

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

1. Focused summary of NAFLD relevant to primary care

NAFLD (non-alcoholic fatty liver disease) is the most common liver disease in Canada, occurring in up to 25% of the population. NAFLD is often associated with obesity, diabetes and/or hyperlipidemia, and results from accumulation of fat (triglycerides) within liver cells, which in turn can lead to liver damage. The term NAFLD actually refers to a group of liver conditions that exist under the same umbrella, including: simple fatty liver (ie. steatosis), non-alcoholic steatohepatitis (ie. NASH), fatty liver with liver fibrosis (ie. 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 (Rinella ME. Nat Rev Gastro Hepatol 2016). Importantly, increasing liver fibrosis stage in people with NAFLD is associated with an exponential increase in risk of liver-related mortality (Dulai PS. Hepatology 2017), which appears to be most pronounced in people with NAFLD who have developed moderate to severe liver fibrosis. Consistent with this, NAFLD has become an increasingly common indication for liver transplantation and liver cancer in North America. Therefore, the identification of people with NAFLD who have developed significant liver fibrosis has become key for designing strategies to help us better manage these individuals to try to prevent progressive liver fibrosis.

Given how common NAFLD is within the Canadian population, specialist referral for all NAFLD patients is not tenable. Therefore, we have developed this clinical care pathway to help facilitate identification of people with NAFLD who are more likely to have significant liver scarring, and therefore would potentially benefit from specialist referral. This pathway employs non-invasive tests to assess a patient for the presence of liver scarring by using blood tests and liver stiffness assessment (measured using shear wave elastography; SWE). SWE is available to primary care physicians within the community for appropriate patients, and SWE reports will be generated by EFW Radiology using a standardized reporting form that clearly identifies patients as LOW or HIGH RISK. For patients who cannot attend SWE testing, please refer to the FIB-4 pathway.

Individuals identified through this pathway as having a HIGH RISK for having more advanced liver scarring should be referred to Hepatology Central Access and Triage (CAT) for care within a multidisciplinary medical team led by a liver specialist. Those identified within this pathway as LOW RISK for having significant liver scarring *at this time* are best managed within their primary care medical home supported by the attached management strategies and physician and patient focused resources. These LOW RISK patients can be placed by their primary care physician in a LOW RISK NAFLD Screening Program with repeat liver SWE testing performed every 3 years to assess for liver scarring progression to HIGH RISK that would potentially warrant referral to Hepatology CAT.

2. Checklist to guide your in-clinic review of your patient with NAFLD before possible referral to the NAFLD clinic

- Risk factor for NAFLD present (obesity, hyperlipidemia, metabolic syndrome and/or type 2 diabetes) and/or an ultrasound has confirmed fatty liver (steatosis).
- Identify medication and lifestyle factors that may be the cause or contribute to fatty liver and/or abnormal liver tests (eg. Excess alcohol consumption (> 2 drinks per day for males, and >1 drink per day for females), medications including corticosteroids, tamoxifen, methotrexate, amiodarone).
- If liver tests are abnormal (elevated ALT and/or AST (for > 6 months) order further investigations to rule out other causes of abnormal liver tests (chronic liver disease work-up - see list of suggested blood tests outlined below).
- Consider ordering SWE through EFW Radiology 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.
- 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)

3. Links to additional resources for physicians and patients

Calgary GI Division:

<http://www.calgarygi.com>

Alberta Healthy Living: Alberta Healthy Living Program provides education sessions and dietary counseling for Fatty Liver disease. This service is free of charge and is available at many locations around the city. To Register call: 403-943-2584 website:

www.albertahealthservices.ca/cdmcalgaryzone.asp

Canadian Liver Foundation:

<http://www.liver.ca>

NICE UK:

<https://www.nice.org.uk/guidance/ng49>

4. Clinical flow diagram with expanded detail

This AHS Calgary Zone pathway incorporates the most current evidence-based clinical guidelines for diagnosis and management of NAFLD, from both Gastroenterology and Primary Care literature:

Rinella ME and Sanyal AJ. Management of NAFLD: a stage-based approach. *Nature Reviews in Gastroenterology and Hepatology*. 11: 196-205, 2016.

Dulai *et al.* Increased risk of mortality by fibrosis stage in NAFLD: Systematic review and meta-analysis. *Hepatology*. 2017 Jan 28. doi: 10.1002/hep.29085. [Epub ahead of print]. PMID: 28130788

<https://www.guideline.gov/summaries/summary/37629/the-diagnosis-and-management-of-nonalcoholic-fatty-liver-disease-practice-guideline-by-the-american-association-for-the-study-of-liver-diseases-american-college-of-gastroenterology-and-the-american-gastroenterological-association>

Festi D. *et al.* Review article: the diagnosis of non-alcoholic fatty liver disease – availability and accuracy of non-invasive methods. *Aliment Pharmacol Ther* 2013; 37: 392–400

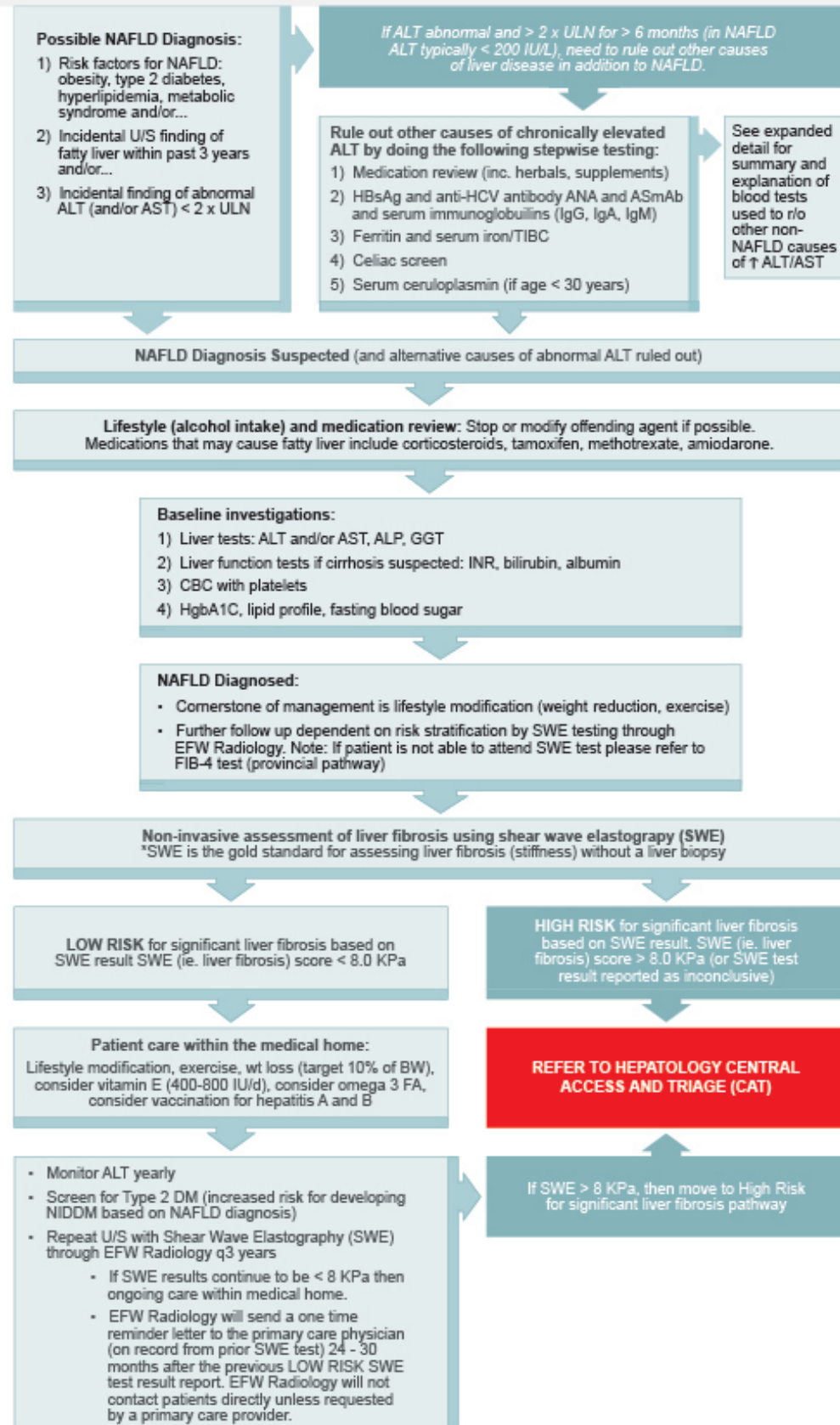
Cassinotto C. *et al.* Liver Stiffness in Nonalcoholic Fatty Liver Disease: A Comparison of Supersonic Shear Imaging, FibroScan, and ARFI With Liver Biopsy. *HEPATOLOGY* 2016; 63:1817-1827.

The following is a best-practice clinical pathway using SWE for management of NAFLD in the primary care medical home, which includes a flow diagram and also an expanded explanation for management suggestions below:

NON-ALCOHOLIC FATTY LIVER DISEASE PATHWAY

Specialist LINK | Local: 403.910.2551 | Toll free: 1.844.962.5465 (LINK) | www.specialistlink.ca

HEPATOLOGY CENTRAL ACCESS AND TRIAGE (CAT) REFERRAL | Fax: 403.944.6555



Flow Diagram: NAFLD Diagnosis and Management - Expanded Detail

- 1. Establish the diagnosis of NAFLD** as defined above through history (risk factors: type 2 diabetes, hyperlipidemia, metabolic syndrome; rule out excessive alcohol intake), physical examination (obesity), abnormal liver tests (persistent elevation of serum ALT; repeat ≥ 6 months; usually < 200 U/L) and/or ultrasound showing fatty liver.
- 2. Review of the patient's medication profile** to identify potential causes of abnormal liver tests including herbal preparations and health supplements (eg. green tea extract), and fatty liver (amiodarone, methotrexate, tamoxifen, valproic acid, corticosteroids). Any new or recently prescribed medication, over the counter or herbal/natural product may be implicated. Many medications can cause liver test abnormalities.
- 3. If increased ALT workup suggests a non-NAFLD diagnosis, consider appropriate referral to Hepatology CAT.**

- 4. If workup for increased ALT is negative, and NAFLD diagnosis is strongly suspected based on risk factors and ultrasound findings, do non-invasive assessment of liver fibrosis with shear wave elastography [SWE].**

*SWE is the gold standard for assessing liver stiffness (a measure of liver scarring) without a liver biopsy and this test is now available through EFW Radiology and can be ordered on an EFW Radiology Liver Programs Requisition under the heading "NAFLD".

- **HIGH RISK** for significant liver fibrosis suspected (SWE value > 8.0 KPa) referral to NAFLD clinic through Hepatology Central Access and Triage (CAT) recommended.
- **LOW RISK** for significant liver fibrosis suspected (SWE value ≤ 8.0 KPa) management of NAFLD in medical home recommended, 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).

*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.

- If evidence for progression to HIGH RISK for significant liver fibrosis (SWE value > 8.0 KPa) then referral to NAFLD clinic through Hepatology CAT recommended.

- 5. Lifestyle management considerations for NAFLD patients within the medical home:**

- Lifestyle modifications are the cornerstone of optimal management of NAFLD:
 - (A) Exercise: 30 minutes of moderate activity 4 times/week [can be in 10 - 15 minute sessions; moderate exercise is when someone feels a little tired, a little short of breath, are sweating, but can still hold a conversation].
 - (B) Diet: lower in carbohydrates and sugars (especially fructose), and higher in protein and vegetables. Avoid saturated fats, simple carbohydrates and sweetened drinks.
 - (C) Target weight loss of $\sim 10\%$ of body weight over 6 months.

- Modify cardiac risk factors where appropriate:
 - Statins for hyperlipidemia. NAFLD patients are at higher risk for developing cardiac disease (3-5 times more likely to suffer a heart attack or stroke). Therefore, patients with increased LDL cholesterol should be strongly considered for statin therapy. *In general, statin therapy is safe in patients with liver disease.* However, ALT monitoring can be considered in NASH patients (3 months after starting therapy) and if the ALT doubles, it should be stopped and a different lipid lowering agent tried.
 - Optimize diabetes control. Patients with NAFLD who are currently not diabetic are at increased risk for developing diabetes in the future.
 - Treat hypertension
 - Encourage smoking cessation.
- Alcohol intake:
 - For NAFLD patients *without* significant liver fibrosis (ie. “Low Risk” NAFLD?), up to 4-5 drinks per week for men and 3-4 drinks per week for women is acceptable.
 - For NAFLD patients *with* significant liver fibrosis (SWE > 8 KPa) alcohol intake ranges outlined above should be cut in half.
 - For NAFLD patients *with cirrhosis*, complete abstinence from alcohol is recommended.
- Encourage coffee consumption (preferably filtered) \geq 2-3 cups per day.
- Consider immunizing NAFLD patients for hepatitis A and B to avoid superimposed preventable liver disease.

6. Therapeutic considerations for NAFLD patients within the medical home:

- Vitamin E: Vitamin E is an antioxidant, which *may* be beneficial in NAFLD (studies are ongoing). The recommended dose of Vitamin E is 400-800 IU/day. Patients should be counselled about the weak epidemiological evidence suggesting possible increased cardiovascular and prostate cancer risk with vitamin E therapy.
- Omega 3 fatty acid (FA) *may* be of benefit for patients with high serum triglycerides (may have an anti-inflammatory effect) (Not OMEGA 3-6-9). Food sources are best, but supplements can also be effective. The supplement should contain a combination of EPA and DHA. In some studies omega 3 FA have been shown to help decrease hepatic steatosis and triglyceride levels. For patients with high serum triglyceride levels and NAFLD the dose of Omega 3 FA would be 2 grams/day if the decision is to try this medication for treating NAFLD.

Summary and explanation of blood tests used to R/O other non-NAFLD causes of ↑ ALT/AST:

- Determine whether only serum transaminases (ALT/AST) are elevated. Perform medication review to rule out medications or herbal supplements as potential cause. ALT/AST can be elevated in cholestatic liver diseases where serum ALP and GGT will be elevated. If ALP and GGT are elevated need to rule out intrahepatic bile flow obstruction (Primary biliary cholangitis [PBC]; anti-mitochondrial antibody [AMA] testing and any titer is significant) or extrahepatic biliary obstruction (U/S of biliary tree). If AMA is positive consider referral to hepatology.
- HB_sAg: if positive then infected with hepatitis B. If positive consider referral to hepatology.
- anti-HCV antibody: if positive do a HCV RNA test through Prov Lab. If negative then has cleared the HCV virus. If positive then infected with HCV. If positive consider referral to hepatology.
- 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 warrants consideration for a referral to hepatology.
- Serum ferritin and iron/TIBC for possible hemochromatosis: *Note: ferritin levels are often elevated in NAFLD (can be > 1000), but transferrin saturation usually <50%.* If ferritin elevated and % transferrin saturation (fasting) is > 50% in females and > 60% in males then consider doing genetic testing for hemochromatosis through molecular laboratory. If genetic testing results suggest increased risk for hemochromatosis consider referral to hepatology for management.
- Celiac screen: Celiac disease can cause abnormal liver tests.
- Ceruloplasmin for Wilson's disease (if age < 30 years). *Note: In Wilson's disease the ceruloplasmin level is typically very low.* If serum ceruloplasmin level is low then consider referral to hepatology for management.

Note: In the routine evaluation of abnormal liver tests abdominal MRI and/or CT are seldom useful and should not be routinely ordered.