1. Possible NAFLD diagnosis (at least one of)
   - Incidental ultrasound finding of fatty liver
   - Incidental finding of abnormal alanine transaminase (ALT)

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

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 (if not completed within one year)
   - HBsAg and HCV antibody, ANA, anti-actin/anti-smooth muscle antibody (depending on local availability), immunoglobulins (IgG, IgA, IgM)
   - Ferritin and iron/TIBC
   - Celiac screen
   - Serum ceruloplasmin (if age <30 years)

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

3. Lifestyle and medication review
   - Complete medication review if not already done in Step 2. Stop or modify offending agent, if possible.
   - Review and address alcohol use.

4. Baseline investigations
   - Liver tests: ALT and AST, ALP, GGT
   - Liver function tests if cirrhosis suspected: INR, bilirubin, albumin
   - CBC with platelets
   - HbA1C, lipid profile

5. NAFLD diagnosed
   - Further follow-up is dependent on risk stratification by FIB-4 score calculation

6. Assess risk of liver fibrosis using FIB-4 index
   - www.mdcalc.com/fibrosis-4-fib-4-index-liver-fibrosis

6a. Low risk (FIB-4 Score <1.30)
   - Exercise and weight loss (target 10% of body weight)
   - Improve diet (increase fibre, lower sugars and saturated fats, choose lean proteins)
   - Limit alcohol intake
   - Consider vaccination for hepatitis A and B
   - Screen for Type 2 diabetes mellitus, hypertension, and hyperlipidemia. Treat/ optimize therapy.
   - Re-calculate FIB-4 score every 2-3 years (order ALT, AST, platelets)
   - If FIB-4 score continues to be <1.30, continue care within Medical Home

6b. Indeterminate/High risk (FIB-4 Score ≥1.30)
   - Refer to Specialist trained in management of liver disease

   - If FIB-4 Score becomes ≥1.30
NAFLD PATHWAY PRIMER

- NAFLD (non-alcoholic fatty liver disease) results from liver damage due to the accumulation of fat (triglycerides) within liver cells.
- It is the most common liver disease in Canada, occurring in up to 25% of the 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 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:

\[
\text{FIB-4 score} = \frac{\text{Age in Years} \times \text{AST level (U/L)}}{\text{Platelet Count (10}^9\text{/L})} \times \sqrt{\text{ALT level (U/L)}}
\]

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

<table>
<thead>
<tr>
<th>Checklist to guide in-clinic review of your patient with NAFLD</th>
</tr>
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<tbody>
<tr>
<td>□ Finding of fatty liver on ultrasound or abnormal ALT</td>
</tr>
<tr>
<td>□ If ALT &gt;2x ULN for &gt;6 months, order further investigations to rule out other causes of liver disease in addition to NAFLD (see algorithm Box 2)</td>
</tr>
<tr>
<td>□ Identify and address medication and lifestyle factors that may cause or contribute to fatty liver or abnormal liver tests. For example, excess alcohol consumption (&gt;2 drinks per day for males and &gt;1 drink per day for females) or medications (e.g. amiodarone, methotrexate, tamoxifen, valproic acid, corticosteroids).</td>
</tr>
<tr>
<td>□ Complete baseline investigations (see algorithm Box 4)</td>
</tr>
<tr>
<td>□ Assess risk of liver fibrosis using the FIB-4 Index</td>
</tr>
<tr>
<td>□ If FIB-4 score &lt;1.3, continue to provide care in the Medical Home (see algorithm Box 6a)</td>
</tr>
<tr>
<td>□ If FIB-4 score ≥1.3, consider referral to a specialist trained in management of liver disease</td>
</tr>
</tbody>
</table>


EXPANDED DETAILS

1. Possible NAFLD diagnosis
   - 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).
       - NB – 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).
       - NB – patients with NAFLD will not necessarily have fatty liver documented on an ultrasound report (more than 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 per day for males, >1 drink per 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:
   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), 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. Visit https://www.albertahealthservices.ca/topics/Page11977.aspx.
      - 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
  o 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.
  o If fasting ferritin elevated and % 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.
  o 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.
  o Excess alcohol consumption (>2 drinks per day for males, >1 drink per day for females) may contribute to abnormal liver tests.
  o 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)
  o 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)
  o 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 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.
   - A free FIB-4 calculator is available at: [https://www.mdcalc.com/fibrosis-4-fib-4-index-liver-fibrosis](https://www.mdcalc.com/fibrosis-4-fib-4-index-liver-fibrosis).

a) **Low risk (FIB-4 <1.30)**

**Patient care within the 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). Moderate exercise is when someone is a little tired, is a little short of breath, is sweating, but can still hold a conversation (e.g. brisk walking, biking, yard work). See [Canadian Physical Activity guidelines](https).
  - **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](https) and [sample menus](https).

- 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 three 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. As a guideline:
    - 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 per week for men and 3-4 drinks per week for women.
    - Abstinence is recommended for patients with cirrhosis.

- There is inconclusive evidence that 2-3 cups of coffee per 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**

- Re-calculate FIB-4 score every 2-3 years to reassess risk of significant liver fibrosis. Continue management in Medical Home if FIB-4 score remains <1.3 or consider referral for specialty care, outlining history and care provided to date if FIB-4 score increases to above 1.3.

**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 400-800IU/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) + 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 FA supplements have an anticoagulant effect in doses >3 grams per day (equivalent to a baby aspirin). Consider other medications and disease states before recommending, and monitor as appropriate.

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

- For patients with FIB-4 ≥1.30, consider referral to a specialist trained in the management of liver disease.

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

This pathway was reviewed and revised under the auspices of the DHSCN in 2020 by a multi-disciplinary team led by family physicians and gastroenterologists. For more information, contact the DHSCN at Digestivehealth.SCN@ahs.ca.

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 June 2023. However, we welcome feedback at any time. Please email comments to Digestivehealth.SCN@ahs.ca.

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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
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). Visit www.albertanetcare.ca/documents/Getting-Started-Advice-Requests-FAQs.pdf for more information.
- Non-urgent telephone advice connects family physicians and specialists in real time via a tele-advice line. Family physicians can request non-urgent advice from a gastroenterologist:
  - In the Calgary Zone at specialistlink.ca or by calling 403-910-2551. This service is available from 8:00 a.m. to 5:00 p.m. Monday to Friday (excluding statutory holidays). Calls are returned within one hour.
  - In the Edmonton Zone by calling 1-844-633-2263 or visiting www.pcnconnectmd.com. This service is available from 9:00 a.m. to 6:00 p.m. Monday to Thursday and 9:00 a.m. to 4:00 p.m. Friday (excluding statutory holidays and Christmas break). Calls are returned within two business days.

<table>
<thead>
<tr>
<th>Resources and References</th>
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## PATIENT RESOURCES

### Information

<table>
<thead>
<tr>
<th>Description</th>
<th>Website</th>
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</table>
| General information on NAFLD (Canadian Liver Foundation)                                     | https://www.liver.ca/patients-caregivers/liver-diseases/fatty-liver-disease/  
https://www.liver.ca/liver-health-month-2018-checkyourengine/                                   |
| Resources on healthy eating (Alberta Health Services)                                        | https://www.albertahealthservices.ca/nutrition/Page11115.aspx                                                                             |
| AHS patient handout on healthy eating for weight management                                 | https://www.albertahealthservices.ca/assets/info/nutrition/if-nfs-healthy-eating-weight-management.pdf                                    |
| AHS patient handout with sample menus for healthy eating                                     | https://www.albertahealthservices.ca/assets/info/nutrition/if-nfs-sample-meal-plans-for-healthy-eating.pdf                              |
| AHS patient handout on omega 3 fatty acids                                                  | https://www.albertahealthservices.ca/assets/info/nutrition/if-nfs-omega-3%20-fats-for-heart-health.pdf                                 |

### Services Available

<table>
<thead>
<tr>
<th>Description</th>
<th>Website</th>
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</thead>
<tbody>
<tr>
<td>Services for patients with chronic conditions, including how to achieve a healthy weight  (Alberta Healthy Living Program - AHS)</td>
<td><a href="https://www.albertahealthservices.ca/info/page13984.aspx">https://www.albertahealthservices.ca/info/page13984.aspx</a></td>
</tr>
<tr>
<td>Supports for working towards healthy lifestyle goals and weight management (Weight Management – AHS)</td>
<td><a href="https://www.albertahealthservices.ca/info/Page15163.aspx">https://www.albertahealthservices.ca/info/Page15163.aspx</a></td>
</tr>
<tr>
<td>Services for people who are struggling with substance use, addiction, or a mental health problem (Addiction and Mental Health Services – AHS)</td>
<td><a href="https://www.albertahealthservices.ca/amh/Page14063.aspx#details-panel14066">https://www.albertahealthservices.ca/amh/Page14063.aspx#details-panel14066</a></td>
</tr>
</tbody>
</table>
| Toll free confidential phone service which provides alcohol, tobacco, other drugs and problem gambling support, information and referral to services. The Addition Helpline operates 24 hours a day, seven days a week (Addiction Helpline – AHS) | 1-866-332-2322  
https://www.albertahealthservices.ca/findhealth/Service.aspx?id=1008399&serviceAtFacilityID=1047128                  |
A Patient’s Pathway for Managing NAFLD

What is NAFLD?

- NAFLD stands for Non-Alcoholic Fatty Liver Disease.
- NAFLD is a build-up of fat within the liver that can lead to liver damage.
- NAFLD often occurs with obesity, diabetes, high blood pressure, and/or high cholesterol.
- NAFLD is the most common liver disease in Canada and occurs in up to 25% of the population.

NAFLD is usually cared for by healthcare provider(s) in your family doctor’s office.

What is the NAFLD patient pathway?

It is a map for you and your healthcare provider(s) to follow. It makes sure the care you are receiving for NAFLD is safe and effective.

You and your healthcare provider(s) may modify the pathway to best suit your healthcare needs.

If your NAFLD cannot be managed over time, you and your healthcare provider(s) may decide a referral to a specialist would be helpful.

Findings of possible liver problems suggesting NAFLD

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

Explore possible causes of liver problems other than NAFLD

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

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)

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 and your healthcare provider(s) will work together to reduce your risks of liver damage and other health problems

Reduce your health risks (see over for details)

- 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 to 3 years to monitor risk for severe liver damage

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.

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

You may need to keep trying other options to find what works best to improve your health.
What do I need to know about NAFLD?

Working through the NAFLD patient pathway can take several months or be ongoing for years:

- Your healthcare provider(s) will ask you questions about your health, review medicines and other treatments you are taking, and review your use of alcohol. They may make some changes with you.
- They may suggest certain tests to look for other causes of liver disease and use your blood tests to check your risk of having severe liver damage.
- If you are at higher risk, you may be referred to a specialist for further assessment.
- If you are at lower risk, you and your healthcare provider(s) will make a plan to reduce your risk and improve your health.
- This plan will address your liver health and other health conditions like diabetes, high blood pressure, high cholesterol, and heart disease risk that may occur at the same time.
- Your healthcare provider(s) will recheck your blood tests every 2-3 years to monitor your risk of severe liver damage.

To manage your condition:

- Exercise moderately for 150 minutes/week (can be 10-15 minute sessions). Moderate exercise is when you are a little tired, a little short of breath, and you are sweating, but you can still hold a conversation.
- Improve your diet. Choose more high-fibre carbohydrates, less refined starches, and less added sugars. Avoid saturated fats. Choose lean meats and plant-based proteins.
- Lose weight if you need to (target 10% of body weight).
- Limit alcohol use to no more than 4-5 drinks/week for men and 3-4 drinks/week for women.
- Drinking up to 2-3 cups of coffee/day may be helpful.

Seeing a specialist is only recommended if:

- Your blood tests suggest you have a higher risk of severe liver damage.
- Concerning symptoms are identified by you and your healthcare provider.

You can find more information in these great resources:

Canadian Liver Foundation [www.liver.ca](http://www.liver.ca)

AHS nutrition handouts [www.ahs.ca/nutritionhandouts](http://www.ahs.ca/nutritionhandouts)

Write any notes or questions you may have here:

If you have any feedback about this patient pathway, contact us at Digestivehealth.SCN@ahs.ca.