Keeping score against NASH: How biomarker assays can help identify patients with non-alcoholic steatohepatitis

The Benefits of NASHnext (NIS4™)

- There is an urgent need for a non-invasive diagnostic test for identifying patients with NASH to prevent disease progression.

- Biomarkers that make up NIS4™ scoring have been shown to be associated with NASH.

- Validation shows that NIS4 scoring can identify patients with NASH and liver fibrosis across clinically-relevant subpopulations.

- Published data has shown NIS4 to outperformed other non-invasive tests in the identification of at-risk NASH.

Nonalcoholic fatty liver disease (NAFLD) 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.[1-3] Within NAFLD 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 nonalcoholic steatohepatitis (NASH), liver fibrosis and NASH-related cirrhosis.[1-3] NAFLD is one of the most common causes of chronic liver disease in developed countries , and the most common cause in North America,[4] largely due to the increased prevalence of comorbidities such as obesity and type 2 diabetes.[2,3] A percentage of patients with NASH and liver fibrosis will eventually progress to cirrhosis and/or hepatocellular carcinoma.[1-3] In fact, NASH 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.[1,2] Currently, the most reliable way to definitively diagnose both NASH and liver fibrosis is with a liver biopsy, which has limitations including patient discomfort as well as risk for bleeding.[3] Therefore, there is an urgent need for a non-invasive diagnostic test for identifying patients with NASH who are at increased risk of developing end-stage liver disease so they can be treated early and aggressively in order to prevent disease progression.

NASHnext™ [504960] is a non-invasive blood test that identifies patients with NASH and liver fibrosis. NASHnext [504960] utilizes NIS4 technology, developed by GENFIT™, to produce a scoring range from 0.00 to 1.00, calculated by combining the results of four individual assays, all of which contribute to the test's predictive performance, in the following equation[5]:

$$NIS4_{score} = e^{y}/(1+e^{y})$$

Where $y = \beta_0 + \beta_1*(miR\text{-}34a\text{-}5p \log [copies/\mu L]) + \beta_2*(A2M [g/L]) + \beta_3*(YKL40 [ng/mL]) + \beta_4*(HbA_{1c} [\%])$

1. miR-34a-5p — Associated with repression/deactivation of SIRT1, AMPK, HNFα, and PPARα, which may contribute to hepatocyte apoptosis, fibrosis, and lipid metabolism[5-7]

2. A2M (α2-macroglobulin) — Promotes liver fibrosis through inhibition of matrix protein catabolism in inflammatory/injured liver[5,8]

3. YKL40 (Chitinase-3-Like 1; CHI3L1) — Associated with activated macrophages; an established biomarker of liver fibrosis[5,9]

4. HbA$_{1c}$ — Established marker of altered glucose homeostasis; associated with inflammation and liver fibrosis in NASH[5,10]

Most of the available tests for NASH to date such as the AST-to-Platelet Ratio Index (APRI),[10] Fibrosis-4 (FIB-4)[12] and the Enhanced Liver Fibrosis (ELF™)[13] are able to identify a majority of patients with advanced liver fibrosis.[14] The NASH FibroSure test produces three separate results for identifying 1) steatosis, 2) NASH and 3) fibrosis.[14-17] NASHnext, however, is currently the only widely available test that produces a single score for identifying patients with both NASH and liver fibrosis.[5] NASHnext™ was developed to identify patients with "at-risk" NASH, which is defined as having a NAFLD Activity Score (NAS) ≥4 and significant liver fibrosis (F≥2) who are at higher risk of disease progression. The FDA has identified patients with at-risk NASH as a focus of drug development given the risk of progression to more severe liver disease.[4]

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NIS4 was developed using stepwise regression and clinical data from the GOLDEN-505 NASH trial as the training or discovery set. To validate its diagnostic performance, NIS4 was tested in a pooled dataset comprised of three independent patient cohorts. These patients were selected using similar criteria to that of the future intended use population, those with metabolic risk factors for NAFLD including type 2 diabetes, prediabetes, obesity, dyslipidemia, and arterial hypertension.[5] The performance of NIS4 was shown to be better than many of the tests that are currently available for identifying patients with NASH and/or liver fibrosis in this pooled cohort.[5] Besides showing strong performance with areas under the curve (AUROCs) of 0.80, NIS4 showed robust diagnostic performance across multiple clinically relevant subpopulations in the pooled cohort.[5] The data revealed that NIS4 can identify patients with NASH and liver fibrosis in clinically relevant subpopulations and, unlike each of the other diagnostic tests, was not impacted by age, sex, body mass index (BMI), aminotransferase levels (ALT or AST), or metabolic comorbidities (type 2 diabetes or obesity).[5] In the combined cohort, patients with NIS4 <0.36 were classified as not having at-risk NASH (ruled out) with 82% sensitivity, 63% specificity and a NPV of 78%, while those with a NIS4 >0.63 were classified as having at-risk NASH (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 NASH, including ELF (AUROC=0·77) and FIB-4 (AUROC=0·70).[5]

Intended use

NASHnext™ [504960] 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 NASH, who are at higher risk of disease progression.[5]

Clinical decision points[5]

1. <0.36 Lower likelihood for at-risk NASH or advanced fibrosis

2. 0.36-0.63 Moderate likelihood for at-risk NASH or advanced fibrosis

3. >0.63 Higher likelihood for at-risk NASH or advanced fibrosis

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