Title

What Does the Future Hold for Patients With Nonalcoholic Steatohepatitis: Diagnostic Strategies and Treatment Options in 2021 and Beyond?

Journal

Hepatology communications, 5(11)

ISSN

2471-254X

Authors

Alkhouri, Naim
Tincopa, Monica
Loomba, Rohit
et al.

Publication Date

2021-11-01

DOI

10.1002/hep4.1814

Peer reviewed

What Does the Future Hold for Patients With Nonalcoholic Steatohepatitis: Diagnostic Strategies and Treatment Options in 2021 and Beyond?

Naim Alkhouri,[1*] Monica Tincopa ,[2*] Rohit Loomba,[3**] and Stephen A. Harrison[4,5**]

Nonalcoholic steatohepatitis (NASH) can progress to cirrhosis and its complications, including hepatocellular carcinoma. Given that the majority of patients with NASH are asymptomatic, developing screening strategies to identify those individuals at risk for progressive NASH remains a highly unmet need. Furthermore, noninvasive tests that accurately predict disease progression as part of the natural history of NASH or regression in response to treatment are urgently needed to decrease the reliance on repeat liver biopsies. To date, there are no US Food and Drug Administration (FDA)-approved medications for NASH that can resolve steatohepatitis and lead to fibrosis regression. The lack of FDA-approved therapy has led to apathy in diagnosis and referral for specialty care. However, several therapeutic agents are rapidly progressing through the different phases of clinical trials with several already in phase 3 programs. In this review, we provide a summary of recent developments in NASH diagnostics and therapeutics that are likely to shape the future management of this underdiagnosed and undertreated disease. (*Hepatology Communications* 2021;5:1810-1823).

Nonalcoholic fatty liver disease (NAFLD) has emerged as the most common chronic liver disease worldwide, with a reported global prevalence as high as 25%.[1] The high prevalence of NAFLD is contemporaneous with epidemics of obesity, type 2 diabetes, unhealthy dietary patterns, and sedentary lifestyle. The spectrum of disease can range from a benign nonprogressive clinical course to a serious state of hepatocellular injury, inflammation, and fibrosis known as nonalcoholic steatohepatitis (NASH), which may then progress to cirrhosis and its complications, including hepatocellular carcinoma (HCC).[2-5]

A recent study prospectively evaluated the prevalence of NASH based on liver biopsy assessment in a large cohort of middle-aged adults in the United States who were asymptomatic. The cohort consisted of 664 individuals with a mean age of 56 years and mean body mass index (BMI) of 30.48 kg/m^2.[6] This study demonstrated that 14% of middle-aged Americans had evidence of NASH while approximately 6% had evidence of significant fibrosis. NASH has become the leading cause of liver transplantation in women in the United States and the second leading cause in men after alcohol-associated liver disease.[7] Screening for NAFLD in high-risk populations and

Abbreviations: ADAPT, algorithm incorporating Pro-C3 with age, diabetes, and platelet count; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUROC, area under the receiver operating curve; BMI, body mass index; CAP, controlled attenuated parameter; CK-18, cytokeratin 18; cT1, corrected T1; ELF, enhanced liver fibrosis; FAST, FibroScan + aspartate aminotransferase; FDA, US Food and Drug Administration; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; FIB-4, fibrosis-4; FXR, farnesoid X receptor; GLP-1, glucagon-like peptide 1; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MetS, metabolic syndrome; MGL-3196, resmetirom; MRE, magnetic resonance elastography; MRI, magnetic resonance imaging; NAFLD, nonalcoholic fatty liver disease; NAS, nonalcoholic fatty liver disease activity score; NASH, nonalcoholic steatohepatitis; NFS, nonalcoholic fatty liver disease fibrosis score; NIT, noninvasive test; NPV, negative predictive value; OCA, obeticholic acid; PDFF, proton density fat fraction; PPV, positive predictive value; RCT, randomized control trial; REGENERATE, Randomized Global Phase 3 Study to Evaluate the Impact on NASH with Fibrosis of Obeticholic Acid Treatment; Sn, sensitivity; Sp, specificity; TLMdX, The Liver Meeting Digital Experience; VCTE, vibration-controlled transient elastography.

Received April 26, 2021; accepted August 1, 2021.

**These authors contributed equally to this work.*

identifying those with NASH and significant liver fibrosis (fibrotic NASH) are the first steps to modify the natural history of the disease, although more data are needed to establish the accuracy and cost effectiveness of different noninvasive tests (NITs) and screening strategies.[8,9]

Despite its high burden on the health care system, there are no US Food and Drug Administration (FDA)-approved medications for fibrotic NASH. However, recent data presented in 2020 provide hope for the future. The aim of the current review is to provide an update on recent advances in NASH diagnostics and therapeutics with a focus on data presented at The Liver Meeting Digital Experience (TLMdX) in 2020.

Diagnostic Considerations

IDENTIFYING PATIENTS AT HIGH RISK IN NEED FOR PHARMACOLOGIC TREATMENT

In current clinical practice , a liver biopsy is required to assess the grade of steatosis, lobular inflammation, hepatocyte ballooning, and fibrosis in order to meet diagnostic criteria for NASH.[10,11] The initial three components are collectively assessed as the NAFLD activity score (NAS), and a separate stage is assigned for fibrosis.[12] Using NAS and fibrosis staging, which have been applied in the NASH Clinical Research Network, an NAS score of 5-8 is considered diagnostic

***These authors contributed equally to this work.*

View this article online at wileyonlinelibrary.com.
DOI 10.1002/hep4.1814

Potential conflict of interest: Dr. Loomba consults for and received grants from AstraZeneca, Bristol Meyers Squibb, Eli Lilly, Galmed, Gilead, Intercept, Inventiva, Janssen, Madrigal, NGM Biopharmaceuticals, and Pfizer; he consults for Aardvark Therapeutics, Altimmune, Alnylam/Regeneron, Amgen, Arrowhead Pharmaceuticals, CohBar, Glympse Bio, HighTide, Inipharm, Ionis, Metacrine, Novartis, Novo Nordisk, Merck, Sagimet, Theratechnologies, 89 Bio, and Viking Therapeutics; he is the cofounder of Liponexus. Dr. Harrison consults for, advises, received grants from, and owns stock in Akero Therapeutics, Galectin Therapeutics, Genfit, Hepion Pharmaceuticals, Metacrine, NGM Biopharmaceuticals, and NorthSea Therapeutics BV; he consults for, advises, and received grants from Axcella Health, CiVi Biopharma, CymaBay Therapeutics, Gilead Sciences, HighTide Therapeutics, Intercept Pharmaceuticals, Madrigal Pharmaceuticals, Novartis Pharmaceuticals, Novo Nordisk, Poxel, and Sagimet Biosciences; he consults for, advises, and owns stock in HistoIndex and Sonic Incytes; he consults for and advises Altimmune, Boston Pharmaceuticals, B Riley FBR, BVF Partners, Canfite Biopharma, Echosens North America, Foresite Labs, Medpace, Prometic Pharma SMT, Ridgeline Therapeutics, and Terns; he consults for and received grants from Enyo Pharma S.A. and Viking; he advises and owns stock in Chronwell; he advises and received grants from Galmed Research and Development; he received grants from and owns stock in Cirus Therapeutics; he consults for AgomAB, Alentis Therapeutics AG, Almentiv, Corcept Therapeutics, Fibronostics, Fortress Biotech, Inipharm, Ionis, Kowa Research Institute, Microba PTY, Nutrasource, Perspectum Diagnostics, and Piper Sandler; he advises 89 Bio, Arrowhead Pharmaceuticals, Indalo Therapeutics, Pathai, and Theratechnologies. Dr. Alkhouri consults for, is on the speakers' bureau for, and received grants from Gilead and Intercept; he consults for and received grants from 89 Bio, Novo Nordisk; he consults for and is on the speakers' bureau for Echosens; he consults for Fibronostics, Perspectum, Pfizer, and Zydus; he is on the speakers' bureau for AbbVie and Alexion and received grants from Akero, Bristol Meyers Squibb, Galectin, Genentech, Ionis, Madrigal, Metacrine, and NGM Bio. Dr. Tincopa has nothing to report.

ARTICLE INFORMATION:

From the [1]Arizona Liver Health, Chandler, AZ, USA; [2]Well Consulting, Los Angeles, CA, USA; [3]NAFLD Research Center, University of California at San Diego, La Jolla, CA, USA; [4]Radcliffe Department of Medicine, University of Oxford, Oxford, United Kingdom; [5]Pinnacle Clinical Research, San Antonio, TX, USA.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

Stephen A. Harrison, M.D.
Radcliffe Department of Medicine, University of Oxford
Oxford, United Kingdom OX3 9DU
E-mail: sharrison@pinnacleresearch.com
Tel.: +44 1865 234657
or

Pinnacle Clinical Research
5109 Medical Drive, Suite 316
San Antonio, TX 78229, USA
E-mail: sharrison@pinnacleresearch.com
Tel.: +1-210-982-0320 ext. 1457

for NASH and NAS scores of 3-4 are considered borderline for NASH, although the gestalt diagnosis of NASH by the pathologist and the presence of ballooning are also required. Among patients with NASH, individuals with NAS ≥ 4 and ≥F2 have been used to distinguish individuals with high-risk features of NASH.[13] Multiple studies have highlighted that, among the histologic parameters of NASH, fibrosis stage is most closely linked with risk of clinical outcomes.[14-16] Clearly, there are several important limitations of liver biopsy that create barriers in diagnosis and risk stratification of NASH. This includes but is not limited to the invasive nature of the procedure with risk for clinical complications, like bleeding, suboptimal inter-reader reliability, and concern for sampling error.[17,18] Artificial intelligence methods, including machine learning, have been developed to address issues with inter-reader reliability of NASH biopsies. These methods have shown high concordance with expert pathologist interpretations and may represent a useful mechanism to standardize histologic scoring for NASH in the future.[19]

Serologic/Circulating Biomarkers

Circulating biomarkers represent an ideal approach for risk stratification as serologic testing can be done with relative ease, although some testing is proprietary and others are not routinely available in clinical practice. Two of the most commonly used serologic-based biomarkers for risk stratification in NASH are the fibrosis-4 (FIB-4) index and the NAFLD fibrosis score (NFS). Both of these clinical decision aides are offered as mechanisms to help risk stratify patients with NAFLD by American Association for the Study of Liver Diseases guidelines.[11] The NFS is computed based on platelet count, albumin, and aspartate aminotransferase (AST)/alanine aminotransferase (ALT), combined with three clinical parameters (age, BMI, and insulin resistance).[20] The key strength of the NFS is its accurate categorization of likelihood of having advanced fibrosis or cirrhosis (area under the receiver operating curve [AUROC], 0.85; sensitivity [Sn], 90%; specificity [Sp], 60%; negative predictive value [NPV], 88; positive predictive value [PPV], 82%).[21] The NFS has limitations in discriminating between lower stages of fibrosis, and approximately 30% of patients will be categorized as having an "indeterminant" NFS.[22,23] FIB-4 is calculated using platelets, AST, ALT, and age and in a meta-analysis was shown to identify advanced fibrosis in NAFLD with accuracy similar to NFS.[24] Similar to these two models, the metabolomics advanced steatohepatitis fibrosis (MASEF) score was constructed using lipids, BMI, platelets, AST, and ALT to detect high-risk NASH. In a cohort of 551 patients with NAFLD with liver biopsies, the MASEF score had an AUROC of 0.91 with Sn 58% and Sp 94%.[25]

There are several other circulating biomarkers that have been extensively evaluated for fibrosis risk stratification in NASH. The enhanced liver fibrosis (ELF) panel consists of the following three extracellular matrix turnover proteins: hyaluronic acid, tissue inhibitor of metalloproteinase 1, and N-terminal procollagen III-peptide. When used to assess likelihood of advanced fibrosis or cirrhosis, the ELF panel has had excellent performance characteristics, with an AUROC of 0.90, Sn 80%, and Sp 90%.[26,27] Pro-C3 is another marker of collagen synthesis that has been evaluated to predict risk of advanced fibrosis and cirrhosis. When used in isolation, Pro-C3 had an excellent AUROC of 0.91 with an NPV of 97% and PPV of 56%.[28] Pro-C3 has been incorporated in combination with other parameters to identify advanced fibrosis in NAFLD and NASH. The FIB-C3 and ABC3D scores incorporate Pro-C3 in combination with age, BMI, platelet count, and diabetes to correlate with the severity of steatohepatitis and fibrosis among patients with NAFLD. Both scores yielded high diagnostic accuracy, AUROC of 0.83 and 0.81, Sn 75% and 66%, and Sp 75% and 75% for FIB-C3 and ABC3D, respectively.[28] A similar algorithm that also incorporates Pro-C3 with age, diabetes, and platelet count (ADAPT) was shown to accurately identify patients with NAFLD and advanced fibrosis.[29] Cytokeratin 18 (CK-18) is a major intermediate filament protein in hepatocytes that has been extensively studied as a potential biomarker in NASH, both in isolation and in combination with other serologic markers and clinical variables. A recent study evaluated the utility of CK18 and wisteria floribunda agglutinin-positive Mac-2-binding protein (M2BP) to classify patients with NAFLD according to disease severity. A combination of M2BP and CK18 predicted the presence of fibrotic NASH with an AUROC of 0.88.[30]

A blood-based biomarker panel (NIS4) comprised of microRNA (miR)-34a-5p, α2 macroglobulin, YKL-40, and glycated hemoglobin yielded similar performance

characteristics, with an AUROC of 0.80 and an NPV of 77.9% to rule out at-risk NASH.[31] In evaluating different screening methods to identify patients with at-risk NASH (NAS ≥ 4 and F ≥ 2), a sequential approach using NIS4 with either FIB-4 or transient elastography yielded the highest PPV.[32] NIS4 levels have also been shown to help predict risk of fibrosis progression among individuals with NASH.[33]

The steatosis-associated fibrosis estimator (SAFE) score, developed using different machine learning methods, was compared to FIB-4 and NFS. The SAFE score incorporated age, sex, BMI, diabetes, AST, ALT, alkaline phosphatase (ALP), hematocrit, platelets, gamma-glutamyl transpeptidase (GGT), albumin, and globulin and outperformed FIB-4 and NFS to predict >F2 among patients with NAFLD.[34] A second machine learning model constructed using data among adults with diabetes and suspected NAFLD included AST, ALT, platelets, triglycerides, and high-density lipoprotein (HDL) and yielded an AUROC of 0.77 to distinguish NASH from NAFLD.[35] Machine learning methods have also been used to try and identify individuals with NAFLD at risk for rapid disease progression. A Light Gradient Boosting Model yielded an AUROC of 0.77 to identify fast progressors (6 months to 3 years) from index diagnosis of NAFLD/NASH to cirrhosis or HCC. Fast progressors had higher mean age, ALP, AST, AST/ALT ratio, bilirubin, rate of change of ALP, and anxiety diagnoses. Fast progressors also had lower mean albumin, low-density lipoprotein (LDL), hematocrit, platelets, and triglycerides.[36]

Whole-transcriptome cell-free messenger RNA has been used to identify patients with NAFLD with clinically significant fibrosis (F ≥ 2). It was able to identify 50% of patients with at least 90% probability of clinically significant fibrosis.[37]

Imaging Biomarkers

Imaging biomarkers have shown great promise to accurately characterize fibrosis in NASH. The primary modalities that have been investigated include vibration-controlled transient elastography (VCTE), magnetic resonance elastography (MRE) ± proton density fat fraction (PDFF), and multiparametric MR imaging (MRI) (LiverMultiScan). In a prospective head-to-head comparison of VCTE, two-dimension shear wave elastography (SWE), and MRE, MRE had the highest diagnostic accuracy for the detection of stage 4 fibrosis (AUROC, 0.92) and the highest intra/interobserver reproducibility among patients with biopsy-proven NAFLD.[38-40] For a detailed discussion on imaging tests for NASH and fibrosis, we refer the readers to an excellent recent review on the topic by Ajmera and Loomba.[41]

Combining circulating biomarkers with imaging data has been shown to enhance diagnostic accuracy to risk stratify NASH and identify those with NAS ≥ 4 and ≥F2. The FibroScan + AST (FAST) score was developed to predict the presence of NASH with fibrosis by combining the following parameters: liver stiffness measurement by VCTE as a biomarker for fibrosis, controlled attenuated parameter (CAP) as a biomarker for steatosis, and AST as a biomarker of activity.[42] The score was initially developed in a cohort in the United Kingdom and then validated in seven additional international cohorts. Based on the knowledge that MRI-PDFF is the most accurate method to quantify liver fat and that MRE is the most accurate imaging test to determine baseline fibrosis stage, the MRI and AST (MAST) score was developed to detect patients with NASH with NAS ≥ 4 and F ≥ 2. In the derivation cohort that included 103 patients with biopsy-proven NAFLD, MAST had an AUROC of 0.93, Sn 85%, and Sp 86%, and in the validation cohort (n = 244), the AUROC was 0.86.[43] A study of 694 patients with biopsy-proven NASH who underwent multiparametric MRI demonstrated that the combination of corrected T1 (cT1), fat, AST, and glucose yielded excellent diagnostic accuracy to identify patients with high-risk NASH.[44]

Jung and colleagues[45] conducted a prospective assessment in a well-characterized cohort of patients with biopsy-proven NAFLD who underwent a liver biopsy as well as a contemporaneous MRE; the aim was to identify patients with stage 2 fibrosis or higher. A combination of MRE ≥ 3.3 kPa plus FIB-4 ≥ 1.6 (MEFIB) yielded a PPV of 97% in the training cohort. They then validated their findings in a geographically and ethnically distinct cohort residing in Japan with a similarly robust PPV.[45] MEFIB appears to have the highest PPV among all NITs for detection of stage 2 fibrosis or higher in NAFLD. Further head-to-head comparative studies are needed to establish hierarchy of these NITs in NAFLD. A summary of NITs that are currently commercially available in the United States, including both serologic and imaging biomarkers, is presented in Table 1.

TABLE 1. SUMMARY OF NITS THAT ARE CURRENTLY COMMERCIALLY AVAILABLE IN THE UNITED STATES

Biomarker	Variables	Utility	Accuracy	Potential Limitations
Serologic				
FIB-4	Age, AST, ALT, platelets	Predicting advanced fibrosis (F3-F4)	High NPV	Cutoff should be modified in elderly; less accurate in young adults
NFS	Age, BMI, AST, ALT, platelets, IGT, albumin	Predicting advanced fibrosis (F3-F4)	High NPV	Less accurate in diabetics and young adults
ELF	HA, TIMP-1, PIIINP	Predicting advanced fibrosis (F3-F4)	Higher specificity/PPV than FIB-4 or NFS	Affected by age and other fibrotic conditions
NIS-4	miR-34a-5p, α2 macroglobulin, YKL-40, HbA1c	Predicting the presence of fibrotic NASH (NAS ≥ 4 and F ≥ 2)	Low cutoff to maximize NPV and high cutoff to maximize PPV	Needs further external validation
Imaging				
VCTE	CAP for steatosis; LSM for fibrosis	Screening for NAFLD; staging fibrosis	High accuracy for predicting advanced fibrosis	Less accurate in severe obesity and those with ALT > 200 U/L
MRI-PDFF	Liver fat fraction	Quantifying liver fat and assessing response to treatment	High accuracy for quantifying liver fat	Lack of prognostic value in terms of liver-related outcomes
MRE	Liver fibrosis	Staging fibrosis	High accuracy for predicting baseline fibrosis stage; prognostic value	Less predictive of histologic fibrosis improvement in response to treatment
cT1	Liver fibro-inflammation	Predicting fibrotic NASH	High accuracy for predicting "at-risk" NASH; prognostic value	Limited utility for NASH cirrhosis

Abbreviations: HA, hyaluronic acid; IGT, impaired glucose tolerance; LSM, liver stiffness measurement; miR, microRNA; NIS-4, blood-based biomarker panel; PIIINP, N-terminal procollagen III-peptide; TIMP-1, tissue inhibitor of metalloproteinase 1.

MONITORING RESPONSE TO PHARMACOLOGIC AGENTS

Methods to Monitor Response to Therapy

The FDA endpoints for NASH clinical trials have focused on NASH resolution without worsening of fibrosis or fibrosis improvement of at least one fibrosis stage without worsening of steatohepatitis. Both histologic endpoints require a repeat liver biopsy at the end of treatment.[46]

Emerging evidence from a series of investigator-initiated studies done at the University of California at San Diego followed by several large multicenter, randomized, controlled trials have helped establish a well-validated criteria, defined as ≥30% relative decline in MRI-PDFF, as recently proposed by Loomba and colleagues.[47-49] MRI-PDFF response is associated with higher odds of both ≥2-point improvements in NAS with at least 1-point improvement in lobular inflammation or ballooning as well as NASH resolution.[50] Further studies are needed to document whether MRI-PDFF response is associated with improvements in fibrosis.

Given the variability in interpretation of histologic changes in response to treatment by pathologists, machine learning techniques were applied to liver histology assessment using data from the Safety and Efficacy of Selonsertib in Adults with NASH and Bridging (F3) Fibrosis (STELLAR 3) or Cirrhosis (F4) (STELLAR 4) trials of selonsertib and the Study to Evaluate the Safety and Efficacy of Selonsertib, Firsocostat, Cilofexor, and Combinations in Participants With Bridging Fibrosis or Compensated Cirrhosis Due to NASH (ATLAS) trial of selonsertib, firsocostat, and cilofexor. Using these data, researchers developed the Deep Learning Treatment Assessment (DELTA) liver fibrosis score to reflect changes in fibrosis stage from baseline to week 48.[51] DELTA scores correlated with changes in NITs, such as ELF and VCTE, among treatment responders.

Several NITs have been used as surrogate markers to assess response to treatment in NASH clinical trials. Data from the Randomized Global Phase 3 Study to Evaluate the Impact on NASH with Fibrosis of Obeticholic Acid Treatment (REGENERATE; NCT02548351) trial of obeticholic acid (OCA) in NASH was used to evaluate NIT-based OCA efficacy endpoints among patients treated with OCA 25 mg or placebo. Those in the OCA arm showed statistically significant improvements in AST-to-platelet ratio index (APRI), FIB-4, ALT, FibroSure, and VCTE compared to placebo.[52,53] A secondary analysis evaluated changes in FibroMeter, FibroMeter VCTE, and FAST among participants in REGENERATE and demonstrated improvement in these NITs among those in the OCA arm.[54] Treatment with OCA also results in dose-dependent improvements in cT1 and liver fat content on multiparametric MRI.[55]

Using data from 252 patients in the Efficacy and Safety Study of Cenicriviroc for the Treatment of NASH in Adult Participants With Liver Fibrosis (CENTAUR), Pro-C3 and Pro-C3 composite score (ADAPT and FIB-C3) levels significantly decreased among patients with fibrosis improvement. Pro-C3, ADAPT, FIB-C3, ELF, APRI, FIB-4, NFS, and CK-18 M30 and M65 were all reduced among patients with regression in their NAS.[56] Histologic changes were also significantly correlated with reductions in MRI-PDFF, ELF, and Pro-C3 among patients with NASH treated with 36 weeks of resmetirom (MGL-3196).[57]

Data from 339 patients in the Study to Evaluate the Safety, Tolerability, and Efficacy of MSDC-0602K in Patients With NASH (EMMINENCE) trial of MSDC-0602K and a meta-analysis of 17 NASH trials that included 3,717 patients evaluated the correlations between changes in biomarkers and histologic response.[58] This study found that a combination of AST, CK-18, and hemoglobin A1c (HbA1c) changes best predicted overall liver biopsy changes in response to NASH pharmacotherapy. This composite score could distinguish between patients with and without NASH resolution without worsening of fibrosis with an AUROC of 0.78 and for fibrosis improvement without NASH worsening with an AUROC of 0.75. Patients with NASH treated with NGM282 similarly demonstrated improvements in NITs, including Pro-C3, ELF and cT1.[59]

Therapeutic Agents for NASH

There are no FDA-approved medications for NASH; however, both vitamin E as an antioxidant

Drug (route of administration)	Efficacy and Safety Endpoints
Hepatic efficacy endpoints	
NASH Resolution	Placebo-adjusted percentage of patients that achieve NASH resolution and no worsening in fibrosis.
Fibrosis Improvement	Placebo-adjusted percentage of patients that achieve fibrosis regression by at least one stage without worsening in NASH.
MRI-PDFF	Percentage of patients that achieve relative liver fat reduction by 30% or more based on MRI-PDFF.
ALT	Percentage of patients that achieve reduction of ALT by 17 U/L or more or percentage of patients that normalize ALT.
Effects on MetS	
Weight	Percentage change in total body weight.
Dyslipidemia	Effects of treatment on TG, HDL, and LDL cholesterol.
Insulin Resistance	Effects of treatment on HbA1c, fasting glucose, and HOMA-IR.
Major AEs	AE of special interest (e.g., pruritus with FXR agonists, GI AEs with GLP-1 agonists, increase in LDL with FGF19 agonists).

FIG. 1. The NASH Drug Score Card. A useful tool to evaluate the potential impact of new drugs and facilitate comparison between different classes of medications. Abbreviations: AE, adverse event; GI, gastrointestinal; HOMA-IR, homeostasis model assessment of insulin resistance; TG, triglyceride.

and pioglitazone as an insulin sensitizer showed some efficacy against NASH in randomized control trials (RCTs).[60,61] The lack of efficacy of vitamin E on liver fibrosis and several adverse events associated with pioglitazone, such as weight gain and edema, have limited the use of these two agents by hepatology providers.

The FDA provided a path forward for conditional approval of NASH drugs if they achieve histologic efficacy endpoints defined by either (a) resolution of NASH without worsening of fibrosis or (b) regression of fibrosis by at least one stage without worsening of NASH.[62-64] Acceptable outcomes for phase 2a trials include improvement in liver steatosis as determined by MRI-PDFF percentage or fibrosis as determined by imaging or blood biomarkers. However, when assessing a new NASH drug, several aspects need to be taken into consideration in addition to hepatic efficacy endpoints. Given the fact that cardiovascular disease remains the main cause of mortality in patients with noncirrhotic NASH,[65] the effects of any new drug on cardiovascular risk factors, such as the metabolic syndrome (MetS), and its components, such as obesity, diabetes, and dyslipidemia, should be evaluated. Furthermore, adverse events of special interest, such as gastrointestinal side effects or pruritus, may affect how the drug is tolerated and its impact on patients' quality of life and patient-reported outcomes. For these reasons, we have created the NASH Drug Score Card to help evaluate the potential impact of new drugs and facilitate comparison between different classes of medications (Fig. 1).

Three drugs are currently in phase 3 RCTs for the treatment of noncirrhotic NASH. OCA is a farnesoid X receptor (FXR), which is a nuclear receptor that regulates bile acid synthesis[66] and lipid/glucose homeostasis and modulates liver fibrosis.[67] OCA was evaluated in the phase 3 REGENERATE trial where patients were randomized to OCA 10 mg or 25 mg daily versus placebo for 18 months. Histologic assessment of patients with NASH and F2-F3 fibrosis demonstrated significant improvement in fibrosis by one stage in 23% of patients on OCA 25 mg daily compared to 12% of those on placebo (P = 0.0002), although there was no significant effect on NASH resolution. In terms of adverse events, compared to placebo, OCA was associated with higher rates of pruritus, and increases in LDL cholesterol and biliary events, including gallstones and cholecystitis.

Resmetirom is a thyromimetic that targets the thyroid hormone receptor beta, the major receptor expressed in the liver with an established role in regulating hepatic triglyceride and cholesterol metabolism.[68-70] Resmetirom was studied in a phase 2b RCT that included 125 patients treated for 36 weeks. Compared to patients treated with placebo, those treated with resmetirom had significantly higher rates of relative liver fat reduction on MRI-PDFF at both

weeks 12 and 36 and higher rates of NASH resolution at week 36 (6.5% with placebo vs. 27.4% with resmetirom, P = 0.02), although there was no significant effect on fibrosis regression.[71] Importantly, resmetirom was well tolerated and had positive effects on the atherogenic dyslipidemia associated with NAFLD with improvement in triglyceride and LDL cholesterol. This drug is being currently evaluated in two large phase 3 RCTs that will evaluate its efficacy on achieving histologic NASH resolution at 52 weeks of treatment in the Study to Evaluate the Efficacy and Safety of MGL-3196 (Resmetirom) in Patients With NASH and Fibrosis (MAESTRO-NASH) (NCT03900429) trial and explore its potential benefits on dyslipidemia and cardiovascular endpoints in the MAESTRO-NAFLD-1 (NCT04197479).

Aramchol is a bile acid and a fatty acid (cholic acid–arachidic acid) conjugate that inhibits the stearoyl-coenzyme A (CoA) desaturase-1 enzyme leading to down-regulation of liver steatosis. In the phase 2b Clinical Trial to Evaluate the Efficacy and Safety of Two Aramchol Doses Versus Placebo in Patients With NASH (ARREST RCT) (NCT02279524), 247 patients with NASH were randomized to receive aramchol at 400 mg or 600 mg daily versus placebo for 52 weeks.[72] Aramchol decreased liver fat and improved liver enzymes, and the 600 mg daily dose showed a trend toward higher NASH resolution rates compared to placebo (16.7% and 5%, respectively, P = 0.051). The Clinical Study to Evaluate the Efficacy and Safety of Aramchol in Subjects With NASH (ARMOR) is a phase 3 RCT (NCT04104321) that plans to evaluate the safety and efficacy of aramchol in 2,000 patients with NASH and F2-F3 fibrosis, with the primary histologic endpoint being NASH resolution/fibrosis improvement at 52 weeks.

Update on NASH Therapeutics From TLMdX

The results of several RCTs that evaluated the safety and efficacy of different NASH drugs were presented at TLMdX. Several therapeutic agents showed promising results in terms of histologic response. Due to space limitation, we will only discuss those agents with histologic data while acknowledging the fact that several other promising agents were effective in improving NITs. We provide an example in Table 2 on how to evaluate these agents using the NASH Drug Score Card. It is important to note that direct comparison cannot be made between these agents because they are in different phases of drug development and lack conclusive phase 3 histologic and long-term outcomes data. Intriguing proof-of-concept data were presented on the potential for combination therapy to increase the efficacy of NASH treatment. On the other hand, some agents failed to show significant histologic improvement in phase 2b and 3 trials.

PROMISING NEW THERAPEUTIC AGENTS WITH HISTOLOGIC DATA

Efruxifermin[73]

Efruxifermin is a synthetic fibroblast growth factor 21 (FGF21) analog with a long half-life and balanced potency on the three FGF receptors (FGFR), FGFR1c, FGFR2c, or FGFR3c. The Phase 2a, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of Efruxifermin in Subjects With NASH (BALANCED; NCT03976401) evaluated three doses of weekly efruxifermin injections (28 mg, 50 mg, or 70 mg) for 16 weeks, with the primary endpoint being liver fat reduction on MRI-PDFF at week 12 and only patients reducing their liver fat by 30% or more being eligible for repeat liver biopsy at week 16. All efruxifermin dose groups met the primary endpoint, with statistically significant absolute reductions in liver fat of 12%-14% and relative fat reduction >60%.

In the 16-week analysis of histologic data in the MRI-PDFF responders, 48% had fibrosis regression by one stage without worsening of NASH and 28% achieved at least a two-stage fibrosis improvement. Moreover, 48% of responders achieved NASH resolution with no worsening of fibrosis. In terms of effects on MetS, efruxiferimin was associated with improvements in weight, insulin resistance, and dyslipidemia. Efruxifermin will be evaluated in an innovative adaptive phase 2b/3 pivotal study in patients with biopsy-confirmed NASH to be initiated in the first half of 2021.

Aldafermin[59,74]

Aldafermin is a modified FGF19 agonist that regulates bile acid synthesis and lipid homeostasis.[75] Patients with NAFLD exhibit a deficiency in FGF19, making it an attractive therapeutic target. The results of

TABLE 2. SUMMARY OF TRIAL RESULTS OF PROMISING THERAPEUTIC AGENTS FOR NASH WITH HISTOLOGIC EFFICACY DATA FROM TLMDX

Drug (Route of Administration)	Lanifibranor (Oral)	Resmetirom (Oral)	Semaglutide (Injectable)	Efruxifermin (Injectable)	Aldafermin (Injectable)	Pioglitazone (Oral)
Hepatic efficacy endpoints						
NASH resolution	Yes	Yes	Yes	Yes	Yes	Yes
Fibrosis improvement	Yes	No	No	Yes	Yes	Yes
MRI-PDFF	No data		No data			No data
ALT	Yes	Yes	Yes	Yes	Yes	Yes
Effects on MetS						
Weight	Weight gain	No	Yes	Yes	Neutral	Weight gain
Dyslipidemia	Yes	Yes	Yes	Yes	Increase in LDL	Yes
Insulin resistance	Yes	No	Yes	Yes	Neutral	Yes
Major AEs	Weight gain; bone loss?	Bone loss?; thyroid effects?	GI AEs; pancreatitis; retinopathy	GI AEs; tremors; bone loss?	GI AEs; malignancies?	Weight gain; bone loss; bladder cancer?

Abbreviations: AE, adverse event; GI, gastrointestinal.

a 24-week RCT that included 78 patients with paired liver biopsies who were randomized 1:2 to receive daily placebo (n = 25) or aldafermin 1 mg (n = 53) subcutaneously were presented at TLMdX. In terms of efficacy endpoints, NASH resolution with no worsening of fibrosis and fibrosis improvement with no worsening of NASH were achieved in a higher percentage of patients in the aldafermin group compared to placebo (24% vs. 9% and 38% vs. 18%, respectively), although the difference was not statistically significant. Interestingly, significantly higher percentage of patients in the aldafermin arm achieved both NASH resolution and fibrosis improvement (22% vs. 0%, $P = 0.015$). A rapid and significant decline in ALT, AST, and fibrosis biomarkers was seen with aldafermin treatment.

Lanifibranor[76]

Lanifibranor is a pan-peroxisome proliferator-activated receptor (PPAR) agonist with well-balanced efficacy for PPARα, δ, and γ.

In the Phase 2b Study in NASH to Assess IVA337 (NATIVE) (NCT03008070), a double-blind RCT, 247 patients were randomized to receive once daily lanifibranor at 800 mg or 1,200 mg or placebo for 6 months. The mean age was 54 years, 42% had type 2 diabetes, and 76% had significant fibrosis (F2/F3). Lanifibranor 1,200 mg daily compared to placebo showed impressive efficacy on hepatic outcome, including significant reduction of the steatosis activity fibrosis score (SAF) (49% vs. 27%, $P < 0.01$), NASH resolution with no worsening of fibrosis (45% vs. 19%, $P < 0.001$), improvement of fibrosis with no worsening of NASH (42% vs. 24%, $P < 0.01$), and the combined endpoint of NASH resolution plus fibrosis regression (31% vs. 7%, $P < 0.001$). In terms of effects on MetS, both doses significantly increased HDL cholesterol and decreased serum triglycerides and lowered HbA1c in diabetics. However, there was a significant weight increase of 2.4 and 2.7 kg in the 800-mg and 1,200-mg arms. Lanifibranor was well tolerated with low discontinuation rate due to adverse events (<5%).

Semaglutide[77]

Semaglutide is a glucagon-like peptide 1 receptor agonist (GLP-1RA) approved for treatment in patients with T2D and has been shown to lead to significant weight reduction in patients with nondiabetic

obesity.[78,79] At TLMdX, the results of a placebo-controlled phase 2b RCT (NCT02970942) that included 320 patients with NASH and F1-F3 fibrosis were presented. Patients were randomized to semaglutide daily injections at 0.1, 0.2, and 0.4 mg or placebo for 72 weeks. In patients with significant fibrosis (F2-F3, n = 230), the primary endpoint of NASH resolution was achieved by a significantly greater proportion of patients on all doses of semaglutide (58.9% in the 0.4-mg daily arm compared to 17.2% in the placebo arm, $P < 0.0001$). Unfortunately, there was no significant fibrosis improvement in the semaglutide arms compared to placebo ($P > 0.05$ for all). Dose-dependent improvements in ALT, AST, and biomarkers of fibrosis were seen with semaglutide. As expected, semaglutide use was associated with significant reduction in weight and HbA1C.

COMBINATION THERAPY[80]

Given the biological heterogeneity of NASH, combining therapies with complementary mechanisms may provide optimal benefit.[81] The ATLAS trial randomized 392 patients with advanced disease (bridging fibrosis in 44% and cirrhosis in 56%) to several combination regimens. This trial demonstrated that the combination of firsocostat (acetyl-CoA carboxylase [ACC] inhibitor that inhibits *de novo* lipogenesis) and cilofexor (FXR agonist) was numerically more effective than placebo in improving fibrosis by one stage or more without worsening in NASH (21% vs. 11%, $P = 0.17$), providing further support to the concept of combination therapy.[82]

A phase 2 trial evaluated the safety and efficacy of semaglutide, a GLP-1RA, alone and in combination with the FXR agonist cilofexor and/or the ACC inhibitor firsocostat in 108 patients with noncirrhotic NASH. There was greater reduction in ALT, liver fat on MRI-PDFF and CAP, liver stiffness on transient elastography, and the FAST score in the combination arms compared to semaglutide monotherapy, especially with the triple combination regimen (semaglutide + cilofexor + firsocostat). Reductions in body weight, AST, GGT, and ELF were noted in all groups. The most common adverse events were gastrointestinal related to semaglutide, with minimal pruritus/increase in LDL noted in the cilofexor-containing arms and increase in triglycerides noted in the firsocostat arms. Overall, the results demonstrated that combinations of semaglutide with cilofexor and/or firsocostat were well tolerated and may provide additional benefits versus semaglutide monotherapy.

FAILED THERAPEUTIC AGENTS

Elafibranor[83]

Results from an interim analysis of the Phase 3 Study to Evaluate the Efficacy and Safety of Elafibranor Versus Placebo in Patients With Nonalcoholic Steatohepatitis (RESOLVE-IT; NCT02704403) RCT evaluating once-daily 120 mg of elafibranor for 72 weeks were presented at TLMdX. The trial did not meet its primary endpoint of NASH resolution without worsening of fibrosis (19.2% with elafibranor compared to 14.7% with placebo) or its secondary endpoint of fibrosis improvement of at least one stage (24.5% with elafibranor compared to 22.4% with placebo). Other key secondary endpoints related to metabolic parameters were not achieved.

Tropifexor[84]

Data from the Study of Safety and Efficacy of Tropifexor (LJN452) in Patients With NASH (FLIGHT-FXR; NCT02855164) phase 2 RCT were presented at the TLMdX. In that trial, 152 patients with NASH and F2-F3 fibrosis were randomized to receive tropifexor 140 μg, 200 μg, or placebo for 48 weeks. Despite achieving high rates of liver fat reduction by ≥30% on MRI-PDFF and marked reduction in liver enzymes in the tropifexor arms (55%-68%), there was no difference in the rates of NASH resolution or fibrosis regression. Pruritus was more common in the tropifexor arms, and there was a modest increase in LDL cholesterol. Combination trials of tropifexor with other agents may provide further clarity on the path for developing tropifexor as a treatment for fibrotic NASH.

Putting This All Together: How Will Patients With NASH Be Managed in the Future?

We foresee a future where patients at high-risk for NAFLD will be screened and risk stratified based

on cost-effective and accurate NITs. Those with suspected fibrotic NASH will be referred to a subspecialist for consideration of pharmacologic treatment. The choice of the first-line treatment will depend on disease severity (e.g., patients with F3 will require agents with proven antifibrotic activity), adverse event profile (e.g., patients with extensive coronary artery disease may benefit the most from drugs such as semaglutide while avoiding drugs that may increase cardiovascular risk or worsen dyslipidemia), and patient preference (e.g., some patients may elect not to use drugs that require subcutaneous injection or intravenous infusion if effective oral alternatives are available). Once treatment with the first-line drugs or regimen starts, assessment for efficacy by NITs should be determined at 12-18 months with one of the following outcomes:

1. Adequate response: continue to current drug and continue to monitor for efficacy with NITs on a yearly basis.
2. Partial response: if the first-line drug is well tolerated, consider add-on therapy with another drug that has a complementary mechanism of action.
3. Futility/lack of response: switch to another drug with a different mechanism of action.

In conclusion, we believe that the management of NAFLD/NASH will have a complete transformation in the next 10 years. More patients will be identified by large-scale screening strategies in at-risk populations and triaged noninvasively with accurate tests to the best management strategies that will rely on personalized lifestyle interventions and effective therapeutic agents.

REFERENCES

1) Younossi Z, Tacke F, Arrese M, Chander Sharma B, Mostafa I, Bugianesi E, et al. Global perspectives on nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. Hepatology 2019;69:2672-2682.
2) Ascha MS, Hanouneh IA, Lopez R, Tamimi TA, Feldstein AF, Zein NN. The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. Hepatology 2010;51:1972-1978.
3) Kabbany MN, Conjeevaram Selvakumar PK, Watt K, Lopez R, Akras Z, Zein N, et al. Prevalence of nonalcoholic steatohepatitis-associated cirrhosis in the United States: an analysis of National Health and Nutrition Examination Survey data. Am J Gastroenterol 2017;112:581-587.
4) Dulai PS, Singh S, Patel J, Soni M, Prokop LJ, Younossi Z, et al. Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: systematic review and meta-analysis. Hepatology 2017;65:1557-1565.
5) Stine JG, Wentworth BJ, Zimmet A, Rinella ME, Loomba R, Caldwell SH, et al. Systematic review with meta-analysis: risk of hepatocellular carcinoma in non-alcoholic steatohepatitis without cirrhosis compared to other liver diseases. Aliment Pharmacol Ther 2018;48:696-703.
6) Harrison SA, Gawrieh S, Roberts K, Lisanti CJ, Schwope RB, Cebe KM, et al. Prospective evaluation of the prevalence of non-alcoholic fatty liver disease and steatohepatitis in a large middle-aged US cohort. J Hepatol 2021;75:284-291.
7) Noureddin M, Vipani A, Bresee C, Todo T, Kim IK, Alkhouri N, et al. NASH leading cause of liver transplant in women: updated analysis of indications for liver transplant and ethnic and gender variances. Am J Gastroenterol 2018;113:1649-1659.
8) Noureddin M, Jones C, Alkhouri N, Gomez EV, Dieterich DT, Rinella ME, et al. Screening for nonalcoholic fatty liver disease in persons with type 2 diabetes in the United States is cost-effective: a comprehensive cost-utility analysis. Gastroenterology 2020;159:1985-1987.e1984. Erratum in: Gastroenterology 2021;160:2226.
9) Loomba R, Adams LA. Advances in non-invasive assessment of hepatic fibrosis. Gut 2020;69:1343-1352.
10) European Association for the Study of the Liver; European Association for the Study of Diabetes; European Association for the Study of Obesity. EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol 2016;64:1388-1402.
11) Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, et al. American Gastroenterological Association; American Association for the Study of Liver Diseases; American College of Gastroenterology. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. Gastroenterology 2012;142:1592-1609. Erratum in: Gastroenterology 2012;143:503.
12) Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, et al.; Nonalcoholic Steatohepatitis Clinical Research Network. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology 2005;41:1313-1321.
13) Kleiner DE, Brunt EM, Wilson LA, Behling C, Guy C, Contos M, et al.; Nonalcoholic Steatohepatitis Clinical Research Network. Association of histologic disease activity with progression of nonalcoholic fatty liver disease. JAMA Netw Open 2019;2:e1912565.
14) Angulo P, Kleiner DE, Dam-Larsen S, Adams LA, Bjornsson ES, Charatcharoenwitthaya P, et al. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. Gastroenterology 2015;149:389-397.e310.
15) Ekstedt M, Hagstrom H, Nasr P, Fredrikson M, Stal P, Kechagias S, et al. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. Hepatology 2015;61:1547-1554.
16) Younossi ZM, Stepanova M, Rafiq N, Makhlouf H, Younoszai Z, Agrawal R, et al. Pathologic criteria for nonalcoholic steatohepatitis: interprotocol agreement and ability to predict liver-related mortality. Hepatology 2011;53:1874-1882.
17) Davison BA, Harrison SA, Cotter G, Alkhouri N, Sanyal A, Edwards C, et al. Suboptimal reliability of liver biopsy evaluation has implications for randomized clinical trials. J Hepatol 2020;73:1322-1332.
18) Sumida Y, Nakajima A, Itoh Y. Limitations of liver biopsy and non-invasive diagnostic tests for the diagnosis of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. World J Gastroenterol 2014;20:475-485.

19) Pokkalla H, Pethia K, Glass B, Kerner JK, Gindin Y, Han L, et al. Machine learning models accurately interpret liver histology in patients with nonalcoholic steatohepatitis (NASH) [Abstract]. Hepatology 2019;70:121A-122A.
20) Angulo P, Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology 2007;45:846-854.
21) Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology 2003;38:518-526.
22) Chan W-K, Treeprasertsuk S, Goh G-B, Fan J-G, Song MJ, Charatcharoenwitthaya P, et al. Optimizing use of nonalcoholic fatty liver disease fibrosis score, fibrosis-4 score, and liver stiffness measurement to identify patients with advanced fibrosis. Clin Gastroenterol Hepatol 2019;17:2570-2580.e2537.
23) Vilar-Gomez E, Chalasani N. Non-invasive assessment of non-alcoholic fatty liver disease: clinical prediction rules and blood-based biomarkers. J Hepatol 2018;68:305-315.
24) Xiao G, Zhu S, Xiao X, Yan L, Yang J, Wu G. Comparison of laboratory tests, ultrasound, or magnetic resonance elastography to detect fibrosis in patients with nonalcoholic fatty liver disease: a meta-analysis. Hepatology 2017;66:1486-1501.
25) Noureddin M, Mayo R, Martínez-Arranz I, Mincholé I, Cusi K, Bril F, et al. The serum-based metabolomics advanced steatohepatits fibrosis score (MASEF) for the non-invasive identification of patients with nonalcoholic steatohepatitis with significant fibrosis [Abstract]. Hepatology 2020;72(Suppl.):948A-949A.
26) Guha IN, Parkes J, Roderick P, Chattopadhyay D, Cross R, Harris S, et al. Noninvasive markers of fibrosis in nonalcoholic fatty liver disease: validating the European Liver Fibrosis Panel and exploring simple markers. Hepatology 2008;47:455-460.
27) Staufer K, Halilbasic E, Spindelboeck W, Eilenberg M, Prager G, Stadlbauer V, et al. Evaluation and comparison of six non-invasive tests for prediction of significant or advanced fibrosis in nonalcoholic fatty liver disease. United Euro Gastroenterol J 2019;7:1113-1123.
28) Boyle M, Tiniakos D, Schattenberg JM, Ratziu V, Bugianessi E, Petta S, et al. Performance of the PRO-C3 collagen neo-epitope biomarker in non-alcoholic fatty liver disease. JHEP Rep 2019;1:188-198.
29) Daniels SJ, Leeming DJ, Eslam M, Hashem AM, Nielsen MJ, Krag A, et al. ADAPT: an Algorithm Incorporating PRO-C3 accurately identifies patients with NAFLD and advanced fibrosis. Hepatology 2019;69:1075-1086.
30) Alkhouri N, Noureddin M, Adams LA, Feldstein AE. The combination of serum MAC-2-binding protein and cytokeratin 18 fragment levels accurately predict the presence of advanced NASH [Abstract]. Hepatology 2020;72(Suppl.):947A-948A.
31) Harrison SA, Ratziu V, Boursier J, Francque S, Bedossa P, Majd Z, et al. A blood-based biomarker panel (NIS4) for non-invasive diagnosis of non-alcoholic steatohepatitis and liver fibrosis: a prospective derivation and global validation study. Lancet Gastroenterol Hepatol 2020;5:970-985.
32) Anstee QM, Harrison SA, Magnanensi J, Stankovic-Valentin N, Hajji Y, Hum DW, et al. Identification of patients with at-risk NASH or advanced fibrosis using NIS4™ alone or in combination as compared with other testing strategies [Abstract]. Hepatology 2020;72(Suppl.):920A-921A.
33) Harrison S, Ratziu V, Anstee QM, Magnanensi J, Hajji Y, Hum DW, et al. Baseline levels of NIS4™ and other fibrosis biomarkers and prediction of histological progression to advanced fibrosis in NASH [Abstract]. Hepatology 2020;72(Suppl.):896A-897A.
34) Sripongpun P, Mannalithara A, Kim D, Kim WR. A machine learning model to safely triage low-risk non-alcoholic fatty liver disease patients: the steatosis-associated fibrosis estimator (SAFE) score [Abstract]. Hepatology 2020;72(Suppl.):888A-889A.
35) Aggarwal M, Singh A, Bansal A, McCullough AJ. Novel machine learning model to predict NASH in NAFLD patients with diabetes mellitus [Abstract]. Hepatology 2020;72(Suppl.):932A-933A.
36) Reinhart B, Doherty M, Balp MM, Tietz A, Cai J, Porwal S, et al. Clinical characteristics used for machine learning identification of fast progressors among patients with NASH [Abstract]. Hepatology 2020;72(Suppl.):45A-46A.
37) Chalasani N, Toden S, Sninsky JJ, Rava RP, Braun JV, Gawrieh S, et al. Non-invasive stratification of nonalcoholic fatty liver disease by whole-transcriptome cell-free mRNA characterization. Am J Physiol Gastrointest Liver Physiol 2021;320:G439-G449.
38) Imajo K, Honda Y, Kobayashi T, Nagai K, Ozaki A, Iwaki M, et al. Prospective head-to-head comparison of diagnostic accuracy for staging liver fibrosis among MR elastography, vibration controlled transient elastography and 2-dimention shear-wave elastography in patients with nonalcoholic fatty liver disease [Abstract]. Hepatology 2020;72(Suppl.):939A-940A.
39) Loomba R, Wolfson T, Ang B, Hooker J, Behling C, Peterson M, et al. Magnetic resonance elastography predicts advanced fibrosis in patients with nonalcoholic fatty liver disease: a prospective study. Hepatology 2014;60:1920-1928. Erratum in: Hepatology 2015;62:1646.
40) Hsu C, Caussy C, Imajo K, Chen J, Singh S, Kaulback K, et al. Magnetic resonance vs transient elastography analysis of patients with nonalcoholic fatty liver disease: a systematic review and pooled analysis of individual participants. Clin Gastroenterol Hepatol 2019;17:630-637.e638.
41) Ajmera V, Loomba R. Imaging biomarkers of NAFLD, NASH, and fibrosis. Mol Metab 2021;50:101167.
42) Aggarwal P, Harrington A, Singh T, Cummings-John O, Kohli A, Noureddin M, et al. Identifying patients who require pharmacotherapy for nonalcoholic steatohepatitis (NASH) using the FAST score [Abstract]. Hepatology 2020;72(Suppl.):922A-923A.
43) Noureddin M, Alqahtani S, Gonzalez B, Gornbein JA, Attar AA, Noureddin N, et al. MRI and AST (MAST) score for non-invasive identification of patients with non-alcoholic steatohepatitis with significant fibrosis [Abstract]. Hepatology 2020;72(Suppl.):928A-929A.
44) Andersson A, Dennis A, Imajo K, Nakajima A, Fallowfield JA, Banerjee R, et al. Diagnostic accuracy of MRI biomarkers cT1 and fat for high-risk non-alcoholic steatohepatitis [Abstract]. Hepatology 2020;72(Suppl.):55A.
45) Jung J, Loomba RR, Imajo K, Madamba E, Gandhi S, Bettencourt R, et al. MRE combined with FIB-4 (MEFIB) index in detection of candidates for pharmacological treatment of NASH-related fibrosis. Gut 2020; https://doi.org/10.1136/gutjnl-2020-322976.
46) Sanyal AJ, Brunt EM, Kleiner DE, Kowdley KV, Chalasani N, Lavine JE, et al. Endpoints and clinical trial design for nonalcoholic steatohepatitis. Hepatology 2011;54:344-353.
47) Loomba R. MRI-proton density fat fraction treatment response criteria in nonalcoholic steatohepatitis. Hepatology 2021;73:881-883.
48) Loomba R, Neuschwander-Tetri BA, Sanyal A, Chalasani N, Diehl AM, Terrault N, et al.; NASH Clinical Research Network. Multicenter validation of association between decline in MRI-PDFF and histologic response in NASH. Hepatology 2020;72:1219-1229.
49) Loomba R, Guy C, Bedossa P, Taub R, Bashir M, Harrison S. Magnetic resonance imaging-proton density fat fraction (MRI-PDFF) to predict treatment response on NASH liver biopsy: a secondary analysis of the resmetirom randomized placebo controlled phase 2 clinical trial. J Hepatol 2020;73:S56.
50) Stine JG, Munaganuru N, Barnard A, Wang JL, Kaulback K, Argo CK, et al. Change in MRI-PDFF and histologic response

in patients with nonalcoholic steatohepatitis: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2020. https://doi.org/10.1016/j.cgh.2020.08.061.
51) Taylor-Weiner AH, Pokkalla H, Han L, Jia C, Huss R, Chung C, et al. Validation of a machine learning-based approach (Delta Liver Fibrosis Score) for the assessment of histologic response in patients with advanced fibrosis due to NASH [Abstract]. Hepatology 2020;72(Suppl.):949A-951A.
52) Alkhouri N, Sanyal AJ, Ratziu V, Rinella ME, Loomba R, Dufour JF, et al. Evaluation of obeticholic acid efficacy in patients with NASH who were monitored using noninvasive tests: a post hoc analysis of the REGENERATE trial [Abstract]. Hepatology 2020;72(Suppl.):53A-54A.
53) Boursier J, Loomba R, Anstee Q, Harrison S, Sanyal A, Rinella M, et al. Obeticholic acid improves experimental non-invasive markers of non-alcoholic steatohepatitis and advanced fibrosis: a secondary analysis of the phase 3 regenerate study. J Hepatol 2020;73:S54.
54) Boursier J, Loomba R, Anstee QM, Harrison S, Sanyal AJ, Rinella ME, et al. 334 obeticholic acid improves experimental non-invasive markers of non-alcoholic steatohepatitis and advanced fibrosis; results of a secondary analysis from the month-18 interim analysis of the REGENERATE study. Gastroenterology 2020;158:S1270-S1271.
55) Anstee Q, Digpal K. P21 Obeticholic acid improves hepatic fibroinflammation as assessed by multiparametric MRI: interim results of the REGENERATE trial [Abstract]. Gut 2020;69(Suppl 1):A17.
56) Leeming DJ, Frederiksen P, Fisker MJ, Daniels SJ, Seyedkazemi S, Sanyal AJ, et al. Biomarkers of liver fibrosis are sensitive to both NAS and fibrosis histological score changes in nonalcoholic steatohepatitis within the CENTAUR study [Abstract]. Hepatology 2020;72(Suppl.):897A-898A.
57) Harrison SA, Guy CD, Bashir M, Frias JP, Alkhouri N, Baum S, et al. In a placebo-controlled 36-week phase 2 trial, treatment with MGL-3196 compared to placebo results in significant reductions in hepatic fat (MRI-PDFF), liver enzymes, fibrosis biomarkers, atherogenic lipids, and improvement in NASH on serial liver biopsy [Abstract]. Hepatology 2018;68:9A-10A.
58) Davison B, Edwards C, Loomba R, Harrison SA, Cotter G, Koch GG, et al. A noninvasive measure of treatment response in non-alcoholic steatohepatitis-insights from emminence and meta-analysis [Abstract]. Hepatology 2020;72(Suppl.):889A.
59) Harrison SA, Rossi SJ, Paredes AH, Trotter JF, Bashir MR, Guy CD, et al. NGM282 improves liver fibrosis and histology in 12 weeks in patients with nonalcoholic steatohepatitis. Hepatology 2020;71:1198-1212.
60) Cusi K, Orsak B, Bril F, Lomonaco R, Hecht J, Ortiz-Lopez C, et al. Long-term pioglitazone treatment for patients with nonalcoholic steatohepatitis and prediabetes or type 2 diabetes mellitus: a randomized trial. Ann Intern Med 2016;165:305-315.
61) Sanyal AJ, Chalasani N, Kowdley KV, McCullough A, Diehl AM, Bass NM, et al.; NASH CRN. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. N Engl J Med 2010;362:1675-1685.
62) Rinella ME, Tacke F, Sanyal AJ, Anstee QM; Participants of the AASLD/EASL Workshop. Report on the AASLD/EASL joint workshop on clinical trial endpoints in NAFLD. Hepatology 2019;71:823-833.
63) Siddiqui MS, Harrison SA, Abdelmalek MF, Anstee QM, Bedossa P, Castera L, et al.; Liver Forum Case Definitions Working Group. Case definitions for inclusion and analysis of endpoints in clinical trials for nonalcoholic steatohepatitis through the lens of regulatory science. Hepatology 2018;67:2001-2012.
64) U.S. Department of Health and Human Services; Food and Drug Administration; Center for Drug Evaluation and Research (CDER). Noncirrhotic nonalcoholic steatohepatitis with liver fibrosis: developing drugs for treatment. Guidance for industry. https://www.fda.gov/media/119044/download. Published December 2018. Accessed December 2019.
65) Vilar-Gomez E, Calzadilla-Bertot L, Wai-Sun Wong V, Castellanos M, Aller-de la Fuente R, Metwally M, et al. Fibrosis severity as a determinant of cause-specific mortality in patients with advanced nonalcoholic fatty liver disease: a multi-national cohort study. Gastroenterology 2018;155:443-457.e417.
66) Ali AH, Carey EJ, Lindor KD. Recent advances in the development of farnesoid X receptor agonists. Ann Transl Med 2015;3:5.
67) Carr RM, Reid AE. FXR agonists as therapeutic agents for non-alcoholic fatty liver disease. Curr Atheroscler Rep 2015;17:500.
68) Sinha RA, Bruinstroop E, Singh BK, Yen PM. Nonalcoholic fatty liver disease and hypercholesterolemia: roles of thyroid hormones, metabolites, and agonists. Thyroid 2019;29:1173-1191.
69) Sinha RA, Singh BK, Yen PM. Direct effects of thyroid hormones on hepatic lipid metabolism. Nat Rev Endocrinol 2018;14:259-269.
70) Sinha RA, You S-H, Zhou J, Siddique MM, Bay B-H, Zhu X, et al. Thyroid hormone stimulates hepatic lipid catabolism via activation of autophagy. J Clin Invest 2012;122:2428-2438.
71) Harrison SA, Bashir MR, Guy CD, Zhou R, Moylan CA, Frias JP, et al. Resmetirom (MGL-3196) for the treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet 2019;394:2012-2024.
72) Ratziu V, de Guevara L, Safadi R, Poordad F, Fuster F, Flores-Figueroa J, et al. One-year results of the global phase 2b randomized placebo- controlled ARREST trial of Aramchol, a stearoyl CoA desaturase modulator in NASH patients. Hepatology 2018;68(Suppl. 1):LB-5.
73) Harrison S, Ruane P, Freilich B, Neff G, Patil R, Behling C, et al. Efruxifermin (EFX), a long-acting FC-FGF21 fusion protein, administered for 16 weeks to patients with NASH substantially reduces liver fat and ALT, and improves liver histology: analysis of a randomized, placebo-controlled, phase 2a study (BALANCED) [Abstract]. Hepatology 2020;72(Suppl.):6A.
74) Harrison SA, Neff G, Guy CD, Bashir MR, Paredes A, Frias JP, Younes ZH, et al. Final analysis of a 24-week, randomized, double-blind, placebo-controlled, multicenter study of aldafermin (NGM282) in patients with nonalcoholic steatohepatitis [Abstract]. Hepatology 2020;72(Suppl):55A.
75) Zhou M, Learned RM, Rossi SJ, DePaoli AM, Tian H, Ling L. Engineered FGF19 eliminates bile acid toxicity and lipotoxicity leading to resolution of steatohepatitis and fibrosis in mice. Hepatol Commun 2017;1:1024-1042.
76) Francque S, Bedossa P, Ratziu V, Anstee QM, Bugianesi E, Sanyal A, et al. The PanPPAR agonist lanifibranor induces both resolution of NASH and regression of fibrosis after 24 weeks of treatment in non-cirrhotic NASH: results of the NATIVE phase 2b trial [Abstract]. Hepatology 2020;72(Suppl.):9A.
77) Newsome PN, Buchholtz K, Cusi K, Linder M, Okanoue T, Ratziu V, et al.; NN9931-4296 Investigators. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. N Engl J Med 2021;384:1113-1124.
78) Permutt Z, Le TA, Peterson MR, Seki E, Brenner DA, Sirlin C, et al. Correlation between liver histology and novel magnetic resonance imaging in adult patients with non-alcoholic fatty liver disease - MRI accurately quantifies hepatic steatosis in NAFLD. Aliment Pharmacol Ther 2012;36:22-29.
79) Kushner RF, Calanna S, Davies M, Dicker D, Garvey WT, Goldman B, et al. Semaglutide 2.4 mg for the treatment of obesity: key elements of the STEP Trials 1 to 5. Obesity (Silver Spring) 2020;28:1050-1061.
80) Alkhouri N, Herring R, Kabler H, Kayali Z, Hassanein T, Kohli A, et al. Safety and efficacy of combination therapies including

semaglutide, cilofexor, and firsocostat in patients with NASH [Abstract]. Hepatology 2020;72:Abstract LO2.
81) Dufour JF, Caussy C, Loomba R. Combination therapy for non-alcoholic steatohepatitis: rationale, opportunities and challenges. Gut 2020;69:1877-1884.
82) Loomba R, Noureddin M, Kowdley KV, Kohli A, Sheikh A, Neff G, et al.; ATLAS Investigators. Combination therapies including cilofexor and firsocostat for bridging fibrosis and cirrhosis attributable to NASH. Hepatology 2021;73:625-643.
83) Harrison SA, Ratziu V, Bedossa P, Dufour J, Kruger F, Schattenberg JM, Francque S, et al. RESOLVE-IT phase 3 trial of elafibranor in NASH: final results of the week 72 interim surrogate efficacy analysis [Abstract]. Hepatology 2020;72:Abstract LP 23.
84) Lucas KJ, Lopez P, Lawitz EJ, Sheikh A, Aizenberg D, Hsia S, et al. Safety and efficacy of tropifexor in patients with fibrotic nonalcoholic steatohepatitis: 48-week results from part C of the phase 2 FLIGHT-FXR study [Abstract]. Hepatology 2020;72(Suppl.):101A-102A.