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Provincial Clinical Guideline

Clinical Guideline Title - Management of Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD) (formerly Non-Alcoholic Fatty Liver Disease, NAFLD)	
Service Area: Primay Care and Medicine (Hepatology)	**Guideline Number:** XX-XXX-XXX V#
Approved By: Provincial Clinical Leadership Team	**Approval Date:** May 28, 2024

1.0 CLINICAL GUIDELINE STATEMENT

1.1 This clinical guideline is intended to serve as a brief resource on metabolic dysfunction-associated steatotic liver disease, MASLD (formerly called non-alcoholic fatty liver disease, NAFLD) and its management.

Its goal is to provide evidence-based support to primary care physicians and their teams who care for patients with MASLD, allow them to adequately manage the majority of these patients in their practice, and improve appropriate access to specialist care, for the subset of MASLD patients who need it.

2.0 GUIDELINE:

2.1 MASLD Essentials

Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common liver disease in Canada, affecting approximately 25% of the general population, and is often associated with obesity, diabetes, dyslipidemia (high triglycerides/low HDL), and/or hypertension.

MASLD results from liver damage due to the accumulation of fat (triglycerides) within liver cells.

The term MASLD refers to a spectrum of liver conditions, ranging from bland liver statosis, to metabolic dysfunction-associated steatohepatitis (MASH, i.e. steatosis with liver cell damage and inflammation), to MASH-related liver fibrosis and cirrhosis.

Bland liver steatosis is generally considered to be benign. However, 2-3% of affected people may progress to MASH and develop advanced fibrosis/cirrhosis within 1-2 decades (even when ALT levels are persistently normal).

In contrast, MASH is considered a potentially progressive disease in which ongoing liver cell injury leads to chronic inflammation and fibrosis, ultimately resulting in cirrhosis in up to 20% of individuals within 20 years. The gold standard for the diagnosis of MASH is a

liver biopsy, but this is rarely necessary and not standard of care in clinical practice.

Increasing liver fibrosis in individuals with MASLD is associated with an exponential increase in risk of liver-related mortality, which appears to be most pronounced in people with MASLD who have developed advanced liver fibrosis or cirrhosis.

MASLD that has progressed to cirrhosis is an increasingly common indication for liver transplantation and liver cancer in North America. Therefore, it is critical to identify people with MASLD who have developed significant liver fibrosis in order to reduce the risk of progression to cirrhosis and its complications by appropriate lifestyle interventions and medical management.

Given the high prevalence of MASLD, specialist consultation for all patients with MASLD is not feasible nor is it necessary. Specialist consultation usually does not add value to the clinical management, particularly in the absence of evidence of advanced fibrosis.

This clinical guideline is, therefore, intended to help **identify individuals with MASLD who are more likely to have advanced liver fibrosis**, and, therefore, may benefit from specialist consultation.

In order to achieve this, simple blood tests are utilized to screen individuals with MASLD for their risk of having relevant liver fibrosis. This screening is based on calculating their Fibrosis-4 score (FIB-4) using the following formula:

FIB-4 score = Age in Years x AST level (U/L) / Platelet Count (10^9/L) x √ALT level (U/L)

Free FIB-4 calculator

A FIB-4 score of <1.30 essentially rules out significant liver fibrosis. A FIB-4 score ≥1.30 may indicate a relevant risk of liver fibrosis and, therefore, warrants further evaluation.

2.2 Stepwise Process for MASLD Diagnosis and Management (see also "Quick Decision Tree")

2.2.1 *Suspicion of MASLD*

MASLD should be considered in patients with one or more of the following:

- Elevated liver enzymes in a hepatocellular or mixed pattern (persistent elevation of serum alanine aminotransferase (ALT) for ≥6 months). In MASLD patients, ALT is usually <200 IU/L).
  - **Note:** Patients with MASLD may have normal liver enzymes.
- Imaging finding of fatty liver (current or past, provided risk factors such as obesity have not changed significantly).

- **Note:** Not all patients with MASLD will have fatty liver documented on an imaging report, as the fatty infiltration may not be extensive enough to reach the detection limit (note that ultrasound is more sensitive for fatty infiltration than conventional MRI and CT). It may also not have been reported on if not specifically asked for.

- **Note:** MASLD typically does not cause symptoms other than occasional right upper quadrant discomfort.

2.2.2a ***History/Review***

- Review presence of **risk factors for MASLD**: overweight/obesity, type 2 diabetes, dyslipidemia, and hypertension, i.e. the metabolic syndrome.
  - **Note:** Not all of these metabolic risk factors are present in all patients with MASLD and normal weight individuals can develop MASLD. In addition to the metabolic risk factors**,** ill-defined and not routinely measurable genetic factors predispose to MASLD. Thus, around 10-20% of MASLD patients may not have any of the above metabolic risk factors at time of diagnosis.
- Review and address **alcohol consumption**: Counsel patients to follow Canada's Guidance on Alcohol and Health (low risk drinking: <3 drinks/week) or to stop alcohol use entirely for 6-8 weeks. Then retest ALT. If it remains abnormal, elevated ALT is unlikely to be the result of alcohol consumption.
- Review **medications**: when assessing whether/how medications or other products may be contributing to abnormal liver tests, consider both the relationship between initiation of the medication and the time of onset of the liver problem (if known), and any improvement in liver function tests after the medication is discontinued.

  Any new or recently prescribed medication, over the counter, or herbal/natural product may be implicated. Some medications and other products may also cause liver damage over a longer term of use.

  Potential medications potentially causing elevated liver enzymes and/or liver steatosis include e.g. amiodarone, methotrexate, tamoxifen, corticosteroids, isotretinoin, some antibiotics, antifungals, anticonvulsants, herbal products, health supplements (e.g. green tea extract), and illicit substances (e.g. cocaine).

  If uncertain, you may consider visiting LiverTox (https://www.ncbi.nlm.nih.gov/books/)

  Discontinue or change medication, reduce dosage, or consider dose frequency modifications. Always weigh risks and benefits of therapy changes. If changes are made, repeat liver tests after 1-3 months. If liver enzymes are very high and/or liver function is impaired (especially elevated bilirubin), contact a liver disease specialist.

2.2.2b ***Baseline Investigations***

- **Liver enzymes**: ALT and AST (to assess for liver cell death or damage), ALP and GGT (to assess for biliary tree injury and/or impairment of bile flow).
- **Liver function**: serum albumin, INR, total serum bilirubin
- **CBC with platelets** (to enable FIB-4 score calculation)
  - **Note:** Platelets are included in the FIB-4 calculation as thrombocytopenia can be an initial sign of cirrhosis/portal hypertension (through splenomegaly and hypersplenism).
- **Ultrasound abdomen** (if not already done within one year to corroborate fatty liver and rule out biliary causes of elevated liver enzymes, especially if the patient complains about right upper quadrant pain suspicious of biliary colic).
- **HbA1C and fasting lipid profile** (to assess for common comorbidities).

2.2.3 ***Rule out Concomitant Liver Disease***

If liver enzymes are elevated for ≥6 months, rule out concomitant causes of chronic liver diseases (other than MASLD) through the following additional testing for:

- ***Autoimmune liver diseases***:
  Anti-nuclear antibodies (ANA), anti-mitochondrial antibodies (AMA), anti-smooth muscle antibodies, and immunoglobulins (IgG) to evaluate for possible autoimmune cause of liverinjury.
  - Autoimmune hepatitis (AIH): ANA (>1:160 titer) and/or anti-smooth muscle antibody (> 1:80 titer) and markedly elevated serum IgG levels may suggest AIH and warrant a referral to hepatology.
  - Primary biliary cholangitis (PBC): AMA (>1:40) and a predominantly cholestatic enzyme picture (without evidence of biliary obstruction on U/S) may suggest PBC and warrant a referral to hepatology.
- ***Hereditary liver diseases***:
  - **Ferritin, iron and transferrin** or total iron binding capacity (to calculate transferrin saturation) (fasting blood sample!) to assess for hemochromatosis
    - **Note:** ferritin is often significantly elevated in MASLD (as an acute phase reactant related to liver inflammation), but transferrin saturation is typically < 50%, i.e. within normal limits. These patients do NOT have iron overload (genetic hemochromatosis) and the respective molecular genetic testing is NOT indicated.

  If fasting ferritin elevated **and** transferrin saturation is >50% in females or >60% in males, consider molecular genetic testing for genetic hemochromatosis. If genetic testing is negative, the patient does not have HFE gene related hereditary hemochromatosis. If genetic testing suggests increased risk for HFE related hemochromatosis, consider referral to Hepatology for assessment of liver fibrosis (patients with hemochromatosis and advanced liver fibrosis are at high risk of liver cancer). Also, HFE related

genetic hemochromatosis is a Celtic disease and does not occur in non-caucasian populations. Non-HFE gene related hereditary iron overload disorders have been described, but are extremely rare.

- **Serum ceruloplasmin** for Wilson's disease
  if low (especially if patient's age <40 years), consider referral to Hepatology.
- **Alpha-1-antitrypsin** for alpha-1-antitrypsin deficiency
  If low (≤50% of lower limit of normal) consider referral to Hepatology.
- **Celiac antibody screen** for Celiac Disease
  If positive, consider referral to GI for gastroscopy to confirm diagnosis. If a diagnosis of Celiac disease is established, initiate/re-instate dietary measures for 6 months, and repeat liver enzymes.

Importantly, in the evaluation of abnormal liver enzymes, abdominal MRI and/or CT are unlikely to add value over and above an ultrasound and should not be routinely ordered.

If workup suggests a non-MASLD diagnosis, treat or consider appropriate referral to specialist (if uncertain, consider eConsult route).

If workup is negative, MASLD diagnosis is strongly suspected (risk factors, elevated liver enzymes, and/or ultrasound findings).

2.2.4 *Assess Risk of Liver Fibrosis using FIB-4 score*

The Fibrosis-4 (FIB-4) score is a non-invasive scoring system based on several laboratory tests that help to estimate the amount of fibrosis (scarring) in the liver. (Free FIB-4 calculator). Further follow-up is dependent on the risk stratification by the FIB-4 score.

- **Note:** the FIB-4 score is best validated in patients aged 35-65 years. In very young patients it may underestimated, in very old patients overestimate the likelihood of relevant fibrosis.

2.2.4.1 *Low risk (FIB-4 < 1.30): Care within the Patient's Primary Care Setting*

Lifestyle modifications are the cornerstone of MASLD management	
Goal	• For overweight and obese MASLD patients: gradual weight loss of 7-10% of baseline body weight through lifestyle measures (physical activity and dietary modifications) over 6 months or more. ○ Of Note: Weight loss of 3%–5% improves steatosis, but greater weight loss (>10%) is generally required to improve MASH and fibrosis).
Physical activity	• 30+ minutes of physical activity/day, aiming for 150 min/week at an intensity where patient is sweating lightly (e.g. walking fast, treadmill, jogging, bicycling, exercycle, elliptical, swimming laps) See the Canadian 24-Hour Movement Guidelines.
Dietary modi-fications	Basic steps: • Patients with MASLD who are overweight or obese are encouraged to follow a diet that leads to a caloric deficit. • Patients with MASLD who are diabetic are encouraged to keep their blood glucose levels under control. • Eat a balanced diet with three meals spread out over the day. Aim for a variety of foods each day including vegetables, fruit, whole grain foods and lean protein foods. Aim for foods with little or no added sugar, salt and fat. • Limit food and beverages that contain added sugar including fruit juice, pop, sports drinks, specialty coffee/teas, candy, desserts and other sweets. ○ Of Note: Sugar (sucrose) is composed of one molecule of fructose and one molecule of glucose. After splitting and absorption in the gut, fructose is taken up in the first pass from portal blood into liver cells where it cannot be metabolized into anything else than fat (triglycerides). • Reduce saturated fat by limiting highly processed meats such as bacon, sausages, hot dogs and high fat deli meat. Choose lower fat daily products. • Increase fiber by choosing whole grains and plant proteins such as beans and legumes. • Regularly include small amounts of healthy fat such as fatty fish (salmon, trout, herring and mackerel), ground flax and nuts. Further information: Follow an eating pattern that includes vegetables, fruits, whole grains and protein foods to get the nutrients you need for good health. The Mediterranean diet is one example of a healthy eating pattern. Patients may benefit from handouts such as the Canada's Food Guide https://food-guide.canada.ca/en/. Referral to a Registered Dietitian can be helpful to support dietary changes. This may be particularly beneficial for individuals who have difficulty accessing healthy food for various reasons.

Cardio-vascular risk factors	• Screen for Type 2 diabetes, hypertension, and dyslipidemia. Treat and/or optimize therapy. • Patients with Type 2 diabetes may benefit from using a glucagon-like peptide-1 (GLP-1) receptor agonist as an antidiabetic because of their weight reduction effects, cardiovascular benefit and improvement in MASH. • Statins are safe and recommended for CVD risk reduction in patients with MASLD across the disease spectrum including compensated cirrhosis.
Alcohol	• Patients with MASLD should be counseled not to consume daily alcohol. Even moderate alcohol consumption increases the probability of advanced fibrosis, particularly in patients with obesity or T2DM, indicating potential synergistic effects of insulin resistance and alcohol on liver disease progression. • MASLD patients with low risk of significant liver fibrosis (i.e. "Low Risk" MASLD; FIB-4 score < 1.30) should be counseled to follow low risk drinking guidance (less than 3 drinks per week; Canada's Guidance on Alcohol and Health). Patients with clinically significant hepatic fibrosis (≥F2) should abstain from alcohol use completely.
Immuni-zations	• The National Advisory Committee on Immunization (NACI) recommends immunization with hepatitis A and hepatitis B vaccination series because patients with MASLD are at risk of more severe disease if infection occurs. Vaccination should be completed early in the course of the disease, as the immune response to vaccine is suboptimal with advanced fibrosis/cirrhosis. That said, hepatitis A and B vaccination is not routinely covered for MASLD patients in Manitoba.
Ongoing Monitoring	• **Re-calculate FIB-4 score every 1-2 years to reassess the likelihood of significant liver fibrosis (order ALT, AST, and platelets). Continue management in the patient's primary care setting if FIB-4 score remains <1.30.** • **If FIB-4 score increases to ≥ 1.30, consider referral to Hepatology or to another specialist trained in managing patients with liver diseases.**

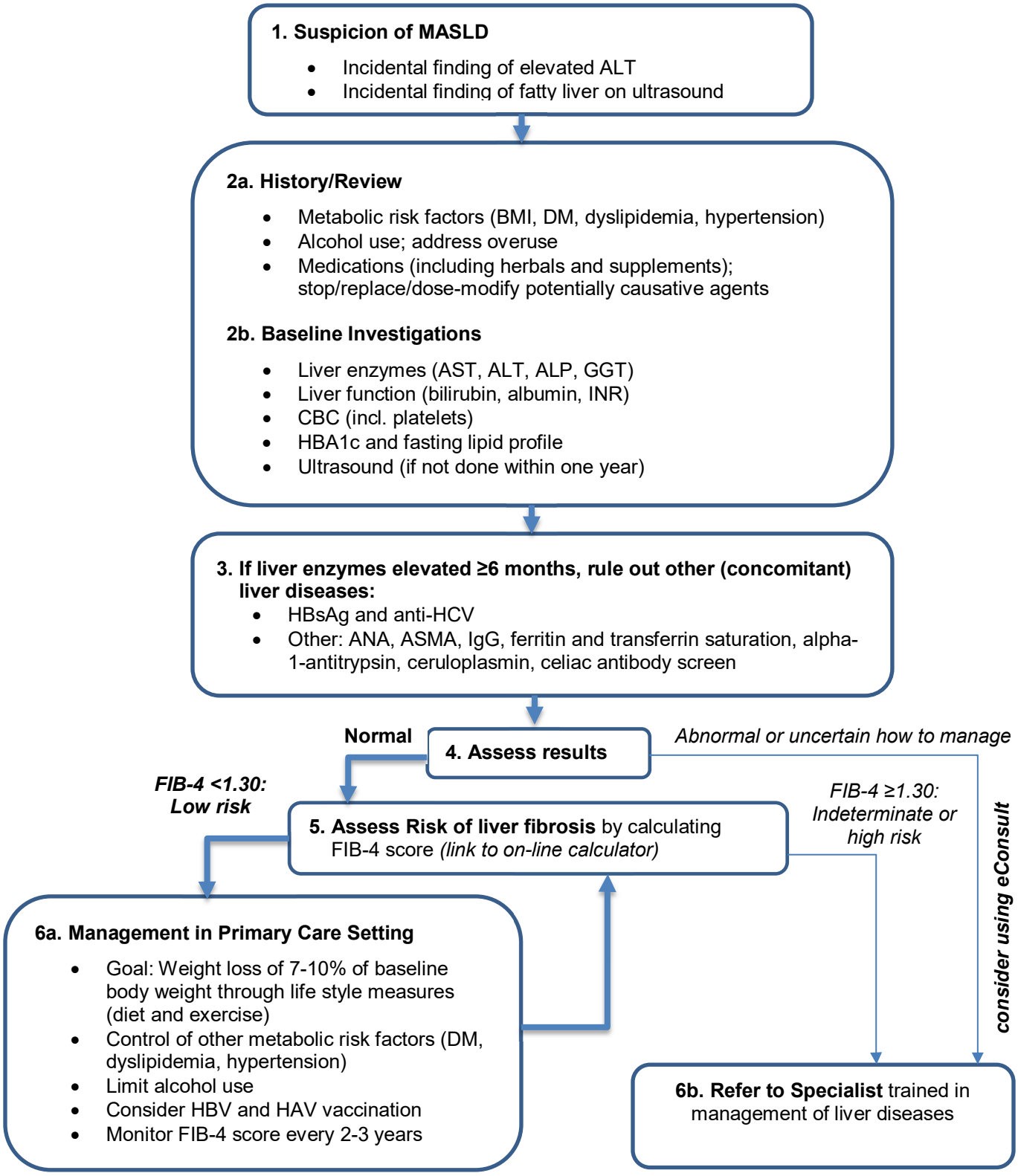
Other Considerations	
Coffee	• **Evidence:** There is some evidence that coffee consumption of at least 3 cups daily (caffeinated or not) is associated with less advanced liver disease.
Vitamin E	• **Evidence:** Vitamin E improves liver histology in patients with biopsy proven MASH and may be considered for MASLD patients. • **Place in therapy:** Until further data supporting its effectiveness become available, vitamin E is not recommended to routinely treat MASH in diabetic patients, MASLD without liver biopsy, MASH cirrhosis, or cryptogenic cirrhosis. If patients choose to trial Vitamin E, they should be counselled about weak epidemiological evidence suggesting increased cardiovascular and prostate cancer risk. • **Dose:** 800 IU/dayM
Omega-3 fatty acids	• This is not the same as OMEGA 3-6-9. • **Evidence:** May have an anti-inflammatory benefit for MASH patients with high serum triglycerides, but this has not been well proven in MASLD on its own. In some studies, Omega-3 fatty acids have been shown to help decrease hepatic steatosis and triglyceride levels. • **Mechanism of action:** Reduces hepatic production of triglyceride-rich very-low density lipoproteins. • **Place in therapy:** Consider for treatment of hypertriglyceridemia in patients with MASLD, however there is insufficient evidence to recommend their use for specific treatment of MASLD or MASH. • **Therapeutic dose:** 2-4 g/day of ecosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) combined. • Patients should be encouraged to eat a diet including fatty fish (salmon, trout, sardines), however a supplement is normally required to obtain sufficient daily EPA + DHA. • **NOTE:** Omega-3 fatty acids supplements have an anticoagulant effect in doses > 3 g/day (equivalent to a baby aspirin). Consider other medications and disease states before recommending. Monitor, as appropriate.
GLP-1 agonists	• Patients with Type 2 diabetes may profit from using a glucagon-like peptide-1 (GLP-1) receptor agonist as antidiabetic because of their weight reduction effects.
Bariatric interventions	• Bariatric interventions may be considered in morbidly obese individuals with MASLD in whom other measures to achieve weight loss were ineffective. Bariatric surgery should be considered as a therapeutic option in patients who meet criteria for metabolic weight loss surgery as it effectively resolve MASLD/MASH in majority of patients without cirrhosis and reduces CVD mortality..

2.2.4.2 ***Indeterminate/high risk (FIB-4 ≥ 1.30)***

Refer to Hepatology or to another specialist trained in management of patients with liver disease.

MASLD – Quick Decision Tree

(Not designed for use in patients with relevant alcohol use since FIB-4 not validated in this population)



3.0 APPLICATION:

3.1 Information for Patients can be found via links below:

- What is MASLD (formerly NAFLD) (www.liver.ca/resource/non-alcoholic-fatty-liver-disease-nafld/)
- Canada's Food Guide (www.food-guide.canada.ca/en/)
- Canadian 24h Movement Guidelines (Canadian 24-Hour Movement Guidelines)
- Canada's Guidance on Alcohol and Health (https://www.ccsa.ca/canadas-guidance-alcohol-and-health)

3.2 Checklist for Clinicians

Checklist to guide in-clinic review of your patient with MASLD	
☐	Finding of fatty liver on ultrasound or abnormal ALT
☐	If ALT > 2x ULN for 6 months, order further investigations to rule out other causes of liver disease in addition to MASLD (see Quick Decision Tree). If other causes identified, treat or refer for specialist consultation
☐	Identify and address medication and lifestyle factors that may cause or contribute to fatty liver or abnormal liver tests; excess alcohol consumption (> 2 drinks/day for males and > 1 drink/day for females) or medications (e.g. amiodarone, methotrexate, tamoxifen, corticosteroids, isotretinoin, antibiotics, antifungals, anticonvulsants).
☐	Complete baseline investigations (see Quick Decision Tree)
☐	Assess risk of liver fibrosis using the FIB-4 Index • If FIB-4 score < 1.3, continue to provide care in the Primary Care setting (see Quick Decision Tree) • If FIB-4 score ≥ 1.3, consider referral to a specialist trained in management of liver disease

3.3 For Health Service Organizations

Incorporate provincial clinical guideline content where applicable into policies and procedures.

4.0 DEFINITIONS:

4.1 Abbreviations:

MASLD, Metabolic Dysfunction-Associated Steatotic Liver Disease

MASH, Metabolic Dysfunction-Associated Steatohepatitis

ALT, Alanine Aminotransferase

AST, Aspartate Aminotranferase

ALP, Alkaline Phosphatase

GGT, Gamma-Glutamyl Transferase

CBC, Complete Blood Cell Count

HBA1c, Hemoglobin A1c

References:

Rinella, Mary E; Neuschwander-Tetri, Brent A; Siddiqui, Mohammad Shadab; et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease Hepatology AASLD Practice Guidance on the clinical assessment and manag... : Hepatology (lww.com).

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Rinella, M. E., and Sanyal, A. J. Management of NAFLD: a stage-based approach. Nature Reviews Gastroenterology & Hepatology, 13: 196; 2016.

Dulai, P. S.; Singh, S.; Patel, J.; et al. Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: systematic review and meta-analysis. Hepatology, 65 1557-1565; 2017.

Update in Prevention: 2021 Canadian Cardiovascular Society Dyslipidemia Guidelines. Gudenkauf, Brent, M; Jacobsen, Allan; Blumenthal, Roger, S et al. FACC; https://www.acc.org/Latest-in-Cardiology/Articles/2021/09/07/12/46/Update-in-Prevention-2021-Canadian-CV-Society-Dyslipidemia-Guidelines#:~:text=The%20initiation%20of%20a%20statin,ApoB%20%3E1.05%20g%2FdL

Alberta Health Services Non-Alcoholic Fatty Liver Disease (NAFLD) Primary Care Pathway www.specialistlink.ca/assets/pdf/Hepatology_NAFLDPathway_CalgaryZone.pdf

Document Review History

Version #	Date	Reviewer	Action
1.0	Jan 18, 2024	Hepatologists	Review and feedback
1.0	March 7, 2024	Primary Care PCT	Review and feedback
1.0	March 12, 2024	Chronic & Complex Medicine & Rehabilitation PCT	Review & feedback
1.0	May 14, 2024	Chronic & Complex Medicine & Rehabilitation PCT	Endorsed
1.0	May 28, 2024	PCLT	Approved

This guideline will be reviewed/revised in a three year cycle.

OUTPATIENT HEPATOLOGY CONSULTATION REQUEST FORM

Health Sciences Centre Winnipeg

For Referrals to HSC & Bairdmore Clinic Only

Fax: (204) 940-8176

All HSC Hepatology Referrals must be received on this form.
Incomplete forms will be returned for completion. To avoid delays, please ensure all appropriate documents are submitted with this form.

Referral Date: _____

Referring Physician Name: _____ Fax Number: _____

Address: _____ Phone Number: _____

Patient Information

Last Name: _____ First Name: _____ Initials: _____

DOB: _____ PHIN: _____ MHSC: _____ Gender:__

Address: _____

City: _____ Province: _____ Postal Code: _____

Phone: Home: Cell: Work:

Reason for Referral:
(Check one of the following and provide one line summary)

- ☐ General Liver Problems (eg. fatty liver, autoimmune liver disease,etc)
- ☐ Viral Hepatitis
- ☐ Cirrhosis / Advanced Liver Disease / HCC / Transplant Assessment

Summary: _____

Current Medications:

Urgent consults will be seen in approximately 2-4 weeks. If you feel that the patient needs to be seen sooner, please page Hepatology-On-Call (204-787-2071)

1) Has your patient been evaluated by Hepatology before?
   ☐ No ☐ Yes - Please attach consultant notes

2) Please ensure to attach all relevant documents (biopsy report, radiology reports, etc.)

Provide the following:
(If available)

ALT: **ALP:** **Bilirubin Total** **Bilirubin Direct**

INR: **Platelet Count** **Creatinine** **BMI:**