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Advances in the Treatment and Management of MASH: More Options, More Decisions

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Chapter 1
MASLD: From Epidemiology to At-Risk

Dr. Rinella:
So welcome, everybody. I think we have a really exciting program today, and we were just sort of introduced, but I'm Mary Rinella. I'm from the University of Chicago. To my left is Professor Naga Chalasani, who really doesn't need much introduction. He's really been an incredibly influential person in this field since the very, very beginning. And to my right is Mazen Noureddin, who is also a star in the field. And actually, I met him when he was a resident, right? Yeah. Or actually, a medical student. I'm older than you, clearly.

Okay. All right, so why don't we go ahead and get started? These are our conflicts of interest, which are also – you have access to them independently as well.

And just to start with the learning objectives, what we're going to do is walk through several key aspects of how to identify patients. So after participating in the activity, you should be able to take the appropriate action in patients with risk factors for MASLD/MASH and give risk stratification or appropriately risk stratify them. You should also be able to demonstrate best practice for management of patients with MASLD and select appropriate treatment for those with at-risk MASH.

The first thing we'll start with is just the new nomenclature. In case you're not aware, there's been a change in the nomenclature which we'll be using throughout the presentation. You've probably seen it at meetings, and certainly in this meeting as well. But basically, NAFLD is now MASLD, metabolic dysfunction-associated steatotic liver disease. And within that we have the non-inflammatory subtype, which is MASLD, and MASH, which replaced NASH. We won't be talking about MetALD or the other categories of steatotic liver disease here.

So an adult with steatosis in whom other causes of steatotic liver disease have been ruled out, what is needed to confer a diagnosis of MASLD? One cardiometabolic risk factor; at least 2 cardiometabolic risk factors; 3 cardiometabolic risk factors; or all 5 cardiometabolic risk factors.

So we made this diagnosis on purpose or intentionally very open, and the reason for that is we wanted to have very significant overlap with the NAFLD population to not alter natural history data. So all you need is one cardiometabolic risk factor in the presence of steatosis and no other disease that would explain that.

So we're going to start with Dr. Chalasani. He's going to walk us through epidemiology and at-risk patients at high risk for disease progression.

Dr. Chalasani:
Yeah, thank you. Mary, I just want to start by congratulating you, as I think about it, in last 15 months, probably 2 of the most influential papers. One is the nomenclature paper, and the other one is the practice guidelines. And really spectacular. Congratulations. And I know it took a lot of work for you to put them together, but I think they've been quite instructive for me and colleagues as well. So to be really a privilege to be on the stage with you, and with you, Mazen, really brilliant, as well.

So just a slide about how common MASLD and MASH in the US. And I think you know; that's why you were sitting here, incredibly common. If you just look at MASLD, up to 1/3 of US adults will have MASLD; it's just a matter how you look for it. If you're looking for MASLD using MRI, it's about 35%. Whereas, if you use only ALT, it's about 7% to 10%. Really a point to be made: ALT is oftentimes not elevated in patients with MASLD. If you're just using ALT, you're going to miss about 2/3 of the cases. MASH is anywhere from 3% to 12%. And importantly, you will see this concept come up repeatedly called at-risk MASH. Basically means you have MASH plus also at least stage 2 fibrosis. This is data from a paper that came from our group, anywhere up to 6% of US adults may have at-risk NASH. Really striking is anywhere from 9% to 22% of type 2 diabetes will have at-risk NASH. Really, you will see this again. At-risk NASH is sort of the kinds of patients we enroll into clinical trials. They are the patients studied in the trials, Madrigal phase 3 trials. These are sort of the potential candidates. So there is a sizable number of patients with at-risk NASH in the US.

Dr. Noureddin:
Can you tell, for those that they don't know, what's the difference between at-risk NASH and MASH?

Dr. Chalasani:
MASH is steatosis, MASLD with ballooning with or without fibrosis. Okay? Really, what distinguishes MASLD from MASH is the fact that they have ballooned hepatocytes. When we started the field, we thought you needed to have some degree of fibrosis. That proved not to be the case. Whereas, at-risk MASH is you need to have at least stage 2 or higher fibrosis, but you need to have MASH as well. They are the kinds of patients that get enrolled into phase 2b and phase 3 trials.

This is from the original practice guideline. On the left side, you see major comorbidities in MASLD, type 2 diabetes, dyslipidemia, obesity, and metabolic syndrome. Up to 80% of type 2 diabetics will have MASLD. 50% of these patients with dyslipidemia will have MASLD. Obesity is just a matter of degree of BMI or higher the body weight more likely you're going to have MASLD. On the right side, the important endocrine disorders, hypothyroidism, sleep apnea, hypopit, hypogonadism. Really, this MASLD is an endocrine disorder. This is as important to us gastroenterologists as it is for endocrinologists as well. Really, the importance of this slide is if you're seeing in a newly identified patient with MASLD, these are the kinds of things that you'd like to drive when you're trying to get your history or when you're trying to do the workup. And the polycystic ovary syndrome is really important as well, because they're going to have premature advanced fibrosis in women with PCOS.

What started as liver NASLD, MASLD being sort of liver centric, now we've come to accept it is a systemic disorder here. Even going back to 20 years ago, people have made a point that it is a component of the metabolic syndrome. You have seen Dr. Rinella has shown 5 components of the metabolic syndrome. People have argued it should be the sixth one. And really, most patients that we see are enriched with metabolic risk factors. That's really what this slide and the cartoon show. Multiple things, gut microbiome plays a role, genetic factors, and so forth.

This is an important slide, though. MASLD occurs in the background of systemic inflammation, but it is a bidirectional. The background inflammation can drive MASLD, but the MASLD can drive inflammation, is linked to atherosclerosis, especially atherogenic dyslipidemia, cardiovascular disease, and so forth. I'll touch on this in a few slides.

MACE stands for major adverse cardiac events. These are sort of if you study cardiovascular literature, are there trials? The cardiac trials use MACE as the primary endpoint. MALO is the major adverse liver outcomes. And others really showing patients with MASLD who are at risk for MACE, MALO, a number of other causes of morbidity and mortality.

Dr. Rinella:
I think Mazen coined that term.

Dr. Noureddin:
I don't know. It's like MASLD, MALO, MARU.

Dr. Chalasani:
Congratulations. You know, I'm sorry. You didn't trademark it, so we've been using it.

So next 2 slides, though, make the point that in patients with MASLD, the most important thing is the degree of fibrosis. This slide is

from the late Dr. Paul Angulo. He published this paper right before he passed away, large multicenter study. Prior to this paper, we were thinking MASH without really attention to fibrosis was the driver of mortality and morbidity. Here he has shown a couple things. It is not the MASH; it is the fibrosis. That is the most important thing for long-term adverse outcomes. Those are the Kaplan-Meier curves. On the right side in the table, I'm not sure how well it is showing up, but he makes the point in 2 different multivariate models, stage 2 or higher fibrosis is what is associated with long-term poor outcomes. Really, I think this is a landmark paper. This is sort of the foundation for at-risk MASH in clinical trials and so forth, even the FDA approval.

This is from our group. The same thing once again. Here, this trial, this study included patients with F3 and F4, bridging fibrosis and cirrhosis. Couple of points I want to make, though, is in this study, in addition to liver-related outcomes, there were a number of vascular outcomes, non-hepatic malignancy, so patients with MASLD are at a higher risk, for example, colon cancer, breast cancer, and so forth. And within the NASH cirrhosis, especially compensated, just the Class A5 versus A6, very compensated versus who are on the verge of becoming B, Class B, there is a striking difference in the natural history. You can see, for example, all deaths or liver transplantation in A6 is about 11% as opposed to 2.1. So that's the important point, when you have a compensated cirrhotic in your office, trying to distinguish A5 versus A6. And then I think this has been the problem in the cirrhosis trials. They have sort of put them all together, A5 and A6, and that's just a very mixed bag.

And on the far right side, you see the risk factors. If you have MASLD cirrhosis, any amount of alcohol is dangerous. That comes out in this paper, and the fact that you have cirrhosis is not very good. And interestingly, if you have MASLD and cirrhosis, the lower the fat, worse the outcome. I think we know as the fibrosis gets worse, the fat disappears. That's why when you have a Child's Class B or Child's Class C MASLD cirrhosis, they may no longer have any fat at all.

This is a question for you to answer: What is the most common cause of death in patients with MASLD? Cardiovascular disease; decompensated cirrhosis; extrahepatic cancer; and hepatocellular carcinoma. We don't have the answers, right? We get the answers at the end?

Dr. Rinella:
I think we know the answer.

Dr. Chalasani:
I know. I'm just asking.

Dr. Noureddin:
Eventually, right?

Dr. Rinella:
Yeah, that's what I was about to look and see if people were answering them. Anyway, go ahead.

Dr. Chalasani:

So we touched on this. So the most common cause of death in all-comer MASLD is cardiovascular disease by far. Original data have come from Rochester, and I think multiple studies have proven that point. However, though, when you have MASH, especially with fibrosis stage 2 and stage 3, liver disease becomes far more important than cardiovascular disease. Let me make this distinction again: all-comers MASLD, cardiovascular disease is the most common cause of death, but if you have MASH and if you have advanced fibrosis, liver-related outcomes become far more important than cardiovascular. Okay?

Just a couple more slides here showing the same thing in a tabular form. Within MASLD, there are 4 sub phenotypes. There is MASL, not MASLD sorry, MASL, there is MASH with stage 0 or 1 fibrosis, then MASH with stage 2 or stage 3 fibrosis, and MASH with cirrhosis. So what you see is in MASL and MASH with early fibrosis, cardiovascular disease is the most common cause of death. If you just look at the fatty liver – excuse me, steatotic liver, that is what about 80% of patients with MASLD will have, just the MASL. CVD is the most common cause of death, non-hepatic malignancy. Actually, top 4, you don't even see the liver disease. Liver disease becomes important as you accumulate fibrosis. On the far right you're seeing is the MASH cirrhosis. Most common cause of death is liver disease, followed by cardiovascular disease, then cancers, maybe renal disease as well. This is one other important point: Patients with MASLD and MASH are at higher risk for kidney disease, rapidly progressive disease as well.

Just the framework, how you manage with MASLD. I think you all know this, but just to put this into perspective for subsequent cases and discussion. So if you have MASL, so you should do lifestyle management but no liver-directed pharmacotherapy, because, as I explained to you, their risk of dying from liver disease is very minimal. But you must manage comorbidities such as diabetes and hypertension and smoking and so forth. If you have MASH with stage 0 or stage 1 fibrosis, it's more or less about the same, lifestyle management, management of comorbidities. You don't do liver-directed pharmacotherapies. For example, the only drug that's

approved, resmetirom, is only approved for patients with MASH and stage 2 or higher fibrosis, of course, without cirrhosis. So in patients with stage 2, stage 3, or stage 4 fibrosis, that is cirrhosis, you do all, just not only liver-directed therapies. You must advise them lifestyle management.

And, Dr. Rinella, you have a great multidisciplinary program where you're really into comanaging patients with a dietitian, and I think you even have a behavioral help.

Dr. Rinella:
Yeah, we have an endocrinologist as well.

Dr. Chalasani:
And the management of comorbidities. And I think it's really important. I think we are hesitant to give statins for patients with dyslipidemia in MASLD. I think it's really important. I think, as I said, they die from heart disease, therefore just the backbone to treating dyslipidemia in MASLD or in general population with statins, the risk of liver toxicity is quite minimal, so I strongly encourage you to consider statins in this population.

Dr. Rinella:
The only thing I'll add too, Naga, is that I think – so the reason why we treat the comorbidities, as Naga mentioned, with statins, but is also true for things like GLP-1, modifying hypertensive agents to not be obesogenic, putting them on the right diabetes medications, because it'll improve cardiovascular outcomes, but it also reduces the risk, potentially, of progression of liver disease when you're starting in an earlier disease stage. So you want to prevent people from getting more advanced disease too.

Dr. Chalasani:
Yeah, you're right. And I think there are a number of papers showing that patients who are on statins have less severe disease. I don't think well-controlled, randomized trials have been done with statins, but I think there are a number of epidemiological studies as well.

Dr. Noureddin:
Yeah, and the cancer too, right? There's been some data showing that it prevents from liver cancer. So we put patients back on statins often when the cardiologist or the primary care is like, oh, that's the cause, and you're like, no, it's actually not. It's MASH and go back on your statins.

Dr. Chalasani:
Can I ask you, both of you, have you actually managed dyslipidemia in your MASLD patients? Or do you send them back to endocrinologists or PCPs?

Dr. Rinella:
It depends. I will treat hypertriglyceridemia, and I'll treat basic elevated LDL with a statin if they're not on a statin. Many times, I'll just have a communication with the primary care doctor, and if they have high ASCVD risk, I'll recommend and if they start it, I'll start it.

Dr. Chalasani:
And obviously, when you put somebody on statins, their ALT will go up. Sometimes, right? I mean, up to 20% in the package insert. I just wonder, what is your comfort zone? How high you will tell the PCPs or endocrinologists it is okay to continue ALT?

Dr. Rinella:
Do you want to answer, or do you want me to?

Dr. Noureddin:
I mean, I usually, to answer the initial question, I do not manage the statins. But you're making a very important point, I will say, in a second. So most of the patients come to me and it's after the fact; they were on statins, the enzymes probably went up a little bit, then they took them off, and they went down a little bit or they did not come down. So I just say go back to your primary care or cardiologist and put them back. But to answer your question, is probably 5 times, and I don't know what's the magic number.

But also, now, things changed a little bit for me, because with the new approved therapy, resmetirom, you have to adjust the statin dose. And it's just like that's the label recommendation. It's not interaction or anything like that, and the resmetirom will lower the lipid panel. So now I pay attention to the medications, and I adjust the statin dose, and I educate them that, hey, listen, tell your cardiologist or the primary care this is because we're starting this drug and just watch. Nothing's going to happen; actually, it might even get better with resmetirom. It does.

Dr. Rinella:
It does, yeah. LDL goes down. It initially developed as a lipid-lowering drug. So it lowers LDL and so, yeah, so you need to dose down

potentially, yeah.

Dr. Noureddin:
But it's one of the things on the label that people need to pay attention to. What's like, Lipitor 80, it shouldn't be 80 and we drop it here. So this is when I started interfering a little bit and say drop it. And I actually initiated and said it's okay, drop it, and then I'll talk to your cardiologist.

Dr. Chalasani:
Just the majority of MASLD patients we see aren't necessarily on resmetirom but they're likely on a statin. And my comfort zone has been up to 150 ALT, 120 to 150.

Dr. Rinella:
I must say, I don't really see much elevation with statins that I initiate. So maybe I'm just, I don't know. I'm not seeing that high elevation. It would make me nervous, 150.

Dr. Chalasani:
Yeah, as long as total bilirubin is normal, they're asymptomatic, and I think you can try, and I think usually they settle down.

I think that's sort of the background discussion. I think next I'll go to case 1, unless we have more discussion here.

Chapter 2
Case 1: A 48-Year-Old Hispanic Woman Referred by Her Endocrinologist

Dr. Chalasani:
So case 1 is a 48-year-old Hispanic woman referred by her endocrinologist. A medical history of type 2 diabetes, sleep apnea. Medications: albuterol, metformin, and spironolactone at a low dose, 50 mg. Denies alcohol or smoking. And the exam shows BMI of 35, waist circumference is about 100 cm. Blood pressure is 130/80.

Mazen, what's your initial impression of this particular patient without looking anything else? What are just your thoughts for that?

Dr. Noureddin:
I'll tell you in a second my impression. But honestly, I got distracted a little bit with the spironolactone.

Dr. Rinella:
Yeah, me too.

Dr. Noureddin:
I didn't see this case earlier, so I'm just wondering why the patient is on spironolactone. But this is my impression. Earlier in my career, I trained on viral hepatitis and all this. We used to look at screens and viral load and hepatitis C viral load and ALT and AST. Here, this is what we're going to look for now. I tell my fellows, now look at the comorbidities. Look what the patients have looked like. So 48, Hispanic, type 2 diabetes. This is a slam dunk. This patient has MASLD and likely has at-risk MASH or significant fibrosis, because the data on type 2 diabetics, they have higher prevalence. Like, multiple risk factors. There's the Hispanic, the age, that's young, type 2 diabetes, the BMI. So multiple, multiple risk factors. So this patient likely will need eventually – I could be wrong and she could be lucky – but this is a patient that definitely we need to work her up.

Another point that, please spread it to your primary care and endocrinologist, and we'll talk about in the guidelines, this patient, if they're sitting in their clinic, it needs to be screened for MASLD, not ignore it. And we'll talk about FIB-4 and all this when we get to the algorithm. So that is my first impression on this lady.

Dr. Chalasani:
And what do you make out of sleep apnea, which is sort of the –

Dr. Noureddin:
Yeah, there's association. We have seen it with MASLD and MASH and all this. So definitely something that, I mean, you talked about hypothyroidism, PCOS, and all these, they come together.

Dr. Chalasani:
Really high-risk, high-risk group. I just wonder, Mary, the age 48, perimenopausal, what are your thoughts about that, particularly with menopause, sex, and the risk for MASLD?

Dr. Rinella:
Yeah, so we think that with menopause or with the reduction in estrogen and a relative increase in testosterone in women, you see

more progression of disease in that population, so you see sort of a concentration or an acceleration of fibrosis in the postmenopausal years. In fact, testosterone is the opposite in men, actually.

Dr. Chalasani:
So as was pointed out, the risk of MASLD and MASH in the US Hispanic, Latino, Latinx is quite high. Poor prevalence can be as high as 60%, and at-risk MASH is close to 1/4 of Hispanic individuals. MASH cirrhosis is 5% and they're just high risk. And maybe you both can sort of discuss about why Hispanics are at a higher risk. I mean, within the Hispanic ethnicity, there are Caribbean, Puerto Rican, and South American. I just wonder what are the differences, and what's sort of the major reason for high risk?

Dr. Rinella:
So I can start, I guess. So, yeah, so that's a really important point. So not all Hispanics are the same. Those that have origin in Mexico and Central America have a very high prevalence of a gene called PNPLA3. Actually, 70% in Mexico, about 60% of Hispanics in the US of Mexican ancestry have this gene. And what this gene does is it accelerates the risk for fibrosis, and it also accelerates the risk for hepatocellular carcinoma.

Mazen, want to add?

Dr. Noureddin:
No, you said it very well.

Dr. Chalasani:
Yeah. Yeah. Right. I think it is certainly PNPLA3 G allele, and I think, as you said, quite high, but just the fact that the diabetes also, right?

Dr. Rinella:
Of course.

Dr. Chalasani:
And the 2 of them together, so, yeah.

Dr. Noureddin:
I mean, this is what I tell my patients, there are a few cultures that they use rice and bread quite often, carbs, you know, Hispanics, tortilla and rice. I'm Middle Eastern, so we use pita bread and rice as well. The Indians, there's naan bread and rice. So you see a lot of MASLD and MASH.

Dr. Rinella:
Yes, in those populations. And actually, Stephen, our dear friend, Stephen Harrison, he used to say call it tortilla poisoning.

Dr. Chalasani:
Tortilla poisoning.

Dr. Rinella:
Yeah, anyway.

Dr. Chalasani:
But I think the take-home is Hispanic ethnicity and diabetes for all purposes, and then you add obesity, like this particular patient, equals to MASLD, just not MASLD/high-risk MASH, likely. You're talking 2/3 to 75% likely that you have clinically very important MASLD here.

Dr. Noureddin:
Do you want to comment on the African Americans by any chance? Like, what is your understanding? Because the data is not quite clear.

Dr. Chalasani:
We just published a paper and Neha is the first author on it from the NASH CRN, highest risk race/ethnic group obviously is Hispanic. Caucasians are in the middle. African Americans have about 1/2 the risk. And that is, once again, tracks to PNPLA3 G allele being about only half as common. And then also, their dyslipidemia is interesting. They don't have hypertriglyceridemia, and their HDL tends to be high as well. And they seem to be biologically protected. But I would say, though, it is not absolute, you know, it's about 12%. There is a large study in the HIV population that we are doing. In Caucasians, it's about 25% prevalent. In Black Americans, it's about 12%, so it's not entirely absent, but it is lower. And then also, it's not as severe.

Dr. Rinella:

Right. And we're a mixture, but most people are a mixture, and that's why I think you see a lot of –

Dr. Chalasani:
Yeah. Interesting, though, if you look at the UNOS database to see how many Black individuals have been listed for transplant for NASH/MASH, very few.

Dr. Noureddin:
It's just access too, right? It's access as well.

Dr. Chalasani:
Yeah. Yeah, totally. It's a combination of biology plus poor access. I agree with you there. Let's keep going.

This is from the guidance document. There is just a beautiful algorithm. And when you suspect steatotic liver disease, how do you work them up? You authored this. Maybe you could walk us through.

Dr. Rinella:
So the intention here, I think, was to provide some guidance for people in the primary care and non-hepatology setting, in addition to those in the hepatology setting. So for everybody, the first thing you start with is a FIB-4, which is basically calculated from ALT, AST, platelets, and age. And the thing to remember about that test is if you're in a low-prevalence setting, that has a very high negative predictive value. So if you have a low FIB-4, the likelihood that your patient has significant fibrosis is really, really low. And so the purpose of it really is to reassure primary care doctors that those patients can remain in their care and they don't need to be referred.

In patients who have a higher FIB-4, then that's where you need to do secondary testing. You can use VCTE. ELF is available and approved by the FDA for prognostication. And then after you have those data, if the patient's high risk based on those or even intermediate risk with risk factors, that's where you can refer for further care. So I think from there, once you're in the gastroenterology space, which is most of you, probably, here, you may want to consider doing additional testing for risk stratification and sometimes liver biopsy, if the NITs are discordant. Okay? So if you get a high value for, let's say, ELF but a low value on VCTE, that's a patient you may want to consider doing a liver biopsy to clarify.

And the other thing I want to note about patients who are high risk, like that Hispanic patient with all those risk factors, sometimes FIB-4 is not very good in that population, actually, so you probably should put a little bit less weight on that.

Maybe, Mazen, you can comment a little bit on that in the enriched population if you know the performance of FIB-4.

Dr. Noureddin:
Yeah. I mean, in my opinion, FIB-4 is a very useful test in the general population and to discover those with high risk. For transparency, I don't use FIB-4 in my office; I go straight to transient elastography. But since the guidelines list this and the AGA pathways and all this, people used not to do anything. And I think one of the key messages there that you need to tell your primary care and endocrine about this test is age, platelet, AST, and ALT. And values less than 1.3, this is what I try to make them focus on. Less than 1.3 stays with you, more than 1.3, they don't like this indeterminate zone, and more than 2.67. So I make it easier on them, although it's going to cause a flood. That's how I do it simply. But also, like, it has some, to your point, some probably performance issues on the type 2 diabetics, so it might be less accurate. And there's also age. So for instance, age of more than 65, you really need to increase that 1.3 to 2. So things that you pay attention to. Sometimes the primary care and endocrine, they get frustrated, but all it takes is you discovering that cirrhotic patient that was embedded in their practice and they did not pay attention to, and then they start paying attention. I think it's a huge step.

Dr. Chalasani:
Yeah. Yeah, that's a really good point. Though, I think I'm sure you're seeing NASH patients with cirrhosis from MASH. And then many times they're sure, right? They have had elevated liver tests for a decade or 15 years. Not common, but many times.

Dr. Rinella:
Or just fatty liver.

Dr. Chalasani:
Yeah, just ultrasound showed something, and that hasn't been worked up. So I think if the primary care used FIB-4, I think it has a lot of problems, but in a primary care setting, I think it can be helpful.

Dr. Noureddin:
Absolutely.

Dr. Chalasani:
I would ask you, though, in the patient that we saw, 48-year-old Hispanic woman with the risk factors, what's the first thing you're going

to do? You going to do imaging, or you're doing VCTE? You're not doing this algorithm, right? You don't have to.

Dr. Rinella:
I know. And we're in a quaternary care clinic setting so we actually just do VCTE on all of our patients that walk in the door, because we have it right there. And especially in her, when diabetes and her performance is a little bit less good. But I think that, just to hammer home the point, if you have a really high-risk patient like the person that Naga just mentioned, you probably shouldn't put a lot of weight on FIB-4. You really do need to do secondary testing in that particular patient, I think.

Dr. Noureddin:
Yeah. And I do FibroScan. So it's 8:30. How many people here have transient elastography? If you want to raise your hand. That's good. How many people use the alternative test in the guidelines, which is the ELF? How many? One person, two. Okay.

Dr. Rinella:
Wow, two.

Dr. Noureddin:
But they are, as Dr. Rinella mentioned, is like FIB-4, and then they come to us. When we have to narrow it down, we do have options between transient elastography versus the ELF. Actually, there are other tests in development out there that you can read through, multiple things. So it's an evolving field, but this is where the guidelines is.

Dr. Rinella:
Right, and you'd be surpris – oh, sorry.

Dr. Chalasani:
I would say one thing, though. I'm surprised ELF isn't being used as widely. It's at least been approved by the FDA for risk stratification of patients with MASLD a while ago, at least 2 or 3 years ago. Really predicts outcomes as well. So I think if you don't have ready access to a FibroScan or MR elastography or MRI-PDFF, etc., it's one that you could order. You know, I think LabCorp or things run it.

Dr. Rinella:
Yeah. No, the only caveat with ELF is that it was really developed in people with a lot of fibrosis, and so the accuracy is not as good if you use it as a single test. So I think if you're going to use that, if you can try to get imaging-based elastography, that'd be better. And a lot of times, in your universities or your local hospitals, you'll have ultrasound-based liver stiffness testing. You can do that too because you probably have access, even if you think you might not.

Dr. Noureddin:
So it's important. Like, you don't have to have a FibroScan. Actually, there are other machines, and they are ultrasound-based elastography. All you need is something to measure the stiffness in any surround. So radiology can have it. Any radiology practice can have an elastography-based test.

Dr. Chalasani:
Just the bottom line, though, is to somehow stratify the risk, whether you do FIB-4 or ELF or VCTE, whatever it is, and trying to say whether this is high risk for complications or not. Really. That's really sort of the core purpose here.

So one of the things is, in this patient, I think you want to rule out other causes of steatotic liver disease, medications you have, alcohol consumption is really important, HIV, and some of these acquired metabolic diseases. I highlight, though, tamoxifen is a really important cause, especially now with tamoxifen has been recommended for up to 10 years for hormonal therapy for breast cancer. It can cause steatotic liver disease, and it can actually rapidly progress within a 5-year time horizon to MASH and cirrhosis as well. Keep that in mind. You may get consults from your oncologist about safe use of tamoxifen, which is fine, by the way.

Dr. Noureddin:
What do you do?

Dr. Chalasani:
What do I do? I let them continue tamoxifen, but I just do serial elastography.

Dr. Noureddin:
And if they go up, do you ask them to switch? What's the other one?

Dr. Rinella:
You can do a biopsy too.

Dr. Chalasani:
You can biopsy them. And I think there's a second-generation of aromatase that is –

Dr. Rinella:
Arimidex.

Dr. Chalasani:
Yep, that I think is safer. You can do that. It can cause, not necessarily fatty liver, but it can cause elevated liver enzymes, ALT. You just have to watch it.

Really an important slide, though. This is the pendulum, back and forth, when we started the field. Actually, we've written papers showing non-heavy drinking in patients with MASLD may be safe, may be protective 15 years ago. It turned out that's not the case. I think the very safe thing you can tell your patients is not to consume any alcohol, especially if there is concern of any degree of fibrosis.

Here's showing couple things, though, is this particular paper found that patients who carry the diagnosis of MASLD, 17% subsequently will end up with either alcohol-associated liver disease or a diagnosis of AUD. That's one point, just common. So self-reported many times can be misleading. And on the right side, these are the data from NHANES showing that compared to MASLD, if you have MetALD, where there is alcohol consumption, your overall mortality is significantly higher. I think we have known this: Metabolic risk plus alcohol consumption, two together are not good news, bad news.

So I just wonder, are you doing PEth routinely in your practice?

Dr. Rinella:
Yeah, I do PEth on every new patient that I see, every single one of them, whether they drink or not. And I also will check it serially if there is alcohol consumption. I also do an AUDIT-C on every patient that I see for the first time. Because I think, ironically, as hepatologists and gastroenterologists, we seem to not really ask people a lot of questions about alcohol consumption, even though we know that it's a really – it's the number one cause for needing a liver transplant, you know, slightly more than MASLD, but it's a big problem. And if you have obesity, your risk of alcohol is about four times. Four times, so it's significant, yeah.

Dr. Chalasani:
Yeah. What about you, Mazen, what are you doing?

Dr. Noureddin:
You're a tough doctor, right now, like everyone is going to get PEth walking in your clinic.

Dr. Rinella:
I won't do it on you, though, Mazen.

Dr. Noureddin:
Well, based on a case actually this last week that –

Dr. Chalasani:
No cocktail for you this evening, Mazen.

Dr. Noureddin:
Based on a case like I had this last week, I should probably PEth a lot of people. I got totally fooled by a patient that I biopsied, did this, this, and this and that, and then she decompensated, and it was PEth in the 500s. So we still get fooled, or I'm not doing a good job asking, as you said. But yeah, there was a paper also on *JHEP*, right, there where they looked at people that they were diagnosed with MASLD and MASH, and they did all kind of testing and –

Dr. Chalasani:
Yeah. Yeah. I just wonder, though, there are geographic differences. For example, in our hands, self-reported alcohol consumption really tracks the PEth. Occasionally, you see a mismatch, to most part in my 20 years and only a handful of times.

Dr. Rinella:
I think it depends on how you ask too. I think that probably they might feel more comfortable with you than they do with Mazen.

Dr. Noureddin:
One of the points to make, actually, it's important. Like, for instance, we're going to talk about MASH therapies –

Dr. Rinella:
Eventually, we will.

Dr. Noureddin:
– and at-risk NASH and give them therapies. And sometimes if they are not responding or something, ask that question. Even if you think you asked, go back and say, hey, tell me about last week and the last 2-3 weeks, and do AUDIT-C or PEth, like Dr. Rinella does everyone. I like it.

Dr. Chalasani:
I just want to add one thing, though, is now I think it's very clear, any amount of alcohol is dangerous, irrespective of MASLD. I think we've gone back and forth. I think even just the one drink increases the risk of cancer. What seemed like alcohol can be cardioprotective, and that isn't the case either. I think multiple national academies are going to come out with a report, and I think WHO also has come up. So there is no such thing as safe type of alcohol; any amount of alcohol is dangerous, regardless of MASLD.

Dr. Noureddin:
These two gentlemen started whispering to each other, except tonight is okay.

Dr. Rinella:
And if you don't have MASLD, that's a whole other question. So, anyway, next. Okay.

Dr. Chalasani:
All right. So, wow, we're still in case 1.

Dr. Rinella:
Naga, I know we've got to keep it moving. He's loving the microphone. I think that's what it is.

Dr. Chalasani:
All right. Well, I think we can skip here. This patient's very last row, pay attention to LSM is 8.6 kPa. CAP score is 371 dB/m.

And the next question is: Does this patient meet the criteria for consideration of treatment with resmetirom?

Okay. I don't know what this is.

Dr. Rinella:
Is it in there? Oh.

Dr. Chalasani:
All right, this is sort of the case conclusion. Do I have a couple minutes here?

Dr. Rinella:
Yeah.

Dr. Chalasani:
So as we talked, every patient with MASLD, lifestyle intervention. This is exercise, any type of exercise, whether it is aerobic, cardiac, or resistance training, equally effective.

And in terms of diet, what are sort of the high-level recommendations you give to your patients, Mary, for lifestyle in terms of, especially, with diet?

Dr. Rinella:
So diet, we recommend a Mediterranean-style diet, so low in saturated fat and modestly low in carbohydrates. The idea being you want something that's going to be sustainable, that people are going to be able to eat and keep over a long period of time and not diets that are going to come in and out of their life.

Dr. Chalasani:
What about you, Mazen?

Dr. Noureddin:
I actually like the low-carb diet if they can do it. And there's some data on low carb. There's some data on intermittent fasting, but to Dr. Rinella's point, the most studied one is the Mediterranean diet. But if I can switch them to low carb, I love it.

Dr. Chalasani:
By far, I think Mediterranean diet has been studied the most, widely recommended, including the guidance document. My recommendation has been about restrict carbohydrates and increase protein intake. And then I also got to believe eggs, I think, are really important, because it's a good source for protein, really a great source for protein, as well as things like betaine and other things

that are protective.

And then in terms of coffee, what do you recommend?

Dr. Rinella:
Up to four cups a day.

Dr. Chalasani:
What about you?

Dr. Noureddin:
If they – sure. We love coffee. All hepatologists love coffee.

Dr. Rinella:
It counteracts alcohol. It's actually true.

Dr. Noureddin:
So after tonight, eggs and coffee for breakfast tomorrow.

Dr. Rinella:
Exactly.

Dr. Chalasani:
One of my partners recommends to his friends, not his patients, for every drink, one cup of coffee next morning. I'm not sure it's evidence based. But I think more so in liver cancer, certainly epidemiological work in chronic liver disease and cirrhosis, coffee seems to be protective as well. There is a strong interaction between G allele as well as coffee drinking as well. The effects of G allele, the PNPLA3 are negated by coffee drinking.

I think we'll skip most of the other things. I just wonder, so this patient, obviously, you would not give liver-directed pharmacotherapy because liver stiffness isn't high enough.

So you've done the lifestyle recommendations. How do you follow up this patient?

Dr. Rinella:
So this person would be, I would say, moderate risk because they have a lot of comorbidities. So I would follow that patient again. I would probably start them on a GLP-1 or recommend that they do that with their primary care, because they have multiple cardiometabolic risk factors. They would benefit from that.

Dr. Chalasani:
And I know we didn't put this in the slide here. I suppose you'll be testing for PNPLA3 in this patient genotype?

Dr. Rinella:
I do, actually. I check it in everybody, every new patient as well. But that's not recommended, I don't think, for we don't really know exactly what to do with that information as far as individual-based risk, but I do check it.

Dr. Chalasani:
And what do you do? Are you testing?

Dr. Noureddin:
I don't. I don’t. It's like access issues and insurance and all this.

Dr. Chalasani:
Yeah. I mean, if you're up to speed on PNPLA3, you can test. I think LabCorp and Quest, I think, you can order it. And the payers haven't balked yet, because I don't think many of us are ordering it, but I think it can be an excellent stratifier especially if you have really exponential risk for fibrosis and so forth. I think that's sort of case 1.

Dr. Rinella:
It's actually perfect for Mazen, because as far as the question goes, about 50% of you thought that this patient would be appropriate for resmetirom, and about half of you thought that it was not or weren't sure about it. So he's going to illuminate us about this, right?

Chapter 3
Case 2: A 56-Year-Old White Woman Referred by Her PCP

Dr. Noureddin:
Yeah, I think a lot of you guys here heard about what happened in 2024, right? We have FDA-approved medication now, and as Naga mentioned earlier, the bull's eye, I guess, to focus on those at-risk MASH. At-risk MASH, again, NASH with F2 and F3 without cirrhosis. We still don't have treatment for cirrhosis. So I'll do this quickly, because Dr. Rinella has a lot of exciting news. So you can go to your alcohol tonight, and Naga has his 3 ventis tomorrow.

So let's look at the case. A 56-year-old white woman referred to her PCP. She's on atorvastatin. So you asked me about statins earlier. Here, I started paying attention. Do I need to change that or not? I can tell you, if she needs resmetirom therapy, that dose needs to be changed. It's on the higher side, nothing above 40. She's also on losartan. Her BMI is 42. Blood pressure 139/84. Those are the labs, ALT of 90, AST of 76, so albumin 4, platelet count 202, LSM 10.9, and CAP 343.

Dr. Rinella, quickly, what does she have?

Dr. Rinella:
She has high-risk MASH, at-risk MASH.

Dr. Noureddin:
At-risk MASH. So does she have cirrhosis?

Dr. Rinella:
No.

Dr. Noureddin:
Why do you say so?

Dr. Rinella:
The AST to ALT ratio is not greater than 0.8. The platelet count is normal. Liver stiffness is only 10.9.

Dr. Noureddin:
Why did you call her at-risk MASH?

Dr. Rinella:
Because she has high liver stiffness and elevated liver enzymes and dyslipidemia and hypertension.

Dr. Noureddin:
So in 2024, we have a treatment for this patient. This is a patient that walks in your office after working so hard for decades. These guys were pioneers in the field. Now we have FDA-approved therapy, and eventually I'll change her atorvastatin. So again, back to the algorithm. If she came to you with the FIB-4 and all this, I didn't calculate the FIB-4 for this patient, but she ended up with the transient elastography. And the transient elastography was in the indeterminate zone, but this is around F2-F3, 8 to 12, more than 12, even advanced fibrosis. And I'll show you what we recommended for approved therapy.

So it's important, I think the elephant in the room, to identify at-risk MASH patients. Again, risk factors, metabolic risk factors, especially type 2 diabetes. You want to find out who has NASH and F2 and F3. So in the primary care setting, we said FIB-4. And then when they show up to our offices, VCTE. And here, our patient who has more than 10 put her, with the ALT and AST and all other comorbidities, put her at risk for at-risk MASH.

Now beyond what we said earlier, there are a few tests if you want to increase your suspicion for that at-risk MASH, and it's a composite score. It combines the fat plus the stiffness plus liver enzymes to tell you the equivalent of those on biopsy that they have NASH and F2 and F3. And those are in the guidelines that, again, published by Dr. Rinella and colleagues.

And for instance, let me tell you about the FAST score. So for those that they have the transient elastography or FibroScan, there's an app. You pull the app and it's going to tell you what is the CAP, which is the amount of steatosis, what is the stiffness, and what's the AST. If the score is more than – 0.35 is the sensitive one, and 0.67 is the specific one. So it gives you an idea where your patients fall. So more than 0.35, they likely have at-risk MASH. More than 0.67, it's highly likely.

There are other scores that are based on MRI, and it's the same concept. You add the CAP, you add the steatosis and stiffness and AST. So for instance, the MAST score has PDFF, transient MR elastography, and AST. It gives you the same kind of idea like the FAST score. There's another score called MEFIB, and this is a dichotomous score, which is MRE more than 3.3 and FIB-4 more than 1.6.

So it's a toolbox that you can use. The most common one that you're probably going to use is the FAST score, which is again based on transient elastography, CAP, stiffness, and AST.

Dr. Rinella:
And you find it on the FibroScan app. Yeah.

Dr. Noureddin:
You find it on the FibroScan app.

So this patient, what additional tests would you like to consider to assess at-risk MASH? Let's say the FibroScan, you're not too happy with, and elevated enzyme, you're still not convinced. Would you do the ELF test? Would you do the FAST score? Would you do FIB-4? Would you do the MRI-PDFF?

And I just presented that in the previous slide, so that's the answer. Okay. Are you going to give us the answers at the end?

Dr. Rinella:
Yeah.

Dr. Noureddin:
Okay. So again, this is the FAST score.

Dr. Rinella:
Most people got FAST score, so you were effective in your teaching.

Dr. Noureddin:
Okay, I was effective. So stiffness plus CAP plus AST, and we talked about the FAST score again. You see it in the CAP. There's a similar one on MRI-PDFF, MR elastography, and AST that can be used as well. And actually, this is what I just talked about earlier. To rule out at-risk MASH is FAST less than 1.35. The rule, the definitive one for having it high specific is FAST score more than 0.67, and it decreases the gray zone. To me, to be honest, Dr. Rinella, I think I just can't start therapy on that patient without even calculating the FAST score, ALT and AST, high metabolic risk factors, the stiffness is high. So I could have started, and I will go to recent recommendations. So here is showing you the FAST score of more than 0.74, at-risk MASH, which is NASH, when MASH with significant fibrosis, and this patient will likely qualify for resmetirom.

Again, we keep beating on the same point: at-risk MASH is MASH and F2 and F3. The people that they're going to require therapy are those that they're going to eventually get in trouble, like Dr. Chalasani showed you earlier, with their liver. So those are where we're trying to target in the clinical trials, NASH and F2 and F3 and NASH and F2 or MASH and F4. We don't have a treatment for MASH and F4. There are multiple clinical trials we're doing. Either resmetirom itself is on clinical trials for MASH cirrhotics, but for MASH and F2 and F3, we just had ASLD guidelines. We had experts' opinion papers. We had FDA approval that if you can treat these patients, you should treat these patients.

How would you initiate treatment in this patient? Vitamin E; resmetirom with lifestyle intervention; resmetirom plus GLP-1 or GLP-1/GIP therapies. And let's answer this question, and hopefully I'll be as effective as the previous one. Did we get that? There's the music now.

Dr. Rinella:
All right, so I think, oh, there we go. You have some answers.

Dr. Noureddin:
Okay? So resmetirom was approved based on this trial that was published earlier this year in *The New England Journal*, and it shows you that they achieved the 2 efficacy endpoints. So the 2 efficacy endpoints we need, on the left is called NASH resolution, which is basically improvement on the steatohepatitis on the biopsy, and we have been able to show that over the 1-year trial. On the right, it's fibrosis improvement. If you are in phase 3, you only need to hit one of them, and they hit both. And this is the music to hepatologists' ears because you have fibrosis improvement, and we talked about morbidity and mortality. So this is, to us, an effective liver-directed therapy. The safety profile was very good. Some people get nausea and GI side effects, and they subside within 20 days or so. So many of us have prescribed it. And it's easy to use in clinical practice.

Anyone have given resmetirom in this room, by any chance? Not as many as I expected, or you're sleeping.

Anyways, so is a liver biopsy ever indicated when evaluating patients for treatment with resmetirom? Yes, when a baseline biopsy was done more than 12 months; yes, when there's discordance between 2 current NITs – so read the question well, hint, hint; no, NITs should be used instead. All right.

So I just want to point out to this paper. That's an effort was initiated by Dr. Rinella, and a group of us put this paper in *Clinical Gastroenterology and Hepatology*. This preceded the ASLD guidelines, and in the recent updated ASLD guidelines, the recommendations was replicated, kind of in the same range, but I'll make it easy for you. So MASLD patient, you look for metabolic risk

factors. They come to you and you do assessment. And I want you to look at the green and orange here. So the VCTE range between 10 and 20 is what we're trying to treat these patients with the resmetirom. Again, so our patient is between 10 and 20. Why it's orange on the middle, because between 15 and 19, you have to start paying attention, making sure this patient is not cirrhotic. And you can do that by looking at the platelet. We all know the platelet, if it starts dropping, especially here, less than 140 in the trial, the patient is likely cirrhotic, or if they have, like nodular liver or collateral. So you have to pay attention to this. The range 10 to 15 is a bit safer. You still have to look for evidence of source of portal hypertension. When you get to red, those are the patients that they don't want to treat, because they're likely to be cirrhotic, until we have further evidence. So VCTE more than 20, if you have a MR elastography more than 5 or ELF more than 11.3. You can also, on the green and orange, use the range using different tests such as MRE or ELF. As Dr. Rinella said, with ELF, maybe you want to add another imaging study. And we talked about the FAST and MAST scores and all this. So it's really improved our understanding how to start treatment, and that biopsy is not needed in such patients.

And this is an algorithm we had in the same paper. So many of you might stop us after this, like, what do I do after I start? So this is what you do. There is some patients, and you probably heard that story, they have some elevation of liver enzymes in the first month if they are on statins. This is not an issue. What I'm doing in my office, I'm checking in 3 months, making sure everything is okay, and then I bring the patient in 6 months and 12 months. And you really have to wait until 1 year, because that's how long it took the trial to show efficacy or not before you make any change in treatment or judgment if that patient was helped or not. Indeed, in my opinion, this is a long disease. It might take longer than that, but this is at least like the first point of real assessment. Before that, they come to you at 3 months, you can draw labs. In 6 months, you can repeat the transient elastography or the MRI if they had and start telling them of the signal, but do not make decisions at that point. Wait until 1 year.

So at 1 year, if you have multiple worsening of NITs, maybe you should consider other etiologies or stop. If no change in NIT, maybe you want to continue or put them on clinical trials or something. And if they're improving, and here we put improving in ALT by 17 unit or transient elastography by 30% or MRI-PDFF, you see the drop by 30%. So these are the things that you want to look at at 1 year. And importantly, again, we don't need a biopsy. We put things together, and if it makes sense, we keep going.

So another point too, which actually, Naga brought it earlier, right? You asked her about what we do with the other patient that did not have high stiffness. So there's a mention of managing with incretins, the comorbidities. And it's mentioned in the AASLD and EASL. So you can treat the type 2 diabetes as well as the obesity with incretins, GLP-1s, or duals, but the liver-directed therapy that's FDA-approved today is resmetirom, not those yet. The clinical trials are ongoing for those patients. So that's what I'm trying to say on this slide. As of today, liver-directed therapy for at-risk MASH, NASH and F2 and F3, is resmetirom, while you can treat the comorbidities with GLP-1 such as obesity and type 2 diabetes. So that, I will leave it here.

Dr. Chalasani:
Mazen?

Dr. Noureddin:
Yes, sir?

Dr. Chalasani:
So can you just explain if somebody is already on a GLP-1 agonist, do patients still respond equally well to resmetirom? Or the patient, you have the follow-up, would it be any different if somebody gets put on, for example, semaglutide?

Dr. Noureddin:
Yeah. So the data is evolving. Let me start with that trial. What we saw in that trial, that patients that were on GLP-1s, and they were mostly like the semaglutide at the 1-mg dose, we still have a lot of patients with NASH and F2 and higher, despite being on a stable dose at least for 6 months. So that means it's not necessarily solving the problem, the GLPs. So they needed resmetirom therapy.

To answer your question directly, it's resmetirom plus weight loss, regardless where it came from, you will see more efficacy data than what we saw on the trial. And those are a lot of sub-analyses here and there. There's actually an oral here in the ACG looking at resmetirom plus weight loss, and the more the weight loss, it adds to already the efficacy of resmetirom.

Dr. Rinella:
And it will also be presented at AASLD, I think, as well.

Dr. Noureddin:
That too. So weight loss matters, and we recommend patients to lose weight and exercise while they're on resmetirom therapy. So, yeah, that's my conclusion of this study. At-risk MASH, NASH and F2 and F3, they need liver-directed therapies. We need to keep an eye on the patients on holistic approach. But there's no alternative for resmetirom, for today, for liver-directed therapy while we're

treating comorbidities, until we see more data. And I think the future, as you guys agree, it will be combination therapy. It could be resmetirom, something else, once they show that efficaciousness in the trial, and it could be like it depends on the stage of the disease, F4 versus F3.

Dr. Chalasani:
Can I just – I know we're running out of time. Vitamin E isn't an option for you anymore? I'm just wondering, you know, because we –

Dr. Rinella:
I've never really used it very much. Sorry.

Dr. Noureddin:
I was going to say this – anymore. So, I mean, I used vitamin E, to be honest, in the past, before that. And I even used pioglitazone. But if you are my family member today and you have F3 and F2, we really don't have fibrosis data on both, right? You guys had this good paper from retrospective analysis from IU showing vitamin E maybe preventing decompensation, but with honesty, it needs to be replicated and maybe, like, you know. But the data on fibrosis, although some people argue pioglitazone had maybe some data, I don't think it's that strong. And to me, as a hepatologist, I want to jump and save this patient, especially when it gets to F3. So if I have FDA-approved liver-directed therapy, that is my go-to, and I'll still manage comorbidities and all this, but I would probably not use vitamin E anymore.

Dr. Chalasani:
That's fair. That's fair. I think the PIVENS trial, the first rigorously done trial, it did not show fibrosis improvement with high-dose vitamin E. Therefore, that's fair.

Dr. Rinella:
And I think that in your trial, I'm going to speculate that in people who have advanced disease, the prevention of decompensation, I would guess, is probably more related to vitamin E's effect on coagulation. And it's through that mechanism, having less sinusoidal sort of obstruction, because there are data also on using all their blood thinners and improving and reducing the risk of decompensation in the future. But I don't know.

Dr. Noureddin:
Anyway, ladies and gentlemen, let's go to the best part of the day, the best speaker, Dr. Rinella. And you're going to see the pipeline is really rich.

Dr. Chalasani:
I know. She is supposed to have 60 minutes.

Chapter 4
Case 3: A 60-Year-Old Black Man With MASH

Dr. Rinella:
That's okay. We're going to do this in 15 minutes. It's going to be great. And then you guys are going to ask questions, hopefully, hopefully.

All right, so third case. This is a 60-year-old Black male with MASH. His medical history is notable for pretty nonspecific symptoms, fatigue, loss of appetite. He's on metformin, sitagliptin, which is an SGLT2 inhibitor. He was diagnosed with type 2 diabetes fairly recently, and that's actually kind of important. He's hypertensive. He's obese. He has edema, no visible stigmata of chronic liver disease. And lab tests show LDL of 95, A1c of 6.9, ALT and AST of 66 and 76, albumin 3.5, and a platelet of 147.

So in the interest of time, I want to walk you through some of the highlights of this case. Okay? Sometimes when you develop diabetes, that, in this context, could mean that that person has developed cirrhosis. That's something that you see fairly commonly, so that at least should raise your level of suspicion. Hypertension, obesity, and diabetes are, of course, all important risk factors. But if you look at the labs, I think you should focus on the ALT and the AST. I always emphasize the importance of looking at these carefully, because the ALT, in your mind, should always be higher than the AST. When it's not, you need to ask yourself a couple of questions. One, does a person have cirrhosis? If the discrepancy between ALT and AST is significant, more than 2:1, could it be alcohol use, or could it be muscle injury? But when the numbers are close like this, this is really cirrhosis territory. And then you look at the platelet count, and that's low, right? So this person, clinically, you should suspect this person has cirrhosis.

Dr. Noureddin:
But also, like, you want to make sure he's not drinking, right? With an AST and ALT inflation. I mean, he's cirrhotic.

Dr. Rinella:
Yes, of course, always ask about alcohol, right? But that ratio is not an alcohol ratio. That really is, not to disagree with you so vehemently, but it really is cirrhosis. What?

Dr. Noureddin:
You going to do PEth on him?

Dr. Rinella:
Yes, I could do that. I would do a PEth on him. All right, so NITs. FIB-4 is high. And I mean, they're just slamming on the points. So ultrasound shows nodular liver, splenomegaly, so this person has cirrhosis without any reasonable doubt.

Okay, so now this is jumping further to something called clinically significant portal hypertension, which basically means that the person is high, high risk for decompensation. So hepatic encephalopathy, variceal bleeding, ascites.

So in this patient, what tests would you do to confirm that the patient has CSPH? So, CT, ELF, FIB-4, MRI, or VCTE and platelet? I'll give you guys a couple seconds to answer that. We're going to move on.

I have most of your answers. Good. Okay, this is interesting. So we have a lot of people saying the first answer, actually, which is interesting. So the correct answer is actually really simple. It's stuff that you already did, other than the FibroScan. Just FibroScan and platelet count, that is really mostly all you need to diagnose people as being high risk. In fact, we can now use this to avoid endoscopy in some patients, and we can use it to initiate beta-blockers when it's over 25, okay, or if there are other features.

So this is really important. The thing to remember about CT scan is it doesn't tell you anything about the risk of decompensation. It can tell you if there are collaterals, but it doesn't really give you more information than telling you there's signs of portal hypertension, and that's, I think, an important point.

Anything else you guys want to note about that?

Dr. Noureddin:
Nope, that's just the Baveno criteria, right?

Dr. Rinella:
Yeah, Baveno criteria.

Dr. Chalasani:
Some of these are Baveno criteria. I agree, Mary, but I still think the large spleen, the collaterals.

Dr. Rinella:
Well, this person has cirrhosis, yeah.

Dr. Chalasani:
And then it's the periesophageal collaterals, etc. But I agree with you, this is easier than doing a cross-sectional imaging.

Dr. Rinella:
But again, the cross-sectional imaging, it's going to tell you there are collaterals, but not that there's specifically – I mean, I guess you can make an argument, fine, but that was maybe a badly worded question, okay, but generally speaking, that's what you need to do. CT does not tell you severity.

Dr. Chalasani:
Are you guys doing spleen stiffness?

Dr. Rinella:
No, are you doing it?

Dr. Noureddin:
I don't have the machine yet.

Dr. Rinella:
Ultrasound with Dopplers? It'll tell you about blood flow, and there are secondary signs like the portal vein can be widened, but really, it's not good enough. If you have ultrasound with liver stiffness, that would be helpful.

Dr. Noureddin:
I mean, this patient eventually is going to move toward – he had ultrasound, right? Yeah, he had ultrasounds for nodular liver. So we're

going to start ATC screening and all this. But your patient, at the end of the day, when they are just at the cusp of cirrhosis, they really want to know. And nodular liver, now we have FibroScan, and it tells you a lot with that 21. It's now slam dunk cirrhotic, and I keep moving on.

Dr. Rinella:
I'm going to skip the last one because it's a little bit in the weeds, just that sometimes the accuracy in stiffness may not be the same in the setting of obesity, but I think that's not so important. ELF, it was 11.0 in this patient. So definitely consistent with high-risk disease, perhaps not decompensating imminently, but definitely in this person in that cirrhosis range.

So what would you do next? Initiate a non-selective beta-blocker; initiate resmetirom; or initiate dietary intervention?

Dr. Noureddin:
Remember that red box that I showed you earlier.

Dr. Rinella:
You're like the teacher that gives you the answers, which is fine. Okay, so this is just the point being that beta-blockers are important to prevent decompensation, and they really should be used much more copiously than we used to use them.

All right, so would you treat this person –

Dr. Chalasani:
What are you using? Are you using carvedilol?

Dr. Rinella:
Carvedilol exclusively pretty much now.

Dr. Noureddin:
Because of the new guidelines? Or I guess I switched, actually, people from propranolol –

Dr. Rinella:
You can just do 6.25 once a day.

Dr. Noureddin:
6.25 once a day.

Dr. Chalasani:
And you're screening for varices with an endoscopy?

Dr. Rinella:
It depends. I mean, we tend to do that because we're endoscopists, but you really don't need to, right? Supposedly, yeah.

Chapter 5
Looking Forward: What's in the Pipeline?

Dr. Rinella:
All right, so we're going to conclude so that we can go look at the pipeline in about 8 minutes. Okay? So what we're going to focus on is really just the drugs that are in phase 3. We would be here for all night long to talk about all the drugs in phase 2, so we're going to focus on phase 3. So resmetirom, we already talked about; we talk about it being FDA-approved. It's conditionally approved. No drug is going to be approved formally by the FDA until we have a benefit of outcomes, and that will be coming hopefully in the first quarter of 2028 for resmetirom, to get that final approval. Semaglutide, again, is also in phase 3. We're going to see the results of that trial. It is a late-breaker at AASLD. Lanifibranor is another oral drug, and we're going to go through that in a minute. Efruxifermin and pegozafermin are FGF21 analogues. So these are kind of the mechanisms that are in play in phase 3 today.

So starting with FGF21, so this is an endogenous hormone, but it has a really short half-life. So there are several drugs in development that play on that and increase the half-life of the drug. And this has many actions, primarily through increasing adiponectin, which is an adipose tissue hormone, which improves insulin sensitivity, it decreases inflammation, so on and so forth. There are also direct effects of FGF21, as you can see illustrated in this graph. And these are typically once-a-week injectables. So these are the results from the efruxifermin phase 2b study. And this was actually also already published, but you can see there are 2 things, I think, to look at. So you know we need to look at the difference over placebo, right? And you need to look at it to see if there's dose dependency. Those are 2 really important features. So in the dark bars, you see modified intention to treat, and the light bars are the intention to treat, meaning every person that came in and got dosed at all is going to be included in the analysis, even if they didn't complete. So here you can see

significant improvement in MASH resolution without worsening of fibrosis and also in fibrosis improvement without worsening of MASH. And those are the 2 registration endpoints that the FDA will be looking for. So in phase 3, that's what they're going to be looking for.

Pegozafermin is another FGF21 analogue, and these are also phase 2b data. This was published in *The New England Journal of Medicine* last year. And you can see very sizable differences between the drug and the placebo arm with respect to MASH resolution. An important point which I should have mentioned before is that this is a much shorter trial. The other trial is a 96-week trial, and those results were sustained over time, and patients actually continued to achieve statistical significance in improvement in fibrosis over time. So that's, I think, really important. So again, here, there's also a nice improvement in fibrosis. So we think that these drugs are probably going to be quite effective in reducing fibrosis. And as I said, they're both in phase 3 right now.

So lanifibranor is an oral agent, and what it does is it agonizes 3 PPARs or peroxisome proliferator-activating receptors. So PPAR-alpha is like your fibrates. So it increases through that; it increases beta oxidation and other things. The PPAR-delta mechanism is going to have more effect on macrophages and inflammatory signaling. And then PPAR-gamma is like pioglitazone in a sense. So that's one of the reasons why this particular drug may cause a little bit of weight gain. It causes less weight gain than pioglitazone does. But that's one of the side effects of the drug.

And actually, before I move on, I should also mention the side effects, to be fair, of the FGF21s, mostly GI, nausea, and diarrhea as well.

Dr. Chalasani:
What do you think about the bone loss part?

Dr. Rinella:
Yeah, so I think that needs to be proven, but there is definitely effect on osteoclastic activity. So that's in the phase 3s being studied specifically. And again, a lot of the patients that had bone loss had low vitamin D. So I think it's critical for us to make sure that people have adequate levels of vitamin D.

What do you think?

Dr. Noureddin:
I agree. And NASH patients in general, they have low vitamin D.

Dr. Rinella:
Yeah. So always check it and replete.

In this oral trial, actually, they looked at a SAF score. That was their primary endpoint, which is the European way to do – it's a very similar score, but for consistency, we're going to present the MASH resolution. Again, it was statistically significant over placebo in both doses; there's dose dependency. And then looking at fibrosis, there was also a difference compared to placebo, and this is still enrolling the phase 3.

So GLP-1s. I'm sure everybody in this room knows about GLP-1s. We're going to talk only about semaglutide, because that's the one that's in phase 3 and actually just finished the phase 3. So there are really multiple effects of GLP-1 agonists on the central nervous system, not directly on the liver, but indirectly to the liver, the kidney, blood vessels, and so on and so forth. There's a reduction in emptying of the stomach, a slowing of motility, increased satiety from the central nervous system perspective. And there are adipose tissue changes that are important for inflammation and insulin resistance as well, in addition to the weight loss. Because with these drugs, you start to see improvements in insulin signaling before you see weight loss.

So these are the data from the semaglutide phase 2 published in *The New England Journal*, gosh, now 3 years ago. And you can see here the 2 endpoints. So importantly, on the left, you see MASH resolution without worsening of fibrosis. And you see in a non-dose-dependent, or not completely dose-dependent manner, you see a very significant improvement of semaglutide 0.4 mg versus placebo. Important difference in this trial, these were daily doses. We use semaglutide as a weekly injection. This is 0.4 mg daily. But if you look over to the right on the fibrosis, there's no difference, no statistically significant difference between sema and placebo with respect to fibrosis. And so that's something that is going to be looked at in the phase 3, and maybe we'll see different results in the phase 3. With respect to safety and side effects, most of you have seen patients on these drugs. Nausea is the most common. Constipation is another important one for this particular mechanism.

Dr. Chalasani:
Mary, for all these incretins and weight loss, how concerned are you about the muscle loss? And what kind of dietary recommendations you're telling your patients?

Dr. Rinella:

So that's a really good question. Weight loss in general, so when you lose weight, the basic rule of thumb is about 25% of your weight loss will be muscle. So it's not completely clear to me that there's anything special about the GLP-1s, or whether it's just the weight loss that's leading to a reduction in muscle mass that's sort of commensurate with what you might expect. That being said, I always recommend a higher-protein diet in my patients. But I don't know if you have any additional comments. Or do you feel differently?

Dr. Noureddin:
Exercise too.

Dr. Rinella:
And exercise, of course. Yeah.

So these are the data from semaglutide in cirrhosis. So this trial was kind of done in parallel, but you can see here that actually placebo did better with fibrosis. And on the right, you see the – what am I trying to – yeah, exactly. So placebo did less well, and there was no statistically significant improvement in MASH resolution; they're just not labeled. But that's what that shows. So the right is MASH resolution. So again, efficacious in non-cirrhotic disease. We did not see a signal. This is a fairly small trial in cirrhosis.

So thank you very much for your attention. We appreciate it very much.

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