# Artificial Intelligence in Precision Medicine

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**Lisa Tomcko:**

Welcome to the latest edition of the College of American Pathologists CAPcast. I'm Lisa Tomcko, content specialist with the CAP. This episode is a joint effort between the CAP’s personalized Health Care Committee and its Digital and Computational Pathology Committee. Artificial intelligence is an exciting technology impacting and advancing the practice of pathology when applied to the area of precision medicine, especially to treat oncologic disease even more frontiers open to provide better patient care.

To learn about some of these developments and future direction and precision medicine. We listened in on a conversation between two CAP member pathologies. Dr. Marilyn Bui, scientific director of the Analytical Microscopy Core Laboratory at Moffitt Cancer Center and Research Institute in Tampa, Florida. And Dr. Eric Walk, the Chief Medical Officer at Path AI in Boston.

Dr. Bui and Dr. Walk, so happy to have you both on. Would you like to introduce yourselves?

**Dr. Marilyn Bui:**

Thank you, Lisa. And thank you, Eric. And this is a really exciting topic. I am a practicing pathologist at Moffitt Cancer Center. I am a senior member. I have been here for 18 years. And as far as the CAP, I've been a member for more than 20 years. So in addition to that, I volunteer for a lot of CAP committees currently and chairing the Digital and the Computational Pathology Committee.

I also serve as Vice-Speaker of the House of Delegates. When we do surveys, ask member what type of topics are they interested? Digital pathology and AI is always one of their top topics they'd love to learn. So today I'm very excited to provide this learning resource for our members and learning from experts like Dr. Eric Walk. Eric.

**Dr. Eric Walk:**

Thank you, Marilyn. And thank you, Lisa, for hosting this podcast. It's great to be here. So my name is Eric Walk. I'm a board-certified pathologist and as Lisa mentioned, the Chief Medical Officer of Path AI, which in full disclosure is a company working in the digital pathology and AI Pathology field. But today, I'll be speaking as a member of the CAP and someone with an avid interest in the fields of precision medicine and AI pathology.

Very briefly, my career as a pathologist has been nontraditional, but today I did practice pathology for a couple of years, but I spent the last 20 years in the drug and diagnostics industry with companies like Novartis and Roche Tissue Diagnostics.

I currently sit on two CAP committees, those being the Precise Health Care Committee. And it's really my pleasure to work with Marilyn on the Digital and Computational Biology Committee as well.

**Dr. Marilyn Bui:**

Thanks, Eric, for all your contribution to pathology as a profession and also College of American Pathologists. So when we started just talking about this topic, we are focusing on this blog on the CAP PHC Committee's Precision Medicine webpage and you and one of your colleagues published that, and it's all framing around AI. So I want to learn about AI a little bit more. And first, I'd like to ask how our AI pathology methods being applied to precision medicine, clinical trials.

**Dr. Eric Walk:**

Well, thanks, Marilyn, and thanks for mentioning that Precision Medicine web page article. It is a pleasure to write that and add that to the web page content. So just in case people are not familiar with that article, let me briefly summarize what we mean by pathology tools overall.

So what we're talking about here are tools that use advanced machine learning and computer vision algorithms. And these algorithms typically input a histopathology slide and they output predictions, information or other pieces of quantitative data that are relevant to diagnosis, predictive drug response, patient outcomes or other clinical parameters. And in my opinion, these tools are best used as inputs for the pathologists to assist them in providing the best information to clinicians and patients.

AI pathology is not about replacing pathologists, it's about enabling pathologists with tools to help them automate, especially some of the tedious tasks like cell counting, and allow them to focus on the bigger picture of patient care. And that really gets to your question, Marilyn, on how is AI pathology being used in precision medicine?

As people know, precision medicine has really become the standard in many diseases, including oncology, over the past 20 years. And the idea is to not treat patients all the same, but really to treat the right patients with the right drugs using the right diagnostics. And so with that AI pathology is being used in precision medicine in all aspects, but in particular in clinical trials to ensure that the right patients are studied and that their correct conclusions about the efficacy of the therapeutic intervention like the drugs are being made.

One specific example I would like to touch on where a pathology is being used in precision medicine trials is patient enrollment. Most people know, precision medicine, clinical trials typically include biomarkers or biomarker enrichment or stratification as a critical part of their design. So, for example, in biomarker or enriched designs, patients are enrolled based on the presence or absence of a biomarker.

So it could be that the trial is only enrolling biomarker positive patients versus biomarker negative patients, or it could be the reverse. Conversely, in a stratified trial design, both biomarker positive and negative patients are enrolled, and then the data analysis is conducted separately for both groups and look for differences in drug response.

However, my point is in both of these scenarios, I think it's obvious that we want the biomarker assessment, which is a key part of the precision medicine paradigm, to be as accurate and reproducible as possible. So the right patients are studied and the drug efficacy results are as close to the biologic truth as possible. And this is where AI pathology methods can be very useful because the data tells us that both reproducibility and accuracy can be improved with AI powered pathology, thereby reducing noise in the analysis phase of the trial and really maximizing the probability that we're seeing the true biologic signal.

And I've seen many examples where clinical trial biomarker data is reanalyzed with AI pathology, and the result is a demonstration of pretty dramatic improvements in the drug with that magnitude sometimes revealing a endpoint that passes the criteria where originally the endpoint had been failed using traditional techniques this approach of applying AI pathology to precision medicine trials is relevant both to cancer trials oncology, but also non-oncology trials in oncology. We're all familiar with common biomarkers like PD-L1, which can be analyzed with greater precision and accuracy with AI pathology. But even outside of oncology, these approaches can be used.

One example there is Nash nonalcoholic steatohepatitis where histology-based measurements based on the H and E. So for example, the naphthalty score or trichrome for the fibrosis score are commonly used to enroll patients in clinical trials and these can benefit from AI pathology analysis.

**Dr. Marilyn Bui:**

Yeah. So from what you said, we learned that pathology and the pathologists are the foundation of precision medicine, and now we have the tool using AI to augment our ability in evaluating biomarkers and the application not only in cancer, precision medicine and also non-cancer. And you give some of the examples.

So I feel like it's a really exciting time to be practicing pathology right now because we're experiencing this third revolution of pathology, like digital pathology and AI. Digital pathology transferred the analog pathology into digital format and that gave rise give birth to AI. That's machine learning, computational pathology. So our pathology is going through a long way from H E to AI to C to molecular pathology.

Now pathology, and AI by combining everything together to augment pathologists ability. So that's great. So my next question is the companion diagnostic now is very important for precision medicine and the pathologists are the people reading these companion diagnostics. Very often they are in that immunohistochemistry form. So these states are not just like any other things by pathologists giving interpretation, the patient will be put on certain clinical trials. So this responsibility for pathologists is a huge. So my question to you, Eric, is how will development of companion diagnostics be affected by pathology?

**Dr. Eric Walk:**

Thanks, Marilyn. I think it's such a great question with a lot of opportunity here. And as you rightly said, it is amazing to retrospectively look at what's happened over the past decade or two where 20 years ago companion diagnostic as a concept was brand new.

And today it's just part of the way we practice medicine, identifying the right patients who respond optimally to specific drugs. And I completely agree with you that pathologists are right in the middle of that whole process. So the role of the pathologists, in my opinion, has become more clinical where they are essentially providing information that's directly tied to the prescription of these drugs. It is a lot of responsibility and of course, all pathologists want to do the best they can with everything with all diagnostic care, but especially with these companion diagnostics. So to answer your question, I think AI has the potential to dramatically change the way certain companion diagnostics are developed and exist in the clinical diagnostics space.

So as I mentioned in my intro, I have a background in IHC CDX development, so really will focus my comments on this particular space of companion diagnostics that are tissue based and using immunohistochemistry technology, which as you know, are many. So currently these IHC based CDX assays are developed with an assumption, and that assumption is that a human pathologists with a pair of eyes will be interpreting that.

And because of this, during the development process, certain decisions must be made during assay development to ensure that the final assay product can be accurately and easily interpreted by the end user pathologist. So let me give an example, no assay developer would launch a companion diagnostic assay that had an unusual cutoff.

So let's just use those example 13% cellular positivity rate. No one would launch an assay like that because we all know that no human pathologist would be able to reproduce this,even if it turned out to be the most predictive and valuable cutoff. So that's the opportunity for AI pathology to improve our ability to develop the best, most predictive companion diagnostics.

And so it's really about creating some new options for codex development due to the increased resolution and also the precision associated with this technology.

I invite everyone to imagine a future where we're no longer bound to ordinal scoring systems like the typical zero one plus two plus three plus scoring system. And also we don't have to be bound with convenient cutoffs like 1%, 50% that we're all used to.

In contrast, AI pathology is natively continuous with close to 100% precision. So the companion diagnostics of the future can really be tuned to outcome data and whatever that scoring system or cutoff is that best predicts drug response or patient outcome. That's what will develop using these tools. So I think it's it really could be game changing. And these are concepts that are actively being explored as we speak.

**Dr. Marilyn Bui:**

Yeah, this is a very important concept because when we got that immunohistochemistry those Brown stains really groundbreaking because we can study the functionality of the proteins at a cellular level that gives birth to the beginning of the precision medicine. The early ones are for breast cancer, the ER PR, the HER2, and then later all the CKID for GIST. But now we realize our human appreciation of that, that the quality of the data is not really quantitative.

So the manual interpretation is always a semi quantitative. So we feel like probably the interpretation of IHC will eventually moving from eyeballing, reading it, interpreting it, then measuring it. Something like AI can give you this continuous value and the highest position and higher reproducibility, especially with the biomarkers at a lower level. For example, in breast cancer, has this a HER2 low new classification and this type of call for action really asking pathology community to develop a tools like what you described, AI to help us solving the problem.

So along the same lines, how will the clinical implementation of companion diagnostic tests be affected by pathology and other work? Is there a future where companion diagnostics must be interpreted with AI assistance, or will manual interpretation always be an option?

**Dr. Eric Walk:**

Yeah. So another really important question, and I'm sure a question that's on the minds of a lot of practicing pathologists and unfortunately I don't have the absolute answer, but it is a critical question. But we don't yet have, in my opinion, enough comparable clinical trial data where we can look at endpoints that have been measured via manual pathology means versus AI. assisted pathology means we have some data, in my opinion, and we need to conduct clinical trials in which the relevant precision medicine biomarkers are interpreted manually and in an AI assisted matter to see prospectively, and especially looking at the discrepancies between these two methods, how do they differentially correlate with patient outcomes.

So we have some intriguing retrospective data, including on PD-L1, that suggests that the sensitivity for detecting response goes up. But we really need to prove this out in a prospective way, it would be remiss of me to not mention that this topic clearly has regulatory implications, as regulators currently associate human pathologists interpretation with the gold standard method.

And so it really creates some interesting questions and some dilemmas about how we might bridge to a future state where human pathologists with AI assistance is a new gold or platinum standard. How we get there is unclear, but it could involve the inclusion or of orthogonal methods and or some degree of outcome data as the ultimate adjudication between manual versus air assisted reading.

And I also wanted to add that there are some advanced AI methods being explored. So, for example, end to end multiple instance learning graph neural networks that are able to reveal spatial patterns at the cellular and histological architecture levels in H and Es and IHC slides that are not accessible by human eyes, but do correlate with drug response or patient outcome.

So this is clearly uncharted territory, especially from a regulatory and validation perspective. So definitely in the area of the field that deserves more attention in analysis in the future. But I think it's safe to say that there will be changes to how CDXs exist in the real world with AI. And so I think there's a lot of potential here, but also a lot of things that we still need to figure out.

**Dr. Marilyn Bui:**

Yes, this is such great insights. It just shows pathology and pathologists that will continue to evolve to provide the quality patient care. Just look at my career in the past 20 some years. I after the medical school, I also finished a PhD in molecular pathology and then immunology without knowing that this tool really helped me to going through the second and third revolution of pathology.

So when I started and of a cancer center 18 years ago, they need a pathologist, a scientist, and I have experience in quality that image analysis to be the scientific director of analytic in my class before. So I took that responsibility and also learned and did not realize that help me to undergo this digital pathology that I transformation.

So we talk about a lot on the precision medicine heading diagnostics. So for the people who are either beginning of the journey of digital pathology, how can I benefit the pathology and the histology, laboratory workflows and beyond just the digitalization. The host like you mentioned.

**Dr. Eric Walk:**

I think this also fits into the precision medicine framework in a broader sense. You know, talking about how A.I can exist in the real world and in the context of the challenges that labs are facing today. And many of those challenges are workflow related, resource related.

And so in my opinion, air pathology has a huge opportunity to improve these workflows. And so we're all familiar with the standard workflow in the anatomic pathology laboratory that really hasn't changed in the past 50 plus years. So starting with specimen acquisition and going to grossing and case distribution and diagnosis, of course. What I envision is a future where downstream of the digitization itself. So just scanning the slide itself, of course unlocks some applications like tele pathology and consoles.

But then when you go to the next step of applying these tools that we've been talking about, in my opinion, it unlocks even more pieces of value that can be directly relevant for lab workflow. So let me go through a few examples and I should say that most of the examples I'm going to cite are more visionary and aspirational, but there are some real-life examples of some of this being done. So it's it really is here and now, and it gives us an exciting runway for the future. Just imagine that we in a lab and we have air pathology as a default. So it is literally looking at every slide being scanned, you know, what can we do? So there are several things we can do. One is, is just purely tactical. So of course there are histology errors, there are digitization out of focus errors. So AI can automatically, from a QC perspective, detect those issues and automatically order re cuts or re scans so the pathologist doesn't have to do it themselves.

But there are other ways that I can pre look at the slides in advance of the pathologist and really frontload a lot of the decision making. One example is IHC reflex so right now and I'll use breast cancer as an example, a pathologist would look at a breast cancer case, decide that it's malignant then order HER2. What if the AI did that the night before, scanned all the breast biopsies, automatically identified the cancers, and then ordered in a reflex way of HER2 and then actually interpreted the HER2 and ordered it only on the two pluses.

You know, that's the sort of concept that we're talking about similarly with NGS, there's a whole class of algorithms being worked on that I'll call molecular prediction where we can not replace NGS, but we can based on H and E, predict the presence of a genomic alteration. We can do this in a high negative predictive value way, eliminate patients who don't need to be subjected to sequencing and only funnel those high probability cases to the time and the cost of sequencing. Another thing that we can do with AI powered pathologies, intelligent case distribution. So especially in large health networks, cases can be sorted based on specialty or even when a sub diagnoses. So when derm, you know, a practical, you may want pigmented lesions to go to one set of pathologies versus inflammatory lesions to go somewhere else, then we've already been talking about biomarker quantification.

So this is the idea of algorithm pre reading of PDL-1 or HER2 in advance and providing those results to the pathologists. So their job is really to review the output from the AI and approve it or reject it. And that's a really important point that all of these workflows, them talking about, lead to the pathologist. They don't replace the pathologist.

So the pathologist really is a pilot in front of this cockpit of tools that they then control and approve and along the way, making them more efficient, more reproducible, more accurate. And most importantly, delivering the most critical information, the most valuable information to clinicians and to the patients.

**Dr. Marilyn Bui:**

Wonderful most of the pathologist taking digital pathology journey, they all aware of the remote sign out rapid onset of the evaluation consultation.

Well, but as we said, any quality pathologist work are rely on the quality workflow, the quality slice and the quality., AI depend on the quality slides and the workflow and everything. So what you described is really going to transform the traditional pathology practice. So we modernize our workflow. So this is just sounds very promising. And as pathologists establish digital and AI pathology solutions in their laboratories because most people, when they start digital pathology, they have AI in mind so almost digital pathologists the means to be able to get to AI to help to augment their practice.

What technical and logical questions should they are asking to best evaluate the different options. I am very passionate about this topic and feel very strongly that all pathologists need to be at least fundamentally fluent in machine learning and AI methods. So it's very similar to all pathologists.

**Dr. Eric Walk:**

I'm sure those listening to this podcast are familiar with the different assay techniques so they know the difference and the pros and the cons of IHC versus ISH versus PCR. The same should be true about machine learning methods and I know it's new and I know it can be a lot of gobbledygook, but there is sort of a high just a very high level of knowledge that I think is sufficient.

You don't need to be a machine learning expert here. This is just about being familiar with the basic techniques, and I can summarize just a few them here. We don't have time to go through them all, but a lot of the methods that you read about are based on something called a convolutional neural network. And I'm not going to get into all the different facets and layers, but essentially this is a method that is highly supervised, meaning you're telling the algorithm what's important.

So let's just say PDL-1 positivity. So you're telling the algorithm that this is a PDL-1 positive cell. So look for that. And so over time, in many applications, this sort of machine learning tool learns based on what you tell it is the difference between a PDL-1 positive tumor cell and a PDL-1 negative tumor cell or a PDL-1 positive immune cell versus a PDL-1 positive tumor cell. So it's very hypothesis driven. In contrast, you have what's called end to end models. An example of that is multiple instance learning.

These are weakly supervised methods and these are rather than hypothesis driven, they're hypothesis seeking. So in this example, you really don't know what you're looking for in terms of a cellular or architectural feature. What you're looking for is a correlation with an endpoint.

And let's just say that drug response, or it could be presence of molecular alteration. So let's just say endtrack fusion. So you give the algorithm two sets of cases, one endtracked fused examples and, endtrack wild type examples. And you ask the algorithm, Is there a pattern of cells or histology architecture that separates these two? And if there is one, it will determine it.

So it's very powerful. The downside is that these algorithms tend to be more black box in nature because the pattern that it sees may not be explainable to a human. You know, we aspire to have as much explainability as possible. But that's one downside of this model. And then in the middle you have something called graph neural networks, where you're creating a graph, a set of polygons that connects cells or tissue elements.

And again, you're making some assumptions that these cells or areas are important, but you're also you're also there is definitely a hypothesis seeking aspect to that as well. So that really falls in the middle. But in general, I think there are some key questions that pathologists should ask about an AI algorithm that they're considering bringing in to their practice.

And I'll just list some here. So you want to know how is the AI model trained, which are those machine learning methods that I just described were a different one were used, how many annotations were in the training set? How many cases? What is the validation data? How was that generated to demonstrate the performance characteristics of this algorithm compared to some ground truth?

And then what was that ground truth? Was it one pathologist? Was the consensus of ten pathologists? Different studies can use different designs. What scanner types has the algorithm been validated on? Many people don't know that these algorithms often are scanner specific. So even though to humanize the images coming off the scanner may look similar or close enough, it really does make a difference in these algorithms.

So that's an important question. What sample types were used during the training? And validation was only trained on biopsies. It was also trained on whole section resections.

As I spoke about earlier, how generalizable is the algorithm? Was the algorithm trained sufficiently to be robust across a diverse set of samples and not biased to any one particular factor that's not related to the biologic signal, like pre analytical factors.

How explainable is the algorithm? Does it visualize its outputs to the pathologist to confirm, or is it a black box? So just to summarize, pathologists don't need to be machine learning engineers, but they do, in my opinion, need to become at least minimally fluent with AI and machine learning pathology methods and approaches so they can make informed decisions about which are the best solutions to meet the needs of their specific lab setup, their current needs, and also their vision for future growth.

**Dr. Marilyn Bui:**

This is really great. On behalf of my committee we’re really grateful that you are part of our digital and Computation Pathology committee. Now after you've finishing up with a PHC committee soon.

And we really thank you for your passion, your dedication, your expertise to pathology and the CHP. At the same time, you know that our committee, we're all volunteers, but we're all trying to come up with useful resources for our members so we can help each other to get on this third revolution of pathology. So in addition to this podcast, which is the joint effort of the PHC and the CPC.

We're going to post it online and provide it to our members. And there are other activities, just a coordinated taking place. For example, I mentioned House of Delegates at the CAP. I'm the vice speaker and our steering committee is organizing the fall meeting, which is taking place during the CAP 2023 annual meeting. So that takes place in Chicago on October 7 to 10.

So the HOD meeting will kick off the CAP 2023. We asked the members, what topic do you like to. They said that they want to learn more current and the future applications of AI in pathology. So we brought into the experts. We're going to have a panel discussion. I will be moderating in addition to Dr. Eric Walk, and there are doctors, Jason Hip and Larissa Furtado. So please check that out.

**Dr. Eric Walk:**

Marilyn, I look forward to the House of Delegates panel discussion and hope everyone on the podcast, listening to the podcast joins us for that session at the CAP meeting.

**Lisa Tomcko:**

Well, thank you both for the great discussion and insights on this exciting topic and precision medicine.

Be sure to check out the Precision Medicine Resource Center on that org for more articles and resources. It's linked in the episode description. There you can find Dr. Walk's article referenced at the beginning of this episode. Machine Learning and Pathology. The potential to predict the future for patients as well as many others. We encourage you to check out the resource center and of course stay tuned for future episodes of CAPcast. For more information about this app, visit CAP.org.