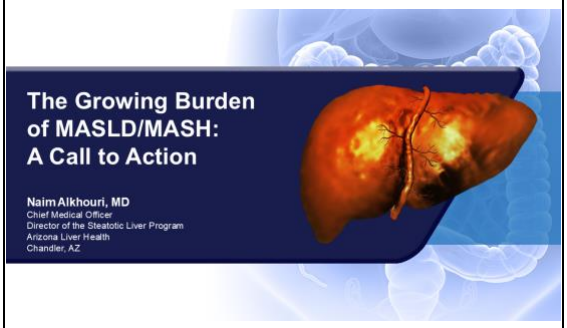
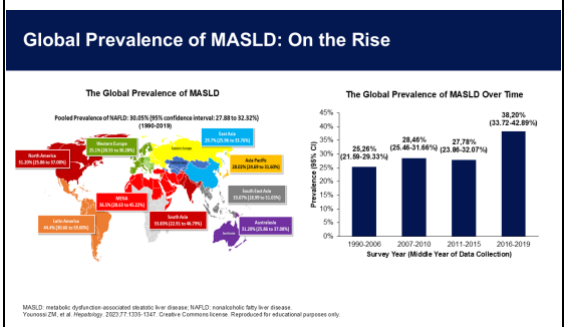
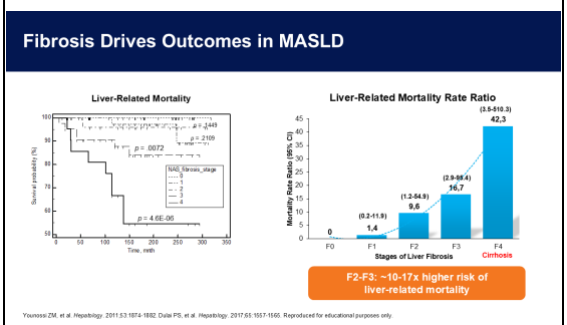
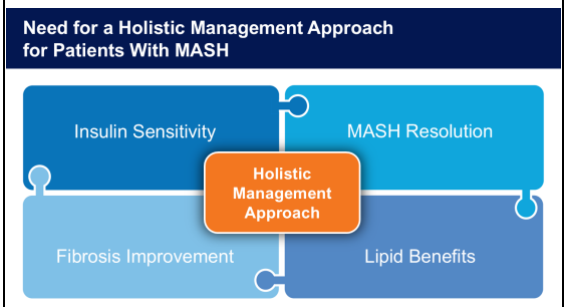
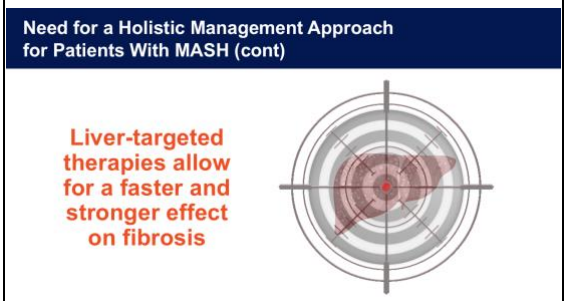
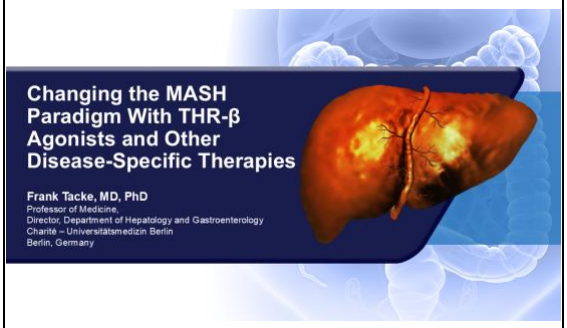
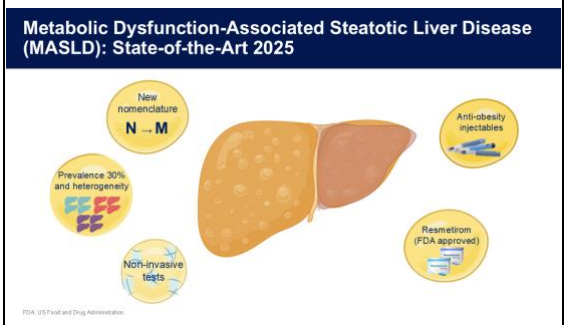
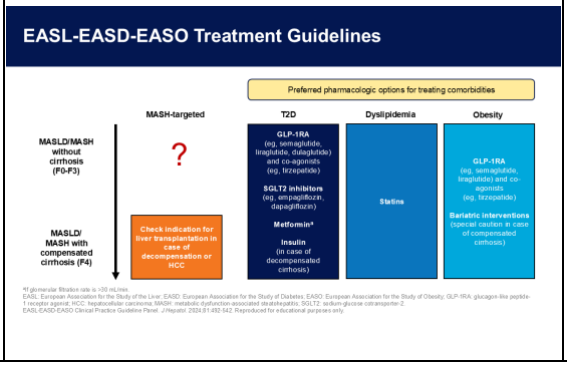
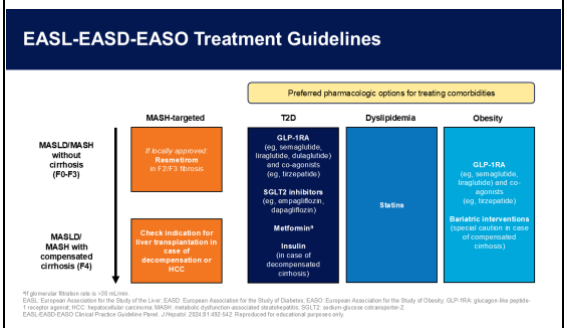
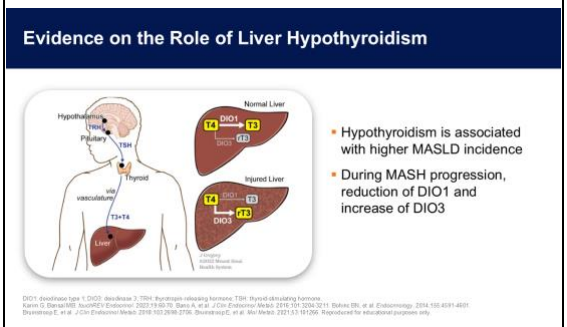
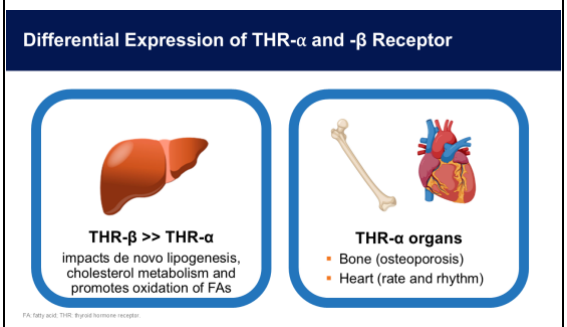
1.		**[Naim Alkhouri, MD, FAASLD]** I'm Dr. Naim Alkhouri, Chief Medical Officer at Arizona Liver Health at Phoenix, United States. The session is titled "A New Era in MASH: How Disease-Specific Therapies Are Changing the Game and Best Practices for Clinical Integration."
2.	**Nonalcoholic Steatohepatitis (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	So, the following presentation contains a discussion of an FDA-approved drug for the treatment of NASH. This is the FDA label in the United States. Here we are referring to it as resmetirom. I know it's not approved in Europe yet, but hopefully this summer it will be available for you guys to use. NASH is now known as MASH, but when we designed the MAESTRO-NASH trial that led to the FDA approval, we used the old terminology, so you may see that the presenters will use NASH and MASH interchangeably.
3.	**Faculty**  **Naim Alkhouri, MD, FAASLD** Course Director Chief Medical Officer Director, Steatotic Liver Program Chief of Transplant Hepatology Arizona Liver Health Phoenix, AZ  **Professor Laurent Castera, MD, PhD** Université Paris-Cité Department of Hepatology Hôpital Beaujon, Assistance Publique-Hôpitaux de Paris INSERM UMR 1149, Centre de Recherche sur l'Inflammation Paris Montmartre Clichy, France  **Prof. Dr. med. Frank Tacke, MD, PhD, MHBA** Director Medical Department of Hepatology and Gastroenterology, Charité – Universitätsmedizin Berlin, Campus Charité Mitte and Campus Virchow-Klinikum, Berlin, Germany	
4.	**Overview and Target Audience** **This activity is jointly provided by AKH Inc., Advancing Knowledge in Healthcare and Catalyst Medical Education, LLC.** **This activity is supported by an educational grant from Madrigal Pharmaceuticals.** **ACTIVITY OVERVIEW –** Mitigating disease progression in MASH has been challenging due to a lack of disease-specific therapies. With FDA approval of the first MASH-specific therapy, and several other agents in advanced stages of development comes, a new era of disease management. This activity will explore the mechanism of action and efficacy of these novel therapies, including thyroid hormone receptor-β (THR-β) agonists, along with data on late-stage investigational therapies. Experts will also focus on case-based scenarios that discuss considerations for disease staging and assessment through non-invasive tests to ensure pharmacological management is tailored to the individual needs of each patient. **TARGET AUDIENCE –** This initiative is intended for hepatology and gastroenterology healthcare providers, as well as other specialty clinicians involved in the management of patients with MASLD/MASH.	

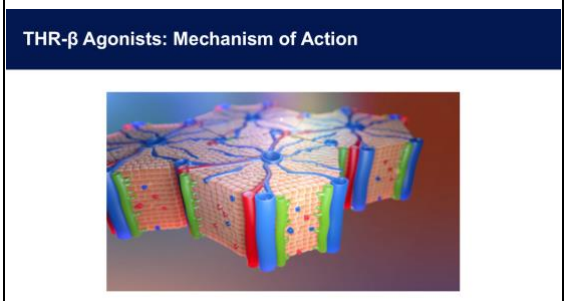
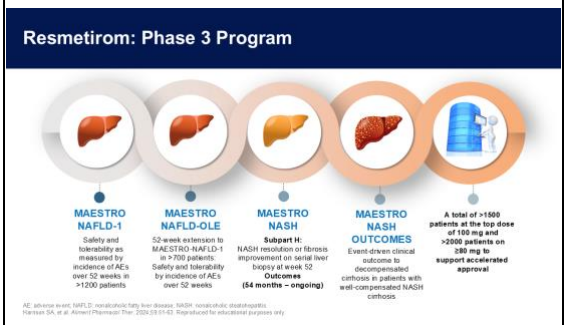
5.	**Learning Objectives** Upon successful completion of this activity, participants should be better able to: ▪ **Describe** the mechanistic and clinical rationale for THR-β agonists as a means of treating MASLD/MASH ▪ **Evaluate** the evidence on THR-β agonists, and other disease-specific therapy classes, considering efficacy, safety/tolerability, and PROs ▪ **Identify** best practices for facilitating and documenting an accurate, non-invasive, and timely diagnosis of MASLD/MASH to support access to disease-specific therapy ▪ **Develop** guideline-aligned management paradigms for MASLD/MASH that incorporate pharmacotherapy tailored to individual clinical scenarios	
6.	**Agenda** ▪ The Growing Burden of MASLD/MASH: A Call to Action ▪ Changing the MASH Paradigm with THR-b Agonists and Other Disease-specific Therapies ▪ Rising to the Need to Improve Diagnosis in the Era of Disease-Specific Therapy ▪ Integrating MASLD/MASH-Specific Therapy into Guideline-Aligned Real-World Practice ▪ Q&A and Closing Remarks	
7.	**Accreditation & Credit Designation Statements** **Criteria for Success** Certificates of completion will be awarded based on the participant's attendance and submission of the activity evaluation/claim credit form. You must participate in the entire activity to receive credit. There is no fee to participate in this activity. If you have questions about this activity, please contact AKH Inc. at tbrignoni@akhcme.com. AKH Credit provided by AKH Inc., Advancing Knowledge in Healthcare In support of improving patient care, this activity has been planned and implemented by AKH Inc., Advancing Knowledge in Healthcare and Catalyst Medical Education, LLC. AKH Inc., Advancing Knowledge in Healthcare is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team. **Physicians** AKH Inc., Advancing Knowledge in Healthcare designates this live activity for a maximum of 1.0 *AMA PRA Category 1 Credit(s)™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity. **Type of Activity:** Application-based **Fee Information:** There is no fee for this educational activity	
8.	**Disclosures** **Disclosure** It is the policy of AKH Inc. to ensure independence, balance, objectivity, scientific rigor, and integrity in all of its continuing education activities. The author must disclose to the participants any significant relationships with ineligible companies whose products or devices may be mentioned in the activity or with the commercial supporter of this continuing education activity. Identified conflicts of interest are mitigated by AKH prior to accreditation of the activity. AKH planners and reviewers have no relevant financial relationships to disclose. **Naim Alkhouri, MD, FAASLD**, has disclosed the following relevant financial relationships: Advisor - 89bio, Akero, Boehringer Ingelheim, Echosens, Fibronostics, Gilead Sciences, Histoindex, Intercept Pharmaceuticals, Ipsen, Madrigal Pharmaceuticals, NorthSea Therapeutics, Novo Nordisk, Perspectum, Pfizer, and Regeneron; Researcher - 89bio, Akero Therapeutics, Arbutus Biopharma, AstraZeneca, BioAge, Boehringer Ingelheim, Bristol Myers Squibb, Corcept Therapeutics, Galectin Therapeutics, Genentech, Gilead Sciences, Healio, Hepagene Therapeutics, Intercept Pharmaceuticals, Inventiva Pharma, Ionis Pharmaceuticals, Ipsen, Lilly, Madrigal Pharmaceuticals, Merck, NGM Biopharmaceuticals, Noom, NorthSea Therapeutics, Novo Nordisk, Perspectum, Pfizer, PharmaNN, Poxel, Regeneron, Viking Therapeutics, and Zydus; Speaker - AbbVie, AstraZeneca, Echosens, Gilead Sciences, Intercept Pharmaceuticals, Ipsen, Madrigal Pharmaceuticals, and Perspectum. **Laurent Castera, MD, PhD**, has disclosed the following relevant financial relationships: Consultant - Boehringher Ingelheim, Boston Pharmaceutical, Echosens, Gilead, GSK, Madrigal, MSD, Novo Nordisk, Pfizer, Sagimet, Siemens Healthineers; Speaker - AstraZeneca, Echosens, Gilead, Inventiva, Madrigal, and Novo Nordisk. **Prof. Dr. med. Frank Tacke, MD, PhD, MHBA**, discloses the following financial relationships: Consultant - Intuitive **STAFF/REVIEWERS** Louis Settembrino, CHCP, Catalyst Medical Education, LLC, President and CEO: has disclosed no financial relationships. Dorothy Caputo, MA, BSN, RN, AKH Lead Nurse Planner/Reviewer, has no financial relationships to disclose. Trish Brignoni, AKH Director Operations & Compliance, has no financial relationships to disclose. Stephanie S. Wenick, MPhil, Medical Writer, has served as a consultant medical writer for REGENXBIO, Inc. AKH and Catalyst Medical Education, LLC Planners and Reviewers, has no financial relationships to disclose. All of the relevant financial relationships listed for these individuals have been mitigated.	

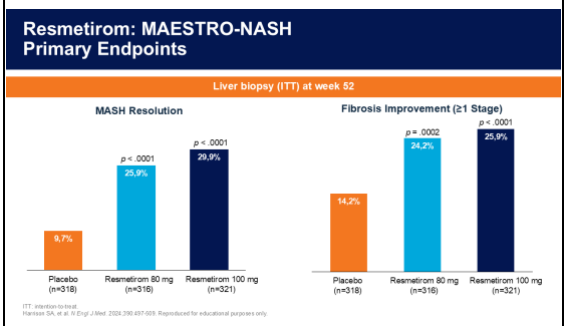
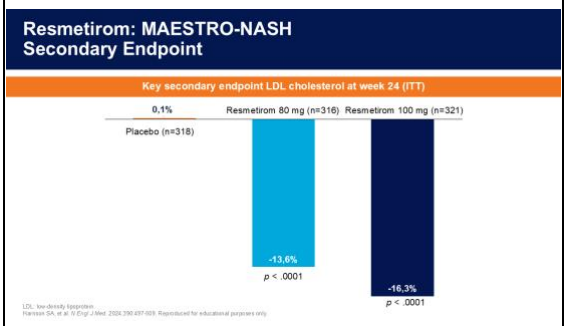
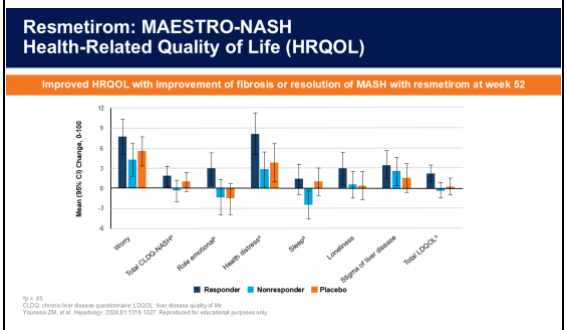
9.	**Disclaimer** This course is designed solely to provide the healthcare professional with information to assist in his/her practice and professional development and is not to be considered a diagnostic tool to replace professional advice or treatment. The course serves as a general guide to the healthcare professional, and therefore, cannot be considered as giving legal, nursing, medical, or other professional advice in specific cases. AKH Inc. specifically disclaim responsibility for any adverse consequences resulting directly or indirectly from information in the course, for undetected error, or through participant's misunderstanding of the content. If you would like to opt out from future communications from AKH please send an email to optout@akhcme.com with your information with "Opt Out" in the subject line. **Disclosure of Unlabeled Use and Investigational Product** This educational activity may include discussion of uses of agents that are investigational and/or unapproved by the FDA. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.	
10.		Okay, so let's get started. "The Growing Burden of MASLD and MASH: A Call to Action."
11.		I think we all know that, MASLD is the most common liver disease globally. It affects about 30% of the adult population, with the highest prevalence in Latin America (up to 44% of adults), followed by the Middle East and North Africa (MENA region, up to 36% of adults have MASLD). And unfortunately, the global prevalence is increasing over time. So, the most recent estimates actually estimate that MASLD affects 38% of the adult population. We also have data on children and adolescents, and the estimates are that MASLD affects about 10% of children.
12.		Fibrosis on the index biopsy is the most important predictor of outcomes, and we have several studies showing that patients with F2-F3 fibrosis have real risk of progressing to cirrhosis in their lifetime and developing older cirrhosis-related complications. The fibrosis stage can predict overall mortality, liver-related mortality, and major adverse liver outcomes. In one

		systematic review, patients with F2-F3 fibrosis had 10- to 17-fold higher risk of liver-related mortality. And that's why when we are developing new therapeutics, you see that we divide the clinical trials into those with MASH, F2-F3 fibrosis, and one of the main objectives in these trials is to prevent progression to cirrhosis. And then we have mass cirrhosis trials that we are conducting separately. And here we are looking at preventing liver-related outcomes such as the development of ascites, variceal bleeding, and encephalopathy. But I think a key message that you're going to walk out with today is that you need to know the fibrosis stage in every patient with MASLD. So staging is key because it has great prognostic implications, and based on the fibrosis stage, the treatment algorithm is going to change.
13.		So, we need a holistic approach to managing patients with MASH. As hepatologists we are always focused on liver outcomes, so in clinical trials you see us reporting on MASH resolution and fibrosis improvement by 1 stage. But with every therapeutic approach, we need to be looking at each component of the metabolic syndrome and see what happens to weight. Are we making the patients lose weight? There are, you know, medications that are weight neutrals. There are medications that are very effective in inducing weight loss. What happens to insulin sensitivity? Are we decreasing HbA_{1c}, helping prevent diabetes and pre-diabetics, and do we have a lipid benefit? And we need to look at the triglycerides, LDL cholesterol, HDL cholesterol. So again, keeping an eye on the entire picture,

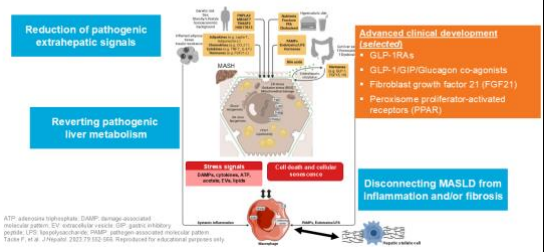
		and we cannot be so myopic and just look at liver outcomes.
14.		There is a definite need for liver-directed therapies. We have medications that can treat several aspects of the metabolic syndrome. But, definitely in patients with F2 and F3, having liver-directed therapies, is, a great need, and I'm glad that in the United States we have 1 FDA-approved medication that should be coming to Europe soon. But we need more medications that can work independently as monotherapy, but also potentially as combination therapy with other medications.
15.		**[Prof. Dr. med. Frank Tacke, MD, PhD, MHBA]** I'm happy to discuss with you how the new therapies that are on the horizon may change our disease-specific approaches to MASLD and MASH.
16.		
17.		And, as a reminder, where do we stand at the moment with our guidelines? So, we know that the base of any therapeutic approach in MASLD/MASH is a lifestyle intervention with a healthy diet, with weight reduction in the case of overweight and obesity, with alcohol abstinence and with

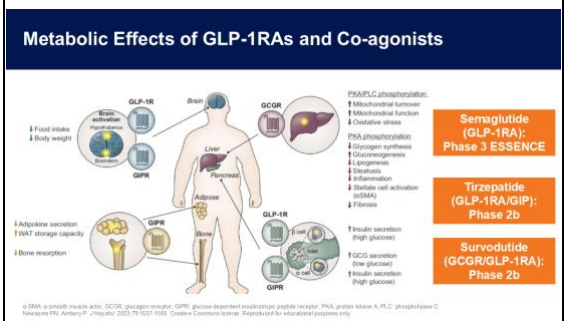
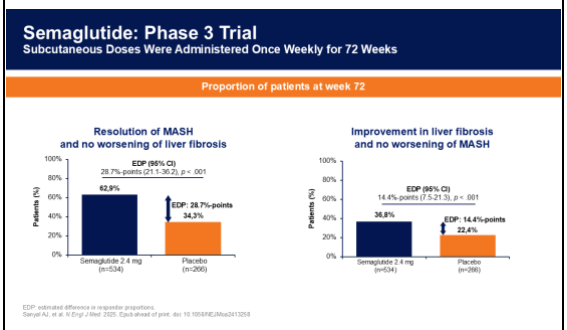
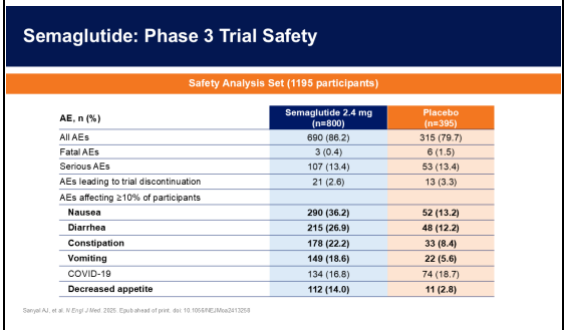
		exercise. And we need to manage our comorbidities in an optimal fashion, meaning that patients with type 2 diabetes will benefit from weight-reducing therapies such as GLP-1 receptor agonists and SGLT2 inhibitors. Dyslipidemia should be treated with statins. Obesity may benefit from pharmacotherapy or bariatric interventions. But what was open so far and still is in Europe is the question of whether we can offer, in patients with at-risk disease, any MASH-targeted therapy.
18.		And for this, the guidelines recommend to use (if it's locally approved) resmetirom in F2-F3 fibrosis.
19.		And why is that? So, we have a lot of evidence over the past decades that we do have hypothyroidism in MASLD that's associated, but we also have a local lack of active thyroid hormone in the liver due to some changes in thyroid hormone metabolism in the liver.
20.		We do understand by now that some of the beneficial actions in the liver are very specific to thyroid hormone receptor β agonism, meaning the increased de novo lipogenesis, cholesterol metabolism, or activation of certain transcription factors that promote oxidation of fatty acids. On the other hand, some of the most systemic effects like tachycardia, bone density loss,

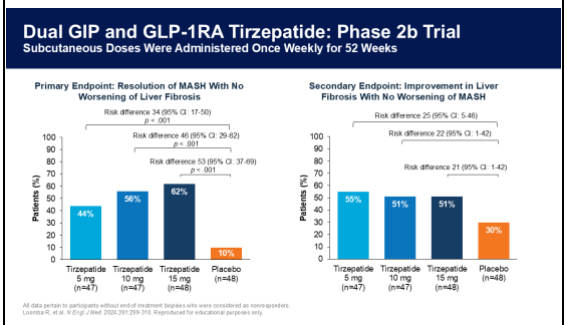
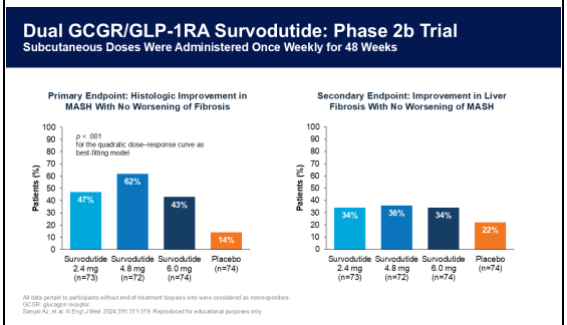
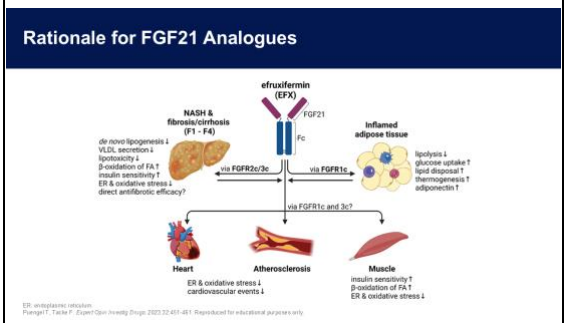
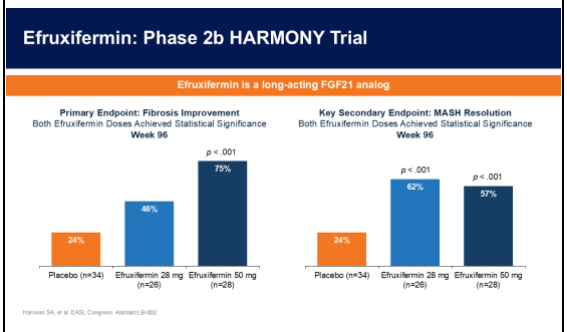
		are actually related to thyroid hormone receptor α actions.
21.		And that's kind of the concept of resmetirom. And this is a little animation that we would like to share with you on how resmetirom works. **[Animation]** Thyroid hormone receptor β agonists or THR-β agonists are small molecules designed 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.
22.		**[Prof. Dr. med. Frank Tacke, MD, PhD, MHBA]** I think the trick is that resmetirom actually is liver-targeted so it accumulates in the liver and specifically activates the thyroid hormone receptor β pathway. And this has been demonstrated in a number of studies, you see here in a brief overview. So, in the end, more than 1500 patients had been treated in the top dose, more than 2000

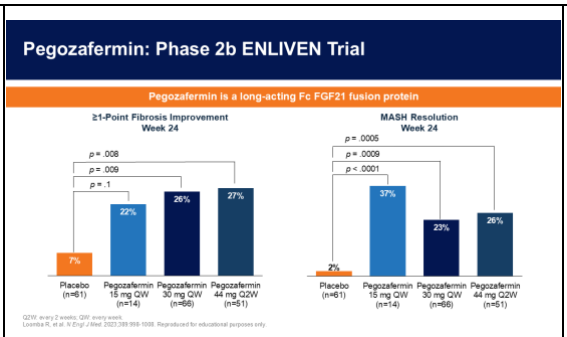
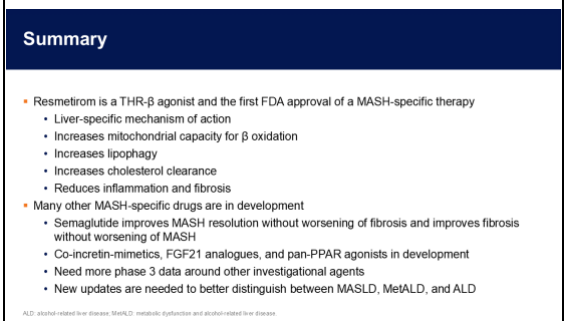
		patients on the lower dose. So, we have a lot of safety and efficacy data.
23.		But the most relevant efficacy data are derived from the MAESTRO-NASH trial, which tested the histological benefit. When you start resmetirom at 80 or 100 mg, and look, after 1 year and you see here MASH resolution was statistically significantly more frequently reached in the resmetirom-treated group and fibrosis improvement (probably the most important outcome) was also statistically significant in the resmetirom-treated participants. The delta to placebo is about 14% to 18%, so maybe not as high as we would hope. On the other hand, we have a lot of noninvasive markers going into the right direction.
24.		An example here, LDL cholesterol is decreasing nicely. Transient elastography values, noninvasive measures of fibrosis are decreasing. So, there's a lot of evidence that the patients benefit from this intervention.
25.		There are also some data that the patients that are responding improve or also have health-related quality-of-life improvement (as you can see here) for different areas that have been tested within the phase 3 clinical trial.

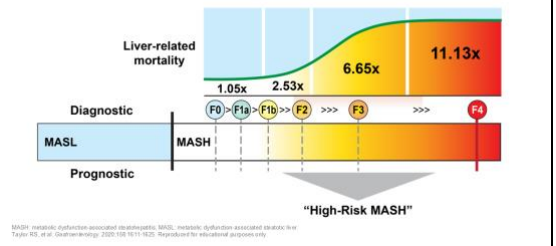
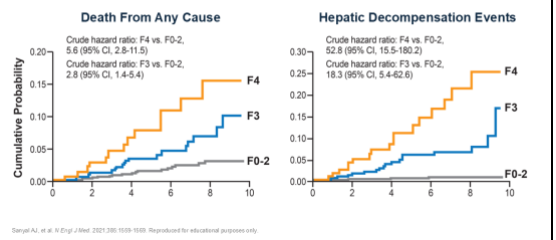
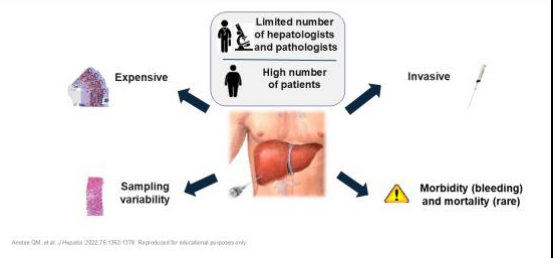
26.	**Resmetirom: MAESTRO-NASH Safety**
	
	AE (%) / Resmetirom 80 mg (n=322) / Resmetirom 100 mg (n=323) / Placebo (n=321)
	Serious AEs / 10.9 / 12.7 / 11.5
	Study discontinuation for AEs / 2.8 / 7.7 / 3.4
	Diarrhea / 27 / 33.4 / 15.6
	Nausea / 22.0 / 18.9 / 12.5
	
	• Resmetirom was well tolerated
	• Consistent with previous phase 2 and phase 3 data, the most common AEs reported with greater frequency in the resmetirom groups vs placebo were:
	  • Excess of generally mild and transient diarrhea
	  • Generally mild nausea at the beginning of therapy
	
	Harrison SA, et al. *N Engl J Med*. 2024;390:497-509. Reproduced for educational purposes only.
		How about the safety? I guess we will learn from Naim how it looks in real life. The clinical trial data are very convincing. So, there are some gastrointestinal side effects, very low number of study discontinuation due to side effects, and overall, a low number of serious adverse events.

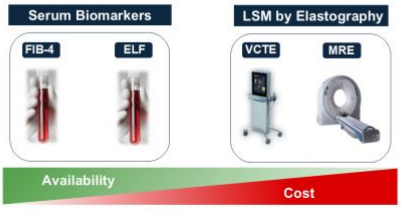
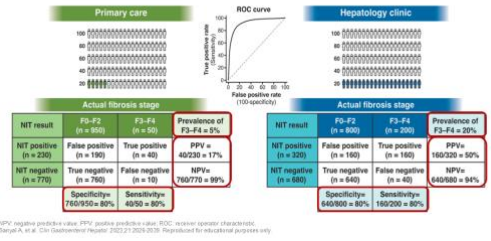
27.	**Other THR-β Agonists in Development** Drug Candidate / Study Stage / Endpoints VK2809 / Phase 2 Biopsy-confirmed MASH (N=248) / 12-week reduction of liver fat content 52-week biopsy data presented at AASLD TERN-501 / Phase 2 Presumed MASH (N=162) / 12-week reduction of liver fat content Results available[a] ALG-055009 / Phase 2 Presumed MASH (N=100) / 12-week reduction of liver fat content Data presented at AASLD TLM 2024 [a]No longer in development. AASLD, American Association for the Study of Liver Diseases; TLM, The Liver Meeting. ClinicalTrials.gov. NCT04171065. ClinicalTrials.gov. NCT05415722. ClinicalTrials.gov. NCT06342947.	Resmetirom is not the only thyroid hormone receptor β agonist in development. So, we do have some different compounds from different companies in different stages of development. So, I guess we can expect that this field will be expanded in the future and will give us more options.
28.	**Therapeutic Strategies Against Steatohepatitis and Fibrosis**  ATP, adenosine triphosphate; DAMP, damage-associated molecular pattern; EV, extracellular vesicle; GIP, gastric inhibitory polypeptide; LPS, lipopolysaccharide; PAMP, pathogen-associated molecular pattern. Tacke F, et al. *J Hepatol*. 2023;79:552-566. Reproduced for educational purposes only.	Nonetheless, if we think about, conceptually, what do we do with the therapy, I guess a lot of our current efforts focus on reducing pathogenic extrahepatic signals. For instance, if we think about modifying nutrition, losing weight, using GLP-1 receptor agonist, so they all act outside the liver. We do not have drugs of the moment to disconnect MASLD from its consequences (from inflammation and fibrosis), but I think with resmetirom we have the first drug that tries to act directly in the liver and reverting some of the pathogenic features of liver metabolism. But this is not the only one. I guess we have some data emerging, how in incretin mimetic GLP-1 receptor agonists, GLP-1/GIP/glucagon co-agonists may work. FGF21 (we just had a very exciting presentation in the general session about it), PPAR agonists are also on the table. Let me just briefly highlight some of the findings using these drugs in clinical trial settings.

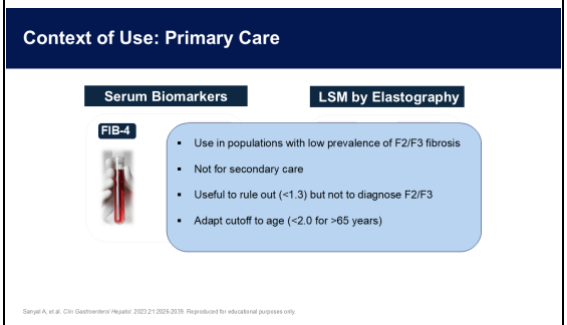
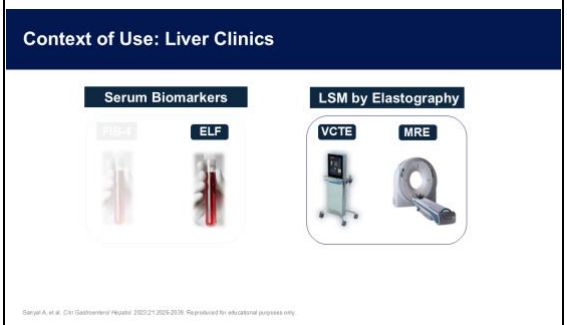
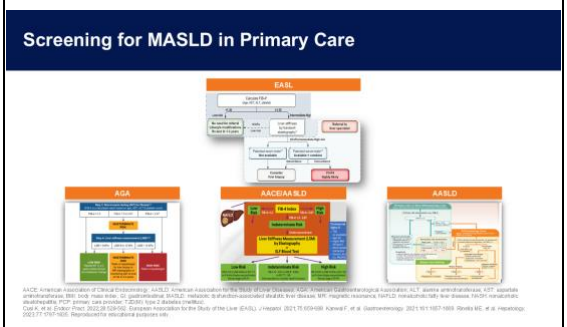
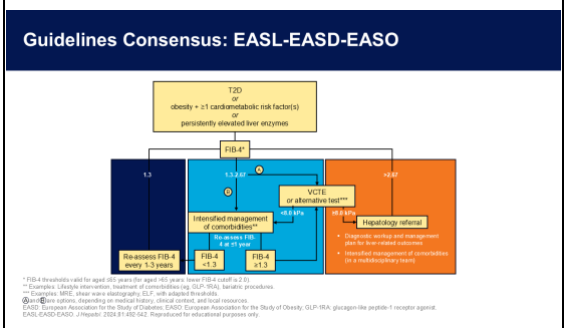
29.		With GLP-1 receptor agonists, they're already approved in clinical practice, they work on the gut and slow down GI motility. But GLP-1 receptor agonism is also active in the brain, also in the pancreas, explaining some of the beneficial effects. And it's very tempting to speculate if you add glucagon receptor agonism or GIP receptor agonism that you'll have more specific effects also on the adipose tissue or on the liver. And this is, how the data look at the moment: we have semaglutide, the traditional GLP-1 receptor agonist in phase 3 (positive phase 3 clinical trial for MASH); with tirzepatide, the clinically approved GLP-1 receptor agonist; GIP, for the treatment of obesity and T2D (with phase 2b data regarding MASH). And we have, for instance, survodutide or others, that may serve as an example for GLP-1 glucagon receptor agonist in the phase 2b trial.
30.		Semaglutide. Those data were just released by the *New England Journal of Medicine* last week, I think, or the 30th of April. Very impressive 1.5 years of treatment, a population with obesity and MASLD/MASH and relevant liver fibrosis. We do see a statistically significant higher number of resolutions of MASH and improvement of liver fibrosis. However, the delta to placebo, about 14% for semaglutide.
31.	 **AE, n (%)** / **Semaglutide 2.4 mg (n=800)** / **Placebo (n=395)** All AEs: 690 (86.2) / 315 (79.7) Fatal AEs: 3 (0.4) / 6 (1.5) Serious AEs: 107 (13.4) / 53 (13.4) AEs leading to trial discontinuation: 21 (2.6) / 13 (3.3) AEs affecting ≥10% of participants **Nausea**: 290 (36.2) / 52 (13.2) **Diarrhea**: 215 (26.9) / 48 (12.2) **Constipation**: 178 (22.2) / 33 (8.4) **Vomiting**: 149 (18.6) / 22 (5.6) COVID-19: 134 (16.8) / 74 (18.7) **Decreased appetite**: 112 (14.0) / 11 (2.8)	And with semaglutide, we do have the expected side effects of nausea, diarrhea, constipation, so GI-related side effects (here highlighted in bold because those were the ones that were statistically significant in this phase 3 trial).

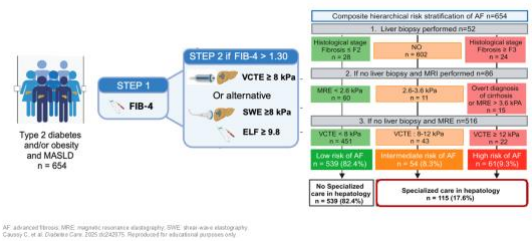
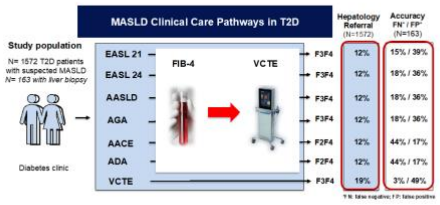
32.		We do have data for tirzepatide, already approved for the treatment of obesity and T2D. These are the data from the *New England Journal of Medicine* paper last year. You can see really the addition of GLP-1 plus GIP seems to increase the number benefiting from resolution of MASH here (assessed after 1 year of treatment). Fibrosis, the delta is about 20% compared with placebo.
33.		Very similar the data for survodutide, the GLP-1 receptor glucagon agonist in phase 2b clinical trial treatment for 1 year or 48 weeks. Not really clearly a dose-dependent effect, but the histological improvement of MASH could be demonstrated, as well as the improvement of liver fibrosis without worsening of MASH.
34.		Some other drugs that receive a lot of or/and deserve a lot of attention are the FGF21 analogues. And 1 example would be efruxifermin, others would be pegozafermin for instance, that have, that are derived from the liver but have very beneficial effects not only for liver metabolism but also for adipose tissue and for the cardiovascular system.
35.		We've just seen in the general session the data for the cirrhosis population. These are the 96-week data for the population without cirrhosis (F2-F3) from the HARMONY trial, where we observed actually in the few patients that got biopsied after 2 years of treatment that the initial observation after 24 weeks of an improvement of liver fibrosis was actually much, much higher if we look after 2 years.

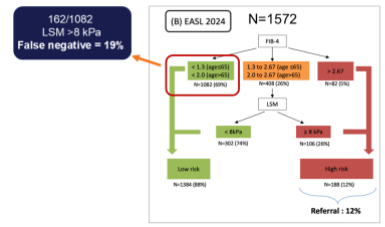
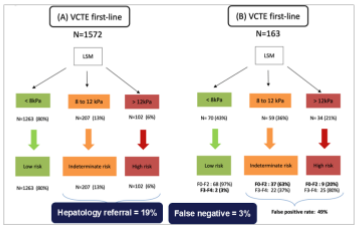
36.		So, this is very encouraging, and just for completeness, I want to show that pegozafermin data as well and long-acting FGF21 analogue. Here, data after 24 weeks, only 0.5 year of treatment and statistically significant improvement of fibrosis and MASH resolution, so very encouraging.
37.		Number of drugs in the pipeline at the moment. So, we will be very interested about your thoughts on how to combine them, how to use them. Resmetirom will be the first THR-β agonist approved in Europe, hopefully very soon (first approved in the FDA). It's liver-specific, increases a lot of the metabolic features that we want to change in MASLD/MASH. But there are other MASH drugs in development which I think we need to watch closely. Semaglutide, I think the extension for the indication has been submitted. The co-incretin mimetics, the FGF21 analogues, pan-PPAR agonists are currently in development. We certainly await more phase 3 clinical data. And I guess, one aspect that we haven't really touched on is to which extent MetALD, ALD patients also would benefit from these drugs, and maybe that's also food for thought for a later discussion. Thank you very much.
38.		**[Professor Laurent Castera, MD, PhD]** This room has a special meaning to me because it's named after Jean-Pierre Benhamou, the founder of our center in Beaujon in Clichy, France.

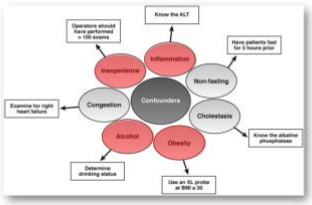
39.	**Outline** 1. Diagnostic target 2. NITs: Advantages and limitations 3. Selecting patients who should be treated (F2/F3) 4. Excluding patients who should not be treated (F4)	So, this is the outline I will be following: diagnostic target, advantage and limitations of NITs, selecting patients who should be treated (F2/F3), excluding patients that should not be treated (F4).
40.	**Defining the Target Condition: High-Risk MASH** 	Diagnostic targets. So, as you know MASL and MASH is a continuum before you reach that stage of cirrhosis. And what we are focusing on, of course, is so-called high-risk MASH, so NAS equal or superior to 4 and F2/F3 fibrosis. And we know that liver-related mortality will increase.
41.	**Fibrosis Is Driving the Prognostic** 	And fibrosis is clearly driving the prognosis. This has been already shown before in terms of deaths from any cause and hepatic decompensation events.
42.	**Liver Biopsy Is Impractical With Many Limitations** 	

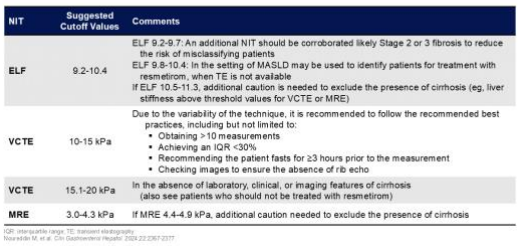
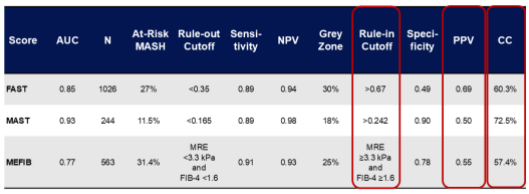
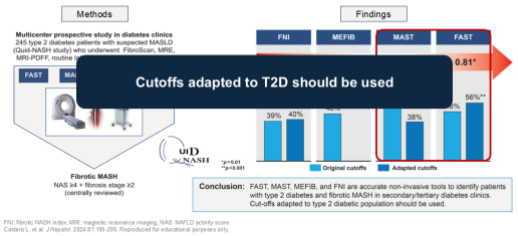
43.	**Outline** 1. Diagnostic target 2. NITs: Advantages and limitations 3. Selecting patients who should be treated (F2/F3) 4. Excluding patients who should not be treated (F4)	So, what are the advantages and limitation of NITs?
44.	**Available NITs** 	These are well known. Among serum biomarkers, we have the FIB-4 and the ELF score. It is an invented score by Siemens. And for liver stiffness measurement by elastography, the pioneer technique is VCTE (better known as FibroScan and MR elastography).
45.	**Critical Issues When Using NITs: Availability and Cost** 	So, there are critical issues when using NITs: availability, cost, and context of use. And of course, FIB-4 is cheap, widely available as compared to MRE for instance. But the cost is inversely proportional to availability in general.
46.	**Critical Issues When Using NITs: Context of Use** 	

47.		Context of use. Of course, the setting where you are going to use this marker is important. Primary care, and this is where FIB-4 qualifies, and it's supposed to be used in populations with low prevalence of F2/F3 fibrosis, and mainly rule out F2/F3 fibrosis but not diagnose F2/F3 fibrosis. And you also need to adapt the cutoff to age (which is part of the formula) to less than 2 for patients older than 65 years.
48.		And the other tests, of course, the VCTE and MRE, are for the liver clinic.
49.		So, for screening in primary care, we have now many algorithms. The first one was published in 2021, so 4 years ago, by EASL. I won't go into detail, but you can see they were followed by many others including AGA, AACE/AASLD, then AASLD and, more recently, the EASL-EASD-EASO algorithm.
50.		So, the philosophy and the concept are to have a sequential algorithm in at-risk populations starting with FIB-4. And then you come up with a second test and I'm not going to discuss it in detail, of course, the cutoff, but we'll have a little clinical case to illustrate this.

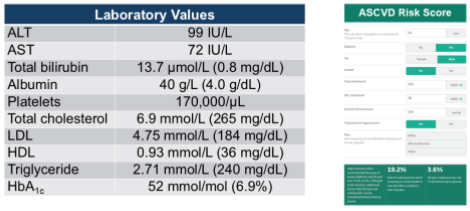
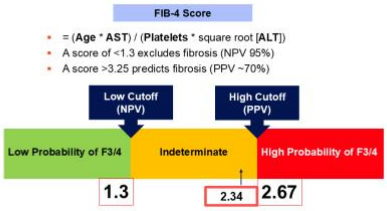
51.	**Implementing Screening in Diabetology**  	Of course, T2D is one of the major risk factors. And these are new data where you can screen for people with diabetes. This is in a diabetology clinic, so it's not the setting like in primary care. This is a study from my colleague Cyrielle Caussie in France, in Lyon. And she tried to apply it in our clinic, but in also other diabetes clinics in France, the FIB-4, followed by either VCTE with a recommended cutoff for ELF or shear wave elastography. And then patients were referred to specialist care. Just to make a long story short, it looks a bit complicated. You end up with a referral to specialized care (around 18%). If you were in primary care, checking, all comer with zero risk factor, you would be around less than 5%.
52.	**Comparison of Algorithms in Diabetology**  	These are data from our group that are now in press and should appear soon. So, we have a large cohort of patients with T2D, and you can see 1500 ended, and a subgroup with liver biopsy. And basically, we look at the effectiveness of all the recommended algorithms, including the EASL 21/24, AASLD, AGA, AACE, and ADA. And what you can see, the percentage of hepatology referral is around 12% for all algorithms. And then we look in the subgroup of patients with liver biopsy at the accuracy in terms of false negative and false positive. And as you can see when you're using the F3F4 as an endpoint, there are more false positives and false negatives, but still, you have close to 20% of false negative using this algorithm.

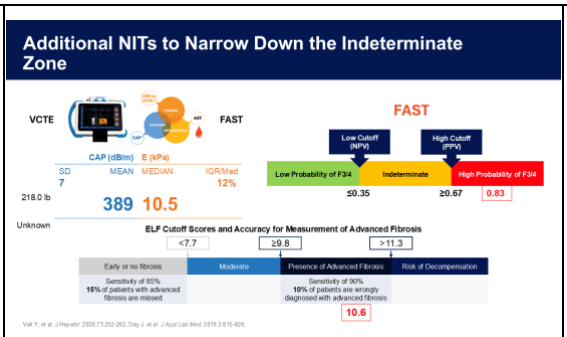
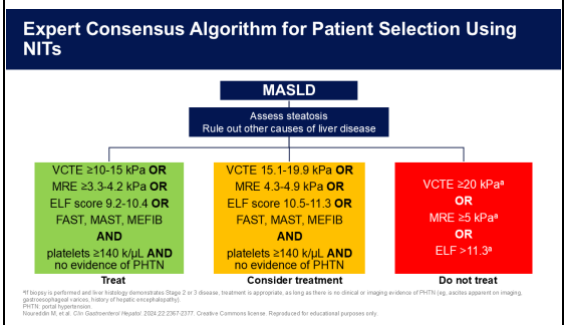
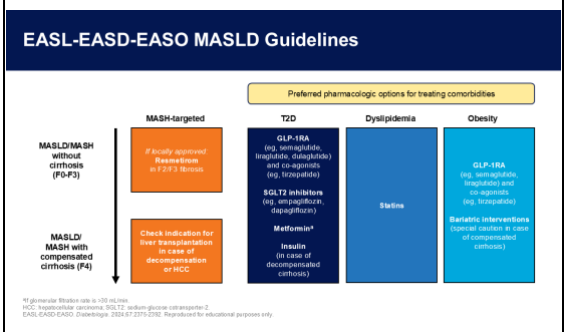
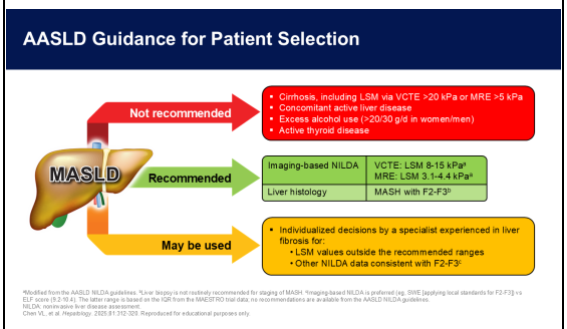
53.	**What Is the Best Strategy: Sequential Algorithm?** 	Now let me focus on the latest EASL recommendation in the large cohorts. And the question is if your FIB-4 is below 1.3 (or below 2 in people older than 65), what happened? They're supposed to be at low risk, but if you look at the result of liver stiffness in the subpopulation, you realize that almost 20% have a liver stiffness measurement above 8 kPa. So, there would be a false negative and it would not pick them up using the algorithm in this setting.
54.	**What Is the Best Strategy: VCTE as First-Line?** 	And if you look at another approach because the pretest probability, so the prevalence, expected prevalence is much higher in this population. So, another possibility is to use a secondary test like VCTE as first line. And this is what we have done, and you can see that you would increase the hepathology referral to almost 20% instead of 12%. And the false-negative rates I showed you was around 20%, then really decreased to 3% at the expense of a higher false-positive rate that we deal with as a specialist.
55.	**Outline** 1. Diagnostic target 2. NITs: Advantages and limitations 3. Selecting patients who should be treated (F2/F3) 4. Excluding patients who should not be treated (F4)	Now, what about patients who should be treated?

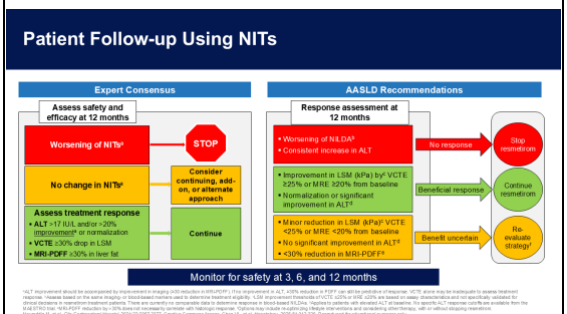
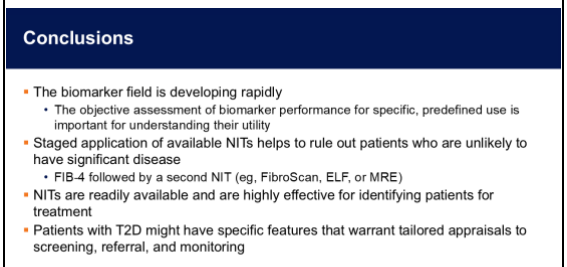
56.	**Package Insert: Baseline Disease Characteristics From the MAESTRO-NASH Trial With Resmetirom** **Eligible Patients**: **CAP** ≥280 dB/m and **LSM** ≥8.5 kPa and **platelets** ≥140 k/μL Assessment of Baseline Disease Severity — Overall (N=888) Liver biopsy — Fibrosis stage, n (%) — F2: 328 (37); F3: 560 (63) Other assessments — VCTE, kPa, median (Q1, Q3)[a]: 12 (10, 15); CAP, dB/m, median (Q1, Q3)[a]: 349 (320, 378); FIB-4, median (Q1, Q3)[a]: 1.3 (1.0, 1.8); ELF, median (Q1, Q3)[a]: 9.7 (9.2, 10.4) [a]<5% misdiagnosis in these variables is omitted. CAP: controlled attenuation parameter. Resmetirom package insert. 2024.	So let me just remind you, the characteristic of the MAESTRO-NASH populations, two-thirds of F3 patients—and when you look at the NITs, CAP was around 350 dB/m, FIB-4 1.3, ELF (these are median) 9.7, and liver stiffness around 12 kPa. But these patients were selected on the basis of CAP and LSM and platelet counts.
57.	**NIT Performance for F2, F3, and F4** Meta-analyses NITs — Studies (n) — Patients (n) — AUROC — Sensitivity (%) — Specificity (%) ELF — 5 — 581 — 0.81 — 69 — 80 VCTE — 37 — 2763 — 0.83 — 80 — 73 MRE — 6 — 209 — 0.91 — 78 — 89 AUROC: area under the receiver operating characteristic curve. Vali Y, et al. J Hepatol. 2020;73:252-262. Selvaraj EA, et al. J Hepatol. 2021;75:770-785.	So, regarding the performance to capture F2, F3, F4 we have a meta-analysis. And clearly among the different markers, the highest level of evidence is for VCTE. As you can see, the AUROCs are quite similar (slightly higher with MRE), but lower number of patients.
58.	**LSM (VCTE) Confounders With Risk of False-Positive Results**  Tapper EB, Cardenas L, Afdal NH. Clin Gastroenterol Hepatol. 2016;13:27-36.	Just to remind you, whatever the technique you're using, liver stiffness is prone to false-positive results with confounders including inflammation, inexperience of the operator, alcohol (that is always the elephant in the room), and obesity. And this is clearly an issue for VCTE, probably more than for MRE.
59.	**VCTE vs MRE: Advantages and Pitfalls** VCTE — Accuracy: • High (AUC 0.85-0.90); Evidence: • High (thousands); Availability: • Widespread; Limitations: • BMI >40 kg/m²; Cost: • Intermediate MRE — Accuracy: • Very high (AUC >0.90); Evidence: • Lower (hundreds); Availability: • Limited; Limitations: • ?; Cost: • High AUC: area under the curve.	Just let me remind you, the advantages and pitfalls of VCTE against MRE. So high versus very high in terms of accuracy; evidence lower for MRE; availability limited; limitation: so, you've seen that BMI is probably not too much of an issue of MRE; and the cost is intermediate and high for MRE.

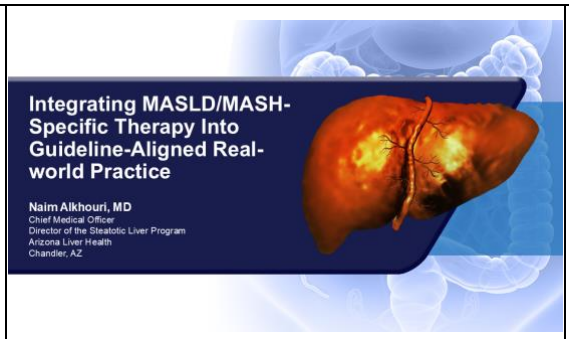
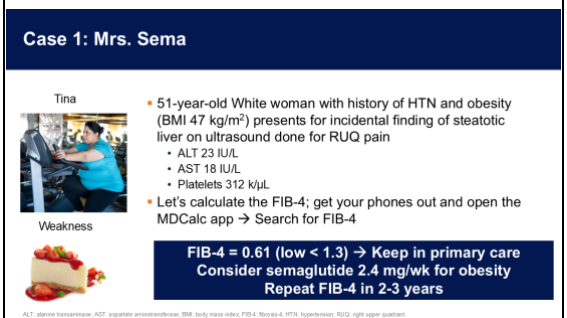
60.	**Suggested Cutoffs for F2-F3**  IQR: interquartile range; TE: transient elastography Noureddin M, et al. Clin Gastroenterol Hepatol. 2024;22:2367-2377	So, this is a very busy slide, but you, I see, are pretty familiar in your practice with the cutoffs that are recommended with the ELF or VCTE from 10 to 15 kPa or 15 to 20 kPa. And MRE should be below 5 kPa. And this I'm going to emphasize again.
61.	**Composite Scores for At-Risk MASH**  FAST: FibroScan-AST; MAST: magnetic resonance imaging AST; MEFIB: MRE combined with FIB-4; PDFF: proton density fat fraction Newsome PN, et al. Lancet Gastroenterol Hepatol. 2025;0:362-373. Noureddin M, et al. J Hepatol. 2022;76:781-787. Jung J, et al. Gut. 2021;70:1945-1953.	A brief word regarding the composite score of at-risk MASH. So, the FAST that is CAP plus AST and LSM using VCTE, the MAST that is a copy-paste of FAST using MRI, and the MEFIB that is MRE and FIB-4
62.	**Summary of Performance**  CC: correctly classified Stern C, Castera L. Clin Mol Hepatol. 2023;29(suppl):S196-S206.	If you look at the performance, so this is just a summary, it's not a comparative study. To summarize the ruling cutoffs are 0.67 for FAST, 0.242 for MAST, and MRE it's a combination, it's slightly different. The PPV is between 0.5 and 0.69, so okay, but not fantastic. And at the end of the day, of course, what matters, the percentage of patients that are correctly classified, true positive and true negative. And again, you can see it's variable.
63.	**Don't Forget Comorbidities: T2D**  FNI: fibrotic NASH index; MRE: magnetic resonance imaging; NAS: NAFLD activity score Castera L, et al. J Hepatol. 2024;81:156-166. Reproduced for educational purposes only.	The point I want to make is that, if you're using the original cutoff and the original cutoff has been defined with 90% sensitivity and 90% specificity and the gray zone. So, the gray zone is important. And let's see how it is translated in practice. So, this is a set of almost 250 patients with T2D with liver biopsy, FibroScan, MRE, MRI-PDFF, and routine tests. And when you compare head-to-head in this population, you can see that in terms of AUROC FAST, MAST outperforms MEFIB and FNI. FNI is more

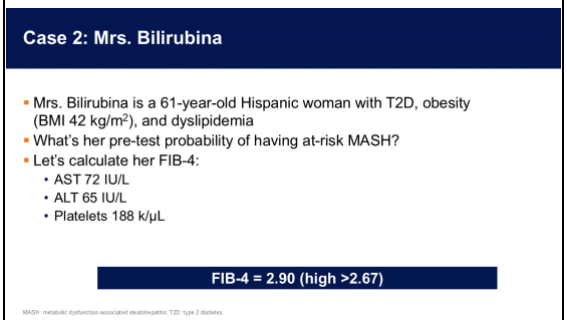
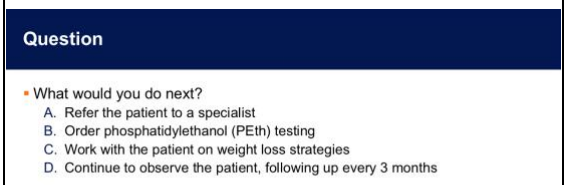
		for primary care. But if you look at the correctly classified patients, it was higher for MAST, and the reason is the gray zone that is smaller. But then if you adapt the cutoff and make them with a different cutoff with 90% sensitivity and specificity in this population, you can see, you come to the opposite: FAST is outperforming MAST in terms of correctly classifying (56% and 38%). So, this has to be adapted to the setting and also to the population in your study, this is important.
64.	**Outline** 1. Diagnostic target 2. NITs: Advantages and limitations 3. Selecting patients who should be treated (F2/F3) 4. Excluding patients who should not be treated (F4)	
65.	**Cutoffs for Diagnosing Cirrhosis** NIT / Cutoff / Comments ELF / ≥11.3 / ELF ≥11.3 is associated with increased risk of hepatic decompensation among patients with cirrhosis Imaging VCTE / ≥20 kPa / LSM by VCTE ≥20 kPa is associated with cirrhosis, but for ruling out, cirrhosis optimal cut point is <8 kPa MRE / ≥5 kPa / LSM by MRE ≥5 kPa has a very good specificity (approaches 95%) for diagnosis of cirrhosis and is associated with increased risk of incident hepatic decompensation Rinella ME, et al. Hepatology. 2023;77:1797-1835.	Most importantly in practice, what are the cutoffs to exclude cirrhosis? Because as you know, the label is for F2/F3, so in your practice you need to exclude cirrhosis, and you can confidently exclude cirrhosis if you're using 11.3 for ELF, or 20 kPa—sorry, not excluding, confirming cirrhosis and MRE of 5 kPa, then of course this patient should be excluded from treatment.
66.	**Case 1: Dhr. Vermeer** ▪ 55-year-old man referred by his PCP due to abnormal liver biochemistry ▪ **Medical history:** T2D for 15 years, dyslipidemia for 2 years ▪ **Family history:** Mother had diabetes, and father had hypertension and IHD ▪ **Social history:** • He exercises occasionally • Mainly sedentary job • Drinks 1 glass of wine every other night, smokes a pipe ▪ **Prior examination:** BMI 27 kg/m², BP 130/80 mm Hg ▪ **Symptoms:** Has some right upper quadrant discomfort ▪ **Medications:** Gliclazide 80 mg by mouth twice daily and fish oil; PCP stopped statin due to abnormal liver biochemistry BP: blood pressure; IHD: ischemic heart disease; PCP: primary care physician.	So, let's go with a clinical case. So, it's a 50-year-old man referred by his GP due to abnormal liver test. He has T2D for 15 years, dyslipidemia for 2 years, and family history of diabetes, hypertension. And although he exercises occasionally, he is mainly sedentary in his job. He drinks 1 glass of wine every other night, smokes a pipe. And BMI of 27 kg/m^2, blood pressure

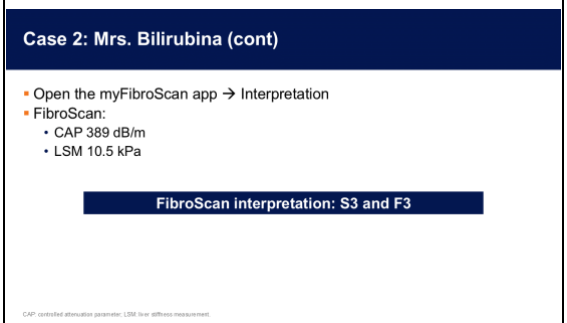
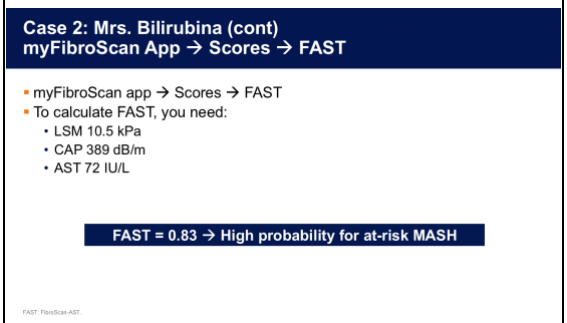
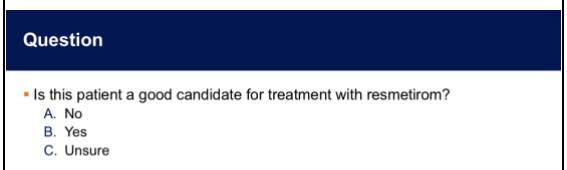
		130/80 mm Hg, has some right upper quadrant discomfort, which is not really very specific, and he's taking gliclazide 80 mg oral, fish oil, and as usual, PCP stopped the statin due to abnormal liver chemistry. So, I think it probably reminds you of your practice, the kind of patients you are seeing.
67.	**Case 1: Dhr. Vermeer (cont)**  **Laboratory Values** ALT 99 IU/L AST 72 IU/L Total bilirubin 13.7 µmol/L (0.8 mg/dL) Albumin 40 g/L (4.0 g/dL) Platelets 170,000/µL Total cholesterol 6.9 mmol/L (265 mg/dL) LDL 4.75 mmol/L (184 mg/dL) HDL 0.93 mmol/L (36 mg/dL) Triglyceride 2.71 mmol/L (240 mg/dL) HbA_{1c} 52 mmol/mol (6.9%) **ASCVD Risk Score** 19.2% 3.6%	So, lab values, ALT, elevated about 2 times the upper limit of normal, bilirubin is okay, so is albumin, platelet counts, cholesterol a bit elevated, triglyceride also elevated, HbA_{1c} is 6.9%, and the cardiovascular risk score is about 20%.
68.	**FIB-4 for Ruling Out Advanced (F3/4) Fibrosis**  FIB-4 Score = (Age * AST) / (Platelets * square root [ALT]) A score of <1.3 excludes fibrosis (NPV 95%) A score >3.25 predicts fibrosis (PPV ~70%) Low Cutoff (NPV) High Cutoff (PPV) Low Probability of F3/4 Indeterminate High Probability of F3/4 1.3 2.34 2.67	So, I think this is now, for you the time to vote, before, after I show you the FIB-4 score. And this guy has a 2.34 score. So, what would you do with him?
69.	**Question** What would you do next? A. Order ELF B. Perform VCTE C. Order liver biopsy D. Continue to follow the patients with annual FIB-4	There are several proposals: would you order an ELF, perform VCTE, order liver biopsy directly, or continue to follow the patient with annual FIB-4? So that's, yeah, the large majority, 80%, okay, we got VCTE. Okay, a few order ELF.

70.		And so, this is what has been done. As you can see, so CAP is 390 dB/m, so very high (remember that it goes from 100 to 400 dB/m), so this is severe steatosis. Liver stiffness is above 10 kPa (10.5 kPa), FAST score is 0.83, and the ELF score is 10.6. So… what would you do with this guy?
71.		So, if you follow the algorithm, the consensus algorithm, you can see that all the values are within what you would expect for patients that could qualify for treatment. It will be in the green box.
72.		And back to the EASL-EASD-EASO guidelines that have been already presented by Frank. This guy is slightly overweight (BMI was 27 kg/m^2), he has diabetes that is well-controlled. So he would be, I think, a good candidate starting with resmetirom. And also, he was on gliclazide for his diabetes and no GLP-1 receptor agonist.
73.		Let me remind you the AASLD guidance for patient selection. So, they're slightly different from the experts' advice (and this we can discuss further later on) because the liver stiffness is 8 kPa instead of 10 kPa as recommended by the MASLD expert group.

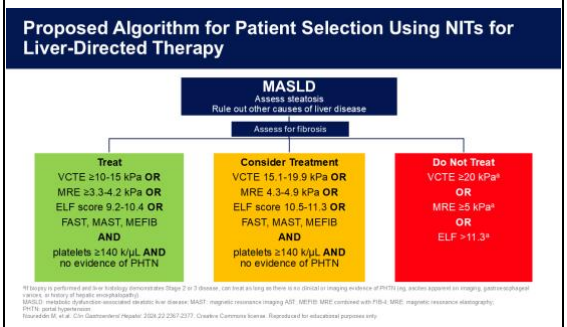
74.		Then, of course, again, I want to reemphasize that if you're above 20 kPa with liver stiffness, you cannot treat these patients. And then, regarding the follow-up of treatment, worsening of NITs should lead to stopping treatment. If there's no change, you could consider continuing, add-on, or an alternate approach. And the treatment response with ALT, a 30% drop in LSM with VCTE, or 30% MRI-PDFF in liver fat, you, of course, may continue. And you can see again that the cutoffs are slightly different between the AASLD recommendation and the expert consensus. So, this also, we can discuss and please do not forget to monitor for safety at 3, 6, and 12 months.
75.		So, in conclusion, the biomarker field is developing rapidly. The objective assessment of biomarker performance for specific, predefined use is important for understanding the utility. Staged application of available NITs helps to rule out patients who are unlikely to have significant disease. FIB-4 followed by a second NIT (FibroScan, ELF, or MRE according to local availability), NITs are readily available and are highly effective for identifying patients for treatment, and patients with T2D may have specific features that warrant tailored appraisals to screening, referral, and monitoring.

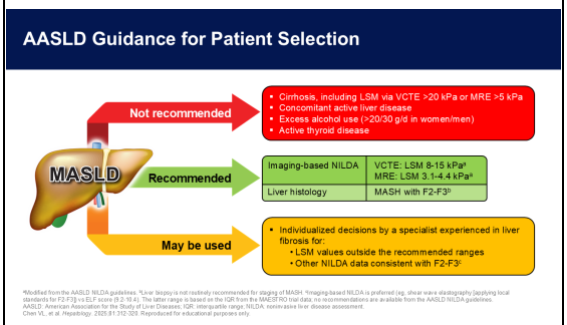
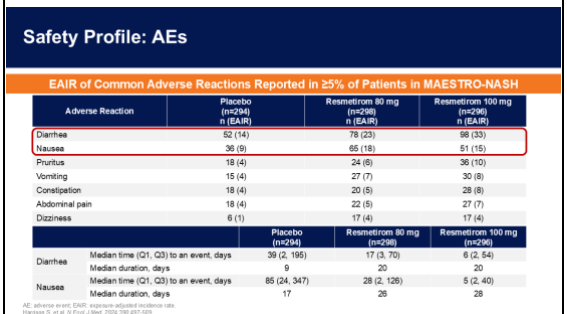
76.		**[Naim Alkhouri, MD, FAASLD]** So, I just have a few cases for you guys at the end and then we'll open it up for the Q&A. But I'm gonna speak to integrating the MASH-specific therapy into guideline-aligned real-world practice.
77.		I highly advise you to download these apps to your phone if you don't have them. One is the myFibroScan app. And this is what Professor Castera was showing you with the first score. So, you can determine the presence of at-risk MASH. I also use it routinely to calculate the score called the AGILE4 score. And this can be a very helpful way to rule out the presence of cirrhosis. I also have a couple of apps on my phone that can help you calculate the FIB-4 index, including the MDCalc app.
78.		So, I have a case for you guys, Mrs. Sema. She is a 51-year-old White woman with a history of hypertension and obesity. Her BMI is typical for the United States at 47 kg/m^2. She presents with incidental finding of steatotic liver on ultrasound and her ALT/AST are within the normal range. You can argue that the ALT might be slightly elevated for a woman, but still not a significant elevation. Platelet count is perfectly fine. So, if we calculate the FIB-4, you can do this on your phone. I can tell you without the calculator, I do a mental FIB-4, and I think she's going to be low because the ALT is higher than AST and the platelet count is perfectly fine. If you calculate the FIB-4 it's going to come out a 0.61. So, this is definitely less than 1.3. And based on the guidelines, we recommend that you keep

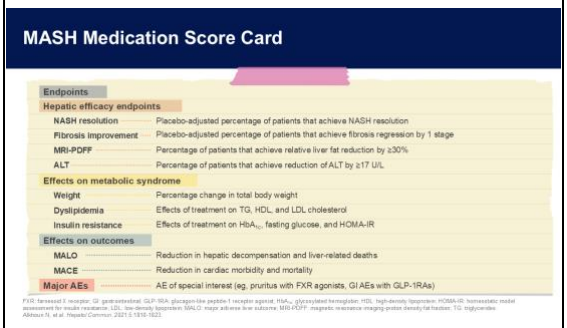
		this patient in primary care. There is no reason to refer her to a hepatologist or do transient elastography. At this point, the focus should be on weight loss and potentially using antiobesity medications with good efficacy like semaglutide. And then the FIB-4 should be repeated every 2 to 3 years.
79.		The second case is Mrs. Bilirubina. She is a 61-year-old Hispanic female with T2D, obesity, BMI 42 kg/m^2, and dyslipidemia. So, when you look at her pretest probability of having at-risk MASH, it's very high based on the data that Professor Castera showed you in patients with T2D. We all know that Hispanic patients also have higher prevalence of MASL, but also more progressive disease. And she has metabolic syndrome and she's older, at 61 years of age. So, when you look at her AST/ALT, you know this, here the AST is higher than ALT. That's always a red flag for advanced fibrosis. And the platelet count, although normal, is still on the lower end at 188 k/µL. So again, a mental FIB-4 will be probably high. If you do the calculation, it is going to come to 2.9. So, this is more than the 2.67.
80.		So, question for you guys. What would you do next? Would you refer this patient to a specialist just based on the FIB-4? Would you order a PEth test to assess for alcohol consumption? Would you work with the patient on weight loss strategies? Or would you continue to observe the patient and follow up every 3 months? Let's vote. Excellent. So, the majority of you guys, based on the FIB-4 being at 2.9, would refer this patient to a specialist. And, of course, in our specialty clinic, we will do transient

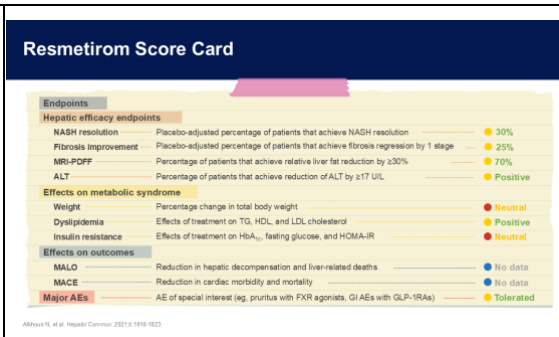
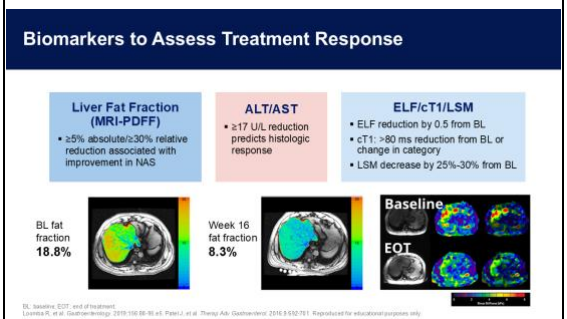
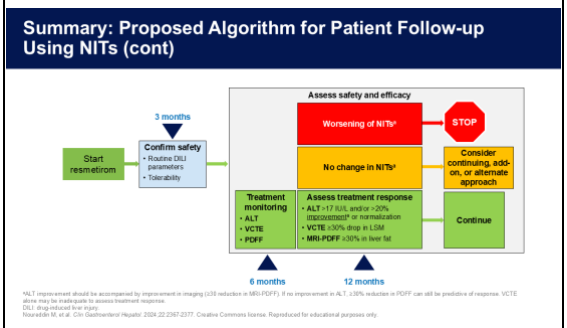
		elastography or ELF to further risk stratify this patient. I don't think it's a bad idea to do PEth testing. And there is a movement now in the field to potentially make it a routine test to assess for alcohol consumption, especially with the new category of MetALD. And, of course, we need to work with all patients on weight loss strategies. But we don't want to keep these patients in primary care if someone with an ELF of 2.9 in the context of diabetes should be seen by specialists.
81.		Okay. So, we did the FibroScan VCTE on this patient and the CAP score came back at 389 dB/m and liver stiffness came back at 10.5 kPa. So, if you actually use the interpretation on the myFibroScan app, you're going to get severe steatosis and potentially F3 fibrosis.
82.		And if you calculate the FAST score based on the liver stiffness, CAP, and AST, your FAST is going to come at 0.83. So, I'm reemphasizing many of the points that Professor Castera highlighted earlier. But you know, again, we have several lines of evidence now suggesting this patient has at-risk MASH, including FIB-4 of more than 2.67, liver stiffness consistent with F2/F3, FAST score consistent with at-risk MASH.
83.		So, is this patient a good candidate for treatment with resmetirom? Let's vote. Okay, so again, 70% of you said, yes, this patient is a good candidate for resmetirom. You know, I mean, I would like to hear from the people that said no, what are your concerns? We would like to hear your

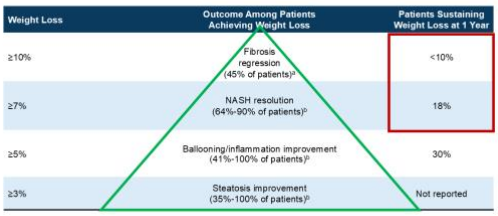
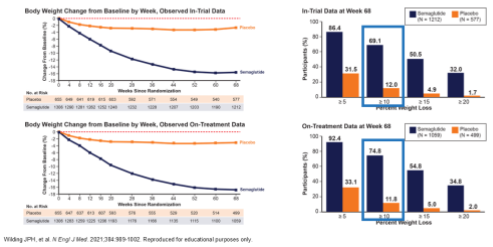
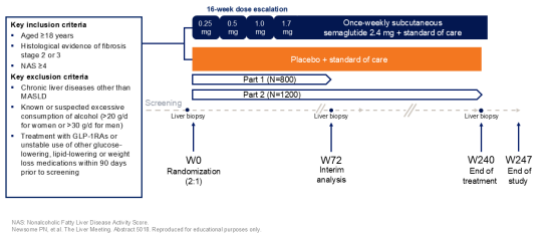
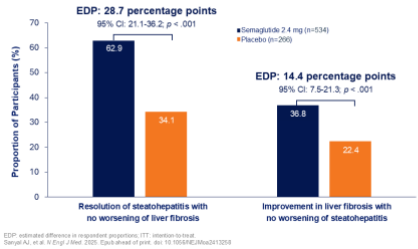
		thoughts on this and happy to answer questions.
84.	**Case 2: Mrs. Bilirubina (cont)** ▪ Absolutely, the patient has T2D and metabolic syndrome with NITs indicating at-risk MASH ▪ How can you rule out the presence of cirrhosis? **FIB-4 <3.48** **LSM <20 kPa** **Platelets >150 k/µL** **Obtain ultrasound: Smooth liver surface and no splenomegaly** NIT, noninvasive testing	Okay. So, in my opinion, I think this is a good candidate. This is exactly what we want to see, not just 1 NIT pointing toward at-risk MASH, but several NITs in a patient with high pretest probability of having at-risk MASH. How can we rule out that she does not have cirrhosis? I think pretty easy. Her FIB-4 is less than 3.48, which is the cut point for cirrhosis. Liver stiffness is less than 20 kPa. Platelet count is more than 150 k/µL. I like to obtain a baseline ultrasound in my patients and make sure that the liver has a smooth contour and that there is no splenomegaly. And this was the case and this patient.
85.	**PI: Baseline Disease Characteristics From the MAESTRO-NASH Trial With Resmetirom** Assessment of Baseline Disease Severity — Overall (N=888) Liver biopsy — Fibrosis stage, n (%) — F2: 328 (37); F3: 560 (63) Other assessments — VCTE, kPa, median (Q1, Q3)[a]: 12 (10, 15); CAP, dB/m, median (Q1, Q3)[a]: 349 (320, 378); FIB-4, median (Q1, Q3)[a]: 1.3 (1.0, 1.8); ELF, median (Q1, Q3)[a]: 9.7 (9.2, 10.4) [a]<5% missingness in these variables is omitted. ELF, enhanced liver fibrosis; NASH, nonalcoholic steatohepatitis; PI, prescribing information; VCTE, vibration-controlled transient elastography. Resmetirom PI. Madrigal Pharmaceuticals, 2024.	Again, Professor Castera showed you this slide, looking at the cut points that we utilize. I want to speak a little bit to the US experience with using resmetirom and implementing the guidelines. We had a poster here at the meeting and I couldn't share slides from the poster. But we treated about 650 patients with resmetirom in the real-world after the FDA approval. So, within 1 year or so at 6 academic centers, and we qualified the majority of patients, 86% based on transient elastography. We had a historic biopsy in about 20% of patients consistent with F2/F3, and about 12% of patients had an additional ELF test. And that was the way we qualified them. And there was a little bit of overlap with having more than 1 methodology to qualify patients. We also found that close to 50% of our patients in the United States were on a statin medicine, and early on we had about 20% on a GLP-1, but now we're closer to

		30% of those with diabetes on a stable dose of GLP-1. And we have successfully added resmetirom. So again, in the MAESTRO-NASH trial we had 15% on a stable GLP-1, and they did well with resmetirom, and there was no effect on the response to resmetirom. And now in the real-world, we're seeing up to 30%. And in MAESTRO-NASH, the highest dose of semaglutide was 1 mg at the time. Just because that was the highest dose approved for diabetes. But now we have patients coming to us on the obesity dose of 2.4 mg, the diabetes dose at 2 mg, and other dual agonists like tirzepatide, which is providing reassurance that combination therapy is acceptable in patients on stable GLP-1.
86.		I think we've all seen the algorithm. I think we talked about the green box where, you know, it's very safe to treat patients with resmetirom. And you really don't have to worry too much about cirrhosis. But I want to focus on the yellow box. And these are kind of the borderline cases where I don't want you to miss the opportunity to treat. So, if you have a transient elastography between 15 to 20 kPa, we have data showing if you biopsy them, that about 35% will have cirrhosis, but 60% will have actually F3. And they might benefit from treatment with resmetirom. And the same story is true for the ELF score. So, I think what we need to do in these cases is to make sure that we look at the platelet count, make sure it's completely normal. We do an ultrasound and again look for splenomegaly and make sure it's absent. And if in doubt you can calculate other scores like the AGILE4 score. That can rule out the presence of cirrhosis if it's less than 0.25.

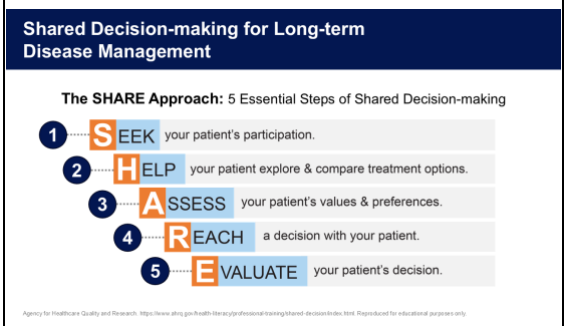
		And if you're still in doubt, you can also do the ELF test. For example, if the transient elastography is between 15 to 20 kPa. But again, the majority of these patients on biopsy will not have cirrhosis. And I don't want you to miss the opportunity to treat F3. But again, with caution, because we are not supposed to treat patients with cirrhosis at this point. The MAESTRO-NASH outcomes trial is still ongoing, and we expect the results by 2027. And that may expand the label to treat those with cirrhosis. Tomorrow, at the late-breaker session, I'll be presenting data also with 122 patients with compensated cirrhosis that we treated with resmetirom, 80 mg, and stay tuned. But very, you know, promising data. And the key message is that it was safe and patients would compensate that cirrhosis.
87.		Again, there are some nuances with the algorithms. Where would you start? I think if you start between 8 to 10 kPa, in terms of treatment, you might be over treating a few patients. But we've definitely seen patients in MAESTRO-NASH between 8 to 10 kPa that had fibrosis of F2 and F3. I take it back actually, in MAESTRO-NASH the lowest kPa that was allowed was 8.5 kPa. So, I would say between 8.5 to 10 kPa.
88.		In terms of the adverse events with resmetirom, the 2 most common adverse events that I discussed with my patients even before they take the first pill are diarrhea and nausea. They start typically after a few days of treatment. Typically, they're mild and self-limited, and they last 3 to 4 weeks. And we have mitigation strategies that we can implement. And in the real-world also we are seeing similar

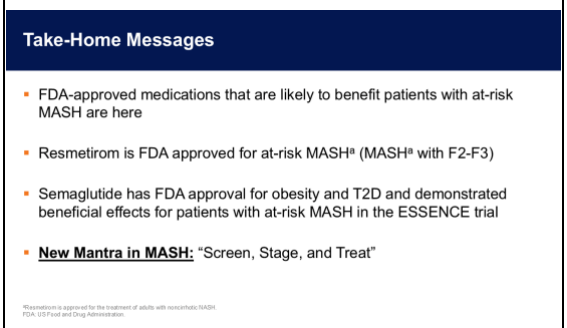
		adverse events to what we saw in MAESTRO-NASH. Other adverse events that we've seen include also pruritus. I had 1 patient that developed a skin rash. Discontinuation rate in the real-world was slightly higher than the trial, but I think that's typical with real-world data.
89.		In terms of looking at different MASH medications, Professor Tacke mentioned many of them that might be coming before the end of this decade. This is something I called the MASH Medication Score Card that I published a few years ago to give you a framework for how to evaluate different trials and different medicines. So of course, we're going to look at hepatic efficacy endpoints. What was the MASH resolution rate? And make sure you adjust for the placebo response. What's the fibrosis improvement rate by 1 stage? But also look at the NITs in every trial including MRI-PDFF, ALT, ELF, PRO-C3. But then you need to look at the trial results in terms of the effects on weight, dyslipidemia, insulin resistance. And this is going to play a significant role in how we select different agents. Eventually we would like to see data on major adverse liver outcomes. And these data don't exist now. I think the first set of data will be the MAESTRO-NASH outcomes trial. And we have some data with certain agents on major adverse cardiac events. And that's also important in our decision-making. With any intervention also you need to look at the adverse events and sometimes we have adverse events of special interest that may limit the use in certain populations.

90.		So, this is the Resmetirom Score Card. You can see the NASH resolution rate, fibrosis improvement with the higher dose, and the effects on dyslipidemia and other metabolic syndrome parameters. And we are still waiting for the data for liver and cardiac outcomes.
91.		In terms of assessing biomarkers for response, I think we discussed this briefly, that MRI-PDFF is actually a very accurate way to assess response to resmetirom, has been shown to be also a good way to assess response with other mechanisms of actions. Reduction in ALT is still important, and the threshold is 17 units absolute reduction or 20% reduction from baseline. If you're going to use liver stiffness, the threshold is 25% to 30%. If you're going to use ELF, it should be more than 0.5 units. And there are other technologies like corrected T1 where the threshold is 80-ms reduction.
92.		And we discussed how we're going to monitor patients. So, for the sake of time, I'm going to skip over this slide. But we are seeing also some of the real-world data now in the United States, especially at the 6-month assessment point, with, in my experience, significant reduction in ALT/AST and steatosis and maybe some slight reduction in liver stiffness. But I think that will take longer than 6 months.

93.	**Weight Loss Through Lifestyle Modification in MASLD** 	Weight loss through lifestyle is, of course, an important aspect of disease management. Weight loss through lifestyle, only 10% of patients are able to achieve the 10% weight loss. So that's why we need medications.
94.	**STEP 1: Effects of Once-Weekly Semaglutide** 	And we have data from semaglutide, tirzepatide showing great efficacy in treating individuals with obesity, with and without diabetes. These are data from the Step 1 study showing 16% to 17%, weight loss. What I wanted to highlight is when you look at that 10% threshold that we try to induce in our patients with MASH, this can be achieved in 70% to 75%, with semaglutide, so much higher percentage than with lifestyle.
95.	**ESSENCE Phase 3 Trial: Semaglutide in At-Risk MASH** 	
96.	**ESSENCE: Primary Endpoints (ITT Population)** 	And I think we've seen the ESSENCE data. So, I'm not going to repeat this, but also very promising on both MASH resolution and fibrosis improvement.

97.	**Case 3: Mr. Hefty** ▪ 29-year-old man with no significant past medical history; presents to your office for a free FibroScan test that you offer ▪ BMI is 46.3 kg/m^2 ▪ VCTE shows the following: • CAP 392 dB/m (S3) • LSM of 21 kPa (F4) with IQR of 27% ▪ You order laboratory tests: • AST 13 IU/L • ALT 21 IU/L • Platelets 401 k/µL ▪ What would you do next?	So, I have a last case for you guys, Mr. Hefty. And he is a 29-year-old man with no significant past medical history, presents to you for a free FibroScan. And his BMI is at 46.3 kg/m^2. Transient elastography shows a CAP of 392 dB/m and liver stiffness of 21 kPa, which is consistent with cirrhosis if you go to the myFibroScan app. But there are several caveats here. Number 1, he's young. He has low pretest probability of having cirrhosis. His BMI is very high, which can affect the accuracy of your liver stiffness. And his IQR is close to 30%, which tells you that the measurements on liver stiffness were all over the place. You order his liver enzymes, and they're completely normal and his platelet count is 400,000/µL. What would you do next? Again, this is a real-life case. And we see this in our clinics. And the last thing I want anyone to do is to tell this 29-year-old patient that, you have MASH cirrhosis and we're going to start HCC surveillance. And next let's do an EGD. Because again the pretest probability is very low. And the FibroScan quality is not ideal. And the BMI is very high and the platelet count is very high. So, it doesn't make any sense.
98.	**Case 3: Mr. Hefty (cont)** ▪ FIB-4: 0.21 ▪ AGILE4: 0.01 ▪ ELF: 7.6 	So, what you can do is you can calculate the FIB-4 and if the FIB-4 is at 0.2, that tells you that probably the FibroScan is not accurate. But you can calculate an AGILE4. And you can see the AGILE4 will come back at 0.01. AGILE4 goes from 0 to 1. And the closer to 1 you are, the more likely you have cirrhosis. The cut point is 0.57 to predict the presence of cirrhosis; less than 0.25 can rule out cirrhosis. And this patient has no chance of having cirrhosis. His ELF comes back at 7.6 also. So again, I just want

		you to interpret liver stiffness and the context of the patient. Look at the entire clinical picture. This is a patient that I would reassure that he doesn't have cirrhosis. But if I want to be 100% sure I have no issues doing a liver biopsy. He may have some degree of fibrosis, but I highly doubt that he will have cirrhosis.
99.		I want to leave you with this slide about shared decision-making. This is what we called the SHARE approach. And I like to implement this in my clinic. So, before you decide on starting resmetirom or other therapeutic interventions, seek your patient's participation, get them engaged in the decision-making, and then help them explore and compare treatment options. We didn't talk about bariatric surgery, but that's another very effective treatment option. And then assess your patient's values and preferences and ask them, you know, does it matter to them if they do an injection? Do they have a problem with injections versus pills? When it comes to lifestyle intervention, what type of diet would they be likely to adhere to? And then reach a decision with your patient. And once you reach a decision, evaluate the decision and then reassess periodically.
100.		So, with this I just want to leave you with the new mantra we have for 2025 about MASH, which is "just do something". It's like the Nike thing, you know, "just do it". But this is "just do something". And the something is the 3 S's approach. S number 1 is screen for MASLD and MASH and all high-risk populations like patients with T2D. And then when you identify MASLD, you need to stage, you need to know the

		fibrosis stage in 2025. It's not okay to tell a patient, “You have fatty liver, lose weight. Come back. We'll see what happens.” This is not acceptable the minute you make the diagnosis. Probably the patient had MASLD for 15 years and MASH for 5 to 6 years.
101.		So, you need to stage, you need to know the baseline fibrosis stage. And once you identify F2/F3, today you can start treatment with a MASH-directed therapy in the United States. And this is coming to Europe soon. So, screen, stage, and start treatment. Thank you for your attention.