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The Updated Role of Non-Invasive Biomarkers in MASLD

Dr. Buch:
Welcome to *GI Insights* on ReachMD. I'm your host, Dr. Peter Buch, and joining me today to discuss the American Gastroenterological Association, or AGA's, Clinical Practice Update on the role of noninvasive biomarkers in nonalcoholic fatty liver disease, or NAFLD, is Dr. Julia Wattacheril. Dr. Wattacheril is an Associate Professor of Medicine at Columbia University Irving Medical Center in New York.

Dr. Wattacheril, welcome to the program.

Dr. Wattacheril:
Thank you so much for this invitation, Dr. Buch. It's a delight to be here.

Dr. Buch:
And we really appreciate having you here to help clarify. So let's dive right in, Dr. Wattacheril. Can you give us some key insights into the AGA's update on noninvasive biomarkers in NAFLD?

Dr. Wattacheril:
Yes. So first things first, we know we in the NAFLD community are overwhelming folks with all sorts of risk stratifies and name changes, but if any members of your audience haven't heard, one of the bigger things that we've been working on is just trying to destigmatize some of the disease naming systems and to include other categories that mimic what humans do, like the influence of alcohol. So I do just want to nod to the fact that we've had some recent naming changes, and you might hear me use the term MASLD, which is metabolic dysfunction-associated steatosis liver disease. It's still a mouthful, but it describes some of the influences of the disease a little better.

So that aside, one of our main points that we want to make is when you have a patient that you're considering the diagnosis of NAFLD, or MASLD, is to make sure that you're evaluating for other causes of liver disease because whenever you have a clinical suspicion that someone may have fat in their liver and it's not due to alcohol, we want the audience first to stratify patients. Imaging with an ultrasound is oftentimes how internists or gastroenterologists find out that there may be some influences of fat in the liver incidentally, and we want them to stratify using what we call a noninvasive test. Once they enter that bucket of MASLD or NAFLD, we really want to start to help clinicians, especially frontline clinicians that are not seeing necessarily transplant patients like many of us in referring centers are to help categorize patients into low-risk and high-risk categories and the risk that we're talking about as advanced fibrosis.

The first test that we recommend in our guidance is something called a FIB-4, Fibrosis-4 test. And we know that it's imperfect, and we know that there are some performance issues across age ranges, and you'll see those in the guidance document, but we want your audience to know that it's free, it's available, it's designed for outpatient testing, not sick inpatients, and we use a general cut point of about 1.3 to help identify patients that are at very low risk for advanced fibrosis, and then we use other cut points 2.67, and these numbers do not need to be memorized. But we just want our audience to know to stratify patients based on their stiffness measures, and they should start with a FIB-4.

We also want to emphasize two other points—sequential testing—when you meet someone in the first visit or you're stratifying them for the first time, and this is very, very important to do based on metabolic risk. And I have to say our internists and gastroenterologists oftentimes do a better job of this than we as hepatologists. So the clinical feature to keep in mind is their diabetes status or metabolic syndrome risk profile. And so those with multiple metabolic risks, so greater than or equal to two or the clinical diagnosis of diabetes fall into a risk category clinically. So what does that mean? In addition to stratifying with a first test, like FIB-4, we want to use a sequential test, an additional test, and one of the ways that we stratify patients is using an imaging-based modality or serum-based test.

Dr. Buch:
Perfect. The other thing that we want to make sure that our primary care colleagues know this about the usefulness and the accuracy of ultrasound in making a diagnosis of NAFLD. Can you please comment on that?

Dr. Wattacheril:
Yes. This comes up a lot. Thank you for asking that question. So the utilization of it, which is not the usefulness, as your question stated, is high. The usefulness depends on the patient's clinical risk, and that's where taking the clinical context of imaging is so important. I think the thing that's most important for anyone seeing a patient in general is knowing when does this test fail, in what circumstances. And we know that ultrasound technology usually picks up steatosis of any cause at around a quantity of 20 percent, and we define the disease as a quantity greater than five percent, so a negative ultrasound does not mean that person does not have fat in their liver, and that's why some of our imaging modalities that we recommend in our noninvasive test algorithm have a higher sensitivity.

Dr. Buch:
Thank you for clarifying that. And to zero in further, can you explain when to use a FIB-4 score and how it compares with proprietary fibrosis biomarkers, like FibroTest or FibroSure?

Dr. Wattacheril:
Yes. So using a FIB-4 score is easy and cheap. It's free. So a FIB-4 score can be calculated based on laboratory values and biometric parameters that you have at your fingertips. For those that are using electronic health records, the dot FIB-4 is something that can be deployed in your clinic note so that you have it automatically calculated again in stable outpatients. The proprietary fibrosis markers, like FibroTest and FibroSure, are send-outs. They are widely used. All of these were derived originally from our hepatitis C population, then subsequently validated in NAFLD and MASLD. But the FibroTest and FibroSure availability and send-out requires access, robust longitudinal validation across all these modalities, and certain ancestry group metabolic risk profiles is ongoing.

So with FIB-4, knowing its limitations, it doesn't perform great in patients under 35 and over 65. We have different parameters that you'll see in our figure for those individuals. But when to use them is based on what's available to the patient in front of you in terms of reimbursement as well as access.

I think one pearl is the more you do this, the more you'll develop a sixth sense for where tests might be wrong, and so not necessarily using all tests that are available but picking one or two that you can develop some local expertise on given the prevalence of the disease would be a good thing for your listeners to start to adopt.

Dr. Buch:
And that's a perfect segue to my next question. What is an enhanced liver fibrosis test, also called and ELF test, and when should it be utilized?

Dr. Wattacheril:
And ELF test is another proprietary test that's a send-out, and so that will incur a cost, so that's something to know about. It's used in sequential testing, as you'll see in our algorithm, and those of us that have sent patients out for it know that we oftentimes use it to help us in the terrain of advanced fibrosis at very high levels or readings greater than or equal to 11.3. We do know that that's associated with an increased risk of hepatic decompensation. So once you're starting to put your patients in buckets of low risk for advanced fibrosis or high risk for advanced fibrosis, or you have someone with known cirrhosis, and you're having the conversation as to what is the likelihood that this liver will fail in my lifetime, an ELF test, where it stratifies greater than 11.3 has been associated with that, and that can help you guide a conversation on when to refer for specialty consultation and potentially transplant evaluation.

Dr. Buch:
Thank you. And, Dr. Wattacheril, could you please describe how you choose between transient elastography, shear wave elastography, and magnetic resonance elastography as confirmatory tests for fibrosis in NAFLD patients?

Dr. Wattacheril:
So much of this decision, quite practically speaking, rests with what is available to you in your area. So those of us with vibration-controlled transient elastography in our offices have developed a practical point of care utilization that's rapid and directly provided by the provider at the instance that they are seen. That's not the majority of your listeners, I imagine.

So shear wave elastography is often pursued and housed in imaging centers that might be more accessible to certain locations, but without transient elastography, we often interpret these results clinically, as many of your listeners may do. So if your listener is looking to stratify patients that have fallen into the bucket of NAFLD or MASLD and are in a low-risk category but they have two metabolic risk categories, those individuals can be seen in follow-up and referred for additional testing. And what that additional test is oftentimes

what's available in your region.

Magnetic resonance elastography, or MREs, are very useful in patients with high BMIs, and so individuals that have heterogeneous diseases, like NAFLD or MASLD, it helps us calculate different regions of interest. So it's not zoning in on one portion of the liver as often we do or we have to do with transient elastography, but it looks over the totality of the liver, so it's often helpful to use MRE when you have preliminary imaging that's suggestive of low bar differences between the right and left lobe.

Dr. Buch:
For those just tuning in, you're listening to *GI Insights* on ReachMD. I'm Dr. Peter Buch, and I'm speaking with Dr. Julia Wattacheril about the use of noninvasive biomarkers in nonalcoholic fatty liver disease.

And continuing on, so if we look at morbidly obese patients with NAFLD, are there special considerations for monitoring these patients?

Dr. Wattacheril:
Best performance is your consideration that you should know about if you're seeing patients with high BMIs. So transient elastography has been validated in morbidly obese or class 3 obesity stratified patients. And that said, those of us that oftentimes operate on these individuals by way of performing the elastography do notice some variability in range and performance in the population at large, so oftentimes this is why third-party payers or insurers, reimburse for MRE. This is a patient population that you may be advantaged by choosing something like an MRE, especially when it comes to higher fibrosis risk patients or patients in whom you're considering weight loss surgery.

Dr. Buch:
And before we close today, can you explain when we should consider a liver biopsy for our NAFLD patients?

Dr. Wattacheril:
Yes. Liver biopsy can be extremely helpful in a couple of clear contexts. So one is determining what is going on in patients with multiple NITs, or noninvasive tests, that don't move in the same direction, so we call these discordant values. Oftentimes, if you're seeing a patient that's referred from another center and putting data together, you may have three different tests that show you three different results. So it's very hard to determine which bucket they fall in, low risk or high risk, so that's one group because we think of MASLD as a relatively slowly progressive disease. There's a lot of room to screen for other influences over time. Just because they've been diagnosed with NAFLD or MASLD in the past doesn't mean there aren't other possibilities for a secondary liver disease, like autoimmune hepatitis, so if you start to see some clinical parameters changing that might indicate something more acute or recent happening, that's also a reason to pursue a biopsy.

They are also very, very helpful with risk stratification for more significant invasive recommendations, like we just covered—weight loss surgical procedures—when you're looking at patients with advanced fibrosis in that category and wondering whether or not they have portal hypertension. In those instances, many times we'll pursue what's called a trans jugular liver biopsy with pressure measurements. So we get liver tissue, but we also get directed portal pressure measurements to help risk stratify those patients prior to surgery. In that terrain, when you start to have patients with advanced fibrosis, when you start to have patients that you're screening for hepatocellular carcinoma, these are all opportunities to have your expert on speed dial such that you can reach out to them if you start to wonder about whether or not a biopsy would be useful. Those are some of the more frequent phone calls and consultations that we get.

Dr. Buch:
I want to thank my guest, Dr. Julia Wattacheril, for a very informative session on noninvasive markers for patients with NAFLD.

Dr. Wattacheril, it was a pleasure speaking with you today.

Dr. Wattacheril:
Thank you so much for this invitation, and thanks to the audience for caring about this disease.

Dr. Buch:
For ReachMD, I'm Dr. Peter Buch. To access this and other episodes in this series, visit *GI Insights* on ReachMD.com where you can Be Part of the Knowledge. Thanks for listening, and see you next time.