostics becomes clearer, there likely will be increased sensitivity to maintaining these samples for future studies," Merriweather agreed.

Another problem that has been hindering the development of new diagnostic tests is the fact that many companies have subsisted on razor-thin profit margins. Typically, academic researchers would identify a new marker that diagnostic companies would then license and develop into a new test. It might take years before physicians became aware of the new test and its value. "Traditionally, diagnostics has stalled because companies haven't been rewarded for the cost of development," Ross said. In fact, such expenditures are daunting in the face of traditionally low-profit margins.

The answer would seem to be to demand higher prices to recoup expenses; yet, no one is certain that insurance companies will be willing to spend more money on diagnostics—the success of Genomic Health notwithstanding. In the short term, diagnostics will therefore have to offer significant cost savings—much like Oncotype DX—to convince insurers to reimburse such tests. Although Burrill thinks that, with time, diagnostic companies will be able to charge higher prices, others are not so sure. Ross cites the many competing technologies—such as reverse transcription-PCR, fluorescence *in situ* hybridization, gene ratio studies and immunohistochemistry—which will allow researchers to develop alternative diagnostic tests. "The best diagnostic assays are built to detect robust biology and robust biology has many measurable components," he said. "There are a lot of solutions to the diagnostics problem, which means we have to deal with competition, and competition brings prices down."

Bill Young, Chief Executive Officer of Monogram, is not convinced that drug prices will drop, although he does see a role for diagnostics: "People are much happier to spend \$50,000 on a therapy if they know it has a 70% or 80% chance of success than if it has a 10% or 20% chance. The system will spend more on drugs, but it will be money much better spent," he said. But Burrill stands by his prediction that diagnostics will become more profitable than pharmaceuticals, although he concedes to having been wrong in the past: "I didn't believe the market was ready for a \$3,500 test," Burrill explained, referring to Burrill & Company's refusal to finance Genomic Health several years ago.

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Regardless of the profitability of diagnostics or pharmaceuticals, tailoring treatment to an individual's biology or specific disease pathology could become a profitable market, if only the industry could work out where that profit will come from. Tailored drugs are only useful if tailored diagnostics can identify appropriate patients—but how the cost will be divided between diagnosis and drug remains unclear. In fact, the only certainty is that no one is certain of anything.

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