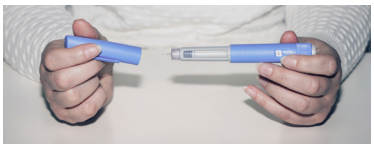
# education

**RESEARCH REVIEWS** Fortnightly round up from the leading medical journals

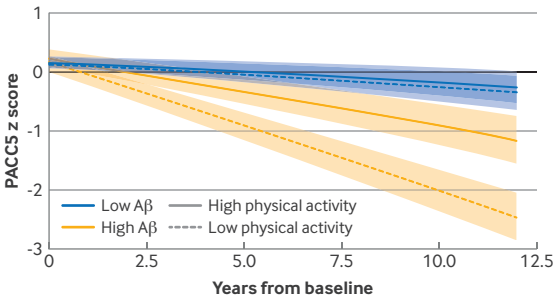
## Liraglutide for minor acute ischaemic stroke

People with diabetes who have a minor acute ischaemic stroke are at high risk of having another stroke within three months. A small open label trial set in China suggests that this may be reduced by liraglutide, the glucagon-like peptide-1 (GLP-1) receptor agonist. Of the 317



patients in the liraglutide arm of the study, 25 (7.9%) had a stroke recurrence within 90 days versus 44 of the 319 patients (13.8%) in the control group (hazard ratio 0.56, 95% confidence interval 0.34 to 0.91). However, the authors caution that the findings need to be validated in larger studies.

*JAMA Intern Med* doi:10.1001/jamainternmed.2025.5684




**Individuals with high baseline physical activity and raised Aβ (solid orange line) showed slower decline in cognitive function, as measured with the Preclinical Alzheimer's Cognitive Composite-5 (PACC5) score**

## Stepping away from dementia

Positron emission tomography (PET) scanning can be used to help identify people with high amyloid β (Aβ) burden, who are at high risk of developing Alzheimer's disease. A longitudinal study suggests that physical activity, even at modest levels of 5000-7500 steps per day, may mitigate this risk. Benefits were seen in tau accumulation—a proxy for dementia progression—and slower rates of cognitive decline (figure) in those with high Aβ burden who were more physically active at the start of the study.

*Nat Med* doi:10.1038/s41591-025-03955-6

## A new class of weight loss drugs: amylin receptor agonists

In the next few years a range of new weight loss drugs are likely to come to market, each hoping to topple tirzepatide—or at least find a profitable niche. One new class of weight loss drugs is amylin receptor agonists. A phase 2 trial recruited 263 people with obesity and randomised them to receive once weekly injections of the amylin receptor agonist eloralintide or placebo. It found dose dependent reductions in body weight of up to 20% after 48 weeks compared with 0.4% in the placebo group. Common side effects were nausea and fatigue.

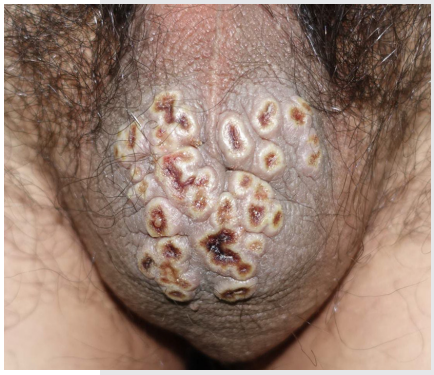
*Lancet* doi:PIIS0140-6736(25)02155-5/

CREDIT: YAU WY, KIRN DR, RABIN JS, ET AL. *NAT MED* 2025 DOI:10.1038/S41591-025-03955-6

## A step forward for knee osteoarthritis pain

The martial art tai chi is said by many to be the secret to longevity and mobility in later life. "My Joint Tai Chi" is a freely available 12 week tai chi programme that requires only access to the internet and enough floorspace to allow you to move two steps forwards and backwards—one more step forward than you need to become a

## CLINICAL PICTURE



### Cerebriform pustules on scrotum

**A man in his 40s with a background of chronic scrotal eczema presented with a four day history of painful scrotal rash and fever (37.8°C), after heterosexual contact with a casual partner using a condom two weeks previously. Physical examination showed hyperkeratosis and lichenification of the scrotal skin, with grey plaques bearing umbilicated pustules that coalesced into a cerebriform pattern. Multiple enlarged lymph nodes were palpable in both inguinal regions. No rash was observed elsewhere. Serological test results for syphilis and human immunodeficiency virus were negative. A swab taken from the scrotal lesions tested negative for herpes simplex virus but positive for mpox clade IIb.**

**Mpox is a viral zoonotic disease caused by the monkeypox virus. Classically, the mpox rash has a centrifugal distribution predominantly affecting the face and extremities. In recent outbreaks, however, presentations have been characterised by fewer lesions, typically affecting the ano-genital and peri-oral regions. In this patient, the rash was present only on**

healthcare leader. A new clinical trial suggests it may help symptoms of knee osteoarthritis. The unblinded study of 178 people in Australia had impressively high retention and adherence rates: 82% reported adequate adherence to the three times a week video tutorials. More than 70% achieved a clinically important improvement in pain and function by the end of the programme, compared with around half in the control group.

*JAMA Intern Med* doi:10.1001/jamainternmed.2025.5723

## Prostate cancer screening study comes of age

In 1993 the European Randomised Study of Screening for Prostate Cancer started randomising men aged 55 to 69 years to receive invitations for repeated prostate specific antigen (PSA) screening or no screening invites. The latest findings, after a median follow-up of 23 years, are that prostate cancer mortality has been 13% lower in the screening group (rate ratio 0.87; 95% CI 0.80 to 0.95). Although no overall mortality benefit has been found, the authors conclude that one death from prostate cancer was averted for every 12 men in whom prostate cancer was diagnosed from screening.

*N Engl J Med* doi:10.1056/NEJMoa2503223

Tom Nolan, clinical editor, *The BMJ*, London; sessional GP, Surrey

Cite this as: *BMJ* 2025;391:r2364

**the scrotal area, a region not protected by a condom. This localised presentation might stem from eczema induced epidermal barrier disruption and impaired immune function, creating an environment conducive for viral entry and propagation. The patient was isolated at home and received symptomatic treatment, and the rash resolved in two weeks.**

Patient consent obtained.

Cite this as: *BMJ* 2025;391:e085243

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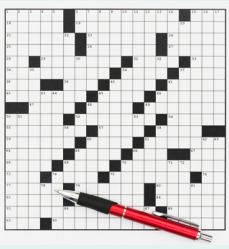
## MINERVA From the wider world of research

### Cognitive outcomes in preterm babies

Although advances in perinatal care have vastly improved survival rates for children born at less than 32 weeks gestational age, a systematic review finds that these children remain at high risk of cognitive impairment (*JAMA Pediatr* doi:10.1001/jamapediatrics.2025.2221). On average, children born very prematurely score 13 points lower on IQ tests than their term born peers. The children in these studies had been born between 1977 and 2016 but, disappointingly, cognitive outcomes didn't improve over time.



### Antenatal corticosteroids

Staying with the subject of prematurity, a study that recruited more than 1.5 million mother-child pairs from Finland and Scotland finds that any short term benefits of antenatal corticosteroids come at the cost of higher risks of infection in childhood (*JAMA Netw Open* doi:10.1001/jamanetworkopen.2025.36809). Both respiratory and non-respiratory infections were around 20% more common in children born between 34 weeks and term who had been exposed to antenatal corticosteroids. The increased risk of infection persisted up to age 21.

### The benefits of trees

Surveys have shown that urban green spaces, especially those containing trees, bring benefits for the health and wellbeing of city dwellers. Sceptics might guess that this would be offset by tree root damage to sidewalks and pavements causing walkers to trip and fall. But a case-control study from the United States that used data from emergency services to plot the locations of pedestrian falls finds, rather surprisingly, that numbers of falls were lower in areas with denser tree canopy cover (*Am J Epidemiol* doi:10.1093/aje/kwaf231).

### Crosswords and other word games

People who took part in cognitively stimulating activities were only half as likely to be diagnosed with dementia as people who didn't, according to data from a longitudinal study of 3000 older people living in France (*Age Ageing* doi:10.1093/ageing/afaf286). Engaging with word games and crossword puzzles seemed especially protective. The benefits of cognitively stimulating activities persisted after adjusting for socio-demographic and genetic variables, but people who didn't get involved with such activities tended to be less healthy overall, so it's possible that unmeasured factors such as impaired vision or reduced hearing are part of the explanation.

### Breastfeeding and breast cancer

We've known for a long time that breastfeeding reduces the risk of breast cancer, but the mechanism underlying the protective effect was a mystery. A series of studies in women with and without breast cancer and in a murine model of breast cancer has now implicated long lived cytotoxic T cells. During pregnancy and the postpartum period, the human breast remodels for lactation and then, after weaning, goes through a process of involution. This sequence induces an accumulation of CD8+ T cells, including cells with a tissue resident memory-like phenotype (*Nature* doi:10.1038/s41586-025-09713-5).

Cite this as: *BMJ* 2025;391:rr2366

# Diagnosis and management of metabolic dysfunction associated steatotic liver disease

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CPD READING

0.5 HOURS

## WHAT YOU NEED TO KNOW

- Metabolic dysfunction associated steatotic liver disease (MASLD) is the most common type of steatotic liver disease and affects one third of the adult population
- MASLD is defined by steatosis plus at least one cardiometabolic risk factor, and patients with the condition are at increased risk of adverse cardiovascular and liver related events
- Patients at risk of liver related adverse events can be identified by performing a blood test (FIB-4) and a measurement of liver stiffness using vibration controlled transient elastography
- Treatment requires a multidisciplinary approach, including advice on lifestyle changes, management of risk factors associated with comorbidities, and, in those eligible, drug therapies

Metabolic dysfunction associated steatotic liver disease (MASLD) is the most common chronic liver disease worldwide. It is characterised by fat accumulation in the liver, in the presence of cardiometabolic risk factors and in the absence of heavy alcohol consumption or other secondary causes of liver disease.[1] It was previously termed non-alcoholic fatty liver disease, but in 2023 the definition was changed to remove potential stigma by excluding the term "fatty" and the reference to alcohol when referring to steatosis.[1]

People with MASLD typically have no symptoms, or vague symptoms, such as fatigue, anxiety, sleep disturbances, abdominal discomfort, and upper right quadrant pain. The condition may be identified incidentally during investigation for other conditions, such as diabetes, obesity, hypertension, or during routine check-ups. MASLD may progress to cirrhosis, and is associated with increased liver related and all cause morbidity and mortality.[2-4]

In this article, we review recent advances in diagnosis, investigation, treatment, and monitoring of adult patients who are suspected to have MASLD.

## How common is MASLD?

Steatotic liver disease is the presence of fat infiltration involving >5% of liver tissue by any imaging modality (abdominal ultrasonography, computed tomography, magnetic resonance imaging, elastography), or liver biopsy.[3 4] It has multiple causes, and includes cryptogenic, MASLD, and alcohol related subtypes (fig 1, and box 1 (bmj.com)).

MASLD is considered the hepatic manifestation of metabolic syndrome, although its pathogenesis is multifactorial and not yet fully understood. Briefly, hepatic lipid accumulation is the primary insult, which is determined by an imbalance between the supply and disposition of lipids in the liver. This is often promoted by insulin resistance, unfavourable lifestyle habits, including adverse nutritional intake and a sedentary lifestyle, and, in some individuals, a genetic predisposition.[3 4] Factors associated with increased hepatic fat accumulation and subsequent inflammation and scarring include immune system activation and pro-inflammatory changes to the gut microbiome.[3 4]

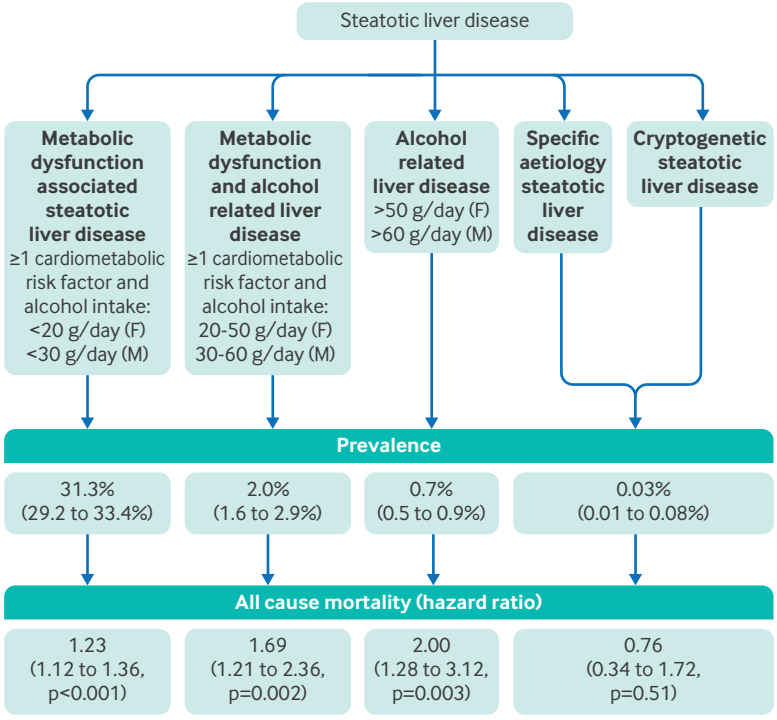


**Fig 1 | Nomenclature and subclassification of steatotic liver disease. Reported data on prevalence (95% CI) and all cause mortality (95% CI, bottom line) are derived from the US population based National Health and Nutrition Examination Survey, which included more than 7300 adult participants and had a median follow-up time of 26.8 years.[2 5] The hazard ratio for all cause mortality was assessed in comparison with people without hepatic steatosis**

## How do I diagnose it?

Diagnosis is most commonly incidental, following abdominal ultrasound or other imaging modalities, or as a result of further investigation following elevated serum liver enzymes.

As MASLD, metabolic dysfunction with alcohol related liver disease, and alcohol related liver disease account for 99.4% of all causes of steatotic liver disease, initial assessment of patients with hepatic steatosis should focus on cardiometabolic risk factors and alcohol intake. The diagnosis of MASLD requires[3 4]:

- Hepatic steatosis, plus
- Presence of at least one cardiometabolic risk factor know to be associated with insulin resistance: obesity/overweight, prediabetes/diabetes, atherogenic dyslipidaemia, hypertension
- Exclusion of significant alcohol consumption (>20 g/day for women and >30 g/day for men).

In figure 2, we propose a diagnostic algorithm for MASLD, based on international guidelines,[3 4] and outline key questions to ask in the history and findings of physical examination and laboratory tests. If metabolic and alcohol related risk factors have been excluded, rule out other causes of steatotic liver disease.

Insulin resistance is present in obese as well as non-obese and lean patients, who represent 40.8% and 19.2% of MASLD population, respectively.[8] Insulin resistance indices (eg, the homeostasis model assessment of insulin resistance, calculated from fasting blood glucose and insulin) may assist in the diagnosis of metabolic dysfunction in adults with suspected MASLD and no other cause of steatotic liver disease.

Assess the amount, pattern, and duration of alcohol intake to classify as mild, moderate, or heavy. European guidelines recommend using validated instruments and/or specific biomarkers for qualitative and quantitative assessment of alcohol intake, as current drinking pattern may not necessarily reflect previous drinking behaviour.[4]

In figure 3 (bmj.com), we outline the natural history and histological spectrum of MASLD. Patients with MASLD have a higher all cause mortality than the general population. In a meta-analysis of 92 population based prospective, retrospective, and cross sectional studies (9 361 716 participants), patients with MASLD had a pooled mortality rate of 17.05/1000 patient years,[7] with the main causes of death being cardiovascular disease (mortality rate 5.54/1000 person years) and liver related complications (mortality rate 1.75/1000 person years).[7]

## How do I assess health related risks?

For patients with MASLD, determine the risk of adverse outcomes based on history, examination, and laboratory tests (fig 2). Assess extrahepatic comorbidities including type 2 diabetes mellitus, dyslipidaemia, cardiovascular disease, and chronic kidney disease in patients with MASLD, while assessment for endocrine disorders and sleep apnoea should be individualised.[24]

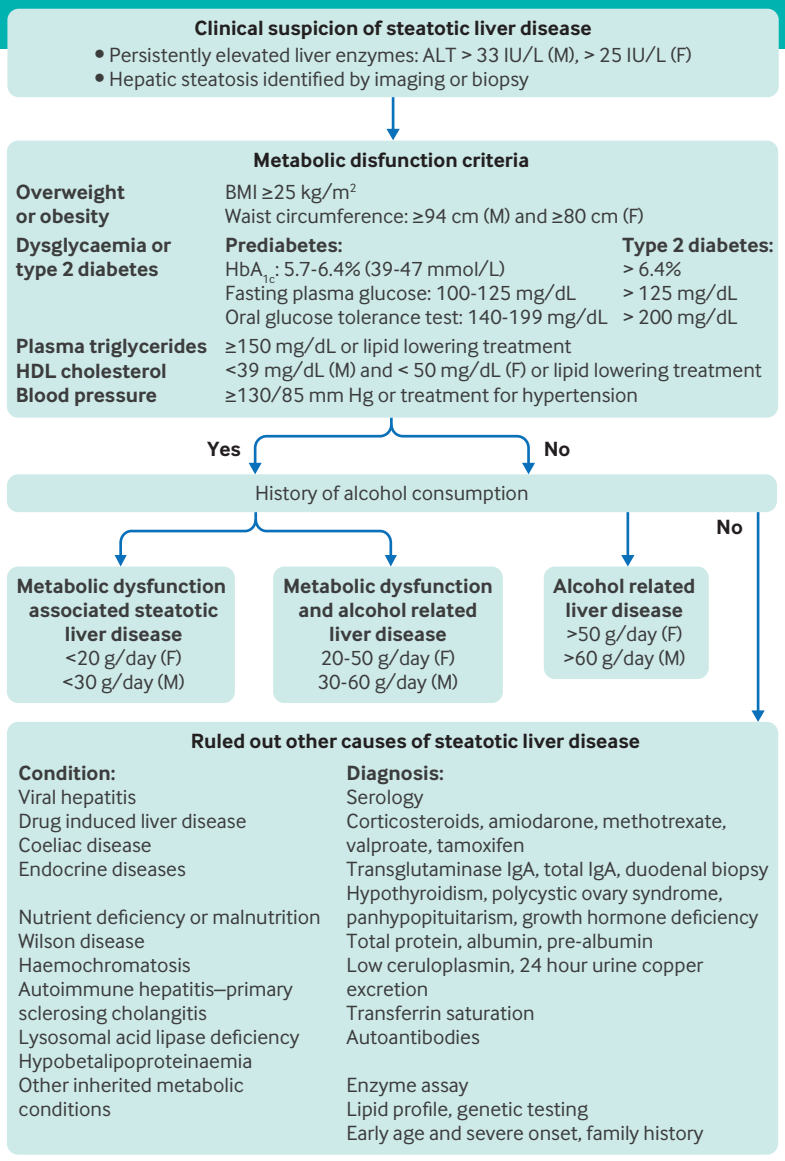


**Fig 2 | Diagnostic algorithm for MASLD[1-4]**

Although about 80% of patients with MASLD are at low risk of liver related complications, with a cumulative five year incidence of liver related events of 0.5%,[25] the rising disease prevalence in high risk patient groups and increased awareness among patients and healthcare professionals will lead to an absolute increase in number of patients diagnosed with advanced liver disease. To assess liver related risk, all guidelines recommend a non-invasive multi-step approach based on sequential application of blood based scores and imaging, measuring mechanical properties of the liver which are modified by fibrosis (fig 4, bmj.com, box 2).[6-32] When available, the fibrosis-4 index (FIB-4)/liver stiffness measurement two step approach can be performed in primary care and effectively classifies patients with MASLD at risk of liver related adverse events[29]:

**Step 1:** FIB-4 is the first line non-invasive test for ruling out advanced fibrosis in patients with MASLD. FIB-4 is cost effective for the initial screening owing to its low cost, simplicity, and high specificity for advanced fibrosis and liver related outcomes.[4] Other non-proprietary diagnostic panels, such as the non-alcoholic fatty liver disease fibrosis score and the aspartate aminotransferase (AST) to platelet ratio index, do not perform better than FIB-4 and are not recommended.[6-32]

**Step 2**: In patients with an indeterminate (or intermediate) risk for advanced fibrosis and adverse liver outcomes (ie, FIB-4 between 1.3 and 2.67, which can occur in 43-51% of patients with MASLD in tertiary referral centres[22]), a second non-invasive test for additional risk stratification is recommended[3-32]:

- Liver stiffness measurement by vibration controlled transient elastography is the next most validated imaging technique for fibrosis risk stratification, and predicts future cirrhosis and all cause mortality. A liver stiffness measurement value <8.0 kPa rules out advanced fibrosis with good negative predictive value.
- If vibration controlled transient elastography is unavailable, guidelines recommend the patented blood based enhanced liver fibrosis test of specific collagen related blood constituents as an alternative.[3-24]

In a multicentre longitudinal study of 12 950 patients with MASLD enrolled at 16 tertiary centres from the US, Europe, and Asia, this two step approach classified 81.5% patients as low liver related risk, 4.6% patients as intermediate risk, and 13.9% patients as high risk, with a five year risk of liver related events of 0.5%, 1.0%, and 10.8%, respectively.[25]

International guidelines recommend referring all patients with MASLD who have an intermediate or high risk of adverse liver related events at the end of the FIB-4/liver stiffness measurement two step approach to a specialist for further investigation.[4-35] Once referred, a liver biopsy or additional non-invasive tests, including magnetic resonance elastography, may be requested to assess fibrosis risk.

### Screening

Guidelines do not recommend systematic, population based screening because it is not cost effective.[6-36] Rather, they recommend investigating and stratifying patients with MASLD with any one of the following features which are suggestive of high liver related risk:

1. Type 2 diabetes mellitus
2. Obesity (overall or abdominal) and ≥1 additional metabolic risk factor(s) (described in fig 2, upper right panel)
3. Persistent aminotransferase elevation (ie, alanine transaminase (ALT) >33 IU/L for men and >25 IU/L for women)[3 4] for ≥6 months, detected by a minimum of two tests, at least four weeks apart.

If only condition 3 is present, rule out other causes of steatotic liver disease before investigating for MASLD as suggested in fig 2.

## How to manage MASLD in primary care

Lifestyle intervention is the cornerstone of management for patients with MASLD, based on established benefits on liver disease and on MASLD associated comorbidities (fig 5, bmj.com).

### Weight loss

The benefits of weight loss have been shown consistently across all international guidelines,[3-35] with a ≥5% weight loss being recommended in patients who are overweight or obese with MASLD. Even in patients whose weight is in the normal range there is a high prevalence of metabolic dysfunction, including insulin resistance and visceral obesity, and a 3-5% weight reduction can resolve liver steatosis and improve cardiovascular risk and glycaemic control.[33] In all patients, a dose-response relation exists between weight loss and histological changes: weight loss of at least 5% improves steatosis and of 7-9% improves steatohepatitis, but improvement in fibrosis occurs only with weight loss ≥10%.[3 4]

In randomised trials, intensive lifestyle interventions, based on cognitive behavioural treatment adopted in a diabetes prevention programme, significantly reduced body weight and liver fat, and improved liver histology.[34] In the same patients with MASLD,[37] a 7-10% weight loss cleared liver fat in obese patients, whereas a 3-5% loss was similarly effective in lean (BMI <25) patients,[37] underlining the weight independent benefits of diet and exercise in patients with MASLD.

### Physical activity

The benefits of physical activity on MASLD are independent of weight loss and are mediated by improved insulin sensitivity and nutrient disposal.[3 4] Both aerobic and resistance exercise are recommended to reduce liver fat and improve cardiometabolic risk factors. European and US guidelines set a threshold of >150 min/week of moderate or 75 min/week of vigorous intensity physical activity.[3 4]

**Box 2 | Non-invasive tests for screening people at increased risk of MASLD**

**Fibrosis-4 index**

- Formula: FIB-4= age × AST/(platelet count × √(ALT)) (age in years, ALT and AST in IU/L, and platelet count in $10^9$/L).
- FIB-4 predicts advanced (stage F3-4) fibrosis with area under the receiver operating curve of 0.77. A FIB-4 <1.3 rules out advanced fibrosis with negative predictive value of 0.92 (95% CI: 0.88 to 0.98), while a FIB-4 cut-off value >2.67 rules in advanced fibrosis with a positive predictive value of 0.83 (0.79 to 0.86).[24]
- In people with diabetes and who are over 65, higher cut-off values (1.9-2.0 rather than >1.3) are recommended. In patients of Indian ethnicity, a lower cut-off value (>1.0 rather than >1.3) is recommended.[24-27]
- FIB-4 has lower accuracy in patients who have had a splenectomy and patients who are thrombocytopenic.[26] Furthermore, predictive value is higher in populations with higher prevalence of advanced fibrosis (for example, those reviewed in specialist clinics) compared with patients reviewed in the primary care setting where the prevalence of advanced fibrosis is lower.[28]

**Vibration controlled transient elastography**

- Liver stiffness measurement by vibration controlled transient elastography is the next most validated imaging technique for fibrosis risk stratification, and it predicts development of cirrhosis and all cause mortality in patients with MASLD.
- It predicts advanced (stage F3-4) fibrosis with an area under the receiver operating curve of 0.89. A value <8.0 kPa rules out advanced fibrosis with negative predictive value of 0.96 (95% CI, 0.86 to 0.99) and rules in advanced fibrosis with a positive predictive value of 0.43 (95% CI, 0.27 to 0.52).[24]
- Technical difficulties in performing the examination may arise if patients are very obese, requiring a large probe, and in patients who have ascites. Severe steatosis may increase liver stiffness and falsely elevate liver stiffness measurement values.[29]

**Other tests**

- If liver stiffness measurement is unavailable, the proprietary enhanced liver fibrosis test of specific collagen related blood constituents represents a valuable alternative[6 7] with an area under the receiver operating curve of 0.81 for advanced fibrosis: individuals with enhanced liver fibrosis <7.7 are considered at low risk for adverse outcomes.
- Once referred, specialists may order liver biopsy or additional non-invasive tests for fibrosis risk stratification, with magnetic resonance elastography having the best overall performance, particularly for fibrosis stages milder than F3-4.

### HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

Co-author LB is a general practitioner and has metabolic dysfunction associated steatohepatitis. She is being treated and monitored for liver disease. Her experience as both a patient with lived experience and a GP helped shape the systematic approach to investigating patients in primary care that is described here. She commented on all aspects of the article, but particularly in relation to screening and treating patients with MASLD in primary care.

#### Healthy diet composition

Guidelines recommend to reduce the consumption of ultra-processed food rich in simple sugars and saturated fats and to avoid fructose sweetened beverages and encourage consumption of fruits, vegetables, legumes, nuts, olive oil, and unprocessed poultry and fish.[3-35]

#### Alcohol

Guidelines recommend stopping alcohol consumption in all patients with MASLD with advanced fibrosis,[3 4] but recent population based studies indicate that there are no safe limits of alcohol intake for patients with MASLD of any severity.[38] Even low to moderate alcohol consumption (5-13 drinks/week in women, 5-20 drinks/week in men) dose dependently increases the risk of liver fibrosis across the whole MASLD spectrum. On this basis, European guidelines discourage alcohol consumption in individuals with steatotic liver disease, particularly those with moderate or high alcohol intake.[4]

#### Coffee

Consuming coffee—whether or not it is caffeinated—shows a protective association with MASLD in observational studies, with more consistent effects on fibrosis than on steatosis.[39] This is because of the possible antioxidant, anti-inflammatory, and antifibrotic effects of coffee phenolic compounds like caffeine, kahweol, and cafestol.[39] Acknowledging the limitations of observational studies and the absence of randomised controlled trials, US guidelines allow drinking three or more cups/day in the absence of contraindications based on the reduced risk of MASLD and liver fibrosis.[3]

#### Smoking

Smoking directly affects the liver through increasing oxidative, pro-inflammatory and pro-oncogenic mechanisms.[40] Smoking is associated with an increased risk of hepatocellular carcinoma in patients with MASLD. In a meta-analysis of 81 studies, pooled odds ratio for development of hepatocellular carcinoma was 1.55 (95% CI, 1.46 to 1.65) in current smokers and 1.39 (95% CI,1.26 to 1.52) in former smokers.[40] These data, together with the adverse extrahepatic health effects of smoking, support smoking cessation in patients with MASLD.

#### Drug therapy

When lifestyle measures alone are insufficient to improve liver disease, pharmacotherapy is recommended as an adjunct.[3-41]

Liver related risk can be reduced by optimising pharmacological treatment of MASLD associated comorbidities, such as diabetes and obesity. Multiple anti-diabetic and anti-obesity drugs, with established cardiometabolic benefits, improved steatohepatitis and hepatic fibrosis in participants in randomised trials and may be considered in patients with MASLD at high liver related risk.[37-46] Most recently, the US Food and Drug Administration (FDA) licensed semaglutide 2.4 mg/week for patients with MASLD and fibrosis stage 2-3 who do not have cirrhosis, based on the results of a registrational phase 3 trial.[37] Use of dual glucagon-like peptide 1 receptor agonists tirzepatide and servodutide and sodium glucose cotransporter-2 inhibitor dapagliflozin have also shown substantial improvements in steatohepatitis and fibrosis improvement in phase 2b trials (table 1, bmj.com).

The selective, liver directed thyroid receptor-β agonist resmetirom was approved by the US FDA and by the European Medicines Agency for treatment of patients with MASLD who have fibrosis stage F2-F3. This was following the publication of a registrational phase 3 trial[47] where resmetirom treatment was associated with steatohepatitis resolution in 30% and with fibrosis improvement in 26% of patients. Treatment with resmetirom does not require liver biopsy and non-invasive tests are sufficient for initiating and monitoring treatment effects.[41]

Saroglitazar is a dual peroxisome proliferator-activated receptor-α/gamma agonist which improved liver histology in non-cirrhotic MASLD in a phase 3 trial from India (table 1, bmj.com).[48] Based on these data, saroglitazar was approved in India in 2020 for patients with MASLD who have F1-3 fibrosis.

#### Surgery

Bariatric surgery is recommended by current guidelines in patients who meet criteria for metabolic weight loss surgery, for example patients with class 2 (BMI 35.0-39.9 kg/m$^2$) or 3 (BMI ≥40.0 kg/m$^2$) obesity.[3 4] In patients with metabolic dysfunction associated steatohepatitis who do not have cirrhosis, bariatric surgery resolves steatohepatitis, improves fibrosis, and reduces mortality from cardiovascular disease and malignancy.[3 4]

#### Monitoring

According to two longitudinal studies that enrolled 1260 and 1403 patients with MASLD and without cirrhosis followed for up to 12.2[50,] and 4.4 years,[27] respectively, changes in FIB-4 and vibration controlled transient elastography values over time are independently and bi-directionally associated with the risk of liver related events in patients with MASLD. These modalities are suitable for monitoring liver related outcomes in clinical practice. The frequency of reassessments depends on the baseline test values and on the concomitant risk factors for fibrosis progression. Clinicians should also take into account patients' frailty status and preferences to make individualised, balanced decisions with respect to treatment and monitoring, which may include less frequent testing than might be advised in guidelines for this patient cohort.

Competing interests: None declared.

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Find the full version with references at doi: 10.1136/bmj-2025-084950

### EDUCATION INTO PRACTICE

- How do you discuss the risk of adverse liver related and extrahepatic events with patients who have just received a diagnosis of MASLD?
- Think about the last time you diagnosed MASLD. What lifestyle interventions did you recommend to the person?

EDITORIAL

# Managing liver disease in primary care

Selective rather than widespread testing is needed

People with chronic liver disease are often diagnosed at a late stage, with decompensated cirrhosis or hepatocellular carcinoma when prevention opportunities have been missed. Two linked education articles in *The BMJ* highlight how this might be avoided: Stewart and colleagues (doi:10.1136/bmj-2024-082648) provide a structured approach to interpreting abnormal liver blood tests in primary care; Musso and colleagues (doi:10.1136/bmj-2025-084950) review advances in the investigation and management of metabolic dysfunction associated steatotic liver disease (MASLD).[1 2] Both articles highlight a more upstream question: not just how to interpret test results or risk stratify patients with established diagnoses, but who should be tested in the first place?

Clinicians frequently describe "incidental" abnormal liver blood tests, yet in practice bloods are usually taken for a reason—whether monitoring hepatotoxic drugs or investigating vague symptoms. Too often, however, liver panels are requested without a clear diagnostic hypothesis, which results in large numbers of patients with abnormal test results that are repeated rarely or remain unexplained.[3] This is not cost effective and might lead to health anxiety. The challenge is to increase the pretest probability that a result will have clinical meaning, for example by confirming a suspected diagnosis or contributing to risk stratification.

The epidemiology of liver disease is evolving. The new umbrella term of steatotic liver disease encompasses MASLD, now the most common cause of steatotic liver disease worldwide and largely driven by obesity and diabetes, and alcohol related liver disease.[5] The overlap between metabolic dysfunction and alcohol intake is considerable—alcohol is calorie dense and promotes obesity, while metabolic dysfunction magnifies alcohol's hepatotoxicity. The prevalence of this overlap condition, newly termed metabolic and alcohol related liver disease (MetALD), represents about 3% of steatotic liver disease, though this is likely underestimated owing to under-reporting of alcohol intake.[6] MetALD is associated with a greater risk of liver related events, hepatocellular carcinoma, and extrahepatic cancers compared with MASLD.[7] In practice, those with this dual risk factor hit should be considered as a priority for further testing and risk stratification.

MALCOLM WILLETT

**When fibrosis tests are applied in unselected populations, the positive predictive value falls**

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### Stepwise investigations

Following blood testing, assessing for the presence of fibrosis is the most important predictor of future liver related outcomes in steatotic liver disease.[8] Non-invasive fibrosis tests such as calculation of the FIB-4 index, enhanced liver fibrosis test, and transient elastography are now embedded in international guidelines.[9 10] The recommended cut-offs for these tests were developed in cohorts of patients whose livers were biopsied and who had a high prevalence of advanced liver disease. When these fibrosis tests are applied in unselected primary care populations, however, their positive predictive value falls, which leads to many false positive results.[11-13] These tools, therefore, work best in selected, high risk groups: people with metabolic risk factors and people with hazardous alcohol use.

Some clinicians ask whether there is any value in diagnosing or staging MASLD at all—given that cardiovascular disease remains the leading cause of death in this population.[14] However, MASLD fibrosis carries an increased risk of liver related mortality, often silent until the end stage of the disease.[5] New drugs, such as resmetirom and GLP-1 receptor agonists, are being used to target MASLD directly.[15 16] Moreover, identifying MASLD could function as a cardiovascular "risk enhancer," in the same way that the presence of chronic kidney disease or diabetes influences thresholds for statin use or blood pressure targets currently. Similarly, a diagnosis of MASLD can and should shift preventive strategies beyond the liver.

Primary care will be central to this effort. General practitioners often do not feel confident in managing liver disease, yet steatotic liver disease has all the hallmarks of a long term condition that could and should be managed largely in the community. Clear referral pathways, decision support including use of automated testing strategies, and shared care models will be crucial, while also keeping in mind the resource implications for primary care. When new drugs are licensed, guidance on who prescribes and monitors them will be needed. Above all, strategies must be embedded and equitable to ensure that patients at highest risk of poor outcomes are identified and managed appropriately.

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Find the full version with references at http://dx.doi.org/10.1136/bmj.r2332

PRACTICE POINTER

# Interpreting abnormal liver blood test results

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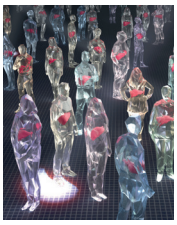


Liver blood tests, frequently and inaccurately called liver function tests, are a collection of core and extended tests commonly requested in both primary and secondary care to screen for, diagnose, and monitor a broad range of liver diseases.[1] The core set of tests include ALT, aspartate aminotransferase (AST), ALP, bilirubin, albumin, and gamma-glutamyl transferase (GGT).[2] Additional initial tests to support assessment of liver health include full blood count (FBC) to measure platelets, and international normalised ratio (INR), followed by a standard and extended non-invasive liver aetiology tests (known informally as the "liver screen").[2]

With 21.7% of all liver blood tests in a large Scottish primary care cohort returning at least one abnormal result[1] (defined as a result outside of the local laboratory reference range), interpretation can be challenging. This stems from a low sensitivity or specificity of each individual liver blood test for detecting liver disease,[2] multiple indications for requesting,[3] and variations in the prevalence of liver disease and its risk factors by geography[3] (box 1, bmj.com). Furthermore, in primary care, clinicians are increasingly managing abnormal blood test results for patients they have never seen or directly cared for.[12] These factors can result in suboptimal management including unnecessary repeat testing and clinician inertia.[3]

In this article, we propose an updated approach and algorithm to managing abnormal liver blood test results, underpinned by new evidence on the evolving epidemiology of chronic liver disease,[4-13] updated international guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD)[7] and steatohepatitis,[11] the evolving multiprofessional landscape within international primary care,[14] and a need to create an integrated approach to managing multisystem manifestations of metabolic disease.

CPD READING

0.5 HOURS

LEARNING MODULE

See learning.bmj.com for linked learning module

## WHAT YOU NEED TO KNOW

- Core liver blood tests have low sensitivity and specificity for diagnosing liver disease, so consider an abnormal result a prompt to use a more specific test
- Repeat a liver blood test only if you know the cause of the abnormality, and if you are not sure, establish the most likely cause first
- Abnormal liver blood test results rarely return to normal within one month
- Liver blood tests should not be interpreted in isolation, but used as part of a diagnostic pathway in conjunction with other investigations
- Risk and prognosis in liver disease are determined by cause, more than degree of liver blood test abnormality

## How should I manage abnormal results?

The infographic shows our proposed algorithm for the management of abnormal liver blood tests in primary care, based on British Society of Gastroenterology guidelines for the management of abnormal liver blood test results,[2] the EASL-EASD-EASO Clinical Practice Guidelines on the management of MASLD published in 2024,[7] and global consensus recommendations for MASLD and MASH in 2025.[11] The algorithm comprises five stages.

### Step 1: Initial clinical assessment

Step 1 reiterates the key information that supports clinicians in assessing for liver disease before serological testing and imaging. Assess hepatitis risk, pregnancy status, medication history, alcohol consumption, liver transplant history, risk factors for liver disease (metabolic syndrome, diabetes, overweight and obesity, family history of liver disease, iron overload), red flags for malignancy and acute illness.[2-16] Clinical examination includes looking for signs of acute and chronic liver disease. Liver disease red flags include falling albumin, substantially raised liver enzymes, jaundice, and signs and symptoms of malignancy.[2-17]

*Alcohol history*

Assess patients' quantity, frequency, and type of alcohol use irrespective of any blood test abnormalities.[18] Screen for alcohol use disorder using an internationally validated tool such as AUDIT-C (alcohol use disorders identification test-C).[18] A score of five points or more is a positive screen and should prompt completion of the full AUDIT questionnaire to assess for alcohol related harm; if alcohol dependence is suspected, assess severity using a more tailored and specific tool (eg, SADQ–severity of alcohol dependence questionnaire).[19] Where indicated, offer a brief intervention to help promote alcohol reduction and/or abstinence.[15 20]

### Step 2: Initial liver health check

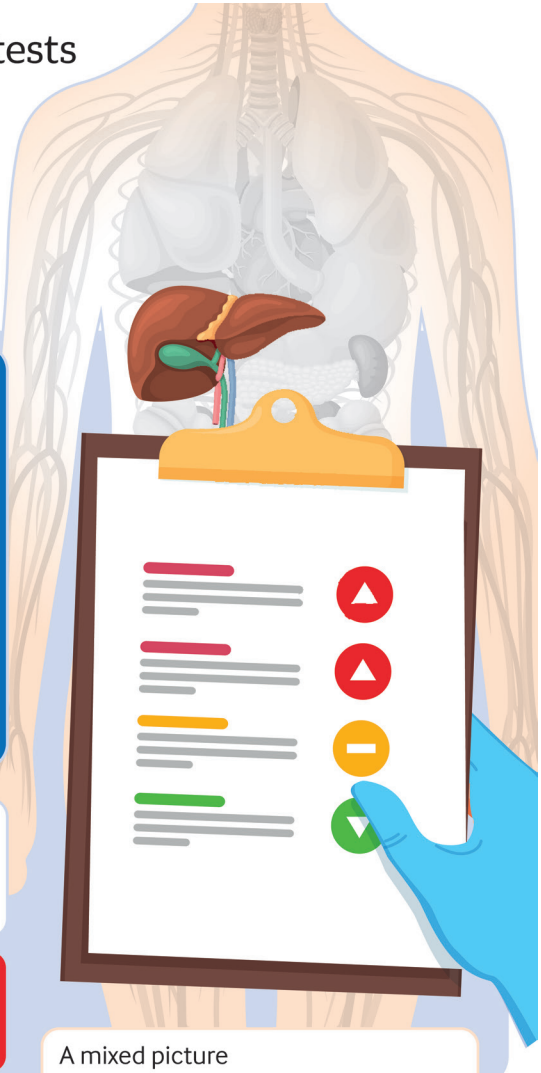
If you are managing an abnormal result and you do not know the patient, go back to step 1 to try to understand the clinical picture and indication for a liver blood test being requested. Indications include screening for liver disease in patients with non-specific symptoms, screening for liver disease in asymptomatic patients at high risk of liver disease, monitoring of hepatotoxic drugs (eg, disease modifying anti-rheumatic drugs,[21] amiodarone, isoniazid, methotrexate[22]), and monitoring of known liver disease or known risk factors for liver disease.[2]

thebmj Visual summary

# Abnormal liver blood tests

## Interpreting and managing results

Interpreting liver blood test results can be challenging. There are a wide range of tests used to screen for, diagnose, and monitor a broad range of liver diseases. Many individual liver blood tests have low sensitivity or specificity for detecting liver disease, and the prevalence of liver disease varies according to individual risk factors and by geographical area.
This visual summary presents a proposed algorithm for the interpretation of abnormal liver blood tests in primary care, based on recent guidelines and recommendations for management of abnormal liver tests and liver disease.



## 1 Initial clinical assessment

### Liver history

**Assess the following**

- Pregnancy status
- Medication history
- Liver transplant history
- Hepatitis risk
- Alcohol consumption
- Red flags for malignancy

**Risk factors** for liver disease

- Metabolic syndrome
- Alcohol consumption
- Hepatitis infection risk
- Diabetes
- Iron overload
- Overweight/obese
- Family history of liver disease

**Clinical examination** for signs of liver disease

- Jaundice
- Spider naevi
- Telangiectasia
- Ascites
- Hepatosplenomegaly
- Pedal oedema

If patient has **acute illness and signs of chronic liver disease** consider same day

- Liver blood tests
- Referral to secondary care

### A mixed picture

A mixed pattern of initial liver blood test abnormalities is common and requires correlation with findings from Step 1 to help determine subsequent investigations.

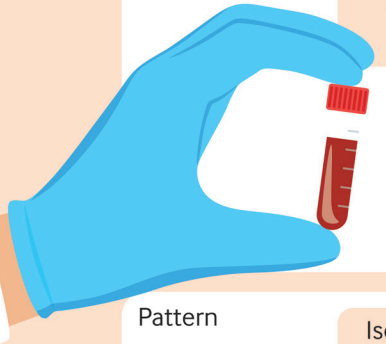
**Consider** the key clinical information from Step 1 alongside the predominant pattern of abnormality from Step 2 to inform which further tests to determine cause of abnormal liver blood test are needed in Step 3.

## 2 Initial blood tests

### Indication for requesting initial liver blood test

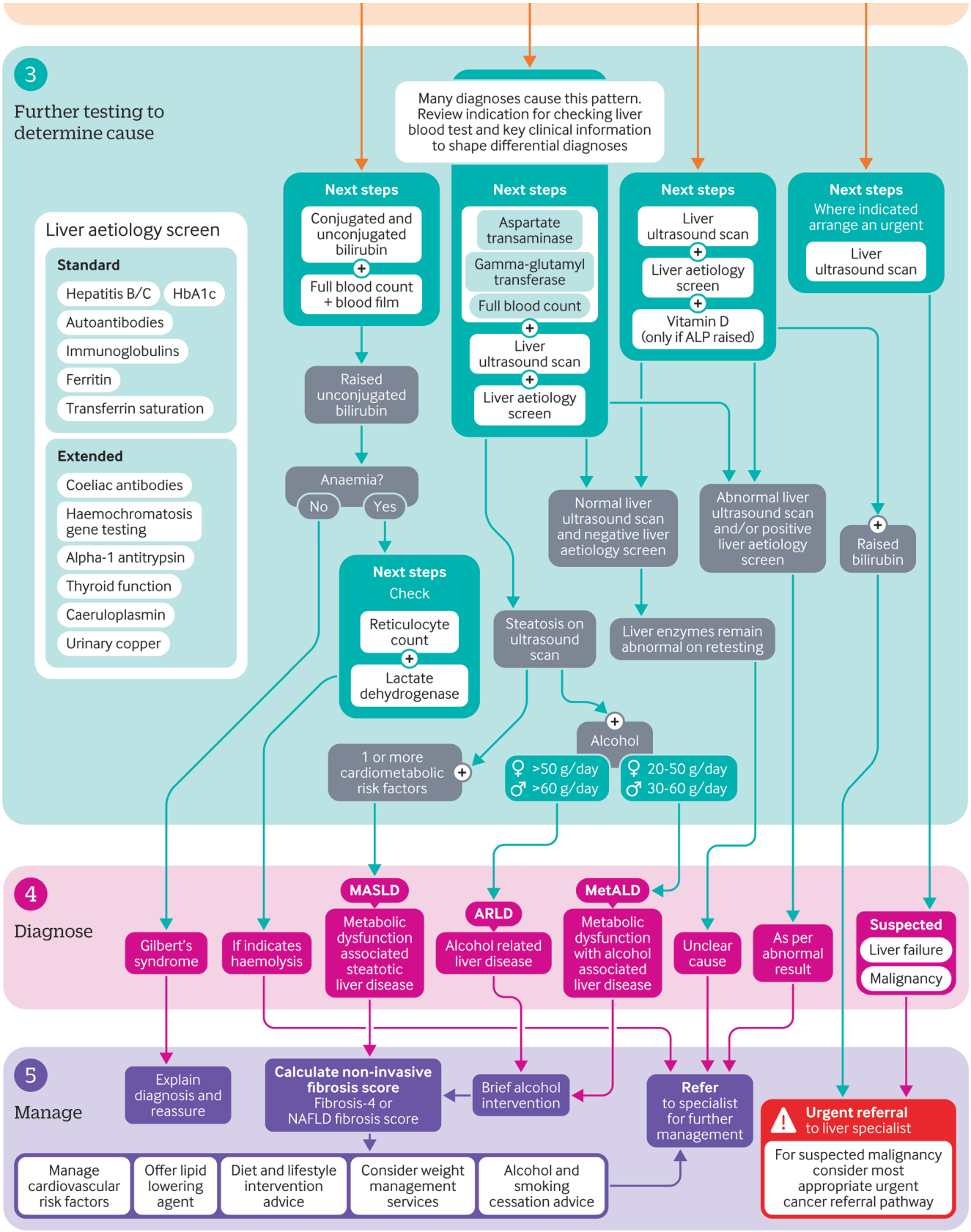
- Monitoring of hepatotoxic drugs
- Monitoring of known liver disease or known risk factors for liver disease
- Screening in patients with non-specific symptoms
- Screening in asymptomatic patients at risk of acute/chronic liver disease

### Abnormality



| Raised | Raised | Raised | Lowered |
|---|---|---|---|
| Bilirubin | ALT Alanine transaminase and/or AST Aspartate transaminase | ALP Alkaline phosphatase and/or GGT Gamma-glutamyl transferase | Albumin and Raised INR International normalised ratio |
| Isolated raised bilirubin | Hepatitic | Cholestatic | Synthetic failure or suspected malignancy |

### Pattern



| Suggested focus of discussion, including rationale for measuring liver blood tests and example explanations | | |
|---|---|---|
| ***Focus of discussion*** | ***Rationale*** | ***Example explanation*** |
| Indication | Explain why the liver blood test is being done | *"As part of routine monitoring because you are taking methotrexate."*<br>*"You had several non-specific symptoms which can be related to liver disease."*<br>Or<br>*"You have known scarring of your liver, so we conducted liver blood tests as part of annual monitoring."* |
| Cause | Explain whether the cause for the abnormal result is known, or whether further tests are needed | *"A raised ALT result is common in patients with diabetes and abnormal cholesterol results like yourself. It does not tell us the cause of your liver problem but it does suggest further investigations would be helpful."* |
| Level of concern | Explain your level of concern regarding the result and remember context is important— "normal results" (within the reference range) can also be abnormal in the context of liver disease, eg, normal ALT in liver cirrhosis. | *"Three of your liver blood tests are elevated and they were all normal when we last checked them three months ago. While we don't know the cause at this stage, I am concerned something serious is affecting your liver and we need to do further investigations urgently."* |
| Next steps | Explain to the patient if a specific action is required on their part and check they understand | *"Two of your liver blood tests are very high which is abnormal, and we need further urgent blood tests, please stop taking your statin medication and paracetamol and seek urgent medical help if you experience the following…"* |

Before requesting a liver blood test, be clear on the indication for doing so. They are non-specific tests and therefore best thought of as an initial liver health check owing to low sensitivity or specificity for individual liver diseases[2] and within-patient and between-patient variation.[23] Abnormal liver blood test results are signals for further testing. Results may follow either a specific pattern which indicates a particular cause of liver disease or a mixed pattern of liver disease.

When determining the pattern of abnormality consider the predominant pattern. Common patterns include:

- Isolated raised bilirubin—hyperbilirubinaemia
- Raised ALT and/or AST—hepatitic pattern
- Raised ALP and/or GGT—cholestatic pattern
- Low albumin
- Raised INR (with or without jaundice)—synthetic failure or suspected malignancy pattern.

A mixed picture of initial liver blood test abnormalities requires correlation with findings from step 1 to help determine subsequent investigations. Following multiple avenues within step 3 of the algorithm may be necessary.

### Step 3: Further testing to determine cause

Abnormality identified in step 2 requires further tests to investigate the hepatic or extra-hepatic cause.[2] Correlation with key clinical information from step 1 will shape differential diagnoses, eg, history of malabsorption, pregnancy status, born in countries where hepatitis B/C virus is prevalent, family history of haemochromatosis.[16] A raised mean corpuscular volume may indicate alcohol related liver disease but is not sensitive or specific for alcohol use.

In some regions of the UK there is a move towards automated reflex testing where laboratories conduct the most appropriate further tests based on the initial liver blood test abnormality.[3] Such a system specific to liver disease is called "intelligent liver blood testing" and was studied in a robust randomised controlled trial which increased specific liver disease diagnoses by 43% while being cost effective.[3]

*Isolated bilirubin*

Raised unconjugated bilirubin is most commonly caused by Gilbert's syndrome (a benign genetic variant) and less commonly by haemolysis.[24] In patients with a raised bilirubin, request fasting conjugated and unconjugated bilirubin, FBC, and blood film. Extremely raised unconjugated bilirubin may indicate the rare Crigler-Najjar syndrome, which presents mainly in childhood and requires referral to a hepatologist.[24 25]

***What to do:***

If anaemia is present, check reticulocyte count and lactate dehydrogenase (LDH) to further assess for haemolysis. Raised conjugated bilirubin is most commonly due to obstructive biliary disease or parenchymal liver disease[2]; correlate with other liver blood tests.

*Hepatitic pattern*

Release of intracellular liver enzymes ALT and AST occurs with hepatocyte injury and death. Many disease processes and drugs cause a raised ALT and/or AST; as such, elevations in these enzymes are the most common liver blood test result abnormalities.[26] ALT has higher specificity for liver disease as it is found mainly in hepatocytes, whereas AST is found in hepatocytes to a lesser degree as well as skeletal and cardiac muscle.[2] The most common causes of raised ALT and/or AST include steatotic liver disease (which encompasses MASLD, alcohol related liver disease, and metabolic-dysfunction associated alcohol-related liver disease), viral hepatitis, autoimmune hepatitis, iron overload, and drug induced liver injury.[2 26]

***What to do:***

To determine the cause of raised ALT and AST, request GGT, FBC, liver ultrasound, and a liver aetiology screen (hepatitis B virus surface antigen; hepatitis C virus antibody; auto-antibodies (anti-smooth muscle, antinuclear, anti-mitochondrial, and anti-neutrophil cytoplasmic antibodies); immunoglobulins; ferritin and transferrin saturation; and $HbA_{1c}$).[2] Where alcohol related liver disease or fibrosis is suspected, calculate the De Ritis ratio (AST:ALT) where a ratio >1 indicates advanced fibrosis/cirrhosis.[2]

*Cholestatic pattern*

ALP is produced primarily in epithelial cells of the biliary system and in bone, and to a lesser degree in hepatocytes.[27] GGT is primarily produced in hepatocytes.[2] As GGT is not produced by bone, it is useful for differentiating raised ALP owing to liver/biliary disease (GGT raised). Although GGT is sometimes elevated in excess consumption of alcohol,[2 28] GGT is a not a reliable indicator of alcohol use.[28] Nevertheless, elevated GGT is an independent predictor of all-cause mortality risk (mildly elevated HR 1.84; CI 1.53 to 2.23; severely (≥ 2.5 × normal limit) elevated HR 6.64; CI 4.96 to 8.88)[1]. Common pathological causes of a cholestatic pattern include biliary obstruction (eg, gallstones, neoplasia), hepatic congestion (eg, secondary to right sided heart failure), drug induced liver injury, primary biliary cholangitis, and primary sclerosing cholangitis.[2] As vitamin D deficiency can cause raised ALP through compensatory mechanisms to maintain normal serum calcium, check vitamin D status for patients with an isolated raised ALP.[27] ALP typically rises during pregnancy due to placental production. During pregnancy, a rise in other liver blood tests in addition to ALP warrants investigation of worsening of pre-existing liver disease or potentially pregnancy related liver disease.

***What to do:***

Request a liver ultrasound (to look for dilated bile ducts and/or focal liver lesions) and a liver aetiology screen.[2]

*Synthetic failure/suspected malignancy*

Synthetic failure refers to when the liver fails to produce sufficient proteins required for key bodily functions; this involves low albumin and prolonged INR.[2] This may also be associated with jaundice owing to decreased hepatic bilirubin breakdown and clearance and reduced urea owing to reduced processing of nitrogenous waste.[29 30] A similar pattern is also seen in a variety of malignancies with associated weight loss and symptoms of cholestasis (pruritis, jaundice, steatorrhoea). Oher causes of low albumin include acute phase response, malabsorption, malnutrition, haemodilution (pregnancy, heart failure, chronic kidney disease), protein loss from gut (protein losing enteropathy) and from kidneys (chronic kidney disease and nephrotic syndrome).[31]

***What to do:***

Request an urgent liver ultrasound and refer urgently to a liver specialist when synthetic failure is suspected.[2] Where malignancy is suspected, refer according to most appropriate suspected cancer pathway.[2]

*Mixed*

A mixed pattern is common. For example, an older adult with reduced protein intake and heart failure may have low albumin (dilutional and reduced synthesis) and raised ALP and GGT owing to hepatic congestion.

***What to do:***

Consider the key clinical information from step 1 alongside the predominant pattern of abnormality from step 2 to inform which further tests to determine cause of abnormal liver blood tests are needed in step 3.[2]


**HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE**

We are grateful to a patient who experienced acute liver failure and received a liver transplant and who shaped this article by helping to refine sections related to how we describe results to patients.


**EDUCATION INTO PRACTICE**

- When interpreting an abnormal liver blood test result, how often are you aware of the indication for testing?
- How often do you assess for the presence of fibrosis in patients with raised ALT or AST?
- How do you explain to patients with MASLD that they have an increased risk of cardiovascular and malignant disease and manage this accordingly?

**Steps 4 and 5: Diagnosis and management**

Based on the clinical picture and test results from steps 2 and 3, clinicians might feel confident to diagnose and manage several of these conditions in primary care with appropriate support from specialists. In table 2 (bmj.com), we outline common differentials, and an approach to diagnosis and management.

*Assessing liver fibrosis*

Patients with metabolic disease and those with signs of steatotic liver disease should undergo non-invasive assessment of liver fibrosis.[7] The most widely available method in primary care is using the FIB-4 (fibrosis-4 index for liver fibrosis) score which calculates a fibrosis risk score based on age, AST, ALT, and platelet count.

- For patients with a score <1.3, FIB-4 has a high negative predictive value for advanced fibrosis and their FIB-4 score should be reassessed every 1-3 years.[7]
- For patients with an intermediate score of 1.3-2.67, intensify primary care management of comorbidities and consider additional assessment of liver fibrosis using local resources (non-alcoholic fatty liver disease fibrosis score, vibration controlled transient elastography—fibroscan, shear wave elastography, magnetic resonance elastography, enhanced liver fibrosis test).[7]
- For patients with a score >2.67, intensify primary care and specialist management of comorbidities and refer to hepatology for further liver fibrosis assessment.[7]
- Limitations of FIB-4: A FIB-4 score <1.3 has a high negative predictive value. FIB-4 has reduced predictive power in adults aged over 65 and under 35, intermediate scores (1.3-2.67), and in patients with type 2 diabetes, therefore consider alternative measures of liver fibrosis for these cohorts. FIB-4 may still be used for patients aged over 65 where intermediate range is defined as 1.30-2.0 and referral to hepatology is warranted for scores >2.0.[7]


Competing interests: None declared.

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Find the full version with references at doi: 10.1136/bmj-2024-082648

WHAT YOUR PATIENT IS THINKING

# Paralysed by migraine

This author describes what it is like to live with chronic hemiplegic migraine, and her search for support

PRIYA SUNDRAM

The normal clinical environment assaults my senses

CPD READING
0.5 HOURS

It took decades for me to receive a diagnosis of chronic migraine, hemiplegic phenotype, with severe aura. My symptoms include tinnitus, upset tummy, severe pins and needles, spreading numbness, hyperacusis, photophobia, reduced cognition, nausea,partial and total paralysis, and muscle weakness. They can be triggered by harsh lighting, strong smells (especially perfume), touch, sudden movements, loud noises, or chaotic environments.

My first partial paralysis was in 1991. A few years later I started to experience daily periods of paralysis that left me unable to get out of bed, and had a host of complex symptoms including severe all-over body and head pain. I also experience frequent, daily stroke-like episodes, affecting half to three quarters of my body.

### Understanding the origin

For years no one could give me an explanation for my symptoms, particularly paralysis. Finding out that whole body paralysis and back-of-head pain can be part of hemiplegic migraine, and that the pain can extend into the body was transformative in my understanding.

Recognising the symptom patterns and effects helped me understand how different parts of my mind and body worked at different times in a repeat pattern. I learnt there would be no possibility of changing the outcome when symptoms started. I also began to understand that there was a crucial relationship between paralysis and headache.

### Lack of information

Most of the information on my condition focuses on treating the migraine headache, but for me the most challenging part of the condition is the aura symptoms, which are often not targeted. I would like to see research and treatments focusing on the biology of paralysis and see new, appropriate aids created that make a difference.

I need appointments to be by Zoom or phone and home visits to be available, as the normal clinical environment assaults my senses. A perfume-free and quiet, low light setting is best for essential examination.

The environment and physical contact cause me massive difficulty, and clinicians need to understand this to safely treat me. Keeping information clear and short can help with cognitive issues. Accepting and respecting my physical difficulties in accessing healthcare are essential for the relationship to work. Feeling heard is key to feeling supported.

LC, patient author

Cite this as: *BMJ* 2025;391:r2268

## WHAT YOU NEED TO KNOW

- Severe hemiplegic chronic migraine is so much more than the migraine headache, and symptoms can be complex, debilitating, and relentless
- It can be helpful to explain to patients the origins of their symptoms so they can begin to understand their whole experience
- Sharing any new, relevant information with patients is important as there is little guidance on how to help and alleviate severe symptoms; so keep up to date and be willing to think outside the box

## EDUCATION IN PRACTICE

- How could you ensure that you provide compassion to anyone experiencing a rare condition like hemiplegic migraine?
- What could you do in your interactions with patients to avoid triggering a migraine attack?

## ADDITIONAL INFORMATION

- https://rarediseases.org/rare-diseases/hemiplegic-migraine/
- https://www.nationalmigrainecentre.org.uk
- https://healthunlocked.com/tag/migraine
- https://journals.sagepub.com/doi/pdf/10.1177/2040622315579627

CASE REVIEW

## A destructive nasal lesion

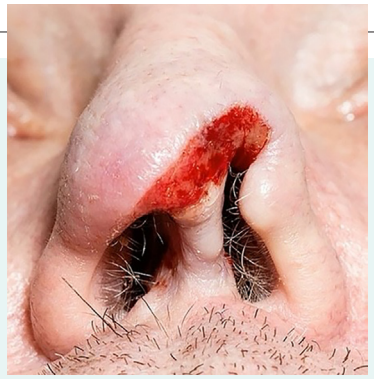
A man in his 50s was referred to the dermatology clinic from the plastic surgery clinic with a two year history of a right sided nasal lesion. The lesion started as a papule that enlarged slowly and appeared to be locally erosive. Topical mupirocin 2% was prescribed but there was no resolution. A biopsy was performed which showed no active inflammation, granuloma, dysplasia, or malignancy. He continued to attend follow up appointments with plastic surgery, however, no definitive diagnosis was reached. No further investigations or treatments were started because the lesion's appearance seemed stable. However, two years from the original onset, similar lesions developed around the nasal tip and superior columella, extending into the left soft triangle and a second opinion was sought from dermatologists. A second biopsy was performed which produced the same result as the first. Further history revealed use of injected drugs and sex with men. The patient did not report any systemic symptoms such as visual or neurological disturbance and reported no history of genital ulcers or rash.

Clinical examination revealed a gummatous lesion involving the skin and underlying cartilage of both nostrils and the nasal septum, with resulting structural collapse and loss of definition at the superior aspect of the nostrils and columella, which extended posteriorly to the level of the middle turbinate. The base of the lesion was copper red with a punched out appearance and scalloped borders (figure). Binocular diplopia on left gaze and reduced visual acuity to the left were seen on neurological exam. Blood count, liver function tests, and autoimmune screen were unremarkable. Relevant investigations and results are presented in the table.

**1 What do the test results show?**

**2 What is the most likely diagnosis?**

**3 What is the management of this condition?**



**Gummatous lesion to the right and left nostrils and septum, involving the superior aspect of the nostril and the columella and resulting in tip ptosis**

Submitted by Holly FitzGerald, Nicholas Laidler, and Graham Thom

Patient consent obtained.

Cite this as: *BMJ* 2025;391:e083645

**Laboratory test results**

| Investigation | Result |
|---|---|
| **Microbiology** | |
| HIV-1 and HIV-2 antigen/antibody confirmation | Not detected |
| **Non-treponemal testing** | |
| Rapid plasma reagin | 1/128 |
| Repeat rapid plasma reagin (after treatment) | 1/4 |
| Venereal Disease Research Laboratory cerebrospinal fluid | Negative |
| ***Treponema pallidum* testing** | |
| Total antibody (chemiluminescence microparticle immunoassay) | Detected |
| Particle agglutination assay (serology) | 3+ |
| Particle agglutination assay (cerebrospinal fluid) | 1/160 |
| Polymerase chain reaction (skin nose swab) | Not detected |
| **Histopathology** | |
| Supplementary review of first biopsy result | No spirochetes identified on *T pallidum* immunohistochemistry |
| **Radiology** | |
| Brain magnetic resonance imaging | Minimal thickening and enhancement of the nasal apex<br>No focal lesion along the trigeminal nerves bilaterally |

answers

CASE REVIEW **A destructive nasal lesion**

**1. What do the test results show?**

Any reactive rapid plasma reagin or VDRL test is considered positive for syphilis, but it must always be confirmed with a treponemal test. The majority of false positive non-treponemal tests show titres <1:4. The positive rapid plasma reagin and high titre along with the detection of *T pallidum* on treponemal testing indicate active treponemal infection.

**2. What is the most likely diagnosis?**

Tertiary syphilis and neurosyphilis. Syphilis is a curable, sexually transmitted disease caused by the spirochete *T pallidum*. Tertiary syphilis presents 2-50 years after infection with primary syphilis and is increasingly rare. The clinical presentation is variable with cardiovascular, gummatous, and neurological manifestations.

**3. What is the management of this condition?**

Both the 2020 European Guidelines and 2025 British Association for Sexual Health and HIV guidelines recommend intramuscular benzathine penicillin G for primary, secondary, early latent, and late latent syphilis.

**LEARNING POINTS**

- **Neurosyphilis occurs when *T pallidum* involves the central nervous system and can be asymptomatic or present with a wide range of neurological or psychiatric manifestations.**
- **Diagnosis of neurosyphilis is challenging and requires reactive serology and cerebrospinal fluid analysis with non-treponemal and treponemal tests.**
- **Penicillin is the cornerstone of treatment for all stages.**

**PATIENT OUTCOME**

See bmj.com.

CPD READING
0.5 HOURS

You can record CPD points for reading any article. We suggest half an hour to read and reflect on each.

LEARNING MODULE

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