



# Screening for liver advanced fibrosis using non-invasive biomarker FibroTest in general population

T. Poynard (1); P. Lebray (1\*); P. Ingiliz (1\*); A. Varaud (1\*); B. Varsat (2); Y. Ngo (1\*); P. Norha (1\*); M. Munteanu (3); R. Morra (1\*); D. Messour (1\*); F. Imbert-Bismut (1\*); JP Carrau (2); J. Massard (1\*); V. Ratziu (1\*); J. Giordanella (2)  
 1. APHP-UPMC Liver Center (\*Hepatology and £ Biochemistry Departments Hôpital Pitié Salpêtrière Paris) 2. Caisse Primaire Assurance Maladie, Paris 3. Biopredictive, Paris 4. Hôpital Pitié Salpêtrière Paris, France

## ABSTRACT

Background: FibroTest (FT) and elastography by Fibrosan have been validated as biomarkers of advanced liver fibrosis (bridging fibrosis) in the most frequent chronic liver diseases: chronic hepatitis C, B, alcoholic and non-alcoholic steatosis, and recently in the fibrosis screening of patients with diabetes. (2)  
 Aim: To use biomarkers for estimating prevalence of advanced fibrosis in the general population, to identify independent risk factors of fibrosis and to propose screening strategies.

## PATIENTS and METHODS

**Cohort**  
 • n=7,554 prospective Informed random subjects aged 40 years or older  
 • Screened in 2 social security prevention centers in Paris

**Exclusion criteria:**  
 • previous history of liver disease  
 • High-risk profiles of false negative and positive biomarkers FibroTest

**Parameters:**  
 • 70 epidemiological, clinical, biological characteristics  
 • Biomarker (FibroTest) on fresh serum centralized  
 • HCV Antibodies in n=3,602  
 • CDT (carbohydrate deficient transferrin) in n=1,074  
 • elastography by Fibrosan in n=893

**Study strategy**  
 • Subjects with presumed advanced fibrosis according to FibroTest (score >0.48) were re-investigated by a hepatologist using:  
 - Fibrosan (FS),  
 - and if necessary to confirm fibrosis one of the following:  
 - **ultrasonography**  
 - **endoscopy**  
 - **liver biopsy**

• All re-investigated subjects had serum markers of chronic liver disease (HbSAg, HCV antibody, hemochromatosis gene mutation, antibody anti-actin, anti-LKM1, anti-DNA, anti-mitochondrial, anti-glutamine)  
 • In a subgroup of consecutive subjects (n=893) Fibrosan was also performed as screening test and re-investigated as well if stiffness >7.1 kPa to assess possible false negative of FibroTest.

**Main end point**  
 Advanced fibrosis (AF) according to FibroTest (cut-off 0.48)  
 The protocol was designed to fully investigate at least 100 patients with presumed AF.

**Biomarkers**

**Fibrosan®**

- Elastography
- Advanced fibrosis confirmed ≥7.1 kPa
- Interpretability criteria:
  - IQR median stiffness < 30%
  - Success Rate > 60%
  - at least 10 valid measures

**FibroTest™**

- patented algorithm
- = estimates fibrosis
- = scores from 0 to 1
- = Advanced fibrosis >0.48
- Combinés:
  - Total bilirubin,
  - GGT,
  - Haptoglobin,
  - Alpha2-macroglobulin,
  - Apolipoprotein A1
  - age, gender
- Non-interpretability criteria: hemolysis, Gilbert, acute inflammation

**FibroTest**

Score 0.14 (FS)

## BACKGROUND & AIMS

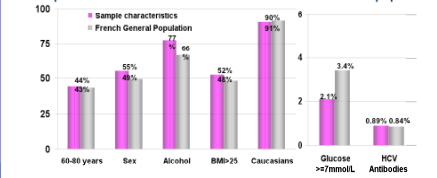
FibroTest (1) and elastography by Fibrosan have been validated as biomarkers of advanced liver fibrosis (bridging fibrosis) in the most frequent chronic liver diseases: chronic hepatitis C, B, alcoholic and non-alcoholic steatosis, and recently in the fibrosis screening of patients with diabetes. (2)

**Aim: To use biomarkers for estimating prevalence of advanced fibrosis in the general population, to identify independent risk factors of fibrosis and to propose screening strategies.**

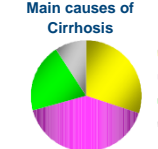
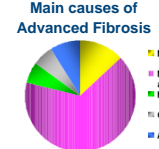
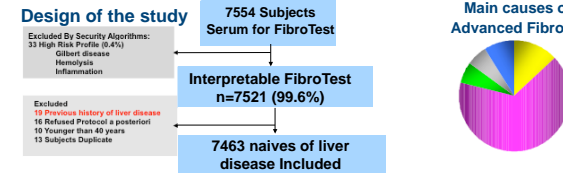
## RESULTS

Characteristics	Presumed fibrosis FibroTest >0.48		without presumed fibrosis (FibroTest <0.48)
	Reinvestigated	Refused re-investigation	
<b>Number of subjects</b>	105	164	7254
Age at serum, years	65.6 (8.9)	63.6 (8.1)	56.7 (8.6)
Male (%)	94 (90%)	95 (91%)	3924 (54%)
Tobacco use	59%	53%	45%
High Education level	17 (16%)	17 (16%)	2028 (28%)
Fatty liver risk factor (Alcohol or metabolic)	93%	83%	65%
Self-declared alcohol consumption at risk**	24 (23%)	28 (27%)	1634/7247 (23%)
Genotype Carbohydrate Deficient Transferrin (CDT1*)	-	-	309/1923 (20%)
IMB† = 2/3	53%	48%	33%
Metabolic factor of ATP-III classification (at least one)	79%	77%	53%
Glucose = 6.1 mmol/L or diabetes treatment	33%	41%	15%
Central obesity waist >102 male >88 female	29%	27%	16%
Triglycerides >= 1.7 mmol/L or fibrate treatment	41%	37%	24%
Hypertension or treatment	41%	41%	26%
HbA1c >= 6.5 mmol/L, male <1.29 mmol/L, female	23%	17%	7%
<b>Other risk factors</b>			
HCV antibody positive	5/105 (5%)	1/62 (2%)	26/3473 (0.8%)
HIV antibody positive	1/63 (2%)	0/8	1/444 (0.1%)
HbSAg antigen positive	2/105 (4%)	0/0	5/604 (0.8%)
Liver stiffness measure kPa	93	0	865

The sample main characteristics were similar to those of French population

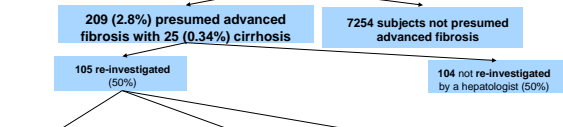


## RESULTS continued



**Independent Risk factors associated with confirmed advanced fibrosis**

Factors	Odds ratio (OR)	P value
Age >60 years	1.12	<0.0001
Male gender	4.1	<0.0001
One metabolic risk factor	2.5	0.02
CDT >1.6%	2.1	0.02
HCV antibody +	2.1	0.02



**N=52 Advanced fibrosis confirmed -stiffness >7.1 kPa**

- 18 NAFLD
- 4 ALD
- 22 mixed alcoholic and non-alcoholic fatty liver
- 4 Chronic hepatitis C
- 1 Hemochromatosis
- 1 Chronic hepatitis B
- 2 No risk factors (One Portal hypertension)

**N=50 Advanced fibrosis still highly suspected -stiffness over 5 kPa -and/or a risk factor**

- 23 NAFLD
- 5 ALD
- 17 mixed ALD and NAFLD
- 1 Chronic hepatitis C
- 1 Chronic hepatitis B
- 1 Autoimmune hepatitis
- 1 No risk factor

**3 undetermined -Stiffness <5kPa -No risk factor identified (2 possible false positive of FibroTest)**

**Liver disease suspected by the GP after screening results:**

- 57 NAFLD
- 6 ALD
- 22 mixed ALD and NAFLD
- 1 Chronic hepatitis C
- 18 No risk factor
- 1 Portal hypertension

**Mode of confirmation in 105 re-investigated subjects presumed advanced fibrosis**

Mode of confirmation	Confirmed	Highly or still suspected	Indeterminate	All
Elastography	47 (>=7.1 kPa)	25 (5kPa-7kPa)	3 (<5kPa)	75
Biopsy	3	1	1	5
Endoscopy	1	0	0	1
Platelet or hyaluronate	2	0	0	2

## References

- Poynard et al. Meta-analyses of FibroTest diagnostic value in chronic liver disease. BMC Gastroenterol. 2007;7:40.
  - Jacquemint et al. Screening for liver fibrosis by using a noninvasive biomarker in patients with diabetes. Clin Gastroenterol Hepatol. 2008;6:829-31.
- DISCLOSURE**  
 TP is the inventor and has a capital interest in Biopredictive the company marketing FibroTest. MM is employee of Biopredictive. Patients belong to the public organization Assistance Publique Hôpitaux de Paris

**Concordance between FibroTest and Fibrosan in N=893 subjects**

FibroTest was interpretable in 887 (99.3%) subjects. Fibrosan was interpretable in 775 (86.8%), 766 subjects had both FibroTest and Fibrosan interpretable

Diagnosis	Concordance	kappa	P value
Advanced fibrosis †	91.2%	0.09	0.009
Cirrhosis ††	99.1%	0.28	<0.0001

† Advanced fibrosis cut-offs: 0.48 for FibroTest and 7.1 kPa for Fibrosan  
 †† Cirrhosis cut-offs: 0.73 for FibroTest and 12.5 kPa for Fibrosan  
 Rate of false negative FibroTest was 0.4% (3 / 766 subjects with interpretable stiffness).

**Predictive values of oriented screening of fibrosis strategies**

Strategy	Confirmed fibrosis n=82 (0.7-1.4%)
<b>Metabolic factors oriented strategy predictive values</b>	
At least one metabolic factor versus None	42/3990 (1.1%) versus 10/3473 (0.3%)
Odds ratio	3.7 (1.8-7.8)
<b>Alcohol-oriented per self-reported consumption screening strategy predictive values</b>	
>10g female/20g male versus <=10g female/<=20g male	16/1686 (1.0%) versus 36/5770 (0.6%)
Odds Ratio	1.5 (0.8-2.9)
<b>CDT oriented strategy predictive value</b>	
CDT >1.6% versus CDT <=1.6%	24/348 (6.9%) versus 8/749 (1.1%)
Odds Ratio	6.7 (2.9-16.8)
<b>Hepatitis Virus-oriented strategy (the standard in the screening centers)</b>	
HbSAg or HCV antibody positive versus negative or not done at baseline	3/36 (8.3%) versus 49/7427 (0.7%)
Odds ratio	14.6 (3.2-48.7)
<b>Transaminase-oriented strategy</b>	
ALT >=50 IU/L versus ALT <50 IU/L	17/513 (3.3%) versus 35/6950 (0.5%)
Odds ratio	6.8 (3.6-12.6)

## CONCLUSIONS

- FibroTest may be used for the detection of fibrosis in general populations with elastography being used as a confirmatory test, strategy fully accepted by 50% of patients.
- In France, the combination of alcohol consumption and NAFLD was highly associated with advanced fibrosis.
- Among subjects 40 years of age or older, the prevalence of suspected advanced fibrosis was 2.8% and suspected cirrhosis 0.34%.

