Technoleg Iechyd Cymru
Health Technology Wales

Topic Exploration Report [1]

Topic explorations are designed to provide a high-level briefing on new topics submitted for consideration by Health Technology Wales. The main objectives of this report are to:

- Determine the quantity of evidence available for a technology of interest.
- Identify any gaps in the evidence.
- Inform decisions on topics that warrant fuller assessment by Health Technology Wales (HTW).

Topic exploration report number	TER506
Topic	ELF (Enhanced Liver Fibrosis) test for the assessment of liver fibrosis
Summary of findings	Two guidelines, three systematic reviews, one HTA, two cost-effectiveness studies, and four primary studies were identified. Across the evidence base, the population, care pathway, and cut-off thresholds for the diagnosis of liver fibrosis varied, and there was variation in the reported the sensitivity and specificity of the ELF test. Two NICE guidelines recommended the use of the ELF test, although the threshold for diagnosing advanced liver fibrosis is higher (10.51) than the suggested threshold of 9.8 from Siemens Healthineers (manufacturer of the ELF test). Within the NICE guideline, the ELF test ranked first compared to other diagnostic strategies, using relevant thresholds for each test, with reference to a cost-effectiveness threshold of £20,000 per QALY (quality-adjusted life years) gained. In a recent prospective study, advanced liver fibrosis was defined as an ELF score of 9.8 or more and in their cost-utility analysis, the ICER was £2541.24 per QALY for the ELF test. Generally, the diagnostic performance of the ELF test across the primary studies was considered good or high. Two primary studies demonstrated that the ELF test was more accurate than the Fibrosis-4 index (FIB-4) and NFS (NAFLD fibrosis score). In general, the evidence suggests that the ELF test is clinically effective and cost effective, and most effective when used in sequence with the FIB-4 test. If this topic were to progress to a fuller appraisal, the population, care pathway and clinical thresholds would need to be explored further.

[1] Cyfieithu dogfennau HTW wedi'u cyhoeddi o'r Saesneg i'r Gymraeg
Translation of published technical HTW documents from English into Welsh

Introduction and aims

Primary non-alcoholic fatty liver disease (NAFLD) or metabolic dysfunction-associated steatotic liver disease (MASLD) is an excess of fat in the liver (steatosis) that is not a result of excessive alcohol consumption or other secondary causes. NAFLD is more common in people who have excessive abdominal fat, insulin resistance or type 2 diabetes, hypertension and dyslipidaemia (NICE 2016b).

The ELF test is a non-invasive blood test which combines three direct serum biomarkers of liver fibrosis. The ELF test has the potential to identify people at high risk of advanced liver fibrosis (such as fibrosis stage three or four) much earlier than the current standard of care. Other key benefits include the reduction in unnecessary referrals to specialists and could therefore reduce the number of unnecessary liver biopsies. The ELF test has several early adopter sites where the technology has been deployed, including six sites in England, The University Hospital of Dundee in Scotland, and the University Hospital of Wales in Cardiff.

In the care pathway, the ELF test would be offered to people with a FIB-4 score between 1.30 and 2.67, who are considered at an intermediate risk of advanced liver fibrosis. People with a FIB-4 score higher than 2.67 are considered at high-risk of advanced liver fibrosis and will be referred to hepatology services for further fibrosis assessment, staging and potentially management. The ELF test can be performed using the same blood sample used for the FIB-4 determination. The manufacturers of ELF, recommend that a score 9.8 or more suggests the presence of advanced fibrosis.

Health Technology Wales researchers searched for evidence on the clinical and cost effectiveness of the ELF test for people with MASLD/NAFLD.

Evidence overview

Guidance

HTW researchers identified two relevant NICE guidelines (NICE 2016b, NICE 2016a). 'Non-alcoholic fatty liver disease (NAFLD): assessment and management [NG49] (NICE 2016b) recommends considering using the ELF test to look for advanced liver fibrosis in people with NAFLD. A total of three studies in the guideline report on the ELF test. If the result of the ELF test is 10.51 or above, and the person also has NAFLD, the guideline recommends diagnosis of advanced liver fibrosis [recommendation 1.2.4]. The guideline reported that among the 13 diagnostic strategies included in the first stage and second stage comparison, ELF ranked first having the highest diagnostic accuracy across the compared tests. 'Cirrhosis in over 16s: assessment and management [NG50]' recommends testing for cirrhosis using transient or ARFI (acoustic radiation force impulse) elastography if the person has a score of 10.51 or above using the ELF test (NICE 2016a).

Health Technology Assessments

Adelaide HTA (AHTA) published a HTA in 2016 on 'Enhanced liver fibrosis test' although at the time of writing this TER, the full text was unavailable (Parsons & Ellery 2016). In the abstract, the authors recommended that the ELF test may be useful in determining liver fibrosis in people with cirrhosis and may be of benefit to people in rural and remote locations with no or limited access to other non-invasive means of measuring liver fibrosis.

Secondary evidence

HTW researchers identified three systematic reviews with meta-analyses about the ELF test (Hinkson et al. 2023, Sharma et al. 2021, Vali et al. 2020), however, there is some overlap of individual studies that are included in the reviews. Populations included those with NAFLD,

advanced liver fibrosis, cirrhosis, and hepatic fibrosis. The diagnostic accuracy of the ELF test varied between different liver diseases across the systematic reviews. For example, Hinkson et al. (2023) reported that the ELF test varied in its ability to distinguish levels of fibrosis depending on the type and severity of disease (e.g., NAFLD, viral hepatitis, and alcohol related liver disease).

There are also variations in the pre-defined cut-offs depending on guidelines. Vali et al. (2020) found the ELF test to have high sensitivity (more than 0.90) for fibrosis at a threshold of 7.7. The study reported that higher cut-off values had lower sensitivity and could not be used to exclude advanced fibrosis, particularly in low-prevalence settings. To achieve a specificity of 0.90 for advanced and significant fibrosis, thresholds of 10.18 (sensitivity: 0.57) and 9.86 (sensitivity: 0.55) were required, respectively. Thus, the ELF test showed high sensitivity but limited specificity for advanced and significant fibrosis at low cut-offs.

Sharma et al. (2021) assessed the diagnostic accuracy of the ELF test for cases of advanced fibrosis, in people who had undergone liver biopsy. The review reported that the ELF test demonstrated good performance in detecting advanced fibrosis in people with NAFLD. This was measured by the area under the curve (AUC). The AUC ranged from 0.78 to 0.97, and good diagnostic performance (AUC 0.85 to 0.92) for detecting cirrhosis in people with NAFLD. The systematic review supported the use of the ELF test across a range of chronic liver diseases as a possible alternative to liver biopsy in selected cases.

Primary evidence

HTW researchers identified a further four primary studies on the ELF test that were published since the latest systematic review in 2023 (Arai et al. 2023, Kjaergaard et al. 2023, Saarinen et al. 2023, Seko et al. 2023). The population, comparator and outcomes varied across the four primary studies. The populations used in the studies included: the general population (Kjaergaard et al. 2023, Saarinen et al. 2023), those at risk of NAFLD (Kjaergaard et al. 2023), people with biopsy-proven NAFLD (Arai et al. 2023, Seko et al. 2023), and people with type 2 diabetes (Arai et al. 2023). Based on their abstracts, the comparators included: the FIB-4 test (Arai et al. 2023, Kjaergaard et al. 2023, Seko et al. 2023) and NFS (Arai et al. 2023, Kjaergaard et al. 2023) and the Mac-2-binding protein glycosylation isomer (M2BPGi) (Seko et al. 2023). The retrospective cohort study by Saarinen et al. (2023) examined data from a survey conducted in 2000-2001 and it is unclear from the abstract whether a comparator was used.

Across the primary studies, outcomes include diagnostic accuracy outcomes (i.e., sensitivity, negative predictive values, and specificity). Generally, the diagnostic performance of the ELF test across the primary studies was considered good or high. Two primary studies demonstrated that the ELF test was more accurate than the FIB-4 and NFS (Arai et al. 2023, Kjaergaard et al. 2023). Arai et al. (2023) reported that the AUC for predicting advanced fibrosis was greater (0.828) than that of the FIB-4 index (0.727) and NFS (0.733). In Kjaergaard et al. (2023), ELF diagnosed advanced fibrosis with significantly better diagnostic accuracy than FIB-4 and NFS: AUC 0.85 (95% CI 0.79-0.92) vs. 0.73 (0.64-0.81) and 0.66 (0.57-0.76), respectively.

Cost-effectiveness evidence

Information from the topic proposer states that the ELF test is estimated to be £55 per test including laboratory costs. It is also stated that within the diagnostic pathway which combines FIB-4 and ELF followed by referral to a liver clinic for fibrosis staging, the combined cost of initial diagnosis and staging is estimated to be £109.19 per person.

HTW researchers identified a cost-utility analysis reported in NG49 (NICE 2016b). The original cost-utility analysis compared 17 strategies for testing adults with NAFLD for advanced fibrosis

Evidence overview

and found that the ELF test ranked first compared to other diagnostic strategies, using relevant thresholds for each test, with reference to a cost-effectiveness threshold of £20,000 per QALY gained.

The latest systematic review (Hinkson et al. 2023) referenced Srivastava et al. (2019), a cost-comparison analysis of FIB-4, ELF and fibroscan in community pathways for NAFLD from a UK healthcare payer perspective. A cut-off threshold of 10.3 was used identify cases at increased risk of advanced fibrosis. The analysis assessed several scenarios including a FIB-4 test followed by the ELF test for people with indeterminate FIB-4 results. This scenario was more effective than the standard of care and yielded the largest cost savings, compared with other scenarios, with a 25.2% budget spend reduction in total healthcare spend from an NHS perspective within a 1-year horizon.

Since the publication of the latest systematic review (Hinkson et al. 2023), HTW researchers identified a prospective study on the prevalence of MASLD in people with type-2 diabetes from a UK perspective (Forlano et al. 2024). The study looked at the cost effectiveness of five different screening strategies compared to standard of care, where ELF was evaluated. In this study, a cut off threshold for diagnosing advanced liver fibrosis was 9.8 or higher. A Markov model was built based on the fibrosis stage, defined by transient elastography (TE). The authors generated the cost per QALY gained and calculated the incremental cost-effectiveness ratio (ICER) over a lifetime horizon. All the screening strategies were associated with QALY gains with TE (148.73 years) having the most substantial gains, followed by FIB-4 (134.07 years), ELF (131.68 years) and NAFLD fibrosis score (121.25 years). In the cost-utility analysis, the ICER was £2480/QALY for TE, £2541.24/QALY for ELF and £2059.98/QALY for FIB-4.

Ongoing research

HTW researchers did not identify any on-going research about the ELF test to be completed within the next 6-12 months.

Areas of uncertainty

The diagnostic accuracy of the ELF test varied across the systematic reviews, and between different liver diseases and similar diagnostic tests, although recent studies suggest the use of the ELF test in sequence with the FIB-4 test yields the greatest benefit in the care pathway, as suggested by the topic proposer. Clarity would also be needed about the most appropriate target population (i.e., whether this would focus on NAFLD or other liver diseases).

Cost effectiveness data suggests clear benefits of the ELF test, although the comparators and standard of care varied. If this topic were to progress to rapid review stage, clarity regarding the intervention, comparator, and standard of care would be needed.

Literature search results

Health technology assessments and guidance
NICE. (2016a). Cirrhosis in over 16s: assessment and management. NICE guideline [NG50]. National Institute for Health and Care Excellence. Available at: https://www.nice.org.uk/guidance/ng50/ [Accessed 18 December 2023]. NICE. (2016b). Non-alcoholic fatty liver disease (NAFLD): assessment and management. NICE guideline [NG49]. National Institute for Health and Care Excellence. Available at: https://www.nice.org.uk/guidance/ng49 [Accessed 18 December 2023]. Parsons J, Ellery B. (2016). Enhanced liver fibrosis test. HTA. Australia: Adelaide Health Technology Assessment. Available at: https://database.inahta.org/article/19117 [Accessed 27 December 2023].
Evidence reviews and economic evaluations
Forlano R, Stanic T, Jayawardana S, et al. (2024). A prospective study on the prevalence of MASLD in people with type-2 diabetes in the community. Cost effectiveness of screening strategies. Liver Int. 44(1): 61-71. Available at: https://doi.org/10.1111/liv.15730 Hinkson A, Lally H, Gibson H, et al. (2023). Meta-analysis: Enhanced liver fibrosis test to identify hepatic fibrosis in chronic liver diseases. Aliment Pharmacol Ther. 57(7): 750-62. Available at: https://doi.org/10.1111/apt.17385 Sharma C, Cococcia S, Ellis N, et al. (2021). Systematic review: Accuracy of the enhanced liver fibrosis test for diagnosing advanced liver fibrosis and cirrhosis. J Gastroenterol Hepatol. 36(7): 1788-802. Available at: https://doi.org/10.1111/jgh.15482 Srivastava A, Jong S, Gola A, et al. (2019). Cost-comparison analysis of FIB-4, ELF and fibroscan in community pathways for non-alcoholic fatty liver disease. BMC Gastroenterol. 19(1): 122. Available at: https://doi.org/10.1186/s12876-019-1039-4 Vali Y, Lee J, Boursier J, et al. (2020). Enhanced liver fibrosis test for the non-invasive diagnosis of fibrosis in patients with NAFLD: A systematic review and meta-analysis. J Hepatol. 73(2): 252-62. Available at: https://doi.org/10.1016/j.jhep.2020.03.036
Individual studies
Arai T, Takahashi H, Seko Y, et al. (2023). Accuracy of the enhanced liver fibrosis test in patients with type 2 diabetes mellitus and its clinical implications. Clin Gastroenterol Hepatol. Availabke at: https://doi.org/10.1016/j.cgh.2023.11.022 Kjaergaard M, Lindvig KP, Thorhauge KH, et al. (2023). Using the ELF test, FIB-4 and NAFLD fibrosis score to screen the population for liver disease. J Hepatol. 79(2): 277-86. Available at: https://doi.org/10.1016/j.jhep.2023.04.002 Saarinen K, Färkkilä M, Jula A, et al. (2023). Enhanced liver Fibrosis® test predicts liver-related outcomes in the general population. JHEP Rep. 5(7): 100765. Available at: https://doi.org/10.1016/j.jhepr.2023.100765 Seko Y, Takahashi H, Toyoda H, et al. (2023). Diagnostic accuracy of enhanced liver fibrosis test for nonalcoholic steatohepatitis-related fibrosis: Multicenter study. Hepatol Res. 53(4): 312-21. Available at: https://doi.org/10.1111/hepr.13871
Ongoing research
No evidence identified

Date of search	27 December 2023
Concepts used	"ELF test" OR "Enhanced Liver Fibrosis Test"

Proposed research question and evidence selection criteria (if selected)

Proposed Research question	**What is the clinical and cost effectiveness of the ELF test to diagnose advanced liver fibrosis for people with MASLD/NAFLD?**

	Inclusion criteria	Exclusion criteria
Population	People considered at risk of advanced liver fibrosis.	Those with or at risk of alcohol related liver disease or other secondary causes.
Intervention	The ELF test, (to be used in sequence with FIB-4 in practice – using same blood test sample)	
Comparison/ Comparators	FIB-4 alone/standard of care	
Outcome measures	Diagnostic accuracy outcomes (e.g., sensitivity, specificity, positive predictive value, negative predictive value). Cost-effectiveness outcomes (e.g., resource use, QALY)	

Proposed speciality	
Proposed specialities	**Endocrine, nutritional, and metabolic**