New Non-Invasive Liver Disease BioMarkers

THE ONLY TESTS FOR THE DIAGNOSIS AND STAGING OF LIVER FIBROSIS AND THE MOST COMMON LIVER DISEASES

• FibroTest-ActiTest
• FibroMAX
The population at risk of liver fibrosis, cirrhosis and hepatocellular carcinoma is alarming

- Insulin resistance: 570 (30)
- Alcohol consumption: 540 (60)
- Hepatitis B: 150 (150)
- Hepatitis C: 90 (90)

Figures are in millions

The majority of HCV patients at risk of liver disease remain undiagnosed

- Worldwide prevalence of risk
- Extensive fibrosis

<table>
<thead>
<tr>
<th>Region</th>
<th>% diagnosed</th>
<th>% treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>22</td>
<td>16</td>
</tr>
<tr>
<td>Europe</td>
<td>19</td>
<td>16</td>
</tr>
</tbody>
</table>

Hepatitis C virus (HCV) prevalence - Pharmaceutical Market Analysis 2004
Liver biopsy is undesirable to patients & associated with serious complications

Traditionally, liver biopsy has been utilized to assess the histological features of the liver and hence estimate the degree of liver damage. However, this procedure has several drawbacks:

- it is invasive
- it is prone to complications, ranging from minor (up to 30% experience pain) through to more severe (including death in approximately 0.03%)
- there is considerable sampling variability (up to 40% for fibrosis staging)
- there is a high intra and inter-pathologist variability

As such,

“...numerous studies strongly suggest that due to the limitations and risks of biopsy, as well as the improvement of the diagnostic accuracy of biochemical markers, liver biopsy should no longer be considered mandatory (1).”
The BioPredictive Patented New Technology...

FibroTest-ActiTest® and FibroMAX®: the innovative diagnostic and staging tools for the most common liver diseases

The BioPredictive tests:
- FibroTest-ActiTest® is the combination of FibroTest® & ActiTest®;
- FibroMAX® is the combination of up to five non-invasive liver tests: FibroTest®, ActiTest®, SteatoTest®, NashTest® and AshTest®.

• FibroTest-ActiTest®
  > FibroTest®: diagnoses hepatic fibrosis
  > ActiTest®: assesses viral necro-inflammatory activity

• FibroMAX®
  > FibroTest®: diagnoses hepatic fibrosis
  > SteatoTest®: diagnoses hepatic steatosis (otherwise known as ‘fatty liver’)
    – the most common cause of ALT and GGT abnormalities
  > ActiTest®: assesses viral necro-inflammatory activity
  > AshTest®: diagnoses severe alcoholic steatohepatitis (ASH) in excessive drinkers
  > NashTest®: diagnoses non-alcoholic steatohepatitis (NASH)
    in patients who are overweight, insulin resistant, have diabetes or hyperlipidemia

The BioPredictive tests work by using an algorithm based on the patients’ sex, age, weight, height and specific blood biomarkers*. These algorithms have been scientifically validated and quality-monitored to ensure that the results delivered are of the highest analytical standards.

The validation and analytical standardization of FibroTest-ActiTest® and FibroMAX® have been established in several clinical studies. There are over 40 publications available that review and assess the tests and these can be found out at:

www.biopredictive.com

The Biopredictive tests provide accurate results instantly

Patient Profile

> BioPredictive test required and result sample

**FibroTest-ActiTest**

Chronic Hepatitis C or B

- **FibroTest-ActiTest**
  - F0
  - F1
  - F2
  - F3
  - F4

- **FibroTest**
  - Score 0.50 (F2)
- **ActiTest**
  - Score 0.38 (A1-A2)

**FibroMAX**

Viral, Metabolic or Alcoholic Hepatitis when symptoms or risk factors are difficult to decipher

- **FibroMAX**
  - S0
  - S1
  - S2
  - S3

- **SteatoTest**
  - Score 0.49 (S1-A2)
- **ActiTest**
  - Score 0.38 (A1-A2)
- **AshTest**
  - Score 0.03 (H0)
- **NashTest**
  - Score 0.75 (Nash)

**FibroTest-ActiTest® and FibroMAX® can be repeated as necessary, according to the patient’s profile and disease severity.**
The FibroTest-ActiTest® results are interpreted as follows*:

<table>
<thead>
<tr>
<th>Score</th>
<th>Fibrosis Stage</th>
<th>METAVIR Fibrosis Stage Estimate</th>
<th>Kendall Fibrosis Stage Estimate</th>
<th>Ishak Fibrosis Stage Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.75-1.00</td>
<td>F4</td>
<td>F4</td>
<td>F6</td>
<td></td>
</tr>
<tr>
<td>0.73-0.74</td>
<td>F3 - F4</td>
<td>F3 - F4</td>
<td>F5</td>
<td></td>
</tr>
<tr>
<td>0.59-0.72</td>
<td>F3</td>
<td>F3</td>
<td>F4</td>
<td></td>
</tr>
<tr>
<td>0.49-0.58</td>
<td>F2</td>
<td>F1 - F3</td>
<td>F3</td>
<td></td>
</tr>
<tr>
<td>0.32-0.48</td>
<td>F1 - F2</td>
<td>F1 - F3</td>
<td>F2 - F3</td>
<td></td>
</tr>
<tr>
<td>0.28-0.31</td>
<td>F1</td>
<td>F1</td>
<td>F2</td>
<td></td>
</tr>
<tr>
<td>0.22-0.27</td>
<td>F0 - F1</td>
<td>F0 - F1</td>
<td>F1</td>
<td></td>
</tr>
<tr>
<td>0.00-0.21</td>
<td>F0</td>
<td>F0</td>
<td>F0</td>
<td></td>
</tr>
</tbody>
</table>

Precautions for Use

The reliability of results is bound with the respect of the preanalytical and analytical conditions recommended by BioPredictive.

The Tests have to be deferred for: acute hemolysis, acute hepatitis, acute inflammation, extra hepatic cholestasis.

The advice of a specialist should be sought for interpretation in chronic hemolysis and Gilbert’s syndrome.

The Test interpretation is not validated in liver transplant patients.

Isolated extreme values of one of the components should lead to caution in interpreting the results.

In case of discordance between a biopsy result and a Test, it is advised to seek for the advice of a specialist. The causes of these discordances could be due to a flaw of the Test or to a flaw in the biopsy: i.e. a liver biopsy has a 33% variability rate for one fibrosis stage.

FibroTest and SteatoTest are interpretable for chronic hepatitis B and C, alcoholic and non-alcoholic steatosis.

NashTest is interpretable for non-alcoholic steatosis.

AshTest is interpretable for alcoholic steatosis.

ActiTest is interpretable for chronic hepatitis B and C.
Like viral hepatitis, the number of patients at risk for metabolic hepatitis (and alcoholic liver disease) is high enough that liver biopsy is not a practical and efficient tool for identifying those at risk of advanced fibrosis.

Based on these tests and within the associated limitations of non-invasive testing, the prevalence (fibrosis, steatosis and NASH) in hyperlipidemic patients appears to be high (3%, 30% and 7% respectively) in this cross-sectional study. This study suggests that biomarkers could be very useful for the screening of advanced fibrosis and NASH in patients with several metabolic syndrome factors to prevent liver mortality. (2)

An additional study also suggests that non-invasive biomarkers could be very useful for the screening of advanced liver fibrosis and its aggravating factors (steatosis and NASH) in type 2 diabetics older than 45 years to prevent liver mortality. (3)
The BioPredictive Tests are simple, convenient and cost-effective

Step 1
Physician prescribes FibroTest-ActiTest® or FibroMAX®

Step 2
Patient has blood sample taken at local biomedical laboratory

Step 3
Data from blood test results are entered directly online at www.biopredictive.com by biologist and results are generated immediately

Step 4
Biologist provides report back to physician

About BioPredictive…
BioPredictive® is a biotechnology company based in Paris, France. The aim of BioPredictive® is the discovery and development of new generation of diagnostic tests employing non-invasive techniques designed to facilitate the care and treatment of patients.

For more information please visit www.biopredictive.com

References:
(2) Ratziu V et al: Screening for advanced fibrosis using non-invasive biomarkers (FibroTest- FIBROSURET) in patients consulting for hyperlipidemia. Aliment Pharmacol Ther. 2006 (Online Accepted).
Poynard T et al; The diagnostic value of biomarkers (SteatoTest) for the prediction of liver steatosis. Comp Hepatol. 2005; 4: 10.
Poynard T et al; Diagnostic value of biochemical markers (NashTest) for the prediction of non alcoholic steato hepatitis in patients with non-alcoholic fatty liver disease. BMC Gastroenterol. 2006; 6: 34.