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OPINION REVIEW

Screening for nonalcoholic fatty liver disease-when, who and how?

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is becoming a frequent liver disease, especially in patients with metabolic syndrome and especially in Western countries. Complications of NAFLD comprise progressive fibrosis, cirrhosis and hepatocellular carcinoma. NAFLD also represents an independent risk factor for cardiovascular disease, extrahepatic neoplasia and other organ damage, such as renal insufficiency. Given the epidemiological importance of the disease, new developments in specific treatment of the disease and the wide availability of noninvasive techniques in estimating steatosis and fibrosis, NAFLD should be subject to screening programs, at least in countries with a high prevalence of the disease. The review discusses prerequisites for screening, cost-effectiveness, current guideline recommendations, suitability of techniques for screening and propositions for the following questions: Who should be screened? Who should perform screening? How should screening be performed? It is time for a screening program in patients at risk for NAFLD.

Key Words: Screening; Nonalcoholic fatty liver disease; Diabetes; Liver fibrosis; Cirrhosis

Core Tip: Nonalcoholic fatty liver disease (NAFLD) is becoming more important in Western countries and leads to serious complications in patients with progressive disease. The epidemiological, clinical and technical requirements for screening for this disease are fulfilled and are outlaid in this review. It is time to consider a screening program for NAFLD.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the most common liver disease world-wide, with rising prevalence to an estimate of 25% in Western populations[1]. NAFLD is regarded as one component of metabolic syndrome, including obesity, insulin resistance or type 2 diabetes mellitus (T2DM), hypertension, and dyslipidemia. Recently, the new term metabolic dysfunction-associated fatty liver disease has been proposed to emphasize this association[2]. Over the next decade, the number of patients with advanced fibrosis stages is expected to rise further together with an increasing incidence of complications [nonalcoholic steato hepatitis (NASH)-related end stage liver disease, *e.g.* hepatic decompensation, liver cancer and mortality][3]. In this recent modeling, the number of NAFLD patients in the United States, the EU5 (France, Germany, Italy, Spain, United Kingdom) and China was estimated to be 85.3 million, 72.2 million and 211 million, respectively, whereby in the same countries, more than 17.3 million, 12.6 million and 32.6 million patients were predicted to have NASH[3]. The number of NASH patients with advanced fibrosis is expected to more than double until 2030. Similar but slightly more conservative calculations have been obtained with different modeling methodologies but confirm the extent of the clinical problem[4]. In addition to liver-related morbidity and mortality, it is important to emphasize that NAFLD patients have increased cardiovascular mortality, which to-gether cause an enormous socioeconomic impact in industrialized countries[4]. The fact that NAFLD has become the most frequent disease entity on the liver transplant waiting list in the UNOS network documents the need for early detection and in-tervention in the future[5]. Given the sheer frequency of patients with obesity, me-tabolic syndrome and NAFLD worldwide, it is remarkable that this disease entity has been overlooked by clinicians and the pharmaceutical industry for a considerable period of time, and no widely established algorithms for screening exist. The global burden of disease documents the burning need to establish clinical care structures and diagnostic algorithms to cope with the increasing number of patients at risk.

A multistep diagnostic screening algorithm is recommended in current guidelines in Western countries and combines an initial ultrasound (US) examination with sub-sequent risk prediction tools such as the Fibrosis-4 (FIB-4) or NAFLD fibrosis score (NFS) followed by transient elastography (TE) stratification for liver biopsy[6,7]. Increasing public and professional awareness as well as the implementation of scree-ning algorithms in primary and secondary care will lead to a more frequent diagnosis of NAFLD patients at different stages of the disease (NAFL, noncirrhotic NASH, NASH with cirrhosis) in the near future. For the histological assessment of NAFLD, different systems are used for scoring in clinical practice [*e.g.*, NAFLD activity score (NAS)][8]. The definite histopathological diagnosis of NAFL *vs* NASH is based on the simultaneous presence of steatosis, ballooning and inflammation, which are required for the diagnosis of "NASH" in the European SAF/FLIP algorithm[9].

Of the different histologic features of NASH, fibrosis has been identified as the strongest predictor of adverse clinical outcomes, including decompensation and liver-related death[10-14]. The latest meta-analysis showed that the stage of biopsy-con-firmed liver fibrosis is a strong predictor of future all-cause mortality and morbidity in NAFLD with and without adjustment for key potential confounding variables[15]. It became clear that evaluation of the fibrosis stage is even more fundamental than scoring necroinflammation or diagnosing NASH. Several options for the noninvasive evaluation of liver fibrosis in NASH, such as elastography devices and blood tests, are available[16]. Despite recent progress in noninvasive tests (NITs) for the evaluation of liver fibrosis in NAFLD, the diagnosis of NASH is still often based on liver biopsy, an invasive procedure not suitable for the large proportion of the general population affected by NAFLD. To identify patients with an increased risk, the NFS was in-troduced in 2007 as a simple scoring system to distinguish NAFLD with and without advanced fibrosis (fibrosis stages 3 and 4)[17]. Subsequently, further fibrosis tests, including the FIB-4 index, Fibrotest/Fibrosure, enhanced liver fibrosis (ELF) test, and liver stiffness measurement (LSM) by vibration-controlled TE, have entered clinical practice[18-21]. Of relevance for fibrosis screening, these NITs show excellent

AUROCs for the diagnosis of advanced fibrosis and cirrhosis[22]. Furthermore, repeated testing of FIB-4 within 5 years improved the identification of individuals at an increased risk of severe liver disease in the general population[23]. In light of a multistep screening algorithm, the performance has been further improved by the sequential combination of different NITs for advanced fibrosis, thereby refining the patient referral pathway between primary care or diabetologists and liver specialists [24]. Sequential combinations of FIB-4 (or NFS) and TE with a lower cut-off to rule-out advanced fibrosis and a higher cut-off to rule-in cirrhosis can increase the specificity and thereby reduce the need for liver biopsies from 33% to 19%[25]. The ultimate goal of screening measures is to identify patients at high risk for liver-related events and unfavorable overall outcomes. Longitudinal retrospective studies have demonstrated that NITs calibrated on liver fibrosis are prognostic markers to stratify the risk of liver-related outcomes and mortality in NAFLD patients[26].

Comparative diagnostic accuracy studies for established and novel biomarkers and combinations thereof are ongoing in the European LITMUS and United States NIBLE consortia[27]. It will be interesting to learn whether and which of the novel biomarkers outperforms the established freely available routine scores NFS and FIB-4. At the same time, biomarker screening strategies are currently being tested to establish validated numbers of patients to test to identify NASH patients with advanced fibrosis suitable for specific treatment.

The following review gives an overview of current guideline recommendations and answers the question of when, whom and how to screen in the different clinical settings.

RECOMMENDATIONS FOR NAFLD SCREENING IN RECENT GUIDELINES

Several guidelines worldwide have already taken a position on screening for NAFLD. The consensus is that screening in the general population is not recommended[6,7,28,29]. AASLD also discourages screening in high-risk groups because of the current lack of treatment options, unclear value of screening tests, and unclear cost-effectiveness. However, "a high index of suspicion" for the presence of NAFLD in diabetes mellitus type 2 patients is advised[7]. The Asian guideline takes a similarly noncommittal view, which also does not explicitly recommend screening in risk groups (here T2DM and obesity) but merely describes it as worth considering[29].

In contrast, specific screening recommendations can be found in the Latin American and European guidelines. Here, NAFLD screening is recommended for patients with repeatedly altered liver enzymes, features of metabolic syndrome, or obesity [body mass index (BMI) > 30] according to Latin American guidelines[28]. In the same direction, patients with insulin resistance and metabolic syndrome, especially manifest type 2 diabetes, should also be screened for the presence of NAFLD according to the European recommendation, regardless of the level of liver enzymes[6]. Both guidelines primarily recommend abdominal US as the initial examination to determine the presence of steatosis. Serum fibrosis tests are considered appropriate for further risk stratification[6,28], with the Latin American guideline decidedly recommending determination of FIB-4 and NFS. Elastography, as a more reliable method, is also mentioned[28] but is considered secondary due to its lack of availability in many places.

The guidelines differ in their treatment of patients in whom serum fibrosis scores indicate intermediate fibrosis risk. While the European algorithm recommends both high-risk and intermediate-risk patients for referral to the hepatologist[6], the Latin American guidelines suggest that this should only be the case for patients > 50 years of age with diabetes or obesity[28].

The basis of the differing recommendations is an ultimate lack of data on the efficacy and efficiency of structured screening and on the effectiveness of the therapeutic efforts that begin after NAFLD has been diagnosed in the context of screening. There are also discrepancies between the lack of widespread availability of specific examination procedures and the desire for screening results that are as sensitive and specific as possible and avoid overloading specialists by referring numerous false-positive screened patients.

SCREENING–WHEN? IS IT TIME FOR A NAFLD SCREENING PROGRAM?

Prerequisites for a disease to justify screening

In 1968, Wilson and Jungner formulated basic criteria for the usefulness of screening procedures for a particular disease in a paper by the WHO[30,31]. These criteria include peculiarities of the disease (significant burden of disease in the population and knowledge of etiology and stages of disease) and of reaching a diagnosis (simple test acceptable to patients) as well as organizational requirements (available facilities for diagnosis and therapy). In general, these criteria already apply for NAFLD for some time.

However, the authors also point out that efficient therapy as well as cost-effectiveness of screening must be present[30]. Here, important new developments have occurred in recent years that make screening for NAFLD much more justified than in the past.

The general progress in diagnosing and treating liver disease led an expert group 2016 to the proposal that screening for liver fibrosis (independent from the underlying disease) may now be feasible even for the general population[32].

For a long time, missing therapeutic options were a major argument against NAFLD screening, since lifestyle changes could only be maintained in a minority of patients and NASH-specific drugs were not even developed. In the meantime, several new drugs acting on various pathophysiological processes in NASH have entered clinical development. Current drug classes being investigated for NASH treatment are agonists of nuclear receptors such as FXR agonists (including FGF19), peroxisome proliferator-activated receptors agonists, chemokine receptor inhibitors, thyroid hormone receptor-β agonists and analogs of enterohepatic hormones such as GLP-1 and FGF21 or SGLT2 inhibitors[33]. Despite disappointment by negative interim results from three out of four recent phase 3 trials, the process of approval is ongoing for obeticholic acid as the only drug with a significant benefit in the phase 3 interim analysis. Obeticholic acid is an obvious candidate for the first conditional approval as a NASH therapeutic in the near future. However, even before approval of new drugs, NAFLD patients "at risk" should be offered to participate in ongoing clinical trials, particularly those with drug combinations, since the future will putatively be a more efficient combination therapy of two different drug classes with complementary effects[33].

Cost-effectiveness of NAFLD screening

Decisions on the target population for screening are mostly driven by cost-effectiveness and depend on the prevalence of the disease in the target population and health outcomes measured as quality-adjusted life-years (QALYs). Unfortunately, the cost-effectiveness of noninvasive liver tests in NAFLD is scarcely available in the literature.

However, the cost-effectiveness of noninvasive screening for alcohol-related liver fibrosis has been investigated in more detail[34]. For low prevalence populations, a screening strategy involving a blood-based noninvasive fibrosis test (ELF) in the first-line follow-up with LSM in intermediate- or high-risk individuals in the second-line follow-up was most cost-effective, both short- and long-term, depending on whether diagnostic testing had lasting or temporary effects on abstinence rates. The study documents that the effect of screening measures strongly depends on the therapeutic options and the size of the treatment effect. Moreover, for high-prevalence populations, direct referral to LSM was highly cost-effective.

In contrast to the growing burden of disease, a cross-sectional study of the public health response to NAFLD among experts in 29 European countries in 2018 and 2019 revealed a general lack of national policies, awareness campaigns and civil society involvement and only a few epidemiological registries[35]. Only one-third of the countries reported having national recommendations for NAFLD screening in all patients with diabetes, obesity and/or metabolic syndrome.

Data on cost-effectiveness need to be interpreted in the context of the national health system, economy and availability of treatment. Nevertheless, available data for certain diagnostic measures allow at least some general insight and can be used as part of evidence-informed decision making. As the most basic diagnostic method, ultrasonography screening for NAFLD has been found to be cost-effective in Thailand for patients with metabolic syndrome participating in an intensive weight reduction program when compared with no screening[36]. Differences in the age of the target population have been observed, since screening before 45 years was cost saving, while screening at 45 to 64 years was cost-effective.

The cost-effectiveness of LSM by TE has only been assessed in comparison to liver biopsy as the invasive reference method. In a systematic analysis covering four cost-effectiveness and four cost-utility studies[37], high-quality cost-effectiveness studies suggested that TE is less costly but also less accurate than liver biopsy (which is not surprising since histology is still regarded as the diagnostic gold standard). The incremental cost-effectiveness ratio (ICER) of TE improves with a greater level of diagnostic accuracy and a higher degree of liver fibrosis. Similar data have been obtained in a Canadian systematic review of existing TE cost-effectiveness studies from the perspective of the Ontario Ministry of Health and Long-Term Care[38]. For a primary economic evaluation, decision analytic models were used to compare short-term costs and outcomes of TE compared to liver biopsy. Again, data suggested that TE leads to cost savings but is less effective than liver biopsy in the diagnosis of liver fibrosis. Of note, TE became more economically attractive in a high-risk population with a higher degree of liver fibrosis. No studies have assessed the cost-effectiveness of TE with controlled attenuation parameter (CAP)-based fat quantification for the diagnosis of liver steatosis.

It remains open whether NAFLD screening can become cost-effective in the near future with a further increasing number of at-risk NAFLD patients in Western countries. Investigators from six prospective cohorts in Europe and Asia used patients with mostly alcohol-related liver disease to explore the cost-effectiveness of TE as a screening method to detect liver fibrosis against standard of care in a primary care pathway[39]. In 6295 participants, TE with the proposed cutoffs for the diagnosis of significant fibrosis (≥ F2) of 9.1 kPa in general population settings and 9.5 kPa in at-risk populations outperformed fibrosis scores in terms of accuracy. Screening with TE was cost-effective, with mean ICER ranging from 2570 €/QALY for a population at risk of alcohol-related liver disease (age ≥ 45 years) to 6217 €/QALY in the general population [39]. Overall, there was a 12% chance of TE screening, even though it was cost saving across countries and populations. This study clearly documents that screening for liver fibrosis with TE can be a cost-effective intervention for European and Asian populations, even in primary care, and may even be cost saving.

For various other screening tools, a comparative cost-utility model analysis of different annual noninvasive screening strategies has been conducted in Canada using a third-party payer perspective in a general population compared to screening in a high-risk obese or diabetic population[40]. The investigated screening algorithms involved the NFS, cytokeratin-18, TE and acoustic radiation force impulse (ARFI) imaging for detecting advanced fibrosis (≥ F3). Liver biopsy and magnetic resonance elastography were compared as confirmation methods. Compared with no screening, screening in high-risk obese or diabetic populations was more cost-effective than in the unselected general population. Interestingly, liver biopsy confirmation was not found to be cost-effective. These data suggest that annual NASH screening can be cost-effective in high-risk obese or diabetic populations in a Western country.

Using a different simulation model in the United States, the effectiveness and cost-effectiveness of US screening for NAFLD followed by liver biopsy has been assessed for type 2 diabetic patients[41]. In this more basic NASH screening strategy, all patients received a one-time screening US, individuals with hyperechogenicity on US underwent subsequent liver biopsy, and those found to have NASH received medical therapy to decrease disease progression. Screening for NASH decreased the number of individuals who developed cirrhosis by 12.9% and resulted in an 11.9% reduction in liver-related deaths. However, the screening strategy resulted in only 0.02 fewer QALYs due to the disutility associated with treatment and was dominated by the "no screening" strategy[41]. The impact of treatment efficacy and treatment-related side effects became clear in this study because when the model excluded the treatment-related quality-of-life decrement, screening became cost-effective. This study documents that treatment-associated side effects are relevant for quality of life and impact QALYs and the suitability of screening.

Referral strategies between primary care and secondary care by specialists have also been investigated. Given the high prevalence of NAFLD in Western countries, the optimal evaluation of NAFLD likely involves triage by a primary care physician (PCP) with advanced disease managed by gastroenterologists or hepatologists. Screening in a cohort of 10000 simulated United States-American patients with NAFLD performed in either PCP or referral clinics was simulated[42]. Risk stratification by the PCP using the NFS alone costs approximately 20% more *per* QALY than usual care costs. In the microsimulation, at a willingness-to-pay threshold of $100000, the NFS alone in the PCP setting was the most cost-effective strategy in 94.2% of samples, followed by the combination NFS/vibration-controlled transient elastography in the PCP setting (5.6%) and usual care in 0.2%[42]. This study indicates that risk stratification of pa-

tients with NAFLD in primary care is a cost-effective strategy that should be further explored in clinical practice.

Finally, the outcome of the entire diagnostic chain is relevant for decision making upon screening. This certainly includes the likelihood of referral to the specialist after obtaining a risk surrogate (which is often moderate at best), the availability of effective drugs for the target disease (in case of NASH to be established) and relevant side effects of the treatment impacting quality of life. Taking into account the emerging awareness campaigns among the public and PCPs and ongoing phase 3 treatment studies for NASH patients, it is likely that the impact of screening on the overall outcome could improve over the near future.

WHO TO SCREEN?

NAFLD is an asymptomatic disease in the early phase, often leading to a late diagnosis [43]. In a large population-based, cross-sectional study from Barcelona, the authors found elevated liver stiffness (as defined with TE > 6.8 kPa) in 9% of the participants, and NAFLD was the leading etiology (followed by alcohol risk consumption)[44]. Risk factors for elevated liver stiffness included obesity, type 2 diabetes and the presence of metabolic syndrome (each with a prevalence of elevated liver stiffness in 20%–30%). This study convincingly underlines the importance of NAFLD in the general population but especially in the known risk groups. While the prevalence of NAFLD in the general population is quite high (20%-30%), only approximately 7%-10% of NAFLD patients develop relevant complications of this disease, such as advanced fibrosis, cirrhosis or hepatocellular carcinoma (HCC)[45,46] (Figure 1). Thus, screening the entire population cannot (yet) be justified because too many patients would suffer overdiagnosis and possibly overtherapy. For advanced testing or invasive diagnostic measures such as liver biopsy, which applies to a selected patient population of still 3%-5%, primary testing to rule out low-risk individuals appears mandatory.

These numbers from the general population, however, do not apply to patient groups with increased NAFLD prevalence and increased risk for advanced disease. In the presence of the risk factors diabetes and obesity, the prevalence of NAFLD increases to 75%[47,48]. Diabetes and obesity are clear independent risk factors for the development of NASH-related fibrosis[46,47] and other factors of the metabolic syndrome are closely associated[49]. In addition, patients with these underlying diseases are more likely to develop complications of NAFLD[48]. Consequently, screening in the group of patients with these risk factors for complications is particularly important[50]. Elevated liver enzymes alone are sufficient as a reason for screening but are not sufficient as a sole decision criterion, as relevant NAFLD with fibrosis or cirrhosis may be present even with normal transaminases[51-53].

These facts warrant screening of this risk population[54], especially at higher HbA1c levels[54]. In some cohorts, patients with NAFLD also had an older age > 50 years in addition to the above risk factors[55-57], and an increased prevalence of NAFLD and advanced fibrosis has been shown in men[57]. These risk factors reflect quite well the collective for which screening for NAFLD is repeatedly discussed in the current literature or even concrete recommendations exist[6,7,28,29].

NAFLD is linked to several other diseases and is connected to metabolic disturbances. It is straightforward to consider the presence of NAFLD in patients with such concomitant diseases, one of the most important being coronary heart disease. Additionally, NAFLD should also be considered, depending on the advancement of the respective disease, in diseases such as polycystic ovary syndrome, sleep apnea, hypothyroidism, depression, renal insufficiency or psoriasis[7,58-60]. Making a specific screening recommendation for these patients is probably not warranted at this time; further risk profiles are needed here to justify such screening in selected patient groups with these diseases.

General screening of close relatives is also not reasonable despite some familial clustering and genetic factors (*e.g.*, *PNPLA3*[61]) that may influence the course of NAFLD. The penetrance of these genetic risk factors is too low to justify screening in the presence alone (RR 3.26 for the histological presence of NAFLD *per* effect allele [62]). However, relatives with the presence of the abovementioned risk factors should definitely be screened for the presence of NAFLD[6]. Screening with diabetes type 2 as a central risk factor again has very recently been shown to be cost effective in the United States by avoiding advanced liver-specific disease and endpoints (all calculated screening models based on US and AST, with an ICER between $17000 and $35000/QALY[63], see also *Cost-effectiveness of NAFLD screening*).
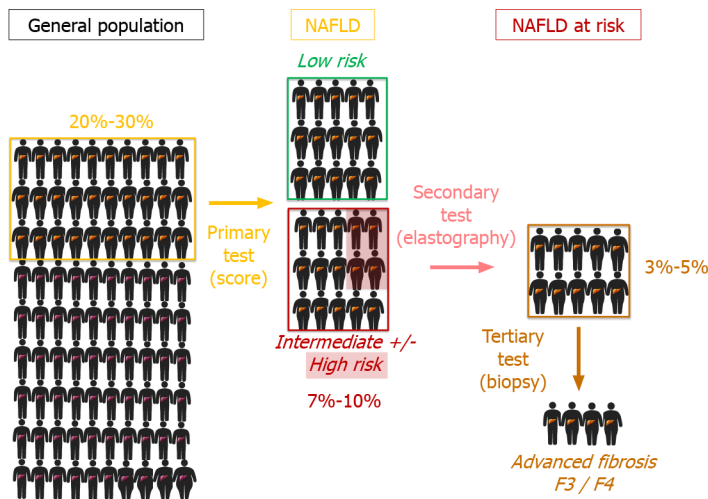
Figure 1 Nonalcoholic fatty liver disease patient proportions according to risk assessment. Stepwise enrichment of nonalcoholic fatty liver disease (NAFLD) patients at risk for advanced fibrosis using a three-step strategy with score-based primary testing in a subgroup of the general population at risk for NAFLD and elastometric secondary testing to identify candidate patients for liver biopsy represents the third and final step in most algorithms. Patients with a diagnosis of NAFLD by either surrogate scores or ultrasound (20%-30% of the general population) are divided into low-risk *vs* intermediate-to-high-risk subgroups (the latter 7%-10% of the general population). After elastometry testing, half of these subjects can be assigned to a high likelihood of advanced fibrosis F3/F4 and should be subjected to liver biopsy. NAFLD: Nonalcoholic fatty liver disease.

WHO SCREENS?

A decision about who carries out screening is determined by the care structures of a particular health care system rather than by the efficacy of particular screening procedures. Even if certain diagnostic procedures proved to be cost-efficient for screening (*e.g.*, LSM as shown above in section 3), the lack of a broad availability of LSM-determining procedures may preclude its application. Consequently, more broadly available blood-based tests are needed, and the design of a screening algorithm must then be aligned with the capabilities of those performing the screening[64-66].

In many countries, almost all patients are primarily cared for by PCPs. A certain proportion of patients defined in the at-risk population (see above) are assigned to specialists (diabetologists/endocrinologists, cardiologists), but numerous patients with diabetes mellitus, obesity, and arterial hypertension are also treated exclusively by PCPs (*e.g.*, in the context of so-called disease management programs). In Europe, screening algorithms are implemented in a total of only 5 countries and are located in the primary health care sector in all of these countries (Belgium, Denmark, Czech Republic, Slovakia, and United Kingdom[35]). However, there are sometimes considerable structural differences in the health care systems of these countries.

Due to access to patients, comprehensive risk population screening in many countries can only be in the hands of PCPs, possibly supported by diabetologists and cardiologists. This group of physicians is particularly suited to broadly identify the major risk diseases for NAFLD and thus to determine the individual NAFLD risk in these patients[67]. This assessment is also in line with existing EASL recommendations [6] and a recently developed algorithm for general practitioners and diabetologists [68]. Direct referral of all patients at risk to hepatologists is not feasible. The need for a screening filter at the primary care level to prevent unnecessary referrals to specialists is shown by data from England ("Camden and Islington NAFLD pathway"[69]) and the United States[70]. In both studies, almost 90% of unnecessary referrals could be avoided by structured screening at the primary care provider level. On the other hand, in an American study, more than 25% of NAFLD patients referred to a hepatologist without screening already had advanced fibrosis (characterized as at least F3 with TE measurement[54]).

Data on awareness of NAFLD at GP level are rare. In the United States, data from the United States Veteran Affairs Database showed that NAFLD is significantly underdiagnosed in primary care patients[71]. Patients with abnormal alanine aminotransferase (ALT)/glutamate pyruvate transaminase (GPT) without other known liver disease (viral hepatitis and alcohol use were largely excluded by data analysis) were detected in only 40% of cases in this study, received a suspected diagnosis of NAFLD in only 21%, received therapeutic counseling in only 15% and were referred to a specialist in only 3% of cases. Initially, there is no reason to assume that the situation

in other countries differs significantly from these results. A study by the professional association of gastroenterologists in private practice in Germany (bng) showed for a cohort of NAFLD patients in secondary care that approximately 10% of these patients already had advanced fibrosis according to FIB-4 screening, but even these patients were not consistently counseled or guided regarding therapy[55]. Only 27% of patients with presumed advanced fibrosis in this study received nutritional counseling. In this respect, education and training activities for PCPs are definitely necessary to increase awareness of the presence and risks of NAFLD and to create acceptance for screening. Diabetologists and cardiologists should also be included by these measures, as they should also be involved in screening due to their spectrum of patients they treat.

Integration of primary care identification of patients at risk for the presence of NAFLD, particularly with advanced fibrosis, into secondary testing facilities at a specialist setting is a crucial issue for the overall efficacy of a screening algorithm (Figure 2). Dedicated elastography platforms have been established at several places, such as in our own center[72]. The likelihood of referral of "intermediate or high risk" individuals to secondary care, the proportion of subjects with "indeterminate" test results (the so-called "gray zone" of respective score-based tests) and the availability of advanced testing platforms for referral are relevant factors at this interface. As pointed out, existing or emerging networks between PCPs and specialists are key to optimizing a bidirectional transition into secondary testing and, in case of "low risk", back to long-term observation and basic treatment in a primary setting.

HOW TO SCREEN?

Value of transabdominal ultrasonography of the liver in NAFLD

US is a widely available, cost-effective, radiation-free method that allows assessment of hepatic fatty degeneration[73]. Hepatic fatty degeneration results in an increase in the echogenicity of the liver parenchyma (*e.g.*, compared with the renal parenchyma). US is thus suitable as a screening method for NAFLD. However, steatosis below 10% of hepatocytes is not detected, and up to 20% is unreliably detected[74] (especially with microvesicular fatty degeneration). In moderate and severe hepatic steatosis, good sensitivity (85%-96%) is achieved with specificity up to 98%[75]. The best results are seen above a liver fat content of 12.5%, where AUROC values under consideration of different echographic parameters reached comparable results to H-magnetic resonance spectroscopy (MRS)[76]. With the above referenced threshold, exclusion of steatosis by US is not completely possible. With regard to possible fibrosis of the liver, US diagnostics do not allow reliable determination and staging[73].

Noninvasive measurement of hepatic steatosis and fibrosis by elastography

US-based shear wave elastography techniques are well suited as a method for measuring liver stiffness to detect or exclude advanced liver fibrosis and cirrhosis in NASH. In addition, FibroScan, for example, now also offers the possibility of quantifying the fat content of the liver *via* the measurement of additional parameters.

The CAP measurement integrated in the FibroScan achieved AUROC values between 0.7[77] and 0.84[78] in studies with more than 400 patients each for (histologically confirmed) steatosis of > 33% and > 66%.

Different elastography techniques are now available on the market, and a differentiated overview cannot be given here but is available elsewhere[79]. While TE using FibroScan requires the purchase of a dedicated device, other techniques, such as ARFI imaging (Siemens), Elast-PQ (Philipps), and supersonic shear-wave elastography (SWE, Aixplorer), offer the advantage of being integrated into routine US equipment [73].

In large cohorts from Europe and Asia, the reliability of TE, its superiority over fibrosis scores, and even its cost-effectiveness have been demonstrated, at least for certain at-risk populations, in determining liver fibrosis of different origins[39]. TE is also well suited for quantifying fibrosis in NAFLD. Here, sensitivity, specificity, and AUROC values improve as fibrosis progresses, reaching values of approximately 92% and 0.89 for cirrhosis (F4), respectively[77,80]. Difficulties in estimating fibrosis in obese patients with the normal (M) probe[81] were countered by the company's introduction of an XL probe for particularly obese patients, which provides reliable values and is automatically chosen if the patient has appropriate physical conditions [82,83].

Apart from slight differences in patients with different body types, the diagnostic value of the different elastography methods in determining liver fibrosis in NAFLD
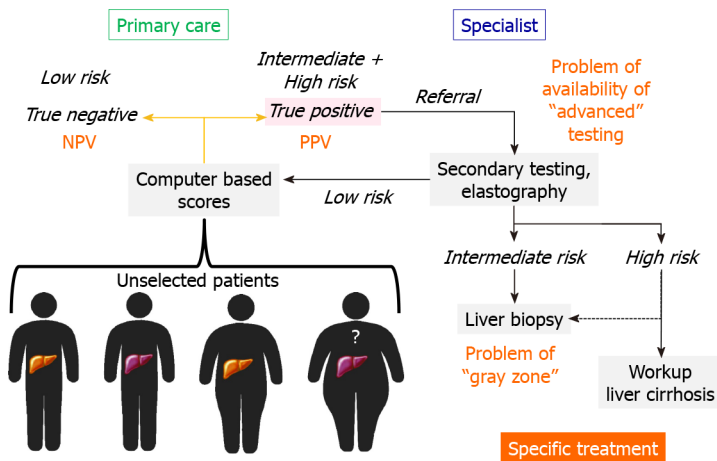
Figure 2 Linking primary care to hepatology. Unselected patients from the general population are most likely in contact with primary care. In primary care, patients at risk for the presence of nonalcoholic fatty liver disease and according to computer-based scores at risk for advanced fibrosis should be transferred into secondary testing facilities at a specialist setting. Critical for the overall efficacy of a screening algorithm are the likelihood of referral of "intermediate or high risk" individuals to secondary care, the proportion of subjects with "indeterminate" test results ("gray zone" of score-based tests) and the availability of advanced testing platforms for referral. NPV: Negative predictive value; PPV: Positive predictive value.

patients appears to be similar. Several studies with different populations and study designs yielded similar AUROC values for TE, SSI, ARFI, and 2D-SWE[84-86]. However, problems with a tendency to overestimate fibrosis occurred in bariatric, extremely obese (median BMI 47 kg/sqm) patients for both TE and ARFI, where the ELF score was actually superior to these two elastography methods[87]. Nevertheless, the procedures should also be well suited for screening most patients. The availability of the methods is very heterogeneous, so broad screening with elastography is currently not possible.

Value of magnetic resonance imaging and computed tomography in the diagnosis and screening of NAFLD

The availability of computed tomography (CT) is bound to institutions with large medical devices but is well reproducible and reliably determines the fat content of the liver by measuring organ density[73]. In a meta-analysis comparing different radiological methods, CT performed rather modestly with a sensitivity of 46%-72%[88]. At least moderate hepatic fatty degeneration can be diagnosed if the density ratio of the liver and spleen on native CT has a cutoff value > 1.1[89]. Dual-energy CT has been able to show promising results for quantifying fat content in the liver in smaller cohorts, even in comparison with magnetic resonance imaging[90]. However, such techniques are poorly validated and not widely available. Overall, CT should not be used as a primary screening method for detecting NAFLD because of its cost, lack of broad availability, and substantial radiation exposure.

Magnetic resonance imaging (MRI), though also a large medical device, is a radiologic imaging modality without any radiation exposure. Certain modalities of MRI can be used to determine both the fat content of the liver and the fibrosis stage quite reliably[73]. MR-based quantification of liver fat content using proton density fat fraction (PDFF) has high linearity and precision with simple postprocessing[91], but it is also not suitable for screening large risk groups because of cost and effort[92]. Compared with histology as a reference standard and in comparison to CAP, PDFF-based determinations have a higher diagnostic accuracy for detecting steatosis (histological grade 1-3) with an AUROC of 0.96 up to 0.99, a sensitivity of 96%, and a specificity of 100%[93,94]. MRS has the highest accuracy for fat assessment in the literature[88,92,95] but is currently limited to research centers due to a lack of standardization of methodology and high costs for hardware and software requirements [73].

MR elastography measures liver stiffness significantly more reliably than US-based elastography techniques[85,96]. In a biopsy-controlled study of 100 patients, an AUROC of 0.98 was achieved at 40 Hz[97]. A joint analysis from 12 studies with over 900 patients still showed summary AUROC values of 0.93-0.95[98]. MR elastography also correlated better to clinical fibrosis parameters and scores than TE[99] but remains restricted to specialized centers[92].

Multiparametric MRI with determination of fat content (by PDFF or spectroscopy) and fibrosis (by MR elastography) was superior to the respective FibroScan-based non-MR methods (CAP for steatosis and TE for fibrosis) in a comprehensive new study [100] and cost-effective for risk stratification of NAFLD in a United Kingdom study [101]. Nevertheless, these methods are not (yet) suitable for broad screening due to lack of availability and high costs.

Laboratory chemistry scores

Because screening must be performed primarily by PCPs, screening tools must be widely available, inexpensive, and noninvasive[58,66,67]. This allows screening to be performed on a day-to-day basis and, more importantly, increases the acceptance of screening by the physicians performing it. The two-step design with the verification of steatosis and fibrosis risk improves the specificity (and in some cases even the sensitivity) of screening[65,102]. Positively screened patients must be transferred to a hepatologist for further evaluation. In this context, the proportion of positively screened patients should not be too large to avoid overloading hepatologists[65,103]. The extent of the diagnostic "gray zone" is of particular importance in this regard and can vary substantially from test to test. In any case, however, patients with prolonged or repeated elevations of GPT/ALT should be referred for further evaluation (as is usually the case), as they are generally at increased risk for liver disease or injury[51, 104,105].

There are significant differences between different countries and health care systems in the availability and cost-effectiveness of different screening tools. However, despite the limited sensitivity of US, this procedure is an attractive screening option for PCPs because of its ease of performance. More technically sophisticated and sensitive procedures such as CAP or elastography are generally not available at this level of care.

Steatosis scores correlate with insulin resistance. Their diagnostic performance for steatosis depends on the degree of fatty degeneration, fibrosis, and inflammation[106]. Assuming at least moderate steatosis is relevant, the performance of the fatty liver index (FLI) and NAFLD liver fat score is best, with the highest AUROC values with a positive predictive value of 99%, but without safe exclusion of steatosis below the cutoff[106-108]. Only the FLI can easily be obtained from routine values in family practice (see Table 1) and should therefore be used when US is not feasible[109].

Fibrosis scores also vary in both availability and quality of information. In this regard, the sensitivity and specificity of each score for significant fibrosis, advanced fibrosis, and cirrhosis are quite different and additionally vary depending on the population screened (population screening *vs* high-risk screening *vs* screening of confirmed NAFLD)[110]. Scores that require the determination of expensive specialty laboratory parameters are not suitable for primary care screening, nor are scores that include, at least in part, unavailable laboratory parameters or instrumental procedures. Although these special scores are superior to routine scores, as expected[111], and would also improve specificity in combination with them[112], the lack of availability and the lack of acceptance of these special scores by general practitioners, based in part on complicated determination, hinder their widespread use. This applies, for example, to the ELF test[113] (hyaluronic acid, TIMP-1, and procollagen peptide), which is of similar prognostic value to liver biopsy[114], and the fibrometer VCTE test (with elastography), which is also superior to purely laboratory chemistry-clinical indices [24].

Scores with readily available routine parameters for fibrosis risk include NFS, FIB-4 score, APRI score, Forns score, and BARD score. The first two (NFS, FIB-4) are superior to the last three (APRI, Forns, BARD) in screening fibrosis in the NAFLD cohort[115,116]. In a recent systematic review, this could be confirmed, especially for the hardest endpoint (mortality)[117]. These two scores (FIB-4 and NFS) are also suitable for screening patients with normal ALT[118] and can be easily determined *via* internet-based calculators.

In population screening, all scores have significant weaknesses and are therefore of limited use for this question[110]. However, the discriminatory performance of all tests is significantly better in high-risk collectives[110]. Although the FIB-4 score was initially developed for the detection of hepatitis C virus fibrosis[119], it has since been validated[120] and compared[121] in NAFLD collectives and may be considered suitable in principle for liver fibrosis of other etiologies. The FIB-4 score has an additional advantage over the NFS in that no albumin value is needed and that the proportion of intermediate tested patients is somewhat smaller[65,116]. However, both scores have lower specificity in patients > 65 years of age[122], which may increase the referral rate to the specialist due to a higher proportion of false-positive screened

Table 1 Scores for diagnosing steatosis and fibrosis with parameters used

Scores for Steatosis	Routine parameters											Special parameters		
	AST	ALT	yGT	Platelets	TG	Bilirubin	BMI	Waist	Age	Sex	Diab.	A2M	HA	Other
FLI			X		X		X	X						
HSI	X	X					X			X	X			
Steato-Test		X	X		X	X			X	X	Gluc	X		Apo-A1, Haptoglobin, Cholesterol
NAFLD-LFS	X	X									X			Insulin
VAI					X		X	X						
TyG					X						Gluc			
Scores for fibrosis														
NFS	X	X		X			X		X		X			Albumin
FIB-4	X	X		X					X					
APRI	X			X										
ELF													X	PIIINP, TIMP-1
Fibrotest		X	X			X						X		Haptoglobin, Apo-A1
Fibrometer (V2G) ((V3G))	X		((X)), for HA	X					X	(X)		X	X	Prothrombin, Urea
NIKEI	X	X				X			X					

New fibrometer versions (V2G, V3G) and their respective parameters labeled with brackets: (V2G) and ((V3G)). AST: Aspartate-aminotransferase; ALT: Alanine-aminotransferase; yGT: gamma-glutamyltransferase; TG: triglycerides; BMI: Body mass index; Diab.: Diabetes; A2M: Alpha-2-microglobulin; HA: Hyaluronic acid; Gluc: Glucose; PIIINP: Procollagen-III-peptide; TIMP-1: Tissue inhibitor of metalloproteinases I; Apo-A1: Apo-A1-lipoprotein; FLI: Fatty liver index; HIS: Hepatic steatosis index; NAFLD-LFS: Nonalcoholic fatty liver-liver fat score; VAI: Visceral adiposity index; TyG: Triglyceride and glucose index; NFS: NAFLD fibrosis score; FIB-4: Fibrosis-4; APRI: AST-platelet-ratio index; ELF: Enhanced liver fibrosis; NIKEI: Noninvasive Koeln-Essen-index.

patients. Data from a screening study of type 2 diabetes patients show that the use of age-adjusted cutoffs on FIB-4 (in delineating negative *vs* intermediate) reduces the number of patients tested intermediate (from 38.3% to 15.4%[65]). Repeated measurements of laboratory scores could also help to identify patients at risk of severe liver disease in the general population, as was recently shown for repeated measurements of FIB-4 within 5 years[23].

The screening strategy proposed in Figure 3 relies on recent proposals and takes into account the aforementioned prerequisites of high-risk screening by PCPs but may not currently be evidence-based in several areas. In particular, this concerns the handling of the intermediate-risk group, the screening interval in low-risk patients, and the cost-effectiveness of the entire algorithm. In addition, the screening recommendation given requires further education and possibly training of PCPs about the prevalence and prognosis of NAFLD.

CONCLUSION

It is time for NAFLD screening. NAFLD is hard to diagnose in the early phase of the disease. The prevalence of this disease is increasing in countries with Western lifestyles, and the complication rate (inflammation, fibrosis, cirrhosis and HCC) is high in patients with metabolic dysfunction. Additionally, there are inexpensive noninvasive tools for the diagnosis of steatosis and fibrosis, leading to a reliable identification of persons at risk who can be referred to hepatologists. Apart from lifestyle modification, there are evolving drug treatments shortly before approval or in the late phases of clinical trials.
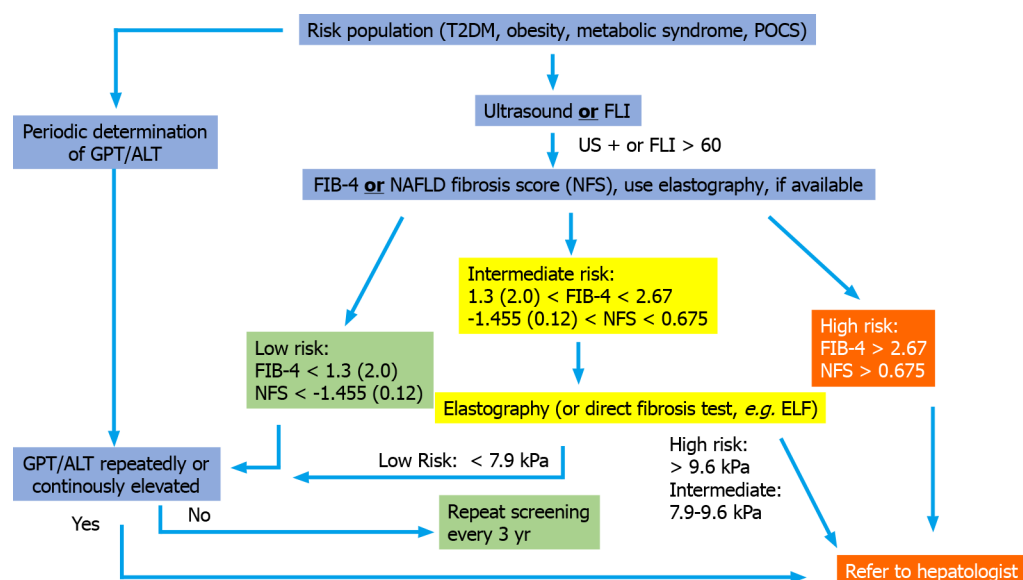
Figure 3 Possible screening algorithm that can be modified according to availability but contains the two main elements (detection of steatosis and fibrosis risk) and can be performed in the primary care physician's office. The algorithm corresponds well to the so-called European algorithm of the EASL-EASD-EASO Clinical Practice Guidelines[6] and to a recently proposed approach for family physicians and diabetologists[68] but is simpler to use. The sequences of fatty liver index and Fibrosis-4 (FIB-4) have been decisively studied for screening in a high-risk population of type 2 diabetes patients[65]. The use of age-adjusted cutoff values (in parentheses) is reasonable to reduce the high proportion of intermediate tested individuals. The sequential use of FIB-4, nonalcoholic fatty liver disease fibrosis score or enhanced liver fibrosis in the intermediate group has not been investigated in studies so far, but there are first studies on the basic sequential use of noninvasive fibrosis scores[123]. FLI: Fatty liver index; FIB-4: Fibrosis-4; T2DM: Type 2 diabetes mellitu; NFS: Nonalcoholic fatty liver disease fibrosis score; GPT: Glutamate pyruvate transaminase; ALT: Alanine aminotransferase.

Studies show that screening for NAFLD, at least for a risk population, is cost effective and will help to prevent serious hepatic consequences of pandemic metabolic dysfunction. However, it will not be easy to implement comprehensive screening programs in all countries since there are large structural differences between national health systems. For example, the extent of availability of elastography will decide in each country, whether this promising technique can be used in broad screening approaches or whether US and lab scores will be necessary for PCPs to conduct screening for NAFLD. Therefore, each screening algorithm (as the one depicted in Figure 3) should be adapted locally depending on the broad availability of methods for detecting steatosis and fibrosis. Additionally, the screening population (*i.e.* the patients with an amount of risk factors high enough for qualifying for the screening program) has to be determined in each country individually depending on the epidemiology of NAFLD in this country.

So what is to be done? We have to increase awareness for NAFLD and its consequences in the population and in primary care. National professional gastroenterology and hepatology societies have to develop guidelines for screening programs depending on the structure of the population and health care system of their respective country. National health systems must implement reimbursement for the tools needed for reliable screening. Hepatologists should prepare for rising numbers of patients referred for risk stratification and specific counseling.

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