SWS measurement(s) as biomarker(s) (BM) of Liver Fibrosis (LF)

Towards a Shared Vision
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Background

- Objective: Determine how SWS can help the physician's assessment of liver fibrosis level.
  1. How
     - Which Technique, which measurement protocol, which applicability criteria
     - Alone or in combination with other measurements;
     - Which clinical framework (Assessment, Diagnosis, Follow up)
  2. Hepatologists, gastroenterologists, radiologists
  3. METAVIR, Fibrosis %, other… (if METAVIR, should we consider all 5 levels F0 to F4?)

- Existing approaches:
  1. Technical / physics based
     Define the formula LF=f(SWS), where f() takes into account all possible relevant influential factors (confounding factors (CF))

  2. Clinical / Biological
     Similar approach to what was used to develop blood tests with BM
     LF = g(SWS, BM_1, ... BM_n), in which SWS may become one of the BM.
Technical versus Clinical Approaches

1. Assess LF from SWS, knowing other CF
   (FibroScan, SWE, VTQ, ElastPQ)

2. Assess LF from a combination of BioM
   (FibroTest, FibroMetre, APRI…)

CFs Found in the Literature for the Technical Approach

<table>
<thead>
<tr>
<th>Technique</th>
<th>Physics &amp; Biology</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technology used</td>
<td>• Visco-Elasticity</td>
<td>• Gender</td>
</tr>
<tr>
<td>SW frequencies used</td>
<td>• Signal attenuation</td>
<td>• BMI</td>
</tr>
<tr>
<td>SNR as a confidence factor</td>
<td>• …</td>
<td>• Metabolic syndrome,</td>
</tr>
<tr>
<td>Mean value</td>
<td>• Serum markers</td>
<td>Diabetes,</td>
</tr>
<tr>
<td>…</td>
<td>• …</td>
<td>Hypertension, Heart rate,</td>
</tr>
<tr>
<td>SWS measurement</td>
<td>• …</td>
<td>Heart failure</td>
</tr>
<tr>
<td>protocol</td>
<td>• …</td>
<td>• Necrosis</td>
</tr>
<tr>
<td>Patient’s position</td>
<td>• …</td>
<td>• Inflammation</td>
</tr>
<tr>
<td>Breathing</td>
<td>• …</td>
<td>• Steatosis</td>
</tr>
<tr>
<td>Fasting</td>
<td>• …</td>
<td>• Congestion</td>
</tr>
<tr>
<td>Liver lobe</td>
<td>• …</td>
<td>• Edema</td>
</tr>
<tr>
<td>…</td>
<td>• …</td>
<td>• Cholestasis</td>
</tr>
<tr>
<td>…</td>
<td>• …</td>
<td>• Beta-blockers</td>
</tr>
<tr>
<td>…</td>
<td>• …</td>
<td>• Ascites</td>
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<tr>
<td>…</td>
<td>• …</td>
<td>…</td>
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</tbody>
</table>

Physics and Biology allow the underlying interpretation of the measurement of a CF
QIBA Group: What role for SWS as a BM?

Is it the primary measurement?

Is it part of the pool of factors?

Towards one single question

• Clinical CF
• Biomarkers
• Ground truth Scale
Towards one single question

- Clinical CF
- Biomarkers
  - Technical measurements
  - Physical properties
- Ground truth
  Scale

Objectives are:

- Determine from literature review:
  - All clinical BM and clinical CF and all technical CF
  - Establish the dependencies between BM and CF

- Design a clinical study protocol to determine the function
  SWS \(\rightarrow\) LF
  - Data acquisition to be collected: need to list all required BM
  - Methodology
    - Patients population
    - Claims / Outcomes
    - Statistical approach
    - Use of a GS
What should be used as the standard of reference?

Current trend: Biopsy is less and less performed. Reasons include: invasiveness, complications (1%), repeated procedures, patient compliance…

Is Liver Biopsy still the Gold Standard (GS)?

**YES**
- Biopsy IS the reference test (« gold standard »)
- Advantages are additional information given about:
  - etiology and cofactors
  - immuno-histochemical, biochemical and biohumoral analysis
  - Iron content assessment
  - Steatosis
  - Necrosis
  - Grading (activity)

**NO**
- Procedure is invasive
  - Complications in ~1% and death in ~1‰
- Reliability is questioned
  - Sampling error
  - Variability in stage assessment
- Unable to assess disease progression beyond F4
- How to reach inflammation and steatosis information?
How are Histological Findings Interpreted?

- LF Scores are all made of a Fibrosis score and an Inflammation activity score.
- Most of them have been developed for the assessment of LF in the context of chronic viral Hepatitis C.
- Fibrosis scores:
  - Metavir (0,1,2,3,4)
  - Ishak (0,1,2,3,4,5,6)
  - Knodell (0,1,3,4)
  - Inuyama (0,1,2,3,4)

**Table:**

<table>
<thead>
<tr>
<th>F0</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>METAVIR stage</th>
<th>Fibrosis area (mean ± SEM)</th>
</tr>
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<tbody>
<tr>
<td>F0</td>
<td>2.0 ± 0.1</td>
</tr>
<tr>
<td>F1</td>
<td>3.4 ± 0.3</td>
</tr>
<tr>
<td>F2</td>
<td>5.8 ± 0.7</td>
</tr>
<tr>
<td>F3</td>
<td>14.7 ± 0.8</td>
</tr>
<tr>
<td>F4</td>
<td>25.1 ± 1.4</td>
</tr>
</tbody>
</table>

The difference in fibrotic area to distinguish between F2 and F3 is very small. Therefore, it is recognized to be less reliable to distinguish between F2 and F3.

Misclassification Rates of Liver Biopsy

- Misclassification of fibrosis stages is higher for F1, F2, and F3 with low length of biopsy specimen (can reach 40%).
- Biopsy procedures should be supported by the adoption of quality criteria:
  - Minimal length: 25 mm
  - Minimal number of portal spaces (6, 10, 12?)
Could Blood Tests be Considered as GS for Liver fibrosis?

- Most of them are good to detect cirrhosis, but not significant fibrosis (F≥2); the misclassification rate is the highest for F1, F2, and F3

Limitations
- Multiplicity of biomarkers
- Availability of dosage methods?
- Standardization/reproducibility of methods?
- Physiological and pathological modifications

Opportunities
- Steatosis and Inflammation could be estimated without Biopsy

Summary Objective
Conclusion: Suggested Action Plan

- Perform a meta analysis to review literature and answer key questions
  - Gather each technology-specific factors (SWS system dependencies)

- Identify and categorize all published confounding factors (CF), and structure their dependencies

- Determine if GS is possible and, if yes, which one

- Design a study protocol to determine the function LF=f(SWS)
  - Data acquisition
  - Methodology

Thank you for your attention!

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