Current Status of Non-invasive Alternatives to Liver Biopsy to Assess Hepatic Fibrosis

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Key Concepts

- The extent of hepatic fibrosis in patients with chronic liver disease is associated with the risk of hepatic morbidity and mortality via the development of portal hypertension and liver cancer.

- Ideal features of a non-invasive test of hepatic fibrosis include simplicity, reproducibility, accuracy, association with disease severity, improvement with therapy, association with clinical outcomes in untreated patients, and widespread availability and cost.

- Liver elastography using ultrasound and magnetic resonance based modalities offers great promise in providing accurate and reliable information in patients with moderate to severe hepatic fibrosis as well as potentially clinically useful prognostic information.

- Panels of routine laboratory tests such as APRI and FIB-4 are simple and widely available indices to estimate the likelihood of advanced fibrosis but they are not liver disease specific, have limited discrimination for milder degrees of fibrosis and their prognostic utility is not well established.

- Serum fibrosis marker panels consisting of PIIINP, hyaluronic acid, and TIMP-1 more directly reflect hepatic fibrogenesis and matrix turnover but have largely been tested in patients with viral hepatitis. Additional testing in prospective cohorts and patients with alcoholic liver disease and NAFLD are needed for further validation and refinement.

- Liver specific physiologic tests based upon hepatic enzyme activity (methacetin breath test), kupfer cell mass (liver-spleen scan ratio), intra-hepatic shunting (cholate shunt), proteomics, and genomics may also provide important information but require further development.

Summary

The extent of hepatic fibrosis is associated with the risk of developing complications of portal hypertension and liver cancer in patients with most forms of chronic liver disease. Therefore, an accurate and reliable assessment of fibrosis severity can help identify patients in need of treatment or more intensive monitoring. Currently, liver biopsy is used to assess the stage of liver disease via the pattern and extent of hepatic collagen content using a trichrome stain. However, liver biopsy is associated with substantial sampling artifact that can lead to fibrosis understaging, inter-observer variability, and patient risk and cost that make it an imperfect “gold standard”. Promising non-invasive modalities include assessment of shear wave propagation to assess liver tissue stiffness (i.e. elastography) which is directly correlated with the extent of hepatic fibrosis on biopsy. However, liver tissue stiffness may also increase with hepatic steatosis and inflammation. Ultrasound based elastography is limited by patient body habitus, limited discrimination of milder degrees of fibrosis, and inter-rater reliability. Magnetic resonance elastography...
The extent of fibrosis on liver biopsy is a consistent predictor of the likelihood of disease progression including the development of complications of portal hypertension, liver cancer, and liver-related death in patients with viral hepatitis, NAFLD, alcohol, and cholestatic liver disease (1,2). In addition to providing staging information on a scale of 0 to 6 (Ishak) or 0 to 4 (Metavir, NAFLD score), a liver biopsy provides important information regarding the grade and type of inflammation, hepatic steatosis, and other histological features that can assist in the accurate diagnosis and characterization of various liver diseases. However, a substantial short-coming of liver biopsy is the potential for sampling artifact and understaging of fibrosis particularly in specimens < 1.5 cm in length or containing < 10 portal triads as well as the inter-observer variability in assigning a fibrosis score due to the subjective nature of liver biopsy interpretation (3,4). Furthermore, liver biopsy is costly and associated with a small but finite risk of pain (33%), hospitalization (1 to 5%) and death (severe bleeding < 0.1%) (5). In light of the large number of patients with chronic HCV and NAFLD, there is a growing need to have simple, reliable and accurate non-invasive tools to assess hepatic fibrosis severity in newly diagnosed patients as well as to monitor them over time (6).

**The Ideal Non-invasive Test of Hepatic Fibrosis Severity**

An ideal non-invasive test would be simple, readily available, inexpensive and accurate in assessing the full spectrum of disease severity (Table 1). Simplicity can be defined by technical aspects of the method used as well as patient convenience with point of care testing that provides immediate results in the outpatient clinic being preferable. Reproducibility requires the use of automated and standardized testing platforms for a test involving a biological fluid such as a blood or urine sample that would yield the same result in different centers. For imaging based tests such as liver elastography, the same or similar result should be obtained by multiple operators using a standardized technique and equipment. The ideal test should not only be able to accurately differentiate between major categories of hepatic fibrosis (cirrhosis vs non-cirrhosis, advanced fibrosis/versus mild fibrosis, normal vs increased fibrosis) but also provide quantitative or semi-quantitative rank order assessment of patients with varying severity of hepatic fibrosis.

In addition to assessing initial disease severity, a non-invasive test should also be able to demonstrate improvement during successful treatment of a chronic liver disease as well as worsening in untreated patients that experience disease progression. These longitudinal studies require paired observations of a large number of individual patients who are followed over several years and are often very difficult, expensive, and cumbersome to conduct. As a result, some studies use a change in histology, portal pressure measurements, or clinical symptoms as a surrogate for more objective findings associated with untreated disease progression such as the development of varices, ascites, encephalopathy or laboratory decompensation.

**Current Non-invasive Tests of Hepatic Fibrosis Severity**

Imaging techniques that assess liver tissue elasticity and serum based tests are most commonly used to estimate liver disease severity worldwide (Table 2).
Liver Elastography

The propagation of either low frequency (50 hertz) (Transient and MR elastography) or high frequency (ARFI, shear wave) waves in liver tissue can provide an assessment of the elasticity or stiffness of the liver tissue using a mathematical equation that converts the observed shear wave velocity (meters/sec) into an estimate of the tissue stiffness (kilopascals). In general, the stiffer the liver tissue the faster the shear wave propagation (7).

**Transient elastography (FIBROSCAN):** The Fibroscan (Echosens, Paris, FR) is the most widely studied device with over 700 published manuscripts and > 1500 units installed worldwide. A 1 cm wide x 4 cm long cylinder of liver tissue can be tested at 25 to 65 mm from the skin surface or at 35 to 75 mm from the skin using the XL-probe (8). Advantages of transient elastography include a relatively short procedure time of 5 to 15 minutes and immediate results at the point of care in an office setting with a broad dynamic range of 2.5 to 75 kilopascals. However, accurate results require the careful interpretation of data based on at least 10 consecutive validated measurements and a success rate of > 60% with an interquartile range of < 30% (7). Although transient elastography has excellent inter and intra-observer agreement, there are 10 to 20% of patients with uninterpretable results due to obesity or limited operator experience (9). In addition, extensive hepatic steatosis and liver inflammation can lead to spuriously high readings in some patients (10). Nonetheless, multiple investigators have developed algorithms and various cut-points for identifying European and Asian chronic HCV and HBV patients with cirrhosis with an overall accuracy of > 90% (Table 3) (7).

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**Table 2. Non-invasive modalities to assess liver fibrosis severity**

<table>
<thead>
<tr>
<th>Imaging based</th>
<th>Technique</th>
<th>Current status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fibroscan</strong></td>
<td>Low frequency (50 Hz) wave propagation in a 1 cm wide x 4 cm long tissue core</td>
<td>+: Many studies worldwide, Recent US approval, Point of care test, immediate results; -: ? accuracy in obese and high BMI, 10 -20% failure rate, poor discrimination of milder fibrosis</td>
</tr>
<tr>
<td><strong>ARFI</strong></td>
<td>Shear wave propagation with USN localization; cylinder 6 mm x 1 cm</td>
<td>+: Localize region of interest, reproducible; -: limited dynamic range, few studies, depth of penetration, USN scanner (Research)</td>
</tr>
<tr>
<td><strong>Shear wave elastography</strong></td>
<td>High frequency (Hz) wave with USN localization; cylinder 2-3 cm wide x 1 cm</td>
<td>+: 3 to 5 rapid measurements, localize region of interest; good accuracy and reproducibility; -: few studies; requires USN scanner (Research)</td>
</tr>
<tr>
<td><strong>Magnetic resonance elastography</strong></td>
<td>Low frequency (90 Hz) external beam and MRI scanner; multiple cylinders 2 -4 cm wide x 4 cm</td>
<td>+: Large tissue sampling, highly reproducible; other MR data obtained (steatosis, surface); -: Costly sophisticated equipment, scanner time, generalizability (Research)</td>
</tr>
<tr>
<td><strong>Serum markers</strong></td>
<td>Routine labs combined into algorithms; disease specific cut-offs for binary categories</td>
<td>+: Routine labs are simple, widely available, inexpensive. -: Indeterminate results; poor NPV; not liver specific, false +, limited dynamic range. FibroSURE not widely available</td>
</tr>
<tr>
<td><strong>Indirect markers</strong></td>
<td>Reflect hepatic fibrogenesis</td>
<td>+: Modest sens &amp; spec &amp; PPV; -: ? Increment vs routine labs, indeterminate results, false +, few longitudinal studies (Research)</td>
</tr>
<tr>
<td><strong>APRI</strong></td>
<td>Serum PIINP, HA, TIMP-1 and others in algorithm</td>
<td>-: Indeterminate results; poor NPV; not liver specific, false +, limited dynamic range. FibroSURE not widely available</td>
</tr>
<tr>
<td><strong>FIB-4</strong></td>
<td>Assess whole liver metabolism, substrate shunting or kupffer cell mass</td>
<td>+: Assess liver specific properties/ function/ portal HTN; semi-quantitative; -: Cumbersome and expense, limited sens &amp; spec for early fibrosis (Research)</td>
</tr>
<tr>
<td><strong>NAFLD index</strong></td>
<td>Genetic markers that associate with future risk of fibrosis</td>
<td>+: Discrete categorical result, easy to automate testing and results reporting. -: Limited studies, do not account for envtl co-factors, epigenetic influences</td>
</tr>
<tr>
<td><strong>Fibrogenesis markers</strong></td>
<td>Serum PIIINP, HA, TIMP-1 and others in algorithm</td>
<td>+: Discover new liver specific proteins involved in liver fibrosis; -: Largely discovery work at this time, compare to routine labs, develop quantitative assays (Research)</td>
</tr>
<tr>
<td><strong>Enhanced liver fibrosis (ELF)</strong></td>
<td>Genetic markers that associate with future risk of fibrosis</td>
<td>+: Discover new liver specific proteins involved in liver fibrosis; -: Largely discovery work at this time, compare to routine labs, develop quantitative assays (Research)</td>
</tr>
<tr>
<td><strong>Hepascore</strong></td>
<td>Methacetin breath test, Cholate shunt, Liver-Spleen scan</td>
<td>+: Assess liver specific properties/ function/ portal HTN; semi-quantitative; -: Cumbersome and expense, limited sens &amp; spec for early fibrosis (Research)</td>
</tr>
<tr>
<td><strong>Liver physiologic tests</strong></td>
<td>Genetic markers that associate with future risk of fibrosis</td>
<td>+: Discover new liver specific proteins involved in liver fibrosis; -: Largely discovery work at this time, compare to routine labs, develop quantitative assays (Research)</td>
</tr>
<tr>
<td><strong>Genomics</strong></td>
<td>Serum proteins detected via GC/Mass spec</td>
<td>+: Discover new liver specific proteins involved in liver fibrosis; -: Largely discovery work at this time, compare to routine labs, develop quantitative assays (Research)</td>
</tr>
<tr>
<td><strong>Proteomics</strong></td>
<td>Serum proteins detected via GC/Mass spec</td>
<td>+: Discover new liver specific proteins involved in liver fibrosis; -: Largely discovery work at this time, compare to routine labs, develop quantitative assays (Research)</td>
</tr>
</tbody>
</table>
staging fibrosis severity have not been established and vary among studies (Table 2).

**ARFI:** Other devices that measure liver elasticity using high frequency shear waves with ultrasound localization include the Acoustic radiation force impulse Imaging (ARFI, Siemens Acuson S200, Virtual Touch) and Aixplorer (Supersonic Imagine, Seattle, WA). With the ARFI device, short duration (260 usec) acoustic pulses (2.7 MHz) that assess a targeted cylinder of liver tissue using B-mode ultrasound that is 6 mm wide x 1 cm in length is performed after identifying the region of interest at 2 to 4 cm below the skin surface. Advantages of the ARFI approach include the adaptation of software to existing ultrasound imaging equipment. However, there is a limited range of potential velocities (0.4 to 4.4 meters/sec) and the optimal location, liver tissue depth, and data acquisition frequency have not been standardized. In addition, this approach is not as generalizable as transient elastography due to the need for an appointment in the radiology suite and may prove to be more costly. Lastly, the number of studies with this technology are limited but results to date appear to be comparable to those obtained with transient elastography (Table 4)(13, 14).

**Real time Shear Wave elastography:** The Aixplorer device (Seattle, WA) uses high frequency shear waves focused on a cylinder of liver tissue that can be adjusted on the instrument console by the operator using B-mode ultrasound (15). This device has very rapid data acquisition that allows the operator to assess fibrosis in a region of interest that can vary from 2.5 to 3.5 cm in diameter and 1 cm in height. Advantages of this approach include the ability to readily adjust the region of interest to a minimum of 1 cm below the liver capsule while avoiding vascular structures using the ultrasound probe. With this technique 3 to 5 consecutive measurements are obtained in the region of interest over a 5 minute period. A recent study of 121 Italian HCV patients demonstrated that use of the Aixplorer device had better discriminatory ability in patients with mild fibrosis compared to the Fibroscan and was able to correctly classify 83% of the patients compared to 67% with transient elastography. The reproducibility of SWE has also been studied in healthy volunteers and shown to be quite good with values of 4.92 to 5.39 kPa (16).

**Magnetic Resonance Elastography**

Magnetic resonance elastography (MRE) utilizes low frequency (65 hertz) longitudinal shear waves delivered by an external transducer with 3-D assessment of shear wave velocity in the whole liver using MRI software (dynamic (17). The volume of liver tissue analyzed can be a cylinder of 2 to 4 cm in length and 2 or more cm in width which is substantially larger than the area tested using ultrasound based methods. A study of MRE compared to TE and APRI demonstrated improved diagnostic performance and accuracy in 141 patients (18). Advantages of MRE include

<table>
<thead>
<tr>
<th>Study</th>
<th>Etiology (N)</th>
<th>% F&gt; 2 (%)</th>
<th>% F4 (%)</th>
<th>Cutoff (kPa)</th>
<th>AUROC</th>
<th>Sens (%)</th>
<th>Spec (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>+ LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Castera</td>
<td>HCV (183)</td>
<td>74</td>
<td>7.2</td>
<td>0.83</td>
<td>67</td>
<td>89</td>
<td>73</td>
<td>66</td>
<td>5.07</td>
<td></td>
</tr>
<tr>
<td>Ziol</td>
<td>HCV (251)</td>
<td>65</td>
<td>8.6</td>
<td>0.79</td>
<td>56</td>
<td>91</td>
<td>68</td>
<td>87</td>
<td>5.94</td>
<td></td>
</tr>
<tr>
<td>Degos</td>
<td>HCV (913)</td>
<td>62</td>
<td>14.6</td>
<td>0.87</td>
<td>86</td>
<td>96</td>
<td>94</td>
<td>96</td>
<td>6.72</td>
<td></td>
</tr>
<tr>
<td>Marcellin</td>
<td>HBV (173)</td>
<td>50</td>
<td>12.9</td>
<td>0.90</td>
<td>72</td>
<td>89</td>
<td>87</td>
<td>87</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>Chan</td>
<td>HBV (161)</td>
<td>25</td>
<td>12-13.4</td>
<td>0.93</td>
<td>98</td>
<td>75</td>
<td>85</td>
<td>85</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>Degos</td>
<td>HBV (284)</td>
<td>42</td>
<td>5.2</td>
<td>0.78</td>
<td>89</td>
<td>38</td>
<td>59</td>
<td>38</td>
<td>59</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from reference # 7
the ability to assess the entire liver and provide measurements in patients with obesity and ascites and perhaps its superior accuracy. Values of MRE in healthy volunteers have been established (2.20 ± 0.31 kPa) and a high degree of reproducibility has been demonstrated but eating a meal can increase values by over 20% (17). In addition, MRE requires longer acquisition time and is substantially more costly than ultrasound based elastography. Furthermore, the generalizability and ability to obtain accurate MRE data may be limited due to costs and the need for sophisticated software and radiologist interpretation.

Serum Based Tests
Serum markers of liver disease severity are attractive due to their low risk and ability to develop standardized and automated testing platforms. Currently available markers can be categorized as indirect markers of liver inflammation and function and direct markers of liver matrix biology and hepatic fibrogenesis (Table 5).

Indirect markers: A number of routinely obtained laboratory parameters correlate with the histological severity of numerous chronic liver diseases (6). A decreased platelet count, decreased haptoglobin level, elevated serum AST/ALT ratio, and increased INR are early indicators of advanced fibrosis but individual markers have limited accuracy in predicting fibrosis. As a result, several algorithms that combine 2 or more laboratory parameters with other patient data such as subject age and medical conditions have been proposed for patients with HCV and NAFLD. The APRI (AST to platelet ratio index) is a simple parameter that has demonstrated ability to confirm or exclude HCV patients with advanced fibrosis (cut off of 1.5 and 0.5, respectively) and cirrhosis (cut off of 2.0 and 1.0, respectively) (19,20). However, 30 to 50% of patients have intermediate values which can not be classified. In addition, the APRI is less useful in chronic HBV patients due to the frequent development of bursts of viral replication and associated inflammation. The FIB-4 index which consists of AST, ALT, platelets and age has also been shown to confirm or exclude the presence of advanced fibrosis in HCV patients but a large number of patients have indeterminate results (21). The NAFLD fibrosis score consists of age, BMI, hyperglycemia, platelet, albumin and AST/ALT ratio and has an AUROC of 0.85 for predicting advanced fibrosis (22). This score was associated with overall mortality in 4,000 NAFLD patients from NHANES and 300 patients from a single center study that were followed for a median of 14.5 and 12.0 years, respectively (23,24).

The FibroTest (Biopredictive, Paris, FR) or FibroSURE (Lab Corp, Raritan, NJ) which consists of a combination of GGT, total bilirubin, haptoglobin, apolipoprotein A1, and \( \beta \)-2-macroglobulin levels adjusted for age and gender has been extensively studied in HCV with a dynamic range of 0 to 1 (25, 26). The AUC of FibroTest ranges from 0.74 to 0.87 for significant fibrosis and from 0.71 to 0.87 for cirrhosis. A systematic review of 1679 HCV patients enrolled in 9 studies found that FibroTest had excellent diagnostic accuracy for cirrhosis but was less useful for lesser degrees of fibrosis (27). FibroTest was also a better predictor of HCV related complications (AUC 0.96 vs 0.91) and HCV related deaths (AUC 0.96 vs 0.87) compared to liver biopsy in 537 patients. Conditions which may lead to diagnostic errors with FibroTest include Gilbert’s syndrome, hemolysis, and extrahepatic cholestasis. A recent systematic review concluded that the APRI and FibroTest are moderately useful for identifying HCV patients with cirrhosis with a similar positive likelihood ratio (8 to 10) (28).

Direct markers: The most commonly investigated serum markers associated with hepatic fibrogenesis are hyaluronic acid, laminin, PIINP, type IV collagen, and YKL-40 (26). Each of these markers is associated with hepatic fibrosis severity in HCV but their diagnostic accuracy alone is insufficient and subjects must be fasting to obtain reliable data. Panels of serum fibrosis markers have also been developed including the Fibrometer (hyaluronan, prothrombin index, AST, \( \beta \)-2-macroglobulin, platelets, age, urea) and the HepaScore (Hyaluronan, ggt, bilirubin, a2-macroglobulin, age, and gender) but neither of

Table 5: Diagnostic performance of serum biomarkers in chronic HCV

<table>
<thead>
<tr>
<th>Index</th>
<th>&gt;F2</th>
<th>F4</th>
<th>Sens (%)</th>
<th>Spec (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>APRI</td>
<td>0.69-0.88</td>
<td>0.61-0.94</td>
<td>41-91</td>
<td>47-95</td>
<td>61-88</td>
<td>64-86</td>
</tr>
<tr>
<td>FIB-4</td>
<td>0.82-0.89</td>
<td>0.71-0.87</td>
<td>37-74</td>
<td>80-98</td>
<td>82</td>
<td>94.7</td>
</tr>
<tr>
<td>FibroTest</td>
<td>0.74-0.87</td>
<td>0.71-0.87</td>
<td>65-77</td>
<td>72-91</td>
<td>76-80</td>
<td>57-81</td>
</tr>
<tr>
<td>ELF score</td>
<td>0.80</td>
<td>90</td>
<td>50-87</td>
<td>70-93</td>
<td>58-93</td>
<td>44-90</td>
</tr>
</tbody>
</table>

Adapted from reference #26.
these have undergone prospective validation with clinical outcomes (29). A combination of serum YKL-40, TIMP-1, and HA levels have demonstrated significant association with the likelihood of disease progression in HCV patients with advanced fibrosis enrolled in the HALT-C trial but the strength of association was inadequate for clinical utility (30).

The ELF panel consisting of hyaluronan, TIMP-1, and PIIINP has also been studied in several patient cohorts in a cross-sectional manner with an AUC of 0.83 for significant fibrosis in HCV patients as well as NAFLD patients (31,32). The baseline ELF panel was superior to the MELD score in predicting clinical outcomes in 161 PBC patients followed over 7.3 years (31). The baseline ELF panel was also similar to liver biopsy in predicting outcomes in 457 chronic liver disease patients followed over time (34).

Other liver disease markers: Studies of individual or combined analytes believed to be involved in NAFLD pathogenesis have also been reported for diagnostic and staging purposes. For example, serum cytokeratin-18 fragments are believed to represent the degree of hepatocellular apoptosis that develops in patients with NASH compared to those with simple steatosis and serum CK-18 levels have an AUROC of 0.82 for correctly identifying NASH patients (22, 35).

Combination Approaches

Due to the limited accuracy of serum biomarkers and the inability to obtain reliable data in all patients with ultrasound based elastography, investigators have proposed synchronous or sequential combination testing for newly diagnosed chronic HCV patients (24). For example, algorithms combining FibroTEST or HEPASCORE and Fibroscan have been proposed in cross-sectional studies of chronic HCV patients with improved diagnostic performance compared to individual test results (Table 6). These studies demonstrate a reduced number of patients with indeterminate test results and greater overall accuracy compared to results obtained with an individual modality. However, further refinement and standardization of the proposed cut-offs are needed in replication cohorts and prospectively completed studies.

Future Approaches

Tests designed to measure global liver function either through assessment of hepatic enzyme activity with a probe substrate or assessment of hepatic functional mass have also been proposed. For example, the C13 Methacetin breath test involves the oral ingestion of a 75 mg dose of 13C labeled methacetin wherein the 13CO2 generated as a result of CYP1A2 mediated metabolism can be detected and quantified over 60 minutes (36). The cholate shunt test and perfused hepatic mass have also been tested in patients enrolled in the HALT-C study and demonstrated to predict the likelihood of clinical decompensation. However, all of these tests require further assessment in other cohorts and may prove to be too complex and expensive for routine clinical use (37).

Omics: The recent expansion of genomics technologies now allows for the rapid determination of multiple SNP’s from a DNA sample at a low cost using high-throughput genotyping platforms. Research to date has demonstrated some association between polymorphisms in genes involved in hepatic fibrogenesis but currently the associations are not strong enough for clinical utility (38). A recent study from Italy demonstrated that the level of expression of 186 genes in a liver tissue sample of 216 compensated HCV cirrhotic patients was also predictive of clinical outcomes during 10 years of follow-up (39). Although liver tissue profiling is invasive, such studies may provide serum biomarkers for further study. Similarly, use of proteomic and glycoproteomic discovery platforms in patients with chronic liver disease may also prove useful in identifying biomarker candidates (40). However, the analytes identified in these studies will need to assessed in multiple cross-sectional and prospective cohorts of well-characterized patients and prove to show incremental value to currently available serum markers.

### Table 6: Proposed combination algorithms to assess liver fibrosis in chronic HCV.

<table>
<thead>
<tr>
<th>Algorithm</th>
<th># Studies (patients)</th>
<th>Type</th>
<th>Tests included</th>
<th>AUC</th>
<th>% Liver bx avoided</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAFE biopsy</td>
<td>5 (3105)</td>
<td>Stepwise</td>
<td>APRI, FibroTest</td>
<td>&gt;F2</td>
<td>0.89-0.94</td>
</tr>
<tr>
<td>Bordeaux</td>
<td>3 (875)</td>
<td>Synchronous</td>
<td>FibroTest, Fibroscan</td>
<td>F4</td>
<td>0.88-0.91</td>
</tr>
<tr>
<td>Angers</td>
<td>1 (390)</td>
<td>Synchronous</td>
<td>FibroTest, Fibrometer</td>
<td>&gt;F2</td>
<td>0.89</td>
</tr>
</tbody>
</table>
References

6. Fontana RJ, Lok ASE. Non-invasive monitoring of patients with chronic hepatitis C Hepatology 2002; 36: S57-S64.


