GUIDELINES ON THE USE OF LIVER BIOPSY IN CLINICAL PRACTICE

FROM THE BRITISH SOCIETY OF GASTROENTEROLOGY, THE ROYAL COLLEGE OF RADIOLOGISTS AND THE ROYAL COLLEGE OF PATHOLOGY

Appendix A: Disease specific indications for liver biopsy

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Although not exhaustive, this section discusses firstly common and then more rare indications for liver biopsy, including within specialised areas.

1 Chronic liver disease

In all chronic liver diseases, histological assessment of severity includes generic features related to disease activity (grade), such as steatosis or inflammation, and features related to disease progression (stage), mainly fibrosis, in addition to features of the specific disease entity. Assessment of both disease grade and stage is important for prognosis and for clinical management. There are promising advances in non-invasive tests for estimating the degree of steatosis and fibrosis, but these do not provide the same detail available from liver histology. At the present time, there are no reliable non-invasive methods for assessing histological inflammatory activity in the liver. Liver histology therefore remains the gold standard in all liver diseases for determining the pattern and severity of necro-inflammatory activity and fibrosis, including any remodelling of the parenchyma.

Increasing numbers of patients have multiple factors that may contribute to liver damage. In these cases, a liver biopsy may help establish the predominant cause of liver damage and guide appropriate interventions to reduce the risk of progressive disease. In the cirrhotic stage, many disease processes such as fatty liver disease (related to alcohol or metabolic syndrome) or autoimmune hepatitis can appear “burnt out” with subtle and sometimes only focal, disease-specific characteristics. Liver biopsy in these cases may not determine the aetiology and the cirrhosis may remain cryptogenic.

In the past, chronic liver disease was thought to be irreversible once cirrhosis had developed but from both animal and human studies it is now clear that cirrhosis is reversible in some patients, especially in those without decompensation such as portal hypertension. It has therefore been suggested that the use of the term advanced chronic liver disease with a statement of the degree of fibrosis better reflects the continuum of chronic liver disease.[1] Although non-invasive liver stiffness

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estimates reflect this continuum well, current histological staging systems include an assessment of architectural disturbance in addition to the amount of fibrosis.[2, 3] In particular, architectural changes involving vascular shunts and liver cell regeneration are best assessed by histology and these findings may be helpful for prognostication. It is also possible to sub-classify cirrhosis histologically, based on the Laennec system, which involves assessing the thickness of fibrous septa compared with the amount of residual liver parenchyma, and this has been shown to give prognostically important information, including complications of portal hypertension and response to anti-fibrotic treatment.[4, 5]

Other limitations of liver biopsy include observer variability and sampling variability. Although not currently generally available, computer-assisted methods may in future help augment conventional histological assessments. These currently include quantifying the amount of fibrosis, such as the collagen proportional area (CPA)[6, 7, 8] and such methods might lead to more precise and reproducible determination of disease progression or regression. For example, CPA has been shown to predict progression both to HCC and liver related death better than the histological Metavir staging system.[3] Another method utilises diffuse reflectance spectroscopy on paraffin embedded liver specimens to assess fibrosis[9] and further advances in automated analysis are expected.

Hepatocyte injury as a determinant of disease activity is usually assessed using liver biochemistry (serum transaminases) although the correlation with histological signs of inflammation is limited. The main histological characteristics that can be estimated through non-invasive tests are hepatic fibrosis, hepatic steatosis and hepatic iron content. The advantage of these non-invasive tests is that they can be used repeatedly to assess disease progression or regression with treatment and have no or minimal clinical risk for the patient.

Hepatic fibrosis: Serological surrogate markers can be disease specific such as the NAFLD fibrosis score, or generic such as Fib4 (Fibrosis 4), ELF® (Enhanced Liver Fibrosis) score or the UIC (Universal Index for Cirrhosis[10]) but these need to be validated for different diseases and clinical situations. Liver stiffness measurements including the transient elastography (Fibroscan®), ARFI®, and MRI based methods also depend on the underlying liver disease (for example cholestatic or hepatitic) and need to be validated accordingly.

Hepatic steatosis: The non-invasive techniques used to determine liver steatosis include the Fibroscan® function of Controlled Attenuation Parameter (CAP)[11, 12, 13] or MRI imaging for example using multi-echo magnetic resonance imaging[14, 15] which may be more accurate than CAP.[16]

Hepatic iron content: Hepatic iron content can be estimated using MRI analysis for example using the liver to muscle intensity ratio, transverse magnetization (R2) relaxometry and the R2* technique with good prediction of iron content compared with liver biopsy.[17, 18, 19] Some techniques are available online for all scanners and their use may be beneficial in both diagnosis of iron storage conditions and management of iron removal.

In addition to these determinants of liver disease assessable by imaging modalities, there are other important factors of progression which will influence prognosis. For example, the portal hepatic venous pressure gradient has been used and might better reflect reversibility or irreversibility and outcome of chronic (and acute on chronic) liver disease than fibrosis stage.[20, 21, 22, 23] This gradient can be measured in a single procedure when a transjugular liver biopsy is obtained and depending on the clinical question, a transjugular biopsy with pressure gradient measurement might be preferential to a transabdominal approach.

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Recommendation: Before proceeding to a liver biopsy, the clinicians involved need to consider whether the necessary information can be gained non-invasively (moderate strength, low evidence).

1.1 Chronic Hepatitis B Virus (HBV) infection

In chronic hepatitis B, patients initially display e antigen positivity (eAg+ HBV) and some later seroconvert to e antibody positivity (eAb+ HBV) with loss of eAg (eAg-). In eAg+ HBV as well as eAb+ infection, the decision to treat patients depends, in part, on the stage of fibrosis, the grade of inflammation and hepatocyte necrosis, and the viral load (HBV DNA concentration). Even at the early stage of infection which was thought to be associated with very little inflammation on the basis of biochemical markers, liver histology can demonstrate significant inflammatory activity.[24] Finding inflammatory or significant fibrosis on histology has implications for disease progression, risk of complications and patient management. Treatment guidelines favour treatment in the presence of biochemical / serological disease activity or signs of advanced disease and in some cases, histology can add to the assessment.[25, 26]

There have been several studies using non-invasive methods to estimate the degree of liver fibrosis in chronic hepatitis B. In one study, transient elastography was superior to APRI (AST to platelet ratio index) for all stages of chronic HBV infection.[27] In a meta-analysis APRI and FIB-4 identified HBV related fibrosis with a moderate sensitivity and accuracy.[28] A combination of liver stiffness measurement using transient elastography with biochemical markers, may predict fibrosis degree accurately and avoid the need for liver biopsy in many cases.[29] The serum γ-GT (gamma glutamyl transferase) to platelet ratio (GPR) seems to be the most sensitive marker to stage liver fibrosis in the absence of biopsy and liver stiffness measurement.[30]

In addition to determining the degree of fibrosis, knowledge of whether the fibrosis is progressive, stable or regressive is important in the management of patients with chronic HBV infection. In particular, regression may be regarded as treatment success and will likely predict improved prognosis. At a given degree of fibrosis, comparison with previous biopsies can give further information and help determine whether fibrosis is progressive or regressive.[31, 32]

In one study, liver stiffness measurement using transient elastography was a better predictor of progression to HCC than fibrosis and necro-inflammatory scores obtained from liver histology.[33] Therefore, algorithms for HCC screening and surveillance (for example when to start) might in the future be determined by liver stiffness measurements. Given therapeutic challenges of HBV treatment, liver biopsies are more often being done in chronic HBV infection but biopsies in chronic HCV infection are declining.[34]

Liver histology can also be useful if other risk factors for liver disease are present or if the extent of fibrosis is unclear.[25, 26] According to current EASL and AASLD guidelines management decisions can often be made on the basis of non-invasive tests[25] (EASL 2017);[26] (AASLD 2018)] but a liver biopsy may be used to determine disease activity where biochemical and virologic markers yield inconclusive results. [25]

Recommendation: Chronic hepatitis B infection can be managed in most cases with currently available treatment regimen without doing a liver biopsy (high strength, high evidence). If other causes are suspected or tests for inflammatory activity or staging are uncertain, liver biopsy is useful in the management of HBV infection (high strength, high evidence).

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1.2 Chronic Hepatitis C Virus (HCV) infection

Previously liver biopsy was frequently used to assess disease severity (mainly fibrosis stage) in patients with chronic HCV infection but this has changed, both as a result of reliable non-invasive methods to assess liver fibrosis and the development of antiviral drugs which have a high efficacy in treating HCV infection irrespective of disease stage. In many countries the current strategy is to treat all patients chronically infected with the HCV and as a consequence, liver biopsies are obtained very infrequently. According to current clinical guidelines, the only indication for liver biopsy is to investigate patients who have additional causes for liver damage,[35] although with short treatment courses, of often 8 weeks, and with very high success rates, it is feasible to eliminate the virus and then re-assess for evidence of on-going liver damage before considering a liver biopsy.

Patients with HCV who have progressed to cirrhosis/advanced stage chronic liver disease will have follow up including HCC screening and surveillance. Liver stiffness measurements such as transient elastography[36] or ARFI[37, 38] and serological scores such as APRI (AST to platelet ratio index)[27] or Fib-4[39] can be used to predict advanced fibrosis and cirrhosis and a combination of serum markers and elastography may improve this prediction.[40] An increased cancer risk remains after eradication of HCV in patients who had cirrhosis, so in this context HCC surveillance is not currently discontinued based solely on evidence of reduced fibrosis.

As in HCV mono-infection, in HIV/HCV co-infection non-invasive tests are useful in fibrosis prediction[41] and in one study FIB-4 was found to be a better predictor of survival and liver related events (decompensation or hepatocellular carcinoma) compared to liver histology and fibrosis staging (using the Metavir score).[42]

Recommendation: Chronic hepatitis C should be managed without a liver biopsy in the majority of cases (high strength, high evidence).

1.3 Non-Alcoholic Fatty Liver Disease (NAFLD)

NAFLD is now defined as fatty liver disease not related to alcohol or other causes such as drug induced liver injury and this condition is considered to be part of the metabolic syndrome. The spectrum of NAFLD includes non-alcoholic fatty liver (NAFL; steatosis without hepatocellular injury) and non-alcoholic steatohepatitis (NASH; steatosis with hepatocyte ballooning degeneration with or without fibrosis). The current thinking is that NAFL and NASH are two points on a disease continuum.[43, 44, 45] Both can progress to fibrosis and cirrhosis with an increased risk of progression in the presence of prominent lobular inflammation.[43, 44] Progression is also more likely in the presence of metabolic risk factors.[46] The presence and degree of liver inflammation is not necessarily reflected in abnormal serum transaminases. Virtually all patients with type 2 diabetes mellitus and many patients with other features of the metabolic syndrome have histological signs of NAFLD on liver biopsy, although not necessarily associated with abnormal liver biochemistry.[47]

The NAFLD fibrosis score (using age, BMI, impaired fasting glucose, AST, ALT, platelet count and albumin) assesses probability of fibrosis in patients with NAFLD.[48] A low NAFLD fibrosis score has a good negative predictive value (NPV) for cirrhosis (NPV for NAFLD Fibrosis score < -1.455 was 93 % in the study group and 88 % in the validation group). However, the positive predictive value (PPV) for significant fibrosis or cirrhosis in patients with a high score was lower (PPV for a NAFLD Fibrosis score > 0.675 PPV was 90 % in the study group and 82 % in the validation group but the PPV was lower in subsequent studies).[48] Therefore, those with a low score should only be investigated further if there are other indications of advanced fibrosis.

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The NAFIC score (**NA**FLD score using **f**erritin, fasting **i**nsulin and type IV **c**ollagen 7S) has been proposed to predict presence of steatohepatitis or advanced fibrosis in NAFLD[49] and an algorithm using this score as well as Fib-4 (age, AST, ALT and platelet count) for investigation of NAFLD has been proposed.[50]

Of the imaging modalities, MRI might be useful estimating the degree of inflammation in NAFLD.[51] Ultrasound scan (the CAP function of the Fibroscan®)[11, 12] and MRI[14, 15, 16] can estimate the fat fraction. There are several ultrasound and MRI based methods of liver stiffness measurement. The methods based on ultrasound scanning (transient elastography, ARFI®) show a reasonably good prediction of degree of fibrosis with relatively little difference between the methods[37, 52, 53] but MRI seems to be more accurate in the identification of liver fibrosis.[16, 54]

In general, consistently low results in non-invasive assessment of disease severity are effective in identifying patients with a low risk of advanced stage NAFLD. When results are indeterminate or conflict with other parameters, then a liver biopsy is justified. Given the epidemiology of NAFLD this has major implications on resources.

Many NAFLD guidelines and guidance documents recommend that liver histology is essential for the diagnosis of NASH and is the only way that reliably differentiates NAFLD from NASH.[55, 56] However, liver biopsy is not uniformly done in NAFLD. At present, there are no licensed drug treatments for NASH, although with their development, the role of liver biopsy in NAFLD would be expected to change.

A further indication for histological assessment is the diagnosis or exclusion of other causes of liver injury and liver biopsy is recommended in these situations by the EASL[56] and AASLD guidelines.[55] With increasing probability of cirrhosis or significant fibrosis on non-invasive tests the guidance suggests to physicians to be more inclined to biopsy to establish fibrosis. However, the guidelines do not state at which thresholds to biopsy. With regards to follow up of diagnosed NAFLD, repeated liver stiffness measurement (using Fibroscan®) predicted clinical outcome comparable with paired liver biopsy[57] suggesting serial biopsies may be unnecessary once the diagnosis is established.

1.3.1 Liver biopsy during bariatric surgery

NAFLD is common in patients undergoing bariatric surgery and many patients have advanced liver disease.[58] Whether there is an additional risk of obtaining a liver sample intraoperatively has not been studied but is likely to be small; routine biopsy during bariatric surgery is not standard.[59, 60] In a recent review, 25 % of patients undergoing bariatric surgery have NASH; non-invasive markers are unable reliably to identify those patients with a normal liver.[61] One group suggests liver inspection during bariatric surgery using a visual liver score as a reliable tool for NAFLD risk stratification with a normal liver appearance reliably excluding significant liver disease thereby avoiding the need for liver biopsy.[62]

Recommendation: Liver histology is recommended to establish the presence of steatohepatitis as well as in patients with indeterminate or contradictory non-invasive tests, or advanced fibrosis, or when there is clinical suspicion for a second pathology, or no improvement in tests after significant metabolic improvement. (high strength, high evidence).

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Recommendation: Liver biopsy in bariatric surgery is not standard practice and should not be done in a macroscopically normal looking liver (low strength, low evidence).

1.4 Alcohol-related liver disease (ARLD)

Acute alcoholic hepatitis which can be the unmasking of chronic disease is discussed in 2.2. The role of liver biopsy in ARLD remains uncertain, with most patients being managed without histopathology available. Biopsy is useful when the non-invasive liver screen suggests an additional or alternative diagnosis, or when the patient presents with the clinical picture of acute hepatitis in which the degree of underlying fibrosis and features of reversibility may be useful in guiding clinical management. The presence of advanced liver disease is high in patients whose first presentation with ARLD is to secondary care.[63] As with NAFLD, the histological diagnoses of fatty liver, hepatitis, fibrosis and cirrhosis cannot be distinguished without biopsy. [64] Despite a history of alcohol excess other factors may often contribute to liver damage and these can be assessed by liver histology. Liver histology is also helpful in estimating the reversibility of the liver disease and demonstrating the severity of liver disease and such knowledge may motivate the patient to abstain from drinking alcohol.

Outside of clinical trials the EASL practice guidance on alcohol related liver disease[64] recommends liver biopsy where there is diagnostic uncertainty or where precise staging is required.

Recommendation: Liver biopsy should be considered in selected patients with ARLD and may be useful where there are multiple risk factors or will help target lifestyle modifications (moderate strength, low evidence)

1.5 Genetic haemochromatosis and iron overload

Iron overload has several causes and the diagnosis is made on the basis of serum iron studies and estimation of iron content in the liver. The diagnosis of genetic hemochromatosis is made by HFE genotyping. MRI methods are able to detect and quantify iron overload in the liver and the spleen as well as other organs. Software for iron quantification for MRI scanners is freely available online and MRI might be more accurate in estimating total body iron than liver biopsy.[65] In future, susceptometry which uses the liver's intrinsic magnetic susceptibility, may become a bedside test.[66]

The role of liver biopsy has changed from quantitative iron measurement to aid diagnosis to determining the degree of fibrosis. The degree of fibrosis is of prognostic value and helps guide clinical management[67] but liver biopsy can be avoided in the majority of cases[68] especially if liver stiffness measurement is clearly indicating the presence or absence of cirrhosis.[69, 70]

In non-HFE iron overload, after exclusion of haematological causes of iron overload, a liver biopsy will determine the histological localisation of iron (in hepatocytes or in Kupffer cells). Liver histology is also useful to rule out other causes of liver disease with stainable iron also found in patients with non HFE iron overload.[67] These include mutations in other iron transporter genes, iron ingestion in related African American iron overload and in patients with other liver diseases (as co-factors) including heavy alcohol consumption, viral hepatitis, alpha-1-antitrypsin variants and any patients with cirrhosis. Excess iron on histology is also found in patients with normal iron parameters.

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Although liver histology can stage fibrosis, measurement of liver stiffness[70] and serum markers such as serum hyaluronic acid may help in determining degree of fibrosis.[71]

Recommendation: Liver biopsy should be considered in selected patients with atypical iron parameters and MRI imaging or atypical HFE genetics in particular with inconclusive liver stiffness measurements or features suggestive of advanced fibrosis. **Liver biopsy is not routinely indicated in most cases of genetic haemochromatosis. (moderate strength, low evidence)**

1.6 Autoimmune hepatitis (AIH)

Liver biopsy is indicated both in the diagnosis and in the follow-up of patients with autoimmune hepatitis. AASLD and EASL guidelines[72, 73] recommend liver histology as part of the workup for the diagnosis of AIH and liver histology is part of standard diagnostic algorithms and scores.[74] AIH may have an acute presentation in up to 30-40% of cases, see section 2.3 below, with or without evidence of underlying chronic disease on biopsy. In atypical clinical presentations, liver histology can identify features that suggest additional pathology, particularly a diagnosis of autoimmune chronic cholestatic liver disease.[75] The role of liver biopsy in monitoring of immunosuppression is less certain. Ongoing histological inflammatory activity is likely to lead to progression of fibrosis and cirrhosis. In autoimmune hepatitis, there is less correlation of fibrosis stage with transient elastography (Fibroscan) than in other chronic liver diseases and fibrosis is best assessed on liver histology.[76]

Histological resolution of disease usually lags behind serological remission by months or years. Despite clinical and serological remission, patients may have significant inflammation on histology. About half of patients with interface hepatitis have a high risk of relapse when immunosuppression is withdrawn and therefore, liver biopsy should be considered prior to cessation of immunosuppressive treatment;[72, 73] some studies suggest that, in well controlled patients, a biopsy may not be necessary.[77]

Recommendation: In autoimmune hepatitis most patients will need a liver biopsy to make the diagnosis at time of treatment initiation. Histology should be considered when withdrawal of immunosuppression is being considered (high strength, high evidence)

1.7 Primary Biliary Cholangitis (PBC)

A persistently raised anti-mitochondrial antibody (AMA) at a titre of ≥1:40 and of the E2 sub-type or other PBC-specific autoantibodies, especially in the presence of an elevated serum alkaline phosphatase, strongly suggests a diagnosis of PBC even in the absence of symptoms or signs of liver disease and a liver biopsy is rarely indicated for diagnosis.[78, 79, 80] In the investigation of cholestatic liver disease with negative serology, or in the presence of other risk factors for liver disease a liver biopsy is indicated.[79, 80] Another indication for a liver biopsy is the suspicion of overlap with autoimmune hepatitis.

Transient elastography[81, 82] as well as the serological enhanced liver fibrosis algorithm ELF®[83] have been shown to correlate with degree of fibrosis, although the presence or absence of cirrhosis is of limited prognostic significance. Changes in transient elastography[81] or a PBC specific serological score (such as the Mayo Risk Score, the Global PBC score and the UK-PBC risk score) might be better in predicting outcome.[79, 84] If information from liver histology is included in the clinical investigations, a staging system based on assessment of fibrosis, duct loss and orcein positive granules has been shown to be more reliable than prognosis based on fibrosis alone.[85, 86] However, it should be noted that sampling variation occurs in PBC as with PSC.[87]

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A liver biopsy may be indicated in those with PBC where the response to treatment is poor and other treatable causes may be present[79] and should be done if second line treatment with Obeticholic acid is considered.

Recommendation: In PBC a liver biopsy should be done if there is uncertainty about the diagnosis, such as absence of PBC specific antibodies, in clinically atypical cases such as failure to respond to UCDA and consideration of second line treatment. Biopsy may also be useful in overlap syndrome (high strength, high evidence).

1.8 Primary Sclerosing Cholangitis (PSC)

Classical PSC is characterised by changes involving large and small bile ducts. PSC is usually suspected in patients with cholestatic liver tests, often in the presence of inflammatory bowel disease; the diagnosis is usually made radiologically with a magnetic resonance cholangiogram (MRCP) or less often with an endoscopic retrograde cholangio-pancreatogram (ERCP). Histopathology is not needed for diagnosis in such cases.[88] However, some other conditions may also show irregularities of the biliary tree, such as IgG4 autoimmune cholangiopathy, ischemia or AIDS cholangiopathy[89]. The main indications for liver biopsy relate to the diagnosis of small duct PSC in which cholangiographic abnormalities are lacking, the assessment of suspected overlap variants (such as PSC/AIH overlap) or instances where the diagnosis is unclear.[90]

The histological finding of periductal fibrosis (onion skin appearance) in needle biopsies is helpful in the diagnosis of PSC. However, fibrosing duct lesions mainly affect medium-sized ducts and are therefore seen uncommonly in peripheral needle biopsy specimens. Furthermore, periductal fibrosis may also be seen in secondary sclerosing cholangitis and rarely in PBC. Liver biopsies from patients with PSC more frequently show non-disease specific features supporting a diagnosis of chronic biliary disease – these include duct loss, ductular reaction, a biliary pattern of periportal fibrosis and changes related to chronic cholestasis such as deposition of copper-associated protein in periportal hepatocytes. Similar changes are also seen in other chronic biliary diseases such as PBC.

It is worth noting that the above features characteristic of a chronic biliary disease are sometimes recognised in liver biopsies taken for other reasons in patients who are not clinically suspected to have a cholestatic disease; this is a relatively common finding in biopsies where the diagnosis is revised on review[91, 92]. In this situation clinicopathological discussion is particularly important and imaging of the biliary tree (or its review if already done) is indicated.

Recommendation: In PSC a liver biopsy should be done if there is doubt about the diagnosis such as overlap syndrome or absence of large duct disease or when other conditions should be considered (moderate strength, low evidence).

1.9 Wilson's Disease

The diagnosis of Wilson's disease is made on clinical history and examination, estimation of serum caeruloplasmin and urinary copper (Leipzig score). If the diagnosis is not clear, this is often followed by liver biopsy which should be used to corroborate the diagnosis.[93, 94, 95] The histological changes seen in Wilson's disease are not specific: they include portal inflammation, steatosis and hepatocyte ballooning; fibrosis / cirrhosis is often present[96] including in patients with an acute/fulminant presentation.[97] Liver histology can be normal in early cases. The presence of copper in hepatocytes can be detected histochemically using stains for copper or copper binding protein. However, copper stains may be negative in Wilson's disease and the absence of stainable

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copper in a liver biopsy does not therefore exclude the diagnosis. In order to obtain an accurate assessment of liver copper content a separate unfixed sample of at least 1 – 2 cm should be taken for chemical pathology analysis.[98] It is possible to determine copper levels on a formalin fixed paraffin embedded sample, but this is less straightforward than in unfixed samples. A cut-off of at least 200 µg/g[99] (or 4 µmol/g = 254 µg/g)[93] was proposed for a firm diagnosis, although such high levels can be seen with severe chronic cholestatic conditions. In contrast to genetic haemochromatosis, there are numerous gene defects described in the Wilson's Disease Gene although genetic analysis of the alleles on chromosome 13 may help in selected cases.

Recommendation: Wilson's disease is often difficult to diagnose in early stages and a liver biopsy will be necessary to confirm the diagnosis in many cases; an adequate sample should be sent for dry copper weight measurement. (high strength, high evidence)

1.10 Investigation of portal hypertension

In cases of portal hypertension where no cause is found, a liver biopsy is often helpful. Although this is a relatively rare indication in the West, it is more common in Asia.[52] The main reason to do a liver biopsy is to diagnose idiopathic non-cirrhotic portal hypertension (NCPH). The histological diagnosis of idiopathic NCPH involves both excluding significant fibrosis and identifying characteristic changes in small portal veins (obliterative portal venopathy) and related secondary vascular changes (e.g. nodular regenerative hyperplasia) There is little guidance as to when liver biopsy should be done and there is no gold standard for diagnosis of NCPH (see for example [100]). The hepatic venous pressure gradient (HVPG) may be better than histological changes at predicting complications of portal hypertension [16496308]. The Baveno VI consensus workshop uses a hepatic venous pressure gradient (HPVG) of > 5 mmHg as indicator of sinusoidal portal hypertension albeit in compensated advanced chronic liver disease.[101] The liver stiffness by transient elastography varies significantly in NCPH with on average higher liver stiffness in causes of portal hypertension other than NRH or PVT.[102]

Recommendation: The role of liver biopsy in idiopathic portal hypertension is unclear but is a useful tool in the absence of portal vein thrombosis (low strength, low evidence).

1.11 Congestive hepatopathy

Obstruction to venous outflow may involve pathological processes occurring anywhere from the sinusoids (sinusoidal obstruction syndrome), small intrahepatic veins (veno-occlusive disease), thrombosis in larger hepatic veins (Budd Chiari syndrome), narrowing of inferior vena cava, or in right sided heart failure either primary or due to advanced lung disease. Characteristic histological features of venous outflow obstruction include sinusoidal dilatation and congestion with extravasated red blood cells lying within the space of Disse. Other changes that may be seen include hepatocyte plate atrophy, fibrosis, fibrous bridging between hepatic veins, and cirrhosis depending on the severity and duration of outflow obstruction. While most patients can be diagnosed on clinical and radiological features, these biopsy findings may occasionally be seen in patients not previously suspected of having venous outflow obstruction and prompt further investigation.

While the diagnosis of congestive hepatopathy can sometimes be made clinically and on imaging, staging of liver damage is difficult. Serological markers including scoring systems such as FibroTest® (FibroSure® in the US) do not correlate well with the degree of fibrosis; imaging in congestive hepatopathy may show a nodular liver contour in the absence of cirrhosis. Patients with advanced

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heart failure are often on anti-coagulants making an estimation of synthetic liver function and prognosis using non-invasive scores (for example Model of End Stage Liver Disease (MELD) score) difficult. A liver biopsy often requires reversal of anticoagulation or a transjugular approach, the latter also allows direct measurement of portal and venous pressures. Although hepatic changes from cardiac congestion can vary markedly within the liver, histological analysis can add to the information obtained with non-invasive measures such as the Model of End-Stage Liver Disease Excluding INR (MELD-XI) score.[103] The main indication for liver biopsy in patients with severe cardiac failure is to evaluate whether there is advanced fibrosis prior to cardiac transplant however, problems with sampling variation result in histology being of limited predictive value for outcome.[104]

Recommendation: Liver biopsy in congestive hepatopathy is indicated in individual cases (for example when heart transplantation is being considered) and should be done after discussion with specialist liver and cardiac centres (moderate strength, low evidence).

1.12 Methotrexate induced fibrosis

Methotrexate (MTX) can be associated with acute drug induced liver injury (acute DILI, see 2.15) but also causes fibrosis at high cumulative doses, often with normal serum transaminases. With long term use, there is a risk of methotrexate induced cirrhosis. Risk factors for methotrexate induced liver injury include obesity, excessive alcohol use and Type 2 diabetes[105] so features of NAFLD and alcohol-related liver disease may also be present on histology.

MTX is for many patients the most effective drug in controlling their dermatological or rheumatological condition. Serial testing may be necessary to help decide whether or when to stop MTX. This decision will depend on stage of liver disease (fibrosis/cirrhosis), presence or absence of other risk factors (such as heavy alcohol consumption or metabolic syndrome) and availability of other effective medications. Hepatic fibrosis and cirrhosis due to MTX is considerably less common than initially reported.[106, 107] Dermatology guidelines are stricter than rheumatology guidelines in surveying for advanced liver disease and risk of hepatic toxicity is greater in patients with psoriasis than in patients with rheumatoid arthritis.[108]

As in other causes of liver damage, serum transaminases and other liver biochemical tests are not very useful for prediction of fibrosis. Routine serial procollagen III peptide (PIIINP) has decreased the need for liver biopsy but some patients with high levels of PIIINP do not have significant fibrosis[109] and high PIIINP may be a less reliable marker of liver fibrosis in psoriatic arthritis because elevated levels may be related to active joint disease.[109, 110] The combination of the serological tests γGT, bilirubin, haptoglobin, apolipoprotein A-1 level and alpha2 macroglobulin corrected for age and gender, has limitations with false negatives in acute inflammation and false positives in haemolysis and Gilbert's syndrome.[111, 112] The results of transient elastography (TE), FibroTest® and serial PIIINP do not correlate with each other[113] but abnormal results in 2 of 3 tests (PIIINP, TE and Fibrotest®) were shown to reduce the need for a liver biopsy in determining degree of fibrosis in patients with psoriasis on MTX. A recent meta-analysis has shown transient elastography has a sensitivity of 87% and specificity of 91 % for the diagnosis fibrosis;[114] MRI might be better in determining fibrosis grade[115] although it is more expensive.

Changes of methotrexate induced fibrosis vary throughout the liver leading to significant sampling variability. Consideration of liver biopsy has been suggested by the 2009 American Academy of Dermatology guidelines[116] in patients with low risk and persistent abnormal liver biochemistry during treatment or after a total cumulative MTX dose of 3.5 to 4.0 g.

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Recommendation: In long term therapy with methotrexate, non-invasive markers of hepatic fibrosis should be used for surveillance for development of significant fibrosis although the reliability and accuracy of these approaches has not been documented prospectively and liver biopsy may be useful in selected cases (moderate strength, low evidence).

1.13 Abnormal liver biochemistry or cirrhosis of unknown cause and rare liver diseases

Liver biopsy may be useful in the investigation of otherwise unexplained abnormal liver biochemistry or cirrhosis. Histology in those with persistently abnormal liver biochemistry and without diagnostic imaging or serology may identify a cause in about 14 % - 18 % and indicate a need for specific treatment.[117, 118] In one study of patients with an isolated rise in the γGT, 11% had evidence of hepatic fibrosis.[117] Other conditions potentially diagnosed on liver biopsy include IgG4 related liver disease,[119] lymphoproliferative disorders and other haematologic malignancies.[120] Lymphoma can be characterised by hepatosplenomegaly but with no other signs nor other accessible tissue a liver biopsy is an important diagnostic approach.[121, 122] Of note, in a series of patients with abnormal liver biochemistry but (almost) normal liver histology, a significant number developed overt liver disease after > 4 years follow up.[123, 124, 125] Occasionally, histological examination can help in the diagnosis of infections such as tuberculosis or other rare causes of pyrexia especially in certain clinical conditions such as HIV infection[126] or in graft versus host disease.[127]

In the investigation and diagnosis of rare liver diseases, liver biopsy may have a role in making a diagnosis, which had not been suspected previously. Examples include diseases such as hereditary haemorrhagic telangiectasia, amyloidosis, glycogen storage disorders, tyrosinaemia and Niemann-Pick disease.

Recommendation: Liver biopsy may be indicated in the investigations of unexplained abnormal liver tests or for investigation of liver disease from rare causes (high strength, medium evidence)

2 Acute hepatitis

In an acute presentation of hepatitis, it is important to diagnose treatable causes of liver disease such as viral hepatitis or autoimmune hepatitis but also to prognosticate the chances of liver recovery (spontaneous or with treatment) or death to make decisions for listing for transplantation. Most causes of viral hepatitis can be diagnosed with serological markers at presentation, using nucleic acid amplification testing if necessary, before relevant antibodies become detectable. Autoimmune hepatitis may be suspected on the basis of autoantibodies and raised serum immunoglobulins and other sero-markers. However, in the acute setting, serological markers of AIH are often absent. In cases with a fulminant presentation of acute hepatitis the cause is frequently not clear and many of these cases are labelled as “seronegative hepatitis”. Progressive liver failure (jaundice, decreased synthetic liver function and hepatic encephalopathy) sometimes requires urgent liver transplantation before a diagnosis is established. Similar difficulties occur in acute on chronic liver failure where an acute injury affects a chronically damaged liver.[128] Some studies suggest that in this situation a mini-laparoscopy guided liver biopsy can be helpful.[129, 130] Although not standard in progressive liver failure, liver biopsy in this situation may help clinical decisions.[129]

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In acute and in fulminant acute liver failure, a transjugular approach is usually the method of choice in view of coagulopathy. Several cores should be obtained in order to obtain adequate material for diagnosis.

Liver biopsy has three main roles in the assessment of patients with a suspected acute hepatitis. The first is confirm that the damage present is acute and to exclude the presence of any underlying chronic liver disease. The second is to help determine disease severity, mainly based on the extent of liver cell necrosis, which has implications for prognosis and treatment. However, heterogeneous distribution of severe liver necrosis may give rise to problems with sampling variability. Thirdly, liver histology may help to determine the cause of acute liver injury, including cases that are not due to acute hepatitis. Examples of the latter include acute alcoholic hepatitis, toxic liver injury (e.g. paracetamol toxicity), ischaemic liver injury, acute presentation of Wilson's disease and diffuse hepatic infiltration by malignancy. In cases with a fulminant presentation, liver biopsy often shows extensive acute cell death without other identifying features, so the usefulness of liver histology in identifying the cause of acute liver failure may therefore be limited.

Recommendation: In acute hepatitis liver biopsy can occasionally be helpful in selected cases where alcohol and viral causes of acute liver injury have been excluded and may provide additional diagnostic and prognostic information (moderate strength, medium evidence).

2.1 Acute viral hepatitis

Acute viral hepatitis with the hepatitis viruses A-E rarely poses a diagnostic challenge since even in the absence of viral antibodies, viral RNA or DNA can be detected. However, in some cases of viral hepatitis, such as Herpes virus infection, liver histology can be useful in making the diagnosis.

Recommendation: In acute viral hepatitis a liver biopsy is usually not necessary to make the diagnosis nor for clinical management (high strength, high evidence).

2.2 Acute alcohol-related hepatitis

Acute alcohol-related hepatitis is a severe form of acute liver inflammation characterised histologically by severe steatohepatitis (lobular inflammation steatosis and hepatocyte ballooning degeneration) has a high mortality when associated with prominent inflammatory activity.[131, 132] There may be significant diagnostic and prognostic uncertainty in individual patients, in particular with regards to the presence of underlying cirrhosis and when corticosteroids may be of benefit. In one study in patients with clinically diagnosed alcoholic hepatitis, a diagnosis of cirrhosis was made in about one third of patients and had significant implications for management and prognosis.[133] A histological activity score may predict response to corticosteroids in alcoholic hepatitis.[134] Also, clinical information (e.g. age) and serological tests (e.g. bilirubin, prothrombin time) and scores (Glasgow alcoholic hepatitis score, AshTest®) correlate with outcome in severe alcoholic hepatitis[135, 136] which will be useful for treatment decisions. Some advocate liver biopsy to confirm the diagnosis since the clinical diagnosis can be incorrect.[131] Liver histology will also detect underlying cirrhosis and may guide treatment. However, in clinical practice a liver biopsy may require transfer of the patient to a central hospital which would potentially delay treatment. Since immunosuppression is the mainstay of treatment in alcoholic hepatitis, this delay might come too late to change the disease process and could increase the already high risk of infection. Thus, the need for histology before instigation of corticosteroid treatment remains uncertain.[132]

Recommendation: In alcohol related hepatitis with or without underlying cirrhosis a liver biopsy may be useful in excluding other diseases and for confirming the diagnosis prior to initiation of immunosuppressant drugs (high strength, high evidence).

2.3 Acute and Fulminant Autoimmune hepatitis

Autoimmune hepatitis (AIH) may have an acute presentation in up to 30-40% of cases and in a small proportion may present as fulminant hepatic failure.[137] AIH may present as acute exacerbation of underlying chronic liver disease with evidence of pre-existing fibrosis or cirrhosis or alternatively as "true" acute hepatitis with histologically no evidence of any underlying chronic liver disease. The clinical diagnosis may be unclear, as in some cases of acute or subacute liver failure caused by conditions other than AIH, autoantibodies are present and, conversely, autoantibodies and hypergammaglobulinaemia may not be present in cases of AIH with an acute presentation.[72, 138] If autoimmune hepatitis is suspected, liver biopsy should ideally be done before initiation of corticosteroids[72] and prednisolone can rapidly improve the liver disease and prevent need for transplantation.

Histological features of acute autoimmune hepatitis include a plasma cell rich inflammatory infiltrate (portal and lobular), perivenulitis, lymphoid aggregates and interface hepatitis. However, none of these changes are specific for AIH and other causes of acute hepatitis (viral and drug induced) need to be excluded. The assessment of other histological features such as the extent of necrosis and the presence/severity of fibrosis[139] may be useful in informing decisions about the need for transplantation and subsequent clinical management. Biopsy should be obtained early, before treatment if possible, since the histological characteristics may resolve with immunosuppression.

Recommendation: In acute hepatitis, where autoimmune hepatitis is considered a possible cause, liver histology may aid the diagnosis; the biopsy ideally should be done prior to treatment initiation (high strength, medium evidence).

2.4. Seronegative acute hepatitis

Patients presenting with acute hepatitis may lack serological features of autoimmune hepatitis, viral hepatitis, and have no history of exposure to hepatotoxic drugs or toxins.[140, 141] The histology in such cases usually shows non-specific features of lobular necroinflammatory activity with varying degrees of confluent necrosis, indicating the pattern but not aetiology of the liver injury. This terminology is generally applied to patients with severe hepatitis leading to acute or fulminant hepatic failure; the role of the biopsy (see 2 above) is as for other acute hepatitides.

2.15 Acute drug induced liver injury

Acute drug induced liver injury (DILI) may present in many ways.[142] The diagnosis of DILI is primarily one of exclusion, assessing the temporal relationship between taking the drug and onset of liver disease, recognising known patterns and risk factors for drug toxicity and the effect of drug discontinuation. In many cases of suspected DILI, a liver biopsy is not necessary for clinical management.

In some situations, liver histology can be helpful in diagnosis. In the context of acute hepatitis, certain histological features, while not specific, would favour a drug induced aetiology and prompt

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more detailed clinical enquiry. These include the following: predominantly zone 3 (centrilobular) inflammation; disproportionately severe/well circumscribed necrosis with relatively little inflammation, unusually prominent cholestasis; eosinophils, granulomas; unusual patterns of necrosis e.g. zone 1 (periportal) necrosis. DILI with autoimmune features cannot be distinguished histologically from autoimmune hepatitis not related to drugs, and diagnosis depends on the drug history.[143]

In addition, the biopsy can contribute by demonstrating or excluding other causes of liver disease. For example, in bone marrow transplant patients where the differential diagnosis of liver injury includes graft versus host disease or drug induced liver injury. There are many patterns of DILI in addition to acute hepatitis, and histological patterns of idiosyncratic liver injury are very variable. Signature patterns of serology and histological changes may not be established for uncommon or newer drugs, and histology does not always show the type of damage expected (hepatocellular, cholestatic or mixed) from serological predictors.[144] Online resources such as the LiverTox website[145] provide comprehensive information about DILI including recognised histological patterns of liver injury. Later on, liver histology may be helpful if presumed DILI fails to resolve or even progresses on drug withdrawal.[146]

Recommendation: In presumed acute drug induced liver disease liver biopsy is indicated if there is doubt of the diagnosis especially with autoimmune features or when the liver tests do not improve with stopping the medication (high strength, high evidence).

3 Transplant related liver biopsies

3.1 Liver biopsy in Liver Transplantation

3.1.1 Donor liver biopsy:

3.1.1.1 Deceased liver donor: liver biopsy may be done to determine the suitability of livers for transplantation. Extended criteria liver donors including livers from DCD or obese donors have a significant risk of inferior clinical outcomes; these are associated with high discard rates and liver histology may help in selecting whether it is appropriate to retrieve / implant the graft.[147] The rapid assessment of the suitability of potential deceased donor livers requires the use of frozen sections, which have problems with logistics and histological interpretation More detailed rapid paraffin assessment may be possible with the use of normothermic perfusion techniques.

Liver histology may be assessed after completion of the transplant to assess any pre-existing abnormalities and changes of reperfusion injury and may help future clinical management. Pre-recovery (pre-retrieval) liver biopsy has been advocated by some to reduce the rate of recovery of unsuitable organs (futile recovery).[148, 149, 150, 151, 152, 153]

Recommendation: Donor liver biopsy may be done before retrieval to help determine the suitability of the liver for retrieval or implantation or to help manage the recipient (high strength, high evidence). Post-perfusion biopsies may be done to identify any pre-existing changes and severity of re-perfusion injury (high strength, high evidence).

3.1.1.2 Healthy Living Donor: The role of liver biopsy in the evaluation of living liver donor candidates is not clear, with many units selecting which candidate to biopsy rather having a protocol to biopsy every potential living liver donor.[154, 155, 156, 157, 158] Studies find abnormalities (steatosis, inflammation or other conditions precluding donation) in 21 to 32 % of (pre-screened) healthy

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donors.[157, 158, 159] For example, magnetic resonance imaging, used to assess substantial steatosis and fibrosis, may decrease the need for biopsy in this indication.[160, 161, 162, 163]

Recommendation: Liver biopsy is currently not routinely recommended for all potential live liver donors but is of value in selected donors (moderate strength, low evidence).

3.1.2 Following liver transplantation

Biopsy of the grafted liver plays an important role in the diagnosis of liver allograft dysfunction and as an aid to improve management of immunosuppression. Interpretation of liver histology is often challenging and there are frequently multiple factors at play. Interpretation of histological findings therefore requires close collaboration between histopathologists and clinicians. Biopsies may be done routinely per protocol but are more often triggered by clinical or biochemical abnormalities. Policies on histological monitoring vary between liver transplant units.[164]

Liver histology is often necessary to determine the cause of liver test abnormalities following liver transplantation since it is not possible to differentiate on the basis of liver tests rejection, preservation-reperfusion injury, viral infection, drug toxicity, recurrent disease and other causes of graft damage[130] and multiple factors may be present. Liver histology is required to diagnose acute cellular rejection (T cell mediated rejection), chronic rejection and antibody mediated rejection.[130, 165]

Planned withdrawal of immunosuppression is standard of practice in some centres for highly selected patients: in addition to normal liver biochemistry, the absence of histological features of rejection is a pre-requisite for immunosuppression withdrawal.[166]

Histology from protocol biopsies may reveal unexpected abnormalities requiring intervention, even in the presence of normal liver tests.[167, 168, 169] This particularly applies to paediatric liver allograft recipients, many of whom develop subclinical graft injury associated with inflammation and progressive fibrosis.[170]

Recommendation: Liver allograft biopsy is often needed to identify the cause(s) of liver test abnormalities and when considering withdrawal of immunosuppression (high strength, high evidence). Allograft biopsy may be done per protocol in patients without abnormalities of liver tests (especially in paediatric patients) as it may detect abnormalities in the graft requiring intervention (medium strength, low evidence).

3.2 Liver biopsy in haematopoietic stem cell transplantation

In haematopoietic stem cell transplantation, there are many reasons for abnormal liver tests, for which the cause can be readily identified but liver histology may be helpful. The diagnosis of hepatic graft versus host disease (GVHD) can be challenging. The risks of liver biopsy need to be considered since in bone marrow transplant patients undergoing a transjugular liver biopsy the risk of bleeding is 2.9 % compared to 0.6 % in other indications (odds ratio 4.9).[171]

Histologically GVHD can be difficult to distinguish from other liver disorders such as infection and drug induced liver injury (DILI). Pre-transplant chemotherapy, immunotherapy and GVHD prophylaxis can be confounding. In one study, over two thirds of patients with possible GVHD had a concurrent disease process, in particular DILI or sinusoidal obstruction syndrome, and bile duct

injury and intraepithelial lymphocytes were helpful diagnostic findings confirming the diagnosis of GVHD.[172]

Recommendation: In haematopoietic cell transplantation, the importance of obtaining a diagnosis needs to be balanced against the higher risk of complications so the decision to biopsy should be limited to specialist teams of haematologists and hepatologists (moderate strength, medium evidence).

4 Liver biopsy in research

Using liver biopsy in the context of research has given invaluable information and advanced understanding of normal and abnormal physiology and pathology and enabled improvements in medical care. A portion of a liver biopsy taken for diagnostic or therapeutic purposes may also be used for research purposes. In both cases, the procedure will need specific approval from the appropriate Research Ethics Committee (or equivalent) as well as fully informed patient consent.

Recommendation: In a research context ethical approval and extensive patient information prior to consent are necessary (high strength, low evidence).

5 Targeted biopsy of focal liver lesions

The role of percutaneous liver biopsy in the diagnosis of focal liver lesions depends largely upon the clinical context including presence or absence of underlying liver disease. The small risk of tumour dissemination which may preclude curative treatment and the risk of bleeding following biopsy which is higher than in diffuse liver disease need to be balanced against the benefit of a tissue diagnosis.

Focal imaging abnormalities in the liver may be detected incidentally, during staging investigations for patients with known malignancy, or as a result of HCC surveillance in patients with advanced chronic liver disease. Biopsy is indicated when the nature of the lesion cannot be determined with reasonable certainty from its imaging characteristics, and when a tissue diagnosis is necessary to inform treatment decisions. The type of biopsy (lesional or background liver) must be clearly indicated on the request form, since these samples are handled differently in the laboratory.

5.1 Metastatic malignancy.

For patients with disseminated malignancy of unknown origin, liver biopsy is often the most accessible means to obtain tumour tissue to guide treatment, including immunohistochemical and molecular diagnosis (ref – RCPath Dataset Malignancy of unknown Origin (MUO)). Targeted liver biopsy is associated with an increased risk of bleeding compared with non-targeted medical biopsy [PMC6339629]; this risk must be balanced against the benefits of establishing a tissue diagnosis of malignancy including prognostic and predictive factors, on which to base treatment.

In malignant disease, liver biopsy of a targeted lesion also carries the risk of needle track seeding.[173, 174, 175, 176, 177, 178, 179] For patients where surgical resection is a potentially curative option (most often in the context of metastatic colorectal carcinoma) diagnosis is based on clinical history and radiology, and biopsy should be avoided because of the risk of chest wall recurrence.[180]

5.2 Primary liver malignancy.

Most cases of HCC develop in the context of advanced chronic liver disease/cirrhosis and 6 monthly ultrasound surveillance aims to enable these to be detected and diagnosed at an early curable stage. For patients with early surveillance detected liver lesions, previous concern that biopsy may promote dissemination and lead to post-transplant recurrence of HCC[181] is now considered exaggerated.[182] The reader should refer to the latest current guidelines[183] because as treatments improve, international societies refresh the indications and contra-indications for use of liver biopsy in patients with HCC.[184, 185]

Usually the combination of two modalities of liver imaging (ultrasound scanning, triple phase CT or MRI of the liver) and the measurement of serum α-fetoprotein will allow a confident diagnosis to be made.[186] There is now agreement among international guidelines that biopsy is recommended or considered for suspicious lesions ≥1cm in diameter that cannot be confidently diagnosed as HCC after bimodality imaging.[185] Also in this context, radiologically malignant lesions that lack characteristics of HCC should be biopsied for diagnosis, in particular for their distinction from intrahepatic cholangiocarcinoma.[187] In future, stratified treatments in HCC requiring molecular subtyping of tumours is likely to increase the requirement for tissue diagnosis in HCC.[188]

In suspected hepatocellular carcinoma, clinical workup will depend on the underlying liver disease. Biopsy of non-lesional liver tissue is often valuable in determining the presence/stage of any background liver disease, which can affect both diagnosis and management. Sampling of non-lesional hepatic tissue can be done using the same, smaller sized needle (18G) to determine whether there is underlying cirrhosis, but parenchymal tissue should be taken at a distance from the lesion to avoid over-interpretation of fibrosis/inflammatory changes in peri-lesional tissue. Use of a large gauge needle, however, does allow for a fuller assessment of fibrosis and liver architecture, The operator should state if the biopsy has had to be taken near the lesion.

Large focal lesions with features suggestive of HCC detected incidentally in non-cirrhotic liver are generally resected without biopsy, since most neoplastic lesions with these features require surgical management, thus avoiding biopsy–associated risks of rupture, haemorrhage and dissemination.

Recommendation: Histology may be needed to characterise focal lesions which cannot be characterised by other means, or to obtain tissue for molecular diagnosis in patients with a known primary malignancy (high strength, high evidence). A smaller needle size than for diffuse liver disease (18 French) should be used and biopsy of non-lesional liver needs to be considered (high strength, high evidence).

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Table A: Table of chronic liver conditions indicating when a liver biopsy is considered. (Lay version)

Type of liver disease	**Useful tests without doing a liver biopsy**	**Examples of when a liver biopsy should be considered**
Hepatitis B virus (HBV) infection	The diagnosis is made with viral blood tests in all cases. Blood tests (including calculated scores), sometimes in combination with a scan measuring liver stiffness[1] can often predict severity of disease and need for treatment and need for cancer screening.	Usually can be managed without a liver biopsy. If additional causes are suspected or if Hepatitis D is present a liver biopsy is useful.
Hepatitis C (HCV) infection	The diagnosis is made with viral blood tests in all cases. Blood tests (including calculated scores), sometimes in combination with a scan measuring liver stiffness[1] is helpful in determining amount of scarring in the liver, urgency to treat and need for cancer screening.	Is managed without a liver biopsy in most cases. If additional causes are suspected a liver biopsy is useful.
Non-alcoholic fatty liver disease (NAFLD)	Blood tests (including calculated scores) and scans measuring liver stiffness[1] are good at estimating the amount of scarring in the liver. Special liver scans (CAP[2]) can also estimate the amount of fat.	Is managed in many cases without a liver biopsy. Only a liver biopsy can determine the amount of inflammation with is a risk factor for future disease progression. A biopsy is needed where other tests are unable to confirm or refute a diagnosis and where additional liver diseases might cause liver damage.
Alcohol-related liver disease (ARLD)	Blood tests (including calculated scores) and scans measuring liver stiffness[1] are good at estimating the amount of scarring in the liver.	Is managed without a liver biopsy in most cases. If a patient denies alcohol excess or additional causes are suspected a liver biopsy is useful.
Autoimmune Hepatitis (AIH)	The diagnosis is suspected from blood tests in many cases with AIH. Blood tests (including calculated scores) and scans measuring liver stiffness[1] are good at estimating the amount of scarring in the liver (although inflammation and other factors may affect readings).	A biopsy is necessary in the diagnosis of patients with AIH in most cases. This can detect overlap with other autoimmune liver diseases and / or where additional liver diseases might cause liver damage. A liver biopsy is also recommended prior to ending (and sometimes

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		reducing) immunosuppressive treatment because of the high risk of relapse.
Genetic Haemochromatosis and other iron overload	The diagnosis is made using blood tests in most cases with iron overload. An MRI scan is good at estimating total liver iron but needs special calculations (freely available over the internet). Blood tests (including calculated scores) and scans measuring liver stiffness[1] are good at estimating the amount of scarring in the liver.	A liver biopsy is not routinely indicated in most cases of genetic haemochromatosis. However, histology can determine the degree of scarring in the liver and can help when gene mutation studies and blood results are not typical and if an additional cause of liver damage is suspected.
Primary Biliary Cholangitis (PBC)	The diagnosis is made using only blood tests in most cases. Blood tests (including calculated scores) and scans measuring liver stiffness[1] are good at estimating the amount of scarring in the liver.	A biopsy should only be done if there is uncertainty about the diagnosis or where there is a suspected overlap with other autoimmune diseases.
Primary Sclerosing Cholangitis (PSC)	Diagnosis is made using imaging, typically magnetic resonance cholangiogram (MRCP) but sometimes an endoscopic retrograde cholangio-pancreatogram (ERCP).	A liver biopsy should be done if there is doubt about the diagnosis, such as overlap syndrome, or when the disease is suspected but large bile ducts look normal on scans.
Wilson's disease (copper overload)	Diagnosis is made using special blood tests (serum caeruloplasmin) and copper in a urine sample.	A liver biopsy is necessary in many patients especially if the diagnosis is not clear and has the advantage that copper weight can be measured in the sample.
Portal hypertension (high pressure in the vein feeding the liver).	Pressure in the vein feeding the liver can be measured through a long cannula usually through a neck vein and in this case often a liver biopsy is done at the same time.	A biopsy is sometimes helpful to identify a cause for portal hypertension, which is often but not always severe scarring (cirrhosis).
Congestive Hepatopathy (liver damage due to the heart failing)	Evidence for a struggling heart can be seen on special heart scans.	Sometimes estimating severity of liver damage for example before having a heart transplant is difficult without a biopsy and liver and heart specialists need to discuss what is best for the patient.
Methotrexate (MTX) induced Fibrosis	In patients who have taken large amounts of the drug over time, blood tests (including special blood tests and calculated scores) and scans measuring liver stiffness[1] can be used to estimate how much liver damage there is from the drug. It is not clear	A biopsy is sometimes useful in making decision on treatment with MTX especially if other factors causing liver damage need to be excluded.

	which test is best, but these test(s) should be used to monitor the patient for the development of scarring and help the decide whether the medicine can still be given safely.	
Abnormal liver tests of unknown causes and rare liver diseases	In all these cases the diagnosis is not clear despite doing many tests to try to find out what the cause of the liver problem might be.	A biopsy is sometimes used in patients with unexplained abnormal liver tests or with liver disease from rare causes. In patients with rare diseases, a liver often helps find out how severe the disease is.

1) Fibroscan®, ARFI®, MRI methods,
2) Controlled Attenuation Parameter of the FibroScan® machine

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Table B: Table of acute liver conditions indicating when a liver biopsy is considered. (Lay version)

Type of liver disease	**Useful tests without doing a liver biopsy**	**Examples of when a liver biopsy should be considered**
Acute liver failure and hepatitis	Viruses, alcohol and drug overdoses can be ruled out as a cause of acute liver disease.	Where the diagnosis is not clear, a biopsy may be useful to find the cause and estimate how likely the liver is to recover.
Acute Viral Hepatitis	The diagnosis can be made using blood tests for the viruses.	A biopsy is very rarely necessary for making the diagnosis or for managing the patient.
Acute and Fulminant Autoimmune hepatitis (AIH)	The diagnosis can often be suspected using blood tests.	Treatment without confirming AIH is rarely done and a biopsy is ideally done before starting treatment.
Pyrexia of unknown origin (PUO) and Infections	It is rare that blood and other tests and scans do not identify the cause of a raised temperature or what infection causes the problem.	A liver biopsy will be helpful when none of these tests show a cause of the liver problem.
Drug induced liver injury (DILI)	Clinicians should suspect drugs causing liver disease in all patients with acute liver problems. Because DILI is rare, doctors compare the signature patterns of drugs listed in a database (LiverTox) with the type of damage seen in the patient.	A biopsy is usually done if there is doubt of the diagnosis, if there are autoimmune features, or the patient does not improve with stopping the medication.

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Table C: Table of transplant related conditions indicating when a liver biopsy is considered (Lay version).

Type of liver disease	**Useful tests without doing a liver biopsy**	**Examples of when a liver biopsy should be considered**
Biopsy of donor livers from deceased donors	How suitable a donated liver is can be difficult to estimate in many cases.	Donor liver biopsy is sometimes done in deceased donors. In most centres a sample is taken during transplantation and can show unexpected findings which need a change in management
Biopsy in health living donors	Sometimes it is not clear whether the liver of a living donor is healthy enough.	A biopsy is currently not routinely done in living donors but is done in some special cases.
Post transplant biopsy from liver recipients .	All transplant patients are monitored with blood tests, at a protocol frequency which diminishes with time post-transplant, or if there is any clinical concern. In addition, imaging tests of the bile ducts or blood vessels may be indicated	A liver biopsy is frequently required to make the diagnosis when the blood tests are abnormal, since there are many potential causes of liver disorder after a transplant. Sometimes the biopsy will suggest the need for an imaging investigation.
Biopsy in haematopoietic cell transplantation	Patients with bone marrow transplants can have many causes for liver disease and can be very unwell with this.	These patients have a higher risk of complications, but it is often very important to understand what the cause of the problem is. Therefore, specialist teams with haematologists and hepatologists need to carefully weigh up the risks and benefits of a liver biopsy.

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Table D: Table of other conditions indicating when a liver biopsy is considered (lay version).

Type of liver disease	**Useful tests without doing a liver biopsy**	**Examples of when a liver biopsy should be considered**
Biopsy of a localised change in a liver.	Sometimes a localised change can be characterised using scans or blood tests. However, sometimes cancer is suspected and it is difficult to find out for sure and in cancer it is important what type of cancer is present to best treat the patient.	In many cases a liver biopsy is key to characterise localised changes when other means can not clarify whether a change is cancer or what type it is.
Routine biopsy in bariatric surgery	Patients undergoing surgery for being morbidly obese often have fatty liver, sometimes complicated by advanced disease. Sometimes the liver can be seen during surgery which can give useful information (nodules and scarring can be seen from the outside of the liver).	A biopsy is not standard practice and should not be done in a liver which looks normal with the naked eye.
Liver biopsy in research	In research many but not all questions can be answered with questionnaires, blood and other tests including scans.	Some difficult questions can only or much easier be answered using liver biopsy samples and sometimes very special tests. This can only be done when a Research Ethics Committee has approved this and the patient has been counselled on this and given consent that the biopsy can be done for research.

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