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The health care experience of adults with metabolic dysfunction–associated steatohepatitis and influence of *PNPLA3*: A qualitative study

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Abstract

Background: Metabolic dysfunction–associated steatohepatitis (MASH) is a progressive form of metabolic dysfunction–associated steatotic liver disease, for which there is limited information about patient experience, including the patient journey.

Methods: In this study, we conducted interviews with patients with MASH to qualitatively evaluate the patient journey and help elucidate the experiences of this patient population. We also investigated if the patatin-like phospholipase domain-containing protein 3 (*PNPLA3*) I148M variant (non-Hispanic) or being of Hispanic ethnicity may influence patient experiences because these 2 subgroups develop advanced liver disease more frequently than other patient groups.

Results: One-to-one interviews were conducted with 28 adults (with *PNPLA3* I148M genetic variant, n = 10; Hispanic, n = 8) living in the United States who had been diagnosed with MASH with liver fibrosis. Patients were asked open-ended questions about their experiences before, at, and after

Abbreviations: F stage, fibrosis stage; FDA, US Food and Drug Administration; MASH, metabolic dysfunction–associated steatohepatitis; MASLD, metabolic dysfunction–associated steatotic liver disease; *PNPLA3*, patatin-like phospholipase domain-containing protein 3; WCG-IRB, WIRB-Copernicus Group Institutional Review Board.

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their diagnosis. The data collected found that patients experienced a long process of misdiagnoses before their diagnosis of MASH, a lack of clear information provided by clinicians, and limited accessibility to support groups. Hispanic patients reported "impact on family/friends" (75%) and "fear of disease progression" (75%) more frequently than the other patient cohorts interviewed. This is the first report of "fear of progression" in patients with MASH. No patients who were White and had the *PNPLA3* I148M variant reported nausea/vomiting, in contrast to other patient cohorts.

Conclusions: This qualitative study identified key aspects of the patient journey that are important for clinical providers and medical teams to recognize. We also propose a new algorithm that could be developed to help screen relatives of patients who are found to carry the *PNPLA3* I148M variant.

INTRODUCTION

Metabolic dysfunction–associated steatohepatitis (MASH) is a chronic and progressive form of metabolic dysfunction–associated steatotic liver disease (MASLD), in which patients have excess fat in the liver as well as inflammation and liver injury.[1,2] MASH can lead to liver fibrosis, which can then progress to cirrhosis and liver cancer.[1,2] MASH is classified based on liver fibrosis stages (F), which range from F0 (no fibrosis) to F4 (cirrhosis).[3] The progression rate of fibrosis is a known predictor of patient clinical outcomes.[2,4–6] Prevalences of MASLD and MASH in the global population are currently estimated to be 32.2% and 5.3%, respectively, with the highest region-specific prevalence of MASH in Latin America (7.1%).[7] A study published in 2018 forecasted that the prevalence of cases of MASLD and MASH will increase by 21% and 63%, respectively, among the US adult population between 2015 and 2030.[8]

The patatin-like phospholipase domain-containing protein 3 (*PNPLA3*) gene variant (rs738409 C > G I148M) is a single nucleotide polymorphism that has been found to be a risk factor for susceptibility to MASLD, MASH, severity of histological features, liver fibrosis progression, and liver cancer.[9–12] It has also been recognized that other factors such as obesity can influence MASH progression, particularly in individuals with the *PNPLA3* I148M variant.[13]

The prevalence of MASLD, MASH, and the *PNPLA3* risk variants differ between ethnic groups. MASH and *PNPLA3* risk variants have been found to be most prevalent in people with Hispanic and Asian ancestry, while White individuals have an intermediate risk and Black ancestry individuals have the lowest risk.[9,14–16] However, whether ethnicity influences advanced liver disease is still disputed. As well as influencing genetic susceptibility to certain conditions, ethnic background could have behavioral or cultural impacts that influence the way in which patients interact with health care professionals or receive information about their health.

Previous research found that patients with MASH reported a variety of symptoms that they felt were associated with their health condition.[17] Directly talking with patients to better understand their experiences of health conditions or therapies can help to improve patient care by allowing health care professionals to be more aware of the factors that can affect patients, such as the type of support required and how that support could be provided. Patients with MASH often experience fatigue, pain in the abdomen, worry, and frustration[17]; however, there is no literature that documents the patient's treatment journey. Patients' insights can provide valuable understanding of their perceptions, concerns, and treatment journeys, from booking their first appointment to receiving a diagnosis and discussing treatment options for their condition. Particularly, understanding an ethnically and genetically diverse population can provide insights into the type of support that patients require and how that support could be provided.

This study aimed to explore and document the patient journey for individuals with MASH, including understanding the barriers that patients experience and the support they may need. In addition, this study investigated how the *PNPLA3* I148M variant or being Hispanic may influence experiences associated with MASH.

METHODS

Study design overview

In this noninterventional qualitative research study, interviews were conducted with adults living in the United States with diagnosed MASH—the study took place while the term non-alcoholic steatohepatitis

(NASH) was still in use, so interviewer questions and patient answers are based on this term. Patients were asked about their experiences before their diagnosis (prediagnosis), while they received their diagnosis (diagnosis) and after their diagnosis (postdiagnosis; their current status). Using their responses, we investigated the patient journey and the similarities and differences between the symptoms and impacts between the general population of interviewed patients and those with the *PNPLA3* I148M variant or who were Hispanic. An overview of the study design is given in Figure 1.

Patient recruitment

Eligible patients were aged at least 18 years, resided in the United States (excluding Puerto Rico), and had received a diagnosis of MASH fibrosis stage F1–3 or compensated F4. This study aimed to recruit 35 patients, of whom ~15 would have the *PNPLA3* I148M variant. All patients with the *PNPLA3* I148M rs738409 C > G variant were tested using a research assay to confirm homozygosity of the polymorphism. Homozygous patients were recruited using consecutive sampling through a clinical trial site at Indiana University and reviewed for eligibility. Potential participants were then contacted through telephone by the site coordinator or clinician. A third-party vendor, Global Perspectives, recruited all other patients with MASH through clinician referrals and social media postings. Patients recruited through Global Perspectives also had their clinicians complete a Confirmation of Diagnosis form. A summary of the patient eligibility criteria is provided in Supplemental Table S1, http://links.lww.com/HC9/A905. Patients received an honorarium following the completion of the interview process.

Patient interviews

The patient interviews were conducted by 3 interviewers (Tara Muma, female, Moderator, IQVIA; Chetan Taylor, male, Engagement Manager, IQVIA; Sarah Phillips, female, Principal, IQVIA) who were experienced in patient interviews and received additional training on concept elicitation methods. Interviewers followed a WIRB-Copernicus Group Institutional Review Board (WCG IRB)-approved semi-structured interview guide with open-ended questions about the patient's experiences. The design of the interview guide was informed by a previous patient interview study about patients with diagnosed MASH.[17] Interviews were performed one-to-one by telephone and lasted ~90 minutes. With the patient's consent, the interviews were audio recorded. Informal field notes were made during the interview, but the audio transcripts were the primary source documents analyzed after the interviews.

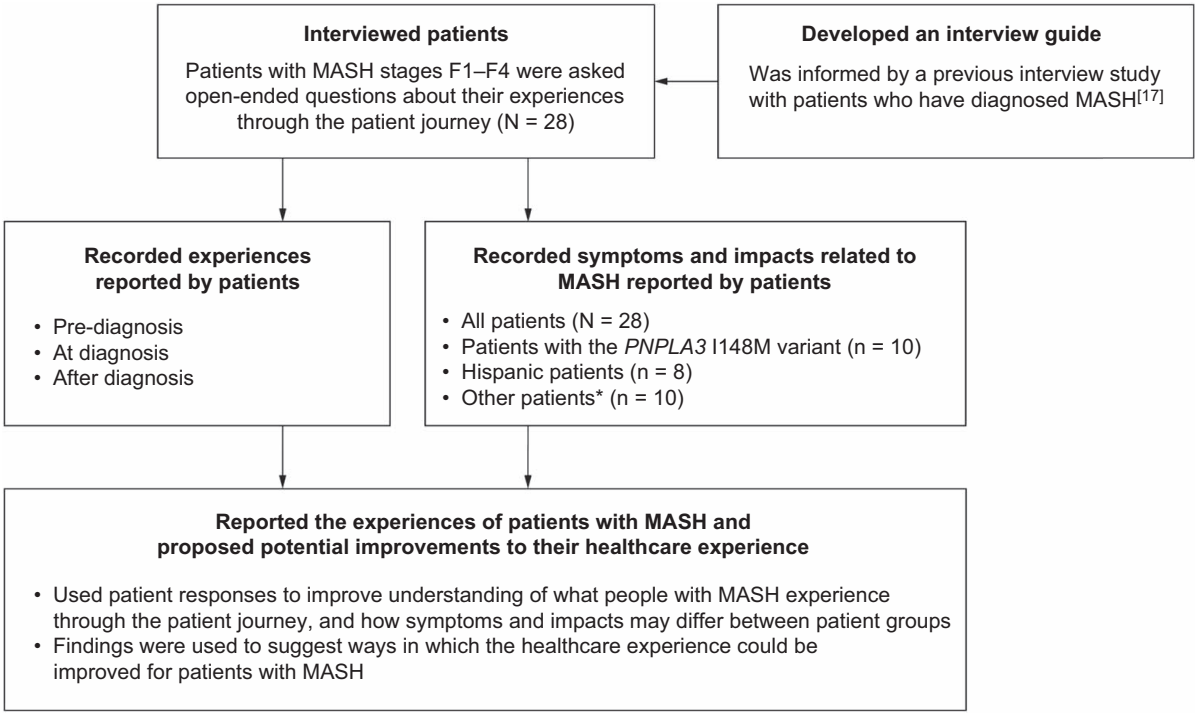

FIGURE 1 Study design. All patient numbers refer to the total number of patients interviewed, including patients with the *PNPLA3* I148M variant and Hispanic patients. During this interview study, health care professionals and patients still referred to MASH as NASH. *Patients who were not known to have the *PNPLA3* I148M variant and were not Hispanic. Abbreviations: MASH, metabolic dysfunction–associated steatohepatitis; NASH, non-alcoholic steatohepatitis; *PNPLA3*, patatin-like phospholipase domain-containing protein 3.

Transcripts were not returned to patients for their comments and no repeat interviews were performed. No relationship was established with the patients before starting the study and they did not know anything about the interviewers.

Data analysis

Transcripts from the recorded interviews were anonymized before coding. Coding of the audio transcripts was conducted by 2 coders (Mahesh Darpelly and Nidhi Saiwal) of IQVIA using the qualitative research software ATLAS.ti (version 8; ATLAS.ti Scientific Software Development GmbH). Coding was performed using a predefined codebook (based on the Swain et al, preliminary conceptual model) and a discussion guide (informed by Swain et al, and patient journey research experience within the study team).[17] The coders coded the transcripts in unison until an intercoder agreement score of >0.7 was established,[18] after which they coded transcripts independently. Grounded theory was applied so that new codes could be added later when deemed appropriate by the coders. Owing to the qualitative objectives of this study and small sample sizes, variations between or within populations could not be fully determined using statistical significance tests.

Ethics

This study was conducted in accordance with the ethical principles of the Declarations of Helsinki and Istanbul and is consistent with Good Clinical Practice and the regulations of the United States Food and Drug Administration, applicable laws, and the institutional review board requirements. Ethics approval was obtained from the WCG IRB (approval no. 1300917). Patients completed an informed consent form that included an explanation of the purpose of the study and the type of questions they would be asked.

RESULTS

Patient demographics

In total, 28 patients were recruited, 10 (36%) of whom had the *PNPLA3* I148M variant and 8 (29%) were Hispanic with unknown genotype (Table 1). No patients were both Hispanic and had the *PNPLA3* I148M variant confirmed. All patients responded to interview questions to the satisfaction of the interviewers. The majority of patients were female (61%) and most had a fibrosis stage of F1–3 (86%). The most common comorbidities were obesity (50%), hypertension (36%), and type II diabetes (29%).

Patient interviews

Prediagnosis

Patients' lifestyle habits and personal priorities. The majority of patients were married (79%) and were either working full-time (29%) or retired (29%, Table 1). Patients' lifestyle habits were reported as active, neutral, or sedentary. Almost all patients provided a response (n = 24; 86%). A similar proportion of patients reported that they were either active (n = 12; 50%) or sedentary (n = 11; 46%). One patient (4%) described themself as neutral. Patients who described themselves as active mentioned a variety of activities including physical exercise, active hobbies (eg, woodworking), active jobs, and participating in family activities (Supplemental Table S2, http://links.lww.com/HC9/A905). Patients who described themselves as sedentary typically reported having desk jobs and engaging in little physical exercise. When asked what the most important aspects of their lives were before their diagnosis, most patients described a sense of strong family bonds and the importance of spending time with loved ones.

> "*My family means everything to me*" (D001-008).

> "*I am a completely family-oriented person. I really like to enjoy my family*" (M001-003).

Many patients were also worried about how a diagnosis of MASH could affect their families in terms of disease inheritance and the implications of worsening health on their ability to be present for their families.

> "*Because I feel like I brought it on myself by being overweight, and then I feel the fear because I don't want to have anything happen where I leave my kids*" (N001-001).

Challenges at the prediagnosis stage. Although the identification of symptoms and impacts experienced by patients were not a focus of this study, those reported by patients spontaneously were documented (Supplemental Table S3, http://links.lww.com/HC9/A905). The most frequently reported symptoms were fatigue/low energy (43%), pain in the abdomen/liver area (39%), and nausea/vomiting (29%). Patients also reported impacts including cognitive problems (7%) and a decreased ability to work (7%).

Several patients mentioned difficulties booking medical appointments to discuss what may be causing their symptoms. These included long wait times to arrange an appointment and difficulty speaking directly with a clinician outside of scheduled appointments.

TABLE 1 Demographic and clinical characteristics of interviewed patients with metabolic dysfunction–associated steatohepatitis

Characteristics	Total patients (N = 28)	*PNPLA3* I148M (n = 10)	Hispanic (n = 8)	Other[a] (n = 10)
Age, y, n (%)				
25–34	3 (10.7)	2 (20.0)	0	1 (10.0)
35–44	5 (17.9)	1 (10.0)	0	4 (40.0)
45–54	5 (17.9)	1 (10.0)	3 (37.5)	1 (10.0)
55–64	8 (28.6)	2 (20.0)	3 (37.5)	3 (30.0)
65–74	7 (25.0)	4 (40.0)	2 (25.0)	1 (10.0)
Gender, n (%)				
Female	17 (60.7)	2 (20.0)	7 (87.5)	8 (80.0)
F stage[b], n (%)				
F1	5 (17.9)	3 (30.0)	0	2 (20.0)
F2	7 (25.0)	3 (30.0)	1 (12.5)	3 (30.0)
F3	6 (21.4)	2 (20.0)	1 (12.5)	3 (30.0)
F3–4	1 (3.6)	0	1 (12.5)	0
F4 compensated	4 (14.3)	1 (10.0)	2 (25.0)	1 (10.0)
Not available	5 (17.9)	1 (10.0)	3 (37.5)	1 (10.0)
Ethnicity, n (%)				
White non-Hispanic	20 (71.4)	10 (100.0)	0	10 (100.0)
Hispanic	8 (28.6)	0	8 (100.0)	0
PNPLA3 I148M GG genotype[c], n (%)	10 (35.7)	10 (100.0)	0	0
Comorbidities, n (%)				
Obesity	14 (50.0)	8 (80.0)	2 (25.0)	4 (40.0)
Hypertension	10 (35.7)	4 (40.0)	2 (25.0)	4 (40.0)
Type 2 diabetes	8 (28.6)	2 (20.0)	2 (25.0)	4 (40.0)
Cardiovascular disease or heart failure	3 (10.7)	1 (10.0)	0	2 (20.0)
Progressive disease associated with MASH[d]	3 (10.7)	0	1 (12.5)	2 (20.0)
Chronic obstructive pulmonary disease	2 (7.1)	0	0	2 (20.0)
Marital status, n (%)				
Married	22 (78.6)	10 (100.0)	5 (62.5)	7 (70.0)
Divorced	4 (14.3)	0	2 (25.0)	2 (20.0)
Separated	1 (3.6)	0	1 (12.5)	0
Single	1 (3.6)	0	0	1 (10.0)
Highest level of education, n (%)				
High school	17 (60.7)	8 (80.0)	3 (37.5)	6 (60.0)
Two-year Technical School	1 (3.6)	0	0	1 (10.0)
Bachelor's degree	8 (28.6)	1 (10.0)	5 (62.5)	2 (20.0)
Current master's student	1 (3.6)	0	0	1 (10.0)
Master's degree	1 (3.6)	1 (10.0)	0	0
Employment status, n (%)				
Full-time employed	8 (28.6)	3 (30.0)	4 (50.0)	1 (10.0)
Part-time employed	3 (10.7)	2 (20.0)	0	1 (10.0)
Homemaker	2 (7.1)	0	0	2 (20.0)
Retired	8 (28.6)	5 (50.0)	1 (12.5)	2 (20.0)
Unable to work due to disability	5 (17.9)	0	1 (12.5)	4 (40.0)
Unemployed	2 (7.1)	0	2 (25.0)	0

Note: MASH was still referred to as NASH at the time of this study.
[a]Patients who were not known to have the *PNPLA3* I148M variant and were not Hispanic.
[b]Fibrosis stages were provided by patients' clinicians.
[c]All patients with the *PNPLA3* I148M mutation were White non-Hispanic.
[d]Including esophageal varices and cirrhosis.
Abbreviations: F stage, fibrosis stage; MASH, metabolic dysfunction–associated steatohepatitis; NASH, non-alcoholic steatohepatitis; *PNPLA3*, patatin-like phospholipase domain-containing protein 3.

TABLE 2 Patient experiences during the process of receiving a diagnosis of metabolic dysfunction–associated steatohepatitis

Experiences when receiving diagnosis	Patient quotes
Lengthy process of elimination of other diseases before diagnosis	"*I **started seeing a gastroenterologist for my IBS-C. He was treating that**, and I went through a dozen medications until I finally found one that worked. **It worked for two or three years until it quit working, and that's when they did the blood work** and found the elevated enzymes.*" (N001-005) "*…'Well, it looks like you had super small stroke.' He goes, **'We need to figure out why.' And then that's when he started running all the tests** and that's kind of when the liver thing came up.*" (ID08)
Accidental diagnosis of MASH	"***I had my gallbladder taken out then and that's when they told me that I had an enlarged liver and fatty liver disease**. Then the actual NASH diagnosis probably was like six months later because I got it from my GI doctor.*" (D001-007) "*Then they found the NASH by doing a CT scan. **When they were looking for something completely different, they found the NASH**. Since then, it's really been about diagnostic testing.*" (D001-005)
Clinicians not familiar enough with MASH	"*I changed liver doctors**. I went to a new liver doctor because I didn't feel like I was getting the proper treatment that I was supposed to be getting**. So, I got a second opinion. They said, 'Yeah, you got NASH and there ain't nothing we can do for it.'*" (ID14)
Patients "not taken seriously"	"*Basically, like I said before, when I was going to our family doctor, he knew that I had NASH, but he **didn't take it like it was anything real serious**.*" (ID07)
Poor quality of information received from clinician	"***It really wasn't discussed**. It was on the paperwork they give you after a doctor's treatment. And it says NASH on it. **They didn't really explain it to me.** So, what I found out, I had found out on my own, it seems like…. I don't recall a deep discussion, if you will.*" (D001-004)

Note: MASH was still referred to as NASH at the time of this study.
Abbreviations: GI, gastrointestinal; IBS-C, irritable bowel syndrome with constipation; MASH, metabolic dysfunction–associated steatohepatitis; NASH, non-alcoholic steatohepatitis.

> "*It was a struggle waiting on getting in with a doctor and being seen*" (D001-005).

> "*They don't call me. The nurses call me. You're not my doctor. I want to talk to the doctor*" (M001-004).

Diagnosis

Process of receiving a diagnosis. Almost all patients described experiencing a lengthy process of elimination of other diseases before their diagnosis of MASH (Table 2). Several patients mentioned that reporting abdominal/stomach pain to their clinician eventually led to their diagnosis. Multiple patients reported that their MASH diagnosis occurred accidentally; this included during surgeries or routine tests, as well as follow-ups for other conditions such as gastrointestinal issues, cancer, or neurological conditions. Some patients reported that their local clinicians were not familiar enough with MASH to make the diagnosis, so they received their diagnosis by attending a specialist center. Several patients stated they felt that their symptoms were not being taken seriously by their clinicians, which meant these symptoms were attributed to other comorbidities or not followed up in detail, leading to a delay in diagnosis. Of patients who received information about the condition from their clinicians, issues were reported regarding both the quality of information received and difficulty receiving information from clinicians in a way that the patients could understand.

Advised treatment options and potential outcomes. Although there are no US Food and Drug Administration (FDA)-approved therapies for MASH, once a diagnosis was received, only 50% of the patients were advised that no treatment was available for MASH aside from diet and exercise.

> "*Some doctors just say there's not anything… I asked my gastro and I asked… Is there anything I can take? And they're like, No, just diet and exercise*" (N001-002).

Patients reported that their clinicians provided varied answers about potential treatment options. Some were advised by their clinicians to start taking vitamin E and/or milk thistle, coupled with weight loss through either surgery or exercise. Others reported that their clinicians did not discuss treatment options with them, so they determined that there were no available treatments for MASH and/or started taking natural treatments following online research.

> "*Later, my dad was telling me that he had gone online and that he had seen a medication called milk thistle and he said, That medication is too good. They say that it is good for the liver*" (M001-003).

Patients received a range of advice from their clinicians about the reversibility of MASH. Several reported that their clinicians explained that the damage caused by MASH could be reversed, largely through weight loss, diet, and exercise.

> "*As long as you don't drink and you change your diet, it could very well go away*" (D001-005).

Some were told that their MASH-related liver damage was permanent and could not be improved—for 1 patient with MASH stage F4, this was likely due to their late MASH stage at the time of diagnosis. Others were told that they could prevent their MASH from progressing or that treatments for MASH were in development but not currently available.

> "*Yeah, they told me I can stop any more progression on it, but I can't reverse the damage that was done*" (N001-001).

Patients' and families' perceived impact of the diagnosis. Patients had varied reactions to their diagnosis. Most were upset by the news and described feeling a combination of worry, shock, fear, anxiety, and stress (Table 3). Others reported being worried about how MASH would affect their lifespan. Some patients reported being unfazed and 1 patient felt relieved to have received a diagnosis.

When telling their families about the diagnosis, most patients described their families reacting with concern or shock (Table 3). Some reported that their families were supportive, such as by trying to gather more information to understand the disease or helping to prepare more healthy meals. A large proportion of patients had negative interactions with their families, including family members having emotional reactions, being unsupportive or reacting negatively to the required lifestyle changes, such as by trying to encourage patients to eat unhealthy foods.

Impact of the PNPLA3 I148M variant diagnosis. Of the patients who had the *PNPLA3* I148M variant (n = 10), 4 clearly remembered being told about their mutation, 2 knew that they had been tested for a mutation but did not fully understand what that mutation was or what it meant, and 4 did not remember or know if they had been tested for it. Patients who recalled being informed that they had the *PNPLA3* I148M variant reported having only short conversations with their clinicians and receiving a minimal explanation of what the genetic mutation meant for their disease or how they might change their behavior to best address the impact of the mutation on their disease.

> "*I just remember they said there was like two genetic markers that they were looking for and I showed one of the two and that meant that I was more prone to NASH than I would be without it. That's kind of all I really remember or took away from it*" (ID17).

The patients who were aware of the mutation reported a range of reactions to the diagnosis, including being relieved there was a reason for them having the disease, feeling nervous or having no concerns. Two patients reported that being informed they had the *PNPLA3* I148M variant helped them to understand why they had MASH and 1 patient mentioned it made them feel less responsible for having their condition.

> "*A little bit relieved that there was kind of a reason for me having liver disease and nobody else in my family has it*" (ID16).

> "*Well, it kind of makes me think that it's a little bit not my fault. I mean, there's a tendency to blame the patient. I think everyone absorbs that a little bit. I think it kind of takes some of that "it's something you did" off of you*" (ID16).

TABLE 3 Patients' and families' perceived impact of metabolic dysfunction–associated steatohepatitis

Reactions to diagnosis	Patient quotes
Patient responses	
Negative	"*When I found out, I was…well, kind of **devastated** because I didn't know…. The first thing the doctor said… because I asked him, 'How is this…' as he was describing it. The words is, 'How will I live long?'*" (D001-002) "*I just felt **depressed** because I felt… I've kind of done this to myself is how it felt. Like, I've made poor health choices. I haven't taken my health seriously.*" (N001-002) "*Yeah. I would say immediately post-surgery I was really pretty **anxious.***" (ID18)
Positive	"*It was **comforting** to know that I did have it and it was at that stage because I really didn't know.*" (D001-013)
Family responses	
Negative	"*Well, I told my mom, but she **wasn't that interested** either.*" (ID16) "*They know, but **I feel like they think it's not true** because they're still like, 'Come on, just eat a taco, come on with this and that.' And I'm like, 'I can't.' We had a gathering and **everybody brought stuff I can't eat.***" (M001-004)
Supportive	"*My husband reacted by, '**What do we need to do**?' He started cooking a lot **healthier***" (D001-013)

Postdiagnosis

How patients identified potential treatments. Most patients (n = 19, 68%) performed their own research (such as searching online resources) or used clinic-provided resources (including books and pamphlets from the clinician's office) to identify potential treatments. Twelve patients (43%) were part of support groups that exchanged information about potential treatment options. Approximately one-third of patients (n = 9, 32%) received information about potential treatments directly from their clinicians. Patients who received guidance from their clinicians tended to be more motivated in enacting changes.

Lifestyle changes discussed. Patients were advised to make lifestyle changes to prevent their MASH from worsening. Suggested changes included diet modifications, weight loss, exercise, and alcohol cessation.

> "*I just recall them saying NASH that it was non-alcoholic fatty liver disease, and to lose weight and exercise*" (N001-005).

> "*They told me to quit alcohol and not to eat anything too fatty*" (M001-001).

One patient was advised to have bariatric surgery to facilitate the weight loss that was needed to control their MASH. Some patients were less motivated to do this until the potential severity of their disease was explained to them.

> "*At first, I didn't really take things serious, but when I…by the time I got to the liver doctor and he explained, You have to change your diet. You have to exercise*" (D001-007)

Lifestyle changes implemented. Most patients attempted to implement the lifestyle modifications recommended by their clinicians or had identified methods using alternative resources themselves. The majority of patients made changes to their diet, including avoiding or eliminating sugars, processed foods, soft drinks, fried foods, and alcohol, as well as including more fruits, vegetables, and whole foods.

> "*I hadn't tried it but instead of frying and stuff, it was baking. Instead of pasta, it was vegetable*" (D001-005).

Patients who were referred to a dietician tended to be more likely to adopt long-term diet changes than patients who were not.

> "*They did send me to an endocrinologist who got me going on my medication. And then they also sent me to a dietician who helped educate me and sent me to a diabetic education class on carbs and that*" (D001-003).

Patients also took up exercise regimens to help them lose weight and be healthier.

> "*Once I got the diagnosis and I started dieting, I started actually spending 30 minutes to 2 hours doing exercises*" (ID17).

Symptoms and impacts reported after diagnosis

A summary of the symptoms and impacts spontaneously reported by all interviewed patients (N = 28) can be found in Supplemental Table S4, http://links.lww.com/HC9/A905. Overall, the symptoms and impacts were generally consistent between these patient cohorts. The most frequently mentioned symptoms among the total population were fatigue/low energy (71%), pain in the abdomen/liver area (68%), and nausea/vomiting (36%). These symptoms were also mentioned by patients who were Hispanic (88%, 38%, and 50%, respectively), and patients who were not known to have the *PNPLA3* I148M variant and were not Hispanic (90%, 80%, and 60%, respectively). Patients with the *PNPLA3* I148M variant reported fatigue/low energy (40%) and pain in the abdomen/liver (50%) but did not report experiencing nausea/vomiting. The most frequently reported impacts from the total population were fear of progression (46%), depression/sadness (39%), impact on family/friends (39%), and anger (29%). These were also among the most frequently reported impacts for patients with the *PNPLA3* I148M variant (40%, 20%, 20%, and 30%, respectively) or who were Hispanic (75%, 50%, 75%, and 38%, respectively). The most frequently reported impacts in patients who were not known to have the *PNPLA3* variant and were not Hispanic were cognitive problems (70%), depression/sadness (50%), and forgetfulness (40%). Hispanic patients reported an impact on family/friends (such as negatively affecting relationships due to patients being unable to engage with family and friends in the same way as they did before their diagnosis), ~2–4 times more frequently than the overall interviewed population patients with the *PNPLA3* I148M variant, and patients who were not Hispanic and did not have the *PNPLA3* I148M variant.

Unmet needs and proposed improvements to the patient journey

When asked about unmet needs, patients described improvements they wanted to see in the diagnosis and treatment process. A summary of patient responses is provided in Figure 2. Patients reported wanting to see improvements in how clinicians listen to and address patients' concerns at the diagnosis stage. These included patients reporting feeling that they were not taken seriously when mentioning signs and symptoms to their clinician, which would further delay diagnosis. Patients were also unsatisfied with the way clinicians communicated their diagnosis, such as providing too little information or providing information too quickly. Patients therefore suggested that there should be improvements in the amount and quality of information delivered about MASH because, overall, they received little information from clinicians and struggled to find information themselves or through support groups.

Patients reported wanting further information on the condition and how to manage it. Many patients felt their clinicians did not understand their condition and suggested that improved education on MASH could enable clinicians to be more aware of the signs/symptoms and stages of the disease, as well as the type of information they should be providing to patients. Patients also suggested that increasing the number and accessibility of support groups would be helpful; these could assist patients in searching for information about MASH, lifestyle changes, and treatment options. One patient suggested creating a group that included both clinicians and patients with MASH to ensure that both clinical and practical information could be gathered. The

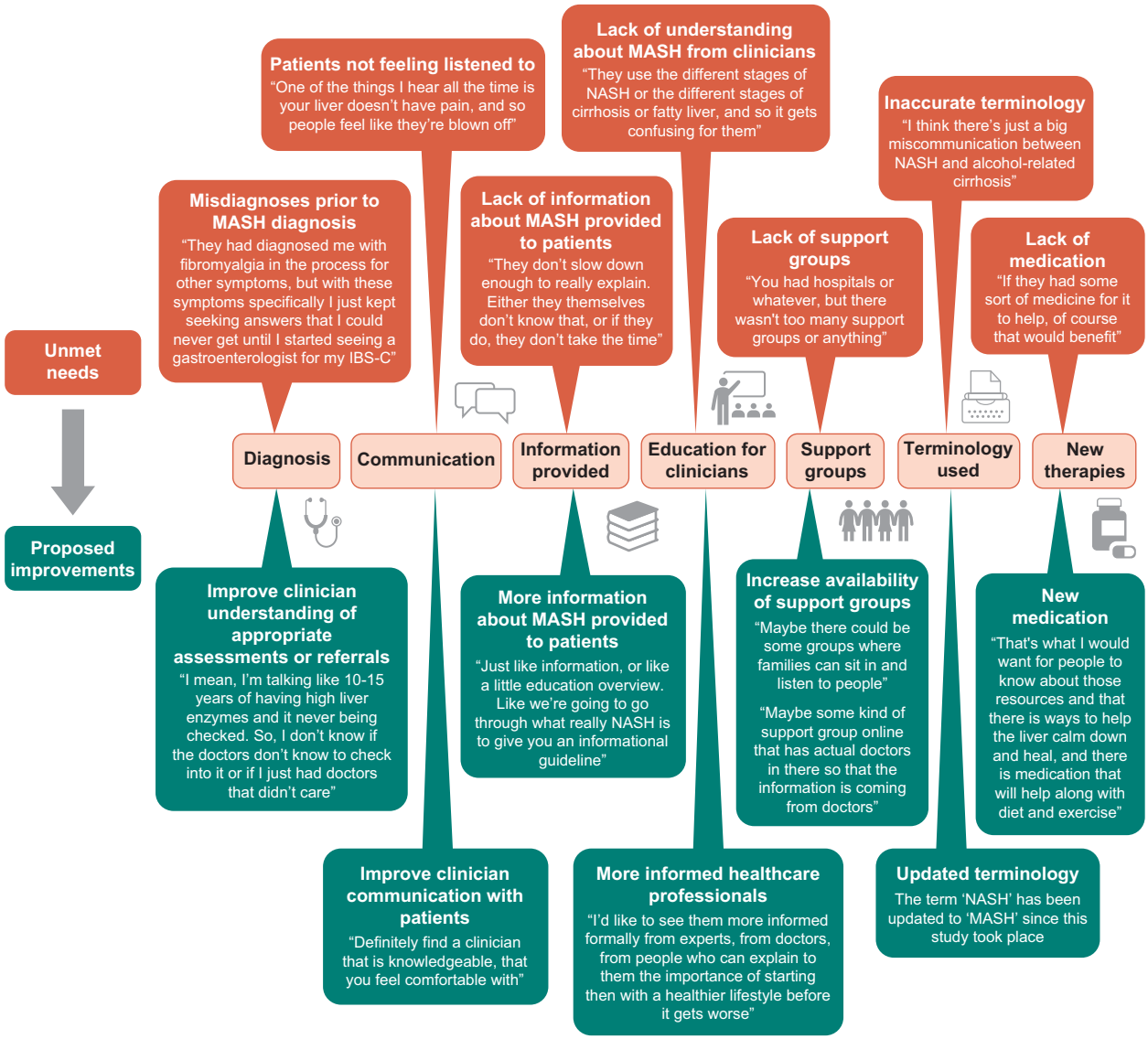

FIGURE 2 Unmet needs and proposed improvements to the patient journey. Abbreviations: IBS-C, irritable bowel syndrome with constipation; MASH, metabolic dysfunction–associated steatohepatitis; NASH, non-alcoholic steatohepatitis.

terminology used to diagnose the condition was also mentioned. Patients highlighted the presence of an incorrect perception of the term NASH being linked to alcohol consumption. Finally, patients expressed their need for proper medicines that could help them control the disease, beyond relying on actions such as diet, exercise, and weight loss.

DISCUSSION

Using in-depth interviews, this study provides a first look at the patient journey (prediagnosis, diagnosis, and postdiagnosis) for individuals with diagnosed MASH. This study also reports the unique perspectives of patients with MASH who have the *PNPLA3* I148M homozygous variant or who self-identified as Hispanic.

MASH can be asymptomatic or perceived as asymptomatic because of long periods of nonspecific symptoms.[19] The majority of patients in this study reported feeling that their symptoms were not taken seriously and received multiple misdiagnoses before their diagnosis of MASH. Others reported MASH as an incidental finding, that was progressed in nature but overlooked. These types of diagnostic delays highlight patients' concerns that they could have been diagnosed earlier, thus limiting potentially preventable disease progression.

At the time of diagnosis, clinicians were reported to provide varying levels of information and support about the condition and potential treatment options, including some clinicians not adequately and clearly explaining the physiology, consequences, and treatment options for MASH. Although clinicians may not be able to recall detailed information about conditions such as MASH, it would be beneficial for them to know how to access suitable resources to be able to correctly advise patients. For patients with the *PNPLA3* I148M variant, it could be beneficial for health care providers to spend more time explaining the impact of the genetic variant, to help patients fully understand their condition. It is also important for clinicians to remain aware of how they communicate with patients so that patients feel supported and are comfortable speaking honestly with them. Without effective communication, doctor-patient interactions could become strained and lead to poorer patient outcomes.[20] In addition, how a diagnosis is communicated to patients is a recognized major barrier for the effective disclosure of a diagnosis.[21] Consequently, refresher training on interpersonal skills for health care staff could be beneficial.

A large proportion of patients reported relying on online sources to understand their condition. A lack of patient-provider partnerships and discussions about online resources could lead to patients finding incorrect information through accessing inappropriate sites.[22,23] By using patient input, resources could be created that answer the types of questions patients typically have. Patients could also be provided with digital support programs to deliver guidance on areas such as the condition itself and therapy options. Many patients reported experiencing unsupportive reactions from family members and friends about their diagnosis of MASH, such as acting disinterested or providing food that the individual should not be eating. The stigma associated with the condition could limit the ability of patients to discuss their condition and so hinder opportunities to raise awareness about the condition. A lack of understanding and support from family members or social groups when receiving a diagnosis of a chronic condition could make it more challenging for patients to manage their condition[24,25] as well as negatively affect patient health-related quality of life.[26–28]

Several patients referred to the term NASH as being related to alcohol consumption, which caused misconceptions about their condition and how they developed it. This supports the recent change to the nomenclature used to discuss fatty liver disease—NASH was amended to MASH and NAFLD was amended to MASLD so that there is more focus on the disease etiology.[29] It was noted that, although widely used, the term "nonalcoholic" does not accurately capture the disease etiology. When interviewed, almost three-quarters of patients reported feeling that the terms NAFLD and NASH were sufficiently flawed to consider a name change, and 61% felt that including "non-alcoholic" in the terms was stigmatizing. Nomenclature that describes the underlying cause of the disease was preferred by 89% of respondents,[29] further reinforcing the importance of the patient experience on the fatty liver disease journey.

In the absence of a regulatory agency–approved drug therapy, all individuals with MASLD or MASH are advised to make lifestyle modifications by implementing dietary changes and increasing physical activity following their diagnosis.[30,31] However, despite this advice, most patients with MASLD are unsuccessful in their attempts to sustain healthy lifestyles.[32] While rates of real-world referral to lifestyle intervention professionals are low,[33] when this is enacted, individuals are more likely to maintain a healthy weight. In this study, patients who were provided with lifestyle intervention support, such as referral to a dietician, made greater improvements and achieved a healthier lifestyle. Clinicians not informing patients of the importance of lifestyle changes, and a lack of social support can also inhibit the motivation of patients to make changes.[34,35] This suggests that further work is required to understand the best ways to support patients in implementing lifestyle changes.[24]

Patients reported a range of emotional responses to *PNPLA3* genetic testing, including relief, reduced shame regarding their diagnosis, and feeling nervous. Understanding patients' reactions can help the development of appropriate support for patients following their diagnosis.

Genetic testing in the clinic is presently not standardized nor routinely recommended by the currently published guidelines.[1,36] The limited awareness and understanding that patients reported about their *PNPLA3* I148M mutation may be a consequence of the lack of genetic testing used for patients with MASH, as well as limited patient resource information available. *PNPLA3* I148M has been well-established with an increased risk of disease progression[37–39] and severity,[40,41] so awareness of the genetic element of MASH may allow patients to make more informed decisions about managing their health care and limit disease progression. Using patient responses as a basis, an algorithm could be developed to help screen the relatives of patients who are found to carry the *PNPLA3* I148M variant. Such an algorithm could identify individuals who have first-degree relatives with MASH, are Hispanic, have a family history of cirrhosis from MASH, or have HCC and progression of MASH despite achieving lifestyle intervention recommendations and/or drug therapy.

Most of the symptoms and impacts reported by patients were similar between those who were *PNPLA3* I148M-positive or Hispanic, and the general population of patients who had diagnosed MASH. The most frequently reported impact, "fear of progression" has not previously been reported for patients with MASH and so reinforces the value of talking with patients. Symptoms such as fatigue/low energy were reported most frequently in Hispanic patients, while no patients with the *PNPLA3* I148M mutation reported nausea/vomiting. In addition, three-quarters of Hispanic patients reported "fear of progression" and "impact on family/friends," whereas less than half of all other interviewed patients reported these impacts. These variations suggest additional data regarding symptoms reported depending on patient genetics or ethnicity is warranted. Differences identified between the overall population of patients interviewed and those who were Hispanic or had the *PNPLA3* I148M mutation also suggest that support may need to be adapted to account for cultural (eg, culturally adapted interventions, support programs, and resources) or genetic differences between patients (eg, genetic education materials). Consequently, understanding variations in the patient experience could help to improve both diagnosis and the support provided.

Although the number of patients interviewed with the *PNPLA3* I148M mutation and of Hispanic ethnicity was small, key insights into their unique and shared experiences are important for providers and patient advocacy groups. While statistical analyses are not suitable for this study, such potential differences between populations could be considered in future analyses of larger cohorts. Understanding variations and similarities in patient experiences among different ethnic groups and genetic backgrounds is important to improve experience and tailor support for patients diagnosed with MASH.

Limitations

Most recruited patients were female; although this skews the demographics of the patients who were interviewed, it is consistent with a recent demographic analysis of the MASH patient population.[42] Representation of the study is limited demographically due to all patients being from the United States. All patients enrolled in this study with the *PNPLA3* I148M risk allele were White-non-Hispanic, yet the risk allele is more common in Hispanic and Asian populations; this could have affected the types of symptoms and impacts reported by patients.[42] Symptoms and impacts were not systematically assessed because this study focused on the patient journey and because such analyses were previously published in a study by Swain et al.[17] The lack of definitions for quantifying patient levels of activity meant that patient interpretations of interview questions varied—some patients thought the question was related to their level of physical activity, whereas others thought it was about how busy their lives were from a social and work perspective. Given that this was a qualitative study, statistical analyses were not performed; however, multiple subgroups were included, which meant that sufficient information could be gathered to assist in making the findings more generalizable to the broader population of patients with MASH.

CONCLUSIONS

This study has furthered the understanding of the patient journey for individuals with diagnosed MASH in the United States. The symptoms and impacts for patients with the *PNPLA3* I148M mutation or who are Hispanic were also evaluated to better understand their unique experiences. Using patient input, potential modifications to manage unique patient experiences have been identified that could improve the patient journey from prediagnosis to postdiagnosis.

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CONFLICTS OF INTEREST

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