FibroMAX™: towards a new universal biomarker of liver disease?

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Among the noninvasive alternatives to liver biopsy, several studies have demonstrated the predictive value and a better benefit-to-risk ratio than biopsy of five combinations of simple serum biochemical markers (the super combination being FibroMAX™ [BioPredictive, Paris, France) in patients at risk of chronic liver diseases: FibroTest™ (BioPredictive) for the quantitative assessment of fibrosis; SteatoTest™ (BioPredictive) for the quantitative assessment of steatosis; ActiTest™ (BioPredictive) for the quantitative assessment of necroinflammatory activity in chronic viral hepatitis C and B; NashTest™ (BioPredictive) for the categorical diagnosis of nonalcoholic steatohepatitis; and AshTest™ for the quantitative assessment of alcoholic steatohepatitis (also known in the USA as HCV-FibroSURE™, HBV-FibroSURE™, ASH-FibroSURE™ and NASH-FibroSURE™; LabCorp, NC, USA). The possible causes of false-negative and false-positive results are also better identified. These tests, which are now available in 50 countries, can facilitate the screening and management of the most frequent liver diseases.

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The consensus conference statements recommended liver biopsy in the management of almost all patients with chronic liver diseases related to hepatitis C, hepatitis B, alcoholic fatty liver diease (AFLD) and nonalcoholic fatty liver disease (NAFLD), but also underline the necessity of developing reliable noninvasive tests [1]. Due to the limitations [2–7] and risks of biopsy [8], as well as the improvement of the diagnostic accuracy of new noninvasive biomarkers, numerous studies strongly suggest that liver biopsy should no longer be considered mandatory as a first-line estimate of injury in these most frequent chronic liver diseases [9,10].

Practices are evolving rapidly and a nationwide survey in France recently found that among 546 hepatologists, 81% used a noninvasive biomarker (FibroTest™ [FT]–ActiTest™ [AT], BioPredictive, Paris, France) and 32% used elastography, with a dramatic decrease in the use of liver biopsy for more than 50% of patients with chronic hepatitis C, and with a subsequent increase in the number of patients treated [11]. A recent overview by French health authorities officially approved noninvasive biomarkers FT and elastography (FibroScan®) as first-line estimates of fibrosis in patients with chronic hepatitis C, recommended reimbursement by social security and approved liver biopsy only as a second-line estimate in cases of discordance or noninterpretability of noninvasive markers [12]. An updated overview is pending for other chronic liver diseases at the end of 2007 [12].

FT (HCV-FibroSURE™, LabCorp®, NC, USA) was initially used in chronic hepatitis C, and thereafter validated in chronic hepatitis B, hepatitis-delta, hepatitis/HIV co-infection, and alcoholic liver disease (ALD) and nonalcoholic liver disease with associated steatosis. Thus, FT is a universal marker of liver fibrosis, at least for the four most frequent chronic liver diseases. AT is the only marketed noninvasive biomarker of necroinflammatory activity. It is used only in chronic viral hepatitis (B and C) patients.

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Table 1. FibroTest diagnostic values according to the cause of liver disease and the independency of authors.

Characteristic	n	Observed area under the ROC curve	Standardized area under the ROC curve
All	29	0.80 0.78–0.82	0.84 0.83–0.86
Disease			
Hepatitis C virus	18	0.79 0.76–0.82	0.85 0.82–0.87
Hepatitis B virus	4	0.77 0.74–0.81	0.80 0.77–0.84
Alcoholic liver disease	2	0.88 0.81–0.84	0.86 0.80–0.92
Nonalcoholic fatty liver disease	2	0.81 0.70–0.91	0.84 0.76–0.92
Mixed	3	0.86 0.81–0.91	0.85 0.80–0.93
Study			
Independent	15	0.80 0.77–0.83	0.85 0.82–0.88
Mixed	5	0.76 0.73–0.80	0.83 0.81–0.86
Inventor	9	0.83 0.79–0.87	0.84 0.81–0.88

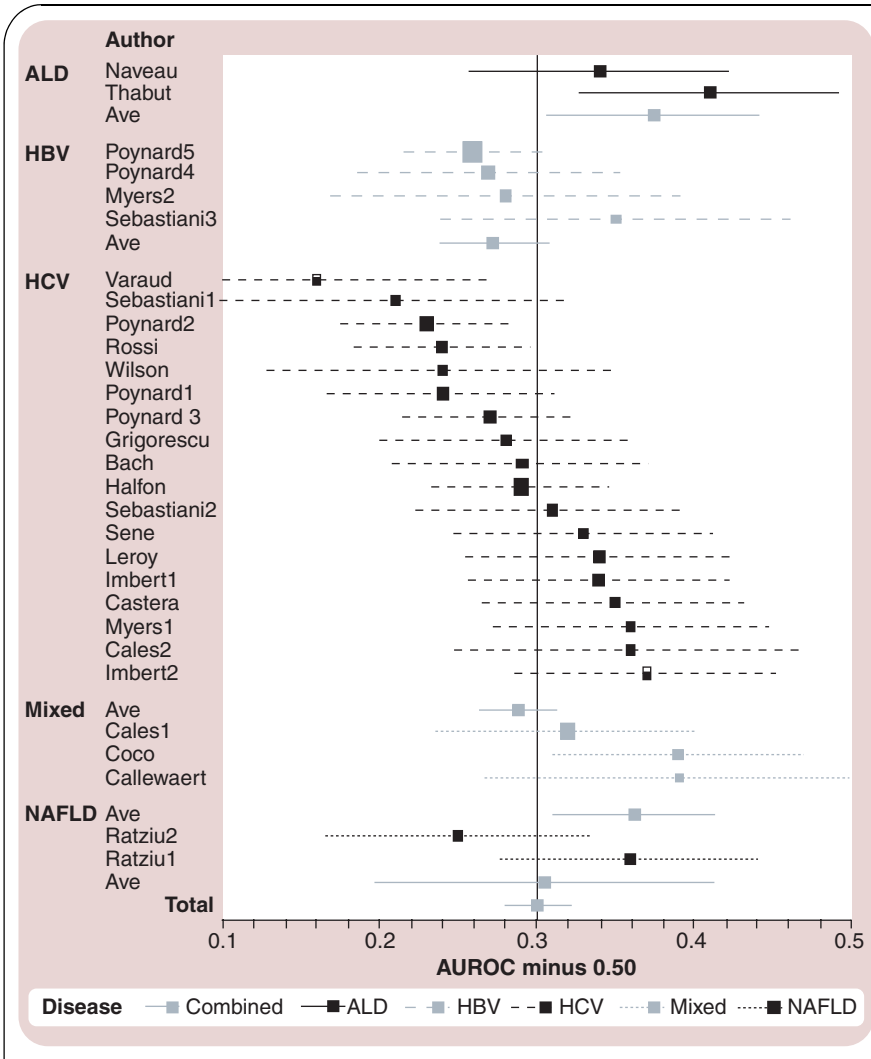

Figure 1. Diagnostic value (AUROC) of FibroTest™ in the most frequent liver disease.
ALD: Alcoholic liver disease; AUROC: Area under the ROC curve; HBV: Hepatitis B virus; HCV: Hepatitis C virus; NAFLD: Nonalcoholic fatty liver disease.

In order to improve this diagnostic tool, three new simple tests were developed to provide an estimate of the associated or worsening factors of fibrosis: liver steatosis (SteatoTest™), nonalcoholic steatohepatitis (NASH; NashTest™) and alcoholic steatohepatitis (AshTest™).

FibroMAX™ (BioPredictive) is a method of concomitant calculation of all these fibrosis-related tests in a single procedure. This provides physicians with simultaneous FT and SteatoTest results on the same sheet and, according to the risk factors, also provides the results of AT for chronic C (HCV-FibroSURE) and B hepatitis (HBV-FibroSURE™, LabCorp), NashTest (NASH-FibroSURE™, LabCorp) for nonalcoholic steatosis and AshTest for alcoholic steatosis (ASH-FibroSURE™, LabCorp).

Like FT, SteatoTest is designed for patients with the most frequent chronic liver diseases: viral hepatitis B and C, NAFLD (overweight, insulin resistance, hyperlipidemia or diabetes mellitus) and ALD. NashTest is intended only for patients with NAFLD, and enables the detection of probable NASH. AshTest is only for patients with excessive alcohol consumption and ALD and is used to detect the presence of severe alcoholic steatohepatitis. The early detection of hepatic fibrosis and its worsening associated factors is essential, because there are now effective treatments that can prevent the occurrence of cirrhosis and thus its complications (liver cancer, digestive hemorrhage and hepatic insufficiency).

For the diagnosis of fibrosis, FT has been extensively studied and validated both alone and combined with elastography or other indexes in various algorithms. Initially, most studies have been performed in hepatitis C (>5000 patients) [9,12], but also in hepatitis B (>2000 patients) [13–19], in patients with NAFLD (>1000 patients) [15,20–23] and 360 patients with ALD [15,24–27]. Between 2001 and 2006, FT has been assessed in 51 publications. A total of 29 studies have been conducted: 15 independent from the inventor group, nine by the inventor group and five mixed with independent and nonindependent authors (TABLE 1 & FIGURE 1). There was no significant difference in the FT accuracy according to the cause of liver disease or the independency of authors. We demonstrated that most of the variability of the observed area under the ROC curves (AUROCs: 0.65–0.89) is related to the variability of fibrosis stage prevalences defining advanced and nonadvanced fibrosis [29]. When standardized, the AUROCs were even more similar (TABLE 1 & FIGURE 1).

Very few patients (n = 19) with hepatitis D have been studied among HBV studies. In HIV co-infected cases, only two full papers have been published and one of these is independent. In ALD patients, only two of the studies are full papers, none are independent. In NAFLD patients, only two studies are full papers, while none are independent.

To date, other diagnostic tests have not been so extensively studied and validated, particularly in ALD and NAFLD [9,12,29]. A prospective study in HCV observed that 18% of discordances were attributable to biopsy failure (mostly due to short length) and 2% to FT-AT failure [30], and that the 5-year prognostic value of FT was at least equal to that of liver biopsy [31].

What are the unmet needs of currently available tests?

No available tests have been extensively validated for the diagnosis of fibrosis, steatosis and specific activity grades. Different combinations of liver tests have been suggested, mostly for fibrosis staging and in patients with hepatitis C. No available test has demonstrated a continuous and linear correlation with fibrosis stage and steatosis and activity grades in the most frequent chronic liver diseases [9,12,29,32].

Isolated biomarkers have smaller diagnostic value than panels of biomarkers [9,32]. Serum alanine aminotransferase (ALT) was the most commonly investigated marker, with low sensitivity of 61–71%. The diagnostic value was lower than the combination of markers in all direct comparisons. Among the extracellular matrix tests, hyaluronic acid correlated best with fibrosis stage overall, but has been demonstrated only for extensive fibrosis. The AUROCs for extensive fibrosis range from 0.65 to 0.86. Procollagen type III peptide and tissue inhibitor of metalloproteinase (TIMP)-1–4 were less predictive than hyaluronic acid [9,32].

Numerous other panels have been elaborated for fibrosis staging. Five panels have been covered in three publications, and not validated by health authorities.

The aspartate aminotransferase (AST)-to-platelet ratio index (APRI) has many publications, but the accuracy is lower than that of FT [9,12,32].

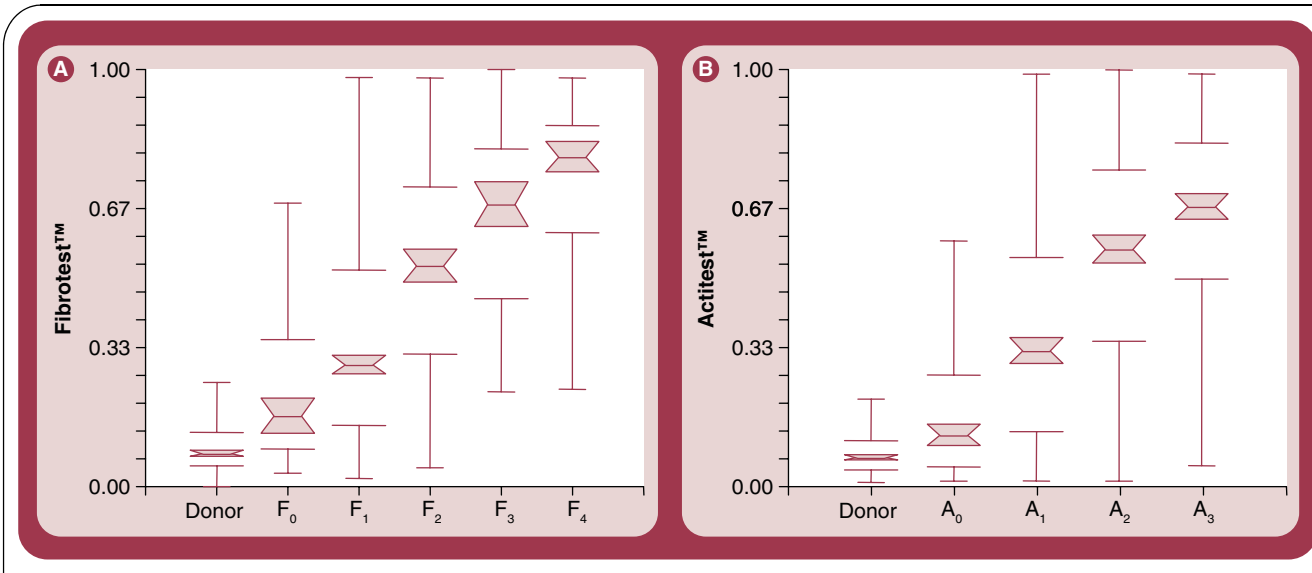

Figure 2. Notched box plots showing the relationship between FibroTest™ and the stage of fibrosis (A) and between ActiTest™ and the grade of activity. (A) FibroTest values according to status, from blood donors to patients with cirrhosis. (B) ActiTest values according to status, from blood donors to patients with severe necrosis. (B). The horizontal line inside each box represents the median and the width of each box the median ± 1.57 interquartile range/ $\sqrt{n}$ to assess the 95% level of significance between group medians. Failure of the shaded boxes to overlap signies statistical signicance ($p < 0.05$). The horizontal lines above and below each box encompass the interquartile range (from 25th to 75th percentile), and the vertical lines from the ends of the box encompass the adjacent values (upper: 75th percentile plus 1.5-times interquartile range; lower: 25th percentile minus 1.5-times interquartile range). Consensus conferences recommend treatment in patients with either F_2 stage or A_2 grade.
A_0: No activity; A_1: Minimal activity; A_2: Moderate; A_3: Severe; F_0: No fibrosis; F_1: Portal fibrosis; F2: Some septa; F_3: Many septa; F_4: Cirrhosis.
Data from [61–63].

Table 2. Conversion between FibroTest™ and fibrosis stages using METAVIR, Knodell and Ishak fibrosis scoring systems.

FibroTest™	METAVIR fibrosis stage estimate	Knodell fibrosis stage estimate	Ishak fibrosis stage estimate
0.75–1.00	F_4	F_4	F_6
0.73–0.74	$F_{3–4}$	$F_{3–4}$	F_5
0.59–0.72	F_3	F_3	F_4
0.49–0.58	F_2	$F_{1–3}$	F_3
0.32–0.48	$F_{1–2}$	$F_{1–3}$	$F_{2–3}$
0.28–0.31	F_1	F_1	F_2
0.22–0.27	$F_{0–1}$	$F_{0–1}$	F_1
0.00–0.21	F_0	F_0	F_0

One panel of biomarkers combining α_2-macroglobulin, hyaluronic acid and TIMP-1 is also on the US market (FIBRO-spect I and II™, Prometheus, USA) [33–35].

The other tests are FibroMeter [15,36,37], Hepascore [36,37,38], and Forns index [39–41]. Few separate studies have been published in different chronic liver diseases. These panels are designed only for fibrosis diagnosis without diagnostic value for necroinflammatory activity, steatosis and steatohepatitis. Contrary to FT [9,31], no study has been presented in community-based population, there are no prognostic studies and the risks of false negatives and positives has not been identified.

Which tests are currently under study?

A study using profiles of serum protein N-glycans found that a profile has a similar AUROC to FT for the diagnosis of compensated cirrhosis. When combined with FT, this marker had 100% specificity and 75% sensitivity for the diagnosis of compensated cirrhosis, which was not significantly different from the 92% specificity and 67% sensitivity of FT alone [42].

Proteomic studies are ongoing, but even if the diagnostic value can be significantly greater than reference panels, cost–utility studies are mandatory. Components of FT have been identified in several proteomic studies [43–46]. A combination of proteomic peaks has been identified with a 7% increase in the AUROC in comparison with FT [45].

How the test works

A physician prescribes the tests according to the possible liver disease, the agreed laboratories measures the components, enters the results into the BioPredictive network, the algorithms are computed, and the results are provided to the laboratory. FT-AT is a noninvasive blood test that combines the quantitative results of six serum biochemical markers (α_2-macroglobulin, haptoglobin, γ-glutamyl-transpeptidase [GGT], total bilirubin, ApoA1 and ALT) with the patient's age and gender in a patented artificial intelligence algorithm (USPTO 6631330) to generate a measure of fibrosis stage and necroinflammatory grade in the liver.

FT-AT is a continuous linear biochemical assessment of fibrosis stage and necroinflammatory activity grade. It provides a numerical quantitative estimate of liver fibrosis ranging from 0.00 to 1.00, corresponding to the well-established METAVIR scoring system of stages $F_{0–4}$ and of grades $A_{0–3}$ (FIGURE 2, TABLES 2–6).

Table 3. Conversion between ActiTest™ and activity grades using METAVIR, Knodell and Ishak necroinflammatory activity scoring systems.

ActiTest™	METAVIR activity grade estimate	Knodell necrosis estimate	Ishak necrosis estimate
0.62–1.00	A_3	A_5	A_4
0.61–0.61	$A_{2–3}$	A_4	A_3
0.53–0.60	A_2	A_3	A_2
0.37–0.52	$A_{1–2}$	$A_{1–3}$	$A_{1–2}$
0.30–0.36	A_1	A_1	A_1
0.18–0.29	$A_{0–1}$	$A_{0–1}$	$A_{0–1}$
0.00–0.17	A_0	A_0	A_0

SteatoTest, NashTest and AshTest each combine six to 12 biomarkers in several patented expert algorithms (USPTO 6,631,330, 0060172286 and 0060173629). The biomarkers include the six components of FT-AT (α_2-macroglobulin, haptoglobin, ApoA1, GGT, total bilirubin and ALT), AST, fasting glucose, total cholesterol, triglycerides and the weight, height, age and sex of the patient.

The analyses should preferably be made on fresh serum, but can be performed with plasma if necessary (blood sample on lithium heparinate). The measurements of the six parameters are made preferably on fresh serum (or plasma) or serum that has been stored between 2 and 8°C for a maximum of 4 days in an unlit area (for the protection of bilirubin). For deferred measurements, the serum should be quickly frozen to -80°C. After thawing, it should be centrifuged for 10 min at 15,000 g [47,48]. A standardization of the parameters is important because of the worldwide distribution of these tests. Laboratories must follow a quality chart in order to be allowed to use the Bio-Predictive algorithms [101]. Several works have validated these preanalytical and analytical recommendations in order to reduce inter- and intralaboratory variability [47–48], fasting conditions [49], transferability between analyzers [50–52] and enzymatic calibration [53].

It has been prospectively demonstrated that FT-AT can be performed on fasting or nonfasting serum samples [49]. SteatoTest, NashTest and AshTest must be performed on fasting serum samples. The results are given in a few days.

Cost–effectiveness

No real cost–effectiveness analysis of FibroMAX has been performed. However, because of the efficacy of FT-AT, the complications of liver biopsy and the difference in direct costs, the results of such cost-effectiveness analysie appears trivial. The cost of FibroMAX varies from €150 to 500 in different countries, versus €1000–2000 for an uncomplicated liver biopsy (TABLE 7).

Sensitivity & specificity

A summary of the FT-AT diagnostic values in chronic hepatitis C according to cut-offs is given in TABLE 8 [54]. In all chronic liver diseases, the liver biopsy is far from a true gold standard and a high percentage of false negatives and positives could be due to errors of biopsy. A prospective study observed that 18% of discordances were attributable to biopsy failure (mostly due to short length) and 2% to FT-AT failure [30,31]. Therefore, the classical expression of accuracy stating that discordances are always due to failure of the biomarkers is obsolete. Classical overviews are interesting [55], but are obsolete if they do not include the discordances data [30,31] as well as standardization according to the prevalence of stages defining advanced and nonadvanced fibrosis [28].

Between September 1, 2002, and May 31, 2004, a total of 32,527 tests have been carried out on the secured internet site [56]. The tests included 55% male and 16% older than 65 years. The most frequent abnormal value observed during postmarketing follow-up was haptoglobin under 0.12 g/l in 1589 patients 4.89%). Among these patients there were 272 cases with high-risk profile of false positives (0.84%) for which the other components were not concordant in favor of significant fibrosis. Patients with extremely low haptoglobin, especially when other exams were hardly modified, could have had hemolysis. A high-risk profile of false positives due to possible Gilbert syndrome was observed in 409 (1.26%) cases. The most frequent cause of abnormally elevated values of bilirubin was Gilbert disease, and acute sepsis for α_2-macroglobulin and haptoglobin. In the presence of acute inflammation (i.e., sepsis) or of acute hemolysis, FT-AT analysis must be postponed.

Table 4. Conversion between SteatoTest™ and steatosis grades in hepatocytes with steatosis.

SteatoTest™	Estimate of steatosis percentage
0.69–1.00	S3S4 >32%
0.57–0.68	S2 6–32%
0.38–0.56	S1 1–5%
0.00–0.37	S0 0%

Table 5. Conversion between NashTest™ and nonalcoholic steatohepatitis categories in patients with nonalcoholic fatty liver disease.

NashTest™	Estimate of nonalcoholic steatohepatitis
0.75	Nonalcoholic steatohepatitis
0.50	Borderline nonalcoholic steatohepatitis
0.25	No nonalcoholic steatohepatitis

Table 6. Conversion between AshTest™ and alcoholic hepatitis categories in patients with alcoholic liver disease.

AshTest™	Estimate of alcoholic steatohepatitis grades
0.78–1.00	A_3 (severe)
0.55–0.77	A_2 (marked)
0.17–0.54	A_1 (mild)
0.00–0.16	A_0 (none)

Clinical profile

FT-AT has been extensively studied in patients with chronic hepatitis C [9,12,54], in more than 2000 patients with hepatitis B [13–19] and less studied in NAFLD [15,20–23] and ALD [15,24–27]. In these four frequent chronic liver diseases (HCV, HBV, ALD and NAFLD), similar diagnostic value has been observed (TABLE 1 & FIGURE 2). Similar diagnostic values have also been observed in preliminary studies of patients with portal hypertension [57] and hemochromatosis [58]. Screening strategies using FibroMAX are ongoing. In patients

Table 7. Summary of advantages and limits of liver biopsy and biochemical markers.

Parameter	Liver biopsy	Biochemical markers
History	Classical standard	New tests or panel tests
Disease diagnosis	Fibrosis, activity, steatosis, steatohepatitis, iron, suspected or unexpected comorbidities, special staining for iron and copper	Fibrosis, activity, steatosis, steatohepatitis
Estimate	Semiquantitative	Quantitative and continuous
False negative	Regeneration nodule, small biopsy	Acute inflammation
False positive	Subcapsular biopsy, small biopsy	Hemolysis, Gilbert disease, acute hepatitis, extrahepatic cholestasis, acute inflammation
Adverse events	Three deaths out of 10,000, three severe adverse events out of 1000, 30 painful out of 100	None
Sampling error	33% discordance in fibrosis staging, 24% discordance in activity grading	None
Observer error	Fibrosis stage discordance (20%), activity grade discordance (40%)	Co-efficient variation <10%
Minimal requirements	≤25 mm size, >5 portal tract	Standardized assays, kits and analyzers
Hospitalization	6–24 h	None
Contraindications	Coagulation disorder, risk of respiratory insufficiency	None
Cost	€1032 for uncomplicated biopsy, €2745 for complicated biopsy	€90–300 for Fibrotest™–ActiTest™–FibroSURE™, €150–500 for FibroMAX™

with diabetes and no history of liver disease, a prospective screening using FibroMAX has identified five patients with cirrhosis, including four patients with hepatocellular carcinoma and two patients with portal hypertension [22]. No studies have been published to date in patients with cholestatic liver diseases and autoimmune hepatitis.

Table 8. Integrated database, with predictive values for significant fibrosis according to METAVIR conversion cut-offs in patients with chronic hepatitis C.

Stage prevalence	AUROC mean (SE)	Cut-off used for METAVIR stages conversion	Sensitivity	Specificity	Negative predictive value	Positive predictive value
FibroTest™ with blood donors (n = 1570)						
$F_2F_3F_4$ 0.31	0.83 (0.01)	0.21	0.92	0.55	0.94	0.48
	0.01 (0.01)	0.27	0.87	0.62	0.92	0.51
		0.31	0.84	0.68	0.91	0.54
		0.48	0.68	0.81	0.85	0.61
		0.58	0.56	0.87	0.82	0.67
		0.72	0.38	0.95	0.77	0.76
		0.74	0.35	0.95	0.76	0.76
		0.75	0.33	0.96	0.76	0.78
FibroTest™ without blood donors (1270)						
$F_2F_3F_4$ 0.38	0.78 (0.01)	0.21	0.92	0.41	0.89	0.49
	0.01 (0.01)	0.27	0.87	0.48	0.86	0.51
		0.31	0.84	0.55	0.85	0.54
		0.48	0.68	0.73	0.79	0.61
		0.58	0.56	0.83	0.75	0.67
		0.72	0.38	0.95	0.70	0.76
		0.74	0.35	0.93	0.70	0.76
		0.75	0.33	0.94	0.69	0.78

SE: Standard error.

Alternative tests

Two biomarkers are on the market for the diagnosis of fibrosis; hyaluronic acid (worldwide) and a panel combining α_2-macroglobulin, hyaluronic acid and TIMP-1 (USA only). For diagnosis of necroinflammatory activity, only transaminases were used.

Studies directly compared FT with hyaluronic acid, Forns index and APRI in the same patients [9,12,32,54]. FT had higher diagnostic values (the AUROC was significantly higher). In particular, FT was more sensitive for discriminating between F_1 and F_2, and more linearly correlated to stages when compared with those three other markers. An advantage of APRI is its availability and low cost. However, a weakness of APRI is the absence of standardized methods and assay calibration, and thus expression of aminotransferase or GGT in multiples of the upper limit of reference values should not be employed [18]. An additional weakness of the Forns index (combining age, platelets, GGT and cholesterol) is the inclusion of cholesterol, which varies greatly in patients with genotype 3 [9,12,32,54].

The FibroScan is another way to perform a histological assessment, using elastography. Elastography has been approved together with FT as a first-line estimate of liver fibrosis in patients with chronic hepatitis C [9,12]. In patients with HCV infection, the sensitivity of FT appears higher for early fibrosis stages, and the combination of FibroScan and FT improves the overall diagnostic value [59]. Preliminary data have been published in other chronic liver diseases and had similar accuracy in chronic hepatitis C [60]. The combination of different biological tests [9] or the complementary use of FT and elastography [59] could also add value for more accurate fibrosis evaluation. The sensitivity of FT appears to be an advantage in comparison with other biomarkers [9] and elastography [37]. Elastography is complementary because of its specificity for severe fibrosis in case of FT high-risk profile of false positives or negatives [59].

Conclusion

Several published studies and overviews have demonstrated the predictive value and better benefit-to-risk ratio than biopsy of these combinations of simple serum biochemical markers in patients with the four most frequent liver disease. They allow a quantitative assessment of both fibrosis and steatosis and, according to the cause of liver disease, an assessment of the necroinflammatory histological activity. The possible causes of false negatives and positives are also better identified. These tests, which are now available worldwide, can facilitate the screening and management of fibrotic liver disease, including hepatitis C, hepatitis B, AFLD and NAFLD.

Expert commentary

According to its poor benefit-to-risk ratio, liver biopsy should be abandoned as a first-line assessment of liver injury in chronic hepatitis C. For chronic hepatitis B, AFLD and NAFLD, similar results are increasingly observed, but few independent validations are still pending. Two noninvasive methods, FT and elastography, have been validated as noninvasive methods for the assessment of liver fibrosis, but markers of other liver injuries, steatosis and necroinflammatory activity, were lacking. The new available markers will better help the clinician. These tests must be interpreted in the overall clinical and biological context. They also have limitations, but one advantage for the FibroMAX combinations is that the profiles of patients at risk of false positives or negatives are well identified. The analytical recommendations are also important to limit the interlaboratory variability of these combinations.

Key issues

- 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.
- In some countries, noninvasive methods are already approved as first-line assessment of liver fibrosis and are reimbursed.
- Among the noninvasive alternatives to liver biopsy, several studies have demonstrated the predictive value and the better benefit-to-risk ratio than biopsy of combinations of simple serum biochemical markers in patients infected with hepatitis C virus and hepatitis B virus: FibroTest™ for the quantitative assessment of fibrosis; and ActiTest™ for the quantitative assessment of necroinflammatory activity.
- New studies have observed the predictive value of combinations of simple serum markers for the quantitative assessment of steatosis (SteatoTest™), alcoholic (AshTest™) and categorical diagnosis of nonalcoholic (NashTest™) steatohepatitis.
- A prospective study observed that 18% of discordances were attributable to biopsy failure (mostly due to small length) and 2% to FibroTest–ActiTest failure (hemolysis, Gilbert syndrome and acute inflammation). The 5-year prognostic value of FibroTest was better than that of liver biopsy.
- These tests, which are now available worldwide, can facilitate the screening and management of the four most frequent chronic liver diseases: chronic hepatitis C and B, and alcoholic and nonalcoholic fatty liver disease.

New studies suggest that these tests can facilitate the screening of the most frequent liver diseases. The development of biomarkers derived from proteomics or glycomics is likely to be important in the future.

Five-year view

Our speculative viewpoint in the next 5 years is that panels of simple biochemical markers, such as as FT-AT, SteatoTest, NashTest and AshTest, will replace the classical liver tests. Large-scale validation in chronic liver diseases other than hepatitis C are ongoing, including prospective screening in general populations. The combination of these markers with elastography and new security algorithms will probably decrease the risk of false positives and false negatives. Markers identified by proteomics or glycomics must be validated in large-scale clinical studies.

These biomarkers will replace liver biopsy in patients with chronic liver diseases, not only for routine assessment of liver injury but also as endpoints in clinical trials. Biopsy will be still useful but as a second line assessment, in very complicated cases.

Financial disclosure

Thierry Poynard is the inventor and has a capital interest in BioPredictive, the company marketing FibroTest, ActiTest, SteatoTest, NashTest and AshTest. Mona Munteanu is a BioPredictive employee.

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