

## Background and aims

The diagnosis of liver fibrosis and cirrhosis may be estimated by blood tests.

However, even well-performing tests may lack optimization; first, most were constructed for significant fibrosis but not for cirrhosis, and second, published accuracies may be overestimated when the model is obtained in a single statistical step, due to optimism bias (Steyerberg et al. 2001).

Finally, several accurate tests include hyaluronate, which results in challenges due to its high cost and low availability.

## Results (1)

- The bootstrap method validated the markers of original FibroMeter2G and provided a modified FibroMeter3G where hyaluronate was replaced by GGT.
- FibroMeter2G and FibroMeter3G were well correlated (**figure 1**).
- The AUROCs (corrected for optimism bias) were:
  - significant fibrosis:
    - original FibroMeter2G: 0.853 (0.847) vs
    - modified FibroMeter3G: 0.851 (0.845),  
p=0.489;
  - cirrhosis:
    - original FibroMeter2G: 0.919 (0.911) vs
    - modified FibroMeter<sup>3G</sup>: 0.911 (0.902),  
p=0.097.

## Aims

Our aim was to check the robustness of an accurate test like FibroMeter (FM), calculate its accuracy (AUROC) corrected for optimism bias, and develop a similar, hyaluronate-free test offering comparable accuracy and reliability for two diagnostic targets: significant fibrosis and cirrhosis.

## Methods

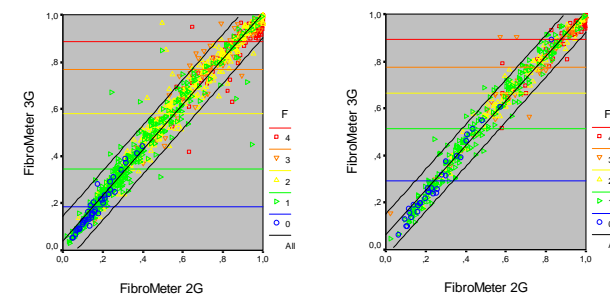
1012 chronic hepatitis C patients with liver biopsy and blood markers were included in a derivation population.

The markers for significant fibrosis (Metavir F $\geq$ 2) were selected by logistic regression repeated in 1000 random bootstrap samples.

Then, specific coefficients were determined for cirrhosis diagnosis.

When models were determined, a second bootstrap resampling was performed to measure optimism bias.

458 chronic hepatitis C patients with liver biopsy and blood markers were included in a validation population.



**Figure 1.** Correlation of FibroMeter2G and FibroMeter3G as a function of Metavir fibrosis (F) stages. Oblique black lines depict linear regression with mean and 95% of population. Horizontal coloured lines indicate the mean FibroMeter3G score as a function of Metavir F. **Panel a:** Derivation population #1 (rp = 0.986). **Panel b:** Validation population #2 (rp = 0.986).

## Results (2)

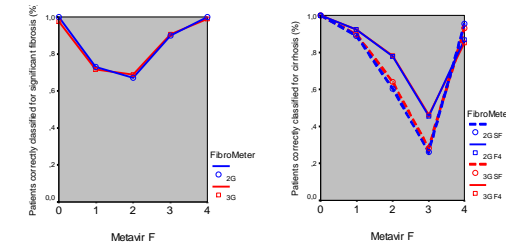
The AUROC of original FibroMeter2G constructed for cirrhosis (0.919) was significantly higher than that of FM constructed for significant fibrosis and applied to cirrhosis diagnosis (0.907,  $p=0.005$ ).

AUROC of original FibroMeter2G and modified FibroMeter3G for significant fibrosis were higher than those of Hepascore (0.787,  $p<0.0001$ ) and Fibrotest (0.810,  $p=0.0002$ ).

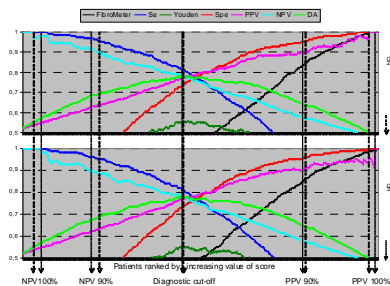
FibroMeter2G and FibroMeter3G had similar performance profiles (figure 2).

The predictive value curves were not different between original FibroMeter<sup>2G</sup> and modified FibroMeter<sup>3G</sup> for the two diagnostic targets (figure 3).

The respective costs were €57 and €31.



**Figure 2.** Comparison of performance profiles between FibroMeter<sup>2G</sup> and FibroMeter<sup>3G</sup>. They depict the rate of correctly classified patients as a function of Metavir fibrosis stage. There was no statistical difference within each stage or whatever the diagnostic target. **Panel a.** Correctly classified patients for significant fibrosis by FibroMeters designed for significant fibrosis. **Panel b.** Correctly classified patients for the diagnosis of cirrhosis by FibroMeters designed for significant fibrosis (SF) or cirrhosis (F4).



**Figure 3.** Curves of diagnostic indices (Y axis) as a function of blood test values (score on X axis) for significant fibrosis. Upper panel: FibroMeter<sup>2G</sup>; bottom panel: FibroMeter<sup>3G</sup>. Se: sensitivity, Spe: specificity, PPV: predictive positive value, NPV: negative positive value, DA: diagnostic accuracy. The bottom line depict cut-offs for diagnosis and different predictive value levels whose crossings with curves are shown by vertical arrows.

## Conclusion

By using the bootstrap method, we validated the original FibroMeter<sup>2G</sup> while developing a similar blood test, FibroMeter<sup>3G</sup>, with comparable accuracy and reliability, but nearly two times less expensive.

The optimism bias was <1% in all AUROCs.

The specific FibroMeter<sup>2G</sup> for cirrhosis had high accuracy (AUROC: 0.92).