Keeping score against MASH: NIS4™, a blood-based score that helps identify patients for treatment for progressive MASH

Metabolic dysfunction-associated steatotic liver disease (MASLD; formerly referred to as nonalcoholic fatty liver disease or NAFLD)[1] is defined by the accumulation of lipids in hepatocytes in the absence of significant alcohol intake, viral infection or other etiologies of fatty liver disease.[2-4] Within MASLD there is a spectrum of histopathologic features that includes hepatic steatosis or fatty liver, steatosis accompanied by liver inflammation and liver cell injury (ballooning), which is referred to as metabolic dysfunction-associated steatohepatitis (MASH, formerly referred to as nonalcoholic steatohepatitis or NASH), liver fibrosis and MASH-related cirrhosis.[2-4]

MASLD is one of the most common causes of chronic liver disease in developed countries, largely due to the increased prevalence of comorbidities such as obesity and type 2 diabetes.[3,4] A percentage of patients with MASH and liver fibrosis will eventually progress to cirrhosis or hepatocellular carcinoma.[2-4] In fact, MASH is expected to become the number one cause for liver transplantation in the United States in the next few years, making it critical to identify high-risk patients earlier in disease progression.[2,3]

Currently, the most reliable way to diagnose both MASH and liver fibrosis is with a liver biopsy, which has limitations including patient discomfort as well as risk for bleeding.[4] Therefore, there is a need for a blood-based diagnostic test for identifying patients with progressive MASH who are at increased risk of developing end-stage liver disease so they can be treated early and prevent disease progression.

NASHnext™ [504960] or NIS4™ is a blood test that identifies patients with MASH and liver fibrosis. The NIS4 test, developed by GENFIT™ and available from Labcorp, produces a score that ranges from 0.00 to 1.00 and is calculated by combining results of four assays that contribute to the test's predictive performance[5]:

NIS4 score = e$^{\gamma}$/(1+e$^{\gamma}$)
Where γ = β0 + β1*(miR-34a-5p log [copies/µL]) + β2*(A2M [g/L]) + β3*(YKL40 [ng/mL]) + β4*(HbA1c [%])

1. miR-34a-5p — Contributes to hepatocyte apoptosis, fibrosis, and lipid metabolism[5-7]
2. A2M (α2-macroglobulin) — Promotes liver fibrosis in inflammatory/injured liver[5,8]
3. YKL40 (Chitinase-3-Like 1; CHI3L1) — Marker of liver fibrosis[6,9]
4. HbA1c — Marker altered glycemia; associated with inflammation and liver fibrosis in MASH[5,10]

Most of the available tests for liver fibrosis or MASH, such as the FIB-4[11] and the Enhanced Liver Fibrosis (ELF™),[12] are able to identify patients with advanced liver fibrosis.[13] The NASH FibroSure test produces three separate results, identifying 1) liver steatosis, 2) MASH and 3) fibrosis.[13-16] NIS4 is the only widely available test that produces a single score for identifying patients with both MASH and liver fibrosis, also known as at-risk MASH, which is defined as having a NAFLD Activity Score (NAS) ≥4 and significant liver fibrosis (F≥2).[5] Patients with at-risk MASH are at higher risk of disease progression, which prompted the Food and Drug Administration to promote at-risk MASH as a focus of drug development, given the risk of progression to more severe liver disease.[17]

NIS4 showed robust diagnostic performance with areas under the curve (AUROCs) of 0.80 in a pooled cohort of subjects with multiple metabolic disease risk factors.[5] The data revealed that NIS4, unlike the other diagnostic tests in the study, was not impacted by age, sex, body, mass index (BMI), aminotransferase levels (ALT or AST) or metabolic comorbidities (type 2 diabetes or obesity).[5] Patients with NIS4 <0.36 were classified as not having at-risk MASH (ruled out) with 82% sensitivity, 63% specificity and a NPV of 78%,

Benefits of NASHnext (NIS4™)

- There is an urgent need for a diagnostic test for identifying patients with MASH so they can be treated and prevent disease progression.
- Validation shows that NIS4 scoring can identify patients with MASH and liver fibrosis across clinically-relevant subpopulations.
- Published data has shown that NIS4 outperforms other blood tests for the identification of at-risk MASH who are at higher risk of disease progression.

while those with a NIS4 >0.63 were classified as having at-risk MASH (ruled in) with 87% specificity, 51% sensitivity and a PPV of 79%. NIS4 significantly outperformed other non-invasive tests in the identification of at-risk MASH, including ELF (AUROC=0·77) and FIB-4 (AUROC=0·70).[5] Importantly, NIS4 was also shown in an independent study called the Non-Invasive BioMarkers of MetaBolic Liver DiseasE (NIMBLE) study to have an AUROC of 0.82 for the diagnosis of at-risk MASH.[18]

Intended use

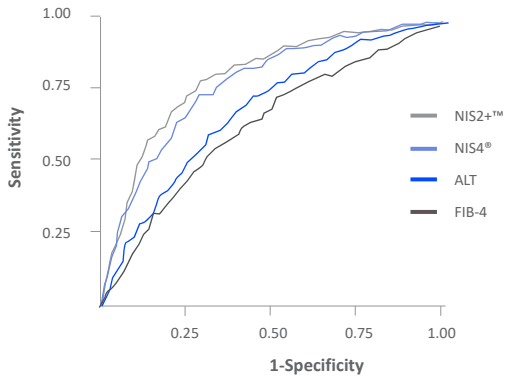
NASHnext™ [504960], or NIS4, is a blood-based diagnostic test that quantitatively measures four independent biomarkers to produce a score that identifies, among patients with metabolic factors, those with at-risk MASH, who are at higher risk of disease progression.[5]

Clinical decision points[5]

1. <0.36 lower likelihood for at-risk MASH or advanced fibrosis
2. 0.36-0.63 moderate likelihood for at-risk MASH or advanced fibrosis
3. >0.63 higher likelihood for at-risk MASH or advanced fibrosis

In 2023, an optimized version of the NIS4 test was released, called NIS2+™. NIS2+ was developed to eliminate the use of HbA1c levels and A2M and lower the volume of serum required for the test.[19]

NIS2+ optimizes the technology of NIS4 by removing 2 biomarkers, allowing for robust detection of at-risk MASH irrespective of patient characteristics



Model	AUROC (95%CI)	*P* value
NIS2+	0.813 (0.795, 0.832)	N/A
NIS4	0.792 (0.772, 0.811)	0.0002
FIB-4	0.653 (0.629-0.676)	<0.0001
ALT	0.699 (0.677, 0.721)	<0.0001

NIS2+ demonstrated superiority for identifying at-risk MASH in patients ≥65 years of age (a particularly vulnerable group) compared to NIS4, FIB-4, NFS, ELF and ALT

As shown above, in using just two of the NIS4 biomarkers (miR-34a-5p and YKL-40), NIS2+ was found to have better performance than NIS4,[19] making it the best blood-based test for the future of identifying patients for the treatment of at-risk MASH.

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