Liver Investigation: Testing Marker Utility in Steatohepatitis

Prof Quentin M. Anstee PhD, FRCP
Project Coordinator (Newcastle University, UK)

Dr Carla Yunis PhD
Project Lead (Pfizer, USA)

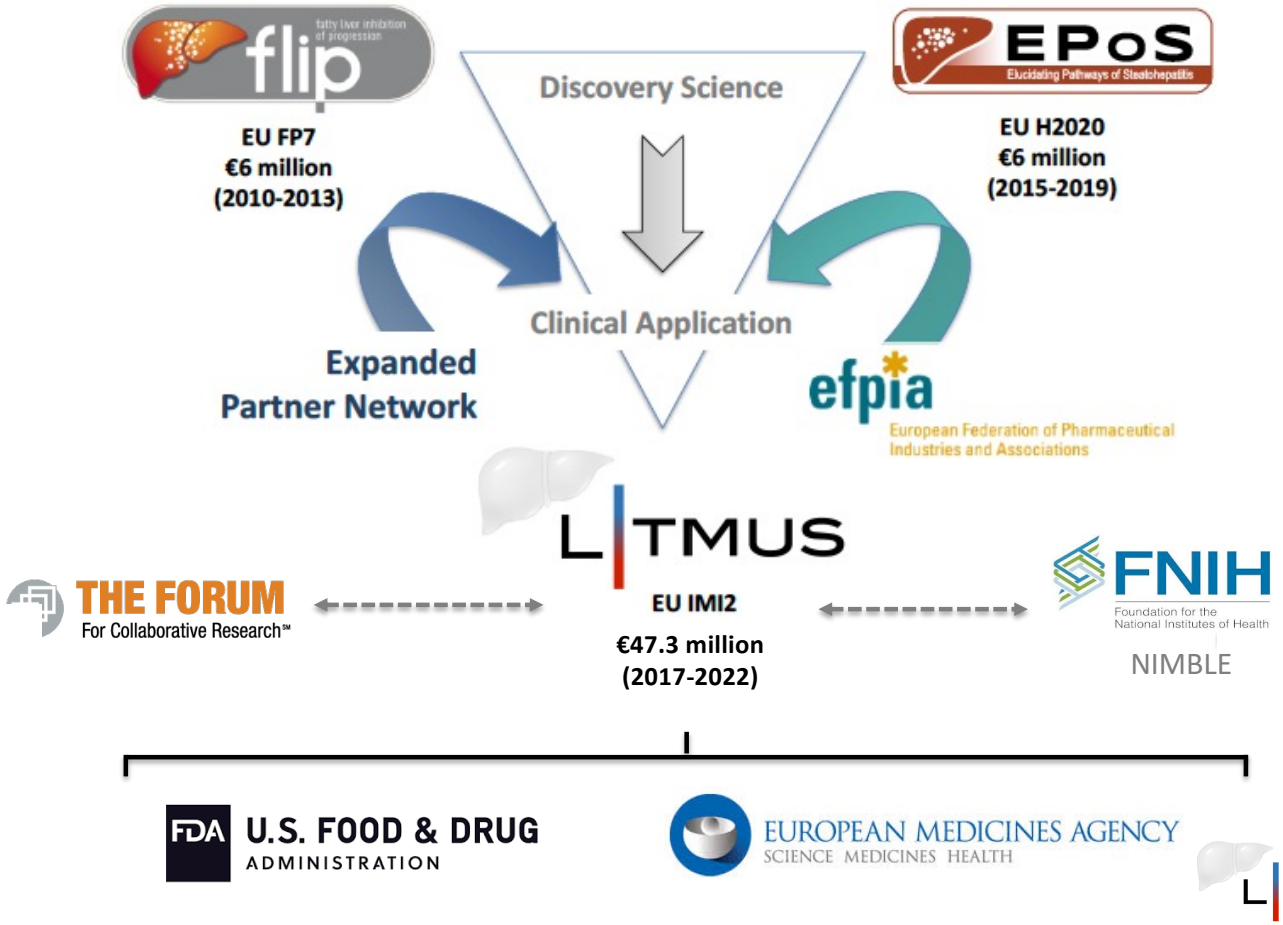
Liver Investigation: Testing Marker Utility in Steatohepatitis (LITMUS)

FACTS & FIGURES

Start Date	01/11/2017
End Date	31/10/2023
Call	IMI2 - Call 9
Grant agreement number	777377

Type of Action:
RIA (Research and Innovation Action)

Contributions	**€**
IMI Funding	15 797 881
EFPIA in kind	25 427 538
Other	6 055 988
Total Cost	47 281 407



Project website:
www.litmus-project.eu

Twitter:
@LITMUS_IMI

Coordinator: Prof Quentin M. Anstee

imi innovative medicines initiative

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- **54 Partners**
  - 30 Academic,
  - 23 EFPIA/Industrial,
  - 1 Professional body
- **14 Countries for Clinical Recruitment**
  - UK, France, Germany, Italy, Switzerland, Netherlands, Austria, Luxembourg, Sweden, Finland, Greece, Spain, Portugal, USA
- **True Public-Private co-funding model**
  - Effective budget approximately €47.3 million (includes >€23 million 'cash' from EU & Industry)

The ultimate goal is to establish a defined set of biomarkers that, singly or in combination, enable detection and monitoring of disease progression to and/or regression from NAFL through NASH to fibrosis and cirrhosis.

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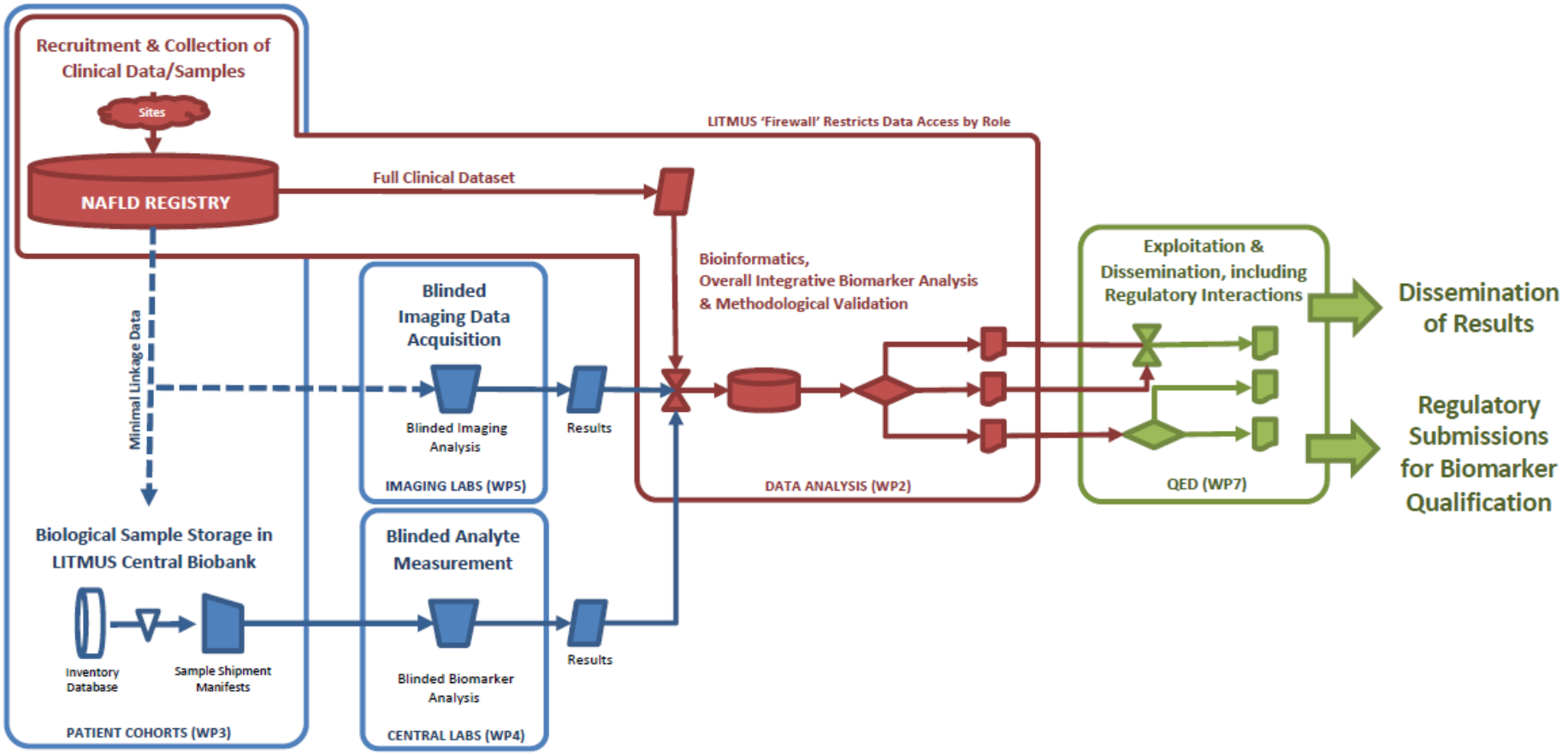
LITMUS



LITMUS has implemented a robust 'technology-unbiased' platform to conduct the systematic study and validation of a broad range of non-invasive biomarkers and imaging technologies with reference to fully-adjudicated liver biopsy data.

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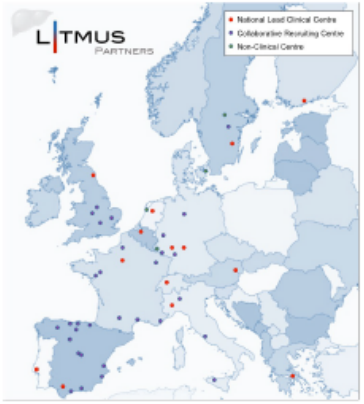
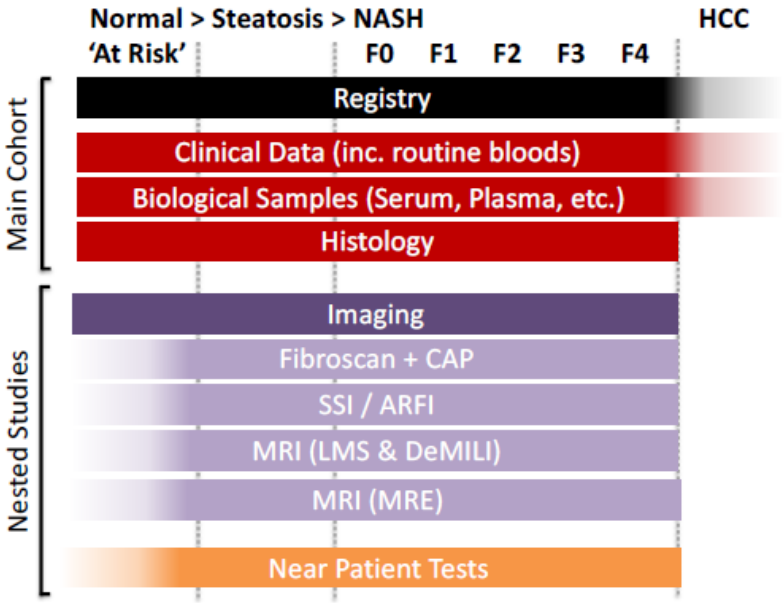
Strong Focus on Robust Data Quality & Technical/Analytic Standards





- Unified Protocol across 13 countries.
- Comprehensive Clinical Dataset (CDISC-ready database):
  - All routinely available clinical data
  - Cross-sectional & Longitudinal/Outcome data
  - PROs
- Robust Quality Management Framework using a risk-based approach that combines iterative Remote and On-site source data verification processes.
- Central reading of liver biopsies by the LITMUS Pathology Group.
- Clearly defined chain of custardy for biological samples.
- Preanalytical variation minimised through standardised sample collection/handling at sites and in LITMUS Central Biobank.
- LITMUS Central Laboratory conducted Technical Validation & QC reports for key biomarkers assessed:
  - Precision & Accuracy
  - Sensitivity
  - Linearity, etc
  - CLSI validation for some

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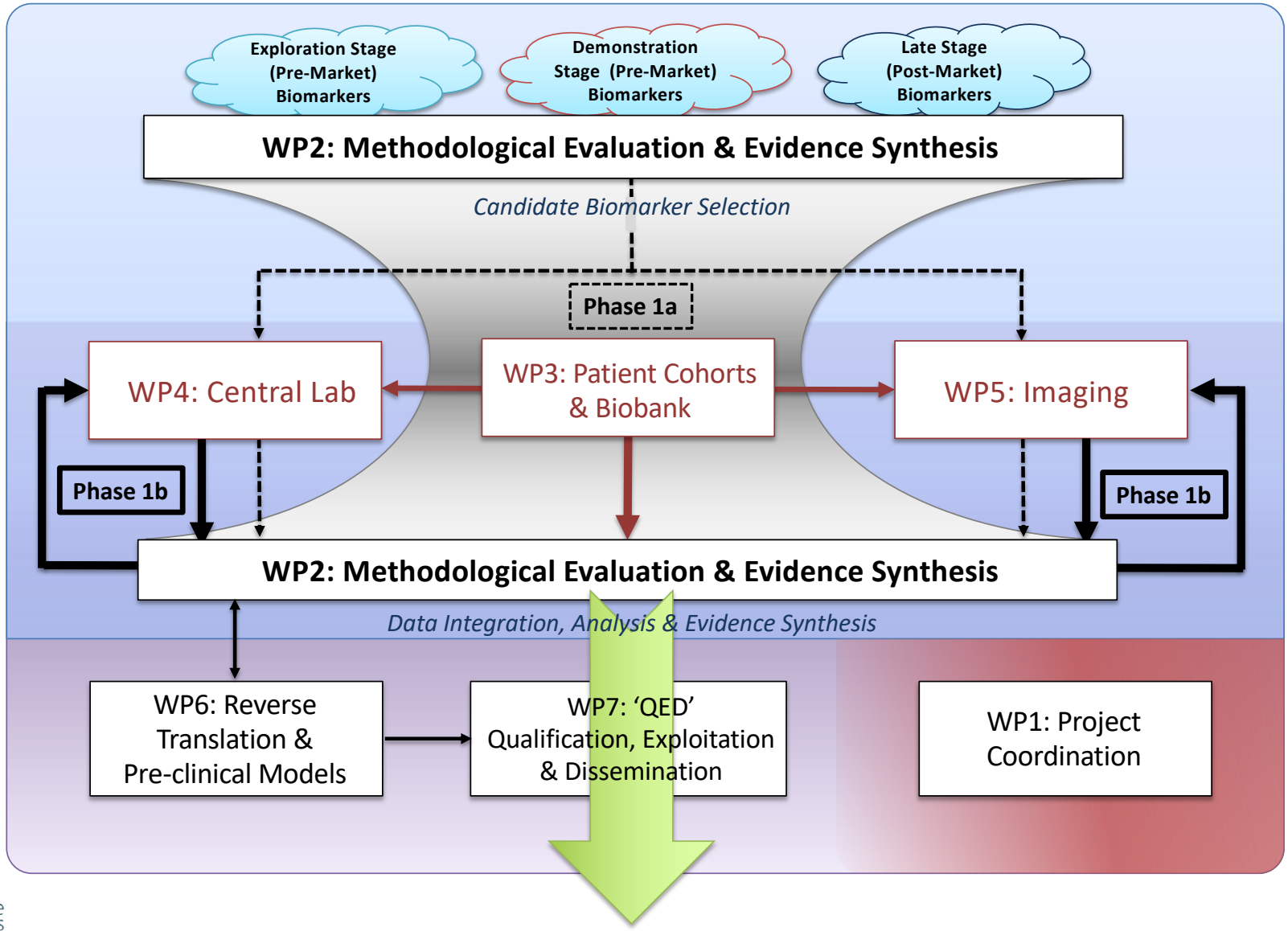
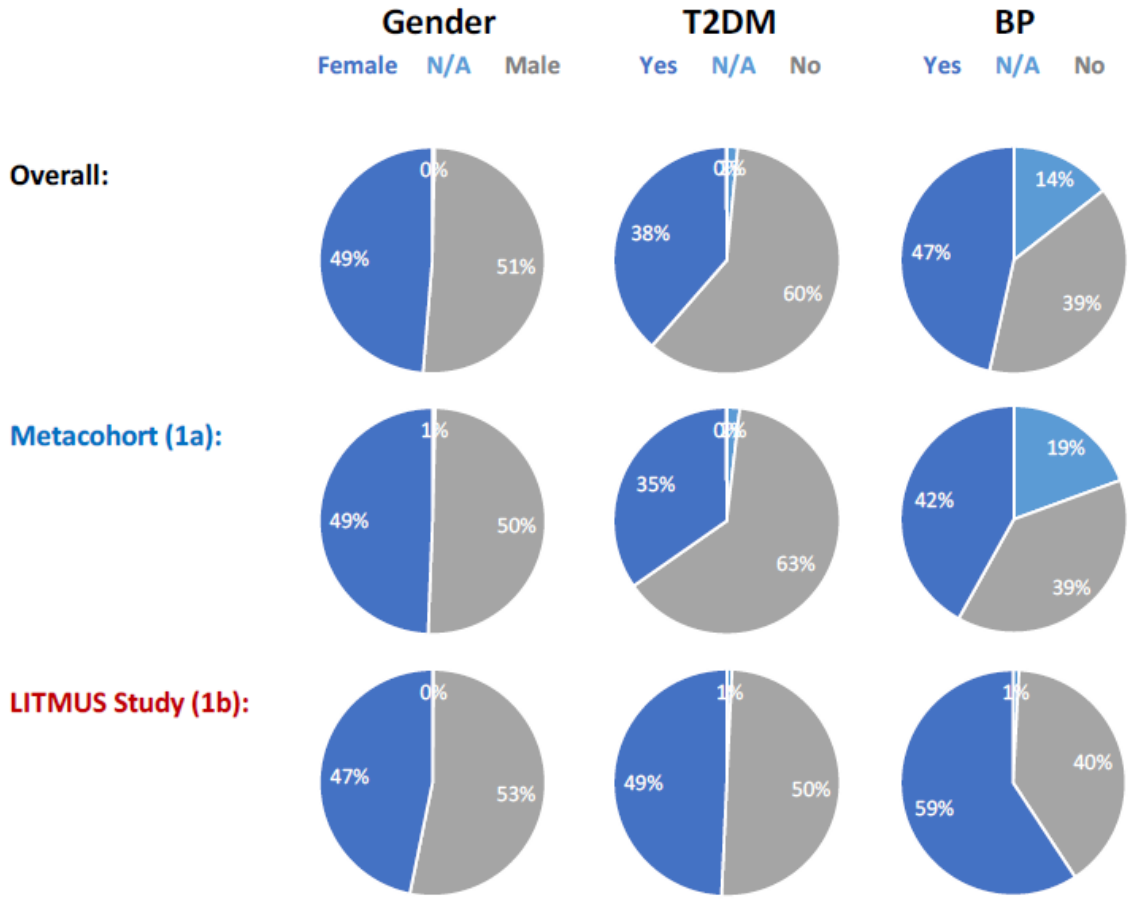


Validated Diagnostic, Prognostic & Dynamic Biomarkers

NAFLD Registry - Recruitment Summary



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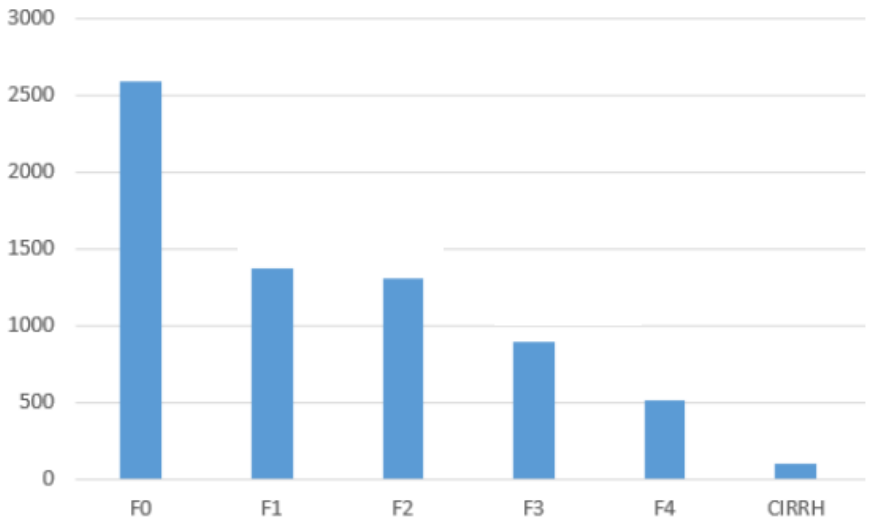
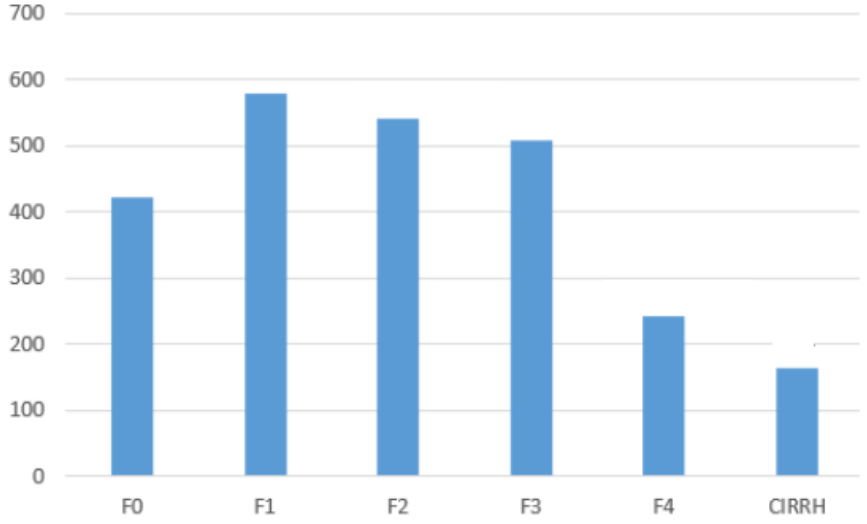
NAFLD Registry - Recruitment Summary

Fibrosis Stage Distribution

Metacohort (1a):



LITMUS Study (1b):



Disease severity distribution representative of the target secondary/tertiary care setting for clinical trial recruitment

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Similarities & Differences in Approach to Biomarker Validation in LITMUS & NIMBLE

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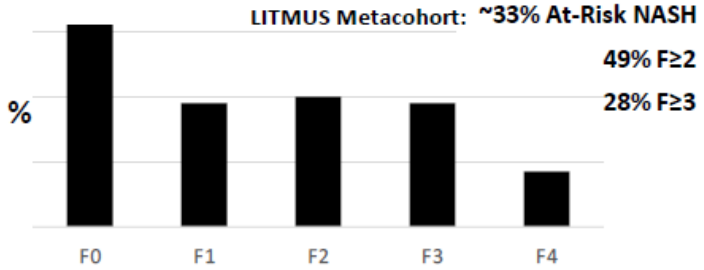
Target Conditions
- Clinically Significant Fibrosis (F≥2)
- Advanced Fibrosis (F≥3)
- At-Risk NASH (NAS≥4 + F≥2)

Acceptable Performance Threshold
- AUROC ≥0.8
- Comparator FIB4

Population
- 'Left Skew' Fibrosis Distribution (as in 2º/3º care)

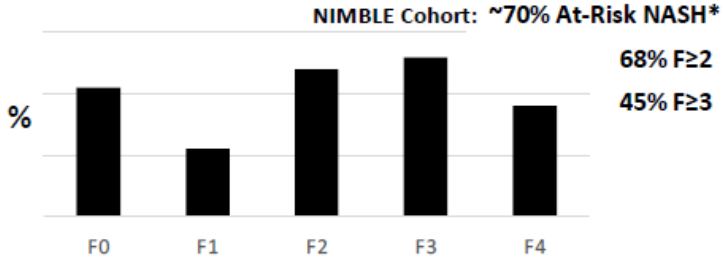


NIMBLE

Target Conditions
- Clinically Significant Fibrosis (F≥2)
- Advanced Fibrosis (F≥3)
- NASH (NAS≥4)

Acceptable Performance Threshold
- AUROC ≥0.7 (+ significantly >0.5)
- Comparator FIB4 (ALT for NASH)

Population
- 'Right Skew' Fibrosis Distribution*



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* NIMBLE Data from Sanyal et al, AASLD 2021

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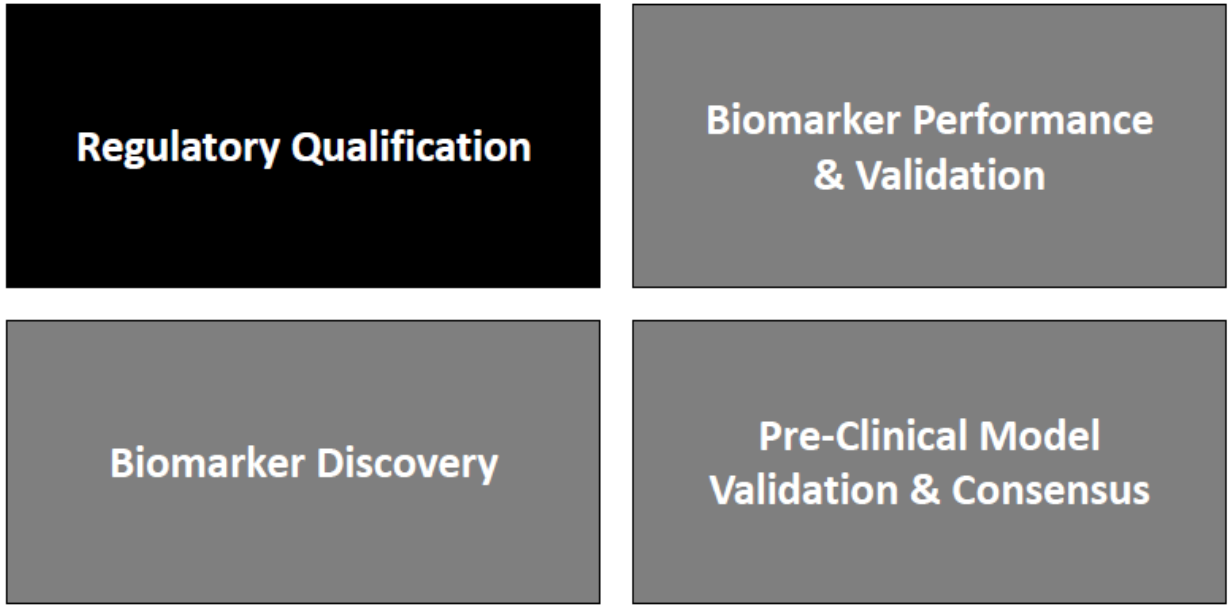
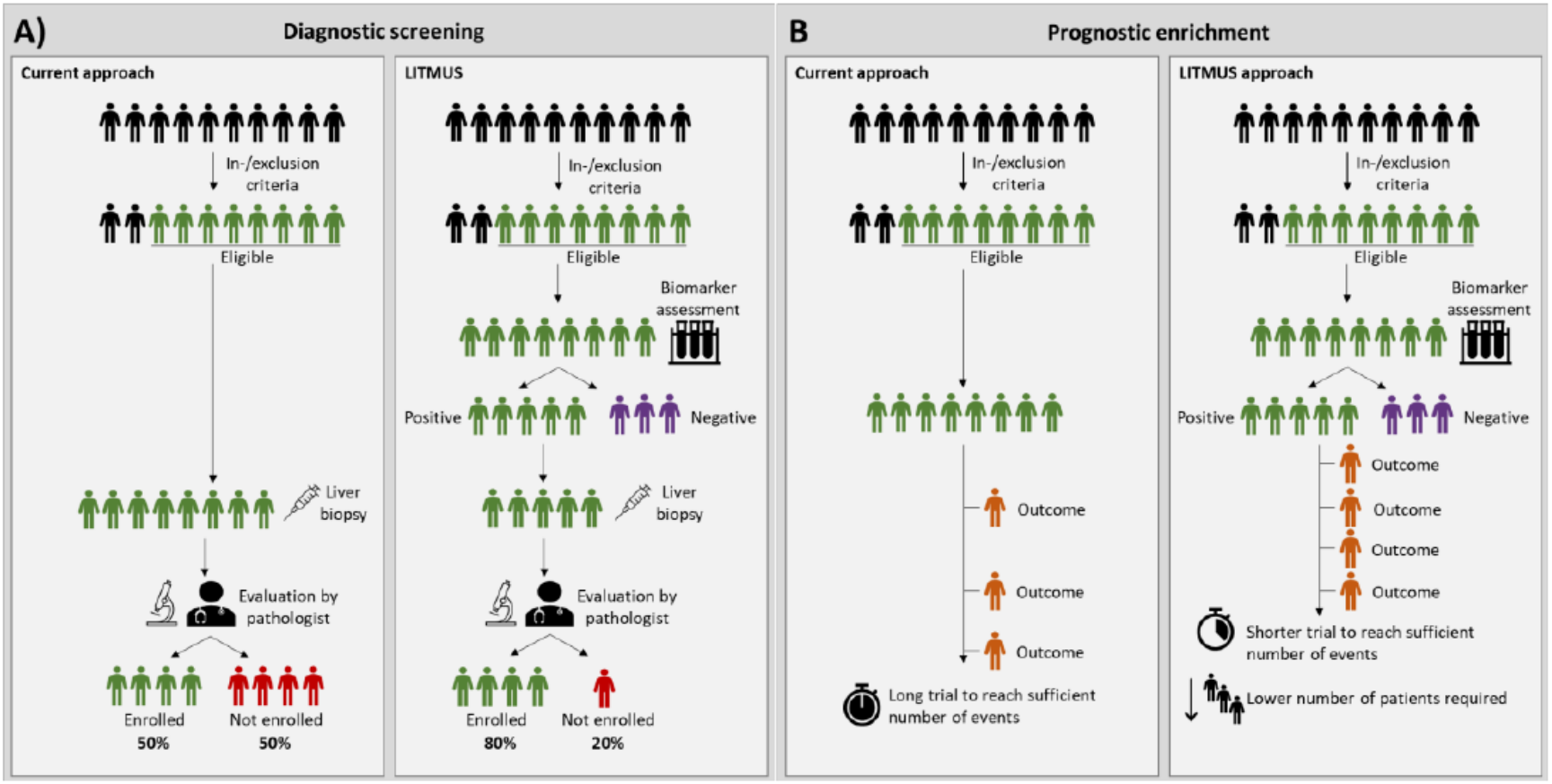
LITMUS Progress Across Key Domains



Regulatory Interactions – LITMUS' Experiences



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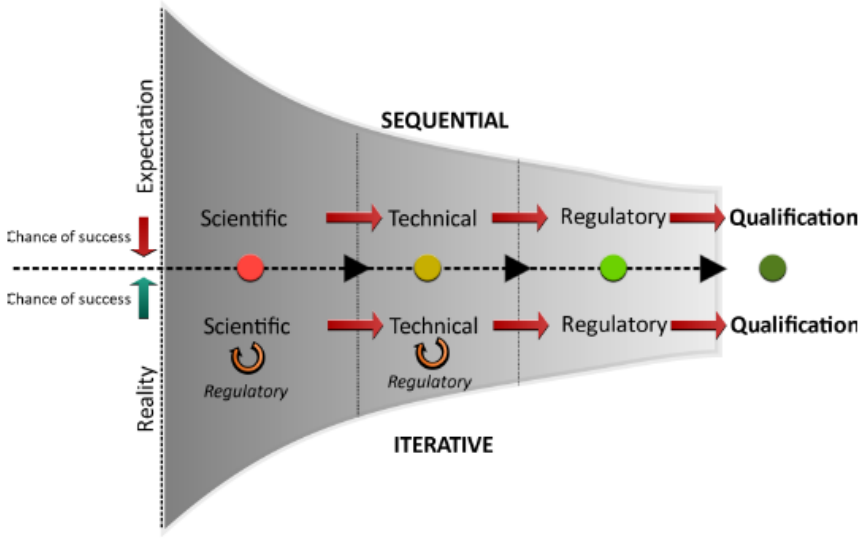
Rasmussen et al, *'NAFLD & NASH Biomarker Qualification in the LITMUS Consortium: Lessons Learned'* Journal of Hepatology 2022, in press.

LITMUS

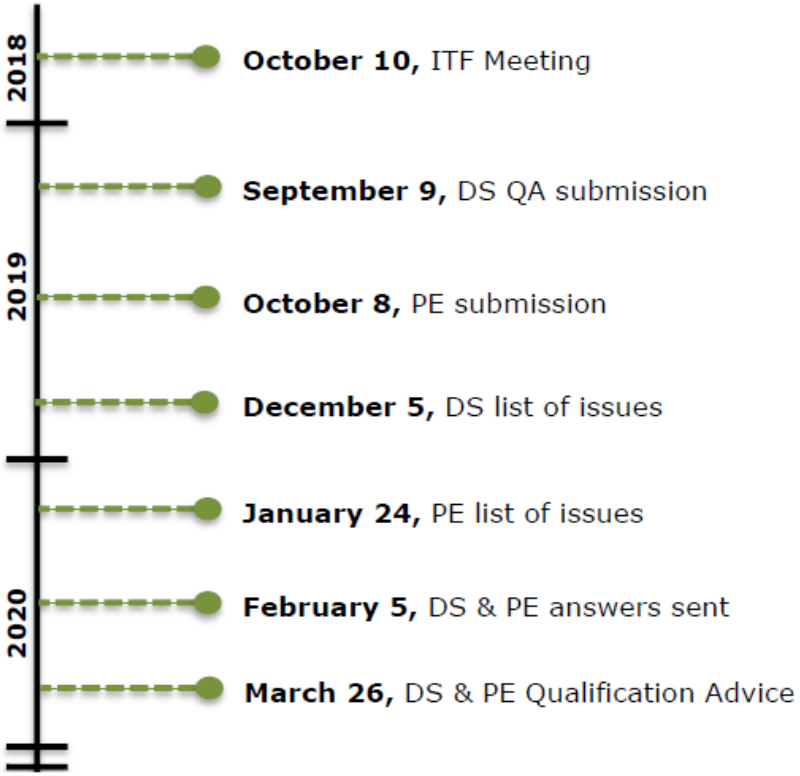
Regulatory Interactions – LITMUS' Experiences



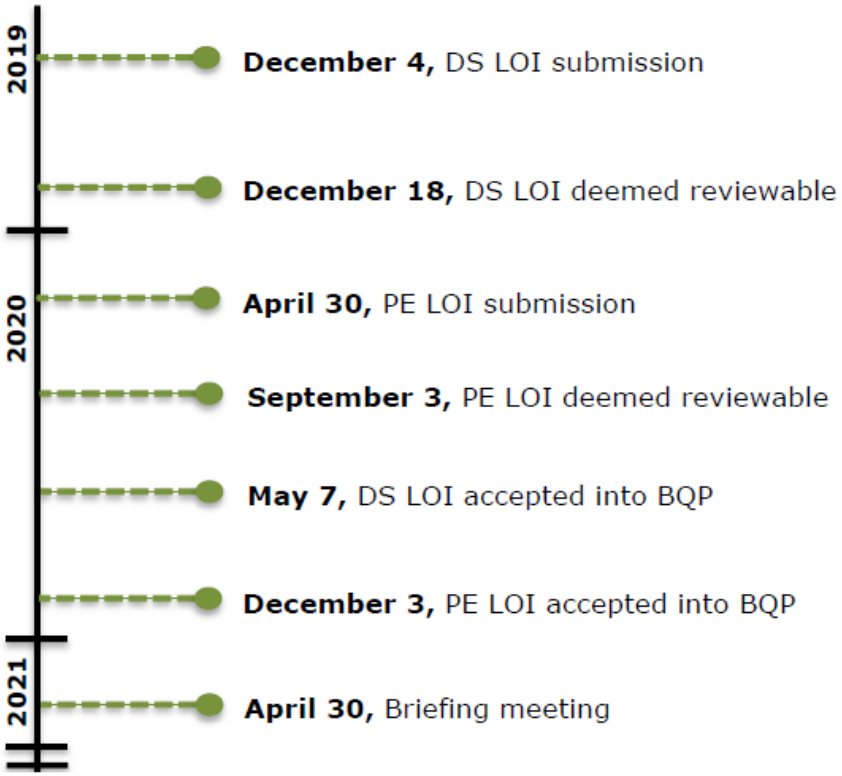
- **The biomarker qualification process is a collaborative and iterative effort, where the agency staff works with the requestor in guiding biomarker development.**
- Feedback from agencies focuses on five key categories: biomarker, context of use (COU), technical and analytical, clinical, and statistical.
- For biomarker qualification, the biomarker will ultimately be qualified independent of the measurement method used to assess the biomarker.
- **The cohorts used for biomarker qualification need to be representative of the intended use population and contain a sufficient sample size to allow meaningful data to be produced to support the COU.**

Rasmussen et al, *'NAFLD & NASH Biomarker Qualification in the LITMUS Consortium: Lessons Learned'* Journal of Hepatology 2022, in press.

EMA



FDA



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DS = Diagnostic screening
PE = Prognostic enrichment

ITF = Innovation Task Force
QA = Qualification Advice

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FDA Letters of Intent Accepted

- **DDTBMQ000095 (May 2020)**
  - Context of Use: Diagnostic Screening
  - Two 'indicative' biomarkers
    - Single 'Wet' Biomarker: PRO-C3
    - Imaging/Composite Biomarker: FAST Score (VCTE+CAP+AST)

- **DDTBMQ000106 (December 2020)**
  - Context of Use: Prognostic Enrichment
  - Two 'indicative' biomarkers
    - 'Wet'/Composite Biomarker: ELF Test
    - Single Imaging Biomarker: cT1

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1. Rasmussen et al, Journal of Hepatology 2022, in press.

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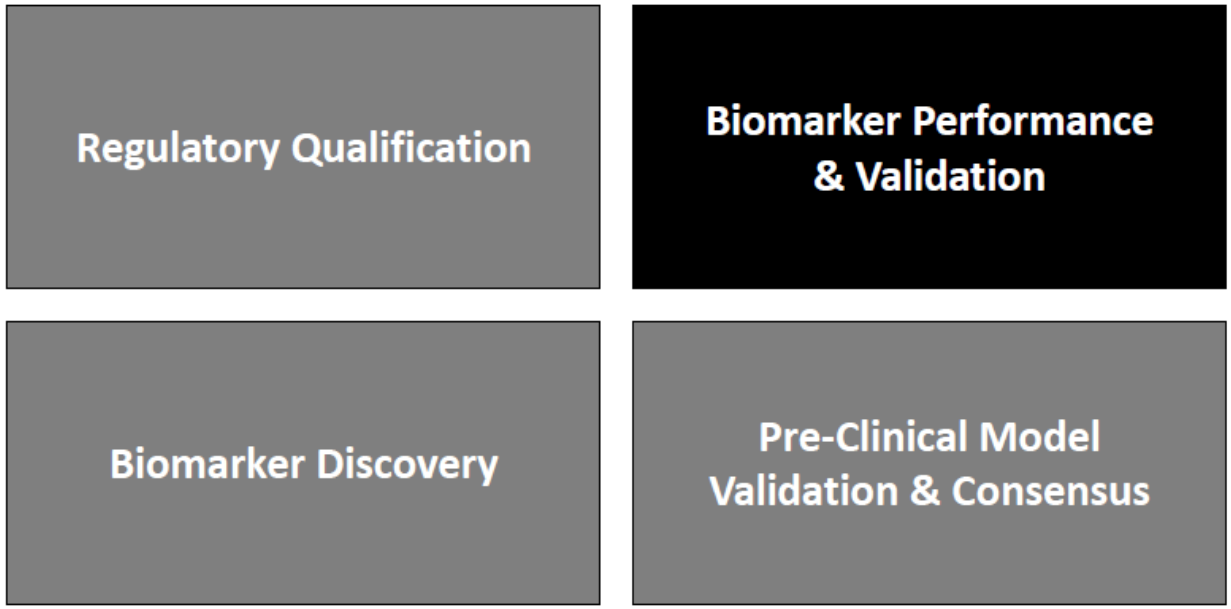
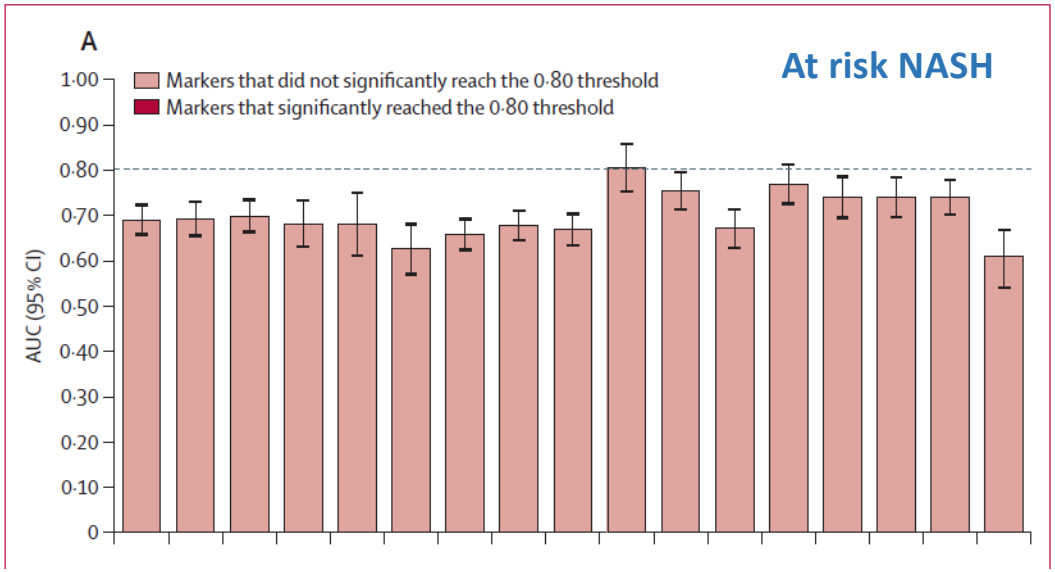
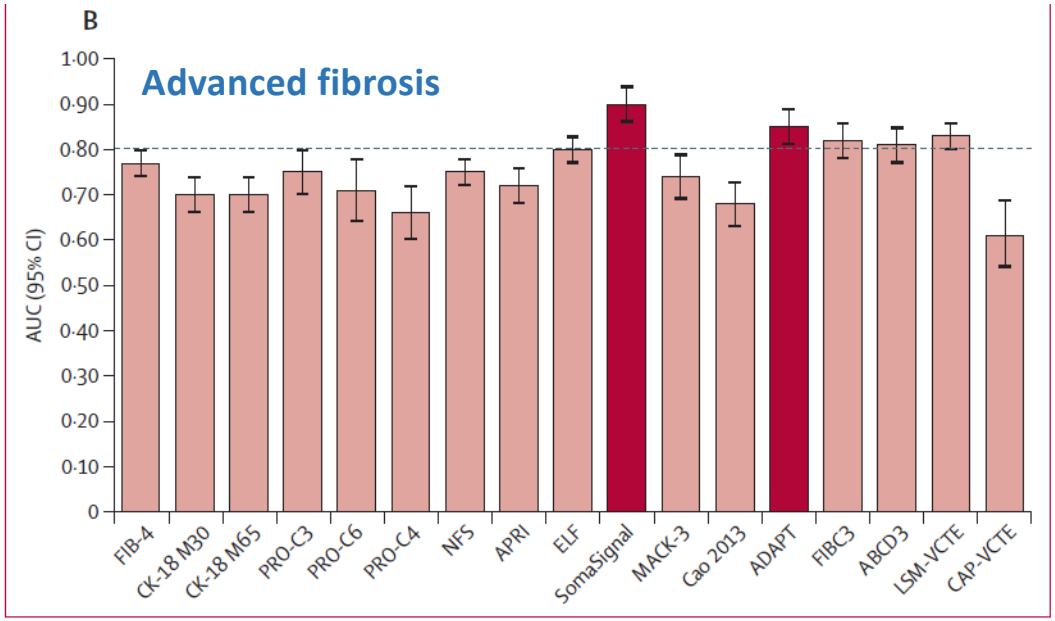
LITMUS Progress Across Key Domains







ging fibrosis and non-alcoholic non-alcoholic fatty liver disease (the comparative diagnostic accuracy study

Salvatore Petta, Kristy Wonders, Dina Tiniakos, Pierre Bedossa, Andreas Geier, Sven Francque, ena Cortez-Pinto, Raluca Pais, Jean-Francois Dufour, Diana Julie Leeming, Stephen A Harrison,

966 Patients incl.

335 at-risk NASH

28% advanced fibrosis

Comparative Accuracy for Pre-Screening to Detect At-Risk NASH in Clinical Trials

Marker	Threshold	Sensitivity	Specificity	Number of positive patients undergoing biopsy (Per 100)	Number of eligible patients found (Per 100)	Number needed to test
SomaSignal	0.06	0.67 (0.59 – 0.75)	0.82 (0.59 – 0.75)	35 (30 – 40)	24 (20 – 26)	4 (4 – 5)
ADAPT	6.91	0.47 (0.39 – 0.55)	0.88 (0.83 – 0.91)	24 (21 – 28)	16 (14 – 19)	6 (5 – 7)
MACK-3	0.53	0.41 (0.34 – 0.48)	0.89 (0.85 – 0.92)	21 (19 – 25)	14 (12 – 17)	7 (6 – 8)
PRO-C3	24.05 ng/ml	0.33 (0.25 – 0.40)	0.92 (0.88 – 0.94)	17 (14 – 20)	11 (9 – 14)	9 (7 – 11)
FIBC-3	0.84	0.28 (0.21 – 0.35)	0.93 (0.89 – 0.96)	14 (11 – 18)	10 (7 – 12)	10 (8 – 14)
CK-18 M30	573.80 IU/L	0.25 (0.20 – 0.30)	0.93 (0.91 – 0.95)	13 (11 – 15)	9 (7 – 11)	11 (9 – 14)
Cao 2013	1.74	0.22 (0.17 – 0.28)	0.94 (0.92 – 0.96)	12 (9 – 14)	8 (6 – 10)	13 (10 – 16)
PRO-C6	14.25 ng/ml	0.18 (0.11 – 0.26)	0.96 (0.91 – 0.98)	9 (6 – 13)	6 (4 – 9)	16 (11 – 26)
PRO-C4	433.35 ng/ml	0.12 (0.08 – 0.18)	0.97 (0.94 – 0.99)	6 (4 – 9)	4 (3 – 6)	23 (16 – 37)
CK-18 M65	1283.55 IU/L	0.12 (0.09 – 0.16)	0.97 (0.95 – 0.98)	6 (5 – 8)	4 (3 – 6)	24 (17 – 33)
No marker	-	-	-	100	35	-

Thresholds correspond to a liver biopsy screen failure rate of 33% at a 35% prevalence
No acceptable threshold was found for ABC3D, APRI, ELF, NFS, or FIB-4

Vali et al, *'Comparative diagnostic accuracy of blood-based biomarkers for staging at-risk NASH in NAFLD: first results of the LITMUS project'* 2023, under review.

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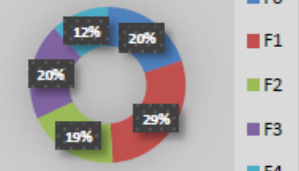
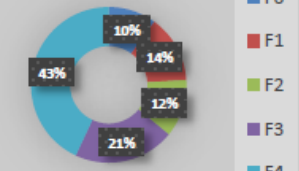
	Sensitivity (%)	Specificity (%)	Youden index	AUROC (95% CI)	Significance (versus ALT or FIB4)
NASH diagnosis					
ALT	63.2	64.8	0.28	0.678 (0.639, 0.717)	
NIS4	77.7	76.2	0.539	0.832 (0.801, 0.864)	<0.001
OWL	77.3	66.8	Categorical data AUROC cannot be computed		
NAS ≥4					
ALT	71.1	64.1	0.352	0.726 (0.694, 0.759)	
NIS4	78.1	73.6	0.517	0.815 (0.786, 0.844)	<0.001
At-risk NASH					
ALT	71.1	64.1	0.352	0.726 (0.694, 0.759)	
FIB4	76.4	58.4	0.349	0.704 (0.671, 0.737)	
NIS4	78.1	73.6	0.517	0.815 (0.786, 0.844)	<0.001
Fibrosis stage ≥2					
FIB4	65.6	80.6	0.462	0.798 (0.768, 0.828)	
ELF	71.8	81.5	0.533	0.828 (0.08, 0.857)	0.013
NIS4	82.3	79.9	0.622	0.874 (0.848, 0.899)	<0.001
PROC3	69.8	81	0.507	0.809 (0.779, 0.839)	0.279
FibroMeter VCTE	66.7	86.4	0.53	0.841 (0.796, 0.886)	<0.001
Fibrosis stage ≥3					
FIB4	70.3	72.4	0.427	0.789 (0.758, 0.819)	
ELF	80.8	70.2	0.509	0.835 (0.807, 0.863)	<0.001
NIS4	72.9	74.8	0.476	0.788 (0.757, 0.820)	0.615
PROC3	71.4	71.4	0.428	0.764 (0.732, 0.795)	0.947
FibroMeter VCTE	76.2	81.3	0.575	0.858 (0.814, 0.902)	<0.001
Fibrosis stage 4					
FIB4	84.7	62.9	0.476	0.810 (0.770, 0.850)	
ELF	82.1	73.3	0.555	0.855 (0.818, 0.892)	<0.001
NIS4	78.1	61.4	0.395	0.725 (0.681, 0.760)	1
PROC3	66.2	68.5	0.346	0.728 (0.685, 0.770)	1
FibroMeter VCTE	94.2	70.4	0.646	0.897 (0.843, 0.951)	0.002

Sanyal, FNIH
Nature Med 2023

Evidence Generation to Support Prognostic Enrichment Context of Use

- **Individual participant data meta-analysis**
- Included studies with baseline LSM-VCTE, FIB4, NFS and liver histology performed within 6 months
- Follow-up period of at least 12 months from baseline
- Composite endpoint of all-cause mortality and/or liver outcomes:
  - Decompensation of cirrhosis
  - Hepatocellular cancer
  - Liver transplantation
  - MELD score > 14 or histological progression to cirrhosis
- Cox proportional hazards regression
  - Univariate
  - Multivariate (adjusted for age, BMI, sex, presence of T2DM)

	Entire group	Participants who reached the composite endpoint
Number of participants	**2518**	**145 (5,8%)**
Median follow-up (months)	64 (54)	65 (60)
Age (years)	53 (13)	62 (14)
BMI (kg/m^2)	29 (5)	29 (7)
BMI ≥ 30 kg/m^2 (%)	39	41
T2DM (%)	50	62
Fibrosis stages (F0/F1/F2/F3/F4), %		

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Mozes et al, Oral Presentation AASLD 2022

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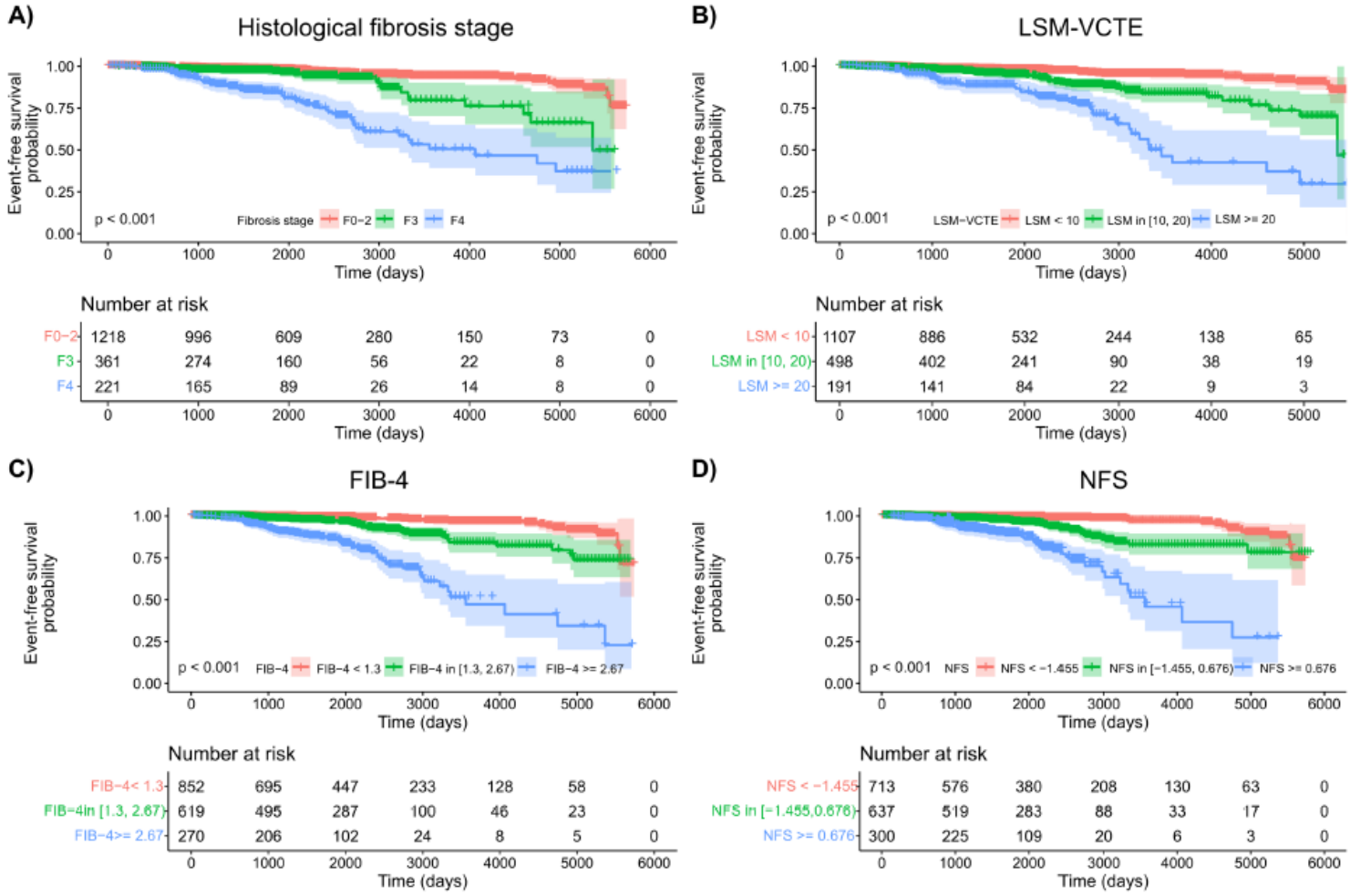
LSM-VCTE, FIB4 & NFS Have Prognostic Utility



Mozes et al, Oral Presentation AASLD 2022

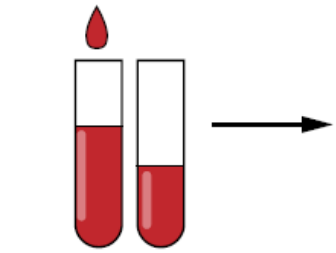
Research Article
NAFLD and Alcohol-Related Liver Diseases

JOURNAL OF HEPATOLOGY

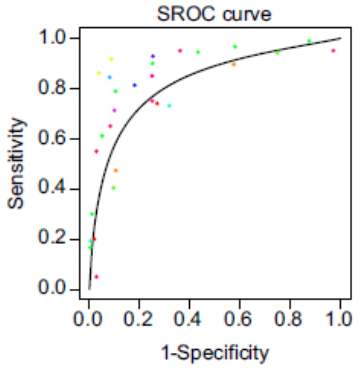
Diagnostic accuracy of elastography and magnetic resonance imaging in patients with NAFLD: A systematic review and meta-analysis

Emmanuel Anandraj Selvaraj[1,2,3,†], Ferenc Emil Mózes[1,†], Arjun Narayan Ajmer Jayaswal[1,†],

AUROC for	VCTE	MRE	pSWE	2DSWE
Significant fibrosis	0,91	0,91	0,86	0,75
Advanced fibrosis	0,85	0,92	0,89	0,72
Cirrhosis	0,89	0,90	0,90	0,88

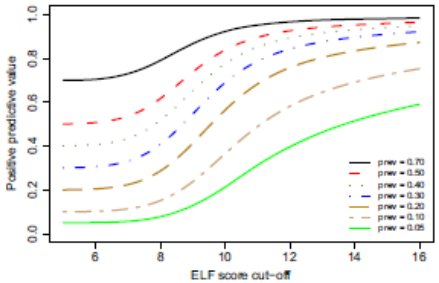


Enhanced Liver Fibrosis test;
A blood based biomarker for diagnosis advanced fibrosis

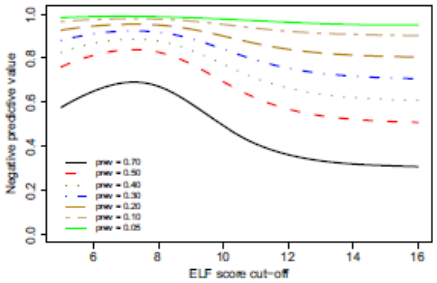


11 studies were included in the meta-analysis of advanced fibrosis
AUC: 0.83 (0.71, 0.90)
Sensitivity: 0.73 (0.60, 0.83)
Specificity: 0.80 (0.68, 0.88)

Summary ROC Curve based on the multiple thresholds model using homogenized thresholds. Circles present information on sensitivity and specificity and each color corresponds to one study.



Corresponding PPV and NPV for different ELF cut-offs based on the multiple thresholds model



In low prevalence settings, the performance of the ELF test for diagnosis of advanced fibrosis is limited and results in low Positive and Negative Predictive Values (PPV and NPV) using different cut-offs. In high thresholds and settings with high disease prevalence (>40%), the test led to high specificity (>90%) and PPV (>80%). However, the PPV fell significantly in primary settings with low prevalence of disease (5-10%).

Research Article
NAFLD and Alcohol-Related Liver Diseases

JOURNAL OF HEPATOLOGY

Enhanced liver fibrosis test for the non-invasive diagnosis of fibrosis in patients with NAFLD: A systematic review and meta-analysis

Yasaman Vali[1,*], Jenny Lee[1], Jérôme Boursier[2,3], René Spijker[4,5], Jürgen Löffler[6], Joanne Verheij[7], M. Julia Brosnan[8], Zsolt Böcskei[9], Quentin M. Anstee[10,11], Patrick M. Bossuyt[1], Mohammad Hadi Zafarmand[1], and the LITMUS systematic review team[†]

PLOS ONE

RESEARCH ARTICLE

Accuracy of cytokeratin 18 (M30 and M65) in detecting non-alcoholic steatohepatitis and fibrosis: A systematic review and meta-analysis

Jenny Lee[1]*, Yasaman Vali[1], Jérôme Boursier[2,3], Kevin Duffin[4], Joanne Verheij[5], M. Julia Brosnan[6], Koos Zwinderman[1], Quentin M. Anstee[7,8], Patrick M. Bossuyt[1], Mohammad Hadi Zafarmand[1]

Journal of Clinical Medicine
MDPI

Review

FibroTest for Evaluating Fibrosis in Non-Alcoholic Fatty Liver Disease Patients: A Systematic Review and Meta-Analysis

Yasaman Vali [1,*], Jenny Lee [1], Jérôme Boursier [2,3], René Spijker [4,5], Joanne Verheij [6], M. Julia Brosnan [7], Quentin M. Anstee [8,9], Patrick M. Bossuyt [1], Mohammad Hadi Zafarmand [1] and on behalf of the LITMUS Systematic Review Team [†]

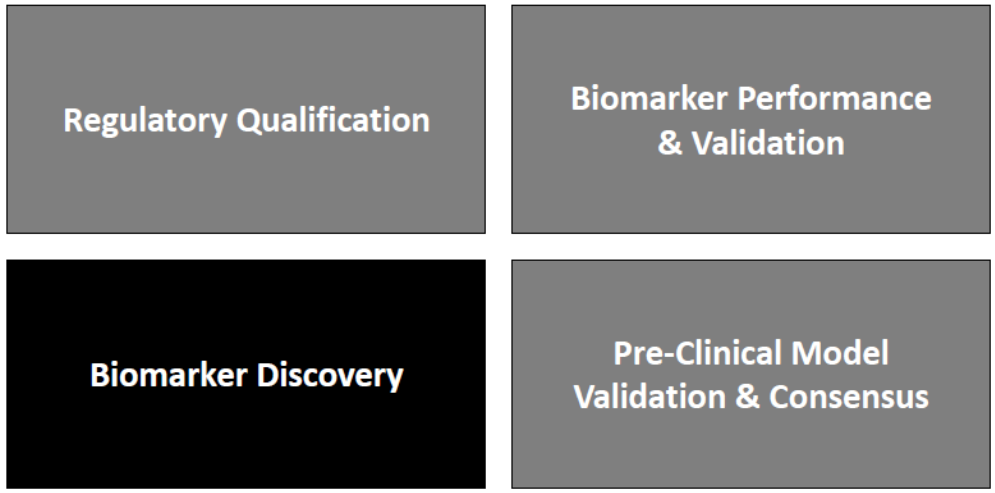
Journal of Clinical Medicine
MDPI

Review

Systematic Review with Meta-Analyses: Diagnostic Accuracy of FibroMeter Tests in Patients with Non-Alcoholic Fatty Liver Disease

Anne-Marieke van Dijk [1,*], Yasaman Vali [2], Anne Linde Mak [1], Jenny Lee [2], Maarten E. Tushuizen [3], Mohammad Hadi Zafarmand [2], Quentin M. Anstee [4], M. Julia Brosnan [5], Max Nieuwdorp [1], Patrick M. Bossuyt [2] and Adriaan G. Holleboom [1]

LITMUS Progress Across Key Domains



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An Integrated Multi-Omics Strategy for Biomarker Discovery

- **Genome-wide genetic variation profiling**
  - Anstee, Q.M., *et al.* Genome-wide association study of non-alcoholic fatty liver and steatohepatitis in a histologically characterised cohort. *J Hepatol* **73**, 505-515 (2020).
- **Hepatic Transcriptomic profiling**
  - Govaere, O., *et al.* Transcriptomic profiling across the nonalcoholic fatty liver disease spectrum reveals gene signatures for steatohepatitis and fibrosis. *Sci Transl Med* **12**, eaba4448 (2020).
- **Circulating epigenetic variation profiling**
  - Cell-free DNA methylation profiling
    - Data on file
  - miRNA expression profiling
    - Johnson, K., *et al.* Increased serum miR-193a-5p during non-alcoholic fatty liver disease progression: Diagnostic and mechanistic relevance. *JHEP Rep* **4**, 100409 (2022).
- **Circulating Proteomic profiling**
  - Goveare et al, Proteo-transcriptomics identifies circulating protein signatures associated with disease activity in Non-alcoholic Fatty Liver Disease, (2022), *submitted*.
- **Circulating Metabolomic/Lipidomic profiling**
  - McGlinchey, A.J., *et al.* Metabolic signatures across the full spectrum of non-alcoholic fatty liver disease. *JHEP Rep* **4**, 100477 (2022).
  - Sen, P., *et al.* Quantitative modeling of human liver reveals dysregulation of glycosphingolipid pathways in nonalcoholic fatty liver disease. *iScience* **25**, 104949 (2022).

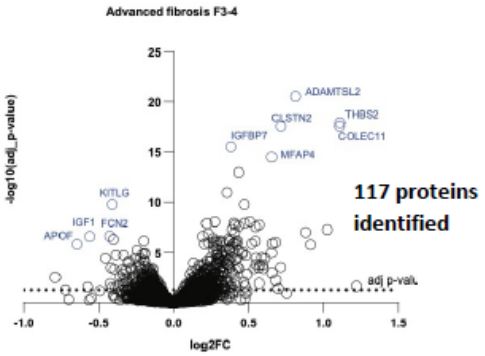
Circulating Proteomic Biomarker Signatures

SOMAscan (v.4.0) in 191 'Discovery' NAFLD samples

Dynamic protein expression changes as disease progresses

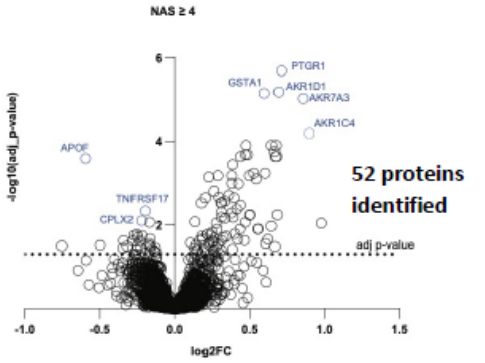
Correlation to Hepatic Gene Expression in 52 paired liver tissue samples to establish source (plus scRNAseq cellular

Model Building & Validation

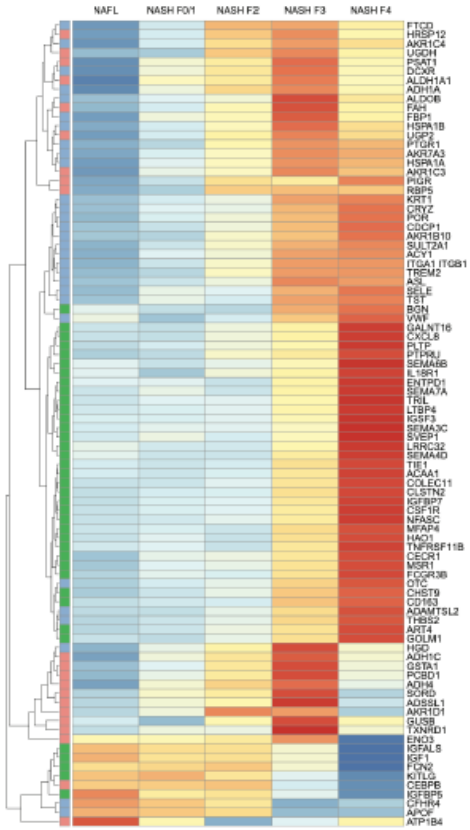


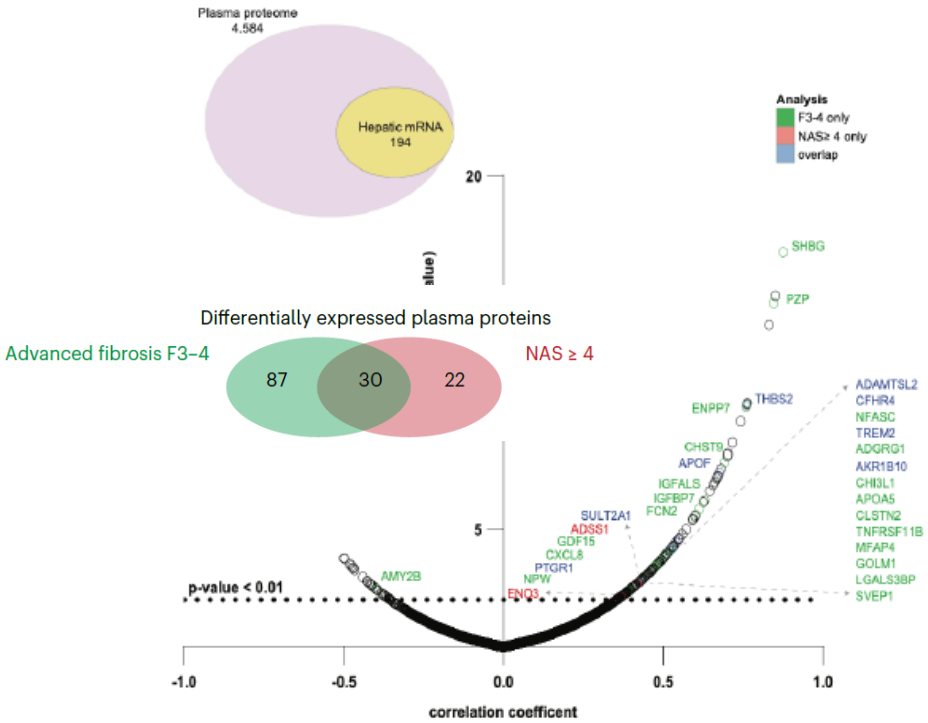
117 proteins identified

30 proteins in common



52 proteins identified





194 genes/proteins correlation between blood/liver.
31 differentially expressed with F≥3/NAS≥4 (8 in both).

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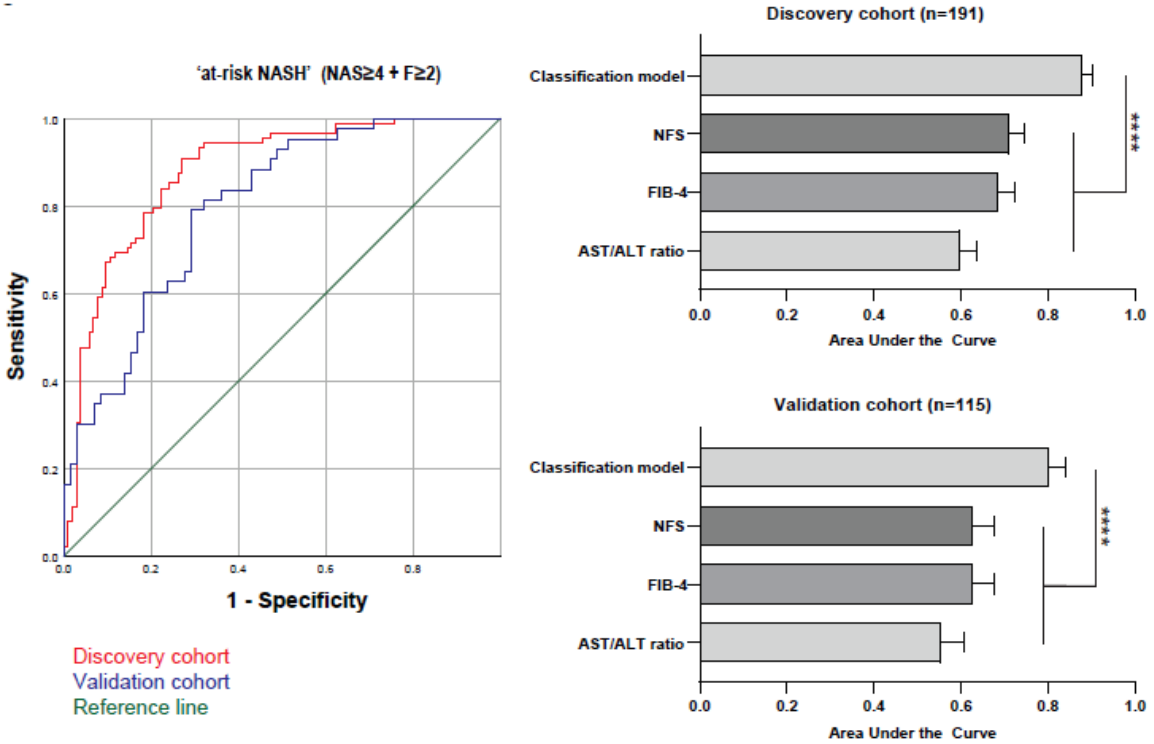
Goveare et al, *Proteo-transcriptomics identifies circulating protein signatures associated with disease activity in Non-alcoholic Fatty Liver Disease,* in review.

Circulating Proteomic Biomarker Signatures

SOMAscan (v.4.0) in 191 'Discovery' NAFLD samples → Dynamic protein expression changes as disease progresses → Correlation to Hepatic Gene Expression in 52 paired liver tissue samples to establish source (plus scRNAseq cellular deconvolution) → Model Building & Validation



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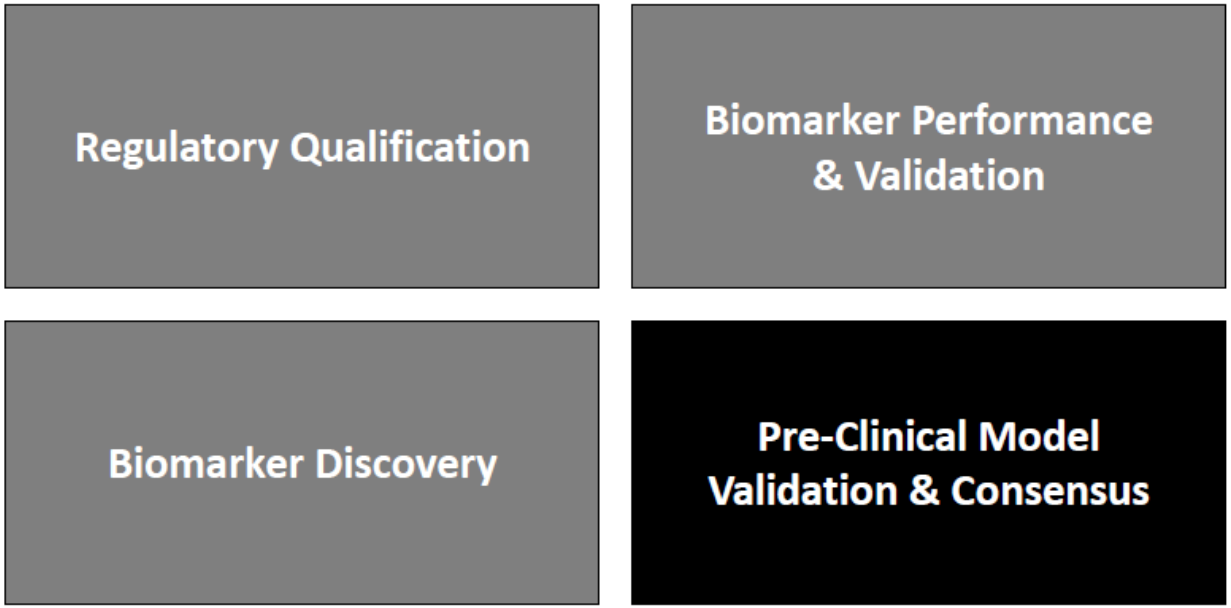
LITMUS Progress Across Key Domains



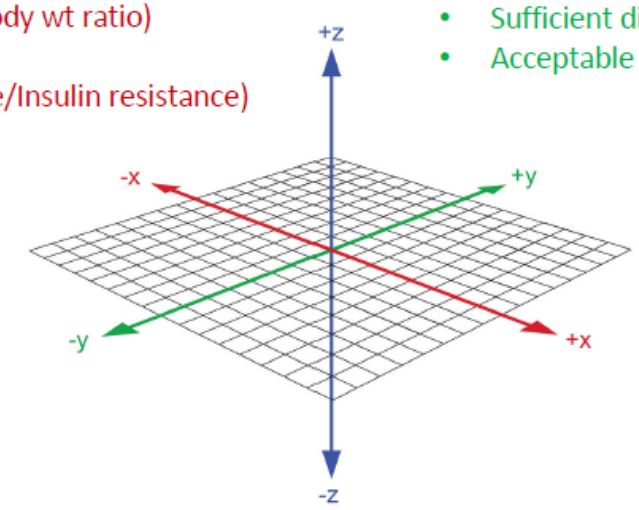
Comparative Biology & The LITMUS 'Human Proximity Score'

PHENOTYPE "Human Proximity Score" (PHPS)

- **Metabolic Syndrome & Obesity as NAFLD drivers**
- Body composition (obesity, liver:body wt ratio)
- Biochemistry (ALT, AST)
- Carbohydrate metabolism (Glucose/Insulin resistance)
- Lipid metabolism

HISTOLOGY "Human Proximity Score" (HHPS)

- **Presence of key histological features (ie NASH + progressive Fibrosis)**
- Sufficient disease grade/stage
- Acceptable disease progression timescale



PHPS + HHPS + DHPS =
Overall "NASH Human Proximity Score"

LITMUS Preclinical Model Biobank

- 42 Murine Models
- 617 Animals

With

- Phenotype
- Centralised Histology
- NGS
- Frozen tissues

- High Fat Diets (HFD)
- Western Diets (WD) AKA "Atherogenic"
- American Lifestyle Diets (ALD)
- Choline Deficient Diets (CD)

DRUG SET ENRICHMENT ANALYSIS "Human Proximity Score" (DHPS)

- **Recapitulates molecular events occurring in humans**
- RNASeq transcriptomic analysis (cf human data: Govaere, 2020; Cazanave 2017, etc)
- Consideration of inflammatory/fibrotic & metabolic signatures

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Vacca et al, Abstract #2704, Oral Presentation EASL 2022

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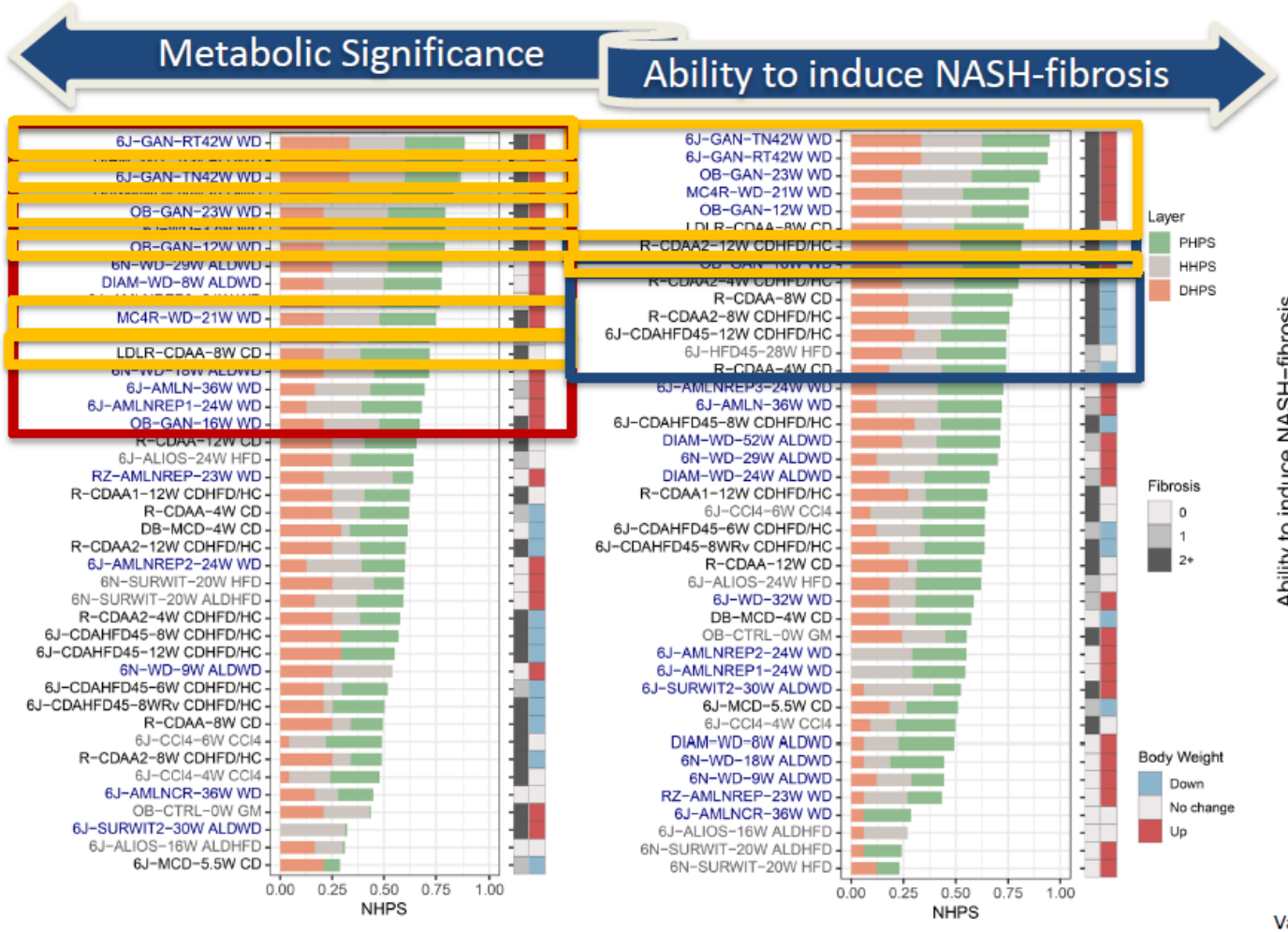
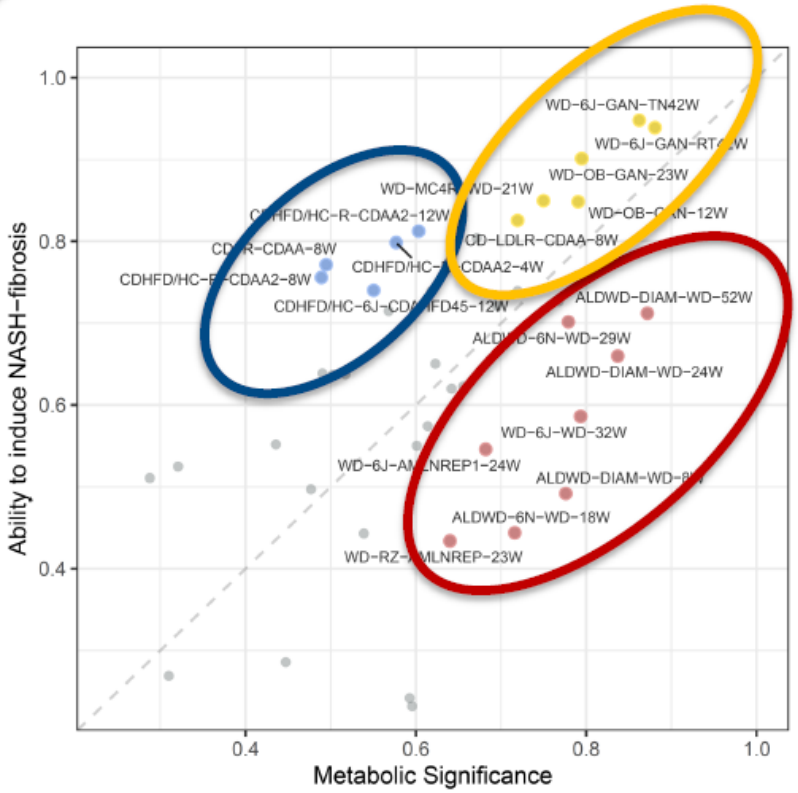
Overall NASH "Human Proximity Score" (NHPS)





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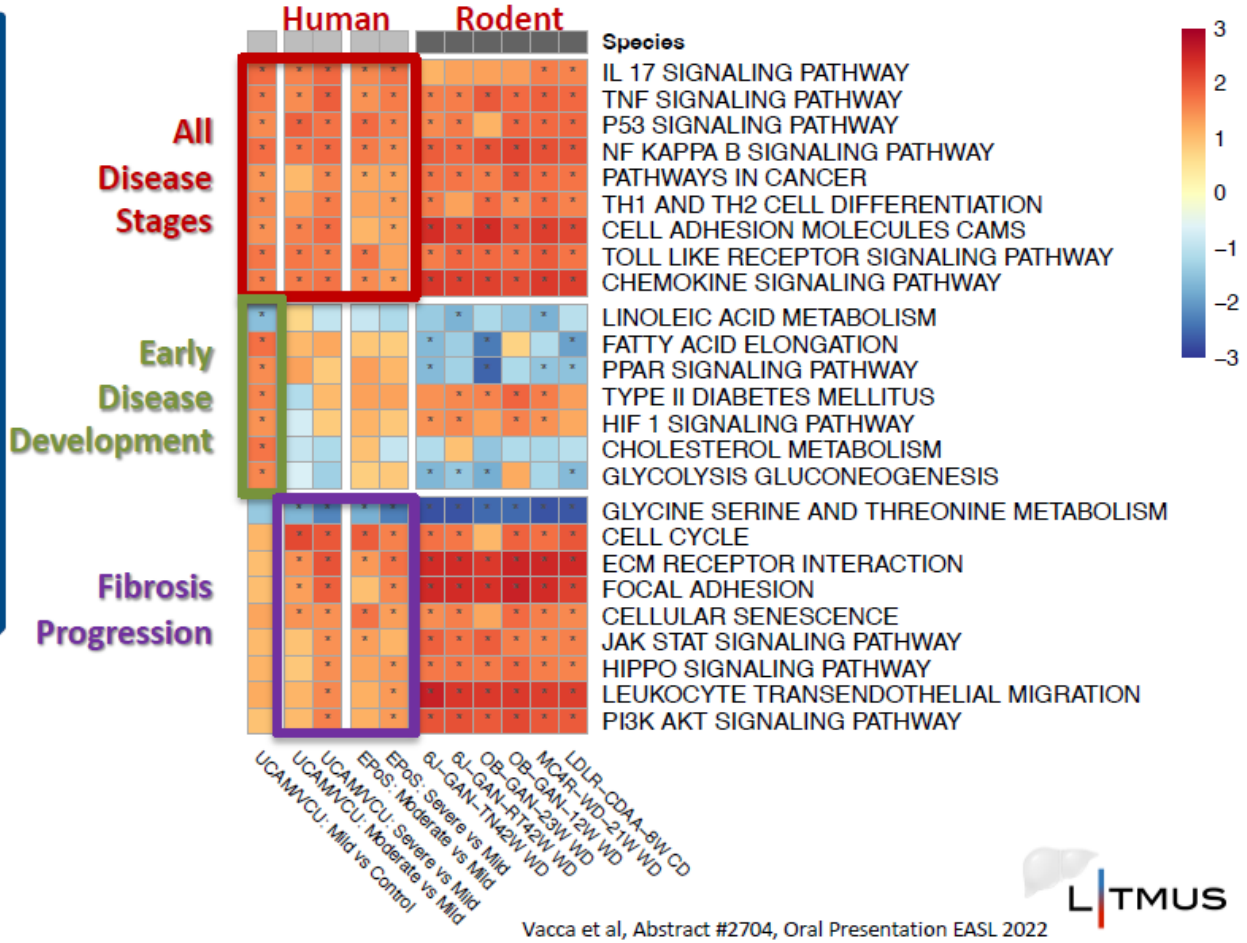
NASH "Human Proximity Score"– Models Highly Ranked

WD2%Chol ("Gubra Amylin NASH" - GAN)
- RD D09100310
- WT(42Weeks) or ob/ob (12/23 Weeks)

WD0.2%Chol ("Atherogenic")
- RD D12079B
- MC4R KO (21 Weeks) – but not in WT!

CD ("Choline-deficient L-amino-defined" - CDAA)
- RD A08111307
- LDLR KO mice (8 Weeks) – but not in WT!



Vacca et al, Abstract #2704, Oral Presentation EASL 2022

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Conclusions

- LITMUS is a focused, pragmatic and goal-oriented programme, founded on a strong track-record of NAFLD research, that addresses the pressing need for validated non-invasive biomarkers.
- The LITMUS ambition is to make a fundamental difference to the way NAFLD/NASH is diagnosed, clinical trials are conducted and the way patients are managed.

LITMUS has the demonstrable capacity to provide much needed clarity on biomarker validity *at scale and pace* and thus deliver a step change in drug development and the care of patients with NAFLD

- LITMUS has made rapid progress across both the clinical platform and the evaluation platform – further outputs expected in coming months.


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