PRIMARY RESULTS OF THE NIMBLE STAGE 1-NASH CRN STUDY OF CIRCULATING BIOMARKERS FOR NONALCOHOLIC STEATOHEPATITIS AND ITS ACTIVITY AND FIBROSIS STAGE

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Background: There are scientific gaps in the literature on non-invasive tests (NITs) for NAFLD impeding their regulatory evaluation as diagnostic tests. The NIMBLE consortium of the FNIH was established to generate the evidence needed to fill these knowledge gaps.

Aim: The current study represents a collaboration between NIMBLE and the NIH/NIDDK NASH CRN to establish the comparative performance of 5 blood-based biomarker panels for NAFLD using AUROCs and sensitivity/specificity at Youden's cutoff for their intended diagnostic use in a multi-center US cohort with NAFLD/NASH.

Methods: Selected biomarker panels were tested in aliquots of the same blood sample from each participant obtained within 90 days of a liver biopsy demonstrating NAFLD. Their performance was tested for their prespecified intended use (in parentheses):

(1) NIS4TM: (NASH diagnosis, high NAFLD activity score (NAS)≥ 4, Fibrosis stage- ≥ 2, ≥ 3 or 4),
(2) OWLiver: (NASH diagnosis, high NAS),
(3-5) Enhanced liver fibrosis (ELF), PROC3 and Fibrometer-VCTE (FM-VCTE): (fibrosis).

The cohort was selected a priori to avoid fibrosis severity spectrum bias. The primary compound statistical hypothesis for the intended use of each of the NITs required: (i) an AUROC estimate numerically > 0.70 and (ii) a lower 95% AUROC confidence limit of at least 0.50. The secondary statistical hypotheses required: (i) the AUROCs of NITs for NASH diagnosis and high NAS were significantly higher ($p < 0.05$) for each intended use. The sample sizes provided a power of 0.8 or higher for AUROC testing. For OWLiver, categorical results were provided; thus, only sensitivity/specificity was reported. Rigorous protocols ensured data-integrity.

Results: 1073 patients with NAFL (n=220) or NASH (n=853) with fibrosis stages 0 (n=222), 1 (n=114), 2 (n=262), 3 (n=277) and 4 (n=198) were studied. The AUROCs, Youden's cutoff with its sensitivity/specificity are tabulated below. NIS4 met criteria for NASH diagnosis and NAS ≥ 4. NIS4, ELF and FM-VCTE all met both criteria for success for diagnosis of fibrosis stage ≥ 2. The performance of ELF and FM-VCTE further improved for fibrosis stage ≥3 and stage 4.

Conclusion: These data establish the sensitivity and specificity of the NITs studied and will inform stage 2 studies in varying intended use populations, alone and in combination, to support regulatory qualification.

AUROC (Youden cutoff) [sensitivity, specificity]							
	FIB4	**ALT**	**NIS4**	**OWLiver**	**ELF**	**PROC3**	**FM-VCTE**
NASH diagnosis	N/A	0.678 (40) [63.2, 64.8]	0.83** (0.4) [77.7, 76.2]	N/A [77.3, 66.8]	N/A	N/A	N/A
NAS ≥ 4	N/A	0.726 (42) [71.1, 64.1]	0.815** (0.6) [78.1, 73.6]	N/A [97.2, 9.1]	N/A	N/A	N/A
F stage ≥ 2	0.796 (1.4) [65.4, 80.8]	N/A	0.874** (0.4) [82.3, 79.9]	N/A	0.828* (9.5) [71.8, 81.5]	0.809 (17.6) [69.8, 81]	0.841** (0.5) [66.7, 86.4]
F stage ≥ 3	0.793 (1.4) [75.1, 68.6]	N/A	0.788 (0.6) [72.9, 74.8]	N/A	0.835** (9.6) [80.8, 70.2]	0.764 (18.8) [71.4, 71.4]	0.858** (0.6) [76.2, 81.3]
F stage 4	0.81 (1.5) [85, 63.4]	N/A	0.725 (0.6) [78.1, 61.4]	N/A	0.855** (10.1) [82.1, 73.3]	0.728 (21.1) [66.2, 68.5]	0.897** (0.6) [94.2, 70.4]

*p < 0.05 for comparison with either ALT or FIB4 for their intended use
**p < 0.001 for comparison with either ALT or FIB4 for their intended use
All AUROCs are significantly superior to AUROC = 0.5 (p < 0.001)

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