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Expert Insights on HER2 Scoring Criteria for Breast Cancer

Announcer:
You're listening to *Project Oncology* on ReachMD. This episode is sponsored Daiichi-Sankyo. Here's your host, Dr. Jacob Sands.

Dr. Sands:
This is *Project Oncology*, and I'm Dr. Jacob Sands. Joining me to talk about the updated guidelines for HER2 mutated breast cancer are Dr. Kathleen Fenn and Dr. Oudai Hassan. Dr. Fenn is an Instructor in Clinical Medicine at Yale School of Medicine. She's also a medical oncologist with a focus on breast and gynecological cancers at Yale Smilow Cancer Center. Dr. Fenn, welcome to the program.

Dr. Fenn:
Thank you.

Dr. Sands:
We're also joined by Dr. Oudai Hassan who's a Senior Staff Pathologist at Henry Ford Health System in Michigan. Dr. Hassan, thank you for joining us.

Dr. Hassan:
Thank you.

Dr. Sands:
Let's begin with a look at the 2018 ASCO/CAP guidelines. Dr. Fenn, what do the latest guidelines tell us about HER2 testing?

Dr. Fenn:
So the 2018 ASCO/CAP guidelines propose several changes and modifications to prior HER2 testing algorithms. So firstly, they redefined the criteria for classifying 2+ immunohistochemical staining. Secondly, they clarified that if HER2 testing on initial biopsy of a primary tumor was negative that it is not mandated to retest this on a surgical excision specimen, whereas before the guidelines did mandate this second testing.

Thirdly and importantly, they addressed several less common clinical scenarios when using ISH testing. So those scenarios are as follows. First, they addressed when the HER2/CEP17 ratio is $\geq$2 and HER2 copy number is <4. Secondly, they addressed when this ratio is <2 and the copy number is $\geq$6. And finally, they addressed when this ratio is <2 and the copy number is between 4 and 6. Previously, the first two scenarios would have been classified as HER2-positive. Now all the scenarios require additional workup including, correlation with immunohistochemical staining and possible re-adjudication of ISH testing. Finally, the panel recommended that dual-probe FISH panels be used instead of single-probe.

Dr. Sands:
And if we focus on one of the key updates, Dr. Hassan, how do the guidelines redefine IHC 2+, or immunohistochemistry equivocal?

Dr. Hassan:
Yeah, so the 2018 guidelines redefined IHC 2+ as weak to moderate immune complete membranous, immunostaining in more than 10% of tumor cells. Previously, in the 2013 guidelines, we used to call this category as +2, but we used also to call weak to moderate immunostaining of incomplete membranous staining in more than 10% of tumor cells as 2+ also. Now we limited the 2+ on IHC to complete membranous staining in more than 10% of tumor cells. And this decreases the number of cases that we would reflect to in situ hybridization. There are also some rare instances where we would call it equivocal still when we have strong complete membranous staining and less than 10% of tumor cells and in some histologic patterns such as micropapillary carcinoma of the breast, we don't

require complete membranous staining. We require only lateral or basolateral, weak to moderate to severe membranous staining to call it equivocal 2+.

Dr. Sands:
Now, if we take a look at the other side of the spectrum, Dr. Hassan, what do the guidelines tell us about the HER2-negative subgroups? So really focusing specifically on HER2-low, HER2-0, HER2-negative. Is there any benefit to monitoring these patient populations?

Dr. Hassan:
So the HER2-negative subgroups include what we call HER2-0 with a score of 0 by immunohistochemistry, HER2 is a score 1 by immunohistochemistry and HER2 is a score too by immunohistochemistry, which went to in situ hybridization and was negative for amplification by in situ hybridization. But so far, we don't have any recommendations from the CAP, but maybe in the next guidelines we will have recommendation on how to monitor these patients.

Dr. Sands:
As we know, the guidelines also explore the use of more rigorous interpretation criteria. With that in mind, Dr. Fenn, what can you tell us about this criteria for IHC and FISH assays, and how might it impact our diagnostic approach?

Dr. Fenn:
So we know that determining accurate HER2 status is really essential to identify patients who will benefit from HER2-targeted therapies, and this certainly is applicable in both the early stage and metastatic settings. In terms of the three less common scenarios with equivocal ISH results that I mentioned previously, these new guidelines really provide a clear pathway for further workup, which includes both reassessment of immunohistochemical assays as well as potentially reassessment of ISH assays if indicated. After performing that workup, the ASCO guidelines really provide clear parameters for determining status as either HER2-positive or HER2-negative. Tumor biologies is on a spectrum and sometimes it's hard to tell where to draw the line. But that being said as a practicing clinician, these guidelines are very helpful for me to feel confident in making treatment recommendations for my patients and really providing guidance to definitively classify patients as either HER2-positive or HER2-negative.

Dr. Sands:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Jacob Sands, and I'm speaking with Dr. Kathleen Fenn and Dr. Oudai Hassan about HER2 scoring criteria for breast cancer.

Now that we've taken a look at these updated guidelines, let's turn our attention to the multidisciplinary care team. Dr. Fenn, from your vantage point as a medical oncologist, what are some of the key factors involved when it comes to taking a multidisciplinary approach to score interpretation for HER2 mutated breast cancer?

Dr. Fenn:
So in many cases, HER2 status by IHC and FISH will be very straightforward and not require a substantial amount of discussion. But in cases where there is any uncertainty or equivocal results, this multidisciplinary conversation between oncologists and pathologists I think is so important. For example, there are some cases where there's a substantial amount of heterogeneity in the tumor. It's really crucial to look at pathology, alongside our pathologists, to understand whether testing is being done on the most enriched samples and really collaborate to understand the biology of the tumor.

Conversely, we can as medical oncologists add flavor in terms of information about the clinical presentation and ensure that the HER2 status and the clinical presentation is concordant, looking at features that are consistent with HER2 amplified disease such as higher grade, higher Ki-67, down-regulated ER/PR expression, for example. In cases where the clinical picture is discordant with a HER2 status, that might drive decisions to retest on a biopsy or surgical specimen or do some more testing to really clarify HER2 status. These conversations in a multidisciplinary way between the specialties really help clinical decision-making and for us to feel confident in making the best recommendations for our patients.

Dr. Sands:
And turning to you, Dr. Hassan, obviously the pathologist plays a really central role in the interpretation of HER2, so can you speak a bit to the pathologist's role in interpreting these scores?

Dr. Hassan:
We start with immunohistochemistry of course on every first time there are nodules of breast cancer, usually we encounter this when we get breast biopsies. The patient goes on screening mammography or ultrasonography, the radiologist sees something suspicious, they biopsy it and send it to us. So when we see cancer at this level, we order what we call prognostic biomarkers, including estrogen, progesterone, Ki-67, and HER2, and this is where we order HER2. Sometimes we would order HER2 also on resection, excision

specimen and certain scenarios, also. So when we get the HER2 slides, we do as a standard at our lab and with every HER2 immunostain slides, we get two controls, what we call controls; this is for our quality assurance. One piece of tissue that we know is negative for HER2 that should not stain and one piece of tissue that we know that is positive for HER2 that should stain and we should look at these controls. Every pathologist who is signing out HER2 looks at these two controls before he looks at the HER2 and the cancer specimen itself to make sure that the staining is working. After we are sure that our immunostaining is working, we would look at our biopsy or the resection specimen, whatever we stain and score the HER2 into score. So we look at the entire tumor. We look at the overall staining of HER2, whatever percentage of tumor cells that stains, what is intensity, what's the pattern of staining. And also, we look at if there is any heterogeneities because some tumors might show heterogeneity. So we might have one clone inside the tumor that's positive for HER2 and the rest of the tumor is negative. This will tell us that there might be some tumor cells in this patient that might respond to treatment, and this is something we might report to our medical oncologists. After we do this immunohistochemistry review, we usually report our HER2 as either negative 0, negative +1, or positive +3, or equivocal.

Dr. Sands:
Now with all that being said, Dr. Fenn, of course we would take all of this from the pathologist and then we utilize it in a clinical way, so you're determining treatment options based upon this. So then speaking to that multidisciplinary team and those efforts, what are some of the ways we can improve communication and collaboration within that multidisciplinary team to better interpret HER2 scores?

Dr. Fenn:
That's so, so true and on an individual patient decision-making level, I think the multidisciplinary tumor board is really one of the best venues to facilitate that conversation, looking visually at the slides together and then talking about the case. It's a great learning opportunity for us in medical oncology, and often from these detailed, more nuanced conversations, we are able to better refine our treatment decisions and sometimes this leads us down further pathways in terms of more testing and workup that can really inform our treatment decisions.

Dr. Sands:
Now before we close, Dr. Hassan, do you have any final thoughts on the updated guidelines, HER2 scoring criteria, or collaborative care that you'd like to share with our audience?

Dr. Hassan:
Yeah, sure. So I think the updated guideline made our reporting of HER2 way more efficient and made a lot of great improvement. The most important and most critical improvement is that with the previous guidelines of 2017 and the one before of 2007, even after we resort to in situ hybridization, we could end up with a category where we would still call it HER2 equivocal. And with these patients we used to leave the medical oncologist with the dilemma on making a treatment decision because they don't have an answer from us. Is this patient a candidate for HER2-targeted therapy or not? And they would have to resort to other clinical information and their own clinical judgement to make a call. With the current guidelines, the equivocal category on in situ hybridization is eliminated. So when we report HER2 at the end of the day, we would report it either as positive or negative after the in situ hybridization. And by that, we would give our medical oncology colleague a clear answer, if this patient is a target for HER2-targeted therapy or is not a candidate for HER2-targeted therapy. And I think this is the most important improvement that happened with the new guidelines.

Dr. Sands:
Well, with those thoughts in mind, I want to thank my guests, Dr. Kathleen Fenn and Dr. Oudai Hassan for sharing their perspectives on HER2 scoring criteria for breast cancer. Dr. Fenn, Dr. Hassan, absolutely wonderful having you on the program.

Dr. Hassan:
Thank you.

Dr. Fenn:
Thank you.

Announcer:
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