FibroMeters: a family of blood tests for liver fibrosis

FibroMètres : une famille de tests sanguins de fibrose hépatique

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Summary

FibroMeters are blood tests for liver fibrosis with several specificities: two main diagnostic targets (fibrosis stage and area of fibrosis); adaptation to specific causes; and results confirmed by an expert system. Thus, FibroMeters comprise six different tests: one for staging and one for quantitation of liver fibrosis in each of the three main causes of chronic liver disease—chronic viral hepatitis, alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD). FibroMeters display a high overall diagnostic accuracy and are the only tests to correctly classify 100% of HCV patients without fibrosis or with cirrhosis. They have 90% predictive values in a higher proportion of patients than with other usual blood tests. A 90% correct classification is available in 100% of HCV patients with the following reliable diagnostic intervals: F0/1, F1/2, F2±1, F3±1. In real-life conditions, the reproducibility of FibroMeters is higher than that of liver biopsy or ultrasonographic elastometry. FibroMeters are robust tests with the most stable diagnostic performance across different centers. Optional tests are also available, such as a specific one for cirrhosis, which has a diagnostic accuracy of 93.0% (AUROC: 0.92) and a 100% positive predictive value for diagnosis of HCV cirrhosis. Determination by FibroMeters of the area of fibrosis—-the only direct, non-invasive, quantitative measurement of liver fibrosis—-are especially useful for following-up cirrhosis as it correlates well with clinical events. FibroMeters are also very accurate in HVB or HIV-HCV co-infected patients. The tests specific for ALD and NAFLD also have a high diagnostic accuracy (AUROCs: 0.96 and 0.94, respectively, for significant fibrosis).

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Résumé

Les FibroMètres sont des tests sanguins de fibrose hépatique avec plusieurs spécificités : deux cibles diagnostiques -stade et aire de fibrose-, adaptation à la cause, et résultats sécurisés par un système expert. Ainsi, il y a six principaux FibroMètres : un pour les stades et un pour la quantification de la fibrose dans chacune des trois principales causes d’hépatopathies : virus, alcool et stéatose. Le FibroMètre a une performance diagnostique globale très élevée et est le seul test à classer correctement 100% des patients infectés par le virus de l’hépatite C (VHC) sans fibrose ou avec cirrhose. Le FibroMètre a des valeurs prédictives à 90% chez une proportion élevée de patients. Une classification correcte à 90% est observée chez 100% des patients dans les intervalles diagnostiques suivants : F0/1, F1/2, F2±1, F3±1. Dans les conditions réelles, la reproductibilité du FibroMètre est plus élevée que celle de la biopsie hépatique ou de l’élastométrie impulsionnelle. Le FibroMètre est un test robuste avec la performance diagnostique la plus stable entre différents centres. Il y a plusieurs tests optionnels. Le FibroMètre spécifique de cirrhose a une performance diagnostique de 93% (AUROC: 0,92) et une valeur prédictive positive de 100% pour la cirrhose VHC. Le FibroMètre aire de fibrose, le seul test non invasif quantitatif de fibrose, est particulièrement utile au suivi des cirrhoses en raison de sa corrélation avec les événements cliniques. Le FibroMètre virus a une performance diagnostique élevée chez les patients co-infectés VHC-VIH ou atteints d’hépatite B. Le FibroMètre spécifique alcool ou stéatopathie métabolique a également une performance diagnostique élevée (AUROC: 0,96 et 0,94, respectivement, pour le diagnostic de fibrose significative). © 2008 Elsevier Masson SAS. Tous droits réservés.

Introduction

In 1997, our laboratory described a diagnostic test for liver fibrosis based on a mathematical algorithm that included several biomarkers [1]. In 2005, we constructed a series of second-generation tests called FibroMeters [2]. The good performance and applicability of these blood tests make them clinically relevant for everyday clinical practice.

FibroMeters have several specificities. First, they are constructed for specific causes of liver fibrosis—namely, chronic viral hepatitis B or C, alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD)—which contributes to their high level of performance. Indeed, our first blood test was not cause-specific [1] but, as the cause was an independent predictor of liver fibrosis, we subsequently developed cause-specific tests [2]. Also, these tests have two main diagnostic targets: fibrosis stage, based on histological staging systems such as METAVIR [3]; and the amount of fibrosis, based on morphometric determinations of the area of fibrosis [4]. Thus, they are the only direct, non-invasive, quantitative tests to measure liver fibrosis. This option of FibroMeters presents the amount of liver fibrosis as a percentage of fibrous tissue. Another specificity is that it validates the results through an expert system that detects and corrects erroneous results (false positives and false negatives).

In this overview, we describe the different characteristics that make FibroMeters a unique series of blood tests with high-quality performance and relevant results for the non-invasive diagnosis of liver fibrosis. FibroMeters offer significant adaptability and flexibility in the clinical setting.

Overall presentation

There are six different tests within FibroMeters (Table 1): one for staging and one for quantification in each of the three main causes of chronic liver diseases—chronic viral hepatitis, ALD and NAFLD. In addition, optional specific tests can be
used for certain circumstances, especially viral hepatitis. Thus, the diagnosis of cirrhosis is optimized because of its own specific FibroMeter test (see details below). Likewise, determining the fibrosis stage in co-infections with HIV is also optimized with a specific test. The expert system uses other algorithms (scores), and these complementary diagnostic steps are all found on a professional website and are easy to use for users. In addition, an ancillary test—the InflaMeter—is intended to grade necroinflammatory activity and is also available. The clinical characteristics and blood biomarkers included in the six main FibroMeters tests and in the InflaMeter are given in Table 1.

### Table 1
Clinical and blood markers included in the FibroMeter tests for determining the stage or area of fibrosis (F) as a function of cause, and in the InflaMeter test.

<table>
<thead>
<tr>
<th>Virus</th>
<th>Alcohol</th>
<th>NAFLD</th>
</tr>
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<tbody>
<tr>
<td>F stage</td>
<td>F area</td>
<td>Activity</td>
</tr>
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<tr>
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<tr>
<td>Gender</td>
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<td></td>
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<tr>
<td>Body weight</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Blood</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha-2 macroglobulin</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Hyaluronic acid</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Platelets</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Prothrombin index</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>AST</td>
<td>x</td>
<td></td>
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<tr>
<td>ALT</td>
<td>x</td>
<td></td>
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<tr>
<td>GGT</td>
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<td>x</td>
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<tr>
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<tr>
<td>Ferritin</td>
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<tr>
<td>Glycemia</td>
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</tbody>
</table>

*aThis FibroMeter virus test includes two other tests—one specific for co-infection, the other for cirrhosis; 
*the InflaMeter test grades the amount of necroinflammatory activity

AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl transferase

The FibroMeter test for fibrosis staging in HCV hepatitis has been evaluated in two independent studies [10, 11] and one meta-analysis, with individual data including the two previous studies, the pivotal study and other available cohorts [12]. We present here the results of the meta-analysis of 1056 patients [12]. In brief, FibroMeters AUROC, or correct classification rate (Fig. 1), for significant fibrosis was significantly higher than those of the other tests evaluated: Fibrotest, Hepascore [13], APRI and Fib-4 [14]. The AUROCs of these other tests did not significantly differ among themselves. In a sensitivity analysis excluding the pivotal study population, these significant differences were maintained.

### FibroMeters in HCV patients

#### Performance

**Overall performance**

**Pivotal study**

In the pivotal study, the FibroMeters tests were mainly evaluated in patients with chronic hepatitis due to hepatitis C virus (HCV) [2]. The overall diagnostic performance for significant fibrosis (METAVIR F2–F4), as reflected by the area under the receiver operating characteristic curve (AUROC, an index summarizing sensitivity and specificity), was significantly superior to the Fibrotest [5], Forns test [6] and APRI [7] in the test population. FibroMeters AUROC was also superior to those of Fibrospect [8] and the European liver fibrosis test [9].

**Validation studies**

The FibroMeter test for fibrosis staging in HCV hepatitis has been evaluated in two independent studies [10, 11] and one meta-analysis, with individual data including the two previous studies, the pivotal study and other available cohorts [12]. We present here the results of the meta-analysis of 1056 patients [12]. In brief, FibroMeters AUROC, or correct classification rate (Fig. 1), for significant fibrosis was significantly higher than those of the other tests evaluated: Fibrotest, Hepascore [13], APRI and Fib-4 [14]. The AUROCs of these other tests did not significantly differ among themselves. In a sensitivity analysis excluding the pivotal study population, these significant differences were maintained.
Although overall diagnostic performance is a necessary descriptor when comparing blood tests, it is not enough. Indeed, overall performance has two limitations: it depends on the prevalence of the diagnostic target—significant fibrosis—and, thus, is not reproducible in different epidemiological settings; and it includes different fibrosis stages with variable definitions. This means that two categories of fibrosis stages have to be distinguished: the median stages (F1–F3) and extreme stages (F0 and F4). Indeed, performance in the median stages is hampered by two drawbacks: it strongly depends on the diagnostic cutoff point that determines the diagnostic target and, more important, it is strongly biased by the reference standard—liver biopsy—as F1–F3 stages have low interobserver reproducibility in histological staging [15]. F0 and F4 are clinically important stages: F0 corresponds to the lack of fibrosis, which is reassuring to the patient; and F4 corresponds to confirmed cirrhosis, a diagnosis that implies stringent management with active screening for esophageal varices and hepatocellular carcinoma. To evaluate this, Halfon et al. have implemented a performance profile that describes diagnostic accuracy at each fibrosis stage [10]. In the meta-analysis described above, FibroMeters had a unique profile [12] as it was the only test to correctly classify 100% of patients in F0 or F4 stages in terms of significant fibrosis (Fig. 2). Thus, no patient of F0 stage at liver biopsy was classified as having significant fibrosis by FibroMeters, and all patients with F4 were diagnosed with significant fibrosis. In addition, this correct classification was significantly superior at each stage of significant fibrosis (F2, F3 and F4) compared with the other usual blood tests.

In fact, the diagnostic performance of FibroMeters was higher than those of the other tests in all values (Fig. 3). However, their main advantage is the use of narrower values at the extreme stages (F0 and F4) as seen in box plots (Fig. 4). This can be attributed to biomarkers such as hyaluronic acid and platelets, which have abnormal results mainly in stages of severe fibrosis in contrast to other markers. Finally, FibroMeters display the highest overall diagnostic accuracy and are the only tests to correctly classify all patients without fibrosis or with cirrhosis.

Applicability

Reliable diagnosis

The reliable diagnosis depicts the intervals of blood-test values where the diagnostic accuracy of these tests is considered sufficiently reliable for clinical practice. This means that, in these patients, liver biopsy can be avoided [12].
Traditional intervals

Previously, intervals of reliable diagnosis were defined by the thresholds provided by 90% negative (NPV) and positive (PPV) predictive values [5, 16]. Using the traditional definition based on 90% predictive values, a reliable diagnosis means that a patient has a ≥90% chance of being F0/1 in the lowest interval and a ≥90% chance of being ≥F2 in the highest interval of blood-test values (Fig. 3). The indeterminate interval is the zone outside of these reliable intervals. Fig. 5 shows the proportion of patients with 90% predictive values and, as FibroMeters included a significantly higher proportion of patients than the other usual blood tests, it was the most highly predictive test.

New intervals

Besides these traditional intervals of blood-test values based on 90% predictive values, it is possible to define new intervals based on ≥90% accuracy for each interval of blood-test values. By including new intervals (between diagnostic cutoff at 0.5 and 90% NPV or PPV; Fig. 3), it was possible to obtain four intervals of fibrosis stages diagnosed by FibroMeters — F0/1, F1/2, F2±1, F3±1 — with reliable diagnosis in 100% of the population, among whom 90% were correctly classified (Fig. 6). Thus, liver biopsy can be avoided in 100% of patients using this new classification. This also provides a simplified fibrosis ‘meter’ with four highly accurate stages. Nevertheless, it is possible to be even more precise (see below).

Meters

Blood tests are usually constructed according to a binary diagnostic process (logistic regression), which provides the probability (predictive value) of having significant fibrosis when the test is above a given cutoff point. However, it is of interest in clinical practice to know the probability of a particular METAVIR fibrosis stage for a given blood-test value. Figure 7 presents the frequency of fibrosis stages as a function of blood-test values in the previously described meta-analysis. For example, a patient with a result close to 0 has a 100% chance of having F0/F1 with FibroMeter F virus test, whereas a patient with a score close to 1 has an 85% chance of having cirrhosis. By expanding this classification, it is possible to derive a more precise meter of fibrosis stages based on the probable METAVIR fibrosis stage, at the cost of a small decrease in overall accuracy compared with binary diagnosis (Fig. 7). Thus, diagnostic accuracy changes from 82% for significant fibrosis to 77% for the meter, including six fibrosis stages [17].

Finally, there are three ways to express FibroMeters results for fibrosis staging (Table 2): by the original diagnosis of significant fibrosis; by the reliable diagnostic intervals (Fig. 6); and by the fibrosis meter (Fig. 7). The fibrosis meter is intended for use by physicians; consequently, this practical information can be found on a website, although the reliable diagnostic intervals are a more accurate descriptor.
Exportability

Reproducibility

We tested the interlaboratory reproducibility of FibroMeters in several studies, including a large series involving different laboratories in France [18]. Globally, reproducibility was excellent, with an intra-class correlation coefficient of 0.991 [18]. The ‘real-life’ simulation from quality controls of blood samples performed in 317 French laboratories, using 25 different dosage methods, indicated a maximum variation of 1.7% in FibroMeter results with a single biomarker [18].

The diagnostic cutoff point for blood-test values distinguishes patients according to the diagnostic target (significant fibrosis). It is usually fixed in the pivotal population at 0.5 to maximize diagnostic accuracy according to statistical rules. However, the best cutoff value may differ, especially in other populations. For this reason, the overall reproducibility of blood tests was evaluated through the variability of the best cut-off values in a large population as a function of centers [17]. FibroMeter tests had the lowest variability (Fig. 8).

We also compared the reproducibility of liver biopsy, Fibroscan and FibroMeter in real-life conditions in several studies carried out throughout France. It was possible to compare the reproducibility of these methods after expressing the results as METAVIR fibrosis stages [19]. The reference standard was a double reading of the liver biopsies by experts. The kappa indices were: liver biopsy: 0.336 (poor agreement); Fibroscan: 0.640 (good); and FibroMeter: 0.874 (excellent).

Robustness

The pivotal studies included several markers with independent significant predictive values, and robustness evaluates the ability of these markers to maintain this independent information in other settings, especially in conditions nearer to real-life conditions. In other words, robustness reflects the diagnostic stability of the blood tests under various conditions. Different indices of robustness have been calculated [19]. For example, the most practical index was the proportion of patients, in a large HCV cohort recruited from primary to tertiary centers, for whom the diagnosis of significant fibrosis consequently changed.
compared with the blood-test scores in the pivotal studies: the variability of FibroMeters was significantly less than with the other usual tests (Fig. 9).

In addition, some variables (sex and/or bilirubin) had no independent value for Fibrotest and Hepascore calculation in this large cohort [17]. In contrast, the performance and the number of independent variables of FibroMeters were stable. The inclusion of all 12 variables used in five blood tests in stepwise logistic regression showed that the 7 variables of FibroMeter kept their independent information in addition to gender. Finally, FibroMeters were the most robust test, having the most stable diagnostic performance across different centers.

Expert system

Briefly, as the first step, the expert system detects putative false positives or false negatives according to rules precisely described by experts. For example, an isolated marked variation (increase) in blood urea is attributed to renal dysfunction whereas an isolated marked decrease in prothrombin index is attributed to vitamin K deficiency. These undesirable abnormal results may also be noted by the patient’s physician. As the second step, the system corrects this putative erroneous result by comparing two FibroMeter results in which the value of the putative culprit variable is replaced by the normal mean and an alternative FibroMeters score where the variable is excluded. Finally, the system validates, or not, the corrected result. If a corrected result is proposed (18% of cases), a personalized caution is provided with the patient’s results. Several ancillary functions are included in the system. The main one is practical in that it provides a diagnosis of exclusion or affirmation of several diagnostic targets that corresponds to 100% NPV or PPV, respectively.

Table 2

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<tr>
<td>(yes/no)</td>
<td>Binary logistic regression</td>
<td>Significant fibrosis (yes/no)</td>
<td>New fibrosis stages (vs METAVIR)</td>
<td>Significant fibrosis + intermediate stages</td>
<td>Area of fibrosis</td>
</tr>
<tr>
<td>Class of fibrosis stage (number)</td>
<td></td>
<td>2</td>
<td>6</td>
<td>4</td>
<td>Multiple: 3.0-55.0%</td>
</tr>
<tr>
<td>Diagnostic accuracya</td>
<td></td>
<td>82%</td>
<td>77%</td>
<td>90%</td>
<td>aR²: 0.65</td>
</tr>
<tr>
<td>Result example</td>
<td></td>
<td>Significant fibrosis present</td>
<td>F2/3</td>
<td>F2±1</td>
<td>10.3%</td>
</tr>
</tbody>
</table>

aCorrect classification rate (%) or adjusted R²
Diagnosis of severe fibrosis and cirrhosis

Standard FibroMeter test

The standard FibroMeter test is targeted on significant fibrosis provided by the pivotal study. AUROC for severe fibrosis and cirrhosis were 0.885 and 0.907 for FibroMeter, 0.837 and 0.882 for Fibrotest, 0.834 and 0.896 for Hepascore, and 0.822 and 0.841 for APRI, respectively (P < 10⁻³, respectively, between blood tests). The proportions of patients in whom severe fibrosis and cirrhosis could be excluded (100% NPV) were significantly higher with FibroMeter than with the other blood tests (Fig. 10). Using the diagnostic thresholds proposed in meters of blood tests [17, 20], the PPV for the diagnosis of cirrhosis was 37.1% for Fibrotest and 68.5% for the standard FibroMeter test.
FibroMeter for cirrhosis

To improve the diagnostic performance for cirrhosis, we implemented a specific score including the same variables as in the previous standard FibroMeter. The correct classification rate (93.0%) of a cirrhosis diagnosis with this specific test for cirrhosis was significantly higher compared with the standard FibroMeter test (90.9%, P = 0.005); AUROC increased from 0.907 to 0.919, respectively. In addition, this specific FibroMeter test provided a 100% PPV for cirrhosis diagnosis that was better than the maximum 88% PPV obtained with the standard FibroMeter test [21].

Comparison to elastometry

We compared several blood tests, Doppler ultrasonography and ultrasonicographic elastometry (Fibroscan) in a large population [22]. Briefly, for a diagnosis of significant fibrosis, two methods were independently accurate and, thus, were synergistic with FibroMeters as step one and Fibroscan as the second step. For a diagnosis of cirrhosis, the same two tests were applicable, but with Fibroscan as step one. A synchronous algorithm was constructed with the two methods and had two main advantages: the diagnostic accuracy in significant fibrosis was significantly increased; and discrepant results were reduced compared with the two methods considered as separate diagnostic procedures.

InflaMeter

The diagnostic accuracy of the InflaMeter test for significant activity (METAVIR grades A2/3) was 74%.

Interpretation of results [23]

Limits of blood tests

The high-quality diagnostic performance of blood tests is attributed to the lack of observer bias and the use of quality controls as well as to efforts towards standardization. Despite the risk of variability due to multiple devices and reagents, blood tests are found to offer the highest reproducibility compared with other diagnostic methods.

Liver biopsy is the reference standard for blood tests and imposes its own constraints. Studies looking at the causes of discrepancy between blood tests and liver biopsy are difficult to perform, being observer-dependent. Several results suggest that the variability of blood tests is less than the original liver biopsy from which they are derived. For example, Fig. 11, based on our first study [1], shows that the progression of the area of fibrosis as a function of clinical events is more plausible with FibroMeter than with liver biopsy [24]. In addition, the variability of the FibroMeters area of fibrosis is less than that of the liver biopsy measurement from which it is derived (Fig. 12). In other words, the manufactured copy—the FibroMeter result—is less variable and more reproducible than the ‘hand-crafted’ original—the liver biopsy—in clinical practice.
We have seen that FibroMeters have several advantages in terms of diagnostic performance, reproducibility and robustness. This can be attributed to the design of the tests and to the multistep diagnostic process. Thus, the FibroMeters F virus test uses the widest spectrum of biomarkers for fibrogenesis and fibrolysis [25]. However, this inconveniently requires several laboratory automates (three as a rule), which increases the cost.

Interpretation of FibroMeters requires validation by a physician, as with any other diagnostic tool. Although the test result is analyzed by an expert system on a professional website, the true expert remains a qualified physician, and the interpretation of non-invasive tests requires expertise in this particular field.

FibroMeters have not been validated for miscellaneous causes of liver diseases, in children and in co-morbidities. However, in our hands, the FibroMeter virus test is the most useful option.

All of the diagnostic improvements provided by FibroMeter optional tests require the use of sophisticated software that is available on a website.

Other conditions

Other viruses

HBV

In the pivotal study, the FibroMeter AUROC was 0.868 in HBV patients vs 0.883 in HCV patients [2]. In an independent study of 255 HBV patients and 255 HCV patients, the FibroMeter AUROC was the highest of four blood tests and not significantly different from that observed in HCV patients [26].

Co-infections

FibroMeter test has been compared with other blood tests in a large series of 272 HCV-HIV co-infected patients [27], and its AUROC was the highest of 7 blood tests. We have also tested several blood tests in a large cohort of 452 HCV-HIV co-infected patients that included the previous cohort, and implemented a specific FibroMeter test for co-infection with an AUROC of 0.85 for significant fibrosis [28].

Other causes

Alcohol

The FibroMeter test for ALD had a good diagnostic performance in the pivotal study with an AUROC of 0.962 for significant fibrosis [2], which was confirmed in a meta-analysis [29]. However, this excellent performance is partially due to the high prevalence of severe fibrosis in ALD with liver biopsy.

NAFLD

The FibroMeter test specific for NAFLD includes glucose, AST, ferritin, platelets, ALT, body weight and age and, thus, includes three markers specific to the metabolic syndrome. It has been evaluated in 235 NAFLD patients [30]. The highest accuracy—91%—for significant fibrosis was obtained with the FibroMeter NAFLD, with an AUROC (0.943) that was significantly higher than those of the NAFLD fibrosis score (NFSA) [31] (0.884, \( P = 0.008 \) vs FibroMeter) and APRI (0.866, \( P < 10^{-3} \) vs FibroMeter; \( P = 0.309 \) vs NFSA). Using thresholds of 90% predictive values (accepted error: 10%), liver biopsy could have been avoided in most patients: FibroMeter, 97.4%, compared with NFSA, 86.8% \( (P < 10^{-3}) \) and APRI, 80.0% \( (P < 10^{-3}) \). The classification of patients, based on the new intervals of reliable diagnosis, provided three reliable diagnostic intervals—F0/1, F2±1 and F3±1—with 91.4% accuracy for FibroMeter NAFLD, avoiding biopsy in all patients.

Particular settings

The FibroMeters virus test has also been validated in hemophiliacs [32].

Quantitation of liver fibrosis

The relationship between the degree of liver fibrosis and the clinical course of chronic liver disease is not established. However, recent studies suggest a close link between the degree of fibrosis and clinical events such as portal hypertension [33]. In addition, as the amount of fibrosis may have
prognostic value, it is likely that quantitative fibrosis tests are clinically useful. In addition, non-invasive tests may substantially contribute to our knowledge of the natural course of chronic liver disease. Previous studies have shown that the amount of fibrosis is mainly developed during cirrhosis [33]. This means that quantification of liver fibrosis is of growing interest.

FibroMeters, as their name suggests, are able to precisely determine the degree of liver fibrosis. The FibroMeter scoring system for staging is intended to be a quantitative index, as there is a strong correlation between blood-test values and stage of fibrosis (Figs. 4 and 7). Also, a specific blood test for cirrhosis provides a more accurate reflection of the degree of fibrosis in patients with cirrhosis than a test designed to detect significant fibrosis (Fig. 13). More important, we have constructed the only direct quantitative measurement of fibrosis with the FibroMeter test for area of fibrosis (Fig. 14) [2]. The amount of fibrosis appears to be closely related to the progression of clinical events (Fig. 11) and degree of liver dysfunction.

**Conclusion**

The FibroMeters family comprises a series of blood tests with several specificities. The first is that they use a wide panel of biomarkers. The second is that they are flexible and can be adapted according to the cause of chronic liver disease. The third is that they include a direct measurement of the amount of fibrosis (via area of fibrosis), a feature unique to this test. The fourth is that the series includes optional tests specific to particular clinical settings such as cirrhosis or co-infection. Finally, an expert system confirms the diagnosis and provides useful information for the clinician such as the exclusion or affirmation of diagnostic targets such as cirrhosis. These improvements all require the use of sophisticated software that is available on a website. Finally, the FibroMeter test for fibrosis staging, especially in viral hepatitis, offers the highest diagnostic performance, reproducibility and robustness compared with other blood tests.

**Conflict of interest:**

**Funding:**

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**Author disclosure:**

Paul Calès, Frédéric Oberti, Isabelle Hubert and Françoise Lunel have stock ownership in BioLiveScale Inc., which has a license for FibroMeters from Angers University.
References


