AI-ECG to Detect Cardiac Amyloidosis: Strengths, Limitations, and Future Directions

Announcer: Welcome to Mayo Clinic's ECG Segment: Making Waves, Continuing Medical Education podcast. Join us every other week for a lively discussion on the latest and greatest in the field of Electrocardiography. We'll discuss some of the exciting and innovative work happening at Mayo Clinic and beyond with the most brilliant minds in the space, and provide valuable insights that can be directly applied to your practice.

Dr. Kashou: Welcome to Mayo Clinic's ECG Segment: Making Waves. We're so glad you could join us. Today, we have an exciting episode planned for you as we discuss an artificial intelligence, AI, enhanced ECG model to detect cardiac amyloidosis. Cardiac amyloidosis is an ominous disease with varying clinical presentations causing it to often evade prompt diagnosis. It is generally considered rare, although recent work appears to suggest a higher prevalence than previously portrayed. Early diagnosis is important due to the significant implications for management, especially with the evolution of effective medical therapy. A previously published artificial intelligence enhanced ECG model showed potential as a tool to screen for cardiac amyloid. We're fortunate to be joined by our expert discussant Dr. David Harmon as we look at the validation of this model to better understand his performance, limitations, and what's next for this model. Dr. Harmon is a first year general cardiology fellow at the Mayo Clinic in Rochester, Minnesota. He attended Texas A&M of medicine, and was selected as a member of the Alpha Omega Alpha AOA National Medical Honor Society. After his graduation, Dr. Harmon completed internal medicine residency at the Mayo Clinic Rochester campus, followed by an NIH funded research year where he focused on the clinical application of AI ECG under the mentorship of doctors Paul Friedman and Zaki Atilla. Dr. Harmon continues his work pushing the clinical limits of AI ECG based technology by assessing the utility of these algorithms on wearable devices, as well as in medically underserved communities. He also continues to push his limit in the daily caffeine consumption. Dr. Harmon, thank you so much for joining us.

Dr. Harmon: Thank you so much for having me here, Anthony. It's great to be here.

Dr. Kashou: You know, so I really want to get into this validation study, but perhaps before we get into that, you could share a little bit about the background as to why AI and why the ECG for detecting and screening for cardiac amyloid?

Dr. Harmon: Sure. Oh, absolutely. So, as you definitely mentioned, amyloid can have variable presentations. You know, not everybody presents with the same symptoms. Sometimes symptoms are very vague. And I was looking at a few studies just earlier today in the diagnosis for amyloidosis patients. About one third of patients with their initial symptomatic presentation will not receive a diagnosis for upwards of a year, and another third of those won't receive a diagnosis within the first six months. Many of these patients will visit upwards of four specialists before actually coming up with this clinical diagnosis. So, frequently this diagnosis is either missed or underdiagnosed, and sometimes you have to have a referral to a major center that can perform the correct testing for this disease entity. Now, while you've had a lot of improvement recently in the diagnosis of amyloid and imaging for amyloid, there's still are clinical cues that go missed just because it's such an elusive disease. You know, the symptoms are very mild, minor, and vague when during the frequent early presentations. So, we've believed that using an

AI enabled algorithm on the electrocardiogram, that this could trigger earlier screening particularly when somebody who's less familiar with this disease entity.

Dr. Kashou: Hmm. So, what I'm hearing is that, you know, as we we've mentioned, is this amyloid is really evading our detection , and from our physicians, and it's kind of going from doctor to doctor and eventually hits maybe the fourth or fifth doctor, and then finally it's caught up. But at that point it's probably a few years into the disease. And so, potentially having a model like this could capture it early and maybe clue in physicians that are less familiar with this.

Dr. Harmon: Exactly.

Dr. Kashou: Now, to the work, and this has been, you know, really exciting work and I've heard you present it, and want the audience to learn more about it. But what are some of the most surprising results of this validation study your team has done?

Dr. Harmon: Sure. So as you mentioned, this is a validation study. So, the original AI algorithm for amyloid has been published by Dr. Grogan and her team in the Mayo Clinic proceedings. And it showed that our AI enabled ECG could accurately detect amyloidosis, even had a positive predictive value of 86% in the original study. But what we wanted to answer were, are there subpopulations that this algorithm may not work quite as well, or subpopulations algorithm works extremely well? And we wanted to really dive into the details because this is still a little bit of a black box technology for us. We know that we have this convolution neural network that looks at the raw ECG files. Not manually selected ECG parameters, but actually the ECG as a whole and makes this prediction. And while we continue to work on the transparency of such an algorithm, it is up to us, currently, to decide what subgroups of patients this algorithm fits best. How can we screen amyloid effectively, and how can we also avoid unnecessary testing in groups where you may not have as well as performance? So in this validation study, we looked across age groups from 20 to 100 years old and 10 year intervals. We also looked at both sexes, male and female. We looked at amyloid subtype. We looked at inpatient and outpatient electrocardiograms. We looked at race and ethnicity with white, black and patients of other race, as well as Hispanic patients and non-Hispanic patients. And then finally, we actually looked at the ECG characteristics itself. So are there certain patterns or underlying arrhythmias that could interrupt the algorithm performance? So, say somebody comes in with atrial fibrillation and a left ventricular hypertrophy, will they have the same type of accuracy as somebody who has normal sinus rhythm? So that was the goal of the study to see which of these groups, the algorithm performed well. And the most surprising, to me personally, was the inpatient and outpatient data. In the earlier study, we looked a little bit at our AI ECG algorithm for heart failure and saw that when a patient was in the hospital that ECG might have some variability in performance. And this is likely due to your external factors. You know, somebody walks into an outpatient ECG lab they're typically well, or well enough, to walk in or be wheeled in by family on a wheelchair, but they don't have a, you know, an endotracheal tube down their throat. They don't have endo tropic medications that are supporting their heart or circulatory system. So they have a lot less impacting factors in the outpatient setting, typically, compared to inpatient. But our algorithm actually showed pretty high performance in both groups, and there wasn't very much difference. So that was a big surprise. The other big surprise that we saw with the ECG characteristics were the patients that presented with low voltage. And in our study, it's not to be misinterpreted, but

the area under the curve was quite high at 0.9 or above there, I'm trying to remember the exact number off the top of my head, but the algorithm performed almost best in this low voltage group. But it is not because low voltage is what you commonly see in cardiac amyloidosis, as it has been reported in prior studies. But it's actually saying that this algorithm can determine ECG low voltage due to cardiac amyloid versus ECG low voltage to other cause, such as extra subcutaneous tissue, lead placement, et cetera. So we saw that this algorithm could even distinguish some of these very small details better than, you know, an average interpreter. The final thing that was a little bit surprising to us was that we could actually see this algorithm work in patients with paste rhythms. It was not as good of a performance, which is to be expected given the differences in the electrocardiogram with paste rhythms. But we did see that it actually had a fair predictive value with these paste arrhythmias that we didn't previously validate in the original study.

Dr. Kashou: It's really fascinating. I love the validation look, the different populations, the in versus out, the different races, sexes, and how that makes a difference, especially the in versus outpatient something we don't really think about, you know, when we're building these models. But it is reassuring that the model validates in that population. And the low voltage, I mean, it speaks to the specificity potentially of the the model to be able to clue in to the unique characteristics of what amyloid and what those features are showing. And I do appreciate the paste rhythm. Sometimes, you know, some of these models will avoid it because certainly it can be a confounder, right? Certainly.

Dr. Harmon: Right. And it was excluded in the original study just for, I think, for simplicity. You know, we had so many things we were already digesting. If we can include these paste rythmns it would be difficult to know what to make of it. So, now is the opportunity to explore is it possible in these groups?

Dr. Kashou: That's really important. And I'm glad this study kind of showed that. Now I do wanna move on to, you know, we have the derivation, we have the testing, the validation now. What have you found in, especially in this validation, some of the biggest limitations in this work?

Dr. Harmon: So this is an excellent question just because it's something that we don't like to ask, you know, how how bad is our algorithm? Is really what what we're getting at. And, you know, in southeastern Minnesota, our population is generally white and 92% of patients were white in the original study, and there was a very small amount of Hispanic patients. They weren't actually evaluated in the original study. And so in our validation we actually looked at the Hispanic population with and without cardiac amyloidosis, and the performance was remarkably lower than the rest of the study. So, at a area under the curve of 0.71, and this is a big drop from our average, which was 0.85 for the entire study. And we were curious why this might have happened. And without the ethnicity data in the original study it's difficult to know how many patients were Hispanic and then how many patients that were Hispanic also had cardiac amyloidosis. And we imagined that there was a very low population that was in this derivation, and therefore we now see this performance drop currently. The other big limitation that we saw was that there potentially a selection bias with our control group because our control patients all had an ECG and all had a transthoracic echocardiogram. And we wanted to make sure that we

were excluding patients who had either diagnostic criteria for cardiac amyloid on echocardiogram or signs of infiltrative cardiomyopathy, which could be undiagnosed amyloidosis. But patients who are getting both an ECG and a TTE, typically, are not quite as healthy as your patients without either of those or with just a ECG alone. So, it's not quite a real world validation just yet. And I think that's one of our next steps is to look into this less, even less selected group. You know, what is somebody's probability of amyloid who's just come off the street? Are they going to have a false positive, false negative? You know, we don't know that data quite yet. And so I think that's our next big exploration point.

Dr. Kashou: And it is really important. I know you mentioned some of the limitations and sometimes we feel we shouldn't admit it, but these are how the field advances and your admittance of those limitations only help us to see where where it works. And that's gonna help us get the buy-in of other providers to use this in the right setting. Now I know you know the ECG, the Echo, but you're building the algorithm, you're validating it. This is important because, yes, we wanna make sure we get it before the the fourth doctor, right? And hopefully the first doctor before they get an Echo, but it makes sense. And, so maybe, I know you've already alluded to that, but where do you see next steps for this algorithm?

Dr. Harmon: So I think first and foremost, we want a very ethnically diverse validation study with this algorithm because we want to see if there's further limits that we haven't identified, especially with what we saw in the Hispanic population. This is a real big next step, not only for this algorithm, but for artificial intelligence in general. Frequently, frequently, you see an underutilization and underdevelopment of this technology with the inclusion of these racial minorities. And in order to help those people who are in these underserved communities who are marginalized in the field of medicine frequently, we also have to make tools that are useful to them. And performing these external validations, these very diverse validation studies, and even deriving algorithms within these underserved and undercared for populations that can help us reach them with a more meaningful tool in the end product.

Dr. Kashou: The AI augmented ECG models continue to show tremendous promise lthough validation of these models is important. And we've seen a lot of that today. We looked at the validation of this cardiac amyloidosis model in a diverse cohort and there's still room to go. Another ethnically diverse group is important. And what's neat is that we've seen the performance in a variety of different settings. The validation in the paste rhythm, validation in different inpatient/outpatient, and this is really important work. It highlights the importance of such studies and the promise of its application for clinical practice. Dr. Harmon, thank you for sharing you and your team's work with us. I always enjoy speaking and learning from you. It's exciting to learn about what is the latest in the field. On behalf of our team, thank you for joining us. I hope you'll come back. It's been a true pleasure.

Dr. Harmon: Awesome. Thank you so much, Anthony. Really appreciate it.

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