



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

Towards a Shared Vision  
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SWS measurement as a biomarker of Liver Fibrosis

## Background



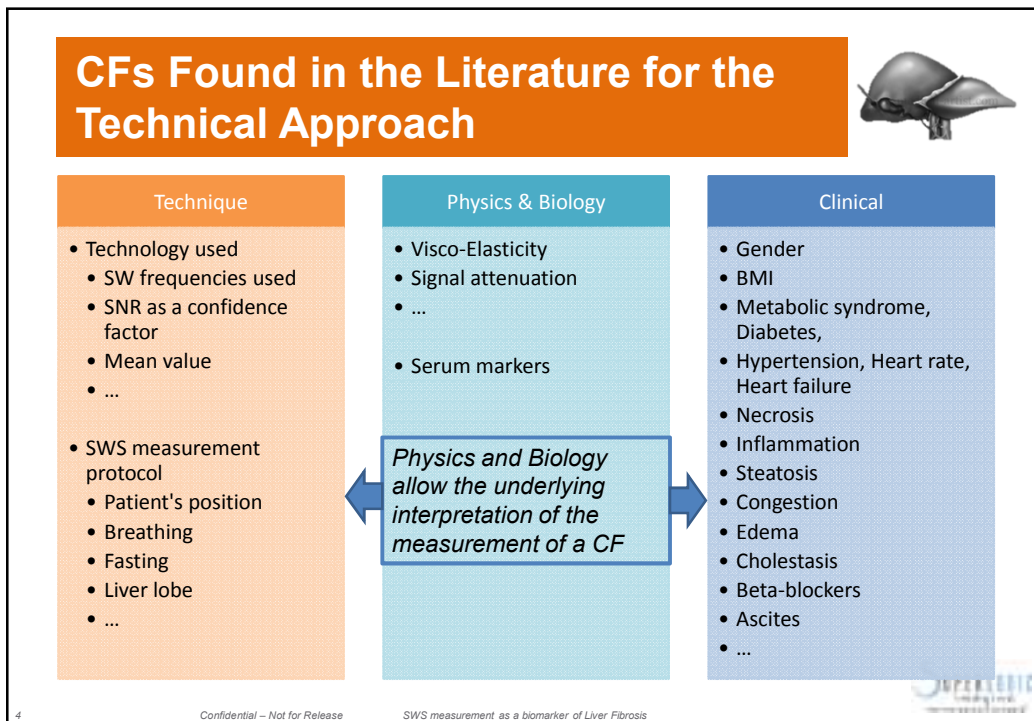
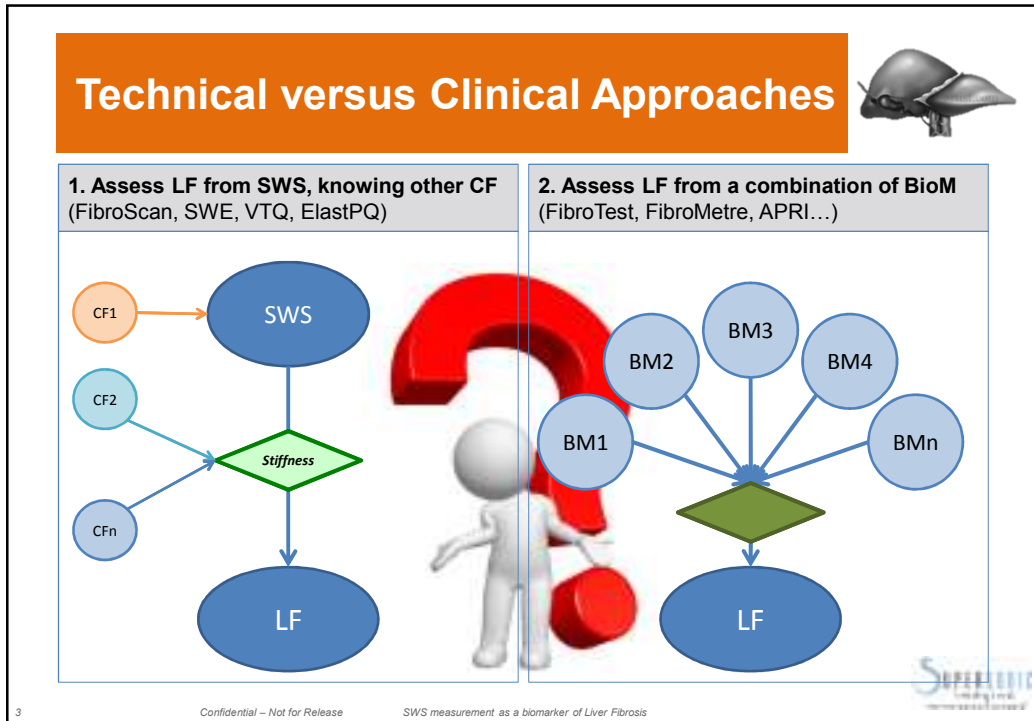
- Objective: Determine **how<sup>1</sup>** SWS can help the **physician's<sup>2</sup>** assessment of liver fibrosis **level<sup>3</sup>**
  1. How
    - Which Technique, which measurement protocol, which applicability criteria
    - Alone or in combination with other measurements;
    - Which clinical 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  
 $LF = g(SWS, BM_1, \dots, BM_n)$ , in which SWS may become one of the BM.




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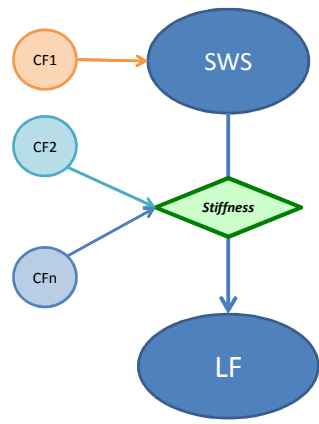
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## QIBA Group: What role for SWS as a BM?



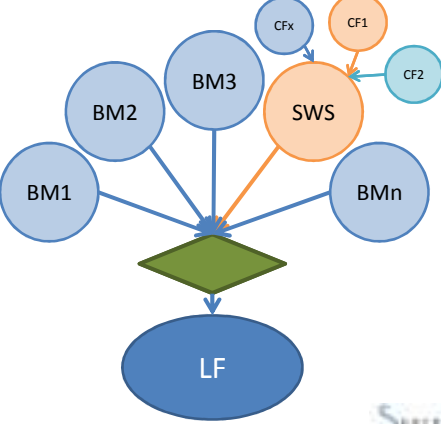
### Is it the primary measurement?



```


graph TD
    CF1((CF1)) --> SWS((SWS))
    CF2((CF2)) --> Stiffness{Stiffness}
    CFn((CFn)) --> Stiffness
    SWS --> Stiffness
    Stiffness --> LF((LF))
        
```

### Is it part of the pool of factors?




```

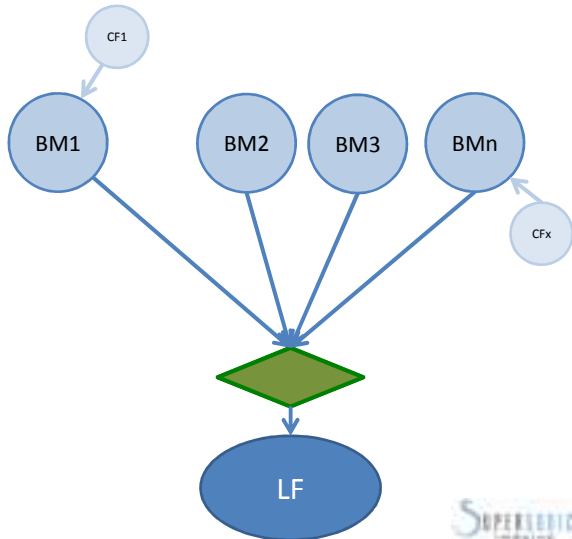
graph TD
    BM1((BM1)) --> Pool{ }
    BM2((BM2)) --> Pool
    BM3((BM3)) --> Pool
    BMn((BMn)) --> Pool
    CFx((CFx)) --> SWS((SWS))
    CF1((CF1)) --> SWS
    CF2((CF2)) --> SWS
    Pool --> LF((LF))
        
```

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## Towards one single question




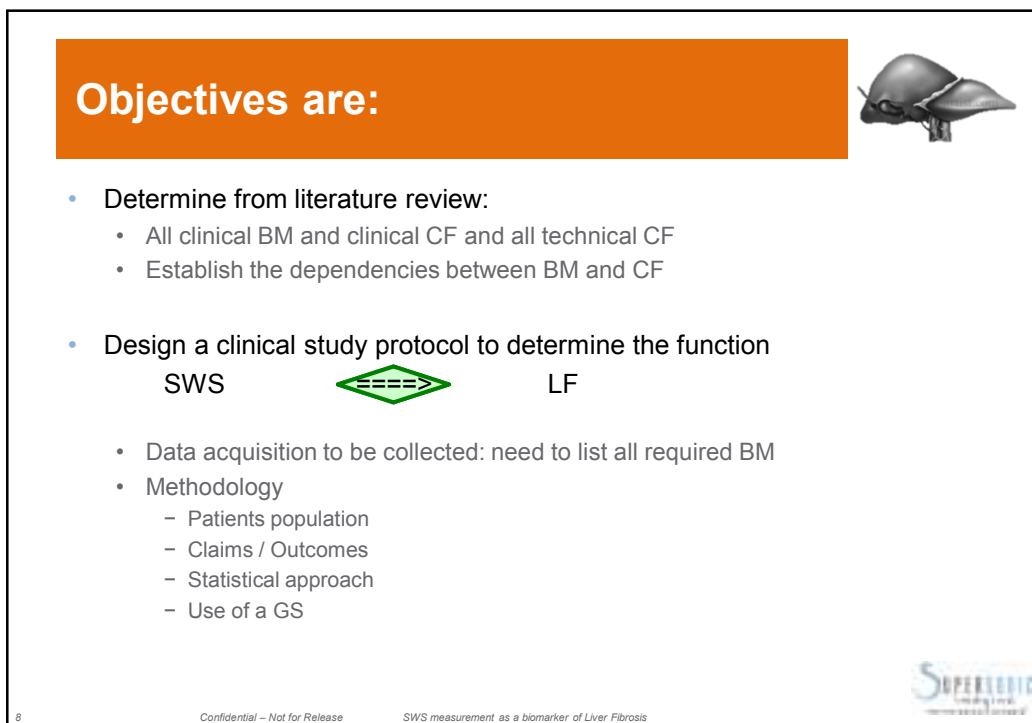
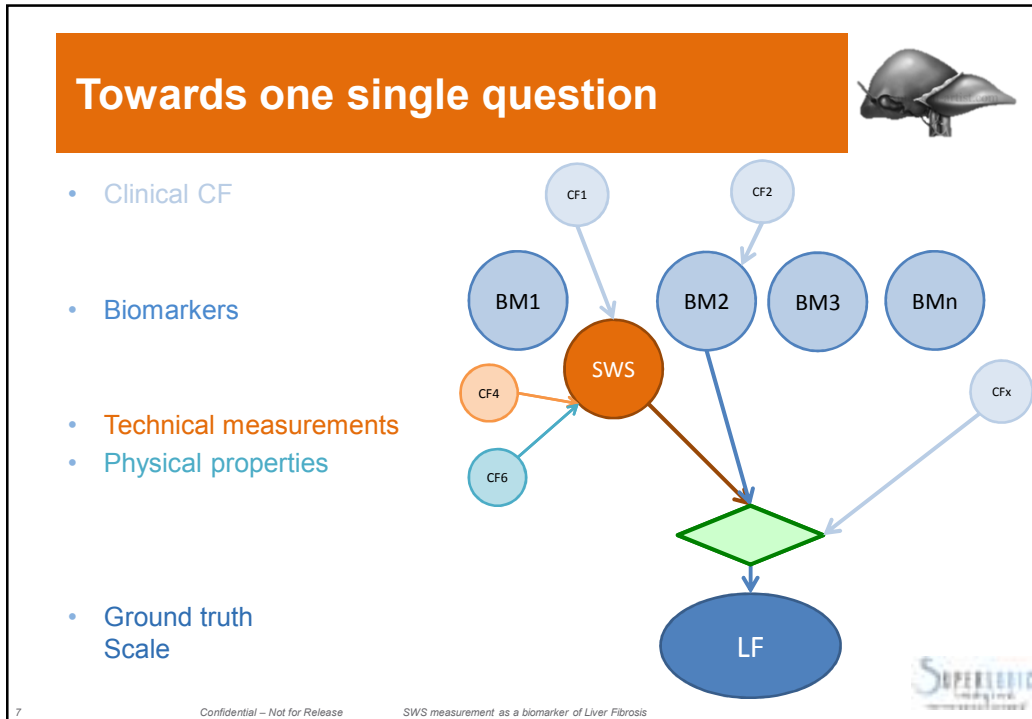
- Clinical CF
- Biomarkers
- Ground truth Scale



```

graph TD
    BM1((BM1)) --> Pool{ }
    BM2((BM2)) --> Pool
    BM3((BM3)) --> Pool
    BMn((BMn)) --> Pool
    CFx((CFx)) --> Pool
    Pool --> LF((LF))
        
```

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## 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...

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## Is Liver Biopsy still the Gold Standard (GS)?

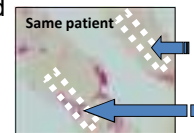


### YES

- 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?



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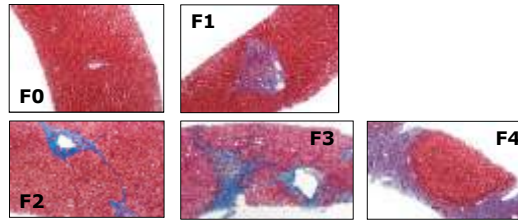
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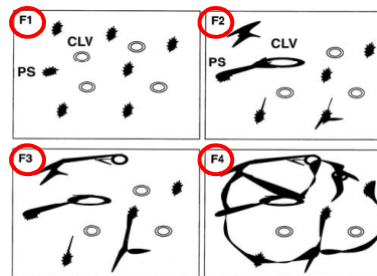
# How are Histological Findings Interpreted?



- 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)



staging	
0	no fibrosis
1	portal fibrosis without septa
2	few septa
3	many septa without cirrhosis
4	cirrhosis



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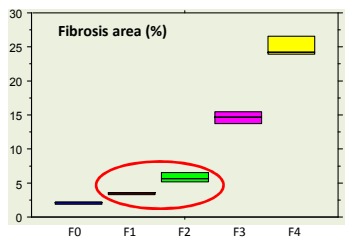
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# Misclassification Rates of Liver Biopsy

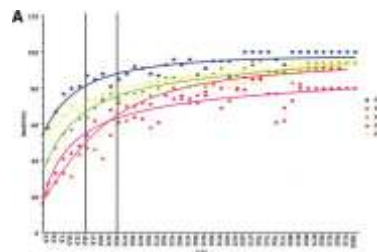


Bedossa Hepatology 2003



METAVIR stage	Fibrosis area (mean ± SEM)
F0	2.0 ± 0.1
F1	3.4 ± 0.3
F2	5.8 ± 0.7
F3	14.7 ± 0.8
F4	25.1 ± 1.4

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.



Percentage of correctly classified biopsies with the converted METAVIR score of fibrosis, according to length of biopsy specimen.

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 :

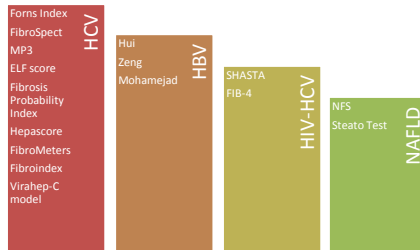
- Minimal length: 25 mm
- Minimal number of portal spaces (6, 10, 12?)

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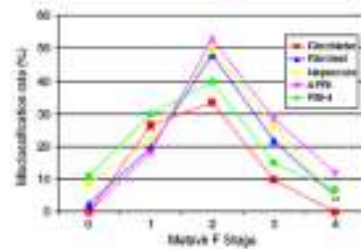
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## Could Blood Tests be Considered as GS for Liver fibrosis?



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



Cales et al. Liver Int 2009



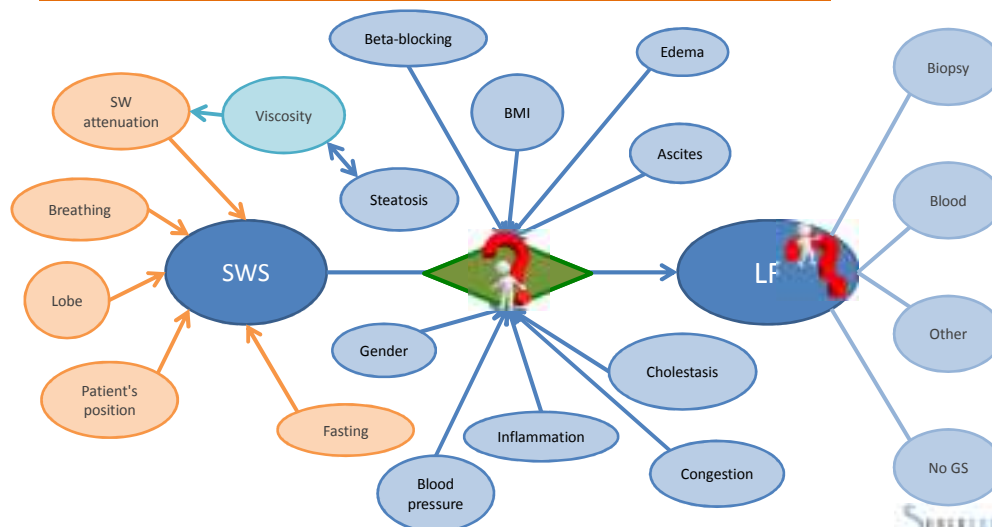
- **Limitations**
  - Multiplicity of biomarkers
  - Availability of dosage methods?
  - Standardization/ reproducibility of methods?
  - Physiological and pathological modifications
- **Opportunities**
  - Steatosis and Inflammation could be estimated without By

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## Summary Objective



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## 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



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Thank you for your attention!

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