Advancing Cancer Prevention, Detection, Diagnosis, Treatment, and Precision Medicine

BY AMANDA PATTON, MA

> "While AI [artificial intelligence]-based systems are currently unable to discern a grimace, notice sweating, or hear a tremor in a patient's voice—skills at which humans excel—these systems offer the unique opportunity to augment clinician performance by creating order and transforming vast amounts of mostly unstructured data into clinically actionable information to support optimal care. This field, although nascent, is rapidly advancing."
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> –ABERNETHY ET AL. [1]

Artificial intelligence (AI) is running in the background and foreground of our lives. Whether it's the fitness app counting our daily steps, the "you may also like" recommendations on our screens, or the GPS telling us where to turn next—AI is everywhere.

Healthcare is no exception. On the business side, AI tools power increasingly sophisticated business intelligence (BI) platforms. In hospitals, as well as oncology programs and practices, AI-based software streamlines operational functions, such as staffing and appointment scheduling, virtual visits, and processes for safety and quality. In cancer research, AI brings together the expertise of biomedical engineers, computer scientists, oncology clinicians, and researchers to imagine, develop, study, and test AI-based solutions to advance early cancer detection, diagnosis, drug development, clinical decision-making, and the boundaries of precision medicine. Consider, for example, the capacity of AI tools to "look" at datasets of images and identify actionable patterns, which are uncovering new ways to "see" cancers with greater granularity and opening the door to the development of non-invasive processes for assessing cancer prognosis and targeting anti-cancer therapeutics.[2]

AI-driven cancer research is uncovering potential approaches for achieving the precision medicine goal: targeting the right treatment to the right patient at the right time.[3] In particular, research on the integration of AI in oncology imaging is progressing with implications for radiology, pathology, and clinical decision-making support for cancer diagnosis, prognosis, and treatment planning.

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In 2017, Dr. Madabhushi received the Institute for Electrical and Electronic Engineering in Medicine and Biology Society award for technical achievements in computational imaging and digital pathology. His work on the use of AI to address health disparities—including identifying differences in prostate cancer "appearance" between Black and White patients—earned national recognition. Dr. Madabhushi co-founded three companies, one of which is Picture Health, where he serves as chief scientific officer.

In a recent conversation with *Oncology Issues*, Dr. Madabhushi and his colleague Trishan Arul, chief executive officer at Picture Health, discussed the expanding role of AI and healthcare professionals in the fields of biomedical engineering and computer science to advance cancer prevention, detection, diagnosis, and treatment, as well as tailor precision medicine for patients with cancer.

OI: Can you share your perspective on AI in cancer research?

DR. MADABHUSHI: I've been working in the biomedical engineering space for about 18 years and [over that time] there have been a lot of developments in AI. Most of those developments have tended to be in diagnostics. That is, thinking about the role of AI for disease diagnosis and disease detection, and that's really good. It's critical. We need technologies to look non-invasively at imaging data to identify presence or absence of disease, but, having said that, our group has also been looking at some of the questions that emerge post-diagnosis.

Nearly 40 percent of the American population will be diagnosed with cancer at some point in their lifetime.[4] In the United States, 1 in 2 men and 1 in 3 women will be diagnosed with cancer during their lifetime.[5] This is a staggering statistic. To me, as we think about diagnosis, we also have to be thinking about how we address the issue of management and care for such a large population of patients.

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OI: Specifically, how can AI tools applied to cancer imaging support clinical decision-making?

DR. MADABHUSHI: Something I feel very passionately about is the development of decision support tools, not just for the radiologist and pathologist to help in diagnosis, but for the clinician to help answer the question: "How should the disease be managed? More aggressively or less aggressively?"

My group and I spend a lot of time thinking about the kinds of AI approaches we can develop that integrate groupings of data that have been acquired as part of routine clinical workup—the initial pathology images, CT [computed tomography] scans, MRI scans. What can we do with these data so that we can really move the needle forward in terms of the decision-making process?

What do I mean by that? For example, figuring out which patients have more aggressive cancer versus less aggressive cancer. We know that in the U.S., unfortunately, there are many, many patients who end up with toxicity, not only because of aggressive anti-cancer therapies, but also from the very real

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issue of financial toxicity. Something like 42 percent of Americans with cancer will lose their life savings within two years of their cancer diagnosis.[6,7]

We think that one way AI can play a significant role is by identifying which patients really require those more aggressive treatments versus patients who will not benefit from aggressive treatment. AI can help advance our ability to more precisely identify which patients need more aggressive therapies and increase precision in treatment selection. Improvements in each area could help patients avoid drug-specific toxicity and treatment-related financial toxicity.

We are also thinking about treatment response. We know that even the best drugs today are not yielding the response rates we would like. So another area our group has been looking at is how can we move forward in terms of early response prediction and monitoring of the changes in the disease and, again, doing this [using] routinely acquired data—off of pathology images or other radiology scans. I think the opportunities here are tremendous.

These tools will no doubt benefit the radiologist and pathologist from a diagnostic perspective. If you think about radiation, medical, and surgical oncology, the ability of these tools in terms of helping provide risk stratification—who to treat more aggressively, who to treat less aggressively, predicting treatment response—to try to identify the right treatment for a given patient. This is where I think AI can really move the needle forward for cancer care providers.

ARUL: With any new technology, concern about integration with existing workflow arises. Picture Health's AI utilizes routine clinical images that already exist [as part of the diagnostic process]. We're not asking anyone to do anything special. We're not asking them [healthcare professionals] to send it [data] out for a specialized test or anything else.

Broader adoption of AI tools will require integration into the [clinical] workflow. We've seen early indications of this with many PACS [picture archive and communication systems] providers. They are building in APIs [application program interfaces] to allow outside AI vendors to plug in to [one's

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electronic health record,] acquire an image, apply their proprietary AI algorithm, and send back the annotated image with additional reporting. It's available in the workflow, but right now it's still fairly clunky. Other AI providers are developing their own cloud-based solutions. But these approaches require users to download and upload images to and from the cloud. We obviously have to solve that workflow challenge in order to achieve wide adoption.

OI: What does the business model look like for implementation of clinical AI tools into oncology practice?

ARUL: AI vendors are still figuring out the business model. It seems to be coalescing around subscription agreements with pay-for-use type arrangements. It's not surprising because it mimics the insurance reimbursement model we have in the U.S. You do something; you get paid for it. That said, Picture Health's AI utilizes routine clinic images like CT images. You can envision a world where all the images come in, we do the AI processing, we send the images back, and there are only alerts on certain images where the AI tool has identified something actionable or something that we can provide a report on. Then, that's a pricing model we've got to sort out. From the AI vendor's perspective, AI applications use a lot of computing horsepower. We have to absorb the cost of the cloud computing to run everything, but, for the clinician, results are available immediately.

OI: Can you say more about Picture Health's goals for its AI tools under development?

DR. MADABHUSHI: We are trying to build decision-support tools for the oncologist. These are AI tools for the treating physician to make some pretty heavy decisions. Moving someone off a particular treatment regimen and putting them on another—these are not trivial decisions. Picture Health is very deliberate and intentional with the AI features invoked in developing its decision support tools.

One of the criticisms around a lot of AI today is that it is very "black box." There is a lack of interpretability. We don't know what's under the hood, how it's working, or how it [the AI tool] got to its prediction. I think clinicians—in particular when it comes to making treatment decisions—set the bar for AI interpretability significantly higher because they are making these life-changing decisions. Because of that, Picture Health has focused on features from both pathology and radiology images that are intuitive and tethered more directly to the biology of the disease. The "anti-black box" if you will. But the beauty of what we are doing is that it also connects within the current paradigm of biomarkers and the way biomarkers are being invoked for treatment management.

Let's talk about immunotherapy, as an example. We all recognize—and I'm not saying anything that is controversial—that PD-L1 [programmed death-ligand 1] is not a good biomarker. And yet it is the status quo for how patients end up getting immunotherapy today. In lung cancer, I think we've gone in some ways beyond PD-L1, where in many cases—independent of the PD-L1 status—patients will end up getting immunotherapy. Four years ago, I think it was different. If you had low PD-L1, you might not be offered immunotherapy. I think it now represents first-line therapy across almost all lung cancers. If it's not there, it's moving toward first-line therapy in many cases.

One of the things we recognized is that in patients with low-PD-L1, even though they are getting immunotherapy, they are probably getting a combination of chemotherapy and immunotherapy. We've done a lot of work around better risk stratification of patients (i.e., seeing how AI tools can add more granularity within patient groups stratified by PD-L1 [low and high PD-L1 status]). These AI tools that we are developing can add further specificity within those buckets to allow further stratification of patient populations.[8,9] Further, compartmentalization of patients within those existing biomarker-defined buckets will add huge value. Now you have the opportunity to look at patients who may have low PD-L1 but potentially have favorable prognosis as determined by our AI tool. Or patients who are candidates for chemotherapy and immunotherapy—the AI application may indicate those patients who are likely to do well and can be given immunotherapy alone. We can avoid chemotherapy for these patients. That is game changing.

It's also valuable because, [although] we know in medicine things are going to change, approaches that try to disrupt the status quo have typically not fared very well. But if you try to be creative and innovative within the context of the existing status quo, I think you can have an impact. That's the way we're thinking about it.

ARUL: If you look at pathology-based AI companies, they are looking at replacing genomic-based biomarkers, doing alternative genomic biomarkers, and recomputing genomic biomarkers without having to take a molecular test. Picture Health is not necessarily taking that approach. We see this [Picture Health's AI approach] as another layer of information on top of what's already there. As Anant said, [a tool to] further stratify the patient population and give the oncologist—and the other physicians, radiologists, pathologists—additional information with which to make these life-saving decisions for their patients.

OI: Is variation in image quality due to site-to-site variation among CT scanners, MRIs, etc., an issue?

ARUL: Much of what we're doing right now is based on the lowest common denominator—the standard H&E (hematoxylin and eosin) slide. The beauty of it is—yes, there is variability across sites—but certainly the variability for H&E slides is significantly lower compared to immunohistochemistry and lower than immunofluorescence, where you have more pre-analytic variations.

Picture Health is unique in that we look at both radiology and pathology. And so, on the pathology side, we are looking at the standard H&E because that's more widely available, with less variability. One of the tools that we've licensed is an algorithm called HistoQC, which is widely used by AI researchers to assess the quality of pathology images.[10] It provides a powerful way for assessing fidelity and computational worthiness. We have ideas on how to use that as a standard quality control mechanism—not just for our AI but for anyone's AI.

DR. MADABHUSHI: There is some variability, but, again that is where these very interpretable features that we've developed are also resilient to variations across sites and scanners. We've been intentional in the way that we've developed these features. Not only are they interpretable, but they are also discriminating, stable, and resilient across variations. So yes, CT scans will be different as a function of the vendor, as a function of the site—there are some sources of variation. But because of the way in which we've constructed our AI tools, they are imbued with more robustness and resilience than a lot of the "black box", non-interpretable AI tools.

OI: ACCC's multidisciplinary membership includes all members of the cancer team—radiation oncologists, medical oncologists, pathologists, molecular pathologists, interventional radiologists, palliative care physicians, and other specialists and subspecialists, including biomedical engineers and data scientists. Can you share your thoughts on how AI may be leading to further integration of the disciplines engaged in diagnosing and treating cancers along the care continuum?

DR. MADABHUSHI: For too long, medicine has been siloed. I think it just goes back to how traditional medicine tends to be. Disciplines were defined decades and decades ago, and they still tend to operate in those departments and siloes. But I think there is also acknowledgement, certainly in many academic medical centers, that this practice has to change. We're hearing terms like "integrated diagnostics" coming up. It is an appreciation that diagnostics is not about radiology or pathology—it's fundamentally about the patient. What you have to be able to do is provide the best decision for the patient. That is where this concept of integrative diagnostics—leveraging the totality and plurality of information—is gaining a lot of traction. It's still a buzzword. It hasn't truly been implemented in practice, but it's something that Picture Health has embraced. Frankly, it's a travesty for us not to be able to use the totality and plurality of information that is being acquired from the patient [for the best possible prognosis]. Philosophically, that's what we've embraced at Picture Health.

As a company, we are unique in being able to meld information together across pathology and radiology to provide a more holistic, integrated prediction of outcome and treatment response for a given patient. The hope is that this will align with changes that are taking place. There is more and more appreciation, certainly within academic medical centers, that the departments of tomorrow will not be radiology or pathology; it will be a diagnostics department. That's the way a lot of the thought leaders and KOLs [key opinion leaders] in the field are thinking. The infrastructure and framework are also starting to change. For the longest time—since the early '90s—radiology has been where the PACS resided. But now, with pathology starting to digitize slides and images becoming available, I think vendors are starting to think about integrated PACS, where you can have radiology and pathology.

Picture Health is very well positioned to take advantage of this coming wave of integrated diagnostics because we think about data differently. We don't think about data in terms of radiology or pathology. We are thinking about data in a more integrated, consolidated fashion. And that, I'd say, is probably the most distinguishing feature of what we do, compared to AI companies that solely leverage either radiology or pathology.

OI: A recent American Society of Clinical Oncology (ASCO) article describes "Artificial Intelligence in Oncology: Current Capabilities, Future Opportunities, and Ethical Considerations."[11] The authors point out that "a major limitation to the broad application of AI algorithms and CDSS [clinical decision support software] in cancer care delivery is the requirement for diverse and inclusive data sets for training."[10] Put another way: the need to address the potential for bias and ethical issues arising with the utilization of AI in oncology.

DR. MADABHUSHI: This something that we've been very deliberate and intentional about. There was a fabulous paper that came out last year that showed that the Oncotype DX® multi-gene assay was actually not accurate in [use among] Black women.[12] That was quite a stunning publication. But when you think about it, it's not that stunning because of the data that Oncotype DX was trained and validated on. The proportion of Black women [who were included] in those data sets for developing and validating that assay was extremely small compared to the number of White/Caucasian women included.

In fact, more and more evidence is coming out, revealing the complexities surrounding health disparities. The worse mortality that we see in underrepresented populations, such as the Black population, has to do with a complex set of socio-political factors, including racism, but apart from social determinants of health, there is also growing evidence that there are fundamental morphological and molecular differences in disease appearance across different populations. This is where I think we have the opportunity to be very deliberate and intentional to make sure those differences are accounted for as we are developing our AI models. It's something I'm very passionate about. It's something I've published on,[13,14] and Picture Health is committed to making sure that we are intentional and deliberate as we develop these models. We don't want to develop models based on a single population; we must be intentional so that models are validated across a plurality of populations.

OI: In your opinion, what are the next steps for community oncology?

ARUL: We think it's important to start the education process through ASCO, ACCC, and other oncology professional organizations to help build understanding for what these AI tools can do. We imagine an AI report that delivers information to end-users that is truly actionable—with a section of the report aimed at each specialty, so that an inter-specialty team can discuss the report in a similar process to a molecular tumor board. OI

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