Cancer biomarker use varies widely, needs a ‘broader view’

Kevin B. O’Reilly

June 2014—Despite an explosion of research into cancer biomarkers and professional guidelines that urge testing for certain genetic mutations that help detect disease, anticipate its course, or predict response to treatment, many cancer centers are out of sync with oncology testing recommendations.

Payment policies, regulatory oversight, clinician preferences, and varying access to testing technology are among the factors that contribute to discrepancies in cancer care.

So says Jan A. Nowak, MD, PhD. And he is worth hearing out on the subject, as did an audience of hundreds of pathologists, oncologists, and others at this year’s Cancer Biomarkers Conference in Houston.

“Adoption of biomarker cancer testing is not high among cancer centers,” Dr. Nowak told the crowd. “It seems high to us because . . . we go to the meetings and we talk to each other, and we’re doing this stuff. But then there are the people who are not going to the meetings, not talking about it, and not doing it.”

Dr. Nowak directs the molecular diagnostics laboratory at NorthShore University HealthSystem, based in Evanston, Ill. He is a former president of the Association for Molecular Pathology, is active in biomarkers work within the CAP, and is a “legend in biomarkers and molecular pathology,” says Philip T. Cagle, MD.

Dr. Cagle organized the Houston conference and is medical director of pulmonary pathology in the Department of Pathology and Genomic Medicine at Houston Methodist Hospital. He is also editor in chief of the *Archives of Pathology & Laboratory Medicine*, in which proceedings of the meeting will be published this fall.
The reasons why many cancer centers fail to make use of recommended cancer biomarker testing are “multiple and complex,” Dr. Nowak said.

Dr. Nowak

“Pathologists don’t practice in isolation, and the motivation to implement effective biomarker usage is multidisciplinary. It requires institutional and infrastructural support, especially from IT, to really make this happen,” he said. “It takes education, from all of our major [professional] societies. And this symposium is intended to educate. I think we’re doing a good job in educating, but the question is: Are we reaching the right people? This is not just about education of pathologists, but education of oncologists, hospital administrators, payers, and on and on.”

The sluggish use of cancer biomarker testing represents “a conservative approach to implementing new knowledge,” Dr. Nowak tells CAP TODAY. “Maybe that’s not bad. Maybe it gives these things time to develop to the point where if it’s really useful and necessary, that information will eventually trickle down, and it gives time to separate the wheat from the chaff. When something is new, there is excitement to be doing this, that, and the other thing. It takes time for all of that to shake out. On the other hand, if there is important information to be implemented and used, you’d like to see that used.”

According to the American Hospital Association, about 2,400 U.S. hospitals offer oncology services. Of programs accredited by the American College of Surgeons' Commission on Cancer, only four percent—68—are National Cancer Institute–designated cancer centers.

Another 13 percent, such as NorthShore University HealthSystem, are academic comprehensive cancer programs. Seventy-one percent of centers are accredited as either community cancer programs or comprehensive community cancer programs. Nearly 900 more programs, ones that treat at least 500 cancer patients a year, do not even have COC accreditation.

"There's a spectrum of pathology services," Dr. Nowak said. "Most cancer treatment is not in the top centers."

The literature on how biomarkers are used is sparse, but some surveys illustrate this spectrum and show wide variations in how U.S. cancer centers are implementing these powerful testing methods.

Using the CAP proficiency testing Survey enrollment numbers as a benchmark, a 2013 CAP Survey found that 1,200 of the participating laboratories are doing ER/PR testing for breast cancer, while another 800 perform HER2 immunohistochemistry, and 600 do HER2 FISH or ISH. But for other cancer biomarkers, the totals are much lower, Dr. Nowak noted. More than 200 offer *BRAF, KRAS,* or *EGFR* testing, yet just 105 do microsatellite instability testing.

"MSI has been around for almost 10 years," Dr. Nowak said. "I would think that the 68 NCI-designated cancer centers are counted in here. Now, not every one has to participate in the CAP PT program, but I'd think that they do. So they account for about 70 of these. . . . This makes me a little bit nervous. I understand the limitations of CAP PT Survey participation, but it makes me wonder: Is there trouble in River City?"

Table 1. Reflex testing practices for Lynch syndrome

Type of cancer program	No IHC or MSI	IHC only	MSI only	IHC and MSI	Plan IHC and/or MSI
National Cancer Institute–designated comprehensive cancer centers	12.5%	29.2%	16.7%	25%	16.7%
Community hospital comprehensive cancer programs	40%	24%	0%	12%	24%
Community hospital cancer programs	80%	5%	0%	10%	5.9%

Data derived from: Beamer LC, et al. *J Clin Oncol*. 2012;30(10)1058–1063. Some totals do not equal 100% due to rounding.

Even at the top cancer centers, there is a gap in meeting goals on turnaround time for some biomarker testing, Dr. Nowak noted. Guidelines from the CAP, the AMP, and the International Association for the Study of Lung Cancer say concurrent or sequential non-small cell lung cancer biomarker testing protocols are OK, but they add that results for all biomarkers should be available within five to 10 days.

For non-small cell lung carcinoma, 96 percent of NCI-designated cancer centers surveyed test for *EGFR, ALK,* and *KRAS,* while the other four percent test only for *EGFR* and *ALK* (Schink JC, et al. ASCO Annual Meeting abstract. *J Clin Oncol.* 2013;31[No. 15 suppl]: e22093). But of the centers offering *EGFR* and *ALK* testing for NSCLC, 76 percent conduct the tests in sequence and achieve a mean turnaround time of 22.8 days. Just 11 percent of these centers achieved the 10-day turnaround time. By contrast, the 24 percent that run the *EGFR* and *ALK* biomarker tests concurrently have a mean TAT of 7.6 days, and 92 percent of these programs meet the 10-day TAT goal.

"Among the elite cancer programs, there is uncertainty about how to carry out high-quality, efficient testing, even for established biomarkers," Dr. Nowak said. "The guideline recommendations are not being achieved."

Other wide variations in biomarker practice appear in reflex IHC and MSI testing of colorectal cancer tumors for Lynch syndrome. In 2009, the Evaluation of Genomic Applications in Practice and Prevention Working Group recommended using genetic tests to look for Lynch syndrome in newly diagnosed patients with CRC to reduce

morbidity and mortality from the syndrome among family members.

A survey of 139 cancer centers found that 42 percent of programs use reflex IHC or MSI testing on CRC tumors. But while 71 percent of the NCI-designated comprehensive cancer programs perform the testing, just 36 percent of community comprehensive cancer programs do so (**Table 1**). Bringing up the rear are community cancer programs, only 15 percent of which screen CRC tumors for Lynch syndrome (Beamer LC, et al. *J Clin Oncol.* 2012;30[10]:1058–1063).

"What's remarkable here is the difference you see in the different categories of cancer programs," Dr. Nowak said. Another "big discrepancy" is seen in how cancer centers handle referrals for positive results on Lynch syndrome testing, he added.

Among NCI programs, a majority of patients with positive results—83 percent—are referred to a genetic counselor by the result recipient or a specialist. But 18 percent are referred automatically for counseling through electronic means. By contrast, none of the community cancer programs or comprehensive community cancer programs offered automatic, electronic referrals. At the elite cancer programs, 23.6 percent of positive Lynch syndrome test reports are sent to genetic counselors or other health professionals in addition to the surgeon (**Table 2**). All of the community cancer programs send their results to the surgeon alone.

"It makes a difference where you send this report, and it also makes a difference what they do with this result," Dr. Nowak said. "We need to worry about reporting mechanisms. Do these things get in the EMR? If they come from the reference lab, do they just get filed and faxed? And who do you send them to?"

At NorthShore, a four-hospital system that handles about 50,000 surgical specimens annually and employs 13 general surgical pathologists, cancer test volume has grown more than fivefold since 2009. The laboratory achieves a turnaround time of less than two days for all biomarker test results, which are available for weekly tumor board meetings subsequent to a patient's procedure. FISH is performed weekly.

Table 2. Who automatically gets IHC/MSI reflex test results

Type of cancer program	Surgeon alone, or with other clinician	Genetic health care professional	Nonsurgeon, nongenetic clinician	No one
National Cancer Institute–designated comprehensive cancer centers	70.6%	11.8%	11.8%	5.9%
Community hospital comprehensive cancer programs	100%	0%	0%	0%
Community hospital cancer programs	100%	0%	0%	0%

Data derived from: Beamer LC, et al. *J Clin Oncol.* 2012;30(10)1058–1063. Some totals do not equal 100% due to rounding.

"I keep it simple," Dr. Nowak tells CAP TODAY, explaining his lab's quick turnaround times. "The way I do things, I test for specific mutations in very simple ways that are adequate to address the issue."

Biomarker test results are automatically transferred into the system's EHR and are available for clinicians to look at in patient records. Doing biomarker testing in-house is key to improving cancer care, Dr. Nowak said.

"The disadvantage of using the reference lab is that it takes time. No one can feel good about going to the tumor board conference three or four weeks after the patient's been discussed and bringing the reference lab reports and saying, 'I've got the results here.' I'm sure that's not in the patient's best interest to do it that way," he said.

But bringing a laboratory up to speed on cancer biomarker testing—or moving toward next-generation sequencing—is no small feat given the financial pressures in health care.

During his talk at the Cancer Biomarkers Conference in March, Dr. Nowak noted how the convoluted nature of payment for biomarker testing complicates health care organizations' investment decisions. There is a wide range of payment for various biomarker tests, from $19.24 in the 2014 Medicare professional fee schedule for MSI test interpretation, compared with $65.61 for *ALK* FISH interpretation. Meanwhile, the clinical lab fee schedule pays nearly $400 for the MSI test, compared with $168.30 for the *ALK* FISH.

"Does this cover costs?" Dr. Nowak asked. "Maybe. Maybe not. . . . There's kind of skimpy reimbursements on these things."

There are some interesting payment wrinkles. Medicare pays pathologists $22.10 to identify a block from the archives to be sent out for molecular testing. That is $2.86 more than pathologists get for interpreting *KRAS, EGFR,* MSI, or *BRAF* tests using the G0452 code.

Pricing issues will continue to evolve this year, Dr. Nowak said. With regard to next-generation sequencing, the American Medical Association's CPT editorial panel is expected to issue codes and descriptors for NGS applications in 2015.

On next-gen sequencing, the practice model—if not the business case—is emerging as actionable cancer biomarkers proliferate. Take colorectal cancer as one example.

"The more recent recommendations call for testing not just KRAS in exon two, but in three and four," Dr. Nowak said. "And you need to worry about NRAS, and maybe HRAS, with those same codons. Then you need to worry about BRAFV600E testing and PIK3CA, and there are probably some others you could include. All of a sudden, you have a panel. Handling these things as single assays or as multiplex assays becomes a little bit more difficult."

NorthShore's lab is assembling a next-generation sequencing CRC test panel, Dr. Nowak tells CAP TODAY.

"We could do this with the old technology, but it's burdensome to do that many tests and have it be immediately useful. I could pretty quickly put together an assay for any one of these mutations in three months, and have it validated," he says. "But for nine different mutations, it's a different story. Those are the NGS applications we will find immediate use for here. They're very practical, and it's not debatable that we need to be doing this stuff."

Despite the hazy financial picture for cancer biomarker testing and next-gen sequencing, ultimately health care organizations that aim to offer first-class oncology care must make hard calls about investments in diagnostics to enable timely, effective care.

"If the plan is to do this testing in-house, you need to invest the money for the appropriate laboratory equipment and hire the people to do the testing. It costs money. It doesn't just happen," Dr. Nowak says. "Administrators ask: What's the return on investment? Well, there may not be a return on investment. Hospitals would save lots of money if they fired the operating room and fired the staff, but don't call yourself a hospital. There are costs to being a hospital or being in health care. If you're looking for immediate return on investment, that's a shortsighted view. You have to look at the broader view."
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