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Biomarker screening strategies to identify at-risk NASH cases for clinical trial recruitment in NAFLD



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1 Introduction

“At-risk NASH”, identified as NAS ≥ 4 with ≥ 1 point in each component plus fibrosis $\geq F2$, is widely adopted recruitment target for NAFLD clinical trials. The ability to accurately pre-select cases for biopsy using non-invasive tests (NITs) could increase the efficiency of recruitment and accelerate drug development.^(1,2)

2 Aim

The LITMUS consortium evaluated blood-based NITs as tools to reduce histological screen failure rates in future trials.

3 Method

- Following a survey among clinicians and leading drug developers, we found that a screen failure rate of 37% would be acceptable for efficient trial enrolment.
- For 10 NITs, we then identified thresholds that yield the corresponding screen failure rate and selected the threshold with the highest sensitivity.

5 Conclusions

Non-invasive pre-screening strategies could lead to substantial efficiency gains in recruitment of trials targeting at-risk NASH, reducing the number of patients biopsied to identify one eligible participant.

Given the high screen failure rate in current trials, such preselection could facilitate trial recruitment and accelerate drug development.

These results also have implications to guide risk stratification in routine clinical practice.

6 Acknowledgements

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7 References

1 **Rinella ME et al.** Report on the AASLD/EASL joint workshop on clinical trial endpoints in NAFLD. *Journal of hepatology*. 2019; 71(4):823-33.

2 **Ratziu V et al.** REGENERATE: Design of a pivotal, randomised, phase 3 study evaluating the safety and efficacy of obeticholic acid in patients with fibrosis due to nonalcoholic steatohepatitis. *Contemporary Clinical Trials*. 2019; 84:105803.

4 Results

- Data from 720 participants from nine centers were included.
- Several NITs such as MACK-3, CK-18 M30, FIB-4 or the SomaScan proteomic algorithm could substantially reduce histological screen failure rates when biopsy was reserved for only biomarker positive patients.
- Table 1 shows the biomarker thresholds that achieved a screen failure rate $<37\%$ when biopsy is selectively performed in participants with a positive biomarker result, as well as the number of eligible patients found among those undergoing liver biopsy.

Table 1: NIT to increase the efficiency in identifying patients with at-risk NASH for trial recruitment

Biomarker	N	Threshold	Number of patients undergoing biopsy (per 100)	Screen failure rate	Number of eligible patients found (per 100)	Number needed to test
No screening	720	-	100	59%	41	-
MACK-3	400	0.36	39	36%	25	4
SomaScan	267	9.30	40	38%	25	4
CK-18 M30	593	365.50	32	34%	21	5
FIB-4	720	1.42	32	38%	20	5
Diafir-Model S	288	3.00	27	33%	18	6
PRO-C3	444	20.60	25	36%	16	6
CK-18 M65	612	553.35	24	38%	15	7
ELF	695	10.04	22	36%	14	7
NFS	673	1.38	4	50%	2	44
GLP-cirrhosis score	323	0.19	3	33%	2	57

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