According to Glaub, Plexxikon sought out a diagnostic partnership when the compound was in phase 1 because only 50% of melanoma patients express the V600E mutation targeted by its small molecule, then called PLX4032. (The mutation also occurs in ~10% of all colorectal cancers and ~8% of solid tumors.)

"We thought that if we could test the drug in a patient-specific way that we could accelerate development," Glaub says. At first, RMS wasn't convinced that Plexxikon had a viable compound. Moreover, the diagnostics company worried that modifying its PCR-based cobas platform to suit Plexxikon's paraffin-imbedded melanoma samples, where much of the DNA is degraded, would be onerous and time consuming. When RMS ultimately did partner with Plexxikon in 2005, Glaub says, it was only because of personal connections with Plexxikon's CEO, Peter Hirth. Development was slow at first, she adds, likely due to RMS's reluctance to invest until clinical signs showing that PLX4032 might be clinically useful first appeared.

In 2006, Plexxikon signed with RMS's parent company, Roche, and Zelboraf and the cobas 4800 BRAF V600 Mutation Test emerged successfully from clinical testing five years later. Still, Hirth and Glaub say the landscape for biotech-diagnostics partnerships remains exceedingly challenging. What they're most critical of is a new FDA draft guidance recommending that therapeutic sponsors incorporate diagnostic development early in drug development plans, to boost chances for simultaneous approval (**Box 1**). This pressure—driven by what FDA claims is a need to ensure diagnostic accuracy in personalized medicine—places biotech companies in a bind, Glaub says. "It's very difficult to get diagnostic companies to invest in a compound that might not turn out to be a drug," she comments. "The alternative is that the companies wait for clinical proof of concept, but then diagnostic development lags behind the drug and you can't get approvals at the same time."

Mark Capone, president of Myriad, says biotech and pharma companies alike worry that companion diagnostics add more risk to drug development and lower returns by shrinking target populations. But echoing a shared view in his industry, Capone counters that the tests boost chances of quick success in clinical trials, by deliberately excluding nonresponders.

Experiences with Xalkori and Zelboraf seem to support that view. Xalkori, in particular, was approved just four years after Pfizer scientists and researchers from Jichi Medical University, in Tochigi-ken, Japan, linked a small subset of NSCLC cases to the *EML4–ALK* translocation in 2006. Soon after, Pfizer partnered with Abbott Molecular Diagnostics of Carlsbad, California for access to its FISH probe test (Vysis' ALK Break Apart FISH Probe Kit), which was already being used for detecting *ALK* mutations. Pfizer used the test to expand an ongoing phase 1 clinical trial with Xalkori to include *ALK* mutation carriers, and by doing so, the drug's objective response rates were dramatically improved.

Whether Pfizer's rapid approval is the norm for targeted drugs developed simultaneously with companion diagnostics is debatable, according to Michael Pellini, president of Foundation Medicine, a diagnostics firm in Cambridge, Massachusetts. The company has forged collaborations with Novartis and Summit, New Jersey–based Celgene, and negotiations are ongoing with a dozen biotech companies, although partnerships have yet to materialize. Foundation Medicine's diagnostic platform relies on deep sequencing of over 300 cancer-related genes with minimal amounts of tissue, an approach with more flexibility than PCR, Pellini claims.

A companion diagnostic may also limit a drug's responder population too tightly. For instance, Zelboraf's approval, based on phase 3 clinical trial results in people carrying the *BRAF* V600E mutation excludes other V600 mutations (V600D, V600M, V600G, V600A, V600R and V600K) more recently linked to melanoma. "That's terrible for patients," Glaub says. "These other mutations could respond to the drug and produce clinical benefits." The test is also prone to false negatives if infiltrating stromal and immune cells bearing wild-type *BRAF* alleles are present in the biopsy.

Until solutions to these challenges are found, it remains unclear how rapid the uptake of companion diagnostics will be by drug developers, particularly smaller companies. Ultimately, though, as McGuire points out, "in the short run, doing diagnostics and drugs at the same time imposes higher costs, but in the long run, it's more cost effective to narrow down your subpopulation." Certainly, constraining a drug market's size by molecular marker shouldn't pose a major economic barrier. "Even drugs that target a few percent of patients with an otherwise common disease like lung cancer can generate hundreds of millions of dollars, and for investors that's a good return," he says. "The biggest risk isn't about the size of the market, it's about whether a drug can cross the finish line."

Charles Schmidt *Portland, Oregon*

IN brief

1,000 pediatric genomes

Complete Genomics will sequence DNA from 500 tumor-normal pairs of childhood cancer cases as part of a National Cancer Institute (NCI) study designed to accelerate pediatric therapies. The Mountain View, California–based company, working for the NCI's contractor SAIC-Frederick of Frederick, Maryland, will provide whole genome sequences to uncover somatic mutations associated with specific tumor types. The initial focus is on acute lymphoblastic leukemia, acute myeloid leukemia, neuroblastoma, osteosarcoma and Wilm's tumor. Complete Genomics will receive $8 million to undertake the work, part of the NCI's TARGET (therapeutically applicable research to generate effective treatments) initiative, funded by the American Reinvestment and Recovery Act of 2009. The biotech will deposit the information in a database as a resource for NCI researchers. "Though the biological relevance of these mutations will be hard to establish, they represent a new unexplored frontier," says Complete Genomics spokeswoman Jennifer Turcotte. Drug discovery efforts have largely avoided the pediatric space because of small sample sizes, varying pharmacokinetics and issues around informed consent. However, a spokesman for Johnson & Johnson Pharmaceutical R&D, of Raritan, New Jersey, points out that translating sequencing information into therapeutics will require "a lot of time and resources". Complete Genomics will also be sequencing 1,000 genomes of healthy elderly people between the ages of 80 and 108 to gather insights into the genetic variants that favor longevity, this time at their own expense. *Karen Carey*

Hedgehog inhibitor single arm

Roche is aiming for accelerated approval of its Hedgehog antagonist vismodegib, a small molecule licensed from Curis, of Lexington, Massachusetts, based on an uncontrolled phase 2 trial. The Basel-based company submitted a new drug application to the US Food and Drug Administration for vismodegib in September undeterred by the agency's refuse-to-file letter issued last year for T-DM1 (trastuzumab-DM1, a conjugate of Herceptin and maytansine) for mid-stage breast cancer. "It really comes down to the question of, 'Is this addressing an unmet medical need?' and that's the crux of it," says analyst Joe Pantginis, of Roth Capital Partners in New York. Whereas for breast cancer several therapeutic options exist, vismodegib is targeted to patients with limited treatment options and no standard of care. "Unmet medical need is a prerequisite for accelerated approval based on single-arm trials," says analyst Jason Kantor, of RBC Capital Markets in San Francisco. Vismodegib shrank tumors or healed lesions in 43% of locally advanced and 30% of metastatic basal cell carcinoma in the pivotal study. The objective response rate was 60% and 46%, respectively, and progression-free survival for both was 9.5 months. If approved, analysts expect a launch next year with sales somewhere north of $150 million. *Karen Carey*