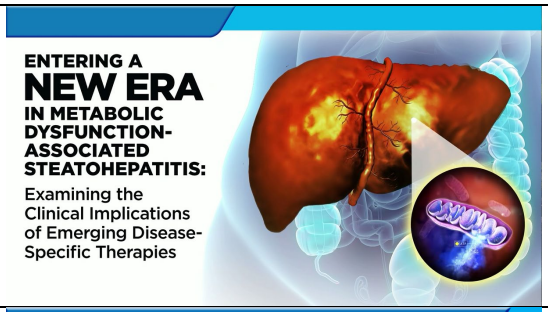
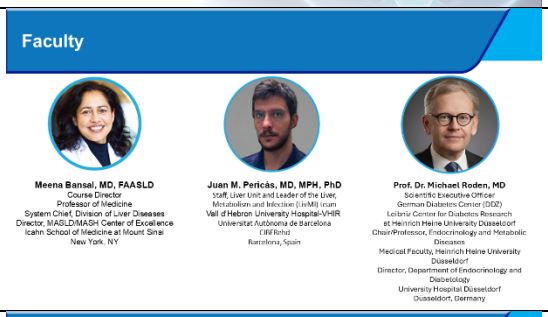
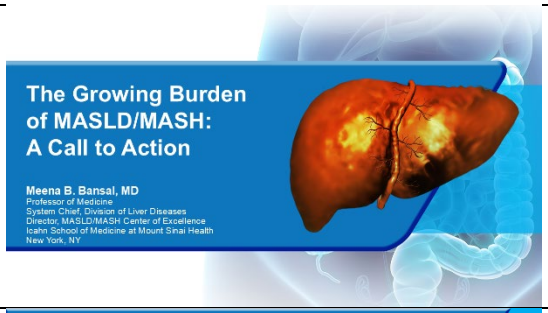
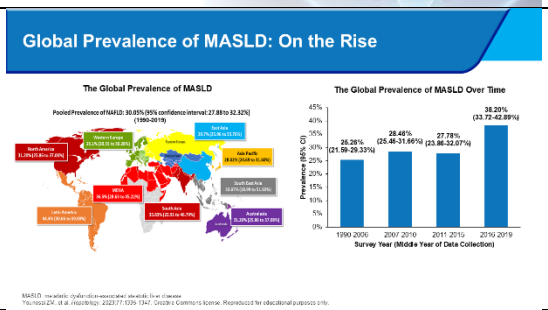
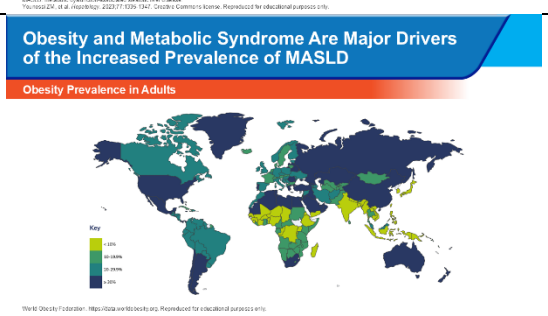
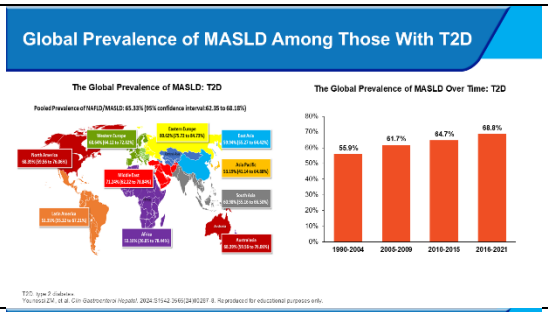
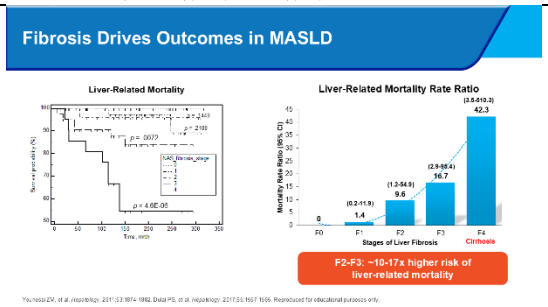
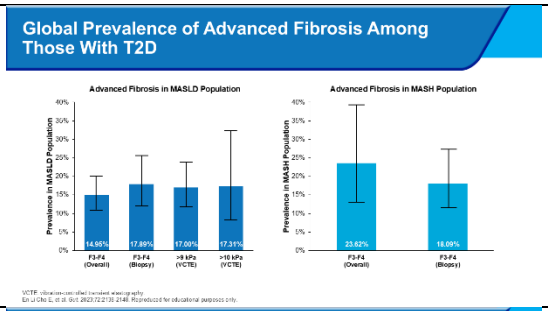
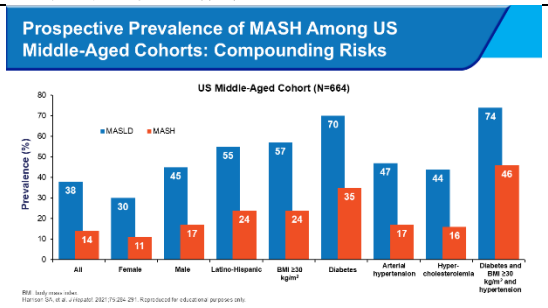
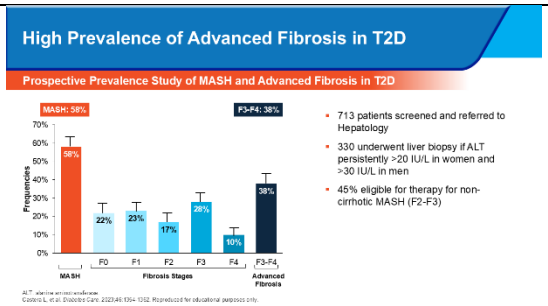
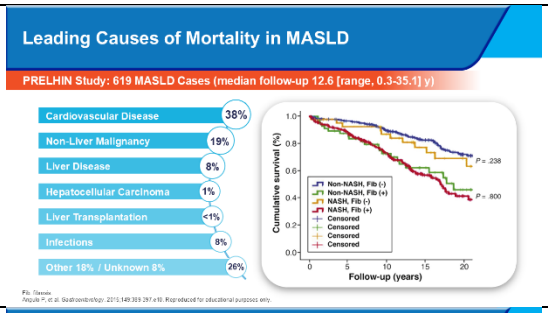
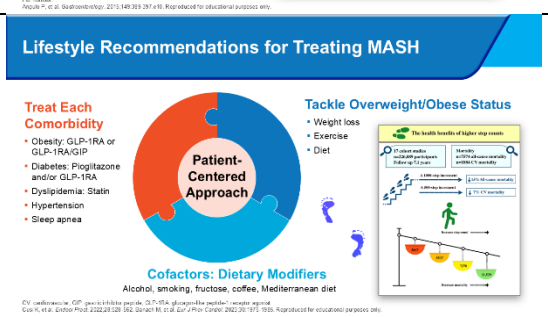
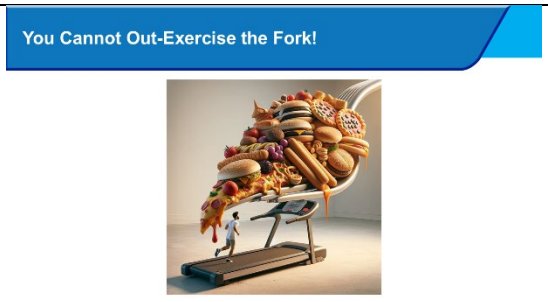
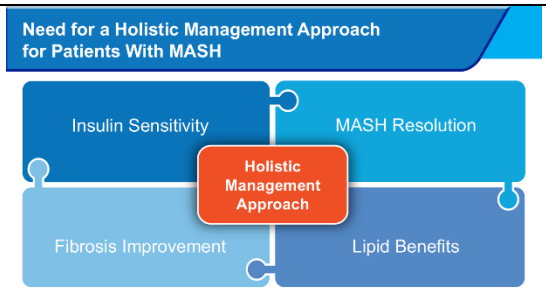
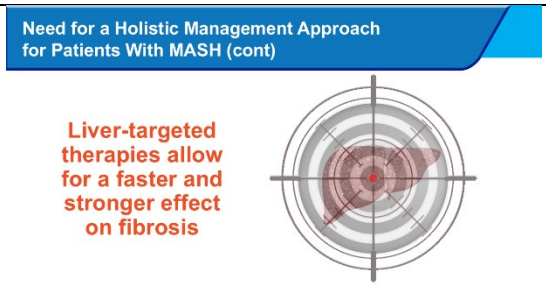
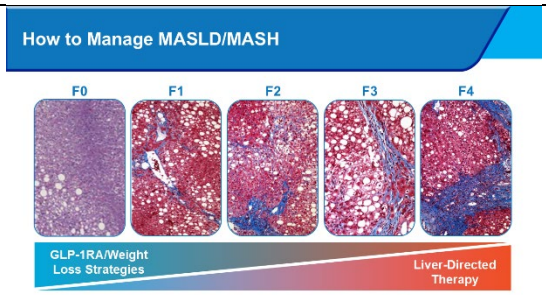
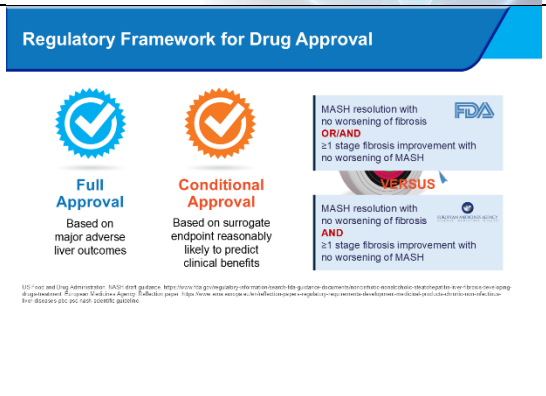
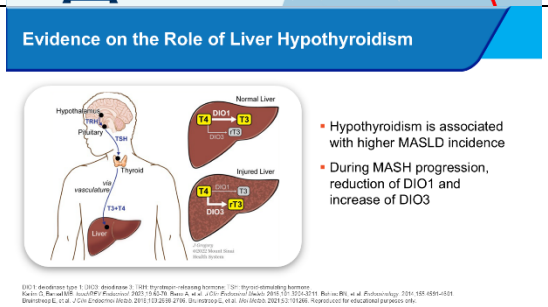
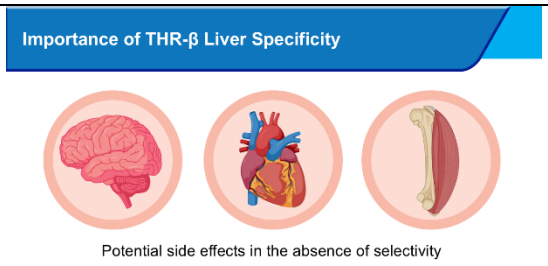
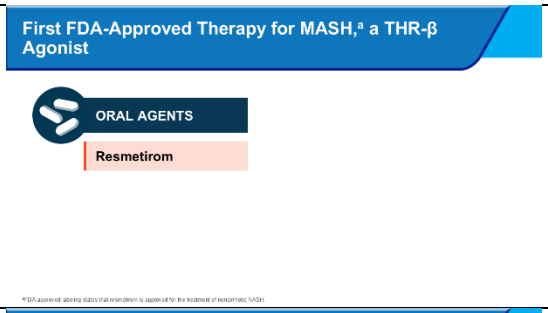
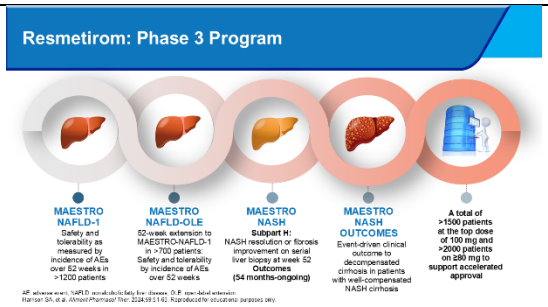
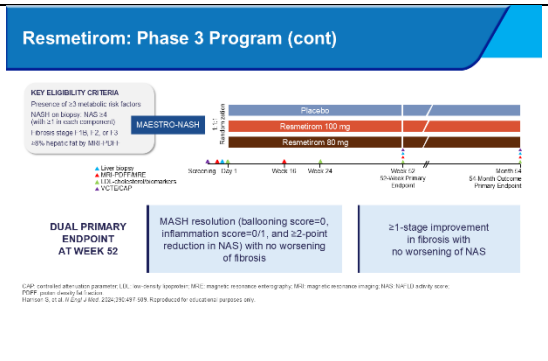
1.		***Meena Bansal, MD, FAASLD*** It's my pleasure to welcome you to, *Entering a New Era in MASH: Examining the Clinical Implications of Emerging Disease-Specific Therapies*.
2.		I'm Meena Bansal, I'm the chief of the Division of Liver Diseases at Mount Sinai in New York. And it's my pleasure to be joined by Dr Pericàs, who's a hepatologist and leader of the Liver, Metabolism and Infectious team in Barcelona, and Prof Roden, who is the chair and professor of Endocrinology and Metabolic Diseases and director of the Department of Endocrinology and Diabetology in Düsseldorf.
3.		I'd like also to take a moment to pause to send our condolences to the family of Dr Stephen Harrison. He was a close friend and colleague to many of us and he is sorely missed.
4.		Okay, so I'm going to kick us off.
5.		I think as many of us know, the global prevalence of MASLD continues to rise—now approaching almost 38%.
6.		And we know that this goes along with the increasing epidemics of both obesity and metabolic syndrome.

7.		And when you specifically look at those with diabetes, you can see that the prevalence of MASLD over time continues to increase in this high-risk group, approaching almost 70%.
8.		But the key thing is that the most important predictor of liver-related mortality is fibrosis. When you achieve Stage 2 fibrosis or F2 fibrosis, you have an increased risk by 10-fold of liver-related mortality, which increases to 17-fold for F3 fibrosis and 42-fold for cirrhosis.
9.		When you look at the prevalence using biopsies, this was a recent systematic meta-analysis. On the right-hand side panel, you can see that among those that have histologic MASH, though, 18% have F3 or F4 fibrosis.
10.		Now, in terms of prospective studies, this was actually a study done by Dr Harrison, where patients were coming in for direct access colonoscopy, if they had steatosis and metabolic risk factors, they were offered a liver biopsy. Six hundred and sixty-four patients agreed to that, and you can see that overall, the prevalence in the total population was 14% of MASH. But when you look at subgroups like Latino and Hispanic patients, those with a BMI greater than 30 kg/m^2 and those with diabetes, you can see increasing prevalence. And when you look at those with diabetes, high BMI, and hypertension, the prevalence of MASH approaches 46%. Now you could say, well, this is in Texas. Is this really applicable to other populations?
11.		So this was a study done by Laurent Castera and colleagues in France. Patients were screened in endocrinology clinics. Those that had steatosis or abnormal liver enzymes were referred to hepatology. Of the 713 patients, 330 underwent liver biopsy if the ALT was persistently greater than 20 IU/L in women and greater than 30 IU/L in men. It's important to point out that those numbers, I think for most of us, you would think, oh gee, that's a really low ALT. But in fact, that is abnormal. And so as the population has

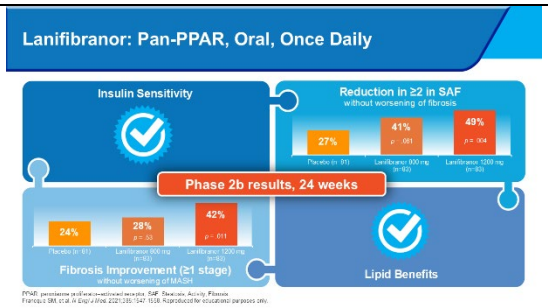
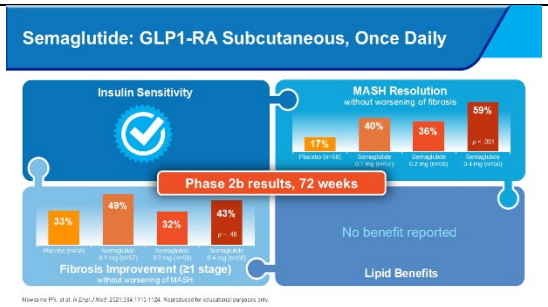
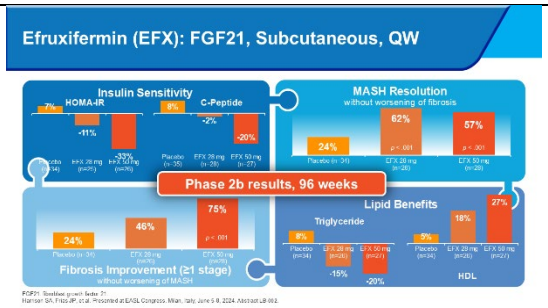
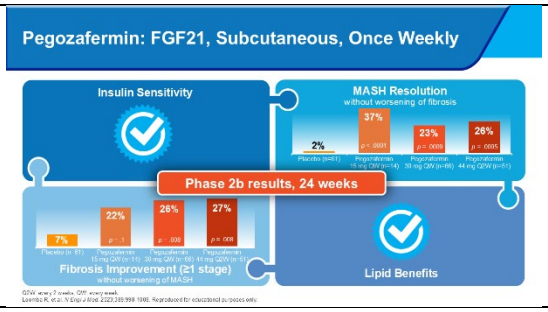
		gotten more and more obese, that upper limit of normal for AST and ALT has also shifted upward. So from a hepatologist perspective, ALT greater than 20 IU/L and ALT greater than 30 IU/L are considered abnormal. When those patients underwent liver biopsy, 45% had either F2 or F3 fibrosis and 38% had F3 or F4 fibrosis.
12.		Now, while we are discussing liver disease here, it's important to recognize that the number 1 cause of death in patients with MASLD is cardiovascular disease, followed by extrahepatic malignancies, and therefore it's paramount in any therapeutic approach to make sure that we're also addressing these comorbidities and we're not increasing the risk for any of these other factors.
13.		So obviously, we know that lifestyle recommendations are central for treating MASH. We want to tackle the overweight obese status through weight loss and exercise. Importantly, exercise, even in the absence of weight loss, was associated with improved all-cause mortality as well as a decrease in cardiovascular mortality. In terms of dietary modifiers, we obviously recommend low alcohol consumption, quit smoking, don't drink fructose-containing beverages, have 2 to 3 cups of coffee a day, and try to adhere to a Mediterranean-style diet. And importantly, we want to aggressively treat each comorbidity, including obesity, whether it be pharmacological or surgical; diabetes; dyslipidemia is very important because often as a hepatologist, I see people don't want to start statins when the underlying liver enzymes are abnormal, but it's absolutely critical that we do start the statins and they're very safe; hypertension; and sleep apnea.
14.		But the key is, is that despite exercise, the reality is that calories matter and you cannot out-exercise the fork.

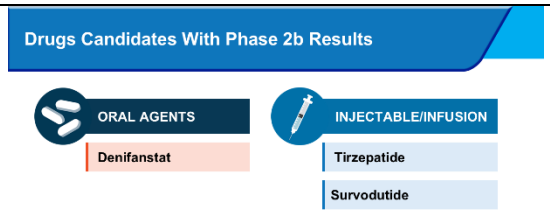
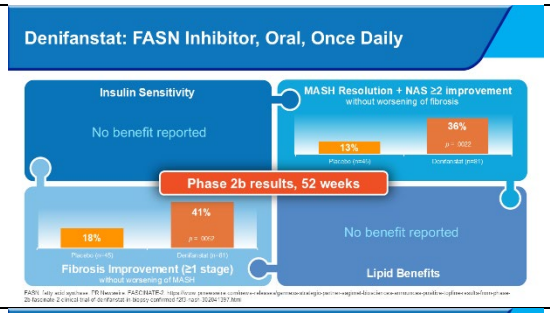
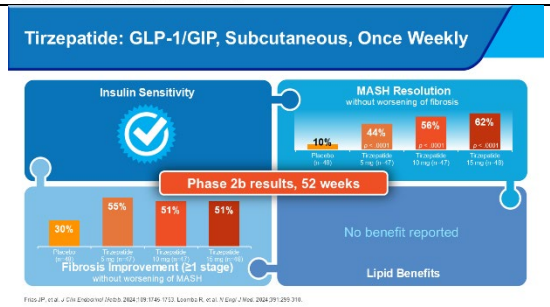
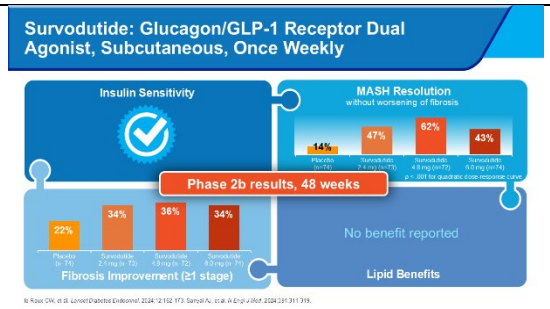
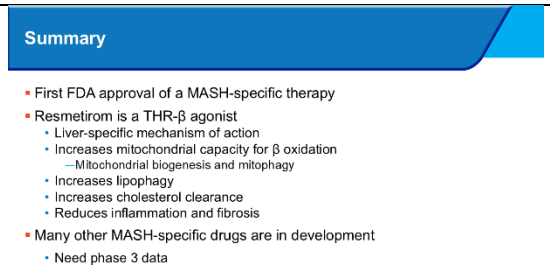
15.		So when we look at these patients, we really need a holistic management approach. Again, as a hepatologist I'm focused on MASH resolution and fibrosis improvement. But I want to make sure that we also are addressing dyslipidemia and any therapeutic approach, if it has additional lipid benefits, that would be a bonus. And of course, we know that insulin resistance and lipotoxicity is a critical driver for MASLD and MASH. And therefore again, any approach, if it also improves insulin sensitivity, is a bonus.
16.		But liver-targeted therapies are going to be necessary when you need to have a stronger antifibrotic effect.
17.		So when you think about the continuum, when patients have minimal fibrosis, F0, F1, really you want to focus on weight loss strategies, whether that be again pharmacologic or surgical approaches. But as the fibrosis increases approaching F3 and F4, we're going to need more liver-directed therapy.
18.		And so now I'm going to pivot to thyroid hormone receptor-β agonists and other disease-specific therapies that are kind of in the mix right now.
19.		So as many of you may know, the regulatory framework for the drug approval for MASH, full approval is contingent upon meeting the endpoint of decreasing major adverse liver outcomes. However, conditional approval is based on a surrogate endpoint reasonably likely to predict clinical benefits; for the FDA that includes MASH resolution with no worsening of fibrosis or at least 1 stage of fibrosis improvement with no worsening of MASH. The EMA, however, has set a higher bar and you need to have both to achieve approval.

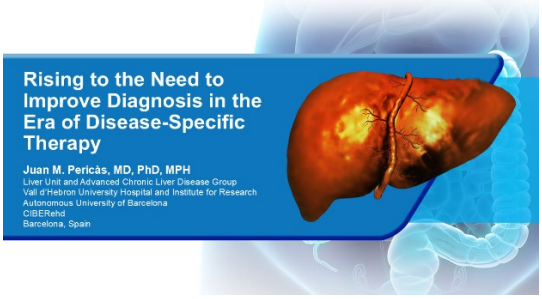
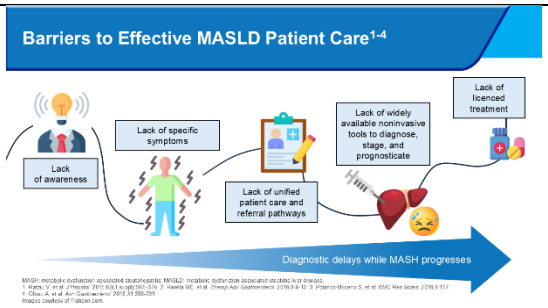
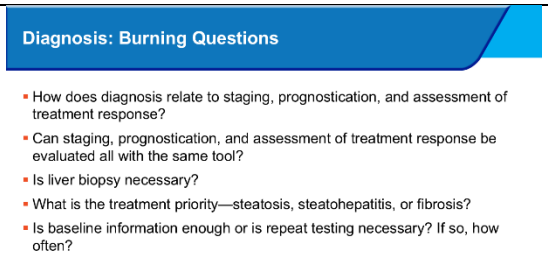
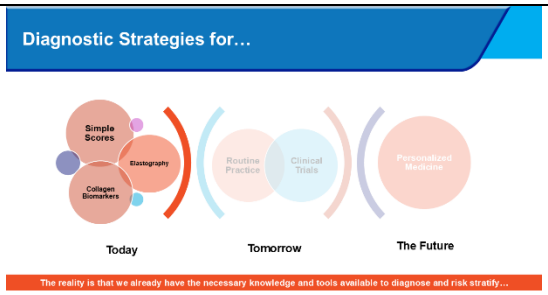
20.		And so this has been a long road for many of you who've been following the field. There've been a number of drugs that have been kind of attempting to get that FDA approval. Some have jumped off the cliff, some have fallen off the cliff. But ultimately, we have our first drug approval of resmetirom, at least in the United States, March 14, 2024, again conditional approval.
21.		So what is the evidence for the role of liver hyperthyroidism in driving MASLD? Well, we know that hypothyroidism is associated with higher MASLD incidence. And normally, as I think this audience knows, even more than me, T4 is the prohormone. It enters the target organ and then is converted to the active T3 in the liver by deiodinase 1. There is some deiodinase 3 that converts it to reverse T3 or the inactive inert form. However, with chronic liver injury there is an upregulation of deiodinase 3, causing kind of this shunting toward the reverse T3 or the inert form causing a relative intrahepatic hypothyroidism.
22.		And so this is a video that shares the mechanism of action of thyroid hormone receptor β-agonists. **Video** Thyroid hormone receptor-β agonists, or THR-β agonists, are small molecules designed to specifically act in the liver. These agents enter the nucleus within the hepatocyte and bind to THR-β to activate target gene expression, which mediates several metabolic pathways. First, enhanced mitophagy removes damaged mitochondria, while mitochondrial biogenesis generates new organelles. At the same time, reductions in reactive oxygen species, or ROS, limit mitochondrial damage and accumulation of toxic long-chain lipids. Finally, increases in lipophagy generate free fatty acids that are then transported to mitochondria to produce ATP via β oxidation. Overall, treatment with a THR-β agonist is effective in reducing hepatic fat content and fibrosis. ***Meena Bansal, MD, FAASLD*** So the key feature is that in MASLD or MASH, the mitochondrial capacity to β-oxidize fatty acids is stressed, and therefore the mechanism by which thyroid hormone receptor-β agonists work is by getting rid of kind of the tired mitochondria through a natural cellular process called mitophagy and allowing for the replenishment of new fresh mitochondria. Therefore, the factory for fat burning is revved up.

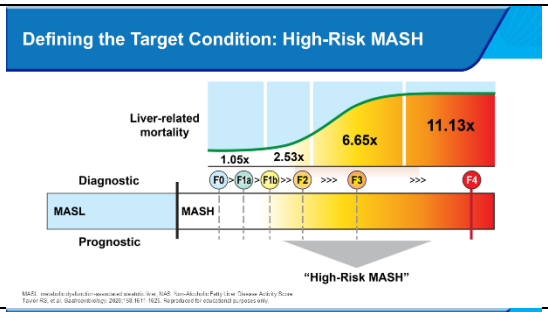
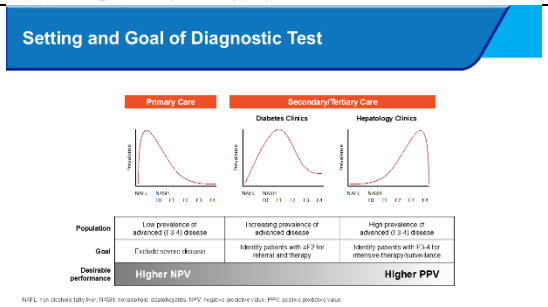
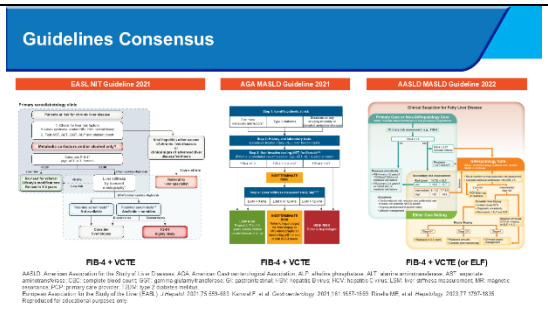
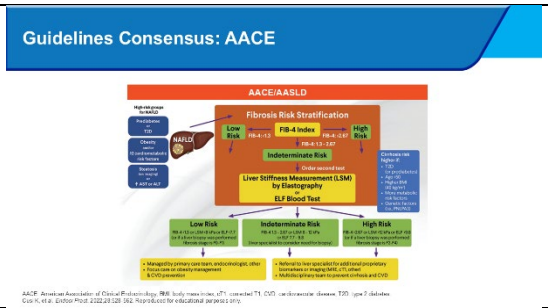
23.		The key is, is that we know that thyroid hormone has a number of effects across different organs. And so the importance of having that β selectivity is to avoid some of the off-target effects, such as in the cardiac or skeletal muscle.
24.		So, we'll go over a little bit of the data for the first FDA-approved therapy for MASH—resmetirom.
25.		So the data supporting the FDA approval in the US were based on a very large phase 3 program. The first was the MAESTRO NAFLD program, which included over 12,000 patients and looked at safety and tolerability. Of those patients, 700 went on to an open-label extension study, again collecting safety and tolerability data over another 52 weeks. The registrational trial that led to the early accelerated approval was the MAESTRO NASH study, in which patients had baseline biopsies and then biopsies at 52 weeks. This study is ongoing, so that we can follow for liver-related outcomes to get full approval. And then there's the MAESTRO NASH OUTCOMES trial, which is an event-driven study that has enrolled well-compensated patients with cirrhosis. So overall, a total of 15,000 patients have received the 100-mg dose and over 2000 have received at least the 80-mg dose.
26.		So just going over the registrational trial, patients had to have at least 3 metabolic risk factors. So very enriched with high-risk patients, at least 8% hepatic fat by MRI-PDFF, and then NASH on biopsy and then various stages of fibrosis up to F3. Patients were randomized to 80 mg, 100 mg, or placebo. And then there was the dual endpoint, which is the biopsy of either MASH resolution without worsening of fibrosis or an improvement in at least 1 stage of fibrosis with no worsening of NASH.

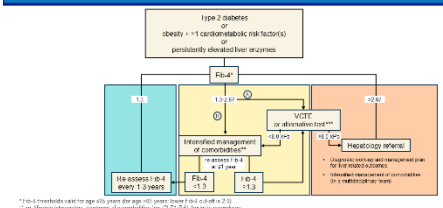
27.	**Resmetirom[a]: THR-β, Oral, Once Daily** Insulin Sensitivity No benefit reported MASH Resolution + NAS ≥2 Improvement without worsening of fibrosis 10% 26% 30% Phase 3 results, 52 weeks 14% 24% 26% Fibrosis Improvement (≥1 stage) without worsening of MASH 0% -14% -16% Lipid Benefits	And so the results that were reported in the *New England Journal of Medicine*, the phase 3 results, you can see that 30% of patients at the higher 100-mg dose achieved MASH resolution compared with 10% of placebo. I didn't mention that thyroid hormone receptor-β also increases LDL receptors on hepatocytes and therefore you see a reduction in LDL. So again, potential lipid benefits as well, with a 16% reduction in LDL in those who were on the 100-mg dose. Fibrosis improvement in approximately 26% compared with 14% on placebo, and no benefit reported on insulin sensitivity.
28.	**Resmetirom: Phase 3 Safety Results** Patients (%) / Placebo (n=321) / Resmetirom 80 mg (n=322) / Resmetirom 100 mg (n=323) ≥1 AE: 298 (92.8) / 296 (91.9) / 296 (91.6) Grade 1: mild: 77 (24.0) / 73 (22.7) / 66 (20.4) Grade 2: moderate: 169 (52.6) / 180 (55.9) / 183 (56.7) Grade ≥3: severe: 52 (16.2) / 43 (13.4) / 47 (14.6) ≥1 treatment-emergent AE: 88 (27.4) / 124 (38.5) / 134 (41.5) ≥1 Serious AE: 37 (11.5) / 35 (10.9) / 41 (12.7) AE leading to discontinuation: 11 (3.4) / 9 (2.8) / 20 (6.2) Death: 1 (0.3) / 1 (0.3) / 2 (0.6) AEs affecting >10% of patients in any group **Diarrhea**: **50 (15.6)** / **87 (27.0)** / **108 (33.4)** COVID-19: 66 (20.6) / 69 (21.4) / 54 (16.7) **Nausea**: **40 (12.5)** / **71 (22.0)** / **61 (18.9)** Arthralgia: 40 (12.5) / 48 (14.9) / 35 (10.8) Back pain: 38 (11.8) / 35 (10.9) / 27 (8.4) Urinary tract infection: 27 (8.4) / 33 (10.2) / 27 (8.4) Fatigue: 28 (8.7) / 33 (10.2) / 26 (8.0) Pruritus: 22 (6.9) / 28 (8.1) / 37 (11.5)	In terms of side effects, the most common were diarrhea and nausea. They tend to occur within the first 2 to 4 weeks of treatment, and they resolve, generally speaking, by 12 weeks.
29.	**EASL-EASD-EASO Treatment Guidelines** Preferred pharmacologic options for treating comorbidities MASH-targeted T2D Dyslipidemia Obesity MASLD/MASH without cirrhosis (F0-F3) If locally approved Resmetirom in F2/F3 fibrosis GLP-1RA (eg, semaglutide, liraglutide, dulaglutide) and coagonists (eg, tirzepatide) SGLT2 inhibitors (eg, empagliflozin, dapagliflozin) Metformin[a] Insulin (in case of decompensated cirrhosis) Statins GLP-1RA (eg, semaglutide, liraglutide) and coagonists (eg, tirzepatide) Bariatric interventions (special caution in case of compensated cirrhosis) MASLD/MASH with compensated cirrhosis (F4) Check indication for liver transplantation in case of decompensation or HCC	And so EASL-EASD-EASO had a very forward-thinking approach. It's not yet approved in Europe, but they do point out in their guidelines that if it's locally approved, resmetirom would be the first MASH-targeted liver-directed therapy for F2 and F3 fibrosis. But importantly, we also must be aggressively managing the comorbidities, including type 2 diabetes, dyslipidemia with statins, and obesity with either pharmacologic or surgical interventions. At the moment, it is not indicated in patients with cirrhosis. That study is ongoing, as I mentioned earlier in the MASH outcomes trial.
30.	**Other THR-β Agonists in Development** Drug Candidate / Study Stage / Endpoints **VK2809**: Phase 2, Biopsy-confirmed MASH (N=248) / 12-week reduction of liver fat content, Recruitment completed, 52-week biopsy data awaited **TERN-501**: Phase 2, Presumed MASH (N=162) / 12-week reduction of liver fat content, Results available **ALG-055009**: Phase 2, Presumed MASH (N=100) / 12-week reduction of liver fat content, Recruitment ongoing	So there are other thyroid hormone receptor-β agonists that are also in development. The furthest along is the Viking drug, which results in a 12-week reduction in liver fat, and we await the 52-week biopsy data.
31.	**Drug Candidates in Phase 3** ORAL AGENTS Lanifibranor INJECTABLE/INFUSION Semaglutide Efruxifermin Pegozafermin	Now, what about other agents that are in phase 3? We'll briefly go over lanifibranor, as well as some of the injectable treatments—semaglutide, efruxifermin, and pegozafermin.

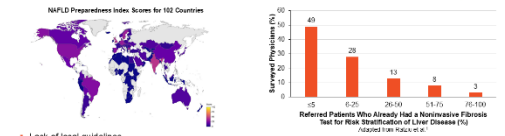
32.		So, lanifibranor is a pan-PPAR agonist. So it has α, δ, and γ activity. The α activity targets the steatotic hepatocyte. The δ activity focuses on infiltrating macrophages and decreasing pro-inflammatory signaling. And then the γ effect is more the stellate cell antifibrotic effect. They saw a 49% reduction in the SAF score, which is another steatosis activity score, compared with placebo. There are lipid benefits with increased HDL and decreased triglycerides. Fibrosis improvement by at least 1 stage at 42% in the 1200-mg dose and of course, increased improvements in insulin sensitivity.
33.		So semaglutide, I think this will be gone over again by Dr Roden, but briefly they saw MASH in their phase 2b 72-week study. Note, this is the daily subcutaneous dose at 0.4 mg, 59% had MASH resolution without worsening of fibrosis compared with placebo. No reported lipid benefits. Fibrosis improvement was not met but note a very high placebo response rate of 33%. We await the phase 3 essence trial and of course, improvement in insulin sensitivity.
34.		Now, FGF21 is a metabolic hormone that has really outstanding effects on energy expenditure, lipid metabolism. It also upregulates adiponectin, which is a potent antifibrotic on stellate cells. The issue is that it has a very short half-life of less than 2 hours. So these are long-acting FGF21 molecules. This is subcutaneous once a week. And what they saw was a MASH resolution without worsening of fibrosis in both the 28- and 50-mg dosing, decreases in triglycerides, and improvement in HDL. Fibrosis improvement at 75% compared with 24% in placebo—but note the small sample size of only 28 patients, so we need to wait for phase 3 data—and improvements in insulin sensitivity, both with a decrease in HOMA-IR and C-peptide.
35.		Now, pegozafermin is a pegylated FGF21, similar kind of data where you see MASH resolution without worsening of fibrosis at all doses that were tested. Improvement in lipid profile and fibrosis improvement also was hit with both the 30-mg once-a-week and 44-mg every-2-week doses and improvement in insulin sensitivity. So this is the phase 2b 24-week study. And we await the phase 3 data.

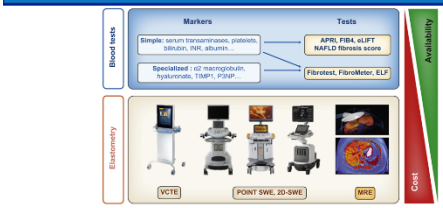
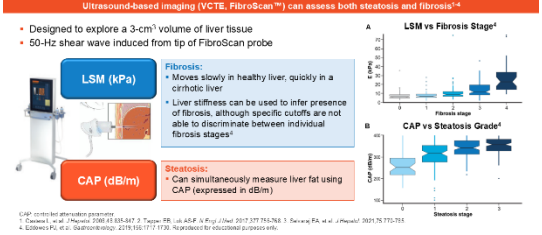
36.		Now what about other drugs that are kind of in the pipeline. Oral agent denifanstat, and then tirzepatide and survodutide.
37.		So denifanstat is a FASN inhibitor, it's oral once daily. And in their phase 2b study, they saw 36% MASH resolution without worsening of fibrosis. No benefit reported on lipids, and fibrosis improvement of 41% compared with 18% in placebo, and no benefit reported for insulin sensitivity.
38.		Now tirzepatide, which is the dual GLP-1/GIP, subcutaneous, once weekly. This was recently reported in the *New England Journal of Medicine*, and you can see that at all doses of tirzepatide, there was MASH resolution without worsening of fibrosis, no lipid benefits reported, and trends toward improvement in fibrosis, but not statistically significant. And of course improvement in insulin sensitivity. So again, we wait for further phase 3 data.
39.		Survodutide is a glucagon receptor agonist as well as a GLP-1, subcutaneous, once weekly. Of note, glucagon receptors are expressed on hepatocytes, so there may be a liver-directed effect here. MASH resolution without worsening of fibrosis was seen in all treatment arms, no benefit reported on lipids, and fibrosis improvement at all doses again trend toward maybe a little—we need to have larger, larger data sets—and improvement in insulin sensitivity. So once again we await their phase 3 study.
40.		So in summary, we have the first FDA approval of a MASH-specific therapy. Hopefully we'll also have it by the EMA. Resmetirom is a thyroid hormone receptor-β agonist, which has a liver-specific mechanism of action. It increases mitochondrial capacity for β oxidation both through biogenesis and mitophagy, increases lipophagy, increases cholesterol clearance, and therefore has a reduction in inflammation as well as fibrosis. But we're in a very hopeful situation with many other MASH-specific drugs in development. But we need the phase 3 data. You cannot compare phase 2 data with phase 3 data—28 patients versus 2000 patients. So we really anxiously look forward to having a full armamentarium to treat these patients.

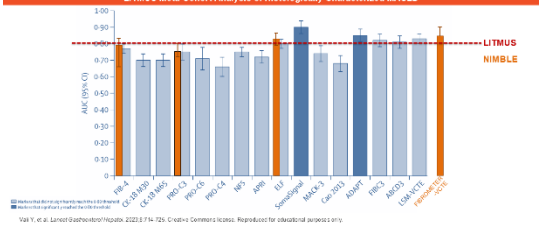
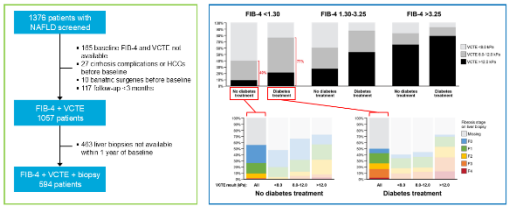
41.		So with that, thank you very much. I'm going to introduce my colleague, Dr Pericàs, who's going to talk to you about the rising need to improve our diagnostics or noninvasive assessments of liver fibrosis in this era of disease-specific therapy. ***Juan M. Pericàs, MD, PhD, MPH*** Good evening, and thank you, Prof Bansal, for the introduction. Let's dive right into it.
42.		So among the most salient barriers we face when trying to provide appropriate care to our MASLD patients, likely the most important is diagnostics. Diagnostic meaning also staging and prognostication. And that's because, our diagnostic tools act as a hinge between our public health epidemiology issues and those related to treatment and clinical challenges. So we lack widely available, noninvasive tools to diagnose, stage, and prognosticate MASLD/MASH in actual clinical care.
43.		And this prompts a series of questions, such as how diagnoses relate to staging prognostication, and assessment of treatment response. Can we do that with just one tool? Do we need a set of different tools? Is liver biopsy still necessary in real clinical care to do such a task? Can we leave it aside for a while, while we try to find our patients and provide them accurate care? And what is now the treatment priority if we leave behind liver biopsies? Still just fibrosis? Do we need to combine with steatohepatitis? Steatosis is still meaningful? And do we need just baseline information, or do we need to repeat testing to monitor treatment response? If so, how often? These are some of the unsolved questions as of yet.
44.		This outlook might be the ideal world, when we have a set of tools which are clearly aligned with what we do in real practice. This largely overlaps with how clinical trials are designed and are conducted, and at the end of the day, we have carefully designed clinical pathways and personalized treatment. However, this is not the current situation. We have a disconnection between how we design and perform trials, as Prof Bansal has explained. We heavily rely on liver biopsy to define our endpoints and to diagnose and monitor treatment response in clinical trials where that's not feasible in actual clinical care. So we need to come up with better noninvasive strategies to find and treat our patients. And although we have such huge knowledge on these NITs and that some of those tools are available, we still don't know how to do that exactly in each epidemiologic and clinical setting.

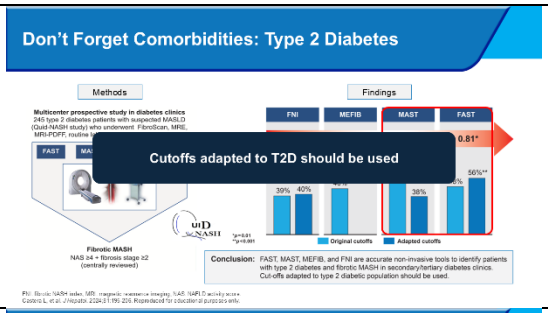
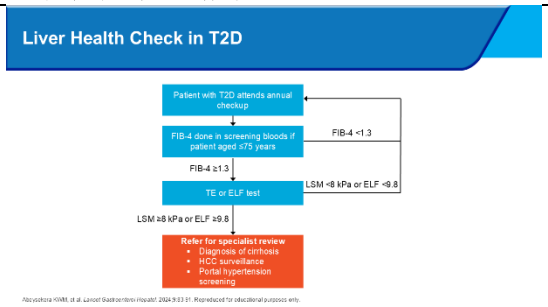
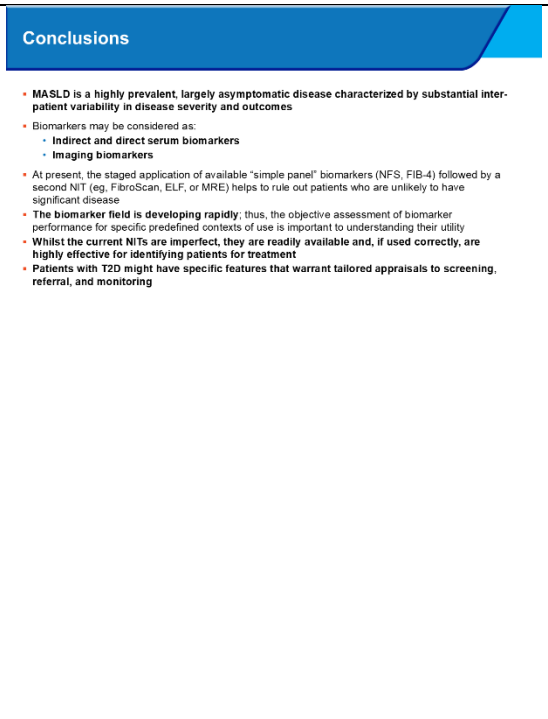
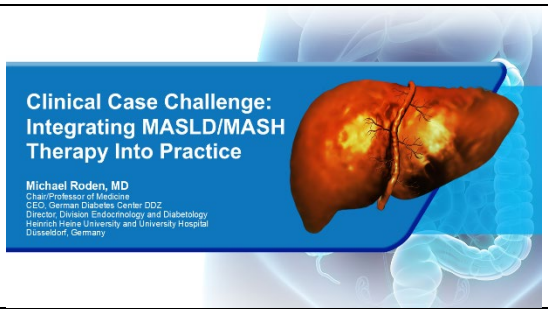
45.		We don't know, however, what is our main priority. We need to find these high-risk patients with MASH, namely those with enough steatohepatitis, meaning moderate to severe steatohepatitis, as well as significant fibrosis. Because, as Prof Bansal has already explained, fibrosis closely relates to prognosis—not only liver-related events, but also cardiovascular, neoplasm, and overall mortality.
46.		Of course, the type of tools we are going to use will differ depending on our priorities. It's not the same to try and diagnose with a screening purpose in a low prevalence setting, such as primary care, where we need very sensitive tools with high negative predictive value to rule out severe disease. Whereas on the other side of the spectrum, for instance, in hepatology clinics, we will try and find those patients with advanced fibrosis in order to prioritize their treatment. And therefore we need specific and with high predictive positive value tools.
47.		So most international societies agree on one thing, which is screening. Screening space in 2 main steps in order to rule out advanced fibrosis. After we have identified our patients with metabolic risk factors that might have fat in the liver according to other imaging tools. Then we go for a first step where we use FIB-4 in all cases. In case FIB-4 is low, we need to repeat FIB-4 assessment perhaps yearly, in other cases every 2 or 3 years, that depends on the guideline. If intermediate, a second test should be performed, either transient elastography or ELF in most guidelines. If FIB-4 is high enough, over 2.67, some guidelines recommend to directly refer the patient to the liver specialist. What's the role of type 2 diabetes in these guidelines? As you can see, for example, in the AGA guideline, type 2 diabetes is stressed as one of the separate risk factors to help identify patients at risk. In the case of the AASLD 2022 Guideline, it affects how often we are supposed to repeat FIB-4 in case it's low in the first case.
48.		In other guidelines, such as the American Association of Clinical Endocrinology Guidelines joined with the AASLD, type 2 diabetes is not only a risk factor for MASLD, but also is considered a direct risk factor for cirrhosis, and the guideline also proposes a 2-step approach to liver fibrosis with FIB-4 and then either ELF or transient elastography.

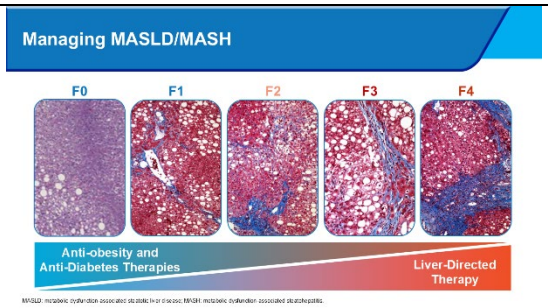
49.	**Guidelines Consensus: EASL-EASD-EASO**  	And the joint guidelines that Prof Bansal has already mentioned, already highlight type 2 diabetes at the beginning as a risk factor for MASLD, and then asked to reassess every 1 to 3 years. They don't go into detail depending on the profile of each patient and highlights transient elastography as the foremost second-line test. Whether there are other suggested alternative tests, such as magnetic resonance elastography, shear wave elastography, ELF, and others.

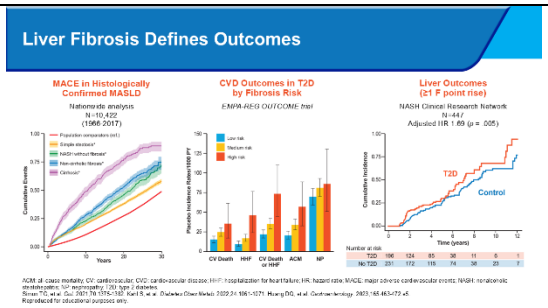
50.	**Identifying Patients With At-Risk MASH: Are We Doing Enough?**
	 
	
	• Lack of local guidelines
	  ▪ Data from over 102 countries revealed that only 32 countries had national NAFLD clinical guidelines[2]
	  ▪ NAFLD was rarely mentioned in public health strategies of related conditions such as diabetes[2]
	• Disconnect between EASL-EASD-EASO guidelines and real-world clinical practice across multiple regions/specialties[1,3]
	  ▪ Suboptimal use of liver function tests, NITs (eg, ultrasound and TE), and tests to exclude other conditions[3]
	  ▪ Use of NITs for patients with NAFLD in primary care is infrequent[1]
		How well are we performing our task in this regard? How well are we screening our patients? Well, we perhaps could say that we could do better. From available reports, we know that, in spite of the presence of very detailed international guidelines, this has not trickled down to a granular local level. And therefore most physicians are not applying such tools in their normal routine care. And as this study in the right-side panel shows, most patients do not perform any type of NIT in order to decide whether they might or not refer a patient to a liver specialist, which highlights, we still have a huge task in front of us in terms of improving education and awareness.

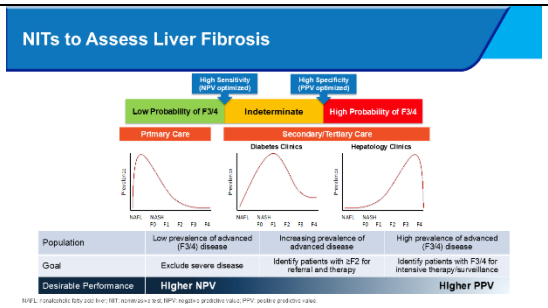
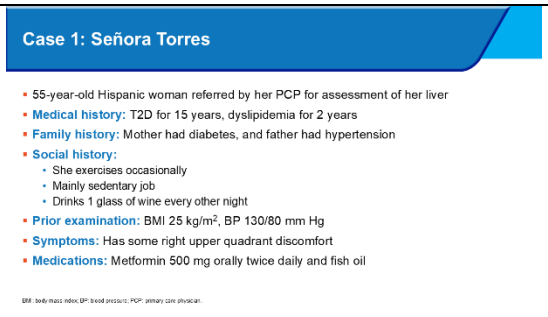
51.	**NITs to Diagnose and Risk Stratify**  	And what about diagnosing and stratifying? Once we have already closed the episode of screening, we have a wealth of different tools that we can use, just noninvasive tools, that might be divided mostly in blood tests, blood tests and elastomeric tests, imaging tests.
52.	**Imaging Techniques Can Assess Both Fibrosis and Steatosis** Ultrasound-based imaging (VCTE, FibroScan™) can assess both steatosis and fibrosis[1-4] • Designed to explore a 3-cm³ volume of liver tissue • 50-Hz shear wave induced from tip of FibroScan probe  	And the most used of all is FibroScan, or vibration-controlled transient elastography, which allows us to assess in a point-of-care manner, both fibrosis and steatosis. It also allows us not only to diagnose, but to stage and prognosticate in one particular act. It has some caveats, however. It requires a prolonged learning curve, and it has some technical issues to it. For instance, patients with morbid obesity might have overestimated liver stiffness. Patients with active alcohol consumption also can be overestimated in terms of fibrosis. And it's not so clear. But it seems that in the case of patients with type 2 diabetes with poor metabolic control, liver stiffness also might be overestimated.

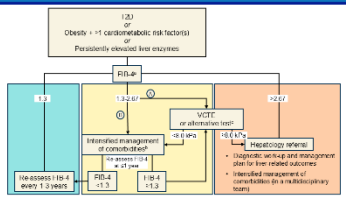
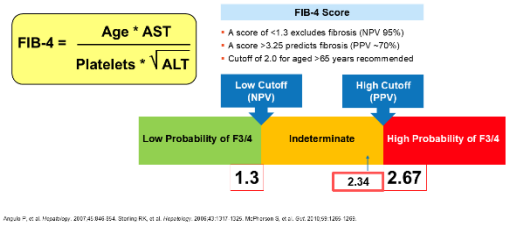
53.	**Comparative Analysis of Biomarkers for Advanced Fibrosis** LITMUS Meta-Cohort Analysis of Histologically Characterized MASLD 	There are other biomarkers that have been assessed and validated in large projects, such as LITMUS in the case of Europe, or NIMBLE in the case of the US, that do perform well, have high area under the curve when compared with the standard of histology as well as to other NITs. And as you can see, for instance, in the case of SomaSignal is a proteomic test combining different proteins, and all of them work quite well in order to identify and monitor advanced fibrosis.
54.	**NITs Are as Accurate as Liver Biopsies for the Prediction of Clinical Events** Prognostic Performance of NITs vs Histology Prognostic Performance of NIT Cutoffs and Histology	And it's also important to note that NITs are as accurate as liver biopsy. Not only to screen, diagnose, but also to prognosticate and monitor treatment response. And in the case of this meta-analysis conducted by LITMUS investigators recently, it also shows 2 important things. The longer the period of assessment, the better accuracy for NITs, as well as for the liver biopsy, of course. But the more information we accumulate, the better the accuracy. And also, and this concerns one of the earlier questions I posed, the higher the number of determination we have available, the better the dynamic specificity. So, this needs to be kept in mind whenever we need to evaluate our patients.
55.	**Resmetirom: Noninvasive Data From MAESTRO-NASH** Sparse Noninvasive Data in Label	And there are already some clinical trials that are using NITs to correlate treatment response to noninvasive assessments. The case of the MAESTRO-NASH was one of the pioneers, and we also are committed to other types of NIT data for other trials in the resmetirom pipeline.
56.	**FIB-4 Has Low NPV for Significant Fibrosis in T2D: Are More Specific Screening Tools Needed?** 	So, before closing, a few words concerning some caveats in patients with type 2 diabetes. We've discussed FIB-4 in terms of screening in the general population as well as diabetic clinics. But we need to be careful because this study and others have shown that the negative predictive value of FIB-4 in low prevalence of fibrosis settings might not be as good as we might want. In this case, 600 patients with available liver biopsy–confirmed MASH diagnoses were assessed in terms of the previous 2-step process, and as you can see, a large proportion of patients with FIB-4 under the cutoff had values of liver stiffness over 8 kPa. And more importantly, both in the group of patients without diabetes and the group with diabetes, in whom there was significant fibrosis of varying proportions. In the case of nondiabetic it was 10%, but in the case of patients with diabetes, as you can see, almost 25% of them had significant

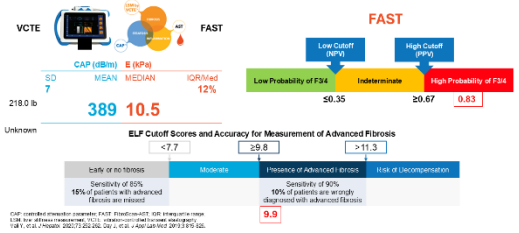
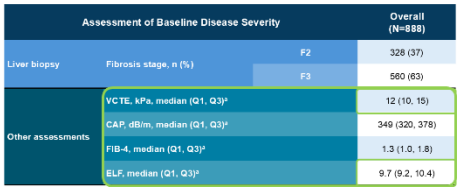
		fibrosis despite having FIB-4 under 1.3. So this requires further data.
57.		And in terms of identifying and diagnosing fibrotic MASH, the high-risk patients we are looking for now, we need to take into account, and this is a beautiful study which I recommend to all of you, led by Prof Laurent Castera, that an adapted cutoff might be necessary in order to identify our patients and treat them.
58.		And finally, there are some authors that are already advocating for universal, systematic, and annual screening of liver fibrosis in patients with type 2 diabetes. Also in diabetes clinics, of course, as they call the liver health check in type 2 diabetes. They advocate for use of the usual tools FIB-4, transient elastography, and ELF and this may warrant further studies. But it's a very interesting matter of study.
59.		So to conclude, we know that MASLD is a highly variable and difficult to diagnose disease. We've been using liver biopsy for a long time, particularly in clinical trials, but now we are approaching the era of treatment. And therefore we need biomarkers that can be derived from blood and imaging. Nowadays, the screening phase is already quite consolidated, and we know that using a 2-step appraisal works with the first step with simple panel biomarkers as a FIB-4 and followed by a second NIT. And while the biomarker field is developing rapidly, we still require some specific predefined context-of-use data in order to apply that in a tailored manner. And while they are imperfect, they are already available, and if used correctly, they may be highly effective to identify patients and start treatment and monitoring. And just a word of caution regarding patients with type 2 diabetes who may have specific features that warrant tailored approaches to screening and referral and monitoring.
60.		And with that, I hand it over to Prof Roden, who's going to talk to us about the clinical cases. Thank you.

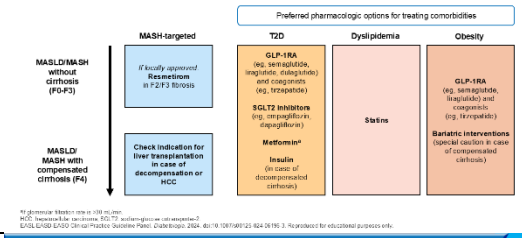
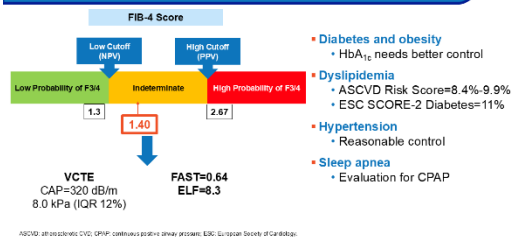
61.		***Prof. Dr. Michael Roden, MD*** So, dear colleagues, first of all, thank you very much for coming here late in the afternoon, already evening, after a very long day. So you are very brave to stay here and even more, you now have heard very specific, to a certain extent, very specific hepatologists' views on the problems that we have to correctly diagnose and case finding in the field on MASLD/MASH. I know that we still have in the field of diabetes, the steatotic liver disease is still not very close to all of us. So I think we still have to learn a lot, so I will try to repeat a little bit on a lower level in order to help us guide in dealing with MASLD/MASH. I just thought before the story that I shared a short oral session yesterday with 8 presentations, and I had 9 different definitions of MASLD, MAFLD, MASH, NASH, NAFLD. So I think we can still learn a lot about this disease. But let's go to what is most important here. We will be talking about management of MASLD/MASH. And we will be sharing together, discussing together 3 specific cases, which should cover or illustrate the different problems of these people, and also the different ways to treat people with MASLD/MASH, particularly in the context of type 2 diabetes. What you see here is, and I think this is very important, we do not focus here on steatosis, which means the amount of fat in the liver. We focus here on fibrosis. So all the case finding, which we agreed upon with the different associations, is that the amount of fat in the liver is a feature, is something, which, of course, is relevant for driving the disease, but it is not the characteristic which defines the progression and the risk for comorbidities. So this means, of course, even if we have people that have a zero fibrosis, F0, it is very important to manage the underlying disease, which in the majority of the people is obesity or type 2 diabetes. Although there is a small group of lean patients with MASH, which we will not directly attach, but probably our hepatologists colleagues will be willing to discuss this specific issue, because this is actually a group which is very insulin-resistant and has specific features. And then later on it is actually the fibrosis and for this, and we heard that already, from the speakers before, there is already the first approved drug, which we soon, hopefully, also will have available in Europe and in other areas of the world.

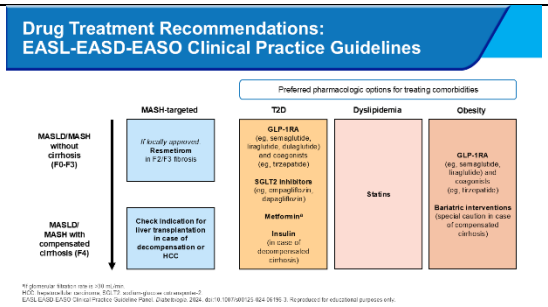
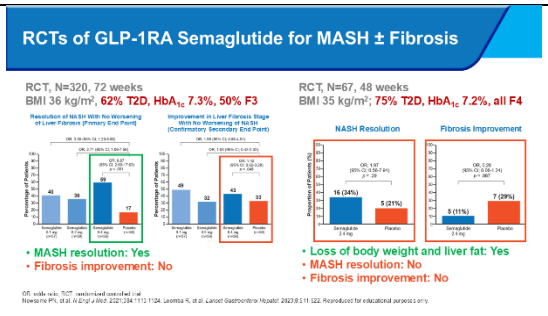
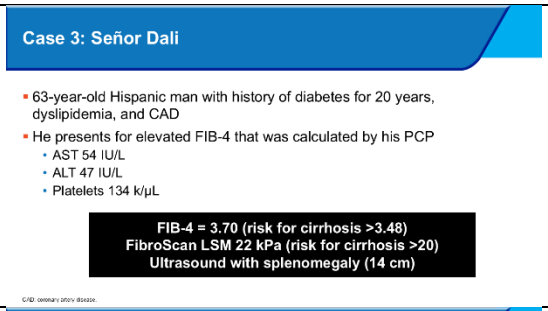
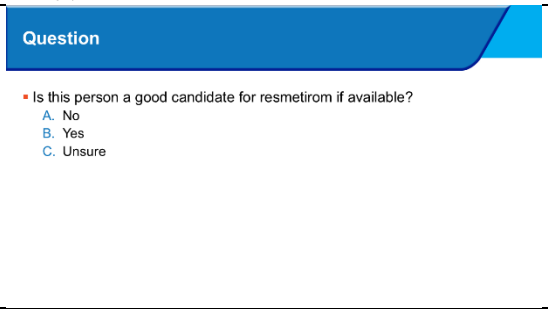
62.		So why is the fibrosis so important? I think the general reason why diabetologists didn't care about stereotactic liver disease is that when you look at epidemiology and you see mortality and the different causes of mortality in people with diabetes, then it's still the majority of people are dying from cardiovascular complications, from stroke, from chronic kidney disease, and the liver, per se, as the cause of death is very rare still in our cohort compared with the other causes. Although it is increasing, and it will be increasing over the years. So, the important point is that liver fibrosis is a major driver of cardiovascular disease. And that is shown here on the left side where you see the MACE, which is the classical endpoint of cardiovascular outcome trials, according to different degrees of histological confirmed MASLD stages. The red line shows you the reference population. I hope you can see it. And then you see the next group in yellow, simple steatosis. There is already an increased risk but it's moderate. But with the increase of inflammation and fibrosis and in particular cirrhosis, there is an excess of cumulative events due to MACE, making the point that fibrosis is a major driver of cardiovascular disease. This study is not done specifically in people with diabetes, but across all the different histologically proven cases with MASLD. The middle panel shows you a study that we published a few years ago, based on the EMPA-REG OUTCOME trial, which you probably all know, it's the large, the first trial with the SGLT2 inhibitor showing significant reduction of cardiovascular outcomes, mainly driven by heart failure, but also kidney disease. And what we did, we took the population independent of the treatment of both groups and we calculated NITs for fibrosis. And you see, the red bars are those with a high risk of fibrosis in this group of people with diabetes. And as you know, from this cohort with a higher cardiovascular baseline risk, had a higher risk for cardiovascular death, heart failure, cardiovascular death and heart failure combined. But of course, not for neuropathy, which we would not expect here. So making the point that this is specifically relevant, fibrosis of the liver is specifically relevant for people with type 2 diabetes plus cardiovascular risk factors. The panel on the right side shows that also, people with type 2 diabetes continuously have a higher risk for worsening of liver fibrosis. Here it's shown the increase of F1, 1 fibrosis point over the course of more than 10 years. Although this slide also shows that probably the progression is similar compared

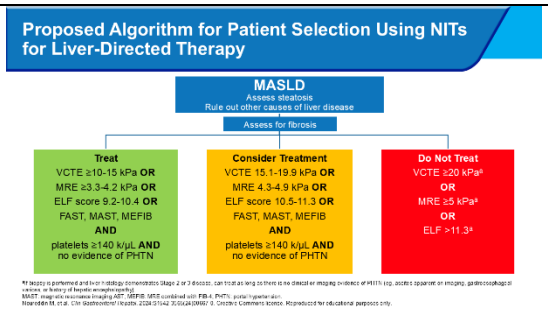
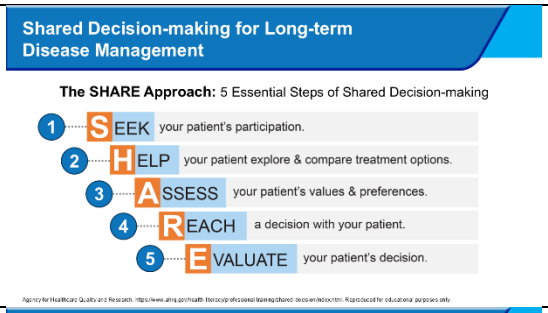
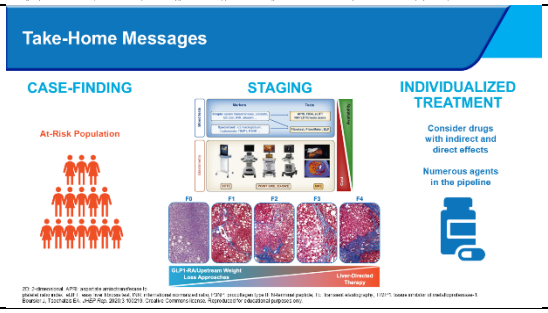
		with patients without diabetes, there are conflicting data at the moment. Some papers show that also the progression of disease is much faster in type 2, but that's not totally clear. But at each level of the year, throughout the course of disease, people with type 2 diabetes have a higher risk of progressing with liver fibrosis. This is the main basis why we are interested in sorting out and finding people with liver fibrosis.
63.		And you have heard about the tests. The experts have shown you their performance, their pros and cons. What is for us interesting is what is the use of these tests for diabetologists and general practitioners, primary care physicians. May I ask you, who is a primary care physician in this audience? And thank you. And who is a diabetologist, endocrinologist? So we have here more endocrinologists than primary care physicians. These graphs show what you can expect from using an NIT in your daily work. The test, the NITs are designed in a way that you would like to identify or clearly exclude a high grade or high stage of fibrosis, which is F3/F4. And in primary care, you have a very high probability of seeing patients that have a low risk of fibrosis and because of the enrichment of obesity in patients with diabetes in the diabetes clinics, you will probably see much more results in this indeterminate range, whereas those with the high probability will be mostly seen in hepatology clinics. Why is this so important? Because we had actually at noon a session, something like an interview, e-learning session with Amalia Gastaldelli, and one of the general practitioners asked the question, “Why should I do the FIB-4? I expect that I wouldn't see anyone.” This is not the case if you do it in all of those who require the test, because still you would need a significant number or relevant number of those with probably F2. So what we can expect that we have tests that would hopefully exclude or rule in the presence of high-grade, high-stage fibrosis.
64.		Okay. First case, it's Señora Torres, a Hispanic woman, 55 years old, and she is referred to a specialist from her primary care physician for the assessment of her liver. The cause of the referral is unclear. Probably it was her symptoms that she had some kind of right upper quadrant discomfort, which is something which all of us might have sometimes, and it's very uncharacteristic. But if the patient has these problems, it could actually lead finally to a specialist referral, which happened in this case. She had a long track record of type 2 diabetes, dyslipidemia for 2 years, family history of diabetes and hypertension with her father. The social history: she is exercising

		only occasionally, mainly sedentary in her job, and regularly, but not intensively using alcohol. The examination revealed borderline normal weight to slightly overweight, something like BMI 25 kg/m^2, blood pressure 130/80 mm Hg, and she is using metformin 500 mg twice daily and a fish oil preparation.
65.	**Case 1: Señora Torres (cont)** Laboratory Values ALT 99 IU/L AST 72 IU/L Total bilirubin 13.7 µmol/L (0.8 mg/dL) Albumin 40 g/L (4.0 g/dL) Platelets 170,000/µL LDL 4.75 mmol/L (184 mg/dL) HDL 0.93 mmol/L (36 mg/dL) Triglyceride 2.71 mmol/L (240 mg/dL) HbA_{1c} 47.5 mmol/mol (6.5%)	These are the lab results clearly showing increased transaminases: ALT and AST both increased, significantly increased, at least for a diabetologist, probably not for a hepatologist, but for us it would be just high; and the platelets are not very high. LDL increased. HDL low. Triglycerides also high. And the HbA_{1c} with metformin perfectly controlled within HbA_{1c} of 6.5% or 47.5 mmol/mol if you use the SI units more frequently.
66.	**Case Finding Instead of Untargeted Screening: EASL-EASD-EASO Clinical Practice Guidelines** 	So what we need in this patient now is the NIT. And this is now again showing you the most recent European Guidelines by both the liver, the diabetes and obesity associations. And what we are actually asking for is the FIB-4 value. Although, and this has been nicely shown before, it has its limitations, unfortunately and particularly, in the type 2 diabetes cohort. Still, it is a very nice initial test, at least in order to sort out those, in many cases with a FIB-4 of less than 1.3, where we can be more or less conservative and just retest, or in the middle range between 1.3 to 2.6/2.7, where actually 2 ways are possible. And when we did these guidelines, there was a lot of discussion. Should we favor 1 pathway? We ended up being democratic and not deciding, but the majority of us actually tended to have a second test as soon as possible in this cohort. And I'd rather belong to this group A, but there is, of course, the alternative that you also can see based on resources and access to FibroScans or other tools that you can do, let's say, close monitoring of these patients and intensify the management of their comorbidities.
67.	**FIB-4 for Ruling Out Advanced (F3/4) Fibrosis** 	So, this is the way to calculate the FIB-4, probably one of the few messages of all of our talks is the FIB-4. FIB-4 is very important, easy to get if you can convince your lab because they can just have it on the printout, which depends on the age, the AST square root of the ALT and the platelets. And most importantly here, we should not only refer to these cutoffs 1.3 and 2.67, but also the age is very important. So it is very important that once your patients are older than 60 or 65 years, then the cutoff should not be 1.3 but moved up to 2, which is very important because of the subsequent test that you would like to do. So our patient had an indeterminate FIB-4 of 2.34.

68.	**Use of Additional NITs for Indeterminate FIB-4** 	And that is where we stand and that, actually based on the guidelines, requires an additional test. And there are a number of different tests which maybe later on in the discussion we could refer to, but not to confuse you here, I think the most easily accessible test is a transient elastography, ultrasound-based, most people use the FibroScan, which gives you a result for the steatosis, the CAP value, which is 389 dB/m, and liver stiffness value of 10.5 kPa, which is already showing an increased risk of fibrosis and significant steatosis 2.
69.	**Question** ▪ Is this person a good candidate for treatment with resmetirom if it were available? A. No B. Yes C. Unsure	And this is now the open question. So we have a patient with an indeterminate, not super high risk but medium increased risk FIB-4 value. We have increased risk based on elastography. And now, is there a specific treatment that we could offer the patient? Let's assume we have the resmetirom already available here. And based on what you have heard, is this person a good candidate for treatment with resmetirom, if it were available? A is no, B is yes, C is unsure. And if you know, please scan the QR code. So, your vote is B, 52%; 23% are unsure; and 23%, no. So that's giving us at least a direction in the right way, because the resmetirom is actually the one that we would suggest to use for these patients.
70.	**PI: Baseline Features From the MAESTRO-NASH Trial With Resmetirom** 	Why? Because the alternatives are not directly acting on the liver and the major problem of this person is the liver. These are actually data from the MAESTRO-NASH Trial that you have heard before. And most of the data of our patient here, the elastography value of 12 kPa, our patient had a little bit more than 10 kPa. Also I didn't address the ELF test. The CAP value was, I think 380 dB/m, and here it's 349 dB/m. The only thing is the FIB-4 in this cohort was rather low. Actually again showing that just having 1 single test is not enough. So with the FIB-4 of 1.3, this would be rather low for this cohort, and our patient had a higher one. And this is the cohort of people that have a high risk of F2 or F3 fibrosis. And this is within the indication, as we have heard, of the resmetirom.
71.	**Question** ▪ Should we consider adding any additional therapy at this time? A. GLP-1RA B. Statin C. SGLT2 inhibitor D. No	The next question, however, is, “Should we consider adding any additional treatment at this time?” So this now brings the experts here in the room to the table. And A, GLP-1 receptor agonist; a statin, B; SGLT2 inhibitor; or nothing. So here we have B, a statin, definitely useful for hyperlipidemia perfectly well. A, GLP-1 receptor agonist, second choice, can be debated. If this is a very high-risk patient for cardiovascular disease, which we have not shown here, then it is an option, but it's not actually, we also could argue that an SGLT2 inhibitor might be relevant

		if this patient, for example, has heart failure. But in general, I can say we are on the right way here. Should we consider anything else at this time?
72.	**Drug Treatment Recommendations: EASL-EASD-EASO Clinical Practice Guidelines** 	Let's think about it. So we now have in this patient resmetirom according to the guidelines. We have a statin for the dyslipidemia. And for the diabetes, per se, with an HbA_{1c} of 6.5%, we actually do not need to do anything more, unless this is a super high-risk cardiovascular or kidney patient, then I would agree with the 20% or 30% of you that we might also consider a GLP-1 receptor agonist.
73.	**Case 2: Señor Quixote**  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 × 10⁹/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	The next one is Señor Quixote. Probably the right name for this place here. Mr. Quixote has high transaminases. He is rather young, 48 years old, obese, BMI 35 kg/m^2, blood pressure like our previous patient. Among the other data, there is also increased cholesterol and LDL and triglycerides. Glucose control—moderate—7.5%. He has medication with metformin, spironolactone, and something for his β-mimetic asthma. He denies alcohol use and smoking.
74.	**Fibrosis Risk Stratification and Comorbidity Assessment** 	So in this case, we just move on to the FIB-4, 1.4, indeterminate like in the previous patient, but much more on the lower side. And the elastography gives us a value of 8 kPa, which is still on the low range, where we say below 8 or 8 kPa is still low risk of fibrosis, and I don't address the other tests here. The patient has a number of issues to be solved, which is of course the HbA_{1c}; the dyslipidemia—he has a moderate to high cardiovascular risk. Hypertension can be seen as more or less well controlled. The sleep apnea also might need further evaluation for intensive treatment.
75.	**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)	Question is here. So we have a patient that has a number of endocrine conditions, but also a liver disease with an indeterminate FIB-4 in the moderate range of fibrosis risk. So should we consider on top of his metformin treatment, any other treatment? Also taking into account that he has fatty liver disease. And this is, as you can see, A, GLP-1 receptor; statin; combination; SGLT2; combination with statin; or resmetirom, which is important, if it's available. So we have here A, very good choice; F, resmetirom, not the perfect choice here; and C, the perfect choice this patient needs. He has obesity. He has dyslipidemia. He has a high cardiovascular risk. He needs to reduce body weight and have a drug that is active in this direction, which is a GLP-1 receptor agonist. And he needs the statin also for the cardiovascular complications. And the GLP-1 receptor agonist might have additional value. Why not resmetirom? At the moment, the data for resmetirom are for fibrosis, F2,

		F3, and not for a patient that most likely has an F1 fibrosis, maybe an early F2 fibrosis. And of course, those of you voting for F are probably in the future, the right ones, we do not know, but at the moment, it is a patient that rather needs intensifying of the metabolic control. So should we consider any additional treatment here?
76.		I think we discussed that. GLP-1 receptor agonist, a statin, and resmetirom—not the perfect drug for this kind of patient. There might be something to consider, I didn't mention it, but maybe you read it, this patient had spironolactone also, so it could be that he has early signs of heart failure, maybe heart failure with preserved ejection fraction. So this patient could additionally maybe have a benefit from an SGLT2 inhibitor, but this needs a workup, probably by a cardiologist.
77.		Why is a GLP-1 receptor agonist good under these conditions? Because we have already heard about this study, I'll just briefly review. We have evidence that at least the inflammatory part of fatty liver disease is improved with semaglutide in a phase 2 study, although there is no significant effect if you statistically compare all the dose groups with regard to fibrosis. A large trial is ongoing, we don't have the results yet. On the right side, something to mention, you do not need to reduce the dose or change it if this patient has a fibrosis, because they have done a study in F4 fibrosis and there were no effects on measured fibrosis, but it was more or less well tolerated, and liver fat at least was reduced. Again, it's not the drug for treating cirrhosis, but if you use it in people with obesity, then it could probably continue to be used.
78.		Last case, very simple, Señor Dali, 63-year-old Hispanic man. Long history of type 2 diabetes, dyslipidemia, cardiovascular disease. Presents with markedly increased FIB-4, which is easy to see here from the low platelets. The FIB-4 is 3.7, very high risk for fibrosis. FibroScan indicates high risk for cirrhosis and ultrasound already shows a clinically progressing cirrhotic disease.
79.		So this is now the question: Do we have a good drug for this patient? Is he a candidate for resmetirom? No. Yes. Or are you not sure. Congratulations to 50% of you. This is not the right patient because it's an F4 fibrosis, it is a cirrhosis, and there is no indication to use resmetirom, again, at the moment, based on the current data and the approval of the drug. It might change in the future, we do not know. Maybe some

		of you are already living in the future, but for the moment, not to be used in cirrhosis.
80.		So, there is an algorithm, I think I don't want to go into detail because that actually just came out, is an expert opinion how you should select people using NITs for liver-directed treatment, which in other terms is treatment for resmetirom. You can take the picture here. You can read it. It is something for the moment, which most likely is more of interest to the hepatologists because they have all the different tests available, and they also can clearly interpret these tests. But be aware that there is already a way to select the people according to tests, NITs, without histology for giving resmetirom.
81.		Of course, at the end it's all about shared decision-making. As you know, it needs the patient, it needs your expertise, it needs the interaction with the patient, and at the end, you need to decide together with the patient particularly, when using novel drugs, and obviously I do not need to tell this to you.
82.		Take-home messages from my side: Try to find the case; use the FIB-4; if you have access to elastography, use it for staging and making the next level of decision; be in very good contact with the hepatologist in order to together come to an individualized treatment of your patients. Thank you very much for your attention.