Application of a Non-Invasive Integrated Screening Approach to Facilitate Enrollment of Clinical Trials with Investigational NAFLD/NASH Therapeutics.

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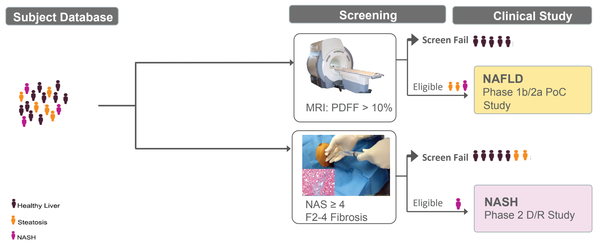
BACKGROUND

- Despite NAFLD/NASH being a prevalent co-morbidity in obesity and type 2 diabetes, the clinical development of NAFLD/NASH therapeutics is currently hindered by significant challenges in clinical trial enrollment.
- Traditional study screening is commonly associated with screen failure rates of approximately 80%. Given the cost- and timeline implications of subjects failing to meet MRI- or biopsy-based inclusion criteria, there is a clear need for optimized screening strategies in NAFLD/NASH clinical studies.

Figure 1. Traditional screening approaches for NAFLD/NASH are commonly associated with high screen failure rates.



AIM

Our goal was to assess the potential utility of an integrated screening approach aimed at pre-identifying individuals who have a high probability of being eligible for NAFLD/NASH clinical studies.

MATERIALS &METHODS

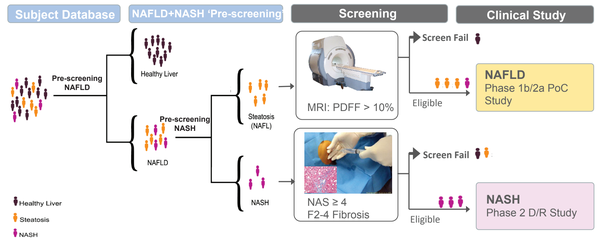
Our integrated screening approach consists of:

1) a NAFLD scoring system based on the combined use and analysis of 2 screening algorithms published in the literature.

2) a lipidomic testing panel for both NAFLD and NASH, developed by One Way Liver (OWL) Metabolomics.
- NAFLD index: BMI + rel conc. of 11 triglycerides
- NASH index: BMI + rel conc. of 20 triglycerides. Testing Both indices have previously been validated against liver biopsy.

- We applied this scoring system (score of 0 to 5, with 5 having the highest probability of NAFLD) to two cohorts of subjects.
- Cohort 1 included subjects with Type 2 Diabetes of whom 145 when pre-screened based on the scoring system had a score of 5. A subset of 18 from those 145 subjects subsequently underwent MRI-PDFF based quantification of liver fat (%).
- Cohort 2 included non-diabetic obese subjects which underwent lipidomic testing to estimate the probability of NAFLD and NASH if their score within the scoring system was 5.

Figure 2. Integrated Screening Approach: Pre-identification of subjects with highest probability of being eligible for NAFLD and/or NASH clinical studies



RESULTS(Cohort 1)

Cohort 1 (T2DM) - 204 subjects with type 2 diabetes

Table 1. Cohort 1 Subjects Characteristics

	Mean (±SD)
n	204
Age (years)	57.2 (7.68)
Gender (n,%)	
Male	130, 63.7%
Female	74, 36.2%
Ethnicity (n,%)	
Caucasian White	102, 50%
Black	0
Asian/Oriental	0
Latino	102, 50%
Height (cm)	167.7 (10.20)
Weight (kg)	89 (17.49)
BMI (kg/m2)	31.3 (4.25)
Waist Circ.	105.1(13.72)
SBP (mmHg)	130.3 (17.87)
DBP (mmHg)	80.7 (8.89)
ALT (u/L)	29 (18.28)
AST (u/L)	23.2 (14.56)
AST:ALT	0.9 (0.29)
GGT (u/L)	43.9 (64.97)
FPG (mg/dL)	164.3 (58.33)
Fasting Insulin	19.2 (17.03)
Triglycerides (mg/dL)	181.2 (124.85)
HDL (mg/dL)	44.4 (11.24)
HbA1C (%)	7.8 (2.04)

Figure 3. 145 of 208 subjects (70%) in cohort 1 had a NAFLD score of 5 (71%).

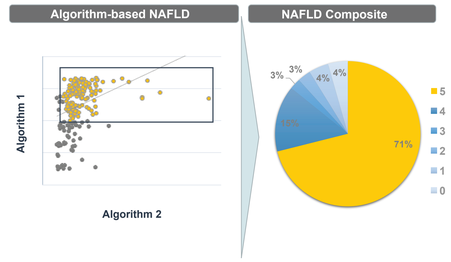
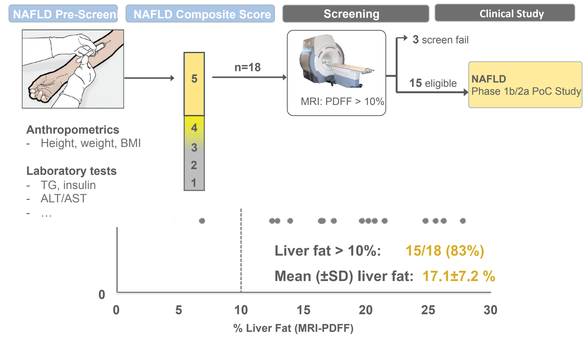


Figure 4. 15 of 18 subjects (83%) undergoing MRI-PDFF had liver fat >10%



RESULTS(Cohort 2)

Cohort 2 (OB/ND) - 55 obese, non-diabetic subjects

Table 2. Cohort 2 Subjects Characteristics

	Mean (±SD)
n	55
Age (years)	47.0 (10.7)
Gender (n,%)	
Male	30, 54.5%
Female	25, 45.4%
Ethnicity (n,%)	
Caucasian White	50, 90.9%
Black	0
Asian/Oriental	0
Latino	5, 9.1%
Height (cm)	168.9 (9.17)
Weight (kg)	101.9 (28.28)
BMI (kg/m2)	33.9 (3.92)
Waist Circ.	105.5 (18.31)
SBP (mmHg)	121.6 (11.48)
DBP (mmHg)	79.1 (6.49)
ALT (u/L)	26.2 (19.29)
AST (u/L)	20.4 (9.06)
AST:ALT	0.9 (0.28)
GGT (u/L)	28.2 (30.47)
FPG (mg/dL)	99.8 (11.23)
Fasting Insulin	16.3 (9.60)
Triglycerides (mg/dL)	128.7 (96.38)
HDL (mg/dL)	49.0 (12.85)
HbA1C (%)	5.7 (0.44)

Figure 5. 35 of 55 subjects (53%) in cohort 2 had a NAFLD score of 5.

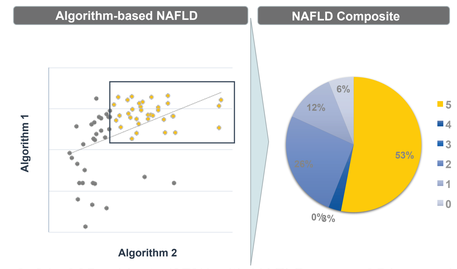
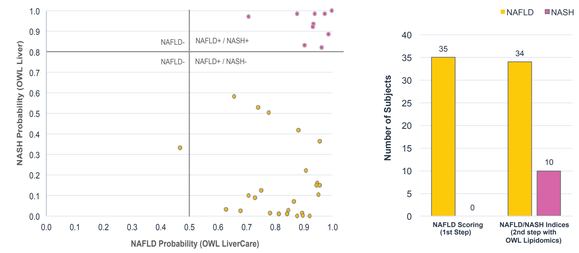


Figure 6. 34 of 35 subjects (97%) with NAFLD score of 5 has positive NAFLD index. Of those, 10 (28.5%) also had a positive NASH index.



CONCLUSIONS

- These preliminary results point to the potential utility of optimized, non-invasive screening algorithms for NAFLD/NASH studies.
- Pre-screening strategies to identify individuals who are most likely to have significant steatosis or steatohepatitis on MRI or biopsy, may be a scalable, efficient means of reducing screen failure rates in NAFLD/NASH clinical trials.
- Refinement and validation in larger cohorts is currently underway.

REFERENCES

1. D. E. Kleiner et al., **Design and validation of a histological scoring system for nonalcoholic fatty liver disease.** Hepatology 41, 1313-1321 (2005).
2. A. Tang et al., **Nonalcoholic fatty liver disease: MR imaging of liver proton density fat fraction to assess hepatic steatosis.** Radiology 267, 422-431 (2013).
3. C. Alonso et al., **Metabolomic Identification of Subtypes of Nonalcoholic Steatohepatitis. Gastroenterology** 152, 1449-1461 e1447 (2017).

Disclosure of Interest: G. Rodriguez-Araujo: Employee: ProSciento, Inc, M. Hernandez: Employee: ProSciento, Inc, C. Weyer: Employee: ProSciento, Inc, L. Morrow: Employee: ProSciento, Inc, L. Millán: Employee: OWL Metabolomics, I. Martínez-Arranz: Employee: OWL Metabolomics, M. Hompesch: Employee: ProSciento, Inc

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