Ready or Not: Personal Tumor Profiling Tests Take Off

By Ken Garber

One vital goal of cancer research is a test that profiles individual tumors at the molecular level in order to guide treatment. Some single-marker predictive tests are now standard, as are two well-validated genomic prognostic tests for breast cancer. But for most tumors, such personalized tests are still viewed as futuristic. At a recent cancer molecular diagnostics conference, many genomic test methods were presented, all of them strictly experimental.

But since 2008, unknown to most oncologists and their patients, three companies have introduced commercial tests that provide genomic profiles of individual patients’ tumors. Along with the profiles, the companies include a list of drugs whose efficacy has been associated, on some level, with the molecular features of each tumor. Marketing materials describe the tests as tools to help oncologists choose appropriate drugs or drug combinations.

These tests have gone largely unnoticed because the companies have relied mainly on limited direct marketing to oncologists and word of mouth for publicity. Only one company has published clinical results in a scientific journal. And because the labs that perform these tests are certified under the federal Clinical Laboratory Improvement Amendments (CLIA), the tests do not require U.S. Food and Drug Administration approval to be sold. Fewer than 13,000 cancer patients have used them.

Unlike the “direct to consumer” genetic tests that assess risk for disease, results for these tests go first to a doctor. But they have not yet proven better at guiding cancer treatment than standard methods. Their effectiveness has not been validated, and no randomized trials have taken place. Claims for their worth hinge on the argument that molecular profiling information should translate to better treatment decisions, but no one knows yet whether that assumption is true. Critics argue that the tests should be used only to direct patients to clinical trials until the tests prove utility in their own randomized clinical trials. Such trials are planned, but these companies aren’t waiting.

Three Tests, Three Approaches

The tests, in order of sales volume, are Caris Target Now from Caris Life Sciences in Irving, Texas; OncInsights from Intervention Insights in Grand Rapids, Mich.; and a profiling service from GeneKey in Boston. All three tests take patient tumor tissue and, from it, generate a genomic profile of the tumor, along with a list of potential drugs. But they vary widely in the methods they use and the information they provide. These methods, which are evolving, range from simply matching overexpressed genes with drugs to systems biology approaches that take into account complex signaling pathways and networks in tumor cells.

By far the most widely used test, with the most accepted methods, is Caris Target Now. It originated in 2003 at the Translational Genomics Research Institute (TGen) in Phoenix, which in 2004 spun off a company, the Molecular Profiling Institute, to further develop and validate the test. In 2008, Caris Diagnostics acquired the Molecular Profiling Institute and later that year launched Target Now commercially. Since then, the company—recently renamed Caris Life Sciences—has sold more than 12,550 Target Now tests.

Target Now uses immunohistochemistry (the staining of tumor sections with antibodies against target proteins) to detect about 20 cancer-related proteins. It employs a standard Illumina oligonucleotide microarray to determine overor underexpression of about 80 other genes. Biomarkers differ by tumor type and subtype. If needed, the test can use fluorescence in situ hybridization, DNA sequencing, and PCR as well. The goal, in all cases, is to detect abnormal gene expression in the tumor. Aberrantly expressed genes are then matched with drugs on the basis of evidence from the scientific literature that response to a given drug is associated (or not) with the abnormalities. For example, high expression of HIF-1 has been associated with benefit from bevacizumab, and low expression of PTEN has been associated with lack of benefit from epidermal growth factor receptor inhibitors. The oncologist receives a report listing these drugs, together with the relevant citations in the literature, weighted according to strength of the evidence. “Think of it more as a literature aggregation profiling platform than an isolated test,” said Caris vice president Alan Wright, M.D., Ph.D.

The report recommends no specific treatment. “We would prefer that that final analysis of candidacies for treatment be undertaken by the oncologist,” he said. The test costs $3,400 and, according to Wright, is fully reimbursable from Medicare and from many private insurers.

OncInsights also uses gene expression to match tumors to drugs, but this test adds analytical methods designed to take advantage of knowledge of signaling pathways in tumors. The test grew from bioinformatics software that cell biologist Craig Webb,
Commercial Tumor Profiling Tests

<table>
<thead>
<tr>
<th>Test (company)</th>
<th>Main analytical method(s)</th>
<th>No. of genes interrogated</th>
<th>Validation/Transparency</th>
<th>Turnaround time</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target Now (Caris Life Sciences)</td>
<td>Biomarker rules</td>
<td>Varies by tumor subtype; -100, by various methods</td>
<td>Pilot feasibility and efficacy study published; methods disclosed</td>
<td>10–14 business days</td>
<td>$3,400</td>
</tr>
<tr>
<td>OncInsights (Intervention Insights)</td>
<td>Biomarker rules, systems biology, connectivity map</td>
<td>Whole genome by expression microarray</td>
<td>Pilot feasibility study published as abstract; methods disclosed</td>
<td>≤10 business days</td>
<td>$3,950</td>
</tr>
<tr>
<td>GeneKey (Formerly CollabRx)</td>
<td>Systems biology</td>
<td>Whole genome by expression microarray, whole-exome sequencing as add-on</td>
<td>No publications; proprietary methods</td>
<td>Varies; generally ≥3 wks</td>
<td>$30,000–35,000 (does not include whole-exome sequencing)</td>
</tr>
</tbody>
</table>

Ph.D., developed at the Van Andel Institute, a cancer research center in Grand Rapids, Mich. Using the software, Webb worked out a system for personalized cancer treatment, and the institute funded a small clinical trial to demonstrate its feasibility. Intervention Insights, a 2009 Van Andel spinoff, licensed the technology and began selling OncInsights in June 2010. The company has sold several dozen tests to date.

OncInsights uses a standard Affymetrix chip to measure RNA expression of about 25,000 genes—essentially whole-genome coverage. The data are analyzed in several ways. Like Target Now, OncInsights incorporates simple biomarker rules—it identifies markers that have been associated with response or resistance to certain drugs in published studies. In other cases, the test links gene expression levels to drugs that target those genes’ products, on the assumption that overexpression indicates drug sensitivity.

OncInsights also uses systems biology approaches. Because gene expression profiling can’t distinguish between “driver” genes, which actively promote tumor growth, and “passengers,” which do not, systems biology incorporates knowledge of signaling pathways and networks. Algorithms assign “scores” to the networks or subnetworks according to their relevance to the growth of a particular tumor, on the basis of data from the patient’s tumor. Algorithms then identify, within the tumor-relevant activated network(s), the most promising drug targets.

OncInsights also applies a “connectivity map” published by investigators at the Broad Institute in Cambridge, Mass., to match the expression pattern of a given patient’s tumor with drugs that may alter expression of those genes, on the basis of cell line experiments. Using such drugs, “the logic is that you could reverse the genotype, hence the phenotype, of the cancer cell,” said Webb.

In its report summary to the treating oncologist, Intervention Insights lists the drugs that appear using all these methodologies, along with a scoring of the evidence and background material. As with Target Now, there is no specific treatment recommendation. The test costs $3,950. Most insurance does not yet cover it.

GeneKey’s service, at $30,000–$35,000 each, is many times more expensive than Target Now and OncInsights. The test profiles the tumor genome through whole-genome mRNA expression profiling and copy number variant detection. Whole-exome DNA sequencing is available as an add-on feature. The test was originally launched in 2008 by CollabRx in Palo Alto, Calif., and called CollabRx ONE, but the company spun off GeneKey earlier this year along with the eponymous test. Between 15 and 20 people have used the service so far, according to company chief scientist Raphael Lehrer, Ph.D. Because of the service’s complexity, “we started out slowly to gain confidence,” said Lehrer. “We’re now ready to scale.”

Using whole-exome sequencing along with gene expression and copy number profiling provides redundancy and thus greater confidence in the data, Lehrer said. Analysis is by proprietary systems biology approaches. “We’re really looking across pathways—not just cancer pathways, but all known biological pathways,” said Lehrer. “Sometimes we find drugs that are not cancer related.”

The test results, as for Target Now and OncInsights, do not include specific drug recommendations. “We call them ‘hypotheses for discussion with the physician,’” said Lehrer. “But we cast a much wider net for potential treatment approaches than either of them does.” This discussion takes place in person with a scientific team dispatched from GeneKey to meet with the doctor and patient.

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Sell Now, Validate Later?
The biggest question about all these tests is whether they work. Do they lead to better outcomes than otherwise would occur? Only one clinical trial, a pilot study, has been published to date. Sponsored by TGen and known as the Bisgrove trial, it monitored 66 patients whose treatments were based on guidance from Target Now. About 27% of the patients, all with recurrent, metastatic disease, had a progression-free survival (PFS) time lasting at least 30% longer than that achieved by their previous treatment. The ratio between PFS on the TGen-guided treatment and PFS on the previous treatment exceeded what would have been expected if the TGen-guided therapy had no effect (in statistical terms, it exceeded the ratio prespecified in the null hypothesis, which was ≥1.5).

“Our conclusion is that the [molecular profiling] approach is promising,” wrote the investigators, whose paper appeared in the Journal of Clinical Oncology in October. But lead author Daniel Von Hoff, M.D., of TGen and colleagues also noted that using patients as their own control subjects can introduce biases that can skew the results; also, a randomized trial would be desirable.

“The study authors are currently trying to obtain support to do such a trial, with added techniques,” wrote Caris spokesperson Holly Clark in an e-mail.

The other two tests have even less validation. Results of the 50-patient pilot study for OncInsights have been published in abstract form only and do not directly address efficacy. “We’ve proven feasibility, it’s logical, everyone’s behind this overall concept,” said Webb. “We now need to do the efficacy trials.” Planning for a randomized efficacy trial is in the early stages. Meanwhile, a nonrandomized feasibility trial in pediatric neuroblastoma will soon begin at 11 sites through the Neuroblastoma and Medulloblastoma Translational Research Consortium. Patients will serve as their own control subjects, as in the Bisgrove trial; the endpoint will compare the individual PFS interval on OncInsights-guided therapy to outcomes from previous treatment rounds. “It’s a start,” said trial principal investigator Giselle Sholler, M.D., of the University of Vermont.

GeneKey has published nothing on its test. In terms of validation studies, “we’re in the early stages of planning and designing controlled trials,” said Lehrer.

Ideally, such trials should occur before any test is used to direct patients to treatments outside clinical trials, said Gordon Mills, M.D., Ph.D., chair of the department of systems biology at the M. D. Anderson Cancer Center in Houston. “If they’re going to direct patients to particular care, it should be part of a clinical trial to determine [whether] this was really working,” he said. “Bisgrove was a start.”

Dan Hayes, M.D., a medical oncologist at the University of Michigan in Ann Arbor, agreed that tumor-profiling tests are best used to direct patients to drug clinical trials. “This is a tricky business,” Hayes wrote in an e-mail. “Since there are only a few molecular changes that actually predict for any of our drugs, [these tests] may lead patients to do things that are not supported by high levels of evidence.”

And the test results are only as good as the technology used. RNA expression, for example, is not a perfect indicator of protein activity. “The correlation between RNA and protein levels are on average between 50% and 60%,” Mills pointed out. “And . . . in many cases protein levels do not track protein function, which is regulated posttranscriptionally and cannot be inferred directly from RNA profiling.” Although two RNA-driven genomic prognostic tests for breast cancer (Oncotype DX and MammaPrint) are well validated, Mills added, DNA sequencing may more reliably predict response to treatment.

Systems biology approaches also are unproven. “Systems biology is critical,” said Mills. “But the evidence to support that a systems biology approach will predict which patients are most likely to respond to therapy . . . remains lacking.”

Defenders of profiling tests argue that molecular information is needed now, outside clinical trials. Profiling “is a tool that’s moving in the right direction,” said Target Now user James Waisman, M.D., a California breast cancer specialist. “We’re compelled by where a patient is: These are people with advanced disease—you’d like to have rational therapy. To wait for phase III trials in all these agents is going to take decades.”

Waisman, who first heard about Target Now from a patient, now sends tumor samples from every patient with metastatic disease to Caris for analysis—more than 100 women to date. “That’s how I got from being an empiricist to being more precise, maybe a ‘precisionist,’ in the way I handle patients,” he said. “You have to be more efficient, you have to be able to avoid undue toxicities of drugs that are not going to be effective, from the data you have.”

Clinical trials are often not an option, he added, because the trials don’t exist, eligibility criteria rule patients out, or geography is a factor. “I live in Los Angeles,” he said. “You can’t get trials for all these patients.” Waisman has even used Target Now to direct first-line treatment—for example, in aggressive triple-negative metastatic carcinoma of the breast. “There is no established clear first-line therapy,” he said. “That’s where you need [the test].”

Even critics admit that the tests can be better than nothing, especially when all validated options are exhausted. Mills considers testing potentially justified when a doctor runs out of standard therapies and must turn to off-label use of approved drugs. “What if I’ve got nothing to do, I’ve got nothing to offer, and there’s an approved drug out there?” said Mills. “Is it wrong to test [the tumor]? I wouldn’t say that. I would say that it should optimally be done within a clinical trial.”

Dr. Wright and Dr. Lehrer are employees of Caris Life Sciences and GeneKey, respectively, and Dr. Lehrer is a principal shareholder in GeneKey. Dr. Webb is a consultant to Intervention Insights and has stock options in the company. Dr. Mills is director of the Kleberg Center for Molecular Markers at M. D. Anderson, which is developing predictive molecular profiling tests. Dr. Hayes is on the scientific advisory board of Halecyon Diagnostics, which is also developing such tests. Dr. Waisman received an honorarium from Caris for giving a talk on Target Now at the 2010 San Antonio Breast Cancer Symposium.