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Can AI Transform How We Diagnose ATTR-CM?

**Announcer:**
This is *On the Frontlines of ATTR-CM* on ReachMD. And now, here's your host, Ryan Quigley.

**Ryan Quigley:**
This is *On the Frontlines of ATTR-CM* on ReachMD. I'm Ryan Quigley, and joining me to discuss the use of artificial intelligence in ATTR-CM diagnosis is Dr. Frederick Ruberg. Dr. Ruberg is Chief of Cardiovascular Medicine at Boston Medical Center, as well as the Thomas J. Ryan Professor of Cardiovascular Medicine at Boston University Chobanian and Avedisian School of Medicine.

Dr. Ruberg, thanks so much for being here today. Appreciate you taking the time out to do this.

**Dr. Ruberg:**
Thanks, Ryan. It's a pleasure to be with you today.

**Ryan Quigley:**
Absolutely. So let's dive right in, Dr. Ruberg. I'm curious, could you walk us through how ATTR-CM is currently diagnosed and where gaps in recognition still exist?

**Dr. Ruberg:**
Well, things have changed a lot over the past 10 years. I'll actually give you a little bit of historical context first. Probably around 10 years ago, the way in which we diagnosed ATTR cardiac amyloidosis was by a heart biopsy. You pretty much had to do a heart biopsy or you had to do a biopsy of some organ in the body. Or you found amyloid, and then you were convinced that the heart was involved and you were able to prove that that amyloid was TTR by histological testing.

In the second half of the 2010s, like 2017, 2018 or so, it became evident that there was a way to diagnose ATTR cardiac amyloidosis just from doing imaging testing in combination with blood testing. And we called that the non-biopsy pathway diagnosis. A major publication that was led by colleagues at the National Amyloidosis Center demonstrated that you could use nuclear scintigraphy and the combination with blood testing to make the diagnosis with a high degree of clinical accuracy and a high sensitivity and specificity. And so that pretty much has supplanted biopsy as the principle way in which cardiac amyloidosis is diagnosed in, now, 2026.

And so the way it works is basically a clinician suspects cardiac amyloidosis for whatever reason: echocardiographic evidence, clinical evidence of congestive heart failure, et cetera. The clinician gets blood testing and looks for a light chain abnormality, because light chain amyloidosis can look like ATTR amyloidosis, and you want to exclude light chain amyloidosis, which can be done by blood and urine testing.

So the blood is tested for a light chain using something called free light chain and free light chain ratio, and the urine is tested using something called immunofixation electrophoresis, which is kind of like an SPEP, but with this extra step. And concurrently—or afterwards if there's no evidence of a monoclonal protein—nuclear imaging using bone seeking radio tracers, tracers like PYROPHOSPHATE, HMDP, or DPD—these are three different tracers that are used—is then acquired. And if that test is positive and it shows uptake in the heart, not in the blood pool, but uptake in the heart, that's more than what you would see in the bone then that is diagnostic of cardiac amyloidosis with ATTR. So the nuclear scan's positive, the light chain test is negative, and the patient's got ATTR amyloidosis. And the only thing left to do is a test of the patient's genes to make sure that the TTR gene is either wild type or variant, because that will determine, in some ways, the treatment.

**Ryan Quigley:**

So I know you just mentioned a few AI tools that are used to help detect ATTR-CM, but what other types of tools are being used or developed to support this earlier recognition?

**Dr. Ruberg:**
The diagnosis of ATTR-CM requires integration across different clinical inputs. So as cardiologists, we think about cardiac imaging and clinical symptoms. So clinical symptoms might be congestive heart failure, conduction disease, unexplained increases in cardiac biomarkers like troponin or pro-BNP, and, echocardiographically, might be unexplained increase in wall thickness that's not explained by hypertension or aortic stenosis, or particular patterns of longitudinal strain or advanced diastolic dysfunction. These are all things that could be indicative of unrecognized cardiac amyloidosis.

But there's other inputs, too, that doctors need to think about. It's pretty well established that ATTR amyloidosis commonly manifests as spinal stenosis or carpal tunnel syndrome before the development of cardiac amyloidosis in a large proportion of people. And so understanding if somebody had spinal stenosis or carpal tunnel syndrome, that may put them at risk for cardiac amyloidosis—a history of something like that as an example.

Looking across different clinical domains is another way in which we recognize disease, but it requires someone to really think about it and to have a careful clinical approach where you're really thinking about not just specifically the problem in front of you, but the entire patient. And that can be really challenging for busy clinicians, and that's where something like AI could be helpful because it looks across those domains or it sees things that clinicians don't otherwise see readily and helps aid in the diagnosis.

**Ryan Quigley:**
So one of the common concerns with AI, of course, and we talk about it all the time, is accuracy. How accurate are these AI driven tools and how are they being validated in clinical settings?

**Dr. Ruberg:**
There are a number of tools that have been developed using echocardiography and electrocardiography to make the diagnosis of cardiac amyloidosis. There has been evidence using machine learning approaches to look at these orthogonal inputs like carpal tunnel syndrome, spinal stenosis, and heart failure using just ICD codes in the electronic health record to help establish a diagnosis.

Using these tools that we apply to imaging or ECG testing, it eliminates, in many ways, pre-bias, because you just apply them and the test will provide an output, right? And so it's not like you're going into it with a presumed outcome, if you will. So that's one of the great advantages of artificial intelligence, is that it allows unbiased appraisal if you apply it broadly.

It also democratizes the capacity to make the diagnosis, because it allows a bunch of people to have almost the same level of expertise. You don't have to be an expert to apply an AI tool. You just have to apply the AI tool.

There are a couple of AI tools for ECG and for Echo and the Echo tools. Two of them have been FDA approved for amyloid diagnosis. So these are available tools now that clinicians can engage with the vendors to actually bring into their clinical workflow. The way they work, basically, is that for all these tools, the ECG or the Echo is uploaded into an interface, typically a cloud interface, and then the output returned is a probability or likelihood of amyloidosis: yes or no. And then the clinician is expected to act on that.

One might order the nuclear testing and the light chain testing that I order if the probability is high. And if probability is low, then you might be reassured and think that testing isn't necessary—the likelihood of amyloidosis is low enough that I don't need a proceed with testing.

**Ryan Quigley:**
Thank you very much for that. And for those just joining us, this is *On the Frontlines of ATTR-CM* on ReachMD. I'm Ryan Quigley, and I'm speaking with Dr. Frederick Ruberg about how AI can help us diagnose patients with ATTR-CM.

So, Dr. Ruberg, with these AI tools gaining FDA approval, what kind of infrastructure or workflow adaptations will clinicians need to make to use them effectively?

**Dr. Ruberg:**
I think that clinicians are very busy, and we have limited time to see patients. And so the tools have to be available to us in a way that doesn't distract us from patient care and enhances our capacity to take the best care of patients. One way in which that's happening now is the AI ECG tool that was developed at the Mayo Clinic. The way it works in the Mayo system is that, basically, a clinician simply clicks a box, the AI output is running in the background, then is populated, and then probabilities for a bunch of different important clinical conditions are provided to the clinician. They include amyloidosis, but it also includes ejection fraction that's high or low, for example, and other kinds of important cardiologic conditions. So that's pretty easy. You click a button and the information is there, and the clinician then can incorporate that right into the workflow.

The Echo workflows are a little bit more complicated, because they require moving the Echo images to the analysis platform. And some of them can be contained behind your firewall, within your network, and some require a cloud-based interface. I think the key issues are going to be the time it takes and the results that you get. Is it going to be clinically actionable to you? Are you going to find it useful as a clinician?

**Ryan Quigley:**
Now, are there any regulatory or ethical challenges you foresee as AI continues to evolve in ATTR-CM care?

**Dr. Ruberg:**
I think the ethical challenge is really, in some ways, derived from the populations on which these models are trained. It's really important that the populations represent a diversity of patient demographics, as well as disease demographics, so that they're as accurate as possible and as broadly applicable as possible.

And so it's really imperative that the developers of these tools make sure that, as they develop these deep learning models, for example, these are quote unquote black box models, where you really don't exactly know what the system is looking at per se, but it's giving you an output. But it's looking at something based upon how it was trained. So it has to be trained on a broad array of patients of different ages, different sexes, different races and ethnicities, and also different diseases, so that it can differentiate amyloid heart disease from hypertensive heart disease or hypertrophic cardiomyopathy, the two principal similarly appearing phenotypes. So that's a potential. I wouldn't say an ethical concern, but it's a concern with just the development of the models.

**Ryan Quigley:**
Yeah, it's very interesting learning more about AI and how it's impacting ATTR-CM care. And Dr. Ruberg, before we wrap up here, how do you think the role of AI will expand in this sphere in the next few years?

**Dr. Ruberg:**
As in every aspect of our society, the role of AI is going to grow. And as far as clinicians and clinical imaging specialists in cardiology are concerned, it's going to be something that helps support our clinical decision making, at least in the very beginning or in the intermediate future.

Will it ultimately supplant? I think probably not. I think that there will always need to be a human doctor for a variety of reasons, not the least of which to articulate the clinical oppression, the treatment plan, and all those sorts of things, but also to look at the output of the AI in the context of the entire patient. But I think that, ultimately, it's still going to require a human doctor to help put that all together. But I see it as decision support. I think it will lead to better recognition of disease. We don't yet know about the prognostic utility of these tools yet, but there'll be, potentially, benefits to prognosis based upon the AI output. And increasing awareness, decision support to get better care to patients and the right diagnosis to the right patient, potentially advantages in prognostic information, and following response to therapy are all promises that AI, I think, will probably realize over the next five years.

**Ryan Quigley:**
And that's a great comment for us to think about as we come to the end of today's program. And I want to thank my guest, Dr. Frederick Ruberg, for joining me to discuss how artificial intelligence can be used in ATTR-CM diagnosis. Dr. Ruberg, thank you so much for joining the program. I really appreciate you doing this.

**Dr. Ruberg:**
It was absolutely my pleasure. Thank you very much for the opportunity.

**Announcer:**
You've been listening to *On the Frontlines of ATTR-CM on* ReachMD. To access this and other episodes in our series, visit *On the Frontlines of ATTR-CM* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!