

## Non-invasive fibrosis markers do not replace liver biopsy

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### Role of Liver Biopsy

To assess fibrosis AND inflammatory activity  
To evaluate for co-etiologicals (ex. HCV and NASH)  
To help determine the need for treatment in hepatitis C infection (mild vs. moderate vs. severe fibrosis)

UIC: 53% of 593 biopsies done in the last 3 years were for staging of HCV

French study 54% (Hepatology 2000)

## Advantages of Liver Biopsy

- Provides a direct, quantitative assessment of fibrosis
- Allows fibrosis to be measured using a standardized system
- Can be used to assess progression of disease/fibrosis over time
- Provides additional information regarding:
  - Degree of inflammation
  - Distribution of fibrosis
  - Co-existing pathology
- Risk of a serious adverse event is rare (<0.2%)

## Limitations of Liver Biopsy: Size Matters

### Specimen length:

1.5 cm

- Fails to recognize cirrhosis in 15-40%
- Even so, NPV 93% (as good or better than most non-invasive tests)

3.0 cm

- PPV and NPV 100%
- Diagnostic accuracy 100%

Colloredo et al. J Hepatol 2003.

## Ideal Characteristics of Non-invasive Fibrosis Markers

Liver Specific  
 Reflect fibrosis irrespective of the cause  
 Simple  
 Readily available  
 Inexpensive  
 Sensitive enough to distinguish between different stages of fibrosis

\*\*\*No tests that are currently available meet all of these criteria

## Non-invasive Fibrosis Markers

Name	Components	Sens/Spec	PPV/NPV
AST/ALT ratio	AST/ALT	<b>53%/100%</b>	100%/ <b>81%</b>
APRI	AST, plts	<b>41%/95%</b>	88%/ <b>64%</b>
Fibrotest	GGT, bilirubin, apolipoprotein A	<b>87%/59%</b>	<b>63%/85%</b>
Fibrospect	Hyaluronic acid, TIMP-1, alpha-2-macroglobulin	<b>83%/66%</b>	<b>72%/78%</b>

Rockey et al Hepatology 2006.

## ■ Limitations of Non-invasive Fibrosis Markers

Indirect measure

Can predict mild (F0/1) or severe (F3/4) fibrosis, not intermediate stages

Either have poor sensitivity and NPV or poor specificity and PPV

Only few of these non-invasive markers have been compared in head-to-head trials

Little evidence is available on patients with non-HCV liver disease

## ■ Elastography

Measures mean hepatic tissue stiffness which is indirectly related to the degree of fibrosis using pulse-echo technology

The velocity of the vibration wave as it passes through the liver correlates directly with tissue stiffness

The stiffer the tissue, the faster the shear wave

## Elastography Limitations

Signal propagation (25-65mm) limited in:

- Obese patients

- Patients with ascites

- Patients with narrow intercostal space

No established optimal cutoff for what is abnormal

Cannot differentiate between fibrosis and steatosis

Cannot track changes in fibrosis as a result of treatment

## Elastography ( $\geq$ F2 Fibrosis)

Study	N	AUC	Sens	Spec	PPV	NPV
Ziol et al	327	0.79	0.56	0.91	0.88	0.56
Castera et al	183	0.83	0.67	0.89	0.95	0.48
Colletta et al	40		100	100	100	100

\*Fibrosis scores are rated by the METAVIR score

## Summary

Liver biopsy has been the gold standard for fibrosis assessment because it is a direct measure.

Biopsy enables an accurate 3-level staging of fibrosis when there is an adequate sample length.

Non-invasive markers assess the extremes of fibrosis, not the clinically relevant intermediate stages.

Non-invasive markers have either a low specificity or sensitivity, circumventing the need for liver biopsy in only a minority of patients.

Many non-invasive markers are not readily available or standardized.

## Conclusions

Liver biopsy remains the most accurate means to directly measure different stages of liver fibrosis.

There is no convincing evidence that non-invasive markers have the precision that is necessary to track disease progression or response to therapy.

While non-invasive markers may prove useful in their ability to assess the extremes of fibrosis, their low specificity and/or sensitivity abolish the need for liver biopsy in only a minority of patients.

Future non-invasive markers need to be able to detect intermediate stages of fibrosis with more sensitivity and specificity before they are ready for routine clinical use.