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## Case finding strategies in non-alcoholic fatty liver disease

Jerome Boursier<sup>1,2</sup>, Emmanuel A. Tsochatzis<sup>3,4</sup>

(1) Service d'Hépatogastroentérologie et Oncologie Digestive, Centre Hospitalier Universitaire d'Angers, Angers, France

(2) Laboratoire HIFIH, UPRES EA3859, SFR 4208, Université d'Angers, Angers, France

(3) Sheila Sherlock Liver Centre, Royal Free Hospital, London, UK

(4) UCL Institute for Liver and Digestive Health, Royal Free Campus, UCL, London, UK

### Corresponding authors:

Jérôme Boursier; Service d'Hépatogastroentérologie, Centre Hospitalier Universitaire, 4 rue Larrey, 49933 Angers cedex 09, France; Tel: (+33) 2 41 35 34 10; Fax: (+33) 2 41 35 41 19; E-mail: JeBoursier@chu-angers.fr or

Emmanuel A. Tsochatzis, UCL Institute for Liver and Digestive Health, Royal Free Hospital, Pond Street, NW3 2QG, London, UK. Email : e.tsochatzis@ucl.ac.uk

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### Key points

- The primary liver lesion to target for the case-finding of at-risk patients with NAFLD is advanced fibrosis
- Diabetics and patients cumulating metabolic factors represent populations with increased prevalence of advanced fibrosis, and should therefore be considered for case-finding strategies
- Non-invasive tests of liver fibrosis, blood tests or elastography devices, can confidently exclude advanced liver fibrosis in low-prevalence populations
- Due to a very low rate of negative result, the NAFLD fibrosis score should not be used for the case-finding of advanced liver fibrosis in diabetics
- Using FIB4 as first-line test followed, if positive, by a specialized blood test or liver stiffness measurement seems the best strategy for the case-finding of advanced liver fibrosis
- Strategies using non-invasive tests of liver fibrosis for the case finding of advanced liver disease in at-risk populations are cost-effective
- Awareness of NAFLD remains insufficient among primary care and non-liver specialists, strong effort must be made to improve the knowledge of the disease and the willingness to detect at-risk patients

## **Summary**

The identification of patients with advanced liver disease among the large NAFLD population remains an unmet challenge, with many patients being diagnosed late at the stage of liver-related complication with poor short-term survival. Accumulating evidence suggests that the use of non-invasive tests targeting liver fibrosis in patients with metabolic risk factors improves the detection of patients in need for specialized management, and is cost-effective. Due to the very high number of patients to evaluate, an active participation of general practitioners and physicians involved in the management of patients with metabolic disorders such as diabetologists is highly required, which requires an increase of awareness of the disease outside liver clinics. The strategies using non-invasive tests for the case finding of at-risk patients must be further validated and generalized, in order to achieve a significant impact of the upcoming drug therapies on the worldwide burden of NAFLD.

## 1. Introduction

Non-alcoholic Fatty Liver Disease (NAFLD) has become the main cause of chronic liver disease with a significant worldwide burden [1]. In some countries, NAFLD is now the first cause of cirrhosis [2], the main cause of chronic liver disease underlying hepatocellular carcinoma [3], and the second cause of liver transplantation with a trajectory foreshadowing it will become the first within 10-20 years [4, 5]. NAFLD encompasses a wide spectrum of liver lesions, ranging from simple steatosis, to non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis and ultimately end-stage liver disease and hepatocellular carcinoma. While NASH is more an indicator of a condition that promotes fibrosis prediction, longitudinal studies have demonstrated that the liver-related prognosis of NAFLD patients is mostly related to the level of liver fibrosis [6, 7], as observed for the other causes of chronic liver disease.

Currently, there is no treatment approved for NAFLD. Major efforts are being made in the research and development of new drugs able to halt the progression of this liver disease, with the aim to prevent cirrhosis and liver-related complication occurrence [8]. In this context, a first positive phase III trial in 2019 gives hopes that new treatments could be available in the near future in clinical practice [9]. In line with the strong impact of liver fibrosis on the prognosis of NAFLD, the current consensus is that pharmacotherapy should be reserved for NASH patients having at least significant fibrosis (stage F2 and higher) [10, 11]. However, since they represent only a small rate of the whole NAFLD population, the case finding of these patients in clinical practice comes back to look for a needle in a haystack. To this must be added that targeted patients have no symptoms, their biology shows non-specific abnormalities, and that awareness of NAFLD among non-specialists is very low. Finally, all of these make the identification of NAFLD patients at-risk of progressive liver disease as a tough challenge in “real life”.

Many tools are now available for the non-invasive evaluation of liver lesions in NAFLD, especially blood tests and elastography devices. With the upcoming arrival of treatments for NAFLD, there is now an urgent need for the development and validation of strategies using these tests for the case finding of patients who will benefit from a specialized management. Indeed, the accurate identification of patients in need of treatment is a mandatory prerequisite if we want the new drugs to decrease the burden of NAFLD. To reach this ambitious aim, several issues still need to be addressed: in which populations case finding

should be concentrated? Which liver lesions are the most relevant to target? What would be the ideal strategy? Are non-specialists aware about NAFLD and would they participate to the case finding of at-risk patients? What are the cost-effective strategies?

## **2. Which liver lesions to target**

When designing case finding strategies and pathways, an important consideration is the target condition to be diagnosed. Factors to consider when making such decisions are the pertinence of the diagnosis to the patients' prognosis and the availability of diagnostic methods to identify the target condition.

Steatosis is prevalent in 25% of the general population and is straightforward to diagnose with the use of an ultrasound. However, unselected patients with NAFLD do not have increased liver-related mortality. Moreover, it is not established whether the presence of NAFLD per se is greater than the sum of its parts (i.e. metabolic comorbidities) in terms of cardiovascular risk [12]. Screening of the general population for the presence of NAFLD is therefore not recommended by learned societies [10, 11, 13]. On the other hand, screening for NAFLD in high risk groups remains a contentious issue, with conflicting guidance from EASL [10] and AASLD [11]. Concerns for a potential screening program for NAFLD include the large number of tests it would involve, lack of effective disease-specific therapies other than lifestyle measures and insufficient data on the cost-effectiveness of the approach.

NASH is considered the progressive form of NAFLD, however it is notoriously difficult to diagnose with non-invasive tests (NITs) and still requires a liver biopsy. CK-18, which was initially considered promising, has limited sensitivity and cannot be used for screening purposes [14]. Moreover, the presence of NASH without significant fibrosis is not associated with increased liver-related mortality [15-17], probably because such patients have the competing mortality risks of cardiovascular disease and non-liver related cancers. Recently, NITs that combine the diagnosis of NASH with a NAS score of  $\geq 4$  and fibrosis stage of  $\geq 2$  were developed; these tests are based on the combination of transient elastography (TE) and simple laboratory values [18] and proprietary algorithms [19, 20] respectively. An immediate application of these tests is for pre-screening patients for clinical trials. However, their use as triaging tests for case-finding pathways is questionable, as they would

potentially miss patients with significant/advanced fibrosis without steatohepatitis, who would still be at increased risk of liver-related events [21].

Advanced fibrosis in NAFLD is unequivocally associated with increased risk of liver related mortality [15-17] and can be reliably diagnosed with a variety of non-invasive tests (NITs) as presented below. Therefore, the primary lesion to target in case finding strategies is advanced fibrosis.

### **3. In which populations case finding should be focused**

Important information can be obtained from population-based studies evaluating the screening of liver fibrosis using transient elastography (TE) [22-25]. These works included large samples of patients in the general population and had similar design, providing the opportunity to delineate the characteristics of the subgroups with increased prevalence of liver fibrosis where the case finding of advanced liver disease ( $\geq$ F3 fibrosis stage) might be the most relevant. Using the 8.0 kPa threshold, the prevalence of patients at-risk for significant liver fibrosis ( $\geq$ F2 fibrosis stage) in the adult general population was similar across studies, around 6-7% (**Table 1**). Multivariate analyses aiming at the identification of the patient characteristic associated with liver stiffness  $\geq$ 8.0 kPa found different results, mainly because different factors were tested across studies, but they also highlighted some interesting similarities. As expected, elevated serum transaminases was associated with increased risk of elevated liver stiffness in all studies, with adjusted Odd Ratio between 2.0 and 4.2 for serum transaminases  $\geq$ 40 IU/l [22, 24]. However, these works also showed that serum transaminases have low sensitivity with result below 40 UI/l in 40-80% of the patients having elevated liver stiffness [22, 24].

Diabetes was also consistently identified as a condition strongly associated with liver fibrosis. In the Rotterdam study, the prevalence of liver stiffness  $\geq$ 8.0 kPa was around 9% in the subgroup of patients with diabetes but no liver steatosis, and it reached 17.2% in patients with both diabetes and liver steatosis [23]. In the Caballería et al study, among 11 factors tested, type 2 diabetes mellitus (T2DM) was the condition associated with the highest prevalence of elevated liver stiffness [22]. These results were confirmed by targeted screening studies which shown the prevalence of elevated liver stiffness  $\geq$ 9.6 kPa was around 20% in T2DM populations from tertiary care centers (**Table 2**) [26-28]. Using the

same cut-off for TE, the Roulot study found a lower 7.3% prevalence, but this work included patient with newly diagnosed and less severe T2DM [29]. Indeed, longer duration of diabetes correlates with higher prevalence of elevated liver stiffness [26]. Moreover, another work using NITs in 338 diabetic patients found higher prevalence of severe fibrosis with increasing T2DM severity: 28.0% in patients with type 2 diabetes, 30.4% in patients >50 years with type 2 diabetes, and 37.9% in patients with a past history of foot ulcer [30]. Otherwise, the study of liver-related outcomes in large population of diabetic patients also gives important information. Indeed, increased risk of death from cancer in diabetics compared to non-diabetics is the highest for liver cancer, and chronic liver disease has the third highest increase in the risk of death from non-cancer and non-vascular disease [31], bringing additional arguments for the case finding of advanced liver disease in this population.

Population-based studies identified other factors associated with elevated liver stiffness (**Table 1**), most of them being related to metabolic conditions: obesity, impaired fasting glucose, low HDL cholesterol, high triglycerides levels, and liver steatosis. NAFLD is now the leading cause of chronic liver disease worldwide [1], therefore it is not surprising that liver fibrosis is mainly related to metabolic risk factors at a population level. A recent work has evaluated the targeted screening of liver fibrosis using TE in a population from primary care center with at least one liver risk factor among obesity, T2DM, or hazardous alcohol use [32]. Age was >40 years in 88% of the patients and the prevalence of elevated liver stiffness  $\geq 8.0$  kPa was 12.4%, which is higher than in the general population of the same age. Elevated liver stiffness was independently associated with obesity and T2DM, with no effect for hazardous alcohol use. The prevalence of elevated liver stiffness was 8.9% in obese patients, 10.8% in T2DM, and it significantly increased to 36.7% in patients having both obesity and T2DM, demonstrating the synergistic effect of metabolic factors on the risk of advanced liver disease. Another study found 25.2% prevalence of elevated liver stiffness  $\geq 8.0$  kPa in 899 patients coming from primary care centers and having at least one liver risk factor among hazardous alcohol use, T2DM or elevated serum alanine aminotransferase [33]. Prevalence was 19.2% among hazardous alcohol users, 31.5% in diabetics, 45.3% in patients with raised serum transaminases, with also synergic effect when liver risks factors accumulated.

Available evidence therefore suggests that overweight/obese patients, even more if they accumulate metabolic risk factors especially T2DM, might be a relevant population for the

case finding of patients with significant liver disease requiring specialized management (**Figure 1**). However, most of the data come from studies focused in adult patients with age >40 years. Since the 80s, we face a dramatic explosion of obesity and T2DM in children, the latter being more aggressive in young people with poorer response to glucose-lowering medication and greater insulin resistance [34-36]. As the length of exposure to the cause is a key factor in the development of advanced liver disease, one can suppose that the picture of chronic liver disease will change with increased cases of advanced liver disease in young adults in the near future. In this context, a very recent population-based study in young adults aged 22-26 years has found a 2.7% prevalence of elevated liver stiffness  $\geq 7.9$  kPa [25]. NAFLD patients have an increased risk of cardiovascular disease and recent data support pathophysiological processes linking NASH and liver fibrosis with cardiometabolic disease [37, 38]. A meta-analysis of studies with paired liver biopsy has shown that arterial hypertension was a strong predictor of fibrosis progression in NAFLD patients [39]. Similarly, a very recent work performed in a long-term community prospective cohort with 65 years follow-up found arterial hypertension as the strongest predictor of chronic liver disease, followed by insulin-resistance/diabetes mellitus and obesity [40]. On the other hand, in a large cohort of 603 biopsy-proven NAFLD patients, there was no independent relationship between liver lesions observed in NAFLD and cardiovascular events, the latter being only driven by the metabolic risks factors [41]. Additional data are needed to demonstrate that patients with cardiovascular disease have an increased risk of advanced liver disease and that screening for advanced fibrosis is relevant in this population.

#### **4. Screening strategies**

##### ***4.1 Which tests to use for the case finding of NAFLD patients with advanced liver fibrosis***

Liver biopsy remains the reference standard for the evaluation of liver lesions observed in NAFLD but, given the large population to be evaluated, this invasive procedure cannot be proposed as first-line evaluation. Several tests are now available for the non-invasive evaluation of liver fibrosis, mainly liver elastography devices and blood tests (**Figure 2**). Diagnostic studies using liver biopsy as reference have demonstrated the good sensitivity (80-90%) and specificity (90-95%) of NITs for the diagnosis of advanced liver fibrosis in NAFLD [42-44]. As these works mainly came from tertiary care centers with enrichment in

patients with advanced liver disease, the negative predictive value is supposed to be even better in populations with lower prevalence of liver fibrosis.

Screening studies using TE have shown this device to be useful in identifying subgroups enriched in patients with liver fibrosis. Using the 8.0 kPa threshold in population-based studies, around half of the patients who further underwent liver biopsy were found to have significant fibrosis (**Table 1**). Moreover, using the 9.6 kPa threshold in T2DM populations, 40-50% of the patients were further confirmed to have advanced liver fibrosis (**Table 2**). It must be however acknowledged that elevated liver stiffness was followed by histological confirmation in only 30-55% of the cases in these works. This low rate was explained by patient refusal, but also by the fact that physicians tend to reserve liver biopsy to more severe patients. Consequently, the true prevalence of liver fibrosis in the at-risk subgroup identified by TE is probably somewhat lower than what has been published. Currently, TE is available only in specialized centers, which is a limitation for the case finding of patients with advanced liver disease in large populations. Many Doppler-ultrasound devices now incorporate elastography technologies (point shearwave elastography, two dimensional shearwave elastography) [45], with similar accuracy for the diagnosis of liver fibrosis in NAFLD compared to that of TE [46, 47]. As these devices are more widely disseminated, they represent an interesting option to increase the availability of elastography.

Blood fibrosis tests represent another attractive option as they can be prescribed by every physician. Blood fibrosis tests include simple blood tests (NAFLD fibrosis score, FIB4) [48, 49], and specialized blood tests (Fibrotest, FibroMeter, Enhanced Liver Fibrosis (ELF) test) [50-52]. Simple blood tests have the advantages to include common and cheap blood markers, with free calculation through websites and smartphone applications. Specialized blood tests are more accurate than simple blood tests [44, 53], but they include more expensive specialized blood markers and they are patented with fees for test calculation. Blood fibrosis tests are mathematical models developed for the diagnosis of advanced fibrosis in cohorts of patients who underwent liver biopsy in tertiary care centers and are therefore well fitted for such populations. The following pitfalls must be avoided when using them for case finding in less selected populations.

The NAFLD fibrosis score (NFS) has been developed in a cohort of 480 NAFLD patients where the diabetes prevalence was 29% [48]. As diabetes is strongly associated with advanced fibrosis, this parameter was selected with age, BMI, AST, ALT, platelets, and albumin in the

final diagnostic model by the multivariate analysis. Two diagnostic cut-offs were calculated: -1.455 to rule-out and 0.676 to rule-in advanced fibrosis. Considering the coefficients attributed to each variable included in the blood test, the presence of diabetes implies an increase in 1.13 point of the NFS result. When NFS is used for the case finding of advanced fibrosis in T2DM populations, these additional points are attributed to all patients. Consequently, 70% of T2DM patients from primary care have an NFS result above -1.455, with only 30% being ruled-out for advanced fibrosis [54]. Moreover, this rate of ruling out dramatically decreases to 3-13% in patients from diabetic clinic [54, 55]. Consequently, NFS should not be used for the case-finding of advanced fibrosis in T2DM populations.

As previously said, the length of exposure to the cause is a key factor in the development of liver fibrosis in chronic liver diseases. Therefore, it is not surprising that age is a variable included in most of the blood fibrosis tests. However, these tests have been developed and therefore their coefficients for age have been calibrated in cohorts of patients aged around 45-50 years [48-50, 52]. Consequently, they are less sensitive in younger people [56], which could become a matter of importance with the expected increase in cases of advanced liver fibrosis in young adults due to the dramatic increase in prevalence of obesity and insulin resistance in children [25]. On the other side, it has been well described that NFS and FIB4 provide higher rates of false positive results in aged populations. It has been recently proposed to adapt their diagnostic cut-offs after 65 years old: 2.0 instead of 1.30 for ruling-out advanced fibrosis with FIB4, and 0.12 for NFS instead of -1.455 [56]. However, such approach induces a "threshold effect": a FIB4 at 1.70 doesn't rule-out advanced fibrosis at 60 years old with thus need for further investigations, whereas the patient will be ruled-out five years after despite 5 additional years of disease evolution. Additionally, a recent study suggested that these adapted cut-offs significantly decreased the sensitivity to only 60% in patients over 65 years of age [44].

In summary, non-invasive tests of liver fibrosis provide acceptable sensitivity for the case finding of advanced liver fibrosis in at risk populations. However, these tests have insufficient positive predictive value, especially in populations with low prevalence of the diagnostic target. Therefore, a strategy using an easy-to-obtain and cheap simple blood test as first-line procedure followed, if positive, by a second line confirmatory test (elastography or specialized blood test) seems the most appropriate strategy. Using such approach, the diagnostic accuracy of the second-line test is likely to match that found in published studies.

Indeed, the first-line test will select an at-risk population enriched in patients with advanced fibrosis whose prevalence will be close to that of the context where specialized fibrosis tests have been developed and validated. At the end, such strategy sequentially using non-invasive tests of liver fibrosis will define the patient pathway from primary care centers and diabetology clinics to liver specialists.

#### ***4.2 Algorithms combining non-invasive tests as referral pathways***

Despite numerous studies on the diagnostic accuracy of NITs, there is a relative paucity of data on their applied use in referral pathways. The rationale of such pathways is the use of an inexpensive readily available first tier NIT for all patients, followed by a second non-invasive test in selected cases [13, 57]. The use of sequential NITs is more effective than single NITs in both low and high prevalence of advanced fibrosis [58]. Based on existing evidence and as mentioned previously, the best performing NIT in such scenarios is the FIB4. The main advantage of using FIB4 as first-tier testing, is the very high negative predictive value (>95%) in unselected populations with low prevalence of advanced fibrosis, providing reassurance in up to 60% of tested patients [59]. The automatic calculation and reporting of the FIB4 (similarly to automatic calculation of glomerular filtration rate to monitor renal function) could potentially improve the uptake of such pathways and facilitate the work up of patients in primary care or non-hepatology specialties. Uptake of referral pathways can be improved if discussed and agreed with primary care providers and adjusted to the local availability and expertise on NITs [57].

Dillon and co-authors reported on the intelligent liver function testing (iLFT), which is an automated system of diagnosing and staging liver disease in primary care [60]. The starting point in the system is the identification of abnormal liver tests, which triggers reflex testing for causes of liver disease and liver fibrosis staging based on simple NITs. Compared to standard of care, the diagnosis of liver disease was increased by 43%, and 80% of patients with NAFLD were appropriately staged according to their risk of fibrosis.

In a pilot study in two primary care practices in the UK, patients at risk of alcoholic liver disease (ALD) or NAFLD were tested with a sequential biomarker algorithm, consisting of ALT/AST ratio in ALD or the BARD score in NAFLD followed by TE in patients with high AST/ALT ratio or BARD score. In total, 504 patients were recruited, and 98/378 had increased liver stiffness [61].

To date, there is a single study that implemented and evaluated a testing and referral pathway in primary care specifically for patients with NAFLD [62]. Srivastava and co-authors prospectively used a two-step algorithm in primary care, combining the use of FIB4 followed by ELF if required in patients with indeterminate FIB4 results. In total, over 3,000 patients were evaluated using the pathway in a two-year period. The uptake of the pathway was 48% highlighting the difficulties of implementation in real life scenarios. Compared to patients not evaluated using the pathway, exposure to the pathway was associated with a 4-fold improvement in the diagnosis of advanced fibrosis and cirrhosis and a 77% reduction of unnecessary referrals. Importantly, there was also a 2.5-fold increase in the number of patients coded as having NAFLD during the evaluation period, implying an increased awareness and recognition of NAFLD at the primary care level.

These results support the introduction of robust guidance and pathways in primary care for the management and testing of patients with NAFLD. A proposed algorithm is shown in **Figure 3**.

## **5. Awareness of NAFLD in non-liver specialists**

In a series of 100 NAFLD-related cirrhosis from a tertiary center, cirrhosis was not diagnosed by intent (incidental diagnosis) in 66% and the majority of these (74%) had a first diagnose of NAFLD concomitantly. [63]. In this work, 80% of the patients with an incidental diagnosis of cirrhosis had NFS or FIB4 result consistent with advanced liver fibrosis, strongly suggesting that a broader use of these tests could facilitate the early detection of patients with asymptomatic severe liver disease. NAFLD patients represent a too large population to be evaluated by liver specialists alone. Moreover, a lack of organization in referrals to liver specialists will contribute to overload liver clinics with patients who do not require specialized evaluation and management, to insufficient case-finding of patients having advanced liver disease, ultimately increasing costs but without a significant impact on the NAFLD burden. In this context, the sequential use of NITs starting with a simple blood test represents a very attractive option, defining a feasible patient pathway between non-liver and liver specialists. The success of such strategy requires an active participation of general practitioners (GPs), diabetologists and the other physicians who must therefore first and foremost be aware of the disease and the use of NITs for their patients.

GPs are those physicians who are the closest to the general population, therefore managing a lot of patients at-risk for advanced NAFLD. A recent evaluation of data from 18 million patients recorded in databases from primary care centers of four European countries (Italy, Netherlands, Spain, UK) showed that the prevalence of codes for NAFLD increased from 0.60% in 2007 to 1.85% in 2014 [64]. Despite significant increase, such prevalence is largely below the estimated 20-25% prevalence in the general population, showing that NAFLD remains under-recognized by GPs. From physician's perspective, 54% of 119 US primary care practitioners reported they did not screen NAFLD in patients with obesity and/or diabetes, and 27% said in fewer than half of the cases [65]. When asked if they refer NAFLD patients to a specialist, 48% reported they did not refer any patients and 37% would refer only some NAFLD patients. In another survey conducted in Australia, 44% of 108 primary care clinicians stated they do not make any referral to liver specialists for an opinion regarding suspected NAFLD/NASH, 80% did not use NITs of liver fibrosis, 60% were not sure that NITs could help to identify advanced fibrosis or cirrhosis, and 70% were unlikely to refer a patient to Hepatology unless liver function tests are abnormal [66]. Similar results were found among GPs from other countries [67-70]. As GPs ask for more information and knowledge about NAFLD [65, 67, 71], an interventional study was performed in Italy with questionnaires filled before and after a dedicated one-day workshop about NAFLD [70]. GPs indicated that this training improved their practice concerning screening of at-risk patients and their referral to the specialist.

Low awareness of NAFLD is not limited to GPs. A retrospective analysis of the French hospitalizations database found a very low 0,4% prevalence of NAFLD/NASH diagnosis codes among 50 million adult patients [72]. In a US survey including 246 physicians across three health systems from a single city, 45% of metabolic specialists did not identify NAFLD as a clinically relevant diagnosis in their patient population, and only half of them would refer suspected NAFLD patients to liver specialists [71]. Patients themselves have also little awareness of NAFLD. As relevant example, despite NAFLD awareness in patients with suspected NAFLD has increased across the different cycles of the US NHANES survey, it remained dramatically low in the 2013-2016 one, not exceeding 3.1% of the participants [73]. A survey conducted in 1790 adult Chinese patients and their family members showed that only 30% of participants had heard of NAFLD prior to the work [74]. Interestingly, after a brief 30 minutes educational seminar conducted by the same team, 46% of the 420

participants achieved improvement in the knowledge about NAFLD and 93% indicated they will improve their diet and physical activity [75].

All this information demonstrates the little awareness of NAFLD outside liver clinics. Therefore, education should be reinforced in specialties involved in the management of patients with metabolic comorbidities, and efforts should be made to directly target and inform patients with metabolic disorders to improve their knowledge of the disease.

## **6. Cost-effectiveness**

The cost-effectiveness of case finding for advanced fibrosis in NAFLD has been evaluated in several models. Limiting factors in all existing models are the absence of a licensed effective treatment and our somewhat limited knowledge on the natural history of the disease. Regarding the natural history of NAFLD, the transition probabilities among fibrosis stages used in modeling approaches are probably over-estimated, as published studies so far include liver biopsies that are performed based on clinical judgment and not per protocol, with over-representation of more severe cases. These important gaps will be hopefully filled in the next few years with the upcoming results of ongoing clinical trials and registries.

Testing patients with NAFLD for advanced fibrosis is cost-effective compared to performing a liver biopsy [76]. A cost-effectiveness study of testing for advanced fibrosis with TE, NFS or a combination of NFS and TE showed that risk stratification with NFS alone or NFS/TE are both cost-effective strategies at approximately \$5,800 per quality-adjusted life years (QALY) [77]. The base case for the analysis was a 50-year-old patient with NAFLD and abnormal ALT. The modeling assumed that patients diagnosed with advanced fibrosis were treated with vitamin E or pioglitazone. Similarly, a UK analysis by the National Institute of Clinical Excellence (NICE) showed that ELF was cost-effective in testing patients with NAFLD for advanced fibrosis. The base case in this analysis was a 50-year-old patient with NAFLD. The modeling assumed that patients diagnosed with advanced fibrosis would be treated with vitamin E or pioglitazone and undergo cirrhosis screening [78]. The NICE analysis was criticized because of the unrealistically high diagnostic accuracy of the ELF test it used (sensitivity of 100% and specificity of 98%). Finally, a decision model to quantify the accuracy and costs of non-invasive strategies to detect cirrhosis in NAFLD, concluded that the

combination of FIB4 and TE had the lowest cost and highest accuracy, followed by the combination of FIB4 and MRE and outperformed liver biopsy or any NIT alone [79].

Furthermore, there are now several cost-effectiveness studies that focus on testing patients in the general population/primary care. Using a hypothetical cohort of 1,000 patients with NAFLD and a 5% prevalence of advanced fibrosis, Crossan et al showed that the sequential use of non-invasive fibrosis tests in primary care (FIB-4 followed by ELF or TE or Fibrotest) is an effective way to rationalize secondary care referrals and is associated with significant cost savings, up to 30% compared to a refer-all strategy or 100% compared to a biopsy-all strategy [59]. A risk stratification pathway for patients with NAFLD in primary care using TE was more effective than standard of care at a cost of £2,138 per QALY gained [80]. The pathway demonstrated an 85% probability of cost-effectiveness at a willingness to pay threshold of £20,000 per QALY. In a cost-effectiveness analysis study across 6 independent cohorts (5 from Europe and one from Asia), screening for liver fibrosis with TE was cost-effective, with incremental cost-effectiveness ratios ranging from 2,570 euros/QALY to 6,217 euros/QALY in patients at risk for alcoholic liver disease and the general population respectively [81]. The target population was >45 years old, with a history of alcohol consumption, type II diabetes, metabolic syndrome or any combination of the above. The number needed to screen to detect one case of significant fibrosis (F2 or above) ranged from 7.0 in patients with diabetes to 34.5 in the general population. A recent US study based on Markov modelling concluded screening patients with type II diabetes for NAFLD was more cost-effective compared with no screening strategies [82]. The model assumed a cohort of patients aged 55 years followed across 1-year cycles. The most cost-effective screening approach was an ultrasound (with or without ALT) followed by a Fibroscan if there was evidence of NAFLD. Finally, in a probabilistic decisional model of a cohort of NAFLD patients in primary care, the sequential use of FIB4 followed by ELF or TE was associated with a reduction of total budget spend of 25% and a reduction in unnecessary referrals by 80%. The cost per case of advanced fibrosis detected was £9,000 with the sequential strategy compared to £25,500 with the standard of care [83].

The above studies support the use of NITs for the initial assessment of patients at risk of NAFLD.

## **7. Conclusions**

The growing burden of NAFLD is changing the landscape of liver disease, with increasing number of patients presenting with cirrhosis and listed for liver transplantation. It is very likely that we are only seeing the tip of the iceberg, as the majority of cases are undiagnosed and under-reported in primary care/non hepatology specialties, and opportunities for early interventions are missed. The accumulated evidence so far supports the implementation of testing pathways for patients with an established diagnosis of NAFLD, with the target lesion being advanced fibrosis. These pathways are feasible and cost-effective, increase the awareness of the disease and lead to an increased rate of early diagnosis of advanced fibrosis and compensated cirrhosis. There are many non-invasive tests available to implement in such pathways, and the choice should be based on local availability and expertise. Further research is required on the effectiveness of case finding in patients at risk of NAFLD, with particular emphasis on the resource required and the cost effectiveness of the approach.

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**Table 1: Population-based studies evaluating screening for liver fibrosis using transient elastography**

	<b>Roulot 2011 [24]</b>	<b>Koehler 2016 [23]</b>	<b>Caballería 2018 [22]</b>	<b>Abeysekara 2020 [25]</b>
Country	France	Netherlands	Spain	United Kingdom
Population	Population-based	Population-based	Population-based	Population-based
Patients	≥45 years	≥45 years	18-75 years	22-26 years
Sample size (n)	1 190	3 041	3 014	3 600
Target	TE ≥8.0 kPa	TE ≥8.0 kPa	TE ≥8.0 kPa	TE ≥7.9 kPa
FibroScan probe used	M probe	M or XL probe <sup>a</sup>	M probe	M or XL probe <sup>a</sup>
Prevalence (%)	7.5%	5.6%	5.8%	2.7%
Independent predictors of the target	Diabetes ALT ≥40 IU/l Elevated WC <sup>b</sup> Age ≥57 years BMI ≥30 kg/m <sup>2</sup> GGT ≥45 IU/l	Diabetes ALT Age Current/former smoking HBs Ag or anti-HCV positive Liver steatosis Spleen size	Type 2 diabetes AST and/or ALT > 40 IU/l Elevated WC <sup>c</sup> Male sex Glucose ≥100 mg/dl Low HDL cholesterol <sup>d</sup> Triglycerides ≥150 mg/dl	Male sex Harmful alcohol use
Liver biopsy (n)	27	-	60	-
Fibrosis stage (n) <sup>e</sup> :				
- 0	1	-	27	-
- 1	8	-	6	-
- 2	9	-	20	-
- 3	0	-	3	-
- 4	4	-	4	-

IFG: impaired fasting glucose; ALT: alanine aminotransferase; AST: aspartate aminotransferase; WC: waist circumference; BMI: body mass index; HBs Ag: HBs antigen; HCV: hepatitis C virus; GGT: gamma-glutamyl transferase

<sup>a</sup> According to the manufacturer recommendation; <sup>b</sup> Waist circumference  $\geq 100$  cm in men or  $\geq 93$  cm in women; <sup>c</sup> Waist circumference  $\geq 102$  cm in men or  $\geq 88$  cm in women; <sup>d</sup> HDL cholesterol  $< 40$  mg/dL in men or  $< 50$  mg/dL in women; <sup>e</sup> according to the NASH CRN staging system, except for viral hepatitis in the Roulot study for which Metavir staging was used

**Table 2: Studies evaluating screening for liver fibrosis in diabetic patients using transient elastography**

	<b>Kwok 2015 [26]</b>	<b>Roulot 2017 [29]</b>	<b>Lai 2019 [28]</b>	<b>Sporea 2020 [27]</b>
Country	China	France	Malaysia	Romania
Population	T2DM	Newly diagnosed T2DM	T2DM	T2DM
Patients	≥18 years	≥18 years	≥18 years	≥18 years
Sample size (n)	1 884	669	557	534
Target	TE ≥9.6 kPa (M probe) or ≥9.3 kPa (XL probe)	TE ≥9.6 kPa	TE ≥9.6 kPa (M probe) or ≥9.3 kPa (XL probe)	TE ≥9.7 kPa
FibroScan probe used	XL probe if M probe failure	XL probe if M probe failure	M or XL probe according to manufacturer recommendations	XL probe if BMI ≥30 kg/m <sup>2</sup> or skin-to-capsule distance >25mm
Prevalence (%)	17.7%	7.3%	21.0%	19.5%
Independent predictors of the target	Diabetes duration ALT BMI HDL-cholesterol Urine ACR	Age ALT BMI GGT	ALT GGT HDL cholesterol Platelets	AST
Liver biopsy (n)	94	47	57	-
Fibrosis stage (n) <sup>a</sup> :				
- 0	5	F0-2: 23	-	-
- 1	29	-	-	-
- 2	13	-	-	-
- 3	20	16	F3-4: 23	-
- 4	27	8	-	-

T2DM: type 2 diabetes mellitus; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; BMI: body mass index; ACR: albumin-creatinine ratio;

<sup>a</sup> According to the NASH CRN staging system

**Figure 1: Populations at-risk for NAFLD-related liver outcomes**

**Figure 2: Non-invasive tests for liver fibrosis**

VCTE: vibration controlled transient elastography, SWE: shearwave elastography; MRE: magnetic resonance elastography

**Figure 3: Testing pathway for patients with a diagnosis of NAFLD in non-hepatology specialties.**

An initial FIB4 is followed by elastography or a patented serum non-invasive test such as ELF or FibroMeter. The target lesion is the presence of advanced fibrosis.

**Overweight / Obese**

**Overweight / Obese  
+ 1 metabolic risk factor**

**Metabolic syndrome**

**Type 2 diabetes**

Prevalence of  
advanced  
liver fibrosis

# BLOOD TESTS

## MARKERS

**Simple:** serum transaminases, platelets, bilirubin, INR, albumin...

**Specialized :**  $\alpha$ 2 macroglobulin, hyaluronate, TIMP1, P3NP...

## TESTS

APRI, FIB4, eLIFT  
NAFLD fibrosis score

Fibrotest, FibroMeter, ELF

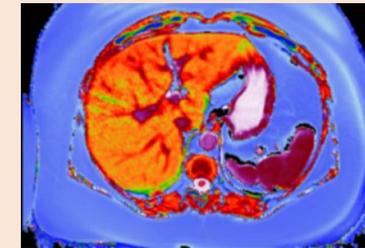
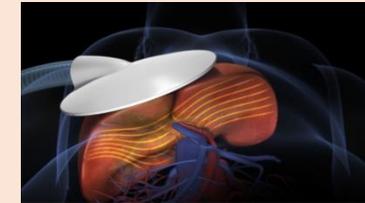
# ELASTOMETRY



VCTE



POINT SWE, 2D-SWE



MRE

Cost

Availability

