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# Fatty Liver or NASH: The Future of Noninvasive Diagnosis and Assessment

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**Dr. Jacobson:**
Hello, and welcome to Fatty Liver or NASH: The Future of Noninvasive Diagnosis and Assessment. I'm Dr. Ira Jacobsen, Director of Hepatology at NYU Langone Health in New York, New York. I'm very happy to be joined today by Dr. Zobair Younossi, Professor and Chairman of the Department of Medicine at Inova Fairfax Medical Campus in Falls Church, Virginia. Zobair, it’s a pleasure to be with you.

**Dr. Younossi:**
Thanks, Ira. It's so great to be with you tonight.

**Dr. Jacobson:**
Now, before we start the program, I'd like to point out that many of the resources that we discussed today can be found on the NASH Clinical Resources Center on www.exchangecme.com.

Today we'd like to discuss findings from a forum of international NASH experts, which focused on the use of noninvasive tests in NASH diagnosis and management. While we encourage you to read more about the full forum findings in our recent publication, today, we'd like to highlight the key findings that are relevant to your practice. To develop this program, the chairs Dr. Younassi and I, developed seven clinical assertion statements, an international panel of NASH experts presented evidence for each statement. After often lively discussion and debate, the panel voted on the nature of the evidence presented, the level of support for the statement, and the level of acceptance of the statement.

In this program, we're going to present a series of questions embedded in the clinical assertion statements that clinicians face every day, we'll focus mostly on the level of consensus reached by the expert panel on these themes in order to provide you with key takeaway points applicable to practice. The nature of the evidence and level of support for each statement are discussed more fully in our paper.

Zobair, could you comment on why it's so important to focus nowadays on the use of noninvasive tests or NITs in NASH diagnosis?

**Dr. Younossi:**
Well, it's important to recognize that NASH is becoming a very common chronic liver disease. The prevalence of NASH has dramatically increased over the past few decades. In fact, in the United States, about 3 to 6% of general population is expec – is estimated to have NASH. Within the spectrum of patients with NASH, those that have significant scarring of the liver or fibrosis, they're at risk for mortality. In fact, those individuals that have a stage 2 or F2 and higher, they're at risk for negative outcomes. It's really not inflammation or grade of steatosis. That's a predictor of mortality, it’s the stage of fibrosis. Now of course stage of fibrosis historically, has been defined by a

liver biopsy. And liver biopsy is limited because it's invasive, there is sampling error, there is some inter and intra-observer variability.

In this context, a number of noninvasive tests have been developed. Some are blood based, and they use clinical parameters such as age to add presence of type 2 diabetes. There are indirect measures of fibrosis and there are some direct measures of fibrosis. Some of these are very easily available in the internet. So the serum for example, based tests, the one that is now approved in the United States as well as Europe in a number of different countries in the world is enhanced liver fibrosis test. FIB-4 which is an algorithm of clinical data as well as some laboratory data that is easily available in the internet and can be utilized in conjunction with the other tests. There are a number of imaging tests that measure basically the stiffness of the liver, based on elastography is also available and trans elastography and MR elastography being the two most common ones available.

So because of the importance of NASH in terms of its impact, its burden, and the fact that biopsy is the only thing that actually can predict the outcome, some noninvasive tests that can replace liver biopsy in terms of staging of fibrosis is important.

So the question that I have for you, Ira, is to maybe you can summarize the themes that were covered by the clinical assertion statements that you and I and the rest of our colleagues put together or addressed.

**Dr. Jacobson:**
Yes, of course, Zobair. So the major themes that we covered started with the issue of screening in patients with type 2 diabetes. That is, should all type 2 diabetics be screened for nonalcoholic fatty liver disease? We'll talk about that. We talked about the role of non-specialists, namely primary care physicians and endocrinologists in particular, but not necessarily restricted to those entirely in screening for NAFLD. And the role of transaminase levels in screening with particular attention to the issue of whether patients with normal ALT levels should be included in any screening program that we propose. We talked about the use of NITs, or noninvasive tests, to defer liver biopsy or avoid having to do it. Obviously, we can't be biopsying 80 to 90 million American adults. So this is a critical issue. We talked about the sequential in combination use of NITs for diagnosis and whether liver biopsy must be obtained as is presently stated in the ASLD guidance prior to initiating pharmacotherapy. We talked about the timing of routine monitoring and what the intervals should be between monitoring tests or if it should be done routinely in a longitudinal sense at all. And finally, we talked about a very hot topic that is still being developed, and that is the utility of genetic testing.

And with that, Zobair, I think we can go to the first question that we prepared for our audience. And that is do patients with type 2 diabetes present a high enough risk for NAFLD that all should be screened? So please take it away.

**Dr. Younossi:**
They should be screened for fibrotic NAFLD, meaning that if you're actually looking at steatosis in patients with type 2 diabetes, almost every one of them will have nonalcoholic fatty liver disease. So assessing for just NAFLD is probably not useful because they all have fatty liver.

On the other hand, patients with type 2 diabetes are also at risk for fibrosis. So they should be screened for fibrotic NAFLD or NASH, and in this context, really one of the noninvasive tests for fibrosis should be used.

Now, let me actually ask you, Ira, about the role of non-specialists in the management of NAFLD and NASH. What do you think their role is?

**Dr. Jacobson:**
Well in a nutshell, Zobair, their role is critical. I think everybody agrees on that. And they're really two questions encompassed here, rolled into one. We actually covered this question in two clinical assertion statements. The first is what test primary care physicians and others like endocrinologists should use? Much of the recent literature and I think real-world experience has focused on the use of the FIB-4, which is a well-validated noninvasive test for liver fibrosis. And just to remind our viewers, that's just a very simple formula of age times the AST and the numerator, and platelets times the square root of ALT in the denominator. And this test has very well accepted and robust cut-offs for negative and positive predictive values for advanced fibrosis or cirrhosis. This test has been shown to be at least as accurate, if not more so than the APRI. It's actually more robust than that, and probably comparable to or maybe a little superior to the NAFLD Fibrosis Score, or the NFS.

We focused on one study of thousands of patients from the UK, in which a FIB-4 cut-off of less than 1.3 was used in a primary care setting to defer referral to a specialist, and a FIB-4 score of over 3.25, which warranted referral to hepatologist. Now in the world of NAFLD, we actually use a score of 2.67 for its positive predictive value of about 80% in adv - for advanced fibrosis or cirrhosis, but that was the score used in that study. And the authors of that study, which we mentioned in our paper, showed that if you added for the patients in the gray zone of 1.3 to 3.25, which is a substantial population actually, the enhanced liver fibrosis score, and I'm just giving that now because we'll discuss it later, as an example of how you can do sequential testing, it greatly reduced the number of unnecessary referrals and it really resulted in a marked increase in the detection of advanced fibrosis or cirrhosis. So with regard to

what tests to use, and whether primary care physicians should do it, yes, the panel consensus was essentially universal.

Then we talked about whether patients with normal transaminases should be included in this net of patients, very large population, who should be screened if there are risk factors for NAFLD especially, but not exclusively type 2 diabetes. And the consensus was that, yes, we should include patients with elevated AL - with normal ALT levels. It's an important point because the American Diabetes Association and even some published algorithms in the hepatology literature specify that an increased ALT should be a trigger for evaluation. So we were kind of debating that point.

And in our paper, we actually cited several studies from around the world, including Asia, Europe, as well as the U.S. showing that in high-risk populations who were screened for fibrosis, especially type 2 diabetics, that mean ALT levels were found to be surprisingly low in those with moderate or advanced fibrosis and the 28 to 35 unit per liter range. So that's kind of a resounding affirmation for those who would favor this of screening for fibrosis in high-risk patients, even if their ALT levels were normal.

In the end, the consensus - the panel - the expert panel was split on whether fibrosis should be considered in patients with NAFLD, even with metabolic risks, regardless of transaminase levels, and I think that's because of the relative paucity of published evidence to support this as a cost effective approach. I think what everybody would agree on is that normal ALT here, if you're going to not screen based on ALT has to be defined very rigorously, it can't be what your lab tells you is the upper limit of normal, it has to be something like what the ASLD has put forward as a level of 19 for women and 30 for men.

**Dr. Younossi:**
I think more importantly, Ira, would be the conundrum that we face in this context is that there is a very low level of understanding and knowledge among primary care and endocrinologists about nonalcoholic fatty liver disease. I think there is probably a good understanding that they should be screened, these patients. But something else that needs to be addressed is how to raise awareness among non-specialists, especially at primary care where they see the vast majority of patients at risk.

**Dr. Jacobson:**
Agree. So, Zobair, back to you for the next question. And this is something that arises in clinical practice regularly, particularly for the many centers now increasing numbers of centers, that have transient elastography available. And that is whether a transient elastography score that predicts F3 to 4 fibrosis, justifies deferral of liver biopsy? Or is liver biopsy still necessary. So, Zobair, please address that question for us.

**Dr. Younossi:**
Well, I think you know, for stage of fibrosis, even today, liver biopsy remains a gold standard. However, because of all the things we talked about previously, it is really not necessary to do liver biopsy in the vast majority of patients. However, the noninvasive tests do have low positive predictive value, they have suboptimal positive predictive value for advanced stages of fibrosis, F3 and F4. So if you really, really want to know that someone has F3 and F4, at the moment, really deferral of liver biopsy cannot be justified.

Now remember, there is another reason to also do liver biopsy, and that's to exclude other liver diseases that could superimpose with nonalcoholic liver disease, autoimmune hepatitis, iron overload, other types of diseases that could exist. So there's some reasons to continue to deliver biopsy. And the panel consensus was that transient elastography of F3 and F4 does not justify deferral of liver biopsy just because of the suboptimal positive predictive value that this test has.

**Dr. Jacobson:**
Zobair, I can't resist drawing upon your expertise and run a question by you that you and I have discussed. It's based on my experience and that of other colleagues with whom I've discussed this, that often when transient elastography shows a high fibrosis score, that the score is lower and MR elastography. Do you have experience with MR at your institution? And can you just say a word about the role of MR elastography in our patients with NAFLD?

**Dr. Younossi:**
I think MR elastography is probably more accurate than trans elastography, and as you pointed out, the biggest problem with the MR elastography with is access. And, for that reason, I really don't use do different modalities of elastography. I go to another modality. So for example, if I have a discrepant FIB-4 and say trans elastography, my next test would be a blood-based fibrosis marker like enhanced liver fibrosis test.

And that's actually a question to you, Ira, what do you think ELF should be? Should it be an alternative to trans elastography in some of our patients in terms of clinical practice?

**Dr. Jacobson:**
Yes, indeed, our panel discussed this at some length. And this is an important new introduction to the diagnostic armamentarium. For

those not entirely familiar with it, this is really a panel of three markers that directly reflect the fibrotic process. And those are hyaluronidase tissue inhibitor of metalloproteinase-III, and procollagen-III, and terminal peptide. And there's a proprietary formula that the laboratory that does this applies to these markers once the results are obtained in the lab, that gives you a numerical score, just like FIB-4 or transient elastography do, respectively. And they are well established cut-offs that estimate with a fairly high level of accuracy, the degree of fibrosis or lack thereof. So just, for example, in ELF, or enhanced liver fibrosis score, or a threshold of 9.8 had a sensitivity and specificity in one study of 72 and 90%, respectively, for advanced fibrosis or cirrhosis, namely F3 to4.

The reason that we thought this test was worth emphasizing, in particular, is that it was approved in Europe over a year ago, and it was approved in the United States by the FDA back in August 2021, not long ago. And interestingly, the literature around this test includes its use as a prognostic marker, specifically it's an algorithm as stated in the literature on it to assess not only the likely to progression to cirrhosis, but also liver-related clinical events because there are a rich data suggesting that it can indeed be used as a clinical prognosticator.

So the interest in it has centered largely on its use as a second line test in a sequential testing algorithm or strategy. And in a clinical trial that we review in our paper with a high prevalence - in a population with a high prevalence of advanced fibrosis, FIB-4 plus ELF compared favorably to FIB-4 plus transient elastography. Our panel discussed this at some length and concluded that ELF, indeed, may provide an alternative to transient elastography.

**Dr. Younossi:**
Now the one thing that I agree with is that the best use of ELF is in conjunction with another test like a FIB-4. In fact, prospectively, we've done a study that was published since we had the consensus group here that was published in JAMA, and it showed that using different cut-off points, you can – of FIB-4 followed by ELF, you can maximize not only the negative predictive value of advanced fibrosis, but you also can actually maximize to over 95% positive predictive value for advanced fibrosis. So by looking at the prevalence of fibrosis in the population, and different thresholds for FIB-4 and ELF, you can actually optimize their performance. So I think that's how we're going to use it in the future.

**Dr. Jacobson:**
Oh, very good. So let's go on to the next question. And this also comes up in practice every day, which is whether a liver biopsy is essential as suggested in the ASLD guidance document from 2018 before initiation pharmacotherapy?

**Dr. Younossi:**
Well, I think, you know, we just want to make sure that we understand sort of the context. If we do - if we are assessing someone for pharmacotherapy in the context of clinical trial, then clinical trials do require a liver biopsy, or at least at the moment. Outside of clinical trial, when you're looking at sort of potential treatment with pharmacotherapy or even weight loss and lifestyle management, at least NITs will give you a better - sort of a better insight about the prognosis of this patient that's in front of you. So you can utilize, of course, in the NITs that we just talked about.

Now, there is also FAST and NS4 tests. These are a combination. FAST is actually AST cap and NS4 is a test that's actually now is also available that not only can give you some assessment of fibrosis, but also activity which has historically been measured or by - or assessed by presence of steatohepatitis, which is really only a histologic diagnosis.

Now, regardless of which test you use, there's going to be, you know, about a third of patients that fall in the indeterminate zone that you can't really call about the - call them as high risk. So, and there's context for most patients, I think that you could probably use an NIT to predict long-term sort of outcome and potential clinical events.

So the consensus panel is probably more aligned with the feeling of other experts in this field. And at least the panel decided that liver biopsy is really not essential prior to initiating formal pharmacotherapy. And I think you have to sort of consider what are some of other comorbidities that you're dealing with? And whether that also can play a role in terms of risk and benefit of the drug that you're using before considering a liver biopsy or not, but I wouldn't use it universally before making a decision at this point.

**Dr. Jacobson:**
Zobair, if I can add one question to that, you know, the other reason arguably that one might want to do a biopsy if you suspect advanced fibrosis, is to determine whether the patient needs to be screened every 6 months for HCC, which we know is a big risk in NAFLD patients with cirrhosis. This gets into the whole question of whether F3 patients should be screened. But without going into all of that, do you think there's an argument that can be made that can solidify your intent or feeling perhaps that you don't need to do screening for HCC?

**Dr. Younossi:**
Now obviously that would be if the patient really wants to know and if you really want to be certain, liver biopsy is of course the only way

to determine that. However, if I have a patient with two tests a FIB-4 or trans elastography, or a FIB-4 followed by an ELF and both are consistent with very high degree of fibrosis, and I really consider F3 and F4 as sort of advanced fibrosis, and they both are probably at risk for HCC. Without liver biopsy, I do screen out those patients. There are athletes in my practice considered as high risk for HCC and they are screened.

**Dr. Jacobson:**
Yeah, I'm pretty expansive about that too.

**Dr. Younossi:**
Right. Right. So, I think you know, one of the things that NITs have not clearly established as whether you can use them for monitoring. However, this is sort of a growing field, whether these in it is have the power to detect small changes and fibrosis or can actually predict either regression or progression of fibrosis. So what do you think, Ira, about NITs and whether it should be used to monitor patients?

**Dr. Jacobson:**
Yeah, in our paper, we do cover some published evidence indicating that increases in NIT values really are associated with increased risks, not only of histologic progression, but also clinical progression. But this includes but is not limited to elastography. It also includes some of the serum markers. Conceptually, of course, it's very easy to accept the idea that an increase in NIT values might well have prognostic significance and/or dictate changes in management, perhaps, you know, going from conservative management with lifestyle interventions to pharmacotherapy, as well as issues like screening for HCC, which we discussed briefly before.

Now we all agree that progression is usually slow. We know from a large meta-analysis that we cover in our paper that one stage progression in fibrosis in a large study population, of those who started with NAFLD alone without steatohepatitis had a mean of 14 years to go from one stage to another, and with NASH, it was half that, 7 years. But in that study that I just quoted, 20% of the patients were actually outliers who had rapid progression from stage 0 to stage 3 or 4 within a much shorter time period covered by the study.

And as in other studies of the major predictors of progression included an inverted ASP to ALT ratio, and importantly, the presence of hypertension, not to mention type 2 diabetes that has unequivocally been associated with faster progression in many published studies.

So the panel consensus here was indeed to perform noninvasive tests. And we had quite a bit of discussion about what the intervals should be, because that's obviously subject to debate. This statement in itself was not accepted by all the panelists, but I think it's fair to say that the disagreement was not so much with the concept of serial monitoring, but with what the intervals should be because I think one can argue for example, whether a patient with NAFLD alone and NAFL without steatohepatitis really needs to be monitored every year.

There was certainly general agreement that type 2 diabetes, metabolic syndrome, hypertension, or the finding of an elevated ASD to ALT ratio, may warrant, in fact does warrant more frequent screening.

And Zobair, this is a question that I picked your brain about repeatedly over the last few years, when I've wondered about the role of genetic testing, because there are some genotypes, as you well know, that are definitely associated with not only steatohepatitis, but potentially rapid progression to clinical complications. So we did pose the question in our clinical assertion statement meetings of whether genetic testing has a role in NASH evaluation management. Can you please comment on that?

**Dr. Younossi:**
Yeah, so there are - obviously, there are a number of genetic tests that have been used to at least associate with progressive liver disease or adverse outcomes, including HCC and advanced fibrosis. PNPLA3 is the one that's been most commonly referred to associated with advanced fibrosis. And there are actually genotypes that that are, quote unquote, protective against adverse outcome. The unfortunate situation is that these studies are not prospective. They're not large, large cohorts of patients. So their validity in terms of predicting outcome has really not been established. There is a low sensitivity for some of these tests in terms of prediction of both risk of fibrosis and HCC.

So the panel discussed this, and we all agreed that genetic testing currently to stratify patients is really premature at this point. So and truthfully, in clinical practice, I don't use these tests, but they are quite interesting. And maybe in the future, they will have a role in terms of individualized sort of assessment and management of these patients.

**Dr. Jacobson:**
So how much is the thought that it's premature related to the fact that the information would not be therapeutically actionable? Is that really the issue? And are these analyses being done retrospectively in some of the clinical trials going on with therapeutic drugs so that we might indeed stratify patients' responses by genetic profiling?

**Dr. Younossi:**

Yeah, I think in the future, if there is going to be effective treatment, there would probably be, you know, biomarkers that will accompany those treatments to stratify who's going to be a responder or a nonresponder, and maybe genetic testing will have a role. I think at this point, the evidence is not strong enough to really put this into clinical practice.

Now let me just actually give you, if you don't mind, Ira, just to summarize some things that we talked about today. And then maybe it will - maybe you can then close with some points at the end, that the manuscript that we have really concludes that that NITs have really a crucial role in the management of NAFLD and NASH. And it seems like actually a combination of blood-based NITs and some of the sort of those clinical algorithms that are available on the internet by primary care physician, endocrinologists to identify high-risk patient and refer to those to liver specialists will be key.

It seems to me that a combination of either a FIB-4 followed by either a trans elastography or ELF or even MR elastography could give us a pretty good predictive value of not only excluding advanced fibrosis, but also including advanced fibrosis with a high-positive predictive value. At least in 2022, a role of liver biopsy is very, very limited. It should be used, of course, for those who go for clinical trials. If you suspect there are superimposed liver disease, of course, that's the situation the liver biopsy will be important. It's really not absolutely required to do a liver biopsy prior to pharmacotherapy outside clinical trial. And it seems that at least our panel agreed that some periodic monitoring using trans elastography and possibly even other tests such as ELF can be justified in the future. At least as we just discussed, Ira, genetic testing is currently a little bit premature to be widely recommended. But we know this is all coming down the pike.

**Dr. Jacobson:**
Thank you, Zobair. So a few final points for our audience. First, thank you very much for joining us and watching our program today. Please do see our publication to review additional data and takeaways that we think you'll find very valuable in your practices from the forum discussion. Please remember to take the post-test and fill out the CME evaluation.

Zobair, it's always been a privilege to have the opportunity to work with you and indeed to be a friend and colleague over the years. I very much enjoyed doing this with you as well today. Thank you.

**Dr. Younossi:**
Same here, Ira. Thank you very much. Appreciate it.

**Announcer:**
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