

# Transient Elastography (FibroScan) for Non-invasive Assessment of Liver Fibrosis

## Summary

- ✓ **Liver fibrosis is associated with significant morbidity and mortality. The major cause is hepatitis C, which affects 240,000 Canadians.**
- ✓ **Assessing the degree of liver fibrosis is critical to its management. Liver biopsy, an invasive procedure, is considered to be the diagnostic gold standard.**
- ✓ **FibroScan is a rapid, non-invasive technology that uses low frequency vibration and ultrasound to assess the stiffness of liver tissue.**
- ✓ **The diagnostic performance of FibroScan is good for identifying severe fibrosis or cirrhosis, but it is less accurate for milder presentations.**
- ✓ **FibroScan is a promising technology, but large multi-centre trials comparing a range of emerging non-invasive fibrosis staging technologies are required.**

## The Technology

Fibrosis of the liver, which is associated with significant morbidity and mortality, occurs as a result of an exaggerated healing response triggered by chronic insults to the liver, such as injury, infection, and inflammation. Fibrosis of the liver develops when scar tissue replaces normal liver tissue. It can be localized or diffuse, and it can progress to cirrhosis, which increases the risk of developing liver cancer. Liver function is impaired. Assessing the degree of fibrosis is important when making decisions about starting treatment, assessing treatment response, and screening for liver cancer.<sup>1-3</sup>

FibroScan (EchoSens, Paris, France) is a non-invasive test that draws on the physics of transient elastography to assess liver fibrosis. A specialized ultrasound transducer placed over the liver transmits a mild amplitude, low frequency vibration. The vibration creates an elastic shear wave that moves through the underlying liver tissue. Its velocity is measured using pulse-echo ultrasound. Shear waves propagate more quickly in stiff tissue, and fibrotic

tissue is stiff. FibroScan takes <5 minutes to perform, and produces immediate, operator-independent results.<sup>4</sup>

## Regulatory Status

FibroScan is not currently licensed for use in Canada (Kathleen Savage, Health Canada, Ottawa: personal communication, 2006 May 3).

## Patient Group

Liver fibrosis can be caused by many diseases, but most of the studies examining the effectiveness of FibroScan have focused on patients infected with hepatitis C (HCV). Up to 3% of the world's population are infected with HCV, and hepatitis C becomes chronic in 85% of infected adults.<sup>5</sup> In the US, HCV accounts for more cases of chronic liver disease than any other single cause.<sup>6</sup> In Canada, about 240,000 people are infected with HCV, with a prevalence estimated at 0.8% of the population.<sup>7</sup>

## Current Practice

Liver biopsy is the gold standard for assessing the degree of fibrosis. Biopsy is recommended, but not mandated, in practice guidelines addressing the management of HCV.<sup>8-10</sup> No information on the proportion of HCV patients who receive a liver biopsy is available, but it is likely to be a subset of the HCV population. The clinical progression of HCV is typically slow, and infected persons may be asymptomatic for  $\geq 20$  years.<sup>5,6</sup> Furthermore, a biopsy may be unnecessary for HCV genotypes 2 and 3, which respond well to treatment.<sup>8</sup>

Liver biopsy is not easily accepted by patients. Pain is reported by one-third, complications occur in three per 1,000 biopsies, and death occurs in three per 10,000 biopsies. In addition, liver biopsy is subject to sampling error, because the typical biopsy specimen represents only 1/50,000 of the total liver volume, and discrepancies of  $\geq 1$  fibrosis stage have been identified in 33% of the samples taken from the right and left lobes of the same patient. There can also be significant intra- and inter-pathologist variation in the interpretation of biopsy samples.<sup>11</sup>

## The Evidence

Seven observational studies address the relative performance of FibroScan, blood tests, or combinations thereof versus liver biopsy. Most of these were conducted in France.<sup>12-18</sup> There is overlap in the authorship of five of the seven studies.<sup>12,14,15,17,18</sup> Four studies<sup>12,13,16,18</sup> include  $\leq 75$  patients in the statistical analysis, while the others include 183 to 711 participants.<sup>14,15,17</sup> Most<sup>12-16</sup> include only HCV patients, one<sup>17</sup> includes patients with chronic liver disease of any origin, and one<sup>18</sup> includes only patients who are HIV and HCV co-infected.

The studies suggest that FibroScan results are reproducible across operators and time.<sup>12,13</sup> All the studies report that FibroScan's diagnostic performance is good, with Colletta *et al.*<sup>16</sup> indicating that it agrees perfectly with liver biopsy. This finding has sparked debate.<sup>3,19</sup> Five studies<sup>12,14,15,17,18</sup> present AUROC (area under the receiver operating characteristic curve) values, a commonly used index of diagnostic accuracy where values close to 1.0 represent high diagnostic accuracy. In terms of FibroScan's ability to discriminate degrees of fibrosis, as staged on the Metavir scale (F0 to F4 where F0=no fibrosis, and F4=cirrhosis), the AUROC ranges across the studies were  $F \geq 2$ , 0.72 to 0.88;  $F \geq 3$ , 0.90 to 0.91; and,  $F=4$ , 0.95 to 0.99. These results suggest that FibroScan performs well in identifying severe fibrosis or cirrhosis, but is less accurate in identifying lesser degrees of fibrosis. This is important because F2 is a threshold for initiating treatment.<sup>9,10</sup>

Two studies consider the performance of FibroScan relative to or with blood tests.<sup>15,16</sup> Castera *et al.*<sup>15</sup> reported that the diagnostic accuracy of FibroScan, FibroTest<sup>®</sup>, (BioPredictive, Paris, France) and APRI (aspartate transaminase to platelets ratio index) are of the same order, and that diagnostic accuracy is maximized when FibroScan and FibroTest are used in tandem. Colletta *et al.*<sup>16</sup> found FibroScan to be superior to FibroTest among HCV patients with normal aminotransferases.

These are early results, so more research is needed. Most of the studies conducted to date are small, focus on a subset of patients with chronic liver disease, fail to consider the full range of non-invasive tests, and arrive at differing thresholds for discriminating among the degrees of fibrosis. It is also unclear whether the studies were independent of industry involvement.

## Adverse Effects

FibroScan is a non-invasive test, and no adverse effects have been reported.

## Administration and Cost

FibroScan can be performed by trained medical or paramedical staff. No studies have addressed the optimal frequency of testing. The only available cost figures for FibroScan were published in 2004. Estimates include equipment costs of €71,760 (C\$100,464), annual maintenance contract costs of €5,400 (C\$7,560), and negligible costs for consumables. Although details of the calculations are not provided, it is estimated that at 20 and 150 examinations annually, the cost per examination would be €1,000 (C\$1,400) and €100 (C\$140) respectively.<sup>20</sup> These estimates focus on equipment-related expenditures, and seem to exclude staffing or indirect costs.

Liver biopsy costs are reported to range from €703 to €1,566 (C\$984 to C\$2,192) in European centres, and US\$1,032 to US\$2,745 (C\$1,146 to C\$3,047) in US centres, depending on whether complications occur.<sup>11,21,22</sup> Canadian costs may be lower; two large British Columbia health care organizations report direct costs of C\$334 and C\$337, and total costs of C\$432 and C\$472 respectively for liver biopsy (Larry Okotinsky, Fraser Health, Surrey, BC: personal communication, 2006 May 15; Chris Haack, Providence Health Care, Vancouver: personal communication, 2006 May 15).

## Concurrent Development

Laboratory tests for liver fibrosis, based on direct and indirect serum markers, continue to be evaluated. Opinions about the reliability of these tests are mixed, but their development is seen as promising.<sup>11,23,24</sup> Another development is magnetic resonance elastography, which may offer an opportunity to assess a larger volume of the liver, and provide three-dimensional information.<sup>25</sup>

## Rate of Technology Diffusion

FibroScan is not widely diffused in any jurisdiction, but if its effectiveness is confirmed, the technology will probably diffuse rapidly, largely on the basis of its low capital cost, widespread providers' familiarity with ultrasound technologies, and consumer demand.

The pattern of diffusion may be irregular, because the geographic prevalence of HCV varies significantly. The economics of FibroScan will be most favourable in centres that perform a significant volume of liver biopsies.

Morbid obesity or narrow intercostal spaces (the area between the ribs) preclude the use of FibroScan in 5% to 8% of patients.<sup>14,15</sup> This has led to speculation that the rate of uncompleted tests will be higher in jurisdictions such as the US, where the average body mass index is high.<sup>3,14,23</sup> This might affect diffusion, but the manufacturer is developing transducers for use in patients who are obese, or who have narrow intercostal spaces.<sup>4,14</sup>

## Implementation Issues

The potential for non-invasive fibrosis staging is promising, but which technology or combination of technologies will be most useful is unclear. Once licensed, FibroScan could enter the Canadian health care system, as none of its features pose a significant barrier to uptake.

Although it might be argued that FibroScan does not need to be used more often than liver biopsy, it could be compelling to use FibroScan more frequently based on its rapid and non-invasive nature. This would be true for baseline fibrosis evaluations, but might also extend to ongoing monitoring, despite the lack of proof for FibroScan's utility for this purpose. If other non-invasive tools for assessing fibrosis gain acceptance, the market for FibroScan may be fragmented. Such scenarios might negatively affect the economics of FibroScan, or where non-invasive technologies are used in tandem, increase the total volume of tests conducted. This situation would be compounded if the indications for FibroScan expand beyond liver fibrosis due to HCV. This trend is evident in the literature.<sup>17</sup>

The degree to which FibroScan can replace liver biopsy is still unclear. Zioli *et al.*<sup>14</sup> and Castera *et al.*<sup>15</sup> indicate that the use of FibroScan alone or in tandem with another test would have permitted 42% and 77% of their respective study populations to avoid biopsy. Given the lack of information about who receives biopsy and for what reason, it is impossible to extrapolate their findings to clinical practice. Any shift to non-invasive testing will affect the system's capacity to perform liver biopsies, and perhaps require a concentration of such specialized services.

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