New noninvasive biomarkers of liver fibrosis the Enhanced Liver Fibrosis score (ELF score)
Liver fibrosis can result from a number of pathological processes, the most common being chronic hepatitis B & C, alcohol abuse, and non-alcohol-related steatohepatitis (NASH). Complications include progression to cirrhosis, end stage liver disease and hepatocellular carcinoma. A worrying trend is the increasing numbers of cases of cirrhosis due to NASH in developed and developing countries. NASH will probably become the major cause of cirrhosis in the near future if current trends in obesity continue.

Liver biopsy is the gold standard for diagnosing and grading the degree of liver fibrosis. Drawbacks to biopsy include cost; a not inconsequential failure rate; complications, including bleeding and shock; and, most importantly, poor patient acceptability. Biopsy samples are often limited and frequently do not reflect the overall fibrotic state of the liver. Noninvasive methods are now being advocated for assessment of fibrosis in patients with chronic hepatitis C rather than resorting to repeated liver biopsies.

A number of noninvasive techniques have been developed to complement or circumvent the need for biopsy. These techniques include serum blood markers, elastography (Fibroscan), ultrasound (acoustic radiation force impulse—ARFI) and functional MRI. Of these, Fibroscan is the only modality that is widely available in Australian capital cities. It is effective but has a higher failure rate in obese patients and is not readily available for remotely situated patients.

Blood markers have been of great interest for decades, but rely on algorithms or calculations incorporating indirect markers such as age, bilirubin, AST, ALT, albumin, gamma GT, triglyceride, platelet count and prothrombin time. They are useful for initial stratification of patients who warrant further investigation for hepatic fibrosis.

Direct blood markers are products of activated hepatic stellate cells (myofibroblasts): the cells responsible for generating fibrosis in the liver. Monitoring these direct markers is indicated when the patient’s history, physical examination, imaging or indirect serum markers are suspicious for fibrosis.

### Stages of liver damage

<table>
<thead>
<tr>
<th>Normal</th>
<th>Liver injury/ inflammation</th>
<th>Liver fibrosis</th>
<th>Liver failure/ liver cancer</th>
</tr>
</thead>
</table>

**Fibrosis Progression**

- Liver injury
- Quiescent stellate cell
- Activated stellate cell

**Extracellular Matrix Proteins**

Fibrosis
Sullivan Nicolaides Pathology has recently introduced a new panel of the most promising direct markers, which are incorporated into a calculation, the Enhanced Liver Fibrosis score (ELF score).

The 3 markers are the N-terminal peptide of procollagen III (P3NP/PIIINP), hyaluronic acid and tissue inhibitor of matrix metalloproteinase 1 (TIMP-1).

Run as automated immunoassays using a serum sample

ELF Score^T = 2.278 + 0.851 \ln(C_{HA}) + 0.751 \ln(C_{PIIINP}) + 0.394 \ln(C_{TIMP-1})

The ELF score has been assessed in a number of studies and has shown comparable accuracy with the Fibroscan. Both the ELF score and Fibroscan can better predict a patient’s long-term survival than a biopsy alone. However, both modalities help prioritise patients for biopsy and can be complementary.

A low ELF score has a very high negative predictive value for moderate to severe fibrosis (Score < 7.7). Thus, unless needed for a diagnosis, these low-risk patients won’t require fibrosis classification via biopsy. Patients with a high score (> 11.2) probably do not need a biopsy as cirrhosis is likely. These patients require six monthly ultrasound and serum AFP to detect hepatocellular cancer, as well as management for end-stage liver disease, including preparation for liver transplantation.

The patients with intermediate scores (7.7–11.2) are candidates for further imaging (Fibroscan) or liver biopsy. However, the ELF score shouldn’t be used as a screening tool in the healthy population as a proportion will have scores above 7.7. It should be reserved for those with known chronic liver disease (e.g. hepatitis B & C, alcohol abuse, haemochromatosis, autoimmune liver disease and NASH). The ELF score can also be elevated in other fibrosing conditions such as scleroderma and is being used to monitor patients.

ELF values falling below 7.7 are associated with limited to no fibrosis in patients that have undergone biopsy. An ELF score of 7.7 or less would be expected to indicate minimal risk of any advanced fibrosis.

Intermediate ELF values of 7.7—9.8 have been associated with moderate fibrosis (relative to biopsy). Clinical pathways for these patients may include subsequent testing to assess the risk of progressive fibrosis, alternate noninvasive assessment of fibrosis/liver stiffness such as imaging, or liver biopsy.

Elevated ELF scores of 9.8 or greater have been associated with significant, biopsy-proven fibrosis or cirrhosis. Patients with elevated ELF scores should be considered at risk and managed appropriately, including further assessment for fibrosis using imaging or liver biopsy.

Some evidence suggests a significant correlation of ELF score of 11.3 and greater with biopsy proven cirrhosis. Use of this additional cut-off is currently outside of claims, but is being explored by the manufacturer. Patients with scores of 11.3 and greater should be considered at significant risk.
P3NP/PIIINP for monitoring methotrexate therapy

Currently P3NP/PIIINP is used to assess the effect of methotrexate on the liver in patients with psoriasis. P3NP will continue to be available for this purpose on its own; however, the Manchester Protocol cut-offs are adjusted to the new assay (Advia Centaur).

<table>
<thead>
<tr>
<th>Indications for biopsy</th>
<th>Manchester protocol PIIINP RIA (ug/L)</th>
<th>ADVIA Centaur PIIINP (ug/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pre-treatment</td>
<td>&gt; 8.0</td>
<td>&gt; 12.2</td>
</tr>
<tr>
<td>during treatment</td>
<td>&gt; 4.2 in at least 3 samples over 12 months</td>
<td>&gt; 6.3 in at least 3 samples over 12 months</td>
</tr>
<tr>
<td>during treatment</td>
<td>&gt; 8.0 in 2 consecutive samples</td>
<td>&gt; 12.2 in 2 consecutive samples</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Indications for withdrawal of MTX</th>
<th>Manchester protocol PIIINP RIA (ug/L)</th>
<th>ADVIA Centaur PIIINP (ug/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>during treatment</td>
<td>&gt; 10.0 in at least 3 samples over 12 months</td>
<td>&gt; 15.3 in at least 3 samples over 12 months</td>
</tr>
</tbody>
</table>

The decision to perform liver biopsy, withdraw treatment or continue treatment despite raised PIIINP levels must also take into account other factors such as disease severity, patient age and the ease with which alternative therapies may be used in place of MTX

*From Chalmers et al. ‘Replacement of routine liver biopsy by procollagen III aminopeptide for monitoring patients with psoriasis receiving long-term MTX: a multicentre audit and health economic analysis’ British J Dermatol. 2005 vol 152 pages 444—450

What to order: Serum Liver Fibrosis Markers or LFM (includes the 3 markers)
Or
Serum PIIINP or P3NP

Charge: No rebate available
Liver Fibrosis Markers $195
P3NP/PIIINP alone $87.50

Test Frequency: Fortnightly

Test Instrument: Siemens Advia Centaur

References: SNP website www.snp.com.au

PLEASE NOTE: To avoid confusion in Australia, where the acronym E/LFT is universally used for electrolytes and liver function tests, this test panel is being described as Serum Liver Fibrosis Markers. When requesting, please use the term Serum Liver Fibrosis Markers or LFM.

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