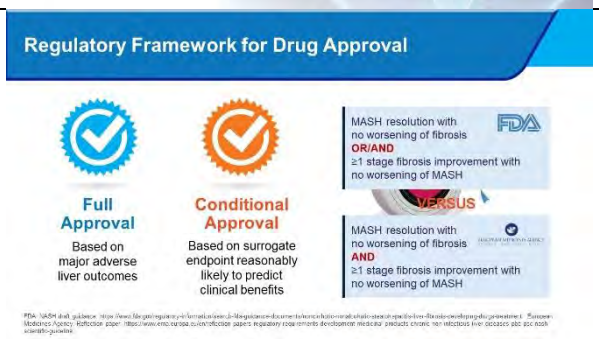
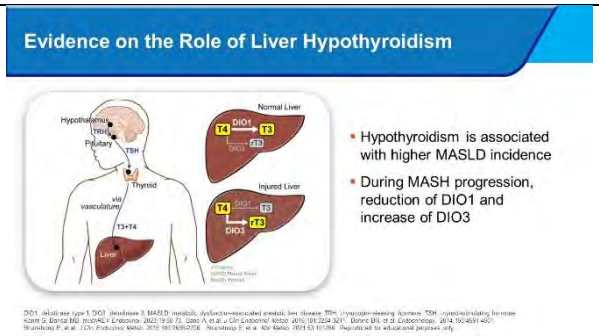
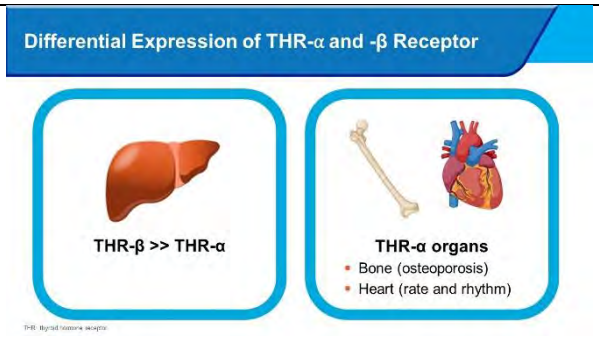
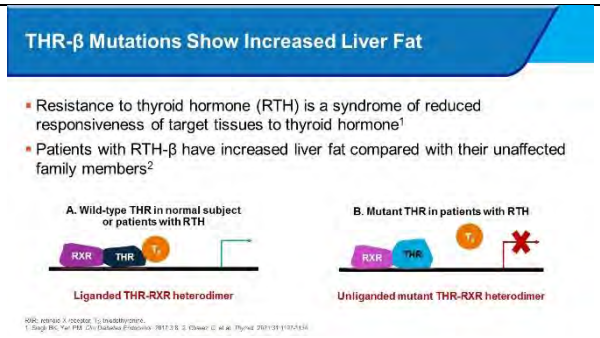
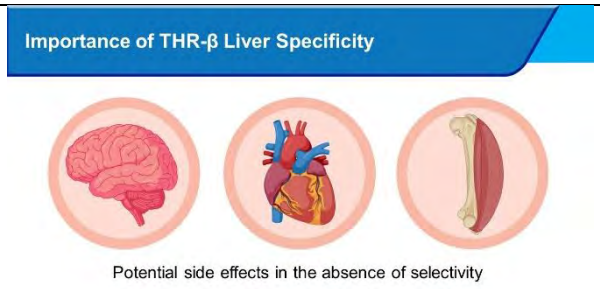
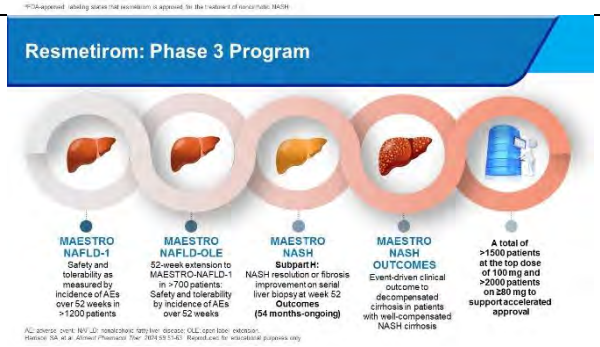
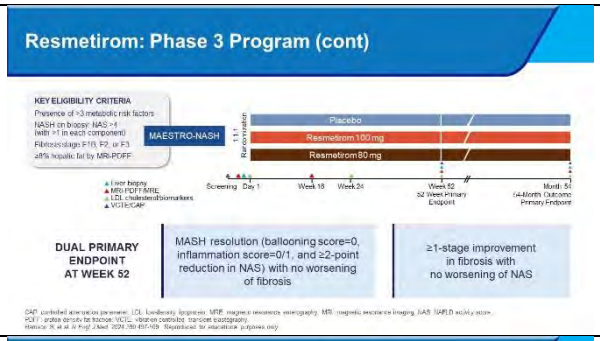
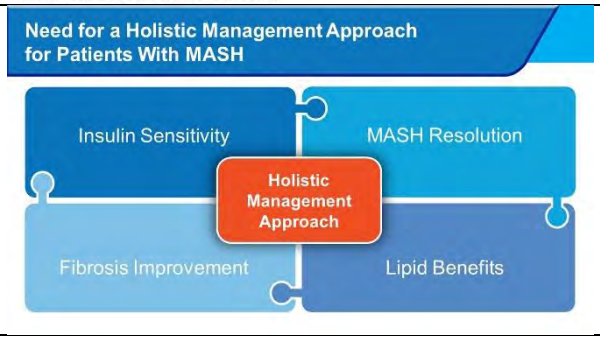
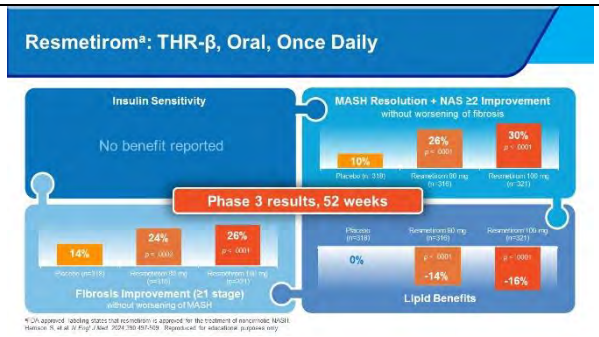
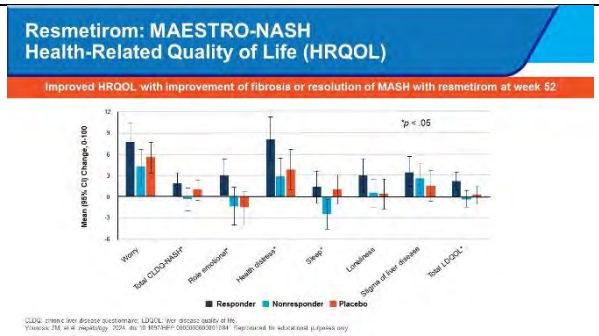
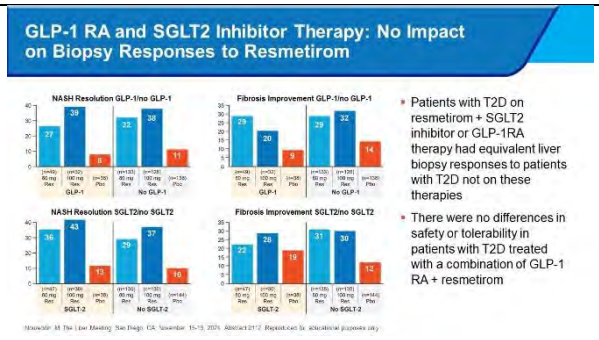
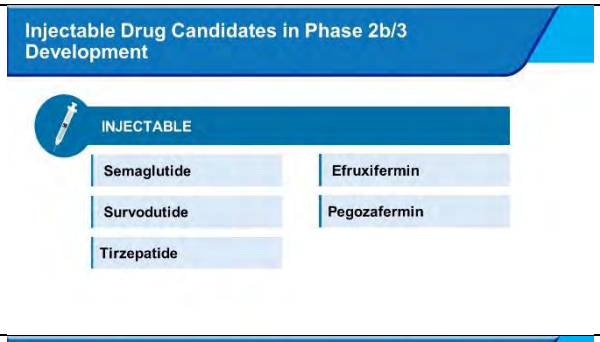
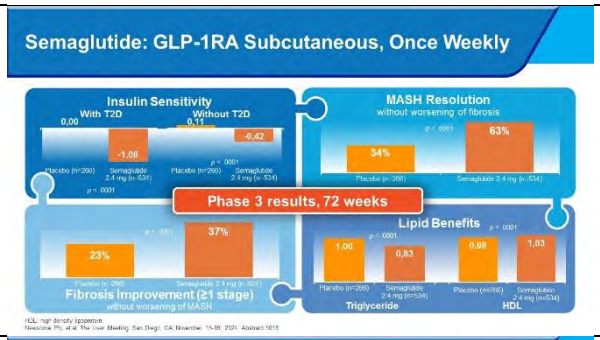
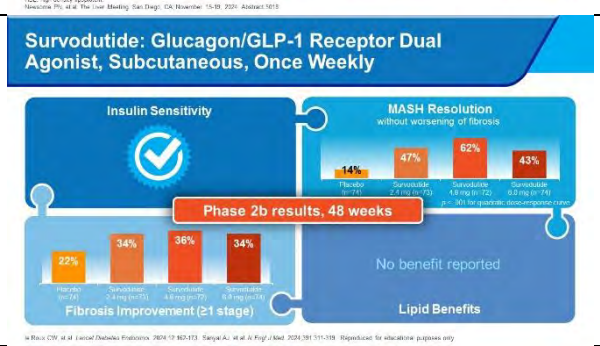
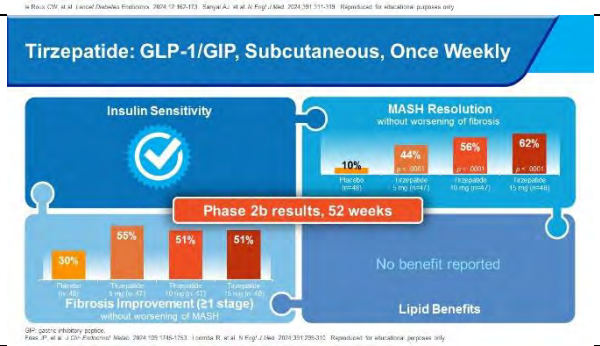
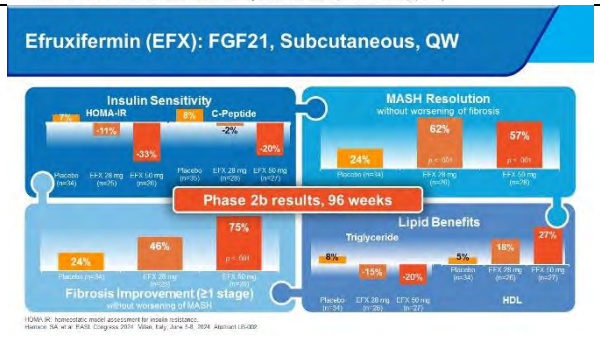
1.		**[Meena Bansal, MD, FAASLD]** Welcome everyone. Welcome to, *A New Eera in MASH: How Disease-Specific Therapies Are Changing the Game and Best Practices for Clinical Integration*.
2.		So, as many of you know, full approval requires us to demonstrate that the therapeutic improves major adverse liver outcomes. However, conditional approval is based on a surrogate endpoint reasonably likely to predict clinical benefits. Now, the FDA requires that you demonstrate either MASH resolution with no worsening of fibrosis or greater than a 1 stage improvement with no worsening of MASH, whereas the EMA requires that you hit both endpoints.
3.		And so this is really a tribute to Dr. Steven Harrison, our dear friend, without whom this field would not be where it is today. As we know, we have finally gotten the first FDA approval on March 14, 2022, of resmetirom, and Steven herald that through. And this is one of his classic slides showing the climb to the goal, all the fatalities on the way. And in fact, many have moved from Base Camp to phase 2 readout, and we'll present some of those data here today.
4.		So we know that hypothyroidism is associated with higher MASLD incidence. We also know that thyroid hormone or T4 is a prohormone and when it gets to its target organ, it's converted to the active form T3 by an enzyme known as deiodinase 1. However, some of that T4 is converted to reverse T3, which is inactivated by the enzyme deiodinase 3. However, with chronic liver injury there is a shift and there's an increase in deiodinase 3, therefore an increase in relative amounts of the RT3 or the inactive hormone and less becoming the active hormone T3. So it's really a relative intrahepatic hypothyroidism.
5.		Now, thyroid hormone β receptors are proportionally expressed much higher in the liver than thyroid hormone α receptors. α receptors are in the bone and in the heart and give rise to thyrotoxicosis, which when you think about it is osteoporosis and tachycardia. **NOTE:** So when we think of leveraging this pathway as a NASH therapeutic, we want it to reduce intrahepatic lipid content, decrease inflammation,

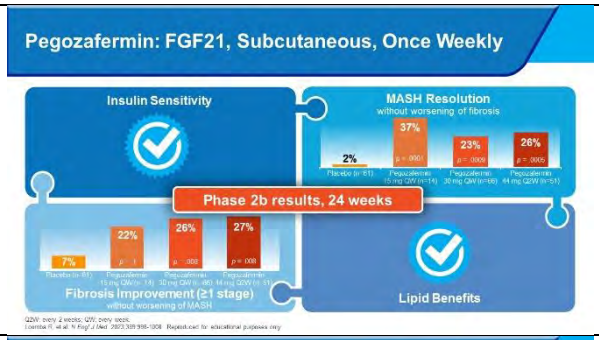
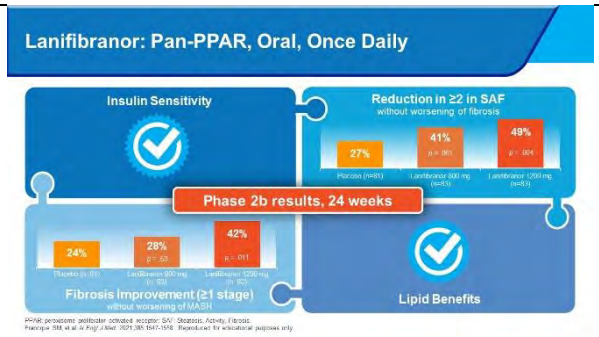
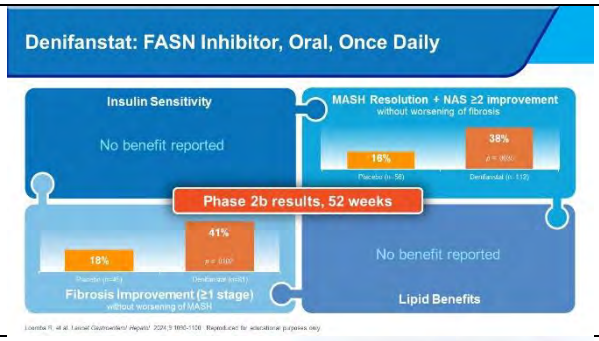
		and ideally fibrosis as fibrosis is the major driver of poor outcomes from NASH. We want to be liver specific with no effect on the hypothalamic-pituitary axis. And we want it to be selective for the β receptor to avoid the side effects of THR-α on the bone and heart.
6.		Now, interestingly, there is a family, actually this family lives in the Portuguese region, Azores, and they have a mutation where they are resistant to thyroid hormone β. And when you look at family members who have the mutation compared with their family members who do not have the mutation, you control for diabetes, BMI, and environmental factors because they're all on the same island. So you're controlling for epigenetic factors as well. Those who have the mutation have an increased amount of hepatic steatosis, really highlighting the importance of thyroid hormone β signaling in the liver and its connection to hepatic steatosis. **NOTE:** Patients with this syndrome have increased liver fat as assessed by CAP on transient elastography compared with their unaffected family members despite controlling for BMI, having similar rates of insulin resistance, and living on the same small island with exposure to similar environmental factors.
7.		So this is a video on the mechanism of action. Thyroid hormone receptor -β agonists, or THR-β agonists, are small molecules designed to specifically act in the liver. These agents enter the nucleus within the hepatocyte and bind to THR-β to activate target gene expression, which mediates several metabolic pathways. First, enhanced mitophagy removes damaged mitochondria, while mitochondrial biogenesis generates new organelles. At the same time, reductions in reactive oxygen species, or ROS, limit mitochondrial damage and accumulation of toxic long-chain lipids. Finally, increases in lipophagy generate free fatty acids that are then transported to mitochondria to produce ATP via β oxidation. Overall, treatment with a THR-β agonist is effective in reducing hepatic fat content and fibrosis.

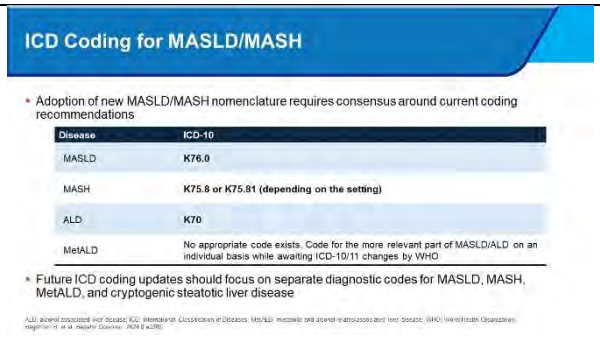
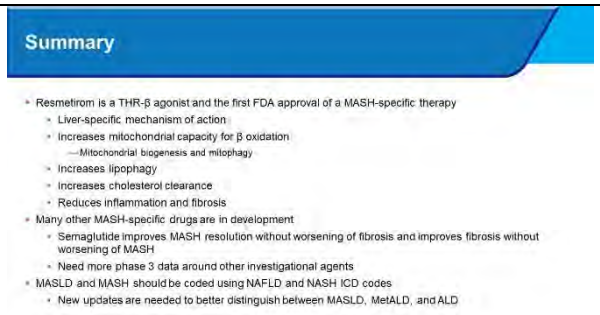
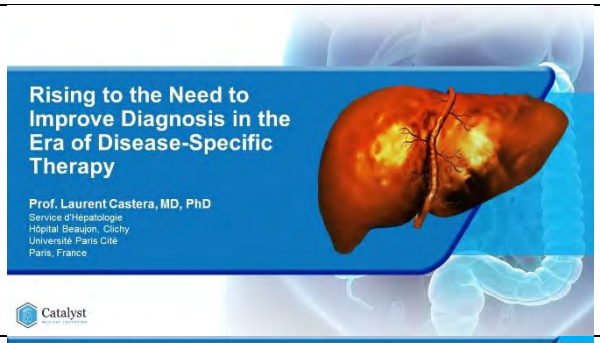
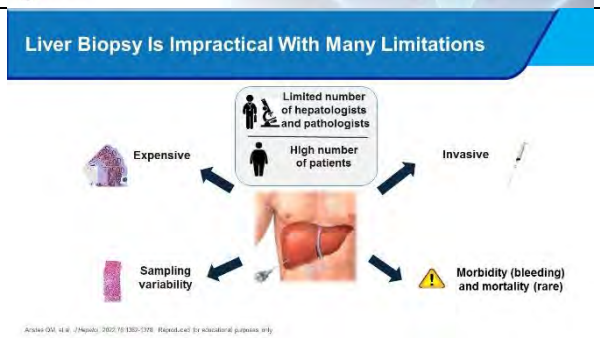
8.		Great. And so, it's that thyroid hormone β liver specificity that helps us avoid potential side effects on other organs.
9.		So the first FDA-approved therapy for MASH—resmetirom.
10.		I think many people have seen this before, but the point is that it's such a robust phase 3 program. So starting with the MAESTRO NAFLD program, which was really safety and tolerability in over 1200 patients of that group, 700 then went into an open-label extension. The MAESTRO-NASH is the registrational trial with the liver biopsy data that led to the accelerated approval. And it continues to be ongoing, where we will look for liver-related outcomes. And then we have the MAESTRO-NASH OUTCOMES study, which is in compensated cirrhosis and is ongoing. So more than 2000 patients have received either the 80- or 100-mg dose that supported accelerated approval.
11.		So for the registrational trial, you can see the patient population was highly enriched with 3 or more metabolic risk factors. They were randomized 1:1:1. And the liver biopsy endpoints were evaluated at 52 weeks. MASH resolution with no worsening of fibrosis and at least 1 stage of improvement in fibrosis with no worsening of MASH.
12.		But whenever we think about an approach to MASH, I think one of the themes of this meeting is really we need to have a holistic view from a liver-centric point of view. Yes, we're very happy to see MASH resolution and fibrosis improvement, but we know that the #1 cause of death is cardiovascular disease. And so ideally, we'd like to see lipid benefits and we know that insulin resistance is a critical underpinning of this

		disease. Thus, the nomenclature change and so ideally, we'd like to see effects on that as well.
13.		So every time we present data on these drugs, if data are available, we share it in all those different realms. So resmetirom, the phase 3 study that was published in the *New England Journal of Medicine*: 52 weeks biopsy, I think people are well aware; 30% MASH resolution in the 100-mg dose compared with placebo 10%; and then 26% fibrosis resolution by 1 stage compared with 14% with placebo. One thing that wasn't mentioned in the video is that resmetirom also increases the expression of LDL receptors on hepatocytes and therefore you see a reduction in LDL. There's no benefit report on insulin sensitivity.
14.		This is critically important. And this slide is for Michael Betel from the Fatty Liver Alliance, where they looked at whether or not histologic response correlated with how the patients felt. And we know we're all concerned about how the patients feel and function, as is the FDA. And so when you look at quality-of-life surveys, in the darker blue is those that had a histologic response, orange is those on placebo, and the light blue are nonresponders. And you can see that over a number of different quality-of-life measures, there was a clinically significant improvement in overall wellness.
15.		Now, about 15% of patients came into the study on a GLP-1. That was the diabetes dose of 1 mg. They had to have been on it for 6 months prior to evaluation for entrance, and they couldn't have greater than 5% weight loss before entering the study. So the question is, does the addition or having both drugs on board impact the histologic endpoint? And I'll focus you on the fibrosis endpoints panels on the right where you see that even if you were on a GLP-1 or not on a GLP-1, there was no difference in the biopsy response. Similar was the case with SGLT2. So whether or not you're on a GLP-1 at that 1-mg dose or on an SGLT2, there was no impact on the histologic response to resmetirom.
16.		Moreover, there was no significant difference in the side effects. Now, what about weight loss by itself? So 22% of patients on resmetirom actually had at least 5% weight loss. And when you look at those that had weight loss—now, this is independent of the GLP-1s. If you had weight loss, those that had fibrosis improvement increased to 41% and those that had MASH resolution on biopsy increased to 57%, underscoring the importance of counseling on

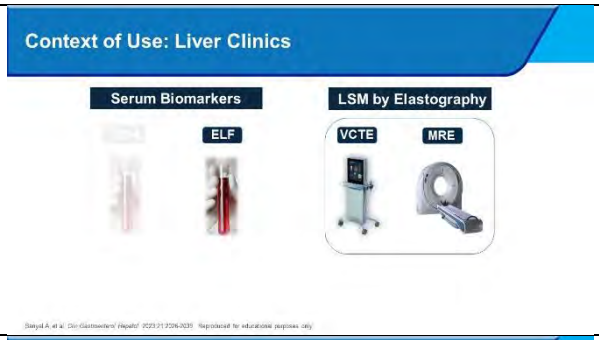
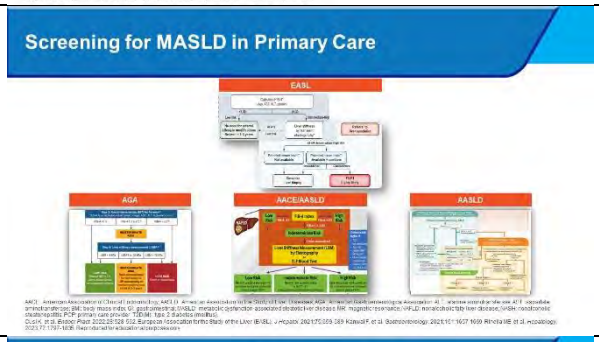
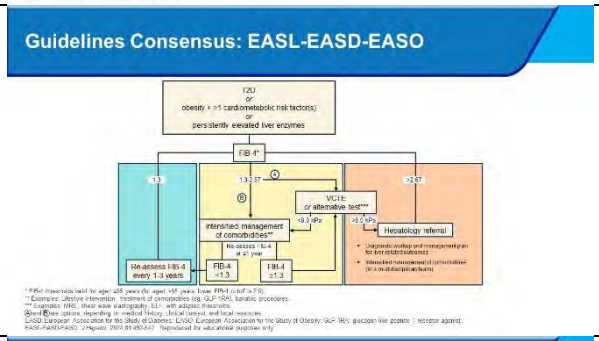
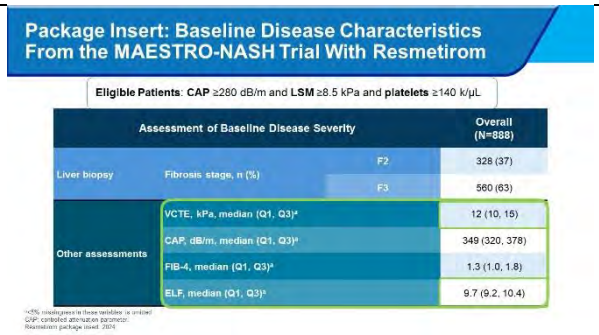
		lifestyle changes even when you have a pharmacologic therapy.
17.	**Resmetirom: Phase 3 Safety Results** Patients (%) / Placebo (n=321) / Resmetirom 80 mg (n=322) / Resmetirom 100 mg (n=323) ≥1 AE: 286 (92.8) / 296 (91.9) / 296 (91.6) Grade 1: mild: 77 (24.0) / 73 (22.7) / 66 (20.4) Grade 2: moderate: 169 (52.6) / 180 (55.9) / 183 (56.7) Grade 3: severe: 52 (16.2) / 43 (13.4) / 47 (14.6) ≥1 Treatment-emergent AE: 88 (27.4) / 124 (38.5) / 134 (41.5) ≥1 Serious AE: 37 (11.5) / 35 (10.9) / 41 (12.7) AE leading to discontinuation: 11 (3.4) / 9 (2.8) / 25 (7.7) Death: 1 (0.3) / 1 (0.3) / 2 (0.6) AEs affecting >10% of patients in any group **Diarrhea: 50 (15.6) / 87 (27.0) / 108 (33.4)** COVID-19: 66 (20.6) / 69 (21.4) / 54 (16.7) **Nausea: 40 (12.5) / 71 (22.0) / 61 (18.9)** Arthralgia: 40 (12.5) / 48 (14.9) / 35 (10.8) Back pain: 38 (11.8) / 35 (10.9) / 27 (8.4) Urinary tract infection: 27 (8.4) / 33 (10.2) / 27 (8.4) Fatigue: 28 (8.7) / 33 (10.2) / 26 (8.0) Pruritus: 22 (6.9) / 26 (8.1) / 37 (11.5) Vomiting: 17 (5.3) / 28 (8.7) / 35 (10.8) Harrison S, et al. N Engl J Med. 2024;390:497-509. Reproduced for educational purposes only	In terms of adverse events, diarrhea and nausea were more common in the treatment groups. This usually occurs within the first 4 weeks and it's gone by about 12 weeks.
18.	**EASL-EASD-EASO Treatment Guidelines** Preferred pharmacologic options for treating comorbidities MASH-targeted / T2D / Dyslipidemia / Obesity MASLD/MASH without cirrhosis (F0-F3) If locally approved: Resmetirom in F2/F3 fibrosis MASLD/MASH with compensated cirrhosis (F4) Check indication for liver transplantation in case of decompensation or HCC GLP-1RA (eg, semaglutide, liraglutide, dulaglutide) and coagonists (eg, tirzepatide) SGLT2 inhibitors (eg, empagliflozin, dapagliflozin) Metformin* Insulin (in case of decompensated cirrhosis) Statins GLP-1RA (eg, semaglutide, liraglutide) and coagonists (eg, tirzepatide) Bariatric interventions (special caution in case of compensated cirrhosis) *If glomerular filtration rate is <30 mL/min. EASL, European Association for the Study of the Liver. EASD, European Association for the Study of Diabetes. EASO, European Association for the Study of Obesity. GLP-1RA, glucagon-like peptide-1 receptor agonist; HCC, hepatocellular carcinoma; SGLT2, sodium-glucose cotransporter 2; T2D, type 2 diabetes. EASL-EASD-EASO. Diabetologia. 2024;67:2375-2397. Reproduced for educational purposes only	And EASL-EASD-EASO were forward-looking in their treatment guidelines. As you know, it's not yet approved by the EMA, but they did specify that if locally approved, the first MASH-targeted therapy should be resmetirom for F2/F3 fibrosis. And of course we want to think about aggressive management of the other comorbidities, and we'll spend some time talking about this in the case discussions. Aggressive management of diabetes, dyslipidemia with statins, and obesity, either pharmacologic or surgical management.
19.	**Other THR-β Agonists in Development** Drug Candidate / Study Stage / Endpoints VK2809 / Phase 2 Biopsy-confirmed MASH (N=248) / 12-week reduction of liver fat content 52-week biopsy data presented at AASLD TERN-501 / Phase 2 Presumed MASH (N=162) / 12-week reduction of liver fat content Results available[a] ALG-055009 / Phase 2 Presumed MASH (N=100) / 12-week reduction of liver fat content Data presented at AASLD TLM 2024 [a]No longer in development. AASLD, American Association for the Study of Liver Diseases.	So what are the other THR-β agonists in development? So I'll present data on VK2809 and ALG-055009 that was presented at The Liver Meeting just recently in November 2024. TERN-501 did report a 12-week reduction in liver fat content but their program is suspended or on hold.
20.	**VK2809: THR-β Oral, Once Daily or Once Every Other Day** Insulin Sensitivity No benefit reported MASH Resolution without worsening of fibrosis 29% / 71% / 65% / 63% / 75% Placebo (n=81) / VK2809 1 mg QD (n=74) / VK2809 2.5 mg QD (n=82) / VK2809 5 mg QOD (n=27) / VK2809 10 mg QOD (n=84) Phase 2b results, 52 weeks Triglycerides -4% / -8% / -31% / -17% / -34% Placebo (n=85) / VK2809 1 mg QD (n=77) / VK2809 2.5 mg QD (n=80) / VK2809 5 mg QOD (n=27) / VK2809 10 mg QOD (n=81) 34% / 57% / 44% / 52% / 57% Placebo (n=81) / VK2809 1 mg QD (n=74) / VK2809 2.5 mg QD (n=82) / VK2809 5 mg QOD (n=27) / VK2809 10 mg QOD (n=84) Fibrosis Improvement (≥1 stage) without worsening of MASH Lipid Benefits QD: once daily; QOD: once every other day. Loomba R, et al. The Liver Meeting. San Diego, CA. November 15-19, 2024.	So VK2809 is also a THR-β agonist. It can be taken once daily or they also looked at every other day, and their 52-week studies were reported in The Liver Meeting. They showed not really a dose dependency but at least a 75% improvement in MASH resolution without worsening of fibrosis at the highest dose. As expected they also saw the reduction of LDL and the lipid benefits and fibrosis improvement at the 2 higher doses of 5 and 10 mg every other day, 57% compared with 34%.
21.	**ALG-055009: THR-β Oral, Once Daily** Insulin Sensitivity No benefit reported Liver Fat Reduction ≥30% 10% / 28% / 33% / 70% / 59% Placebo (n=21) / ALG-055009 0.3 mg (n=18) / ALG-055009 0.5 mg (n=21) / ALG-055009 0.7 mg (n=20) / ALG-055009 0.9 mg (n=17; >95 kg) Phase 2a results, 12 weeks LDL-C -4% / -12% / -5% / -16% / -12% Placebo (n=21) / ALG-055009 0.3 mg (n=18) / ALG-055009 0.5 mg (n=21) / ALG-055009 0.7 mg (n=20) / ALG-055009 0.9 mg (n=17; >95 kg) No benefit reported Fibrosis Improvement (≥1 stage) without worsening of MASH Lipid Benefits Loomba R, et al. The Liver Meeting. San Diego, CA. November 15-19, 2024. Abstract 1226.	ALG-055009 has just a phase 2a result. So they only had liver fat reduction but needless to say they saw 70% reduction in liver fat at the 0.7-mg dose. Similarly, lipid benefits, and we wait to see further data.

22.		In terms of injectable drug candidates, phase 2b in development, the GLP-1RA, also known as glucagon receptor agonist, and the GIP family and then we have the FGF21 family.
23.		So semaglutide. This was obviously the big news at The Liver Meeting presented by Phil Newsom in the ESSENCE trial 72-week, phase 3 data with MASH resolution of 63% compared with 34%, slight decrease in triglycerides, slight increase in HDL. So good lipid benefits. Fibrosis improvement in 37% compared with 23% improvement in insulin sensitivity as expected.
24.		And then survodutide, which has now the glucagon receptor in addition, which is expressed on hepatocytes. And there we see MASH resolution without worsening of fibrosis across all of the doses tested, a trend toward fibrosis improvement. And so we wait to see phase 3 data.
25.		Tirzepatide now is the GIP combo with GLP-1. MASH resolution without worsening fibrosis across all 3 doses tested. Similarly trend toward increased fibrosis improvement at all doses tested and improvement in insulin sensitivity.
26.		The FGF21 family. As you know it's an endogenous hormone that has really many effects on many organs including antifibrotic effects. And you can see here in their 96-week study—MASH resolution without worsening of fibrosis at both the 28- and 50-mg dose, improvement by reduction in triglycerides, improvement in HDL, and a 75% fibrosis stage, improvement by 1 compared with 24% in placebo. And good benefits on insulin sensitivity, HOMA-IR, and a reduction in C-peptide.

27.		Pegozafermin, similar class of family, phase 2b results at just 24 weeks. You can see MASH resolution without worsening of fibrosis is statistically significant at all doses tested as well as fibrosis improvement at the 2 higher doses of 30 mg per week and 44 mg every 2 weeks.
28.		Now what about our oral candidates?
29.		We have lanifibranor which is a pan-PPAR, so α has effects on steatotic hepatocytes, the delta has effects on macrophage inflammatory signaling, and the gamma carries the antifibrotic effects on stellate cells. And so you can see they similarly see a reduction in SAF score without worsening of fibrosis and fibrosis improvement in the 1200-mg dose, 42% compared with 24% in placebo, and good benefits both on lipids and insulin sensitivity. So we look forward to seeing the phase 3 data.
30.		Denifanstat is a FASN inhibitor, which inhibits de novo lipogenesis. We see mass resolution without worsening of fibrosis, and we see fibrosis improvement by 1 stage, 41% compared with 18%.
31.		So just one quick note on ICD coding because this has come up in many questions.

32.		Just let people know that now if you put in MASLD or MASH, it maps to the exact same codes as NASH or MetALD. So those should not affect any of the studies that we do when we look at ICD coding. However, moving forward we will work with the organizations like WHO, which we're not a part of anymore apparently. And we will need to work with them to have more and more diagnostic codes that are more specific for MetALD, etc.
33.		So in summary, resmetirom is a THR-β agonist and the first FDA approval of a MASH-specific therapy. It has a liver-specific mechanism of action, specifically focusing on increasing the mitochondrial capability of β oxidation through biogenesis and mitophagy, increases lipophagy, increases cholesterol clearance, and also reduces inflammation and fibrosis. There also are many other drugs that are in development, we know that now. Phase 3 data have been released for semaglutide, which were very positive. And just the point of ICD codes, we need to do more work there, but it shouldn't impact anything at the moment.
34.		And I'm going to pass it on to my colleague Dr. Laurent Castera, who's going to talk to us about NITs. **[Professor Laurent Castera, MD, PhD]** It's my pleasure to present today on NITs.
35.		So you know that liver biopsy is impractical with many limitations. Not only it's invasive, but it's prone to morbidity and mortality, also rare, sampling variability and it's expensive. So as a result, given the high number of patients, there is a very limited number of hepatologists and even more limited of pathologists. So we need other methods and this what has fueled the NITs.
36.		So basically to make a long story short, we have serum biomarkers, which are validated with FIB-4 and ELF, and liver stiffness by elastography, either with vibration control transient elastography, better known as FibroScan, or MRE.

37.	**Outline** 1. Critical issues when using NITs 2. Selecting patients who should be treated (F2/F3) 3. Excluding patients who should not be treated (F4)	So I just want to outline a few critical issues when you're using NITs that are critical and you should not forget.
38.	**Critical Issues When Using NITs** 1. Availability 2. Cost 3. Context of use	First, availability, cost, and context of use.
39.	**Availability and Cost** Serum Biomarkers: FIB-4, ELF LSM by Elastography: VCTE, MRE Availability → Cost	So for instance, the serum biomarkers are widely available and come at a reduced cost as compared with MRE for instance.
40.	**Impact of Fibrosis Prevalence on NIT Performance** Primary care / Hepatology clinic ROC curve Actual fibrosis stage NIT result: F0–F2 (n = 950) / F3–F4 (n = 50) / Prevalence of F3–F4 = 5% NIT positive (n = 230): False positive (n = 190) / True positive (n = 40) / PPV = 40/230 = 17% NIT negative (n = 770): True negative (n = 760) / False negative (n = 10) / NPV = 760/770 = 99% Specificity = 190/950 = 80% / Sensitivity = 40/50 = 80% Actual fibrosis stage NIT result: F0–F2 (n = 800) / F3–F4 (n = 200) / Prevalence of F3–F4 = 20% NIT positive (n = 320): False positive (n = 160) / True positive (n = 160) / PPV = 160/320 = 50% NIT negative (n = 680): True negative (n = 640) / False negative (n = 40) / NPV = 640/680 = 94% Specificity = 640/800 = 80% / Sensitivity = 160/200 = 80%	Context of use. Let me guide you through this slide and figure. But let's say you have a good test of 80% sensitivity and specificity. According to the prevalence, so if you're in the primary care setting where the prevalence (in other words the pretest probability) is low (around 5%), then you end up with a very high NPV (close to 100%) and a PPV that is poor (17%). Using the same test at the hepatology clinic where the prevalence is much higher (between 20% and 30%) you still have high NPV, but look—the PPV is not perfect, they go from 17% to 50%. So always keep this in mind when interpreting NITs.
41.	**Context of Use: Primary Care** Serum Biomarkers: FIB-4 LSM by Elastography ▪ Use in populations with low prevalence of F2/F3 fibrosis ▪ Not for secondary care ▪ Useful to rule out (<1.3) but not to diagnose F2/F3 ▪ Adapt cutoff to age (<2.0 for >65 years)	So primary care, clearly now FIB-4 is the test of choice. It's really designed for use in populations with low prevalence of F2/F3 fibrosis, not for secondary care. Useful to rule out 1.3, but not to diagnose F2/F3. And you should adapt the cutoff to age as well.

42.		As for the others, they are most suited as second testing (either VCTE or MRE).
43.		So if we're screening for MASLD in primary care, the good news is we have many algorithms, starting with the EASL algorithm published in 2021, but many other algorithms use the same philosophy.
44.		And recently, last year, the EASL-EASD-EASO guideline. So just to make a long story short, because you're all very familiar with this algorithm, you basically start with a very simple first test and use a second test, and we can discuss the cutoff.
45.		So now the key question is how are we going to select patients who should be treated? Because you know, the label came without a liver biopsy.
46.		Let me take you to this table. But just to remind you, what were the eligible patients in the MAESTRO-NASH trial: so, CAP of at least 280 dB/m, liver stiffness above 8.5 kPa, and platelets above 140 k/µL. So you have two-thirds of patients with F3 and one-third with F2. And you see that the median VCTE was 12 kPa, median CAP was almost 250 dB/m, FIB-4 median 1.3, and ELF median 9.7.

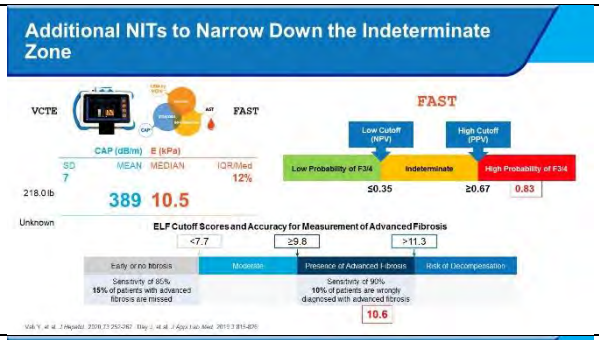
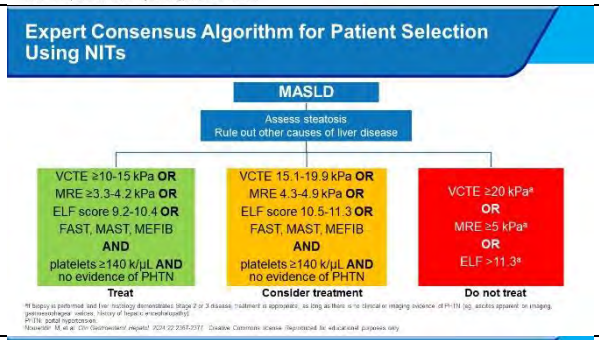
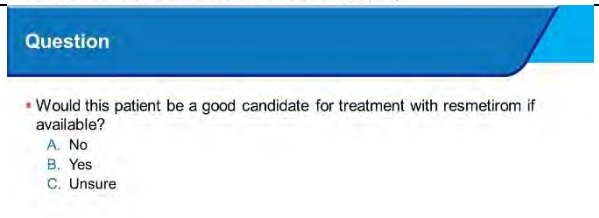
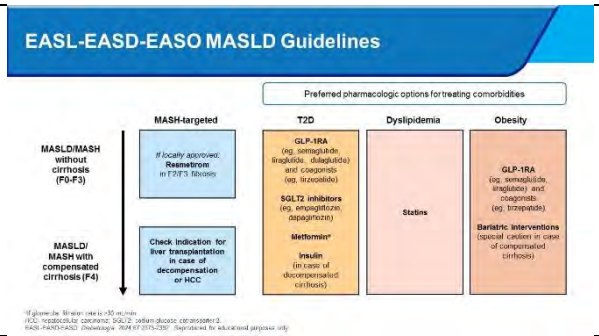
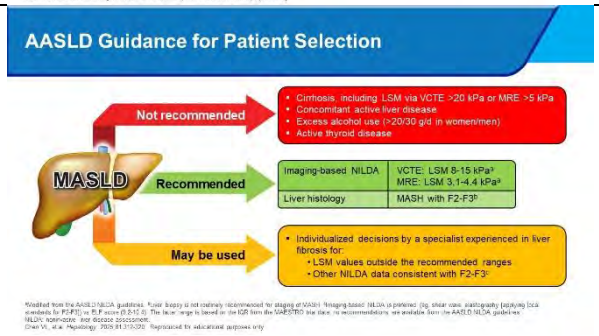
47.	**NIT Performance for F2, F3, and F4** Meta-analyses AUROC, area under the receiver operating characteristic curve; VCTE, vibration-controlled transient elastography.	Now what are the performances of this test for diagnosing significant fibrosis? So again, to make a long story short, you see that the performances are good, with AUROC ranging from 0.81 to 0.91, but clearly the level of evidence is much higher for VCTE.
48.	**LSM (VCTE) Confounders With Risk of False-Positive Results** Know the ALT Operators should have performed > 100 exams Have patients fast for 3 hours prior Inexperience Inflammation Non-fasting Confounders Congestion Examine for right heart failure Cholestasis Know the alkaline phosphatase Alcohol Obesity Determine drinking status Use an XL probe at BMI ≥ 30	Don't forget that when you're using liver stiffness, whatever the technique, there are confounders with the risk of false-positive results. The main one of course, inflammation and steatohepatitis; inexperience of the operator (this is for VCTE); alcohol use—we have a lot of discussion about that, but it's related to inflammation; and finally, obesity of course is a major factor. And this is for VCTE more than MRE.
49.	**VCTE vs MRE: Advantages and Pitfalls** AUC, area under the curve	If you just look at the advantages and pitfalls of the 2 techniques, the accuracy is high for both, but even higher for MRE as compared with VCTE. The level of evidence is by thousands of patients and hundreds for MRE. Availability is widespread for VCTE, more limited for MRE. The range of value also is different, 2 to 75 kPa for VCTE and 2 to 11 kPa, meaning that you have probably more granularity using VCTE, especially in the patients with severe disease (if you want to look at liver-related events for instance). The main limitation of VCTE in practice, as you know, is BMI. When it's above 35 kg/m^2, it should ring a bell, but when it's above 40 kg/m^2, you should be very cautious interpreting the data.
50.	**Suggested Cutoffs for F2-F3**	For the sake of time, I will not go into detail for this very busy slide. Just to give you a flavor of the suggested value of cutoff for diagnosing F2/F3, ELF 9.2 to 10.4, VCTE 10 to 15 kPa and 15 to 20 kPa, and MRE is 3 to 4.3 kPa.

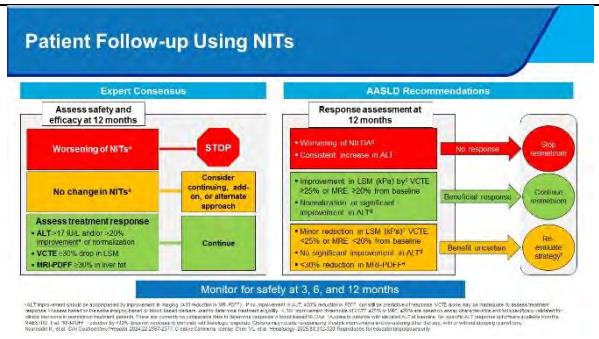
51.	**Composite Scores for At-Risk MASH** **FAST** = CAP + AST + LSM (VCTE) - Rule-in: ≥0.67 - Rule-out: ≤0.35 - Grey zone: 0.35-0.67 **MAST** = PDFF + AST + LSM (MRE) - Rule-in: >0.242 - Rule-out: <0.165 - Grey zone: 0.165-0.242 **MEFIB** = LSM (MRE) + FIB-4 - Rule-in: MRE ≥3.3 kPa + FIB-4 ≥1.6 - Rule-out: MRE <3.3 kPa + FIB-4 <1.6 - Grey zone: Neither rule-in nor rule-out	Okay, just brief words regarding composite score for at-risk MASH. You know the score FAST, MAST, and MEFIB.
52.	**Summary of Performance** Score / AUC / N / At-Risk MASH / Rule-out Cutoff / Sensi-tivity / NPV / Grey Zone / Rule-in Cutoff / Speci-ficity / PPV / CC FAST 0.85 1026 27% <0.35 0.89 0.94 30% >0.67 0.49 0.69 60.3% MAST 0.93 244 11.5% <0.165 0.89 0.98 18% >0.242 0.90 0.50 72.5% MEFIB 0.77 563 31.4% MRE <3.3 kPa and FIB-4 <1.6 0.91 0.93 25% MRE ≥3.3 kPa and FIB-4 ≥1.6 0.78 0.55 57.4%	And again the summary of performance. As you can see they come with dual cutoff and a grey zone. So the rule-in cutoff is 0.67 for FAST, 0.242 for MAST, and MRE is not linear, it's a combination of FIB-4 and MRE. At the end of the day, what matters, PPV as you can see is far from perfect going from 0.5 to 0.7, but the correctly classified basically varies to 57% to 72%. So this has to be taken into account.
53.	**Don't Forget Comorbidities: T2D** Methods Findings FNI MEFIB MAST FAST Cutoffs adapted to T2D should be used 0.81* 39% 40% 38% 56%** Original cutoffs Adapted cutoffs Fibrotic MASH Conclusion: FAST, MAST, MEFIB, and FNI are accurate non-invasive tools to identify patients with type 2 diabetes and fibrotic MASH in secondary/tertiary diabetes clinics. Cut-offs adapted to type 2 diabetic population should be used.	I would just like to draw to your attention that you should not forget comorbidities, including type 2 diabetes. These were results published last year from the QUID-NASH cohort. And again, when you compare the different tests, you can see that MAST and FAST outperform MEFIB and also FNI. But this is no surprise with FNI because this is intended for primary care. Now if you look at the percentage of correctly classified using the original cutoffs that have been published in the literature (not addressing type 2 diabetes population with a high pretest probability), you'd think that the MAST outperformed FAST. Now if you adapt the cutoff to the setting, look what is happening. Then it's the opposite, FAST is outperforming, MAST in terms of correctly classified patients. So don't forget cutoff should be adapted to the context. This is just I think an example for type 2 diabetes, but this may apply to other settings.
54.	**Outline** 1. Clinical issues when using NITs 2. Selecting patients who should be treated (F2/F3) 3. Excluding patients who should not be treated (F4)	Now how can we exclude patients?

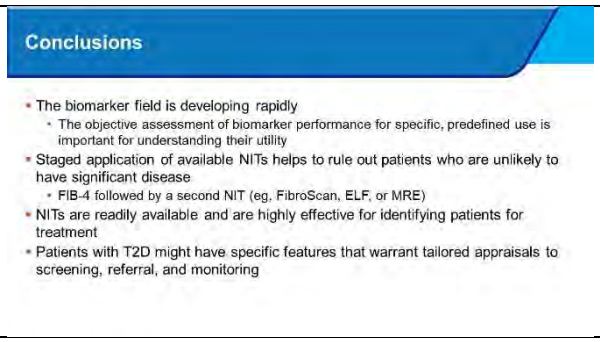
55.	**Cutoffs for Diagnosing Cirrhosis** | NIT	Cutoff	Comments | |---|---|---| | ELF | ≥11.3 | ELF ≥11.3 is associated with increased risk of hepatic decompensation among patients with cirrhosis | | Imaging | | | | VCTE | ≥20 kPa | LSM by VCTE ≥20 kPa is associated with cirrhosis, but for ruling out, cirrhosis optimal cut point is <8 kPa | | MRE | ≥5 kPa | LSM by MRE ≥5 kPa has a very good specificity (approaches 95%) for diagnosis of cirrhosis and is also associated with increased risk of incident hepatic decompensation |	And this is of course very important in practice because the label is for F2/F3. So you want to be confident to exclude patients with cirrhosis where you could be detrimental in the absence of label. So the cutoff of 11.3 for ELF if you're over, and for VCTE would be 20 kPa and 5 kPa, so quite easy to remember cutoff.

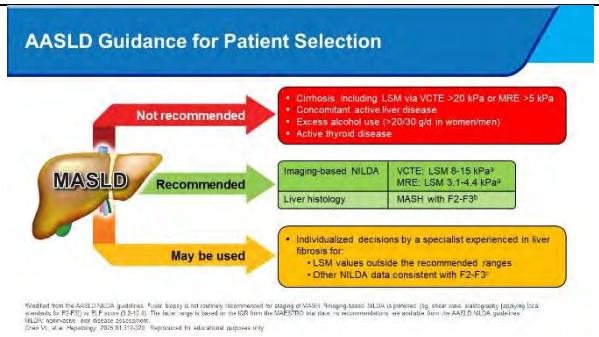
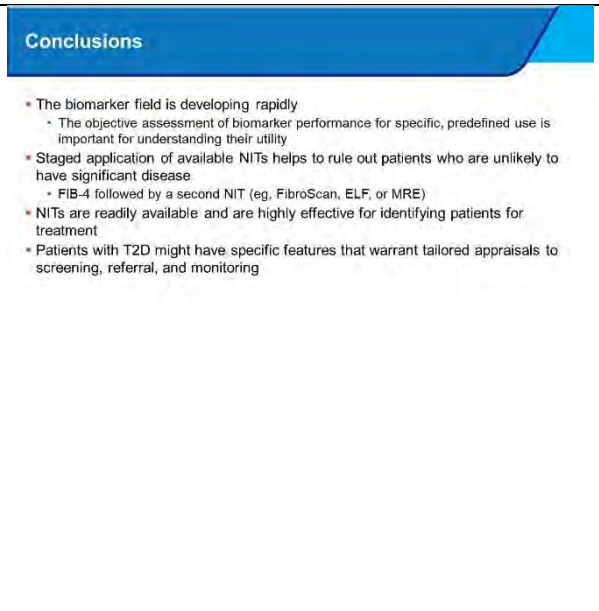
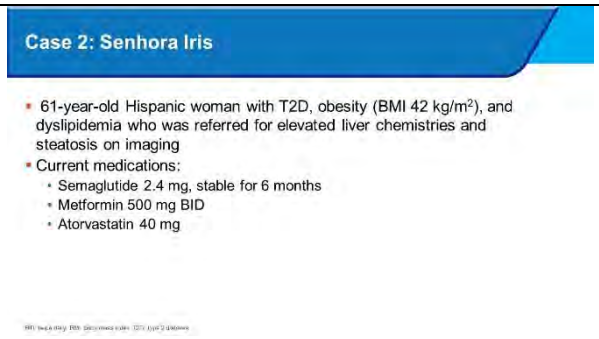
56.	**Case 1: Senhor Diogo**
	
	- 55-year-old man referred by his PCP due to abnormal liver biochemistry
	- **Medical history:** T2D for 15 years, dyslipidemia for 2 years
	- **Family history:** Mother had diabetes, and father had hypertension and IHD
	- **Social history:**
	  - He exercises occasionally
	  - Mainly sedentary job
	  - Drinks 1 glass of wine every other night, smokes a pipe
	- **Prior examination:** BMI 27 kg/m^2, BP 130/80 mm Hg
	- **Symptoms:** Has some right upper quadrant discomfort
	- **Medications:** Gliclazide 80 mg by mouth twice daily and fish oil; PCP stopped statin due to abnormal liver biochemistry
		This is Senhor Diogo, a 55-year-old man referred by PCP due to abnormal liver biochemistry. He has a medical history of type 2 diabetes for 15 years and dyslipidemia, more recent, for 2 years. Family history: mother has diabetes and father has hypertension. Social history is mainly sedentary; he drinks a glass of wine every other night and smokes a pipe. His BMI is 27 kg/m^2, his blood pressure is 13/8 mm Hg. He has some right upper quadrant discomfort, and his medication includes gliclazide 80 mg and his PCP stopped his statin due to his abnormal liver biochemistry. So this is I'm sure a common situation that you've encountered in your practice.
		
		NOTE:
		The patient should continue statin therapy.

57.	**Case 1: Senhor Diogo (cont)** | Laboratory Values | | |---|---| | ALT | 99 IU/L | | AST | 72 IU/L | | Total bilirubin | 13.7 µmol/L (0.8 mg/dL) | | Albumin | 40 g/L (4.0 g/dL) | | Platelets | 170,000/µL | | Total cholesterol | 6.9 mmol/L (265 mg/dL) | | LDL | 4.75 mmol/L (184 mg/dL) | | HDL | 0.93 mmol/L (36 mg/dL) | | Triglyceride | 2.71 mmol/L (240 mg/dL) | | HbA_{1c} | 52 mmol/mol (6.9%) | ASCVD Risk Score	So let's go to the laboratory values. For the sake of time, I would just emphasize that of course there's a slightly elevated ALT, higher than AST. Bilirubin is normal, platelet is normal, but you see that the lipid profile is elevated with elevated triglyceride, cholesterol, LDL, and low HDL. HbA_{1c} is okay and ASCVD risk score is close to 20%, so this patient is clearly at risk given his diabetes and his lipid profile.
58.	**FIB-4 for Ruling Out Advanced (F3/4) Fibrosis** FIB-4 Score - = (**Age** * **AST**) / (**Platelets** * square root [**ALT**]) - A score of <1.3 excludes fibrosis (NPV 95%) - A score >3.25 predicts fibrosis (PPV ~70%) Low Cutoff (NPV) / High Cutoff (PPV) Low Probability of F3/4 / Indeterminate / High Probability of F3/4 1.3 / 2.34 / 2.67	So if you look at the FIB-4 results, the FIB-4 is intermediate.

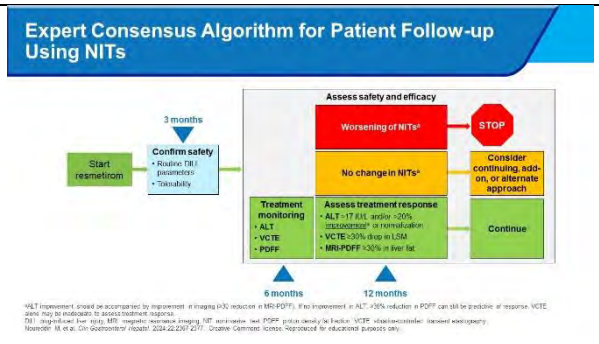
59.		The FAST score is elevated (0.83) and the liver stiffness is 10.5 kPa.
60.		So this, the expert consensus recommendation published last year in *Clinical Gastroenterology and Hepatology*.
61.		**[Meena Bansal, MD, FAASLD]** Okay, so if you scan that QR code, so would this patient be a good candidate for treatment with resmetirom if available? Yes. Okay, great. **[Professor Laurent Castera, MD, PhD]** This is amazing votes. Right, 84% for yes, 8% for no, and still 8% of people are unsure. Okay, so I close the voting and I go back.
62.		So this has been already shown by Meena. These are the guidelines recently from EASL and resmetirom (if locally approved because we don't have experience yet in Europe) should be considered if you have F2/F3 fibrosis. Of course if you have diabetes, then you use a diabetes treatment.
63.		For the sake of time, I will move forward and just look at the AASLD guidance for patient selection. So as I already emphasized, clearly not recommended in patients with suspected cirrhosis on the criteria we mentioned or concomitant active liver disease, excess alcohol use; clearly recommended, and you see that the cutoffs are not completely consistent, for vibration controlled transient elastography (VCTE), the recommendation for treatment with resmetirom is 8 kPa instead of 10 kPa in the other recommendation (expert consensus algorithm by Noureddin 2024) or liver histology; and when resmetirom may be used, then you will individualize decisions by a specialist

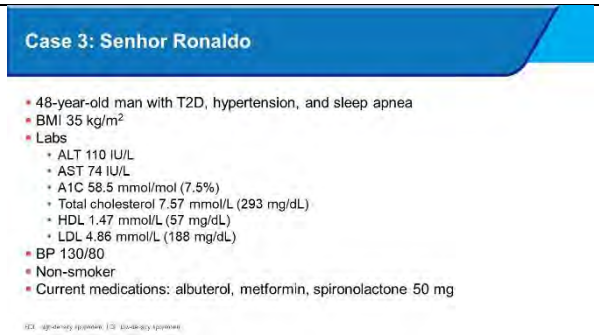
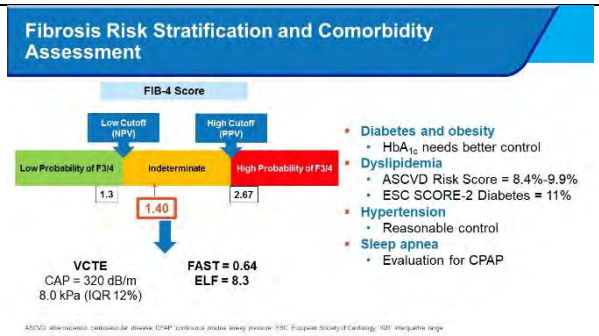
		experienced in liver fibrosis for LSM values outside of the recommended range or other NILDA testing data consistent with F2/F3.
64.		Regarding the follow-ups, these are the expert consensus and the AASLD recommendations, and they're basically aligned, which is reassuring. Of course, if there would be worsening of NITs (we can discuss about the definition of worsening of NITs), then of course the treatment should be stopped. Otherwise, in case of treatment response assess, on VCTE 30% drop, MRI-PDFF 30% drop in liver fat, and improvement of AST of 20%, then you should continue treatment. Otherwise if there's no change, you can consider continuing, add-on, or an alternate approach. And this is basically what the 2 recommendations are, and this we can discuss of course. **[Meena Bansal, MD, FAASLD]** Yeah, I think we can even discuss a little bit why the case that you presented is kind of the Goldilocks case, right? So the perfect case where the liver stiffness, all the NITs are consistent with F2/F3 fibrosis, there's clearly no cirrhosis, and then when you look at the other comorbidities, their diabetes is reasonably well controlled, they're overweight (BMI 27 kg/m^2), but you know, still worth focusing on the liver fibrosis here and starting resmetirom. I think the other important point to make, which many of you may see (I know I see all the time; interested to hear Mary's opinion), but there's a hesitancy to start statins in patients when their liver enzymes are at this level of 80-90 IU/L (like this patient). So oftentimes we're the ones that need to start the statin. I would say don't fear the statin, and this patient was inappropriately taken off the statin. So I don't know if you have a comment on that. **[Mary E. Rinella, MD]** That's a very common misconception that patients like this should not be—I mean, I think—I calculate ASCVD risk on all of my patients and if it's over 7%, the patient should be on a statin. Most of the patients that you're going to see with this disease should be on a statin anyway. And this person has a mixed dyslipidemia, so we also can expect resmetirom to reduce the LDL in this patient. So you could either start both or you can wait, do resmetirom first and then add a statin, or you could do the reverse. But ultimately, if you're going to have a liver-directed approach in this particular patient, then you would focus on that. But the LDL should come down nicely also with resmetirom. **[Meena Bansal, MD, FAASLD]**

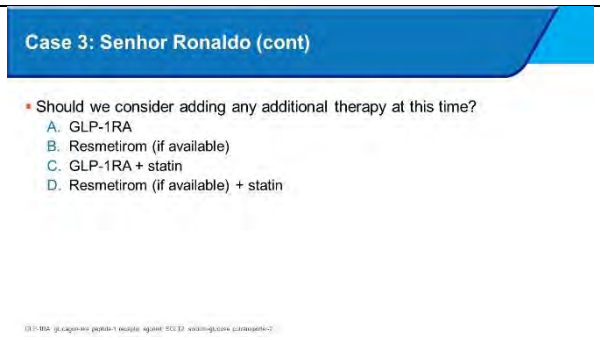
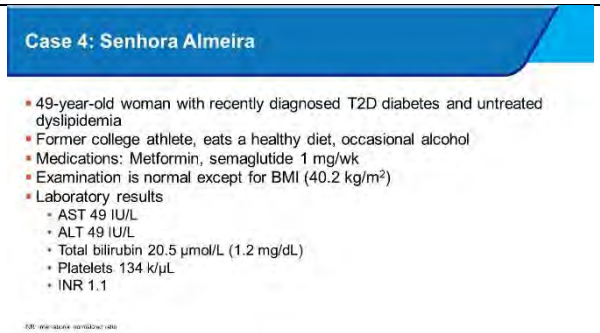
		Yeah, that's a great point. So maybe see where you land after resmetirom for 6 months, and then look at the lipid parameters, and then make your choice accordingly. **[Mary E. Rinella, MD]** And the caveat though is that we haven't yet seen proven cardiovascular benefit. I would not be surprised if we, you know, someday we'll show that. But just to be fair, with statins that is clearly shown. So I don't know if we can 100% say we wouldn't need to also add the statin later. **[Meena Bansal, MD, FAASLD]** Yeah, and I think about 45%, almost 50% of the patients who were enrolled in the MAESTRO-NASH study were on a statin. **[Mary E. Rinella, MD]** Exactly. **[Professor Laurent Castera, MD, PhD]** So would you like to comment on the transaminase? Because this is what worries the GP, and this is a very common situation, but we as specialists know that we do not worry about transaminase. But what about the combination of statin and resmetirom? **[Meena Bansal, MD, FAASLD]** Yeah, so in the study, those that were on a baseline statin saw a tiny blip in their liver enzymes early on, but that goes away. So we need to educate our PCPs to not overreact to this, don't check it, really, you don't need to check it after 1 month. There's no recommendation to check liver enzymes after starting resmetirom 4 weeks later. People think it's reasonable to check at 3 months just to kind of make sure they're taking it, take a look at it. But again, you're not looking for efficacy at that point. And there's really no DILI events that were reported. Mary, I don't know if you have another comment.
65.		**[Mary E. Rinella, MD]** No, in fact, I think the next case that we're going to do just highlights that it's a very simple concept, but I think that it's an important one because I think it's a reflex when you start somebody on a medication to look at their liver chemistries. But in this particular case, you should not be making any treatment decisions based on early assessment of liver enzymes.

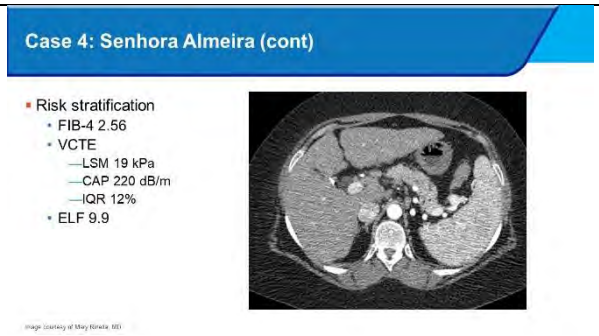
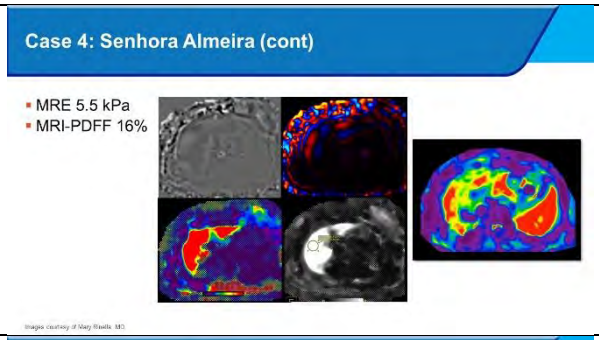
		[Meena Bansal, MD, FAASLD] We can make a comment about the thyroid also and the differences between the ASLD guidance and the expert opinion. You know, hypothyroidism is associated with MASLD. As part of the workup, before you even got to this point, a patient probably had a TSH.
66.		They should, you know, hepatologists often check that in their workup, but about 15% of patients were on, you know, levothyroxine on a thyroid hormone replacement therapy coming into the study. And so here they're calling out active thyroid disease. But again, if you're euthyroid on treatment, there's no expectation that that will change and it really doesn't have to be monitored specifically. Again, you're monitoring them, but it has nothing to do with the resmetirom. **[Mary E. Rinella, MD]** Yeah, I think it's misleading to say that, to have that, because it does raise those questions, right? But no, I completely agree with you.
67.		**[Professor Laurent Castera, MD, PhD]** Okay, so maybe it's time to move to the conclusion and hear what Mary is going to say afterward. So you're, I think, very convinced that the biomarker field is developing rapidly and the objective assessment of biomarker performance for specific, predefined use is important for understanding their utility. Staged application of available NITs helps to rule out patients who are unlikely to have significant disease, and [it should be] FIB-4 followed by a second NIT (FibroScan, ELF, or MRE). NITs are readily available and highly effective in identifying patients for treatment. And patients with type 2 diabetes might have specific features that warrant tailored appraisals to screening, referral, and monitoring. Thank you very much for your attention.
68.		**[Mary E. Rinella, MD]** Okay, so we're gonna start with our first case. This is a 61-year-old Hispanic female with diabetes, obesity with a BMI of 42 kg/m^2, dyslipidemia, who's referred for elevation of liver chemistries, and steatosis on imaging, a very typical scenario. They're on semaglutide, 2.4 mg. They've been stable on this dose for 6 months. They're also on metformin and atorvastatin 40 mg.

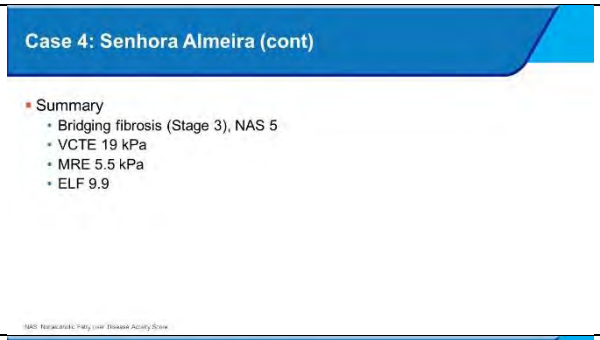
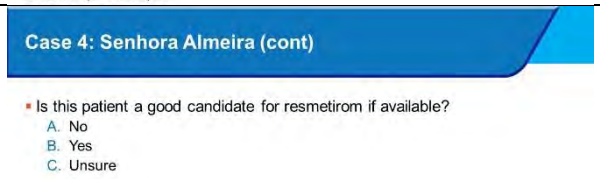
69.	**Case 2: Laboratory Data and Risk Stratification** ▪ Lab testing • AST 55 IU/L • ALT 62 IU/L • Platelets 188 k/µL • A1c 54 mmol/mol (7.1 %) • Bilirubin 20.5 µmol/L (1.2 mg/dL) ▪ FIB-4 2.90 ▪ CAP 389 dB/m ▪ LSM 10.5 kPa ▪ FAST 0.83	So the initial laboratory assessment is the AST 55 IU/L, ALT 62 IU/L. In our laboratory, 30 IU/L is the upper limit of normal, approximately. Platelets 188 k/µL, HbA_{1c} is 7.1%, bilirubin is 1.2 mg/dL, and FIB-4 is elevated at 2.9. Elevated CAP and then modest liver stiffness in a FAST is 0.83. Do you guys have any initial comments before we move on? If there's anything interesting to point out? **[Meena Bansal, MD, FAASLD]** Certainly looking like consistent with F2/F3 fibrosis. Platelet count is good, so that's reassuring. The AST/ALT ratio is favorable. **[Mary E. Rinella, MD]** Oh, you can't hear that, you're saying. But essentially the Goldilocks. This is Goldilocks right here. That's Laurent, do you have any other comments about? This is a very quick case. **[Professor Laurent Castera, MD, PhD]** So just be cautious giving the BMI with the liver stiffness. **[Mary E. Rinella, MD]** Yes, that's a very good point. **[Professor Laurent Castera, MD, PhD]** Basically, the other NITs are pretty concordant.
70.	**Case 2: Senhora Iris (cont)** ▪ Resmetirom is started ▪ 4 weeks later she sees her PCP who checks her liver enzymes • AST 68 IU/L • ALT 75 IU/L • Bilirubin 18.8 µmol/L (1.1 mg/dL) ▪ The PCP reaches out concerned about the liver enzymes	**[Mary E. Rinella, MD]** Yeah. So this patient was started on resmetirom and I really do... This is actually a very common type of patient. About half of my patients come in already on a GLP-1. So this is pretty typical at least for my practice. And the pieces in case for the PCP checks, liver chemistries, and they are as they are here. So they are continued to be elevated. They're actually a bit more elevated. I don't know if the numbers were flipped but in any case, bilirubin is about the same and the PCP is now worried after you've done this.
71.	**Case 2: Senhora Iris (cont)** ▪ What is the next best step in the management of this patient? A. Stop resmetirom immediately B. Continue resmetirom and monitor liver enzymes in 4 weeks C. Continue resmetirom and monitor liver enzymes in 2 months	So now we're gonna answer. Okay. Okay. Interesting. Well, yeah, so this is a little bit. So it's good that nobody said "A". Because you don't really, you don't need to do that. Whether you do your assessment at 3 months or a little bit later, a little bit earlier, that's fine. I think either probably are okay. But we recommend 3 months as the first assessment and again that's really focused mostly on safety as you would do with the new medication. Efficacy really needs to be done later, assessed later rather. **[Meena Bansal, MD, FAASLD]** And I think this is the point that we were talking about, with if you're on a baseline stage and sometimes you see that little blip but it will get better. **NOTE:**

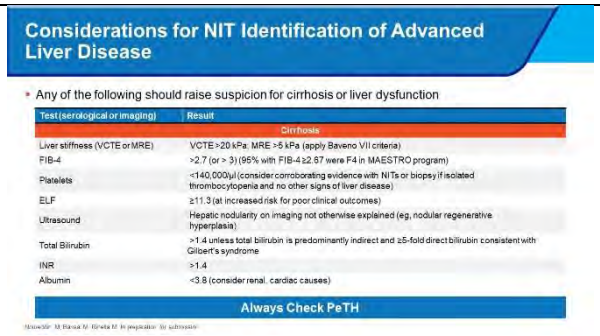
		https://www.ncbi.nlm.nih.gov/books/NBK603251 Resmetirom Mild, transient serum aminotransferase elevations develop in a high proportion of patients receiving resmetirom, generally within the first 4 weeks of therapy. These elevations are typically mild, self-limited, and not associated with symptoms or jaundice. Furthermore, these early changes were usually followed by a decrease in serum enzymes which were often within normal range 3 to 6 months later. These improvements in liver-related enzymes correlated to some extent with the decrease in hepatic fat and histologic evidence of steatohepatitis. After 52 weeks of treatment, liver biopsies demonstrated resolution of NASH in 26% to 30% of patients. Whether these changes are sustained or increase with further therapy is not known. Therapy does not result in weight loss, and the improvements in hepatic histology and fibrosis may be lost once therapy is discontinued. Analysis of liver tests from more than 1300 adults with NASH treated with resmetirom in doses of 80 or 100 mg daily for up to 1 year identified 2 patients with liver injury that was considered at least possibly due to resmetirom. The latency to initial onset was 2 and 3 months (ALT 236 U/L and 578 U/L, ALP unknown and 64 U/L, bilirubin 0.6 and 1.1 mg/dL). Both patients recovered completely within 1 to 2 months of stopping treatment. One patient was restarted on treatment and redeveloped liver injury within 28 days (ALT 3226 U/L, ALP 140 U/L, bilirubin 10.9 mg/dL) that was more severe than the initial episode, but that resolved spontaneously within 2 months of stopping. In both cases, other diagnoses remained possible.
72.		**[Mary E. Rinella, MD]** Yeah. So here are the recommendations that we proposed. So, safety assessment at 3 months and then really you can start to make I think, get a gestalt, an assessment as far as if there's any efficacy at 6 months but really not making a treatment changing decision, I would say, for 12 months would be appropriate. Do you have any additional comments about that, Meena or Laurent? **[Meena Bansal, MD, FAASLD]** No, I agree, I agree. I think, you know, there's... You're just treatment monitoring it at 6 months but not really looking for efficacy yet till 12 months.

		NOTE: Assessment of safety and treatment response on resmetirom. Changes in NITs at 3 months were not reliably predictive of treatment response in the MAESTRO-NASH trial, thus the 3-month assessment should be reserved to confirm the absence of DILI. Assessment of response in patients with resmetirom should ideally not be made until the 12-month time point. Although an improvement in PDFF was most predictive of response, this may not be routinely performed and other NIT benchmarks to consider are provided. *ALT improvement should be accompanied by improvement in imaging (≥30 reduction in MRI-PDFF). If no improvement in ALT, ≥30% reduction in PDFF can still be predictive of response. VCTE alone may be inadequate to assess treatment response. Based on MAESTRO-NASH, histologic improvements may occur without corresponding changes in VCTE or liver enzymes, emphasizing the importance of considering MRI-PDFF or liver biopsy before labeling patients as unresponsive to treatment.
73.		**[Mary E. Rinella, MD]** Okay. So now it starts to get a little bit more complicated. So this is Ronaldo, 48-year-old patient with diabetic hypertension with sleep apnea. BMI is 35 kg/m^2. Liver enzymes are a little bit more elevated. HbA_{1c} is 7.5%. Total cholesterol 293 mg/dL. HDL 57 mg/dL. LDL is 188 mg/dL. I would say borderline blood pressure. Non-smoker and he's on albuterol, metformin, and spironolactone only, which is remarkable.
74.		Okay. So, he gets a FIB-4 calculated and it's 1.4. Why don't you comment, Laurent, on how we might interpret these? **[Professor Laurent Castera, MD, PhD]** I think it's indeterminate. **[Mary E. Rinella, MD]** Yes. **[Professor Laurent Castera, MD, PhD]** Seriously. I think it means, of course you need a second test. And you see that the ELF is 8.3, the FAST 0.64, and VCTE is 8 kPa. So, we're kind of in the grey zone. We're not sure about significant or advanced fibrosis. **[Mary E. Rinella, MD]** Right. But there's no evidence really for very significant fibrosis. Certainly. You could argue that the HbA_{1c}, that the diabetes, could use a little bit better control. The patient could, you know, use a little bit more weight loss. The ASCVD Risk Score would state that the patient also

		would benefit from a statin and better control of hypertension, sleep apnea. Again, not. You do your due diligence, what you're supposed to do with that.
75.		And then, I guess, the next question then is, what do you do? Right? This is also a very, very common scenario. So we'll do, we'll start the voting. Okay. Any comments or... **[Meena Bansal, MD, FAASLD]** Yeah, no, I think the choice "C" definitely makes a lot of sense. This person has sleep apnea. They have a number of other risk factors for, you know, obesity. So, I think a GLP-1 receptor agonist makes total sense. Their ASCVD risk score also is elevated. And in a patient with diabetes, you definitely want to start a statin. And I guess we get back to that same question. Do you start 2 things at the same time just for monitoring purposes, or just kind of phase them just a little bit so that you can kind of monitor and see your impact? **[Professor Laurent Castera, MD, PhD]** I would agree as well. **[Mary E. Rinella, MD]** Yeah. I mean, you could do one and then the other, but at the end of the day, I think the patient really needs to be on a statin also in addition to a GLP-1, even though there's, you know, cardiovascular benefit also with a GLP-1. So that this would be a very, I think, solid case for GLP + or - statin. **[Meena Bansal, MD, FAASLD]** And I think that clearly, you know, with an 8 kPa, with that BMI, you know, more likely they don't have significant fibrosis, but that can change. So, the key is then annual monitoring for longitudinal changes in time. As we saw a lot of data during this meeting, it's those longitudinal changes—you know, getting to that 10 kPa. Right? Is where there's a clear inflection point. So we definitely want to do annual fibrosis assessment.
76.		**[Mary E. Rinella, MD]** Yeah, it's a high-risk patient. Okay, so the next patient is a 49 year old. Again, diabetes, untreated dyslipidemia, who used to be very fit but gained quite a bit of weight, is on metformin, semaglutide 1 mgm and as I mentioned, she's overweight. AST/ALT ratio is 1 and they're 49 IU/L, respectively. Bilirubin is 1.2 mg/dL, platelets are 134 k/µL, INR is 1.1.

77.		You rule out other causes of liver disease, of course. And you get a FIB-4 of 2.56. Liver stiffness is elevated—19 kPa and the ELF is 9.9. Any quick comments on what you would do next or any thoughts? **[Meena Bansal, MD, FAASLD]** So the platelet count was on the lower side. So now I'm kind of a little bit concerned for more advanced disease. And if you look, the CAP is actually quite low, right, and you see that with more advanced liver disease. So I'm concerned about cirrhosis in this patient. **[Professor Laurent Castera, MD, PhD]** Yeah, I share your concern. I would suspect the so-called burnout NASH or cirrhosis. **[Mary E. Rinella, MD]** Yeah, no, I agree. So, in fact cross-sectional imaging is done. You can see that this is a bit of a nodular liver and the spleen is a little bit generous.
78.		And then an MRE was actually done in this patient and the liver stiffness was quite elevated with a stiffness of 5.5 kPa.
79.		**[Meena Bansal, MD, FAASLD]** So by now, this actually brings up the point. See here the PDFF is 16%. So on a much better test at looking at fat, you can see it, whereas the CAP did not pick it up. **[Mary E. Rinella, MD]** It's also not the same day and all of that. But yes, I agree. So, this is the biopsy. What was interesting about this biopsy, this is read as a stage 3 with an NAS of 5. HVPG is just above the upper limit of normal. So it's in technically early portal hypertension. I would personally look at this biopsy and say this patient has cirrhosis. Period. Even without the biopsy. But the point I think with this case is that it is not uncommon to get a read that says F3 and it's not actually F3. And that's important because you need to use all the data that you have at your disposal, you know, whether it's laboratory assessment, physical, you know, assessment and non-invasive testing to sort of get a gestalt as to what the right answer is for this patient. So this patient, like I said, definitely I would disagree that this is just a stage 3.

80.		This is a patient that has definitely exceeded that.
81.		I'm gonna go a little bit through this because we have 1 more. So, what do you do with this patient? Yes, that's a correct answer. So, I think, you know, until we know more and there's nothing intrinsic, there's no major reason why we'd say, "Oh, you can't treat somebody with cirrhosis." But we don't have the evidence yet. And there's a lot of evidence that's been developed. It just hasn't read out. And we just don't have that recommendation. That's not on the label and that's why you just wouldn't do that in this particular patient. **NOTE:** **Figure 1: Proposed algorithm for patient selection using noninvasive tests.** In patients with MASLD (steatosis confirmed on imaging or suspected by the presence of cardiometabolic risk factors and exclusion of other causes of liver disease), fibrosis burden should be approximated using NITs, with the goal of targeting those with clinically significant fibrosis (F2 or F3) and excluding those likely to have cirrhosis or portal hypertension. Phosphatidylethanol (PeTH) measurement should be considered to identify those who may have MetALD or ALD. While treatment with resmetirom may be effective in the setting of moderate or heavy alcohol use, this requires further study. Thus, it is suggested that those with a PeTH >200 not be treated with resmetirom. If liver biopsy is available and demonstrates stage 2 or 3 fibrosis, NIT based parameters can be overridden, provided there is no clinical or imaging evidence of portal hypertension (see text for specifics).

82.		**[Mary E. Rinella, MD]** This is basically just the other things you should be thinking about, which we sort of discussed in the course of the discussion. Very elevated ELF greater than 11.3, abnormalities in bilirubin. That's the direct bilirubin, not just the total. You need to look at the direct to see if there's any signal for liver impairment and any other evidence of synthetic dysfunction or impairment. That really should be a warning sign to you that the patient has impaired synthetic function. And that's not the right person to be starting on new medication. The other thing that's an important point is PeTH. We've talked a lot about PeTH in this meeting, but it is very important. In my practice I check it on every new patient that I see and depending on the level that I see or the history, I may check it again. It's important because patients who have high alcohol intake may have, you know, more impairment in synthetic function and are at higher risk. And those patients are really not tested, especially if the level, PeTH level, comes back, certainly above 200. **NOTE:** Noureddin, Bansal, and Rinella, In Preparation for Submission. Additional Clinical Criteria • Any history of clinical manifestations of hepatic decompensation (ascites, varices, hepatic encephalopathy) • Elevated bilirubin (ensure no symptoms of jaundice, dark urine, clay-colored stools; predominately indirect bilirubin if Gilbert's syndrome suspected) • Trends of albumin and platelets • Physical examination findings: palmar erythema, spider angioma, Dupuytren contracture
83.		**[Meena Bansal, MD, FAASLD]** Just let you close with this kind of concept of shared decision-making for long-term disease management, seeking your patient's participation. Obviously, a patient-centered approach, understanding their values, and then making a collective decision.