Primary Care Management Pathway
Non-Alcoholic Fatty Liver Disease

Background

Primary care management pathways are being developed by specialist and primary care groups to support the management of common, non-urgent conditions for which long wait times to specialty care currently exist. The pathways will help identify patients with high-risk features and facilitate early referral to specialists as needed.

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease in Canada, occurring in up to 25% of the population. It is often associated with obesity, diabetes and/or hyperlipidemia, and results from accumulation of fat (triglycerides) within the liver cells, which can lead to liver damage. NAFLD is an increasingly common indication for liver transplantation and cause of liver cancer in North America. Therefore, the goal is to identify people with NAFLD who have developed significant liver fibrosis in order to initiate cancer surveillance and variceal screening.

Defining condition and/or other important definitions

NAFLD refers to a group of liver conditions that exist under the same umbrella: simple fatty liver (steatosis), non-alcoholic steatohepatitis (NASH), fatty liver with liver fibrosis (liver scarring), and fatty liver with advanced liver fibrosis/cirrhosis.

The clinical care pathway facilitates identification of people with NAFLD who are more likely to have advanced scarring and therefore potentially benefit from specialist referral. The pathway employs bloodwork-based tests to assess a patient for high risk or low risk of significant liver scarring based on calculating the **FIB-4 score**.

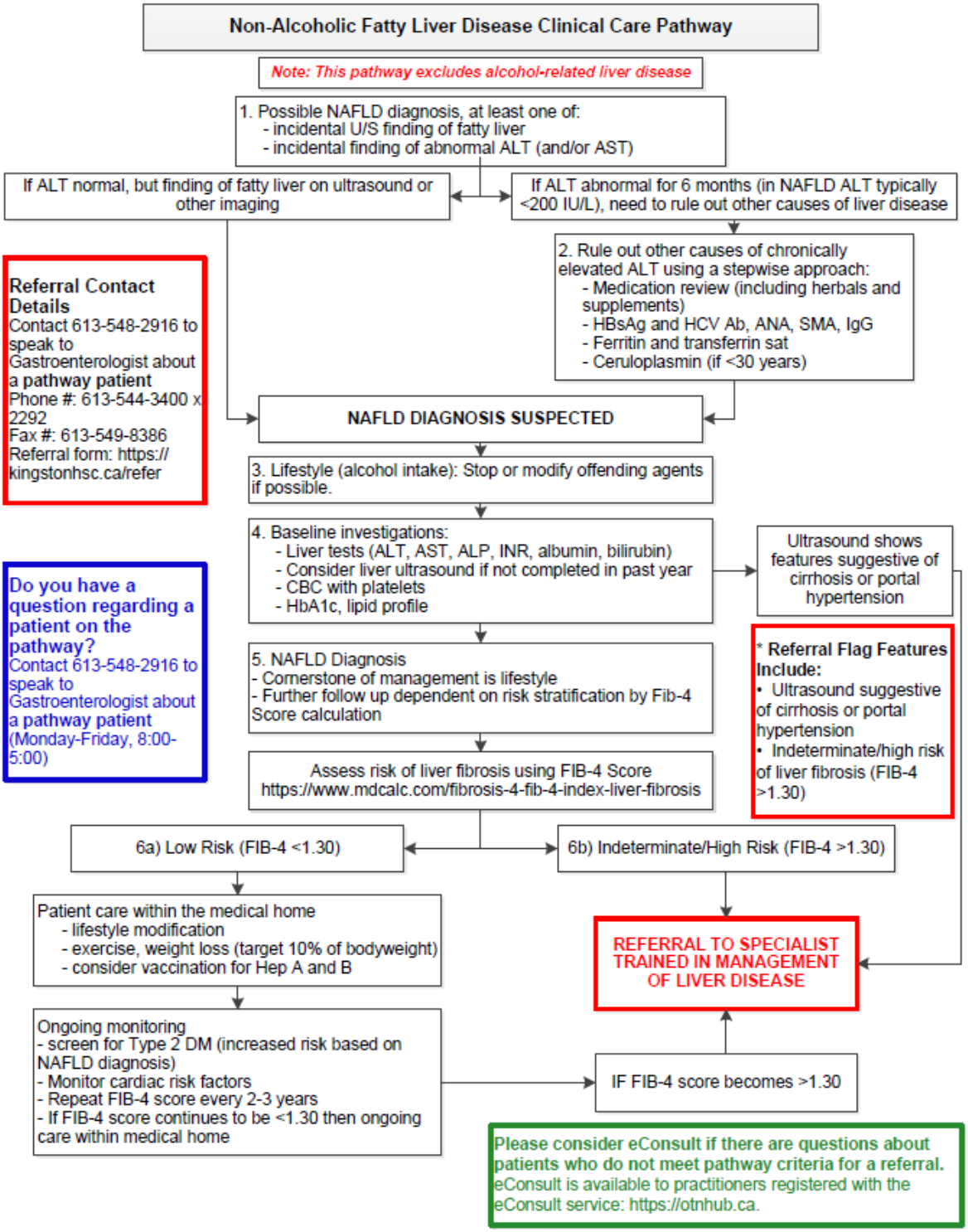
FIB-4 Score = Age in Years x AST level (U/L) / Platelet Count (10^9/L) x √ALT level (U/L)
(*This formula is readily accessible as an online calculator:
www.mdcalc.com/fibrosis-4-fib-4-index-liver-fibrosis)

The FIB-4 score has a diagnostic accuracy of 0.84 (AUROC) for the identification of advanced fibrosis (Xiao, 2017). A FIB-4 score of <1.3 essentially rules out significant liver fibrosis. A FIB-4 score over 1.3 could potentially indicate presence of liver fibrosis and warrants further evaluation.

Patient information

It is possible that your patient and/or their family member may express a desire for additional information about the primary care management pathway and their role or experience throughout the process of being on a pathway. Additional information for patient education has been provided in “Appendix B – Patient Information”.

Primary Care Management Pathway – Clinical Flow Diagram
Non-Alcoholic Fatty Liver Disease



Appendix A – Expanded Detail

Possible NAFLD Diagnosis

NAFLD diagnosis should be considered for patients with **one or more** of the following:

- Abnormal liver tests (persistent elevation of serum ALT; usually ALT <200)
- Ultrasound finding of fatty liver

Risk factors for NAFLD include obesity, type 2 diabetes, hyperlipidemia and metabolic syndrome. Patients with NAFLD will not necessarily have elevated liver enzymes and will not necessarily have fatty liver documented on an ultrasound report.

The pathway is not designed for use with patient with significant alcohol consumption (>14 drinks/week for males, >9 drinks/week for females). Counsel patients to reduce their alcohol consumption for 6-8 weeks and then repeat ALT at that time. If ALT remains abnormal then use of this pathway is appropriate.

Rule Out Other Causes of Elevated ALT

For patients with a chronically elevated ALT (>6 mos) **other causes must be ruled out**.

Review and address excess alcohol use (>14 drinks/week for males, >9 drinks/week for females)

Medication Profile Review

- Identify potential causes of abnormal liver tests including herbal preparations and health supplements and medications (this pathway is **not intended for patients on amiodarone, methotrexate, tamoxifen—they should be referred for further fibrosis assessment).**
- Any new or recently prescribed medications, over the counter or herbal/natural product may be implicated.
- If abnormal ALT correlates with a new medications or recent dose increase then consider stopping or modifying the offending agent if possible, then repeat liver enzymes in 3-6 months.

Hepatitis B and C Screening

- HBsAg: If positive, refer to hepatology.
- HCV Ab: If positive, order HCV RNA (PCR). If HCV RNA is positive, then refer to hepatology.

Other Testing (if abnormal ALT >6 months).

- ANA, anti-smooth muscle antibody, IgG (for autoimmune hepatitis). The higher the titer, the more significant the test results may be.
    - ANA (>1:80) and/or smooth muscle antibody (>1:20 titer) **and** elevated IgG may suggest autoimmune hepatitis and warrants consideration for referral to hepatology
- Ferritin and iron/TIBC
    - Note: Ferritin is often significantly elevated in NAFLD but transferrin saturation is typically <50%. These NAFLD patients do not have iron overload.
    - If ferritin is elevated and % transferrin saturation is >50% then consider doing genetic testing for hemochromatosis which can be ordered through Life Labs at no cost to the patient. If genetic testing is negative then it is unlikely the patient has genetic hemochromatosis.
- Note: In the routine evaluation of abnormal liver tests **abdominal MRI and/or CT scan or seldom useful and should not be ordered routinely.**

If work-up suggests a non-NAFLD diagnosis, consider appropriate referral to specialist trained in managing liver disease.

If work-up for other causes is negative, NAFLD diagnosis is strongly suspected based on risk factors, elevated liver enzymes and/or ultrasound findings.

NAFLD Baseline Investigations

There are certain laboratory tests outlined in the baseline investigation section of the NAFLD pathway that are accompanied with a cost to the patient if the test is requested and administered at a community medical laboratory. To ensure that cost is not a barrier to patient care, Kingston Health Sciences Centre has **developed a unique laboratory requisition to be used only for baseline investigations as outlined on the NAFLD pathway**.

The unique laboratory requisition is meant to be completed by referring primary care physicians for patients who are following the NAFLD pathway and would prefer to have these tests completed at KHSC (KGH: Armstrong 1 or HDH: Jeanne Mance 5) at no cost to the patient. Patients may still prefer to have these tests completed at a community medical laboratory and pay for the associated costs.

This requisition can be accessed and downloaded by primary care physicians at: https://kingstonhsc.ca/refer/gastroenterology-1.

NAFLD baseline investigations include:
Liver tests (ALT, AST, ALP, bilirubin, INR, albumin), CBC, platelets, lipid profile, HbA1c, and ultrasound (if not done in past year).

A diagnosis of NAFLD can be assumed if no other causes of fatty liver/elevated liver enzymes have been identified, even in the presence of a normal ultrasound.

Assess risk for liver fibrosis using the FIB-4 score

- A FIB-4 calculator is available at www.mdcalc.com/fibrosis-4-fib-4-index-liver-fibrosis

NAFLD with Low Risk of Fibrosis (FIB-4 <1.3)

Lifestyle modifications are the cornerstone of optimal management of NAFLD.

Exercise	30 minutes of moderate activity 4 times/week (can be in 10-15 min sessions).
Diet	Lower in carbohydrates and sugars (especially fructose) Higher in protein and vegetables Avoid saturated fats, simple carbohydrates and sweetened drinks
Weight loss	Target weight loss of 5-10% from lifetime maximum weight over 6 months
Modify cardiac risk factors where appropriate	NAFLD patients are at higher risk of developing cardiac disease (3-5 times more likely to suffer a heart attack or stroke) 1. Statins for hyperlipidemia Patient with increased LDL cholesterol should be strongly considered for statin therapy. ***In general, statins are safe in patients with liver disease.*** However, ALT monitoring can be considered in NAFLD patients (3 months after starting therapy) and if the ALT doubles, stopping should be considered and a different lipid lowering agent tried. 2. Screen for type 2 diabetes Patients with NAFLD who are not diabetic are at increased risk of developing diabetes in the future. 3. Optimize diabetes control 4. Treat hypertension 5. Encourage smoking cessation
Alcohol intake	Risk of alcohol consumption for patients with NAFLD is unknown. As a general guideline: • NAFLD patients with low-risk of significant liver fibrosis (FIB-4<1.3) up to 4-5 drinks/week for men and 3-4 drinks/week for women may be acceptable • Abstinence is recommended for patients with cirrhosis or advanced fibrosis

Coffee: There is substantial evidence that coffee consumption (2-3 cups per day) may be beneficial for patients with fatty liver.

Vitamin E: Vitamin E is an antioxidant that **may** be beneficial in patients with NAFLD **without cirrhosis** and **without diabetes** (studies are ongoing—has only been studied in patient with biopsy proven NASH). The recommended dose if one is going to try it is 400-800 IU daily.

Patients should be counselled that the epidemiological evidence suggesting possible increased cardiovascular risk and prostate cancer risk with vitamin E therapy is weak.

Consider immunizing NAFLD patients for hepatitis A and B to avoid superimposed preventable liver disease.

Ongoing Monitoring

Re-calculate FIB-4 score every 2-3 years to reassess the risk of significant liver fibrosis. Continue management in the medical home if FIB-4 score remains <1.3. Consider referral to specialty care if FIB-4 score increased to above 1.3.

NAFLD with Indeterminate/High Risk of Fibrosis (FIB-4 >1.3)

For patients with FIB-4 >1.3, consider referral to a specialist trained in the management of liver disease.

When Should I Refer my Patient to a Specialist?

1. **If FIB-4>1.3 indicated indeterminate or advanced fibrosis**
2. **Ultrasound has features suggesting cirrhosis or portal hypertension**

Appendix B – Patient Information

Please note: This information is intended to be given to the patient, either as a handout or in the form of a conversation with their primary care provider.

What is nonalcoholic fatty liver disease (NAFLD)?

- NAFLD is a build of fatty tissue in the liver.
- It tends to be associated with obesity, or can also occur in patients with increased fatty tissue around the waist line and those who consume more sugary foods and drinks.
- There is an association between NAFLD and diabetes, high cholesterol and high blood pressure.
- It occurs in approximately 25% of Canadians.

How will my doctor follow my condition?

- Majority of patients with NAFLD are managed by their primary care provider.
- Your primary care provider will do blood work to monitor your liver enzymes and to monitor for potential damage to the liver.
- They will help counsel you on weight loss and dietary changes. They will also monitor for diabetes, high cholesterol and high blood pressure and manage these conditions as needed.

You are enrolled on the NAFLD primary care pathway. What does this mean?

- The pathway helps to provide a map to ensure the care you are receiving is safe and helpful in managing your condition.
- Patients can be enrolled on the pathway for several months, or possibly even for years.
- Your primary care provider will ask you questions about medications or supplements and your alcohol use. They may ask you to do blood work to rule out other conditions affecting the liver.
- They will do blood tests to check if you are at risk of having severe liver damage.
- If you are at higher risk, then you may be referred to a specialist for further assessment.
- If you are low risk, then your primary care team will make a health to help reduce your risk of progression and improve your health.

Additional resources

The Canadian Liver Foundation: Fatty Liver Disease. 2021
https://www.liver.ca/patients-caregivers/liver-diseases/fatty-liver-disease/

Mediterranean-Style of Eating. Alberta Health Services. 2017
https://www.albertahealthservices.ca/assets/info/nutrition/if-nfs-mediterranean-style-of-eating.pdf

Appendix C – Endnotes

Chalasani N et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. *Hepatology*. (2018) 67:328-57

EASL. EASL-EASD-EASO clinical practice guidelines for the management of non-alcoholic fatty liver disease. *Journal of Hepatology*. (2016) 64:1388-1402

McPherson S et al. Simple non-invasive fibrosis scoring systems can reliably exclude advanced fibrosis in patients with non-alcoholic fatty liver disease. *Gut*. (2010) 59: 1265-69

NAFLD Primary Care Pathway. Alberta Health Services and Primary Care Networks. 2021. https://www.albertahealthservices.ca/assets/about/scn/ahs-scn-dh-pathway-nafld.pdf

Xiao G et al. Comparison of laboratory tests, ultrasound, or magnetic resonance elastography to detect fibrosis in patient with non-alcoholic fatty liver disease: A meta-analysis. *Hepatology* (2017) 66: 1486-1501