**NAFLD and the interface between primary and secondary care**

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**Abstract**

Non-alcoholic fatty liver disease (NAFLD) has a prevalence of 25-30% in unselected populations and has become the main reason for referrals to hepatology services. From a liver point of view, NAFLD is a disease of high prevalence but relatively low severity. Screening studies in people at risk show a prevalence of advanced fibrosis of 5%, which underlines the need for robust pathways for risk stratification in primary care with subsequent referrals as required. In this review, we discuss the interface between primary and secondary care with regard to risk stratification and management of patients with NAFLD. We focus on selected issues of epidemiology and natural history and discuss the burden of disease in primary care, the evidence on screening for NAFLD, the rationale for testing for advanced fibrosis and the optimal management in primary care.

## Introduction

Non-alcoholic fatty liver disease (NAFLD) has a prevalence of 25-30% in the general population and has thus become the main reason for referrals to hepatology services[1,2]. The number of patients diagnosed and referred is projected to rise further secondary to the growing epidemic of obesity and diabetes but also the increasing awareness of the disease.

NAFLD is a systemic disease and is often perceived as an inconsequential hepatic manifestation of the metabolic syndrome; although some patients will develop progressive liver disease that can lead to cirrhosis and liver cancer, the majority of those affected will never develop hepatic complications. Indeed, cardiovascular disease is the main cause of mortality in patients with NAFLD followed by non-liver related malignancies[3]. Therefore, from a liver point of view, NAFLD is a disease of high prevalence but relatively low severity. It is therefore critical that primary care physicians are actively involved in the screening and management of patients, with community pathways in place for selecting patients at risk of liver disease for secondary care referral and adequate education for following up and treating those deemed at low risk. In this review, we discuss the interface between primary and secondary care as regards risk stratification and management of patients with NAFLD. We focus on selected issues of epidemiology and natural history and discuss the burden of disease in primary care, the evidence on screening for NAFLD, the rationale for testing for advanced fibrosis and the optimal management in primary care. This review is relevant for primary care and/or other specialties that make the first diagnosis of NAFLD or treat the majority of people at risk of NAFLD. Parts of the

manuscript on screening and testing are also relevant for secondary care clinicians developing services for NAFLD and for commissioners of those services. We further highlight areas of uncertainty and needs for future research.

## Search strategy and selection criteria

We searched MEDLINE (2005-2017) using the search term "NAFLD" or "NASH" combined with the terms "non-invasive fibrosis tests" or "primary care" or "prevalence" or "incidence" or "treatment". Articles were also selected through searches of the authors' own files. We selected further relevant publications from the reference lists of articles identified by this search strategy. We largely selected publications in the past 5 years, but did not exclude highly relevant older publications. Review articles are cited to provide more details and references than this Seminar has room for.

## Epidemiology

NAFLD is an increasingly common global entity which is defined by the presence of hepatic steatosis and varying degrees of liver injury and fibrosis, occurring in the absence of any other aetiological factors notably alcohol excess[4]. Its emergence over the past 20 years has been driven by the dramatic rise in levels of obesity and type 2 diabetes mellitus with which it is closely linked[5].

Population and other studies have used different methods to diagnose NAFLD, which in turn has a major impact on the prevalence figures generated; in general studies requiring abnormal liver blood tests to make the diagnosis of NAFLD

generate much lower figures compared to those utilising imaging modalities. The observation that patients with NAFLD, and indeed those with significant liver damage, may have entirely normal liver blood tests is widely accepted but has impacted on case-finding in clinical practice[6]. In addition, NAFLD refers to patients with the full spectrum of the condition, ranging from indolent steatosis through to progressive inflammation, non-alcoholic steatohepatitis (NASH), and fibrosis culminating in cirrhosis[7]. As the distinction often requires recourse to additional investigations, some invasive such as liver biopsy, there are more limited data on the prevalence of NASH and progressive fibrosis. This is relevant as there is a growing recognition that complications related to liver disease arise only after many years and predominantly in those individuals with NASH and fibrosis.

The global data on prevalence of NAFLD and NASH have been reviewed recently by Younossi *et al*[8]*;* 86 studies from 22 countries included 8,515,431 patients and established a global prevalence of 25.24% (95% CI: 22.10-28.65) with the highest prevalence found in the Middle East and South America. Nevertheless, there were broadly similar prevalence figures across the different geographical regions, with prevalence plateauing after the age of 40 before rising further beyond the age of 70. Pooled overall prevalence estimate in those patients with NAFLD being 59.10% (95% CI: 47.55-69.73), but extrapolating this to the population prevalence of NASH is more difficult given the inherent biases in such figures, which are commonly generated in specialist centres. Modeling data, again from Younossi and colleagues, suggests a prevalence of 2-5% of NASH across the US and major European countries[8].

Finally data on the prevalence of NASH with advanced fibrosis are even sparser yet of greater clinical importance. Population based studies report lower prevalence figures than those from specialist centres highlighting ascertainment bias in the latter. Nonetheless these figures conservatively suggest a prevalence of 0.3-1% for NASH with advanced fibrosis in the US and Europe[8].

**Natural History**

There is an uncertain understanding of the progression of liver damage in the setting of NAFLD/NASH; in the main this is due to the reliance on liver biopsy to track changes in liver injury. Moreover, most of the datasets reported are single centre studies from specialist units where repeat biopsy occurred in response to clinical events – inevitably this results in a bias as repeat biopsy will be driven by clinical concerns in many patients providing a non-representative understanding of the overall rate of change. When analysed, Singh and colleagues, determined that rate of histological progression differed depending on severity of baseline NAFLD[9]; those with more indolent disease at the outset appeared to progress more slowly, whereas those with NASH progressed more rapidly. These data are helpful in informing the field but it should be noted though that the rates of progression were still slow; the time taken to advance by one stage of liver fibrosis was 7 years in `fast` progressors versus 14 years in `slow` progressors[9].

A relevant consideration is the method of evaluating changes in fibrosis in patients with NASH. This uses the established NASH Clinical Research Network

(CRN) classification which stages fibrosis from 0 to 4 depending on the histological pattern observed[7]. This system whilst useful has some limitations; the fibrosis is graded categorically yet analysed as if it was a continuous variable. Moreover, the staging system is not linear with absolute differences in fibrosis between the earliest stages being modest whereas later stages have more marked increases in collagen. This is relevant as in the systematic review by Singh most patients had fibrosis within the earliest categories of fibrosis and hence the reported changes in stage represent relatively small changes in fibrosis[9]. Of note these studies also demonstrate that there is a significant amount of spontaneous improvement in fibrosis seen at these early stages in NASH highlighting the dynamic nature of disease.

To understand which factors predicted histological change Singh and colleagues undertook logistic regression followed by a multi-variate analysis. A number of features were observed as predicting progression at univariate analysis, although notably only hypertension remained as a predictive factor after multivariate analysis[9]. This could represent a chance finding, although there may be logic in the link between activation of the renin angiotensin axis and ongoing liver fibrogenesis, as highlighted by the potential beneficial role of angiotensin converting enzyme inhibition in liver fibrosis[10].

Whilst there is an understandable focus on liver morbidity and mortality in patients with NASH, analysis of outcomes in such cohorts demonstrates that deaths from cardiovascular disease and non-liver malignancy are the top two causes[11,12]. Given the co-existence of often multiple metabolic syndrome factors in patients with NASH this is not surprising. This knowledge is of particular

relevance for the shared management of such patients in primary care where there should be a clear focus on the optimal management of the metabolic syndrome. Identification of the factors predicting the development of overall and liver-related mortality has been the focus of many recent studies, with the finding that metabolic factors such as diabetes mellitus and HMG co-A reductase usage are important prognostic factors. Similarly the presence and severity of liver fibrosis has been reported in several studies to be a strong predictor of overall and liver-related mortality. The link with liver-related mortality is to be expected, and the data by Dulai *et al* suggest that the risk manifests after the development of more significant liver fibrosis (F2) and rises exponentially thereafter[13]. The link with overall mortality pertains at even lower levels of fibrosis and rises in a more proportionate fashion with fibrosis. This could represent a surrogate for the number of metabolic risk factors, although there remains an ongoing discussion about the direct role of NASH on cardiovascular risk once concomitant metabolic syndrome factors are controlled for.

Several studies have highlighted the link between fibrosis and outcome, whilst also noting that the presence of NASH did not seem to have a similar effect[11,12]. At one level this has been considered a controversial finding suggesting that the presence of inflammatory liver injury *per se* is not as important a driver of outcomes than the subsequent development of liver fibrosis. However, the presence of NASH, and ballooning in particular, is the hallmark of liver injury which in the presence of concomitant factors such as steatosis is a recognised driver of liver fibrosis. Without being too dogmatic this is the accepted paradigm by which liver injury results in fibrosis irrespective of the nature of liver damage,

although caveats here may include the direct fibrogenic effect of certain fat moieties including free cholesterol. Accepting that the diagnosis/mis-diagnosis of NASH on liver biopsy occurs frequently[14] and that this more so than fibrosis is a dynamic entity it is still likely that NASH is a principal driver of progression in such patients. Moreover, there are likely to be different fibrogenic susceptibilities to the development of fibrosis in response to a similar amount of inflammatory liver injury, thus the presence of NASH is one risk factor amongst others that determines the likelihood of liver fibrosis and hence clinical outcomes[15].

**NAFLD in primary care**

In the absence of population screening, the diagnosis of NAFLD in primary care is usually triggered by the incidental diagnosis of abnormal liver blood tests or steatosis on an imaging modality performed for a separate indication. Liver blood tests are often requested in primary care when there is general clinical uncertainty as opposed to a specific query about liver disease, and thus, primary care physicians are often confronted with abnormal liver blood tests without any prior clinical clues. Further investigation of the underlying aetiology and severity is often driven by the magnitude of the liver blood test abnormality, which whilst appropriate when referring to markers of liver synthetic function is not so when it relates to liver enzymes. Significant liver disease can exist in the setting of normal or minimally abnormal liver enzymes and thus unless there is an obvious transient cause such as sepsis or concomitant time-limited drug prescription the focus should turn to the underlying cause.

Analysis of causation of abnormal liver blood tests in primary care indicates that most are caused by NAFLD or alcohol excess with a significant proportion having no discernible aetiology. Whilst the latter may be caused by transient illnesses they may also be a reflection of under-reported alcohol consumption or NAFLD that is not captured by ultrasonography[16]. In a primary care cohort of over 1,000 patients with incidentally diagnosed abnormal liver tests, NAFLD was the underlying abnormality in 26% of cases, while the cause was not identified in 45% of cases[16]. For patients with NAFLD there has been an *ad hoc* approach to referral resulting in cases of advanced liver disease being over-looked and patients with minimal disease being referred to secondary care. A systematic response to abnormal liver blood tests is required to standardize the approach for such patients[17]. This should include testing for viral hepatitis B and C, testing for autoimmune liver disease, simultaneous serum ferritin and transferrin saturation, a1-antithrypsin levels, serum ceruloplasmin in patients younger than 40 years, an abdominal ultrasound and a detailed history of alcohol use and concomitant medication.

**Screening for NAFLD in primary care**

Although screening for NAFLD in unselected populations is not warranted, case-finding in groups deemed at high risk of having the condition remains a contentious issue with conflicting guidance from the major learned societies and commissioning bodies[1,2,17,18]. These reflect the paucity of data on disease progression and long-term outcomes in unselected population, the lack of an

optimal screening test and the lack of effective disease-specific therapies that all hinder cost-effectiveness analyses.

Magnetic resonance imaging (either with proton density fraction images or with spectroscopy) is the gold standard for the diagnosis of NAFLD in research settings, however due to accessibility and costs is not fit for clinical use at the moment. Abdominal ultrasound can only diagnose steatosis if it is in excess of 20-30% and therefore will miss patients with NAFLD and a steatosis grade between 5% and 20%. Compared to blood-based tests, ultrasound has the benefit of direct visualization of the liver and the potential of diagnosing additional pathologies such as liver lesions. The Controlled Attenuation Parameter (CAP) of the Fibroscan can identify steatosis with a reasonable sensitivity and specificity; in an individual patient meta-analysis of almost 4,000 patients, the AUROCs for the diagnosis of any degree and >33% of steatosis were 0.82 and 0.86 respectively at cut-offs of 248 and 268 dB/m[19]. Notably, CAP values were influenced by the aetiology of liver disease and the presence of diabetes[19]. There are no standardized CAP cut-offs using the XL Fibroscan probe in obese patients. Serum based algorithms include the Fatty Liver Index (FLI), the NAFLD Liver Fat Score, the Hepatic Steatosis Index and the Steatotest[20]. Although these tests are useful for population-based studies, their utility is less optimal for population screening due to an unacceptably high number of false positive results. Overall, the sub-optimal specificity is an issue with all widely available methods for NAFLD screening[21].

The diagnosis of NASH is of more clinical relevance than the diagnosis of NAFLD, however it is hindered by the lack of non-invasive diagnostic methods. The circulating fragments of cytokeratin 18, which is an apoptotic marker, is the most studied biomarker, but has low sensitivity and does not correlate with ballooning, which is the hallmark of NASH[22].

The European Associations for the Study of the Liver (EASL), Diabetes (EASD) and Obesity (EASO) guidelines advocate case-finding for NAFLD with an abdominal ultrasound in individuals with obesity, type II diabetes, presence of the metabolic syndrome or incidentally discovered abnormal transaminases[1]. They advocate the use of ultrasound over serum-based algorithms because of the additional diagnostic information an ultrasound can provide. They also advocate a comprehensive evaluation of NAFLD-associated disease in patients with an incidental diagnosis of steatosis. In contrast, the American Association for the Study of Liver Disease (AASLD) guidelines do not recommend routine screening in high risk patient groups or any further investigation of incidental steatosis unless there is evidence of chronic liver disease or abnormal liver tests[2]. They do suggest a high index of suspicion in patients with type II diabetes, however with no specific recommendations for a diagnostic or monitoring approach. The recent British Society of Gastroenterology guidelines on abnormal liver blood tests also do not recommend screening for NAFLD until further evidence on cost-effectiveness becomes available[17].

The National Institute for Clinical Excellence (NICE) in the UK performed a cost-effectiveness analysis for NAFLD screening in the general population[18]. The base

case for NAFLD testing was a 45-year old person with type II diabetes or presence of the metabolic syndrome. A variety of tests were compared for the diagnosis of >5% and >30% of steatosis. Screening for NAFLD was more cost-effective than not; fatty liver index was the most cost-effective tests, followed by abdominal ultrasound. Due to the wide confidence intervals for the sensitivity of the fatty liver index that could potentially result in a high number of false positives, there was no recommendation for a specific test to diagnose NAFLD or for screening for NAFLD. A slightly different cost-effectiveness analysis was performed by Corey and co-authors[23]; this assumed a 50-year old with type II diabetes as the base case, and ultrasound for screening for NAFLD followed by a liver biopsy if this was positive. Patients diagnosed with NASH were treated with pioglitazone. There was an allowance of a 21% incidental diagnosis of NAFLD in the non-screened group. Screening was not cost-effective, which was mainly due to the decrement in the quality of life due to the side effects of pioglitazone.

An important question is the burden of advanced liver disease that will be missed if patients at risk are not screened for NAFLD and subsequently for advanced liver fibrosis. It is well recognized that the severity of liver disease in NAFLD is independent of increased ALT values and indeed the entire histological spectrum can be seen in patients with normal ALT values[24]. In the Rotterdam Study, that included over 3,000 participants older than 45 years, 5.6% had probable clinically relevant fibrosis using Fibroscan, and this was strongly associated with steatosis and type II diabetes[25]. In a study from Hong Kong with almost 2,000 patients with type II diabetes and no history of chronic liver disease, increased liver stiffness measurements (indicating the presence of

fibrosis) was found in 17.7% of patients; of the 94 patients who had a subsequent liver biopsy, 50% had advanced fibrosis or cirrhosis[26]. A UK study of 919 patients at risk for chronic liver disease across four general practices, reported 25.6% and 2.9% prevalence of increased liver stiffness and confirmed cirrhosis in that population, with obesity, type II diabetes and alcohol misuse being the main risk factors[27]. In a systematic review of non-invasive tests to stratify patients at risk of advanced liver disease in a general population setting, the prevalence of advanced fibrosis ranged from 0% to 2.7% depending on the population characteristics[28]. Normal liver blood tests were found in approximately 50% of patients with advanced fibrosis or cirrhosis.

Therefore, although screening for NAFLD is not universally recommended at the moment, there is a possible rationale for case finding in risk groups rather than relying on the incidental diagnosis of abnormal liver tests or fatty liver on ultrasounds. Given the limitations of existing screening methods for the presence of NAFLD, looking directly for fibrosis could be alternatively explored. Strong collaboration with primary care and commissioners is important for the design of pathways for testing and referral, and the clinical effectiveness of such pathways will need to be tested in pragmatic studies[29]. The placebo arm of the ongoing randomized controlled trials will provide important data on the natural history of NAFLD that will decrease the uncertainty in cost-effectiveness models[30]. The advent of effective pharmacological treatments will also make case finding more relevant for physicians and patients[31].

**Testing for advanced fibrosis**

Although screening for NAFLD is currently contentious, testing for advanced fibrosis (F3 on the NASH CRN staging system) in patients with an established diagnosis of NAFLD was recommended in all recent guidelines[1,2,17,18]. The presence of advanced fibrosis is the most important factor that determines clinical outcomes in patients with NAFLD[11,12]. Although it would be desirable to target patients with significant fibrosis (F2 on the NASH CRN staging system) for testing strategies due to the higher risk of progression, this is currently not feasible due to the suboptimal diagnostic accuracy of existing non-invasive fibrosis tests for F2. The NAFLD fibrosis score (NFS)[32] and the FIB-4[33] are well-validated simple non-invasive tests with a high negative likelihood ratio for the exclusion of advanced fibrosis. Importantly, patients with values below the lower-cut offs have excellent liver-related prognoses over ten years follow-up[34]. Assuming a prevalence of advanced fibrosis of less than 5% in unselected patients with NAFLD, their negative predictive value is more than 98%[35]. The FIB-4 consists of fewer variables and is thus simpler to calculate and incorporate in primary care pathways for triaging patients, and performs slightly better than NFS in head to head comparisons[35]. These tests have dual cut-offs, a low and a high cut-off to exclude and diagnose the presence of advanced fibrosis respectively. The cut-offs of both scores need to be adjusted for people older than 65 years to account for the inappropriate weighting of age in the algorithms above this age that leads to reduced specificity[36]. A proportion of patients, approximately 40-50%, fall into an indeterminate category between the two cut-off values and thus require further testing[37]. Therefore, a two-tier testing strategy is required for almost half of the patients encountered in primary care

(Figure 1). The choice of the second tier test could be either an elastography technique or a proprietary serum algorithm, based on local availability and expertise.

Fibroscan is the most widely available elastography technique, with adequate validation in NAFLD in both European and American cohorts[38,39]. The XL probe has allowed the performance of the technique in obese patients and has largely addressed the challenge encountered in NAFLD with the M probe[40]. Less than 5% of examinations fail or show unreliable results in the hands of experienced operators, as recently reported in an audit of more than 1,500 exams[39]. Alternative elastography techniques, such as Acoustic Radiation Force Impulse (ARFI) and Supersonic Shear Imaging have comparable results in terms of diagnostic accuracy[41]. Magnetic resonance elastography is superior to other elastography techniques for lesser fibrosis stages but has similar diagnostic accuracy for advanced fibrosis[42]. It is currently available only in specialist centres and thus not suitable for population screening.

There are a number of proprietary serum tests that were developed mainly in cohorts of patients with chronic hepatitis C. These include Fibrotest, the Enhanced Liver Fibrosis (ELF) test, Hepascore and Fibrometer [35]. Both the ELF score [43] and Fibrometer [44] were subsequently validated in patients with NAFLD.

The EASL guidelines recommend the use of non-invasive fibrosis tests to rule out advanced fibrosis in patients with NAFLD and normal transaminases, although no specific non-invasive fibrosis testing algorithm is recommended; they further

advocate direct referral to a liver specialist in patients with abnormal transaminases without prior non-invasive fibrosis assessment[1]. It should be noted that the above guidance refers to individuals with cardiometabolic risk factors only and is intended for secondary/tertiary non-hepatologist care rather than primary care. The AASLD guidelines state that the NFS and FIB4 are clinically useful tools for identifying (rather than ruling out) advanced fibrosis despite the unsatisfactory positive likelihood ration of these tests and also mention Fibroscan and MRE, however there are no recommendations for a stepwise approach[2]. The BSG guidelines recommend the use of either NFS or FIB4 as a first step in all patients diagnosed with NAFLD. Patients at low risk of advanced fibrosis are managed in primary care, while patients at high risk are directly referred to secondary care. Patients at indeterminate risk undergo second tier testing with either ELF score or an elastography technique, based on local availability and expertise[17]. This is a pragmatic approach indicating the need for action and further consideration, without being too prescriptive.

NICE deemed that testing for advanced fibrosis was cost-effective in NAFLD, although controversially concluded that the use of ELF score alone was the most cost-effective approach[18]. This was most likely due to the fact that the diagnostic accuracy of the ELF score imputed in the modeling was extrapolated from a pediatric study of 112 patients that reported a sensitivity and specificity of 100% and 98% respectively[45]. Tapper and co-authors compared the cost-effectiveness of the NFS versus Fibroscan versus a combination of NFS and Fibroscan versus a liver biopsy, and NFS alone or its combination with Fibroscan were the most cost-effective options, depending on the scenario used[46]. Similarly, our cost

analysis indicated that a two-tier approach with a combination of a simple non-invasive test with either ELF or Fibroscan results in a referral rate of 10% and resulted in significant cost savings[35]. A testing strategy is summarized in Figure 2. The diagnostic accuracy of the most commonly used non-invasive fibrosis tests is summarized in Table 1.

There is therefore an increasing realization that non-invasive testing for advanced fibrosis is required in patients with NAFLD and that it should be even extended to patients at risk of NAFLD even if a firm diagnosis is not present[47]. The latter has several potential benefits, as it would overcome the suboptimal specificity of diagnostic tests for steatosis, it would increase testing uptake by simplifying current algorithms and would increase awareness and shift the focus of physicians to a clinically meaningful diagnosis.

Patients should be re-tested after 3-5 years to capture disease progression or potential false negatives of the initial testing episode.

**Management in primary care**

The main focus of NAFLD management in primary care should be the treatment of the metabolic comorbidities in order to reduce the cardiovascular risk, which will also prevent the future development of NASH and fibrosis (Table 2). Indeed, primary care physicians are much better equipped to address these risks than hepatologists in secondary care. Lifestyle interventions with diet and exercise are a key first step for all such patients. Weight loss of 10% was, in one study, associated with resolution of NASH and improvement of fibrosis in 90% and 45% of patients respectively[48]. Bariatric surgery is an effective option in selected

patients that fulfill certain obesity and/or comorbidity criteria[49]. Moreover, regular exercise reduces visceral and hepatic effect even in the absence of weigh loss[50].

Regarding pharmacotherapy, certain drugs could be preferentially considered for the treatment of metabolic comorbidities, due to a suggested benefit in NAFLD. Most of the data presented, with the exception of pioglitazone, are from observational or pilot studies and will need to be verified in adequately powered randomized controlled trials. In a nationwide case-control study from Taiwan, metformin was associated with a reduced risk of hepatocellular carcinoma (HCC) in diabetic patients and is currently recommended as first line treatment for type II diabetes[51]. Pioglitazone has positive effects in liver histology and is a reasonable choice for add-on treatment in some patients without relevant contraindications[52]. Liraglutide results in weight loss and improved histology in patients with NAFLD as shown in a proof of concept randomized controlled trial[53]. Angiotensin II blockers may have anti-fibrotic effects and could be the first line treatment for hypertension[54]. The overall cardiovascular risk should be calculated in all patients using the appropriate tools (such as the QRISK2 score) and statins should be initiated if required. There is an unfounded perception of increased risk of hepatotoxicity from statins in patients with abnormal transaminases amongst non-liver specialists, which results in patients being potentially denied an essential medication. A post-hoc analysis of 437 patients with moderately elevated transaminases most likely due to NAFLD that participated in the GREACE study, demonstrated that statin treatment was safe and could improve transaminases and reduce cardiovascular morbidity[55].

Moreover, individuals with elevated baseline transaminases are not at higher risk for hepatotoxicity[56].

## Conclusions

The growing burden of obesity is a deeply concerning public health issue and has resulted in a global prevalence of NAFLD in excess of 25%[57]. Primary care has an important role in preventing the development and progression of NAFLD and screening patients at risk for chronic liver disease with referral to secondary care as required. The vast majority of patients will remain in primary care and therefore a focus on the active management of cardiovascular risk factors is essential. There is an urgent need for an integrated management plan between primary and secondary care, with robust pathways for testing for advanced fibrosis and subsequent referrals. Currently, the lack of such widespread pathways results in *ad hoc* referral strategies that potentially miss a significant proportion of the population at risk [58,59]. The deployment of community hepatologists and specialist nurses might help in educating general physicians and raising awareness. Research is required on the need for screening for NAFLD and also the best pathway to screen for advanced fibrosis.

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**Table 1.** Summary of most widely available non-invasive fibrosis tests for advanced fibrosis (NASH CRN stage 3) in patients with non-alcoholic fatty liver disease (NAFLD).

| **Test** | **Components** | **Cut-off** | **Sensitivity** | **Specificity** | **NPV** |
|---|---|---|---|---|---|
| NFS | Age, BMI, T2DM, AST, ALT, PLT, albumin | -1.455, 0.676 | 0.80 | 0.66 | 0.98 |
| FIB4 | AST, ALT, age, PLT | 1.3, 2.67 | 0.84 | 0.74 | 0.98 |
| ELF | Hyaluronic acid, PIIINP, TIMP-1 | 10.3 | 0.80 | 0.90 | 0.99 |
| Fibrotest | A2 macroglobulin, haptoglobin, apo-A1, bilirubin, GGT, g globulin | 0.3, 0.7 | 0.88 | 0.73 | 0.99 |
| Fibroscan | Imaging modality | 8.7-9.8 KPa | 0.82 | 0.82 | 0.99 |
| ARFI | Imaging modality | 1.2-1.3 m/s | 0.81 | 0.78 | 0.99 |

The negative predictive value is based on a prevalence of advanced fibrosis of 5%. The diagnostic accuracy data are derived from Crossan[35].

Abbreviations: NPV: Negative Predictive Value, NFS: NAFLD Fibrosis Score, T2DM: Type II Diabetes Mellitus, PIIINP: Amino-terminal propeptide of type III collagen, TIMP-1: Tissue Inhibitor of Matrix Metalloproteinase-1, PLT: platelets, ELF: Enhanced Liver Fibrosis test, apo-A1: apolopoprotein A1, GGT: gamma glutamyltranspeptide, ARFI: Acoustic Radiation Force Impulse

**Table 2.** Primary care management of patients with NAFLD

| **Condition** | **Treatment modality** | **Therapeutic Target** | **Suggested benefits** |
|---|---|---|---|
| Obesity | Lifestyle changes, diet, exercise. Bariatric surgery in selected cases. | 10% weight loss | Resolution of NASH; fibrosis regression; Reduced cardiovascular events |
| Hypertension | ACE inhibitors | Blood pressure <130/80 mmHg | Less fibrosis progression & Reduced cardiovascular events |
| T2DM | 1. Metformin<br>2. Pioglitazone<br>3. Liraglutide | HBA1c<6.5% | 1. Associated with reduced incidence of HCC<br>2. Resolution of |

| | | | |
|---|---|---|---|
| | | | NASH<br>3. Resolution of NASH<br>Reduced cardiovascular events |
| Hyperlipidaemia | Statins | QRISK2 score<10% | Improvement of transaminases &<br>Reduced cardiovascular events |
| Smoking | Counselling;<br>nicotine patches;<br>medication | Smoking cessation | Less fibrosis progression &<br>Reduced cardiovascular events |

Abbreviations: NASH: non-alcoholic steatohepatitis, ACE: angiotensin converting enzyme, T2DM: Type II Diabetes Mellitus; HBA1C: glycated hemoglobin

**Figure 1.** A general concept of the interface between primary and secondary care, with decision-making based on the stage of fibrosis. Although ideally patients with significant fibrosis (F2) should be followed in secondary care due to higher risk of progression, this is not feasible due to lack of available tools for detection of F2 and advanced fibrosis (F3) is targeted instead.

**Figure 2.** An algorithm of two-step testing for advanced fibrosis in primary care. Percentages that appear in the figure are based on a prevalence of advanced fibrosis of 5% and the diagnostic accuracy of non-invasive tests as outlined in Table 1.