Oncologists Push Beyond New Lung Cancer Genomic Testing Guidelines

By Ken Garber

Personalized treatment for lung cancer is evolving faster than professional organizations can issue treatment guidelines. In October, the American Society of Clinical Oncology (ASCO) endorsed the 2013 molecular testing guidelines issued jointly by the International Association for the Study of Lung Cancer and two pathology organizations. These guidelines set standards to test for epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) gene translocations. Randomized clinical trials underlying these guidelines showed that, in patients with these tumor mutations, targeted drugs yield better response rates and progression-free survival than chemotherapy. These drugs include the EGFR tyrosine kinase inhibitors gefitinib and erlotinib and ALK inhibitors crizotinib and ceritinib.

But practices had already widely adopted such testing. Lung cancer specialist Paul Bunn, M.D., of the University of Colorado, estimated that only 20% of U.S. oncology practices don’t test advanced lung tumors for EGFR and ALK mutations.

“It’s not totally clear how to get to that 20%,” he said. “ASCO can help with adoption by making [the guidelines] well known.”

As those remaining practices gradually adopt tumor genetic testing, academic medical centers and many community oncology practices have already moved on, greatly expanding its scope. Besides EGFR and ALK, research has found more than a dozen other genetic alterations in driver oncogenes in non–small-cell lung cancer. Doctors are already testing for these and prescribing drugs according to the results. They are doing this without guidelines—and mostly without reporting clinical outcomes. Philip Stella, M.D., medical director for the St. Joseph Mercy cancer center in Ann Arbor, Mich., calls this the Wild West.

“The idea is to identify not only expected mutations and expected tumors but [also] unexpected mutations and unexpected tumors that may be amenable to targeted therapy.”

“I’m not necessarily endorsing that everybody should have this testing, but the testing is being done,” said Richard Schilsky, M.D., ASCO’s chief medical officer. In the U.S., only 10%–15% of lung cancers bear EGFR mutations, and another 3%–5% have ALK translocations. Many of the remaining tumors bear rarer activating mutations in more than a dozen other known genes, including ErbB2, BRAF, MEK, MET, and PI3KCA. U.S. Food and Drug Administration (FDA)–approved drugs for other tumor types target these driver oncogenes (crizotinib targets MET). To use these drugs off-label for lung cancer, many oncologists order comprehensive genomic testing to detect the mutations, despite a $4,000–6,000 cost that insurance might not cover.

Stella has ordered such testing for lung cancer patients who have failed multiple lines of chemotherapy but are feeling relatively well and don’t want hospice care.

“It makes sense in this day and age [to] do molecular testing to see if there is something out there that might have a different mechanism of action,” he said.

Both academic centers and for-profit companies offer this testing, based on “next generation” sequencing technology, which sequences DNA fragments in flow cells in a massively parallel manner. Memorial Sloan–Kettering Cancer Center in New York, for example, launched an assay in May 2014 that tests for mutations in 341 cancer-associated genes. As of late November, the center was on track to test 10,000 patient tumors by year’s end.

“The idea is to identify not only expected mutations and expected tumors but [also] unexpected mutations and unexpected tumors that may be amenable to targeted therapy,” said Memorial Sloan–Kettering pathologist Natasha Rekhtman, M.D., Ph.D.

Meanwhile, Foundation Medicine, a for-profit company in Cambridge,
The Eastern Cooperative Oncology Foundation Medicine will test up to The Southwest Oncology Group news in progress: experimental targeted therapies are also more lung cancer patients to panels of lung cancer.

genetic alterations in non–small-cell cal trials. Such trials are under way indi those,” Bunn said. In theory, patients no established approved treatment for mon EGFR mutations, because there’s look for RET fusions or look for uncom cancer, “there’s no guidelines to say that patients who test positive? In lung can continue,” Stella said.

in just a year, and we’re going to see that oncologists. Orders coming from community-based geneticists in 2013 and was on pace for 23,500–25,000 test reports in 2014, with half of orders coming from community-based oncologists.

“That’s phenomenally rapid growth in just a year, and we’re going to see that continue,” Stella said.

How should oncologists advise patients who test positive? In lung cancer, “there’s no guidelines to say that you should look for BRAF mutations or look for RET fusions or look for uncommon EGFR mutations, because there’s no established approved treatment for those,” Bunn said. In theory, patients can enroll in investigational drug clinical trials. Such trials are under way individually for most, but not all, identified genetic alterations in non–small-cell lung cancer.

Several large trials designed to steer more lung cancer patients to panels of experimental targeted therapies are also in progress:

- The Southwest Oncology Group launched the Lung Cancer Master Protocol (Lung-MAP) trial in June 2014 for advanced squamous-cell lung cancer.
- Foundation Medicine will test up to 1,000 patients per year for mutations in 200 genes and match them with one of four targeted agents or anti-PD-L1 immunotherapy.
- The Lung Cancer Mutation Consortium 2 trial has already tested more than 800 lung adenocarcinoma patients for 14 oncogenic drivers and matched them with targeted therapies in an ongoing trial.
- The Eastern Cooperative Oncology Group sponsors the Molecular Analysis for Therapy Choice (NCI-MATCH) trial, which will enroll patients with solid tumors and lymphomas that have progressed on standard therapy. Testing for alterations in 200-300 genes will result, for an estimated one-third to one-half of patients, in treatment with one of 40 investigational targeted agents, matched to tumor genetic profile.

But these trials will capture only a few patients, and other important trials will remain undone. Although many geneticists believe that FDA-approved drugs target are mutated in multiple tumor types, “there just aren’t enough patients in these rare subsets, there’s not enough money to do all these trials, there’s not enough time to do them all,” Schilsky said.

So doctors simply offer patients the drugs.

“There’s nothing right now, of course, to stop a doctor from prescribing one of these drugs off-label, except for the fact that these drugs tend to be very expensive and oftentimes the payer won’t cover them,” Schilsky said.

With a monthly drug cost of at least $8,000, many patients cannot afford to pay out-of-pocket. Yet doctors increasingly prescribe such drugs after tumor genomic testing, and some insurance companies are paying “under the radar,” Stella said. Unfortunately, the clinical data are lost to the field.

“We have no idea what’s happening out there in the country where all these one-offs are being done,” Stella said. “You have no idea if the patient responded or not.”

ASCO has a plan to help patients get off-label treatment with FDA-approved drugs and to capture outcome data from such use. The Target Agent Profiling and Utilization Registry (TAPUR) calls for doctors who order tumor genomic profiling to check results against a molecular treatment protocol and treat patients accordingly, or otherwise to submit a treatment plan to a molecular tumor board. Drug companies will supply the drugs at no cost and insurance companies will cover routine clinical care. In return, the patient and doctor agree to submit the clinical data to a registry that all parties can access. These data could help drug companies decide whether an approved drug is worth formally testing in a different indication. Companies have been receptive to the TAPUR concept, Schilsky said, and ASCO will launch a pilot project in a limited number of sites.

So even without formal guidelines, a system for off-label use of targeted cancer drugs (and data collection) should soon be available to community oncologists. Stella embraces the concept, in part because broad genomic testing, beyond EGFR and ALK, is so available.

“It’s becoming the standard of care,” he said.

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New Mouse Models Mimic Biology of Human Cancer

By Charlie Schmidt

Scientists always try to develop mouse models that better represent human cancer and therapy. With two recent developments, those efforts have turned a corner. In one, investigators have published proof-of-principle findings with a highly outbred mouse that shows diverse responses to benzene, which causes human leukemia. This diversity outbred (DO) mouse represents an advanced model to derive human exposure limits for carcinogens. In the other development, clinical trials are expanding the array of decision-making tools by incorporating patient-derived xenograft (PDX) models that can grow human tumors.

Varied Reactions to Benzene

Developed over years of successive cross-breeding, the DO model addresses a substantial limitation in toxicology: Cohorts of traditional inbred mice—which show little genetic diversity—respond similarly to drug or chemical exposures in a study. By contrast, human populations are genetically diverse, and individual responses vary depending on susceptibility to a particular outcome. This disparity is problematic, assuming that inbred strains misrepresent the typical human response can lead to a standard that over- or underprotects human health.

During the new study, slated for February publication in Environmental Health Perspectives, investigators exposed