ASSESSMENT OF NIS4 CLINICAL UTILITY FOR IDENTIFICATION OF PATIENTS WITH ACTIVE NASH (NAS≥4) AND SIGNIFICANT FIBROSIS (F≥2) IN PATIENTS AT RISK OF NASH

SAT-299

Remy Hanf[1], Pierre Chaumat[1], Zouher Majd[1], Geneviève Cordonnier[1], John Brozek[1], Emilie Praca[1], Fouad Ben Sudrik[1], Prof. Pierre Bedossa[2], Prof. Quentin M. Anstee[3], Prof. Sven Francque[4], Prof. Stephen A. Harrison[5], Prof. Vlad Ratziu[6], Sophie Mégnien[7], Alice Roudot[1], Suneil Hosmane[7], Dean W. Hum[1], Arun J. Sanyal[8]

[1]GENFIT SA, Loos, France; [2]Hôpital Beaujon, Department of Pathology, Paris, France; [3]Faculty of Medical Sciences, Newcastle University, Newcastle, United Kingdom; [4]Antwerp University, Antwerp, Belgium; [5]Pinnacle Clinical Research Center, San Antonio, United States; [6]Pitié-Salpêtrière Hospital, Paris, France; [7]GENFIT CORP, Cambridge, MA, United States; [8]Virginia Commonwealth University, Richmond, United States

BACKGROUND

NASH is dramatically under-diagnosed largely because a liver biopsy is required for diagnosis. Given the global burden of NASH, new non-invasive tools are needed to identify millions of patients at higher risk of developing liver related outcomes. We recently described a new non-invasive score, NIS4 for detection of patients with active NASH and significant fibrosis (NAS≥4 and F≥2) who should be considered for therapeutic intervention.

AIM

The aim of this study was to assess the clinical utility of NIS4 by determining clinically useful cut-offs for NIS4 to efficiently rule-out patients with no or mild disease or rule-in patients with active NASH and significant fibrosis (NAS≥4 with F≥2).

METHODS

- The «merged» cohort comprised 714 patients prospectively screened for inclusion in two interventional trials (GOLDEN-505 and RESOLVE-IT).
  - Blood samples and liver biopsy were collected during the screening periods.
  - Centralized reading of liver biopsy according to NASH-systems: NAFLD activity score (NAS) and Fibrosis stage (F)
- Receiver Operating Curve (ROC) for identification of active NASH (NAS≥4) and significant fibrosis (F≥2) were used to define and calculate:
  - AUROC with 95% CI
  - Optimal cut-off
  - Low cut-off set at 85% sensitivity
  - High cut-off set at 85% specificity
  - Diagnostic metrics at each cutoff with 95% CI: sensitivity, specificity, negative and positive predictive values (NPV and PPV)
- Head to head comparison of NIS4 performance with other non-invasive scores (FIB4, NFS, ELF, BARD, APRI, FibroTest or FLI) to detect patients with active NASH and significant fibrosis was performed (De Long test).
- Clinical utility of NIS4 in the «merged» cohort was assessed by calculating:
  - Percentage of ruled out patients (NIS4 below the low cut-off) and histological characteristics.
  - Percentage of ruled in patients (NIS4 above the high cut-off) and histological characteristics.
  - Percentage of patients in the "grey zone", i.e. indeterminate risk.

COHORT CHARACTERISTICS

MERGED Cohort	All	NAS<4-F<2	NAS≥4-F≥2	*P-value*
DEMOGRAPHY				
n	714	350	364	
Male (%)	48.32	47.71	48.90	*0,7514*
Age (y)	**53.85 ± 11.69**	**51.57 ± 11.57**	**56.07 ± 11.36**	***<0.0001***
BMI (kg/m2)	33.14 ± 5.77	32.81 ± 5.91	33.47 ± 5.62	*0.0648*
T2D (%)	**38.51**	**30.29**	**46.43**	***<0.0001***
Dyslipididemia (%)	**50.14**	**46.29**	**53.85**	***0,0258***
Hypertension (%)	**57.42**	**50.29**	**64.29**	***0.0001***
BIOCHEMISTRY				
Glucose (mmol/l)	**6.05 ± 1.76**	**5.72 ± 1.46**	**6.36 ± 1.96**	***<0.0001***
HbA1c (%)	**6.13 ± 0.94**	**5.90 ± 0.82**	**6.36 ± 0.99**	***<0.0001***
TG (mmol/l)	1.94 ± 1.12	1.95 ± 1.23	1.94 ± 1.01	*0.4588*
TC (mmol/l)	**4.92 ± 1.21**	**5.01 ± 1.27**	**4.85 ± 1.14**	***0.0423***
HDL (mmol/l)	1.25 ± 0.35	1.27 ± 0.34	1.24 ± 0.36	*0.1245*
LDL (mmol/l)	**2.79 ± 0.99**	**2.89 ± 1.00**	**2.73 ± 0.97**	***0.03540***
LIVER FUNCTION TESTS				
ALT (IU/l)	**63.88 ± 42.99**	**53.27 ± 34.48**	**74.08 ± 47.69**	***<0.0001***
AST (IU/l)	**44.91 ± 28.81**	**34.59 ± 20.04**	**54.82 ± 32.30**	***<0.0001***
GGT (IU/l)	**75.99 ± 84.03**	**65.14 ± 73.72**	**84.47 ± 91.98**	***0.001***
ALP (IU/l)	**80.73 ± 28.76**	**78.79 ± 26.82**	**82.61 ± 30.43**	***0.0378***
HISTOLOGY				
NAS≥4/F≥2 (%)	50.98			
Mean F-stage	**1.72 ± 1.04**	**0.89 ± 0.74**	**2.51 ± 0.53**	***<0.0001***
Mean NAS	**4.80 ± 1.55**	**3.96 ± 1.56**	**5.61 ± 1.02**	***<0.0001***

Table 1: Characteristics of the «merged» Cohort.
Results are expressed as Mean±SD, p-values for differences between groups were determined by Pearson's Chi Squared and Wilcoxon tests for categorical and continuous data, respectively.

- Almost all patients of the «merged» cohort have risk factors for NASH: overweight/obesity, Type 2 diabetes, hypertension, dyslipidemia, metabolic syndrome and/or elevated liver function tests (ALT≥30 IU/L or AST≥35 IU/L or GGT≥35 IU/L).
- The «merged» cohort covers the complete histological spectrum of NAFLD: NAS from 0 to 8 and fibrosis stage from 0 to 4.

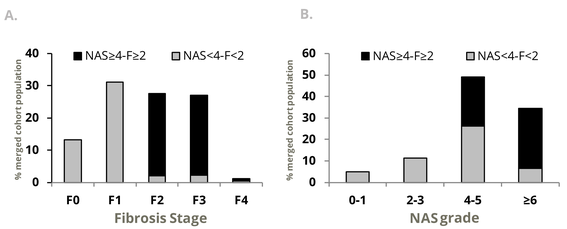


Figure 1: Patient distribution according to fibrosis stage (A) or NAS grade (B) in the «merged» cohort (N=714)

- The vast majority of patients with F≥2 have active disease (NAS≥4).
- The proportion of patients with significant fibrosis increases with NAS.

The «merged» cohort is representative of the target population at risk of NASH who should be tested for identification of patients with active disease (NAS≥4) and significant fibrosis (F≥2) who should be considered for intervention.

NIS4 CUTOFFS AND DIAGNOSTIC PERFORMANCES

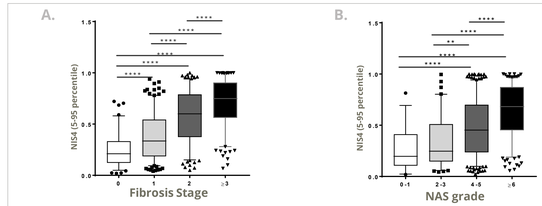


Figure 2: NIS4 score according to fibrosis stage (A) or NAS grade (B) in the «merged» cohort (N=714).
One-way ANOVA with post hoc Tukey test : **p<0.01. ****p<0.0001

- NIS4 value is an accurate reflection of histological lesions in the liver.

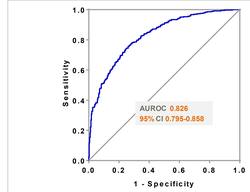


Figure 3: NIS4 ROC to detect NAS≥4 and F≥2 patients (N=714)

	NIS4		
AUROC [95% CI]	0.827 [0.795-0.857]		
cutoffs	Low (85% sens.) 0.3642	Optimal 0.5014	High (85% spe) 0.6137
Accuracy [95% CI]		74.6%	
Sensitivity [95% CI]	85% [81.1 - 88.6]	74% [69.1 -78.3]	**60%** [55.2 - 65.5]
Specificity [95% CI]	**60%** [54.9 -65.5]	75% [70.6 - 79.9]	85% [80.9 - 88.7]
NPV	**79.5%**	73.5%	67.2%
PPV	69.5%	76.0%	**81.2%**

Table 2: NIS4 diagnostic performance for the detection of patients with NAS≥4 and F≥2
(at 85% sens., optimum cutoff and 85% spec.)

- Below the low cutoff of 0.3642, 60% of all patients without the target condition are identified with good accuracy (NPV=80%).
- Above the high cutoff of 0.6137, 60% of all patients with the target condition are identified with good accuracy (PPV=81%).

HEAD TO HEAD COMPARISON OF NIS4 AND PREVIOUSLY DESCRIBED SCORES

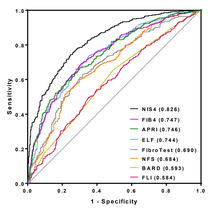


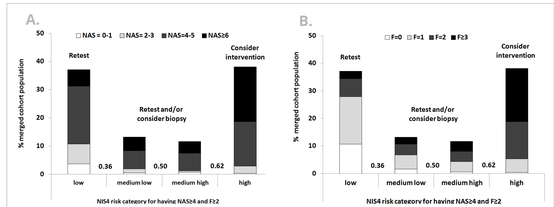
Figure 4: Comparison of ROCs

Comparison score	Number of patients with score value and NIS4 value	Number of patients with the condition	Score AUROC [95% CI]	NIS4 AUROC [95% CI]	*P value*
Target condition = NAS≥4 and F≥2					
NIS4	714	364	0.826 [0.798; 0.855]	-	-
FIB4	710	364	0.747 [0.711 ; 0.783]	0.827 [0.799; 0.858]	<0.0001
NFS	702	358	0.684 [0.642 ; 0.722]	0.826 [0.798; 0.854]	<0.0001
ELF	709	362	0.744 [0.708 ; 0.778]	0.825 [0.795; 0.853]	<0.0001
BARD	714	364	0.593 [0.552; 0.635]	0.826 [0.798; 0.855]	<0.0001
APRI	710	364	0.750 [0.709 ; 0.784]	0.827 [0.795; 0.855]	<0.0001
FibroTest	708	361	0.690 [0.644 ; 0.724]	0.825 [0.794; 0.855]	<0.0001
FLI	711	362	0.684 [0.543 ; 0.621]	0.826 [0.796; 0.855]	<0.0001

Table 3: Comparison of tests performance

- NIS4 significantly (P<0.001, De Long test) outperforms existing scores to identify patients with NAS≥4 and F≥2.
- NIS4 favorably compares with the other scores for detection of patients with advanced fibrosis (F≥3): AUROC=0.79 vs AUROC=0.767 for ELF (data not shown).

NIS4 CLINICAL UTILITY



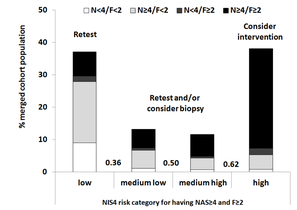


Figure 5: NASH histological distribution across NIS4-defined risk categories in the «merged» cohort. A: F-stage, B: NASH activity C: histological category

- A low cutoff of 0.3642 classifies 37% (264/710) of the total cohort as "low risk" of active NASH (NAS≥4) and significant fibrosis (F≥2).
  - **These patients should be retested because of persistent risk of disease evolution.**
- A high cutoff of 0.6173 classifies 38% (271/710) of the total cohort at "high risk" of active NASH (NAS≥4) and significant fibrosis (F≥2).
  - **These patients should be considered for intervention because of risk of cirrhosis.**
- 25% of the patients are in the "grey zone" (i.e. between low and high cutoffs).
  - **These patients should be either retested or considered for confirmatory liver biopsy and/or other tests and/or imaging techniques.**

CONCLUSIONS

- **This study strengthens use of NIS4 as a new clinical tool for the detection of active NASH and significant fibrosis (NAS≥4 with F≥2) in a population of patients presenting with risks of NASH.**
- **It supports clinical utility of using NIS4 to non invasively eliminate patients at low probability of having active NASH and significant fibrosis and to accurately identify those at high probability of progressive disease who should be considered for therapeutic intervention.**
- **Direct comparison showed that NIS4 significantly outperformed existing scores for the discrimination of patients with NAS≥4 and F≥2 in the «merged» cohort.**
- **Overall, 75% of the target population will be accurately classified as low- or high-risk of having active NASH and significant fibrosis.**

Corresponding author's email: remy.hanf@genfit.com - **EASL-ILC 2019**

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Remy Hanf
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