Investigating and Referring Incidental Findings of Abnormal Liver Tests

Note on Referral Guidelines: these revised guidelines are presented as a tool to aid appropriate referral and management of common liver-related problems. The text below supplements the flowchart (Appendix 1 and available separately). The revisions are a response to an increasing prevalence of non-alcoholic fatty liver disease (NAFLD), incidental finding of hepatic steatosis on US scanning and our awareness that standard liver biochemistry (so-called liver function tests, LFTs) does not indicate the severity of NAFLD. We need to target those at high risk of advanced liver disease, who may previously have been missed (see NICE Guidance NG 49, NG 50).

These guidelines are not nuanced and are not intended to be restrictive: they do not supersede good clinical judgement. If you would like any advice regarding these topics, please contact the Hepatology email advice line using orh-tr.oxon.hepatologyadvice@nhs.net.

Hepatology Red Flags

Please investigate urgently and consider early Hepatology referral for patients with the following:

- Jaundice
- Severely deranged liver biochemistry
- New ascites
- Hepatomegaly/irregular liver/splenomegaly
- Prolonged prothrombin time (PT) / low albumin in the context of abnormal LFTs/thrombocytopenia

A. Mildly elevated Alanine Aminotransferase (ALT <4x ULN, +/- abnormalities in other LFTs)

1. Lifestyle; history and intervention
   a. Assess alcohol history and abstinence
      i. If alcohol intake regularly greater than 35 units/ week for a woman or 50 units/ week for a man → offer Direct Access FibroScan via Choose and Book
   b. Assess metabolic syndrome components and encourage weight loss
   c. Stop potentially hepatotoxic medications (NB Herbal medications, steroids and over-the-counter medications)
   d. Recheck LFTs 2-3 months after intervention
      i. If normal → consolidate lifestyle advice and recheck in 1 year
      ii. If still abnormal →

2. Please arrange full chronic liver disease screen, including:
   i. Abdominal ultrasound (US abdo)
   ii. Viral serology (Hepatitis B surface antigen, Hepatitis C antibody)
   iii. Autoimmune serology (antinuclear antibody (ANA); Immunoglobulins; Liver autoantibodies (anti mitochondrial, anti smooth muscle, anti liver kidney microsomal); coeliac serology (anti endomysial or tissue transglutaminase, TTG))
iv. **Metabolic** (Lipid profile; HbA1c; Ferritin; TSH; Caeruloplasmin (if age <40); alpha-1 antitrypsin levels)

a. If **POSITIVE** for viral or autoimmune markers →
   refer Hepatology (Viral Hepatitis clinic for positive hepatitis virus tests, otherwise General Hepatology clinic)

b. If screen **NEGATIVE** and persistently elevated or rising alkaline phosphatase (ALP) (>1.5 x ULN), need to exclude primary sclerosing cholangitis →
   refer Hepatology

c. If screen **NEGATIVE** for viral or autoimmune markers →
   likely NAFLD, request Risk Stratification Test

3. Request risk stratification test (Fib4-ELF) on ICE (searchable by “Fib4” or “ELF” or “NAFL”)

a. Table for interpretation of results available as link from result page and Appendix 2 below

b. If “low risk” →
   address cardiovascular risk factors and recheck risk stratification test in 3 years
   i. assess cardiovascular risk factors and modify as appropriate (note: NAFLD and mildly abnormal LFTs is not a contraindication to statin use)
   ii. aim for 7-10% weight loss over 6-12 months (consider MoreLife, WeightWatchers, Slimming World)
   iii. repeat risk stratification in 3 years

c. If “high risk” →
   refer to Metabolic Hepatology clinic

**Note:** Moderately to severely elevated ALT (>4x ULN, with or without abnormalities in other LFTs)

1. As per mildly elevated ALT, but check liver screen directly and do not wait 3 months
2. Consider direct referral to Hepatology clinic or contact orh-tr.oxon.hepatologyadvice@nhs.net

**B. Increased hepatic echogenicity or steatosis on ultrasound scanning**

1. Check LFTs
   a. If ALT elevated → Go to **A**.
   b. If ALT not elevated → assess alcohol intake
      i. If alcohol intake regularly greater than 35 units/ week for a woman or 50 units a week for a man → offer Direct Access FibroScan via Choose and Book
      ii. If alcohol intake exceeds national guidelines, provide brief intervention advice to reduce alcohol intake
      iii. Consider referral to alcohol services (Alcoholics Anonymous, Turning Point)
   iv. If alcohol intake not excessive, likely NAFLD, request Risk Stratification Test
   v. Look for and address metabolic syndrome components/ cardiovascular risk factors/potential steatogenic medications

2. If irregular liver contour and/or splenomegaly, suggests cirrhosis →
   please send chronic liver disease screen and refer directly to Hepatology
Note: components of the metabolic syndrome-
- Abdominal obesity
- Type 2 Diabetes or Impaired Glucose tolerance
- Hypertension (treated or untreated)
- Dyslipidaemia (low HDL or elevated fasting triglycerides, treated or untreated)

C. Isolated elevated gamma-Glutamyl Transferase (γGT)

*Please note: due to lack of sensitivity and specificity, we do not recommend use of γGT for routine liver function testing, nor to indicate excessive alcohol intake.*

1. If ALT elevated, proceed as per A-1
2. If ALT normal, proceed as per B

D. Isolated elevated Alkaline Phosphatase (ALP)

1. Check γGT
   a. If γGT normal → likely bone origin- please exclude pregnancy, check Bone profile and Vitamin D. Consider PTH testing and look for evidence of malignancy
   b. If γGT elevated → proceed as per A-1

E. Isolated elevated Bilirubin

1. Check conjugated/unconjugated (“split”) Bilirubin
   a. If elevated unconjugated Bilirubin and haemolysis excluded → likely Gilbert’s syndrome- reassure
   b. If predominantly conjugated hyperbilirubinaemia,
      i. look for and stop (if appropriate) potentially hepatotoxic medications then
      ii. proceed with abdominal US and chronic liver disease screen as per A-1.
      iii. If jaundiced (“red flag”) please consider early referral.

Note on statins: there is no contraindication to statin use in chronic liver diseases if indicated.
Statins are occasionally associated with elevated liver enzymes, frequently a manifestation of NAFLD and thus an association. Statin-induced abnormalities in liver biochemistry are usually low-grade and not associated with clinical sequelae. If there is concern that a rise in LFTs is statin-related (i.e if ALT rises to 3x ULN at 3 months from normal at baseline, or in association with new fatigue myalgia), consider stopping the statin and proceeding as per guidance (section A).
Appendix 1. Flowchart summary

**Guidelines Summary: Investigating Mildly Abnormal Liver Tests**

- **A. ↑ ALT + other LFT abnormalities**
  - **A-1. Lifestyle, Drug and Alcohol History and Intervention: Recheck LFTs in 2-3/12**
    - Normal
    - Abnormal

- **B. Steatosis on US**
  - Lifestyle and Alcohol review and intervention
  - Excessive alcohol: >35u (F) or >50u (M)
  - Chronic liver disease screen* + US abdo

- **C. Isolated ↑ GT**
  - Offer Direct Access FBroadsheets Unless Abnormal
  - Alcohol within recommended limits

- **D. Isolated ↑ ALP**
  - Go to A-1

- **E. Isolated ↑ Bil**
  - Go to A-1

- **Risk Stratification Test (Fib-4 ELF)²**
  - Low risk
  - High risk

- **Consolidate Lifestyle changes and recheck LFTs in 1 year**
  - Refer Hepatology
  - Weight loss, address cardiovascular risk and recheck Fib-4 ELF in 3 years

- **Refer Metabolic Hepatology**
  - Likely bony origin
  - Likely Gilbert's


- *mildly elevated ALT: <4x ULN; moderate >4x <10x ULN; severe >10xULN. If moderate or severe, refer directly to Hepatology (urgent if severe)
- Chronic Liver Disease Screen consists of: Hep B Ag, Hep C ab, ANA, Liver autoantibodies, Immunoglobulins, Ferritin, HbA1c
- Risk stratification test requested on ICE (search “Fib-4” OR “ELF” OR “NAFL”)
## Appendix 2. Interpretation of Fib4/ELF

### Interpretation of Fib-4 and ELF test in NAFLD

| Age < 35 | ELF < 9.0 | **Low risk for advanced liver fibrosis.**
|          |          | Treat metabolic risk factors and if there is ongoing risk suggest repeating test in 3 years. |
|          | ELF > 9.0 | **High risk for advanced liver fibrosis.**
|          |          | Recommend referral to Metabolic Hepatology Clinic. |

| Age > 35 | FIB-4 < 1.3 | **Low risk for advanced liver fibrosis.**
|          |          | Treat metabolic risk factors and if there is ongoing risk, consider repeating FIB-4 in 3 years. |
|          | FIB-4 1.3-2.67 (Indeterminate) | ELF < 9.5 | **Low risk for advanced liver fibrosis.**
|          |          | Treat metabolic risk factors and if there is ongoing risk consider repeating FIB-4 in 3 years. |
|          | FIB-4 > 2.67 | **High risk for advanced liver fibrosis.**
|          |          | Recommend referral to Metabolic Hepatology Clinic. |
|          | FIB-4 > 2.67 | **High risk for advanced liver fibrosis.**
|          |          | Recommend referral to Metabolic Hepatology Clinic. |

If you have any queries regarding the interpretation of the results, if there are any atypical clinical features or hepatic comorbidity, please contact the Hepatology email advice line on orh-tr.oxon.hepatologyadvice@nhs.net

We like to offer all patients with NAFLD access to clinical trials. If your patient is interested then please email: Nellia.Sande@ouh.nhs.uk