Article:
Rowe, IA orcid.org/0000-0003-1288-0749 and Parker, R (2022) The Placebo Response in Randomized Trials in Nonalcoholic Steatohepatitis Simply Explained. Clinical Gastroenterology and Hepatology, 20 (3). E564-E572. ISSN 1542-3565

https://doi.org/10.1016/j.cgh.2021.05.059

The placebo response in randomised trials in nonalcoholic steatohepatitis simply explained

Ian A Rowe PhD MRCP(UK)[1,2] i.a.c.rowe@leeds.ac.uk

Richard Parker PhD MRCP(UK)[2] richardparker@nhs.net

[1]Leeds Institute for Medical Research, University of Leeds, Leeds, LS9 7TF, UK

[2]Leeds Liver Unit, St James's University Hospital, Leeds, LS9 7TF, UK

Address for correspondence: **Dr. Ian A Rowe PhD MRCP(UK)**
Room 6.1, Clinical Sciences Building
University of Leeds
St James's University Hospital
Leeds
LS9 7TF
UK
T: +44 (0) 113 206 5667
E: i.a.c.rowe@leeds.ac.uk

Conflict of interest

The authors have no relevant conflicts to declare. Dr Parker has received personal fees from Sandoz and Norgine outside the submitted work. Dr. Rowe has received personal fees from Abbvie and Roche outside the submitted work.

Data transparency statement

Code to reproduce the simulations is at github.com/iacrowe/sampling_variability

Abbreviations

NASH, nonalcoholic steatohepatitis

Author contributions

IAR: concept, development of simulation model, analyses, drafting of manuscript

RP: concept, analyses, review of manuscript

Both authors approved submission of the final manuscript

Abstract: 259

Word count: 3994

Abstract

Background & Aims Liver histology is the primary endpoint in phase 3 trials in nonalcoholic steatohepatitis (NASH). There is an appreciable response to placebo that confounds endpoint assessment. The aim of this study was to quantify contributors to the placebo response and its impact on liver fibrosis improvement.

Methods Estimates of fibrosis improvement in placebo treated participants were made using probabilistic simulation. Each simulated trial included 120 participants. Parameters considered in the model included sampling and observer variability, regression to the mean, and net fibrosis progression calibrated to reported trial outcomes.

Results In large phase 2b and 3 trials, 22% of placebo treated participants with fibrosis stage 2 or 3 NASH at baseline improved by at least one fibrosis stage with minimal net disease progression. Estimates of sampling and observer variability in simultaneous biopsy studies highlighted an imbalance where apparent fibrosis improvement was more likely than worsening. Using these estimates and known trial outcomes, net fibrosis progression was estimated at 0.05 stages per year. Simulations of the placebo response rate showed a rate of 22% with 80% of trials falling between 15 and 30%, in keeping with trials reported to date. Additional increases in observer variability further increased the placebo response.

Conclusions The analyses presented simply define the placebo response in liver fibrosis in trials in NASH in terms of sampling and observer variability, regression to the mean, and fibrosis progression. Factors relating to liver biopsy are largely unmodifiable and the variation in placebo response rates, both simulated and observed, challenges the role of biopsy in trial endpoint assessment.

Keywords: histology, NAFLD, outcomes, pathology

Introduction

Liver biopsy forms an integral aspect of the assessment of nonalcoholic steatohepatitis (NASH) for enrollment in randomised clinical trials and also endpoint assessment.[1] The histological assessment in NASH encompasses two main aspects; disease activity and severity of liver fibrosis, and of these, it is liver fibrosis that is most clearly associated with clinical outcomes.[2,3]

In clinical trials in NASH there is an appreciable response in patients treated with placebo. This placebo effect has not been adequately explained and has been variously attributed to the Hawthorne effect, lifestyle change and reduction in body weight, and the stringency of trial entry criteria.[1] The impact of factors relating to variability in liver biopsy define outcomes, including the role of sampling and observer variability in this placebo response has not been described. Sampling variability has long been recognised in the assessment of liver fibrosis on histology. In a landmark study in hepatitis C virus infection, Bedossa and colleagues described the impact of sampling variability with misclassification of fibrosis stage in excess of 25% on biopsies measuring <25mm in length.[4] Moreover, this variability is described in simultaneous biopsy studies in NASH.[5–7] Recently, observer variability in the overall interpretation of trials in NASH has been highlighted as a major issue. Additionally, where patients are having repeated measurements as part of a trial protocol, there is the potential for the regression to the mean phenomenon to be observed on repeat biopsy.[8] This occurs when repeated measurements are made on the same population and, due to random error, relatively high (or relatively low) observations are likely to be followed by less extreme values. In the context of eligibility for trials in NASH where a relatively extreme phenotype (NASH plus advanced fibrosis) is required, regression to the mean may be seen as apparent fibrosis regression.

In this study we aimed to characterise factors contributing to the placebo response in fibrosis improvement in randomised trials in NASH to inform estimates of key parameters in the design of future trials.

Patients and methods

This is a simulation study of the placebo response in fibrosis in NASH. The simulations were built considering four factors: sampling variability, regression to the mean, inter- and intra-observer variability, and fibrosis progression over an 18 month horizon, in line with current trial designs.

Parameter estimation

Study selection for sampling variability

Systematic searches were done to find reports of studies describing sampling variability in nonalcoholic steatohepatitis (NASH) using a simultaneous liver biopsy approach (**Supplementary methods**). One study[5] was directly applicable to evaluating sampling variability in the identification of patients with fibrosis stage 2 or 3, who are currently considered as the optimal patient group for enrollment in clinical trials.

Randomised trial identification

Large, recent, placebo controlled randomised trials were identified from searches previously used[9] and were updated for this study. Specifically, trials reported in 2015 or later and including >50 placebo treated participants were included. Data on trial design and outcomes were extracted into a standardized spreadsheet. The outcomes of interest were changes in fibrosis, both regression and progression, regardless of any change in disease activity. Of note, all trials used the same histological staging system to report these outcomes.[10]

Fibrosis progression calibration

Fibrosis change due to progressive liver disease was modelled recognising that there may be progression in some trial participants and regression in others. The net fibrosis progression rate described accounts all possible changes. Fibrosis progression in liver diseases has been modelled using a gamma distribution where the majority of persons have little progression over time whereas an important minority show more rapid progression[11]. A sequence of distributions were applied to the baseline sampling variability estimates with escalating mean rates of net fibrosis progression to identify what rate of progression produced simulated outcomes in keeping with the reported trials.

Model development

A probabilistic simulation model was built to estimate the probability of fibrosis improvement in patients with NASH and fibrosis stage 2 or 3 at baseline who are the prioritised target group for treatment.

The impacts of sampling variability and regression to the mean were identified together based on published estimates that were directly applicable to the research question. Recognising that inter- and intra-observer variability was already present in the assessments of sampling variability in simultaneous liver biopsy studies, the initial simulations were done without addition of parameters to account for observer variability.

Each simulated trial consisted of 120 placebo-treated participants studied over a period of 18 months with all participants undergoing repeat liver biopsy to mimic a large phase 2b trial. A total of 1000 trials was done in each simulation to assess the distribution of likely trial

outcomes. All analyses were done in R using code developed specifically for this study.[12] Analytic code is available at https://github.com/iacrowe/sampling_variability for re-use.

Sensitivity analyses

A series of sensitivity analyses were done to explore aspects of the analyses. First, the number of placebo-treated participants included in simulated trials was varied between 15 and 150 to understand the range of potential values for the apparent placebo response from small phase 2a exploratory studies to large phase 2b or phase 3 trials. Second, the proportion of participants who apparently improve fibrosis due to sampling variability was varied. To maintain calibration to the published trials, the net fibrosis progression rate was also varied as described above. Only simulations with net fibrosis progression (rather than net regression) were considered to be plausible. Finally, a sensitivity analysis was done to explore the impact of observer variability above that seen in the simultaneous biopsy studies.

Results

Overall burden of fibrosis appears stable in placebo-treated patients in clinical trials

Eight trials including 901 placebo-treated participants were identified and data extracted.[13–20] These trials are summarised in **Table 1**. At the trial level there was no evidence of a significant change in body weight or other metabolic parameters that might be driving the placebo response. Fibrosis improvement over a median of 18 months was observed in 21.7% of participants in all eight trials (**Figure 1A**). The observed proportion where fibrosis progressed was similar (21.1% among 729 participants in six trials since two trials did not report the number or proportion of participants with worsening of fibrosis, **Figure 1B**). The similarity in these proportions suggests either that the net progression of fibrosis in trial participants with NASH and F2/F3 fibrosis is negligible overall, or, more likely, there are additional factors including sampling variability and regression to the mean that explain this apparent stability in the overall degree of fibrosis present.

Apparent fibrosis changes in simultaneous biopsy studies

The nature of sampling variability in NASH has been described.[5] The proportion of participants with F2 or F3 in either biopsy who had apparent fibrosis improvement is 29.6% whereas 14.6% had apparent worsening. Importantly these proportions are not symmetrically distributed. Rather, where patients are selected by a relatively extreme phenotype, apparent improvement (towards the patient's mean fibrosis level) is more frequent indicating that regression to the mean is a likely contributor to fibrosis changes observed in trials in NASH.

Calibrated fibrosis progression rate

Fibrosis progression is probable in trial participants who have been selected on the basis that fibrosis has already progressed. Using data from the simultaneous biopsy study as a baseline a net fibrosis progression rate of 0.05 stages per year gave the closest calibration to the rates of fibrosis change observed in large contemporary randomised trials (**Table 2)**.

Estimated placebo rates in simulated randomised controlled trials

We included sampling variability, regression to the mean, and fibrosis progression rates in probabilistic analyses to identify ranges of change in fibrosis in placebo treated participants (**Suppl. Table 1, Figure 2**). For example, the estimate for the proportion of placebo-treated participants with improvement of fibrosis fell between 15% and 30% in 80% of simulations. Importantly, the range of values predicted for fibrosis improvement was comparable to the values observed in a wider range published trials of fibrosis response where nine of 26 trials fell outside 80% of simulations (**Figure 3**).[5]

Sensitivity analyses

The role of trial size was explored to understand the range of plausible values for the apparent placebo response in both early and later stages of drug development. In these simulations, the mean percentage of placebo-treated patients with improved fibrosis was stable at 22%. In small trials, including 15 placebo-treated participants, 80% of simulations showed the

proportion of participants with fibrosis improvement was between 7 and 40%. In trials including more than 45 participants the proportion of participants improving fibrosis was similar to that seen in the base case analysis including 120 participants (**Supplementary Figure 1**).

To explore the range of plausible values for the proportion of trial participants appearing to improve fibrosis due to sampling variability we varied this parameter within the models. To maintain the calibrated outcomes it was also necessary to vary fibrosis progression. It was not possible to maintain calibration below 23% apparent improvement due to sampling variability. At this level, net fibrosis progression was set to 0.01 stages per year and calibrated outcomes were 20.3% improved fibrosis and 20.6% worsened.

Finally, in a recent report the intra-observer variability in fibrosis assessments of patients with F2 or F3 on the index assessment was less than the variability seen due to sampling variability.[21] The proportion of biopsies where there was apparent improvement in fibrosis was 13% and worsened fibrosis was reported in 3%, again favouring regression of fibrosis. The impact of this additional variation was simulated across a range of plausible values in addition to sampling variability and regression to the mean simulated as in the previous analyses. Increasing observer variability resulted in an increase in the rate of fibrosis improvement (**Table 3**).

Discussion

Summary of findings

The studies presented define the placebo response in terms of the known limitations of liver biopsy, namely sampling and observer variability, regression to the mean, and fibrosis progression. These simulations define the likely placebo response rates that are expected in clinical trials and, furthermore, clarify the likely rates of fibrosis progression amongst persons with NASH and significant liver fibrosis.

Findings in the context of current knowledge

Current understanding of the principal drivers of the placebo response is limited.[1] This study highlights limitations inherent in liver biopsy, together with regression to the mean, as the main drivers of fibrosis regression seen in placebo treated patients in randomized controlled trials. Indeed, it was not possible to reduce sampling variability and regression to the mean to less than 22% and maintain calibration with recently reported trials highlighting the pivotal role of these factors in the apparent placebo response.

The importance of sampling variability in apparent fibrosis improvement in clinical trials is supported by observations from recently reported trials.[15,22] Trial participants in the simtuzumab trials who apparently improved fibrosis had lower non-invasive fibrosis test scores suggesting that liver disease was less advanced than was defined on the index biopsy. Similarly, those who progressed had higher non-invasive scores at baseline. Furthermore, in the recently reported study of semaglutide there was a high placebo response (**Figure 3**). This response was associated with lower enhanced liver fibrosis scores and transient elastography values in the placebo treated participants at baseline despite identical fibrosis staging. These observations

illustrate likely overestimation of fibrosis by the index biopsy through sampling variability as the key determinant of apparent placebo response.

Additionally, sampling variability as a predictor of fibrosis change in clinical trials is relevant to liver diseases other than NASH and to earlier stage disease. For instance, histological changes in biliary diseases particularly can be patchy with the associated potential for sampling variability. Notably the placebo response rate in a biopsy controlled study in primary sclerosing cholangitis including patients across the full spectrum of fibrosis stages was similar to those observed for persons with NASH.[23]

Fibrosis progression in NASH

Current estimates of fibrosis progression are derived from small observational studies, largely in persons with little or no fibrosis.[24] The currently defined mean fibrosis progression rate of 0.14 stages per year from observational studies is far in excess of values that could reasonably be calibrated to observed fibrosis changes in randomised trials when sampling variability and regression to the mean were also considered. There are several possible explanations for this. It is possible that selection for, and participation in, a clinical trial is sufficient to identify a patient group at substantially lower fibrosis progression rates. Whilst there is supporting evidence for behaviour change in a proportion of placebo-treated trial participants in NASH, such as a reduction in liver fat as measured using magnetic resonance imaging,[25] it is not clear to what extent this impacts fibrosis progression. In the light of minimal changes in weight and other metabolic parameters such as HbA1c in the studies included here it seems unlikely that this is sufficient to substantially reduce mean fibrosis progression overall. It is also possible that the rate of fibrosis progression is underestimated by its calculation from the variability associated with liver biopsy. For fibrosis progression to be substantially greater in this context

would require that sampling variability, regression to the mean, and observer variability to be greater than was estimated. It is more likely therefore, that in persons with NASH in whom fibrosis has already developed and who enrolled in clinical trials, progression is less rapid than currently anticipated.

The information available regarding the rate of fibrosis progression in persons in whom fibrosis has already progressed is uncertain. Data from observational series is derived from relatively few patients with significant fibrosis. 41 patients were included in the noted systematic review from Singh, Allen and co-workers, with approximately 320 person years of follow-up and the net fibrosis change was negative in persons starting with fibrosis stage 2 or 3.[24] . Using clinical trial data, it has been stated that there is a risk of progression to cirrhosis in a substantial proportion of persons with advanced fibrosis due to NASH.[22,26] There will however be an important contribution to that figure of 20% from sampling variability. As noted in the original sampling variability reports, the risk of apparent progression is 14.6%, again suggesting that the true rate of progression is in fact substantially lower than 20%. The description of a fibrosis progression rate from significant liver fibrosis in NASH, at a rate that is slower than the pooled population estimate, provides an important insight into the progression of this disease.

Considering the role of liver histology as an endpoint in trials in NASH

The role of liver histology has been challenged as a surrogate outcome in trials in NASH.[27] The recent description of clinically important observer variation in biopsy interpretation has heightened the importance of this debate.[21] The factors included in the simulations here are inherent characteristics of liver biopsy. Sampling and observer variability can be tackled by ensuring appropriately sized samples are taken and multiple pathologist reads, but this will inevitably limit trial enrollment and the applicability of treatments in the longer term. There is

growing interest in the use of novel technologies in the interpretation of liver histology but it remains an open question as to whether these will be sufficient to overcome its limitations particularly as they relate to sampling variability.[28,29]

Substantial variation in the primary outcome measure of trials aiming to provide evidence for conditional licensing is a major issue in drug development in NASH. A deeper understanding of this issue is likely to benefit interpretation of trials as they are reported but it remains a priority to develop and refine biomarkers. For use in clinical practice, the primary aim of a biomarker is that it is prognostic for future liver events in a way that enables treatment decision-making. Existing noninvasive tests, including transient elastography, provide prognostic information and likely meet the need for risk stratification if not yet the need for treatment decision-making in NASH. Additionally, response biomarkers that identify a change in prognosis with treatment are critical so that the field can ultimately move away from liver biopsy and its inherent limitations. It may be that existing biomarkers (alone or in combination) being developed and evaluated in parallel with ongoing clinical trials will fulfill these needs.[30]

Strengths and limitations

In this study we have integrated data from a number of sources to provide a clearer understanding of the nature of the placebo response in trials in NASH including an important estimate of fibrosis progression for patients with significant and advanced liver fibrosis. The clinical trial populations provide a consistent baseline for estimates of fibrosis progression and regression but there are potential limitations. First, the estimates of sampling variability and regression to the mean come from a small patient population as simultaneous liver biopsy studies are infrequently done. Additionally, the staging scheme used in this study was according to the original description by Brunt[31] rather than the NASH CRN staging system that

has been used subsequently[10]. There is substantial overlap between these two systems and in our view it is unlikely that this has had a significant impact on the outcomes reported. Second, there is incomplete information regarding factors that might impact sampling variability. For instance, it is known that biopsy length impacts sampling variability.[4,32] In the original report on sampling variability, the mean biopsy length was 20mm with 17 portal tracts included. Only one of the trials included in the analysis included a description of the length of biopsy at enrollment, reporting a similar length. Third, there is incomplete information regarding the impact of additional benefits that may have accrued in the context of a clinical trial that might impact on fibrosis progression. While there was no evidence of significant weight loss or positive change in metabolic parameters at the trial level it may be that there were changes at the individual level. As such the defined net fibrosis progression rate may not be applicable to populations outside clinical trials.

Conclusions

In conclusion, the analyses presented define the apparent placebo response in liver fibrosis in randomised trials in NASH in terms of sampling and observer variability, regression to the mean, and fibrosis progression. The factors relating to liver biopsy are largely unmodifiable with current techniques and the variation in placebo response rates, both simulated and observed, challenges the role of biopsy in trial endpoint assessment.

Figure legends

Figure 1**. Pooled fibrosis change in contemporary phase 2 and phase 3 trials enrolling participants with NASH and fibrosis at baseline**. (**A**) Fibrosis regression, (**B**) fibrosis progression. Trials not reporting fibrosis progression are excluded from that analysis

Figure 2. **Simulated trial outcomes**. The distribution of fibrosis change in simulated trials is shown for a probabilistic evaluation of 1000 trials to illustrate the likely outcomes in placebo treated participants in controlled randomised trials in NASH.

Figure 3. **Distribution of fibrosis changes in placebo treated participants in reported randomized controlled trials**. The distribution of simulated trials is shown to illustrate the range of values for fibrosis improvement (**A**) and fibrosis worsening (**B**) likely in placebo controlled randomized trials in NASH. 26 trials reported fibrosis improvement (**A**), and 15 trials reported fibrosis worsening (**B**). The area of each point is proportional to the number of trial participants. Trials falling outside 80% of predicted simulations are annotated.

References

1. **Rinella ME, Tacke F, Sanyal AJ, Anstee QM**, et al. Report on the AASLD/EASL joint workshop on clinical trial endpoints in NAFLD. J Hepatol 2019;71:823-833.

2. Dulai PS, Singh S, Patel J, et al. Increased risk of mortality by fibrosis stage in non-alcoholic fatty liver disease: Systematic Review and Meta-analysis. Hepatology 2017.

3. Taylor RS, Taylor RJ, Bayliss S, et al. Association between fibrosis stage and outcomes of patients with nonalcoholic fatty liver disease: A systematic review and meta-analysis. Gastroenterology 2020;158:1611-1625.e12.

4. Bedossa P, Dargere D, Paradis V. Sampling variability of liver fibrosis in chronic hepatitis C. Hepatology 2003;38:1449-1457.

5. Ratziu V, Charlotte F, Heurtier A, et al. Sampling variability of liver biopsy in nonalcoholic fatty liver disease. Gastroenterology 2005;128:1898-1906.

6. Merriman RB, Ferrell LD, Patti MG, et al. Correlation of paired liver biopsies in morbidly obese patients with suspected nonalcoholic fatty liver disease. Hepatology 2006;44:874-880.

7. Larson SP, Bowers SP, Palekar NA, et al. Histopathologic variability between the right and left lobes of the liver in morbidly obese patients undergoing Roux-en-Y bypass. Clin Gastroenterol Hepatol 2007;5:1329-1332.

8. Barnett AG, van der Pols JC, Dobson AJ. Regression to the mean: what it is and how to deal with it. Int J Epidemiol 2005;34:215-220.

9. Roskilly A, Hicks A, Taylor EJ, et al. Fibrosis progression rate in a systematic review of placebo-treated nonalcoholic steatohepatitis. Liver Int December 2020.

10. Kleiner DE, Brunt EM, Van Natta M, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology 2005;41:1313-1321.

11. Kim WR, Poterucha JJ, Benson JT, et al. The impact of competing risks on the observed rate of chronic hepatitis C progression. Gastroenterology 2004;127:749-755.

12. R Core Team. R: A Language and Environment for Statistical Computing., 2020. https://www.R-project.org/.

13. Neuschwander-Tetri BA, Loomba R, Sanyal AJ, et al. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. Lancet 2015;385:956-965.

14. Friedman SL, Ratziu V, Harrison SA, et al. A Randomized, Placebo-Controlled Trial of Cenicriviroc for Treatment of Nonalcoholic Steatohepatitis with Fibrosis. Hepatology 2017.

15. Harrison SA, Abdelmalek MF, Caldwell S, et al. Simtuzumab Is Ineffective for Patients With Bridging Fibrosis or Compensated Cirrhosis Caused by Nonalcoholic Steatohepatitis. Gastroenterology 2018;155:1140-1153.

16. Harrison SA, Goodman Z, Jabbar A, et al. A randomized, placebo-controlled trial of emricasan in patients with NASH and F1-F3 fibrosis. J Hepatol 2019;27.

17. Harrison SA, Alkhouri N, Davison BA, et al. Insulin sensitizer MSDC-0602K in non-alcoholic steatohepatitis: A randomized, double-blind, placebo-controlled phase IIb study. J Hepatol 2019.

18. **Younossi ZM, Ratziu V**, Loomba R, et al. Obeticholic acid for the treatment of non-alcoholic steatohepatitis: interim analysis from a multicentre, randomised, placebo-controlled phase 3 trial. Lancet 2019;394:2184-2196.

19. Harrison SA, Wong VW, Okanoue T, et al. Selonsertib for patients with bridging fibrosis or compensated cirrhosis due to NASH: Results from randomized phase III STELLAR trials. J Hepatol 2020.

20. Newsome PN, Buchholtz K, Cusi K, et al. A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis. N Engl J Med November 2020.

21. Davison BA, Harrison SA, Cotter G, et al. Suboptimal reliability of liver biopsy evaluation has implications for randomized clinical trials. J Hepatol 2020;73:1322-1332.

22. Sanyal AJ, Harrison SA, Ratziu V, et al. The Natural History of Advanced Fibrosis Due to Nonalcoholic Steatohepatitis: Data From the Simtuzumab Trials. Hepatology 2019;70:1913-1927.

23. Muir AJ, Levy C, Janssen HLA, et al. Simtuzumab for Primary Sclerosing Cholangitis: Phase 2 Study Results With Insights on the Natural History of the Disease. Hepatology 2019;69:684-698.

24. **Singh S, Allen AM**, Wang Z, et al. Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. Clin Gastroenterol Hepatol 2015;13:643-654 e1-e9; quiz e39-e40.

25. Harrison SA, Bashir MR, Guy CD, 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.

26. Loomba R, Adams LA. The 20% Rule of NASH Progression: The Natural History of Advanced Fibrosis and Cirrhosis Caused by NASH. Hepatology 2019;70:1885-1888.

27. Rowe IA. The devotion to surrogate outcomes in drug development for liver disease. Nat Rev Gastroenterol Hepatol 2018;15:1-2.

28. **Liu F, Goh GB-B**, Tiniakos D, et al. qFIBS: An Automated Technique for Quantitative Evaluation of Fibrosis, Inflammation, Ballooning, and Steatosis in Patients With Nonalcoholic Steatohepatitis. Hepatology 2020;71:1953-1966.

29. Taylor-Weiner A, Pokkalla H, Han L, et al. A Machine Learning Approach Enables Quantitative Measurement of Liver Histology and Disease Monitoring in NASH. Hepatology February 2021.

30. Rowe IA, Wai-Sun Wong V, Loomba R. Treatment candidacy for pharmacologic therapies for NASH. Clin Gastroenterol Hepatol March 2021.

31. Brunt EM, Janney CG, Di Bisceglie AM, et al. Nonalcoholic steatohepatitis: a proposal for grading and staging the histological lesions. Am J Gastroenterol 1999;94:2467-2474.

32. Vuppalanchi R, Unalp A, Van Natta ML, et al. Effects of liver biopsy sample length and number of readings on sampling variability in nonalcoholic Fatty liver disease. Clin Gastroenterol Hepatol 2009;7:481-486.

Author names in bold designate shared co-first authorship.