In checklists, new approach for predictive markers

Valerie Neff Newitt

November 2019—In the 2019 edition of the CAP accreditation program checklists, released in September, requirements for predictive marker testing were revised to make them general so they apply to all types of such testing performed by immunohistochemistry and in situ hybridization, wherever possible.

Dr. Nakhleh

The revision will prevent an overload of new requirements as the number of new predictive markers grows, but still ensure the quality of the testing, say those who led the 18-month effort to, in effect, build a new system.

“HER2 was the first widely used predictive marker, so we used that experience as a foundation. And yet every marker has its own unique challenges, so we needed to figure out a system that would fit an ever-increasing list of predictive markers so as to avoid producing new requirements for each new marker,” says Raouf Nakhleh, MD, chair of the CAP Council on Scientific Affairs and professor of pathology, Mayo Clinic Jacksonville.

Until now, once a new predictive marker came into clinical use, “a CAP guideline would grow around it,” says Andrew Bellizzi, MD, chair of the CAP Immunohistochemistry Committee and clinical associate professor, Department of Pathology, University of Iowa Hospitals and Clinics. “Then each new CAP guideline was typically translated into one, two, or as many as five new checklist requirements. And because predictive markers can be done by different methodologies, the predictive marker requirements needed to be placed in several different checklists.”

Just when the Checklists Committee was considering adding checklist requirements about gastric HER2, “six or seven additional predictive markers moved into prime time. It was time for a rethink,” he says.

There were two ways to go, they say. “We could continue to add checklist requirements or we could reorganize around a common framework,” Dr. Bellizzi explains. The former created the risk of unwieldy checklists and difficult inspections. So the CAP chose the latter and assembled a team drawn from its Checklists, Cytogenetics, Surgical Pathology, Immunohistochemistry, Molecular Oncology, Cancer, and Center committees, led by Harris Goodman, MD, Checklists Committee chair. “He did it masterfully,” Dr. Bellizzi says of his leadership.

The team’s work culminated in revised or new requirements for the all common, anatomic pathology, cytogenetics, molecular pathology, and laboratory general checklists. While generalizing the requirements was the aim, some requirements that pertain only to breast cancer markers have been retained.

“Many committee members wanted to keep breast cancer specific requirements in place,” explains Dr. Goodman, of Alameda Health System’s Highland Hospital, Oakland, Calif. “The anatomic pathology checklist has a section on predictive markers that applies only to assays performed on breast cancer. So, at least at this time, it was felt that we would keep some checklist requirements specific to tumor types. But the goal to move toward more general checklist requirements as they apply to predictive markers remains.”

The more substantive revisions pertaining to predictive markers are found in the following checklist requirements:

• COM.01520 PT and Alternative Performance Assessment for IHC and ISH Predictive Marker Interpretation. “This is

new and very important," Dr. Bellizzi says. "In the past we've had Surveys pertaining to many predictive markers that provided a lab with tools to show how well they were doing with some tests. Participation was optional; now participation in something is required. So of all the checklist requirements this one is perhaps the most impactful for laboratories. It requires them to do something new—PT or alternative performance assessment, and evidence of compliance must be maintained."

• ANP.22969/MOL.39295/CYG.47880 Report Elements. "If you do an IHC or ISH predictive marker test," Dr. Goodman says, "your report has to include information on specimen processing, the antibody clone or probe used, and the scoring method used."

It is not a new requirement, "but it has gotten more teeth," Dr. Bellizzi says. "This is an excellent checklist requirement that is being used as a linchpin to capture all of the reporting requirements around a predictive marker. This was already the most general guideline in IHC regarding predictive markers, but now we have trimmed some of the fat and folded various other checklist requirements into this one requirement."

• ANP.22978/MOL.39323/CYG.48399 Predictive Marker Testing—Validation/Verification. "In this requirement, assay validation and verification no longer refer only to HER2, but to all predictive marker test validations and verifications," says Jeffrey Goldsmith, MD, CAP Center Guideline lead, associate professor of pathology at Harvard Medical School, and director of GI pathology, Boston Children's Hospital.

Dr. Bellizzi

"We're taking advantage of something that was already on the books," Dr. Bellizzi adds, "and using it to its best generalized purpose. We took an excellent checklist requirement that specifically referred to validation and verification of HER2. Then, instead of alternatively adding a PD-L1 validation checklist requirement, and a BRAF checklist requirement, et cetera, we used this as a tool to help labs best validate and verify their new predictive markers, and as a tool to help laboratory inspectors inspect labs on the validations and verifications of new predictive markers. Because this requirement had been worked out so proficiently for its original purpose, it seemed smart to call it into action for everything else."

The requirement's note says test verification of FDA-cleared or -approved assays must be performed on a minimum number of 40 cases and that labs should consider using higher numbers of cases when validating laboratory-developed tests. For HER2 and ER/PR predictive marker testing performed on breast cancer specimens using LDTs, 40 positive and 40 negative samples must be used at a minimum.

• MOL.39315/CYG.47885 Annual Result Comparison—Breast Carcinoma. This new requirement, based on ANP.22970, calls for the lab to compare at least annually its patient results for ISH tests performed on breast carcinoma with published benchmarks and evaluate interobserver variability among those performing the technical component.

Dr. Goodman

Laboratories that perform ISH should know their annual rate of ISH positivity in their breast cancer cases, Dr. Bellizzi says. “Is it 10 percent? Is it 90 percent? If it’s some number that’s way off from what would be expected, then it’s a tool for laboratories to suspect that their assay might be performing suboptimally.” This requirement serves two purposes. “It has to do with how the assay is doing globally, and it is also one of the only tools we have to assess how individuals are doing reading the assay,” Dr. Bellizzi says, adding that it also compares the performance of individual pathologists who read the assay. “This is totally new for the cytogenetics and molecular checklists. Labs need to know about it because they need to establish internally a new policy and procedure to satisfy this requirement. And they have to compile their data and be able to spit it out.”

• MOL.39365/CYG.48950 Predictive Marker Testing—Decalcified Specimens. This is a new requirement for the validation and reporting of results from decalcified specimens and is based on ANP.22985. “Basically this says that decalcification needs to be taken into account when validating an assay and in reporting an assay,” Dr. Bellizzi says.

• GEN.40125 Handling of Referred Specimens; ANP.22983 Fixation—HER2 and ER/PgR Breast Cancer Predictive Marker Testing; and MOL.39358/CYG.48932 Fixation—HER2 (ERBB2) Breast Predictive Marker Testing. GEN. 40125 describes the specimen handling responsibilities of laboratories that refer specimens to other laboratories. “A main change, specifically referring to breast tissue here, is that for pathology specimens, the cold ischemia time and total fixation time must be recorded and submitted to the referral laboratory,” Dr. Bellizzi explains. “It is the responsibility of the lab referring out to provide it, and the responsibility of the reference lab to ask for it. These checklist requirements work in tandem to say, ‘You’re both responsible for this important parameter.’”

In general, Dr. Bellizzi says, revisions will provide clarity that may have been lacking previously. “Because of the way checklist requirements were structured before, with many that applied specifically to breast predictive biomarkers but not to others, it almost seemed as if there were two different standards for predictive markers. These revisions make clear that, for certain aspects, all predictive markers should be held to the same standard.”

Until fairly recently, Dr. Nakhleh says, there were so few predictive markers in use that writing new checklist requirements for them was manageable. But the number of emerging markers now demands a more universal approach to checklist requirements, which the 2019 checklist edition provides, he says.

The highest hurdle, Dr. Bellizzi says, was getting all team members to think broadly across the disciplines and understand how the changes might affect the laboratory as a whole. “As pathologists we tend to be in silos, operating in these huge, complex interconnected systems, but doing work that’s fairly specific. For this project we had to work together, think more broadly than any of us were accustomed.”

The new and revised requirements will help laboratories that implement new predictive marker testing, Dr. Goodman says. “They will help them ensure they’re doing testing properly, appropriate validation and verification studies, appropriate proficiency testing, and that the specimens are undergoing appropriate preanalytic handling.”

Dr. Goldsmith agrees, calling the checklists “the 10 commandments of running a laboratory.”

“Revised and improved checklists help those in laboratory medicine understand why predictive markers are different from nonpredictive markers and how to treat them differently. The revisions are instructive and ensure quality. In the end,” he says, “all of it serves patients and improves outcomes.”

And that, Dr. Nakhleh adds, “serves our membership as well.”

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