NASH Screening and Diagnosis in Specialty Clinics: The Role of Radiologic Modalities, Serum Fibrosis Tests and Algorithm

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Outline

• Epidemiology – Genetics
• New advances in non-invasive assessment
• Predictors of treatment response
Epidemiology: Burden of NAFLD

• Globally, nonalcoholic fatty liver disease (NAFLD) is present in 1 in 4 people\textsuperscript{1}

• Ethnic predisposition
  – More common in Asian Indians > Hispanics > Caucasians > African Americans

• Risk factors include MetS
  – Obesity, hypertension, hypertriglyceridemia, insulin resistance and diabetes
  – PNPLA3, TM6SF2, MBOAT7 genotype
  – HSD17B13

• NAFLD is diagnosed
  – Either on biopsy or imaging evidence of hepatic steatosis (≥ 5% liver fat) in individuals who consume little or no alcohol without any other cause for liver disease or hepatic steatosis

\textsuperscript{1} Younossi et al. Hepatology. 2015;64:73–84.
Stage 2 Fibrosis Is the Tipping Point for Liver Related Mortality

Impact of fibrosis on clinical outcomes in a meta-analysis of five multinational cohorts (17,452 patient-years of follow-up)

Risk of liver-related mortality increases exponentially with increasing fibrosis stage

CI, confidence interval; PYF, patient-years of follow-up; NASH, non-alcoholic steatohepatitis.
Who Needs to Be Treated?

- NAFLD: Stage 0-1
- NASH: ≥ stage 2 fibrosis
- NASH with advanced fibrosis (stage 3 and 4)
- NASH/NAFLD cirrhosis
- NAFLD cirrhosis with decompensation

Organisations Are Currently Reflecting on the Future Use of Non-Invasive Testing

Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment
Guidance for Industry


EMA: European Medicines Agency; FDA: Food and Drugs Administration.
Exploring Non-Invasive Tests: Fibrosis-4 (FIB-4) Index and NAFLD Fibrosis Score

Fibrosis-4 (FIB-4) index
- Predicts advanced fibrosis in the liver
  - Age (years)
  - ALT (U/L)
  - AST (U/L)
  - Platelet count (x$10^9$/L)

Understanding the score:
- Score <1.3
  - Rules out advanced fibrosis
    (Sn: 74%; Sp: 71%)
- Score >2.67
  - Predicts advanced fibrosis
    (Sn: 33%; Sp: 98%)
- Indeterminate

NAFLD fibrosis score (NFS)
- Predicts liver fibrosis in patients with NAFLD
  - Age (years)
  - Albumin (g/dL)
  - ALT (U/L)
  - AST (U/L)
  - BMI (kg/m$^2$)
  - Hyperglycaemia
  - Platelet count (x$10^9$/L)

Understanding the score:
- Score <1.455
  - Rules out fibrosis
    (Sn: 82%; Sp: 77%)
- Score >0.676
  - Predicts fibrosis
    (Sn: 51%; Sp: 98%)
- Indeterminate

Sn: sensitivity; Sp: specificity.
Exploring Non-Invasive Tests: Enhanced Liver Fibrosis (ELF) Score

- Proprietary blood test that delivers information on liver fibrosis severity
- Algorithm incorporating 3 common serum biomarkers:
  - HA (hyaluronic acid)
  - PIIINP (amino-terminal propeptide of type III procollagen)
  - TIMP-1 (tissue inhibitor of metalloproteinase-1)

Understanding the score:

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
<th>Sn (%)</th>
<th>Sp (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.7</td>
<td>Rules out fibrosis</td>
<td>97</td>
<td>33</td>
</tr>
<tr>
<td>9.8</td>
<td>Predicts fibrosis</td>
<td>69</td>
<td>98</td>
</tr>
<tr>
<td>11.3</td>
<td>Predicts cirrhosis</td>
<td>83</td>
<td>97</td>
</tr>
</tbody>
</table>

ELF ≥9.8 is associated with advanced fibrosis

Can Longitudinal ELF Data Predict Progression to Cirrhosis and Liver-Related Outcomes?
In a Patient With NAFLD and Bridging Fibrosis, What Cutpoint Predicts High Risk of Progression to Cirrhosis?

- A: ELF $\geq 8.8$
- B: ELF $\geq 9.8$
- C: ELF $\geq 11.3$
- D: ELF $\geq 14.0$
In a Patient With NAFLD and Fibrosis, What Cutpoint Predicts High Risk of Progression to Cirrhosis?

A. ELF >8.8
B. ELF >9.8
C. ELF >11.3
D. ELF >14.0
ELF Predicts Progression More Accurately Than Biopsy

- Phase 2 simtuzumab in NASH and F3–F4

Higher baseline ELF and greater change in ELF were associated with increased risk of progression to cirrhosis.

Optimal threshold of baseline ELF: 9.76 (sensitivity 77%, specificity 66%)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Adjusted HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline ELF</td>
<td>3.20 (2.33, 4.39)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change in ELF</td>
<td>1.60 (1.19, 2.16)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Ishak stage 4 vs 3</td>
<td>0.87 (0.47, 1.59)</td>
<td>0.64</td>
</tr>
</tbody>
</table>

CI, confidence interval; ELF, enhanced liver fibrosis; HR, hazard ratio.

Patients with NASH and bridging fibrosis (n=219) or compensated cirrhosis (n=258) enrolled in two Phase 2b SIM studies.
ELF Predicts Progression More Accurately Than Biopsy

- Phase 2 simtuzumab in NASH and F3–F4

Higher baseline ELF and greater change in ELF were associated with liver-related clinical events

Liver-Related Clinical Events According to Baseline ELF

<table>
<thead>
<tr>
<th>Month</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
<th>36</th>
<th>42</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival Free From Liver-Related Clinical Events, %</td>
<td>100</td>
<td>80</td>
<td>60</td>
<td>40</td>
<td>20</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Log-rank $p<0.001$

HR 2.93 (95% CI 1.64, 5.23)

Predictors of liver-related clinical events

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Adjusted HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline ELF</td>
<td>2.40 (1.70, 3.38)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change in ELF</td>
<td>1.53 (1.09, 2.14)</td>
<td>0.01</td>
</tr>
<tr>
<td>Ishak stage 6 vs 5</td>
<td>0.89 (0.47, 1.68)</td>
<td>0.71</td>
</tr>
</tbody>
</table>

Optimal threshold of baseline ELF: 9.76 (sensitivity 77%, specificity 66%)

CI, confidence interval; ELF, enhanced liver fibrosis; HR, hazard ratio.
Noninvasive Assessment of Steatohepatitis and Advanced Fibrosis in NAFLD

- **NAFLD Fibrosis Score and FIB-4**
  - Identification of NAFLD patients with higher risk of stage 3–4 fibrosis

- **VCTE and MRE**
  - Identification of advanced fibrosis in NAFLD patients

Optimal Strategy for Population at Risk Management
Optimizing Risk Management

100 million Americans with suspected NAFLD

Rule-out advanced fibrosis (FIB-4 or NAFLD Fibrosis Score)

- **FIB-4 < 1.3**
  - NFS ≤ −1.455
  - NPV 88–95%
  - **Low risk**
  - No further assessment
  - Repeat evaluation at 1 year

- **FIB-4: 1.3–2.67**
  - NFS: −1.455–0.672
  - **Intermediate risk**
  - 60–70 million can be excluded

- **FIB-4 > 2.67**
  - NFS > 0.672
  - PPV 75–90%
  - **High risk**
  - Next step – elastography
  - or ELF ≥ 9.8
  - Or FIBROspect2 ≥ 17

ELF, Enhanced Liver Fibrosis; NFS, NAFLD Fibrosis Score; NPV, negative predictive value.
Step 2: Suspected NAFLD referral (excluded low FIB-4)

- Ascites, CHF, severely high ALT
  - Risk factors for other liver disease
    - Yes: Clinical work-up and consider biopsy if needed
    - No: VCTE/SWE/ARFI

- BMI >35 kg/m²
  - No: MRE
  - Yes: MRE

  - Failed or unreliable results
    - Yes: Liver biopsy
    - No: MRE <2.55 kPa

  - VCTE/SWE/ARFI
    - No: Failed or unreliable results
      - Yes: MRE
      - No: VCTE <6 kPa
        - No biopsy

  - VCTE <7.9 kPa
    - Low risk for advanced fibrosis
  - MRE <2.99 kPa
    - High risk for advanced fibrosis
      - VCTE >9.9 kPa – 83% accuracy
      - MRE >3.63 kPa – 93% accuracy
Hierarchy of Imaging-Based Modalities Upon Evidence

Accuracy

CPR | Fib-4 | VCTE | MRE
Genetic Risk Score of Cirrhosis

C. Multi-trait cirrhosis GWAS

-log_{10}(p)

Chromosome

1 2 3 4 5 6 7 8 9 11 13 15 17 20

PNPLA3

EFNA1
MARC1
HSD17B13
ARHGEF28
TOR1B
SERPINA1
APOE
TM6SF2

Role of FAST in Detection of High-Risk NASH

**FAST for NASH**

```
<table>
<thead>
<tr>
<th>AUROC (95% CI)</th>
<th>n</th>
<th>Prevalence of NASH + NAS ≥ 4 + F≥2</th>
<th>Rule-out zone (FAST ≥ 0.35)</th>
<th>Grey zone (FAST 0.35-0.67), n (%)</th>
<th>Rule-in zone (FAST ≥ 0.67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Derivation cohort</td>
<td>0.80</td>
<td>(0.76-0.85)</td>
<td>350</td>
<td>174 (50%)</td>
<td>113 (32%)</td>
</tr>
<tr>
<td>French bariatric surgery cohort</td>
<td>0.95</td>
<td>(0.91-0.99)</td>
<td>110</td>
<td>16 (15%)</td>
<td>69 (63%)</td>
</tr>
<tr>
<td>USA screening cohort</td>
<td>0.86</td>
<td>(0.80-0.93)</td>
<td>242</td>
<td>28 (12%)</td>
<td>194 (80%)</td>
</tr>
<tr>
<td>China Hong-Kong NAFLD cohort</td>
<td>0.95</td>
<td>(0.76-0.93)</td>
<td>83</td>
<td>36 (43%)</td>
<td>28 (34%)</td>
</tr>
<tr>
<td>China Wuhan NAFLD cohort</td>
<td>0.84</td>
<td>(0.72-0.95)</td>
<td>104</td>
<td>9 (9%)</td>
<td>55 (53%)</td>
</tr>
<tr>
<td>French NAFLD cohort</td>
<td>0.80</td>
<td>(0.73-0.86)</td>
<td>182</td>
<td>78 (43%)</td>
<td>67 (37%)</td>
</tr>
<tr>
<td>Malaysian NAFLD cohort</td>
<td>0.85</td>
<td>(0.78-0.91)</td>
<td>176</td>
<td>36 (20%)</td>
<td>78 (44%)</td>
</tr>
<tr>
<td>Turkish NAFLD cohort</td>
<td>0.74</td>
<td>(0.65-0.82)</td>
<td>129</td>
<td>74 (57%)</td>
<td>26 (20%)</td>
</tr>
<tr>
<td>Pooled external patients cohort</td>
<td>0.85</td>
<td>(0.83-0.87)</td>
<td>1026</td>
<td>277 (27%)</td>
<td>517 (51%)</td>
</tr>
</tbody>
</table>
```

**FAST: CAP+LSM+AST**

Main issue is low PPV: 0.33-0.83

Utility of Magnetic Resonance Elastography in Accurate Identification of Candidates for Pharmacologic Treatment of NASH Related Fibrosis: A Prospective Cohort Study

Combination of imaging and serum markers (MRE ≥ 3.3kPa and FIB-4 ≥ 1.6) yielded a high positive predictive value (97.1) for a clinician to rule in clinically significant disease that needs pharmacologic treatment in NAFLD.

Predicting Treatment Response
A ≥ 17 IU/L decline in serum ALT is associated with higher odds of histologic response to OCA/Placebo
Key Clinically Useful Predictors of Response Assessment With OCA

In addition, significant reductions in AST, GGT, APRI and FIB-4 were also noted

Loomba et al. Poster LBP-019.
Combination Therapy and NIT Data
Safety and Efficacy of Combination Therapies Including Semaglutide, Cilofexor, and Firsocostat in Patients With NASH

There were similar relative reductions in body weight across groups

Data collected beyond 30 days after last dose of any study drug excluded from analysis. Changes in PDFF based on ANCOVA models adjusted for BL and diabetes status.

*p<0.05 vs SEMA alone.

Numerically Greater Improvements in Liver Stiffness by VCTE in Combination Therapy

### Absolute Change at Week 24

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean Change (95% CI), kPa</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEMA</td>
<td>-2.9 (-7.5, 2.3)</td>
</tr>
<tr>
<td>SEMA + FIR</td>
<td>-3.5 (-5, 0)</td>
</tr>
<tr>
<td>SEMA + CILO 30 mg</td>
<td>-3.2 (-5, 0)</td>
</tr>
<tr>
<td>SEMA + CILO 100 mg</td>
<td>-2.3 (-5, 0)</td>
</tr>
<tr>
<td>SEMA + FIR + CILO 30 mg</td>
<td>-3.7 (-5, 0)</td>
</tr>
</tbody>
</table>

### ≥25% Reduction at Week 24

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Response Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEMA</td>
<td>36</td>
</tr>
<tr>
<td>SEMA + FIR</td>
<td>14/19 (72%)</td>
</tr>
<tr>
<td>SEMA + CILO 30 mg</td>
<td>20/12 (66.7%)</td>
</tr>
<tr>
<td>SEMA + CILO 100 mg</td>
<td>16/6 (25%)</td>
</tr>
<tr>
<td>SEMA + FIR + CILO 30 mg</td>
<td>17/9 (52.9%)</td>
</tr>
</tbody>
</table>

- Similar reductions in LS by VCTE between treatment groups
  - No differences in changes in LS by MRE

Changes in LS by VCTE based on ANCOVA models adjusted for BL and diabetes status. ANCOVA, analysis of covariance; BL, baseline; CI, confidence interval; CILO, cilofexor; FIR, firsocostat; LS, liver stiffness; LSmean, least squares mean; MRE, magnetic resonance elastography; SEMA, semaglutide; VCTE, vibration-controlled transient elastography.

FAST Score: Greater Improvements With Combinations

- All combinations, except CILO + FIR 100 mg, led to significantly greater improvements in FAST score vs SEMA alone.

Changes in FAST score based on ANCOVA models adjusted for BL and diabetes status. * p<0.05 vs SEMA alone.

ANCOVA, analysis of covariance; BL, baseline; CI, confidence interval; CILO, cilofexor; FAST, FibroScan-aspartate aminotransferase; FIR, firsocostat; IQR, interquartile range; LSmean, least squares mean; SEMA, semaglutide.

What Is a Clinically Significant Reduction in MRI-PDFF?
Hypothesis: A 30% reduction in MRI-PDFF may be associated with a 2-point improvement in NAFLD Activity Score
A Secondary Analysis of the FLINT Trial

Histologic improvement by relative 72-week change in MRI-PDFF

MRI-PDFF decline by 29% higher odds of histologic response p<0.001

- A 30% reduction in MRI-PDFF is associated with a 2-point improvement in NAS

MRI-PDFF responders had significantly higher odds of histologic response with OR 4.86 (95% CI, 1.6-14.4, p-value <0.0005)

Magnetic Resonance Imaging-Proton Density Fat Fraction (MRI-PDFF) to Predict Treatment Response on NASH Liver Biopsy: A Secondary Analysis of the Resmetirom Randomized Placebo Controlled Phase 2 Clinical Trial

Cutoff 41.5% (Se 82% [61–93%], Sp 83% [74–90%])

- MRI-PDFF >30% reduction: OR 9.1-18.0 NASH Resolution
- MRI-PDFF >40% reduction: OR 16.5
- MRI-PDFF >50% reduction: OR 25.3

Loomba R et al. EASL dILC2020. #AS077.
Rate of histologic response between MRI-PDFF responders versus non-responders

Odds of histologic response between MRI-PDFF responders versus non-responders

- >2-point NAS reduction
  - MRI-PDFF non-responders: 14%
  - MRI-PDFF responders: 51%
  - Odds Ratio: 6.98
- NASH resolution
  - MRI-PDFF non-responders: 7%
  - MRI-PDFF responders: 41%
  - Odds Ratio: 5.45

Stine …….Loomba. CGH 2020 in press.
MRI-PDFF Response Criteria

MRI-PDFF response is defined as a relative decline in MRI-PDFF of ≥ 30% from baseline is associated with

- 2-point improvement in NAFLD activity score
- NASH Resolution
- Not only associated with steatosis improvement but also with ballooning with FXR
- And steatosis, ballooning, inflammation and fibrosis with Resmetirom

• Non-invasive assessment is taking the center stage in risk stratification

• Fibrosis improvement requires longer-term treatment and typically requires liver specific targeted therapies

• MEFIB (MRE ≥ 3.3 Kpa and FIB-4 ≥ 1.6) and/or FAST may be used to screen patients in liver clinics

• MRI-PDFF response defined as ≥ 30% relative decline is associated with 2-point improvement in NAS and NASH resolution
Thank you

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