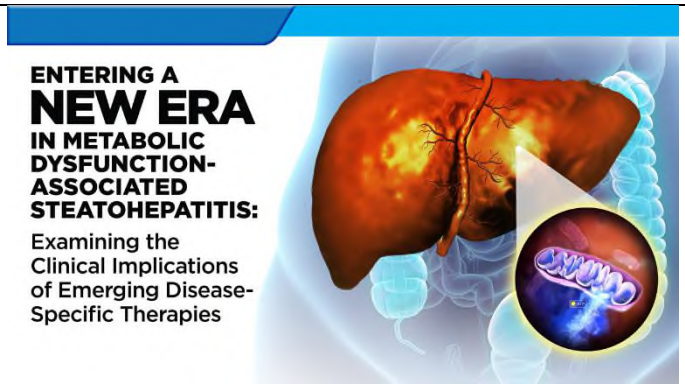
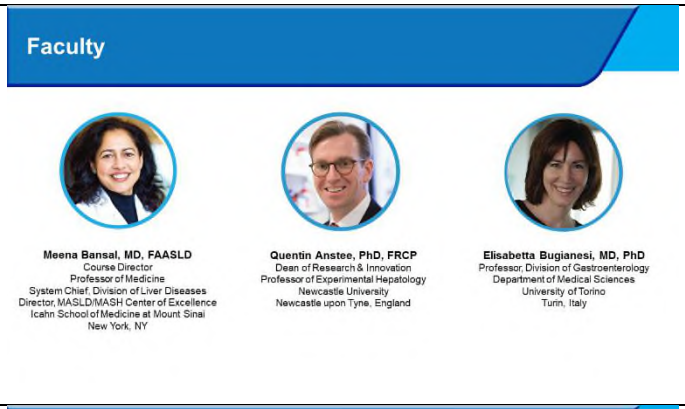
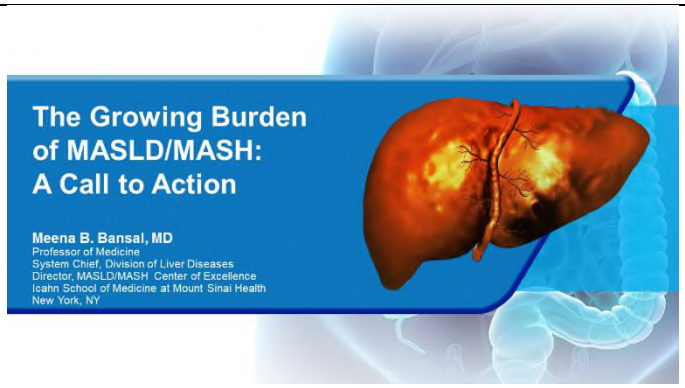
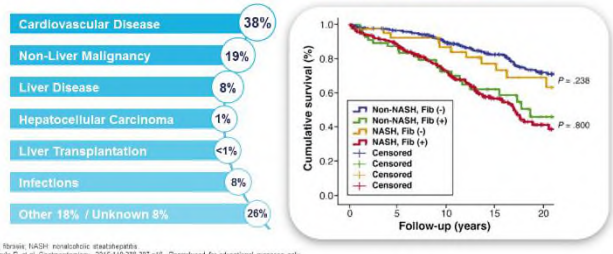
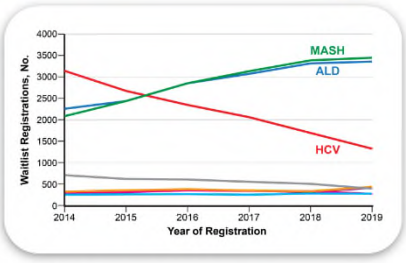
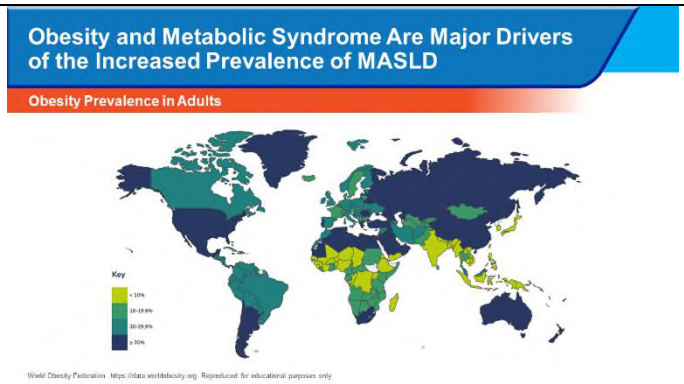
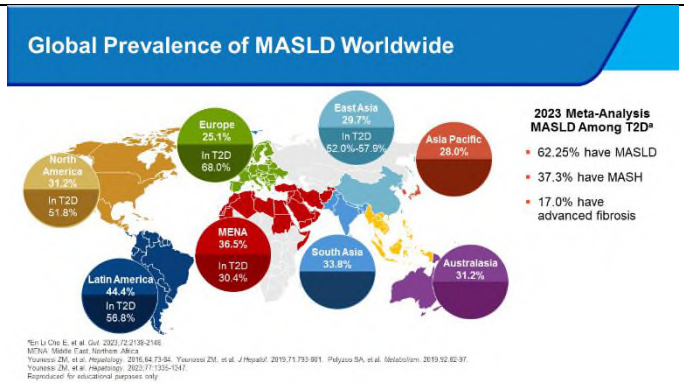
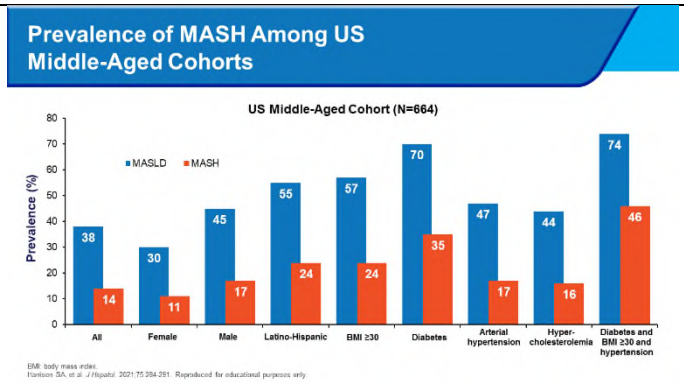
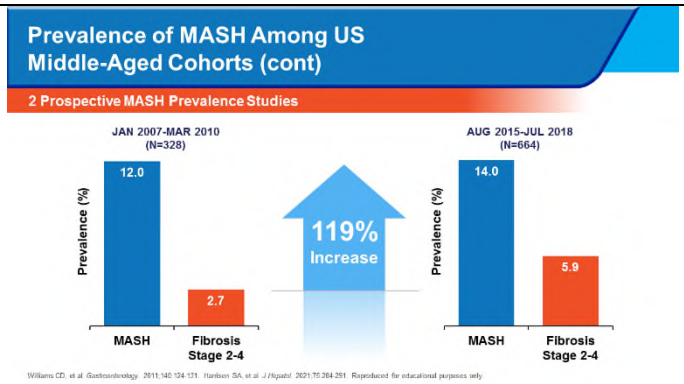
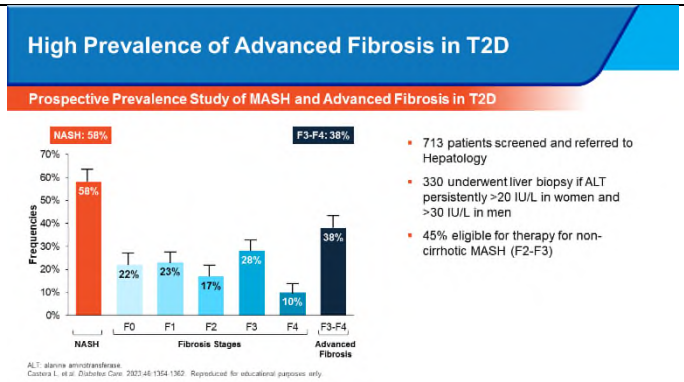
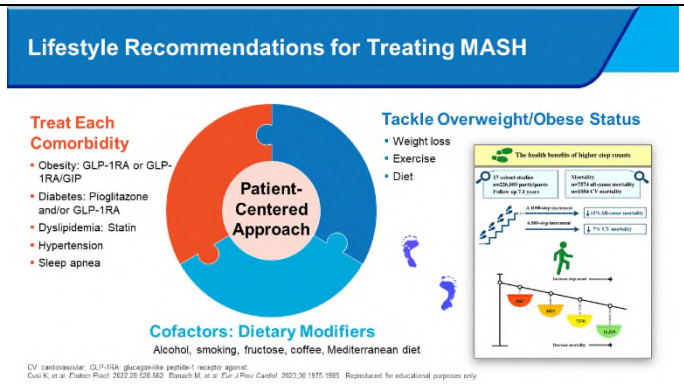
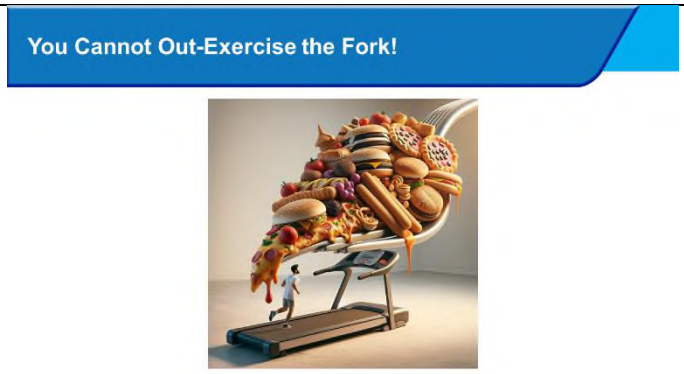
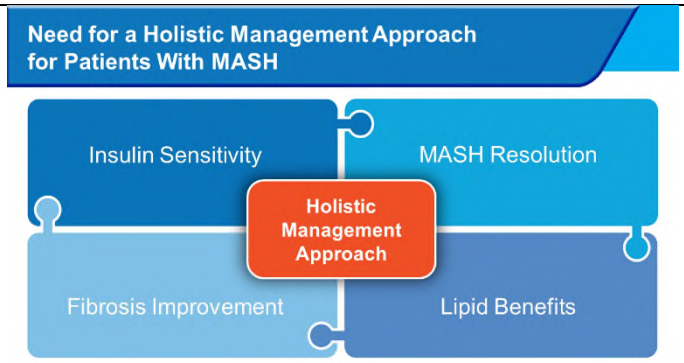
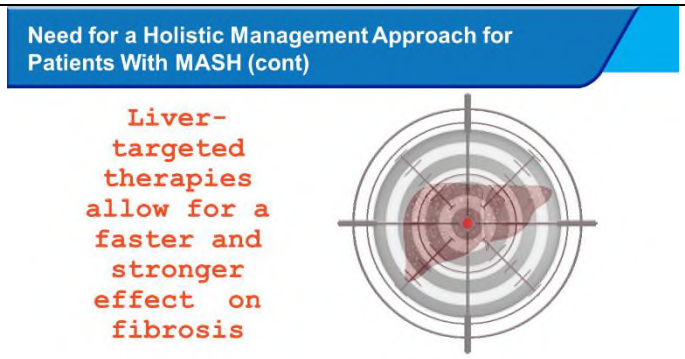
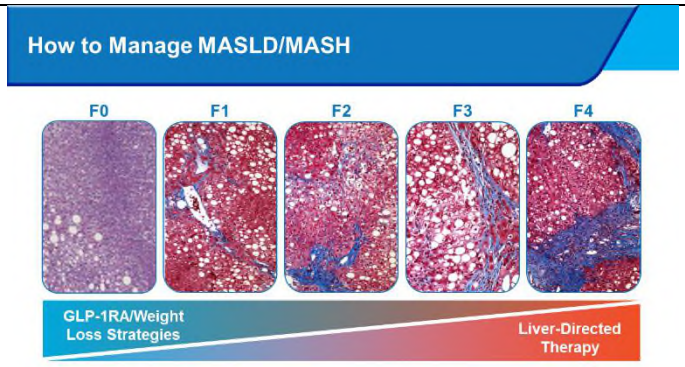
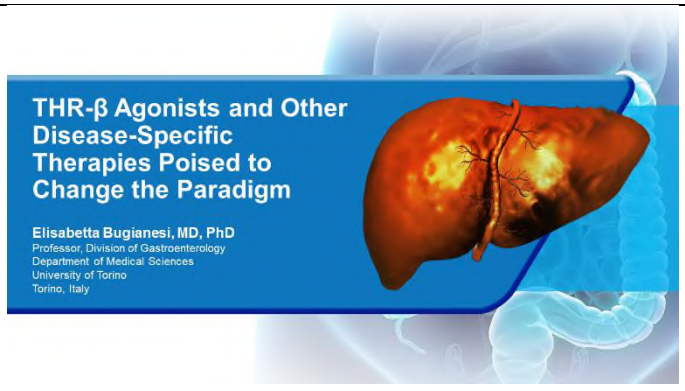
1.		***[Meena B. Bansal, MD, FAASLD]*** Welcome, everyone, to this session "Entering a New Era in Metabolic Dysfunction-Associated Steatohepatitis: Examining the Clinical Implications of Emerging Disease-Specific Therapies."
2.		I'm Meena Bansal. I am professor of medicine and chief of the Division of Liver Diseases at Mount Sinai, New York. I'm so pleased to be joined by Dr. Anstee, dean of research and innovation and professor of experimental hepatology at Newcastle University. And Dr. Elisabetta Bugianesi, professor of the division of gastroenterology at the University of Torino.
3.		But I'm very sad and heartbroken that we're missing a very important part of our family. Dr. Stephen Harrison. For those of you who knew him, he was a fierce competitor, but he was not competitive. He made everyone around him feel good about themselves, and he was extremely generous with his time and his friendship. We've purposely kept some kind of classic Stephen Harrison slides in here just to commemorate him, but we miss him dearly.
4.		So I'm going to kick us off by just setting the stage.

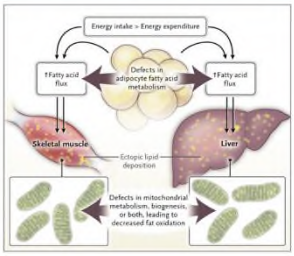
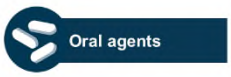
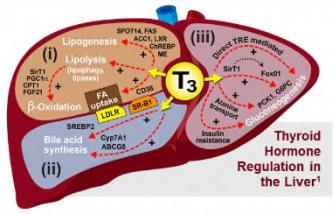
5.	**Nonalcoholic Steatohepatitis (NASH) vs Metabolic Dysfunction-Associated Steatohepatitis (MASH)** ▪ The following presentation contains a discussion of an FDA-approved drug for the treatment of NASH ▪ NASH is now known as MASH to emphasize the underlying pathophysiology of this liver condition ▪ Presenters may use NASH and MASH interchangeably	I think many of us have been hearing about this since the opening ceremony, and just keep in mind that the following presentation contains a discussion of an FDA-approved drug for the treatment of NASH, though the nomenclature MASH and NASH will be used interchangeably throughout the discussion.
6.	**A Worldwide Epidemic** 	So, as we know, obesity is a worldwide epidemic associated with insulin resistance, type 2 diabetes, cardiovascular disease, MASLD/MASH, as well as major adverse liver events and CKD.
7.	**Leading Causes of Mortality in MASLD** PRELHIN Study: 619 MASLD Cases (median follow-up 12.6 [0.3-35.1] years) 	Importantly, cardiovascular disease is the number one cause of death in this population, followed by non-liver malignancy and liver disease.
8.	**Etiology Trends Among Adult Liver Transplantation Waiting List** Lack of effective therapies for ALD and MASH contribute to increasing disease severity, leading to cirrhosis and end-stage liver disease requiring liver transplantation 	In the United States, MASH is now a leading indication of transplantation, particularly in women.

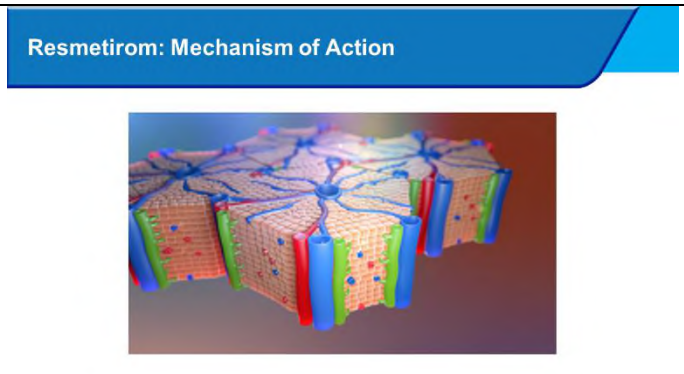
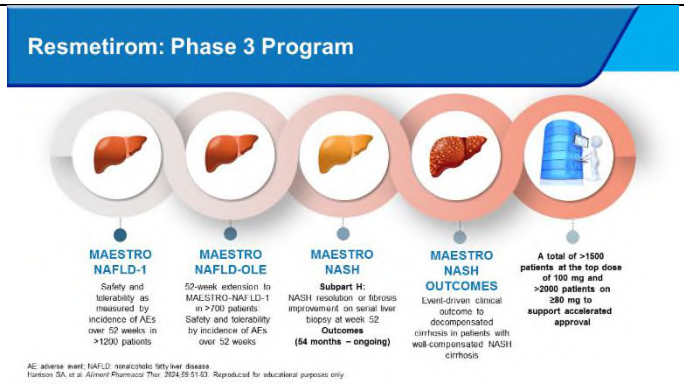
9.		And as we've been hearing, as I said, since the opening ceremony, the obesity prevalence is a global issue, and those regions denoted in blue represent areas where the prevalence is over 30%.
10.		When you look at the global prevalence of MASLD worldwide, that also is nondiscriminatory. You can see the numbers of MASLD in those, particularly in those with type 2 diabetes. And a recent meta-analysis in 2023 showed that about 62% of patients with diabetes have MASLD, 37% have MASH, and about 17% have advanced fibrosis.
11.		And this was a study done by Stephen Harrison looking prospectively at the prevalence of MASH in the general population. These were patients who were coming for screening colonoscopy, had metabolic risk factors, and were offered a biopsy. You can see that 38% had MASLD, 14% of whom had MASH, and that was higher in those who are of Latino-Hispanic ethnicity, were obese, or had diabetes. And looking to the right, when you had diabetes, obesity, and hypertension, the prevalence of MASLD was 74% and that of MASH, 46%.

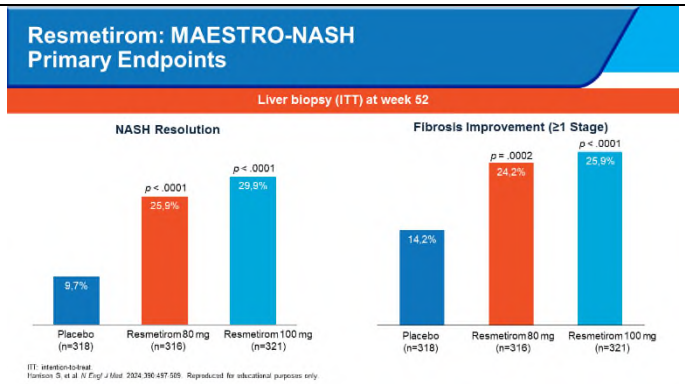
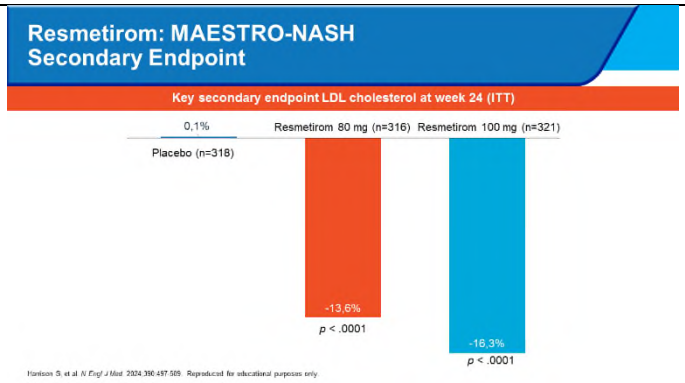
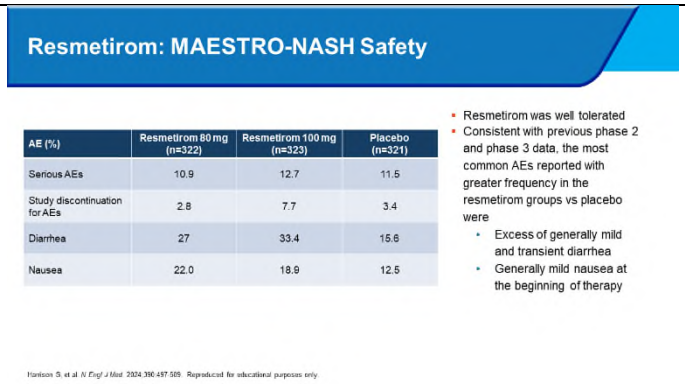
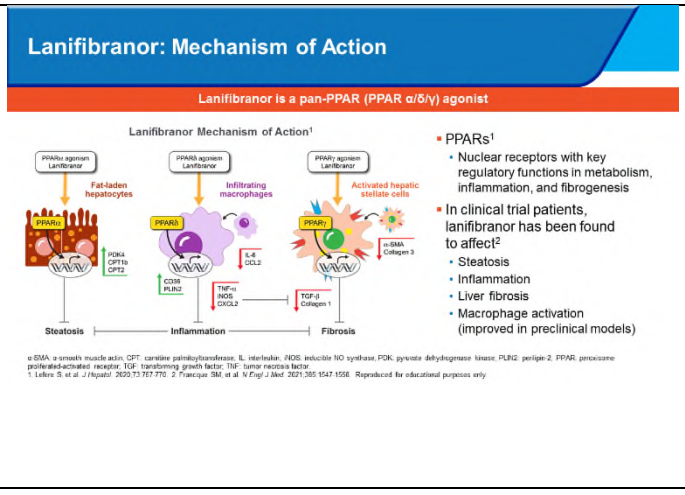
12.		And when you compare with a cohort about a decade ago, you can see that there's been an increase, not only of MASH, but more importantly, a 2-fold increase in those with stage 2 or 4 fibrosis.
13.		But then you could say “Oh, this is Texas, Stephen. This isn't the way it works around the rest of the world.” So this is a study by Dr. Castera and colleagues from the QUID-NASH investigators in France. This was a prospective study specifically looking at patients with diabetes: 713 patients were screened in a diabetes clinic and then referred to hepatology. Of those, 330 underwent liver biopsy if their ALT was persistently over 20 IU/L in women and over 30 IU/L in men. And you may say those are really low. And that's an important point to make here. The normal ALT is not just the range you see on the laboratory reports. As the obesity epidemic has moved forward, the average ALT has also gone up. So you really want to be concerned at lower level than what that range might be. In those patients who then underwent liver biopsy, 58% had MASH, of which 38% had advanced fibrosis, consistent with F3 and F4; 45% would be eligible for a therapy for non-cirrhotic MASH.

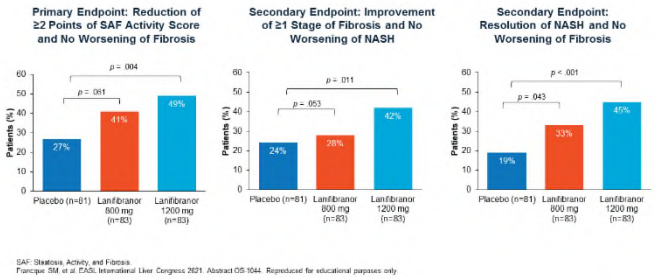
14.		And so, of course, we talk about lifestyle modifications. It's absolutely critical. A weight loss of about 10% is associated with fibrosis regression. Importantly, even in the absence of weight loss, exercise can be protective. For each 1000-step increment, there's a decrease of 15% in all-cause mortality. We talk about stopping alcohol, stopping smoking, stopping fructose, drinking 2 to 3 cups of coffee a day, and a Mediterranean diet. And then aggressive management of each of the comorbidities: obesity, diabetes, dyslipidemia, hypertension, and sleep apnea.
15.		And this is a classic Stephen slide, where you cannot out-exercise the fork.
16.		So we have a need for a holistic management approach for patients with NASH. While as hepatologists or gastroenterologists, we certainly are focused on NASH resolution and fibrosis improvement. But we can't forget about the lipid benefits of any kind of therapy and improving insulin sensitivity.

17.		So when we think about fibrosis, a liver-targeted therapy allows for a faster and stronger effect on fibrosis.
18.		So when you think about patients who do not have significant fibrosis—and remember fibrosis is the most important predictor of clinically meaningful liver-related outcomes. So early we want to tackle upstream weight loss strategies, whether that be pharmacologic or surgical. But as you progress to increasing stages of fibrosis, there's a need for more liver-directed therapy.
19.		And this is perhaps Stephen's most famous slide, where he talked about all of the kind of people who fell off the cliff and those who are still climbing. But thankfully, he was able to see the first FDA approval of resmetirom on March 14, 2024.
20.		So with that, I'm going to pass it on to my colleague, Dr. Bugianesi, to give us an outline on thyroid hormone receptor-β agonists and other disease-specific therapies. ***[Elisabetta Bugianesi, MD, PhD]*** Thank you. Good afternoon to everyone. Thank you for this kind introduction, and thanks to the sponsor for inviting me.

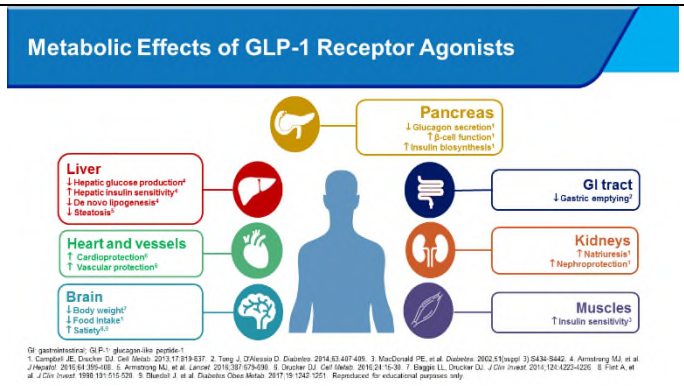
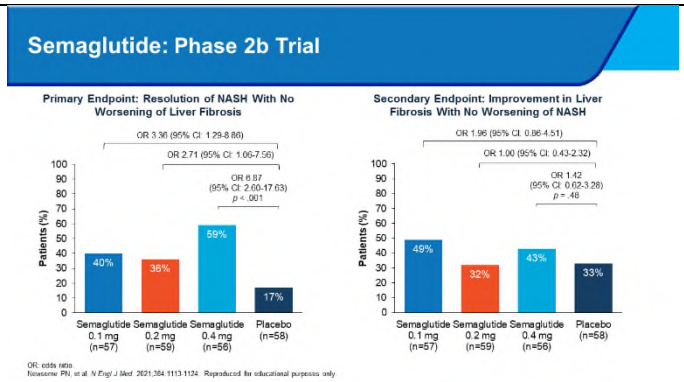
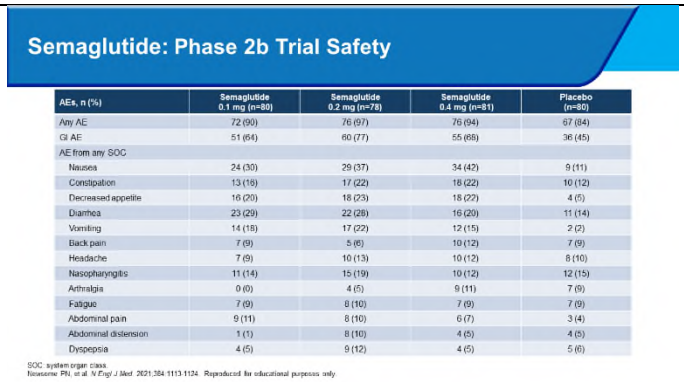
21.	**Ectopic Fat Deposition and Mitochondrial Dysfunction: Main Drivers of Liver Damage in MASLD**  MASLD: metabolic dysfunction-associated steatotic liver disease. Lee E, et al. *J Hepatol.* 2023;79:1540-1562. Reproduced for educational purposes only from Shulman GI. *N Engl J Med.* 2014;371:1131-1141.	So we know that the main drivers of liver damage in MASLD are either ectopic fat deposition coming from an expanded and inflamed adipose tissue that is leading to skeletal muscles as well as liver incremental free fatty acid. And in turn this leads to lipotoxicity defects in mitochondrial metabolism biogenesis alone leading to decreased fat oxidation. So many of the drugs that I'm going to discuss and that are currently in advanced phase for the treatment of MASH belong to these 2 mechanisms of action, either reducing the free fatty acid flux or improving the mitochondrial health.
22.	**Select Drugs With Phase 2b or Phase 3 (Interim) Results**  	So let's start with the oral agents.
23.	**Resmetirom: Mechanism of Action** Resmetirom is a THR-β agonist  ▪ Thyroid hormone[2,3] ▪ Important in maintaining metabolic homeostasis ▪ Acts via THR-β on the liver and kidneys ▪ In the liver, impacts de novo lipogenesis and cholesterol metabolism and promotes oxidation of FAs ▪ In clinical trial patients, resmetirom has been found to[4]: ▪ Lower liver fat ▪ Resolve NASH ▪ Lower LDL cholesterol ▪ Lower TGs ABCG5: ATP binding cassette sub-family G member 5; ACC1: acetyl CoA carboxylase 1; ChREBP: carbohydrate responsive element binding protein; CPT1: carnitine palmitoyltransferase 1; FA: fatty acid; FAS: FA synthase; FoxO1: forkhead box O1; G6PC: glucose-6-phosphatase; LDL: low-density lipoprotein; LDLR: low-density lipoprotein receptor; LXR: liver X receptor; ME: malic enzyme; NASH: nonalcoholic steatohepatitis; PGC1α: peroxisome proliferator-activated receptor γ coactivator 1α; PK01: phosphoenolpyruvate carboxykinase 1; SirT1: sirtuin 1; SREBP2: sterol regulatory element-binding protein-1c; SR-B1: scavenger receptor class B1; THR: thyroid hormone receptor; TRE: thyroid hormone response element. 1. Sinha RA, et al. *Trends Endocrinol Metab.* 2014;25:536-545. 2. Ritter MJ, et al. *Hepatology.* 2020;72:742-752. 3. Sinha RA, Yen PM. *Cell Biosci.* 2016;6:46. 4. Harrison SA, et al. *Lancet.* 2019;394:2012-2024. Reproduced for educational purposes only.	As Meena was saying, resmetirom is the first drug approved by FDA for the treatment of MASH with F2 and F3 fibrosis. Resmetirom is a thyroid hormone receptor-β agonist. The thyroid hormone receptor-β acts mostly in the liver where it impacts the de novo lipogenesis, cholesterol metabolism, and also promotes oxidation of free fatty acids. So in all the previous trials, resmetirom has been found to lower liver fat, resolve NASH, and lower LDL cholesterol as well as triglycerides.

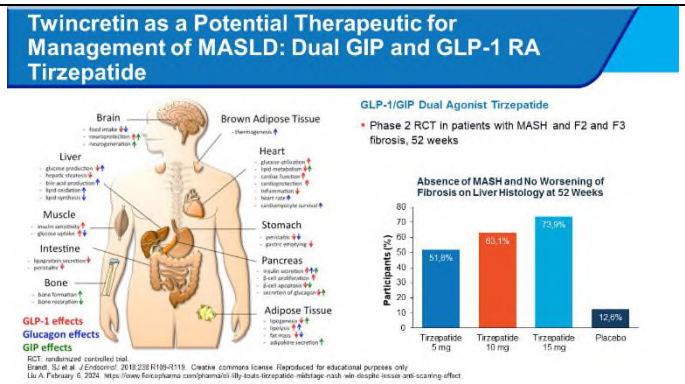
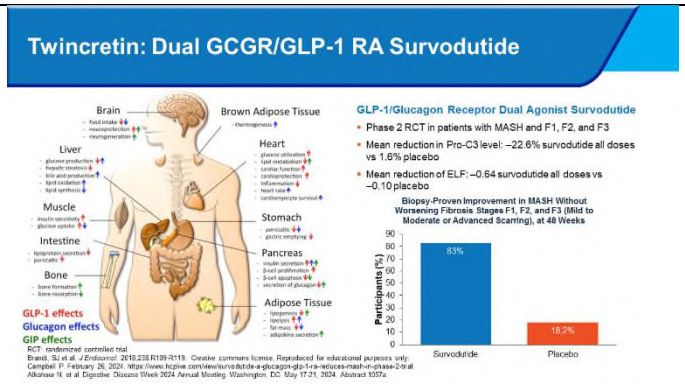
24.		But I'll better show you the mechanism of action. Thyroid hormone receptor-β agonists, or THR-β agonists, are small molecules designed to specifically act in the liver. These agents enter the nucleus within the hepatocyte and bind to THR-β to activate target gene expression, which mediates several metabolic pathways. First, enhanced mitophagy removes damaged mitochondria, while mitochondrial biogenesis generates new organelles. At the same time, reductions in reactive oxygen species, or ROS, limit mitochondrial damage and accumulation of toxic long chain lipids. Finally, increases in lipophagy generate free fatty acids that are then transported to mitochondria to produce ATP via β-oxidation. Overall treatment with a THR-β agonists is effective in reducing hepatic fat content and fibrosis.
25.		Well, this is a very important mechanism for mitochondrial health. And resmetirom has also a direct anti-fibrogenic effect. We know that the resmetirom phase 3 program is a very strong program because it started with safety and tolerability over almost 2000 patients and then continues with MAESTRO NASH, which is the trial that led to the FDA approval of this drug. And we'll continue also with MAESTRO NASH OUTCOMES, which is a trial in patients with well-compensated NASH cirrhosis. And it is an event-driven clinical outcome trial of compensated cirrhosis. So in the end, a total of more than 1500 patients at the top dose of 100 mg and more than 2000 patients at more than 18 mg to support accelerated approval.

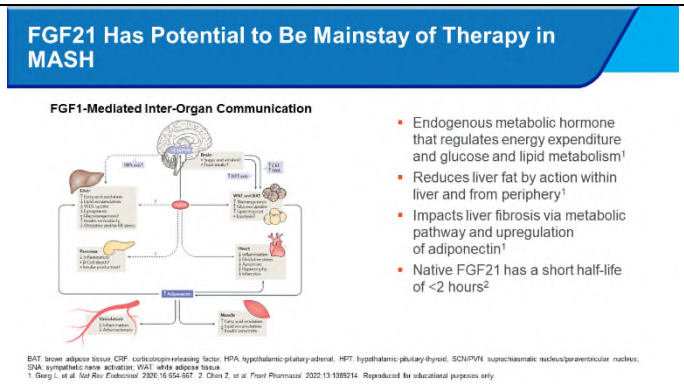
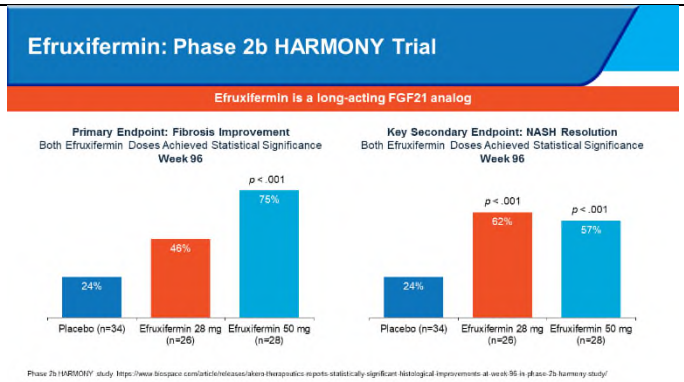
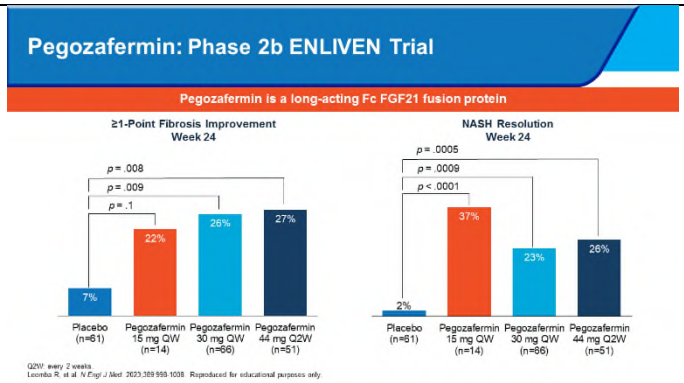
26.		And these are the results of the interim analysis of the phase 3 study that led to the FDA approval. So resmetirom was able to hit both NASH resolution and fibrosis improvement of at least 1 stage. You see that there is a nice dose-related response of up to 30% in patients in the resmetirom 100-mg arm for NASH resolution and up to 26% in the same dosage for fibrosis improvement of at least 1 stage.
27.		On top of that, resmetirom is also able to protect from cardiovascular disease by decreasing LDL cholesterol. You see compared with no change in placebo there is a 13.6% decrease at the resmetirom 80-mg dosage and a minor 16.3% decrease in the highest dosage of 100 mg.
28.		Now resmetirom is also a very well-tolerated drug. Generally patients suffer from mild and transient diarrhea that can be experienced at the beginning of the therapy but then disappear.
29.		Then let's go to another oral drug, lanifibranor. Lanifibranor is a pan-PPAR agonist (alpha, delta, and gamma). Thanks to the alpha action it increases the oxidation of free fatty acid. Thanks to the delta action it is able to decrease the activity of infiltrated macrophages. So decrease in pro-inflammatory cytokines and thanks to the gamma action, besides diverting the lipid from the liver to the deposed tissue is also able to inhibit collagen production in the activated hepatic stellate cells.

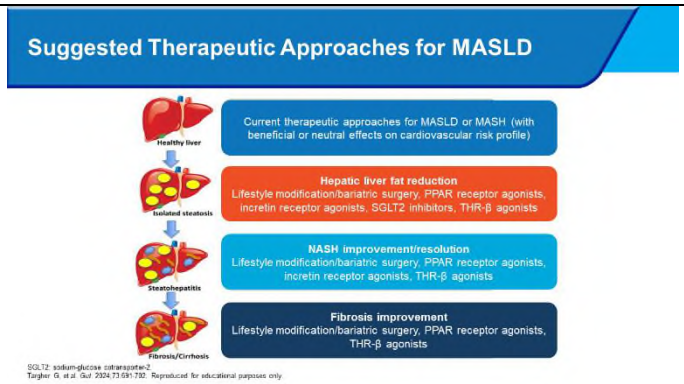
30.	**Lanifibranor: Phase 2b NATIVE Trial**  SAF: Steatosis, Activity, and Fibrosis. Francque SM, et al. EASL International Liver Congress 2021. Abstract OS-1044. Reproduced for educational purposes only.	And these are the results of the phase 2b NATIVE trial where again both endpoints of NASH resolution and fibrous improvement were met. Here this is a particular endpoint of reduction of at least 2 points of the SAF activity score. Without worsening of fibrosis, which was achieved in almost 50% of patients. And the same is true also for resolution of NASH and no worsening of fibrosis. In up to 45% of patients with lanifibranor 1200 mg. And a secondary endpoint of improvement of at least 1 stage of fibrosis was met in 42% of patients. Again at the highest dosage.
31.	**Lanifibranor: NATIVE Trial Safety** Francque SM, et al. N Engl J Med. 2021;385:1547-1558.	Well, the gamma activity usually leads to an increased body weight. Here the increase in body weight was lower compared with pioglitazone, is still there, but 2, 3 kg. Then there are also some diarrhea, fatigue, nausea, but no serious adverse events for this drug.
32.	**Drugs With Phase 2b or Phase 3 (Interim) Results** Injectable/infusion	And now let's move to the injectable drugs.

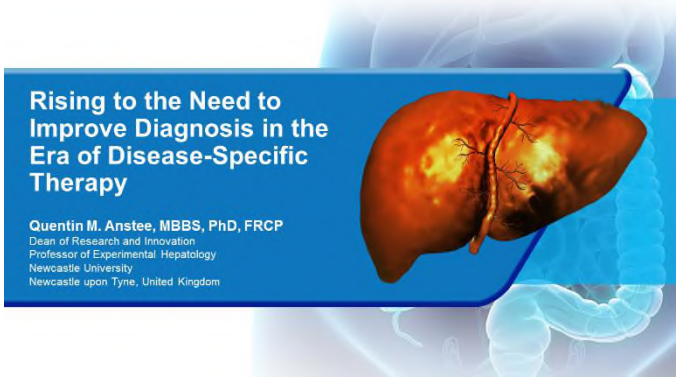
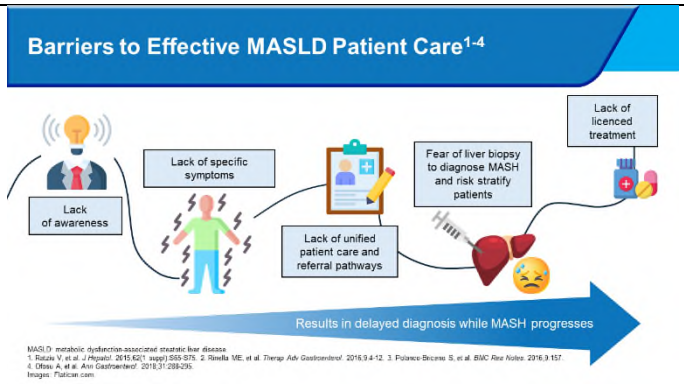
Most Frequent AEs, n (%)	Lanifibranor 1200 mg (n=83)	Lanifibranor 800 mg (n=83)	Placebo (n=81)
Diarrhea	10 (12)	8 (10)	1 (1)
Fatigue	11 (13)	3 (4)	8 (10)
Nausea	7 (8)	8 (10)	3 (4)
Weight gain	7 (8)	8 (10)	0 (0)
Peripheral edema	7 (8)	5 (6)	2 (2)
Headache	7 (8)	4 (5)	4 (5)
Abdominal pain	5 (6)	4 (5)	4 (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)

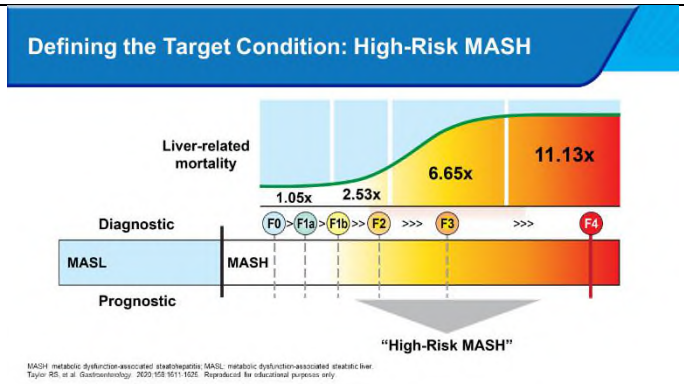
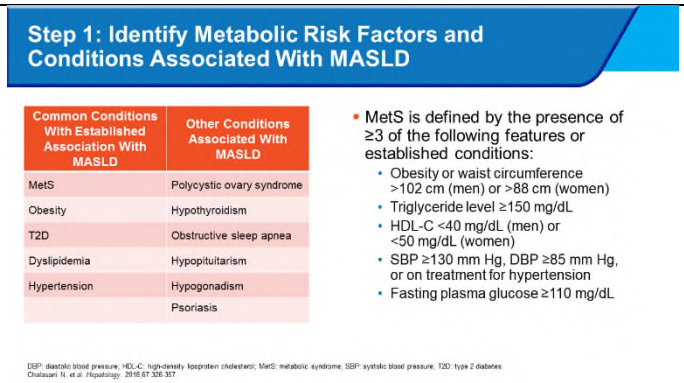
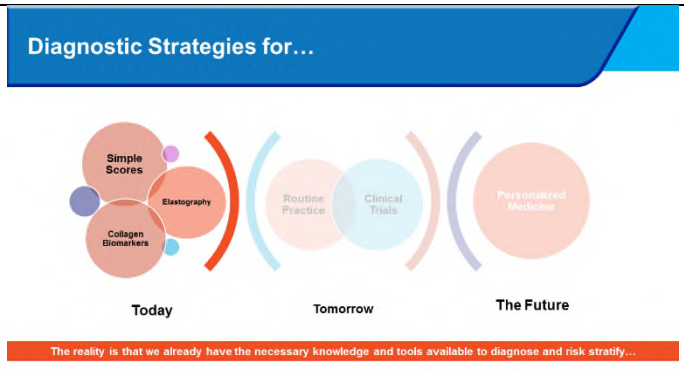
33.		Of course, you all know by now, GLP-1 receptor agonist is a pleiotropic drug that first acts to improve insulin sensitivity by increasing β-cell function, but also acts on the brain to decrease body weight by increasing satiety and decreasing gastric emptying. On top of that, the drug has also a cardioprotective effect and a nephroprotective effect.
34.		So these are the results of the phase 2 trial of semaglutide. The primary endpoint was resolution of NASH with no worsening of liver fibrosis. That was achieved in 59% of patients who were on semaglutide 0.4 mg subcutaneously once a day. But the secondary endpoint, which is improvement in liver fibrosis, was high enough, but not enough to be significantly different from the placebo arm. And the highest response rate was seen with semaglutide 0.1 mg daily (49%) compared with 33% in the placebo arm.
35.	 AEs, n (%) / Semaglutide 0.1 mg (n=80) / Semaglutide 0.2 mg (n=78) / 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 these drugs. Many gastrointestinal side effects, nausea, constipation, and of course decreased appetite is an actual mode of action of this drug. But again, no serious adverse events.

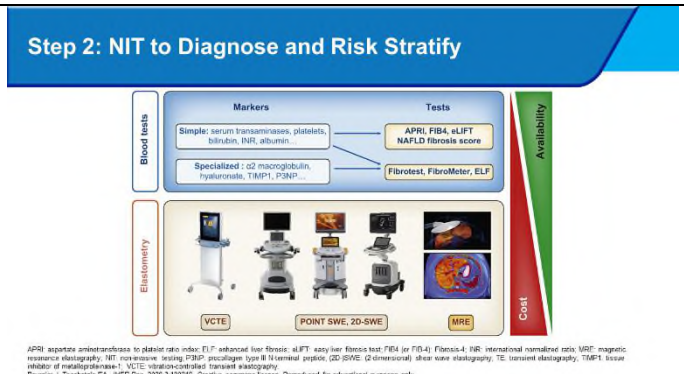
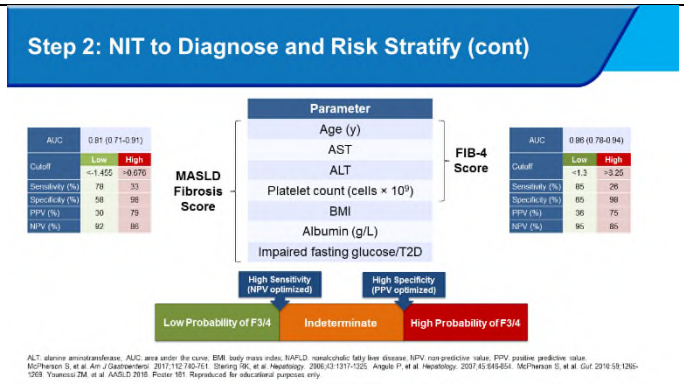
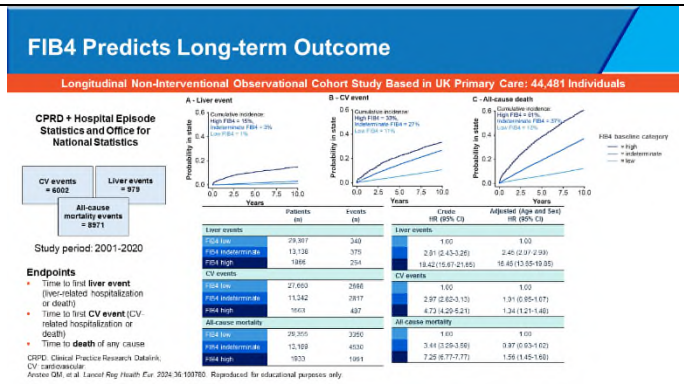
36.		And now let's go to the twincretin as a potential therapeutic for the management of MASLD. So one of the incretins that has been tested is tirzepatide, which is a dual GLP-1/GIP receptor agonist. Compared with the single action of GLP-1, adding GIP action improves the action of insulin secretion in the pancreas. So this is a more powerful GLP-1 receptor agonist and also in the adipose tissue, which improves the adipokine secretion, so the anti-inflammatory adipokine secretion. These are the preliminary results of the phase 2b randomized control trials where tirzepatide was given at 5, 10, or 15 mg weekly. And you see that after 52 weeks, up to 74% of patients in the highest dosage were able to achieve the absence of MASH without worsening of fibrosis. We know that there is a late-breaking abstract tomorrow and we are looking forward to the results on fibrosis.
37.		Survodutide. Survodutide is a dual GLP-1/glucagon receptor dual agonist. So adding the glucagon effects made the drugs much more effective in the liver because here it increases lipid oxidation, decreases lipid synthesis, increases bile acid production, and increases thermogenesis for the same amount of weight loss. So the amount of fat loss in the liver is higher compared with the single GLP-1 receptor agonist. So the phase 2b randomized controlled trials in patients with F1, F2, and F3 have been shown this morning in the general assembly, so the highest dosage of survodutide was able to improve MASH without worsening of fibrosis in 83% of patients, and this morning they also showed there was an improvement, a loss of at least 1 stage of fibrosis in 65% of patients.

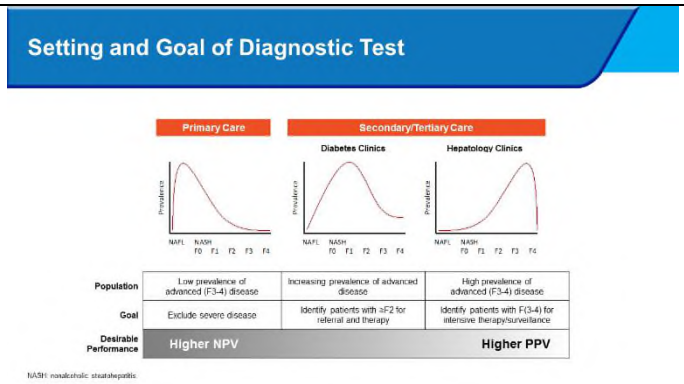
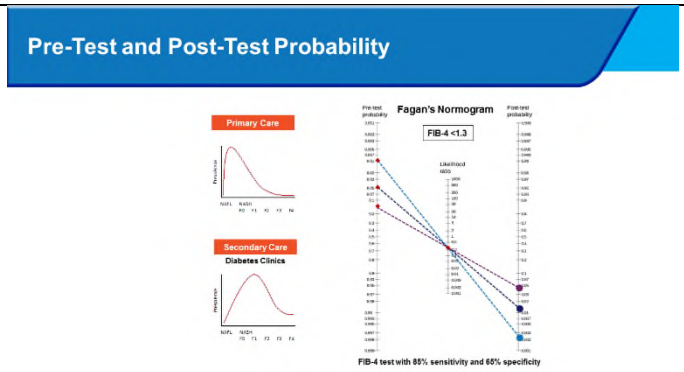
38.		FGF21 has a potential to be a mainstay of therapy in MASH. This is an endogenous metabolic hormone that regulates energy expenditure, glucose and lipid metabolism. It has direct action on the liver by increasing fatty acid oxidation, decreasing lipid accumulation, and decreasing oxidative and ER stress. It also acts on the heart where it reduces inflammation and oxidative stress and apoptosis. The only problem with the native FGF21 is that it has a short half-life, less than 2 hours.
39.		So this is the reason why long-acting compounds were synthetized, and this is efruxifermin. The results of the phase 2b HARMONY trial. The primary endpoint was fibrosis improvement, and this was achieved in up to 75% of patients in the highest subcutaneous dosage of 50 mg. The secondary endpoint was natural resolution and was achieved as well in 62% [28 mg] and 57% [50 mg] of patients with no difference between the 28 mg and 50 mg doses.
40.		And then pegozafermin is another long-acting FGF21 fusion protein. Again, fibrosis improvement was hit in 26% [30 mg QW] and 27% [44 mg Q2W] in the highest dose of pegozafermin and natural resolution at week 24. So this is earlier compared with the previous trial in up to 37% of patients in the lowest dosage 50 mg QW, although the numbers are still low.

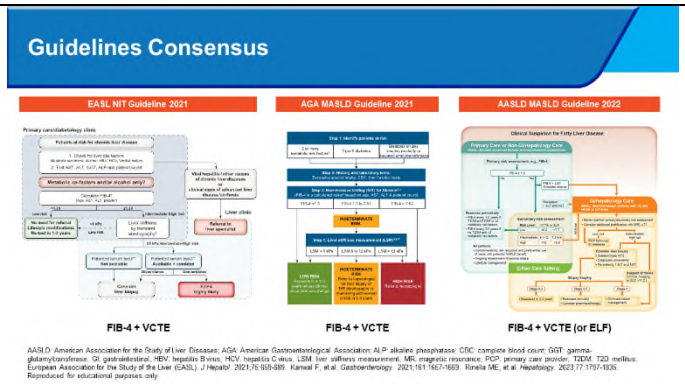
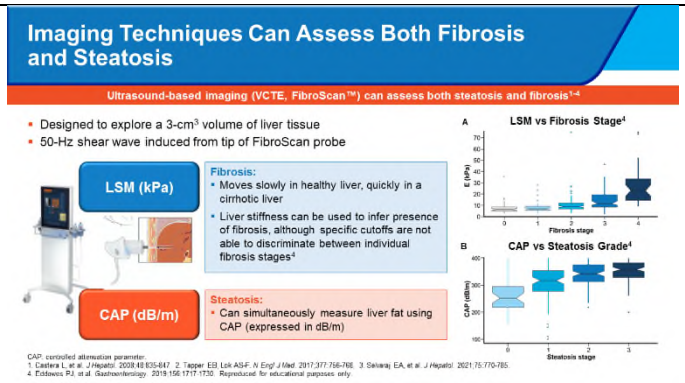
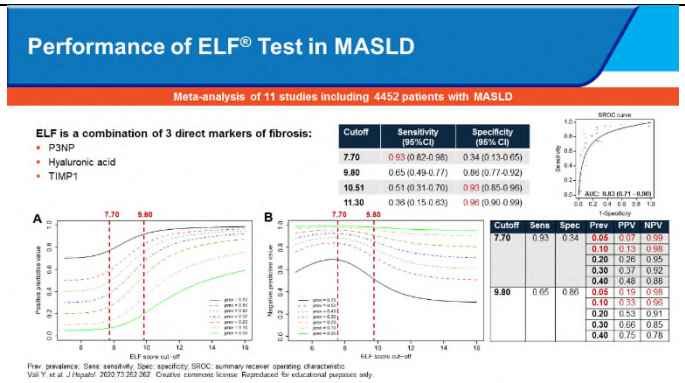
41.		So in the end, if we have a patient with MASH, of course we have to personalize, to tailor the therapy according to the degree of liver damage. So if we want to decrease just steatosis we have lifestyle modification, we have bariatric surgery according to the current indication. We have PPAR receptor agonist; incretin and twincretins; SGLT2 inhibitors, but just in type 2 diabetes; and of course resmetirom. If we want to improve NASH or resolve NASH, again, lifestyle modification, but it is a little bit harder to maintain at least this improvement. Bariatric surgery, but in a limited number of patients, pan-PPAR receptor agonist incretin and twincretins and again resmetirom. If you want to achieve fibrosis improvement, this is the most ambitious target for lifestyle modification. It can better be achieved by bariatric surgery, pan-PPAR receptor agonist, resmetirom, and now let's see for the twincretins. This is something that we need to sort out also with the presentation at the late-breaking session tomorrow. Current therapeutic approaches for MASLD or MASH with beneficial or neutral effects on the cardiovascular risk profile—there are currently no licensed treatments for MASLD or MASH. The figure summarises the evidence mainly derived from phase 2 or phase 3 randomized placebo-controlled trials of current therapeutic approaches showing promise in the treatment of this common and burdensome liver disease, in terms of improvement in liver steatosis, steatohepatitis, or fibrosis. Licensed treatments for type 2 diabetes (eg, GLP-1 receptor agonists, pioglitazone, or SGLT2 inhibitors) are among the most promising treatment options for MASLD or MASH and effectively also decrease the future risk of fatal and nonfatal CVD events.

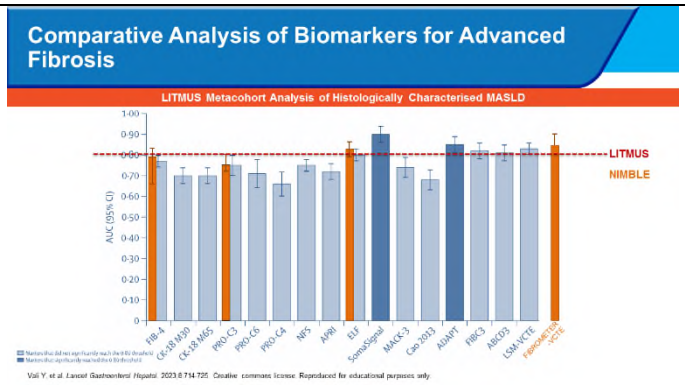
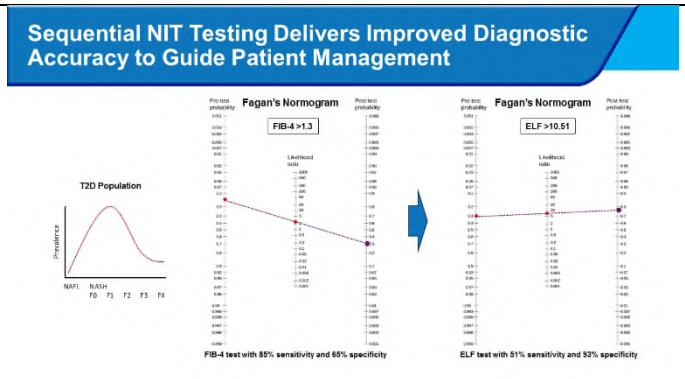
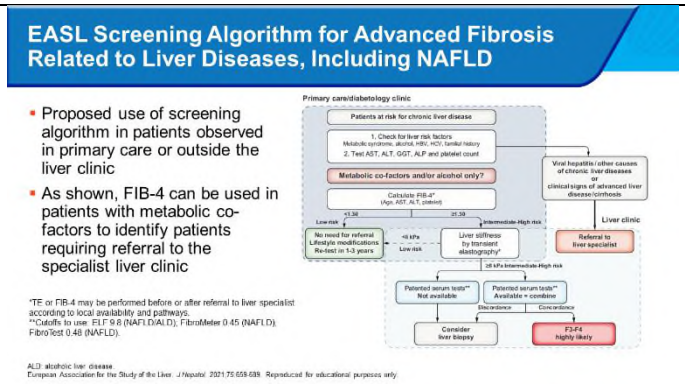
42.		And I thank you so much for your attention. And it's my pleasure to introduce Prof. Quentin Anstee to talk about the rising to the need to improve diagnosis in the era of disease-specific therapy. ***[Quentin M. Anstee, MBBS, PhD, FRCP]*** Thank you very much indeed. It's an absolute pleasure to be here. What I think we can all agree is one of the exciting turning points in the journey with MASLD, because for the first time, we're starting to see, as Prof. Bugianesi demonstrated, a burgeoning pipeline of new medication coming through which gives real hope to our patients that treatments will be available in the not too distant future in Europe, as they already are in the North America. But of course, all of that is academic if we don't find the patients who need to be treated and identify them.
43.		My disclosures were, I think, shown at the start, but they're available online. So we've got to think about what are the barriers, what's actually preventing us treating patients with MASLD right now. And there are a number of checkpoints along the way that are holding us up. There are issues with a lack of awareness. We know that MASLD doesn't have very many pathognomonic-specific symptoms. We know in many countries right now, there aren't unified care pathways or referral pathways to target individuals at high risk and get them to see the necessary specialists. And then there are other systematic issues. There's a fear of liver biopsy. Many of us here in the room are hepatologists, we do liver biopsies. I think we can all agree that it is a very useful and important diagnostic tool, but we probably do not want one ourselves. And I think that is the thing we need to build on

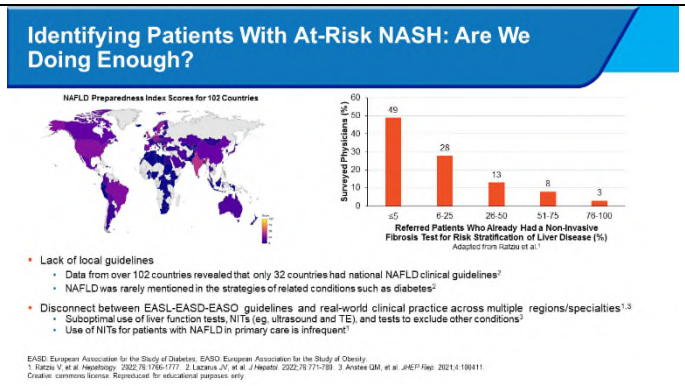
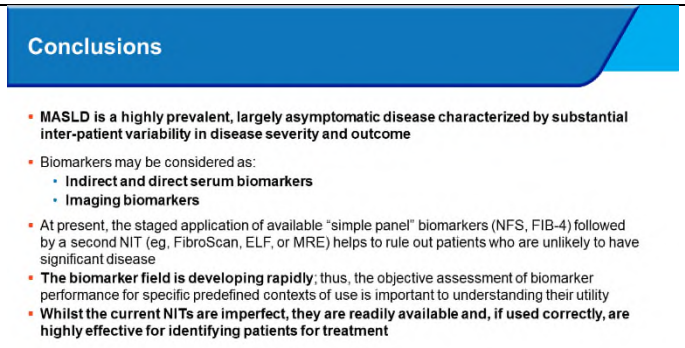
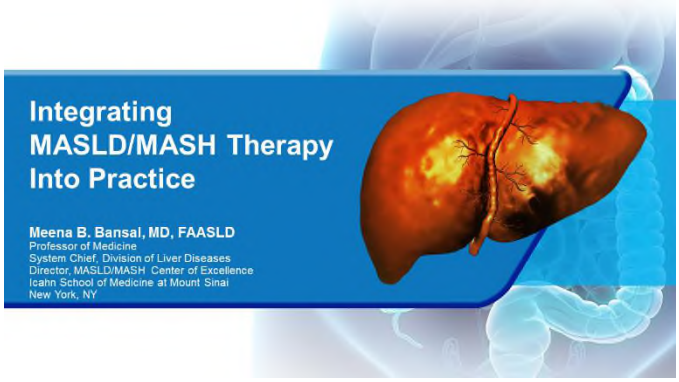
		here. And then, of course, we need licensed treatments that we can use. So what we need to do is think about how we can knock down those barriers and go beyond it.
44.		The first step in that is to understand which patients we're looking for. What is our target condition? And the target condition here is high-risk MASH. In other words, patients who are pre-cirrhotic with F2 or F3 fibrosis and have active steatohepatitis. And the reason we want to target those individuals is very nicely summarized here. It's because as that fibrosis increases in the liver from F2 to F3, that's when the increased risk of liver-related mortality creeps in. So that's the sweet point where we can begin to affect change. And so we need to work to find patients with that.
45.		The first step is to appreciate the risk factors that drive MASLD in terms of the features of the metabolic syndrome. And I always say "I count them off on my fingers". Obesity, type 2 diabetes, dyslipidemia, hypertension. When I get to about 2, I'm thinking "This patient has a very high probability of MASLD and is also very likely to have the MASH, the inflammatory, progressive form of the condition". But there are also a number of other associated conditions that are relevant.
46.		Now, the next thing, then is, well, what's our approach to screening these patients? How are we going to find and diagnose the patients? And the short answer is, we've got effective tools today. Yes, we can talk about what there is tomorrow and personalized medicine in the future, but the reality is that right now, we have the necessary tools and knowledge. We just need to put them into practice and employ them. So don't let—what's the word? Perfection be the enemy of good. We've got the right tools, let's

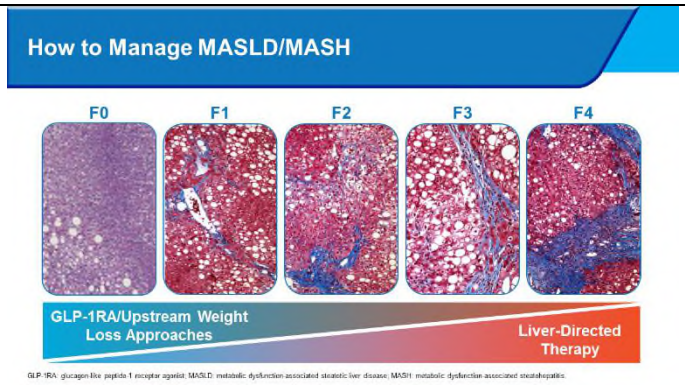
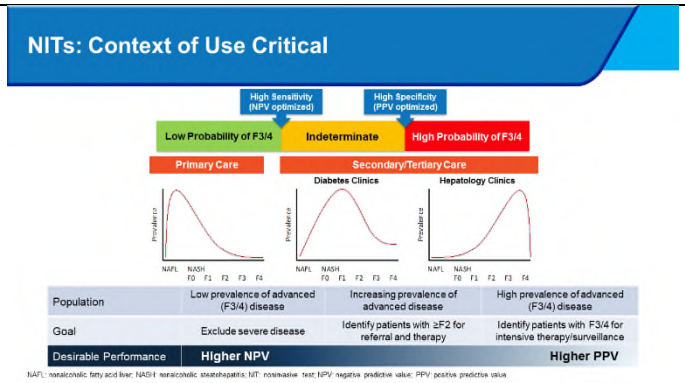
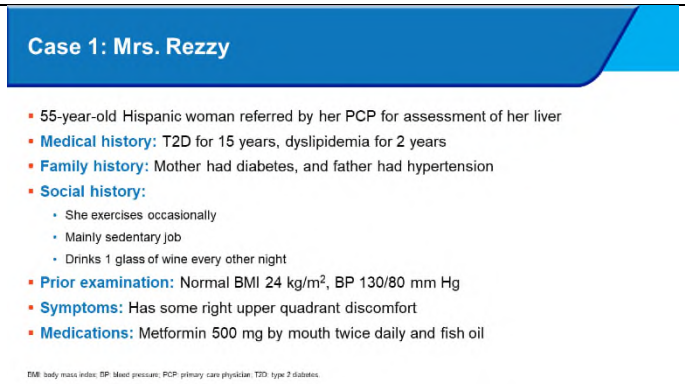
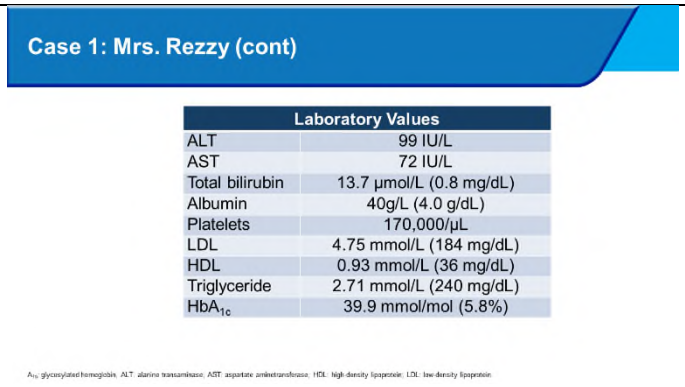
		start using them now.
47.		And this is just a very quick summary of what we've got. So, we have the blood test, the blood-based noninvasive tests. They can be things as simple as the FIB-4 score. And I'm going to talk about that a little bit more in a moment. And then we also have more advanced noninvasive tests, such as the ELF test, PRO-C3, et cetera, et cetera, FibroMeter and so on. And then elastometry, whether that's FibroScan or any of the other technologies that are now available, going all the way through to MRE. So we have a huge range of options in our war chest, but we can pick out a few that really work for us.
48.		Let me start off with the FIB-4 score, and the reason I'm such a proponent for this one is because it's cheap and it works. It's got a very high negative predictive value, so it's great for reassuring our patients that right now they don't have advanced fibrosis. And that would be using the 1.3 cutoff if you're under the age of 65. And there are data from our group demonstrating a cutoff of 2 if you're over the age of 65.
49.		Beyond the performance as a diagnostic test, we also know that FIB-4 is a prognostic tool. These are data from Europe, from a large UK primary care database, demonstrating that FIB-4 stratification into low, intermediate, or high categories is prognostic not only for liver-related events, but also cardiovascular events. And better than that. And crucially, it isn't a one-off shot with a test like this. We can repeat it 12 months later, and when you do that, you can refine and adjust your hazard ratios to improve your prognostication. So this is a monitoring tool and it costs peanuts. So this is a really useful thing to bear in mind.

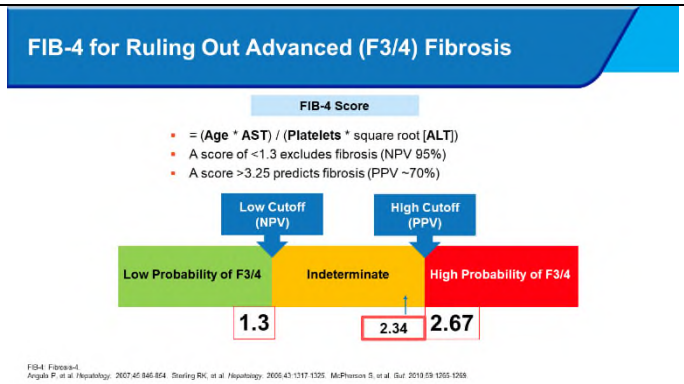
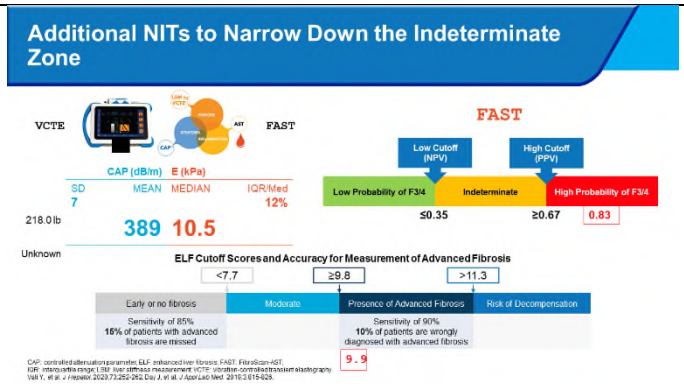
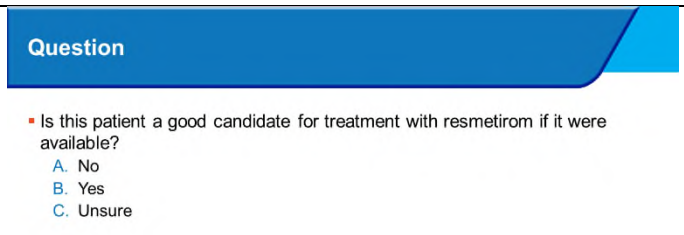
50.		The next thing we need to think about is where we're using the test, because the prevalence of the disease will change dramatically whether we're in the primary care setting, secondary care, tertiary care, if we're in a diabetes clinic, and so on. And we need to think about that because it influences test performance. It also changes what questions we want to answer. In primary care, by and large, we want negative predictive value. We want to be able to reassure people. In secondary and tertiary care practice we want to be picking out the people we focus specifically on. And actually, that's a key feature to think about.
51.		Let me just show you what I mean. This is the Fagan's Normogram that converts your pretest probability—in other words, the prevalence in a particular population—through the performance of a specific biomarker, to the post-test probability—in other words, letting you know what it means to an individual patient. And if we look on the left-hand side of that as we go up, hopefully go up. There we go, go up as the prevalence increases. Here I'm showing you between 1% and 15% pretest probability. You can see that the performance increases reciprocally with that. So the more of the disease there is in the population you're sampling, the better the test will perform as a pretest probability. It's a bit like that concept. When I used to take my son fishing many years ago, I took him to one of those heavily stocked ponds where you could virtually walk across the water because there were so many fish in it. And this is what we're doing here. We add reaching the population.

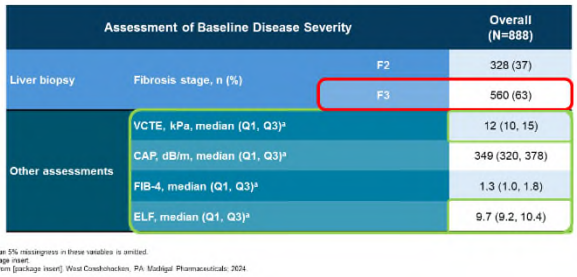
52.		And I'm going to come back to this because it's crucial. Across all the guidelines, whether you're in Europe or North America, they all use a 2-test probability, starting with FIB-4, simply because it sets up the next test to perform well.
53.		And what is the next test we can use? Well, we have some options again. Two of the most widely used are liver stiffness. Here I'm showing you the FibroScan data, which gives us, again, diagnostic and prognostic information.
54.		And then the other one that's also very useful is the ELF test, a circulating biomarker, again, with data for both diagnostic and prognostic use. So these are excellent second-line tests. And what these graphs are showing you, is again, exactly the same features I was describing. As the pretest probability goes up, the negative predictive value begins to reduce and the positive predictive value begins to increase. And one of the key things to just pull out here, if you look on the right-hand side, if you look at the prevalence column in red, we really need to get to a prevalence level of 20% to 30% before the positive predictive value of a test, whether it's ELF or FibroScan, really peaks.

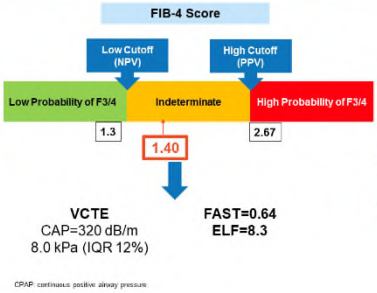
55.		And that's an important principle, because whether you're looking at data from LITMUS in Europe or NIMBLE from North America, the reality is most of the fibrosis biomarkers we have perform relatively similarly relative to histology. It's not that one of them is better than another, it's how we use it. We need to work smarter and better.
56.		And that's why a 2-step process works so well, which is demonstrated here, because this is working through what would happen if we applied FIB-4, followed by ELF test, starting maybe, in a type 2 diabetes clinic population, where, let's conservatively say, 15% of them had advanced liver disease. FIB-4 will bring us up to a post-test probability of about 30%, which I've demonstrated to you is that key deflection point where the next test works so well. And going from that through with ELF test, we see, we get ourselves up to a post-test probability of almost 80%. So it's working that way to play the statistics to make this a more effective diagnostic principle, which is the basis here.
57.		I'm showing you the EASL guidelines accepting metabolic risk, moving on to FIB-4, using that to set us up for a high-performing second-line test to risk stratify individuals.

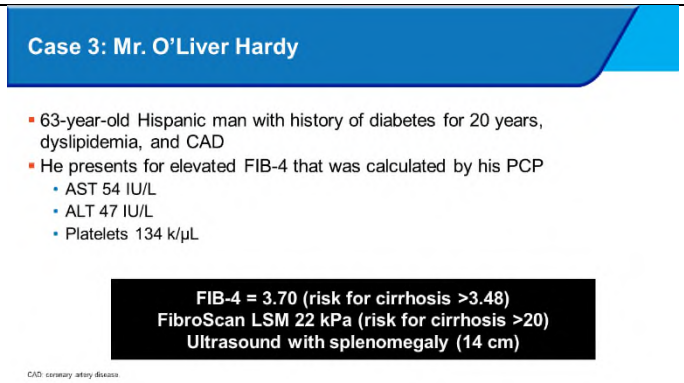
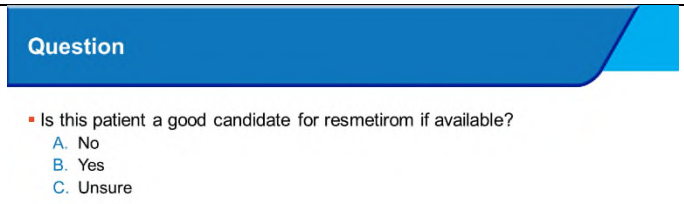
58.		The final point I want to make in the last few seconds is, of course, that we need not only the right tools, but we need the right ecosystem, the right infrastructure to support us. This is work that we did with Jeff Lazarus a few years ago, where we surveyed first of all European countries for readiness to deal with the challenges of MASLD, and then moved on to a worldwide survey. And one of the key things—and we all need to go home from this meeting and advocate with our colleagues—is to ensure that we have the right care pathways in place, the right regional and national infrastructure to allow us to deliver the best care we possibly can for our patients.
59.		So I'm going to leave it there and just conclude with the fact we have the right tools. We just need to use them well. And thank you all very much indeed for your attention.
60.		***[Meena B. Bansal, MD, FAASLD]*** Okay, now we're going to engage you a little bit. So I know everybody's had their food, they're probably settling in, but we want you to engage with us now. So we're going to have some cases where you actually scan the QR code and vote, and we'll have a robust discussion on managing patients.

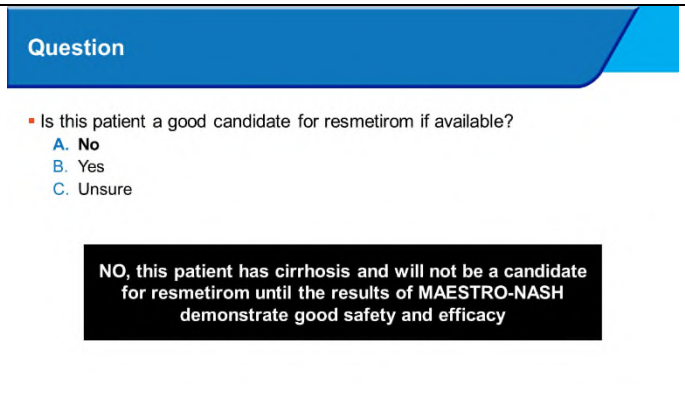
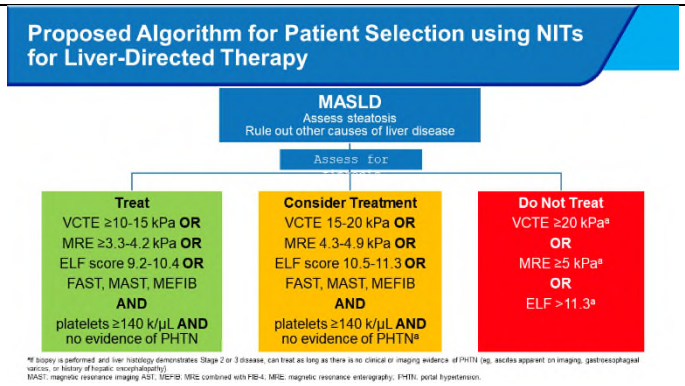
61.		So, remember, some of the key concepts were that early on, we need to have upstream interventions that focus on weight loss approaches, whether that be pharmacologics or whether that be surgical. But as we move down that fibrosis progression, we need to think about liver-directed therapy, as liver fibrosis is the most important predictor of liver-related outcomes.
62.		And as Dr. Anstee just pointed out, context of use is absolutely critical. So you need to know, what is the population that you're looking at when you apply a test? And I think the other most important message was that sequential testing is the best way for us to identify with a higher positive predictive value of those likely to have advanced disease.
63.		So we start with the first case. So, Mrs. Rezzy. She's a 55-year-old Hispanic woman referred by her PCP for assessment of her liver. She's had type 2 diabetes for 15 years, dyslipidemia for 2 years, mother had diabetes, father had hypertension. She exercises occasionally, she drinks occasionally, has mainly a sedentary job, normal BMI, blood pressure 130 over 80, has some mild upper quadrant discomfort. Metformin, 500 mg, she takes twice daily, and fish oil.
64.		When you look at her liver enzymes, you see that both her AST and ALT are elevated. Her synthetic function is fairly well preserved. She has elevated LDL and triglycerides, low HDL, and her hemoglobin A_{1c} is reasonably well controlled.

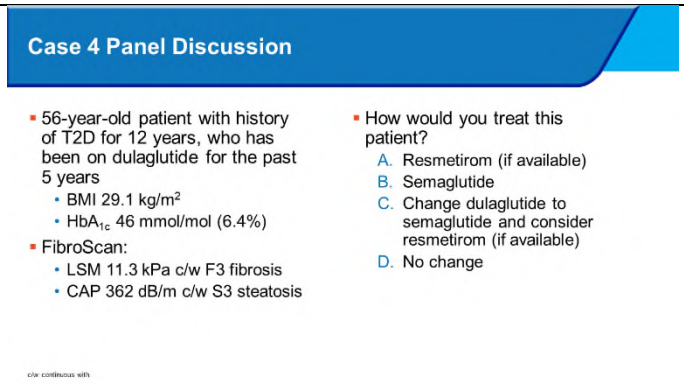
65.		So what's the first test we do? Obviously, we first do a FIB-4 test. And in her, her FIB-4 value was 2.35. Still in the gray zone, but at a higher level.
66.		So the next thing we want to do is our sequential testing. So Dr. Anstee said you use what you have available. What we see most frequently is VCTE and ELF. So in this case, her VCTE was 10.5 kPa. Importantly, you want to look at that IQR of less than 20% to know that you have a good study. Her CAP is 389 dB/m, consistent with significant steatosis. Now, if you use the FibroScan app, there's other scores on there, too. One such score is the FAST score, which now brings in that inflammation or that at-risk MASH component. And so the FAST score has a rule in cutoff of about 0.67. And in her case she had a 0.83. And then her ELF score was 9.9. And remember, this is both a little bit diagnostic, but also prognostic, more importantly. So greater than 9.8 carries a risk of progression to cirrhosis and reflects the presence of advanced fibrosis.
67.		So is this patient a good candidate for treatment with resmetirom, if it were available? Okay, so we have 64% feel that it is a good choice, 28% no, and 8% are unsure. Thoughts from my panel? She has her glycemic indices are okay, she's non-obese. She has evidence of advanced fibrosis. So this is somebody who would benefit from a liver-targeted therapy.

68.	**PI: Baseline Disease Characteristics From the MAESTRO-NASH Trial With Resmetirom**  [a]Less than 5% missingness in these variables is omitted. PI: package insert. Resmetirom [package insert]. West Conshohocken, PA: Madrigal Pharmaceuticals; 2024.	And now look at the, let's look at the baseline characteristics of the patients that were in the registrational trial or the MASH trial, MAESTRO NASH. Yes, sorry. So they had 63% had F3 fibrosis. The median kPa was 12 with a range of 10 to 15 kPa. So she is in that range. That's the interquartile range, elevated CAP. And the ELF score, hers was 9.9. And the median ELF in the study was 9.7.
69.	**Question** ▪ Should we consider adding any additional therapy at this time? A. GLP-1RA B. Statin C. SGLT2 inhibitor D. No SGLT2: sodium-glucose cotransporter-2	Okay, should we consider any additional therapy at this time? Okay, so 27% would start a GLP-1 receptor agonist. But what are we treating? So you're talking about. She's not obese. Her diabetes is well-controlled. So what are we treating with that? But certainly to be considered, statin, we talked about how it's really important to look at dyslipidemia in these patients, and one of the reasons, including this patient where she wasn't started on a statin because of elevated baseline liver enzymes, and we see this all the time, you cannot fear the liver enzymes. These patients do fine on a statin and should get a statin. The determination of starting a statin should be on their cardiovascular risk score. So there's a number of calculators out there. In the United States, there's the ASCVD risk score, and in Europe, there's the European Society of Cardiology, which actually is regional specific, as you guys may know. And so you want to calculate the risk of having a cardiovascular event in the next 10 years and then determine the need for statin therapy based on that SGL2 inhibitor. Again, her diabetes is under good control, and we can have some discussion at the end as well.

70.	**Case 2: Mr. Semastat**  Aged 48 years BMI=35 kg/m² WC=100 cm BP=130/80 mm Hg **Laboratory Test** / **Values** Liver function tests: **ALT 110 IU/L; AST 74 IU/L** ALP 60 IU/L; albumin 44 g/L (4.4 g/dL); bilirubin 8.55 µmol/L (0.5 mg/dL); BUN 3.57 mmol/L (10 mg/dL); creatinine 0.057 µmol/L (0.65 mg/dL) Lipids: **Total cholesterol 7.57 mmol/L (293 mg/dL); HDL 1.47 mmol/L (57 mg/dL); LDL 4.86 mmol/L (188 mg/dL); triglycerides 3.05 mmol/L (270 mg/dL)** Blood sugar: **Glucose 5.1 mmol/L (91 mg/dL); HbA_{1c} 58.5 mmol/mol (7.5%)** CBC: WBC 5.5 × 10^9/L; hematocrit 37.8%; platelets 241 G/L Medications: Albuterol, metformin, spironolactone (50 mg) Viral hepatitis: HCV-; HBcAb+; HBsAg-; HBsAb+ Medical history: T2D; sleep apnea Social history: Denies alcohol use and smoking ALP: alkaline phosphatase; BUN: blood urea nitrogen; CBC: complete blood count; CRP: C-reactive protein; HBcAb: hepatitis B core antibody; HBsAb: hepatitis B surface antibody; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; WBC: white blood cell; WC: waist circumference	Okay, let's go to the second case, Mr. Semastat. He is 48 years old, BMI of 35 kg/m^2, liver enzymes are elevated. He's got some dyslipidemia. His hemoglobin A_{1c} is not adequately controlled. He's on metformin. Other comorbidities include sleep apnea.
71.	**Fibrosis Risk Stratification and Comorbidity Assessment**  FIB-4 Score Low Cutoff (NPV) High Cutoff (PPV) Low Probability of F3/4 Indeterminate High Probability of F3/4 1.3 1.40 2.67 VCTE CAP=320 dB/m 8.0 kPa (IQR 12%) FAST=0.64 ELF=8.3 CPAP: continuous positive airway pressure ▪ Diabetes and obesity • HbA_{1c} needs better control ▪ Dyslipidemia • ASCVD Risk Score=8.4%-9.9% • ESC SCORE-2 Diabetes-11% ▪ Hypertension • Reasonable control ▪ Sleep apnea • Evaluation for CPAP	So we first say fibrosis, hepatic fibrosis risk assessment. So in his case, his FIB-4 score is a 1.4, again in the indeterminate range. Sequential testing, VCTE of 8 kPa, consistent with F0/F1. The FAST score is below the rule in cutoff and the ELF is the below the high positive predictive value. So, from a liver perspective, he falls on that left-hand side of the spectrum, right? So now we say, okay, what are the other comorbidities? So, he's got both diabetes and obesity. His hemoglobin A_{1c} needs better control. In calculating his cardiovascular risk score, he's between 8.5% and 10% on the ASCVD risk score for the European score, I used Italy as the prevalence risk here. So he's got an 11% chance of having a cardiovascular event in the next 10 years, reasonable control for hypertension, and then the sleep apnea you want to consider for CPAP, although if he has substantial weight loss, it may improve in and of itself.
72.	**Question** ▪ Should we consider adding any additional therapy at this time? A. GLP-1RA B. Statin C. GLP-1RA + statin D. SGLT2 inhibitor E. SGLT2 inhibitor + statin F. Resmetirom (if available)	So we going to start voting. Should we consider adding any additional therapy at this time? Yes. So, 70% GLP receptor agonist and statin. He's almost like a poster child, right? He's got obesity, needs better glycemic control, doesn't have advanced fibrosis so would benefit from a GLP-1 receptor agonist; also has sleep apnea. So again, GLP-1 kind of poster child. In addition, he has high risk of cardiovascular

		disease and so you would want to have statin therapy.
73.		Okay, Mr. O'Liver Hardy, a 63-year-old Hispanic man with a history of diabetes for 20 years, dyslipidemia, and CAD. He presents for elevated FIB-4 that was calculated by his PCP, AST 54 IU/L, ALT 47 IU/L, and platelets of 134 k/µL. So this is kind of like the FIB-4 sniff test, right? You just, like, look at this patient. And the key is, is if you saw in the FIB-4 calculation, AST is weighed heavier than ALT. So when you see the AST greater than ALT, you almost know, okay, this person's FIB-4 is likely going to be higher. Secondly, you see these platelets of 134 k/µL, so you're very concerned. He's kind of got the cirrhosis sniff test. So his FIB-4 calculation is 3.7 and risk of fibrosis at 3.48 has a high positive predictive value. His FibroScan is 22 kPa. Again, greater than 20 is highly predictive of cirrhosis. And then you want to get a sense he's already got low platelets, right? So you're concerned about portal hypertension. So ultrasound with splenomegaly. So he's got splenomegaly. So this is all concerning for portal hypertension.
74.		So is this patient a good candidate for resmetirom, if available? No. Yes and unsure.

75.		No, this patient has cirrhosis and will not be a candidate for resmetirom until the results of the MAESTRO NASH demonstrate good safety and efficacy. So remember, this is for non-cirrhotic MASH consistent with F2, F3 not indicated in patients with cirrhosis at this time.
76.		That being said, there's a group that's trying to put together guidance for liver-directed therapies and NITs. This is still in draft form, but I'm sharing it with you here today. So if you look in the green box, what's that sweet spot? That Goldilocks area, for treating non-cirrhotic MASH. You don't want to treat too early. We need to have upstream therapies for them. So VCTE between 10 to 15 kPa if you have availability for MRE, we do in the United States. I'm told it's mostly clinical trials and research here, but if you have it 3.3 to 4.2 kPa, an ELF score between 9.2 and 10.4. And there's some combination. I mentioned FAST, but then there's some combination tests that can be done if available to you. And no evidence of portal hypertension. So platelets greater than 140 k/µL and no clinical signs of portal hypertension, splenomegaly, etc. Now you come to the middle box, kind of like you might want to put. There's certain patients you might want to push the envelope on a little bit. And we know that also in patients with obesity, that VCTE can be higher. So you could consider treatment for a liver-directed therapy between 15 and 20 kPa or an MRE between 4.3 and 4.9 kPa. ELF score between 10.5 and 11.3. And again, no evidence of portal hypertension. And do not treat anybody with cirrhosis or concern for portal hypertension.

		In patients with MASLD (steatosis confirmed on imaging or suspected by the presence of cardiometabolic risk factors and exclusion of other causes of liver disease), fibrosis burden should be approximated using NITs, with the goal of targeting those with clinically significant fibrosis (F2 or F3) and excluding those likely to have cirrhosis or portal hypertension. Phosphatidylethanol (PEth) measurement should be considered to identify those who may have MetALD or ALD. If liver biopsy is available and demonstrates stage 2 or 3 fibrosis, NIT-based parameters can be overridden, provided there is no clinical or imaging evidence of portal hypertension.
77.		Okay, now I'm going to ask my panel. I'm going to ask my expert panel faculty to contribute here. So you guys are off the hook. You can rest. No more QR codes. These are going to be rapid-fire cases that should stimulate discussion. We also welcome anybody from the audience who wants to give us some input or ask a question to do so. So, 56-year-old patient with a history of type 2 diabetes for 12 years. They've been on dulaglutide for the past 5 years. Still in the overweight grouping. BMI of 29 kg/m^2, reasonable glycemic control. FibroScan, the liver stiffness is 11.3 kPa, consistent with F3 fibrosis, significant steatosis. How would you treat this patient? All right, Dr. Anstee, tell us what you think. ***[Quentin M. Anstee, MBBS, PhD, FRCP]*** The pressure's on now. Thank you very much indeed. So we've got a middle-aged man, he's got diabetes, he's overweight, and his diabetes is actually suboptimally controlled. The noninvasives with the FibroScan suggest that

there is moderate or advanced fibrosis. We don't know if his statins, if his lipids are controlled, but one thing I would say is, I would definitely be doing that. I think it's a really important message. Most of our patients are going to die of cardiovascular disease, and so we need to be good at this. So that's the first thing I'd be thinking about in terms of our options there. I would be changing the dulaglutide to semaglutide based on the current evidence, although it's really important to remember that there are no licensed medications for fatty liver disease in Europe, and so we are doing that off-label. If we do make that change, and we're really looking to treat his diabetes when we make that change. And so I would be wanting to optimize the diabetic control for those reasons. I think if I did have a liver-targeted therapy like resmetirom available to me, I'd also be considering that as well. So I'm probably looking at something along those lines. But my reasons for the semaglutide switch would be to improve the diabetes, even though it has an additional benefit.

[Meena B. Bansal, MD, FAASLD]

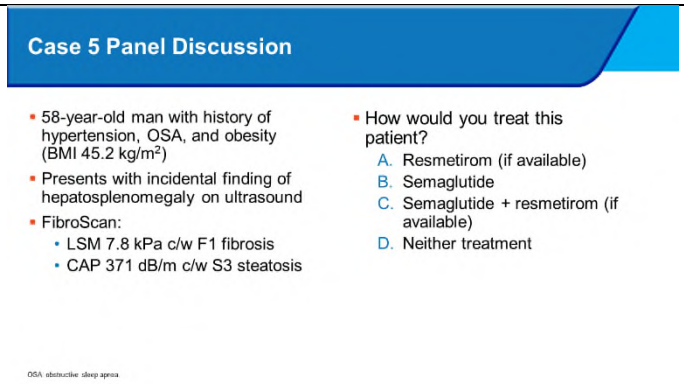
And maybe some additional weight loss is still possible. Elisabetta, anything you would add to that? And if anybody has a comment in the audience, please step up to a mic.

[Elisabetta Bugianesi, MD, PhD]

It's a question for you. Would you consider them for bariatric surgery?

[Meena B. Bansal, MD, FAASLD]

BMI of 29 kg/m^2? I don't have evidence here. Like, if he had sleep apnea, like the number of comorbidities are limited, it's to be considered

		and discussed with the patient, but I might think that they're on the lower end of the spectrum for bariatric surgery. ***[Elisabetta Bugianesi, MD, PhD]*** Well, actually, yes, if he's overweight, but with 2 comorbidities, at least, because he has MASH and he has type 2 diabetes and dulaglutide is insufficient to make him lose weight. The problem is how much, how many signs of portal hypertension may this guy have? So anyway, you should do an endoscopy, upper GI endoscopy, before the bariatric surgery to be sure that there are no signs of portal hypertension. No under evaluation of fibrosis by LSM, because sometimes it may happen. So, yes, it's something that might be discussed. ***[Meena B. Bansal, MD, FAASLD]*** Okay. Okay. Any other questions or comments on the answer? So I think that certainly we're talking about managing comorbidities here, and we'll see to what extent there is fibrosis reversal if you had a liver-targeted therapy and you're not getting the desired effect, and hepatic fibrosis, say, after 1 year, you might consider add-on therapy. Okay.
78.		All right, next case—58-year-old man with a history of hypertension, sleep apnea, obesity, BMI of 45 kg/m^2, presents with an incidental finding of a hepatosplenomegaly on ultrasound. The FibroScan is consistent with F0, F1 fibrosis and significant steatosis. This guy looks like perfect for some bariatric surgery. So bariatric surgery, that's an option. But a lot of people don't want bariatric surgery, right? This is a patient's choice. So bariatric surgery would be an option. I would say that, you know, when we talk about, he doesn't have significant fibrosis,

right? So F1 fibrosis, we really want to focus on managing the sleep apnea, the hypertension, the obesity. And so this is a person who's perfect for a weight loss strategy. Pharmacologic GLP-1 receptor agonist. Quentin, you want to add anything?

[Quentin M. Anstee, MBBS, PhD, FRCP]

Yeah, just one thought. I mean, as you rightly say, this patient has multiple metabolic risk factors. They're also significantly overweight. We do know that elastography can be adversely affected by that. And I would be concerned, particularly given evidence of hepatosplenomegaly here, that that liver stiffness is falsely reassuring. So I'd probably…

[Meena B. Bansal, MD, FAASLD]

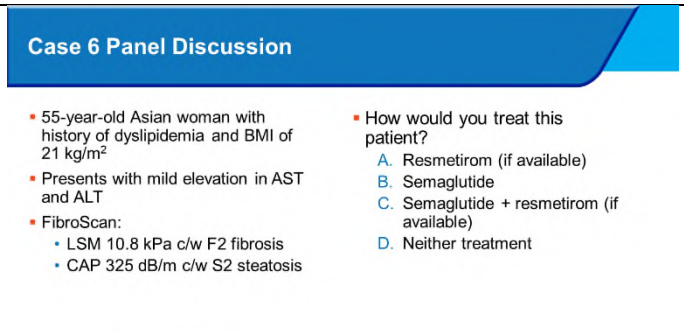
So what would be your next test in him?

[Quentin M. Anstee, MBBS, PhD, FRCP]

I'd be strongly considering, I mean, you need to look at a holistic view of a patient, but I'd be strongly considering a liver biopsy or something additional at this point. I don't have MRE available to me. MRE is less subjective or subject to influence of BMI. So, yeah, the other option would be to use a circulating biomarker like ELF and then get a triangulation across. But I think I'd want more information before I was completely reassured about this patient's liver stiffness.

[Elisabetta Bugianesi, MD, PhD]

I do agree with Quentin because that splenomegaly doesn't fit very well with LSM 7.8 kPa.

		[Meena B. Bansal, MD, FAASLD] Yeah, and I think sometimes, you know, obviously, it's quite obese, so sometimes you do see enlarged spleens, just in big people. But absolutely, so some other assessment and also perhaps longitudinal assessment over time. I think, Quentin, you made a big point of, like, no one point in time is what you want to use to assess a patient. So, obviously, repeat testing, different modalities of testing that might not be susceptible to his weight status would all be great things to do. Okay.
79.		All right, 55-year-old Asian woman with a history of dyslipidemia and a BMI of 21 kg/m^2 presents with mild elevation of AST and ALT. FibroScan with a liver stiffness of 10.8 kPa consistent with F2 and moderate steatosis. Dr. Anstee, what would you do in this case? ***[Quentin M. Anstee, MBBS, PhD, FRCP]*** Keep going in alphabetical order here. This is very tough. ***[Meena B. Bansal, MD, FAASLD]*** I'll switch it around for the last one. ***[Quentin M. Anstee, MBBS, PhD, FRCP]*** So this is interesting because obviously this patient's Asian. So although her BMI is 21 kg/m^2, certainly in the UK, we're trained to sort of add 3 to that to give us a slight ethnicity adjustment to it. Still would be within what would be considered to be the healthy weight range. That said, we need to factor in other details. So, you know, there's this great concept of the personal fat threshold. I think that's really important. You can be having, you know, what

might be considered the appropriate weight, but it can be too much for you based on your genetic makeup and so on. I'm not overly bothered, there's only mild changes in biochemistry. I don't think that's particularly pertinent here. It doesn't track well. The liver stiffness is high, and there's certainly an increased fat accumulation in the liver, so we're dealing with a degree of fibrosis. I'd want to know that the liver screen is completely clear, that the patient's adequately treated for their dyslipidemia. It's a tricky one where we go from there, actually.

[Meena B. Bansal, MD, FAASLD]

So if you had a liver-directed therapy.

[Quentin M. Anstee, MBBS, PhD, FRCP]

If I had a liver-directed therapy, I'd certainly be considering it, but I'd possibly want to know about trying to get this patient's weight down to a weight that is appropriate for them. So a combination of approaches there may be, stepwise.

[Meena B. Bansal, MD, FAASLD]

Okay.

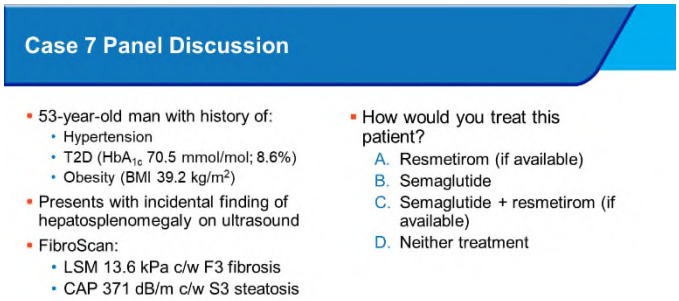
[Quentin M. Anstee, MBBS, PhD, FRCP]

Elisabetta?

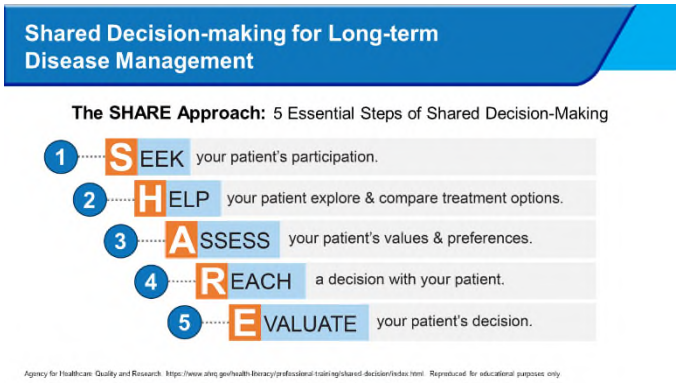
[Elisabetta Bugianesi, MD, PhD]

Well, actually, I would like to know a little bit more about the risk factors of this woman because, okay, history of dyslipidemia, but how much, how long, has she been be treated or not? Then I would do an alcohol test, just to be sure,

		because you never know. ***[Meena B. Bansal, MD, FAASLD]*** You said what? ALT test? ALT test you said? ***[Elisabetta Bugianesi, MD, PhD]*** Alcohol. ***[Meena B. Bansal, MD, FAASLD]*** Oh, alcohol. ***[Elisabetta Bugianesi, MD, PhD]*** Alcohol questionnaire. ***[Meena B. Bansal, MD, FAASLD]*** Okay. ***[Elisabetta Bugianesi, MD, PhD]*** And the third is. I would do a genetic testing for *PNPLA3.* ***[Meena B. Bansal, MD, FAASLD]*** Interesting. Okay. Okay, you're seeing a high prevalence in Asian patients of *PNPLA3*. ***[Elisabetta Bugianesi, MD, PhD]*** Well, there is. There is a significant prevalence, 30%. ***[Meena B. Bansal, MD, FAASLD]*** Interesting. Okay. Okay, so you want to know a little bit more about the patient, possibly a liver-directed therapy, because let's assume her comorbidities are controlled in terms of the dyslipidemia. But, Quentin, you still feel like extra weight loss could be important with a BMI

		of 21 kg/m^2. ***[Quentin M. Anstee, MBBS, PhD, FRCP]*** I think we have to recognize this would be somebody at a high risk of cardiovascular disease, and so we'd want to optimize management there as well. ***[Meena B. Bansal, MD, FAASLD]*** Absolutely. ***[Quentin M. Anstee, MBBS, PhD, FRCP]*** There's no right or wrong here, is there?
80.		***[Meena B. Bansal, MD, FAASLD]*** Yeah. No, no, no. We're just, we're having fun. Okay, excellent. All right. And then the last case, and then I'll open up if there's any burning questions? We have a 53-year-old man with a history of hypertension, type 2 diabetes, 8.6% not well-controlled obesity presents with incidental finding of a hepatosplenomegaly ultrasound. See, we get that all the time. Like, almost so many patients have a hepatosplenomegaly. I don't know if it's just an overread by the radiologist, and then a FibroScan of 13.6 kPa consistent with F3 fibrosis and significant steatosis. So, Elisabetta, what do you think? ***[Elisabetta Bugianesi, MD, PhD]*** Well, first of all, this guy has never seen a physician in his life because, I mean, 8.6% of type 2 diabetes, so almost 40 kg/m^2 of BMI and presents with an incidental finding of hepatosplenomegaly. So the first ultrasound that he did was too late. And, I mean, this is already

		cirrhotic or very close to be cirrhotic. And how would I treat? Well, actually, to control type 2 diabetes and obesity, of course, semaglutide, resmetirom. Yes. I should be sure that he is not cirrhotic. I would perform, how many platelets does he have? I mean, either… ***[Meena B. Bansal, MD, FAASLD]*** One side. No evidence of portal hypertension. ***[Elisabetta Bugianesi, MD, PhD]*** Okay. No portal hypertension. ***[Meena B. Bansal, MD, FAASLD]*** No portal hypertension. ***[Elisabetta Bugianesi, MD, PhD]*** No portal hypertension so resmetirom. ***[Meena B. Bansal, MD, FAASLD]*** Okay, great. Anything to add, Quentin? So this is a patient who clearly needs better glycemic control, needs to lose weight, would benefit from a GLP-1. Semaglutide is a no-brainer. Perhaps since he's got advanced fibrosis, F3, maybe even more if we're not getting a good fibrosis, resolution or improvement, would add on another therapy. ***[Quentin M. Anstee, MBBS, PhD, FRCP]*** So I mean, I completely agree with Elisabetta here. We need to start from the ground up. We've got a lot of remedial work in terms of this patient's care, in lifestyle change, we've not even mentioned it yet. We'd be talking about that. He'd be seeing my dietitian, my exercise physiologist, would be optimizing his lipids,

		certainly getting that diabetes well controlled, following guidelines. I think the thing to remember is we don't have to do it all in 1 day. So, you know, we'll start with some things. We'll build up on that. Then we'll build on, yes, this is somebody who's pre-cirrhotic. So if available, resmetirom could be available here. But I've got several steps I'd want to get through on the way to that.
81.		***[Meena B. Bansal, MD, FAASLD]*** Okay. I think we're actually exactly on time. So if there's no other burning questions, we thank you for your engagement and joining us.