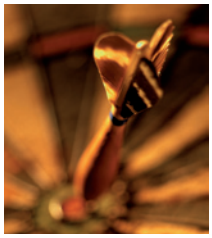

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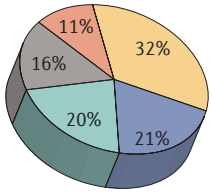

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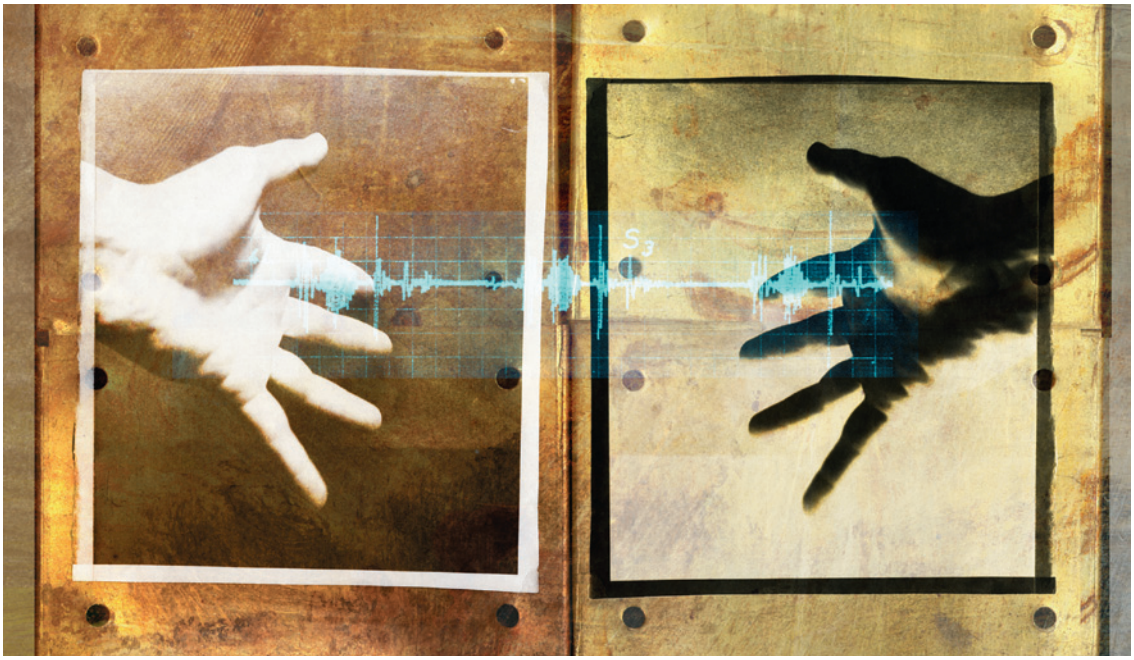

Bridging the drug–diagnostic divide

The delivery of personalized medicine depends on closer collaboration between drug and diagnostics firms.

Alisa Opar

Personalized medicine has been hailed as a transformational force for the pharma industry for over a decade. But a report released in April by consulting firm Diaceutics finds that few firms have developed the requisite commitment to companion diagnostics, including genetic screening, that are critical for delivering tailored therapies.

"The main challenge that these two industries face is that the business models are completely misaligned. To a great extent, they still do not understand what the other does, how the other works or how to effectively work with each other," says Mollie Roth, Chief Operating Officer of Diaceutics, which published the report *Pharma Readiness for Personalized Medicine*.

In part, the differences in view stem from the commercial incentives inherent in the application of personalized medicine data. That is, how can companies best share the value generated between diagnostics firms (who make relatively low-cost, one-use products) and drug makers (who may gain long-term access to a market for a high-cost treatment) (see also *Nature Rev. Drug Discov.* **8**, 279–286; 2009)? Other problems include the fact that drug companies often do not see the need for a companion diagnostic until they are considering submitting a product for marketing approval, says Randy Scott, the Executive Chairman of diagnostics developer Genomic Health. "By that time it's almost too late, because the Phase II trials weren't designed for discovering biomarkers," he says. "You really want to combine the diagnostic and the therapeutic through the research and development (R&D) phases."

"It's not realistic to expect people sitting in drug research and translational medicine to know all this stuff automatically," says Mike Nohaile, Head of the Novartis Molecular Diagnostics unit, which launched in 2008. "It's a whole new world."

In-house or in-licensing?

Pharma and diagnostics companies have tended to work separately. For example, many of the currently commercially available companion diagnostics — such as molecular tests for epidermal growth factor receptor (EFGR) mutations to guide

the use of EGFR kinase inhibitors in lung cancer — were developed independently of the treatments they are used with. But two main strategies for more effective coordination are emerging among those at the forefront of integrating drug discovery and diagnostic development: some are building dedicated in-house diagnostics units, which may include acquiring existing companies, whereas others are forming innovative partnerships with external developers.

Novartis and Roche are among those with internal diagnostics divisions. Both aim to align R&D activities between their pharma and diagnostics branches early on.

"We have diagnostics liaison managers that work in pharma teams — in each disease area — to have a strong and integrated linkage between the pharma and diagnostics divisions," says Thorsten Gutjahr, Head of Diagnostics Biomarkers in Roche's Diagnostics Division, whose projects include companion diagnostic assays for the BRAF inhibitor PLX4032 in melanoma and for the interleukin-13-targeting lebrikizumab in asthma. "They help ensure we have an extremely good understanding of what the questions are, how the science is progressing and what we can do to support pharma with our diagnostic, scientific and technological capabilities. It's key to our success."

The Novartis Molecular Diagnostics unit usually gets heavily involved at the drug candidate selection stage, when the targets have been defined, says Nohaile. Having an internal unit allows Novartis to protect proprietary information and ensures that the diagnostics unit can focus on supporting pharma from the earliest stages of development. "We do have external partners, but we have sufficient [internal] capability to be successful in diagnostics, especially now that we've bought Genoptix." Novartis acquired the haematology and oncology tests company in January for US$470 million.

AstraZeneca, meanwhile, has opted to remain a 'pure' pharma company. Nevertheless, it also begins to think about the need for diagnostics early: "Usually starting at the interface between the preclinical and clinical stages, we assess whether a project is suitable for a personalized health-care approach," says Ruth March, AstraZeneca's personalized health-care leader. To facilitate the co-development of drugs and tests, AstraZeneca forms strategic alliances with independent diagnostics developers. In 2010, for instance, it teamed up with cancer diagnostics company Dako to develop companion diagnostics for multiple oncology drug programmes. The approach "allows us to talk to our partner much earlier than we would have done otherwise, and to share our needs so that they can then show us products coming through their pipeline that might be a good match," says March.

Another benefit of the strategic alliance is that it reduces the effects the discontinuation of a drug programme will have on the diagnostics company. "One project may end, but they can pick up the next project," says March.

Companies keep agreement details confidential, providing little information on who pays for early diagnostic development — which can cost $10 million or more — marketing costs and the division of future royalties. Rosanne Welcher, Dako's Vice President of R&D, says that a risk-sharing model is agreeable. She adds that there has been a "definite improvement" in pharma understanding the risks for diagnostics companies, which have a much lower return on investment for their tests than pharma does for its drugs.

Genomic Health, meanwhile, uses three business models. In its fee-for-service model, pharma pays to use its clinical platforms and then owns and controls everything. At the other end of the spectrum, Genomic Health works independently to develop stand-alone diagnostics that can be used to guide treatment for established drugs, such as oxaliplatin and taxanes. "Then there's the collaborative zone, where maybe a riskier or unproven drug is involved and so we are hesitant to spend a lot of money developing a diagnostic in case the drug fails," says Scott. "There's going to have to be some shared risk-taking there."

In addition to partnering with big pharma, Dako and Genomic Health have seen a big surge in interest from smaller biotechs, who see diagnostics "as an avenue to develop drugs from the early stages at lower cost and higher efficiency," says Scott.

Regulatory evolution

While companies continue to experiment with different business models, regulators are developing their own approaches to companion diagnostics. "It's absolutely critical that if a drug company's therapy depends on a companion diagnostic for it to be safe and effective, then they have to have an approved companion diagnostic," says Elizabeth Mansfield, the US Food and Drug Administration's (FDA's) Director for Personalized Medicine in the Office of In Vitro Diagnostics in the Center for Devices. "That has been a hurdle in some cases, where people just walk in completely unaware that this is a requirement and then are stuck doing post-hoc planning. It's really, really important that they understand this and start at an early stage to plan for it."

> The main challenge that these two industries face is that the business models are completely misaligned.

Mansfield adds that many more drugs with companion diagnostics are on their way into the pipeline. Although personalized medicine so far has focused primarily on oncology — for which the science is rich — pharma and diagnostics companies alike say the next wave will target autoimmune diseases and inflammation, for which the biomarkers are readily available.
A key challenge for these companies is the FDA's lack of regulatory guidance for co-development of drugs and diagnostics. A draft is written, which the agency hopes will be released to the public soon.

One central issue will be whether it is possible to gain regulatory approval of a diagnostic with the same data from clinical trials that are used to support the drug approval, says March. "I don't know whether that's twice the challenge or the challenge squared."

Nohaile adds that it is much more challenging to develop analytically validated tests that will pass regulatory muster than it is to create those that are applied only to facilitate clinical trials. "Take sequencing," he says, "there aren't really any FDA-approved sequencing tests available in the way one normally thinks about them, and so we're still working with the agency to establish ground rules as we move forward. We are focused on what it will take to leverage these technologies to get the content to market — and there is still a lot to work through because it's all new."

It's a difficulty the agency acknowledges. "A challenge for us at the FDA is actually trying to interweave two different sets of regulations that were written at different times. We never really contemplated the idea that the approval of a drug would depend on some kind of companion diagnostic," says Mansfield. "Every situation so far has had its own unique challenges."

But on the upside, she adds that drug companies are increasingly coming to the FDA earlier with questions, recognizing that their therapy depends on having a companion diagnostic to pick the right population or dose. "It's starting to get better," she says.