FibroTest/FibroMax Scientific Publications

Key Publications for 2018

AASLD 2018

Metabolic Liver Diseases (MLD)

Prognostic validation of FibroTest and quantitative NashTest 2 in patients with NAFLD

Long term prognostic value of the FibroTest in patients with non-alcoholic-fatty-liver disease, compared to chronic hepatitis C, B, and alcoholic liver disease.

Munteanu M, Pais R, Peta V, et al., for the FibroFrance Group. Aliment Pharmacol Ther 2018 (in press)

FibroTest (FibroSure in USA) validated for the diagnosis of the stages of fibrosis in NAFLD (Aliment Pharmacol Ther 2016) had demonstrated a significant prognostic value for the overall survival and to predict cardiovascular events in patients with type-2 diabetes (T2D) or dyslipidemias. (Aliment Pharmacol Ther 2014). Therefore, since 2016, FibroTest has been integrated in the diagnostic strategy to assess disease severity in the presence of suspected NAFLD and metabolic risk factors. (EASL-EASD-EASO guidelines J Hepatol 2016)

The present study proposed to validate FibroTest for the 10-years prediction of liver-related mortality in the prospective NAFLD FibroFrance-cohort from a tertiary center (Pitié-Salpêtrière Hospital, Paris)*. The comparator was it's performance in chronic hepatitis C (CHC), the most validated population.

A total of 7,082 pts were included: 1,079 NAFLD, 3,449 CHC, 2,051 CHB and 503 ALD with a median (range) follow-up of 6.0 years (0.1-19.3). FibroTest significantly predicted overall survivals all in chronic liver diseases with similar performance in NAFLD as in CHC.

FibroTest significantly predicted survival without liver-related death (LRD) in NAFLD patients

The prognostic value of FibroTest for the survival without LRD was validated for the first time in NAFLD patients and was even higher than in patients with CHC [AUROC (95%CI)]: 0.941 (0.905-0.978) and 0.875 (0.849-0.901; P=0.01), respectively.

FibroTest could stratify the risk of death in NAFLD cirrhosis

The present study demonstrated the FibroTest ability to stratify NAFLD cirrhosis in 3 classes with increased probabilities of death: F4.1 (non-complicated cirrhosis; scores >0.74-0.85), F4.2 (oesophageal varices risk; scores >0.85-0.95) and F4.3; severe complications risk, scores >0.95-1.00): 0.90 (0.80-0.99), 0.96 (0.88-1.00), and 0.67 (0.43-0.91) (Logrank=8.1; P=0.018).

Prognostic performance of quantitative markers, NashTest-2 (see article below) and SteatoTest-2 (Poster #1750)

The new validated surrogate quantitative markers of NASH, NashTest 2, and SteatoTest 2, (patents upcoming), had significant predictive values for liver-related deaths (AUROC 95%CI) 0.94 (0.88-1.00) and 0.73 (0.58-0.88).

In conclusion, this study conducted on a large sample size of patients with long-term follow-up, has demonstrated that FibroTest has a high predictive value for the liver-related mortality in patients with NAFLD. The severity of NashTest 2 score at baseline, was also predictive of mortality, independently of baseline fibrosis severity.

*ClinicalTrials.gov number, NCT01927133

MUNTEANU 2018

NashTest 2
FibroTest
NASH-FibroTest

Metabolic Steatohepatitis

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BIO Predictive

NASH-Test V2 : a new quantitative test for the diagnosis of nonalcoholic steatohepatitis (NASH)

Impact of steatosis and inflammation definitions on the performance of NASH tests.

Poynard T, Munteanu M, Charlotte F, et al. FLIP consortium, the FibroFrance-CPAM group; and the FibroFrance-Obese group. Eur J Gastroenterol Hepatol. 2018;30:384-91.

Authors aimed to construct a new noninvasive quantitative test for the diagnosis of steatohepatitis (NashTest 2) using a simplified histological definition* permitting to identify more cases of NASH than the standard histological NASH-CRN definition (Eur J Gastroenterol Hepatol. 2018).

For this purpose, a total of 1,081 metabolic liver disease (MLD) patients were included from the FibroFrance Project (USA- ClinicalTrials.gov number, NCT01927133) and the FLIP European Consortium (http://www.flip-fp7.eu/). The new NashTest 2 does not include BMI and fasting glucose to avoid variability in obese and type2 diabetic (T2D) patients. The NashTest 2 performances [AUROC (95%IC)] were high (0.77 and 0.81), in both training and control groups, respectively, with higher performances than NAFLD fibrosis score, BARD, FIB-4 and ActiTest. Significant MLD (A2 or F2 as per NashTest 2 combination with FibroTest) was strongly associated with type 2 diabetes, when applied to larger populations (US and French cohorts).

In conclusion, the new NashTest 2 enables a quantitative assessment of NASH in subjects with MLD risk. Important fact, this new diagnosis of NASH **(NashTest 2) does not require BMI and glucose any longer**.

** The new definition of MLD no longer requires the presence of steatosis and the presence of both lobular inflammation and ballooning and enables the diagnostic of NASH in patients with steatosis less than 5%, and a grade 2 lobular inflammation without ballooning. (Poynard et al. Eur J Gastroenterol Hepatol. 2018) (see next abstract)*

Simplified definition for metabolic liver diseases

Impact of steatosis and inflammation definitions on the performance of NASH tests.

Poynard T, Munteanu M, Charlotte F, et al. FLIP consortium, the FibroFrance-CPAM group; and the FibroFrance-Obese group. Eur J Gastroenterol Hepatol. 2018;30:384-91.

Authors proposed to improve the identification of NASH cases by using a SAF-simplified score, which does not require the presence of steatosis and of both activity features as the standard definition does [NASH-CRN (Kleiner Hepatology 2005)]. Patients were from the FibroFrance project (USA-NCT01927133) and from the FLIP consortium (http://www.flip-fp7.eu/).

The impact of definitions variability on the prevalence of NASH (evaluated by FibroMax tests) was studied for the following clinical situations: 1/ less 5% steatosis for NASH; 2/ no steatosis requirement for NASH; and 3/ severe NASH based on the SAF-activity grade at least A2. The present study confirmed that the variability in the estimated performance of NIT-NASHs is related to the diverse histological definitions of NASH.

In conclusion, a simplified definition of NASH based on activity only and not requiring >5% steatosis, has a lowest risk of false-positives and false-negatives.

POYNARD 2018

NashTest 2
NASH-FibroTest
Metabolic
Steatohepatitis

POYNARD 2018

Methodology
NashTest 2

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Improvement of quantitative NashTest 2 and SteatoTest and after bariatric surgery in morbidly obese

Circulating Endocannabinoids Are Reduced Following Baiartric Surgery and Associated with Improved Metabolic Homeostasis in Humans.

Azar S, Sherf-Dagan S, Nemirovski A, et al. Obes Surg. 2018. doi: 10.1007/s11695-018-3517-0.

The present study, based n=65 morbidly obese patients, aimed to investigate the changes in the circulating levels of endocannabinoid (eCBs) system, key factors in obesity, at 1 year following sleeve gastrectomy surgery, in relation with liver biomarkers estimating steatosis (SteatoTest), fibrosis (FibroTest) and steatohepatitis (NashTest-2 quantitative score).

One year after bariatric surgery, a significant improvement was observed in SteatoTest (0.55 vs 0.25, $p<0.001$) and in NashTest-2 quantitative scores (0.41 vs 0.32, $p<0.001$).

At one year after surgery, arachidonic acid (AA) serum changes were found to be positively associated with SteatoTest changes (0.452, $p<0.05$), stronger than the associations with other factors as serum ALT levels, fat-free mass and waist circumference. In the same way, the 2-arachidonoylglycerol (2-AG) delta change was positively correlated with SteatoTest score (0.266, $p<0.05$) and also with circulating triglyceride and total cholesterol levels.

These results suggest that eCB changes (AA and 2-AG) at 1 year after bariatric surgery are correlated with clinical and liver benefits and with a significant regression of both steatosis and inflammation as per SteatoTest and NashTest-2 quantitative scores, respectively.

FibroTest and SteatoTest identified NASH in Type 2 Diabetes without elevated liver enzymes

European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO) clinical practice recommendations for the management of non-alcoholic fatty liver disease: evaluation of their application in people with Type 2 diabetes.

Sberna AL, Bouillet B, Rouland A, et al. Diabet Med. 2018;35:368-75.

This study aimed to evaluate the application of the recently proposed European EASL-EASD-EASO NAFLD-guidelines (J Hepatol 2015) in n=179 type-2 diabetic (T2D) patients.

According to the guidelines, the following non-invasive tests (NIT) were used for steatosis and fibrosis evaluation: SteatoTest and FibroTest [FibroMax panel, (BioPredictive, France)], proton magnetic resonance spectroscopy (H-MRS), fatty liver index score (FLI) and nonalcoholic fatty liver disease fibrosis score (NFS).

68.7% of participants had steatosis (liver fat content >5.5%) according to H-MRS, and 78.7% according to SteatoTest (score >0.57) with 70% concordant results with H-MRS.

FibroTest identified clinically advanced fibrosis (FibroTest >0.57) in 2.2% T2D patients having normal liver enzymes (ALT, AST and GGT), so otherwise not detected.

AZAR 2018

NASH-FibroTest
NashTest 2
SteatoTest
FibroTest

Obesity

SBERNA 2018

SteatoTest
FibroTest

T2D
Obesity

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BIO Predictive

Non-invasive assessment of non-alcoholic fatty liver disease: Clinical prediction rules and blood-based biomarkers.

Vilar-Gomez E, Chalasani N. J Hepatol. 2018;68:305-15.

Based on the assumption that the diagnostic accuracy can be improved by combining biomarkers, the authors proposed an algorithm using non-invasive tests (NIT) that includes FibroTest, to assess patients with NAFLD risk.

The algorithm combines several prediction rules, free biomarkers (e.g. NAFLD fibrosis score, FIB-4 index and BARD score, Pro-C3 tests) and patented biomarkers (e.g. FibroTest, ELF). The algorithm discriminates between the "high risk" patients for fibrosis F3 or more (FibroTest >0.70) in whom to consider a liver biopsy and the "low risk" patients (FibroTest <0.30) to be monitored with repeated NIT every 2 years.

Authors acknowledged that patented markers of fibrosis such as FibroTest are more specific and have higher positive predictive values for detecting advanced fibrosis and adverse outcomes.

VILAR-GOMEZ 2018

FibroTest
NAFLD
NASH

Alcoholic Liver Diseases (ALD)

New validation of FibroTest in excessive drinkers from primary and secondary healthcenters

Transient and 2-dimensional shear-wave elastography provide comparable assessment of alcoholic liver fibrosis and cirrhosis.

Thiele M, Stæhr Madsen B, Fuglsang Hansen J, et al. Gastroenterology 2018 Jan 4. doi: 10.1053/j.gastro.2018.01.005

Authors proposed to compare prospectively the accuracy of the Enhanced Liver Fibrosis test (ELF), FibroTest, liver stiffness measurements by TE and 2D-SWE and 6 other biomarkers in detection of advanced liver fibrosis in patients with excessive dinking recruited in primary (n=128) and secondary (n=161) healthcenters.

Diagnostic accuracy of FibroTest was high (AUROC 0.90) for advanced fibrosis (AF) (Kleiner stage >=F3 using biopsy), comparable to ELF (0.92, p=NS). In intention-to-diagnose analyses, FibroTest has comparable performances to TE and 2D-SWE for AF (all p=NS).

For the primary care patients, FibroTest values below 0.58 had 94% negative predictive values for AF.

The main strengths of study are the analyses in intention-to-diagnose and the inclusion of patients with metabolic syndrome features and ongoing drinking, which reflect real-life situations.

In conclusion, in excessive drinkers from primary and secondary care, FibroTest can ruled out AF (scores below 0.58) with high diagnostic performances.

THIELE 2018

FibroTest
ELF
TE
2D-SWE

Alcohol

AshTest to rule-out alcoholic steatohepatitis (ASH) in a proof-of –concept metabolomics study

What's in Metabolomics for Alcoholic Liver Disease?

Suciu AM, Crisan DA, Procopet BD, Radu CI, Socaciu C, Tantau MV, Stefanescu HO, Grigorescu M. J Gastrointestin Liver Dis. 2018;27:51-58.

The aim of this proof-of-concept study was to identify and further characterize the potential metabolomic biomarkers for the diagnosis, staging and severity assessment of alcoholic liver disease (ALD). The study included 30 patients with alcoholic liver diseases and 10 controls and the prevalence of cirrhosis was 57% and 75% of cirrhotic had an AshTest score ≥ 0.18. The study revealed the usefulness of surrogate marker of alcoholic hepatitis, AshTest, in the context of a lack of biopsy-proven alcoholic liver disease.

SUCIU 2018

AshTest

Alcohol

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BIO Predictive

Drug Induced Liver Injury (DILI)

DILI-ActiTest a new prognostic biomarker of drug-induced-liver-injury (DILI).

Evidence-based Translation consortium. Serum apolipoprotein A1 and haptoglobin, in patients with suspected drug-induced liver injury (DILI) as biomarkers of recovery.

Peta V, Tse C, Perazzo H, et al; Drug Induced Liver Injury- Groupe Hospitalier Pitié-Salpêtrière; Drug Induced Liver Group of the Injury Safer and Faster PLoS One. 2017;12:e0189436.

The primary objective was to analyze in patients with DILI the prognostic performance of ActiTest and FibroTest proteins apoliprotein-A1 (APOA1), haptoglobin (HAPTO) and alpha-2-macroglobulin (A2M), as predictors of recovery* outcome. N=115 adjucated DILI cases from the European DILI Consortium had at least two samples during 12-weeks follow-up.

APOA1 and HAPTO, both acute phase reactants, have had the strongest negative correlation with DILI during the follow-up.

A new biomarker, DILI-ActiTest combining ApoA1, Hapto, A2M, GGT, age and gender, resulted in a significant prediction of recovery with 67% accuracy and an significant AUROC of 0.72 ($p<0.001$ vs hazard). Further validation of the panel DILI ActiTest should be performed in another group of DILI cases.

** Recovery outcome was defined as an ALT <2x and BILI <2x the upper limit of normal.*

PETA 2017

DILI-ActiTest
Haptoglobin
Apolipoproten A1

HBV-HIV coinfected

New validation of FibroTest in HIV-HBV

FibroTest and other biomarker assessment in HIV-HBV coinfected patients Diagnostic accuracy of the Coopscore to predict liver fibrosis in human immunodeficiency virus/ hepatitis B virus co-infection.

Taibi L, Boyd A, Bosselut N, et al. Ann Clin Biochem. 2018;55:236-243.

The authors proposed to compare the diagnostic performances of several biomarkers of liver fibrosis: FibroTest, Coopscore (CS) Hepascore (HS), Zeng score (ZS), Fibrometer (FM) and transient elastography (TE) in 97 HBV- HIV co-infected patients.

High standards of methodology were used as the Obuchowski's method was done in addition to standard AUROC and the study performed direct comparison between markers.

- The diagnostic performances for significant fibrosis (METAVIR stages F2-F4), were similar for FibroTest (0.778), CS (0.836) and FM (0.790) and superior to HS (0.727) and ZS (0.746).
- The diagnostic performances for severe fibrosis (F3) or cirrhosis (F4) all scores had similar performances.

In conclusion, this study confirms the diagnostic value of FibroTest in the classification of clinically significant fibrosis in coinfected HIV-HBV patients.

TAIBI 2018

FibroTest
Hepascore

HIV+HBV

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BIO Predictive

Improve of FibroTest and AFP in HCV-SVR

Potent viral suppression and improvements in alpha-fetoprotein and measures of fibrosis in Japanese patients receiving a daclatasvir/asunaprevir/beclabuvir fixed-dose combination for the treatment of HCV genotype-1 infection.

Akuta N, Toyota J, Karino Y, et al. J Gastroenterol. 2018 Mar 2. doi: 10.1007/s00535-018-1445-3.

The present study assessed the dynamics of hepatic fibrosis with FibroTest and alpha-fetoprotein (AFP) in pre- and post-treatment HCV-genotype 1 patients that achieved SVR in UNITY-3 trial with DAA therapy (daclatasvir/ asunaprevir/ beclabuvir).

A total of 217 patients were included, 46% were aged >65 years and 21% had compensated cirrhosis. Both FibroTest and AFP values improved significantly post-treatment with numerically greater score improvement in cirrhotic patients. FibroTest stage decreased in 44%, remained stable in 50%, and worsened in 6% of patients at SVR.

Improvements in both FibroTest and AFP scores suggest that HCV-SVR may reduce the risk of future liver disease progression and hepatocellular carcinoma, particularly in those with compensated cirrhosis.

AKUTA 2018

FibroTest, HCV, HCC

HCV Treatment Prioritization in trials using FibroTest

Sofosbuvir/Velpatasvir in Patients With Hepatitis C Virus Genotypes 1-6 and Compensated Cirrhosis or Advanced Fibrosis.

Asselah T, Bourgeois S, Pianko S, et al.. Liver Int. 2018;38:443-450.

ASSELAH 2018
SOFO-VELPA

100% sustained virological response and fibrosis improvement in real-life use of direct acting antivirals in genotype-1b recurrent hepatitis C following liver transplantation.

Iacob S, Cerban R, Pietrareanu C, et al. J Gastrointestin Liver Dis. 2018;27:139-144.

IACOB 2018
Liver Transplantation

Risk of hepatitis B virus reactivation in hepatitis B virus + hepatitis C virus-co-infected patients with compensated liver cirrhosis treated with ombitasvir, paritaprevir/r + dasabuvir + ribavirin.

Preda CM, Popescu CP, Baicus C et al. J Viral Hepat. 2018;25:834-841.

PREDA 2018

Real-world efficacy and safety of ombitasvir, paritaprevir/r+dasabuvir+ribavirin in genotype 1b patients with hepatitis C virus cirrhosis.

Preda CM, Popescu CP, Baicus C, et al. Liver Int. 2018;38:602-610.

PREDA 2018

Diagnostic value of combined serum biomarkers for the evaluation of liver fibrosis in chronic hepatitis C infection: A multicenter, noninterventional, observational study.

Köksal, Yılmaz G, Parlak M, et al., Study Group TCHC. Turk J Gastroenterol. 2018;29:464-72.

KÖKSAL 2018

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BIO Predictive

Fontan Syndrom

Noninvasive monitoring of the liver after Fontan completion, two clinical studies

Hepatic and renal end-organ damage in the Fontan circulation:A report from the Australian and New Zealand Fontan Registry.

Wilson TG, d'Udekem Y, Winlaw DS, et al.; Australian and New Zealand Fontan Registry. Int J Cardiol. 2018.pii: S0167-5273(18)30069-X.

Survivors of the Fontan procedure may have hepatic and renal dysfunction at an unknown incidence. A total of 152 participants (19.8±9.3 yrs) were selected from a Registry of 1528 patients underwent abdominal ultrasound (US), transient elastography (TE), FibroTest, along with other analyses.

Features suggestive of hepatic fibrosis were observed on ultrasound in 61%, 46% had a FibroTest score ≥0.49 (equivalent to ≥F2 fibrosis) and 88% TE median was ≥10 kPa. FibroTest score correlated with FibroScan value (r=0.24, p=0.015) and with albumin-creatinin ratio (r=0.29, p=0.002). More than a third of participants had renal impairment.

Based on these results, authors recommend in the second decade after Fontan completion hepatic and renal function monitoring.

FibroSURE and elastography poorly predict the severity of liver fibrosis in Fontan-associated liver disease.

Schachter JL, Patel M, Horton SR, Mike Devane A, Ewing A, Abrams GA. Congenit Heart Dis. 2018 Aug 12. doi: 10.1111/chd.12650

This second study was conducted on 14 patients (mean age 26.4 +7.5) with Fontan surgery, all being evaluated concomitantly with FibroSURE-FibroTest, shearwave elastography (SWE), hepatic duplex ultrasonography (US) and liver biopsy (LB). FibroTest agreed with LB in 36% while SWE in 0% of cases. None of the US indices predicted the presence or severity of liver fibrosis.

These results have shown some contradictions compared to the study of Wilson et al. Int J Cardiol 2018 but highlighted that, despite the limited concordance with LB, the FibroTest had the best accuracy compared to SWE and US.

WILSON 2018

FibroTest
TE

Fontan

SCHACHTER 2018

FibroTest
TE
Biopsy

Fontan

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