The Southwest Oncology Group will test up to 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 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 genes 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...
DO mice to various levels of benzene and looked for evidence of micronuclei in the blood. Micronuclei are chromosomal fragments that fail to incorporate into daughter nuclei during cell division, and their numbers increase in proportion to benzene exposure. Mice exposed at the highest dose—100 ppm in air for 28 days—showed different responses. The frequency of micronuclei ranged from 2.29 for every 1,000 reticulocytes (immature red blood cells) in the most resistant mouse to 92.7 in the most susceptible mouse. The range mirrors that in exposed humans, according to lead author Gary Churchill, Ph.D., a geneticist and professor at Jackson Laboratories in Bar Harbor, Maine. Some workers tolerate benzene at the federal standard of 1 ppm for 8 hours, whereas others at that level show evidence of blood poisoning. When Churchill and colleagues modeled the dose–response curve, the safe exposure limit (e.g., the benchmark concentration) was 10 times lower in DO mice than in more standard inbred strains.

Repeating the experiment 4 months later, the investigators got the same results, suggesting that DO mice generate reproducible findings for use in setting regulatory exposure standards for carcinogens, according to coauthor Kristine Witt, M.S., a toxicologist at the National Institute of Environmental Health Sciences.

Kent Hunter, Ph.D., senior investigator in the National Cancer Institute’s cancer biology and genetics laboratory, says DO mice and a related outbred model with less genetic diversity—the collaborative cross—offer better opportunities to search for cancer genes. Each DO and collaborative-cross mouse is extensively sequenced, he said. Investigators in the benzene study used linkage analysis to map mouse genes on chromosome 10 that boost resistance to the carcinogen, and Hunter uses DO mice to study the genetics of cancer progression. After breeding transgenic males prone to spontaneous mammary tumors with DO females, he looks for genes that confer susceptibility to metastasis in the offspring.

“And most of the susceptibility genes we identify in the F1 mice have analogues in human patients,” he said.

**Engrafting Mice With Human Tumors**

PDX models, meanwhile, better predict how patients respond to cancer treatment. To make these models, scientists engraft cancer cells or tumor tissue from patients into immune-compromised mice. Models that guide personalized treatment decisions for individual patients are known as N-of-1 models, or avatars. They are available commercially from companies, including Champions Oncology in Hackensack, N.J., costing $10,000–$30,000 (not covered by insurance) depending on the number of treatments evaluated. Getting from engraftment to results that could guide therapy takes about 4–5 months, according to Angela Davies, M.D., Champions’ chief medical officer. That long duration is often cited as a limitation, and Davies says the company is working to shorten it.

> “Ultimately, we’ll have enough data to correlate a patient’s tumor genome signature with information captured in the knowledge base. Then we won’t have to wait for a model to establish a treatment plan, and that will be both faster and cheaper than the current approach.”

“But we have to avoid unduly influencing the tumor and compromising the model’s accuracy,” she said.

Carol J. Bult, Ph.D., a geneticist at Jackson Laboratories, says that PDX models are yielding a knowledge base of tumor genetics and drug response data.

> “Ultimately, we’ll have enough data to correlate a patient’s tumor genome signature with information captured in the knowledge base. Then we won’t have to wait for a model to establish a treatment plan, and that will be both faster and cheaper than the current approach.”

Scott Kopetz, M.D., Ph.D., associate professor at the University of Texas M. D. Anderson Cancer Center in Houston, says PDX models are increasingly replacing traditional cell lines used to develop drugs. That’s largely because the models recapitulate the genetic heterogeneity and histology of human tumors. Kopetz cites a 2012 paper by French investigators in Clinical Cancer Research showing that PDX mice engrafted with human colorectal cancer (CRC) closely mimicked what occurs in patients with the illness: The tumors exhibited many of the same genetic mutations, such as KRAS and BRAF, and they responded similarly to standard chemotherapies.

> “This is something we would have never been able to observe with cell lines,” Kopetz said.

Clinical trials at M. D. Anderson are now using PDX models, including a new trial in CRC sponsored by the Southwest Oncology Group. Led by Kopetz, this trial investigates whether BRAF inhibitors improve progression-free survival in CRC patients. According to results presented at Chicago’s 2014 annual meeting of the American Society of Clinical Oncology, tumors regressed similarly in patients and their PDX models after treatment with experimental BRAF-inhibiting drugs during a pilot study.

> “We’re still in the proof-of-principle phase,” Kopetz said. “We’re embedding PDX models into clinical trials now and expect to gain experience with them.”

PDX mice aren’t suitable to study immune therapies for cancer. And the mice have other shortcomings: Whereas CRC and some other human tumors engraft easily, others—especially prostate tumors—don’t. Moreover, mouse stroma—the tumor’s supportive tissue—tends to replace human stroma over time, limiting the usefulness of PDX models to investigate stroma-targeting drugs.

Bult says that humanizing the animals’ immune systems with human cytokines and other immune system components can overcome some of those shortcomings.

> “That’s an exciting trend in PDX research,” she said. “Humanized PDX models will more accurately recapitulate human biology and disease, including any disease process where the mouse orthologue does not functionally replace the human gene.”

But Hunter emphasizes that no matter how sophisticated, mice are still a different species.

> “The new models are extraordinarily useful as long as you know their limitations,” he said. “We have to continually validate results in human patients.”

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