Non-Alcoholic Fatty Liver Disease (NAFLD) Primary Care Pathway

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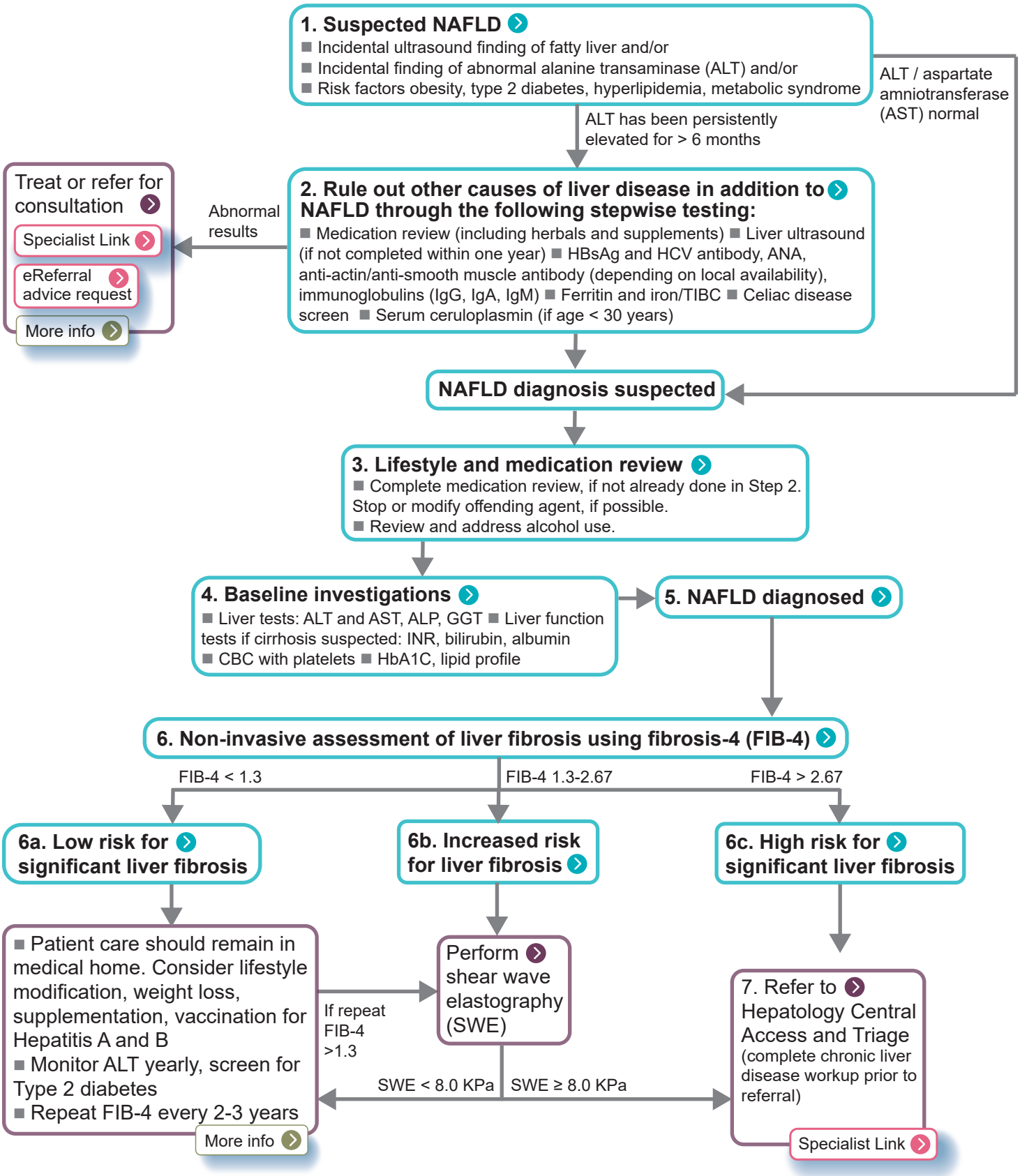

This primary care pathway was co-developed by primary and specialty care and includes input from multidisciplinary teams. It is intended to be used in conjunction with specialty advice services, when required, to support care within the medical home. Wide adoption of primary care pathways can facilitate timely, evidence-based support to physicians and their teams who care for patients with common low-risk GI conditions and improve appropriate access to specialty care, when needed. To learn more about primary care pathways, check out this short video.

NAFLD PATHWAY PRIMER

- Non-alcoholic fatty liver disease (NAFLD) results from liver damage due to the accumulation of fat (triglycerides) within liver cells.
- It is the most common liver disease in Canada, affecting approximately 25% of the general population, and is often associated with obesity, diabetes, and/or hyperlipidemia.
- The term NAFLD actually refers to a group of related liver conditions, including simple fatty liver (i.e. steatosis), non-alcoholic steatohepatitis (steatosis with liver damage/NASH), fatty liver with liver fibrosis (i.e. liver scarring), or fatty liver with advanced liver fibrosis/cirrhosis.
  - In general, steatosis is considered to be relatively benign, but can still progress to cirrhosis in 2-3% of people within 1-2 decades (even when ALT levels are persistently normal).
  - In contrast, NASH is considered a potentially progressive disease that can lead to cirrhosis in up to 20% of people within 20 years[1]. The gold standard for NASH diagnosis is a liver biopsy, though this is rarely done in practice.
  - Increasing liver fibrosis in people with NAFLD is associated with an exponential increase in risk of liver-related mortality[2], which appears to be most pronounced in people with NAFLD who have developed moderate to severe liver fibrosis.
  - NAFLD 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 NAFLD who have developed significant liver fibrosis in order to better manage these individuals to try to prevent progressive liver fibrosis.
- Given the prevalence of NAFLD, specialist consultation for all patients with NAFLD is not feasible.
  - This clinical care pathway helps to **identify people with NAFLD who are more likely to have advanced liver scarring**, and, therefore, may benefit from specialist care.
- This pathway employs two tests – fibrosis-4 (FIB-4) and shear wave elastography (SWE) to assess the risk of liver fibrosis. Both tests are available to primary care physicians within the community for appropriate patients. SWE reports will be generated by EFW Radiology or Mayfair Diagnostics using standardized reporting.

[1] Rinella, M. E., & Sanyal, A. J. (2016). Management of NAFLD: a stage-based approach. *Nature Reviews Gastroenterology & Hepatology*, *13*(4), 196.
[2] Dulai, P. S., Singh, S., Patel, J., Soni, M., Prokop, L. J., Younossi, Z., ... & Stal, P. (2017). Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: systematic review and meta-analysis. *Hepatology*, *65*(5), 1557-1565.

Checklist to guide in-clinic review of your patient with NAFLD	
☐	Finding of fatty liver on ultrasound or abnormal ALT or risk factors for NAFLD present (obesity, hyperlipidemia, metabolic syndrome, and/or type 2 diabetes) (see algorithm Box 1)
☐	If ALT > 2x ULN for 6 months, order further investigations to rule out other causes of liver disease in addition to NAFLD (see algorithm Box 2). 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, valproic acid, corticosteroids). (see algorithm Box 3)
☐	Complete baseline investigations (see algorithm Box 4)
☐	Order FIB-4 to assess liver fibrosis. If increased risk for liver fibrosis, order SWE through EFW Radiology or Mayfair Diagnostics, if NAFLD has been diagnosed (as per flow diagram); other causes of chronic liver disease have been ruled out; or, it has been greater than 3 years since the last abdominal ultrasound showing steatosis and risk factors for NAFLD present (see algorithm Box 6)
☐	Continue to manage patients identified as “Low Risk” NAFLD within the medical home using the care plan outlined.
☐	Refer patients identified as “high risk” NAFLD to Hepatology Central Access and Triage (CAT). **Complete chronic liver disease workup for all referrals to hepatology** (see algorithm Box 7)

EXPANDED DETAILS

1. Suspected NAFLD

- NAFLD should be considered for patients with one or more of the following:
  - Abnormal liver tests (persistent elevation of serum alanine aminotransferase (ALT); repeat > 6 months. In patients with NAFLD, ALT is usually < 200 U/L).
    - **Note:** Patients with NAFLD will not necessarily have elevated liver enzymes.
  - Ultrasound finding of fatty liver (current or past, if risk factors, such as obesity, have not changed significantly).
    - **Note:** Patients with NAFLD will not necessarily have fatty liver documented on an ultrasound report (> 30% fat infiltration is required to visualize fatty liver on ultrasound).
- Risk factors for NAFLD include obesity, type 2 diabetes, hyperlipidemia, metabolic syndrome, and hypertension.
- The pathway is not designed for use with patients with significant alcohol consumption (> 2 drinks/day for males, > 1 drink/day for females).
  - Counsel patients to reduce their alcohol consumption below these levels. After 6-8 weeks, retest ALT. If it remains abnormal, use of this pathway is appropriate.

2. (If ALT > 2x Upper Limit of Normal (ULN) for 6 months) Rule out other causes of liver disease in addition to NAFLD through the following stepwise testing

a) Medication profile review

- 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 liver problems (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 culprits include medications (e.g. amiodarone, methotrexate, tamoxifen, valproic acid, corticosteroids), herbal products, health supplements (e.g. green tea extract), and illicit substances (e.g. cocaine).
  - The Medication and Herbal Advice Line through AHS PADIS is a free service that provides information on a wide range of products, including information on toxicity.
- 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 3-6 months.

b) Liver ultrasound

- Order if not completed within one year.

c) Hepatitis B and C screening

- Hepatitis B surface antigen (HbsAg) – if positive, consider referral to hepatology.
- Hepatitis C antibody (anti-HCV) – if positive, see Hepatitis C pathway.

d) Other testing

- Anti-nuclear antibody (ANA), anti-actin/anti-smooth muscle antibody, and immunoglobulins (IgG, IgM, IgA) - to evaluate for possible autoimmune cause of liver injury.
  - Autoimmune hepatitis (AIH): ANA (> 1:80 titer) and/or anti-smooth muscle antibody (> 1:20 titer) and elevated serum immunoglobulin levels (especially IgG) may suggest AIH and warrant consideration for a referral to hepatology.
- Ferritin and iron/TIBC (done while fasting) to assess for hemochromatosis
  - **Note:** ferritin is often significantly elevated in NAFLD (as an acute phase reactant related to liver inflammation), but transferrin saturation is typically < 50%. These patients do not have iron overload.
  - If fasting ferritin elevated **and** percentage transferrin saturation is > 50% in females or > 60% in males, consider molecular genetic testing for hemochromatosis. If genetic testing suggests increased risk for hemochromatosis, assessment of liver fibrosis is recommended as patients with hemochromatosis and advanced liver fibrosis are at high risk of liver cancer. If genetic testing is negative, it is highly unlikely that the patient has hereditary hemochromatosis.
- Celiac screen – if positive, consider referral for gastroscopy to confirm diagnosis.
  - Once under control for 6 months, repeat liver function tests.
- Serum ceruloplasmin (if age < 30 years) – if positive, consider referral to hepatology.

e) Note: In the evaluation of abnormal liver tests, abdominal MRI and/or CT are unlikely to add diagnostic benefit and should not be routinely ordered.

If increased ALT workup suggests a non-NAFLD diagnosis, consider appropriate referral to specialist.

If workup for increased ALT is negative, NAFLD diagnosis is strongly suspected based on risk factors, elevated liver enzymes, and/or ultrasound findings.

3. Lifestyle and medication review

- Complete medication review if not already done in Step 2. Stop or modify offending agent, if possible, then repeat liver function tests after 3-6 months.
- Review and address alcohol use
  - Excess alcohol consumption (> 2 drinks/day for males, > 1 drink/day for females) may contribute to abnormal liver tests.
  - Counsel patients to reduce their alcohol consumption below these levels. After 6-8 weeks, retest ALT. If it remains abnormal, elevated ALT is unlikely to be the result of alcohol consumption.

4. Baseline investigations

- ALT and AST (to assess for liver cell death or damage)
- ALP and GGT (to assess for impairment of bile flow)
  - If elevated, and extra-hepatic biliary obstruction ruled out by ultrasound, test anti-mitochondrial antibody. Any positive titer is significant and is highly specific for primary biliary cholangitis (which affects ~1:1000 women over the age of 40). If positive, consider referral to hepatology.
- CBC with platelets (to assess liver function and enable FIB-4 score calculation)
  - Platelets are included in the FIB-4 calculation as thrombocytopenia can be an initial sign of cirrhosis
- HbA1C and lipid profiles (to assess for common comorbidities)
- **If cirrhosis is suspected,** also test INR, bilirubin, albumin (to assess liver function)

5. NAFLD diagnosed

- NAFLD is the diagnosis of exclusion if no other causes of fatty liver/elevated liver enzymes have been identified, even in the presence of normal ultrasound. Remember that 30% fat infiltration in the liver is required for it to be visualized on ultrasound.

6. Assess risk of liver fibrosis risk using FIB-4 and SWE

- Fibrosis-4 variable index (FIB-4) is a score calculated from an individual's age, platelet count, and blood ALT and AST levels. It was initially developed and validated to evaluate liver fibrosis stages related to chronic HCV infection. Over the last two decades, it has been validated in other chronic liver diseases including MASLD/NAFLD. FIB-4 should be used as a first step "screening" tool to risk stratify patients with MASLD/NAFLD who are at risk of liver fibrosis. Values below 1.30 are indicative of low risk of significant or advanced fibrosis. Values above 2.67 warrant assessment by hepatology and need to be further evaluated using a radiological assessment tool such as Transient Elastography (i.e., Fibroscan). Indeterminate values between 1.30 and 2.67 warrant further assessment by SWE[3][4].

a) **Low risk** (FIB-4 value < 1.3). Management of NAFLD in medical home recommended, with reassessment every two to three years using FIB-4 score for evidence of significant liver fibrosis progression/development.

[3] Xiao, G., Zhu, S., Xiao, X., Yan, L., Yang, J. and Wu, G. (2017). Comparison of laboratory tests, ultrasound, or magnetic resonance elastography to detect fibrosis in patients with non-alcoholic fatty liver disease. *Hepatology*, *66* (5).
[4] Kanwal, F. Shubrook, J. et al (2021). Clinical care pathway for the risk stratification and management of patients with non-alcoholic fatty liver disease. *Hepatology*, 161 (5), 1657-1669.

If repeat FIB-4 >1.3 , move to increased risk for significant liver fibrosis and perform SWE. Ongoing management in medical home if FIB-4 value remains < 1.3 (LOW RISK).

Patient care within the Patient's Medical Home

- Lifestyle modifications are the cornerstone of NAFLD management.
  - **Exercise:** 20+ minutes of moderate exercise almost daily, aiming for 150 min/week (can be in 10-15 minute sessions). See Canadian Physical Activity guidelines.
  - **Diet:** Aim to choose more high-fibre carbohydrates, less refined starches, less added sugars, and less saturated fats. Replace foods high in saturated fat with monounsaturated fat and omega-3 fats. Choose lean meats and plant-based proteins to preserve lean body mass while losing body fat. Consider referral to a dietitian for support.
  - **Weight loss:** As needed, target weight loss of ~10% of body weight over 6 months. Patients may benefit from handouts on healthy eating for weight management and sample menus.
- Modify cardiac risk factors where appropriate. NAFLD patients are 3-5 times more likely to suffer a heart attack or stroke compared with the general population.
  - Statin therapy is strongly recommended in patients with increased LDL cholesterol. In general, statins are safe in patients with liver disease, however ALT monitoring can be considered in NASH patients. Tests should be done 3 months after starting therapy. If ALT doubles during this time, the statin should be stopped in favor of a different lipid lowering agent.
  - Screen for type 2 diabetes and hypertension. Treat and/or optimize therapy.
  - Encourage smoking cessation. Provide information, treatment, or referral, as appropriate.
- Alcohol intake:
  - Patients with NAFLD should not consume heavy amounts of alcohol. The risk of moderate alcohol consumption for patients with NAFLD is unknown.
    - An acceptable intake for NAFLD patients with low risk of significant liver fibrosis (i.e. "Low Risk" NAFLD; FIB-4 score < 1.30), up to 4-5 drinks/week for men and 3-4 drinks/week for women.
    - Abstinence is recommended for patients with cirrhosis.
- There is inconclusive evidence that 2-3 cups of coffee/day (preferably filtered) may be beneficial for patients with fatty liver.
- Consider vaccinating NAFLD patients for hepatitis A and B to avoid superimposed preventable liver disease.

Ongoing monitoring

- ALT yearly
- Screen for Type 2 DM (increased risk for developing NIDDM based on NAFLD Diagnosis)
- Repeat FIB-4 every 2-3 years. Ongoing management in medical home can continue if Fib-4 value remains LOW RISK, at <1.3 or if a SWE is done and the results are <8.0 KPa. If evidence for progression to HIGH RISK for significant liver fibrosis (Fib-4 >2.67 OR SWE value > 8.0 KPa) then referral to NAFLD clinic through Hepatology CAT recommended.

Note: EFW Radiology will send a one-time only reminder letter to the primary care physician, who is on record from prior SWE test, 24-30 months after the previous LOW RISK SWE test. EFW Radiology will not contact

patients directly unless requested by a primary care provider. Mayfair Diagnostics will send a reminder to referring physician on record for LOW RISK patients 6 months prior to the 3 year due date for next Fib-4 / SWE measurement.

Therapeutic considerations for NAFLD patients within the Medical Home

- Vitamin E is an antioxidant. Studies are ongoing to determine whether it is beneficial in treating NASH in non-cirrhotic and non-diabetic patients.
  - Until further data supporting its effectiveness become available, vitamin E is not recommended to routinely treat NASH in diabetic patients, NAFLD without liver biopsy, NASH 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.
  - The suggested dose is 400-800 IU/day.
- Omega 3 fatty acid (FA) (Note: this is not the same as OMEGA 3-6-9) may have an anti-inflammatory benefit for NASH patients with high serum triglycerides, but this has not been well proven in NAFLD on its own. In some studies, Omega 3 FA have been shown to help decrease hepatic steatosis and triglyceride levels.
  - The therapeutic dose of Omega 3 FA would be 2-4 grams/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 and DHA.
  - **Note:** Omega 3 FA supplements have an anticoagulant effect in doses > 3 grams/day (equivalent to a baby aspirin). Consider other medications and disease states before recommending, and monitor as appropriate
- There is evidence that GLP-1 receptor agonists demonstrate benefit in NAFLD. Particularly in patients with Type 2 DM and NAFLD who have inadequate glycemic control, the preferential use of GLP-1 RA should be considered.

b) **Increased risk for liver fibrosis** is suspected if FIB-4 value 1.3 – 2.67. Recommendation with this finding is to perform a shear wave elastography (SWE) assessment.

SWE is the gold standard for assessing liver stiffness (a measure of liver scarring) without a liver biopsy and this test is now available. EFW and Mayfair radiology groups have fulfilled quality assessment for the Calgary NAFLD pathway SWE measurement. Currently they are the recommended providers for SWE in the Calgary Zone. EFW can be ordered through EFW Radiology Liver Programs Requisition under the heading “NAFLD”.

SWE finding of ≥8.0 KPa is a HIGH RISK for significant liver fibrosis suspected (SWE value > 8.0 KPa) referral to NAFLD clinic through Hepatology Central Access and Triage (CAT) recommended.

SWE find of <8.0 KPA is a LOW RISK for significant liver fibrosis suspected (SWE value < 8.0 KPa) management of NAFLD in medical home recommended (information above), with reassessment every three

years using SWE score for evidence of significant liver fibrosis progression/development. Ongoing management in medical home if SWE value remains < 8.0 KPa (LOW RISK).

c) **High risk for significant liver fibrosis** suspected if FIB-4 value > 2.67. In this instance, a referral to NAFLD clinic through Hepatology Central Access and Triage (CAT) recommended. Complete chronic liver disease workup must be done for all referrals to hepatology. Referral information can be found at https://albertareferraldirectory.ca/PublicSearchController?direct=displayViewServiceAtFacility&serviceAtFacilityId=1131966&pageNumberToDisplay=1&sortOrder=1&publicSearch=true&backToPage=solrSearchScreen1

BACKGROUND

About this Pathway

- Digestive health primary care pathways were originally developed in 2015 as part of the Calgary Zone's Specialist Link initiative. They were co-developed by the Department of Gastroenterology and the Calgary Zone's specialty integration group, which includes medical leadership and staff from Calgary and area Primary Care Networks, the Department of Family Medicine, and Alberta Health Services.
- The pathways were intended to provide evidence-based guidance to support primary care providers in caring for patients with common digestive health conditions within the patient medical home.
- Based on the successful adoption of the primary care pathways within the Calgary Zone, and their impact on timely access to quality care, in 2017 the Digestive Health Strategic Clinical Network (DHSCN) led an initiative to validate the applicability of the pathways for Alberta and to spread availability and foster adoption of the pathways across the province.

Authors & Conflict of Interest Declaration

The content has been created by the Calgary Zone Specialty Integration Task in 2018, and was revised in 2024 to represent the Calgary Zone resources. This update pathway format was modified from work by DHSCN.

Pathway Review Process

Primary care pathways undergo scheduled review every three years, or earlier, if there is a clinically significant change in knowledge or practice. The next scheduled review is January 2027. However, we welcome feedback at any time. Please email comments to info@calgaryareapcns.ca.

Copyright Information

Disclaimer

This pathway represents evidence-based best practice, but does not override the individual responsibility of healthcare professionals to make decisions appropriate to their patients using their own clinical judgment given their patients' specific clinical conditions, in consultation with patients/alternate decision makers. The pathway is not a substitute for clinical judgment or advice of a qualified healthcare professional. It is expected that all users will seek advice of other appropriately qualified and regulated healthcare providers with any issues transcending their specific knowledge, scope of regulated practice or professional competence.

PROVIDER RESOURCES

Still concerned about your patient?

The primary care physician is typically the provider who is most familiar with their patient's overall health and knows how they tend to present. Changes in normal patterns, or onset of new or worrisome symptoms, may raise suspicion for a potentially serious diagnosis, even when investigations are normal and typical alarm features are not present.

There is evidence to support the importance of the family physician's intuition or "gut feeling" about patient symptoms, especially when the family physician is worried about a sinister cause such as cancer. A meta-analysis examining the predictive value of gut feelings showed that the odds of a patient being diagnosed with cancer, if a GP recorded a gut feeling, were 4.24 times higher than when no gut feeling was recorded[5].

When a "gut feeling" persists in spite of normal investigations, and you decide to refer your patient for specialist consultation, document your concerns on the referral with as much detail as possible. Another option is to seek specialist advice (see Advice Options) to convey your concerns.

Advice Options

Non-urgent advice is available to support family physicians.

- Gastroenterology advice is available across the province via Alberta Netcare eReferral Advice Request (responses are received within five calendar days). View the Referring Provider – FAQ document for more information.
- Non-urgent telephone advice connects family physicians and specialists in real time via a tele-advice line.
  - In the Calgary Zone, contact a hepatologist at specialistlink.ca or by calling 403-910-2551. This service is available from 8 a.m. to 5p.m. Monday to Friday (excluding statutory holidays). Calls are returned within one hour.
  - In the Edmonton Zone, contact a gastroenterologist by calling 1-844-633-2263 or visiting pcnconnectmd.com. This service is available from 9 a.m. to 6 p.m. Monday to Thursday and 9 a.m. to 4 p.m. Friday (excluding statutory holidays and Christmas break). Calls are returned within two business days.

[5] Friedemann Smith, C., Drew, S., Ziebland, S., & Nicholson, B. D. (2020). Understanding the role of General Practitioners' gut feelings in diagnosing cancer in primary care: A systematic review and meta-analysis of existing evidence. *British Journal of General Practice*, 70(698), e612-e621.

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Resources	
Poverty: A Clinical Tool for Primary Care Providers (AB)	cep.health/media/uploaded/Poverty_flowAB-2016-Oct-28.pdf
Nutrition Guidelines: Household Food Insecurity	ahs.ca/assets/info/nutrition/if-nfs-ng-household-food-insecurity.pdf
Calgary GI Division	http://www.calgarygi.com
Canadian Liver Foundation	https://www.liver.ca/professionals/health-professionals/
NICE UK: Non-alcoholic fatty liver disease (NAFLD): assessment and management	https://www.nice.org.uk/guidance/ng49

PATIENT RESOURCES

Information

Description	Website
General information on NAFLD (Canadian Liver Foundation)	• liver.ca/patients-caregivers/liver-diseases/fatty-liver-disease/ • liver.ca/liver-health-month-2018-checkyourengine/
General information on weight management (MyHealth.Alberta.ca)	myhealth.alberta.ca/health/pages/conditions.aspx?Hwid=center1038
Online learning module on weight management (MyHealth.Alberta.ca)	myhealth.alberta.ca/learning/modules/Weight-Management
Nutrition Education Material	ahs.ca/NutritionResources
Patient handout on healthy eating for weight management	ahs.ca/assets/info/nutrition/if-nfs-healthy-eating-weight-management.pdf
Patient handout with sample menus for healthy eating	ahs.ca/assets/info/nutrition/if-nfs-sample-meal-plans-for-healthy-eating.pdf
Patient handout on omega 3 fatty acids	ahs.ca/assets/info/nutrition/if-nfs-omega-3%20-fats-for-heart-health.pdf
Canadian Physical Activity Guidelines	csep.ca/CMFiles/Guidelines/CSEP_PAGuidelines_0-65plus_en.pdf

Services Available

Description	Website
Alberta Healthy Living Program: Eating Well for fatty liver disease	Registration information at: ahs.ca/info/page13984.aspx
Lyfe^{MD} (paid subscription) : Self-management support tool that will empower the patient to make changes in lifestyle, and provide the support to maintain the changes	https://www.lyfemd.ca/patients/nafld
Supports for working towards healthy lifestyle goals and weight management (Weight Management – AHS)	ads.ca/info/Page15163.aspx
Services for people who are struggling with substance use, addiction, or a mental health problem (Addiction and Mental Health Services – AHS)	ad.ca/amh/Page14063.aspx#details-panel14066
Toll free confidential phone service which provides alcohol, tobacco, other drugs and problem gambling support, information and referral to services. The Addiction Helpline operates 24 hours a day, seven days a week (Addiction Helpline – AHS)	1-866-332-2322 ahs.ca/findhealth/Service.aspx?id=1008399&serviceAtFacilityID=1047128