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Revolutionizing Diagnostic Precision: AI-Driven Approaches in Digital Pathology and HER2 Expression

Chapter 1

Dr. Bui:
Hi. Welcome to this educational program on AI-driven approaches in digital pathology and HER2 expression.

This is CME on ReachMD, and I'm Dr. Marilyn Bui.

Dr. Salomon:
Hi everyone. I'm Dr. Anne Vincent-Salomon.

Dr. Bui:
Today, we will start our program with an overview of the current role of digital pathology in AI and machine learning in oncology diagnostics.

As we all know, a patient's medical journey begins with their diagnosis. As pathologists, we provide a forecast of their diagnosis, prognosis, and the therapy selection, so pathologists impact the life of every single patient. We are the most essential doctors that patients rarely meet or rarely know of. We are doctors in a multidisciplinary care team. With all those qualities, it makes us become the inherent leaders in precision medicine, because we're close to the patient's sample and the important data generated from the patient's tissue.

It is now a very exciting time to practice in pathology because we're experiencing the third revolution of pathology; that's digital pathology, artificial intelligence. Our profession was born with microscope and HE slides that give us that opportunity to study disease at a cellular level.

Currently, we're experiencing a shortage of pathologists. In addition, people are living longer, and there will be more cancer cases coming out. We anticipate in 2030 there will be 26 million new cancer cases worldwide. But pathologists are the first-line diagnostic physicians. All patients' cancer journey start with accurate and timely diagnosis.

So how will these 26 million patients get accurate diagnosis and allowed appropriate treatment? Pathologists are pivotal in solving diagnostic challenges. With digital pathology, we are connected. So instead of moving slides around between hospitals, we can move digital slides through the hospital care system, and the information can be shared easily.

So digital pathology is the foundation of AI. So this slide shows human cognitive capacity has limitations. Pathologists are used to manual reading, eyeballing things. However, when the data are so complex as proteomics or genomics, this is really beyond the eyeballing ability of the pathologist, so we need the help from computational pathology to analyze this data.

Traditional pathology is analog, subject to interpretational variation. It barely scratched the surface of the significant amount of data. Computational pathology, machine learning, is reproducible and robust in data analysis.

So this technology is to assist humans, enhance our ability doing our job rather than replacing it. So when I'm referring to AI, we're talking about augmented AI. pathologists are really empowered. We're using computational pathology to help us generate impact for data to help our clinicians.

In precision pathology, what are the AI algorithms there? So I would say there are 5 big categories. First is detection. Even as early as in 2016, the National Artificial Intelligence Research Development Strategic Plan already thought breast cancer diagnosis is a good area to apply this technology, because the top AI algorithms can have an error rate in 7.5%. We're talking about finding metastatic breast cancer in the sentinel lymph node. Then when you ask the highly trained breast pathologist to do that, the error rate is 3.5%. At that time, the AI wasn't highly sophisticated. However, when you combine those 2, AI-augmented pathologist, the error rate is reduced to 0.5.

So this is a newer data to show this is the new nature of cancer, and this is also clinical implementation of AI-assisted detection of breast cancer metastatic to the lymph node. So this is a single-center, non-randomized clinical trial. What they found is their primary endpoint, there is a significant reduced relative risk of IHC rate use. Secondary endpoint shows significant time reduction and up to 30% improved sensitivity for AI-assisted pathologists. So this trial really demonstrated the safety and potential saving in cost of AI assistant. So this is a great example for detection.

So we're going to talk about the second classification. So these 2 publications are from my group. The top one is we developed AI to diagnose bladder cancer reliably. The second is to use AI to diagnose or classify sarcoma. The third category is quantification. On the left is immunofluorescent. You can see cytokeratin, you can see PD-L1, and you can see immunohistochemical markers, like a CD3, CD8.

Dr. Salomon, on the left is an immunofluorescent multiplex biomarker testing for clinical trial. So my question is, what kind of cancer are we detecting?

This cancer has cytokeratin positivity. It's TTF1 positive, but it's not shown here. And we were studying PD-L1, CD3, CD8. What cancer is this?

Dr. Salomon:
Huh. Is it lung cancer? Or –

Dr. Bui:
Yes. It's non-small cell lung adenocarcinoma. So in this case, we have so many biomarkers tested at the same time, as you can see. We can't eyeball this, so we've got to use computer and AI algorithms and do quantitative image analysis.

On the right-hand side, and what diagnosis is that?

Dr. Salomon:
Yes, a melanoma.

Dr. Bui:
Yeah, it has S100, PD-L1, and also those immunomarkers. So that's one example to show AI can help with the quantification.

So this study showing on the right is manual reading compared among pathologists. There are 12 pathologists. You see there's a lot of variability. On the left is a comparison versus pathologist. So there's a greater consent using AI across 4 clones of antibodies used for companion diagnostics and across 5 frequently used scanners.

Another example, further showing that AI can identify more patients that are PD-L1 positive even at the lower cutoff point, subsequently identify those patients for immunotherapy. So if you're looking at the line here, the orange one is patients classified as positive greater than 5% by both AI and the manual reading. And the orange ones are the negative ones, so the negative one has the worst prognosis. So whenever it's identified by AI or AI plus manual, it has better prognosis.

So this is an interesting line. It's green, the patient classified as PD-L1 positive greater than percent by manual only. Because the human's quantification of 5%, 10%, it's not very reliable, so you see this very sharp demarcation. You can't evaluate the patients as reliable, as continuously, as AI. So this is very interesting study.

So let's talk about the fourth class. That is prognosis. So this is one of our studies to use radiology, pathology, and the AI information to predict on radiology which ductal carcinoma of the breast may be aggressive to become invasive carcinoma in subsequent sessions. Our next step is to study histology, to look at the HE on DCIS to find the AI biomarkers to predict the aggressive variant and then the more/less aggressive variant.

The last category is for prediction. So this is a very nice example from ArteraAI. They have this prostate biomarker test predicting therapeutic benefits from patients using a large volume and a variety of clinical data, digital pathology images, the AI-enabled prediction of the outcome that commercial technology does not allow. See in this patient, when the AI marker is negative, the patient will not benefit from the hormonal therapy. In this case, the biomarker is positive; the patient will respond to the hormonal therapy. So this is the higher level of AI algorithms.

So this is a summary of what's the role of digital pathology and the AI in precision oncology and the 5 categories of algorithms.

Dr. Salomon, what's your thoughts about these?

Dr. Salomon:
Definitely, the pathologists are augmented pathologists thanks to AI. And truly, our patients deserve that we are the best as we can and provide to them the best information as we can. So I think that we are experiencing, really, a revolution by using these AI tools.

Dr. Bui:
I agree.

Chapter 2

Dr. Bui:
So now we're going to do the next chapter. We're going to change gear. And because we have this global view now, we're going to stay from the forest and focus in on a specific tree. So that is breast cancer-targeted therapy.

Dr. Salomon:
These progresses with antibody-drug conjugates challenged the pathologist to better define the HER2 status of the breast cancers, and that's where you're going to explain how AI tools can help us.

Dr. Bui:
DESTINY-Breast04 is really a ground-shaking landmark study to demonstrate patients with HER2-low metastatic breast cancer have superior response to these antibody-drug conjugates to HER2 and compared to conventional therapy. Most recently, in 2025, there is a further expanded approval for metastatic hormone-positive HER2-low or HER2-ultralow patients; they can be benefiting from this therapy. So these approvals have really broadened the use of T-DXd, offering new treatment options for patients across a spectrum of HER2 expression of breast cancer

So currently, the histology workflow for HER2 testing is pretty much a one-way street. We start with specimen acquisition, and then the specimen will be processed in histology, and then the case will be distributed as HE slides and go to the pathologist. We'll make the diagnosis of breast cancer, and then we realize, oh, the invasive breast cancer needs a HER2 testing or send it back to histology lab for HER2 testing or for other genomic testing. Then it comes back to us review and sign off. So this is just a one-way street. Then you can see when you have a single road to travel, if there's a traffic accident somewhere, and then the whole thing become a bottleneck.

So we talk about the pathologist's role is important. So our effort is not to become a bottleneck but become enabler to our patient care.

So as pathologists, we follow the ASCO, American Society of Clinical Oncology, and the CAP, College of American Pathologists, HER2 testing guideline. These guidelines had a couple of updates. So before, we were only doing dichotomy type of interpretation. We identify HER2-positive or HER2-negative patients. Now we've got to identify HER2-positive, HER2-low, HER2-ultralow, and HER2-null patients. HER2 positive are IHC 3+ positive or ICH2+, ISH positive. HER2-low are IHC 1+ or IHC 2+, ISH negative. HER2-ultralow are HER2 IHC incomplete faint staining equal or less than 10%. And HER2-null is completely no staining. And the HER2 positive is in 15% of the patients, HER2-low 45%-55%, HER2-ultralow or HER2-null is 30% to 40%.

So this is what we're following, ASCO/CAP HER2 testing guideline. And now we need to educate all our pathologists to be able to recognize all levels of HER2 expression.

So now let's talk about, manually, how do we review HER2 cases? So here we have a HE slide. Dr. Salomon, this is a 60-year-old woman. This is from her left breast. And you have an HE slide of this core biopsy. What is the diagnosis?

Dr. Salomon:
Probably invasive carcinoma of no special type, I would say, as a first look.

Dr. Bui:
Yeah. Invasive ductal carcinoma. And then all those newly diagnosed breast cancer by the ASCO/CAP guideline are supposed to be tested for HER2. So this is the negative control. So what's your interpretation of this control sample?

Dr. Salomon:

It's correct because no staining. So no –

Dr. Bui:
Yeah, there's no staining at all. And we have over here, this is a patient sample. This is a negative control slide, and the patient is also negative, right?

Dr. Salomon:
Perfect.

Dr. Bui:
So we have another slide. This is the positive control. Did a positive control work?

Dr. Salomon:
Beautifully. A 3+ staining, membranous. Intense.

Dr. Bui:
And how about this, the core biopsy?

Dr. Salomon:
Well, it looks like it's positive too. So it seems to be the same intensity as the control, the positive control, so staining is membranous on the invasive cells. It's complete and in more than 10% of the tumor cells. I would say it's a 3+.

Dr. Bui:
I agree. It's a first complete membrane staining, intense, strong, diffuse, greater than 10%. This is almost all cells are stained. So this is 3+. So we have no problem with this one.

So let's look at another case. So what is your diagnosis?

Dr. Salomon:
Again, it seems to be an invasive carcinoma. Truly of no special type too, so invasive ductal carcinoma.

Dr. Bui:
So this is the IHC. You see the control worked. Now we're going to go with high power.

Dr. Salomon:
Okay, the staining is lower and probably no complete membranous staining so far clearly seen. So maybe we could be in the category of a 1+.

Dr. Bui:
I agree with you. So when we have stains like that, do you normally consult another pathologist?

Dr. Salomon:
Yes.

Dr. Bui:
Yes. It's always good to share with other colleagues.

So you see, this is how we do this manually. And there are a couple of things. This is already a digital slide. So with a digital slide, even I do the manual screen, I'm able to cover the entire area. But if it's a microscope, that's a lot of hand moving to move the stage to be able to see the entire spectrum. So we're actually showing you the manual screen of a digital slide. But in a lot of pathology practice, people are going to be doing the manual screen using the microscope.

Now we're going to move to the next area, is to show how can we use AI to augment pathologists' ability to make a HER2 interpretation. So this is an example using PathAI, HER2 breast workflow. It is optimized through pathologists and also the labs. At the beginning it was for research, but now it is implemented in clinical practice. So the workflow will be, first, digitalize the slides. When there is specimen received, the HER2-stained slides are prepared, scanned, uploaded for this image analysis and AI. This algorithm is right on the slide and generates predictive HER2 scores and the visual overlaying for the slide. When pathologists receive the slides, they will review the HE slides to make diagnosis first. And then when they determine HER2 is needed, and they're going to look at the HER2 algorithm and confirm the quality of the options, the areas that the machine scored, review the slide with the algorithm score and the overlays in preferred order, agree or disagree with the predicted algorithm, and then finalize assessment.

So this is the workflow. So that means when the pathologists read the cancer case, the biomarker predictive value is already available for them to be able to review, agree and disagree, and sign off case. So that's time saving there.

So now I'm going to use an example to show AI-assisted HER2 scoring assessment.

Video Narrator:
Demo of the Mindspeak Breast HER2 AI module. Let's review the first case. As shown in the results panel on the right, the AI has primarily identified tumor cells with complete, intense staining, suggesting a HER2 score of 3+. The pathologists can review these results at the single-cell level to confirm the analysis. In this instance, the AI has identified a more heterogeneous staining pattern. To visually confirm the results, classes are filtered to highlight the approximately 9% that show complete weak to moderate staining and the 2% that exhibit complete intense staining, indicating an overall HER2 score of 2+. By using the filter, areas of interest can be quickly identified to aid in completing the diagnosis.

In the third case, the AI has detected a substantial amount of incomplete membrane staining, which indicates a score of 1+. By using filters, areas of clinical relevance can be quickly identified, facilitating an efficient diagnosis.

When AI detects less than 10% incomplete membrane staining resulting in a score of 0, a whole-slide analysis can help focus attention on small areas of positivity. This approach allows pathologists to identify small positive lesions in situations where ultralow positivity levels could be clinically significant.

In cases where there is 0% staining observed, conducting a comprehensive full-slide, single-cell-level analysis of all tumor cells can accurately confirm the slide as truly negative. This approach ensures that any potential focal areas of positive staining are reliably excluded.

Dr. Bui:
So this is such a great example to show the power of AI-assisted HER2 score.

And this is a research showing how HER2 breast AI algorithm is highly concordant to pathologist’s interpretation of HER2, pointing to the potential utility of algorithm as a standardization for pathologists.

So this performance assessed 770 HER2 IHC slides across 52 board-certified pathologists. So here we have HER2 0, 1+, 2+, and 3+. So the dark blue is AI versus pathologist. The purple is pathologist versus pathologist. As you can see, the performance concordant rate is like 95% so that's pretty decent.

And furthermore, there are other studies showing the role of AI in accurately interpreting HER2 IHC score 0 and then 1+ in breast cancer. As we know, for 3+, there is a higher concordance, but for 2+, 1+, and 0, there is a lower concordance. And in this case, it’s showing AI can help us to improve the accuracy of distinguishing HER2 IHC 0 and the 1+ consistently.

Chapter 3

Dr. Bui:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Marilyn Bui, and here with me today is Dr. Anne Vincent-Salomon. We're discussing the role of digital pathology in AI or machine learning in oncologic pathology.

Within this session we have discussed how digital pathology and the AI are the third revolution in pathology and play a critical role in precision pathology.

AI assists identification, quantification, classification, prognosis, and prediction. The role of HER2 in breast cancer is evolving, and the HER2-targeted antibody-drug conjugates offer the opportunity to treat patients with HER2-low and the HER2- ultralow breast cancer.

It is challenging to score HER2-low and HER2-ultralow accurately and reproducibly manually, but the AI-assisted tools are promising to standardize HER2 scoring and augment pathologists.

So this is showing, this is just my 2 cents, that AI will not replace pathologists, but rather, it will empower us, because AI can do a lot of work very efficiently. However, we are playing a vital role in integration of AI into healthcare and will guide the AI development and ensure the algorithms are high quality. The collaboration between pathologists and AI enhance the diagnostic proficiency; the human element is essential for patient care.

What's your thoughts on this, Dr. Salomon?

Dr. Salomon:
I absolutely do agree. And with the example of HER2 evaluation, before the availability of antibody-drug conjugates, it was quite straightforward to analyze 3+ cases or 0 cases, and negative cases. The 2+ were quite challenging, but we were quite used to assess

them. And now to really interpret 1+ appropriately or ultralow HER2 cases, we have to spend some time, and we are probably less reproducible. And if AI tools can do it for us more efficiently and more accurately, it will save us time to deal with more challenging diagnostic cases. So really, I share your views. The pathologist will forever validate the reports, but they are augmented, and they can save time using AI tools. So I fully agree with your 2 cents.

Dr. Bui:
Thank you.

All right, so that's the end of the presentation. I'd like to introduce you to this wonderful educational resource, and it's HER2Know.com. So this is an educational resource made by pathologists for pathologists, and some of the whole-slide images with the HER2 staining were from this website.

Thank you, Dr. Salomon. It's wonderful working with you. Bye.

Dr. Salomon:
Thank you, Dr. Bui. It was a very interesting session. Thank you to all.