Northern England
Strategic Clinical Networks

Liver Network

Guidelines for the Management of Adults with Asymptomatic Liver Blood Test Abnormalities

Prof Stuart McPherson
On behalf of the North East & North Cumbria Hepatology Network

Version History:	Date:	Feb 2024	Version:	V3.0	Review Date:	Feb 2026

Introduction

This guideline relates to **adults** with only vague or no symptoms or signs of liver disease, found to have abnormal liver blood tests**.** This guideline does not apply to children.

It is recognised that abnormal liver blood tests are an increasingly common presentation in primary care, in part due to the growing number of individuals with metabolic dysfunction associated steatotic liver disease (MASLD; formerly named non-alcoholic fatty liver disease [NAFLD]).

This guideline makes recommendations for the diagnosis and management of adults with abnormal liver blood tests with little or no symptoms, and is intended for use by all clinicians in the North East and North Cumbria in the diagnosis and management of these patients. The interventions should be offered to all people who are likely to benefit, irrespective of race, disability, gender, age, sexual orientation or religion. Information should be provided to patients in an accessible format and consideration should be given to mobility and communication issues, and being aware of sensitive and cultural issues.

STEP 1 – PATTERN RECOGNITION

What sort of abnormality do the abnormal liver blood tests suggest?

a. **Isolated raised bilirubin** – most commonly due to Gilbert's syndrome. This is a benign condition and does not need referral. It occurs in about 5% of the population.

   Repeat Liver blood tests on a fasting sample with an FBC. The bilirubin should rise further and there should be no evidence of anaemia. If the patient is anaemic haemolysis needs to be excluded (reticulocyte count, LDH).

b. **Cholestatic pattern** – Alkaline phosphatase (Alk phos) raised significantly more than ALT. Remember bone causes of raised Alk phos e.g. Paget's Disease. Repeating Liver blood tests with a GGT can help confirm a liver cause.

c. **Hepatitic pattern** – Most marked abnormality is a raised ALT (and AST if reported), though Alk phos and/or GGT may also be raised. These can be short-lived, due to intercurrent illness or muscular injury, reverting to normal a few days or weeks later. The bulk of this guidance refers to patients with this pattern of abnormality.

d. Isolated raised GGT (GGT is not routinely analysed in a liver enzyme panel in many Trusts unless specifically requested) - GGT is the most common liver enzyme abnormality in people with alcohol-related liver disease and metabolic dysfunction associated steatotic liver disease (MASLD). It can also be raised in other liver conditions such as drug-induced liver injury, hepatic congestion secondary to heart failure, liver metastases and cholestatic liver disorders (usually with raised ALP). While a particularly high level of GGT, such as >1000 U/L, is frequently associated with excessive alcohol consumption, more modest elevations (up to 500 U/L) are very commonly seen in patients with MASLD and can be accompanied by a normal or raised ALT.

STEP 2 – FIRST ASSESSMENT

Given that the most common causes of abnormal liver blood tests are MASLD (fatty liver associated with features of the metabolic syndrome), potentially harmful alcohol consumption and adverse drug reactions, a careful drug/alcohol history should be taken and other features of the metabolic syndrome (hypertension, diabetes, obesity and abnormal lipids) should be sought. Consider using the AUDIT or FAST questionnaire for detecting hazardous or harmful drinking. Patients should be given general advice as appropriate (reduction in alcohol intake, weight reduction by diet and exercise) and any drugs known to be associated with drug induced liver injury should be suspended if possible. Of particular note are NSAIDs. These should be stopped and liver blood tests repeated after 3 months. In cholestatic abnormalities antibiotics, especially flucloxacillin, are relatively common cause.

Many other drugs that cause abnormal liver blood tests are more difficult to stop (e.g. neuroleptics, anti-epileptics). Referral to liver advice and guidance or obtaining advice from the prescribing specialist may be appropriate in these circumstances. Patients with high risk alcohol consumption (AUDIT ≥15) should be referred to addiction services when appropriate.

Repeat the liver blood tests, **requesting AST and γGT** also, with an FBC.

When to repeat the liver blood tests?

a. Isolated raised bilirubin – **fasting sample** when convenient
b. Isolated raised Alk phos (confirmed as liver with GGT) – no delay needed
c. Isolated ALT –repeat in 1-3 months
d. Isolated GGT - repeat in 1-3 months
e. A raised ALT or Alk phos that is over 3x the upper limit of normal should have the above done without delay at the same time as a liver screen and USS (step 3)
f. A raised ALT or raised Alk phos, in combination with raised bilirubin should be referred routinely to a liver clinic or gastroenterologist.

Please order an USS of liver / spleen / pancreas routinely at the same time.

The presence of unexplained clinical jaundice should lead to immediate referral.

STEP 3 – SECOND ASSESSMENT (PERSISTENTLY ABNORMAL LIVER BLOOD TESTS)

If the abnormalities have persisted for 1-3 months despite the above measures, then a liver screen should be arranged (see below). In some parts of the region (Durham and Cumbria) intelligent liver function tests (iLFT) can be requested which is an automated approach to conducting this testing:

a. Viral screen (HBsAg, HCVAb, HIV test)
b. Autoantibodies – ANA, AMA, ASMA and immunoglobulins
c. Coeliac screen (TTG Ab)
d. Ferritin and Transferrin Saturation
e. HbA1c and fasting lipids
f. USS liver, biliary tree, pancreas - request for all patients with cholestatic liver enzymes or patients aged ≥ 50 years with hepatitic or mixed pattern of liver enzymes**. An USS liver is not essential for patients with suspected steatotic (fatty) liver disease under 50 years who have a low FIB-4 score (<1.3) as these scans do not usually add any additional information.**

STEP 4 – DECIDE WHO TO REFER

The history taken and results so far should point to possible pathologies causing the abnormal liver blood tests. Most of the list below will need referral for further assessment and management.

- Chronic viral hepatitis – history of risk behaviours, blood transfusion and positive viral hepatitis serology.

- Primary biliary cholangitis – raised Alk phos (cholestatic pattern), positive anti-mitochondrial antibody.
- Primary sclerosing cholangitis – history of inflammatory bowel disease, cholestatic pattern on liver blood tests.
- Autoimmune hepatitis – positive autoantibodies (smooth muscle, antinuclear antibodies and typically a raised IgG), might have history of other autoimmune diseases,
- Haemochromatosis – raised ferritin and transferrin saturation (>45%). Might have history of diabetes and joint pain.
- USS – the presence of dilated bile ducts requires further assessment and **URGENT** hospital referral on an NCA Upper GI pathway. Any reported dilation of the biliary tree is significant.

Many of these patients in the list below will not require referral. Low risk patients with steatotic liver disease can be managed in primary care.

- Alcohol-related liver disease
    - from history, raised MCV, raised ferritin with normal transferrin saturation, steatosis on USS.
    - Advanced alcohol-related liver disease is indicated by nodular liver, splenomegaly or other signs of portal hypertension on USS, low platelets, low albumin or raised bilirubin
- Metabolic dysfunction steatotic liver disease (MASLD; formally named NAFLD)
    - Patients likely to have raised BMI or increased waist circumference, hypertension, pre-diabetes or diabetes, raised fasting triglyceride and low HDL cholesterol.
    - Not consuming more than 14 units alcohol per week for females and 21 units per week for males
    - An USS may show a steatotic liver, but a ‘normal ultrasound’ does not exclude mild steatosis
    - The Liver screen is usually negative, although 10% will have low level liver autoantibodies (with a normal IgG level). A raised ferritin (with transferrin saturation <45%) is seen in a third of cases. IgA is raised in about half of cases.

- MetALD (people with metabolic associated steatosis who consume moderately excessive alcohol)
    - Same clinical features as above
    - Alcohol consumption 14-40 units per week for females and 21-50 units per week for males.

The hazardous drinker without evidence of advanced liver disease requires advice, regular counselling and, where appropriate, referral to secondary care alcohol specialists (AUDIT score ≥15). These patients do not require referral to liver clinics.

STEP 5 – RISK STRATIFICATION OF PATIENTS WITH MASLD or MetALD

Steatotic liver disease represents a spectrum of metabolic syndrome-associated liver disease progressing from simple steatosis (fat but no inflammation or hepatocellular injury), through to steatohepatitis (MASH = fat + inflammation+ hepatocellular injury) and fibrosis to cirrhosis. Estimates suggest that up to a third of the population has MASLD. Approximately 40% of patients with MASLD develop progressive fibrosis, which can progress to cirrhosis in 10%. Patients with cirrhosis are at risk life threatening liver related complications, such as hepatocellular carcinoma, portal hypertension and liver failure.

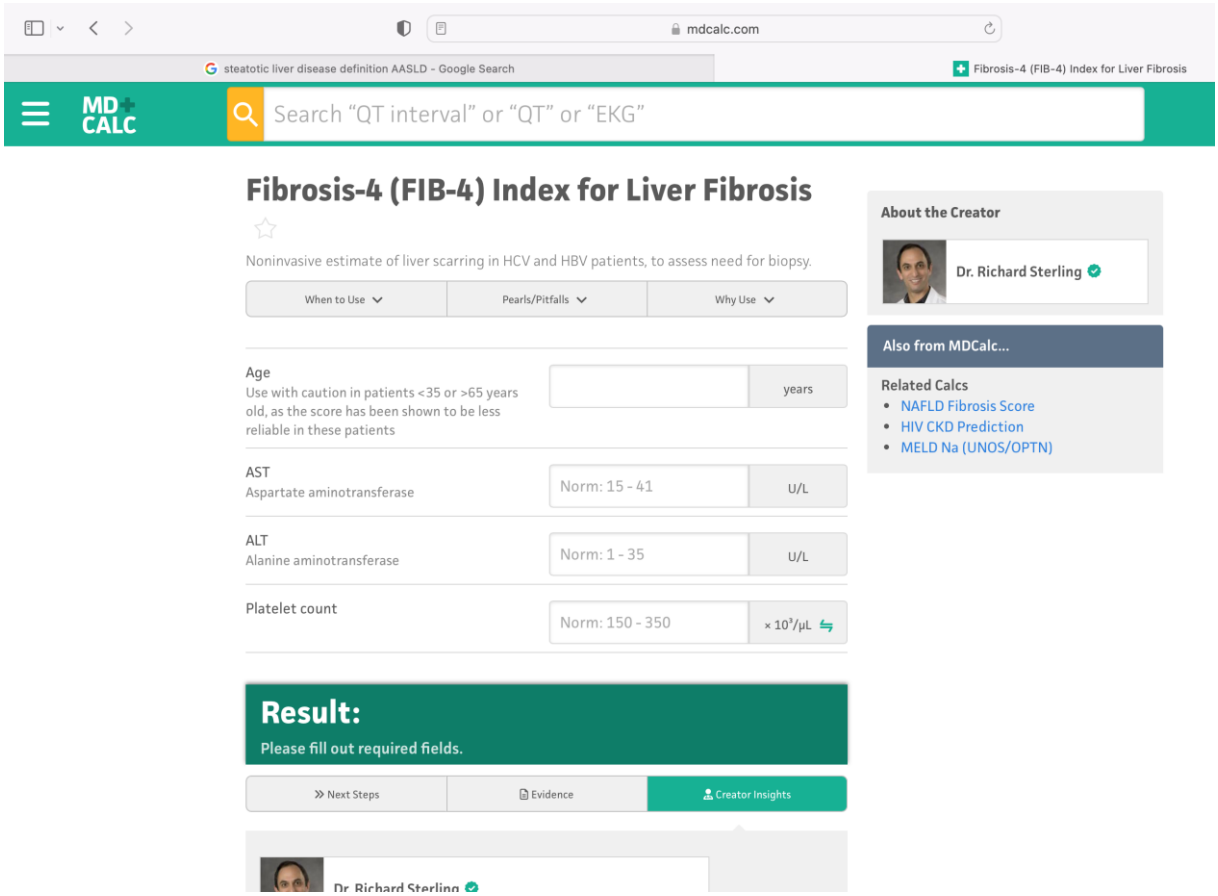
Stage of liver fibrosis is the most important prognostic factor and patients with moderate or severe liver fibrosis are at significant risk of liver-related complications in the future. There are algorithms based on simple blood tests and clinical parameters that can accurately exclude advanced fibrosis, and these can be used to triage patients who require referral to secondary care for further investigation and management. The FIB-4 score and NAFLD fibrosis score have been well validated for this purpose. We recommend using the FIB-4 score as it is the most accurate simple score available and is simpler than the NAFLD fibrosis score to calculate.

For all patients with a clinical diagnosis of MASLD or MetALD who have had other causes of liver disease excluded the FIB-4 score should be calculated.

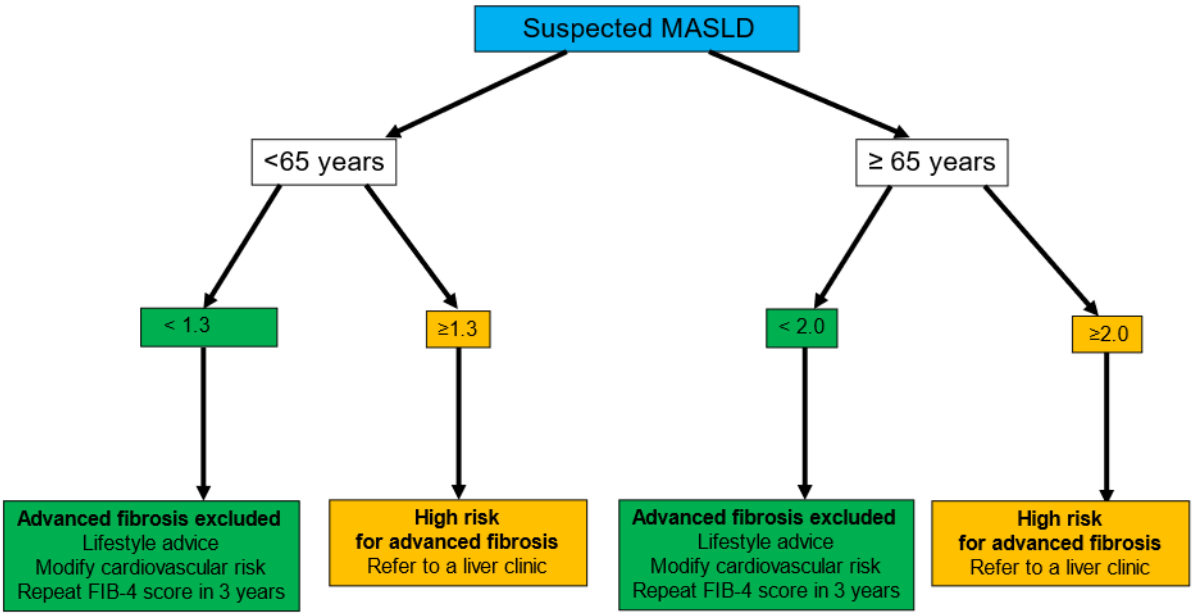
To calculate the FIB-4 score you need

- Age
- AST
- ALT
- Platelets

An online calculator for this is available at: Fibrosis-4 (FIB-4) Index for Liver Fibrosis - MDCalc



- There are different cut-offs for patients depending on whether their age.
- **For patients under 65 years of age a FIB-4 score < 1.3 reliably excludes advanced fibrosis.** These patients can be managed in primary care
- **For patients ≥65 years old: a FIB-4 score <2.0 reliably excludes advanced fibrosis.** These patients can be managed in primary care.
- **If the FIB-4 score is ≥1.3 (for under 65 year olds) or ≥2.0 for ≥65 years olds patients have a significant risk of having advanced fibrosis.** Referral to a liver clinic or for fibroscan is recommended. If significant/advanced fibrosis is confirmed patients will receive appropriate treatment in secondary care.



Referrals to the liver clinic will be reviewed by a consultant and some patients with suspected MASLD or MetALD where it is clear that they need a fibroscan to stage fibrosis will be triaged directly to a fibroscan. This will typically be patients with a modestly raised FIB-4 score. This will more rapidly triage patients who need a subsequent liver clinic appointment. Direct access fibroscan is also available in some parts of the region.

Patients whose fibroscan is < 8 kPa will be given lifestyle advice by the fibroscan technician and discharged back to primary care with appropriate follow up advice. Individuals with a fibroscan ≥ 8kPa will be reviewed in the liver clinic for a more detailed assessment. Those with suspected cirrhosis will be offered a “soon” appointment.

STEP 6 – MANAGE PATIENTS WITH LOWER RISK MASLD or MetALD

Currently the mainstay of management for patients with steatotic liver disease without advanced fibrosis is lifestyle modification and optimisation of diabetes and cardiovascular risk factors.

- A care bundle is available for the management of MASLD (appendix 5)
- Give patients advice about MASLD and its treatment. This leaflet from LIVErNORTH provides comprehensive information about steatotic liver disease. NAFLD liver north leaflet
- Lose weight if BMI >25 or raised waist circumference
  - Aim for at least a loss of 10% of body weight.
  - Refer to dietetics where appropriate
  - Consider referral to specialist weight management services if patients meet the criteria for bariatric surgery or GLP-1 analogues
  - Advise exercise at least 30 minutes 3 times per week (both cardiovascular and resistance exercise are beneficial even independent of weight loss)
- Optimize control of diabetes
  - Use metformin, GLP-1 analogue or SGLT2 inhibitor where possible
- Treat hypertension as per NICE guidelines
- Drink sensibly – within current limits (<14 units per week for males and females). There is no evidence at present to recommend abstinence, except for patients with cirrhosis where abstinence is recommended.
- Reduce other risk factors for vascular disease (https://nescn.nhs.uk/wp-content/uploads/2021/07/NEELI-Final-10.2.pdf) Statins are safe in patients with MASLD and should be actively prescribed as per NICE guidelines
- Undertake an annual vascular disease risk score as patients with MASLD are more at risk from this than from direct effects on the liver.
- Calculate the FIB-4 score every 3 years and refer if the FIB-4 score increases above the age-related cut-off. For patients >80 years old or those with significant other co-morbidity further FIB-4 testing may not be appropriate as it will be unlikely to change their management

APPENDIX 1

Testing for Gilbert's syndrome

A solitary abnormal raised bilirubin result is likely to be due to Gilbert's. Repeat testing should confirm that none of the other Liver blood tests are abnormal. A repeat **fasting** sample should show a further isolated rise in bilirubin.

If you wish to confirm that the rise in bilirubin is unconjugated, send the sample wrapped (e.g. in a small envelope) within the usual pathology bag. This will reduce light exposure (which leads to conjugation). At low levels of bilirubin, testing for conjugation is unreliable (e.g. up to 25µmol/L).

Confirm there is no evidence of haemolysis – reticulocytes and LDH will be normal (raised retics/LDH seen in haemolysis). There is no need to test the urine.

Samples required to confirm Gilbert's:

1 x SST 11 (gold top) wrapped
1 x EDTA (lavender top)

APPENDIX 2

Samples required for full liver screen (Step 3)

3x SST 11 (gold top)
1 x Fluoride oxalate (grey top)
2 x EDTA (lavender top)

FBC
Liver enzymes, AST and GGT
HbA1c
lipids
ferritin
Liver autoantibodies and TTG
Immunoglobulins
HBsAg, HCVAb and HIV.
Transferrin saturation (if ferritin increased)

APPENDIX 3

After consideration, screening for Wilson's disease and alpha-1-antitrypsin deficiency has been left out of our recommended liver screen (Step 3). This is due to the rarity of these conditions and the significant cost of the relevant tests. However, you may want to consider these conditions in patients presenting with atypical features at a young age.

Wilson's disease

An autosomal recessive disorder of hepatic copper metabolism. Wilson's disease most commonly presents in the teenage years and should always be considered in this context particularly in the presence of neuropsychiatric features. However, Wilson's disease can be very difficult to diagnose and there is no single diagnostic test that can exclude or confirm Wilson's disease with 100% certainty. Suspicion should be alerted in the patient with a low alkaline phosphatase level or Coomb's negative haemolytic anaemia. A low serum caeruloplasmin level is a useful screen but can be normal.

Alpha 1 antitrypsin deficiency (AAT)

AAT is a proteinase inhibitor and mainly produced in the liver. AAT disease of the liver is rare in adults. Most commonly presenting within the first week of birth with jaundice. AAT deficiency is particularly important in the lungs, especially with a history of smoking. Be suspicious in the patient with COPD who has evidence of chronic liver disease but in the absence of obvious risk factors. Heterozygous carriers have an increased susceptibility to liver injury in the presence of a "second hit" on the liver as with excessive alcohol consumption. However, patients should be advised not to smoke and keep alcohol intake within recommended safe drinking limits.

Coeliac disease

Coeliac disease can present with cryptogenic liver disease with persistent "transaminitis" in up to 5 – 10% patients. This will often resolve with a gluten free diet but may persist and can be associated with autoimmune liver disease. There is a reported increased association with haemochromatosis and a three-fold higher incidence of coeliac disease in MASLD as compared to the general population.

However, be aware that in the presence of chronic liver disease tissue transglutaminase (TTG) antibodies can be falsely elevated.

Hereditary Haemochromatosis

Hereditary haemochromatosis is a common inherited (recessive) disorder of iron absorption. This can result in iron deposition in tissues, mainly the liver but also other organs including the pancreas and heart. The C282Y and H36D mutations within the HFE gene account for > 90% cases seen in our region. There are at least 4 other mutations that have been identified that account for the remaining 10% of cases but the tests are not widely available for clinical use.

Generally speaking, we recommend HFE genotyping if the Transferrin saturation is > 45% in the presence of a raised serum ferritin.

Ferritin is an acute phase reactant and can be raised in a wide range of inflammatory conditions, obesity and Type 2 diabetes. In addition, a raised serum ferritin is often seen in other liver conditions such as alcohol-related liver disease, hepatitis C and non–alcoholic steatohepatitis.

Hereditary haemochromatosis is an important condition to diagnose as it is readily treatable (venesection) and has implications for other family members. Those parents, siblings and children over the age of 20 years will require screening.

Some patients ask for dietary advice. They should avoid iron – rich foods and vitamin C supplements, minimize alcohol to within recommended safe drinking limits and advise weight loss in patients with central obesity.

APPENDIX 4

Adverse drug effects on the liver are important and should be considered when assessing patients with liver function abnormalities.

This is not a comprehensive list but some of the commonest culprits are:
NSAIDs

Antibiotics: Flucloxacillin, Co-amoxiclav,

Antiepileptics: Phenytoin, Carbamazepine, Sodium Valproate

Antituberculous drugs: Rifampicin, Isoniazid, Ethambutol

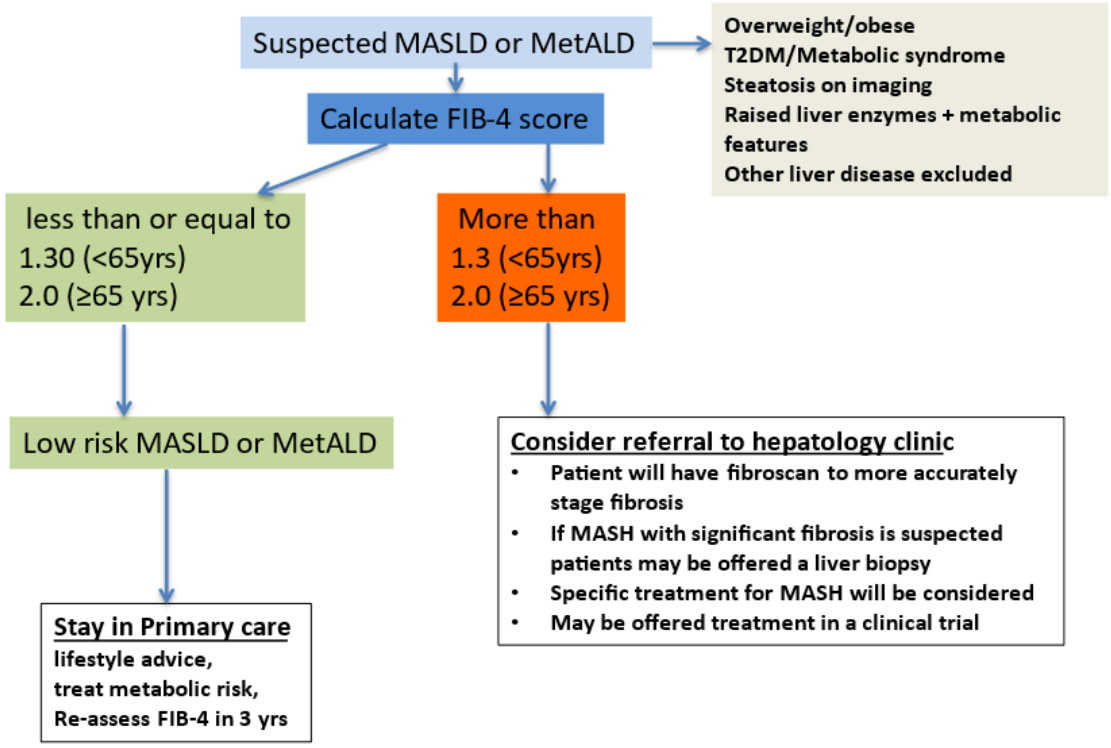
NB: Statin induced hepatotoxicity is very rare, and most abnormal liver blood tests in the setting of statin use are due to underlying metabolic dysfunction associated steatotic liver disease.

APPENDIX 5

Care bundle: Management of patients with steatotic (fatty) liver disease in primary care

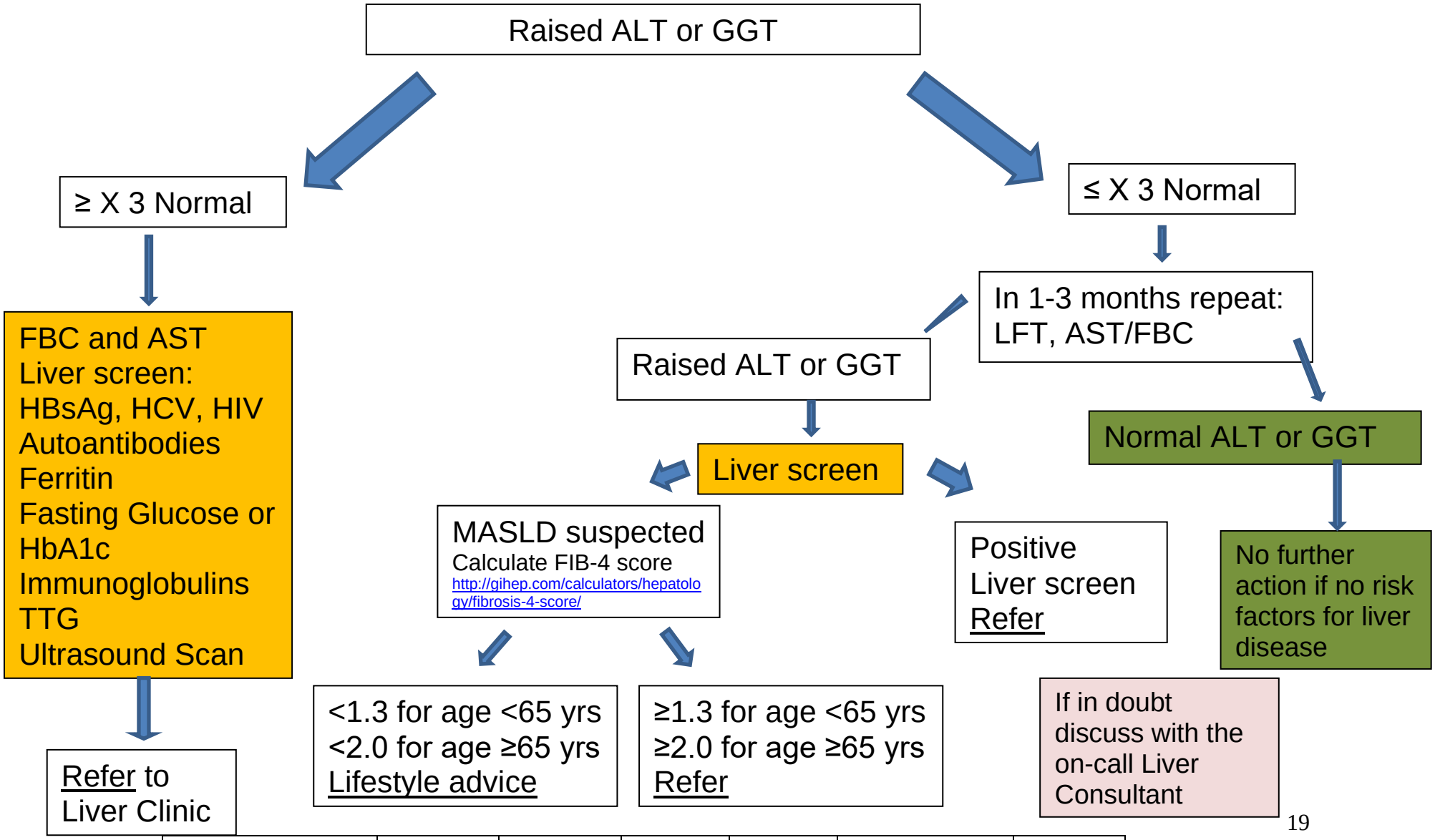
Date seen……

Weight (kg)	Height (m)	BMI	BP (mmHg)
Overweight/ Obesity □	Type 2 diabetes □ Year diagnosed: ……	Hypertension □	Dyslipidaemia □
Current alcohol consumption units/week If alcohol consumption is greater than 14/21 units per week for females/males then advise reduction or abstinence			
Current FIB-4 score …….. **Last staging date**: …….. Stage with FIB-4 at diagnosis and then re-stage every 3 years or more frequently			
Lifestyle changes			
Ensure information leaflets on NAFLD given		Y N	
Change in weight since last review (+ or -)		kg %	
Target weight (aim >5% weight loss if overweight and >10% if obese)		kg	
Discuss/reinforce dietary advice		Y N	
If not losing weight offer referral to dietician		Y N N/A decline	
Discuss increasing activity/exercise		Y N	
Managing metabolic risk factors			
Review BP		Y N	
Review diabetic control/ screen for diabetes		Y N	
Ensure on statin - If no, why not? Not tolerated □ Low risk □ (statins are recommended for patients with T2DM or a QRISK2 >10%)		Y N	
Smoking cessation advice		Y N N/A	
When to refer to hepatology			
Consider referral if FIB-4 score >1.3 for <65 years and >2.0 for ≥ 65yrs		Y N N/A	
Routine investigations: FBC, U/E, LFT, AST, GGT, HbA1c, glucose, lipids.			



- **MASLD:** metabolic dysfunction associated steatotic liver disease = steatosis, metabolic risk factor(s) and alcohol <14 (F) or 21 (M) units alcohol/week
- **MetALD:** steatosis, metabolic risk factors, alcohol 1440 (F) or 21-50 (M) units alcohol per week

Asymptomatic Liver Blood Test Abnormalities
Raised ALT or GGT



Asymptomatic Liver Blood Test Abnormalities