Put It on the Board, 11/15

Approvals mark ‘tip of the iceberg’ for PD-L1 testing

What the FDA giveth, the FDA may taketh away.

On Oct. 2, the agency approved the use of Merck’s immunotherapy drug Keytruda (pembrolizumab) to treat patients with metastatic non-small cell lung cancer whose disease has progressed after chemotherapy and whose tumors express the PD-L1 protein. Dako’s IHC 22C3 pharmDx test kit was approved as a companion diagnostic for use with the drug.

Dr. Cagle

Aside from offering patients another, less toxic treatment option, the FDA action seemed to portend a big boost to the surgical pathologist’s role in lung cancer care, says Philip T. Cagle, MD. He is medical director of pulmonary pathology at Houston Methodist Hospital and editor in chief of *Archives of Pathology & Laboratory Medicine.*

“Almost all of the lung cancer patients, one would expect, would be potential candidates for immunotherapy. They may get some other therapy first, but eventually they would be candidates for this,” he says. “The test is immunohistochemistry, and the good news about that is pathologists are already mostly set up to do IHC….And they can bill and get reimbursed for immunohistochemistry, in contrast to a lot of the issues we have with molecular tests. There are many positives for pathologists, surgical pathologists, and cytopathologists to do this test themselves rather than simply collect tissue for the molecular lab. That’s the good news.”

Dr. Bernicker

The sheer volume of cases potentially involving PD-L1 testing could create a "watershed" moment for surgical pathology's role in patient care, says an editorial co-written by Dr. Cagle and Houston Methodist oncologist Eric H. Bernicker, MD (*Arch Pathol Lab Med.* 2015;139[11]: 1329–1330). More than 221,000 new cases of lung cancer were diagnosed in the U.S. in 2015, and more than 158,000 Americans died of the disease (Siegel RL, et al. *CA Cancer J Clin.* 2015;65[1]:5–29).

Yet just a week after making PD-L1 testing a requisite for Merck's immunotherapy drug, the FDA took an action that could undermine some clinicians' imperative to order such testing. On Oct. 9, the agency expanded its approval for Bristol-Myers Squibb's Opdivo (nivolumab), another immune checkpoint therapy, to treat patients with nonsquamous metastatic non-small cell lung cancer whose disease progresses during or after platinum-based chemotherapy.

But in this case, the FDA approved another Dako test—the PD-L1 IHC 28-8 PharmDx assay—as a "complementary diagnostic," rather than a companion. This designation means that while the test could inform treatment decisions, it is not required in order to start a patient on Opdivo, and insurers likely won't make payment for the treatment contingent on the PD-L1 testing.

"If I want to order Keytruda, I've got to have that test, or otherwise my infusion administrator is going to be screaming at me that we won't get reimbursed," Dr. Bernicker says. "Now that it [Opdivo] is approved without the bar of having a companion diagnostic, I can tell you what most medical oncologists are going to do. They're going to order the drug that doesn't need a companion diagnostic because we don't have data that one of these drugs is superior to the other."

Richard Pazdur, MD, director of the FDA's Office of Hematology and Oncology Products, said in a statement that "it appears that higher expression of PD-L1 in a patient's tumor predicts those most likely to benefit" from Opdivo. But Dr. Bernicker predicts that many oncologists will find little reason to order the PD-L1 testing.

"When you're dealing with a patient with metastatic lung cancer and they've already failed front-line therapy, and they're sitting there in the room, even if the doctor knows they have very low PD-L1 expression, it's not like we have other awesome treatments that would challenge it [Opdivo]," he says. "Patients and families and treating oncologists will go straight to Opdivo as a default second line."

For the minority of patients treated in cancer centers such as Houston Methodist, the clinicians' thinking on PD-L1 testing is likely to be different. In that type of cancer center, patients with low expression of the protein who are unlikely to respond well to Opdivo or Keytruda could be offered access to nearby clinical trials.

For laboratories, the challenge in PD-L1 testing goes beyond the immediate Opdivo versus Keytruda question, Dr. Cagle says. These two therapies, and several others recently approved or in clinical trial, have each used a different PD-L1 biomarker assay during testing, and it is possible the FDA may require the specific assay to be used in determining eligibility for each therapy.

"This is the sort of bad news, at least at the moment," he says. "When the FDA approves a companion diagnostic, then in theory everyone is supposed to use that one, and you have to buy that and validate it in-house, which is a real pain. And administrators may not go for it, especially if you have to do this multiple times over for the different drugs."

That kind of burden could impede patients' timely access to this testing as hospital laboratories rely on send-outs, Dr. Cagle says. He hopes the FDA will approve universal, standard criteria for PD-L1 testing, whether it is designated as a companion or complementary diagnostic for a given therapy.

It is clear that oncologists' requests for PD-L1 testing will be on the rise in the coming months and years, Dr. Bernicker adds.

"Pathologists…will be asked more and more to be assessing PD-L1 on tumor and immune cells and scoring immune infiltrates, as we're clearly moving from the experimental arm to the practical clinical aspects now," he says. "They

are going to have to be able to provide some of that information to clinicians in a useful way. It's coming. There's absolutely no question this is the tip of the iceberg." *—Kevin B. O'Reilly*

BioFire's meningitis/encephalitis panel cleared

The FDA has given BioFire Diagnostics a de novo clearance for the FilmArray Meningitis/Encephalitis Panel. This panel is designed to address the need for quick and accurate identification of central nervous system infectious agents by using a comprehensive panel to test cerebrospinal fluid for the 14 most common pathogens responsible for community-acquired meningitis or encephalitis in about an hour. Now, testing CSF for multiple organisms is not always possible because it can be difficult to obtain enough fluid from each patient to run multiple tests.

In June 2015, the installed base of FilmArray systems reached 1,900 instruments and sales more than doubled year over year, said a company statement. The ME Panel is cleared for the FilmArray and FilmArray 2.0 systems and will be commercially available in the U.S. this month, followed by CE-marking shortly after.
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C. diff. molecular testing linked to overtreatment

Relying solely on molecular tests for *Clostridium difficile* diagnosis is likely to result in overdiagnosis and unnecessary treatment, said a study led by pathologists at the University of California, Davis, Medical Center.

"Molecular tests are great at detecting *C. difficile* DNA in the laboratory but probably overdiagnose a lot of patients in hospitals, if doctors assume that everyone with a positive result needs treatment," the study's lead author, Christopher R. Polage, MD, said in a statement. He is associate professor of pathology and infectious diseases at UC Davis Medical Center.

Dr. Polage and colleagues examined clinical outcomes in patients with conflicting results by common tests used to diagnose *C. difficile* infection in the U.S. They evaluated 1,416 hospitalized patients tested for *C. difficile* at UC Davis, tracking the outcomes and severity of infection according to the results of toxin tests versus molecular tests such as PCR. The study concluded that newer molecular tests, which have been adopted by nearly half of U.S. hospitals over the last six years, are unable to distinguish infected patients who need treatment from patients who are colonized with the bacteria and do fine without treatment (*JAMA Intern Med.* 2015;175[11]:1792–1801).

In the study, patients diagnosed with *C. difficile* using a traditional toxin test had more severe disease, a longer duration of symptoms, and greater risk of bad outcomes, validating their need for treatment. In comparison, patients who were positive by the new molecular test but negative by the traditional toxin test had milder symptoms and outcomes that were similar to patients without *C. difficile*, even without treatment.
"This finding caused us to question whether these patients really had a *C. difficile* infection or needed treatment at all," Dr. Polage said.

"The reality is that diarrhea has many causes in hospitalized patients and sometimes patients with *C. difficile* colonization have diarrhea that has nothing to do with *C. difficile*.…So, if you only detect DNA or the presence of the organism, you haven't necessarily proven that the organism is what's causing those symptoms. Yet, doctors routinely assume that all patients with positive molecular test results are infected and treat everyone with antibiotics, even when they might be better off left alone."

Dr. Polage recommends that physicians and laboratories move in a direction of defining *C. difficile* disease based on the detection of toxins and limit molecular tests to screening, similar to what is done in Europe.
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23andMe offers new version of genome service

23andMe has launched a new version of its personal genome service. Following two years of work with the FDA, extensive user comprehension testing, and a complete redesign, 23andMe's offering includes carrier status, wellness, trait, and ancestry reports. The announcement follows an October 2013 FDA order that 23andMe stop marketing the previous version of its direct-to-consumer genomics service.

"We've worked with the FDA for nearly two years to establish a regulatory path for direct-to-consumer genetic testing. We are a better company with a better product as a result of our work with the FDA," 23andMe cofounder and CEO Anne Wojcicki said in a statement.

For $199, customers receive a detailed genetic report that is designed to be easy to understand. The company said that ease of use was validated by user testing.

In addition to more than 60 health, ancestry, wellness, and trait reports, the service includes reports on genetic research and new genetic discoveries, personalized insights based on analysis of 650,000 genetic variations, segment-level data for advanced genetic genealogy research, and the chance to find and connect with DNA relatives in a database of more than 1 million customers.

23andMe's service also offers consenting customers the chance to participate in ongoing research by answering survey questions. In turn, they will receive insights along the way to help them learn more about their genetics, see early findings from 23andMe research, and learn how they compare with others.
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FDA clears Cepheid's trichomoniasis test

Cepheid has received clearance from the FDA to market Xpert TV, a qualitative in vitro diagnostic test for identification of trichomoniasis in symptomatic and asymptomatic female patients, using urine, endocervical swab, or vaginal swabs collected by the patient in a clinical setting. Xpert TV is the 18th test available to run on Cepheid's GeneXpert System in the United States.

"The commercial launch of Xpert TV is particularly timely given the CDC's recently revised recommendation to use highly sensitive and specific NAAT testing for the detection of Trichomonas vaginalis in both symptomatic and asymptomatic patients," Cepheid chief medical and technology officer David Persing, MD, PhD, said in a statement. Xpert TV began shipping in the U.S. this month.