Algorithm to identify non-alcoholic steatohepatitis (NASH) patients with a NAS≥4 and F≥2:

Derivation in an American screening cohort and validation in a British non-alcoholic fatty liver disease (NAFLD) cohort

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Disclosure

- C. Fournier: Presenter – Full time employee of Echosens.
- The British cohort is from a study sponsored by Echosens.
- The American cohort is from a study financially supported by Echosens.
Agenda

1. Introduction
2. Material and Methods
3. Results
4. Conclusion
Background

- Many ongoing drug clinical trials in NASH
- Depending of the drug mechanism of action different type of patient profiles are needed
- Several ongoing phase 3 trials are looking for patients with biopsy proven NASH AND NAS ≥ 4 AND F23
- The lack of non invasive tools to prescreen patients leads to a relatively high screening failure rate which in turns leads to:
  - Slow patients enrollment
  - Increased trial cost and duration
Objective

- To develop and validate a simple triage algorithm based on routine clinical, biological and/or imaging parameters to screen for patients with **NASH AND NAS ≥ 4 AND F ≥ 2**
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Population

**Derivation population – American cohort**

- One US center
- Patients referred for a colon cancer screening
- FibroScan/MRE/MRI-PDFF/LiverMultiScan performed on all patients without known history of CLD
- Underwent a liver biopsy if:
  - LSM by FibroScan ≥ 7 kPa
  - OR LSM by MRE ≥ 3 kPa
  - OR MRI-PDFF ≥ 5%
  - OR LIF by LiverMultiScan ≥ 2

**Validation population – British cohort**

- 7 UK centers
- Patients undergoing liver biopsy for suspicion of NAFLD

**In all cases:**

- Liver biopsy read centrally by the two same expert pathologists in double-blind with consensus
- Use of NASH CRN scoring system for NAS and fibrosis
- Use of FLIP definition for presence of NASH
Definitions and constraints

In order to assess the performance of the triage algorithm in the context of its use to screen patients for a trial, the following indicators will be used:

➔ **Target patients:**
   Histological enrollment criteria

➔ **Screen failure rate – SFR**
   Proportion of patients sent to liver biopsy that are not the target patients

➔ **Missed case rate – MCR**
   Proportion of patients that meet the target but are not sent to liver biopsy

➔ **Screening improvement rate – SIR**
   Proportion of avoided liver biopsy compared to all patients being sent to liver biopsy

\[
\text{MCR} \quad \frac{\text{SFR}}{\text{SIR}}
\]
Methods

▪ “Target patients”: NASH AND NAS ≥ 4 AND F ≥ 2
▪ Decrease SFR without exceeding 25% of MCR
▪ The following steps were repeated 3 times in the derivation cohort without any a priori:
  1. Univariate analysis between the target patients and all the bio-clinical parameters
  2. Among bio-clinical parameters significantly linked to the target patients, selection of the one with the best diagnostic performance
  3. Definition of selected parameter cut-off value with a high sensitivity
  4. Exclusion of the patients for which the selected parameter is below that cut-off value
▪ The final triage algorithm was then applied to the validation cohort
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## Patient’s characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Derivation</th>
<th>Validation</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>177</td>
<td>381</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>55 [10]</td>
<td>54 [18]</td>
<td>0.05</td>
</tr>
<tr>
<td>Female gender</td>
<td>65 (37%)</td>
<td>170 (45%)</td>
<td>0.10</td>
</tr>
<tr>
<td>BMI</td>
<td>32.5 [6.0]</td>
<td>33.8 [9.3]</td>
<td>0.01</td>
</tr>
<tr>
<td>Obesity</td>
<td>128 (72%)</td>
<td>266 (70%)</td>
<td>0.61</td>
</tr>
<tr>
<td>T2DM</td>
<td>43 (24%)</td>
<td>192 (50%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HTA</td>
<td>88 (50%)</td>
<td>206 (54%)</td>
<td>0.39</td>
</tr>
<tr>
<td>Hypercholema</td>
<td>84 (47%)</td>
<td>198 (52%)</td>
<td>0.40</td>
</tr>
<tr>
<td>LSM</td>
<td>5.8 [3.5]</td>
<td>8.8 [7.8]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CAP</td>
<td>319 [80]</td>
<td>336 [74]</td>
<td>0.006</td>
</tr>
<tr>
<td>NASH</td>
<td>69 (39%)</td>
<td>244 (64%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Target</td>
<td>20 (11%)</td>
<td>173 (45%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Distribution:
- Continuous variable: median [IQR]
- Ordinal/categorical variable: figure (%)

### Group comparison:
- Continuous variable: Mann-Whitney test
- Ordinal/categorical variable: χ² or Fisher-exact

[All these parameters were used as potential candidates to built the triage algorithm]
Optimal algorithm performances

- **Derivation population**

  \[
  \begin{align*}
  \text{N} &= 177 \\
  \text{N}_{\text{Target}} &= 20 \\
  \text{SFR} &= 89\% \\
  \text{MCR} &= 0\% \\
  \text{SIR} &= 0\%
  \end{align*}
  \]

  \[
  \begin{align*}
  \text{STEP 1} &: \text{LSM} \geq 6.8 \text{ kPa} \\
  \text{N} &= 69 \\
  \text{N}_{\text{Target}} &= 16 \\
  \text{SFR} &= 77\% \\
  \text{MCR} &= 20\% \\
  \text{SIR} &= -61\%
  \end{align*}
  \]

  \[
  \begin{align*}
  \text{STEP 2} &: \text{CAP} \geq 300 \text{ dB/m} \\
  \text{N} &= 47 \\
  \text{N}_{\text{Target}} &= 16 \\
  \text{SFR} &= 66\% \\
  \text{MCR} &= 20\% \\
  \text{SIR} &= -73\%
  \end{align*}
  \]

  \[
  \begin{align*}
  \text{STEP 3} &: \text{ALT/ULN} \geq 0.49 \\
  \text{N} &= 37 \\
  \text{N}_{\text{Target}} &= 16 \\
  \text{SFR} &= 57\% \\
  \text{MCR} &= 20\% \\
  \text{SIR} &= -79\%
  \end{align*}
  \]

- **Validation population**

  \[
  \begin{align*}
  \text{N} &= 381 \\
  \text{N}_{\text{Target}} &= 173 \\
  \text{SFR} &= 55\% \\
  \text{MCR} &= 0\% \\
  \text{SIR} &= 0\%
  \end{align*}
  \]

  \[
  \begin{align*}
  \text{STEP 1} &: \text{LSM} \geq 6.8 \text{ kPa} \\
  \text{N} &= 263 \\
  \text{N}_{\text{Target}} &= 147 \\
  \text{SFR} &= 44\% \\
  \text{MCR} &= 15\% \\
  \text{SIR} &= -31\%
  \end{align*}
  \]

  \[
  \begin{align*}
  \text{STEP 2} &: \text{CAP} \geq 300 \text{ dB/m} \\
  \text{N} &= 201 \\
  \text{N}_{\text{Target}} &= 132 \\
  \text{SFR} &= 34\% \\
  \text{MCR} &= 24\% \\
  \text{SIR} &= -47\%
  \end{align*}
  \]

  \[
  \begin{align*}
  \text{STEP 3} &: \text{ALT/ULN} \geq 0.49 \\
  \text{N} &= 195 \\
  \text{N}_{\text{Target}} &= 131 \\
  \text{SFR} &= 33\% \\
  \text{MCR} &= 24\% \\
  \text{SIR} &= -49\%
  \end{align*}
  \]
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Conclusion

▪ It is possible to derive a simple algorithm to help screen patients for clinical trials which leads to a significant improvement of SFR without exceeding a MCR of 25% (both in derivation and validation cohorts)

▪ In this study, without any a priori, LSM, CAP and normalized ALT were the most pertinent parameters to use in the triage algorithm

▪ This type of algorithms can be adapted to different target populations and by adding a priori information such as the type of parameters and their order in the sequence

▪ Such triage algorithms could also be used to help find patients to be treated once drugs will be on the market
Acknowledgments

▪ The patients and their family

▪ Brooke Army Medical Center
  - Dr Stephen Harrison
  - Dr Angelo Paredes
  - Jennifer Whitehead
  - Joseph Macaitis
  - Dr Katherine Cebe
  - Dr Katherine Roberts
  - Megan Wise

▪ M118 study
  - University of Birmingham
    • Pr Philip Newsome
    • Dr Peter Eddowes
    • Dr Sarah Townsend
  - Newcastle University
    • Dr Quentin Anstee
    • Elisabeth Enderson
    • Lorna Brownlee
    • Hannah Stevenson
  - Royal Free Hospital, London
    • Dr Emmanouil Tsocatzis
    • Pr Massimo Pinzani
    • Audrey Esson
    • Cristina Agapuyan
  - University of Nottingham
    • Dr Neil Guha
    • Angela Andrew
  - Plymouth University
    • Dr David Sheridan
    • Linda March
    • Susan Inniss
    • Amanda Aquilina
  - Cambridge University
    • Dr Michael Allison
    • Julie Ellis
  - Cambridge University
    • Dr Jeremy Cobbold
    • Denise O’Donnell
    • Mark Ainsworth
    • Lizzie Stafford

▪ Pathologists
  - Pr Pierre Bedossa
  - Pr Valérie Paradis

▪ Echosens
  - Remko Enserink
  - David Goyard
  - Saliha Haddag
  - Aymeric Labourdette
  - Anne Llorca
  - Veronique Miette
  - Magali Sasso
  - Khalide Seddik