

Section I - FibroTest compared to APRI, FIB-4 and  
transient elastographyHouot 2015  
FibroTest, TE, FIB-4, APRI  
Meta-analysisFibroTest is superior to TE by Fibroscan, APRI and  
Fib-4 using direct comparisons**Systematic Review with Meta-analysis: Direct Comparisons of Biomarkers for the Diagnosis of Fibrosis in Chronic Hepatitis C and B.***Houot M, Ngo Y, Munteanu M, Marque S, Poynard T. J Hepatol 2015; 62. Abstract. (Aliment Pharm Dig Tract (APT) In press)*

Direct comparisons permitted to improve standard methods of meta-analysis and the evidence based comparisons between the most used noninvasive tests Fibrotest, APRI and transient elastography (TE) by Fibroscan. 71 studies were eligible including 185 direct comparisons in chronic hepatitis C and B.

✓ 12,725 patients for the diagnosis of significant fibrosis (F2F3F4)

FibroTest has superior performances than TE by Fibroscan for identifying significant fibrosis.

✓ 10,929 patients for the diagnosis of significant fibrosis (F4)

FibroTest has not lower but similar performance to TE by Fibroscan for identifying cirrhosis.

✓ FibroTest is more applicable than TE by Fibroscan (99% versus 88%)

✓ FibroTest is more accurate than APRI and FIB-4 For both cirrhosis and fibrosis

Haseltine 2015  
FibroTest, APRI, FIB-4  
HBVHBV carriers follow-up: FibroTest more realistic than  
APRI and FIB-4 for SVR**Successful treatment with telaprevir-based regimens for chronic hepatitis C results in significant improvements to serum markers of liver fibrosis.***Haseltine ELI, Penney MS, George S, Kieffer TL. J Viral Hepat. 2015.*

This retrospective analysis was done on 1208 patients from Phase 2 and two Phase 3 telaprevir clinical studies (PROVE3, ADVANCE, REALIZE) with repeated biomarker: FibroTest, APRI, FIB-4 and Forns' Score before and after HCV treatment (at 24 weeks). Consistent with previous studies, patients who attained SVR exhibited significant improvements in scores from each of these tests after treatment.

✓ Overall FibroTest improvement in SVR was more moderate at 24 weeks (i.e. fibrosis regression of less than a Metavir stage) suggesting a more realistic approach as FibroTest not being related to necroinflammatory improvement as ALT is not included in its algorithm, contrary to APRI and Fib-4.

# FibroTest/FibroSure Scientific Publications

## Key Publications for 2015

Perazzo 2014  
APRI  
Methodology

### Fibrosis biomarker APRI is impacted by AST variability and definition

**Variability in definitions of transaminase upper limit of the normal impacts the APRI performance as a biomarker of fibrosis in patients with chronic hepatitis C: "APRI c'est fini ?".**

*Perazzo H et al.; FibroFrance & EPIC3 Groups. Clin Res Hepatol Gastroenterol. 2014;38:432-9.*

Despite its low cost and availability, authors highlighted two major limits of the APRI score related to AST transaminases:

1. The variability of the definition of the upper limit of normal for AST (ULN) and
2. The risk of overestimating fibrosis stage due to necro-inflammatory activity.

Moreover, AST-ULN variability seemed high highly associated with the variability of metabolic risk factors between the different control groups. The AST-ULN variability could cause misleading interpretations of APRI performance for the staging of fibrosis and comparisons of APRI with other non-invasive tests.

Xu 2014  
FibroTest  
HBV

### APRI has lower performances than FibroTest among HBV-infected patients also

**The effectiveness of noninvasive biomarkers to predict hepatitis B-related significant fibrosis and cirrhosis: a systematic review and meta-analysis of diagnostic test accuracy.**

*Xu XY, Kong H, Song RX, et al. PLoSOne. 2014;9:e100182.*

A systematic review was conducted on records in PubMed, EMBASE and the Cochrane Library electronic databases, in order to assess the accuracy of FibroTest, APRI and FIB-4 for predicting HBV-related fibrosis. The meta-analysis contained 30 studies; performances of Fibrotest were superior to APRI and FIB-4 for both clinically significant fibrosis and cirrhosis. Therefore, authors claimed that FibroTest have excellent diagnostic accuracy for identification of HBV-related significant fibrosis and cirrhosis and APRI and FIB-4 have only modest benefits.

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# FibroTest/FibroSure Scientific Publications

## Key Publications for 2015

### Section 2 - FibroMax is SAF ready

**SAF**  
**ready**

SAF score is the new simplified histologic classification for the main liver lesions (steatosis, activity and fibrosis) in NAFLD risk patients.

**FibroMax = FibroTest + ActiTest + SteatoTest + NashTest + AshTest**

FibroMax is a liver panel used in the diagnosis and the follow-up of liver fibrosis, steatosis and inflammations with a blood sample and is done at a local laboratory:

- FibroTest: estimates the liver fibrosis
- ActiTest: estimates the necroinflammatory activity
- SteatoTest: estimates the liver steatosis
- NashTest: estimates the non-alcoholic steatohepatitis
- AshTest: estimates the alcoholic steatohepatitis

Perazzo 2014  
FibroTest, SteatoTest  
NAFLD

### FibroMax (FibroTest and SteatoTest) validated as severity markers in NAFLD-risk patients

**Prognostic value of liver fibrosis and steatosis biomarkers in type-2 diabetes and dyslipidaemia.**

*Perazzo H, Munteanu M, Ngo Y et al., FLIP Consortium. Aliment Pharmacol Ther. 2014;40:1081-93.*  
N=2312 patients with type-2 diabetes and/or dyslipidaemia were included and followed up for 5–15 years.

✓ FibroTest and SteatoTest have robust prognostic values in patients with metabolic disorders. The presence of advanced fibrosis (FibroTest) or severe steatosis (SteatoTest) was associated with an increased risk of mortality.

✓ FibroTest and SteatoTest and allows a better evaluation not only of the hepatic risk, but also of the cardiovascular risk.

In type-2 diabetes patients, advanced fibrosis at baseline FibroTest or with progression to advanced fibrosis during follow-up predict cardiovascular events.

Pais 2015  
FibroTest, SteatoTest  
CHB

### Epidemiology of steatosis according to FibroMax in chronic hepatitis B (CHB)

**Prevalence of steatosis and insulin resistance in patients with chronic hepatitis B compared with chronic hepatitis C and non-alcoholic fatty liver disease.**

*Pais R, Rusu E, Zilisteanu D et al. Eur J Intern Med. 2015;26:30-6.*

The authors proposed to compare the prevalence and determinants of steatosis (FibroMax) and insulin resistance (IR) in CHB compared to CHC and pure NAFLD as evaluated by biomarkers of steatosis (SteatoTest), IR (HOMA-IR) and fibrosis (FibroTest). The lowest degree of IR, of steatosis >5% and of fibrosis F2 or more was in CHB. CHB patients with steatosis had higher BMI, waist circumference and HOMA-IR than those without steatosis as per SteatoTest. However, metabolic risk factors and HOMA-IR were not associated with significant fibrosis as in CHC.

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# FibroTest/FibroSure Scientific Publications

## Key Publications for 2015

Zelber-Sagi 2015  
FibroTest, SteatoTest  
Coffee

### FibroTest and SteatoTest for the evaluation of coffee consumption effects

**Coffee consumption and nonalcoholic fatty liver onset: a prospective study in the general population.**

Zelber-Sagi S, Salomone F, Webb M. et al. *Transl Res.* 2015 Mar;165(3):428-36.

This cross-sectional study evaluated the association between coffee consumption and fatty liver onset in the general population. Fatty liver was diagnosed with abdominal ultrasound (US) and SteatoTest (FibroMax), whereas FibroTest was used to assess fibrosis degree.

- ✓ High coffee consumption was associated with a lower proportion of clinically significant fibrosis F2 (FibroTest higher than 0.48)
- ✓ High coffee consumption is not able to counteract steatogenesis as per SteatoTest and liver US, whereas was associated with lower odds for significant fibrosis as per FibroTest {OR(95%CI) =0.49(0.25–0.97); P<.05}, the more important determinant of clinical outcomes in NAFLD.

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The screenshot shows the BioPredictive Library website interface. At the top, there are navigation tabs: 'by Test', 'by Comparison', 'by Disease', and 'by Liver Injuries'. A search bar is located in the top right corner. Below the navigation, the main heading is 'BioPredictive Publications'. A brief description states: 'FibroTest-ActiTest is the non-invasive liver test benchmark. Launched more than 10 years ago FibroTest success relies on the quality of its scientific background. Consecutively, SteatoTest, NashTest and AshTest were finalized with the same demanding quality. BioPredictive offers with this site the exhaustivity of its extensive scientific work - 244 studies have been published by 1009 authors in 76 journals - all publications are tagged for an easy browsing.' The BioPredictive logo is in the top right. The main content area displays two publication entries. The first entry is '#249' and is titled '2013 - Nature reviews. Gastroenterology & hepatology - Castéra, Laurent'. It describes a 'Noninvasive evaluation of NAFLD.' and lists the author 'Castéra L, Vilgrain V, Angulo P'. Below the title, there are several colored tags: 'Review', 'FibroTest', 'ActiTest', 'SteatoTest', 'NashTest', 'Independent Team', 'Ultrasound', 'Elastography', 'Metabolic Diseases', 'Fibrosis', and 'Genetics'. The second entry is '#247' and is titled '2013 - HIV medicine - Castéra, Laurent'. It describes a 'Comparison of transient elastography (FibroScan), FibroTest, APRI and two algorithms combining these non-invasive tests for liver fibrosis staging in HIV/HCV coinfecting patients: ANRS CO13 HEPAVIH and FIBROSTIC collaboration.' and lists the authors 'Castéra L, Winrock M, Pambrun E, Paradis V, Perez P, Loko MA, ...'. On the right side of the page, there is a sidebar with filters. It shows '214 publications' and 'Articles'. Under 'by Journal', there is a dropdown menu 'Select a journal'. Under 'by Authors', there is a dropdown menu 'Select an author'. Under 'by Kind', there are checkboxes for 'Article' (checked), 'Letter', 'Guidelines', and 'Health Authorities'. Under 'by Test', there are checkboxes for 'FibroTest', 'ActiTest', 'SteatoTest', 'NashTest', and 'AshTest'.

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# FibroTest/FibroSure Scientific Publications

## Key Publications for 2015

### Section 3 - FibroTest in unique populations

Schmid 2015  
FibroTest, APRI, FIB-4  
HIV/HCV coinf.

FibroTest better than APRI and FIB-4 in HIV/HCV co-infected Swiss cohort

**Progression of Liver Fibrosis in HIV/HCV Co-Infection: A Comparison between Non-Invasive Assessment Methods and Liver Biopsy.**

*Schmid P, Bregenzer A, Huber M, et al.; Swiss HIV Cohort Study. PLoS One. 2015;10:e0138838.*

A new study on 105 HIV/HCV co-infected patients from the Swiss cohorts with liver biopsy taken as gold-standard were evaluated the performance by AUROC (95% CI) of several liver fibrosis non-invasive tests:

- ✓ For significant fibrosis, FibroTest diagnostic performance was 0.75 (0.65–0.85)
- ✓ For cirrhosis, FibroTest diagnostic performance was 0.84 (0.75–0.92).
- ✓ FibroTest sensitivity and specificity for cirrhosis were high: 85.7% and 72.4%, respectively.
- ✓ FibroTest performances were higher than that of Hyaluronic acid both for advanced fibrosis.
- ✓ FibroTest has 90% negative predictive value (NPV), higher than Fibroscan (85%), APRI (80%), FIB-4 (80%) and Hyaluronic acid (76%).

Lynch 2014  
FibroTest  
Psoriasis

FibroTest monitors hepatotoxicity in patients receiving methotrexate for psoriasis

**The use of transient elastography and FibroTest for monitoring hepatotoxicity in patients receiving methotrexate for psoriasis.**

*Lynch M, Higgins E, McCormick PA, et al. JAMA Dermatol. 2014;150:856-62.*

The study proposed to evaluate the use of FibroTest (FibroSURE in the United States), PIIINP and transient elastography (TE) in a population receiving methotrexate therapy for psoriasis.

- ✓ FibroTest abnormal scores were correlated with the duration of methotrexate therapy ( $r=0.36$ ,  $P=0.002$ ).

Authors proposed to reduce the need for liver biopsy and to be required only if abnormalities in at least 2 serial noninvasive FibroTests or other noninvasive biomarkers exist.

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# FibroTest/FibroSure Scientific Publications

## Key Publications for 2015

### Sadler 2015 FibroTest Cystic fibrosis

#### FibroTest for cystic fibrosis

**Noninvasive methods, including transient elastography, for the detection of liver disease in adults with cystic fibrosis.**

*Sadler MD, Crotty P, Fatovich L, et al. Can J Gastroenterol Hepatol. 2015;29:139-44.*

N=127 Canadian patients with cystic fibrosis (CF) were evaluated non-invasively for CF-associated liver disease (CFLD) using FibroTest, transient elastography (TE) by Fibroscan and APRI.

CFLD was defined as two or more the following criteria: abnormal liver biochemistry, hepatomegaly or sonographic abnormalities other than steatosis.

- ✓ FibroTest, APRI and TE had similar performances for CFLD
- ✓ Individuals with CFLD had higher median FibroTest compared with those without CFLD

Authors concluded that FibroTest along with other biomarkers could be useful noninvasive methods for detecting CFLD in adults.

### Bonnard 2015 FibroTest Genotype 4 HCV Egypt

#### FibroTest revalidated in HCV genotype 4 Egyptian patients

**French National Research Association (ANRS) Funded Study. Comparison of liver biopsy and noninvasive techniques for liver fibrosis assessment in patients infected with HCV-genotype 4 in Egypt.**

*Bonnard P, Elsharkawy A, Zalata K, et al. J Viral Hepat. 2015 ;22:245-53.*

The study proposed to revalidate against biopsy in 312 HCV mono-infected genotype 4 Egyptian patients, several fibrosis biomarkers: FibroTest, APRI, FIB-4, and transient elastography (TE) by Fibroscan

- ✓ FibroTest diagnostic value by Obuchowski method was comparable to TE, with higher applicability.
- ✓ No influence of schistosomiasis on FibroTest was noticed.

Authors judged TE less applicable than FibroTest in this population with high BMI and focused on FIB-4 interest because of epidemic context of HCV. However, precautions must be taken with respect to FIB-4 combining not standardized (i.e. platelets) and transaminases, being more subject to variability with necro-inflammatory activity.

### Yakoob 2015 FibroTest HCV Middle East

#### FibroTest experience in Middle East patients

**Noninvasive biomarkers FibroTest and ActiTest versus liver biopsy in chronic hepatitis C patients: the Middle East experience.**

*Yakoob R, Bozom IA, Thandassery RB, et al. Ann Gastroenterol. 2015;28:265-270.*

The study evaluated once more FibroTest and ActiTest in predicting fibrosis and activity in N=107 chronic hepatitis C (CHC) patients with liver biopsy (LB) and compared to 106 blood donors (n=106) taken as controls.

- ✓ Fibrotest and ActiTest had high observed and standardized diagnostic values for predicting fibrosis and activity respectively.
- ✓ Specificity of FibroTest and ActiTest in the control population were 95% and 100% respectively.

### Section 4 - FibroTest brings liver prognosis

Poynard 2014  
FibroTest  
HBV  
Cirrhosis

HBV: FibroTest reclassify cirrhosis into 3 levels in chronic HBV carriers

**Staging chronic hepatitis B into seven categories, defining inactive carriers and assessing treatment impact using a fibrosis biomarker (FibroTest®) and elastography (FibroScan®).**

*Poynard T et al.; FibroFrance and Bordeaux HBV Study Groups. J Hepatol. 2014;61:994-1003.*

The 10-year updated individual data of 1434 HBV- carriers patients were pooled from two prospective cohorts.

✓ FibroTest-ActiTest identify inactive carriers

Low risk carriers were better identified by normal FibroTest-ActiTest than the ALT-based standard

✓ FibroTest is predictive of liver complications independently of treatment, viral load, HBeAg status and ALT

✓ Cirrhosis can be fine-tuned into 3 levels using FibroTest:

▶ F4.1 (Cut-off 0.74): Cirrhosis without complications

▶ F4.2 (Cut-off 0.85): Cirrhosis with oesophageal varices only

▶ F4.3 (Cut-off 0.95): Cirrhosis with severe complications: including primary liver cancer, bleeding or decompensation

✓ FibroTest increasing scores predict hepatocellular carcinoma

FibroTest scores increased in the majority of patients that developed hepatocellular carcinoma

✓ FibroTest still needed to monitor fibrosis progression and HCC occurrence in viral responders

Despite virological response, the overall incidence of cirrhosis increased.

Hepatocellular carcinoma incidence was 5.8% among virological responders.

# FibroTest/FibroSure Scientific Publications

## Key Publications for 2015

Park 2015  
FibroTest, TE  
HBV

### HBV: Risk assessment according to FibroTest and FibroTest-stiffness combi

**Prognostic value of the combined use of transient elastography and fibrotest in patients with chronic hepatitis B.**

*Park MS, Kim SU, Kim BK, et al. Liver Int. 2015;35:455-62.*

Authors investigated the prognostic role of the combined use of liver stiffness and FibroTest in predicting liver-related events in 127 consecutive patients with chronic hepatitis B (CHB) with a 5 years median follow-up.

- ✓ Combinations of FibroTest and livers stiffness was predictive of liver-related events better than histological fibrosis staging, but with a marginal additional benefit compared to FibroTest alone.
- ✓ Combinations of FibroTest and livers stiffness permitted to classify patients in 3 levels of prognosis according to complications: high, intermediate and low grades.

Rudler 2015  
AshTest  
Alcohol

### Alcohol: AshTest for a new definition of severe alcoholic hepatitis (ASH)

**Validation of AshTest as a Non-Invasive Alternative to Transjugular Liver Biopsy in Patients with Suspected Severe Acute Alcoholic Hepatitis.**

*Rudler M, Mouri S, Charlotte F, et al. PLoS One. 2015;10:e0134302.*

AshTest is an non-invasive alternative to transjugular liver biopsy in patients suspected for severe ASH.

N=123 cirrhotic patients with severe ASH were included.

- ✓ AshTest performance was significantly higher than the AST/ALT.
- ✓ AshTest performance was confirmed in the appropriate context of use: cirrhotic patients with severe ASH with corticosteroid treatment
- ✓ Finally, according to the limitation of biopsy, authors proposed to simplify the definition the ASH from the non-activity features of ALD (steatosis, fibrosis), as it had been achieved recently for NAFLD with the SAF score of Bedossa et al.
- ✓ FibroTest had 100% positive predictive value for cirrhosis in severe ASH patients

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