Future therapies in NAFLD/NASH

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Non-Alcoholic Fatty Liver Disease

Healthy liver

15-30% → NAFLD

12-40% → NASH

15-25% → Cirrhosis

~7% → Hepatocellular carcinoma

100% → Liver transplant / Death

FAT → INFLAMMATION → FIBROSIS
NASH is associated with mortality

- Retrospective series - biopsies from 1980s
- N=118 NAFLD

NASH liver mortality OR 5.71 (2.31-14.13)
NASH + Fibrosis OR 10.06 (4.35 – 22.35)

Soderberg et al 2010
Musso et al 2011
Fibrosis is associated with mortality

Figure 2. Overall Mortality by (A) Steatofibrosis and (B) NASH Status

- 209 patients with biopsy-proven NASH vs non-NASH NAFLD
- Fibrosis or not

Younossi et al, EASL 2017
Advanced fibrosis predicts mortality

Survival by NAS and fibrosis stage

- Survival by NAS 0-4, F0-2
- Survival by NAS 5-8, F0-2

Survival by fibrosis stage

- Survival by F0-F2
- Survival by F3-F4

Log-rank test: P=0.17

Log-rank test: P<0.001

Cohort study of biopsy-proven NAFLD patients (N=229) in Sweden followed for a mean of 26.4 years (range: 6-33)

Ekstedt M, et al. 2015
Lack of clarity

• Optimal target is unclear
  – Steatosis
  – Inflammation
  – Fibrosis

• Aims of treatment poorly defined
  – Reversal of NASH / fibrosis?
  – Prevent progression to cirrhosis?
  – Prevent cancer development?
Trial Endpoints

• NASH

• Fibrosis

• Liver endpoints

• Cardiovascular endpoints
Insulin resistance is a feature of NAFLD

- **Increased glucose** (activates ChREBP)
  - De novo lipogenesis (SREBP1)
  - Activates PKCε (inhibits IR tyrosine kinase)

- **Inappropriate gluconeogenesis**
  - FOXO1-mediated

- **Impaired glycogen synthesis** (muscle and liver)
  - Akt2-mediated

- **Impaired suppression of lipolysis in adipocytes**
  - Glycerol and FFA

J C Cohen et al. Science 2011;332:1519-1523
What is metabolic inflammation?

- Macrophages infiltrate adipose tissue in obesity
  - Secrete TNFα and cytokines
  - Adipokines e.g. adiponectin, visfatin, IL-6

- NKT and CD8⁺ T cells

- Hypothalamus, liver, muscle, pancreas and gut

- Interferes with glucose metabolism
Mechanistic link to IR

- Adoptive transfer of CD8+ T cells to CD8-/- mice
  - adipose inflammation
  - systemic IR
  - glucose intolerance

The obese liver is both inflamed and insulin resistant.
Metabolic inflammation

• Activation of tissue injury pathways impacts on metabolic function
  – Common signalling elements

• NASH: tissue injury AND metabolic dysfunction

• If target those elements, can we impact the liver disease in NASH?
Thiazolidinediones

• Peroxisome proliferator-activated receptor - γ
• Reduce IR
  – Induce insulin sensitising genes
• Promote favourable lipid profile
  – Enhance clearance of VLDL
• Maintains adipocyte function
  – Reduce adipocyte inflammation / increase adiponectin
  – Improves insulin-suppression of lipolysis
PIVENS Study

• N=247 with NASH
  – Non-diabetic
• 2 point reduction in NAS
  – 96 weeks
• Improved inflammatory
• No improvement in fibrosis
  – no worsening
• Improved IR

• NB – weight gain / fluid retention / osteoporotic fractures

Sanyal et al. 2012
Hepatic PPAR $\alpha/\delta$

- **PPAR$\alpha$**
  - regulates fatty acid transport
  - inhibits gluconeogenesis
  - inhibits inflammation
- **PPAR$\delta$**
  - inhibits lipogenesis
  - anti-inflammatory in Kupfer cells
- **Elafibrinor** – combined agonist (mostly $\alpha$)
  - Mouse models of NASH
  - LFTs in abdominally obese individuals
GOLDEN 505

- N=274 non-cirrhotic NASH
  - Placebo vs 80mg vs 120mg for 52 weeks
  - NASH reversal without worsening of fibrosis

Ratziu et al 2016

<table>
<thead>
<tr>
<th>Population</th>
<th>Selection</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All NAS ≥4</td>
<td>234b</td>
<td>3.52 (1.32–9.40)</td>
<td>.013</td>
</tr>
<tr>
<td></td>
<td>202c</td>
<td>3.26 (1.17–9.02)</td>
<td>.024</td>
</tr>
<tr>
<td>NAS ≥4 with fibrosis (any stage)</td>
<td>204b</td>
<td>3.75 (1.39–10.12)</td>
<td>.009</td>
</tr>
<tr>
<td></td>
<td>176c</td>
<td>3.22 (1.15–8.99)</td>
<td>.026</td>
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<tr>
<td>NAS ≥4 with moderate/advanced fibrosis (F2, F3)</td>
<td>118b</td>
<td>18.46 (4.80–70.96)</td>
<td>.0001</td>
</tr>
<tr>
<td></td>
<td>99c</td>
<td>10.59 (2.52–44.50)</td>
<td>.002</td>
</tr>
</tbody>
</table>

4-5 point rise in serum creatinine

Ratziu et al 2016
IVA337 (a pan-PPAR agonist) improves insulin resistance, steatosis and inflammation in HF/HS and MCD diet models.

**High Fat**
(12 weeks diet followed by 4 weeks diet + IVA337)

**Body weight**

**Insulin**

Wettstein et al, EASL 2016
ASK1 and response to oxidation

Effect of ASK1 inhibition

Phase 2 N=72 24 weeks
5 arms
Cenicriviroc CCR2/5 inhibitor

- CENTAUR Phase 2b; N=289
- Primary outcome: ≥2 point in NAS / no worsening of fibrosis
- Key secondary outcomes
  - resolution of NASH and no worsening of fibrosis
  - improvement in fibrosis by ≥1 stage and no worsening of NASH

Benefit of treatment in:
- NAS >4
- Ballooning
- Higher fibrosis at baseline
- Non-diabetics

Phase III AURORA Study on-going

Friedman et al 2017
FXR Agonists

- **Obeticholic acid**
  - Semi-synthetic bile acid that selectively activates FXR
  - Reduces fat and fibrosis in animal models
  - Improve hepatic insulin sensitivity
  - Decrease steatosis
  - Inhibit lipogenesis
  - Cause regression of atherosclerosis
  - Anti-fibrotic

- **Fully synthetic FXR agonists**
  - GS-9674 / LJN452 / EDP-305
FLINT study

• Phase IIb double blind placebo controlled multicentre RCT
• Non-cirrhotic NASH patients
  – Histology
• N=283
  – 53% diabetes
• Primary outcome
  – Improvement in NAS by at least 2 points
    • No worsening of fibrosis
<table>
<thead>
<tr>
<th></th>
<th>Obeticholic acid</th>
<th>Placebo</th>
<th>Relative risks or mean changes from baseline* (95% CI) (obeticholic acid vs placebo)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome‡</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients at risk‡</td>
<td>110</td>
<td>109</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with improvement</td>
<td>50 (45%)</td>
<td>23 (21%)</td>
<td>1.9 (1.3 to 2.8)</td>
<td>0.0002</td>
</tr>
<tr>
<td><strong>Changes from baseline in histological features</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients with biopsy specimens at baseline and 72 weeks</td>
<td>102</td>
<td>98</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resolution§ of definite non-alcoholic steatohepatitis</td>
<td>22 (22%)</td>
<td>13 (13%)</td>
<td>1.5 (0.9 to 2.6)</td>
<td>0.08</td>
</tr>
<tr>
<td>Fibrosis¶</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with improvement</td>
<td>36 (35%)</td>
<td>19 (19%)</td>
<td>1.8 (1.1 to 2.7)</td>
<td>0.004</td>
</tr>
<tr>
<td>Change in score</td>
<td>-0.2 (1.0)</td>
<td>0.1 (0.9)</td>
<td>-0.3 (-0.6 to -0.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Total NAFLD activity score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in score</td>
<td>-1.7 (1.8)</td>
<td>-0.7 (1.8)</td>
<td>-0.9 (-1.3 to -0.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hepatocellular ballooning</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with improvement</td>
<td>47 (46%)</td>
<td>30 (31%)</td>
<td>1.5 (1.0 to 2.1)</td>
<td>0.03</td>
</tr>
<tr>
<td>Change in score</td>
<td>-0.5 (0.9)</td>
<td>-0.2 (0.9)</td>
<td>-0.2 (-0.5 to 0.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>Steatosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with improvement</td>
<td>62 (61%)</td>
<td>37 (38%)</td>
<td>1.7 (1.2 to 2.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Change in score</td>
<td>-0.8 (1.0)</td>
<td>-0.4 (0.8)</td>
<td>-0.4 (-0.6 to -0.2)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Lobular inflammation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with improvement</td>
<td>54 (53%)</td>
<td>34 (35%)</td>
<td>1.6 (1.1 to 2.2)</td>
<td>0.006</td>
</tr>
<tr>
<td>Change in score</td>
<td>-0.5 (0.8)</td>
<td>-0.2 (0.9)</td>
<td>-0.3 (-0.5 to -0.1)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Portal inflammation¶</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with improvement</td>
<td>12 (12%)</td>
<td>13 (13%)</td>
<td>1.0 (0.6 to 1.7)</td>
<td>0.90</td>
</tr>
<tr>
<td>Change in score</td>
<td>0.2 (0.7)</td>
<td>0.2 (0.7)</td>
<td>0.0 (-0.1 to 0.2)</td>
<td>0.59</td>
</tr>
</tbody>
</table>
Change in liver enzymes and weight

Main side effects:
Pruritis (23%) / Increase HOMA-IR / Raised LDL - 0.22
Thyroid hormone receptor $\beta$ agonist

- MGL-3196
- 36 week trial
- NAS $\geq$4; F1-3

**Fig 1. Relative Change in MRI-PDFF (%)**

<table>
<thead>
<tr>
<th>Group</th>
<th>wk 12</th>
<th>wk 36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-9.6</td>
<td>-7.6</td>
</tr>
<tr>
<td>MGL-3196</td>
<td>-36.3</td>
<td>-37.3</td>
</tr>
<tr>
<td>High Exp/SHBG</td>
<td>-42.0</td>
<td>-49.3</td>
</tr>
<tr>
<td>Low Exp/SHBG</td>
<td>-22.5</td>
<td>-25.0</td>
</tr>
</tbody>
</table>

*Placebo vs MGL-3196, p<0.0001

**Fig 2. ALT (IU/L)**

<table>
<thead>
<tr>
<th>Week</th>
<th>Placebo</th>
<th>MGL-3196</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>80</td>
<td>70</td>
</tr>
<tr>
<td>24</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>36</td>
<td>50</td>
<td>30</td>
</tr>
<tr>
<td>38</td>
<td>40</td>
<td>20</td>
</tr>
</tbody>
</table>

**Fig 3. 2-pt NAS reduction with $\geq$1 pt decrease in ballooning or inflammation**

<table>
<thead>
<tr>
<th>Group</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>32.4</td>
</tr>
<tr>
<td>MGL-3196</td>
<td>50.7</td>
</tr>
</tbody>
</table>

*Placebo vs MGL-3196, p=0.09

**Fig 4. Nash Resolution (%)**

<table>
<thead>
<tr>
<th>Group</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo, no fibrosis</td>
<td>6.4</td>
</tr>
<tr>
<td>MGL-3196, no fibrosis</td>
<td>27.4</td>
</tr>
<tr>
<td>MRI-PDFF $\geq$50%</td>
<td>24.6</td>
</tr>
<tr>
<td>MRI-PDFF $\geq$30%</td>
<td>24.6</td>
</tr>
</tbody>
</table>

*Placebo vs MGL-3196, p=0.018

*Placebo vs MGL-3196, p=0.0013

*Placebo vs MGL-3196, p=0.032

*Placebo vs MGL-3196, p=0.0026
Thyroid hormone receptor $\beta$ agonist

- **VK2809**
- **12 weeks**
- **MRI-PDFF $\geq 8\%$**

### Median relative % change in liver fat at 12 weeks

<table>
<thead>
<tr>
<th>% Change from Baseline</th>
<th>Placebo (n=11)</th>
<th>VK2809 10 mg QOD (n=13)</th>
<th>VK2809 10 mg QD (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Change</td>
<td>-8.9%</td>
<td>-56.5%</td>
<td>-59.7%</td>
</tr>
<tr>
<td>p-value</td>
<td>-</td>
<td>0.0014</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

### Patients with $\geq 30\%$ reduction in liver fat at 12 weeks

<table>
<thead>
<tr>
<th>% Responders</th>
<th>Placebo (n=11)</th>
<th>VK2809 10 mg QOD (n=13)</th>
<th>VK2809 10 mg QD (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders</td>
<td>18.2%</td>
<td>76.9%</td>
<td>90.9%</td>
</tr>
<tr>
<td>p-value</td>
<td>-</td>
<td>0.012</td>
<td>0.0019</td>
</tr>
</tbody>
</table>

Loomba et al AASLD 2018
Eat less, move more?

- Low/moderate intensity (n=141)
  - 9x more likely to exercise >1hr/week
- 150 mins / week or increase by >60mins
  - improvement in ALT
  - Metabolic indices (HOMA-IR)
- Independent of weight loss

St George et al, 2009
Weight loss improves NAS

<table>
<thead>
<tr>
<th>Authors [ref]</th>
<th>Mean difference IV, fixed, 95% CI</th>
<th>Mean difference IV, fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harrison et al, 2009 [12]</td>
<td>-2.50 (-3.52, -1.48)</td>
<td></td>
</tr>
<tr>
<td>Nobili et al, 2008 [11]</td>
<td>-1.10 (-2.11, -0.09)</td>
<td></td>
</tr>
<tr>
<td>Vilar Gomez et al, 2009 [98]</td>
<td>-2.40 (-3.51, -1.29)</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI)  
-2.05 (-2.58, -1.53)

Heterogeneity: $\chi^2=4.71$, df=3 ($p=0.19$); $I^2=36\%$  
Test for overall effect: $z=7.63$ ($p<0.00001$)
Weight loss – the more the better

- 293 patients with NASH
  - BMI 31.3
- 52 week lifestyle
- 750kcal/day deficit
- Walk 200 mins / week
- 8 weekly f/up

Vilar-Gomez et al, 2014
GLP-1

- Incretin gut hormone
- Induces insulin / reduces glucagon secretion
- Weight loss
- Appetite suppression
- Delayed gastric emptying
Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study


N=52
40% Stage 3
12% Cirrhotic
1.8mg liraglutide

Resolution of NASH
Liraglutide – 39%
Placebo – 9%

Semaglutide taken forward
Is all weight loss the same?

• Liraglutide non-responders lost as much weight as responders
• Bariatric surgery has been shown to improve liver indices
  – RYGB
  – Sleeve gastrectomy
• Resolution of diabetes and sustained weight loss
How will we find patients for treatment?
Population Study

Total for 3 Boroughs n=813,700

- How much liver disease is out there?
- How much has been ‘worked up’
Liver abnormalities are common

• 690,683 adults registered in 150 East London practices

• 218,032 adults had LFTs tested (31.6%)

• 31,672 (14.5%) at least 1 abnormal results
  – ALT or AST
## Risk of Abnormal LFTs

<table>
<thead>
<tr>
<th>Explanatory Variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (continuous)</td>
<td>0.97</td>
<td>0.97 - 0.97</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male</td>
<td>2.80</td>
<td>2.65 - 2.97</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Excess alcohol</td>
<td>1.85</td>
<td>1.73 - 1.97</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.69</td>
<td>1.60 - 1.77</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.23</td>
<td>1.17 - 1.28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>BMI Category</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI underweight</td>
<td>0.96</td>
<td>0.75 - 1.23</td>
<td>0.748</td>
</tr>
<tr>
<td>BMI normal (ref)</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI overweight</td>
<td>1.52</td>
<td>1.42 - 1.62</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI obese</td>
<td>2.20</td>
<td>2.05 - 2.36</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Multivariate analysis
Alazawi et al, BJGP 2014
Prevalence of Liver Diagnoses

- NAFLD
- Viral Hepatitis
- Alcohol
- Inherited
- Pregnancy-related
- Autoimmune
- Venous thrombosis

N=690,683  
Alazawi et al, 2014
## Independent Risk Factors for NAFLD

<table>
<thead>
<tr>
<th>Explanatory Variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bangladeshi</td>
<td>1.38</td>
<td>1.14</td>
<td>1.69</td>
</tr>
<tr>
<td>Indian</td>
<td>0.83</td>
<td>0.63</td>
<td>1.11</td>
</tr>
<tr>
<td>Pakistani</td>
<td>1.12</td>
<td>0.83</td>
<td>1.53</td>
</tr>
<tr>
<td>White (reference cat)</td>
<td>1.00</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>African</td>
<td>0.53</td>
<td>0.42</td>
<td>0.66</td>
</tr>
<tr>
<td>Age (continuous)</td>
<td>0.998</td>
<td>0.994</td>
<td>1.003</td>
</tr>
<tr>
<td>Male</td>
<td>0.85</td>
<td>0.78</td>
<td>0.92</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.25</td>
<td>2.08</td>
<td>2.44</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.32</td>
<td>1.13</td>
<td>1.53</td>
</tr>
<tr>
<td>Cardiovascular Disease</td>
<td>0.94</td>
<td>0.84</td>
<td>1.07</td>
</tr>
<tr>
<td>BMI underweight</td>
<td>0.85</td>
<td>0.35</td>
<td>2.08</td>
</tr>
<tr>
<td>BMI normal (ref)</td>
<td>1.00</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>BMI overweight</td>
<td>2.90</td>
<td>2.40</td>
<td>3.51</td>
</tr>
<tr>
<td>BMI obese</td>
<td>5.00</td>
<td>4.08</td>
<td>6.12</td>
</tr>
</tbody>
</table>

Alazawi et al 2014
NAFLD and Type II Diabetes

• NAFLD most common cause of liver disease
  – 75% of diabetic population
  – 10-20% per mmol/l increase in plasma glucose\(^1,2\)

• Temporal association
  – Diagnosed 3.7-5.5 years after DM\(^3\)

• Associated with
  – Microvascular & Macrovascular complications
  – 2.2-fold increase in all-cause mortality

• No routine screening for NAFLD

\(^1\)Sung et al 2012
\(^2\)Jimba 2005
\(^3\)Adams 2010
Obesity in East London

Adult Obesity

Year 6 Obesity

Barking
Newham
Waltham Forest
Tower Hamlets
Hackney

PHE Atlas
How will we select patients for treatment?

• ‘Fat and fibrosis’

OR

• NASH
Liver Biopsy

<table>
<thead>
<tr>
<th>PROs</th>
<th>CONs</th>
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<tbody>
<tr>
<td>Staging</td>
<td>Invasive</td>
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<tr>
<td>Grading</td>
<td>Cost</td>
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<tr>
<td>Diagnosis</td>
<td>Sampling</td>
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<tr>
<td>Co-Pathology</td>
<td>Reluctance</td>
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<tr>
<td></td>
<td>Static information</td>
</tr>
</tbody>
</table>

– 30 % pain / 0.3-0.6% bleeding

Pathologist – dependent
Methods of Assessment

- Biopsy – Gold Standard
- Fibroscan
- CT – no significant role (HCC)
- MR Elastography
- Other MR techniques
- Serum Markers
Transient Elastography

- Pulse-echo ultrasound to measure stiffness
- Samples 1 x 4 cm cylinder
- Confounded by
  - Obesity
  - Inflammation / Cholestasis
  - Post-prandial / Alcohol
  - Heart failure
Liver stiffness is not fibrosis stage

- Indicates high or low probability of advanced fibrosis
- Stiffness correlates with HVPG 5-10 mmHg
Non-invasive tests for fibrosis

• ELF
  – Age / hyaluronic acid / P3P / TIMP1
  – Only 61 of 912 patients had NAFLD

• FibroTest
  – 5 serum markers
  – 267 patients with NAFLD
  – 33% Indeterminate
Assessing risk of fibrosis

• NAFLD-FS
  – Age / BMI / DM / AST:ALT / Plt / Albumin

• APRI
  – AST / Plt

• FIB-4
  – Age / AST / ALT / Plt

• BARD
  – BMI / DM / AST:ALT
Composite Scores

A

Survival probability [%]

Duration (months)

0  60  120  180  240  300

NAFLD-FS: < 1.455
NAFLD-FS: 1.455 to 0.676
NAFLD-FS: > 0.676

B

Survival probability [%]

Duration (months)

0  60  120  180  240  300

APRI: < 0.5
APRI: 0.5 to 1.5
APRI: > 1.5

C

Survival probability [%]

Duration (months)

0  60  120  180  240  300

FIB-4: < 1.30
FIB-4: 1.30 to 2.67
FIB-4: > 2.67

D

Survival probability [%]

Duration (months)

0  60  120  180  240  300

BARD: 0/1
BARD: 2/3
BARD: 4
NAFLD Fibrosis Score

Age
BMI
IGF / diabetes
AST
ALT
Platelets
Albumin

Retrospective
N=320
105 months (3-317)

www.nafldscore.com

Angulo et al 2013
Abnormal liver function tests and/or ultrasound showing fatty liver

**Primary Care:**
- Symptoms & comorbidities
- Detailed drug history
- Careful family history
- Alcohol review – **AUDIT-C**
- Metabolic risk factors inc BMI

**Blood Tests**:  
- Viral hepatitis – **HBV & HCV**
- FBC, U&E, INR, TFT
- LFTs inc AST / GGT
- Lipid profile
- Ferritin
- Autoantibodies
- Immunoglobulins
- Consider need for ultrasound

**AUDIT-C Positive**
- Brief Intervention
- Repeat tests in 3 months

**Abnormalities resolve**

**Abnormalities persist**

**Hepatology**

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All patients with clinical jaundice or bilirubin >40 should be referred urgently for assessment

*A complete liver screen would additionally include testing for alpha1-antitrypsin, caeruloplasmin and alphafetoprotein. *Chronic viral infection should be excluded by testing for hepatitis B virus surface antigen and antibodies against hepatitis C virus. If abnormalities are acute, exclude hepatitis A and hepatitis E virus infection.
Abnormal liver function tests and/or ultrasound showing fatty liver

**Primary Care:**
- Symptoms & comorbidities
- Detailed drug history
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- Alcohol review – **AUDIT-C**
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**Blood Tests***:
- Viral hepatitis – **HBV & HCV**<sup>*</sup>
- FBC, U&E, INR, TFT
- LFTs inc AST / GGT
- Lipid profile
- Ferritin
- Autoantibodies
- Immunoglobulins
- Consider need for ultrasound

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**AUDIT-C Positive**
- Brief Intervention
- Repeat tests in 3 months

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**Screen Positive or uncertain**

**Hepatology**

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*All patients with clinical jaundice or bilirubin >40 should be referred urgently for assessment*

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* A complete liver screen would additionally include testing for alpha1-antitrypsin, caeruloplasmin and alphafetoprotein. *Chronic viral infection should be excluded by testing for hepatitis B virus surface antigen and antibodies against hepatitis C virus. If abnormalities are acute, exclude hepatitis A and hepatitis E virus infection.*
Abnormal liver function tests and/or ultrasound showing fatty liver

Primary Care:
- Symptoms & comorbidities
- Detailed drug history
- Careful family history
- Alcohol review – AUDIT-C
- Metabolic risk factors incl BMI

Blood Tests*:
- Viral hepatitis – HBV & HCV
- FBC, U&E, INR, TFT
- LFTs inc AST / GGT
- Lipid profile
- Ferritin
- Autoantibodies
- Immunoglobulins
- Consider need for ultrasound

AUDIT-C Positive
- Brief Intervention
- Repeat tests in 3 months

Screen Positive or uncertain

Likely NAFLD: Calculate non-invasive score
- Behaviour / lifestyle advice
- Alcohol
- Exercise
- Diet
- Cardiovascular risk factors

Primary Care:
- Symptoms & comorbidities
- Detailed drug history
- Careful family history
- Alcohol review – AUDIT-C
- Metabolic risk factors incl BMI

Blood Tests*:
- Viral hepatitis – HBV & HCV
- FBC, U&E, INR, TFT
- LFTs inc AST / GGT
- Lipid profile
- Ferritin
- Autoantibodies
- Immunoglobulins
- Consider need for ultrasound

Negative or Metabolic Risk:

Hepatology

I / H risk
- Low risk
- Follow-up in Primary Care
- Annual review

Abnormalities resolve

Abnormalities persist

All patients with clinical jaundice or bilirubin >40 should be referred urgently for assessment

*A complete liver screen would additionally include testing for alpha1-antitrypsin, caeruloplasmin and alphafetoprotein.

†Chronic viral infection should be excluded by testing for hepatitis B virus surface antigen and antibodies against hepatitis C virus. If abnormalities are acute, exclude hepatitis A and hepatitis E virus infection. § The Diagnostic Liver Clinic will return patients to GP with a diagnosis and advice on future management
Key challenges

• Multiple endpoints - ?comparisons
• Clinical meaning of endpoints - ?outcomes
• What will be the indication for treatment
  – How do we know it’s working (when to stop)?
• What is the role for behaviour and lifestyle?
• How will we find the patients?