



Topic Brief: Screening and Treating Non-Alcoholic Fatty Liver Disease

Date: 10/30/2020

Nomination Number: 0939

Purpose: This document summarizes the information addressing a nomination submitted on 7/7/2020 through the Effective Health Care Website. This information was used to inform the Evidence-based Practice Center (EPC) Program decisions about whether to produce an evidence report on the topic, and if so, what type of evidence report would be most suitable.

Issue: Although non-alcoholic fatty liver disease (NAFLD) impacts millions of Americans, there is little guidance or expert consensus regarding best practices for screening and treatment.

Program Decision: While the scope of this topic met all EHC Program selection criteria and was considered for a systematic review, it was not selected.

Key Findings

- We found one systematic review on the diagnostic accuracy of imaging tests for NAFLD, and two primary studies (from a sample of 200 studies) on non-imaging diagnostic accuracy tests.
- We did not find any evidence for screening of asymptomatic adults for NAFLD.
- We found one systematic review on the effectiveness and harms of weight-loss interventions for NAFLD, but did not find any studies on combination therapies.
- A new systematic review on non-imaging diagnostic tests for NAFLD could be used in the development of updated guidelines for NAFLD.

Background

Non-fatty alcoholic liver disease (NAFLD) is defined as excess fat in the liver that cannot be attributed to secondary causes of hepatic fat accumulation such as significant alcohol consumption, long-term use of steatogenic medication, or monogenic hereditary disorders. There are two kinds of NAFLD, simple fatty liver and nonalcoholic steatohepatitis (NASH). As many as 80 million Americans have NAFLD, and between 10 and 30 percent of people with NAFLD have NASH.¹ NAFLD is diagnosed as fatty liver on ultrasound, negative serological liver screen, and alcohol consumption ≤ 30 and ≤ 20 g/day in males and females, respectively. The diagnosis of NASH is made when there is evidence of inflammation that can cause liver damage which, in turn, can lead to cirrhosis, liver failure, or hepatocellular carcinoma. The rising prevalence of obesity is thought to account for the rapid increase in NAFLD over the past 20 years.²

The epidemiology of NAFLD has not been adequately studied, but large, well-conducted observational studies indicate that NAFLD and NASH are underdiagnosed in primary care.³

Lower-quality evidence suggests that about half of patients who have NAFLD do not have abnormal liver function tests (LFTs). Among primary care patients who have abnormal LFTs, NAFLD accounts for about 25 percent and excess alcohol use accounts for a similar proportion. About 8 percent of the NAFLD patients seen in primary care already have some fibrosis.⁴

Currently, the United States Preventive Services Task Force (USPSTF) does not have guidelines regarding screening for NAFLD. Guidelines from the American Association for the Study of Liver Diseases do not recommend screening for NAFLD in primary care due to uncertainties surrounding diagnostic testing and treatment options, and lack of knowledge related to long-term benefits and cost-effectiveness.⁵ The guideline determined that evidence was also insufficient to recommend screening for NAFLD in overweight or obese pediatric populations. However, an older guideline from the European Association for the Study of the Liver recommended screening high-risk primary care patients, such as patients over the age of 50 who have diabetes or features of metabolic syndrome.⁶ However, there is uncertainty regarding the choice of screening and confirmatory tests, and the effectiveness of treatment, which may include diet and exercise, as well as medications to treat associated metabolic comorbidities (e.g. hyperglycemia, obesity, and hyperlipidemia).

Nomination Summary

The nominator feels that not enough attention is being paid to this condition in primary care. In many respects, this nomination is a “classic” screening question that may come before the USPSTF in the future. Current USPSTF recommendations regarding weight loss to prevent obesity-related morbidity and mortality; lipid disorders in children and adults, healthful diet, and cardiovascular risk reduction, overlap with the population and interventions that a review of NAFLD would address. However, the USPSTF has not assessed tests for NAFLD, such as liver ultrasound, liver function tests, fibrosis markers, or transient elastography, in any of these reviews.

For treatment of NAFLD, we found one systematic review of a range of weight-loss interventions. The nominator felt that this review covered the key questions regarding treatment with the exception of combination therapies (e.g. diet combined with pharmaceutical interventions). The original nomination did not include these combination therapies.

Scope

Table 1 shows the overarching PICO for the question of whether to screen in any or all of these populations.

Table 1. Table of relevant PICO (population, interventions, comparators and outcomes)

Population	Asymptomatic adults a) without risk factors or b) “high risk” with BMI>27, diabetes, or other features of metabolic syndrome. c) Patients with elevated LFTs
Interventions	Screening, additional tests, treatment
Comparators	No screening
Outcomes	Reduced incidence of cirrhosis, liver failure, hepatocarcinoma

Screening strategies for NAFLD in primary care include (a) screening everyone, and (b) screening only people at high clinical risk or (c) no screening. The corresponding populations addressed in the PICOs are:

- a) Asymptomatic adults without risk factors. We did not find a specific screening and testing strategy aimed at this population. However, it is likely that screening would be done with laboratory tests rather than universal ultrasound. The EPC will need to explore possible screening strategies with experts before the PICOs for this population can be specified.
- b) “High risk” asymptomatic adults with BMI>27, diabetes, or other features of metabolic syndrome. A testing algorithm for this population has been proposed (See Figure 1). For this population, the initial screening tests are ultrasound and alanine transaminase (ALT). If these indicate fatty liver, the NAFLD fibrosis score (NFS) or the Fibrosis-4 (FIB-4) index for liver fibrosis is performed. The NFS consists of serum glucose, platelet count, albumin, aspartate transaminase (AST)/ALT ratio, age, Body Mass Index (BMI), and diabetes status. The FIB-4 is an alternative prediction tool using just ALT and AST, age, and platelet count. Both tests are intended to distinguish between patients at high risk of fibrosis from those who are unlikely to have fibrosis.
- c) In addition, any screening strategy in primary care needs to account for patients who have elevated LFTs found incidentally in the course of primary care. We did not identify an algorithm for additional testing in this population, which may contain some people who do not have risk factors and others who do. The options for next steps might be 1) no additional testing for NAFLD; 2) additional testing for everyone who has abnormal LFTs; and 3) additional testing for those who are “high risk” by the definition given in “b” above. In any case, if additional testing were done, it would be an ultrasound, since this test was not done initially. If the ultrasound shows a fatty liver, these patients would join the algorithm in Figure 1 at the step labeled “use NFS and FIB-4 score to assess risk for fibrosis.”

We developed key questions (KQs) that apply primarily to the high-risk populations and, with some modifications, to the other populations. KQs 1a, 1b, and 1c cover the test performance of the screening tests (ALT, ultrasound, or a combination of the two) as well as the accuracy of follow-up tests to identify patients with fibrosis (NFS and FIB-4 and transient elastography). In these KQs, we considered transient elastography as a confirmatory test for use in intermediate-risk patients.

- 1a. What is the comparative accuracy of different screening tests or combinations of screening tests for non-alcoholic fatty liver disease (NAFLD)?
- 1b. For a positive NAFLD screening test, what is the accuracy of NAFLD Fibrosis Score (NFS) or Fibrosis-4 (FIB-4) for estimating the risk of fibrosis?
- 1c. If the NFS or FIB-4 indicate an intermediate probability of fibrosis, what is the accuracy of transient elastography to confirm or rule out fibrosis?
- 1d. What is the yield of screening in primary care for each strategy (no screening, screening all patients, and screening high risk patients)?

2. Does screening asymptomatic adults reduce the incidence of cirrhosis, liver failure, and hepatocarcinoma?

3a. What is the effectiveness and harms of treatments for NAFLD?

3b. What factors influence the effectiveness and harms of treatments for NAFLD? (ex. severity of disease, comorbidities, patient characteristics, socioeconomic factors)

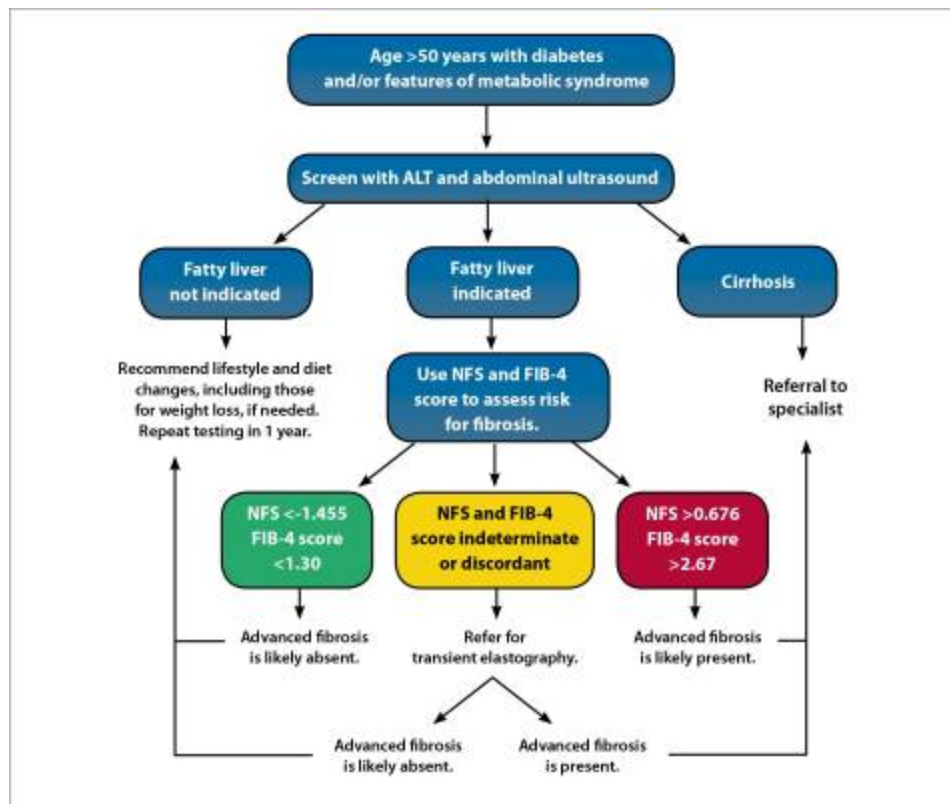
KQs 1a-1c do not include all possible tests or combinations of tests. For example, it is possible that transient elastography could be used as an initial screening test, either as an add-on or as a substitute for ultrasound. Also, we did not include other forms of elastography, such as acoustic radiation force impulse (ARFI), magnetic resonance elastography (MRE) or magnetic resonance (MR), computed tomography, and scintigraphy. We leave these possibilities open; an EPC will need to consult experts to determine which combinations and sequences of tests should be added to the scope of the review. It would be premature to include these tests in the PICOs now since we did not encounter any expert opinion that suggested they be part of the testing strategy for screening in primary care.

KQ 1d concerns the “yield” of screening; that is, based on the prevalence of disease and the accuracy of the tests, how many patients with NAFLD will be identified correctly with each screening strategy?

KQ 2 indicates “direct” evidence; that is, evidence from randomized trials or other comparative studies of screening that report the effect on health outcomes such as cirrhosis and liver failure. Currently, there are no studies that would be eligible for Question 2.

KQs 3a and 3b pertain to treatment studies in patients who have been diagnosed with NAFLD. The ideal study would examine treatment outcomes in patients who had been identified by screening, but we expect that most or all studies were performed in patients who were diagnosed by other means.

Figure 1. Algorithm for screening high-risk patients in Primary Care; From Reference 3



Assessment Methods

See Appendix A.

Summary of Literature Findings

We found two systematic reviews that address portions of the nominated scope, and only found primary studies sufficient for a new systematic review for KQ regarding diagnostic accuracy tests for NAFLD.

The systematic review addressing KQ 1 was published in 2019, and evaluated imaging tests for diagnosis of NAFLD in patients known to have liver disease.⁷ This systematic review adequately addressed imaging diagnostic tests, but did not include non-imaging diagnostic tests. We then found two studies on the diagnostic accuracy of non-imaging diagnostic tests.^{8,9}

For KQ 2, addressing the effectiveness of screening asymptomatic adults for NAFLD, we did not find any systematic reviews or primary studies.

For KQ 3, we found one systematic review published in 2019 that evaluated a range of weight loss interventions, including behavioral, pharmaceutical, and surgical interventions.¹⁰ The nominator expressed that this was largely an adequate review of NAFLD treatment, but communicated interest also in an evaluation of combination therapies (e.g., diet plus pharmaceutical intervention), which were not included in the review. We did not find any studies of combination therapies.

Table 2. Literature Identified for Each Key Question

Question	Systematic reviews (10/2017-10/2020)	Primary studies (10/2015-10/2020)
Question 1: Diagnostic accuracy of screening, and followup testing	Total: 1 <ul style="list-style-type: none"> • Cochrane: 0 • AHRQ: 0 • Other: 1⁷ 	Total: 2 ^{8,9} non-imaging diagnostic tests (from a sample of 200 studies)
Question 2: Screening in asymptomatic adults	Total: 0	Total: 0
Question 3: Effectiveness/comparative effectiveness and harms of treatments	Total: 1 <ul style="list-style-type: none"> • Cochrane: 0 • AHRQ: 0 • Other: 1¹⁰ 	Total: 0 combination therapies

Abbreviations: AHRQ=Association for Health Research and Quality

See Appendix B for detailed assessments of all EPC selection criteria.

Summary of Selection Criteria Assessment

The benefits and harms of screening for NAFLD in the primary care setting may be important to determine, but we did not find existing evidence to address this issue. Furthermore, though one systematic review on individual weight loss treatments was identified, no studies evaluating combination treatments for NAFLD were found, which may be important. Our search did find one systematic review on the diagnostic accuracy of imaging tests for NAFLD, as well as evidence to inform a potentially a new systematic review on the accuracy of non-imaging diagnostic tests. A new systematic review could be used in the updating of guidelines for NAFLD.

Please see Appendix B for detailed assessments of individual EPC Program selection criteria.

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Appendix A: Methods

We assessed nomination for priority for a systematic review or other AHRQ Effective Health Care report with a hierarchical process using established selection criteria. Assessment of each criteria determined the need to evaluate the next one. See Appendix B for detailed description of the criteria.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance.

Desirability of New Review/Absence of Duplication

We searched for high-quality, completed or in-process evidence reviews published in the last three years October 21, 2017 - October 21, 2020 on the questions of the nomination from these sources:

- AHRQ: Evidence reports and technology assessments
 - AHRQ Evidence Reports <https://www.ahrq.gov/research/findings/evidence-based-reports/index.html>
 - EHC Program <https://effectivehealthcare.ahrq.gov/>
 - US Preventive Services Task Force <https://www.uspreventiveservicestaskforce.org/>
 - AHRQ Technology Assessment Program <https://www.ahrq.gov/research/findings/ta/index.html>
- US Department of Veterans Affairs Products publications
 - Evidence Synthesis Program <https://www.hsrp.research.va.gov/publications/esp/>
 - VA/Department of Defense Evidence-Based Clinical Practice Guideline Program <https://www.healthquality.va.gov/>
- Cochrane Systematic Reviews <https://www.cochranelibrary.com/>
- PROSPERO Database (international prospective register of systematic reviews and protocols) <http://www.crd.york.ac.uk/prospetro/>
- PubMed <https://www.ncbi.nlm.nih.gov/pubmed/>

Impact of a New Evidence Review

The impact of a new evidence review was qualitatively assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether it was possible for this review to influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.).

Feasibility of New Evidence Review

We conducted a limited literature search in PubMed from the last five years (October 21, 2015 - October 21, 2020) on parts of the nomination scope not addressed by previously identified systematic reviews. Because a large number of articles were identified, we reviewed a random sample of 200 titles and abstracts for each question for inclusion. We classified identified studies by question and study design, to assess the size and scope of a potential evidence review. We then calculated the projected total number of included studies based on the proportion of studies included from the random sample.

Search strategy

Ovid MEDLINE(R) ALL 1946 to October 21, 2020

Date searched: October 22, 2020

1 *Non-alcoholic Fatty Liver Disease/ (8952)
 2 (((nonalcoholic or non-alcoholic) adj2 ("fatty liver" or steatohepatitis or steato-hepatitis)) or nafld).ti,kf. (18326)
 3 or/1-2 (19887)
 4 *Diagnosis/ or *Mass Screening/ (68163)
 5 (diagnos* or elastograph* or "function test*" or imaging or screen* or "steatosis score*" or ultrasound*).ti,kf. or (dg or di).fs. (4155192)
 6 limit 3 to "diagnosis (best balance of sensitivity and specificity)(2394)
 7 or/4-6 (4163984)
 8 exp *Bariatric Surgery/ or exp *Behavior Therapy/ or exp *Diet Therapy/ or exp *Drug Therapy/ or exp *Exercise Therapy/ or *Therapeutics/ (541195)
 9 (agents or "bariatric surgery" or behav* or diet or diets or drug or drugs or exercis* or intervention* or medication* or nonpharmacol* or pharmacol* or surger* or therap* or treat* or weight-loss).ti,kf. or (dh or dt or su or th).fs. (7949881)
 10 (lorcaserin or (naltrexone adj3 bupropion) or orlistat or phentermine-topiramate or sibutramine or liraglutide or metformin or pioglitazone or statin or statins or "vitamin E").ti,kf. (49211)
 11 or/8-10 (8094489)
 12 and/3,7 (5653)
 13 limit 12 to english language (5275)
 14 limit 13 to yr="2017 -Current" (2336)
 15 (meta-analysis or systematic review).pt. or (metaanaly* or meta-analy* or ((evidence or systematic) adj2 (review or synthesis))).ti,ab,kf. (328158)
16 14 and 15 (106) KQ1-2 Systematic Reviews / Meta-analyses
 17 randomized controlled trials as topic/ or exp clinical trial as topic/ or placebos/ or comparative study/ or exp evaluation studies/ or follow up studies/ or prospective studies/ (3260044)
 18 ("randomized controlled trial" or "controlled clinical trial" or "clinical trial").pt. or (((control* or random*) adj3 trial) or control* or evaluation or follow-up or placebo* or prospectiv* or random*).ti,kf. (2075211)
 19 or/17-18 (4635188)
 20 19 not ((exp Animals/ not Humans/) or (mice or mouse or rat or rats or rattus).ti.) (4032771)
 21 and/13,20 (1330)
22 limit 21 to yr="2015 -Current" (844) KQ1-2 Trials
 23 and/3,11 (7009)
 24 limit 23 to english language (6575)
 25 limit 24 to yr="2017 -Current" (3400)
26 and/15,25 (124) KQ3 Systematic Reviews / Meta-analyses
27 limit 24 to yr="2015 -Current" (4609)
28 and/20,27 (773) KQ3 Trials

Ovid EBM Reviews - Cochrane Central Register of Controlled Trials September 2020

Date searched: October 22, 2020

1 Non-alcoholic Fatty Liver Disease/ (940)
 2 (((nonalcoholic or non-alcoholic) adj2 ("fatty liver" or steatohepatitis or steato-hepatitis)) or nafld).ti. (2294)
 3 or/1-2 (2531)
 4 Diagnosis/ or Mass Screening/ (3246)
 5 (diagnos* or elastograph* or "function test*" or imaging or screen* or "steatosis score*" or ultrasound*).ti. (45880)
 6 or/4-5 (47014)
 7 exp Bariatric Surgery/ or exp Behavior Therapy/ or exp Diet Therapy/ or exp Drug Therapy/ or exp Exercise Therapy/ or Therapeutics/ (167921)

8 (agents or "bariatric surgery" or behav* or diet or diets or drug or drugs or exercis* or intervention* or medication* or nonpharmacol* or pharmacol* or surger* or therap* or treat* or weight-loss).ti. (579531)

9 (lorcaserin or (naltrexone adj3 bupropion) or orlistat or phentermine-topiramate or sibutramine or liraglutide or metformin or pioglitazone or statin or statins or "vitamin E").ti. (14492)

10 or/7-9 (686912)

11 and/3-6 (1)

12 limit 11 to yr="2015 -Current" (1) KQ1-2 Trials

13 and/3,10 (1124)

14 limit 13 to yr="2015 -Current" (700) KQ3 Trials

Ovid EBM Reviews - Cochrane Database of Systematic Reviews 2005 to October 22, 2020

Date searched: October 22, 2020

1 (((nonalcoholic or non-alcoholic) adj2 ("fatty liver" or steatohepatitis or steato-hepatitis)) or nafld).ti. (12)

2 (diagnos* or elastograph* or "function test*" or imaging or screen* or "steatosis score*" or ultrasound*).ti. (342)

3 (agents or "bariatric surgery" or behav* or diet or diets or drug or drugs or exercis* or intervention* or medication* or nonpharmacol* or pharmacol* or surger* or therap* or treat* or weight-loss).ti. (4761)

4 (lorcaserin or (naltrexone adj3 bupropion) or orlistat or phentermine-topiramate or sibutramine or liraglutide or metformin or pioglitazone or statin or statins or "vitamin E").ti. (68)

5 and/1-2 (1) KQ1-2 Systematic Reviews

6 or/3-4 (4817)

7 and/1,6 (5)

8 limit 7 to last 3 years (1) KQ3 Systematic Reviews

ClinicalTrials.gov

Date searched: October 22, 2020

KQ1-2

107 Studies found for: Non Alcoholic Fatty Liver | diagnosis OR diagnostic OR elastograph OR "function test" OR imaging OR screen OR "steatosis score" OR ultrasound | First posted from 01/01/2015 to 10/22/2020

KQ3

167 Studies found for: (agents OR behavior OR diet OR drug OR exercise OR intervention OR medication OR nonpharmacological OR pharmacological OR surgery OR therapy OR treatment OR weight-loss OR lorcaserin OR naltrexone OR orlistat OR phentermine-topiramate OR sibutramine OR liraglutide OR metformin OR pioglitazone OR statin OR statins OR EXPAND[Concept] "vitamin E") AND (EXPAND[Concept] "Non Alcoholic Fatty Liver" OR steatohepatitis OR NAFLD) | First posted from 01/01/2015 to 10/22/2020

☑Clinical Trials.gov

KQ1-2 Link (107 results): [link](#)

KQ3 Link (167 results): [link](#)

Value

We assessed the nomination for value. We considered whether or not the clinical, consumer, or policymaking context had the potential to respond with evidence-based change; and if a partner organization would use this evidence review to influence practice.

Appendix B. Selection Criteria Assessment

Selection Criteria	Assessment
1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the US?	Yes.
1b. Is the nomination a request for an evidence report?	Yes.
1c. Is the focus on effectiveness or comparative effectiveness?	Yes.
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes.
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	The global prevalence of NAFLD is estimated to be 25 percent, ¹¹ and a recent systematic review and meta-analysis reported that the disease affects 75 to 100 million Americans. ¹²
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	Yes. A 2016 assessment of economic burden found that NAFLD was projected to generate approximately \$103 billion in direct medical costs annually. ¹¹ One 2016 meta-analysis found that a number of metabolic comorbidities were associated with NAFLD, and concluded that rising levels of obesity will continue to fuel such comorbidities, thus increasing the clinical and economic burden of NAFLD globally. ²
2c. Incorporates issues around both clinical benefits and potential clinical harms	Yes.
2d. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Yes. A 2016 assessment of economic burden found that NAFLD was projected to generate approximately \$103 billion in direct medical costs annually. ¹¹ One 2016 meta-analysis found that a number of metabolic comorbidities were associated with NAFLD, and concluded that rising levels of obesity will continue to fuel such comorbidities, thus increasing the clinical and economic burden of NAFLD globally. ²
3. Desirability of a New Evidence Review/Absence of Duplication	
3. A recent high-quality systematic review or other evidence review is not available on this topic	We found 2 systematic reviews that cover portions of the nomination. One addressed the diagnostic accuracy of imaging tests for NAFLD, but did not include non-imaging diagnostic tests. ⁷ The other covered the effectiveness and harms of weight-loss interventions for NAFLD, but did not include combination therapies. ¹⁰
4. Impact of a New Evidence Review	
4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?	There is a lack of consensus among experts on screening and treatment of NAFLD. ¹³
4b. Is there practice variation (guideline inconsistent with current practice, indicating a	There is a lack of consensus among experts on screening and treatment of NAFLD. ¹³

potential implementation gap and not best addressed by a new evidence review)?	
5. Primary Research	
<p>5. Effectively utilizes existing research and knowledge by considering:</p> <ul style="list-style-type: none"> - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies) 	<p>We found 2 studies (from a random sample of 200) for KQ 1 on the accuracy of non-imaging diagnostic tests.</p> <p>We did not find any studies for KQ 2 on benefits and harms of screening in the primary care setting.</p> <p>We did not find any studies for KQ 3 on combination therapies.</p> <p>A new systematic review on the accuracy of non-imaging diagnostic tests is estimated to be limited, with an estimated 8 studies.</p>
6. Value	
6a. The proposed topic exists within a clinical, consumer, or policy-making context that is amenable to evidence-based change	Yes. Evidence in this area could influence practice guidelines.
6b. Identified partner who will use the systematic review to influence practice (such as a guideline or recommendation)	A partner has not yet been established, but a systematic review could contribute to guideline development.

Abbreviations: AHRQ=Agency for Healthcare Research and Quality; KQ=key question; NAFLD=non-alcoholic fatty liver disease; US=United States.