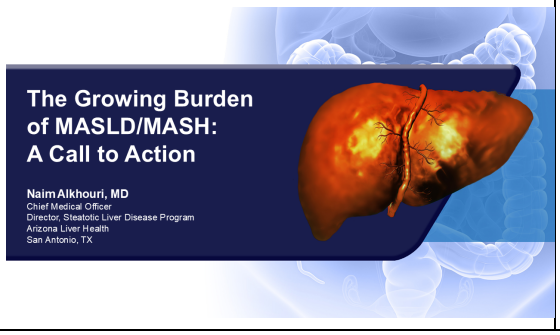
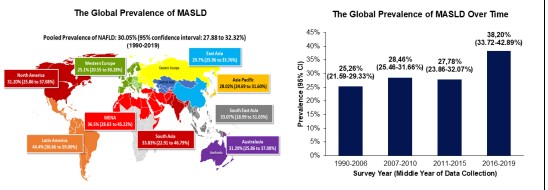
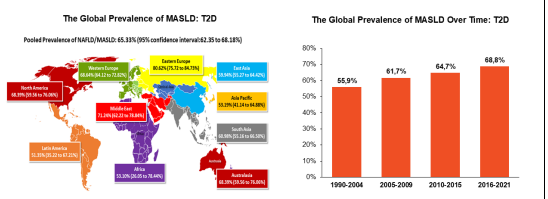
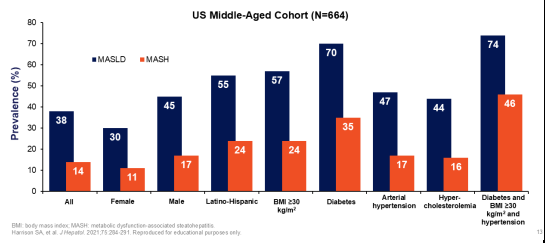
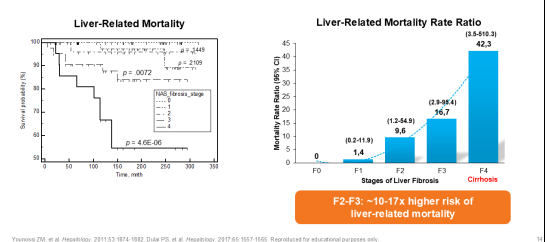
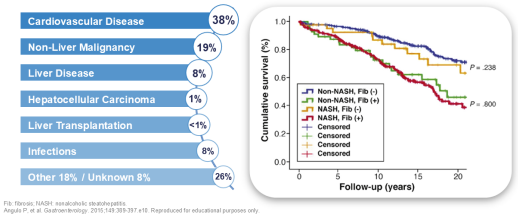
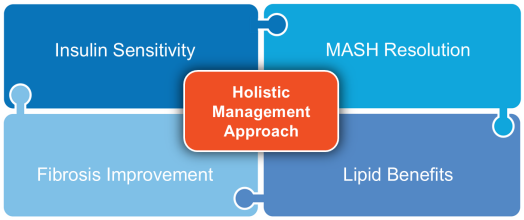
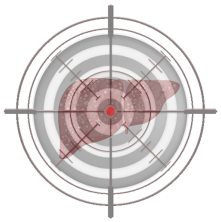
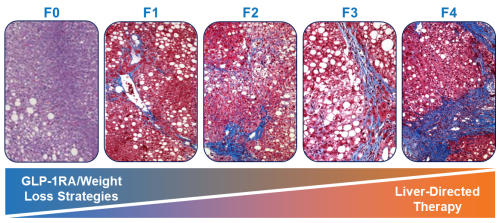
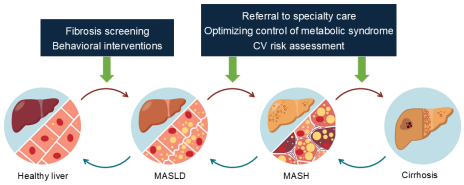
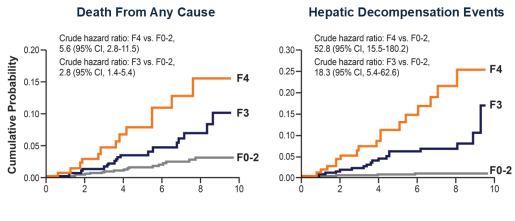
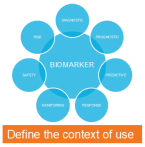
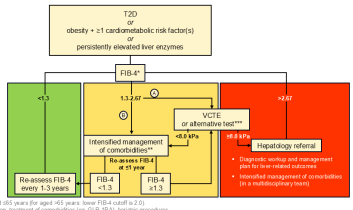
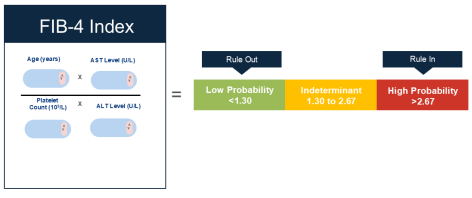
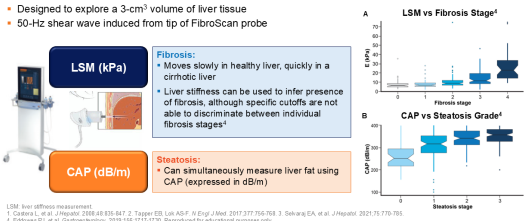
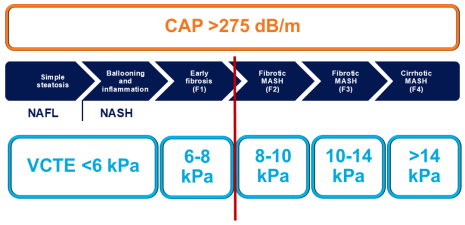
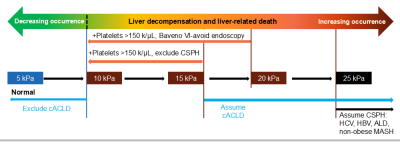
1		**[Naim Alkhouri, MD, FAASLD]** All right, welcome everyone. I'm Dr. Naim Alkhouri, Chief Medical Officer at Summit Clinical Research in San Antonio, Texas, United States, visiting you guys here in Europe. I welcome you to our symposium, "A New Era in MASH: How Disease-Specific Therapies Are Changing the Game". I am thrilled to be here in beautiful Berlin with you guys as part of the UEG meeting. I think throughout this whole conference you heard the theme in steatotic liver disease, that we need to screen high-risk patients, identify patients with significant fibrosis, and get them started on appropriate pharmacologic treatments. So this is going to be the main theme for today.
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	I think everyone is aware that we changed the nomenclature. So now we use metabolic dysfunction-associated steatotic liver disease and steatohepatitis, so MASLD and MASH.
3	**Faculty**  **Naim Alkhouri, MD, FAASLD** Chief Medical Officer Director, Steatotic Liver Disease Program Summit Clinical Research San Antonio, TX  **Jörn M. Schattenberg, MD** Professor of Medicine Director of the Department of Medicine II Saarland University Medical Center and Saarland University Homburg, Germany  **Frank Tacke, MD, PhD, MHBA** Director Medical Department of Hepatology and Gastroenterology Charité – Universitätsmedizin Berlin Campus Charité Mitte and Campus Virchow-Klinikum Berlin, Germany	And I am joined today by 2 esteemed faculty and good friends, Professor Jörn M. Schattenberg, who is Professor of Medicine and the Director of the Department of Medicine, Chief of Gastroenterology at Saarland University, and Professor Frank Tacke, who is the Director of the Medical Department of Hepatology and Gastroenterology at Charité University here in Berlin. So thank you guys for joining me.
4		Okay, so let's get started. "The Growing Burden of MASLD and MASH: A Call to Action".

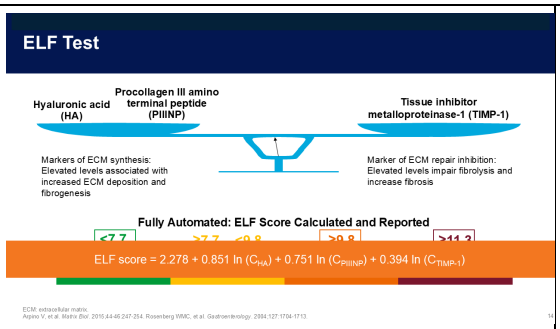
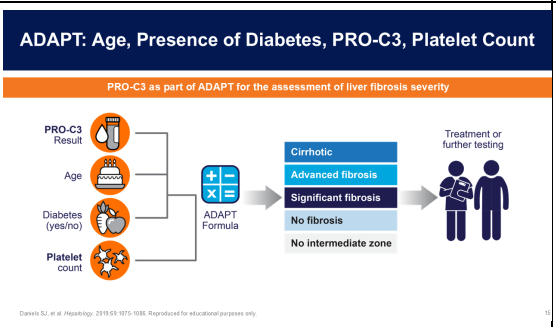
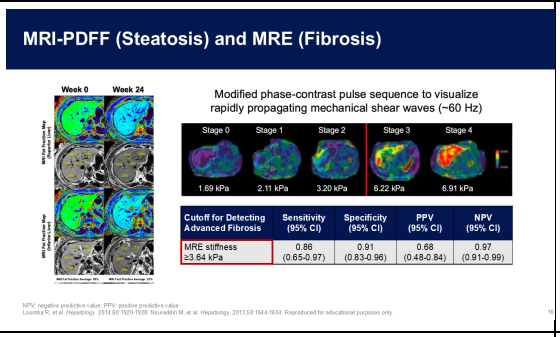
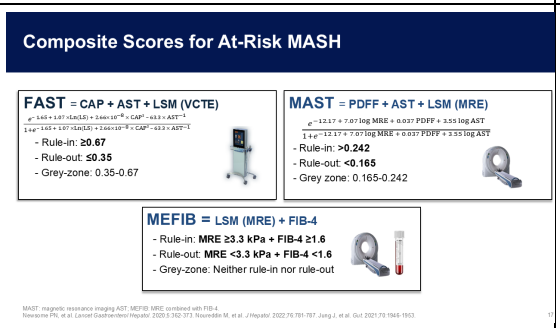
5	**Global Prevalence of MASLD: On the Rise**  MASLD: metabolic dysfunction-associated steatotic liver disease; NAFLD: nonalcoholic fatty liver disease. Younossi ZM, et al. *Hepatology*. 2023;77:1335-1347. Creative Commons license. Reproduced for educational purposes only.	We know that MASLD is the most common chronic liver disease globally, and the estimates between 1990 to 2019 are that 30% of the global population has MASLD or MASH. Actually, we have data showing that there is a progressive increase in the prevalence. So in 1990, the global prevalence was around 25%. And move forward to 2016 to 2019, and now the estimates are around 38%. The regions with the highest prevalence of MASLD globally are actually the MENA region (Middle East and North Africa) and Latin America. Up to 44% of Latin Americans may have MASLD or MASH.
6	**Global Prevalence of MASLD Among Those With T2D**  T2D: type 2 diabetes. Younossi ZM, et al. *Clin Gastroenterol Hepatol*. 2024:S1542-3565(24)00287-8. Reproduced for educational purposes only.	We know that the problem is even bigger in patients with type 2 diabetes. So the global estimates for the prevalence of MASLD in diabetics are around 65%. And again, there is also a progressive increase in the prevalence of MASLD in diabetics. The most recent estimates put that at 68%. So two-thirds of diabetics have MASLD, and they absolutely need to be screened, and we need to do case findings of patients with significant and advanced fibrosis.
7	**Prevalence of MASH Among US Middle-Aged Cohorts: Compounding Risks**  BMI: body mass index; MASH: metabolic dysfunction-associated steatohepatitis. Harrison SA, et al. *J Hepatol*. 2021;73:284-291. Reproduced for educational purposes only.	This is a study that I did in San Antonio, Texas, with the late Stephen Harrison, where we looked at the middle-aged cohort coming to the military hospital in San Antonio, Texas, highly enriched for Hispanic patients. And they're coming just for screening colonoscopy without any known history of MASLD or elevated liver enzymes. And we offered them a state-of-the-art MRI-PDFF to diagnose MASLD. And then, if they had MASLD on the MRI, we offered a liver biopsy because we wanted to prospectively determine the prevalence of MASH and the stage of fibrosis. And in this study, we found that in the entire cohort, 38% had MASLD. But more importantly, 14% had MASH, the aggressive form of the disease that can lead to progression to cirrhosis and its complications. If you actually look at patients with type 2 diabetes, up to 35% will have MASH. And then, if you look at patients with obesity, type 2 diabetes, and Hispanic ethnicity, up to 46% have the aggressive form of MASH.
8	**Fibrosis Drives Outcomes in MASLD**  Younossi ZM, et al. *Hepatology*. 2011;53:1874-1882. Dulai PS, et al. *Hepatology*. 2017;65:1557-1565. Reproduced for educational purposes only.	We also know from several studies that fibrosis stage, based on biopsy or noninvasive tests, is the most important prognostic factor that can tell you who are the patients that will develop cirrhosis, who are the patients at risk to develop major adverse liver outcomes. These are decompensating events such as ascites, encephalopathy, and variceal bleeding. And this inflection point starts at F2 fibrosis. So our goal is to find patients with F2 and F3, get them on the appropriate treatment to prevent progression to cirrhosis. Because once you have cirrhosis, there is an exponential increase in liver outcomes, and there is an increase in hepatocellular carcinoma.

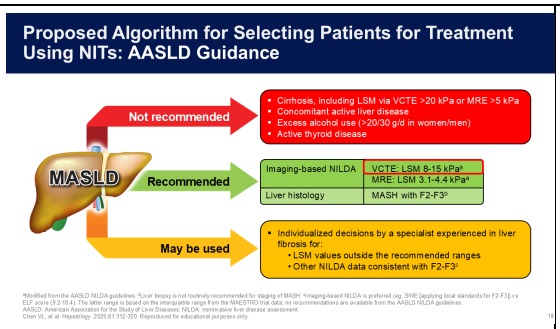
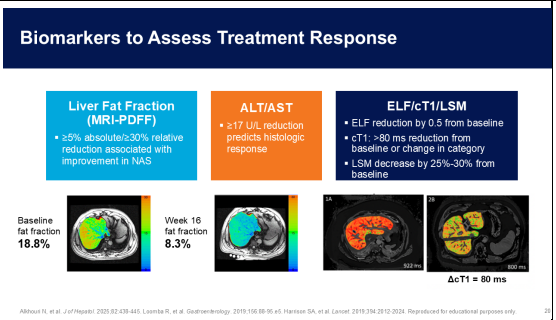
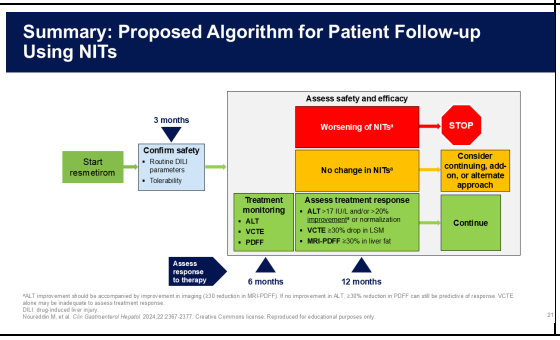
9	**Leading Causes of Mortality in MASLD** PRELHIN study: 619 MASLD cases (median follow-up 12.6 [range, 0.3-35.1] y)  Fib: fibrosis; NASH: nonalcoholic steatohepatitis Angulo P, et al. Gastroenterology. 2015;149:389-397.e10. Reproduced for educational purposes only.	These are data from the PRELHIN study by the late Paul Angulo from the Mayo Clinic, looking at causes of mortality in a MASLD population. And similar to the general population, the number 1 cause of mortality is cardiovascular disease, followed by non-liver malignancy. But the main finding here is that in patients with MASLD and MASH, liver disease is the number 3 cause of mortality. In the general population, liver disease is typically number 9 in the United States. So these patients have higher rates of progressing, and many of them unfortunately die from liver disease or may require liver transplant. Also in the study, they showed clearly that fibrosis stage was the most important prognostic factor.
10	**Need for a Holistic Management Approach for Patients With MASH** 	Now, when we talk about the management of MASH, we really need a holistic approach. We need to focus on liver outcomes, so achieving MASH resolution and fibrosis improvement, but we also need to look at the metabolic syndrome and see if there is a lipid benefit. Can we improve insulin sensitivity? And this is very important early on in the disease.
11	**Need for a Holistic Management Approach for Patients With MASH (cont)** Liver-targeted therapies allow for a faster and stronger effect on fibrosis 	But we also want to highlight the need for liver-directed therapy. And this becomes more important as patients progress to more advanced fibrosis. We really need to target the liver directly to reverse fibrosis and potentially also implement this therapy with lifestyle intervention and other medications to enhance the liver-directed effect.
12	**How to Manage MASLD/MASH** 	So when we think about the spectrum of MASH, we have 4 fibrosis stages, with stage 4 being cirrhosis. And we do believe that lifestyle intervention and medications that target weight loss and insulin resistance are very important early on in the disease spectrum. But as you progress to significant fibrosis and advanced fibrosis—and hopefully in the future we'll also have liver-directed therapy for cirrhosis—then we need to focus on agents that target fibrosis and can work in conjunction with lifestyle intervention to reverse fibrosis. So this is my call to action, and now I would like to invite Professor Schattenberg to educate us about how to utilize noninvasive tests to identify high-risk patients.

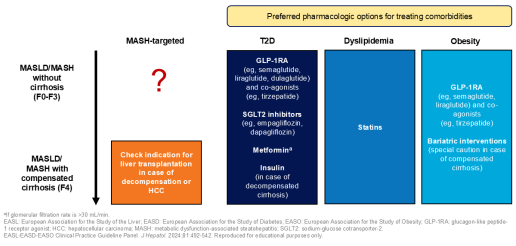
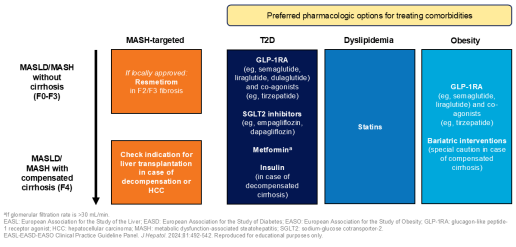
13		**[Jörn M. Schattenberg, MD]** Thank you, Naim, and thank you, dear colleagues, for being here for your lunch break. I think this is a very important topic, and I'm very happy to continue that theme. You've shown how high the prevalence of disease is, and clearly that's not all the patients we want to have in the gastroenterologist's office. We need to fine-point this and fine-tune and identify the patients at risk where we can prevent the relevant outcomes—development of cirrhosis, carcinoma, and decompensation. So, improving screening and diagnosis is my task, and I'm going to lead you through this.
14	**Introduction** ▪ In this section, we will discuss • Available NITs for MASH, including blood-based, imaging, and combination tests • Use of NITs to risk stratify patients with MASH and monitor treatment response MASH: metabolic dysfunction-associated steatohepatitis; NIT: noninvasive test.	I will be discussing the available so-called noninvasive tests, or NITs, blood-based and imaging. We use combinations to increase the accuracy of these. And then I'm also going to show you a little bit of data because we have an approved treatment. The EMA has had a favorable response. There's been a drug available in Germany now for 2 weeks and it should be coming to your European countries soon.
15	**MASLD Is a Slowly Progressive Disease** Building pathways of comprehensive care will allow for prevention and treatment  CV: cardiovascular; MASLD: metabolic dysfunction-associated steatotic liver disease. Wong VWS, et al. *Liver Int* 2022;42:2377-2389. Reproduced for educational purposes only.	Let's reflect again about MASLD. This is a disease that's not going to kill the patient overnight. It's a slowly progressive disease, but as with all metabolic diseases, it produces end-organ injury to an organ, in this case, the liver. It's the steatohepatitis subtype that leads to scarring and then eventually terminal degradation of liver tissue into fiber, which makes the liver lose function. We screen for fibrosis and use behavioral interventions more like a preventive approach in earlier stages, but we should utilize the referral systems in the respective countries to identify the patients with steatohepatitis, the inflammatory fibrosing subtype, for them to be managed and treated. Even in the cirrhotic space, we have recommendations for screening and follow-up in these patients.
16	**Liver-Related Outcomes: Linked to Liver Histology**  Sanyal AJ, et al. *N Engl J Med* 2021;385:1559-1569. Reproduced for educational purposes only.	As Professor Alkhouri has shown, the fibrosis stage, as with many liver diseases, but also with MASLD, is the strongest predictor of mortality in our patients. And these are data that have been generated in prospective studies, recruiting patients in the United States, published in one of the highest medical journals we have. You can see how the histological fibrosis stages F3 and F4 single out with regard to increased cumulative death from any cause. This is also true for hepatic events, but these patients do have additional causes of death, including cardiovascular disease, but also cancer that's even outside of the liver. As a field, we have successfully moved beyond liver histology to stage these patients.

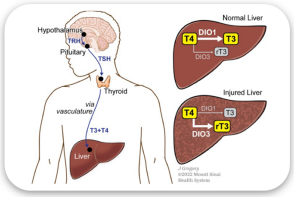
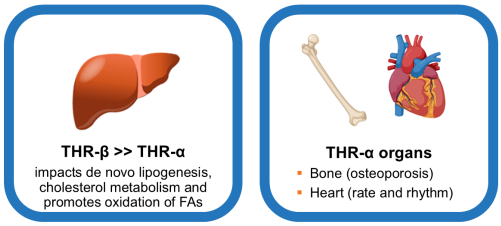
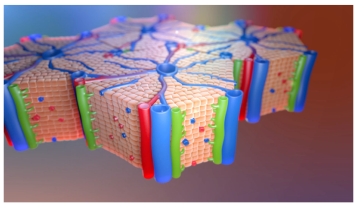
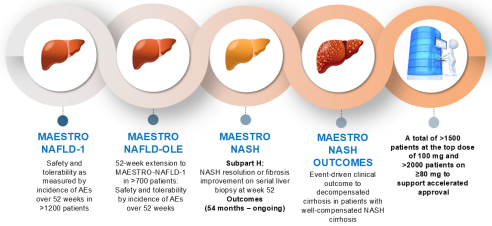
17	**Let's Talk About Biomarkers** From the Regulatory Authority's Standpoint FDA Biomarker Qualification What Are Biomarkers and Why Are They Important?  The Biomarkers, EndpointS, and other Tools (BEST) • An indicator of normal biologic processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions  Define the context of use US Food and Drug Administration. What are biomarkers and why are they important? Transcript. https://www.fda.gov/drugs/biomarker-qualification-program/what-are-biomarkers-and-why-are-they-important-transcript.	And for that reason, there were a lot of interactions with the regulatory authorities, the FDA, and there's guidance on how to use biomarkers to diagnose and stratify that patient population. If you want to take a deep dive into the biomarker field, there are many different biomarkers. As clinicians, we tend to simplify their context of use. It means a specific biomarker has been developed for a certain population. It doesn't mean it's the same biomarker you use for treatment response. I recommend you look into the BEST criteria. The FDA has sorted this out. I'm going to be discussing diagnostic and prognostic biomarkers today.
18	**Overview of Biomarkers** ✓ Diagnostic, prognostic, predictive? ✓ Pathophysiology and biology in relation to disease stage with biomarkers  Blood-Based Biomarkers: FLI; NFS; HIS; OWLiver®; ALT and AST; CK18; SomaSignal™; PRO.C3; **ELF Test**; **FIB-4**; APRI score; NIS4; ADAPT score; NFS; SomaSignal™; FibroTest; AST/ALT ratio Imaging Biomarkers: **Ultrasound**; **FibroScan® (CAP)**; **MRI-PDFF**; **MRI Liver MultiScan™**; **FibroScan® (VCTE)**; **Ultrasound: SSI, ARFI**; **MRI Liver MultiScan™**; **MRE** Combination: AGILE3+, AGILE4; **FAST score** ADAPT, age, diabetes, PRO-C3, and platelets; ALT, alanine aminotransferase; APRI, AST to platelet ratio index; ARFI, acoustic radiation force impulse; AST, aspartate aminotransferase; CAP, controlled attenuation parameter; CK18, cytokeratin 18; ELF, enhanced liver fibrosis; FAST, FibroScan-AST; FIB-4, Fibrosis-4; FLI, fatty liver index; HIS, hepatic steatosis index; MRE, magnetic resonance elastography; MRI, magnetic resonance imaging; NFS, Nonalcoholic Fatty Liver Disease Fibrosis Score; NIS4, noninvasive score 4; PDFF, proton density fat fraction; PRO-C3, N-terminal type III collagen propeptide; SSI, supersonic shear imaging; VCTE, vibration-controlled transient elastography. Sanyal AJ, et al. Clin Gastroenterol Hepatol. 2023;21:2026-2039. Armandi A, et al. Expert Rev Mol Diagn. 2023;23:771-782.	This is a diagram to show you that there are different contexts of use or target conditions we can use to identify patients. There are some biomarkers for steatosis, and we're using ultrasound as clinicians in our daily practice. It's a good one. There are more advanced quantifying methodologies of fat. It's been a challenge to develop a biomarker specifically detecting the degree of hepatic inflammation for MASH. Our transaminases do show some correlation, but not perfect. And based on the relevance of the fibrosis stage for the overall survival of our patients, I think most focus has been on the fibrotic markers. And I'm going to be discussing the ones that are in bold letters here briefly.
19	**Guidelines Consensus: EASL-EASD-EASO 2024**  * FIB-4 thresholds valid for aged ≤65 years (for aged >65 years, lower FIB-4 cutoff is 2.0). ** Examples: Lifestyle intervention, treatment of comorbidities (eg, GLP-1RA), bariatric procedures. Examples: MRE, SWE, ELF, with adapted thresholds. and/or more options, depending on medical history, clinical context, and local resources. GLP-1RA, glucagon-like peptide-1 receptor agonist. EASL-EASD-EASO. J Hepatol. 2024;81:492-542. Reproduced for educational purposes only.	The guidelines, and Professor Tacke, who joins us up here, has been crucial in developing the EASL guidelines, among others, are very firm in recommending sequential testing. We identify patients based on metabolic risk, for example, type 2 diabetes or obesity with cardiometabolic risk factors. We use a very simple test called the FIB-4 test, and we risk-stratify the entire population into low prevalence of liver disease, or high risk of liver disease, and an intermediate or indeterminate stage where additional management could be useful.
20	**FIB-4** Identification of Advanced Fibrosis  Hepatitis C Online. FIB-4 calculator. https://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4. Sterling RK, et al. Hepatology. 2006;43:1317-1325. Reproduced for educational purposes only.	Now, the FIB-4 is an old test, and it's robust, it's biologically plausible, it's cheap, it's not perfect, but it's a risk stratifier. And you can use it using age, AST, platelets, and ALT levels to rule out a large population or a large group of patients that do not show advanced disease. Its ability to rule in is weaker; however, it serves us as a risk stratifier.

21	**Limitations of FIB-4 in Certain Populations**  1. Kim W.G. et al. *Diabetes Care*. 2022;45:2449-2451. 2. Kaltenbach M. Why are non-invasive risk scores such as FIB-4 used in clinical practice? https://www.aasld.org/liver-fellow-network/core-series/why-series/why-are-non-invasive-risk-scores-such-fib-4-used. Reproduced for educational purposes only.	Some of the weaknesses come from age as a part of the FIB-4. It's important to factor in age because the time of exposure to the injurious agent, namely inflammation in the liver from the sick metabolism, is crucial. But you have to consider that, in particular, in older patients you might have to use different cutoffs. Patients with type 2 diabetes are at higher risk and have a higher prevalence of disease. Here, there is also a little bit more inaccuracy in that test, which then allows for sequential testing.
22	**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  LSM: liver stiffness measurement. 1. Cardoso L., et al. *J Hepatol*. 2008;48:835-847. 2. Tapper EB, Lok AS-F. *N Engl J Med*. 2017;377:756-768. 3. Selvaraj EA, et al. *J Hepatol*. 2021;75:770-785. 4. Eddowes PJ, et al. *Gastroenterology*. 2019;156:1717-1730. Reproduced for educational purposes only.	A second-step test is available and needed, and the guidelines recommend elastography methodologies for that. One of the elastography methodologies I'm showing you here is VCTE, or FibroScan. It's a simple point-of-care test that allows the quantification of fibrosis based on the stiffness of the liver. And you can see in the upper part that discrimination of the fibrosis stages, in particular in the advanced stages, is happening well, and you can use the attenuation of the ultrasound to quantify the hepatic steatosis.
23	**FibroScan: Identification of Significant Fibrosis**  NAFL: nonalcoholic fatty liver; NASH: nonalcoholic steatohepatitis.	To break it down and simplify it a little bit, it could look like this, where you have the continuous spectrum of metabolic liver disease up until cirrhosis, and those correlate to different cutoffs. Now, they're not identical. Liver disease is a continuum at all times, as are these tests. So I caution you not to replicate a certain cutoff to an exact histological stage, but it gives you a good risk stratification tool, in particular when using it sequentially.
24	**Algorithm for Noninvasive Assessment of Clinically Significant PHTN** Baveno VII consensus in PHTN ▪ HVPG values >5 mm Hg indicate sinusoidal PHTN ▪ In patients with MASH-related cirrhosis, HVPG ≥10 mm Hg is strongly associated with the presence of clinical signs of PHTN[a]  [a]Note that these signs can also be present in a small proportion of patients with HVPG values <10 mm Hg. ALD: alcohol-related liver disease; cACLD: compensated advanced chronic liver disease; CSPH: clinically significant portal hypertension; HBV: hepatitis B virus; HCV: hepatitis C virus; HVPG: hepatic venous pressure gradient; IV: independent variable; PHTN: portal hypertension. Adapted for educational purposes only from de Franchis R, et al. *J Hepatol*. 2022;76:959-974.	There have been prospective trials looking at the value of these elastography tests. The Baveno criteria for the risk stratification of portal hypertension, or the concept of advanced chronic liver disease - compensated advanced chronic liver disease—in strata of 5 kPa holds up, and actually, mortality starts to rise with a 10-kPa cutoff. We've seen data published, so we are very firmly believing that using the elastography devices, we can risk stratify our patients and talk about prognostic values.
25	**Available Ultrasound-Based Radiologic Tests**  |	TE (kPa)	Velacur™ (kPa)	ARFI (m/s) – SWE (kPa)
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Advantages	▪ Can be performed in clinic with real-time results	▪ Can be performed in clinic with real-time results	▪ Can be integrated into a conventional ultrasound
Disadvantages	▪ Increased failure rate with obesity ▪ Expensive device ▪ Cutoff values with XL probe are slightly different from M probe	▪ More time consuming than TE (although time can be reduced significantly with training) ▪ Limited availability	▪ Increased failure rate with obesity ▪ Cutoff values for advanced fibrosis vary significantly | SSW: supersonic shear wave.	I've shown you VCTE; there are a number of ultrasound devices that can be used to assess this liver stiffness, which is the physical phenomenon underlying the changes in elastography, the FibroScan device. But there are other ones—Velacur, or ARFI and ShearWave elastography—that might be integrated into an ultrasound machine that you have in your office. So I think that's an important message every gastroenterologist could support in risk stratifying that population.

26		Moving away from imaging, there are potential other blood-based biomarkers. The UK has established the ELF test as a second-line test for referral to hepatology. It's a composite of 3 peptides that are tightly linked to fibrosis. It's a little complicated formula, but you get an ELF test result. Don't worry about the formula. It does, as other tests, risk stratify your population into mild disease or even high likelihood of future decompensation, and it's very practical if you have access to it. The advanced disease stages, severe stages, are encountered in an ELF score above 9.8.
27		Good news is more developers have identified direct fibrosis markers. And another example I'd like to highlight here is the ADAPT score that uses a collagen PRO-C3 in conjunction with age, diabetes, and platelet count—so all biological factors linked to advanced liver disease to do the same job, namely identify the patient population with advanced fibrosis.
28		If we think of high-end testing, MR technology, Professor Alkhouri mentioned they've done a population-based study using MR. That's easy in the research setting, more difficult in clinical practice. But MRI-PDFF, quantifying liver fat, and you see this on the right-hand side of this picture, or MRE, elastography, quantifying the stiffness using MR technology, is available and is used in particular in phase 2a and 2b trials.
29		You can increase the accuracy of the single tests by combining, for example, the ultrasound elastography device with liver enzymes, the so-called FAST score. Or if you have access to MRE, you can use the same parameters, fat quantification by MR and stiffness by MR with AST, and end up with a MAST score. Or third one, and I'm going to stop giving you abbreviations after that, the MEFIB. They are all combinations of imaging and plus-based biomarkers to identify patients that have inflammation and fibrosis in the liver, particularly useful in the context of enriching populations for clinical trials, but also potentially for monitoring and identifying patients for treatment.

30		How should we identify patients for treatment? And I'm showing you recommendations of the AASLD here. I can highlight that the German Association for Gastroenterology has also published a consensus statement on how to use noninvasive tests to identify patients eligible for treatment. The only treatment we have available in Germany at this time is resmetirom. It's not recommended according to label in cirrhosis, so you have to rule out that patients have cirrhosis. It's recommended in patients with liver histology stages F2, F3. I said in the beginning, we're not talking about histological stages in our patients anymore. We focus on NITs using liver stiffness. You can use MRE, the guidelines have that included. I would say in most practical settings, you have a transient elastography device available, and we try to push this to the limit in patients that have not just cirrhosis because I think the benefit in that population is the highest, but you have to rule out cirrhosis.
31		The important question is also how long to treat patients. And there are some NITs we currently use to assess response to pharmacologic treatment.
32		The available data, the MAESTRO-NASH trial has studied patients for a year to come up with a treatment response. So that's an important aspect. And from that trial and other trials, it has been shown that changes in MRI-PDFF that exceed 30% relative reduction, hepatic steatosis is going down, correlates to a histological improvement. You can see that if transaminases are going down, AST and ALT, and there are other biomarkers. I mentioned ELF, some MR imaging technologies, cT1, for example, or stiffness measures. And I think we're going to be learning more in this session from Professor Alkhouri, who will share his real-world experience with us.
33		For that reason, I'm going to skip this summary slide here. That pretty much tells you if there's no benefit for the patient, you should stop the treatment. But even in the context of unchanged NITs, there might be individual benefit. I think this is something we'll be discussing with Professor Alkhouri in a little bit.

34	**Summary** ▪ NITs have replaced liver biopsy in managing patients with non-cirrhotic MASLD ▪ Guidelines recommend FIB-4 followed by a second NIT ▪ Imaging and blood-based tests for MASLD helps with: • Staging • Prediction • Treatment response ▪ The context of use and accuracy of testing varies	And in summary, I think it's important to recognize that NITs have replaced liver biopsy. We recommend sequential testing using very cheap diagnostic risk stratifiers, FIB-4, with sequential tests. This can be imaging or blood-based. And then it's important to remember that these tests were developed in a certain context of use, and they help us to guide patients' identification today. So thank you, and with that, I think we're going to turn to the next presentation, and it's an honor and pleasure to invite Frank Tacke up here, who's responsible for the guidelines, and he's going to be talking about hormonal, about treatment options at this time. Frank.
35		**[Frank Tacke, MD, PhD, MHBA]** Yes, thank you very much. My name is Frank Tacke. I welcome you all to Berlin. But let me remind you, this is not really the center of Berlin. So really take your time also and visit the Berlin nightlife. I would like to discuss with you the scientific evidence that we have nowadays for treatment options for MASLD/MASH. And Professor Schattenberg has introduced to you that we want to focus on the ones with steatohepatitis and relevant fibrosis. Of course, lifestyle is like the basis for everything, healthy lifestyle, but we do have nowadays treatment options.
36	**EASL-EASD-EASO Treatment Guidelines** 	And this is what the guidelines recommend. The European guidelines have been developed by 3 societies: EASL (liver society), EASD (diabetology), and EASO (obesity management). And you see here that the preferential choice for co-medication to treat the comorbidities is very important. For instance, using the GLP-1 receptor agonists for the treatment of diabetes or obesity because they are also beneficial, presumably due to their weight loss effect, for MASLD/MASH. But so far, we did not really have anything that was specific as a MASH-targeted therapy.
37	**EASL-EASD-EASO Treatment Guidelines** 	And this has changed now in Germany for 2 weeks now, as we have resmetirom, a thyroid hormone receptor-β–specific agonist that we can use in F2 and F3 fibrosis.

38	**Evidence on the Role of Liver Hypothyroidism**  ▪ Hypothyroidism is associated with higher MASLD incidence ▪ During MASH progression, reduction of DIO1 and increase of DIO3 DIO1: deiodinase type 1; DIO3: deiodinase 3; TRH: thyrotropin-releasing hormone; TSH: thyroid-stimulating hormone Karim G, Bansal MB. *touchREV Endocrinol*. 2023;19:68-78. Bano A, et al. *J Clin Endocrinol Metab*. 2016;101:3204-3211. Bohinc BN, et al. *Endocrinology*. 2014;155:4591-4601. Braunstein E, et al. *J Clin Endocrinol Metab*. 2018;103:2696-2706. Braunstein E, et al. *Mol Metab*. 2021;53:101266. Reproduced for educational purposes only.	So what do we try to achieve with that? We know that hypothyroidism is associated with higher MASLD incidence, but there's also a phenomenon of local hypothyroidism in the liver.
39	**Differential Expression of THR-α and -β Receptor**  FA: fatty acid; THR: thyroid hormone receptor.	And in the liver, thyroid hormones work through a receptor called thyroid hormone receptor-β, whereas a lot of the systemic effects that we associate with thyroid effects like sweating, tachycardia, or bone loss are actually mediated via thyroid hormone receptor-α. So what does resmetirom, as a liver-specific thyroid hormone receptor-β agonist, do? And for this, we prepared a little video for you because the video can probably explain this much better than any of us. So let's have a look into the liver.
40	**THR-β Agonists: Mechanism of Action** 	Thyroid hormone receptor-β agonists, or THR-β agonists, are small molecules designed to specifically act in the liver. These agents enter the nucleus within the hepatocyte and bind to THR-β to activate target gene expression, which mediates several metabolic pathways. First, enhanced mitophagy removes damaged mitochondria, while mitochondrial biogenesis generates new organelles. At the same time, reductions in reactive oxygen species, or ROS, limit mitochondrial damage and accumulation of toxic long-chain lipids. Finally, increases in lipophagy generate free fatty acids, which 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.
41	**Resmetirom: Phase 3 Program**  AE: adverse event; NAFLD: nonalcoholic fatty liver disease; NASH: nonalcoholic steatohepatitis. Harrison SA, et al. *Aliment Pharmacol Ther*. 2024;59:51-63. Reproduced for educational purposes only.	Well, this sounds all great, but let's look at the data. Do they support what the scientific rationale behind this actually is? And you can see here the large study program that has led, in the end, to the approval of resmetirom for the treatment of MASH with F2 and F3 fibrosis. And the most important trial was probably the MAESTRO-NASH, because here the patients underwent 2 liver biopsies, 1 before the start of the treatment and 1 year after starting resmetirom.

42	**Resmetirom: MAESTRO-NASH** **Primary Endpoints** Liver biopsy (ITT) at week 52 MASH Resolution $p < .0001$ 25,9% $p < .0001$ 29,9% 9,7% Placebo (n=318) Resmetirom 80 mg (n=316) Resmetirom 100 mg (n=321) Fibrosis Improvement (≥1 Stage) $p = .0002$ 24,2% $p < .0001$ 25,9% 14,2% Placebo (n=318) Resmetirom 80 mg (n=316) Resmetirom 100 mg (n=321) ITT: intention-to-treat Harrison SA, et al. *N Engl J Med*. 2024;390:497-509. Reproduced for educational purposes only.	And what was achieved was a significant increase in the proportion of patients achieving MASH resolution after 1 year, as well as fibrosis improvement, which is, of course, very important to a hepatologist—more than or equal to 1 fibrosis stage. And you can see here significant differences for the 2 doses that were tested.
43	**Resmetirom: MAESTRO-NASH** **Secondary Endpoint** Key secondary endpoint LDL cholesterol at week 24 (ITT) 0,1% Placebo (n=318) Resmetirom 80 mg (n=316) Resmetirom 100 mg (n=321) -13,6% $p < .0001$ -16,3% $p < .0001$ LDL: low-density lipoprotein Harrison SA, et al. *N Engl J Med*. 2024;390:497-509. Reproduced for educational purposes only.	Importantly, resmetirom also has some beneficial effects on cholesterol levels, so you can see here LDL cholesterol going down.

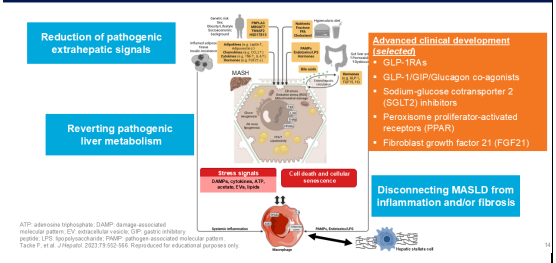
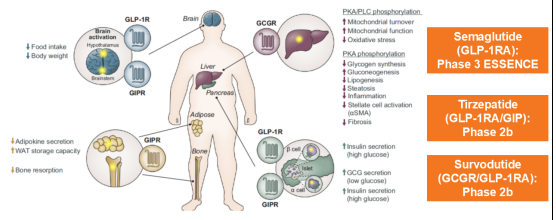
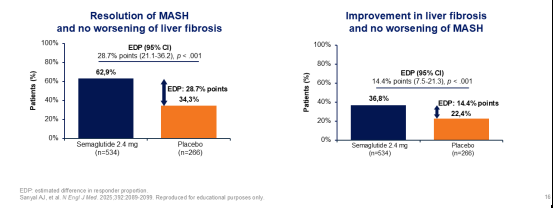
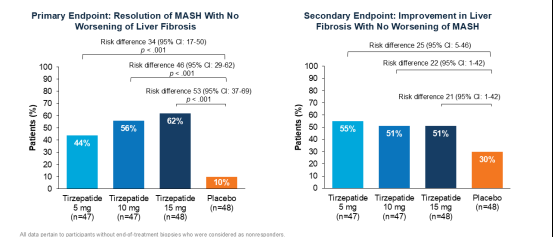
44	**Resmetirom: MAESTRO-NASH Safety**
	• Resmetirom was well tolerated
	• Consistent with previous phase 2 and phase 3 data, the most common AEs reported with greater frequency in the resmetirom groups vs placebo were:
	  • Excess of generally mild and transient diarrhea
	  • Generally mild nausea at the beginning of therapy
	Harrison SA, et al. *N Engl J Med*. 2024;390:497-509. Reproduced for educational purposes only.
		And from the safety data that we have from the phase 3 trial program, it's actually a quite well-tolerated drug. So you see here a relatively low number of serious adverse events, very similar to the placebo rate. The most important side effects are diarrhea and nausea, which have been reported in these trials. We're very excited to hear from Naim Alkhouri how it's been used in the US thus far.

45	**Current Utilization of Disease-Directed Therapy in the United States** ~7% of eligible patients with MASH are receiving treatment with resmetirom 25 000 20 000 15 000 10 000 5 000 0 > 2000 > 23 000 2Q 2024 2Q 2025 Resmetirom 9,000,000 Adult MASH population 3,100,000 Individuals with MASH F2/F3 315,000 Patients diagnosed with MASH F2/F3 ~7% patients on resmetirom 2Q 2025 Fortan Claims Data; Clearview Analysis; figure adapted for educational purposes only from Fishman J, et al. *Adv. Ther.* 2024;41:4172-4190.	If we look from Europe to the United States, we see that the uptake of the medication in the United States is quite high. There's still only a small fraction of the eligible patients currently on the drug, and we'll learn about the experiences from Naim in a minute.
46	**Other THR-β Agonists in Development** Resmetirom is not the only THR-β agonist in development, so there is a whole program from other companies, and they are not approved yet, but I think we will learn more about the use of thyroid hormone receptor-β agonists and also whether some of the drugs have more advantages than others.	

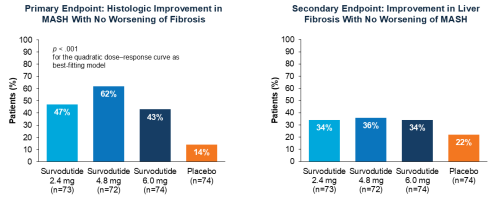
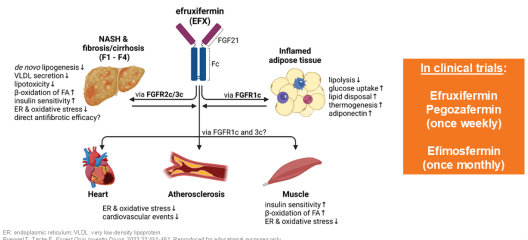
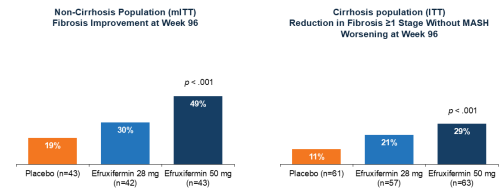
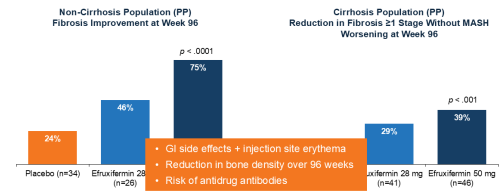
AE (%)	Resmetirom 80 mg (n=322)	Resmetirom 100 mg (n=323)	Placebo (n=321)
Serious AEs	10.9	12.7	11.5
Study discontinuation for AEs	2.8	7.7	3.4
Diarrhea	27	33.4	15.6
Nausea	22.0	18.9	12.5

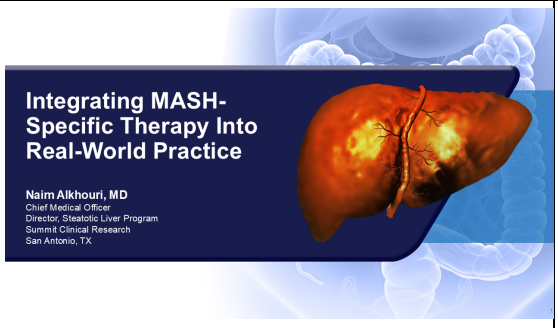
Drug Candidate	Study Stage	Endpoints
VK2809	Phase 2 Biopsy-confirmed MASH (N=248)	12-week reduction of liver fat content 52-week biopsy data presented at AASLD
TERN-501	Phase 2 Presumed MASH (N=162)	12-week reduction of liver fat content Results available[a]
ALG-055009	Phase 2 Presumed MASH (N=100)	12-week reduction of liver fat content Data presented at AASLD TLM 2024

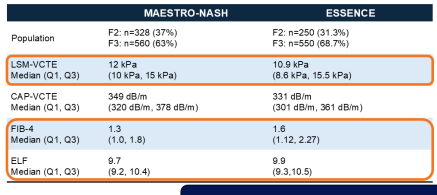
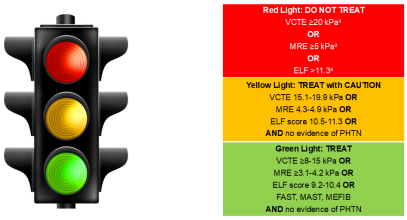
[a]No longer in development.
AASLD: American Association for the Study of Liver Diseases; TLM: The Liver Meeting
ClinicalTrials.gov: NCT04171050; ClinicalTrials.gov: NCT05415722; ClinicalTrials.gov: NCT06342947.

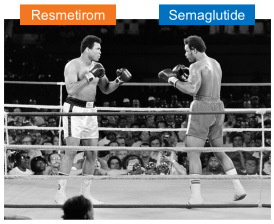
47	**Therapeutic Strategies Against Steatohepatitis and Fibrosis** 	If we think about how to place these new drugs into the treatment of steatohepatitis and fibrosis, I think we do have some drugs and some approaches that target pathogenic signals outside the liver. And I would think losing weight, either by nutritional interventions or by GLP-1 receptor agonists, would be one of the mechanisms that is very efficacious in MASLD/MASH. With thyroid hormone receptor-β agonists, we have the first drug that really targets liver metabolism. We do not really have that many drugs that work on the inflammation or fibrosis side. So we can't, at the moment, improve metabolism in order to get the beneficial effects on the metabolic consequences of injury, meaning steatohepatitis and fibrosis.
48	**Metabolic Effects of GLP-1RAs and Co-agonists** 	Of course, I would like to mention that the GLP-1 receptor agonists, the obesity drugs, are also important in the management of patients with MASLD/MASH. We do have phase 3 clinical data for semaglutide, an obesity drug, for the treatment of MASH. We also have data from a phase 2 trial for tirzepatide, a GLP-1 receptor and GIP agonist, and the concept of using GLP-1 receptor agonism and glucagon agonism, for instance with survodutide, is being tested at the moment.
49	**Semaglutide: Phase 3 Trial** **Subcutaneous Doses Were Administered Once Weekly for 72 Weeks** FDA Conditional Approval Proportion of patients at week 72 	For semaglutide, the phase 3 clinical trial data have led to the FDA approval of semaglutide for the treatment of MASH. You can see here that resolution of MASH without worsening of liver fibrosis was significantly more often achieved after 1.5 years, resmetirom trials were 1 year histology and this is 1.5 years. Improvement in liver fibrosis was also achieved.
50	**Semaglutide: Phase 3 Trial Safety** Safety analysis set (1195 participants) See table below	Semaglutide, of course, has the known gastrointestinal side effects, particularly nausea, diarrhea, constipation, and vomiting, which were more frequently observed in this high-dose group compared with placebo.
51	**Dual GIP and GLP-1RA Tirzepatide: Phase 2b Trial** **Subcutaneous Doses Were Administered Once Weekly for 52 Weeks** 	Looking at tirzepatide, which is approved for the treatment of obesity already in Europe and the United States, data after 1 year of therapy show MASH resolution and fibrosis improvement was significantly more often achieved in this early phase clinical trial with different doses of tirzepatide.

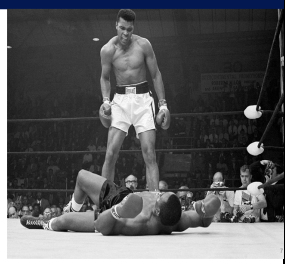
AE, n (%)	Semaglutide 2.4 mg (n=800)	Placebo (n=395)
All AEs	690 (86.2)	315 (79.7)
Fatal AEs	3 (0.4)	6 (1.5)
Serious AEs	107 (13.4)	53 (13.4)
AEs leading to trial discontinuation	21 (2.6)	13 (3.3)
AEs affecting ≥10% of participants		
Nausea	**290 (36.2)**	**52 (13.2)**
Diarrhea	**215 (26.9)**	**48 (12.2)**
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)**

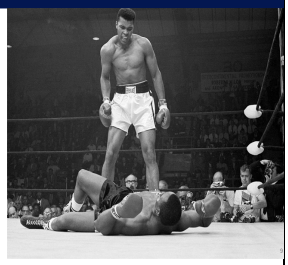
52	**Dual GCGR/GLP-1RA Survodutide: Phase 2b Trial** **Subcutaneous Doses Were Administered Once Weekly for 48 Weeks**  All data pertain to participants without end-of-treatment biopsies who were considered as nonresponders. Sanyal AJ, et al. *N Engl J Med*. 2024;391:311-319. Reproduced for educational purposes only.	And we have similar data for this dual glucagon and GLP-1 receptor agonist, survodutide, in a phase 2 clinical trial. No clear dose dependency was observed, but that may be because at the higher doses, some participants switched back to the lower dose, which may have impacted the results. But also significant effects on MASH resolution and a clear trend in fibrosis improvement.
53	**Rationale for FGF21 Analogues**  ER: endoplasmic reticulum; VLDL: very low-density lipoprotein Fruergaard T, Taicle F. *Expert Opin Investig Drugs*. 2023;32:451-461. Reproduced for educational purposes only.	One drug or one class of drugs that I would like to mention to you is FGF21 receptor agonists or FGF21 analogues. FGF21 is a hormone produced by the liver with a lot of beneficial metabolic effects in the body, also on the cardiovascular system. We have several compounds currently in clinical trials. What's really exciting is that the new components or new drug formulations allow a once-weekly or even once-monthly injection of the drugs. And what is exciting is that we have, from some trials, not only data after 24 weeks of intervention, which showed a delta of about 20% fibrosis improvement.
54	**Efruxifermin: Phase 2b HARMONY and SYMMETRY Trials** **Efruxifermin is a long-acting FGF21 analog**  mITT: modified intention-to-treat. Noureddin M, et al. *Lancet*. 2025;406:719-730. Noureddin M, et al. *N Engl J Med*. 2025;392:2413-2424. Reproduced for educational purposes only.	We now also have data after 96 weeks, so 2 years of treatment. If you look here on the left side, one trial was using efruxifermin in the non-cirrhotic population. And if you look on the right side, 96-week data show fibrosis improvement in the cirrhotic population—people reverting from cirrhosis to fibrosis. It's quite impressive.
55	**Efruxifermin: Phase 2b HARMONY and SYMMETRY Trials (cont)** **Efruxifermin is a long-acting FGF21 analog**  GI: gastrointestinal; PP: per protocol (biopsy completers). Noureddin M, et al. *Lancet*. 2025;406:719-730. Noureddin M, et al. *N Engl J Med*. 2025;392:2413-2424. Reproduced for educational purposes only.	If this is the ITT analysis, looking at the protocols—so the ones that really had 2 biopsies available—you can see that there seems to be an effect on fibrosis improvement that becomes even better over time. That makes us very hopeful for the use of antifibrotic drugs or drugs with an effect on fibrosis, that if we treat longer, we may even see more benefits. Particular side effects of FGF21 analogues include GI side effects and reduced bone density, so this needs to be carefully monitored.

56	**Summary** ▪ Resmetirom is a THR-β agonist and the first FDA/EMA approval of a MASH-specific therapy • Liver-specific mechanism of action • Increases mitochondrial capacity for β oxidation • Increases lipophagy • Increases cholesterol clearance • Reduces inflammation and fibrosis ▪ Many other MASH-specific drugs are in development • Semaglutide improves MASH resolution without worsening of fibrosis and improves fibrosis without worsening of MASH (FDA approval) • Co-incretin mimetics, SGLT2 inhibitors, FGF21 analogues, and pan-PPAR agonists in trials • Need more phase 3 data around other investigational agents • New updates are needed to better distinguish between MASLD, MetALD, and ALD ALD: alcohol-related liver disease; MetALD: metabolic dysfunction and alcohol-related liver disease	Let me summarize. Resmetirom is the first drug approved by the FDA and EMA and is now available also in Europe as a MASH-targeted therapy with a lot of beneficial actions in the liver: increases mitochondrial capacity for β oxidation, lipophagy, cholesterol clearance, and reduces inflammation and fibrosis. There are many other drugs currently in development, and we reviewed a bit of the clinical trial data for semaglutide and the co-incretin mimetics. We do need more phase 3 data around these agents. And of course, we are aware that some of the patients do not have pure MASLD, but also MetALD. And we need to understand which of the drugs are very important for this subclass of patients as well. And with this, I'm very excited that Naim Alkhouri will discuss with us some cases on how we should use all these drugs in clinical practice. Thank you.
57		**[Naim Alkhouri, MD, FAASLD]** Thank you very much. That was a wonderful overview of the entire therapeutic pipeline. So over the next few minutes, I'm going to try to help you integrate everything you heard into your practice. We're going to make this interactive. We have some polling questions, so please participate in these.
58	**2 FDA-Approved Medications for MASH With F2/F3** ▪ Resmetirom • Conditional approvals • FDA March 14, 2024 —NASH with moderate to advanced liver fibrosis (consistent with stages F2 to F3) • August 19, 2025 —Non-cirrhotic MASH with moderate to advanced liver fibrosis (fibrosis stages F2 to F3) ▪ Semaglutide • Conditional approval • FDA August 15, 2025 —Non-cirrhotic MASH, formerly known as NASH, with moderate to advanced liver fibrosis (consistent with fibrosis stages F2 to F3) in adults	But everything changed for us in March of 2024 when the FDA approved resmetirom as the first liver-directed therapy for patients with MASH and F2 or F3 fibrosis. It really changed everything we do in our clinics, the conversation we have with the patients, and the ability to give them hope that this is a reversible disease and that we can actually slow its progression, at least based on the data we have today from the MAESTRO-NASH trial. And then, of course, resmetirom was just recently approved in Europe, and in Germany, you guys have it now. It's available to prescribe from my understanding. Semaglutide was also approved in the United States on August 15th of this year. So in the United States, now we have 2 FDA-approved medications. They both have the indication for patients with MASH and F2 or F3 fibrosis.

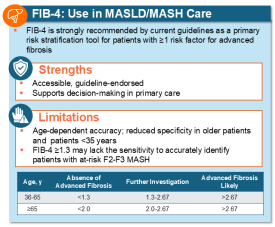
59	**Comparison of Overall Baseline NITs**  Use of quartiles: Q1 to Q3 represents 50% of the overall data Use of mean/SD: [mean-SD] to [mean+SD] represents ~68% of the data CAP: controlled attenuation parameter; ELF: enhanced liver fibrosis; FIB-4: Fibrosis-4; LSM: liver stiffness measurement; NIT: noninvasive test; VCTE: vibration-controlled transient elastography. Harrison SA, et al. *N Engl J Med*. 2024;390:497-509. Newsome PN, et al. *Aliment Pharmacol Ther*. 2024;60:1525-1533.	We select patients in clinic based on noninvasive tests. We do not biopsy patients, although all the trial data that you saw were based on 2 biopsies at baseline and after 52 to 72 weeks of treatment. So here I'm summarizing the NIT data from the MAESTRO-NASH trial and the ESSENCE trial to show you that the data that Professor Schattenberg shared with you actually will help you select the right patient population that was treated in the clinical trial. So if you look at transient elastography, liver stiffness measurements. You can see in the MAESTRO-NASH trial, the median was 12 kPa, and the interquartile range was between 10 to 15 kPa. In MAESTRO-NASH, we required that all patients have liver stiffness of at least 8.5 kPa. So that's why the lower cut point was a little bit higher. If you look at the ESSENCE trial, the median liver stiffness was 10.9, and the range was between 8.5 to 15.5. And this is what's recommended by the guidelines. The sweet spot is between 8 to 15 kPa. I also want to highlight that in both studies, FIB-4 was actually on the lower side. And that means that we're going to miss a lot of patients if we just rely on FIB-4. So in MAESTRO-NASH, the median FIB-4 was 1.3. That means that 50% of patients with biopsy-proven MASH with F2 or F3 had FIB-4 less than 1.3. So keep this in mind. In the ESSENCE trial, the median was 1.6. And then finally, the ELF score (Enhanced Liver Fibrosis test)—this is something we use commonly in the United States. The median was around 9.7 to 9.9, and the range was between 9 to 10.5. So maybe that 7.7 cut point that is recommended by some guidelines is set too low. So I start treating patients when the ELF is 9 or above.
60	**Proposed Algorithm for Patient Selection Using NITs**  If biopsy is performed and liver histology demonstrates stage 2 or 3 disease, treatment is appropriate, as long as there is no clinical or imaging evidence of PHTN (eg, ascites apparent on imaging, gastroesophageal varices, history of hepatic encephalopathy). FAST: FibroScan-AST; MAST: magnetic resonance imaging AST; MEFIB: MRE combined with FIB-4; MRE: magnetic resonance elastography; PHTN: portal hypertension. Noureddin M, et al. *Clin Gastroenterol Hepatol*. 2024;22:2347-2357. Chen VL, et al. *Hepatology*. 2025;81:312-330. Image from pngtree.com.	I think we've seen a similar figure to this one. But this is kind of the traffic light concept for how to select patients for treatment with pharmacologic therapy. We have the green zone, which is based on liver stiffness between 8 to 15 kPa. And we have cut points also for MR elastography and ELF. We have the red zone, where we don't want to treat with resmetirom or semaglutide, and these patients are likely to have cirrhosis if the liver stiffness is more than 20 kPa or MR elastography is more than 5 kPa. And then we have the yellow zone. So, for example, liver stiffness between 15 to 20 kPa. Many of these patients will actually have F3 fibrosis, but some of them will have cirrhosis. So you really need to do a full abdomen ultrasound, make sure your liver is smooth, there is no splenomegaly, your platelet count is completely normal, and then you can treat them also with liver-directed therapy.

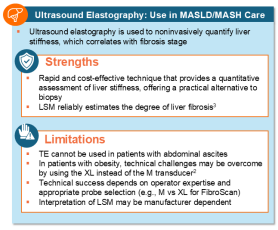
61	**Real-World Evidence With Resmetirom (N=669): Baseline Characteristics/NITs** ▪ A total of 97 patients (14.5%) were diagnosed via liver biopsy ▪ The majority 608 (90.9%) were assessed using transient elastography ▪ 111 (16.6%) had ELF testing ▪ **38% on statin, 18% of GLP-1RA** | Parameter	
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Age, median (IQR), years	57 (47-67)
Sex (male), n (%)	242 (41.6)
T2D (yes), n (%)	335 (50.1)
Hypertension (yes), n (%)	340 (50.8)
Low HDL	219 (55.6)
Elevated triglycerides	209 (47.2)
Obesity, n (%)	476 (82.4)
BMI, kg/m^2	36 (32-41)
LSM, median (IQR), kPa	10.9 (8.9-13.6)
CAP, dB/m	322 (296-352)
ELF score, median (IQR)	9.9 (9.5-10.6)
FIB-4 Index	1.27 (0.82-1.87)
AST, U/L	35 [24-52]
ALT, U/L	42 [27-66]
Platelet, x10^3/µL	241 (198-301) | AST: aspartate aminotransferase; HDL: high-density lipoprotein; IQR: interquartile range. Akhoundi N, et al. EASL Congress 2025. Poster SAT-438.	This is the real-world evidence that we generated back in the United States at 6 academic centers, where we actually treated, after the FDA approval, 669 patients. And in this population, about 14% of them had a historic biopsy. We went back 3 years, and anyone who had a biopsy showing F2 or F3, we considered them for treatment. So I encourage you today in Germany, if you biopsied patients over the last few years, to go back and recall the patients that have F2 and F3. But the vast majority of patients that we treated and qualified for treatment, and who were approved by insurance, were based on transient elastography. So 91% met the elastography criteria between 8 to 15 kPa, and we had about 15% that had ELF testing also. I also want to highlight that you can use resmetirom with statins, no problem. There is a dosing consideration for the statin you need to be aware of, but 38% of patients in this real-world cohort were on a statin, and also 18% of these patients came to us on a stable dose of GLP-1. And they still had MASH with F2 or F3. And then we added resmetirom on top of the GLP-1. In the table, you can see the patient characteristics. I was surprised how similar they are to the MAESTRO-NASH trial, including the liver stiffness measurements and the ELF test. So this validates these cut points for NITs in the real world.
62	**The Big Fight/The Rumble in the Jungle**  	So now we have a big fight in the United States. We have 2 FDA-approved medications, resmetirom and semaglutide. As clinicians, we have to make decisions and decide which agent is the right first choice. And of course, as I showed you, you can actually add resmetirom on top of a stable GLP-1. But I'm going to share with you a few cases. We're going to have some questions. There is no right answer. So I'm very curious to see how you guys respond.

63	**Fight 1**
	▪ 56-year-old woman
	▪ Past medical history of T2D for 12 years
	  • Treated with dulaglutide for the past 5 years
	▪ BMI 29.1 kg/m^2
	▪ HbA$_{1c}$ 6.4%
	▪ FibroScan
	  • **LSM 11.3 kPa c/w F3** fibrosis
	  • CAP 362 dB/m c/w S3 steatosis
	
	HbA$_{1c}$: hemoglobin A$_{1c}$
	
	
		But this is fight number 1 or patient number 1. We have a 56-year-old woman with a past medical history of type 2 diabetes for 12 years. She has been treated with a GLP-1, specifically dulaglutide, for the past 5 years. She actually achieved weight loss. Her BMI is down to 29.1 kg/m^2. Her HbA$_{1c}$ is under control for someone with diabetes. But then you do a liver stiffness measurement, and it comes back as 11.3 kPa. So this is consistent with stage F2–F3 fibrosis, and her CAP score is consistent with significant steatosis. So again, this is a patient with diabetes who has been on a GLP-1, with good diabetes control, and BMI in the overweight but not obesity range.

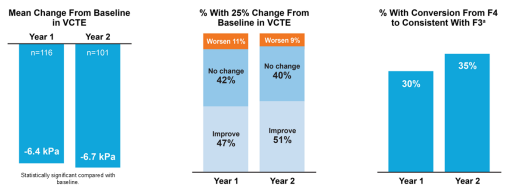
64	**Question** How would you treat this patient? A. Resmetirom B. Semaglutide C. Resmetirom + semaglutide D. Neither treatment	Question for you guys: How would you treat this patient? Would you start her on resmetirom? Would you switch to semaglutide from dulaglutide? Would you do both resmetirom and semaglutide, or neither treatment? Let's vote. So I see that the majority of you selected to start this patient on resmetirom. I agree because this patient has been on a GLP-1. The diabetes is under good control, and potentially this is a patient with F3. So I would like to start with liver-directed therapy here, given the fact that she's been on a GLP-1, and then we can reassess and potentially consider switching the GLP-1.
65	**Fight 2** ▪ 53-year-old man ▪ Past medical history of HTN, OSA, and obesity (BMI 39.2 kg/m^2) ▪ Presents with incidental finding of hepatosplenomegaly on ultrasound ▪ FibroScan • **LSM 8.6 kPa** c/w F2 fibrosis • CAP 371 dB/m c/w S3 steatosis  HTN: hypertension; OSA: obstructive sleep apnea	Now we have case number 2: a 53-year-old man with a past medical history of hypertension, obstructive sleep apnea, and class II obesity with a BMI of 39.2 kg/m^2, presents with an incidental finding of hepatosplenomegaly on ultrasound. Liver stiffness is 8.6 kPa, indicating potentially early F2 fibrosis, and CAP is high at 371 dB/m.
66	**Question** How would you treat this patient? A. Resmetirom B. Semaglutide C. Resmetirom + semaglutide D. Neither treatment	The question for you guys: How would you treat this patient? Resmetirom, semaglutide, both agents, or neither treatment? **[Jörn M. Schattenberg, MD]** You're throwing me off with hepatosplenomegaly in this case? Or was it just a large liver? **[Naim Alkhouri, MD, FAASLD]** You know, sometimes we see this reported, and the splenomegaly is like 12.5 cm. But you're right, when you see splenomegaly, you always worry about cirrhosis. But with this kPa, if it's like 12.5 cm, usually I don't react to it. But if it's more than 14 cm, I'm always worried about splenomegaly. So good point, but sometimes we overcall it. All right, let's see what you guys came up with for this. Okay, so I think, given the highest metabolic burden, the higher BMI, and the fact that this is early-stage disease, many of you selected to start semaglutide, but many of you also decided that maybe resmetirom is a good option. And some of you want to do combination therapy. Again, there's no right answer. I think we need to take into account patient preference, whether they want to do an injection or a tablet, and any prior exposure to a GLP-1. So these are all things you have to consider. But I do agree with this choice.

67	**Fight 3** ▪ 53-year-old man ▪ Past medical history of T2D (HbA_{1c} 7.4% on metformin) and obesity (BMI 34.2 kg/m²) ▪ Presents with incidental finding of hepatosplenomegaly on ultrasound ▪ FibroScan at baseline: • LSM 10.9 kPa c/w F3 fibrosis • CAP 371 dB/m c/w S3 steatosis ▪ After 1 year of treatment with semaglutide: BMI 32.8 kg/m² and HbA_{1c} 6.1% ▪ **VCTE** • **LSM 13.6 kPa** • CAP 326 dB/m • Add resmetirom 	Now case number 3: a 53-year-old man with a past medical history of type 2 diabetes. His HbA_{1c} is 7.4%, only on metformin, and not perfect control. He still has obesity with a BMI of 34.2 kg/m². He presents with, for Dr. Schattenberg, hepatomegaly—again, it should be hepatomegaly, fine—and FibroScan liver stiffness of 10.9 kPa, so maybe early stage F3, and CAP score of 371 dB/m. The patient was treated by his endocrinologist with semaglutide. After 1 year of treatment, his BMI dropped and the HbA_{1c} is under very good control. But this is a key message today: when you start someone on a GLP-1, such as semaglutide, you need to reassess after 1 year. Even if they lose weight and have better diabetes control, not everyone will achieve fibrosis response. This patient's transient elastography showed worsening liver stiffness, from 10.9 to 13.6 kPa, and the CAP went down, so there might be loss of steatosis. This is important because the weight loss here, the BMI dropped but very slightly so they did not achieve optimal response.
68	**Question** How would you treat this patient? A. Add resmetirom B. Add resmetirom and continue semaglutide C. Neither treatment	The question for you guys: How would you treat this patient? Would you add resmetirom and stop semaglutide completely because of the worsening liver fibrosis, or would you add resmetirom to semaglutide and have the patient on dual therapy? Or neither treatment. Let's vote. Okay, excellent—no one wants to stop semaglutide because we achieved better glycemic control, but I think this is a perfect patient to add resmetirom on top of semaglutide, since semaglutide did not achieve fibrosis response, and we need to use liver-directed therapy.

69	**Juanita**
	▪ 61-year-old Hispanic woman with T2D and obesity
	▪ Presents for elevated liver enzymes
	▪ Family history: mother died from MASH-cirrhosis complications
	▪ Laboratory tests
	  • ALT 71 U/L
	  • AST 45 U/L
	  • Platelets 265 k/µL
	▪ Abdomen US: smooth liver with normal spleen size
	▪ FIB-4 index: 1.23
	▪ Current Medications
	  • GLP-1 RA for T2D
	
		Now, finally, I have a longer case for you to walk through some monitoring of treatment response. This is Juanita, a 61-year-old Hispanic woman with type 2 diabetes and obesity. She presents with elevated liver enzymes and has a significant family history, with her mother dying from MASLD cirrhosis complications. Her labs show elevated ALT at 71 U/L, AST 45 U/L, normal platelet count at 265 k/µL. You do a full abdominal ultrasound. It shows a smooth liver with normal spleen size, and you calculate the FIB-4, and it comes at 1.23, so less than 1.3, okay? And she has been on a GLP-1 to treat her diabetes. What would you do next? Would you say, you know, I'm going to reassure this patient her FIB-4 is less than 1.3 and just come back in 2 years. I think the message I want to drive here is no, please don't do that. This is a patient with very high pre-test probability of having significant disease. She is Hispanic with type 2 diabetes. And she has elevated liver enzymes. And there is family history of MASH cirrhosis. So again, this is a patient where I'm going to doubt this FIB-4. And I would still do another test. In fact, the cutoff of 1.3 was initially developed to rule out advanced fibrosis, not significant fibrosis, not F2, F3. And if you read the EASL guidelines by Professor Tacke, he actually mentions a lower cut point for FIB-4, right, between 0.7 to 0.9 if you want to rule out F2 or higher. So this is a patient where, you know, again, I'm going to do another test. I'm not going to stop at the FIB-4. Keep in mind this FIB-4 is also borderline.

70	**Are You Confident Ruling Out Advanced Fibrosis in Juanita?**  Juanita's VCTE ▪ CAP 371 dB/m (S3) ▪ LSM 12.4 kPa 	So when we are looking at these patients, I want you to look at the entire picture. So what is the age? Do they have diabetes or not? What's the AST to ALT ratio? What's the platelet count? Do we have family history of MASH cirrhosis? And I encourage you in specialty care and GI hepatology clinics to do transient elastography in these patients. Transient elastography is not perfect. It has limitations. If the AST, ALT are very high, above 200 U/L, you're not supposed to do transient elastography. If someone has very high BMI, above 40 kg/m^2, that can impact the accuracy of your transient elastography. So the key message here is these NITs should not be interpreted in a vacuum. You need to look at the clinical picture, pre-test probability, and then interpret the NITs. But in this patient, I would not stop at FIB-4. I would actually do the transient elastography. And this is what happened in Juanita's case. So transient elastography came back with the liver stiffness of 12.4 kPa. So she would have been missed if we just followed the guidelines and stopped at the FIB-4. So this is consistent with F3 fibrosis.

71	**Additional Tests With Discordant Diagnostic Findings** ▪ Juanita's FIB-4: 1.23 (<1.3 = low probability for cirrhosis) • FIB-4 in this case failed to appropriately risk stratify this patient • A phase 3 trial in MASH patients with moderate to advanced fibrosis reported a mean baseline FIB-4 score of 1.3–1.5 ▪ Juanita's Agile 4: • 12.4 kPa • T2D • Female • AST 45 U/L, ALT 71 U/L • Platelets 265 k/μL Agile 4 = 0.09 Agile 3+: 0.7 = **high risk** for advanced fibrosis Rule Out <0.45 | Indeterminate ≥0.45 - <0.68 | Rule In ≥0.68 Agile 4: 0.09 = **low risk** for advanced fibrosis Rule Out <0.25 | Indeterminate ≥0.25 - <0.57 | Rule In ≥0.57	You may tell me, you know what, I'm not convinced because the FIB-4 is too low. Now I have discordant NIT, so I need something else. You can consider doing a liver biopsy, but we have additional tests that can increase your positive predictive value from your liver stiffness. And one such test is called the Agile 3+. This is developed to predict F3 and F4 fibrosis. And this includes your liver stiffness plus AST, ALT, platelet count, age, presence of diabetes, and it ranges from 0 to 1. The closer you are to 1, the more likely you have F3 fibrosis or higher. So in this case, we calculated the Agile 3+, and it was at 0.7, above the 0.6 cut point. That increases your positive predictive value. You may also be worried maybe this patient has cirrhosis, especially with the family history. So you want to rule out cirrhosis. I showed you she has a normal platelet count. There's no splenomegaly, smooth liver. But there is a score also called the Agile 4 score that was developed to also rule out and rule in cirrhosis based on 2 different cut points. If you calculate the Agile 4 in this patient, it comes as a very low score at 0.09. So this is a patient with F3 without cirrhosis that would definitely treat with liver-directed therapy.
72	**Ruling in Noncirrhotic MASH With Advanced Fibrosis (F3)** Clinical imaging and laboratory tests available to assist clinicians in accurately identifying patients likely to have noncirrhotic MASH with F3 fibrosis **Clinical parameters** Metabolic risk factors: Diabetes, obesity, hyperlipidemia, hypertension with no signs of portal hypertension **Imaging** Liver stiffness (VCTE): >8 to <20 kPa (~33% of patients with biopsy-confirmed F3 had VCTE ≥15 kPa) MRE: <4.2 kPa Ultrasound: No hepatic nodularity or evidence of portal hypertension on ultrasound, MRI or CT scan **Standard blood tests** Platelets: >140,000/μL (trajectory of platelet count showing stability over time can be helpful) Bilirubin: Normal total bilirubin <1.3 mg/dL (unless consistent with Gilbert Syndrome, where total bilirubin is ≥5-fold direct bilirubin and direct bilirubin levels are normal) Albumin: ≥4.0 g/dL **Special blood tests** ELF: 9.0 to <10.3 PEth: <50 ng/mL - Can be used to rule out excessive alcohol intake. PEth >50 ng/mL investigate chronic alcohol use	So again, to rule in F3 fibrosis, rule out cirrhosis, I want you to look at the clinical picture. How old is the patient? What are the metabolic risk factors? Diabetes is the most important one. Then I want you to look at your imaging test. What is my liver stiffness? Do I have an ultrasound? Is there splenomegaly? Do I have a nodular liver or not? So we look at imaging tests. Then I want you to look at the routine labs. What is my platelet count? That's the most important one. But I also want you to look at your bilirubin, your albumin, because we do not want to treat patients with cirrhosis today with resmetirom or semaglutide. We do not have that indication yet. If you have the ELF score, that can also help you in controversial cases. And this is a blood-based test. Also, PET testing is something that we are using commonly in the United States to rule out significant alcohol consumption. So make sure that you are treating the right patient population, which is MASLD and MASH, not a patient with ALD.
73	**Juanita (cont)** ▪ Based on Juanita's high pre-test probability of having at-risk MASH (Hispanic woman with obesity and T2D + family history of MASH cirrhosis) + VCTE showing LSM of 12.4 kPa + high AGILE3+ score + lack of evidence for cirrhosis • She is started on resmetirom 80 mg daily —Weight 179 lbs	So based on Juanita's high pre-test probability of having advanced disease because of diabetes, family history, VCTE showing F3, high Agile 3+, and lack of cirrhosis, she was started on resmetirom, 80 mg/day. This is weight-based, so less than 100 kg or 220 lb, you start with the 80 mg/day.

74	**Question** Juanita's primary care physician (PCP) checks her liver enzymes 4 weeks after starting resmetirom. The PCP observes that ALT has increased from 71 U/L to 91 U/L. What should you do next? A. Stop resmetirom due to lack of efficacy B. Increase resmetirom to 100 mg daily C. Order a PEth test D. Continue therapy	And Juanita's primary care, after we started the resmetirom, decided to check liver enzymes 4 weeks after we started treatment. And the PCP observed that the ALT increased from 71 to 91 U/L. Okay. What should we do next? Should we stop resmetirom because of the increase in liver enzymes? Should we increase the resmetirom to 100 mg/day? Should we order a PET test to see if she's drinking too much alcohol? Or should we continue therapy and measure liver enzymes in 3 months or so? Let's vote. **[Jörn M. Schattenberg, MD]** Thank you, Naim. While we wait, can you remind us? There are 2 doses, and the recommendations are? **[Naim Alkhouri, MD, FAASLD]** If you weigh less than 100 kg, you go on the 80-mg dose. If you weigh more than 100 kg, you go on the 100-mg dose. This is how we dose resmetirom. All right, let's see what you guys came up with. All right, continued therapy. So I put this question together to highlight that it is expected to see a slight bump in ALT and AST when you start resmetirom if you check at 4 weeks. We think this is related to the sick hepatocytes dying, releasing these enzymes, and some remodeling in the liver. And typically by 8 weeks, you see the enzymes go back to baseline. And by 12 weeks, you see a reduction in liver enzymes. But this increase is usually within 1.5 times the baseline value. So if you start at 60 U/L, you can go up to 90 U/L. You're not going to go from 60 to 500 U/L. If that happens, you stop treatment immediately. This could be a very concerning scenario. Very unlikely, but that's why we monitor liver enzymes.
75	**Resmetirom in MASH Cirrhosis: Sustained Reductions in Liver Stiffness (LSM) After 2-Year Treatment** After 2 years on resmetirom, >50% of patients achieved sustained ≥25% reduction in LSM by VCTE  *Patients with confirmed F4 at baseline (liver biopsy, F4 and/or platelets <140/MRE ≥5 with VCTE ≥15) showed a transition from F4 to potential F3 at year 2 (VCTE<15 and ≥25% decrease from baseline). Alkhouri N, et al. EASL Congress 2025. Abstract LBO-002.	Finally, I just want to leave you with this teaser slide. I said do not treat patients with cirrhosis, but we have some data in patients with cirrhosis. This is from an open-label study that treated 122 patients with MASH cirrhosis, compensated cirrhosis, with resmetirom 80 mg, up to 2 years of treatment, and we measured liver stiffness. We showed a clinically significant reduction in liver stiffness from baseline by up to 6.7 kPa. And we know that reducing liver stiffness by 5 kPa is clinically meaningful. We also showed that more than 50% of patients reduced their liver stiffness by 30% or more from baseline, and about one-third of patients potentially reversed their cirrhosis by achieving a liver stiffness less than 15 kPa and decreasing the stiffness by 30% or more.

76	**Just Do Something About MASH**    **Screen** **Stage** **Start Rx**	So my take-home message is just do something about MASH, okay? And I've been preaching this for the last year, but I call it the 3 S's approach. S number 1 is please screen all high-risk patients. That includes all diabetics and all patients with obesity and other metabolic risk factors. Once you diagnose MASLD, you need to stage the disease. From day 1, you need to know if they have F2, F3, because we can treat these patients and potentially reverse the disease or slow its progression. And once you identify patients with F2, F3, please start treatment. And in Germany now, you have 1 EMA-approved medication, which is resmetirom. So please identify these patients and get them on treatment.
77	**Take-Home Messages** ▪ FDA-approved medications that are likely to benefit patients with at-risk MASH are here ▪ Resmetirom and semaglutide are FDA approved for at-risk MASH[a] (MASH[a] with F2-F3) ▪ Semaglutide has additional FDA approval for obesity and T2D ▪ **New Mantra in MASH:** "Screen, Stage, and Treat" [a]Resmetirom and semaglutide are approved for the treatment of adults with noncirrhotic NASH.	So to conclude, we have FDA-approved medications today to treat at-risk MASH, defined as MASH and F2, F3. Resmetirom is the only medication approved in Europe. The FDA approved semaglutide recently. Of course, semaglutide has other indications such as obesity and diabetes in Europe. And the new mantra is screen, stage, and treat. Thank you so much for your attention.