CPG NAFLD GUIDELINES

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DISCLOSURES

Lectures and advisory board fees from Intercept, Genfit, MSD and Gilead
EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease

European Association for the Study of the Liver (EASL)*, European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO)


Journal of Hepatology 2016

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Clinical Practice Guidelines

Non-alcoholic fatty liver disease

SLIDE DECK
Definitions of NAFLD, NAFL and NASH

NAFLD
- Excessive hepatic fat accumulation
- Steatosis in >5% of hepatocytes*
- Exclusion of secondary causes and AFLD†

NAFL
- Pure steatosis
- Steatosis and mild lobular inflammation

NASH
- Early F0/F1 fibrosis
- Fibrotic ≥F2 to ≥F3 fibrosis
- Cirrhotic F4 fibrosis

HCC

Definitive diagnosis of NASH requires a liver biopsy

*According to histological analysis or proton density fat fraction or >5.6% by proton MRS or quantitative fat/water-selective MRI;
†Daily alcohol consumption of ≥30 g for men and ≥20 g for women
Spectrum of lesion from steatosis to steatohepatitis, where fibrosis can progress to cirrhosis and HCC.
Significant overlap of obesity and excessive alcohol consumption

Fatty Liver disease

Alcoholic
Alcohol >30 M; >20 F

Non-alcoholic
Alcohol <30g M; 20g F
• NAFLD is the most common liver disorder in Western countries, affecting 17–46% of adults\(^1\)
  – Parallels the prevalence of metabolic syndrome (MetS) and its components, which also increase the risk of more advanced disease
  – NAFLD is also present in 7% of normal-weight (lean) individuals\(^2\)

Non-alcoholic fatty liver disease is present in about 25% of adult population.
In Europe, NAFLD/NASH represents a very small proportion of liver-related mortality.
Should we screen for NAFLD? Who to screen?

- Limited value of screening for NAFLD in the community
  - High direct and indirect costs
  - Low predictive value of non-invasive tests
  - Risks associated with liver biopsy
  - Lack of effective treatments
### Screening

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Grade of evidence</th>
<th>Grade of recommendation</th>
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<tbody>
<tr>
<td>All individuals with steatosis should be screened for features of MetS, independent of liver enzymes.</td>
<td>A</td>
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<tr>
<td>All individuals with persistently abnormal liver enzymes should be screened for NAFLD</td>
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<tr>
<td>In subjects with obesity or MetS, screening for NAFLD should be part of routine work-up.</td>
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<td>In high-risk individuals, such as:</td>
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<tr>
<td>• T2DM,</td>
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<td>• age&gt;50 years,</td>
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<td>• MetS</td>
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<td>finding of advanced disease is advisable</td>
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</table>
Assessment of **steatosis**

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<thead>
<tr>
<th>Recommendations</th>
<th>Grade of evidence</th>
<th>Grade of recommendation</th>
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<tbody>
<tr>
<td><strong>US is the preferred first-line diagnostic procedure</strong> for imaging of NAFLD, <em>as it provides additional diagnostic information</em></td>
<td>A</td>
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<tr>
<td>Whenever imaging tools are not available or feasible, serum biomarkers and scores are an acceptable alternative for the diagnosis of steatosis</td>
<td>B</td>
<td>2</td>
</tr>
<tr>
<td>A quantitative estimation of liver fat can only be obtained by $^1$H-MRS. This technique is of value in clinical trials and experimental studies, but is expensive and not recommended in the clinical setting</td>
<td>A</td>
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</tbody>
</table>
A Western diet/lifestyle has been associated with weight gain and obesity, and NAFLD\(^1\)

- High calorie intake
- Excess (saturated) fat
- High fructose intake
- Sedentary behaviour

**Recommendation**

Unhealthy lifestyles play a role in the development and progression of NAFLD. The assessment of dietary and physical activity habits is part of comprehensive NAFLD screening.

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<th>Grade of evidence</th>
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High red and processed meat consumption is associated with non-alcoholic fatty liver disease and insulin resistance.

- **Healthy liver**
  - Saturated fat
  - Cholesterol
  - Heme-iron
  - Sodium
  - Preservatives
  - Advanced-Glycation End-Products (AGEs)

- **Fatty liver**

- Red and/or processed meat
  - OR = 1.47, 95% CI 1.04-2.09

- Non-alcoholic fatty liver disease
  - OR = 1.55, 95% CI 1.07-2.23

- Insulin resistance (both among general population and NAFLD subjects)
  - OR = 2.22, 95% CI 1.28-3.86
  - OR = 1.92, 95% CI 1.12-3.30

- Unhealthy cooking methods
  - Grilled or broiled to well-done level
  - Fried

Zelber-Sagi et al, J Hepatol, 2018
Several genetic modifiers of NAFLD have been identified\(^1\)
- A minority have been robustly validated
\- \textit{PNPLA3 I148M} and \textit{TM6SF2 E167K} carriers have a higher liver fat content\(^*\)
- Increased risk of NASH
- NAFLD not systematically associated with features of IR

**Recommendation**

<table>
<thead>
<tr>
<th>Genotyping</th>
<th>Grade of evidence</th>
<th>Grade of recommendation</th>
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<tbody>
<tr>
<td>may be considered in selected patients and clinical studies but \textbf{is not recommended} routinely</td>
<td>B</td>
<td>2</td>
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</table>

*Grade of evidence B, grade of recommendation 2
Liver biopsy

- Liver biopsy is essential for the diagnosis of NASH
  - Clinical, biochemical or imaging measures cannot distinguish NASH from steatosis
- NAFL encompasses
  - Steatosis
- NASH requires
  - Steatosis
  - Lobular or portal inflammation
  - Ballooning

NAFLD indicates disease severity*

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<th>Grade of recommendation</th>
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<tbody>
<tr>
<td>NASH has to be diagnosed by a liver biopsy showing <strong>steatosis, hepatocyte ballooning and lobular inflammation</strong></td>
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*Should not be used for initial diagnosis
Role of non-invasive assessments

- Non-invasive markers should aim to:
  - Identify the risk of NAFLD among individuals with increased metabolic risk in primary care
  - Identify those with a worse prognosis in secondary and tertiary care
    - E.g. severe NASH
  - Monitor disease progression
  - Predict response to therapeutic interventions

Achieving these aims could reduce the need for liver biopsy
Liver Investigation: Testing Marker Utility in Steatohepatitis

The LITMUS project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No. 777377. This Joint Undertaking receives support from the European Union’s Horizon 2020 research and innovation programme and EFPIA.

www.litmus-project.eu
www.imi.europa.eu
Fibrosis was the only histological finding with prognosis significance

Median follow-up: 12.6–0.3 to 35.1 years

Analysis of 619 NAFLD patients, from 1975 to 2005 – US, Europe and Thailand

Angulo et al, Gastro, 2015
Fibrosis was the stronger predictor of disease specific mortality

NAS score (Kleiner)
Fibrosis score 0 to 4

Median follow-up: 26.4 – 6 to 33 years

229 NAFLD
In Sweden

Ekstedt et al, Hepatology, 2015
Screening for liver fibrosis

**Simple**
- NAFLD Fibrosis Score (NFS)
  - <= -1.455 → F0-F2
  - -1.455 → 0.675 → indeterminate
  - > 0.675 → F3-F4

**Complex (Patented Tests):**
- FIB-4
  - <1.30 → F0-F1
  - >2.67 → F3-F4
- ELF
  - Fibrotest
  - Fibrometer

**Fibroscan**
Elastography in NAFLD has a spectrum bias, with cut-offs ranging from 10.3 to 22.3 KPa for cirrhosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnosis</th>
<th>Year</th>
<th>Count</th>
<th>n.a.</th>
<th>Cut-off</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yoneda et al. [156]</td>
<td>NAFLD</td>
<td>2008</td>
<td>97</td>
<td>50</td>
<td>6.6</td>
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<td>9</td>
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<td>17.0</td>
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<tr>
<td>Wong et al. [85]</td>
<td>NAFLD</td>
<td>2010</td>
<td>246</td>
<td>41</td>
<td>7.0</td>
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<td>10</td>
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<td></td>
<td></td>
<td>10.3</td>
</tr>
<tr>
<td>Gaia et al. [82]</td>
<td>NAFLD</td>
<td>2011</td>
<td>72</td>
<td>46</td>
<td>7.0</td>
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<td>12.5</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>10.5</td>
</tr>
<tr>
<td>Myers et al. [66]</td>
<td>NAFLD</td>
<td>2012</td>
<td>75</td>
<td>n.a.</td>
<td>7.8</td>
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<td>n.a.</td>
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<td></td>
<td>22.3</td>
</tr>
<tr>
<td>Wong et al. [68]</td>
<td>NAFLD</td>
<td>2012</td>
<td>193</td>
<td>45</td>
<td>7.0</td>
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<td>13</td>
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<td>10.3</td>
</tr>
</tbody>
</table>

Noninvasive, EASL/ALEH CPG, 2015
Potential algorithm for non-invasive assessment: prediction rules and blood-based biomarkers

*Estimated prevalence for low-, intermediate- and high-risk groups
Vilar-Gomez E, Chalasani N. J Hepatol 2018;68:305–15
Copyright © 2017 European Association for the Study of the Liver Terms and Conditions
Natural history and complications: CVD

- Prevalence and incidence of CVD is higher in NAFLD than in matched controls
  - Driven by the association between NAFLD and MetS components
- CVD should be identified in NAFLD, regardless of traditional risk factors
- CVD and metabolic risk factors are also reported in adolescents and children with NAFLD

### Recommendations

<table>
<thead>
<tr>
<th>Screening of the cardiovascular system is mandatory in all individuals with NAFLD because CV complications frequently dictate the outcome</th>
<th>Grade of evidence</th>
<th>Grade of recommendation</th>
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<tbody>
<tr>
<td>A</td>
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</tbody>
</table>
Meta-analysis of the risk of fatal and non-fatal CVD events associated with more severe NAFLD

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>log [odds ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Odds ratio</th>
<th>Odds ratio % CI</th>
<th>% 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fatal CVD events (only)</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Ekstedt 2015</td>
<td>1.472</td>
<td>0.328</td>
<td>18.1%</td>
<td>4.36</td>
<td>[2.29, 8.35]</td>
<td></td>
</tr>
<tr>
<td>Haring 2009 men</td>
<td>0.879</td>
<td>0.423</td>
<td>13.3%</td>
<td>2.32</td>
<td>[1.01, 5.43]</td>
<td></td>
</tr>
<tr>
<td>Haring 2009 women</td>
<td>0.343</td>
<td>0.756</td>
<td>5.4%</td>
<td>1.54</td>
<td>[0.61, 3.88]</td>
<td></td>
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<tr>
<td>Kim 2013</td>
<td>1.241</td>
<td>0.303</td>
<td></td>
<td>4.82</td>
<td>[2.15, 10.87]</td>
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<tr>
<td><strong>Subtotal (95% CI)</strong></td>
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<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 2.56, df = 3 (p = 0.89)</td>
<td></td>
<td></td>
<td></td>
<td>13.3%</td>
<td>2.45 [1.07, 5.61]</td>
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<tr>
<td>Test for overall effect: Z = 6.23 (p &lt; 0.0001)</td>
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<tr>
<td><strong>Fatal and non-fatal CVD</strong></td>
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<tr>
<td>Emre 2015</td>
<td>0.089</td>
<td>0.710</td>
<td>6.0%</td>
<td>1.23</td>
<td>[0.71, 2.09]</td>
<td></td>
</tr>
<tr>
<td>Moon 2015</td>
<td>0.398</td>
<td>0.248</td>
<td>24.2%</td>
<td>1.49</td>
<td>[0.93, 2.39]</td>
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<tr>
<td>Pisto 2014</td>
<td></td>
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<tr>
<td><strong>Subtotal (95% CI)</strong></td>
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<tr>
<td>Heterogeneity: Tau² = 0.19; Chi² = 2.59, df = 2 (p = 0.27); I² = 23%</td>
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<td></td>
<td></td>
<td>43.5%</td>
<td>1.94 [1.17, 3.21]</td>
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<tr>
<td>Test for overall effect: Z = 2.59 (p = 0.010)</td>
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<tr>
<td><strong>Total (95% CI)</strong></td>
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<tr>
<td>Heterogeneity: Tau² = 0.09; Chi² = 9.77, df = 6 (p = 0.13); I² = 39%</td>
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<tr>
<td>Test for overall effect: Z = 5.00 (p &lt; 0.00001)</td>
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<tr>
<td>Test for subgroup differences: Chi² = 2.71, df = 1 (p = 0.10), I² = 63.1%</td>
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</tbody>
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The risk of fatal and non-fatal CVD associated with more severe NAFLD
Natural history and complications: HCC

- Cumulative incidence of NAFLD-associated HCC varies according to study population
- Large number of NAFLD cases at risk of HCC makes systematic surveillance largely impracticable
  - *PNPLA3* rs738409 C>G gene polymorphism is associated with increased HCC risk
  - However, **HCC surveillance in NAFLD is not yet considered cost effective**

### Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Grade of evidence</th>
<th>Grade of recommendation</th>
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</thead>
<tbody>
<tr>
<td>Although NAFLD is a risk factor for HCC, which may also develop in the pre-cirrhotic stage, and the risk is further increased by the presence of the <em>PNPLA3</em> rs738409 C&gt;G polymorphism, no recommendation can be currently made on the timing of surveillance and its cost effectiveness</td>
<td>B</td>
<td>1</td>
</tr>
</tbody>
</table>
Treatment: diet and lifestyle changes

- Diet and lifestyle changes are mandatory in all patients
  - Modest weight loss reduces liver fat, improves hepatic IR, and can result in NASH regression
  - Weight loss of 7% is associated with histological improvement

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<tr>
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<tbody>
<tr>
<td>Structured programmes aimed at lifestyle changes towards healthy diet and habitual physical activity are advisable in NAFLD</td>
<td>C</td>
<td>2</td>
</tr>
<tr>
<td>Patients without NASH or fibrosis should receive counselling for healthy diet and physical activity but no pharmacotherapy</td>
<td>B</td>
<td>2</td>
</tr>
<tr>
<td>In overweight/obese NAFLD, a 7–10% weight loss is the target of most lifestyle interventions, and results in improvement of liver enzymes and histology</td>
<td>B</td>
<td>1</td>
</tr>
</tbody>
</table>
Components of a lifestyle approach to NAFLD

**Energy restriction**
- Calorie restriction (500–1,000/day)
- 7–10% weight loss target
- Long-term maintenance approach

**Fructose intake**
- Avoid fructose-containing food and drink

**Coffee consumption**
- No liver-related limitations

**Macronutrient composition**
- Low-to-moderate fat
- Moderate-to-high carbohydrate
- Low-carbohydrate ketogenic diets or high protein

**Daily alcohol intake**
- Strictly below 30 g men and 20 g women

**Physical activity**
- 150–200 min/week moderate intensity in 3–5 sessions
- Resistance training to promote musculoskeletal fitness and improve metabolic factors

Comprehensive lifestyle approach
Bariatric Surgery induced the disappearance of NASH in 85%, and was maintained at 5 years.

Lassailly, Mathurin et al, ILC, 2018

198 with biopsy proven NASH

Evolution of NASH*

*Paired biopsies
Bariatric Surgery reduced the fibrosis severity at 1 year, and continued to improve at 5 years.

198 with biopsy proven NASH
Treatment: Bariatric surgery

- Bariatric surgery is an option in patients unresponsive to lifestyle changes and pharmacotherapy
  - Reduces weight and metabolic complications
  - Stable results in the long term

Recommendations for bariatric surgery

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<tr>
<th>Grade of evidence</th>
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</table>

Bariatric surgery reduces liver fat and is likely to reduce NASH progression; prospective data have shown an improvement in all histological lesions of NASH, including fibrosis.
Treatment: pharmacotherapy

- Treatment should be indicated in:
  - Progressive NASH
  - Early-stage NASH with risk of fibrosis progression*
  - Active NASH with high necroinflammatory activity
- Treatment should reduce NASH-related mortality and progression to cirrhosis or HCC
  - Resolution of NASH-defining lesions accepted as surrogate endpoint
- Safety and tolerability are prerequisites
  - Extensive comorbidities associated with significant polypharmacy and increased likelihood of DDIs

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<tbody>
<tr>
<td>Pharmacotherapy should be reserved for patients with NASH, particularly for those with significant fibrosis (stage F2 and higher). Patients with less severe disease, but at high risk of disease progression could also be candidates for treatment</td>
<td>B</td>
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</table>

*Age > 50 years, diabetes, MetS, increased ALT
**Treatment: pharmacotherapy**

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<th>Grade of recommendation</th>
</tr>
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<tbody>
<tr>
<td>While no firm recommendations can be made, pioglitazone* or vitamin E† or their combination could be used for NASH</td>
<td>B</td>
<td>2</td>
</tr>
<tr>
<td>The optimal duration of therapy is unknown; in patients with increased ALT at baseline, treatment should be stopped if there is no reduction in aminotransferases after 6 months of therapy‡</td>
<td>C</td>
<td>2</td>
</tr>
</tbody>
</table>

*Most efficacy data, but off-label outside T2DM; †Better safety and tolerability than pioglitazone in the short-term; ‡No recommendations can be made in patients with normal baseline ALT  
### Recommendations

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Statins may be confidently used to reduce LDL cholesterol and prevent cardiovascular risk, with no benefits or harm to liver disease.
No medications approved by the FDA or EMA for the treatment of NAFLD/NASH

Any drug treatment is off label