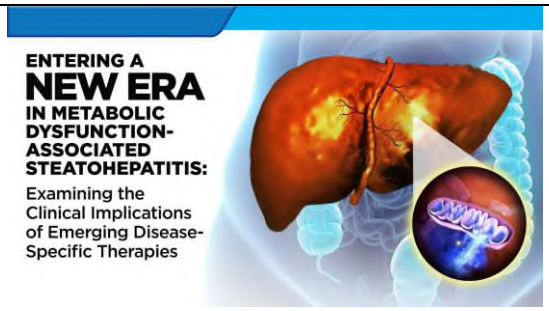
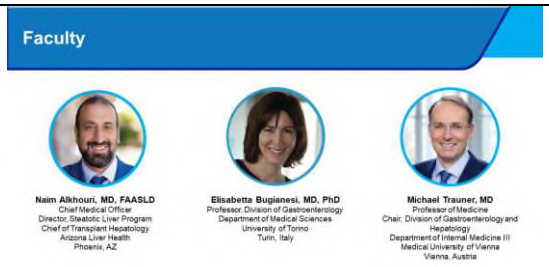
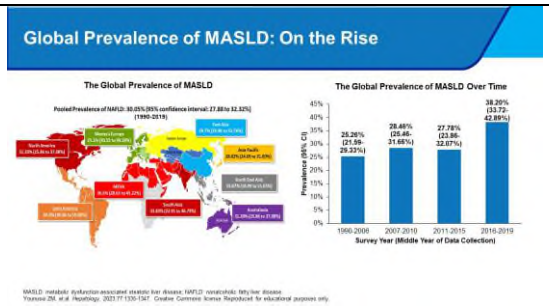
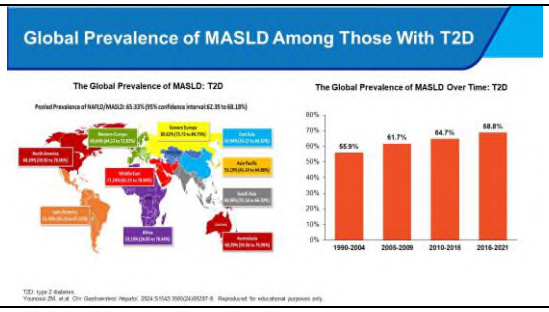
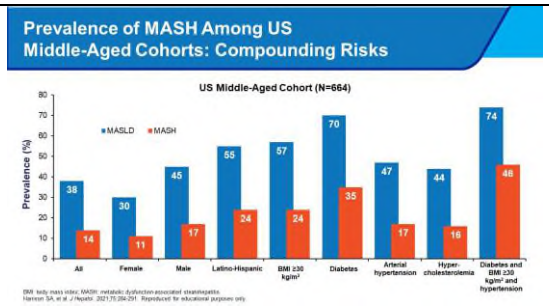
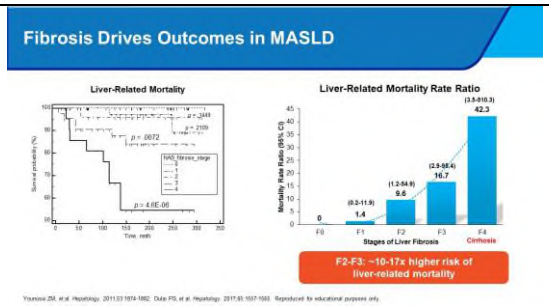
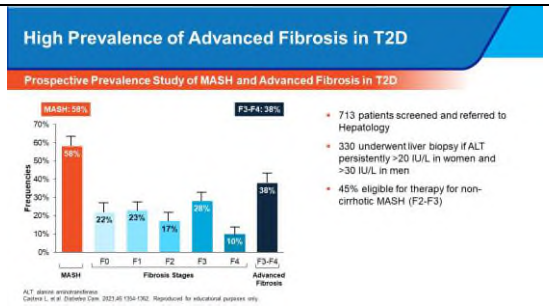
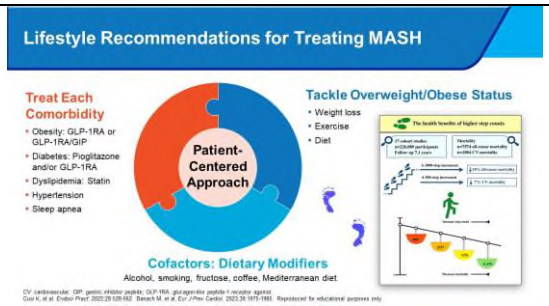
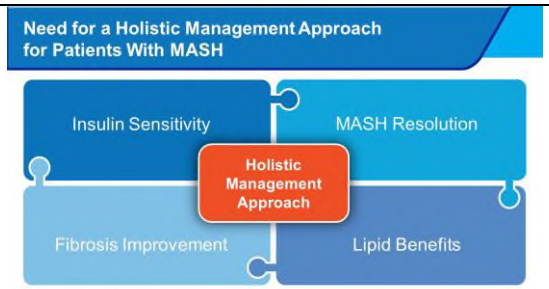
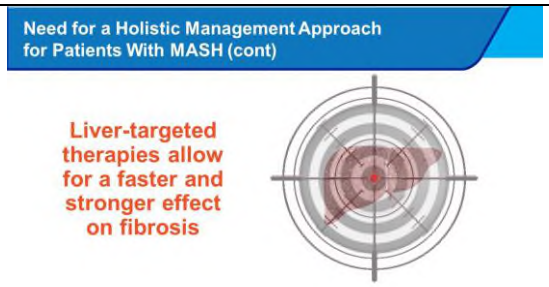
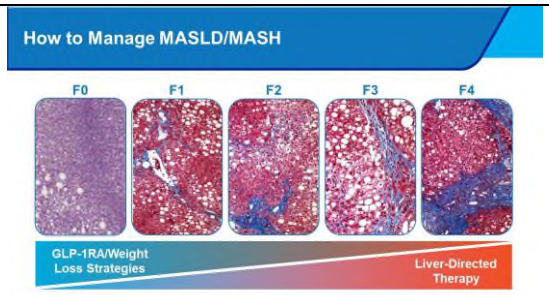
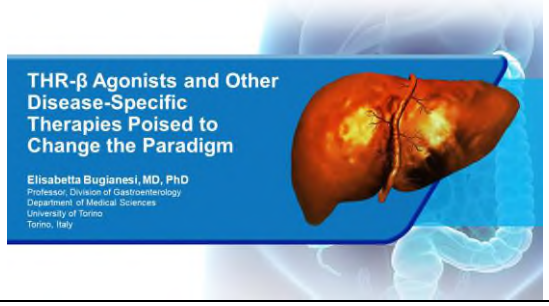
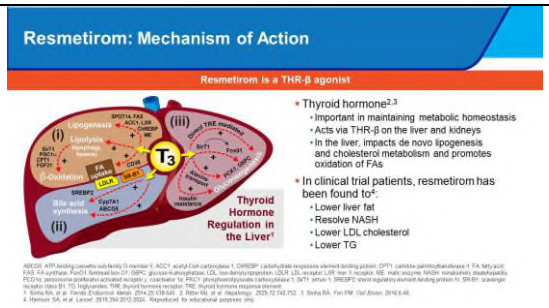
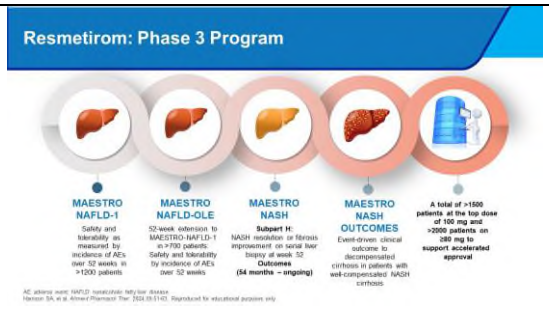
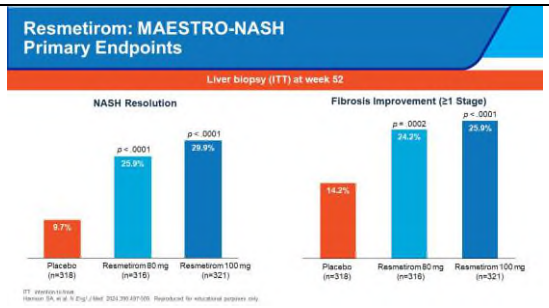
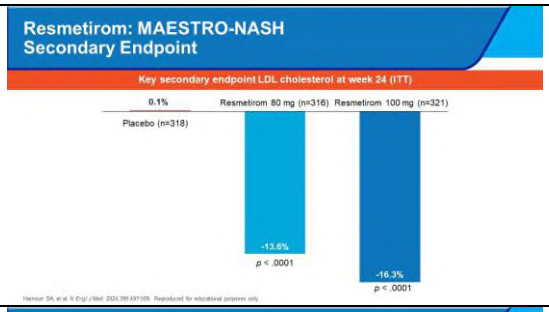
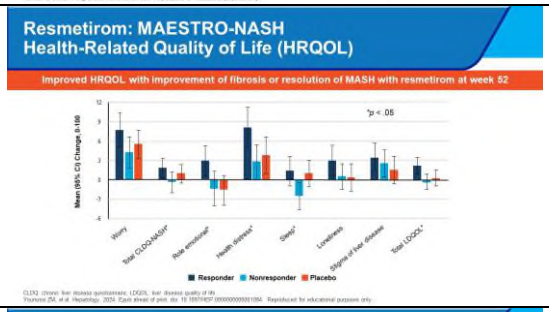
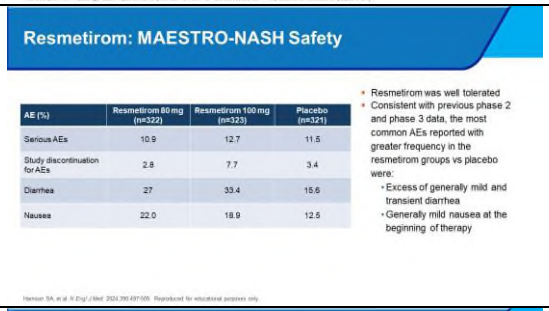
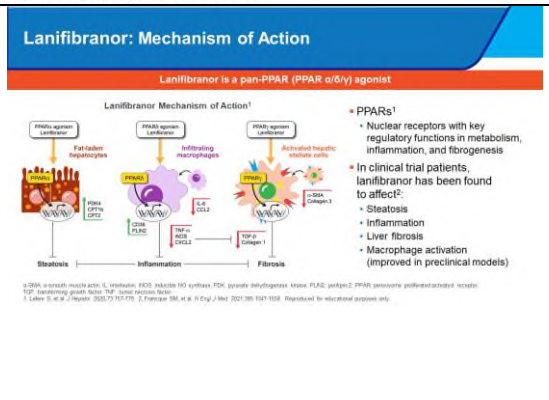
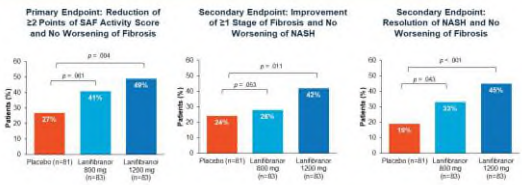
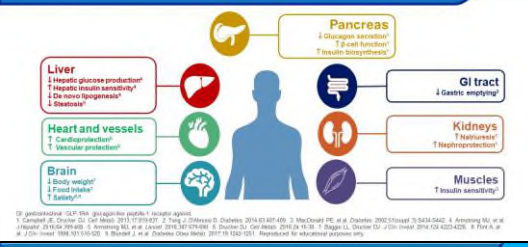
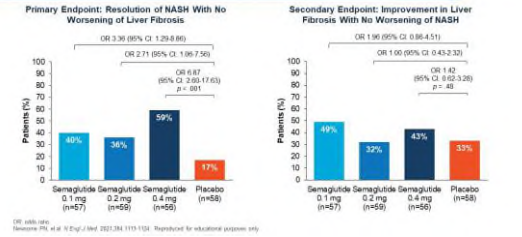
1.		***Naim Alkhouri, MD, FAASLD*** Thank you so much for joining us. I'm Dr Naim Alkhouri, a chief medical officer at Arizona Liver Health in Phoenix, Arizona. And I'm pleased to have you this evening to go over our program, *Entering a New Era in Metabolic Dysfunction-Associated Steatohepatitis*, or MASH. This is an exciting year for us, 2024, in the United States, we witnessed the FDA approval of the first medication to treat patients with MASH and moderate-to-advanced fibrosis, resmetirom. And I had the privilege to treat a few patients, so far about 200 patients that we prescribed in our clinics. So hopefully this will be approved in Europe next year and you guys also will be prescribing. So, let's make this interactive, and if you have any questions related to resmetirom, or other drugs in the pipeline, let's have a nice discussion at the end of this session.
2.		So, I introduced myself already, and it gives me great pleasure to introduce my distinguished speakers tonight. Dr Elizabetta Bugianesi, she is professor of medicine at the Division of Gastroenterology, Department of Medical Sciences at the University of Torino, and Prof Michael Trauner. I don't think he needs an introduction in his city of Vienna, but he is professor of medicine and the chair of the Division of Gastroenterology and Hepatology at the Medical University of Vienna.
3.		So, in terms of the global prevalence of MASLD, we know it's on the rise. So, we estimate now that in the adult population, about 30% of adults globally have evidence of MASLD or MASH. And the highest prevalence is actually in South America, up to 44% and in the Middle East, and North Africa region. And we have recent data showing an actually progressive increase in the prevalence with the latest data from 2016 to 2019, showing as high as 38% prevalence of MASLD.
4.		That prevalence is even double in patients with type 2 diabetes. So, the global prevalence of MASLD in those with diabetes is at 65%, and most recent data from 2016 to 2021 show a prevalence of 68%. So patients with type 2 diabetes at are at higher risk of MASLD. They're also at higher risk of having MASH, the aggressive form of MASLD, and significant fibrosis.

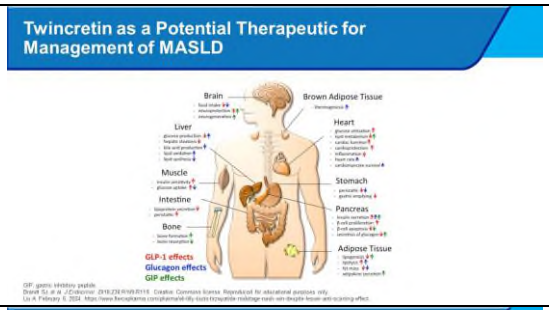
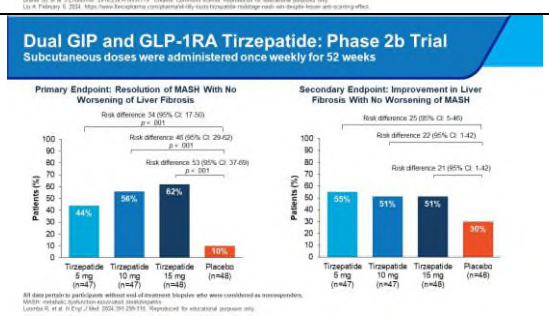
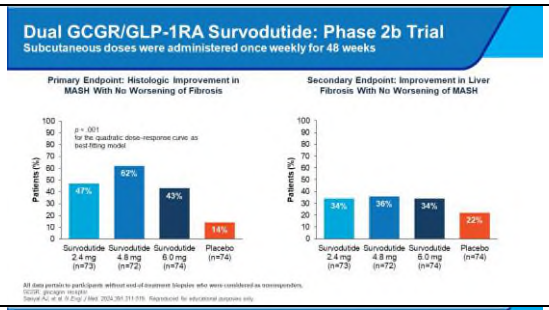
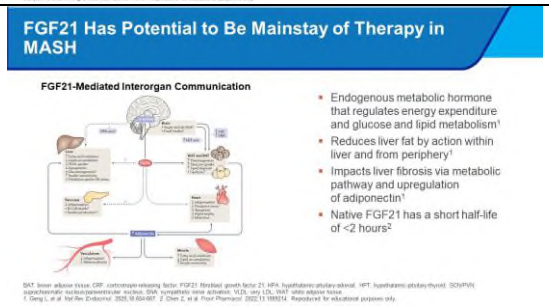
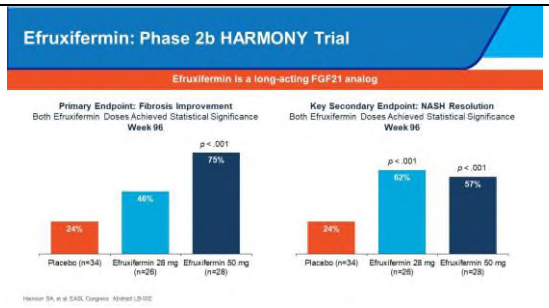
5.		This is from a study I did with the late Steven Harrison in San Antonio, Texas, where we offered patients coming for a screening colonoscopy—so middle-aged adults in San Antonio, Texas—we offered them the opportunity to learn more about their liver health, and if they agreed, we did MRI-PDFF to quantify liver fat and diagnose MASLD. And if they had more than 5% liver fat on the MRI, we offered the liver biopsy to diagnose MASH and to determine the stage of fibrosis. And we found in this cohort of middle-aged Americans that 38% had MASLD. But more importantly, 14% of the total cohort had evidence of MASH, which is the progressive form of the disease. When we looked at Latinos/Hispanics, 55% had evidence of MASLD and 24% had MASH. And then when you look at the combination of diabetes, obesity, Hispanic, up to 45% had evidence of MASH. And this cohort also we found about 6% that had evidence of F2-F3 fibrosis.
6.		Fibrosis is the main prognostic factor on a biopsy that correlates with clinical outcomes. So we have several studies showing as you progress to fibrosis stages 2 and 3, these are the patients that are likely to develop severe liver disease and develop liver-related mortality. And the bar graph, you see a systematic review that looked at several studies showing that exponential increase once you reach the F2 stage. So F2 and F3, they have higher rates of progression to cirrhosis but also dying from liver disease.
7.		And this study from Laurent Castera in France, he followed a large cohort of patients with type 2 diabetes, more than 700 patients and in patients with diabetes and persistently elevated ALT, they offered a liver biopsy. And what they showed in this study is very high prevalence of MASH—up to 58% of patients with diabetes. More importantly, though, he showed high prevalence of F3-F4 fibrosis, 38%, and up to 45% of patients with diabetes had F2-F3 fibrosis. These are the patients that we are targeting with resmetirom and other therapeutic agents.
8.		In terms of lifestyle recommendations for MASH, we always want to use a patient-centric approach. We start with lifestyle changes, focus on exercise and eating healthy. We have this systematic review that included 17 cohort studies showing a decrease in overall mortality and cardiovascular mortality. Based on the numbers of steps you do every day. And it seems like the magic number is that 8000 steps a day. So that should be our goal for patients with MASLD and MASH. We also want to modify the diet and decrease or eliminate alcohol consumption and

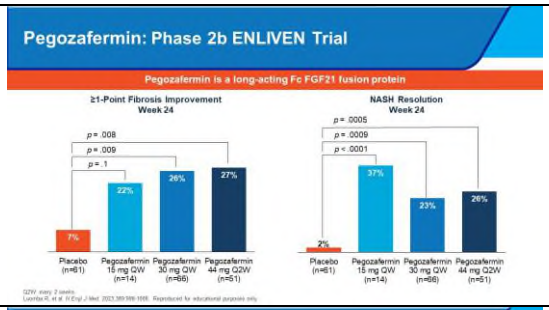
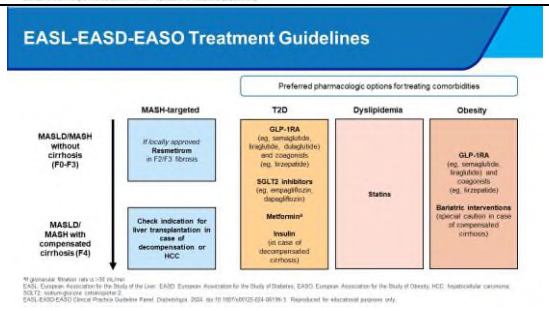
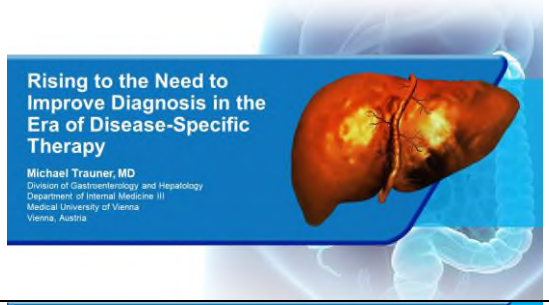
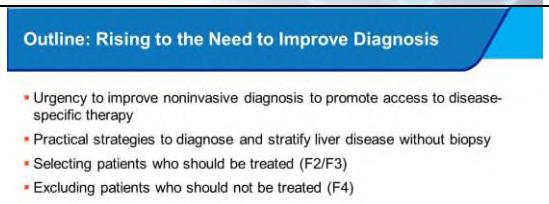
		smoking, decrease high fructose corn syrup, coffee is good for the liver, but black coffee, no sugar, no cream, and Mediterranean diet. And then we want to treat each comorbidity that coexists with the MASLD, including obesity, optimize the management of type 2 diabetes, dyslipidemia, hypertension, and obstructive sleep apnea.
9.		And one key message for our patients is you cannot out-exercise the fork, okay. You cannot burn enough calories just exercising. So, you have to eat healthy.
10.		Now we need a holistic management approach for patients with MASH. And the focus should not just be on liver outcomes such as MASH resolution and fibrosis regression, but we also need to improve the metabolic syndrome components, including dyslipidemia, insulin sensitivity, and also induce weight loss.
11.		There is a need also for liver-targeted therapies, especially in patients with F2-F3 fibrosis, because, you know, the focus should be on trying to halt progression of fibrosis toward cirrhosis. But even better if we can actually reverse fibrosis.
12.		So, this is how we think about the management of MASLD and specifically MASH. As you start with F0-F1 no significant fibrosis, the focus should be on weight loss, whether it's lifestyle intervention or maybe anti-obesity medications like GLP-1 receptor agonists. But as you progress to F2 and F3-F4, this is where we need liver-directed therapies that have proven anti-fibrotic effects.
13.		So, this is just an introduction to the topic. And now I'd like to hand it to Dr Bugianesi to go over THR-β agonists and other disease-specific therapies. ***Elisabetta Bugianesi, MD, PhD*** Thank you and thanks to the organizer.

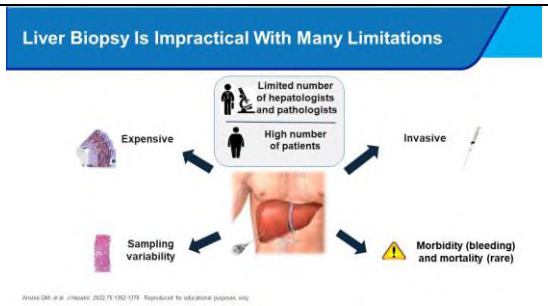
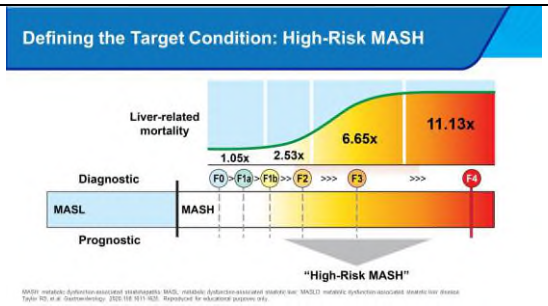
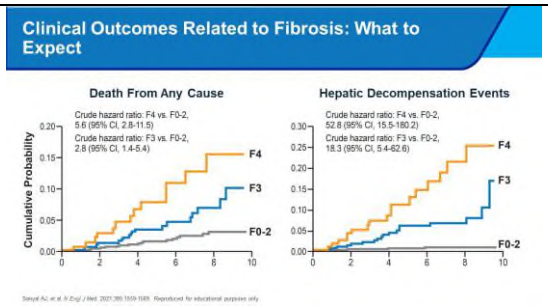
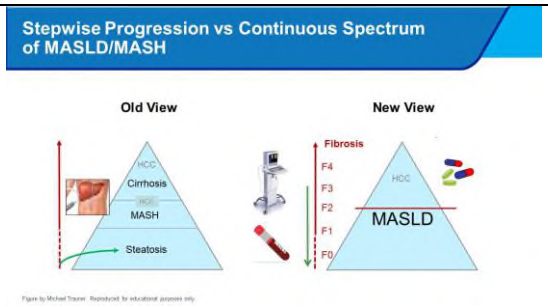
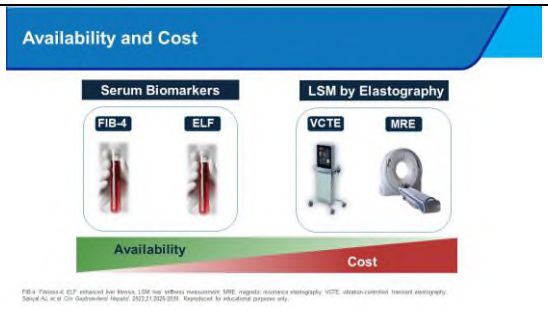
14.		So, let's start from the oral agents right away with resmetirom.
15.		Resmetirom is a thyroid hormone receptor-β agonist. So this receptor acts on the liver and on the kidneys, but mainly in the liver, to impact de novo lipogenesis cholesterol metabolism and promote oxidation of free fatty acids. But the main mechanism of resmetirom actually is to improve and restore mitochondrial health, which is very, very important in all the metabolic diseases driven by insulin resistance. And you will see.
16.		**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 agonist is effective in reducing hepatic fat content and fibrosis.
17.		***Elisabetta Bugianesi, MD, PhD*** And so the resmetirom phase 3 program actually encompasses a lot of studies for a total of more than 1500 patients at the top dose of 100 mg, and more than 2000 patients for at least 80 mg to support accelerated approval. Among these studies, of course, you are aware of the MAESTRO-NASH study, the one that led to the conditional approval of resmetirom as liver-targeted therapy for MASH and F2 and F3 fibrosis.

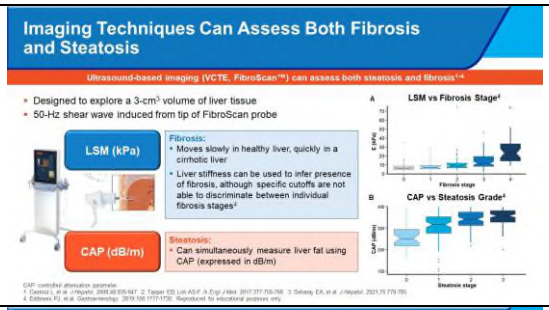
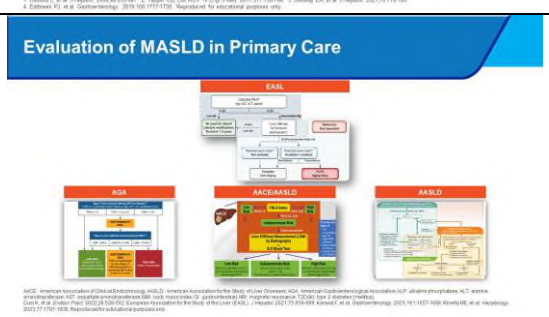
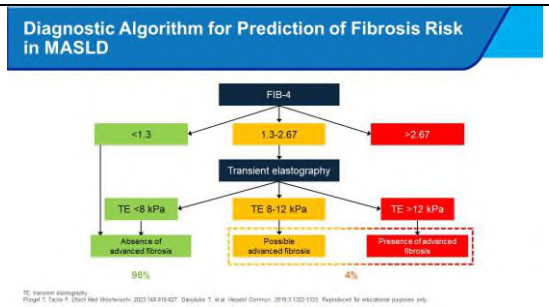
18.		So this is the MAESTRO-NASH study. There were 2 primary endpoints. And these are the results by intention-to-treat analysis. The first is NASH resolution which was achieved in 30% of patients at high resmetirom dosages of 100 mg, compared with 9.7% in the placebo group. And fibrosis improvement of at least 1 stage was similarly achieved in 26% of patients at the highest resmetirom dose, compared with 14% in placebo arm.
19.		Now, resmetirom has also favorable effects on lipid profile, it decreases the cardiovascular risk by decreasing LDL cholesterol, and this is very early at week 24. You see, at the highest dosage, LDL cholesterol is being reduced by 16%.
20.		Not just that, but resmetirom also is able to improve the health-related quality of life. If you compare responders, which is the dark bar, to nonresponders, which is the blue, to placebo, which is the orange, you see that there is overall an improvement in health-related quality of life for patients who were responders. And the main improvement was in the domain of emotional, health distress, and sleep.
21.		Resmetirom is very well tolerated. The most common adverse events are at the beginning of the therapy. Generally mild and transient diarrhea.
22.		But let's move to another molecule that is currently tested—lanifibranor. Lanifibranor is a pan-PPAR agonist α, δ, and γ. You know that PPARs are nuclear receptors with key regulatory functions in metabolism, inflammation, and fibrogenesis. In particular, the α components improve steatosis. The δ components decrease the activity of infiltrated macrophages and decrease the production of pro-inflammatory cytokines, and the γ components act on fibrogenesis and decrease TGF-β and collagen 1 production.

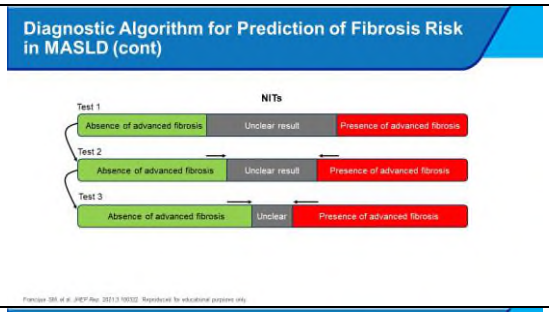
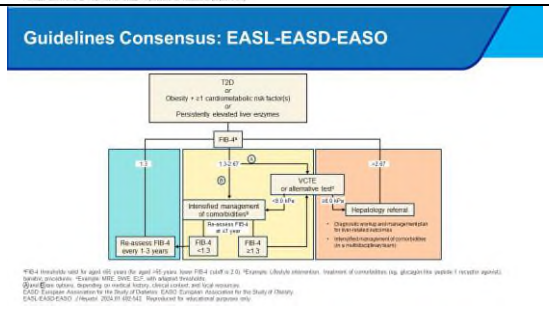
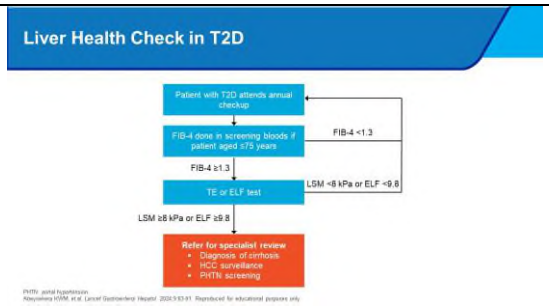
23.	**Lanifibranor: Phase 2b NATIVE Trial** Primary Endpoint: Reduction of ≥2 Points of SAF Activity Score and No Worsening of Fibrosis Secondary Endpoint: Improvement of ≥1 Stage of Fibrosis and No Worsening of NASH Secondary Endpoint: Resolution of NASH and No Worsening of Fibrosis  	So these are results of the phase 2b NATIVE trial. The primary endpoint here was a reduction of at least 2 points on the SAF Activity Score. And you see that this goal was achieved for the highest dosage, lanifibranor 1200 mg, 49% responder compared with 27% in the placebo. The secondary endpoints were improvement of at least 1 stage of fibrosis. Again obtained in 42% of patients in the high dosage lanifibranor, compared with 24% in placebo, and resolution of NASH worsening of fibrosis, with similar results 45% in the highest dosage compared with 19% in placebo.
24.	**Lanifibranor: NATIVE Trial Safety** Most Frequent AEs, n (%) / Lanifibranor 1200 mg (n=83) / Lanifibranor 800 mg (n=83) / Placebo (n=81) Diarrhea 10 (12) 8 (10) 1 (1) Fatigue 11 (13) 3 (4) 8 (10) Nausea 7 (8) 8 (10) 3 (4) Weight gain 7 (8) 8 (10) 0 (0) Peripheral edema 7 (8) 5 (6) 2 (2) Headache 7 (8) 4 (5) 4 (5) Abdominal pain 5 (6) 4 (5) 4 (5) Dizziness 6 (7) 2 (2) 3 (4) Anemia 6 (7) 1 (1) 0 (0) Constipation 5 (6) 3 (4) 6 (7) Increase in aminotransferase levels 3 (4) 5 (6) 1 (1)	Lanifibranor is quite well tolerated with some diarrhea, some fatigue. There is some weight gain, which is on average 2.5 kg, but nevertheless is lower compared with pioglitazone.
25.	**Metabolic Effects of GLP-1RAs**  	Then let's move to GLP-1 receptor agonist. By now you all know the effects of these excellent pleiotropic drugs. The main mechanism is central in the brain where it changes behavior. And on top of that it also has cardioprotective and nephroprotective effects.
26.	**Semaglutide: Phase 2b Trial** Primary Endpoint: Resolution of NASH With No Worsening of Liver Fibrosis Secondary Endpoint: Improvement in Liver Fibrosis With No Worsening of NASH  	So these are the results of the phase 2b trial for semaglutide, where 4 different doses—0.1, 0.2, and 0.4 mg given subcutaneously once a day—were compared with placebo, and for the primary endpoint of resolution of NASH they obtained 60% response rate in the high doses of semaglutide, compared with 17% in placebo. But for the improvement of at least 1 stage of fibrosis, although the response rate was quite high, 43%, they could not achieve a significant difference with the placebo arm, where the response rate was 33%.
27.	**Semaglutide: Phase 2b Trial Safety** AEs, n (%) / Semaglutide 0.1 mg (n=80) / Semaglutide 0.2 mg (n=79) / Semaglutide 0.4 mg (n=81) / Placebo (n=80) Any AE 72 (90) 76 (97) 76 (94) 67 (84) GI AE 51 (64) 60 (77) 55 (68) 36 (45) AE from any SOC Nausea 24 (30) 29 (37) 34 (42) 9 (11) Constipation 13 (16) 17 (22) 18 (22) 10 (12) Decreased appetite 16 (20) 18 (23) 18 (22) 4 (5) Diarrhea 23 (29) 22 (28) 16 (20) 11 (14) Vomiting 14 (18) 17 (22) 12 (15) 2 (2) Back pain 7 (9) 5 (6) 10 (12) 7 (9) Headache 7 (9) 10 (13) 10 (12) 8 (10) Nasopharyngitis 11 (14) 15 (19) 10 (12) 12 (15) Arthralgia 0 (0) 4 (5) 9 (11) 7 (9) Fatigue 7 (9) 8 (10) 7 (9) 7 (9) Abdominal pain 9 (11) 8 (10) 6 (7) 3 (4) Abdominal distension 1 (1) 8 (10) 4 (5) 4 (5) Dyspepsia 4 (5) 9 (12) 4 (5) 5 (6)	You all know the side effects of this drug. So nausea, some GI effects. But anyway, they are quite well-tolerated and for sure widely used.

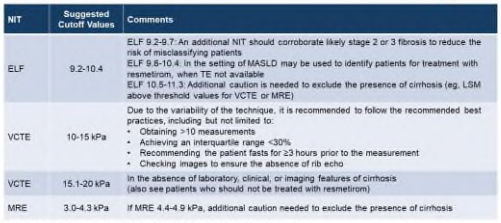
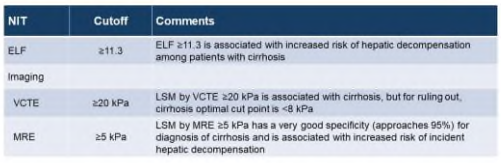
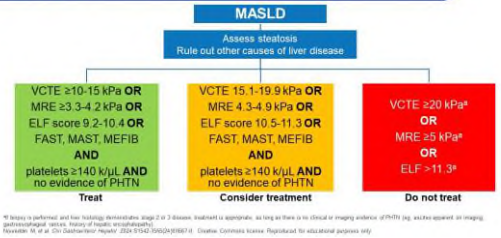
28.		Then twincretin. Twincretins have a potential therapeutic for the management of MASLD. So far, 2 kinds of twincretin has been tested: the combined GLP-1 and GIP effects, which in total is a more powerful GIP receptor agonist, and GLP glucagon effects, where the effects on the liver on reducing fat steatosis is higher compared with the weight loss.
29.		So this is the results of the randomized control trial phase 2b for tirzepatide dual GIP and GLP-1 receptor agonist. You see 62% of response rate for resolution of MASH in the highest dosage, 15 mg, that was given once a week subcutaneously, compared with 10% in placebo, and for improvement in liver fibrosis, they went up to 51%. But again, this was not sufficient because the response rate in placebo was 30% so it was not significantly different in the intention-to-treat analysis.
30.		Similar results we see for the dual glucagon GLP receptor agonist survodutide phase 2b trial, again up to 62% response rate for the histologic improvement of MASH, compared with 14% in placebo, and up to 36% for improvement in liver fibrosis, compared with 22% in placebo. Again, not significant.
31.		But another molecule is getting center stage for this disease, which is the fibroblast growth factor 21, which has the potential to be a mainstay of therapy in MASH. This is an endogenous metabolic hormone that regulates energy expenditure, glucose and lipid metabolism, and is able to reduce liver fat, to reduce liver fibrosis via metabolic pathway and upregulation of adiponectin. The only problem is that the native FGF21 has a short half-life of less than 2 hours.
32.		So long-acting FGF21 analogs are currently being tested. This is efruxifermin, the result of the phase 2b HARMONY trial. A high response rate up to 75% for the primary endpoint that this time was fibrosis improvement, and this was significantly different from the 24% response rate in placebo. The secondary endpoint here was NASH resolution. And again up to 62% in efruxifermin 28 mg, compared with 24% in placebo.

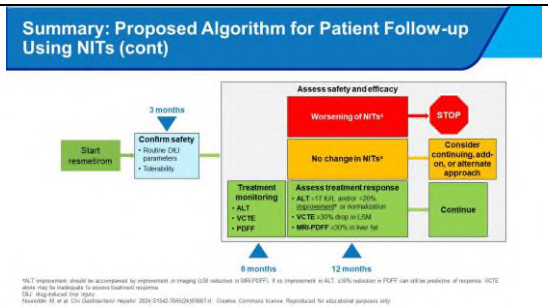
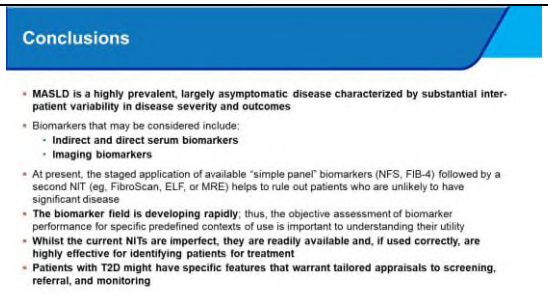
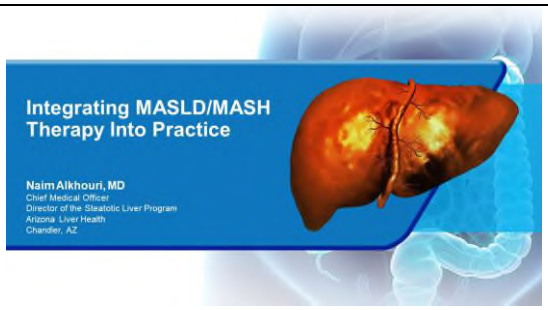
33.		Similar data were also observed for pegozafermin. Here you see that for fibrosis improvement, they had a response rate of 27%, compared with 7% in placebo, and for NASH resolution, up to 37%, compared with 2% in placebo.
34.		But let's summarize what European guidelines suggest about the treatment in patients with MASH. So the drugs should be given, liver-targeted drugs should be given only to patients with MASH and F2 to F3 fibrosis. So if locally approved, resmetirom will be the liver-directed drug for MASH with F2, F3 fibrosis. But it has not been tested in cirrhosis, so it shouldn't be given in cirrhosis yet. Then we have to optimize the comorbidities therapy. First of all type 2 diabetes. So here we have GLP-1 receptor agonist and coagonist. We have SGLT2 inhibitors. But we do not have any histological proof that these drugs can improve liver damage. We have metformin and insulin should be given just in case of decompensated cirrhosis. Dyslipidemia statin should be given to all patients without problems. And for obesity of course we have GLP-1 receptor agonist and coagonist. And for selected cases bariatric intervention, which should be used with special caution in cases of compensated cirrhosis.
35.		And now I hand over the stage to my co-chair, Prof Michael Trauner, for a talk on rising to the need to improve diagnosis in the era of disease-specific therapy. Michael. ***Michael Trauner, MD*** Thank you very much, Elisabetta.
36.		You've heard we are targeting patients with F2, F3 fibrosis. So how can we noninvasively diagnose those patients? I want to take you through this journey of new, noninvasive tests, which are now available to select patients with F2, F3 fibrosis and also identify those we do not want to treat at the moment with resmetirom, because the studies are still ongoing and also dosage adjustments may be necessary, which are the patients with cirrhosis.

37.		So I think we are all aware that liver biopsy is not feasible for a disease, which is as common as we've heard. So liver biopsy is invasive, it has a certain morbidity and even mortality. And I would say the acceptance by patients and also referring physicians is limited. We have the sampling variability, the cost issue, and perhaps most importantly, only a limited number of hepathologists interpreting these biopsies and also pathologists and hepatologists doing these biopsies.
38.		So from this, it's clear that we have to move to a noninvasive strategy. And here it comes in very handy that the fibrosis is actually the prognostic, most important, determining factor as you've heard. And it's this space of F2, F3 fibrosis where actually the prognosis of patients is changing, that liver-related mortality increases 6-fold in F3 fibrosis. And of course patients with F4 with liver cirrhosis are going to have liver-related events.
39.		And this is also nicely depicted by this study. On the right you see the hepatic decompensation events, which, of course, are more prevalent in F3 and F4 fibrosis. Little or no events in F0-F2. But actually on the left-hand side you see that death from any cause also is influenced by the degree of fibrosis. The liver, the fibrotic liver, seems to be a central hub, also determining extrahepatic outcomes. This is also very important to keep in mind in terms of interorgan crosstalk in this systemic disease.
40.		So we now have a new view of MASLD/MASH that we no longer can categorize. You know, different categories of MASH and non-MASH where we require liver biopsy. We continuously monitor liver fibrosis as we do in other diseases. And this can be done noninvasively with FibroScan or noninvasive tests to help to determine which patients actually require intensified therapy, such as pharmacotherapy, which starts with the F2, F3 category.
41.		So what are our tools? On the one hand, we have serum biomarkers, indirect fibrosis markers such as FIB-4, or direct fibrosis markers such as ELF. We have the liver stiffness measurements by elastography. Either FibroScan or other ultrasound-based methods such as ARFI (acoustic radiation force impulse) or more costly MR elastography. And the availability of these tests, of course, is inversely related to the costs, but certainly serum biomarkers and increasingly also FibroScan are widely available.

42.		With FibroScan, it's not only possible to measure liver stiffness, which nicely correlates with histological fibrosis stages, but also to a certain degree, assess steatosis by CAP, which also correlates with steatosis grade.
43.		So when you look at the evaluation algorithms for MASLD in primary care, they all look pretty much the same. Whether you look at EASL, AGA, or AASLD guidelines. It always comes down to the same paradigm that we want to rule in or rule out advanced fibrosis, which is F3 or significant fibrosis, F2 fibrosis. And here, on the one hand, we have FIB-4, where patients below 1.3 are basically in the green area. Those are the patients who can be managed in primary care who require lifestyle and metabolic therapies. And then on the other hand, we have the red space with a FIB-4 above 2.67. Those are the patients who have a very high risk of advanced fibrosis. And in between we have this intermediate, you know, traffic light orange area between 1.3 and 2.67 where patients require a second test, which would be, for example, transient elastography to determine whether we can again rule out or rule in advanced fibrosis. But still we have this indeterminate population with possible advanced fibrosis. And using this strategy of 2 consecutive tests, it's actually possible to restrict the number of patients requiring a specialized hepatology assessment to 4%. So 95% of the patients with this algorithm can be managed in primary care.
44.		It always comes down to the same paradigm that we want to rule in or rule out advanced fibrosis, which is F3 or significant fibrosis, F2 fibrosis. And here, on the one hand, we have FIB-4, where patients below 1.3 are basically in the green area. Those are the patients who can be managed in primary care who require lifestyle and metabolic therapies. And then on the other hand, we have the red space with a FIB-4 above 2.67. Those are the patients who have a very high risk of advanced fibrosis. And in between we have this intermediate, you know, traffic light orange area between 1.3 and 2.67 where patients require a second test, which would be, for example, transient elastography to determine whether we can again rule out or rule in advanced fibrosis. But still we have this indeterminate population with possible advanced fibrosis. And using this strategy of 2 consecutive tests,

		it's actually possible to restrict the number of patients requiring a specialized hepatology assessment to 4%. So 95% of the patients with this algorithm can be managed in primary care.
45.		And the principle is just simply that through this consecutive application of noninvasive tests, you limit this gray intermediate zone or orange zone as it was on the previous slide.
46.		And basically the same principle also is applied with the recent EASL guidelines, that we focus on higher risk populations, patients with diabetes, cardiometabolic risk factors, and persistently elevated liver enzymes to assess fibrosis with FIB-4. And then you have the same values 1.3, 2.67 with the categories which I've mentioned, or the second test in this intermediate zone category with vibration control, transient elastography, FibroScan, or alternative tests such as ELF for further evaluation.
47.		What about diabetes? We've heard that in diabetes we have had an even higher prevalence of MASH and advanced fibrosis. The current guidelines, also the EASD guidelines actually, recommend to screen or assess fibrosis in patients with diabetes, but they don't tell us how often this should happen. And actually, from this publication, there's a very, you know, intriguing recommendation to perform annual checkups with the cutoffs, which we've mentioned, you know, the FIB-4 or here comes in the ELF test, which may be more widely available as a laboratory test. And basically, patients with an ELF of 9.8 or higher to a liver stiffness above 8 kPa or higher should be referred to specialized hepatology care for HCC screening and screening of portal hypertension. I would add that also you can apply the Baveno VII criteria here.
48.		So how to select patients with F2, F3?

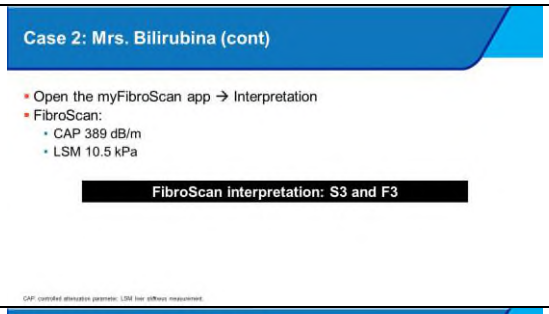
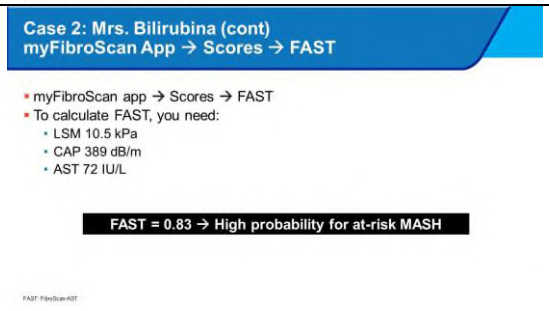
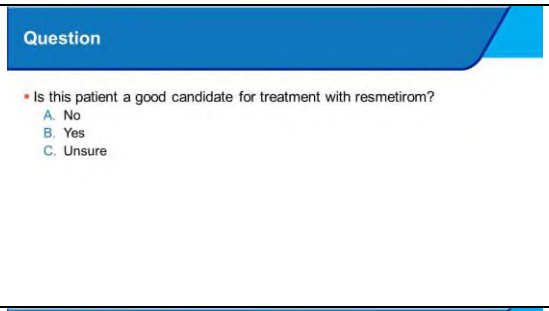
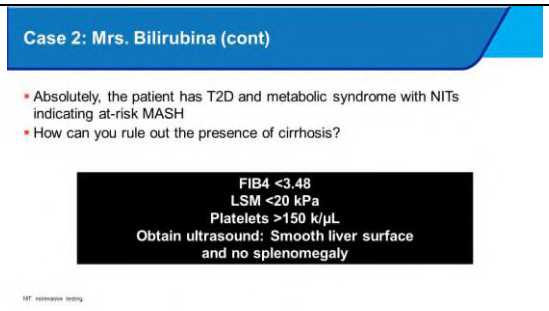
49.	**Suggested Cutoffs for F2-F3**  NIT / Suggested Cutoff Values / Comments ELF — 9.2-10.4 — ELF 9.2-9.7: An additional NIT should corroborate likely stage 2 or 3 fibrosis to reduce the risk of misclassifying patients. ELF 9.8-10.4: In the setting of MASLD may be used to identify patients for treatment with resmetirom, when TE not available. ELF 10.5-11.3: Additional caution is needed to exclude the presence of cirrhosis (eg, LSM 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 interquartile range <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	What are the cutoffs? Actually for FibroScan we have this 10 to 15 kPa cutoff range. It's important to obtain measurements in sufficient quality. With ELF we have this 9.2 to 10.4. So when we are in the lower range, 9.7, 9.2 to 9.7, we may want another additional confirmatory test such as FibroScan. And these are actually data which all come from the MAESTRO trial. In this trial I should add that FIB-4 did not perform very well to categorize F2, F3 fibrosis. So here we need these additional tests to assess the target population. And this can be done with ELF and FibroScan.
50.	**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	We also have other, you know, new composite scores for identification of persons at risk for advanced MASH with high activity and advanced fibrosis, such as the FAST score, which is the FibroScan, you know, AST combination combining both stiffness and CAP. A similar principle, the MAST score using MR PDFF for steatosis and MR elastography together with AST or also an MRE FIB-4 score. And also here we have those rule-in, rule-out cutoffs, which may help to identify the risk population. This is not yet in guidelines. But this will probably a direction where those scores have a better performance than FIB-4 and conventional FibroScan.
51.	**Rising to the Need to Improve Diagnosis** ▪ Urgency to improve noninvasive diagnosis to promote access to disease-specific therapy ▪ Practical strategies to diagnose and stratify liver disease without biopsy ▪ Selecting patients who should be treated (F2/F3) ▪ Excluding patients who should not be treated (F4)	So how to exclude patients with liver fibrosis?
52.	**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 associated with increased risk of incident hepatic decompensation	This is basically above 11.3. These also are data from the MAESTRO trial. Those are basically patients at an increased risk for hepatic decompensation. Those are patients who we do not want to treat at the moment or with a FibroScan above 20 kPa. MR elastography, I think, is not that widely available, but also here we have cutoffs.
53.	**Summary: Proposed Algorithm for Patient Selection Using NITs**  MASLD Assess steatosis Rule out other causes of liver disease VCTE ≥10-15 kPa OR MRE ≥3.3-4.2 kPa OR ELF score 9.2-10.4 OR FAST, MAST, MEFIB AND platelets ≥140 k/µL AND no evidence of PHTN Treat VCTE 15.1-19.9 kPa OR MRE 4.3-4.9 kPa OR ELF score 10.5-11.3 OR FAST, MAST, MEFIB AND platelets ≥140 k/µL AND no evidence of PHTN Consider treatment VCTE ≥20 kPa[a] OR MRE ≥5 kPa[a] OR ELF >11.3[a] Do not treat	So with this, it's possible to propose an algorithm for patient selection. Again, with this traffic light algorithm. Green are the patients who should be treated with the FibroScan cutoff of 10 to 15 kPa. You can push up the value up to 19.9, close to 20 kPa. Above 20 kPa is basically the cirrhotic space, if you're sure, or if you have other indices such as, you know, platelet counts and no evidence of portal hypertension on imaging or endoscopy to rule out

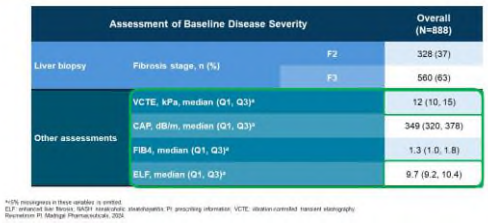
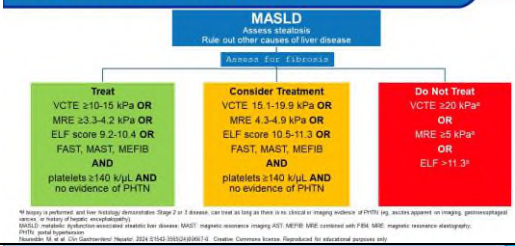
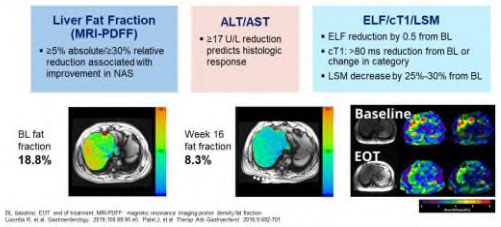
		cirrhosis. So those are patients who can be considered. The green space are the patients who should be treated and maybe here the FAST and the new course, which I've briefly introduced to do, may come into play.
54.		We also can use those noninvasive tests to monitor patients, you know, certainly when there's a worsening of needs, we would consider stopping treatment. On the other hand, improvement of FibroScan, and we know this from other advanced chronic liver disease studies that, for example, a drop of 25% to 30% is associated with the risk reduction of 50% for clinical outcomes. So this is certainly helpful to monitor the development of these noninvasive tests in addition to liver enzymes.
55.		So with this, without further ado, I want to summarize. You know, it's a complex area. We have those new biomarkers. It's rapidly developing. We have new scores coming in. We improve the current needs. They are not perfect, but they can be used for clinical practice already and probably for diabetes. I think this is also a lesson that we've learned. We not only may have to adjust our values, but also have to develop additional tests to better risk stratify this population.
56.		So without further ado, Naim, I'm handing it over to you, and I think you have brought us some exciting cases. You are going to challenge us a little bit or the audience. Right? ***Naim Alkhouri, MD, FAASLD*** Thank you so much for this excellent presentation. So let's have some fun. Now I want to ask you guys, with a show of hands. How many of you calculates FIB-4 routinely in your clinic? Let's see. Only 2 people. Okay. We have a lot of fun to have here, okay. Maybe 4 or 5. And do you guys have any online calculators or anything on your phone that you utilize to calculate FIB-4? If you don't, there is an app called MDCalc and it has FIB-4, all you need is AST, ALT, platelet count, and age. Let me see also, show of hands. How many of you guys have the MyFibroScan app, which is the app to calculate the FAST score. Okay, we have a few people. This is another app that I highly encourage you to download on your phone. It's called the MyFibroScan app. It helps with some of these scores that Prof Trauner showed you. All right. So let's do a few cases. We will have some interactive questions here.

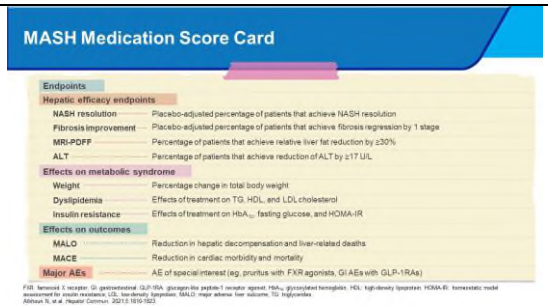
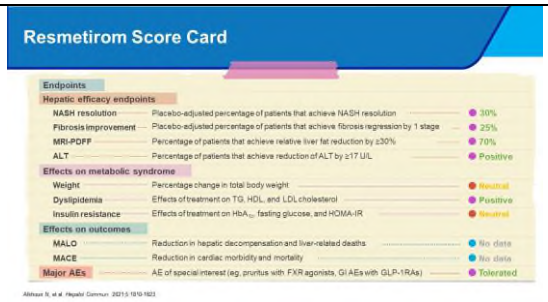
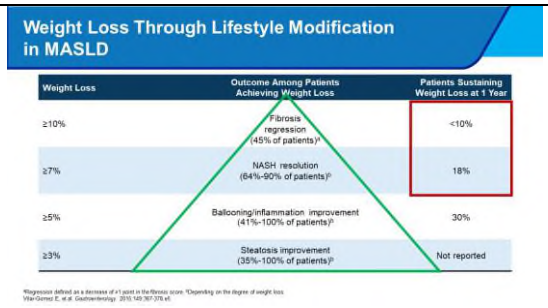
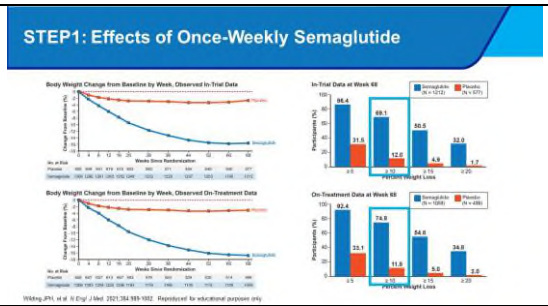
57.	**Case 1: Mrs. Sema**
	Tina
	 
	Weakness
	 
	• 51-year-old White woman with history of HTN and obesity (BMI 47 kg/m²) presents for incidental finding of steatotic liver on ultrasound done for RUQ pain
	  • ALT 23 IU/L
	  • AST 18 IU/L
	  • Platelets 312 k/µL
	• Let's calculate the FIB4; get your phones out and open the MDCalc app → Search for FIB4
	FIB4 = 0.61 (low < 1.3) → Keep in primary care
	Consider semaglutide 2.4 mg/wk for obesity
	Repeat FIB4 in 2-3 years
	ALT: alanine transaminase; AST: aspartate aminotransferase; BMI: body mass index; FIB4: fibrosis-4; HTN: hypertension; RUQ: right upper quadrant
		So we'll have you vote on some of these questions using the QR code and the UEG app. So we'll start with the first case. This is Mrs. Sema and she is a 51-year-old Caucasian woman. History of hypertension and obesity. She loves her cheesecakes, and she gained some weight unfortunately over the years. And she presents with incidental finding of steatotic liver on ultrasound. Her ALT and AST are relatively normal and platelet count is perfectly fine at 312 k/µL. So let's calculate the FIB-4. If anyone has it on their phone, and you can give me the answer quickly, that would be great. But I did the calculation for you guys in my mind, I do a mental FIB-4, so when I look at normal ALT, AST, normal, platelet count, relatively younger patient, I know it's probably going to be low and the FIB-4, when you calculated, is at 0.61. So less than 1.3. So this is considered the green zone, low likelihood of having significant fibrosis. So this is a patient you want to keep in primary care or an endocrine clinic. You do not need to refer to a hepatology clinic. And you should consider weight loss strategies, including anti-obesity medications. And then you repeat the FIB-4 every couple of years to assess for progression.

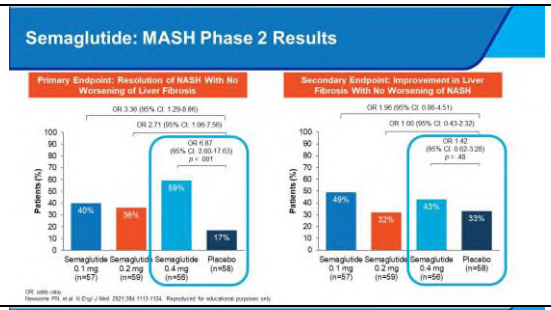
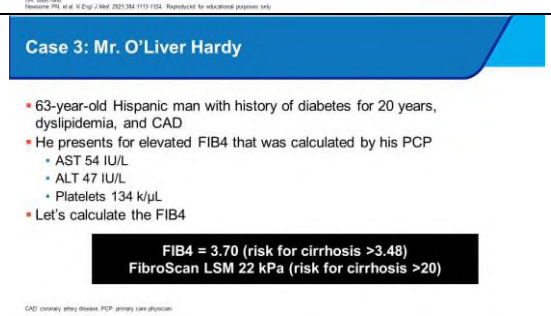
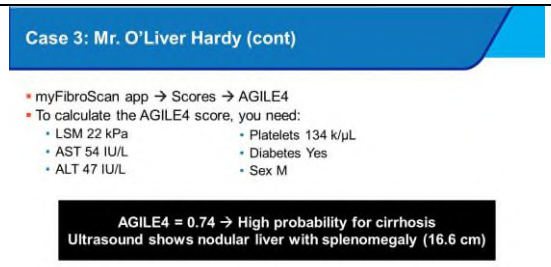
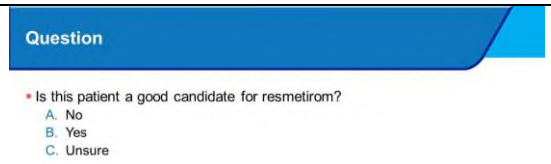
58.	**Case 2: Mrs. Bilirubina**
	• Mrs. Bilirubina is a 61-year-old Hispanic woman with T2D, obesity (BMI 42 kg/m²), and dyslipidemia
	• What's her pre-test probability of having at-risk MASH?
	• Let's calculate her FIB4:
	  • AST 72 IU/L
	  • ALT 65 IU/L
	  • Platelets 188 k/µL
	FIB4 = 2.90 (high >2.67)
	MASH: metabolic dysfunction-associated steatohepatitis; T2D: type 2 diabetes
		Second case is Mrs. Bilirubina. She is a 61-year-old Hispanic woman with type 2 diabetes, obesity with high BMI of 42 kg/m^2, and dyslipidemia. So what's her pretest probability of having at-risk MASH? I would say high, based on the data that I showed you because of the Hispanic ethnicity, the presence of type 2 diabetes, class 3 obesity, and the presence of metabolic syndrome. And you can see her AST and ALT. Typically in MASLD, ALT is higher than AST. When you see AST is higher than ALT, that indicates either advanced fibrosis or that the patient is lying to you and they're drinking alcohol and they're not disclosing that they're drinking. And the platelet count is a little bit lower at 188 k/µL. So let's calculate a FIB-4 here. And when you calculate the FIB-4 it comes at 2.9. So this is more than the 2.67. This is a high-risk patient who I would refer to a hepatologist. You don't need to do an additional test. Again she has high pretest probability of having MASH with significant fibrosis. And you calculate the FIB-4 and it's more than 2.67.

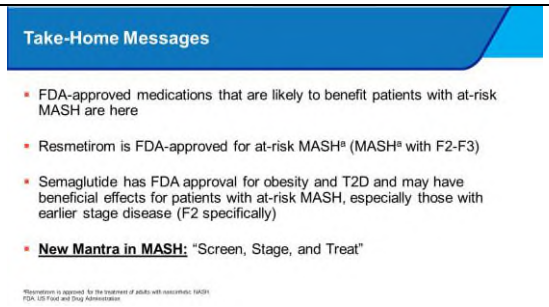
59.	**Question**
	• What would you do next?
	  A. Refer the patient to a specialist
	  B. Order phosphatidylethanol (PEth) testing
	  C. Work with the patient on weight loss strategies
	  D. Continue to observe the patient, following up every 3 months
		Now what would you do next? Refer the patient to a specialist; order a PEth test to assess for alcohol consumption; work with the patient on weight loss strategies, or continue to observe the patient, following up every 3 months. I kind of gave you the answer, but let's see if the voting system works. All right, so I think there is not one correct answer, but I would have picked the first one, which is refer the

		patient to a specialist based on the FIB-4 being at 2.9. But, you know, some of us are doing PEth testing routinely on patients with MASLD. And actually we shared some data earlier today that 10% of patients in clinical trials for MASH, they have evidence of significant alcohol consumption. Of course, weight loss is always a good idea.
60.		All right. So if you have the MyFibroScan app, you know, we did a FibroScan on this patient. And the CAP score for steatosis came out at 389. And the liver stiffness is at 10.5 kPa. So how do we interpret this? If you put these numbers in the MyFibroScan app, this will come at steatosis grade 3, which is severe steatosis and stage 3 fibrosis.
61.		If you want to increase your positive predictive value and confidence that this patient has at least F2 fibrosis or higher, you can calculate the FAST score that Prof Trauner explained earlier. This has the CAP score for steatosis, liver stiffness for fibrosis, and the liver enzyme AST for disease activity. So you need these 3 variables, which I provide. And if you calculate the FAST score, it comes at 0.83. Anything more than 0.67 is consistent with MASH and at least significant fibrosis of F2 or higher. So this is a patient clearly with MASH and at least F2 fibrosis.
62.		Is this patient a good candidate for treatment with resmetirom? We have 3 options for you guys: No, yes, or unsure. Let's vote again. We'll give you a few seconds. All right. Let's see the results if available. All right. Wow. I guess we did a good job convincing you that patients with evidence of, you know, MASH with F2 or higher on NITs are good candidates, so 100% said yes to resmetirom.
63.		All right, so the answer is absolutely yes. The patient has type 2 diabetes, metabolic syndrome, with NITs indicating at-risk MASH. Now, how can you rule out the presence of cirrhosis in this patient, because we don't want to use resmetirom on patients with cirrhosis. And these are the NITs that were shown earlier. So FIB-4 less than 3.48 typically is useful for, you know, cirrhosis; liver stiffness less than 20 kPa. Make sure your platelet count is more than 150 k/µL. And then I typically like to obtain a baseline ultrasound in my patients with MASLD if they don't have one. And make sure you have a smooth liver contour and no splenomegaly. If you see any signs of portal hypertension or anything suggestive of cirrhosis, then we have to wait for more data with resmetirom as treatment for cirrhotic MASH.

64.	**PI: Baseline Disease Characteristics From the MAESTRO-NASH Trial With Resmetirom**  Assessment of Baseline Disease Severity / Overall (N=888) Liver biopsy — Fibrosis stage, n (%): F2 328 (37); F3 560 (63) Other assessments: VCTE, kPa, median (Q1, Q3)[a] 12 (10, 15); CAP, dB/m, median (Q1, Q3)[a] 349 (320, 378); FIB4, median (Q1, Q3)[a] 1.3 (1.0, 1.8); ELF, median (Q1, Q3)[a] 9.7 (9.2, 10.4)	All right. So these are some of the data that were actually shared from the MAESTRO NASH trial that helped us establish the cut points for NITs to select patients that have F2 and F3. And if you look at the liver stiffness, you see the median was at 12 kPa and the interquartile range was between 10 to 15. And this is how we got that green zone between 10 to 15 kPa as the sweet spot for treating patients with resmetirom. And then if you look at the ELF score, the median was at 9.7 and the interquartile range was between 9.2 to 10.4. One thing I want to highlight in the MAESTRO-NASH trial is that the FIB-4 median was at 1.3. So if you utilize FIB-4 to select patients for treatment, you're going to miss 50% of patients who will have a FIB-4 of less than 1.3. So FIB-4 is great for primary care clinics to select patients for referrals. But they're not. It's not the way to select patients for treatment and [for patients seen in] GI and hepatology clinics.
65.	**Proposed Algorithm for Patient Selection Using NITs for Liver-Directed Therapy**  MASLD Assess steatosis Rule out other causes of liver disease Assess for fibrosis Treat: VCTE ≥10-15 kPa OR MRE ≥3.3-4.2 kPa OR ELF score 9.2-10.4 OR FAST, MAST, MEFIB AND platelets ≥140 k/µL AND no evidence of PHTN Consider Treatment: VCTE 15.1-19.9 kPa OR MRE 4.3-4.9 kPa OR ELF score 10.5-11.3 OR FAST, MAST, MEFIB AND platelets ≥140 k/µL AND no evidence of PHTN Do Not Treat: VCTE ≥20 kPa[a] OR MRE ≥5 kPa[a] OR ELF >11.3[a]	This is the same algorithm that Prof Trauner went over. So I'm not going to repeat this. But just know that we have a green zone. We have a yellow zone and a red zone. And you can select different biomarkers, including transient elastography, MR elastography, or the ELF score. Or you can use some of these combination biomarkers like the FAST and MAST.
66.	**Biomarkers to Assess Treatment Response**  Liver Fat Fraction (MRI-PDFF): ▪ ≥5% absolute/≥30% relative reduction associated with improvement in NAS ALT/AST: ▪ ≥17 U/L reduction predicts histologic response ELF/cT1/LSM: ▪ ELF reduction by 0.5 from BL ▪ cT1: >80 ms reduction from BL or change in category ▪ LSM decrease by 25%-30% from BL BL fat fraction 18.8% Week 16 fat fraction 8.3% Baseline EOT	We have biomarkers also to assess response to treatment. So we learned from clinical trials. And this has been validated in several studies that if you see reduction and MRI-PDFF, which is a way to quantify liver fat by 30% relative reduction from baseline that predicts histologic response in terms of MASH resolution and potentially even fibrosis regression. When we look at the improvement in ALT, which is commonly utilized in our clinics, reduction in ALT by 17 units from baseline or more typically corresponds with histologic improvement. A reduction in the ELF score by 0.5 from baseline also can predict histologic improvement and reduction in liver stiffness. Transient elastography by 25% to 30% from baseline can predict histologic response. So if I start with someone with liver stiffness of 10 kPa and then I treat with resmetirom for 1 year, the ideal outcome will be that they decrease their liver stiffness to less than 7.5 kPa or more. That would be a good responder. Typically, I would like to see a reduction in the ALT, and then reduction in liver fat on the CAP score or MRI-PDFF.

67.		So I wrote a paper a few years ago looking at how we're going to compare MASH treatments, as we have more and more that are FDA and EMA approved. And this is what I call the MASH medication scorecard. So when we look at these medications it's very important to look at hepatic efficacy endpoints. So what was the rate of MASH resolution, fibrosis improvement, reduction in liver fat, improvement in ALT. But we cannot be so myopic and just look at liver efficacy endpoints. We need to look at the effects of each drug on every component of the metabolic syndrome. And the ideal drug also should help you lose weight and improve lipids and improve insulin resistance. And then eventually, we would like to see the effects of the drugs on liver outcomes, what we call major adverse liver outcomes, or MALOs, like progression through cirrhosis, decompensation with ascites, encephalopathy, and also look at cardiovascular outcomes, overall mortality. And of course, we have to take into account the adverse events of each drug.
68.		So this is how resmetirom scored based on my card. So you see the NASH resolution rate, the fibrosis improvement, reduction in liver fat. It's weight neutral and it's neutral on HbA_{1c}. But it helps with dyslipidemia. We showed the data with reduction in LDL cholesterol by 16% and reduction in triglycerides by 22% from baseline. We do not have data on liver or cardiac outcomes at this point, and the medicine was very well tolerated in the clinical trials.
69.		Weight loss is still very important. And actually in the FDA label, it is recommended that you use resmetirom with the comprehensive lifestyle intervention. Our goal for our patients should be to lose 10% of their total body weight or more. This has been shown to be associated with NASH resolution and fibrosis regression. So for someone who's 250 pounds, they need to lose 25 pounds. Unfortunately, even in clinical trials, only 10% of patients are able to lose that 10% total body weight, which leaves 90% of patients needing help with weight loss outside of lifestyle.
70.		We talked about semaglutide, and these are data from the STEP1 trial that led to the obesity indication. And I just want to highlight that with semaglutide and tirzepatide, about 70% to 75% of patients actually lose that 10% weight, which is great.

71.		But as Dr Bugianesi showed you earlier, there was no effect on fibrosis. So we only saw improvement in MASH resolution with semaglutide. But at least in the phase 2b trial, there was no clear signal on fibrosis. So we have this paradox that with semaglutide you lose the 10% total body weight in the majority of patients. But at least at this point, we don't have convincing data that this helps with liver fibrosis.
72.		Last case I have is Mr. O'Liver Hardy. He's a 63-year-old Hispanic man with a history of diabetes for 20 years, dyslipidemia, and coronary artery disease, so already high risk. He presents with elevated FIB-4 that was calculated by his PCP. His AST is higher than his ALT and his platelet count is low. So already I'm worried that he has very advanced disease. If we calculate the FIB-4, it comes to 3.7. So more than the 3.48, which is the cut point for cirrhosis. And we did a FibroScan transient elastography. And that showed liver stiffness of 22 kPa. So this is more than the 20 kPa cut point for cirrhosis. So this is a patient that I'm very comfortable diagnosing with MASH cirrhosis. I don't need to do a liver biopsy.
73.		You also can calculate a score called the AGILE4. This is another score you can calculate in the MyFibroScan app. This combines the FIB-4 plus liver stiffness so you have your liver stiffness, platelets, AST, ALT, presence of diabetes, and sex male versus female. If you calculate an AGILE4, this will be a very high at 0.74. The cut point for cirrhosis is 0.58. So this increases your positive predictive value that this patient has cirrhosis. We also obtained an ultrasound. And that shows a nodular liver with splenomegaly.
74.		So is this patient a good candidate for resmetirom treatment? Let's vote. No. Yes. Unsure. Okay I guess we have 1 person who would still treat. I would love to hear from you, whoever you are at the end, why you think treating at this point is indicated? Again, we're not saying that we know for a fact that resmetirom is a bad idea in patients with cirrhosis, but we are doing the phase 3 trial now called the MAESTRO-NASH outcomes. So the answer may change in a couple of years. But at least at this point, this is not in the FDA label and it's not going to be in the EMA label.

75.		All right. So my last slide is about SHARE decision-making for long-term success with our patients. So this is the SHARE approach that has 5 steps that we utilize in our clinics. So first you need to seek your patient's participation. You want to engage the patient. You want to help them to explore and compare the treatment options and what works for them. You want to assess their values and preferences. If a patient has an issue with injections, probably going on semaglutide is not going to be the way to go. If a patient does not eat meat, probably going on a keto diet is not a good way to go. So you need to assess their values and preferences, and then you need to reach a decision with the patient. So again engaging them in the decision-making. And then you want to evaluate your patient's decision.
76.		So my take-home message is that FDA-approved medications that are likely to benefit patients with at-risk MASH are here, at least in the United States, and should be here for you guys in Europe next year. Resmetirom is FDA approved for at-risk MASH, which is MASH with F2, F3 fibrosis; semaglutide has FDA approval for obesity and type 2 diabetes, 2 common comorbid conditions in patients with MASH. So use it appropriately. And I have a new mantra in MASH in 2024, which is, "Just do something." And that should include screen all high-risk patients, all patients with diabetes, and patients with metabolic syndrome. And then, when you identify fatty liver or MASLD, you need to determine the stage. It's not okay to say you have MASLD, lose weight, and we'll monitor you. You need to know the stage of fibrosis. And then when you identify patients with MASH and F2 or higher, start treatment, we have effective treatments today.