Optimizing Prescreen Strategies to Minimize Screen Failures

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Goals

- Screen more – utilizing effective screening strategies
- Biopsy only those in need
- Screen fail less
- Complete enrollment of trial on time or even early!

Current Requirement for NASH Patients in Phase 2 & 3 Clinical Trials

Ph 3 trials: 7600 Subjects
Ph 2 trials: 2400 Subjects

10,000

Majority F2/3 Fibrosis

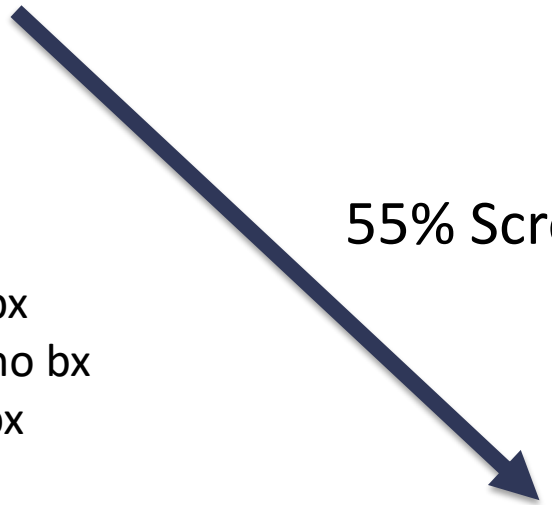
Likely 1-2000 more NASH subjects required in 2018 for new phase 2 and 3 studies starting

Screen Fail Rates for Current and Recently Completed NASH Trials

~55-60%

Number of NAFLD Patients Required to Screen for Current NASH Studies Given Screen Fail Rate

22,225 NAFLD Subjects Screened



55% Screen Fail Rate

~ cost per SF:
-$2000 w/o MRI or bx
-$5000 w/MRI, but no bx
-$8000 w/MRI and bx

10,000 NASH Subjects Randomized

*Also includes indirect CRO costs (logistics, central reading, monitoring of screening visits, etc
* Historical biopsies are still being utilized in about 1/3 of cases. This would bring the cost down some

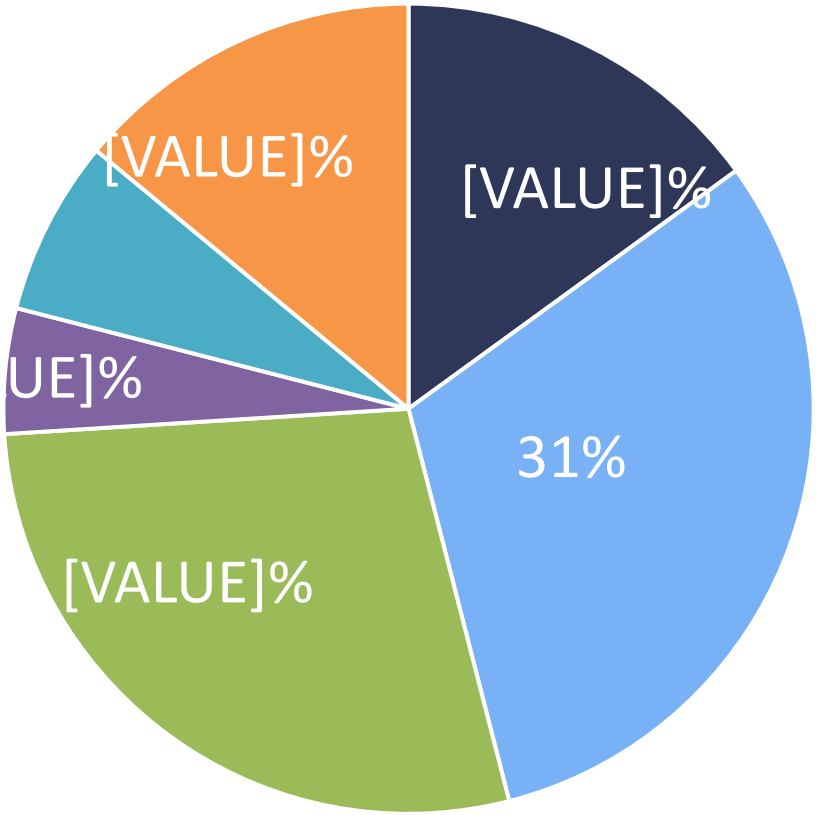
Why Do Patients Screen Fail

- Failed biopsy qualification- majority (>50%)
- Do not meet Inclusion/Exclusion criteria
  - Screening labs, medical history (not known at prescreening), con-meds, AE/SAE during screening period
- Failed image qualification
  - Focus on prescreen fibroscan with CAP feature if available
- Withdrew consent

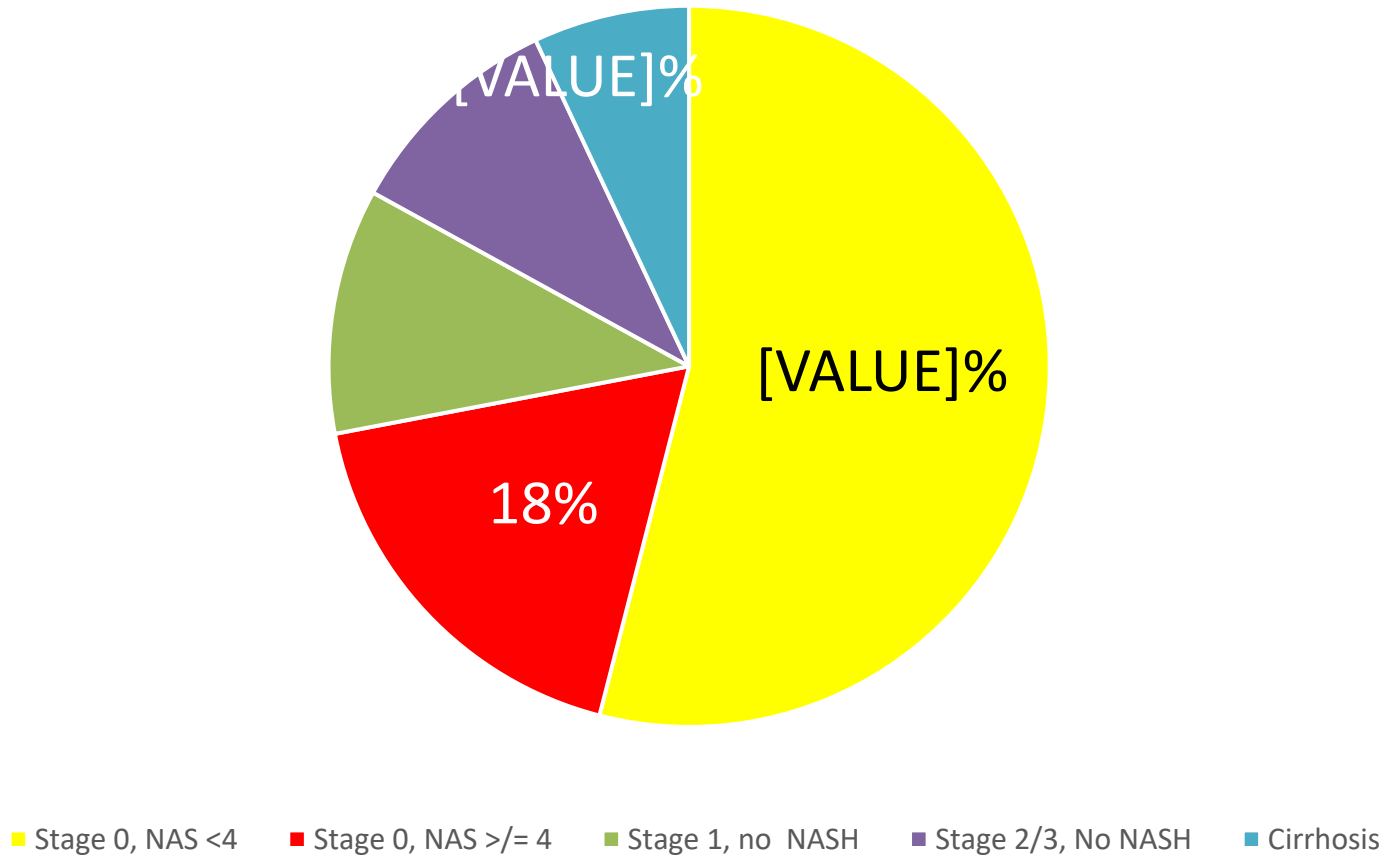
Non Histological Reasons for Screen Fail in large phase 3 trials

- Lab: 20%
- Consent withdrawn: 7%
- Medical history: 5.5%
- Con-meds: 5%
- Compliance: 4%
- AE/SAE: 1%

Histological Reasons for Screen Failing in a Large Phase 3 trial (Based on F2/F3 and NAS of at Least 4)



Histological Reasons for Screen Failing in a Large Phase 2 Trial

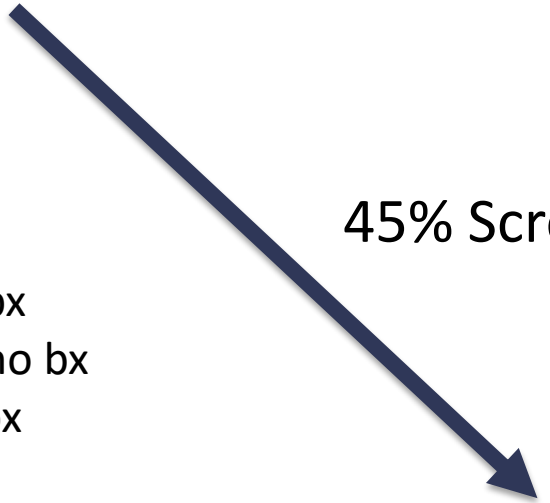


What if???

- The screen fail rate dropped by 10%
  - Cost Savings-Huge
  - Shorten recruiting timelines (additional cost savings)
  - Maintain site motivation
  - Patients remain optimistic about therapeutic options (not discouraged because they screen fail once or sometimes more than once)

Number of NAFLD Patients Required to Screen for Current NASH Studies Given Screen Fail Rate

18,180 NAFLD Subjects Screened



45% Screen Fail Rate

~ cost per SF:
-$2000 w/o MRI or bx
-$5000 w/MRI, but no bx
-$8000 w/MRI and bx

10,000 NASH Subjects Randomized

Dropping SF rate from 55% to 45%, reduced the number needed to screen by 4,045 subjects. Assuming all made it to liver biopsy, this would be a cost savings of 20 to 30 million US dollars.

Shorten Recruiting Timelines

- A phase 2 study enrolling 200 subjects
  - 50 sites
  - Screening 1.50 subjects per site/month = 75 screens/month
  - Screen fail rate 55%: 33.75 subjects randomized per month
  - 5.9 months to enroll study
- Dropping screen fail rate to 45%:
  - 4.8 months to enroll study

This 10% Improvement Can Be Achieved by Focusing On Biopsy Qualification

Utilization of Non-Invasive Surrogates Can Help Risk Stratify Patients and Decrease Screen Failure due to Histopathology

Patient case: 56-year-old hispanic female with obesity, T2DM, and ALT elevation

Referred by PCP for:

- Mild ALT/AST elevation (70/63)
- Other liver chemistries normal over past year
- Ferritin 500 ng/ml
- No current medication

Past medical history

- Dyslipidemia
- T2DM

Family history

- Mother: diabetes, hypothyroid
- Father: alcohol-related cirrhosis

Physical exam

- BP 130/85
- BMI: 32, central obesity
- Acanthosis nigricans
- No stigmata of cirrhosis, liver 3 cm below costal margin
- Normal cardiopulmonary exam
- No splenomegaly
- Normal skin and nails

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; PCP, primary care physician; T2DM, type 2 diabetes mellitus.

Non-invasive tests for liver fibrosis

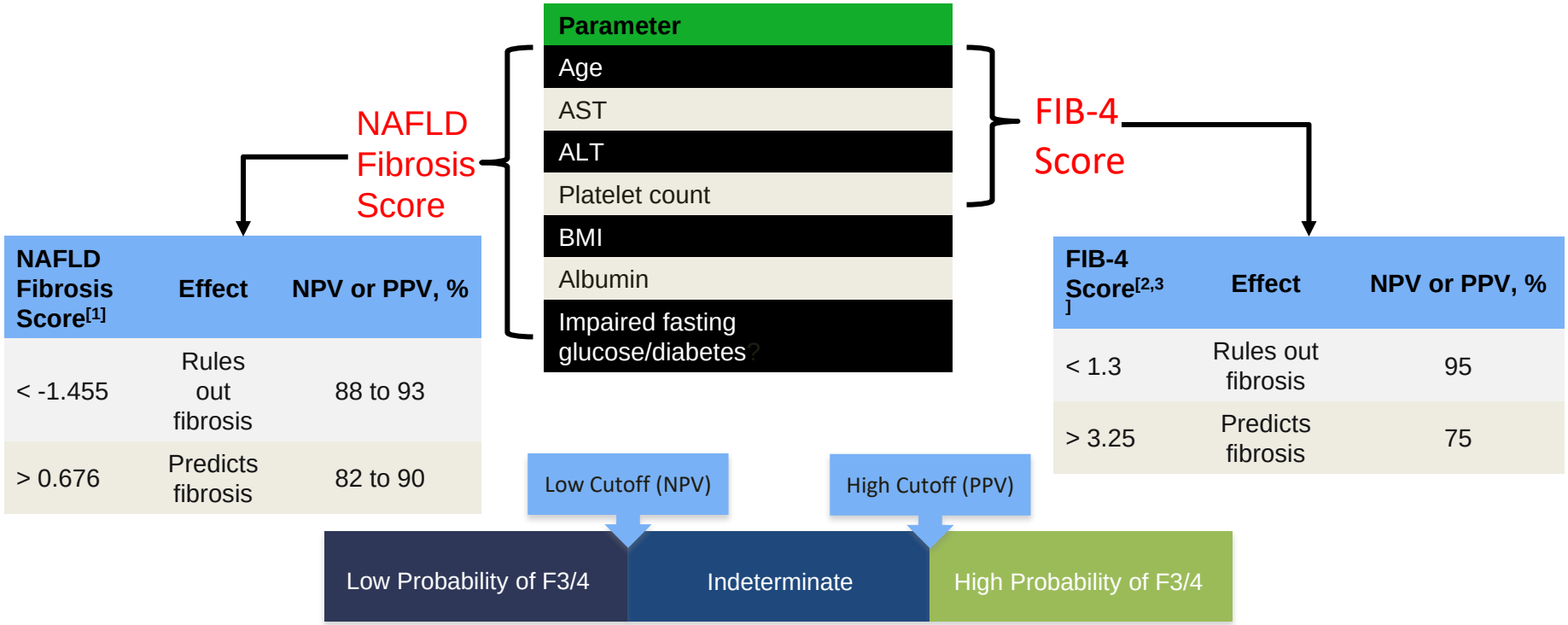
Clinical or laboratory tests

- NAFLD fibrosis score
- FIB-4 index
- BARD
- AST/ALT ratio

Imaging modalities

- Shear-wave elastography
  - SWE, VCTE, ARFI
  - MRE
- MRI-based
  - Liver MultiScan

ALT, alanine aminotransferase; ARFI, acoustic radiation force impulse; AST, aspartate aminotransferase; MRE, magnetic resonance elastography; MRI, magnetic resonance imaging; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis



NAFLD Fibrosis Score[1]	Effect	NPV or PPV, %
< -1.455	Rules out fibrosis	88 to 93
> 0.676	Predicts fibrosis	82 to 90

FIB-4 Score[2,3]	Effect	NPV or PPV, %
< 1.3	Rules out fibrosis	95
> 3.25	Predicts fibrosis	75

1. Angulo P, et al. Hepatology. 2007;45:846-854. 2. Sterling RK, et al. Hepatology. 2006;43:1317-1325.
3. McPherson S, et al. Gut. 2010;59:1265-1269.

Back to our case…
NAFLD fibrosis score and FIB-4

NAFLD fibrosis score: **2.00**

Parameter	Patient
Age, years	56
AST	63
ALT	70
Platelet count, cells x 10^9	200
BMI	32
Albumin, g/L	4.0
Impaired fasting glucose/diabetes?	Yes

FIB-4 score: **2.11**

NAFLD cutoff value[1]	Stage
<−1.455	F0–F2
−1.455 to 0.676	Indeterminate
> 0.676	F3–F4

FIB-4 cutoff value[2]	Stage
< 1.45	F0–F2
1.45 to 3.25	Indeterminate
> 3.25	F3–F4

May not be accurate at extremes of age[3]

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; NAFLD, non-alcoholic fatty liver disease.

1. Angulo P, et al. *Hepatology*. 2007;45:846-854. 2. Sterling RK, et al. *Hepatology*. 2006;43:1317-1325. 3. McPherson S, et al. *Am J Gastroenterol*. 2016;[Epub ahead of print].

- Study comparing identification of F3/4 in pts with NAFLD (N = 145)

Test	AUC (95% CI)	Cutoff	Sens, %	Spec, %	PPV, %	NPV, %
AST/ALT ratio	0.83 (0.74-0.91)	0.8 1	74 52	78 90	44 55	93 89
APRI	0.67 (0.54-0.8)	1	27	89	37	84
BARD score	0.77 (0.68-0.87)	2	89	44	27	95
FIB-4 score	0.86 (0.78-0.94)	1.30 3.25	85 26	65 98	36 75	95 85
NAFLD fibrosis score	0.81 (0.71-0.91)	-1.455 0.676	78 33	58 98	30 79	92 86

McPherson S, et al. Gut. 2010;59:1265-1269.

VCTE (FibroScan) technology overview

Non-invasive quantification of two physical biomarkers of the liver within a 10 minute examination:

Liver stiffness	CAP
• Obtained through a VCTE measurement • Correlated to extent of fibrosis	• Quantification of ultrasound attenuation obtained in VCTE measurement • Correlated to liver steatosis

Both biomarkers can be used to assess disease severity in different etiologies including NASH

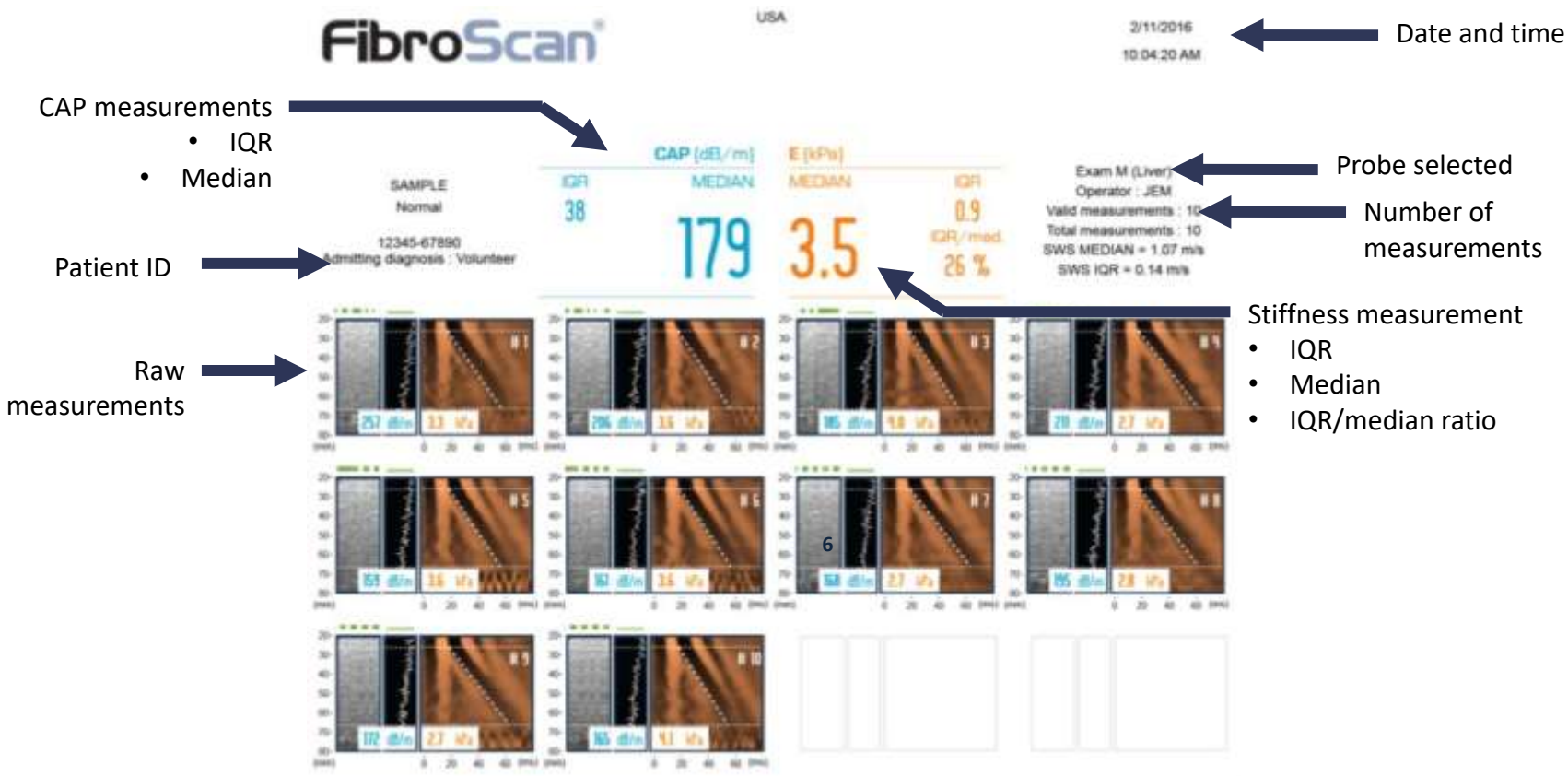
FibroScan 502 Touch

FibroScan 530 Compact

FibroScan M & XL Probes

CAP, controlled attenuation parameter; NASH, non-alcoholic steatohepatitis; VCTE, vibration-controlled transient elastography.

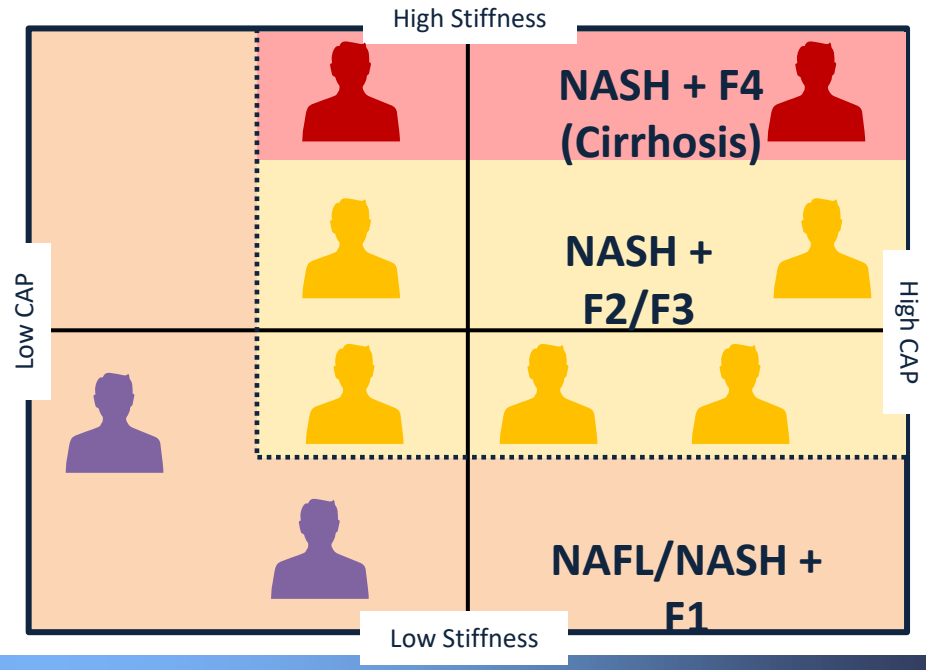
The FibroScan output interface



Patient enrollment will be a challenge without non-invasive technology

Mixed patient population with suspected NASH

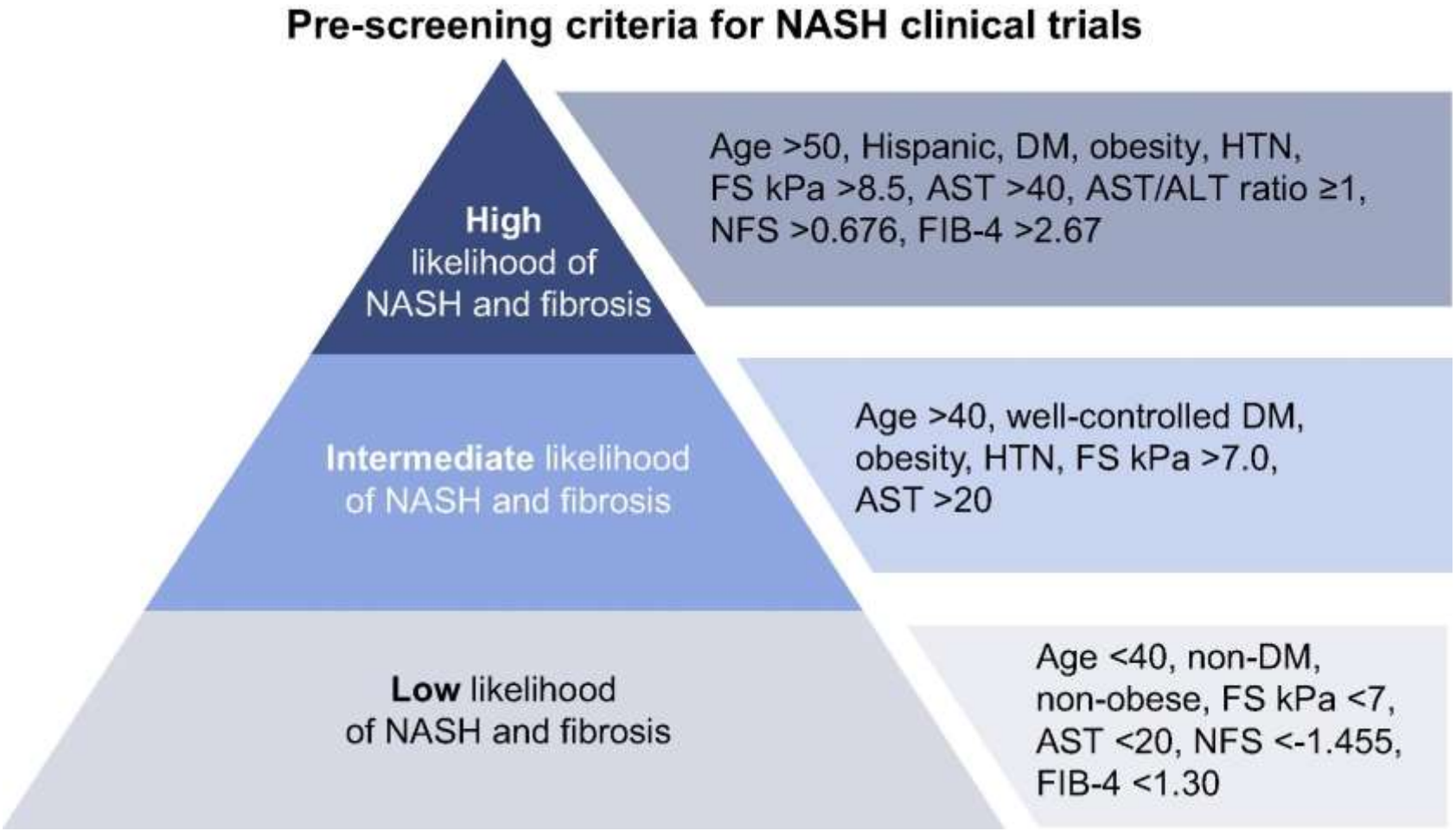
Stratify patients



Non-invasive technologies allow for **rapid patient stratification** for efficient patient selection into NAFL / NASH clinical trials.

NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.

Putting It All Together



Konerman et al, J Hepatol 2018

Ongoing Phase 2 Study: Real Life Example

- Pre-protocol amendment
  - Screen failure due to liver biopsy was 70%
- Amendment included the following changes:
  - Addition of Fibroscan CAP ≥ 270
  - Addition of Fibroscan kPa >8.4
  - AST >20 U/L
- Post-protocol amendment
  - Screen failure due to liver biopsy 52% (Δ 18%)!!

Next Steps

- Obtain clinical, serological and imaging (fibroscan) data from screening activity for as many studies as possible (completed and ongoing)
- Collate the data in an agnostic format
- Assess data for combination criteria that correlate best with:
  - NASH and stage 1 fibrosis
  - NASH and stage 2-3 fibrosis
  - NASH and cirrhosis

Thank You