Table 1 Commercially available genomic diagnostic tests using complex algorithms

Company	Test description
Agendia	MammaPrint, a 70-gene signature that provides the ability to identify which early-stage breast cancer patients are at risk of distant recurrence after surgery, independent of estrogen receptor status and any prior treatment.
CardioDx	Corus CAD, a blood test that integrates the expression levels of 23 genes involved in the development of and/or response to atherosclerosis into a single score that can help quickly assess whether or not a patient's symptoms are due to obstructive coronary artery disease.
Genomic Health	Oncotype Dx tests predict the likelihood of chemotherapy benefit as well as recurrence in invasive cancer. The tests also predict the likelihood of recurrence in ductal carcinoma *in situ* (breast cancer); and assess the risk of recurrence in patients with stage II and stage III disease (colon cancer).
Pathwork Diagnostics (Redwood City, California)	Pathwork Tissue of Origin Test measures expression levels of 2,000 genes and compares the pattern to that of 15 tumor types to help diagnose cancer type and guide therapy.
Veracyte	Afirma promises to help physicians reduce the number of avoidable surgeries by preoperatively reclassifying indeterminate nodules as benign, measures the gene expression of 142 genes and applies a multidimensional algorithm to classify whether a nodule with cytopathology indeterminate diagnosis is benign or suspicious.
xDx (Brisbane, California)	AlloMap measures the expression levels of 20 genes from a blood sample to help identify heart transplant recipients with stable allograft function who have a low probability of moderate/severe acute cellular rejection at the time of testing in conjunction with standard clinical assessment.

Source: company websites

That's changing. "If you take most any one of these genomic technologies and stick with it and make it standardized, they are technically going to perform extremely well," Perou says. Instrument companies are becoming more involved in transitioning into test kit development. Life Technologies, for example, a leading provider of genomic instrumentation for the research market in Carlsbad, California, recently acquired the personal genomics firm Navigenics of Foster City, California, in part to be able to use Navigenics's specialty laboratory to develop diagnostic kits, not LDTs or services, according to Life Technologies's CEO Greg Lucier.

Today, picking the right test format may be a matter of understanding your customer and your market—what's going to happen with your sample, says Bonnie Anderson, CEO of thyroid cancer test developer Veracyte, in S. San Francisco, California. Veracyte's gene expression test is used when results from a thyroid fine needle aspirate (FNA) biopsy are indeterminate, which happens up to 30% of the time. "If a sample is collected in an academic center, or patients in a particular cancer area go to a particular academic center to be treated, I would argue you very well could serve your business better by enabling those labs to perform your test," she says. However, most thyroid FNAs are collected by doctors in their offices or in a clinic unassociated with a hospital or an academic center. So they are going to send that sample off somewhere anyway for cytopathology.

Reimbursement is also far from assured for those molecular tests that require a complex algorithm for interpretation. Veracyte's test, Afirma, and Palo Alto, California–based CardioDx's cardiovascular test Corus CAD are the only LDTs to have completed a technology assessment and received a determination that they meet criteria under Medicare's newly established "MolDx" program (**Box 1**). MolDx is run by Medicare regional contractor Palmetto, and was established to determine coverage and reimbursement for laboratories conducting complex molecular tests in Palmetto's jurisdiction, which includes California.

In pushing for the adoption of a test, reimbursement is one challenge, instrumentation is another. Most kit providers, as Nanostring aims to be, generally make their money off the robotics systems, instrumentation and reagents that make up their technology platform, says Peter Kolchinsky, managing director at RA Capital in Boston. And it takes a lot of work, he says, to have critical mass in placement, because when you become the platform, you have to be sufficiently established. The hardware has to be trustworthy and disseminated before people start developing content for it. "If you're not willing to carry the hardware company on your back as a unique content provider," he says, "you may discover that your content is in demand but the hardware provider is only halfway to profitability and halfway is not enough."

Mark Ratner *Cambridge, Massachusetts*

IN brief

First gene therapy approved

uniQure

Jörn Aldag, uniQure CEO

The first person to be administered a commercial gene therapy will be treated in Germany in the middle of 2013. The European Commission granted marketing authorization for Glybera (alipogene tiparvovec) for the treatment of the ultra-rare inherited disorder, lipoprotein lipase (LPL) deficiency, on November 2. The approval marks the beginning of a significant growth path for gene therapy, says Jörn Aldag, CEO of Glybera's developer, uniQure BV (formerly Amsterdam Molecular Therapeutics), based in Amsterdam. "The world has been watching very skeptically, questioning if a gene therapy could be approved at all. We have overcome all the barriers and now the European Medicines Agency (EMA) has validated Glybera and said it can be applied in [a] market environment." One of Europe's leading advocates for rare-disease patients, Alastair Kent, says he is "very pleased with the outcome." However, Kent, who is director of Genetic Alliance UK in London and president of the European Genetic Alliances' Network located in Amsterdam, cautions that it remains to be seen if this really will open up the gene therapy market. "We'll have to watch and wait, but hopefully EMA will be more confident about assessing risks and balances." uniQure is in the thick of negotiations with reimbursement bodies, trying to agree on a price for a one-off treatment that has lasting effects. The aim is to get a price comparable to the €250,000 ($318,000)-a-year cost of enzyme replacement therapies for treating other rare metabolic disorders. While waiting on approval, the company has screened 319 patients, identifying 32 with the relevant mutation of the LPL gene. In all, Aldag estimates there are 400–500 patients in Europe, and he says Glybera will be profitable going forward. Now uniQure intends to engage with the US Food and Drug Administration, with the aim of launching Glybera in the US in 2014. More ambitiously still, over the next nine months the company will begin phase 1/2 trials of gene therapies in four other disorders. *Nuala Moran*