DR. PERE GINES (Orcid ID : 0000-0003-4657-4504)

DR. ALINA M. ALLEN (Orcid ID : 0000-0002-8393-8410)

DR. VINCENT WAI-SUN WONG (Orcid ID : 0000-0003-2215-9410)

DR. ROBERT DE KNEGT (Orcid ID : 0000-0003-0934-6975)

PROF. EMMANUEL A TSOCHATZIS (Orcid ID : 0000-0001-5069-2461)

PROF. JÖRN M. SCHATTENBERG (Orcid ID : 0000-0002-4224-4703)

PROF. INDRA NEIL GUHA (Orcid ID : 0000-0002-6940-5861)

PROF. NURIA FABRELLAS (Orcid ID : 0000-0001-6720-0291)

DR. ANN THU MA (Orcid ID : 0000-0002-9059-111X)

PROF. PHILIP N NEWSOME (Orcid ID : 0000-0001-6085-3652)

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pgines@clinic.cat

CONCISE REVIEW

POPULATION SCREENING FOR LIVER FIBROSIS: TOWARDS EARLY DIAGNOSIS AND INTERVENTION FOR CHRONIC LIVER DISEASES

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Pere Ginès[1,2,3,4] Laurent Castera[5,6,7], Frank Lammert[8,9,10], Isabel Graupera[1,2,3,4], Miquel Serra-Burriel[11], Alina M. Allen[12], Vincent Wai-Sun Wong[13], Phillipp Hartmann[14], Maja Thiele[15], Llorenç Caballeria[16], Robert J. de Knegt[17], Ivica Grgurevic[18], Salvador Augustin[3],[19,20,], Emmanuel. A Tsochatzis[21], Jörn M. Schattenberg[22], Indra Neil Guha[23], Andrea Martini[24] , Rosa M Morillas [3,20,25,] Montserrat Garcia-Retortillo[26], Harry J de Koning[27], Núria Fabrellas[2,28], Judit Pich[29], Ann T Ma[1,2,4], Mª Alba Diaz[30] Dominique Roulot[31]. Philip N Newsome[,32,33], Michael Manns[8], Patrick S. Kamath[12], and Aleksander Krag[15], ***for the LiverScreen Consortium Investigators***. *****

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Affiliations

[1]Liver Unit Hospital Clínic,

[2] Institut D'investigacions Biomèdiques August Pi I Sunyer (IDIBAPS),

[3]Centro de Investigación En Red de Enfermedades Hepáticas Y Digestivas (Ciberehd), Barcelona, Spain;

[4]Dept of Medicine, Faculty of Medicine and Health Sciences, University of Barcelona, Spain.

[5]Department of Hepatology, Hôpital Beaujon, Assistance Publique-Hôpitaux de Paris, Clichy, France

[6]Université de Paris, Paris. France

[7]Inserm UMR 1149, Centre de Recherche Sur L'inflammation, Paris, France.

[8]Department of Medicine II, Saarland University Medical Center, Homburg, Germany.

[9]Institute for Occupational Medicine and Public Health, Saarland University, Homburg, Germany

[10] Health Sciences, Hannover Medical School MHH, Hannover, Germany

[11]Epidemiology, Statistics, and Prevention Institute, University of Zurich, Switzerland

[12]Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine and Science, Rochester, Minnesota, USA

[13]The Chinese University of Hong Kong, Dept. of Medicine and Therapeutics, Hong Kong

[14] Division of Gastroenterology, Hepatology & Nutrition, Department of Pediatrics, University of

California San Diego,La Jolla, USA
[15] Centre for Liver Research, Department of Gastroenterology and Hepatology, Odense University Hospital, and Institute for Clinical Research, University of Southern Denmark Odense, Denmark
[16]USR Metropolitana Nord, IDIAP Jordi Gol, ICS Institut Català de la Salut, Spain.
[17]Department of Gastroenterology and Hepatology, Erasmus MC University Medical Centre, Rotterdam, the Netherlands
[18] Department of Gastroenterology, Hepatology and Clinical Nutrition, University Hospital Dubrava, University of Zagreb School of Medicine and Faculty of Pharmacy and Biochemistry, Zagreb, Croatia
[19]Liver Unit, Department of Internal Medicine, Hospital Universitari Vall d´Hebron, Vall d'Hebron Institut de Recerca (VHIR) , Vall d'Hebron Barcelona Hospital Campus, Spain.
[20]Universitat Autònoma de Barcelona, Barcelona, Spain.
[21] UCL Institute for Liver and Digestive Health, Royal Free Hospital, University College of London (UCL), London, UK.
[22] Metabolic Liver Research Program, Department of Internal Medicine I, University Medical Centre of the Johannes Gutenberg-University Mainz, Mainz, Germany.
[23]NIHR Nottingham Biomedical Research Centre, Nottingham University Hospitals NHS Trust and the University of Nottingham, Nottingham, UK.
[24] Unit of Internal Medicine and Hepatology (UIMH), Dept. of Medicine (DIMED), University-Teaching Hospital of Padova, Italy
[25]Liver Unit, Hospital Germans Trias i Pujol, IGTP, Badalona, Spain
[26] Liver Section, Gastroenterology Department, Hospital del Mar, Departament of Medicine, IMIM, Barcelona, Spain
[27] Department of Public Health, Erasmus University Medical Center, Rotterdam, the Netherlands
[28]School of Nursing, Faculty of Medicine and Health Sciences, University of Barcelona,Spain.
[29]Clinical Trial Unit, Hospital Clínic, 08036 Barcelona, Spain.
[30.] Department of Pathology. Centre of Biomedical Diagnosis. Hospital Cínic. Barcelona, Spain
[31]Unité d'Hépatologie, Hôpital Avicenne, AP-HP, Université Paris 13, Bobigny, France
[32] European Association for the Study of the Liver (EASL), Geneva Switzerland.
[33]National Institute for Health Research Biomedical Research Centre at University Hospitals Birmingham NHS Foundation Trust and the University of Birmingham, UK.

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SUMMARY

Cirrhosis, highly prevalent worldwide, develops after years of hepatic inflammation triggering progressive fibrosis. Currently, the main etiologies of cirrhosis are non-alcoholic fatty liver disease (NAFLD) and alcohol-related liver disease (ALD), although chronic hepatitis B and C infections are still major etiological factors in some areas of the world. Recent studies have shown that liver fibrosis can be assessed with relatively high accuracy non-invasively by serological tests, transient elastography, and radiological methods. These modalities may be utilized for screening for liver fibrosis in at-risk populations. Thus far, a limited number of population-based studies using non-invasive tests in different areas of the world indicate that a significant percentage of subjects without known liver disease (around 5% in general populations and a higher rate –18 to 27%- in populations with risk factors for liver disease) have significant undetected liver fibrosis or established cirrhosis. Larger international studies are required to show the harms and benefits before concluding that screening for liver fibrosis should be applied to populations at risk for chronic liver diseases. Screening for liver fibrosis has the potential for changing the current approach from diagnosing chronic liver diseases late when patients have already developed complications of cirrhosis to diagnosing liver fibrosis in asymptomatic subjects providing the opportunity of preventing disease progression.

Cirrhosis is the 11th commonest cause of death globally accounting for an estimated 2 million deaths per year (1) with data from the Global Burden of Disease Study indicating cirrhosis deaths have risen from 899 000 to more than 1·32 million from 1990 to 2017 (2). Moreover, there is marked geographical variation with Central Asia having the highest age-standardized death rate (39 deaths [36.2-41.5 95% CI] per 100,000 population) in contrast to the lowest rates seen in Australasia (5.4 [4.9-6.0 95% CI] per 100,000 population) (2).

Approximately 75 million individuals worldwide have an alcohol-use disorder putting them at risk for alcohol-related liver disease (ALD). With over 2 billion adults being obese/overweight and over 400 million with diabetes, the increase in age-standardized prevalence of compensated and decompensated cirrhosis has been higher with non-alcoholic fatty liver disease (NAFLD) as compared with other etiologies of liver disease (increase of 33% for compensated cirrhosis and 55% for decompensated cirrhosis, with NAFLD as compared to other etiologies of cirrhosis) (2). The recognized interaction between obesity and alcohol will contribute further to a marked increase in liver disease including hepatocellular carcinoma (HCC) which now accounts for 3.5% of all deaths worldwide (3). The absolute burden of viral hepatitis has also increased, although the availability of effective vaccines and treatments may reduce the burden of these diseases in the years to come.

In terms of morbidity, cirrhosis is now the 7th leading cause of disability associated life years (DALY) in people aged 50-74 years and the 12th cause in the 25-49 age range (4), with annual in-hospital costs for cirrhosis in the U.S. alone accounting for over $10 billion (5). Thus, there is an urgent need to try to identify patients with chronic liver diseases (CLD) at an earlier stage and intervene effectively before they progress to cirrhosis and decompensation and/or HCC.

This review article discusses the rationale and available evidence for screening for liver fibrosis in the population.

Rationale for screening for liver fibrosis

In order to justify the application of a screening policy by health authorities, the 10 criteria of Wilson and Jungner are often still seen as guiding principles (table 1). CLD with a long asymptomatic phase before cirrhosis develops, is characterized by a relatively well-defined natural

history and a high death rate, meeting the first three criteria (6). Most patients at risk of CLD, however, are seen in primary care where optimal diagnostic strategies are undefined.

In population screening, the sensitivity and specificity of the test used is paramount for minimizing the risk of false negative and false positive cases, respectively. Conventional liver tests, such as serum aminotransferases, have poor sensitivity and specificity for identifying cirrhosis, and a liver biopsy is too invasive for a screening test. Non-invasive tests of fibrosis, such as transient elastography (TE) or serum biomarkers, are widely available and well validated for this purpose, with good acceptability (7). However, longitudinal data using these tests for screening are scarce. Finally, screening using non-invasive tests may be cost-effective but requires validation (8).

Early diagnosis of CLD enables initiation of specific measures or treatments to prevent disease progression and improve survival, including antiviral therapy for HBV or HCV, alcohol abstinence in ALD and behavioral changes and treatment of diabetes and obesity in NAFLD. In addition, patients with cirrhosis, once diagnosed, require surveillance for varices and HCC.

Non-invasive tools for population screening

A key challenge is that a test's performance varies with prevalence of the disease. This is the "spectrum effect", meaning that in low prevalence populations the sensitivity and the positive predictive value are lower. Further, any test, depending on the nature of the test and the chosen cut-off, is associated with false positive and false negative test results, an inherited limitation of binary decision making. A step-wise algorithm of combining noninvasive tests could reduce the rate of false positive tests (9). In addition, it is important to recognize the limitation of liver biopsy as reference standard and the potential variability of all blood based biomarkers (10) which can challenge the potential as screening tool.

Hagström et al. found only modest prognostic performance (AUROC from 0.54-0.71) of five indirect markers of fibrosis (APRI, FIB-4, BARD, Forns and NFS) to predict future development of cirrhosis and severe liver disease in the general population (11). More successful approaches involve TE, which has been applied as screening tool in >6,000 people from population studies from France, China, Spain and the UK (12-15). TE was in general acceptable, and after availability of the XL probe, which was designed to obtain accurate values for obese subjects, reliable results were obtained in >97% of participants. However, the true diagnostic accuracy with liver biopsy as gold standard is less investigated in the screening setting. In a subgroup analysis of

a biopsy-controlled study, TE had a sensitivity of 86% and specificity of 97% in a population where 6% had advanced fibrosis (15). Some of the tools that could be used in population screening are shown in table 2. Enhanced liver fibrosis test (ELF) has also been proposed, but studies with information about its potential as screening tool of fibrosis are limited (16,17).

Prevalence of liver fibrosis in general population in different parts of the world

Europe

A limited number of studies have reported results on liver fibrosis screening using different non-invasive methods and cutoffs (table 3) (11,12,14,18-24). Liver fibrosis detection rates ranged between 0.7% and 7.5% in populations-based cohorts vs 18-27% in cohorts at risk for CLD (25). Prevalence of cirrhosis reported in half of the studies ranged from 0.25 to 0.76%. NAFLD was the main cause of liver fibrosis in all studies.

North America

Between 1988 and 2016, NAFLD prevalence increased from 20.0% to 31.9%, while that of chronic hepatitis C decreased nearly twofold: 1.6% to 0.9% and chronic hepatitis B and ALD remained stable: 0.3%–0.4% and 0.8%–1.0%, respectively (26).

In NAFLD, prevalence estimates of advanced fibrosis have ranged between 3.2% and 10.3%, depending on the assessment method and population (27,28).

Asia

Despite the success of universal infant vaccination and antiviral therapy, chronic hepatitis B affects 0.6-9.8% of the general population and remains a leading cause of cirrhosis and HCC. NAFLD now affects 29.6% of the general population (29). Alcohol consumption is also on the rise.

Few studies have determined the prevalence of liver fibrosis, both in general population and at risk populations (supplementary table 1). Studies from Hong Kong reported increased TE values suggestive of advanced fibrosis in 2% and 17.7% of these two populations, respectively (13,30).

Other parts of the world

A Markov simulation based on obesity data in Australia projects a 25% increase in NAFLD by 2030, with 85% increase in cirrhosis and NAFLD-related liver deaths (31). Most cirrhosis deaths

in Latin America are due to alcohol, except for tropical Latin America where the major cause of cirrhosis is hepatitis C. No data on population screening for liver fibrosis are available from Latin America or Africa**.** In Africa, the major causes of death due to cirrhosis are hepatitis B and hepatitis C (2).

Potential strategies for screening and Limitations

A major reason for the low proportion of patients with early diagnosis of advanced fibrosis and/or cirrhosis is the lack of referral pathways, even if elevated liver enzymes are identified in primary care. In addition, the care pathways for ALD or NAFLD are not always well structured. In general, strategies for early diagnosis of CLD, advanced fibrosis and/or cirrhosis can be designed as population-based or targeted screening. A population-based, cross-sectional study with 3,076 participants in the Barcelona area using TE for "at front" screening in primary care reported that TE values <9.2 kPa had highest accuracy to exclude fibrosis stages F2 - F4 (14). A more targeted approach focusing on patients with risk factors, such as harmful alcohol consumption or type-2 diabetes, may result in a higher rates of cirrhosis detected than a global approach (25). The Nottingham liver disease stratification pathway for the identification of advanced CLD (32) used (i) raised AST/ALT ratio ≥ 0.8, (ii) harmful alcohol use or iii) fatty liver index (FLI) ≥ 60 as criteria for referral from primary to secondary care. Among patients fulfilling these criteria, 23% of 968 patients had TE values ≥8 kPa, of whom 39% would have gone undetected. Markov modeling estimated the pathway to be cost-effective (33). Similar one-step pathways but based on APRI score in primary care with subsequent TE, are being evaluated in the population-based screening program for asymptomatic cirrhosis (SEAL) in Germany (https://www.lebervorsorge.de/seal/). To assess two-step screening algorithms, a primary care referral pathway combining FIB-4 and ELF for patients with NAFLD was evaluated in a longitudinal study in London (18). Five times more cases of advanced fibrosis and cirrhosis were detected and unnecessary referrals from primary to secondary care decreased by almost 90% using this strategy.

The implementation of a screening program has to take into account not only region-specific health risk profiles (age, sex, comorbidities, ethnicity) but region-specific participation barriers and health inequities (socio-economic differences, distance and mobility), the structure of the health care system (in particular community and primary care, links to other screening programs

such as colon and breast cancer) as well as regulatory requirements (ethics, data protection, coverage of costs).

A general strategic framework for early diagnosis of CLD based on current knowledge is proposed in figure 1.

Cost-effectiveness of liver fibrosis screening

In recent years, evidence regarding the cost-effectiveness of liver fibrosis screening has been mounting. Using non-invasive procedures for risk stratification, and compared to the current standard of care pathways, various economic models show highly cost-effective results. These results are consistent across a wide range of target populations and healthcare systems, mostly in European settings. (8,33-37) Estimates range between $6,000 per quality-adjusted life-year (QALY) in low-prevalence general population settings to $2,000 per QALY in at-risk populations, such as heavy alcohol consumers or patients with metabolic syndrome. These numbers are well below the thresholds that allow new therapies to enter the portfolio of covered services in most developed countries, $100,000 in the US and between $25,000 and $50,000 in Europe. Their importance lies in their opportunity cost. Provided that less cost-effective therapies are being administered, using the same budget but shifting it towards liver fibrosis screening would yield a better societal return.

Screening in pediatric populations

Approximately 9.6% of children and adolescents have fatty liver; and 1-2% of the general pediatric population have at least some histopathological evidence of portal and/or perisinusoidal fibrosis associated with fatty liver based on autopsy studies (38), which is lower than the liver fibrosis prevalence in adults. In light of this low prevalence in children, universal screening for liver fibrosis in that population cannot be recommended at this time, but screening should be guided by risk factors, such as personal and family history of liver disease or presence of obesity.

Screening for liver fibrosis with serum ALT levels is insufficient in children, as fibrosis can be detected on liver biopsy in 12% of children with suspected NAFLD and normal ALT levels (39). The gold standard in the assessment of pediatric liver fibrosis is still liver biopsy (39), but it might soon be replaced by noninvasive serum and imaging screening modalities, which are getting better at diagnosing (early) liver fibrosis in children (supplementary table 2) (40,41).

Conclusions and future directions

There is an urgent need to change the paradigm of diagnosis of CLD from late diagnosis (i.e. decompensated cirrhosis) to early diagnosis (i.e. fibrosis or compensated cirrhosis). This new approach would require identification of asymptomatic patients using non-invasive methods of assessment of fibrosis in large portions of the population. A main lesson learned from cancer screening is that selection of individuals with a high pre-test probability leads to higher economic efficiency. Early research points towards 3-fold improvements in efficiency when at-risk populations are targeted (8). However, there is need for studies with large sample sizes addressing the most important gaps of knowledge, particularly comparing existing non-invasive tests of fibrosis in terms of accuracy and applicability in specific settings, evaluating cost-effectiveness of screening, and investigating potential beneficial effects in the long-term.

There are several initiatives worldwide evaluating the implementation of different methods of screening for liver fibrosis in the population (table 4). When implemented, screening will likely have a remarkable impact on the practice of hepatology. Most patients with CLD may subsequently be detected in early stages, thus potentially decreasing the incidence of hepatic decompensation and HCC and the need for some specialized therapies, such as liver transplantation.

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Figure 1. Proposal of a general strategic framework for screening of liver fibrosis in primary care. Current evidence suggests that the target population for screening should have risk factors for chronic liver diseases, including high-risk alcohol consumption and/or components of the metabolic syndrome; the prevalence of liver fibrosis is very low in subjects without these risk-factors (risk stratification I). The first additional step needed is based on a serum surrogate marker of fibrosis with high negative predictive value to rule-out subjects with very low likelihood of fibrosis (risk stratification II). Some screening studies suggest that FIB-4 could be used as marker to rule-out fibrosis, but further studies are necessary (7,25). A single large study suggests that FLI could also be useful, but more information is clearly needed (13). The second step avails of a non-invasive marker of fibrosis to rule-in subjects with high likelihood of significant fibrosis who then should be referred to secondary care or a liver center for further evaluation (screening test in high-risk individuals). Tools/tests to be used in this second step include TE, but this strategy may be expensive and not usually available in primary care settings (7,8,25). ELF has been shown to be accurate in cohorts with high prevalence of fibrosis, but studies are needed in screening populations that have low prevalence of fibrosis (16,25).

* Tests that may be used to rule out hepatic fibrosis include FIB-4 and FLI (fatty liver index)

** Tests that may be used to rule in hepatic fibrosis include TE (transient elastography) and ELF.

ELF, enhanced liver fibrosis test; FIB-4, fibrosis-4 score; FLI, fatty liver index; TE, transient elastography.

Table 1. Summary of the 10 criteria proposed for screening for a disease in the general population *

Factors	Criteria	Comment regarding screening for liver diseases
Disease	1. The condition sought should be an important health problem	Criterion met
	2. There should be a recognizable latent or early symptomatic stage	Criterion met
	3. The natural history of the condition, including development from latent to declared disease, should be adequately understood	Criterion met
Setting	4. Facilities for diagnosis and treatment should be available	Further research needed.
Diagnosis	5. There should be a suitable test or examination	Criterion met
	6. The test should be acceptable to the population	Criterion met
	7. Case-finding should be a continuing process and not a "once and for all" project	Further research needed
Treatment	8. There should be an accepted treatment for patients with recognized disease	Criterion met
	9. There should be an agreed policy on whom to treat the patients	Criterion met**
Cost-effectiveness	10. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole	Further research needed

*Adapted from Wilson and Jungner for World Health Organization

** does not apply to ALD, NAFLD, or viral hepatitis in low-income countries

Table 2. Advantages and limitations of non-invasive tests of fibrosis used in population screening

	Evidence to support			**Practical issues**		
	Accuracy in low prevalent populations	Tested in screening setting	Cost effectiveness in screening	Price	Require operator training	Point of care assessment
Transient elastography	++	++	++	+++	++	+++
Direct fibrosis markers e.g. ELF test	+	+	+	++	+	-
Indirect markers e.g. FIB-4	+	+	+	+	+	-
Sequential testing, e.g. FIB-4 and ELF	+	+	+	++	+	-

The table rate the current evidence base to support different screening tools and the level of practical barriers for implementation. The rating is arbitrary and combines strength and amount of data. -; none or no data, +; limited, ++; moderate, +++; significant

Table 3. Prevalence of liver fibrosis and cirrhosis in general population-based studies in Europe

Author, Year, (Reference)	Country	Sample Size	Setting	Non Invasive Fibrosis Test	Definition of Fibrosis	Prevalence of Fibrosis ≥2	Definition of Cirrhosis	Prevalence of Cirrhosis
Poynard 2010 (15)	France	7463	Consecutive subjects >40 yr attending health examination centers	FibroTest TE	FibroTest ≥0.48 LSM ≥ 7.1kPa	0.7-2.8%	FibroTest ≥0.48, LSM ≥ 7.1kPa & clinical sings or liver biopsy	0.1-0.3%
Roulot 2011 (10)	France	1358 (1190 with valid results)	Consecutive subjects >45 yr attending a medical check-up	TE	LSM ≥ 8 kPa	7.5%	LSM ≥ 13 kPa & Liver Biopsy	0.76%
Zelber-Sagi 2012 (16)	Israel	375 (338 with valid results)	National Health Survey	FibroTest	FibroTest ≥0.22; FibroTest ≥0.32; FibroTest ≥0.59	25.7%; 12.8%; 0.9%	FibroTest ≥0.75	0.3%
Koehler	Netherland	3439 (3180 with valid	Population-based,	TE	LSM ≥ 8 kPa	5.6%	LSM ≥ 13 kPa	0.6%

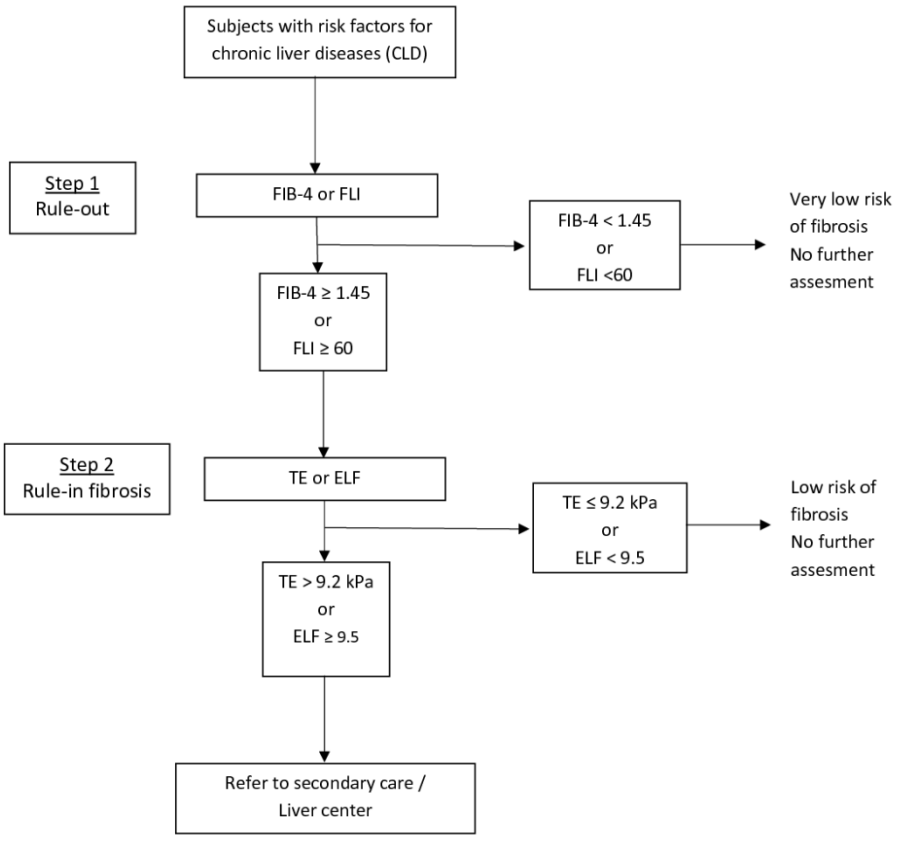
2016 (17)	s	results)	randomly selected					
Fabrellas 2018 (18)	Spain	295 (292 with valid results)	Population-based randomly selected (2/3 with metabolic factors)	TE	LSM ≥ 8kPa	4 %	-	-
Petta 2018 (19)	Italy	890	Population-based study	TE	LSM ≥ 9.6 kPa	4%	-	-
Caballeria 2018 (12)	Spain	3076 (3014 with valid results)	Population-based, randomly selected 18-75 yr	TE	LSM ≥ 9.0 kPa	3.6%	-	-
Abeyseker a 2020 (20)	UK	4021 (3600 with valid results, mean age 24)	Avon Longitudinal Study of Parents and Children	TE	LSM ≥ 7.9 kPa	2.4%	LSM ≥ 11.7 kPa	0.25%
Hagström, 2020 (9)	Sweden	126,941	Cohort of health check-ups and outpatients from primary care setting	FIB-4, BARD, APRI, Forns, NFS	FIB-4 > 2.67; BARD>3, APRI> 1.5, Forns >6.9, NFS >0.676	0.3-1.4%	-	-

TE, transient elastography; LSM, liver stiffness measurement

Table 4. Examples of projects evaluating screening for liver fibrosis in the population in different areas of the world

Name	Geographical area	Area and/or Number of subjects	Characteristics
RENOWN	Nevada (USA)	30,000	Subjects with risk factors for NAFLD
SCARRED LIVER PROJECT	Nottingham (UK)	GP practices in a population of 700,000	Subjects with risk factors for chronic liver disease
LIVERSCREEN	7 countries in Europe	30,000	Population-based
SEAL	Germany (2 federal states: Rheinland-Pfalz + Saarland)	12,000 plus 22,500 controls	Detection of asymptomatic cirrhosis in primary care

Figure 1



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