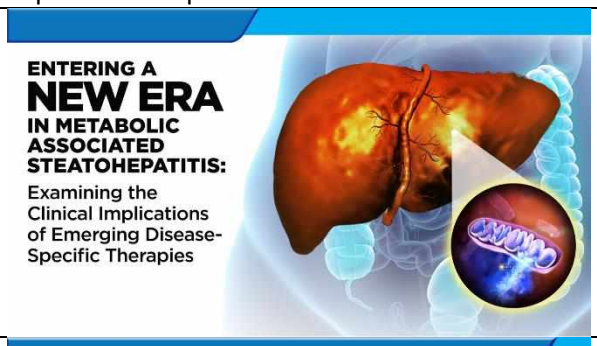
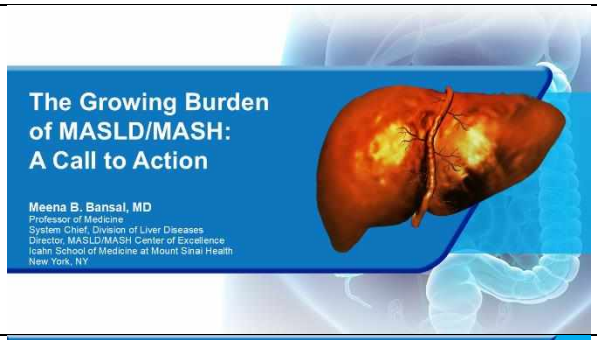
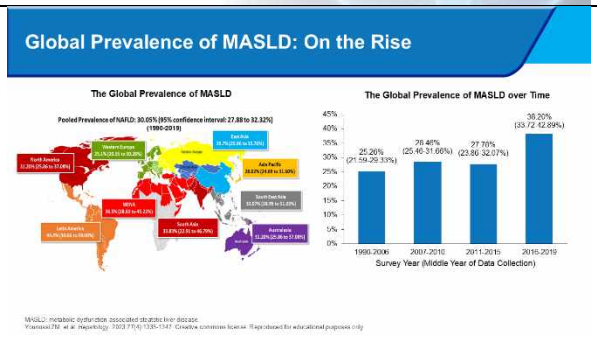
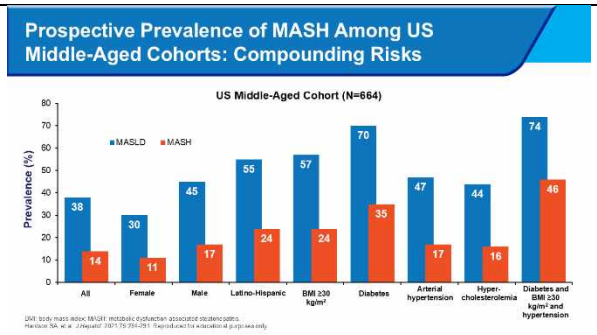
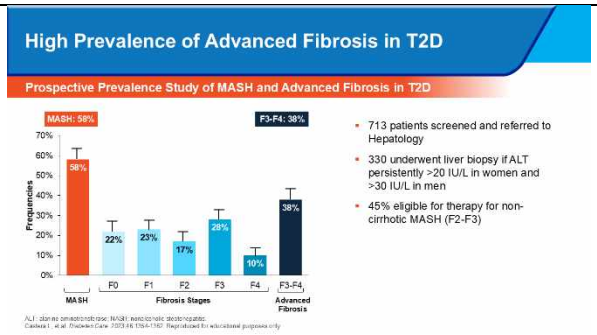
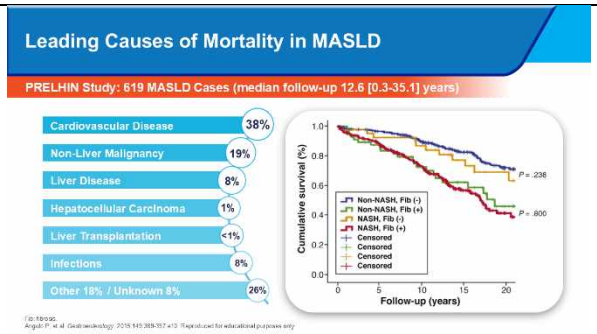
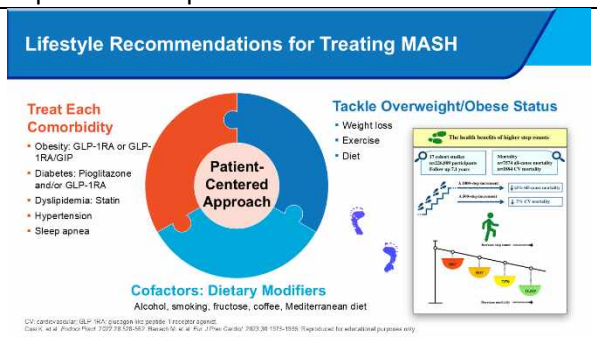
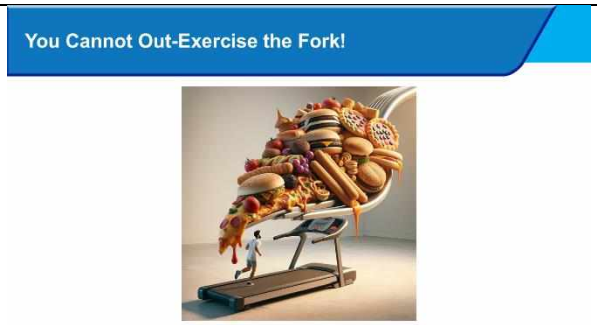
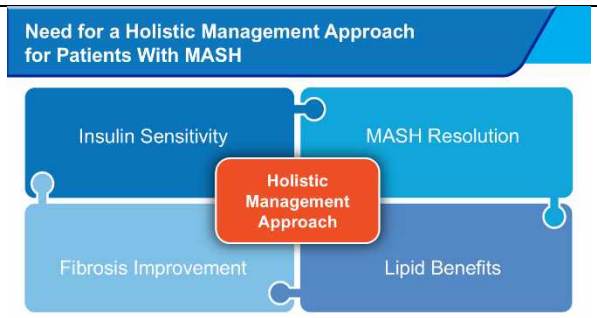
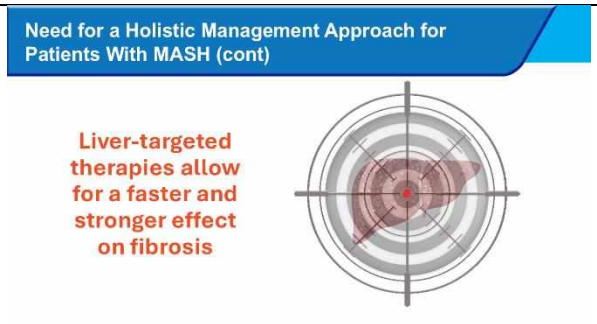
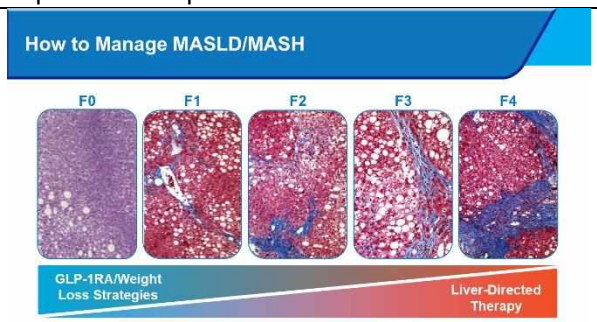
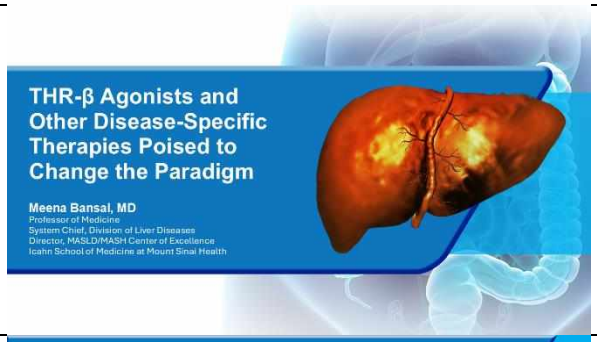
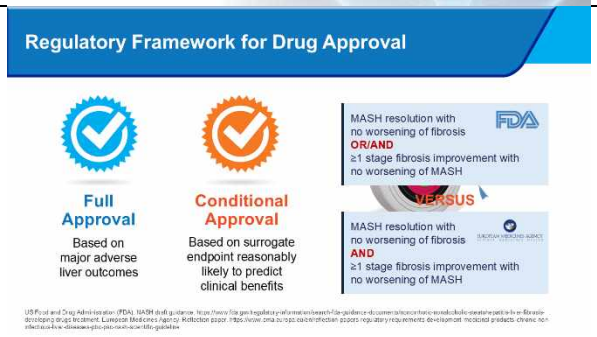
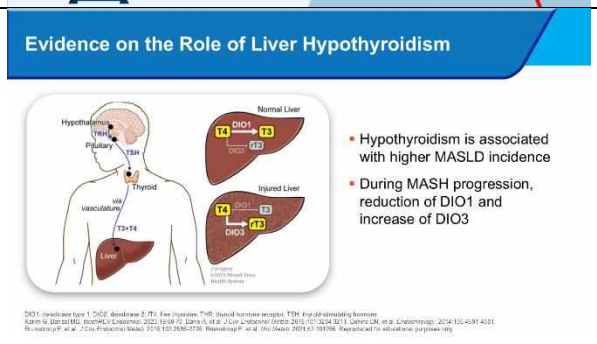
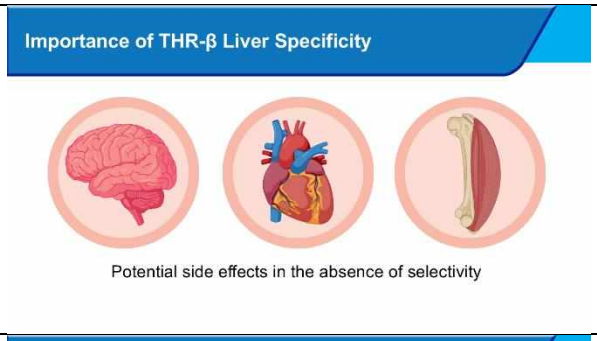
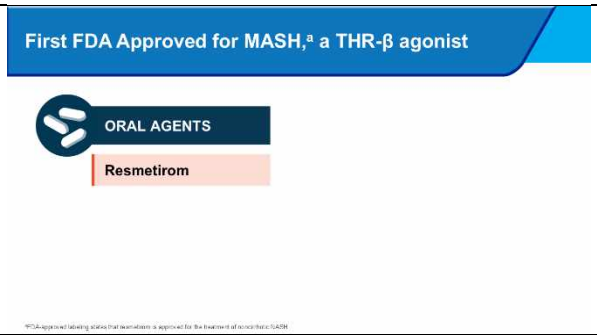
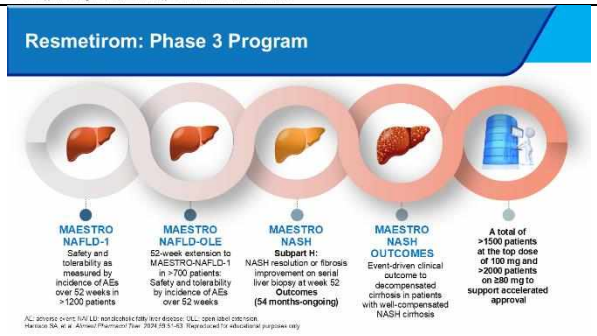
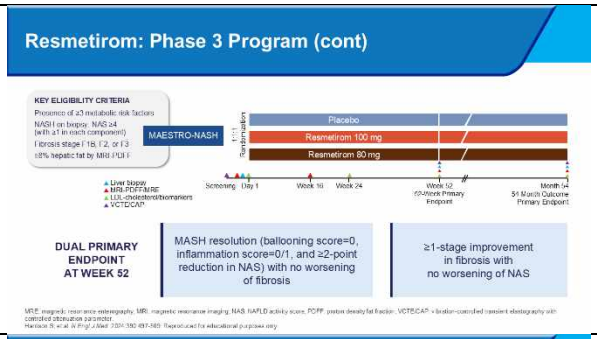
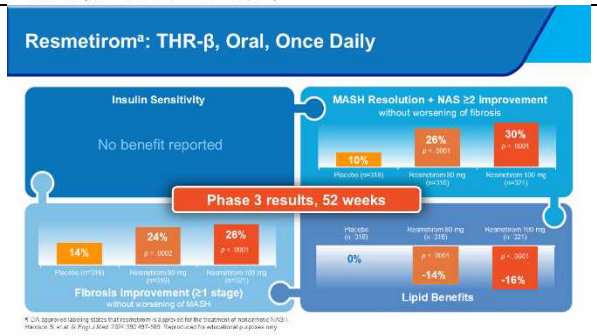
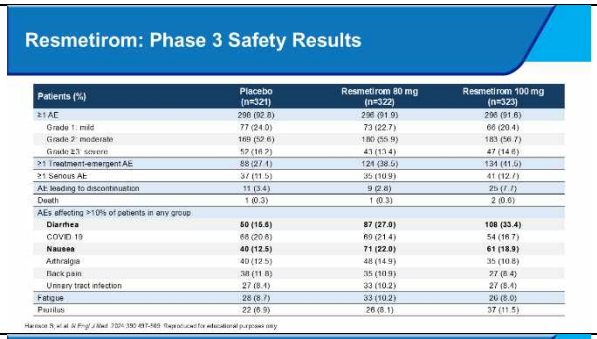
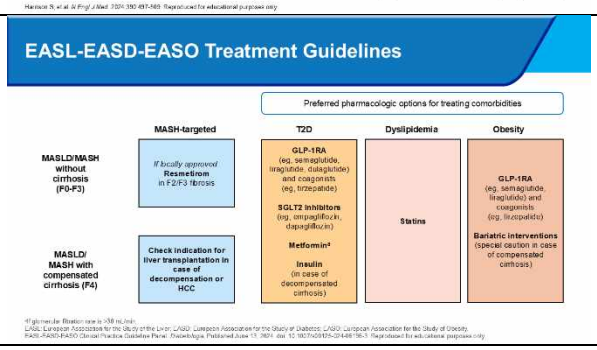
1.		**Meena Bansal, MD, FAASLD** So it's my pleasure to welcome you on this very rainy morning as we enter a new era in metabolic-associated steatohepatitis.
2.		I am Meena Bansal. I'm chief of the Division of Liver Diseases at Mount Sinai in New York, and I am joined by my esteemed colleagues, Dr Quentin Anstee, Dean of Research and Innovation at Newcastle, and Prof Laurent Castera from the University of Paris and the Department of Hepatology.
3.		So I'd like to start with honoring our dear friend. As many of you know, we lost Dr Harrison earlier this year. And, you know, he was such a generous friend with his time, with his support. And it would be remiss not to include him in this talk. And many of the slides are kind of classic Stephen Harrisonisms. And I think what most people know about Stephen is that while he was a fierce competitor, he was never competitive, and we all enjoyed that collaboration with him.
4.		Okay, so we're going to start by discussing the growing burden of MASLD and MASH, which I think this audience knows all too well.
5.		So the global prevalence of MASLD has continued to increase over time specifically, and quite notably in those who have Type 2 diabetes.

6.		And this is a prospective cohort study, actually done by Stephen Harrison, where they looked at patients who were referred for direct colonoscopy, who had metabolic risk factors and steatosis on imaging. And they offered them a liver biopsy. Of those patients, 14% had MASH. And when you look at specific categories, there was an increased prevalence in those who were Latino or Hispanic, a BMI greater than 30 kg/m^2, and those who had diabetes. If you had diabetes, were obese, and had hypertension, there was a 46% chance of having MASH. And of note, out of this entire cohort, about 35% had F2 fibrosis or higher. You may say, well, that's Stephen's, Texas, but this is Laurent's, France.
7.		And when he partnered with endocrinology clinics, patients were referred to hepatology when they were screened in endocrine with elevated liver enzymes or steatosis on imaging: 713 patients were screened and referred to hepatology; 330 underwent liver biopsy if the ALT was persistently greater than 20 IU/L in women and greater than 30 IU/L in men. So those are pretty low numbers, right? If you saw your patients with 20 and 30 IU/L, many would not even think that that is abnormal. But we know that when you talk about true normal, it's much, much lower. Of those patients who underwent liver biopsy, 45% had F2 or F3 fibrosis and so would be eligible for a therapy for non-cirrhotic MASH. Importantly, 38% had F3 or F4 fibrosis.
8.		And it's important to note that the number 1 cause of death in these patients is CVD, followed by extrahepatic malignancy. And so when we talk about any therapeutic approach, we must keep in mind that we also want to make sure that we are paying attention to cardiovascular risk factors.

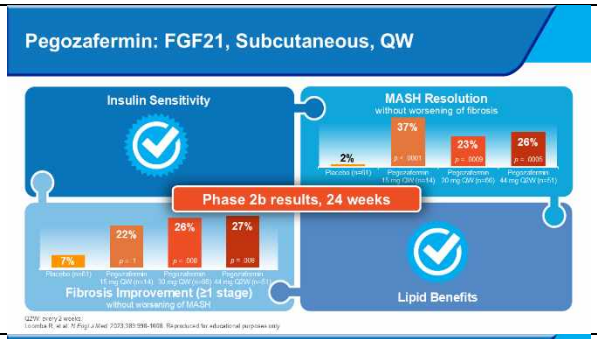
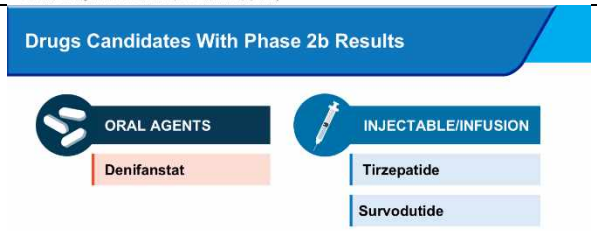
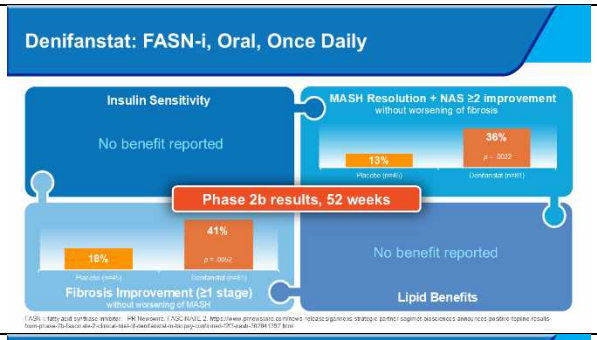
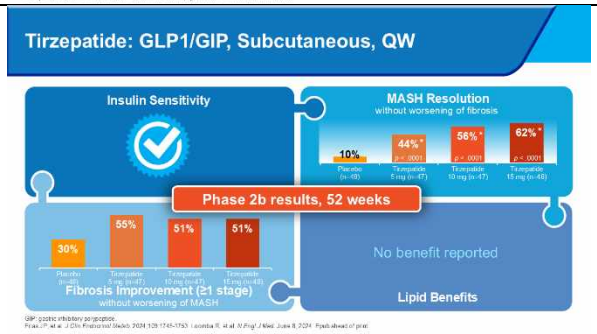
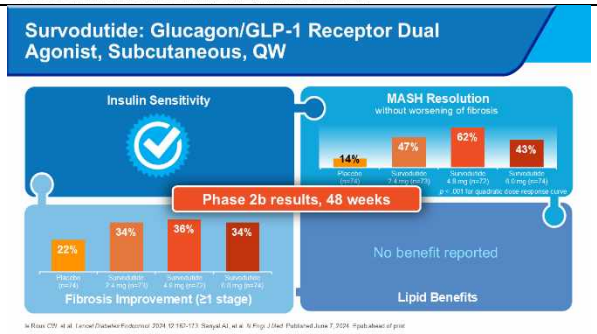
9.		And so this is one of Stephen's classic pictures with the feet going. We have to have a patient-centered approach focusing on tackling overweight or obese status through exercise and weight loss. Importantly, exercise, independent of weight loss, is also beneficial, for every 1000-step increase increment in step count, a 15% reduction in all-cause mortality. We tell our patients not to drink, not to smoke. Avoid fructose-containing beverages. Drink 2 to 3 cups of coffee a day and adhere to a Mediterranean diet. And of course, we have to aggressively treat each comorbidity, obesity with GLP-1s or combos, diabetes. Dyslipidemia is critically important because we often see that patients are not started on a statin, even if they meet criteria by CVD risk score, because of the concern of baseline abnormal liver enzymes.
10.		But this is perhaps another classic. You can exercise a lot, but the bottom line is that you cannot out-exercise the fork.
11.		So we need to have a holistic management approach for patients with MASH. As hepatologists we're certainly concerned for MASH resolution and fibrosis improvement. But given that CVD is the number one cause of death, we have to look for beneficial effects on the lipid profile. And as insulin resistance is central to lipotoxicity in many end organs, ideally you want therapies that also may address insulin sensitivity.
12.		Nevertheless, liver-targeted therapies allow for the fastest and strongest effect on fibrosis.

13.		And so you want to really think about this as a continuum. For those who have minimal fibrosis F0, F1 the strategy can be more upstream using GLP-1 receptor agonists, other weight loss strategies, bariatric surgery. However, as fibrosis accumulates and you develop more advanced disease, F3, F4, it's time for more liver-directed therapy.
14.		And so let's talk a little bit about thyroid hormone receptor-β agonists and other new therapies in the pipeline.
15.		So we know that for full approval, the mandate is to achieve a decrease in major adverse liver outcomes. And those studies are ongoing. However, in the meantime, we have the conditional approval based on surrogate endpoint, reasonably likely to predict clinical benefits. And I learned a new term yesterday. Now RLSE [reasonably likely surrogate endpoint]. So that conditional approval is based on surrogate markers. And for the FDA that's MASH resolution with no worsening of fibrosis or at least a 1-stage improvement in fibrosis, with no worsening of MASH versus the EMA where both are required.
16.		And so this has been a long road. Many of you in the room have been part of a lot of these programs. Some have fallen, some have jumped off the cliff. But at the end of the day, we were happy that we have our first FDA approval of resmetirom on March 14, 2024.
17.		So what is the evidence on the role of liver hypothyroidism? We know that overall hypothyroidism is associated with higher MASLD incidence. T4 is a prohormone. It enters the liver, and it is converted to active T3 by the enzyme deiodinase 1. Some of that T4 is converted to reverse T3, which is inactive by deiodinase 3. During chronic liver injury, there is an upregulation of deiodinase 3, so you have more of that T4 going to reverse T3, which is inert, and less going to

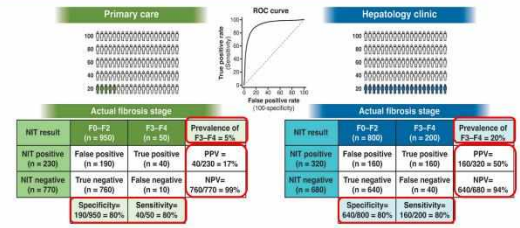
		the active form of T3. So you have relative intrahepatic hypothyroidism.
18.		So this is a video explaining, and we can talk about it more, the mechanism of action of thyroid hormone receptor-β agonists. **Video** Thyroid hormone receptor-β agonists, or THR-β agonists, are small molecules designed to 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 agonists is effective in reducing hepatic fat content and fibrosis.
19.		**Meena Bansal, MD, FAASLD** And it's important to have this thyroid hormone receptor-β selectivity. The liver is the organ in which β receptors are expressed much more than α receptors, and the α receptors are what you typically think of, like the side effects of thyrotoxicosis with tachycardia and bone loss.
20.		And so the first FDA-approved therapy for MASH, a thyroid hormone receptor-β agonist, is resmetirom.
21.		And we've seen this slide, and I mean, the bottom line here, the point to make is this is a very robust phase 3 program. First, the MAESTRO-NAFLD, which looked at safety and tolerability over 52 weeks in more than 1200 patients. Of that, 700 patients went on into an open-label extension study, again tracking safety and tolerability. The registrational trial matched MAESTRO-NASH, which is the liver biopsy study, at

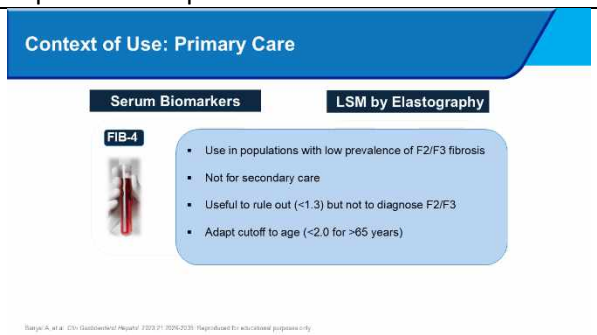
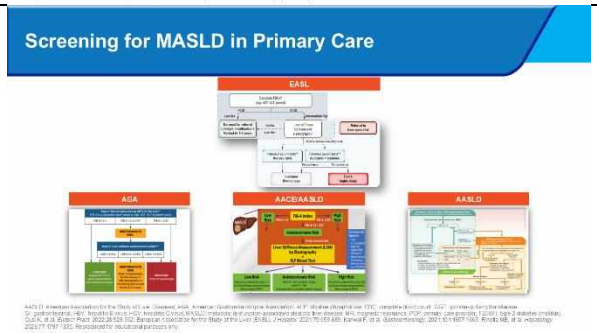
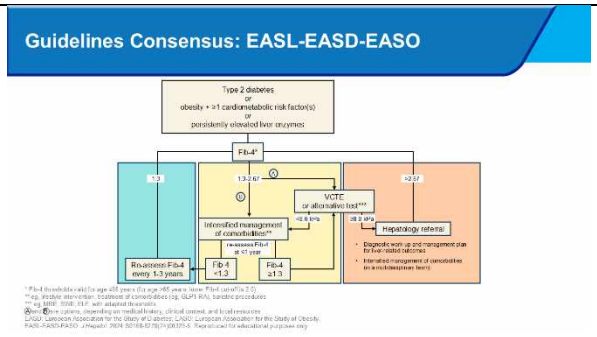
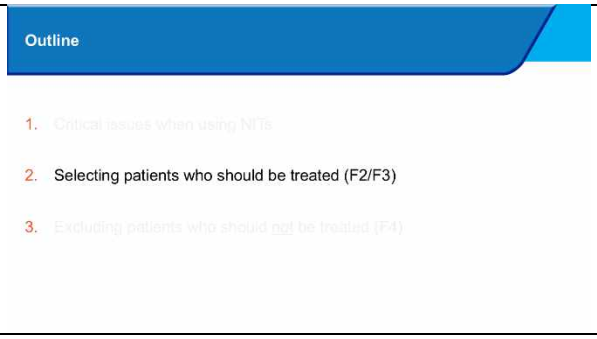
		baseline and at 52 weeks, which is ongoing, to look at those liver related outcomes. And finally, MAESTRO-NASH outcomes, which is event-driven clinical outcomes in patients with compensated NASH cirrhosis. So, in totality, over 1500 patients have seen that top dose of 100 mg and over 2000 patients have seen at least 80 mg, all supporting the accelerated approval.
22.		These are the phase 3 data that supported that approval. They enriched the population with those who had at least 3 metabolic risk factors, at least 8% hepatic fat by MRI-PDFF. The randomization was 1:1:1, placebo, 100 or 80 mg, with a liver biopsy at 52 weeks looking at either MASH resolution with no worsening of fibrosis, or at least 1-stage improvement in fibrosis with NAS.
23.		The results showed that MASH resolution without worsening of fibrosis was seen in 30% of those at the 100-mg dose, compared with placebo. What wasn't mentioned in the video, but is very important, is that resmetirom also increases the expression of LDL receptors on hepatocytes and therefore reduces LDL. Again, thinking about the lipid benefits and potential cardiovascular outcomes. Fibrosis improvement of at least 1 stage was seen in 26% compared with placebo, and no benefit report on insulin sensitivity.
24.	 Patients (%) / Placebo (n=321) / Resmetirom 80 mg (n=322) / Resmetirom 100 mg (n=323) ≥1 AE: 296 (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) / 20 (6.0) Pruritus: 22 (6.9) / 26 (8.1) / 37 (11.5)	When you look at the adverse events in the clinical trial, you can see the top row, they were pretty balanced across all 3 arms. However, diarrhea and nausea did occur more commonly in those treated with resmetirom. That usually occurred within the first 4 weeks of treatment and resolved by 12 weeks.
25.		And so the EASL, EASD, and EASO treatment guidelines are forward thinking, and even though it's not yet approved, if locally approved, resmetirom is considered the MASH-targeted therapy in F2 and F3 fibrosis, keeping in mind that we do also want to focus on the comorbidities and the pharmacologic options, as well as bariatric options for obesity.

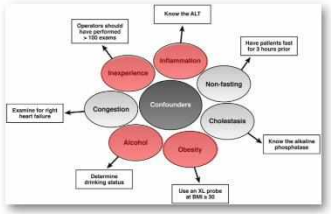
26.	**Other THR-β Agonists in Development** | Drug Candidate	Study Stage	Endpoints | |---|---|---| | VK2809 | Phase 2 Biopsy-confirmed MASH (N=248) | 12-week reduction of liver fat content Recruitment completed 52-week biopsy data awaited | | TERN-501 | Phase 2 Presumed MASH (N=162) | 12-week reduction of liver fat content Results available | | ALG-055009 | Phase 2 Presumed MASH (N=100) | 12-week reduction of liver fat content Recruitment ongoing |	There are other thyroid hormone receptor-β agonists in the pipeline. Furthest along is the Viking drug, which showed a 12-week reduction in liver fat content. And now we await the 52-week biopsy data.
27.	**Drug Candidates in Phase 3** ORAL AGENTS Lanifibranor INJECTABLE/INFUSION Semaglutide Efruxifermin Pegozafermin	Now, what about other drug candidates in phase 3? We have oral agents as well as injectable agents.
28.	**Lanifibranor: Pan-PPAR, Oral, Once Daily** Insulin Sensitivity Reduction in ≥2 in SAF without worsening of fibrosis 27% 41% 49% Phase 2b results, 24 weeks 24% 28% 42% Fibrosis Improvement (≥1 stage) without worsening of MASH Lipid Benefits	And we'll briefly go over some of these. So lanifibranor is a pan-PPAR. The α affects the steatotic hepatocyte. The δ impacts infiltrating macrophages resulting in decreasing pro-inflammatory signaling. And then the γ is the direct stellate cell or antifibrotic effect. They saw a reduction in the SAF score without worsening of fibrosis at the 1200-mg dose, 49% versus 27% placebo. There are some potential lipid benefits, fibrosis improvement again at the higher dose of 42 weeks compared with 24% of placebo, and improvements in insulin sensitivity.
29.	**Semaglutide: GLP1-RA Subcutaneous, Once Daily** Insulin Sensitivity MASH Resolution without worsening of fibrosis 17% 40% 36% 59% Phase 2b results, 72 weeks 33% 49% 32% 43% Fibrosis Improvement (≥1 stage) without worsening of MASH No benefit reported Lipid Benefits	Now what about semaglutide? This is the daily subcutaneous dosing. So not the weekly obesity dosing. They looked at semaglutide 0.1, 0.2, and 0.4 mg. Those with a demonstrated MASH resolution without worsening of fibrosis, no clear lipid benefit reported, and fibrosis improvement did not hit, although note the high placebo response rate. And of course these are small numbers. So we await the phase 3 data and certainly improvement in insulin sensitivity.
30.	**Efruxifermin (EFX): FGF21, Subcutaneous, QW** Insulin Sensitivity HOMA-IR 7% -11% -33% C-Peptide 8% -2% -20% MASH Resolution without worsening of fibrosis 24% 62% 57% Phase 2b results, 96 weeks 24% 46% 75% Fibrosis Improvement (≥1 stage) without worsening of MASH Lipid Benefits Triglyceride 8% -15% -20% HDL 5% 18% 27%	Now the FGF21 is a hormone that has really a number of effects that increase energy expenditure, decrease liver fat, as well as in the periphery. The problem is that it has a very short half-life. So this is a weekly subcutaneous dose of FGF21. And they saw MASH resolution at both doses compared with placebo. They saw good impact on lipids with decreased triglycerides as well as increased HDL. Fibrosis improvement in 75%. Only 28 patients, but nevertheless very

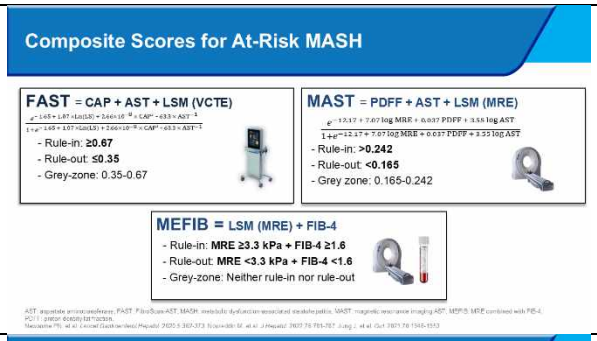
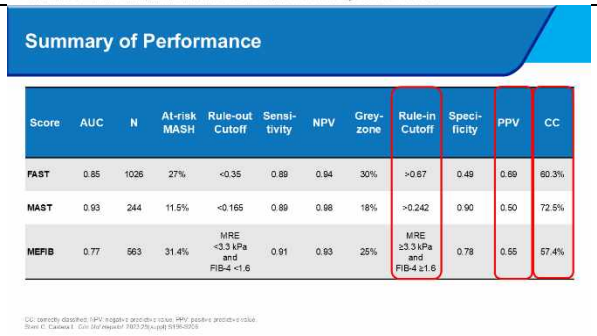
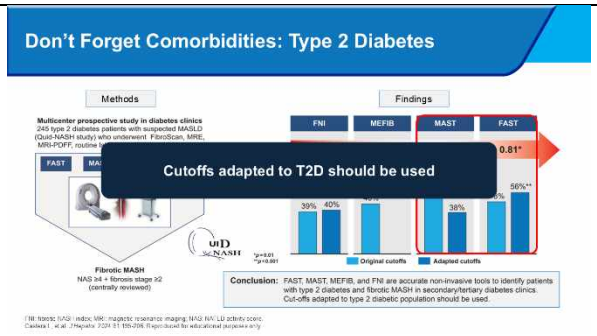
		nice to see. That's probably the biggest δ we've seen in fibrosis. And this is at 96 weeks compared with 24% at placebo. And they also saw improvements in insulin sensitivity as reflected by HOMA-IR and C-peptide levels.
31.		Now pegozafermin is also a long-acting FGF21. They saw MASH resolution at all doses compared with placebo. Potential lipid benefits as well, and fibrosis improvement at the 2 higher doses, 26% and 27%, respectively, compared with 7% placebo. So again, we look forward to phase 3 data and improvement in insulin sensitivity.
32.		So drug candidates with phase 2b results. We'll quickly go over those.
33.		So denifanstat is a FASN inhibitor which was shown to have MASH resolution without worsening of fibrosis in 36% compared with 13% in placebo, no lipid benefit of reported and fibrosis improvement of at least 1 stage without worsening of MASH, and no reported benefit on insulin sensitivity. So we await further data.
34.		Tirzepatide, the dual GLP1/GIP demonstrated MASH resolution without worsening of fibrosis at all doses. No benefit was reported, and fibrosis improvement by of at least 1 stage in the 50% range, compared with 30% in placebo and improvement in insulin sensitivity. So again, we look forward to phase 3 results.
35.		Survodutide, which is a glucagon receptor agonist along with a GLP receptor dual agonist. The glucagon receptor, importantly is expressed on hepatocytes. They saw MASH resolution without worsening of fibrosis at all doses. No lipid benefit was reported. They also saw fibrosis improvement as well as an improvement in insulin sensitivity.

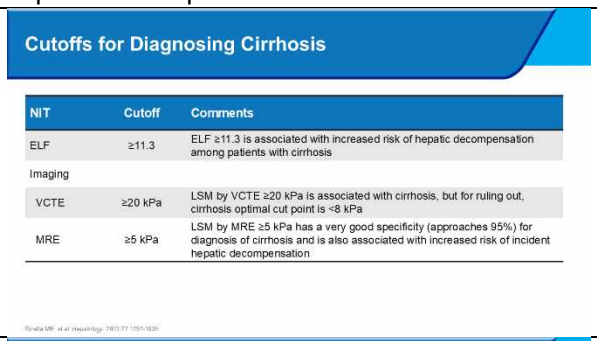
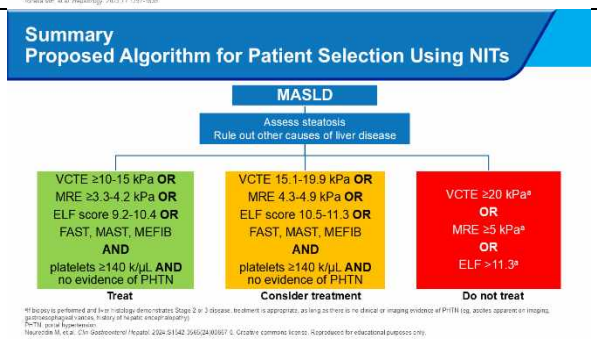
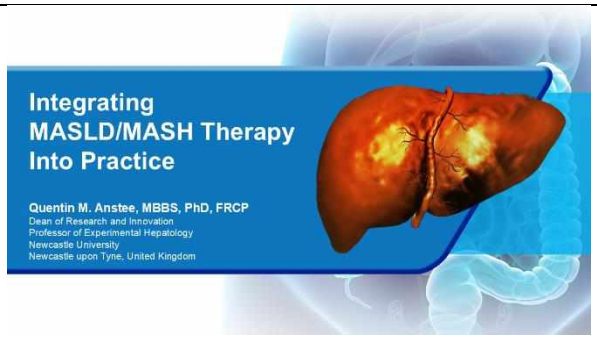
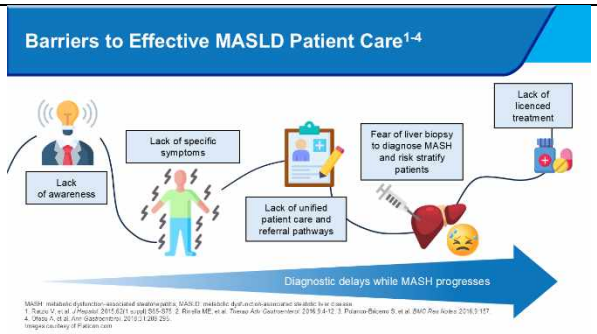
36.	**Summary** ▪ First FDA approval of a MASH-specific therapy ▪ Resmetirom is a THR-β agonist • Liver-specific mechanism of action • Increases Mitochondrial Capacity for β oxidation —Mitochondrial biogenesis and Mitophagy • Increases lipophagy • Increases cholesterol clearance • Reduces inflammation and fibrosis ▪ Many other MASH-specific drugs are in development • Need phase 3 data	So in summary, we have the first FDA approval of a MASH-specific therapy. Resmetirom is a thyroid hormone receptor-β agonist with a liver-specific mechanism of action. It increases mitochondrial capacity for β oxidation, not only by mitochondrial biogenesis or fresh new mitochondria, but also the removal of kind of tired mitochondria, thereby kind of ramping up the factory for fat β oxidation. In addition, it increases lipophagy, increases cholesterol clearance, as I mentioned, and reduces inflammation and fibrosis. With many other specific drugs in development, it's a very exciting time for our field. Keep in mind we need phase 3 data, and we have got to be careful comparing phase 3 data with phase 2 data.
37.	**Rising to the Need to Improve Diagnosis in the Era of Disease-Specific Therapy** Prof. Laurent Castera, MD, PhD Service d'Hépatologie Hôpital Beaujon, Clichy Université Paris Cité Paris, France	And with that, I'm going to pass it on to my colleague, Professor Laurent Castera, who's going to talk about NITs in helping us improve diagnosis in this exciting era. **Laurent Castera, MD, PhD** Thank you very much, Meena. Good morning, everyone.
38.	**Liver Biopsy Is Impractical With Many Limitations** Limited number of hepatologists and pathologists High number of patients Expensive Invasive Sampling variability Morbidity (bleeding) and mortality (rare)	So within the next 10 minutes, I will try to go through the NITs. So, as you know, liver biopsy is impractical with many limitations. Not only is it invasive, it comes with morbidity, even though the complications are rare. Sampling variability, it's expensive. But most importantly, given the magnitude of the epidemic, there's a limited number of hepatologists. And most importantly, pathologists specialized in liver given the high number of patients, so we'd never be able to tackle the epidemic using liver biopsy. And it's a major bottleneck to access to treatment for most patients.
39.	**Available NITs** Serum Biomarkers FIB-4 ELF LSM by Elastography VCTE MRE	So these are basically the available candidates for an NIT serum biomarker—FIB-4, ELF—and liver stiffness by elastography—VCTE with a pioneer technique and more recently, magnetic resonance elastography.

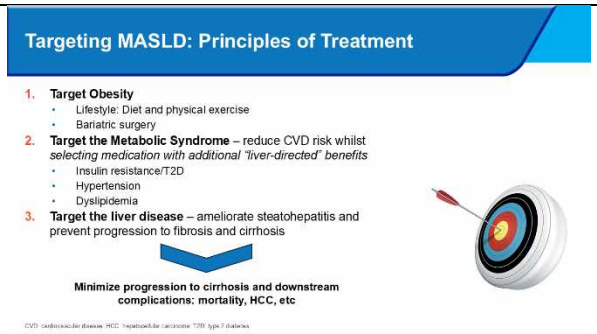
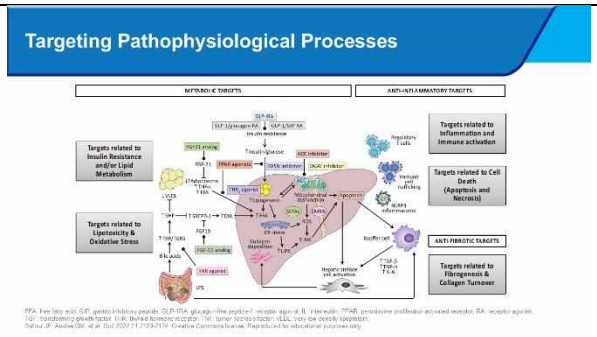
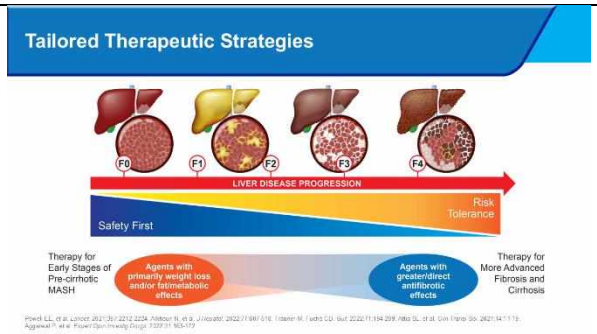
40.	**Outline** 1. Critical issues when using NITs 2. Selecting patients who should be treated (F2/F3) 3. Excluding patients who should not be treated (F4)	So this is the outline. There are critical issues when using NITs.
41.	**Critical Issues When Using NITs** 1. Availability 2. Cost 3. Context of use	Availability of course. Cost and context of use. This may seem obvious, but this is critical in practice because you can have fabulous AUROC. But if your test is too costly or not available, it's going to not make it.
42.	**Availability and Cost** 	And context of use as well. So of course availability, FIB-4 is much more available than MRE and also less costly.
43.	**Impact of Fibrosis Prevalence on NIT Performance** 	Context of use is very important. So I just want to take 1 minute to go through this slide. Let's say you have a test with good specificity and sensitivity, 80% each. According to the prevalence, the pretest probability. So if you're in primary care where the prevalence of advanced fibrosis is usually less than 5%, you end up with a very high NPV, close to 100%, but the PPV is poor. This is the case for FIB-4 for instance. On the other hand, when you're in the pathology clinic with an enriched population with prevalence of advanced fibrosis, around 20%, you see the NPV is still good, but the PPV increased from 70% to 50%. So you have to take this into account when using an NITs.

44.		So for instance, FIB-4 is a good test for primary care. Use in a population with low prevalence, it is not for secondary care. You can rule out but not diagnose patients with F2, F3 and you need to adapt the cutoff according to age when you're older than 65 years.
45.		The other tests are for secondary or tertiary setting.
46.		You know these slides. I don't have time to go into detail, but we have at least 4 different algorithms from EASL, AGA, AACE, and AASLD. And the good news is, they are all aligned. And basically the philosophy is to start with a very simple test and the candidate is clearly FIB-4 and then followed by a second, more specific test with better PPV. VCTE is the first candidate, but it's not available everywhere. So you might use an alternative such as ELF or MRE.
47.		I don't have time to discuss the cutoff, because we're going to focus on the candidate for treatments. Very recently at EASL in Milan, 2 months ago, were presented the new EASL, EASD, EASO guidelines. Same philosophy, we can discuss during the discussion, he loop with the FIB-4 test, whether you should repeat after intensified management of comorbidities.
48.		Now back to the outline.

49.	**F2/F3 Population Treated in Resmetirom Phase 3 Trial** **Eligible Patients**: **CAP** ≥280 dB/m and **LSM** ≥8.5 kPa and **platelets** ≥140 k/μL Baseline / Patients (n=888) / IQR CAP (dB/m) / 349 / (320-378) ELF / 9.7 / (9.2-10.4) LSM-VCTE (kPa) / 12 / (10-15)	How do we select the patients that should be treated? So let me remind you that in the phase 3 trial, eligible patients were patients with CAP above 280 dB/m, LSM above 8.5 kPa using FibroScan, and platelet count above 140 k/μL. So this has been already shown by Meena, but I just want to remind you that the median CAP was around 350 dB/m, ELF 9.7, and LSM 12 kPa.
50.	**NIT Performance for F2, F3, and F4** **Meta-analyses** NITs / Studies (n) / Patients (n) / AUROC / Sensitivity (%) / Specificity (%) ELF / 5 / 581 / 0.81 / 69 / 80 VCTE / 37 / 2763 / 0.83 / 80 / 73 MRE / 6 / 209 / 0.91 / 78 / 89	So this is just a summary of the meta-analyses to diagnose F2, F3, and F4 using these 3 tests. And in a nutshell, you can see that VCTE clearly has the highest level of evidence compared with MRE and ELF.
51.	**LSM (VCTE) Confounders With Risk of False-Positive Results** 	Nevertheless, there are some confounders with the risk of false positives. Of course, inflammation. If transaminases are above 5 times the upper limit of normal, you should not interpret the result. Operator experience also matters. Alcohol intake, patients should be abstinent or close to abstinent. This is not an issue, of course, in MASLD usually, and obesity, has been the major drawback for years.
52.	**VCTE vs MRE: Advantages and Pitfalls** VCTE / MRE • High (AUC 0.85-0.90) / Accuracy / • Very high (AUC >0.90) • High (thousands) / Evidence / • Lower (hundreds) • Widespread / Availability / • Limited • 2-75 kPa / Range / • 2-11 kPa • BMI >40 kg/m^2 / Limitations / • ?	Just to briefly summarize advantages and pitfalls of VCTE and MRE. Accuracy is higher for MRE. Lower level of evidence for MRE. Limited availability. Apart from the United States. Range is much narrower and BMI above 40 kg/m^2 is clearly a limitation of liver stiffness using FibroScan. We don't really know with MRE.
53.	**Suggested Cutoffs for F2-F3** NIT / Suggested Cutoff Values / Comments ELF / 9.2-10.4 / ELF 9.2-9.7: An additional NIT should be corroborated likely Stage 2 or 3 fibrosis to reduce the risk of misclassifying patients ELF 9.8-10.4: In the setting of MASLD may be used to identify patients for treatment with resmetirom, when TE not available If ELF 10.5-11.3, additional caution is needed to exclude the presence of cirrhosis (eg, liver stiffness above threshold values for VCTE or MRE) VCTE / 10-15 kPa / Due to the variability of the technique, it is recommended to follow the recommended best practices, including but not limited to: • Obtaining >10 measurements • Achieving an IQR <30% • Recommending the patient fasts for ≥3 hours prior to the measurement • Checking images to ensure the absence of rib echo VCTE / 15.1-20 kPa / In the absence of laboratory, clinical, or imaging features of cirrhosis (also see patients who should not be treated with resmetirom) MRE / 3.0-4.3 kPa / If MRE 4.4-4.9 kPa, additional caution needed to exclude the presence of cirrhosis	So, the suggestive cutoff that you can use in practice for ELF, if your score is going from 9.2 to 9.7, an additional NIT should be corroborated, likely stage 2 or 3 to reduce the risk of misclassifying patients. If ELF is above 9.8 and below 10.4, in the setting of MASLD, it may be used to identify patients for treatment with resmetirom when TE is not available. If ELF is below 10.5 and 11.3, additional caution is needed to exclude the presence of cirrhosis. As for VCTE, you can see there 2 cutoffs, 10 to 15 kPa, very common situation. And you must be sure that you have 10 measurements. IQR ratio on median should be less than 30%. This is the most important quality criteria. As you all

		know in practice, fasting patients. So you need to check for the quality of the examination. If you're above 15 and less than 20 kPa, patients might be treated in the absence of laboratory, clinical, or imaging features of cirrhosis. Last but not least, for MRE between 3 and 4.3 kPa. If MRE is above 4.4 to 4.9 kPa, additional caution is needed.
54.		What about composite score for at-risk MASH? Again, don't have time to go too much into detail, but they include FAST, MAST, and MEFIB. So combination basically of AST liver stiffness by VCTE or MRE and FIB-4 and MRE.
55.		Just to briefly summarize, it's a dual cutoff strategy. And we're interested in the rule-in cutoff point of 67 for FAST, 0.242 for MAST. And MRE is not linear. So it's the association of a cutoff for MRE and FIB-4. The PPV is not perfect, as you can see, going from 0.5 to 0.70. But at the end of the day, what really matters is the percentage of correctly classified patients. So as you can see, basically between 60% and 70%. These are the original study.
56.		I just want to ring a bell. This has been already mentioned by Meena initially. Don't forget comorbidity and Type 2 diabetes is a very common comorbidity. This is a study we have performed in 20 to 45 patients who underwent liver biopsy, but also MRI and FibroScan. And we compare the 4 tests in the same population. And you can see that MAST and FAST were at similar performance but outperform MEFIB and FNI. In terms of correctly classified, this was to the advantage of MAST as compared with FAST if you were using the original cutoff, but if you adapt the cutoff to our population, this was the opposite. So the take-home message is, "Cutoff might need to be adapted to the context of use, especially in Type 2 diabetes."

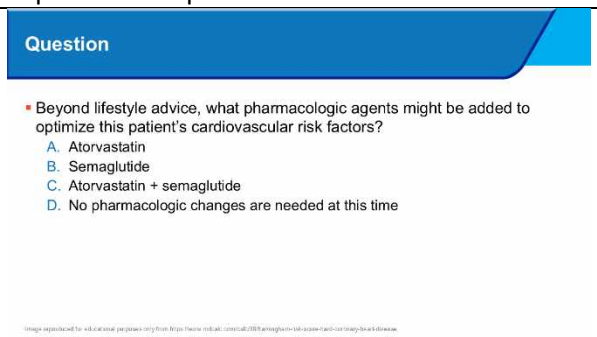
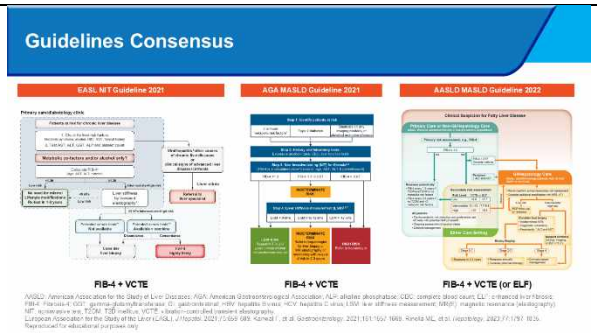
57.		So just before concluding, you need to exclude the patients for diagnosing cirrhosis. And the cutoffs I already mentioned is 11.3 for ELF, 20 kPa for VCTE, and 5 kPa for MRE.
58.		So just to summarize, of course, I think you really need to focus on the right part. Patients that should not be treated because they likely have cirrhosis. So VCTE of 20 kPa or higher, MRE of 5 kPa or higher, or ELF above 11.3—do not treat. You should treat the green part. So I don't want again to go too much into detail. Don't forget about the platelet counts. Should be above 140 k/µL. No evidence of portal hypertension, and you might consider treatment in a yellow box intermediate zone. Thank you very much for your attention.
59.		I might introduce my colleague, Quentin Anstee, who is going to go to clinical practice and ask our opinion about different cases. **Quentin Anstee, MBBS, PhD, FRCP** Thank you very much, Laurent, and I'd like to thank the organizers. It's a great pleasure to be here. So, you alright? It's an exciting time in the world of hepatology, isn't it? Because the drug development pipeline is really burgeoning. And for the first time, at least in North America, there is now a drug that's licensed to prescribe specifically for MASLD/MASH, which makes it all the more timely to start thinking about how we actually integrate treatments into our current clinical practice.
60.		Up until now, there have been a range of barriers which have inhibited our ability to deliver effective care for our patients. We've had challenges with lack of awareness. We know that MASLD has no pathognomonic symptomatology, so there is a lack of specific symptoms. There's been a great deal of work needed to start to build effective care pathways so that we can triage individuals and identify the right people for treatment. We've had barriers around testing, so that concern regarding invasive tests like liver biopsy that Laurent just explained. And then up till now, at least in the United States, the lack of a licensed treatment. That last one has been something

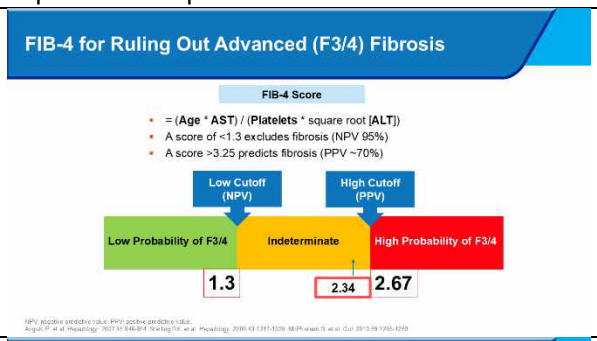
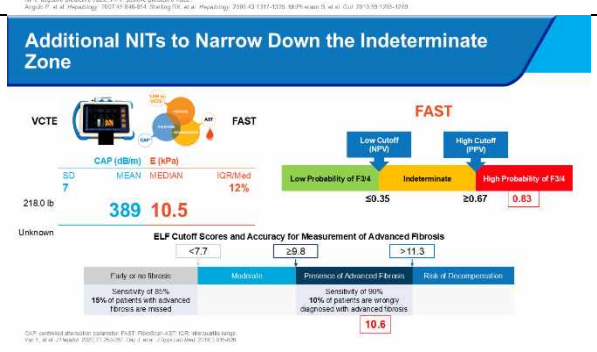
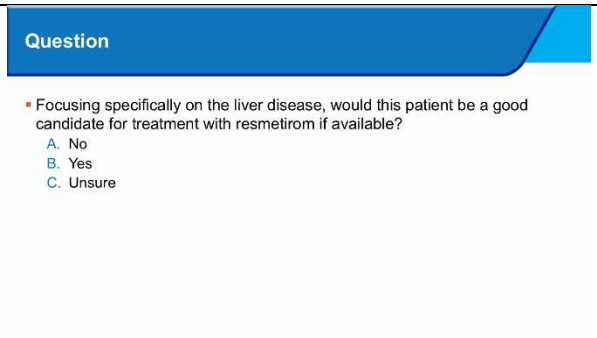
		that now we do have some viable options available to us. And so we're slowly working our way through these problems, addressing them.
61.		So, when we think about the therapy for MASLD, there are a number of principles that I think we need to take into account. We need to be aware of the pathophysiological features that are driving that disease. So we need to be targeting the obesity, targeting metabolic syndrome. And then, once those risk factors, which are basically cardiometabolic in nature, have been addressed. We want to be targeting the liver itself to make sure that we are ameliorating steatohepatitis, preventing that progression of fibrosis towards cirrhosis. And hopefully, if we can achieve all of that, we will reduce the number of patients who progress to cirrhosis. We will improve their cardiovascular risk profile and therefore have a positive impact on both morbidity and mortality for our patients. So there's a very clear strategy here. And it's really a case of how we put that into place.
62.		As we heard from Meena, there are a range of different treatments being assessed at the moment. The majority of those that have had most success in clinical trials tend to be ones addressing metabolic targets. So that may be insulin resistance; lipid metabolism; drugs like resmetirom, which are targeting the thyroid axis—all of these very much in that metabolic space, but the benefits potentially read through towards the liver as well.
63.		So. An exciting time in that respect. We also need to think a little bit about how we select treatments and how we may use them as more and more become available. This is very similar to one of the cartoons that I think Meena demonstrated with this idea that we may tailor the drugs we select to different stages of disease. So with very mild disease, of course, we prioritize safety at all times, but it's even more so important when we have mild disease. And we're probably looking at agents that may be beneficial in terms of weight loss or fat and metabolic effects. However, as disease progresses and we get more and more advanced fibrosis, we're looking for greater liver-targeted benefits as well. And indeed, if agents become available in cirrhosis, we may well alter our risk benefit ratio to tolerate agents that possibly are less

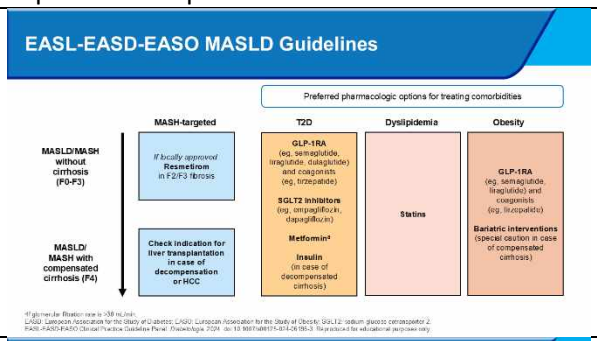
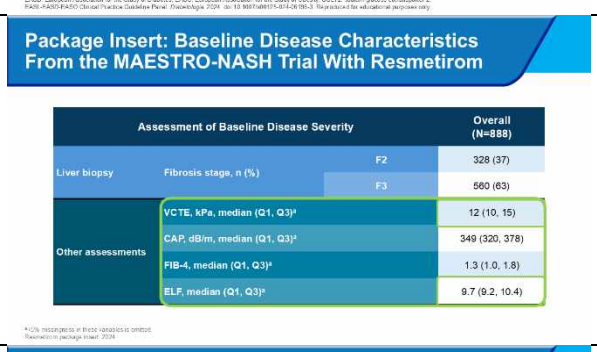
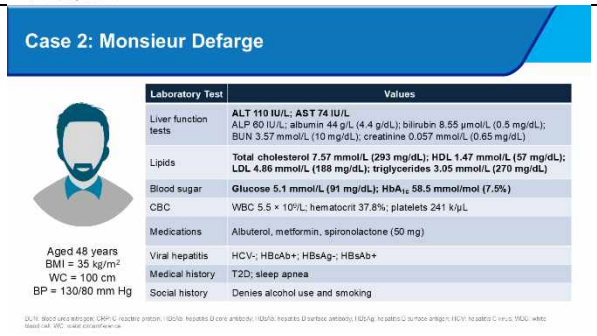
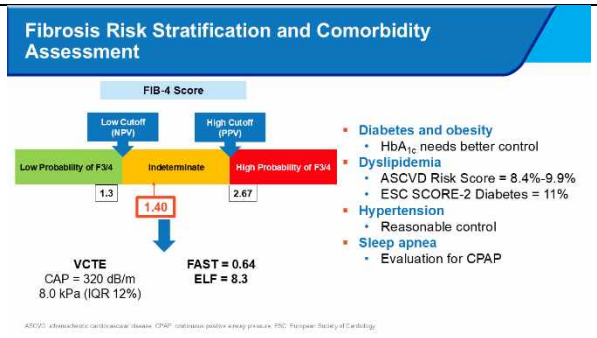
		well tolerated if they are highly efficacious. That's a point for speculation, but I think it's worth considering how we're gonna put this together.

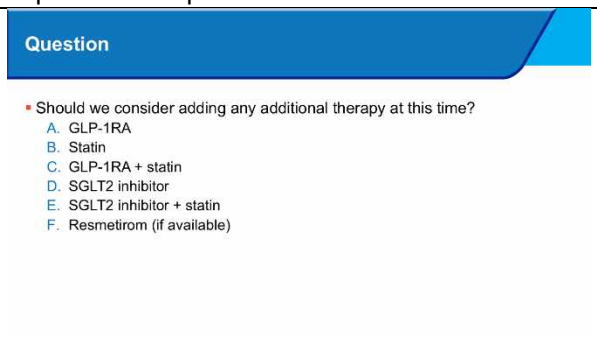
64.	**Case 1: Monsieur Hulot**
	• 55-year-old man referred by his PCP due to abnormal liver biochemistry
	• **Medical history:** T2D for 15 years, dyslipidemia for 2 years
	• **Family history:** Mother had diabetes, and father had hypertension and IHD
	• **Social history:**
	  ◦ He exercises occasionally
	  ◦ 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
		So with that in mind, what I'd like to do is take a few minutes and go through a couple of cases. So let's start off with Monsieur Hulot. He's a 55-year-old man who's been referred by his primary care physician due to abnormal liver function tests. Just before we get into this, there's gonna be some voting in a moment or 2, so I don't know if you all scanned the Slido app at the start when Meena showed the barcode, but if not, we'll do this by a show of hands, so don't worry. But there's an audience participation element to go through here. So, 55-year-old man, he's diabetic, he's dyslipidemic. He's got a really strong family history of diabetes, hypertension, and ischemic heart disease. He exercises occasionally, drinks a little bit of wine, as you'd expect with Monsieur Hulot, and does smoke a pipe. He's overweight with a BMI of 27 kg/m^2, and he's mildly hypertensive. No real specific symptoms. He's on gliclazide for his diabetes. His GP stopped the statin because he noticed that the liver biochemistry was slightly abnormal. And of course, that's something we see very commonly in our practice.

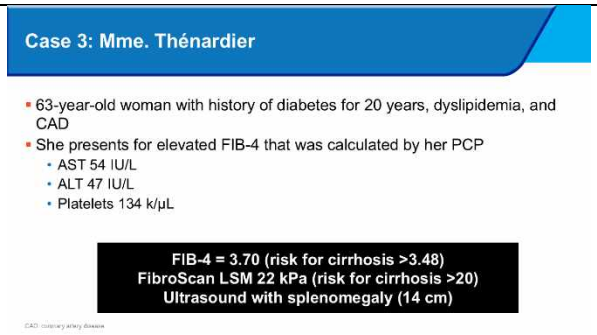
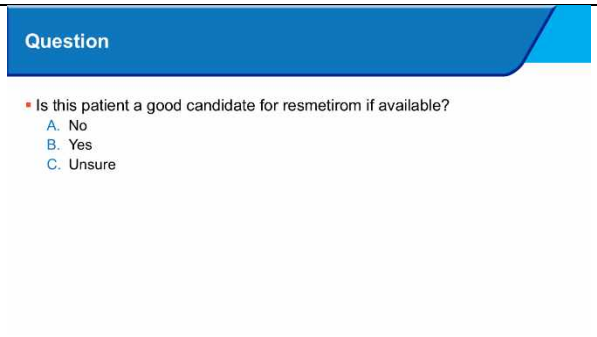
65.	**Case 1: Monsieur Hulot (cont)** **Laboratory Values** ALT 99 IU/L AST 72 IU/L Total bilirubin 13.7 µmol/L (0.8 mg/dL) Albumin 40 g/L (4.0 g/dL) Platelets 170,000/µL Total cholesterol 6.9 mmol/L (265 mg/dL) LDL 4.75 mmol/L (184 mg/dL) HDL 0.93 mmol/L (36 mg/dL) Triglyceride 2.71 mmol/L(240 mg/dL) HbA$_{1c}$ 52 mmol/mol (6.9%) Framingham Risk Score for Hard Coronary Heart Disease	If we actually look at his blood tests, we can see that derangement in the liver biochemistry with the ALT at 99 IU/L, AST at 72 IU/L. His liver function looks to be pretty good. Platelets edging towards the bottom of the normal range, but still very much within the normal range. His cholesterol is up a little bit at 6.9 mmol/L, and his diabetes is suboptimally controlled at 52 mmol/mol or 6.9%. So if we stick all that into the Framingham Risk Score calculator, we'll get a cardiovascular risk of about 25%. So this is clearly somebody who we need to be thinking about in terms of that cardiovascular risk profile and addressing that side of things.

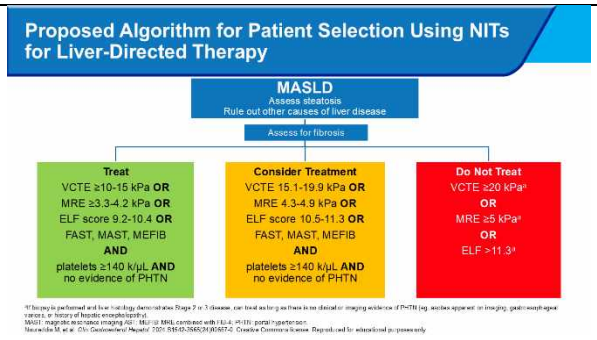
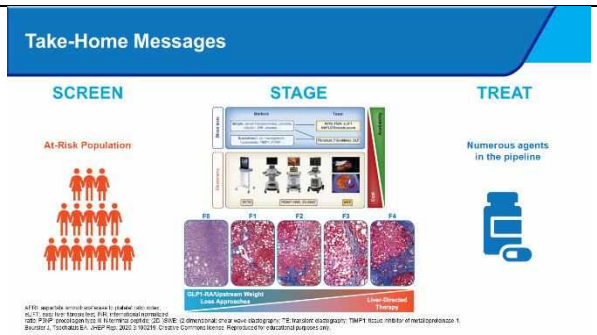
66.		Let's go on to our first question. So beyond lifestyle advice, what pharmacologic agents might be added to optimize this patient's cardiovascular risk profile? So is it just atorvastatin? Would you go for a GLP-1 like semaglutide? Maybe you go for both or nothing at all. Now either that's just one vote or we have possibly the most informed audience I've ever come across. Oh, no. Hang on, you've got 10 seconds. After that, we're defaulting to a show of hands, because I think we've only got two people who've got the app. Okay. So we could do it this way. Does the audience agree with the majority on the vote? Hands up if you agree. Yep. Hands up now if you disagree. Wonderful. So. Maybe a conflict of interest in the front row, but thank you. Okay, so the majority of the audience, I think to improve that cardiovascular risk profile, we need to be addressing a statin. And of course this is something we very commonly see, isn't it? Primary care physicians are worried about inducing abnormal liver function tests and discontinue statin therapy in people who need it. And it's probably one of the first interventions I do in many of the patients I see is restart that statin. Then there's the question about improving the diabetic control, maybe bringing the weight down, and an agent like a GLP-1 could be beneficial in that sense. So great, I think. I think we're all on the same page with that one. So thank you. Let's see if I can move on.
67.		So having addressed the cardiovascular risk profile, we then need to think a little bit further about how we would actually risk stratify this individual because of course we're hepatologists. It's great that we keep the heart going. But the most important organ in the body, I think we can all agree, is the liver. And therefore we need to keep that one functioning well. As we've heard, we've got a great deal of consensus across guidelines in Europe and North America in terms of how we should be risk stratifying these patients, FIB-4 and then often FibroScan, maybe ELF is also recommended.

68.		If we think about their FIB-4 score, this patient's FIB-4 score comes out at about 2.3. So they're just at the top end of that indeterminate zone. So they've got at least a 1 in 20 chance on FIB-4 alone of having advanced fibrosis. Probably more than that. We go on and we do a FibroScan.
69.		Now in my routine practice I don't use FAST, I just use good old-fashioned FibroScan, gives me the information I need. This patient's CAP is up at 390 dB/m. Their median liver stiffness is up at 10.5 kPa. And if we did do an ELF—10.6. So this is an individual who's likely to have advanced fibrosis but probably not cirrhotic. So it's the sort of individual I'm thinking about therapy for without a doubt.
70.		So back on with the voting focusing specifically on liver disease. Would this patient be a good candidate for treatment with resmetirom if it's available in the territory in which you practice medicine? So it's a no, a yes, or an unsure. Again, I'm loving this audience. **Meena Bansal, MD, FAASLD** This is Paris. **Quentin Anstee, MBBS, PhD, FRCP** Great. So again, show of hands. Does everybody agree with our 1 voter? **Meena Bansal, MD, FAASLD** That's 14 votes. **Quentin Anstee, MBBS, PhD, FRCP** Thank you very much. Okay, so we've got a lot of agreement there. So absolutely once addressed those metabolic factors, one needs to be thinking about what else we can do. And this is an individual at high risk of an active steatohepatitis. He's got advanced fibrosis. So definitely we'd need to look at liver-targeted therapies. And if we're practicing in the United States, resmetirom is available to us. And an option.

71.		Okay. And that again is very much in line with the EASL guidelines. So very forward thinking. We don't have the agent yet, but if locally approved, this is exactly the sort of patient for whom an agent like this would fit within the guidelines and would be recommended for pre-cirrhotic MASLD/MASH.
72.		And if we look at the data from the MAESTRO-NASH trial, we can see that this individual broadly fits within that range in terms of the noninvasive markers. So Monsieur Hulot is very much somebody who could have been recruited into MAESTRO-NASH.
73.		Okay, let's move on. I should say there are going to be bonus points for putting into the Slido, the 3 films or books that our patients are drawn from today, and I will be asking the panel if they can help me with this later on. So the next is Monsieur Defarge. He's a 48-year-old gentleman. Body mass index of 35 kg/m^2. Mildly hypertensive gain. ALT 110 IU/L, AST 74 IU/L. His cholesterol is through the roof 7.6 mmol/L. Diabetic control suboptimal with an HBA_{1c} of 58.5 mmol/mol and 7.5% in old money. He's on some metformin, a bit of spironolactone, his liver screens otherwise negative and apart from diabetes and the sleep apnea, that's about it. He denies alcohol use or smoking, which is surprising because he runs a wine shop in Paris.
74.		Let's think about the NITs. If we think, first of all, about the FIB-4 score, again, we're into intermediate, but we're at the lower end of the intermediate score here. Just 1.4 FibroScan. There's a lot of fat in that liver, but liver stiffness just 8 kPa, FAST score low, ELF score 8.3. So if we think about therapy here, clearly we need to improve that diabetic control. We need to sort out his cardiovascular risk profile and his dyslipidemia. And certainly we need to think about CPAP for the obstructive sleep apnea, but what else might we be considering?

75.		Should we be considering adding on any of these therapies at this time? Maybe a GLP-1 receptor agonist, maybe resmetirom, an SGLT2 inhibitor, a statin, maybe a GLP-1 and a statin or an SGLT2 inhibitor and a statin. What are what are our thoughts here? Okay. Oh, oh. Thinking better of it. Let's have a look here. There's a lot of movement this time. I'm getting some. I didn't know you could change your vote. This is very good, actually. Okay, great. So again, does everybody in the audience agree? Hands up if you agree. Yeah. We've got a lot of agreement here. So this is a gentleman. He's got mild disease. He's very early on in terms of disease stage. He's got a lot of cardiometabolic risk factors. So I mean I would agree. And Meena, what do you think? **Meena Bansal, MD, FAASLD** Yeah, I mean I think that, you know, clearly he needs to be on a statin. So that's a no-brainer. Needs better glycemic control, is overweight, has sleep apnea. All of those things might be, you know, might be benefited by a GLP-1 receptor agonist. And right now, luckily he's at the low-end of the fibrosis spectrum so doesn't really need a liver-targeted therapy at this time. But that can change. **Quentin Anstee, MBBS, PhD, FRCP** Fantastic. Laurent, do you concur? **Laurent Castera, MD, PhD** Yes, I concur, but Meena, do you really trust FibroScan results in a patient with a BMI of 35 kg/m^2? **Meena Bansal, MD, FAASLD** So I think we have the other confirmatory test, right? So his ELF. We never depend on 1 test. And as you point out, MRE will perform much better in somebody with that body habitus. But the fact that we have other data that are supportive and, you know, you need to continue to follow the patient over time. If you have access to MRE, that's certainly appropriate. **Laurent Castera, MD, PhD** But I think in practice you should not hesitate to repeat, of course, the FibroScan. And also there are more false positives than false negatives. So 8 kPa would be reassuring.

		Meena Bansal, MD, FAASLD Yeah, absolutely. **Quentin Anstee, MBBS, PhD, FRCP** Okay.
76.		Okay, so, 1 more case. So Madame Thénardier, a 63-year-old innkeeper's wife with a history of Type 2 diabetes, dyslipidemia, and coronary artery disease. She presents with an elevated FIB-4 score that was calculated by her general practitioner, AST 54 IU/L, ALT 47 IU/L, platelets 134 k/µL. So below the bottom of the normal range. An individual like this, when you calculate the FIB-4 score, it's pretty sporting, 3.7 the FibroScan you're bouncing off the patient at 22 kPa. And when we do the ultrasound scan, we're seeing some splenomegaly here, which is making me think about portal hypertension. Laurent, what are your thoughts on somebody like this? **Laurent Castera, MD, PhD** I think it's pretty consistent. I mean, with the age, the clinical case, the platelet counts, the splenomegaly. So it's suggestive of cirrhosis.
77.		**Quentin Anstee, MBBS, PhD, FRCP** Okay. Thank you. So with that in mind, would this patient be a good candidate for resmetirom therapy if it was available to prescribe in your territory? No, yes, or unsure? No votes. I'm counting that as unsure. Hands up if everyone here is unsure. Oh, there we go. We have a vote. So some unsure. So I think that's a fair question. And some nos here. All right then. So I think that's quite a useful thing to be thinking about here. So right now we have evidence for resmetirom for pre-cirrhotic MASH. So that's where we can use that agent if it's available to prescribe. And there are trials ongoing for those. So for MAESTRO-NASH outcomes where we'll be beginning to look at that and also for cirrhosis. But until we get the results of that, I don't think we can be using resmetirom in the cirrhotic patients. Meena, what would your thoughts be? **Meena Bansal, MD, FAASLD** Yeah, absolutely not yet. We need the data from the outcome study. So right now, you know, we're hopeful that it will pan out that way. But right now we cannot treat cirrhosis.

		Quentin Anstee, MBBS, PhD, FRCP Absolutely. So I think I think we're going to read the unsure as optimistic and hopeful that the trial reads out in the way we want it to. But I think that's a really important point to think about.
78.		And it brings us nicely onto this algorithm, which we've already seen, this idea that we need to stratify individuals, identify that sweet spot for treatment where people have significant liver disease but have not yet progressed all the way to cirrhosis. And I think that's a very useful tool in terms of guiding our thinking here. But as Laurent pointed out, noninvasive. It's really helpful to look at consistency of readings and to factor in where the limitations are in terms of BMI and how that can actually affect overcalling of elastography techniques and so on. Okay, good.
79.		Of course, when we're thinking about treatment, it's essential to remember that this is a shared decision-making process and that there isn't a one-size-fits-all response. It's really key that we work in partnership with our patients to tailor our treatment approach to their needs. We know that lifestyle change is a key aspect of the therapy of MASLD. We also know that it's very hard to initiate, it's hard to sustain, and it is particularly difficult once you've achieved your goal, your weight loss targets, if you can achieve them to maintain that into the longer term. So it's an ongoing process with our patients in terms of supporting them to make the right lifestyle choices, but then also to tailor their medical therapy to their needs, taking a holistic approach that addresses both that cardiovascular risk and also liver-focused therapeutics.
80.		So, take-home messages. Identify at risk groups. Type 2 diabetics would be a clear example of that. But anybody with cardiovascular risk, be thinking about questions about whether this individual has advanced liver disease. Many of us, particularly if we're working not in liver disease, but in other areas, will be coming across patients day in, day out who have undiagnosed liver disease. And we need to think about that when we screen those high-risk populations and identify individuals, we then need to accurately stage it. And that's where the more advanced NITs come into

		play. And then it's an exciting time in the MASLD space. Lots of opportunities for therapies. And we already have in the United States, 1 agent that's licensed, that is a fantastic start in that process.