





# Liver biopsy in the real world—reporting, expert concordance and correlation with a pragmatic clinical diagnosis

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### Summary

**Background:** Patients with non-alcoholic steatohepatitis (NASH) and fibrosis stage  $\geq 2$  comprise a target population for pharmacotherapy. Liver biopsy, the reference standard for identifying this population, requires complete and accurate assessment of steatohepatitis and fibrosis.

**Aims:** To investigate the completeness of real-world NASH-related pathology reports, assess concordance between site pathologists and central expert interpretation of the histologic elements of NASH, and determine concordance between biopsy-diagnosed NASH and a pragmatic clinical definition of NASH.

**Methods:** Liver pathology reports from 222 patients across 38 TARGET-NASH sites were analysed for documentation of the histologic features of NASH. Biopsy slides were over-read by a blinded central expert pathologist. Concordance of histologic scores and interpretation was assessed. Histologic concordance with a clinical definition of NASH was determined. TARGET-NASH clinically defined NASH: elevated ALT, hepatic steatosis on biopsy or imaging and  $\geq 1$  of the following: BMI  $\geq 30$  kg/m<sup>2</sup>, type 2 diabetes mellitus and dyslipidaemia.

**Results:** Documentation of steatosis, lobular inflammation, portal inflammation and ballooning were missing from 21%, 35%, 46% and 40% of reports, respectively. There was slight-to-fair concordance (weighted kappa 0.01-0.35) between site and central pathologists for inflammatory features, and moderate concordance (weighted kappa 0.56-0.57) for fibrosis staging. Clinical definition of NASH was 75%-91% concordant (94%-95% sensitive) with biopsy-diagnosed NASH.

**Conclusions:** There is substantial variability in reporting and grading NASH and fibrosis staging in clinical practice. This heterogeneity may adversely impact patient assessment and translation of practice guidelines into reality. The TARGET-NASH pragmatic clinical definition may serve as a valuable tool to accurately identify NASH patients in clinical practice.

## 1 | INTRODUCTION

The growing prevalence of non-alcoholic fatty liver disease (NAFLD) contributes to the increasing burden of cirrhosis and need for liver transplantation.<sup>1,2</sup> Those with non-alcoholic steatohepatitis (NASH) comprise a subset of individuals with NAFLD who have a more aggressive disease phenotype marked by inflammation and fibrosis that is associated with increased morbidity and mortality.<sup>3-5</sup> The American Association for the Study of the Liver Diseases (AASLD) practice guidelines recommend a biopsy to identify patients with NASH and advanced fibrosis.<sup>6</sup> Liver biopsy interpretation requires accurate, reliable and consistent reporting of the key components that define NASH and fibrosis. As novel therapeutics continue to be developed, the ability to accurately diagnose individuals is fundamental in identifying patients who may benefit from interventions that may lead to a reduction or reversal in disease progression.

The general indications for performing liver biopsy in NAFLD/NASH patients are to confirm or exclude the diagnosis of NASH and to assess disease severity.<sup>7,8</sup> Liver biopsy remains the reference standard for diagnosing and assessing the histologic features of NASH, particularly the reversible necroinflammatory components, and has been used in drug development and clinical trials to enrol patients and assess disease response. These *clinical trial* biopsies are interpreted by central expert pathologists.<sup>9-11</sup> However, the utility of a liver biopsy in routine clinical practice is dependent on the accuracy and reliability of its interpretation and whether or not all essential features are reported. Indeed, in real-world clinical practice, there is a paucity of data regarding the completeness and quality of liver pathology reports.

Since liver biopsies are invasive procedures that require post-procedural monitoring, increase healthcare utilisation and may be associated with serious complications, they are not scalable to the population as a whole.<sup>12,13</sup> The desire to avoid or limit the use of invasive testing, as well as the need to be able to apply diagnostics to a large population of patients, has led to research into non-invasive tests (NIT) to diagnose and stage NASH.<sup>14,15</sup> Such NITs have not yet met regulatory approval. Thus, there is a critical unmet need for an inexpensive, practical, non-invasive method for diagnosing and clinically staging NASH.

Therefore, the aims of this study were to (a) describe the completeness of real-world histologic interpretation and reporting in patients who had liver biopsies to evaluate for NASH, (b) evaluate the concordance of histologic interpretation of NASH-related pathology slides between local pathologists and a central expert pathologist and (c) assess the concordance between a pragmatic TARGET-NASH clinical definition of NASH and a histologic determination of NASH.

## 2 | METHODS

### 2.1 | TARGET-NASH cohort

TARGET-NASH is an ongoing longitudinal, observational real-world cohort that includes patients with NAFLD managed at academic and

community hepatology, gastroenterology, and endocrinology practices in the United States (NCT02815891).<sup>16,17</sup> The study is sponsored by Target Real World Evidence (Target RWE), a company designed to collect pragmatic clinical information from routine clinical practice and provide phase 4 post-marketing surveillance of new medications where applicable. Clinical information, including demographics, comorbidities, concomitant medications, laboratory results, pathology reports and imaging data, is abstracted from the electronic medical records for a period of up to 3 years prior to enrolment and for up to 5 years prospectively, as previously described.<sup>16-20</sup> Institutional Review Board Approval was obtained for each study site prior to enrolment and all enrolled participants provided written informed consent.

### 2.2 | Study population

The current analysis includes adult patients enrolled in TARGET-NASH between 8 November 2016 and 10 December 2020 with the following characteristics: (a) age 18 years or older; (b) from United States sites; (c) with a needle liver biopsy date on or after 1 January 2014 and (d) a site pathologist overall interpretation of NAFLD, NASH or steatohepatitis. Patients with an inconclusive biopsy according to interpretation by the central pathologist were excluded. Additionally, patients were excluded if they had wedge biopsies, biopsies of a liver explant or for whom a formal pathology report was unavailable for comparison. Patients with comorbid non-NAFLD liver diseases (eg autoimmune hepatitis and chronic hepatitis C) were also excluded.

### 2.3 | NAFLD definitions and severity

Patients enrolled in TARGET-NASH have been diagnosed with NAFLD based on usual clinical practice by their treating physician. Once enrolled into TARGET-NASH, patients are classified via biopsy and/or clinical criteria as having non-alcoholic fatty liver (NAFL), NASH or cirrhosis due to NAFLD as previously described.<sup>16-20</sup> NASH is defined by the presence of steatosis, ballooning and inflammation, with or without fibrosis, based on histologic interpretation.<sup>6</sup> A pragmatic clinical diagnosis of NASH was created by a panel of NASH experts and is based on an elevated ALT (>19 IU/L for women and >30 IU/L for men), hepatic steatosis on biopsy or imaging and at least one of the following: BMI  $\geq 30$  kg/m<sup>2</sup>, type 2 diabetes mellitus (HbA1c >6.5% or identified by review of the patient's medical history) or dyslipidaemia (identified by review of the patient's medical history).<sup>16</sup> Patients' clinical information from  $\pm 2$  years of their liver biopsy date was reviewed to determine whether or not they met criteria for a clinical diagnosis of NASH.

### 2.4 | Pathology reports

Liver pathology reports from academic and community practices were analysed by two readers (HPK and ASB) for documentation of

steatosis, lobular inflammation, portal inflammation, hepatocyte ballooning and fibrosis stage. Disagreements were adjudicated. Specific quantification of each histologic element was recorded using the NAFLD activity score criteria (NAS).<sup>21</sup> Additionally, an overall NASH activity score according to a standardised scoring system (NAS or Brunt grade) was recorded.<sup>21,22</sup>

## 2.5 | Central read of digitised biopsy slides

Biopsy slides from 150 participants were scanned, digitised and over-read by a blinded central expert pathologist. An overall interpretation was made, including categories of definite NASH, possible NASH and not NASH. Definite NASH was defined as the presence of steatosis, lobular inflammation and unequivocal hepatocyte ballooning. Possible NASH was included as a category for sensitivity analysis given the heterogeneous distribution of NASH-related lesions and the potential for sampling error that might lead to inaccurate diagnosis and staging.<sup>15,23</sup> Possible NASH required the presence of steatosis, as well as lobular inflammation but no unequivocal ballooning. In the presence of cirrhosis and absent inflammation and ballooning, NASH was still considered possible if there was any amount of steatosis. Not NASH was defined as the absence of steatosis and hepatocyte ballooning. These definitions are summarised in Table 1. For biopsy slides with a central interpretation of definite or possible NASH, hepatic steatosis, lobular inflammation, portal inflammation, hepatocyte ballooning and fibrosis stage were assessed. Each slide was also assigned scores using the NAS and Brunt grade.<sup>21,22</sup>

## 2.6 | Statistical analysis

Descriptive statistics were reported for baseline characteristics for all patients and by pathologist/biopsy read type, central vs the local site pathologist. Continuous variables were summarised using the frequency, median, minimum and maximum values. Categorical variables were summarised using the frequency and the percentage relative to those with non-missing values. Demographic information summarised included age at enrolment, gender, race, ethnicity, pathologist type (ie central vs site) and site type. Pathologist documentation of hepatic steatosis, lobular inflammation, portal inflammation, hepatocyte

ballooning, fibrosis and standardised NAFLD scoring systems, NAS and Brunt grades were reported as percentages of the total number of pathology reports. Pathologists' concordance for quantifying steatosis, lobular inflammation, portal inflammation, hepatocyte ballooning and fibrosis, assessed using weighted kappa statistics, was reported.<sup>24</sup> The concordance between the central pathologist biopsy-defined NASH and the TARGET-NASH clinical definition was summarised using frequency counts and percentages. The sensitivity and specificity of the TARGET-NASH clinical definition were calculated in reference to the histologic definition as the reference standard. All analyses were performed in SAS, version 9.4, and JMP Pro.

## 3 | RESULTS

### 3.1 | Baseline characteristics

A total of 222 pathology reports representing unique individuals from 38 TARGET-NASH sites were included and reviewed to assess pathology report completeness when evaluating NASH (Figure 1, Table 2). Of these, scanned pathology slides from 150 participants enrolled across 13 TARGET-NASH sites were scanned and digitised for interpretation by the central expert pathologist to evaluate concordances of histologic interpretation between local and central pathologists, and between a pragmatic TARGET-NASH clinical definition of NASH and a histologic determination of NASH. These pathology slides represented 150 unique patients with a median age of 55 years (range 21-75), 63% female and 86% white; 75% were interpreted at academic (ie academic teaching or university affiliated hospital) sites and 25% at community (ie private practice) sites. Available scanned liver biopsy slides that were centrally read came from patients who were slightly younger (median age 55 vs 58 years), more frequently Hispanic (19% vs 10%) and were more commonly interpreted at academic sites (75% vs 63%) as compared to patients whose biopsies were not available for central read.

### 3.2 | Histologic reporting by local pathologists

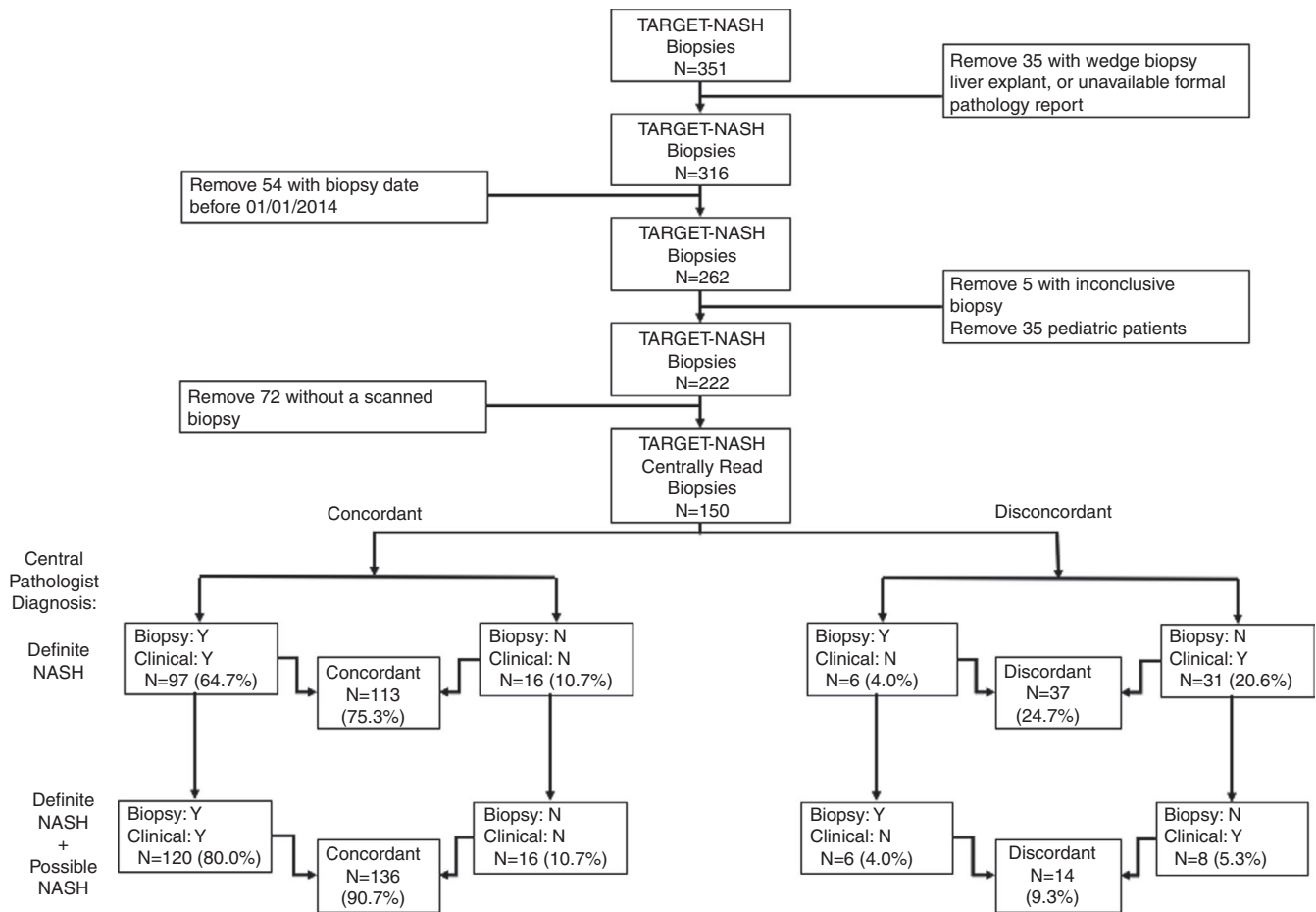
Of the 222 pathology reports that were reviewed, documentation of steatosis, lobular inflammation, portal inflammation and ballooning

TABLE 1 Histologic definitions of definite NASH, possible NASH and not NASH

	Steatosis	Ballooning	Inflammation
Definite NASH	Present, >5%	Unequivocal hepatocellular ballooning	Present
Possible NASH without cirrhosis <sup>a</sup>	Present, >5%	Absent	Lobular inflammation present
Possible NASH with cirrhosis <sup>b</sup>	Present, >5%	One may be present but not required	
Not NASH	Absent, <5%	Absent	Absent or present from another aetiology

<sup>a</sup>Possible NASH without cirrhosis was present with >5% steatosis and the presence of lobular inflammation but no unequivocal ballooning.

<sup>b</sup>Possible NASH as the aetiology for cirrhosis was considered possible if only steatosis was present due to the possibility of "burnt out NASH" as ballooning and inflammation may disappear with advanced disease.



N = no; Y = yes

**FIGURE 1** Consort diagram for centrally interpreted liver biopsies and concordance between biopsy-defined NASH versus clinically defined NASH. Diagram reflects the selection of the population for this study based on data from the TARGET-NASH study. Liver biopsy reports were obtained for participants from participating study sites; scans of biopsy slides were available for a subset of these biopsies and were read by a central pathologist. Concordance between the central pathologist diagnosis and that based on the clinical definition was assessed

were missing from 21%, 35%, 46% and 40% of reports respectively. Grading of NASH was more commonly performed using the NAS compared to the Brunt criteria; however, 55% of reports did not include either of these validated grading scores. Fibrosis was frequently reported with only 5% of reports missing a fibrosis score and only 3% of reports missing any description of fibrosis (data not shown).

### 3.3 | Concordance of histologic interpretation of NASH features

Of the 150 biopsy slides that were centrally interpreted, there was substantial discordance in the quantification of NASH components and fibrosis staging by local vs central expert pathologists (Table 3). Based on kappa scores, there was slight-to-fair concordance (weighted kappa range 0.01-0.31) for steatosis, lobular inflammation, portal inflammation and hepatocyte ballooning. Fair

concordance was observed for overall assessment of disease using the NAS (weighted kappa=0.35; 95% CI 0.23, 0.46) and Brunt grading criteria (weighted kappa=0.34; 95% CI 0.11, 0.58), and concordance was moderate for fibrosis staging with a weighted kappa statistic of 0.57 (95% CI 0.48, 0.66). When limited to concordance among biopsies with advanced fibrosis or cirrhosis (F 3-4), concordance was substantial (weighted kappa=0.61 95% CI 0.52, 0.71).

### 3.4 | Concordance of TARGET-NASH clinically defined NASH vs biopsy-defined NASH

Of the 150 centrally interpreted biopsy slides, 103 (69%) were interpreted as definite NASH, 23 (15%) possible NASH and 24 (16%) not NASH according to histologic interpretation. The 23 biopsy specimens that were judged to be only possible NASH based upon central reading of the liver biopsy were all from patients who met pre-established clinical criteria for NASH. Despite the presence of

**TABLE 2** Baseline characteristics for the study population and stratified by biopsy read type

Summary	Centrally read biopsy (N = 150)	Non-centrally read biopsy (N = 72)
Age at study entry (years)		
Median (n)	55.0 (150)	57.5 (72)
Min-Max	21.0-75.0	30.0-74.0
Gender, n (%)		
n	150	72
Female	95 (63.3)	44 (61.1)
Male	55 (36.7)	28 (38.9)
Race, n (%)		
n	145	71
White	124 (85.5)	60 (84.5)
Black or African American	11 (7.6)	3 (4.2)
Asian	7 (4.8)	7 (9.9)
Other	3 (2.1)	1 (1.4)
Not available	5	1
Ethnicity, n (%)		
n	149	70
Hispanic or Latino	28 (18.8)	7 (10.0)
Not Hispanic or Latino	120 (80.5)	63 (90.0)
Other	1 (0.7)	
Not available	1	2
Site type, n (%)		
n	150	72
Academic	112 (74.7)	45 (62.5)
Community	38 (25.3)	27 (37.5)
Pathology type, n (%)		
n	150	72
Central	150 (100.0)	–
Local	–	72 (100.0)

several histological features of NASH including evidence of steatosis (23/23), portal and/or lobular inflammation (22/23) and fibrosis (16/23), the absence of definitive ballooning in all of these specimens precluded the histological definition of NASH (Table 4). Across the study population, 31 patients had significant fibrosis (fibrosis stage  $\geq 2$ ) but no ballooning.

In 113 (75%) cases, there was concordance between the TARGET-NASH clinical and histologic diagnoses, where 96 cases were determined to represent NASH and 16 cases were determined as not meeting criteria for NASH (Figure 1). The remaining 37 (25%) patients included 31 patients with a clinical diagnosis of NASH but without definite histologic NASH. However, 23 of these 31 cases were classified as representing possible NASH by the central pathologist. When categorising these cases as histologic NASH, the concordance between clinical and biopsy-driven NASH diagnosis

increased to 91%. Only 6 of the 150 patients (4%) with biopsy-diagnosed NASH did not meet all the criteria for clinically defined NASH due to the absence of obesity (BMI  $\geq 30$  mg/kg<sup>2</sup>), although all were overweight (BMI  $\geq 25$  mg/kg<sup>2</sup>). Using the biopsy-defined definite NASH diagnosis as the reference standard, the clinical NASH definition was 94% sensitive (95% CI 87.8-97.8) and 34% specific (95% CI 20.9, 49.3). When defining biopsy-defined NASH as those with definite or possible NASH, the sensitivity and specificity of the clinical definition increased to 95% (95% CI 89.9, 98.2) and 67% (95% CI 44.7, 84.4), respectively, with a positive predictive value of 94% and a negative predictive value of 73% (Table 5).

## 4 | DISCUSSION

In this real-world observational cohort of patients with NAFLD, there is substantial heterogeneity in the local histological reporting of NASH with a large proportion of reports missing important descriptors of NASH disease activity, as well as only slight-to-moderate concordance between local and central pathologists when interpreting specific features of NASH and stages of fibrosis. Of note, we also found that the TARGET-NASH clinical definition of NASH was accurate in identifying biopsy-defined NASH, as confirmed by a central expert pathologist, in the vast majority of cases.

In the appropriate context, liver biopsy remains a necessary step in staging the activity and severity of NASH and in excluding or identifying comorbid liver diseases. While liver biopsy remains the reference standard for assessing the histologic elements of NASH, the utility of a liver biopsy is limited by its interpretation, reporting and selection of who receives a liver biopsy.<sup>17</sup> The degree of heterogeneity and missing components in pathologic reporting observed in this study limits the value of these biopsies in routine clinical care. Furthermore, the concordance for biopsy interpretation was moderate at best. Useful reporting should clearly document and quantify hepatic steatosis, lobular and portal inflammation, hepatocyte ballooning and degree of fibrosis, with the goal of accurately staging disease severity and being able to differentiate between NAFL and NASH. When not all the diagnostic criteria for NASH are reached, it is useful to underline in the descriptive remarks of the histological report if there are elements of steatosis and associated with ballooning or lobular inflammation or, due to possible sampling error, NASH cannot be entirely excluded. A descriptive conclusion should be provided in these cases. Recommendations for such reporting have recently been put forth by the AASLD NASH Task Force, which was composed of a multidisciplinary team of hepatologists and pathologists and underscores the importance of these constituencies working closely together.<sup>25</sup> Such heterogeneity and lack of reliability in reporting and interpretation may adversely impact patient assessment and application of new NASH therapies. Utilising specific standardised scoring mechanisms may improve concordance between pathologists' interpretations and increase the utility of performing liver biopsies, which are not without complications.

**TABLE 3** Kappa statistics for concordance of histological interpretation of NASH for central vs local read of biopsies

Histological characteristic	Number of pathology reports compared	Weighted Kappa statistic (95% CI)	Concordance interpretation <sup>a</sup>
Steatosis	66	0.31 (0.15, 0.46)	Fair
Lobular Inflammation	37	0.01 (-0.19, 0.22)	Slight
Portal inflammation	35	0.18 (-0.05, 0.40)	Slight
Hepatocyte ballooning	34	0.20 (0.02, 0.38)	Slight
Fibrosis stage	109	0.56 (0.46, 0.65)	Moderate
NAFLD Activity Score	77	0.35 (0.23, 0.46)	Fair
Brunt grade (inflammation)	27	0.34 (0.11, 0.58)	Fair
Brunt stage (fibrosis)	112	0.57 (0.48, 0.66)	Moderate

Abbreviation: NAFLD, non-alcoholic fatty liver disease.

<sup>a</sup>Concordance: 0-0.20 as slight; 0.21-0.40 as fair; 0.41-0.60 as moderate; 0.61-0.80 as substantial and 0.81-1 as almost perfect.<sup>24</sup>

**TABLE 4** Histological and clinical characteristics of patients with possible NASH by central pathologist

Subject	Histologic features of NASH					Clinical features of NASH			
	Steatosis	Ballooning	Inflammation		Fibrosis	Steatosis	Elevated ALT <sup>a</sup>	BMI ≥30 kg/m <sup>2</sup>	Diabetes and/or dyslipidaemia <sup>b</sup>
			Portal	Lobular					
1	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No
2	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No
3	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No
5	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes
6	Yes	No	No	Yes	No	Yes	Yes	Yes	No
7	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes
8	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes
10	Yes	No	Yes	Yes	No	Yes	Yes	No	Yes
11	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes
13	Yes	No	Yes	Yes	N/A	Yes	Yes	Yes	Yes
14	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
15	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes
16	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No
17	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
18	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
19	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No
20	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No
21	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No
22	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
23	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes

<sup>a</sup>Adults: ALT > 19 U/L for female and >30 U/L for male at any time.

<sup>b</sup>The presence of type 2 diabetes was defined by HbA1c >6.5% or medical history; dyslipidaemia identified by review of the patient's medical history.

Another important limitation of performing liver biopsies is related to the heterogeneous or uneven distribution of NASH-related lesions throughout the liver parenchyma.<sup>15,23</sup> Therefore, even in the

presence of optimal histologic interpretation and reporting, liver biopsies are subject to sampling error that can lead to inaccurate diagnoses and disease staging. According to our histologic definitions of

Biopsy-defined NASH	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV
Definite NASH	94.2 (87.8, 97.8)	34.0 (20.9, 49.3)	75.8	72.7
Definite or possible NASH	95.2 (89.9, 98.2)	66.7 (44.7, 84.4)	93.8	72.7

**TABLE 5** Sensitivity and specificity of the TARGET-NASH clinical definition of NASH according to biopsy-defined NASH categories

Abbreviations: NASH, non-alcoholic steatohepatitis; NPV, negative predictive value; PPV, positive predictive value.

NASH, slides were determined to represent definite NASH, possible NASH and not NASH. All cases of possible NASH were related to the absence of unequivocal hepatocyte ballooning. In the correct clinical context, therefore, it is reasonable to conclude that these cases represent true NASH. This additional limitation of liver biopsies brings into question the role of liver biopsy in NAFLD and contributes to our understanding that the utility of liver biopsies for clinical decision making in the real world may not be practical.

In light of the current limitations of liver biopsy and histologic interpretation, one important unmet need is a pragmatic and accurate clinical definition for the diagnosis of NASH. With the growing prevalence of NAFLD, it has become increasingly important to be able to screen for and diagnose NASH early, ideally using non-invasive methods with clinical information that is readily available. As an observational cohort, TARGET-NASH developed a clinical definition of NASH with such pragmatism in mind, only requiring information that is available as part of routine care. This is in contrast to studies that have evaluated, or are evaluating, specific biomarkers to identify that NASH that include variables that are not routinely measured.<sup>14</sup> Using a biopsy interpretation for definite NASH, the TARGET-NASH clinical diagnosis was able to detect 94% of NASH cases as interpreted by a central expert pathologist. The performance of the TARGET-NASH clinical definition improved when including cases of biopsy-defined possible NASH in the reference standard, with favourable operating characteristics that would not only allow for the detection of cases but also reasonably rule them out, as well. The high sensitivity we observed is essential when using a tool or test to screen for a disease.

There are some limitations of the current study that must be acknowledged. In evaluating the TARGET-NASH clinical definition of NASH, we were only able to assess for concordance between a clinical diagnosis and a biopsy-defined diagnosis rather than validating the clinical definition. A validation study would require large cohorts of individuals with and without clinical NASH to undergo liver biopsies, something that is beyond the scope of what is possible through the TARGET-NASH cohort. Another possible limitation is that the subset of slides available for central interpretation represented only 13 of the original 38 sites and more often came from academic sites. If there is a difference in the histologic reporting between academic vs community sites, then the assessment of concordance of histologic interpretation may be subject to bias. Further limitations include missing data such as pathology reports that were unavailable for comparison and race/ethnicity descriptors that were unavailable in two patients.

This study highlights important and relevant limitations of liver biopsy interpretation and reporting in the real-world clinical setting. As liver biopsy currently remains the reference standard for diagnosing and staging NASH, major efforts must be made to improve the comprehensiveness and consistent reporting of histologic findings to improve the utility of biopsies in patient assessment and management. Additionally, this study importantly demonstrates that a pragmatic clinical definition of NASH can be used to accurately identify individuals who may require more aggressive management and benefit from future therapeutics. This clinical NASH definition developed by TARGET-NASH warrants further investigation in future validation studies.

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## AUTHORSHIP

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## DATA AVAILABILITY STATEMENT

Author elects to not share data.

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## APPENDIX 1

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