Letters, 4/14

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HER2 testing guideline update

Karen Titus' article "New guideline takes on tough HER2 cases" (October 2013) nicely captures the deliberations behind the new HER2 testing guideline, issued by the American Society of Clinical Oncology and the CAP last October. But as her article makes clear, the new guideline leaves open a question—and I would like to suggest an answer.

That answer is based on new studies of molecular diagnostics, to which my institution and several others are contributors, and my own experience as a practicing medical oncologist.

The issue the new guideline attempts to address is what to do when standard laboratory HER2 testing with immunohistochemistry or fluorescence in situ hybridization yields inconclusive results. The guideline tries to reduce the number of cases with such results, by improving the way pathologists perform the tests and clarifying the difference between positive and negative tests.

But as the guideline's authors are well aware, this approach has serious limitations. Even when the guideline is perfectly followed, some equivocal results will still occur. So as they suggest, additional testing could be useful in many of these cases.

I feel that enough evidence now exists to demonstrate what that additional testing should be: next-generation genomic tests that provide risk of recurrence testing and molecular subtyping like Mamma-Print and BluePrint. Our research shows molecular subtyping is more accurate than subtyping by IHC/ FISH and can provide better guidance about appropriate therapies. These next-generation genomic tests also definitively stratify breast cancer recurrence risk as high or low, without ambiguous "intermediate" results.

I co-led one of the studies supporting this approach that I presented at SABCS '13, and other studies have come to the same conclusions. I also rely on these genomic tests in my practice, with excellent outcomes to date.

It is only a matter of time before a new iteration of the HER2 testing guideline recognizes the contribution being made by these molecular diagnostic tests, as well as the mounting evidence behind them. In the meantime, this more accurate approach to molecular subtyping is the best way to make sure that HER2 patients who fall between the cracks with IHC/FISH are matched to the targeted therapies that can best help them.

Massimo Cristofanilli, MD
Director, Jefferson Breast Care Center
Kimmel Cancer Center
and Thomas Jefferson University and Hospitals Philadelphia

Members of the steering committee of the ASCO/CAP HER2 Testing Guideline Update Panel reply: We read with interest the letter to the editor by Dr. Cristofanilli in response to the October 2013 CAP TODAY story on the publication of the ASCO/CAP HER2 testing guideline update,[1,2] which echoes his separate opinion piece (*Oncology Times*, January 2014[3]) and interview (*Oncology Nurse Advisor*, March 2014[4]) published recently in other trade publications. While the ASCO/CAP HER2 testing update only addressed the issue of multiparametric tests when it pertained to providing a read-out for HER2, such as in the Oncotype DX test report[5] (Genomic Health, Redwood City, Calif.), a common theme by Dr. Cristofanilli is his unequivocal endorsement of the microarray-based MammaPrint and BluePrint genomic assays (Agendia, Irvine, Calif.) as standard tests for routine practice based on what he describes as the "greater accuracy and utility of molecular subtyping."[3] While he bases his personal

decision to adopt these two tests routinely in his clinical practice ("… with excellent outcomes to date") on research he and others conducted, we caution the CAP TODAY reader against assuming that such public endorsements imply that evidence of clinical utility exists. Therefore, we find that Dr. Cristofanilli's comments are premature and could in some cases negatively impact patient care.

The opinions Dr. Cristofanilli expresses reflect a common failure by many assay supporters to account for basic standards of biomarker development, such as well-established principles to determine analytical validity, clinical validity, and clinical utility set forth by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP)[6] and endorsed by the Institute of Medicine.[7] The EGAPP Working Group defines clinical utility of a genetic test as "… its usefulness and added value to patient management decision making compared with current management without genetic testing." In other words, do decisions guided by the test result lead to an improvement in clinical outcomes? In regards to MammaPrint and Blue-Print, and despite Dr. Cristofanilli's enthusiastic endorsement, based on the prevailing peer-reviewed evidence (or to be more precise the lack of supportive evidence at present), we cannot conclude yet whether or not use of MammaPrint leads to an improvement in outcome.

As described in the clinical test report itself, MammaPrint was cleared by the Food and Drug Administration after a clinical validation study that showed it to "… correlate with high or low outcome risk for distant metastases in women with invasive breast cancer."[8] However, the clinical validation of MammaPrint as a prognostic marker for outcome (i.e. the ability to accurately and reliably predict a clinically defined entity of interest[6]) does not imply clinical utility.

Despite analyses of prognosis from uncontrolled retrospective[9] and prospective observational[10] studies and an attempt to retrospectively evaluate prediction of chemotherapy benefit from pooled study series,[11] data on the clinical utility of MammaPrint await the results of the prospective MINDACT trial (NCT00433589) that has as primary objective to determine whether cancer patients with no more than three lymph nodes involved and with a "low risk" molecular prognosis and "high risk" clinical prognosis can safely be spared chemotherapy.

As for the BluePrint, the test report indicates that this "… molecular subtyping profile was designed to distinguish the Basal-type, Luminal-type and ERBB2-type (HER2/neu positive) intrinsic subgroups of tumors."[12] An informal PubMed literature search using the terms "blueprint" and "breast" identifies about seven publications on this assay, though none of them addresses issues of clinical validity or clinical utility.

As an anecdotal example, one of us recently reviewed the case of a 50-year-old woman with a 0.8-cm node-negative, low-grade, strong ER-positive/HER2-negative breast cancer, whose surgeon unbeknownst to the oncologist had submitted a sample of the lumpectomy specimen for microarray testing. The test result indicated a "high risk" tumor by MammaPrint that was "Basal-type" by BluePrint, and both results were discordant with the other pathology measures routinely available. Absent high-quality clinical utility data at this time to show that this patient had a high-risk cancer as suggested by the microarray test result and that her outcome (disease-free or overall survival) would have improved with adjuvant chemotherapy (and its potential toxicities), the oncologist appropriately maintained their initial recommendation and the patient began adjuvant endocrine therapy without chemotherapy.

Companies are under enormous commercial pressure to market their assays even before evidence of clinical utility becomes available. Breast surgeons have been the target of intense marketing to order some diagnostic tests before evidence is mature. Regarding MammaPrint, most medical oncologists are aware of current practice guidelines and await the results of the MINDACT trial before deciding if this genomic assay should be incorporated into routine practice. Breast cancer patients deserve to receive care that is coordinated among all their doctors, including the pathologist. Tests should be ordered if they will guide clinical decision-making. Therefore, decisions to adopt new tests that could influence treatment decisions should be guided by evidence, not just beliefs, and preferably discussed among members of the multidisciplinary team.

Antonio C. Wolff, MD, The Johns Hopkins Kimmel Comprehensive Cancer Center, Baltimore, Md.

M. Elizabeth H. Hammond, MD University of Utah School of Medicine and Intermountain Healthcare, Salt Lake City,

Utah

David G. Hicks, MD University of Rochester Medical Center, Rochester, NY

Mitch Dowsett, PhD Royal Marsden Hospital London, United Kingdom

Daniel F. Hayes, MD University of Michigan Comprehensive Cancer Care Center, Ann Arbor, Mich.

Lisa M. McShane, PhD National Cancer Institute, Bethesda, Md.

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Ordering prognostic studies

In regard to the question whether the diagnosing pathologist may order prognostic studies (Q&A, March 2014), I respectfully disagree with the hospital compliance officer and with Jane Pine Wood. These markers are not only prognostic but also critical components of the diagnosis. The CAP's cancer protocols and the required synoptic reporting list prognostic studies as part of the report. It has become part of the diagnosis to include prognostic parameters in these cases. Moreover, often the best time to do these studies is at the time of initial diagnosis. In addition, an initial treating physician may not think to order these studies, but if the patient is referred to another physician, that physician might need them to best treat the patient. It seems to me that some rules and regulations stand in the way of doing what is in the best interest of the patient, and I believe this is a case of that.

Arthur H. Mensch, MD, Pathologist, West River, Md.

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CAP TODAY online

In the past, I was not too impressed with my monthly e-mail about the newest CAP TODAY issue. I would click a link and it took me to the whole magazine. I'm not sure when you changed the way that e-mail works—I've probably been avoiding clicking the links because of my previous experience. However, I clicked the links in my notification e-mail today, and was I impressed! I absolutely loved being able to click the article title, and the link taking me directly to my point of interest. Congratulations on a job well done.

Brenda L. M. Franks, MT(ASCP) POCT Coordinator Methodist Hospital Pathology Omaha, Neb.
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Send letters to Editor, CAP TODAY, 325 Waukegan Road, Northfield, IL 60093. Fax: 847-832-8873; srice@cap.org.