Non-Invasive Serum Markers for the Diagnosis and Monitoring of Liver Fibrosis: Diagnostic Accuracy, Clinical Effectiveness/Utility, Cost-Effectiveness, and Guidelines
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Acknowledgments:

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada’s health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.
Research Questions

1. What is the diagnostic accuracy of non-invasive serum markers to detect liver fibrosis in patients with or suspected of having liver disease?
2. What is the clinical effectiveness and clinical utility of non-invasive serum markers to detect liver fibrosis in patients with or suspected of having liver disease?
3. What is the cost-effectiveness of non-invasive serum markers to detect liver fibrosis in patients with or suspected of having liver disease?
4. What are the evidence-based guidelines associated with the use of non-invasive serum markers to detect liver fibrosis in patients with or suspected of having liver disease?

Key Findings

Four systematic reviews (three including meta-analyses), two meta-analyses, three randomized controlled trials, and 36 non-randomized studies were identified regarding non-invasive serum markers for the diagnosis and monitoring of liver fibrosis. Additionally, eight evidence-based guidelines were identified.

Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, economic studies and guidelines. The results of a second focused search (with main concepts appearing in the title or subject heading) were also included. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2012 and August 2, 2017. Internet links were provided, where available.

Selection Criteria

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.
**Table 1: Selection Criteria**

<table>
<thead>
<tr>
<th><strong>Population</strong></th>
<th>Adult and pediatric patients with liver disease or suspected of having liver disease with accompanying liver fibrosis (e.g., but not limited to, chronic viral hepatitis, non-alcoholic fatty liver disease, alcoholic liver disease, liver malignancies, etc.)</th>
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<tr>
<td><strong>Intervention</strong></td>
<td>Serum markers (e.g., Aspartate Aminotransferase to Platelet Ratio Index [APRI], Fibrosis-4 [Fib-4]), Fibrotest</td>
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| **Comparator** | Q1-3: Liver biopsy; Placebo; No treatment  
Q4: No comparator |
| **Outcomes** | Q1: Diagnostic accuracy (in diagnosing/detecting fibrosis or staging/grading fibrosis severity, validity, reliability, sensitivity, specificity)  
Q2: Clinical effectiveness and utility (e.g., monitoring of liver fibrosis once treatment is initiated, use to make treatment decisions); Safety (e.g., false positives/false negatives, harms to the patient)  
Q3: Cost-effectiveness (e.g., incremental cost per QALY or health benefit gained)  
Q4: Guidelines (for both diagnosis and monitoring) |
| **Study Designs** | Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic evaluations, evidence-based guidelines |

**Results**

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, non-randomized studies, economic evaluations, and evidence-based guidelines.

Four systematic reviews (three including meta-analyses), two meta-analyses, three randomized controlled trials, and 36 non-randomized studies were identified regarding non-invasive serum markers for the diagnosis and monitoring of liver fibrosis. Additionally, eight evidence-based guidelines were identified. No relevant health technology assessments or economic evaluations were identified.

Additional references of potential interest are provided in the appendix.

**Health Technology Assessments**

No literature identified.

**Systematic Reviews and Meta-analyses**

   PubMed: PM24308774


Randomized Controlled Trials


Non-Randomized Studies

Adult Populations


24. Huang, H. et al. CHI3L1 is a liver-enriched, noninvasive biomarker that can be used to stage and diagnose substantial hepatic fibrosis [Internet]. OMICS. 2015 Jun 1 [cited 2017 Aug 14];19(6):339-345. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4486713/


PubMed: PM26110613

PubMed: PM26341864

PubMed: PM24798655

PubMed: PM25761184

PubMed: PM24472062

PubMed: PM25253959

PubMed: PM24942271

PubMed: PM24742130

PubMed: PM23742243


Pediatric Populations


Mixed Population


Economic Evaluations

No literature identified.
Guidelines and Recommendations

https://www.nice.org.uk/guidance/ng50/chapter/Recommendations
See: Recommendation 1.1.9

https://www.nice.org.uk/guidance/ng49
See: Identifying adults, young people and children with advanced liver fibrosis

See: Assessment of liver disease severity

See: Other liver elasticity-based imaging techniques – Recommendations, page 242

http://apps.who.int/iris/bitstream/10665/154590/1/9789241549059_eng.pdf?ua=1&ua=1
See: Recommendations: noninvasive assessment of liver disease stage at baseline and during follow up

http://apps.who.int/iris/bitstream/10665/111747/1/9789241548755_eng.pdf?ua=1&ua=1
See: 6.2 Assessing the degree of liver fibrosis and cirrhosis

http://www.sign.ac.uk/assets/sign133.pdf
See: 8.2 FIBROSIS MARKERS

See: Non-invasive assessment of steatohepatitis and advanced fibrosis in NAFLD
Appendix — Further Information

Previous CADTH Reports


Systematic Reviews and Meta-Analyses

Unclear Comparator/Reference Standard


Alternative Comparator


Non-Randomized Studies

Unclear Reference Standard


Alternative Comparator


Clinical Practice Guidelines – Uncertain Methodology


Additional References