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Key Insights on Diagnostic Tools for NASH

**Announcer:**
You're listening to *GI Insights* on ReachMD, and this episode is sponsored by Siemens Healthineers. Here's your host, Dr. Charles Turck.

**Dr. Turck:**
Welcome to *GI Insights* on ReachMD. I'm Dr. Charles Turck, and joining me to explore the latest diagnostic tools for nonalcoholic steatohepatitis, or NASH for short, is Dr. Kenneth Cusi. Dr. Cusi is the Chief of the Division of Endocrinology, Diabetes and Metabolism in the Department of Medicine at the University of Florida.

Let's begin with some background, Dr. Cusi. What tools are currently available to diagnose NASH?

**Dr. Cusi:**
Well, within the clinical context the first thing doctors have to think is if a patient fits the profile of a high-risk person for developing nonalcoholic steatohepatitis. And the three highest risk groups are those with type 2 diabetes, those with obesity, particularly with metabolic risk factors, and if you found an individual having elevated liver enzymes or steatosis during a blood test or a random exam. Once you have that clinical context and the history, the tests that we have are broadly divided into three types. Number one, blood tests or diagnostic panels, biomarkers that tell us about the underlying mechanisms that are leading to NASH and fibrosis. Second would be imaging, and third, a liver biopsy, which is something we try to avoid but many times will be the needed final test to decide management.

**Dr. Turck:**
And as a quick follow-up to that, are there any considerations clinicians should keep in mind when choosing between a noninvasive test and a liver biopsy?

**Dr. Cusi:**
Well, of course. So, a liver biopsy is invasive and entails some risk. It is costly and we resort to liver biopsies of course in clinical trials, but in the clinical practice we would do that only if the noninvasive tests don't allow us enough precision to decide the management. In that case, you know, the liver biopsy will be the final word. But I think in the future, a vast majority of people will be managed with noninvasive biomarkers and imaging. And there are several of them, and I think that this will help manage the vast majority of people. So, liver biopsy will be restricted to differential diagnosis or some special circumstances.

**Dr. Turck:**
Now if we take a look at one noninvasive test in particular, can you tell us about the FibroScan test and its potential limitations?

**Dr. Cusi:**
Of course. So, the transient elastography is championed by the FibroScan in many, many studies and has had value in giving us two types of information. Number one –what is the degree of steatosis, which is important because steatosis is a cardiometabolic risk factor associated with cardiovascular disease and type 2 diabetes, and the fundamental piece of the diagnosis, to say that the patient has nonalcoholic fatty liver disease once we rule out other causes. However, it is the liver stiffness measurement that is going to tell us what is the risk of this person of having severe disease or cirrhosis. So, the pros and cons are multiple. It is simple. Can be done fairly quickly. Can be done in the point of contact in the clinic. The device itself is expensive but the tests are rapidly inexpensive, usually less than $100.

And, again, there is a lot of data validating it as a test for future prognosis and sometimes management as is emerging from the clinical trials, but in particular it does help people who have very advanced disease and need additional workup. And this is gonna come to

when we get into the guidelines, that the second-line test that's been for a long time now a FibroScan, once you identify people at risk. And we can discuss the importance of FIB-4 when we talk about the diagnostic panels and biomarkers. But we do think that in current management, elastography with the FibroScan is important. There are other devices that also provide similar information, but the best validated so far has been the FibroScan.

**Dr. Turck:**
And what about the ELF test? How does this tool work and what kind of prognostic utility does it have?

**Dr. Cusi:**
Yeah. Well, the ELF test is something new for the American physicians. It's been broadly validated and used overseas in many countries and many studies. There are meta-analysis that have shown its value. For those who are new to the liver field, or non-hepatologists, ELF stands for enhanced liver fibrosis, and it's a score that measures three proteins that are from the extracellular matrix linked to the pathophysiology of fibrosis in the liver. One is TIMP1, which is a tissue inhibitor of metalloproteinases. The other one is P3NP or amino-terminal propeptide of type III procollagen, that's pretty complicated, and the other one is hyaluronic acid. And, in short, these three measurements that come from a blood test combine to give you a number that will give you the risk of having advanced fibrosis or not, and this number has been validated on many, many studies. So, the idea is that it's a test to help doctors guide therapy when you are screening people at high risk, and so far, again, no test is perfect. All tests have areas of uncertainty, but we think, as we're going to mention about the guidelines, after a first stratification with the FIB-4, which I think most people are familiar with it which comes from an index that comes from age liver transaminases and platelets.

A second line would be the FibroScan and if unavailable, to use the ELF as a decisive factor, or sometimes the second test doesn't get you out of the gray zone so you need to combine proprietary biomarkers like ELF with the FibroScan before making a decision to refer to the hepatologist. So, this is really important because it's truly important, number one, that primary care doctors, endocrinologists, family doctors learn how to screen with a FIB-4 and know how to interpret ELF and how to interpret FibroScan, to not overwhelm gastroenterologists and hepatologists with inappropriate consults. So that's what the guidelines are for and hopefully we'll optimize this referral pattern.

**Dr. Turck:**
For those just joining us, this is *GI Insights* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Kenneth Cusi about noninvasive tests versus liver biopsy for diagnosing nonalcoholic steatohepatitis, or NASH.

Now, Dr. Cusi, can you give us a sense of how these tests are used in clinical practice? And can a combination of noninvasive tests be used?

**Dr. Cusi:**
There was a consensus reached in mid-2021 in a meeting that later led to a white paper and a clinical care pathway. And it's important to mention that this white paper was published in *Diabetes Care*, which is the official journal of the ADA. It was published in *Obesity*, which is the official journal of the Obesity Society, and in *Gastroenterology*, as you know, and also *Metabolism*, another endocrine journal. And basically, it goes to tell primary care doctors to remember just a few things: Number one, that there are three groups of risk: people with type 2 diabetes, obesity, or elevated liver enzymes or steatosis. We do then a diagnostic panel which is the FIB-4. The FIB-4, if it's above 1.3, deserves a second test. At the time, we did the AGA 2021 guidelines, the ELF had not been approved, so it wasn't incorporated. Now, I was fortunate to chair with Dr. Isaacs from Atlanta and Emory, the American Association of Clinical Endocrinologists guideline, which is not meant to be a different guideline. It was just meant to be deeper into the management of these patients, by endocrinologists and primary care doctors. And in addition to what the work done with AGA clinical care pathway, we added ELF, that had been approved in mid-2021.

So, ELF is a test that based on the pathophysiology of the disease, would help in that decision-making. We think there are other proprietary tests that are being evaluated and will be eventually incorporated but the combination of FIB-4 with a second deciding test, either imaging with elastography test, or with ELF, I think will help identify most of the patients. Again, no test is perfect, but using combination, there are many papers that now, that have shown that it helps, and the message for primary care doctors, endocrinologists, cardiologists, obesity management doctors and nurses and nurse practitioners is to think of NASH as something that you can diagnose today, and the importance is because cirrhosis is just too late to do the kind of treatment that will prevent end-stage liver disease. To diagnose people early so they can be referred to the hepatologists to do things such as lifestyle changes and promote weight loss and diabetes medications like pioglitazone or GLP-1 receptor agonists that are proven to slow the progression and reverse that hepatitis. So, there are things to be done today, while we wait for drugs to be FDA approved.

**Dr. Turck:**
With all of that in mind, how important is it to utilize professional guidelines when screening patients for NASH?

**Dr. Cusi:**
Well, really important, as you can tell, because just to give you some examples, I mean, if you screen 100 people coming to a clinic today, with type 2 diabetes and obesity, about one in five have liver fibrosis, and among them, about 15 percent have advanced liver disease. So, these are studies we and others have published in the last 12 months, and it's been consistent around the world. So, you have a disease that's affecting one out of six people with diabetes, and about one in ten with obesity without diabetes, and that we can treat today with weight loss, we can treat today with obesity medications such as GLP-1 agonists or diabetes medications like GLP-1 or pioglitazone. So, it's critical that we do this, not only these guidelines, and I need to mention that the American Association of Clinical Endocrinology, or AACE guideline, were cosponsored by the Liver Society, AASLD. Now, in November at the annual meeting, the Liver Society updated the guidelines with pretty much the same algorithm, and the American Diabetes Association in January is going to also publish an expanded recommendation in their standard of care to screen with FIB-4 and with the imaging and ELF, as we mentioned. So there still has to be a final consensus on that, and on those recommendations that have been discussed, but the ADA is very proactive in preventing cirrhosis.

**Dr. Turck:**
And before we come to a close, Dr. Cusi, do you have any final thoughts or takeaways you'd like to share with our audience today?

**Dr. Cusi:**
Yes, number one, thank you for listening. Number two, educate your patients about the importance of a healthy liver. If you have steatosis, you have someone at risk of cardiovascular disease. The American Heart Association, this year for the first time, put fatty liver disease as a cardiovascular risk factor. You also double your chance of having type 2 diabetes. But from a liver perspective, an early diagnosis will save people from end-stage liver disease, and I have seen many young adults going for liver transplantation, or dying from cirrhosis, and it is in your hands to identify these people today with a simple test such as FIB-4 and with the stepwise approach we discussed to really change the life of many people. So, I think this is possible. There are drugs used for obesity and diabetes today that you can use and are explained in the guidelines, and I think very soon, we're going have some approvals by the FDA, of drugs for the treatment of NASH. So, it's everybody's work, patients and their doctors to change this starting tomorrow.

**Dr. Turck:**
Well, with those key takeaways in mind, I want to thank my guest, Dr. Kenneth Cusi, for sharing his insights on the latest tools to diagnose nonalcoholic steatohepatitis. Dr. Cusi, it was great having you on the program.

**Announcer:**
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