NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) PRIMARY CARE PATHWAY

1. Diagnostic criteria

- Incidental finding of abnormal alanine aminotransferase (ALT)
- Incidental ultrasound finding of fatty liver

Note: this pathway is not designed for use in patients with significant alcohol consumption because FIB-4 has not been validated in this population.

Is ALT > 2x ULN for 6 months?

YES

2. Rule out other causes of liver disease in addition to NAFLD through the following stepwise testing

- Medication review (including herbals and supplements)
- Liver ultrasound (order if not completed within 1 year)
- HbsAg and anti-HCV
- Other testing: ANA, anti-actin/anti-smooth muscle antibody, immunoglobulins (IgG, IgM, IgA), ferritin and iron/TIBC, celiac disease screen, serum ceruloplasmin (age < 30 years)

ABNORMAL RESULTS

Refer to Gastroenterology
Click here for Referral letter

NAFLD diagnosis suspected (and alternative causes of abnormal ALT investigated)

3. Medication and lifestyle review

- Complete medication review if not already done in Step 2. Stop or modify offending agent, if possible.
- Repeat liver function tests after 3-6 months.
- Review and address alcohol use.

4. Baseline investigations

- Liver tests: ALT, AST, ALP, GGT
- CBC with platelets
- HbA1C and lipid profiles
- If cirrhosis is suspected: test INR, bilirubin, albumin

5. NAFLD diagnosed

- Further follow-up is dependent on risk stratification by the FIB-4 score

6. Assess risk of liver fibrosis using FIB-4 index

- Free FIB-4 calculator

FIB-4 < 1.30

FIB-4 >/= 1.30

6a. Low risk

6b. Indeterminate/high risk

6a. Care within the Patient Medical Home

- Physical activity (20+ minutes/day aiming for 150 minutes/week)
- Diet and weight loss (increase fibre, lower sugars and saturated fats, choose lean proteins)
- Screen for type 2 diabetes, hypertension, and hyperlipidemia. Treat/optimize therapy. Consider the use of newer hypoglycaemic agents such as Ozempic which can also aid in weight loss
- Encourage smoking cessation
- Limit alcohol intake
- Consider immunizations for hepatitis A and B

Ongoing monitoring: re-calculate FIB-4 every 2-3 years (order ALT, AST, platelets). If FIB-4 continues to be < 1.30, continue care within the Patient Medical Home.

If FIB-4 becomes ≥ 1.30

Refer to Gastroenterology
Click here for Referral letter

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Non-Alcoholic Fatty Liver Disease (NAFLD) - What is it?

- Non-alcoholic fatty liver disease (NAAFLD) 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 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. The gold standard for NASH diagnosis is a liver biopsy, though this can rarely be done in practice.
    - Increasing liver fibrosis in people with NAFLD is associated with an exponential increase in risk of liver-related mortality, 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.
    - The 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 blood tests to assess a patient's risk of significant liver scarring, based on calculating their Fibrosis-4 score (FIB-4) using the following formula:

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

    - An FIB-4 score of < 1.30 essentially rules out significant liver fibrosis. An FIB-4 score ≥ 1.30 could potentially indicate risk of liver fibrosis and warrants further evaluation.

CHECKLIST TO GUIDE IN-CLINIC REVIEW OF YOUR PATIENT WITH NAFLD

☐	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 NAFLD. 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, isotrentinoin, antibiotics, antifungals, anticonvulsants).
☐	Complete baseline investigations
☐	Assess risk of liver fibrosis using the FIB-4 index • If FIB-4 score < 1.3, continue to provide care in the Patient Medical Home • If FIB-4 score ≥ 1.3, consider referral to GI specialist

Expanded Details of NAFLD Clinical Pathway

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) because FIB-4 has not been validated in this population.
    - 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

- **Medication 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, corticosteroids, isotretinoin, antibiotics, antifungals, anticonvulsants), herbal products, health supplements (e.g. green tea extract), and illicit substances (e.g. cocaine).
    - 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.
- **Liver ultrasound**
    - Order if not completed within one year.
- **Hepatitis B and C screening**
    - Hepatitis B surface antigen (HbsAg) - if positive, consider referral to hepatology.
    - Hepatitis C antibody (anti-HCV) - if positive, consider referral to hepatology.
- **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 is elevated **and** percentage transferrin saturation is > 50% in females or > 60% in males, proceed to molecular genetic testing for hemochromatosis. If genetic testing suggests increased risk for hemochromatosis, assessment of liver fibrosis is recommended as patient 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 disease screen - if positive, please refer to GI for gastroscopy to confirm diagnosis.
        - Once under control for 6 months, repeat liver function tests.
    - Serum ceruloplasmin (if age < 30 years) - if positive, please refer to hepatology.

Note: in the evaluation of abnormal liver tests, abdominal MRI and/or CT are unlikely to add diagnostic benefit and <u>should not be routinely ordered.</u>

If workup suggests a non-NAFLD diagnosis, treat or consider appropriate referral to specialist.

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

3. Medication and lifestyle review

- Complete a 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 the 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 about 1:1000 women over the age of 40). If positive, then please refer 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% of fat infiltration in the liver is required for it to be visualized on an ultrasound.

6. Assess risk of liver fibrosis risk using FIB-4 index

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

a) Low risk (FIB-4 < 1.30): Care within Patient Medical Home

CARE WITHIN THE PATIENT MEDICAL HOME	
Lifestyle modifications are the cornerstone of NAFLD management.	
Physical activity	• 20+ minutes of physical activity/day, aiming for 150 minutes/week • See the Canadian 24-Hour Movement Guidelines
Dietary modifications and weight loss	• Aim to choose more high-fibre carbohydrates and less refined starches, added sugars, and 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. • Referral to a Registered Dietician can be helpful to support dietary changes. • As needed, target weight loss of about 10% of body weight over 6 months
Cardiac risk factor modifications	• Screen for Type 2 diabetes, hypertension, and hyperlipidemia. Treat and/or optimize therapy. • Statin therapy is strongly recommended in patients with increased LDL cholesterol to manage cardiac risk factors, not to specifically treat NASH. 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 his time, the stating should be stopped in favour of a different lipid lowering agent. • Encourage smoking cessation.

Alcohol intake	• Patients with NAFLD should not consume heavy amounts of alcohol. The risk of moderate alcohol consumption for patient with NAFLD is unknown. • An acceptable intake for NAFLD patients with low risk of significant liver fibrosis (FIB-4 score < 1.30) is up to 4-5 drinks/week for men and 3-4 drinks/week for women. • Abstinence is recommended for patients with cirrhosis.
Immunizations	• The National Advisory Committee on Immunization (NACI) recommends immunization with hepatitis A and B vaccination series because patients with NAFLD are at a risk of more severe disease if infection occurs. Vaccination should be completed early in the court of the disease, as the immune response to vaccine is suboptimal in advanced liver disease. Post-immunization serologic testing may be used to confirm hepatitis B vaccine response. Serologic testing is not recommended after receiving the hepatitis A vaccine due to the test's poor sensitivity.

OTHER CONSIDERATIONS	
Vitamin E	• **Evidence:** Vitamin E improves liver histology in patients with biopsy proven NASH and may be considered for NAFLD patients. • **Place in therapy:** Until further data supporting its effectiveness become available, vitamin E is not recommended to routinely treat NASSH 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. • **Dose:** 800 IU/day
Omega-3 fatty acids	• **This is not the same as Omega 3-6-9.** • **Evidence:** 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 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 NAFLD, however there is insufficient evidence to recommend their use for specific treatment of NAFLD or NASH. • **Therapeutic dose:** 2-4g/day of ecosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) combined. • **Note:** Omega-3 fatty acid supplements have an anticoagulant effect in doses > 3g/day (equivalent to baby Aspirin). Consider other medications and disease states before recommending. Monitor, as appropriate.
Coffee	• There is inconclusive evidence that 2-3 cups of coffee per day (preferably filtered) may be beneficial for patients with fatty liver.

Ongoing monitoring

- Re-calculate FIB-4 score every 2-3 years to reassess risk of significant liver fibrosis (order ALT, AST, and platelets). Continue management in the Patient Medical Home if FIB-4 score remains < 1.30.
- Refer to a specialist trained in the management of liver disease if FIB-4 score increases to > 1.30. Outline history and care provided to date.

b) Indeterminate/high risk (FIB-4 ≥ 1.30)

- Referral to a specialist trained in the management of liver disease.

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.

When a "gut feeling" persists in spite of normal investigations, and you do decide to refer your patient for specialist consultation, document your concerns on the referral with as much detail as possible.

Additional Information About this Pathway

About this pathway

This primary care pathway was created using resources from Alberta Health Services and Alberta Primary Care Networks and further adapted by gastroenterologists at Kelowna Gastroenterology Associates from Kelowna, British Columbia. 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.

- 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 GI and the Calgary Zone's speciality integration group, which includes medical leadership and staff from Calgary and area Primary Care Networks, the Department of Family Medicine and Alberta Health Services.
- This pathway has been reviewed by the Kelowna Gastroenterology Associates and its physicians for content and use.

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Patient Information Sheet for Managing Non-alcoholic Fatty Liver Disease

What is NAFLD?

- A build-up of fat within the liver that can lead to liver damage.
- Often occurs with obesity, diabetes, high blood pressure, or high cholesterol.
- The most common liver disease in Canada and occurs in up to 25% of the population.
- Usually cared for by healthcare providers in your family doctor's office.

What is the NAFLD patient pathway?

It is a map for you and your healthcare providers to follow. It makes sure the care you are getting for NAFLD is safe and helpful in managing your symptoms.

You and your healthcare providers may modify the pathway to best suit your healthcare needs.

If symptoms cannot be managed over time, you and your healthcare providers may decide a referral to a specialist would be helpful.

1. Check your symptoms

- Abnormal bloodwork or liver test results
- Fatty liver seen on an ultrasound

2. Explore possible causes of liver problems

- Review all medicines, herbals, and supplements you are taking
- Review your use of alcohol
- Make the changes recommended by your healthcare providers, then you liver tests will be repeated

3. Tests that may be done

- Blood tests to check for other causes of liver disease
- Blood tests to check for other conditions that can be associated with NAFLD (e.g. diabetes)

4. Assess risk of severe liver damage (scarring of the liver)

- Based on your blood test results
- If higher risk, you may be referred to a specialist for further assessment
- If lower risk, you are your healthcare providers will work together to reduce your risks of liver damage and other health problems.

5. Reduce your health risks

- Exercise
- Make changes to your diet
- Lose weight, if you need to
- Limit alcohol use
- Complete screening for heart disease, high blood pressure, diabetes, and high cholesterol, and treat, as required
- Redo blood tests every 2-3 years to monitor risk for severe liver damage

6. Once you find something that works for you, stick with it

You may need to keep trying other options to find out what works best to manage your symptoms.

7. Talk to your primary care provider about being referred to a specialist if:

- Your blood tests suggest you have higher risk of severe liver damage.
- You and your healthcare providers identify concerning symptoms or test results.

Most people with NAFLD do not develop severe liver damage. Ongoing monitoring is important because NAFLD can cause serious health problems in some people. If you are concerned about your liver health, ask your primary care provider.

Resources

1. Canadian Liver Foundation
   - liver.ca

2. Nutrition Information
   - https://www.hsph.harvard.edu/nutritionsource/

3. Healthy Eating Plate
   - https://www.hsph.harvard.edu/nutritionsource/healthy-eating-plate/