Community pathways for the early detection and risk stratification of chronic liver disease
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KWMA: conceptualization, methodology, validation, formal analysis, data curation, writing – original draft, review & editing; IM: conceptualization, methodology, validation, formal analysis, data curation, writing – review & editing; KGO: methodology, validation, formal analysis, data curation, writing – original draft; SM: writing – original draft, review & editing; RP: writing – original draft, review & editing; RH: conceptualization, methodology; AY: writing – review & editing; IAR: writing – review & editing; JFD: conceptualization, methodology, writing – review & editing, supervision.

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Abstract

Patients with chronic liver disease are often diagnosed during an index presentation to hospital with decompensated cirrhosis or liver-related events, and the Lancet Commission for Liver Disease has highlighted the high mortality associated with such presentations. However, there is often a long asymptomatic phase, in which there is an opportunity for earlier diagnosis and interventions to prevent progression to advanced disease. Therefore, strategies enabling diagnosis and interventions (including behavioural change and pharmacological treatments) that prevent patients progressing to cirrhosis and its associated complications likely have substantial benefits for patients and healthcare services.

Many community pathways have been generated in the last 10 years. Some focus on abnormal liver function tests as the entry point to diagnosing liver disease. Others centre around targeting groups at greater risk of chronic liver disease - particularly persons with harmful alcohol consumption, type 2 diabetes, and obesity. This systematic literature review is the first attempt to summarise the existing strategies available for the early detection and/or risk stratification of liver disease, focusing primarily on alcohol related liver disease and nonalcoholic fatty liver disease.

Future randomised clinical trials comparing different strategies will be vital to elucidate which pathways are acceptable to patients, feasible, provide high diagnostic accuracy for the detection of liver disease, improve liver-related outcomes and are most cost effective at a population level.
Introduction

Chronic liver disease (CLD) is a major burden to healthcare systems and society globally. Recent estimates suggest that there are 2.14 million deaths from CLD each year worldwide, an increase of over 10% in under a decade (1). Persons with advanced CLD have high rates of hospitalisation and use of healthcare resources with a significant financial cost (2).

In the United Kingdom overall mortality due to liver disease has been increasing over the last three decades in contrast to other common diseases (3). Liver disease is now one of the commonest causes of death in people of working age (4, 5). In contrast to the global picture, the commonest causes of CLD in the UK are alcohol related liver disease (ALD) and non-alcohol related fatty liver disease (NAFLD) (6). These are both typified by long disease trajectories (7, 8) in the development of hepatic fibrosis that should allow for detection of disease before it progresses to the point of causing morbidity or mortality.

Early detection of liver disease, here defined as identification of advanced fibrosis, has been the focus of considerable attention over recent years with the ambition to reduce the burden of ill-health. The experience of using highly effective new treatments for hepatitis C has shown that concerted action can improve outcomes for patients. However, the role of early detection of liver disease is different in ALD or NAFLD to that of hepatitis C, where specific treatments over a short period can be used to cure infection. No specific, licensed therapies exist for ALD or NAFLD. Moreover, interventions that might prevent the development of fibrosis - alcohol reduction/cessation, control of metabolic risk factors - are indicated regardless of the presence of liver disease.

Reports from groups across the UK have shown that proactive case finding can detect advanced liver disease at a greater rate than standard pathways (9), and that feedback to patients about the presence of liver disease can help address risk factors (10). Individualisation of risk of future liver disease may increase the effectiveness of current interventions, for instance, those aimed at reducing alcohol consumption (11) or weight. Additionally, it is known that cirrhosis can be clinically silent for some time before initial decompensation, so screening for and managing complications of portal hypertension in
persons with cirrhosis may reduce morbidity. The caveat to this is the significant burden of extra-hepatic ill health in ALD (12) and NAFLD (13) where the competing risk of other adverse health outcomes may render liver-specific treatments ineffective.

The role of early detection is further complicated by uncertainties over the tests, or combinations of tests, which are used to detect hepatic fibrosis. Multiple tests have been developed to accurately predict the presence of hepatic fibrosis and these tests have been trialed alone and in combination. Finally, the optimal delivery of early detection of liver disease remains to be clarified with debate over the starting point for detection - whether this should be based on an individual’s risk factors, or a prior finding of abnormal liver blood tests, or an established diagnosis of liver disease.

The purpose of this review is therefore to summarise existing published pathways that are in use to detect, and risk stratify liver disease, focusing on NAFLD and ALD. The methodology of the various pathways, and, where the possible, the outcomes will be compared. Finally, we suggest a set of metrics that should be recorded and reported to allow for the evaluation of early detection initiatives.
Methods

Search Strategy

We performed electronic searches of Pubmed, Ovid Medline, Web of Science, Cochrane Library from 1st January 2000, until 30th June 2021. We manually searched clinical guidelines, relevant professional websites, social media and reference lists of included papers. Study authors were contacted for further information where required. Medical search headings (MeSH) terms were agreed between authors and are described in supplementary Table 1. Rayyan software (www.rayyan.ai) was used by the review team for all stages of the review process. Reasons for study exclusion are detailed in supplementary Table 2. Study quality assessment for risk of bias was performed using the QualSyst tool (see supplementary Table 3).

Inclusion criteria

The inclusion criteria were deliberately broad, to capture as many pathways as possible. Criteria for studies included in the review were:

Population: Adults (≥19 years) without known liver disease in general population, community or primary care settings. Studies targeting adults at high risk of liver disease due to another condition e.g. Type 2 diabetes were included, as well as those targeting the general population.

Intervention: An established community-based liver disease detection pathway utilising non-invasive test(s) to risk stratify and/or diagnose liver fibrosis. Cross-sectional prevalence studies were not included.

Control/comparison: Not applicable.

Outcomes: Outcomes were detection of incident cases of liver fibrosis or cirrhosis, diagnosed by any of appropriate diagnostic imaging, histology, cancer registry, ICD code, or clinician's diagnosis.
Exclusion criteria

Studies that only involved strategies for detection of other specific liver diseases e.g. Hepatitis B and C were excluded. Also excluded were studies not in English and those involving paediatric patients (<19 years).

Study Selection

Studies were initially screened by title and abstract, and then by full text, to determine which studies met the a priori selection criteria. Two team members (KGO and KA) completed title and abstract screening independently and with blinding to the others’ decisions in place. Blinding was then removed, and any conflicting decisions were discussed with a third team member (IM). Full text review was performed individually, and decisions discussed with all three team members. Further information was requested from authors directly, where needed. Where multiple publications existed related to a pathway, the paper which best described a pathway in its entirety was presented.

Where the same pathway was detailed in more than one published study that met the eligibility criteria, only one study was included. Figure 1 shows the study selection process.

Data extraction

Data collected were:

a) General study information (authors, year, country, study design, enrolment period and funding source)

b) Study population details (sample and setting, participants, age, sex, inclusion and exclusion criteria)

c) Pathway details (entry to pathway, detection method used, subsequent steps, follow up)
d) Outcome details (outcome measures collected e.g. change in liver disease diagnosis rate with pathway, loss to follow-up, cost effectiveness analysis)

Data synthesis

Study characteristics were tabulated. The stated goals of a pathway including a brief description were reported e.g. risk stratification of NAFLD, and the non-invasive tests involved to achieve this. Detection of advanced fibrosis (as defined by individual studies) was considered the main endpoint of interest within each study.
Results

Our systematic search of databases and grey literature identified 4478 records. After screening of the titles and abstracts, 4441 studies were excluded. The full text of 37 studies were assessed for inclusion and exclusion criteria, which resulted in a further 25 articles being excluded, leaving 12 studies for final review (see Figure 1). The final results of the search strategy, pathway descriptions and main findings are presented in Table 1.

Pathways utilising abnormal liver function tests (LFTs)

Six studies were identified that used abnormal LFTs, predominantly alanine transaminase (ALT), as the point of entry into a liver disease detection pathway, all based in the UK. All six studies described two-step processes for fibrosis assessment; two studies first used NAFLD Fibrosis Score (NFS) (14, 15); three studies first used Fibrosis-4 score (FIB4) (16-18); and one study used aspartate aminotransferase (AST)/ALT ratio >1 to trigger further assessment (19). Secondary assessment was either with Enhanced Liver Fibrosis (ELF) test or transient elastography (TE). Harman et al reported on performing TE in patients who had had an elevated ELF test in the setting of an intermediate FIB4 score (17). Four of these studies focused primarily on identification and risk stratification of suspected NAFLD, all of which used a two-step risk stratification assessment of fibrosis (13-15, 17). The Intelligent Liver Function Tests (iLFT) Pathway based in Tayside, Scotland, was distinct from other pathways utilising abnormal LFTs as it provides a diagnostically holistic automated cascade tool that primary care practitioners (PCPs) can select at the point of ordering a test (17).

Case-finding pathways in high-risk groups

Three pathways were identified that focused primarily on screening high risk groups for liver disease, two of which were in the UK. The Gateshead pathway involved the addition of a FIB4 to an annual diabetes review, with intermediate or high results triggering referral for a community-based TE (20). El-Gohary and colleagues presented the LOCATE study, a cluster randomised controlled trial which embedded a specialist hepatology nurse clinic in the primary care setting, receiving referrals from PCPs, patients with high AUDIT
scores on mail out questionnaires (questionnaire response rate was low at 21·7%), and

Case finding performed by the nurse specialist using primary care records (21). Hayward and colleagues presented an Australian study for the risk stratification of suspected NAFLD by PCPs; local guidelines defined this as ultrasound evidence of steatosis in the presence of metabolic risk factors and absence of excess alcohol consumption. The pathway was unique amongst those identified as it performed both a NFS and FIB4 in all referred patients and only if both were low were patients discharged back to primary care, by a community-based liver fellow or liver nurse specialist. Intermediate results were referred for TE and high FIB4 or NFS was referred to direct to secondary care clinic (22).

Case finding pathways in high-risk groups and/or elevated LFTs

Three pathways presented results which incorporated evaluation of patients with abnormal LFTs and those with known liver disease risk factors primarily included harmful alcohol consumption, obesity, type 2 diabetes (T2DM) and dyslipidaemia, with the latter three variables focusing on NAFLD (9, 22-24). Shaheen et al described a Canadian pathway dedicated to NAFLD detection and risk stratification utilising shear wave elastography in conjunction with abdominal ultrasound amongst patients with risk factors for NAFLD, facilitating the diagnosis of NAFLD in 94·1% of cases (23).

Ong et al presented the Leeds Community Hepatology Clinic (CHEP), a pilot study designed to detect NAFLD and ALD. If PCPs had a clinical suspicion of either disease process, they could order an ELF test. If the ELF test was elevated (defined as >9·5), the patients could be referred for a community-based TE (24). The Scarred Liver Project in Nottingham, UK describes a large, predominantly ALD and NAFLD case finding pathway, involving 110 primary care practices across four clinical commissioning groups. PCPs are advised to refer all patients with evidence of harmful alcohol consumption or risk factors for NAFLD to a TE clinic. In addition, the pathway also had a referral arm to accommodate patients with abnormal LFTs, where PCPs are encouraged to complete a non-invasive liver screen (NILS) and refer if the AST/ALT ratio is > 0·8. This was the commonest arm for referral (36·9% of referrals) (9).
Fibrosis detection

When comparing fibrosis detection, where possible the denominator reported is the number of patients referred for second step risk stratification e.g. following an intermediate FIB4 score, or secondary care referral e.g. due to a high FIB4 (see Table 1). This denominator was chosen as two step risk stratification is utilised to reduce false positives (25). The exception to this was the fibrosis detection rate reported for iLFTs, where the denominator reported is patients referred through iLFTs with an abnormal LFT in their step wedged trial (26). Fibrosis detection rates ranged from 3·4% in the Calgary NAFLD Care Pathway to 43·1% in the Gateshead Pathway (23). This could partly be explained by the absence of a two-step stratification within the Calgary NAFLD Care Pathway, resulting a larger denominator. Furthermore, Mansour et al took a pragmatic “real-world” approach of screening referrals for TE, and actively not referring in some cases e.g. amongst patients with frailty or life limiting conditions (20).

Amongst pathways using abnormal LFTs as the entry point to detect and risk stratify NAFLD, fibrosis detection rates ranged from 16·0% in the Camden and Islington NAFLD pathway to 26·6% in the Portsmouth Hospitals NHS Trust NAFLD Pathway. The former was a prospective longitudinal cohort study over 2 years, and the latter a retrospective service evaluation over a three-year period.

Amongst pathways that incorporated abnormal LFTs and screening patients with risk factors for liver disease, fibrosis detection rates were highest in the Scarred Liver Project pathway (22·9%). However, the CHEP pathway primarily reported TE results >15kPa i.e. cirrhosis, which was higher than the cirrhosis rate found by Chalmers et al in the Scarred Liver Project (5·8%) (9, 24).

Clinic attendance

A comparable assessment of attendance was possible between pathways that required TE, which were reported in five studies. Three studies reported attendances above 90%, two of which had clinics embedded in the primary care setting. The Gwent AST Project
reported the lowest clinic attendance rate of 53·6% but it was also the largest study, with over 2000 patients referred with an AST/ALT ratio >1.

Cost-effectiveness analysis

Cost-effectiveness of early diagnosis has been described in terms of both costs per diagnosis (26), and gains in quality adjusted life years (QALY) following interventions that occur downstream of diagnosis (26, 27). Two of the reported cost-effectiveness evaluations compared early diagnosis to standard of care testing, those evaluating the iLFT pathway and the Scarred Liver Project (Dillon, Tanajewski). The increase in diagnosis that is associated with the use of the iLFT pathway was associated with an increased cost of testing with an incremental cost per diagnosis of £284 (€334, $377). Extrapolating this increase in early diagnosis to a change in QALY requires an estimation of the impact of that diagnosis on the progression of liver disease. In the models developed for the lifetime evaluation of iLFT and the Scarred Liver Project a reduction in disease progression was incorporated. It is recognised in Tanajewski et al, which considers persons with NAFLD alone, that there were no published data to support the estimation of this effect size. The reduction in disease progression of 37% was modelled based on a phase 2 trial of rosiglitazone in persons with NASH (27). The modelled estimate in the reduction in disease progression in the evaluation of iLFTs is not reported in Dillon et al but was 25% for both alcohol-related liver disease and NAFLD (personal communication).

The lifetime cost-effectiveness was substantially different in the two models. For the iLFT evaluation it was found that early diagnosis would both reduce lifetime costs and increase life expectancy in the base case analysis. No deterministic sensitivity analyses are presented to understand whether changes in parameters where there is considerable uncertainty (including the probability of reduced disease progression after diagnosis) changed this estimate of cost-effectiveness. In the evaluation of the Scarred Liver Project for persons with NAFLD the incremental cost-effectiveness ratio (ICER) was £2,318 (€2,717, $3,073) per QALY gained in the base case. This was sensitive to both the rate of disease progression and the probability that treatment as a consequence of early
diagnosis results in reduced progression. In a scenario analysis where early diagnosis does not change the trajectory of disease the ICER was £18,130 (€21,246, $24,039).

Discussion

Summary of findings

This systematic review has identified 12 studies with established pathways for the early detection of liver disease in the community. Ten of these studies were based in the UK. This reflects the benefits of integrated care delivery between primary and secondary services that can be utilised within a National Health Service framework. Importantly, whilst this study has presented published established pathways, focusing on NAFLD and ALD, we acknowledge that there are many more similar unpublished pathways that have been developed to improve services locally between PCPs and specialist services, committed to the early detection and risk stratification of liver disease. This would indicate that clinical practice is ahead of the data in terms of detection and risk stratification of liver disease in the community. This possibly reflects an acknowledgement by clinicians that the status quo of waiting for patients with NAFLD or ALD to be referred by PCPs or present as hospital admissions creates unnecessary barriers for PCPs and represents poorer care for patients. As alcohol misuse and ALD continue to rise following the COVID-19 pandemic (28, 29), the value of refined pathways to identify and risk stratify individuals with suspected ALD becomes even more pertinent.

Where lifetime cost-effectiveness evaluations have been done, these are largely favourable in supporting the implementation of pathways to early diagnosis of liver disease. The base case estimates, where there is a significant impact of disease progression resulting from early diagnosis, are however substantially below the UK National Institute for Health and Care Excellence (NICE) willingness to pay threshold of £20,000 per QALY (30). The apparent difference between the findings of the two reported lifetime cost-effectiveness models may relate to differences in the populations considered (all patients vs. NAFLD alone) or to critical parameter estimates. It is important to note however that the lifetime cost-effectiveness of these pathways is critically dependent on the impact of early diagnosis of strategies to reduce fibrosis progression (31). It remains
unclear whether early diagnosis of liver disease in the primary care setting is associated with behaviour change that impacts fibrosis progression (11, 32). As novel treatment options are developed for the management of persons with NAFLD (33) there are likely to be substantial changes in the cost-effectiveness estimates of early diagnosis. This further highlights the need for high quality prospective studies of early diagnosis that capture sufficient data (including diagnosis and downstream changes in patient management) to improve existing cost-effectiveness models.

**Strengths and Limitations**

To the best of our knowledge this is one of the first attempts to describe pathways that focus on early detection and/or risk stratification of NAFLD and ALD in the community. However this systematic review has limitations. Studies did not report outcomes of advanced fibrosis in a uniform manner, thus we were unable to synthesise and meta-analyse studies to compare fibrosis detection rates between studies. This review focused solely on pathways presented in English and we cannot comment on or present early detection pathways from non-English scientific literature, thereby potentially missing relevant studies. With ten of the twelve studies presented based in the UK, how these results translate to healthcare services that are not free at the point of entry remains unclear. Furthermore, the studies presented are all set in urban areas. Alternative strategies may be required to detect liver disease in rural areas, where access to TE or ELF may be limited. Finally, by choosing to focus on ALD and NAFLD, the two commonest chronic liver diseases, in the general population, we excluded pathways designed to detect Hepatitis C. Many of these pathways were designed to detect and risk stratify Hepatitis C in patient groups that are traditionally hard to reach, and there remains valuable strategies to explore and replicate, for example in patients with alcohol dependency and no fixed abode.

**Selection of Non-Invasive Tests**

Many non-invasive tests (NITs) have been developed to identify fibrosis in patients with liver disease. AST/ALT ratio, ELF, FIB4, NFS and TE have been repeatedly validated in
ALD and NAFLD in secondary care populations with known liver disease, often histologically proven (25, 34-36). However, how NITs for liver fibrosis perform in the general population where liver fibrosis prevalence is much lower is still not well understood. Given low community prevalence of fibrosis, NITs are perhaps best used for their negative predictive value in ruling out clinically significant liver disease (25). Furthermore, tests like AST/ALT ratio, FIB4 and NFS have the additional benefit of being cheap, composite markers that are easily accessible to all PCPs.

When improving community detection of clinically significant liver disease, consensus appears to have been achieved in a two-step fibrosis risk stratification process amongst eleven of the twelve pathways presented. Pathways that utilise this have demonstrated a reduction in unnecessary referrals and simultaneously an increase in detection and specialist referral of clinically meaningful fibrosis, i.e. ≥F3, which is associated with increased liver related events and mortality (13, 37). In separate modelling studies of pathways, including those done alongside pathways identified in this review, a two-step risk stratification has been demonstrated to be the most cost-effective modality for stratifying liver disease (38).

Where pathways differ is in which components constitute their two step-approach, and particularly whether ELF or TE is used as the second fibrosis assessment. Both have excellent receiver operator characteristics in the detection of advanced NAFLD and ALD fibrosis (25). ELF has the benefit of being analysed along with all other serological investigations through a single blood test. This is even more valuable in the post pandemic era where patients are being asked to minimise journeys to the hospital. However, laboratories are required to purchase the patented Siemens® equipment to process an ELF test, which is expensive. As a result, access to ELF, at least in the UK, is mixed. Alternatively, TE is a simple, non-invasive, point of care assessment which can provide immediate results to patients and the clinician. However, it requires patients to attend clinic, training of the operator, and maintenance of the equipment.

*Entry point to testing*
Based on the twelve pathways present, there appears to be equipoise amongst the hepatology community as to the entry point for pathways that detect advanced fibrosis, using abnormal LFTs versus case finding based on known risk factors for NAFLD and ALD, the two commonest liver diseases in the western world. LFTs can often be normal and falsely reassuring in advanced liver disease, with a systematic review by Harris et al demonstrating normal LFTs in significant liver disease ranged from 41·0-74·6% (39). Conversely, the sheer volume of LFTs performed in primary care does provide an opportunity to risk stratify those with abnormal LFTs, with over 20% of LFTs having at least one elevated marker (6, 40).

A national survey by Jarvis et al of clinical commissioning groups across the UK, with 99% of groups responding, found only 29% and 40% of regions had some pathway in place to manage liver disease or abnormal LFTs respectively in the primary care setting (41). This is despite all the pathways presented in this review having demonstrated superiority over “standard of care” in detection of liver disease, with robust cost benefit being illustrated in modelling from iLFTs and Scarred Liver Project.

This review also noted a lack of consensus on which upper limit of normal (ULN) to constitute an abnormal LFT. Using lower ALT levels may facilitate earlier detection of liver disease but concerns remain over how this impacts service delivery. Notably laboratories often use ULN levels of ALT not accounting for age, sex or BMI, despite evidence suggesting these variables affect the value (42-44).

Implications for future research

Future research in this area should focus on trials comparing and contrasting pathways with the different entry points of abnormal LFTs versus case finding amongst patients with risk factors for ALD and NAFLD (see Table 4). These trials should be performed across geographical areas with varying prevalence of obesity and harmful alcohol use. To allow better comparison, future early detection and risk stratification pathway studies should preferably report on:
• Measures of liver-related morbidity and mortality that might include unplanned admissions due to liver disease in tested and untested populations
• ≥F2 equivalent fibrosis and cirrhosis detection in intervention arm compared to standard of care.
• Secondary care clinic attendance following risk stratification.
• Cost effectiveness evaluation, reporting QALYs gained per pathway versus standard of care.
• How a pathway has impacted secondary care referrals.
• Behaviour changes – weight loss, alcohol consumption – after testing

Finally, future prospective work is required to address how early detection of liver disease truly impacts survival. Globally, the gastroenterology and hepatology community must be proactive, not reactive, in collaboration with primary care colleagues to reduce the burden of liver disease and positively impact on our patients' lives.
References


C3 - EMBASE 621859599.


### Table 1. Pathways included in literature review

<table>
<thead>
<tr>
<th>Entry point to pathway</th>
<th>Study, Country</th>
<th>Pathway goal</th>
<th>Pathway description</th>
<th>Fibrosis assessment</th>
<th>Study size (mean age; %female)</th>
<th>Main findings</th>
<th>Fibrosis detection (n)</th>
<th>TE attendance rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Camden &amp; Islington NAFLD Pathway. Srivastava et al. 2019. England (16)</td>
<td>Detection and risk stratification of NAFLD</td>
<td>PCPs were instructed to perform a FIB4 in patients with a raised ALT +/- steatosis and negative NILS in absence of excessive alcohol consumption. If this was high, patients were referred to Hepatology clinic, and if intermediate, an ELF test &gt;9.5 triggered referral.</td>
<td>FIB4 (1-30;2-25)</td>
<td>ELF (&gt;9-5)</td>
<td>3012 (54-4 years; 46-7%)</td>
<td>3012 patients were analysed. Authors found a 2-step pathway reduced unnecessary referrals by 88% in practices using the pathway. There was also a 4-fold increase in the detection of advanced fibrosis and cirrhosis compared to SoC.</td>
<td>16-0% (232/1452)</td>
<td>n/a</td>
</tr>
<tr>
<td>COMMANDS. Burke et al, 2018. England (14)</td>
<td>Detection and risk stratification of NAFLD</td>
<td>Randomised controlled trial. Electronic integrated care pathway (eICP) developed to guide primary care practitioners (PCPs) through NAFLD diagnostic assessment. x2 ALTs &gt;70UI and suspected NAFLD (e.g., steatosis on US) required for pathway entry. †</td>
<td>NFS**</td>
<td>ELF **</td>
<td>52 (52 years; 29%)</td>
<td>52 patients involved in initial pilot, with 100% of the eICP intervention arm having appropriate exclusion of alternate diagnoses vs 57-7% in the SoC arm. NAFLD diagnosis made in 64% of patients within intervention arm. No diagnoses could be made in SoC arm due to lack of investigations.</td>
<td>18-2% (4/22)</td>
<td>n/a</td>
</tr>
<tr>
<td>iLFTs Pathway. MacPherson et al 2020. Scotland (17)</td>
<td>Diagnosis and risk stratification of liver diseases</td>
<td>Automated investigation algorithm on initial abnormal LFT samples (ALT&gt;30U/l), with full NILS and non-invasive fibrosis scores +/- ELF where indicated. GPs required to enter alcohol consumption, BMI and metabolic syndrome at point of request. Once diagnosis established through reflex testing, GPs are sent a link to management plan.</td>
<td>FIB4 (≥1-45 if &lt;65yrs; ≥2-00 if ≥65yrs) and/or NFS (≥-1-455 if &lt;0-120 if ≥65yrs)</td>
<td>ELF (&gt;9-8) ‡</td>
<td>554 (52-9 years; 44-4%)</td>
<td>Increase in liver diagnosis by 43%, with diagnostic accuracy of &gt;90% (26). Since going ‘live’ in August 2018, annually iLFTs instructs secondary care referral in 25-3% of outcomes with primary care management in 74-7%. The commonest outcome was an isolated ALT without fibrosis (23-5%). Cost-effectiveness modelling suggested a low incremental cost-effectiveness ratio of £284 per correct diagnosis.</td>
<td>12-5% (8/64)</td>
<td>n/a</td>
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<tr>
<td>Gwent AST Project. Yeoman et al, 2020. Wales (19)</td>
<td>Detection of advanced fibrosis of any cause</td>
<td>Automatic calculation of AST/ALT ratio if ALT raised; referral for TE in secondary care if ratio &gt;1.</td>
<td>AST/ALT ratio (&gt;1)</td>
<td>TE (≥8kPa)</td>
<td>17,770 (age/sex demographics not stated)</td>
<td>17,770 patients with elevated ALT. 2117 (12%) with AST/ALT ratio &gt;1. 750 patients referred for TE, substantial clinic nonattendance rate (&gt;40%). Of those that attended TE clinic, 29% had cirrhosis, with NAFLD accounting for 49% of diagnoses.</td>
<td>9-1% (192/2117)</td>
<td>53-6%</td>
</tr>
<tr>
<td>Oxford University Hospitals NHS Foundation Trust NAFLD Pathway. Harman et al, 2020. England (18)</td>
<td>Detection and risk stratification of NAFLD</td>
<td>In patients with an ALT&lt;4x ULN with negative NILS, PCPs are instructed to perform a FIB4 (with reflex ELF testing if intermediate score). Patients with an intermediate FIB4 + high ELF (≥9.5) or high FIB4 are referred to hepatology clinic. In secondary care clinic patients have TE.</td>
<td>FIB4 (≥1-30-2-67)</td>
<td>ELF (≥9-5) +/- TE (≥8kPa)</td>
<td>670 (age/sex demographics not stated)</td>
<td>Of 670 patients enrolled in this pathway, 139 were referred to liver clinic. The study was primarily evaluating concordance of FIB4, ELF and TE within the pathway, finding 56% of patients with an elevated ELF had an elevated liver stiffness measurement (LSM). No clear factors associated with discordant FIB4/ELF/LSMs could be identified.</td>
<td>20-7% (139/670)</td>
<td>Not stated</td>
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<td>Location</td>
<td>Risk Factors</td>
<td>Abnormal LFTs and Risk Factors</td>
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<td>Portsmouth Hospitals NHS Trust NAFLD Pathway. Fowell et al, 2021. England (15)</td>
<td>Detection and risk stratification of NAFLD PCPs managing patients with steatosis on US +/- elevated ALT in absence of alcohol abuse and a negative NILS, are asked to send NFS. High NFS are referred directly to Hepatology clinic and intermediate scores are referred to a nurse-led one stop FibroScan clinic. NFS (-1.455 – 0.675) TE (≥7.9kPa) 904 (59 years; 47-1%) 87-4% of referrals through this pathway were diagnosed with NAFLD. Amongst this group 70-6% had an LSM&lt;7.9kPa, and the pathway was able to discharge 70-9% of referrals back to primary care overall. 26-6% (210/790) 97-2%</td>
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<td>Gateshead Pathway. Mansour et al, 2021. England (20)</td>
<td>Detection of advanced fibrosis, primarily in NAFLD Routine FiB4 screening at annual review of T2DM. If intermediate or elevated and deemed appropriate to investigate further, referred for TE. FiB4 (≥1:3 if 35-65yrs; ≥2:0 if &gt;65yrs) TE (≥8kPa) 466 (63-8 years; 37-1%) 18-5% of diabetic patients screened had an elevated FiB4 (n=85/467). Of the 58 patients referred, 43-1% had an elevated LSM of &gt;8kPa. Over a fifth of patients referred for TE had cirrhosis. 43-1 % (25/58) 93%</td>
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<td>LOCATE Study. El-Gohary et al, 2018. England (21)</td>
<td>Detection of advanced fibrosis, primarily in NAFLD and ALD Cluster randomised feasibility trial. Nurse-led primary care-based clinic accessible via 3 routes: (1) PCPs referral (2) Community based liver nurses performing case finding of patients with risk factors for liver disease (e.g. type 2 diabetes) risk factors using electronic records (3) Patients with high AUDIT scores based on mailed out questionnaires. Liver Traffic Light Test (Green/ Amber/ Red) TE (6-8kPa – liver warning; 8-12-9kPa) 14,622 (49 years; 50-7%) Of the 910 patients seen in community nurse led clinic – 4-8% had probable cirrhosis and a further 15-5% had advanced fibrosis. Over half of new cases of liver disease identified through the nurse-led case finding intervention arm. The intervention arms identified more than double the number of new cases of liver disease compared to SoC. 15-5% (141/910) n/a</td>
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<td>Towards Collaborative Management of NAFLD (TCM-NAFLD). Hayward et al, 2021. Australia</td>
<td>Risk stratification of NAFLD Pilot study. PCP diagnosis of suspected NAFLD, referred to pathway. Liver Fellow or Hepatology nurse visiting practice perform NFS and FiB4, in referrals if one or both were high, referral to secondary care made. If one or both indeterminate (but not high) – TE performed, if &gt;8kPa referred to secondary care. NFS (-1.455 – 0.675) AND/OR FiB4 (1.3-2.67) TE (≥8kPa) 220 (58-7 years; 69-1%) 220 patients referred through pathway. 153 had completed assessment; 9-1% had ≥F2 fibrosis, 3-9% had cirrhosis. Concordance for low risk NFS ad FiB4 scores was found in 34-0%. 9-2% (14/153) 97-8%</td>
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<td>Calgary NAFLD Care Pathway. Shaheen et al. 2020. Canada (23)</td>
<td>Detection and risk stratification of NAFLD Patients with risk factors for NAFLD including T2DM, elevated BMI, dyslipidaemia, previous imaging suggesting steatosis or elevated liver enzymes (in absence of alcohol abuse or viral hepatitis) were referred for abdominal USS and SWE. A SWE &gt;8kPa triggered Hepatology referral. USS + SWE (≥8kPa) n/a 2084 (55 years; 53-7%) 2084 patients with possible NAFLD were assessed, with 94-1% having confirmation of diagnosis. 167 patients were referred to Hepatology clinic (67 with SWE &gt;8kPa; 100 with inconclusive SWE). Authors noted that using an intermediate FiB4 cut-off would have more than doubled the secondary care referrals. 3-4% (67/1958) n/a</td>
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<tr>
<td>Leeds Community Hepatology Clinic (CHEP). Ong et al,</td>
<td>Detection of advanced fibrosis, primarily in NAFLD and ALD Pilot study. Patients with clinically suspected NAFLD or ALD had an ELF test performed by PCPs. If ELF was ≥9.5 patients had TE in the community. ELF (&gt;9.5) TE (≥15kPa defined significant fibrosis) 1450 (age/sex demographics) Of 1450 patients assessed through the community pathway, 572 had an elevated ELF, with 71% attending their TE appointment. 66% of these patients had NAFLD and 31% had ALD. The pilot pathway was demonstrated to be cheaper than SoC. 53 3% of patients were discharged after clinic vs 9.6% in SoC. 11·1% (45/405) 71%</td>
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<td>Scarred Liver Project. Chalmers et al, 2020. England (9)</td>
<td>Detection of advanced fibrosis of any cause</td>
<td>Patients with risk factors for NAFLD or ALD (obesity, T2DM, harmful alcohol consumption) can be referred to nurse led TE clinic. Simultaneously patients with elevated LFTs, a negative NILS and AST/ALT ratio ≥0·8 could be referred to the clinic. *</td>
<td>AST/ALT ratio (≥0·8) OR FLI * (≥60)</td>
<td>TE (8-14kPa consider referral; ≥15kPa all referred)</td>
<td>968 (56·3 years; 51%)</td>
<td>In population of &gt;700,000, 968 patients referred for TE in one year, most commonly through abnormal LFTs pathway. Of this group 22·9% has an LSM &gt;8kPa, with 5·9% having cirrhosis. Without case finding strategy, authors demonstrated 38·7% of cases of liver disease would go undetected.</td>
<td>22·9% (222/968)</td>
<td>Not stated</td>
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</table>

† Authors confirm pathway has since changed with FIB4 used instead of NFS. Patients with an indeterminate FIB4 are supported via electronic advice and guidance system and are stratified with TE. Patients with high FIB4 are referred direct to hepatology clinic for assessment.
‡ Authors confirm a liver nurse led pathway remains embedded within the community rather than each individual GP practice.
γ Authors confirm the pathway is now established throughout the local area, incorporating a stepwise risk stratification using FIB4 and ELF testing. PCPs can refer directly for TE in community.
¥ Authors confirm the abnormal LFTs arm of the pathway has been updated with AST/ALT and FLI being replaced with FIB4 – individuals with an intermediate FIB4 referred for TE or ELF and high FIB4 scores being referred to Hepatology clinic.
Θ Authors confirm cut-off values. Pathway altered from initial published trial to include ELF as second stage rather than specialist clinic review.
** Authors have not published cut-off values
* Amongst assessed and risk stratified as intermediate/high risk. Fibrosis detection defined as >/=F2 based on TE or ELF result

** Abbreviations: ALD – alcohol related liver disease; ALT – alanine transaminase; AST – aspartate aminotransferase; ELF – enhanced liver fibrosis; FLI – Fatty Liver Index; FIB4 – Fibrosis-4; LSM – liver stiffness measurement; NFS – NAFLD fibrosis score; NILS – non-invasive liver screen PCPs- primary care practitioners; SoC – standard of care; SWE – shear wave elastography TE – transient elastography; T2DM – type 2 diabetes mellitus; ULN – upper limit of normal; USS – ultrasound scan.**
Table 2. Cost-effectiveness analysis available amongst pathways

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Cost-effective analysis</th>
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<tr>
<td>LOCATE Study. El-Gohary et al, 2018. (21)</td>
<td>No formal costing analysis but service costing for local business case was a third of the pre-existing liver outpatient referral service.</td>
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<td>iLFTs Pathway. Dillon et al 2019. (26)</td>
<td>ICER £284 per correct diagnosis Modelled cost-saving of £3216 per patient lifetime to the NHS Additional 0.021 QALY gained (26)</td>
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<td>Leeds Community Hepatology Clinic (CHEP). Ong et al, 2020. (24)</td>
<td>Overall costs of liver investigations in referred patients was £162 in the pilot pathway vs £258 for patients referred through SoC. Cost savings were mainly through elimination of duplicate testing</td>
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<td>Scarred Liver Project. Chalmers et al, 2020. (9)</td>
<td>Markov modelling following pilot study demonstrated the pathway costs £2138 per QALY gained compared to SoC for a patient diagnosed with NAFLD. There was an 85% probability of cost effectiveness at the NICE willingness to pay threshold of £20,000 per QALY (31).</td>
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<td>Calgary NAFLD care pathway (45)</td>
<td>Decision analytic model suggested FIB4 followed by SWE was most cost effective strategy for detecting F2 and F3 NAFLD fibrosis in patients compared to all other NITs. (45)</td>
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<tr>
<td>Term</td>
<td>Description</td>
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<td>----------------------------------------------</td>
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<td>Disability-adjusted life-years (DALY)</td>
<td>A DALY represents one year of healthy life. It can be expressed as DALYS lost compared with the maximum achievable life-expectancy without disease or disability, i.e. the number of healthy years lost. (46)</td>
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<td>Quality-adjusted life-years (QALY)</td>
<td>Outcome measure used to quantify effectiveness of a specific intervention. To accommodate for the multifarious impacts of an intervention, QALYs incorporate gains in quality of life and quantity of life (47). One quality adjusted life year is equal to 1 year of perfect health. The National Institute for Clinical Excellence (NICE) considers interventions costing the NHS less than £20,000 per QALY gained as cost-effective (30).</td>
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<td>Incremental cost-effectiveness ratio (ICER)</td>
<td>Summary measure reflecting the economic value of an intervention. It is the difference in the change in mean costs in the population of interest (incremental cost) divided by the difference in the change in mean outcomes in the population of interest (incremental effect). QALYs can used as the denominator in this calculation, providing an “extra cost per extra unit of health effect” (48).</td>
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### Table 4. Key research questions

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<th>Key questions for future early detection pathways research</th>
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<td>What is the optimum entry point to detect and risk stratify liver disease in the general population? Is it focusing on patients with abnormal LFTs or those with risk factors for NAFLD and ALD?</td>
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<td>Does early detection of liver disease actually impact morbidity and mortality associated with liver disease?</td>
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<td>What is the efficacy of lifestyle and pharmacological interventions following the early detection of liver disease? Furthermore, does this vary by stage of liver disease detected?</td>
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<td>At a population level, does the diagnosis of alcohol related fibrosis/cirrhosis reduce harmful alcohol consumption? Is alcohol consumption maintained or increased in those without disease, a “free pass” to drink more?</td>
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