
FAMILY
MEDICINE
SUMMIT
2019
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Rimrock Resort Hotel | Banff, AB
Alberta College of
Family Physicians

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

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Conflict of Interest Disclosure

- Faculty: Kelly Burak
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  - Other: Office of CME&PD has received an unrestricted grant from the *Cal Wenzel Chair in Hepatology* to support development of CME materials for the Specialist Link NAFLD Pathway

I was not involved in the development of the Specialist Link NAFLD pathway…
but I endorse its use

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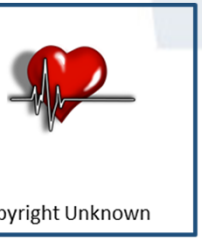

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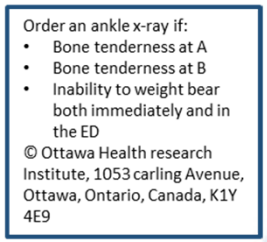

Order an ankle x-ray if:
- Bone tenderness at A
- Bone tenderness at B
- Inability to weight bear both immediately and in the ED

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Objectives

By the end of this session, participant will learn to:

1. Recognize NAFLD as the most common liver disease in Canada
2. Identify common causes of secondary hepatic steatosis
3. Identify risk factors associated with NAFLD
4. Offer appropriate workup in patients suspected to have NAFLD
5. Identify population at highest risk for complications → know when to refer
6. Have an approach managing low risk NAFLD in primary care medical home
7. Refer to current practice guideline in diagnosis and management of NAFLD

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NON-ALCOHOLIC FATTY LIVER DISEASE PATHWAY

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www.specialistlink.ca

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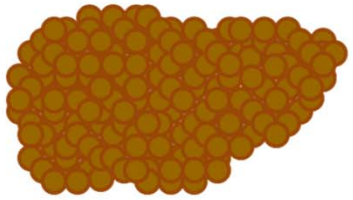
Normal liver

Acute Hepatitis

Chronic Hepatitis

Cirrhosis



Decompensation

Malignancy

Causes of Cirrhosis

- Infectious = HBV, HCV
- Toxin = ETOH
- Metabolic = NAFLD
- Immune = AIH, PBC, PSC
- Genetic = HH, A1AT, WD

Image Source: HepAPPtology @kwburak

Definitions

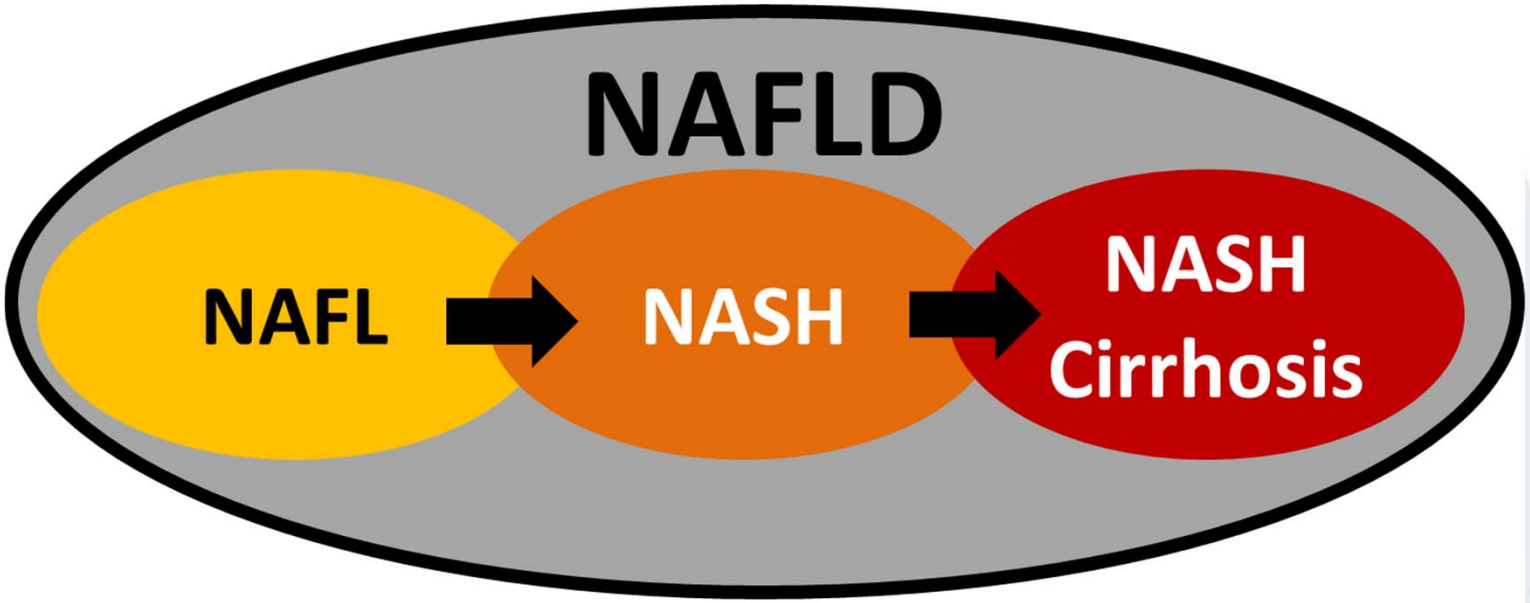


Image Source: HepAPPtology @kwburak

Case
Mrs. DF

Image Source:
https://www.imdb.com/title/tt0107614/mediaviewer/rm4228632064

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History

- 65-year-old retired nanny new to your practice
- elevation of liver test for 3 years
- asymptomatic, no history of jaundice or hepatitis
- overweight (75 kg)
- diet controlled diabetes for 10 years
- drinks alcohol socially and is a life-long nonsmoker
- traveled to Mexico 2 years ago with her husband
- Meds = atorvastatin (Lipitor) 10mg daily

Physical Exam

- Weight 75 kg, Height 5 feet (152 cm)
- BP 95/60, HR 90
- No stigmata of chronic liver disease
- Chest and cardiovascular exams normal
- Abdomen obese, soft and non-tender, with no hepatosplenomegaly or ascites
- Extremities showed no peripheral edema

Lab Tests

	[Normal Range]	2y ago	1y ago	now
ALT	[1-40 U/L]	**100**	**120**	**65**
AST	[8-32 U/L]	**100**	**140**	**95**
ALP	[30-115 U/L]	**95**	**115**	**230**
GGT	[8-35 U/L]	**200**	**350**	**300**
Bili	[0-24 umol/L]	**12**	**10**	**14**
Hemoglobin	[120-160 g/L]		**140**	**150**
WBC	[4-11 $x10^9$]		**7.0**	**6.0**
Platelets	[150-400 $x10^9$]		**180**	**145**
Cholesterol	[4.2-5.2 umol/L]			**7.2**
Fast glucose	[3.6-11.1 mmol/L]			**8.0**
HbA1C	[0.043-0.061]			**8.1%**

Ultrasound

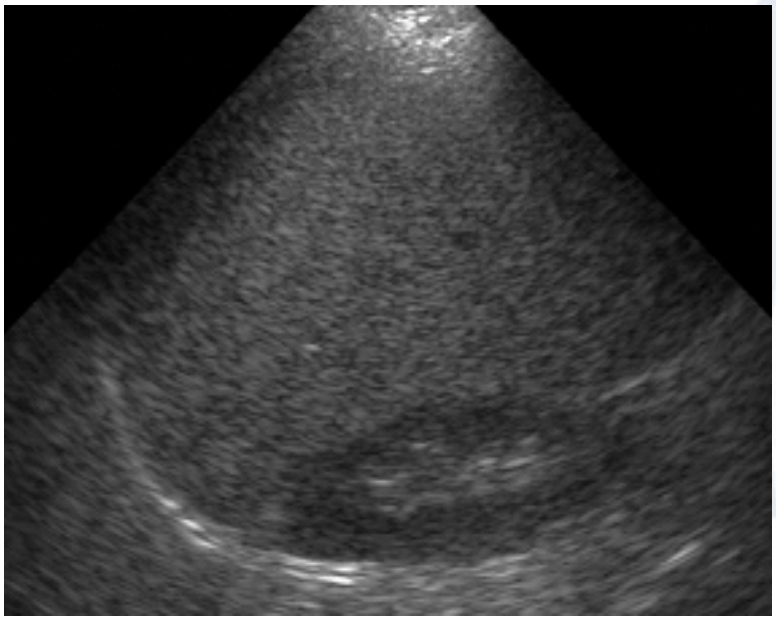


Image Source:
Courtesy Dr. Stephanie Wilson

Conclusion: The normal sized liver, with increased echogenicity, likely due to fatty infiltration. There is no dilatation of the biliary system. Other organs are unremarkable, although the spleen is at 15cm, which is the upper limit of normal.

NAFLD Risk Factors

#3

- Obesity
- Type 2 Diabetes
- Dyslipidemia
- Metabolic Syndrome (≥3)
  1) Waist >102 cm in men or >88 cm in women
  2) TG ≥ 1.7 mmol/L
  3) HDL <1.0 mmol/L in men or <1.3 mmol/L in women
  4) sBP ≥ 130 mmHg or dBP ≥ 85 mmHg
  5) fasting glucose ≥ 6.1 mmol/L

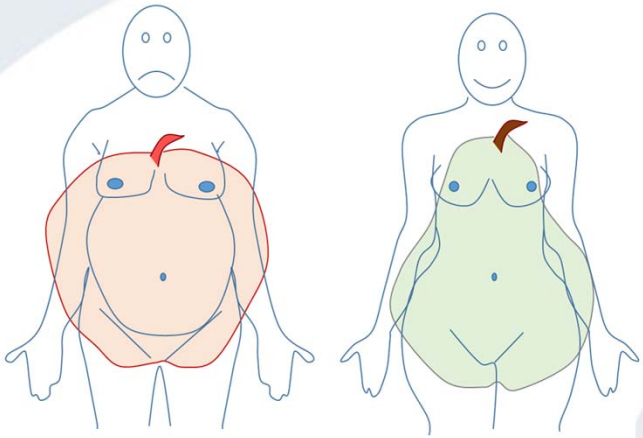
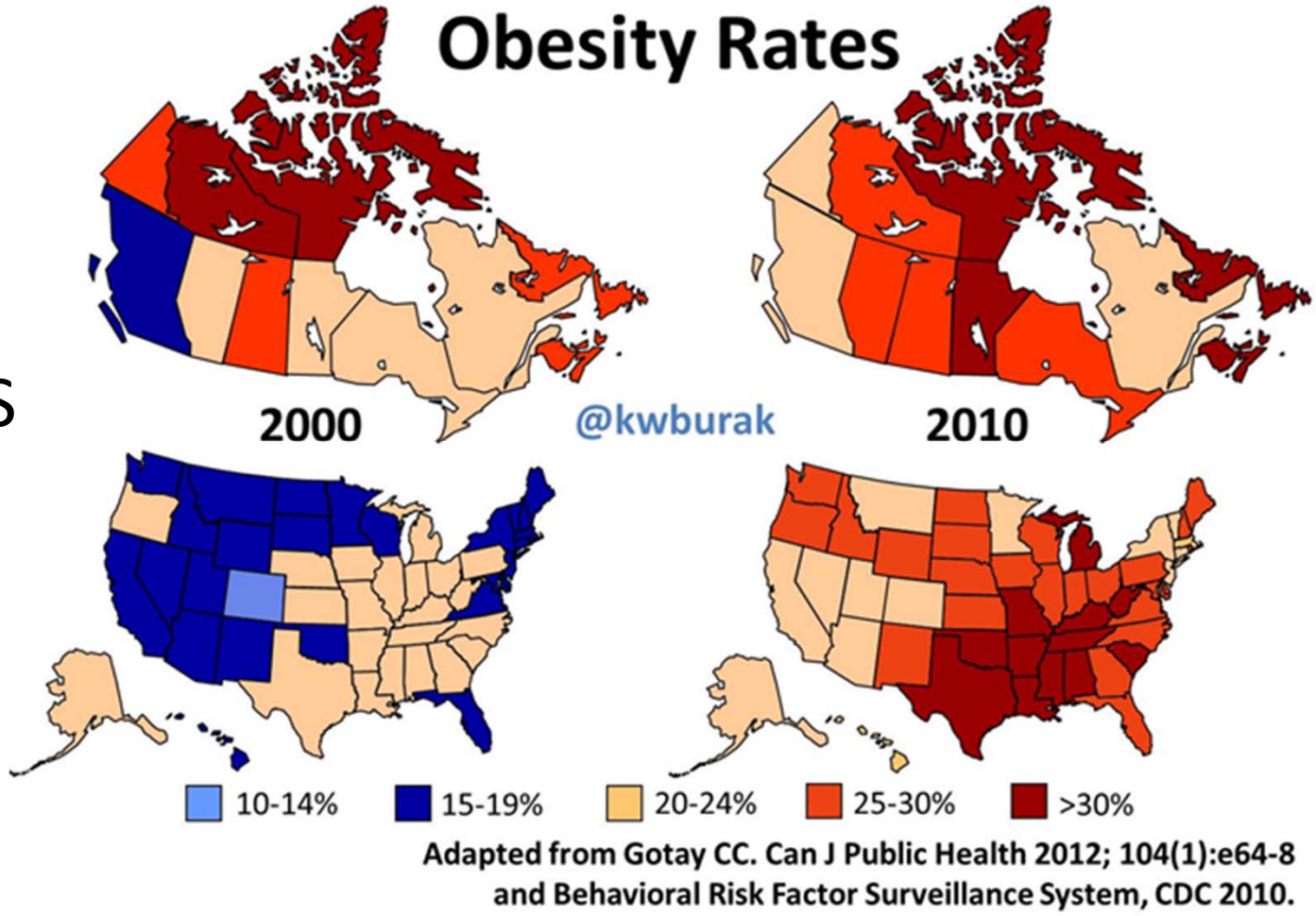


Image Source: HepAPPtology @kwburak

NAFLD Prevalence

- 30% obese
- 25% NAFL on US
- 10% ↑ ALT
- ¾ due to NAFLD



#1

Source: National Health & Nutrition Survey III

Image Source: HepAPPtology @kwburak

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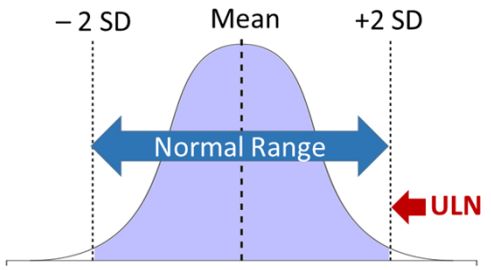
If ALT abnormal and > 2 x ULN for > 6 months (in NAFLD ALT typically < 200 IU/L), need to rule out other causes of liver disease in addition to NAFLD.

What is a normal ALT?

- Varies from lab to lab
- Depends on "healthy" popn
- Gender differences
- New "true normal" for ALT[1]
  - Men ≅ 30 (29 – 33) U/L
  - Women ≅ 20 (19 – 25) U/L



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[1]Kwo PY. ACG Clinical Guideline: Evaluation of Abnormal Liver Chemistries. *Am J Gastroenterol* 2017; 112: 18 -35.

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Other Causes of Steatosis

#2

- Alcohol – must exclude by history
- HCV (genotype 3)
- Wilson's disease
- Starvation and Total Parenteral Nutrition
- Pregnancy = AFLP, HELLP
- Medications
  - Amiodarone, methotrexate, tamoxifen, steroids, valproate, HAART

Further Testing

#4

Step 1 = rule out viral hepatitis and check for NAFLD risk factors

- HBsAg [HBV] , anti-HCV [HCV] → if + get HBVDNA or HCVRNA
- HbA1C, fasting glucose, lipids

Step 2 = rule out genetic and autoimmune liver disease

- Fe/TIBC (TS), ferritin [HH] → if TS >45% get HFE genetic test
- A1AT level [A1AT def] → if low get phenotype
- ceruloplasmin [WD] → if low get 24h urine Cu
- ANA & ASMA [AIH], AMA [PBC]
- Immunoglobulins: IgG [AIH], IgA [Alcohol/NAFLD], IgM [PBC]

Step 3 = rule out other causes of abnormal liver tests

- TSH
- Celiac disease screen

Testing for Chronic Liver Diseases

Classification	Diagnosis	Screening Test	Confirmatory / Additional Tests
Viral	**HBV**	HBsAg	HBVDNA, HBeAg, anti-HBe
	HCV	Anti-HCV	HCVRNA, genotype
Toxin	**Alcohol**	History *Note: AST>ALT, ↑↑ GGT, ↑IgA*	Biopsy if uncertain
Metabolic	**NAFLD**	None (obesity, DM, ↑ lipids) *Note: check fasting glucose and lipids, rule out other diseases*	Biopsy if uncertain
Autoimmune	**AIH**	ANA, ASMA, ↑IgG (all non-specific)	Biopsy **required** for diagnosis
	PBC	AMA *Note: ↑IgM*	AMA is diagnostic
	PSC	None *Note: autoantibodies (ANCA)*	MRCP
Genetic	**HH**	Fe/TIBC (TS) >45%	HFE gene testing (C282Y)
	A1AT def	A1AT level (low)	A1AT phenotype (ZZ)
	WD	Ceruloplasmin (low)	24h urine copper, slit lamp (KF rings)

Adapted from Burak KW. MEDSKL: Approach to Abnormal Liver Tests, www.medskl.com

Results

anti-HAV antibody (total)	positive
HBsAb	positive
HBsAg	negative
anti-HCV antibody	negative
Fe/TIBC	40%
Ferritin	1200 [13-375 ug/L]
A1AT level	0.7 [0.9-2.0 g/L]
ceruloplasmin	0.4 [0.16-0.45 g/L]
ANA	positive @ 1:80
ASMA	negative
AMA	negative
IgA	8.0 [0.6-4.2 g/L]
IgG	16.0 [6.8-18.0 g/L]
IgM	1.0 [0.4-3.0 g/L]

DDx of ↑Ferritin

1) **Chronic Liver Disease**
   - NAFLD, Alcohol, HCV, HBV
2) **Chronic Inflammation**
   - RA, IBD, etc.
3) **Hemochromatosis**
   - Hereditary (HFE)
   - Others

Choosing Wisely Canada

Canadian Association for the Study of the Liver CASL ACEF Association Canadienne pour l'étude du foie

3 **Don't order HFE genotyping based on serum ferritin values alone to diagnose hereditary hemochromatosis.** ▲

Image source: https://choosingwiselycanada.org/hepatology/

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NAFLD Diagnosis Suspected (and alternative causes of abnormal ALT ruled out)

So what, should I care?

- NAFLD does cause ↑ overall mortality
- Becoming a leading cause for LT and HCC
- #1 cause of death is cardiovascular disease
- NASH (but not NAFL) has ↑ liver related mortality

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Chalasani N, et al. AASLD, ACG, AGA Guidelines. Hepatology 2012; 55(6):2005-23.

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Lifestyle (alcohol intake) and medication review: Stop or modify offending agent if possible.
Medications that may cause fatty liver include corticosteroids, tamoxifen, methotrexate, amiodarone.

Baseline investigations:

1) Liver tests: ALT and/or AST, ALP, GGT
2) Liver function tests if cirrhosis suspected: INR, bilirubin, albumin
3) CBC with platelets
4) HgbA1C, lipid profile, fasting blood sugar

NAFLD Diagnosed:

- Cornerstone of management is lifestyle modification (weight reduction, exercise)
- Further follow up dependent on risk stratification by SWE testing through EFW Radiology. Note: If patient is not able to attend SWE test please refer to FIB-4 test (provincial pathway)

Why pay attention to the platelet count?

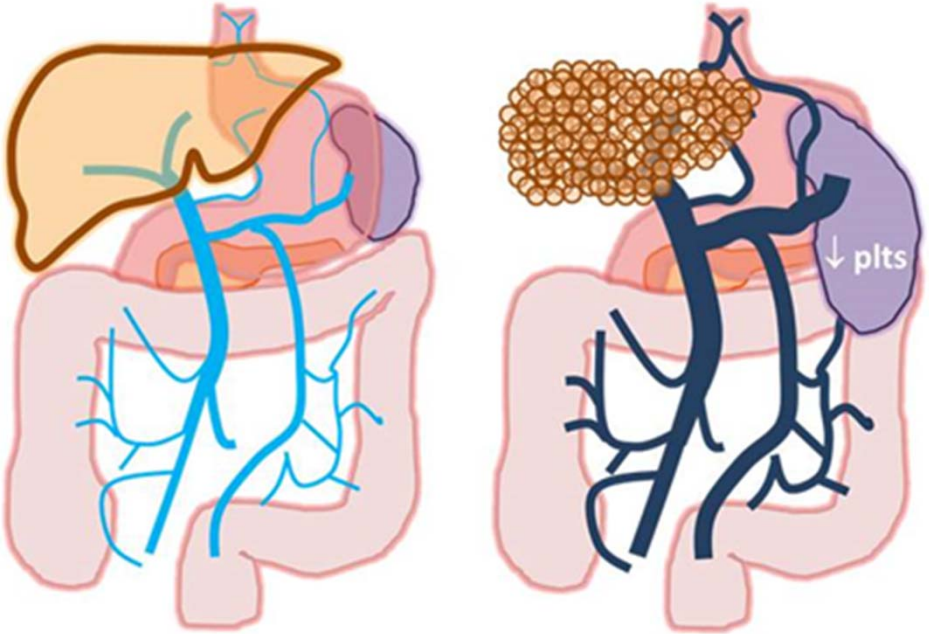

Image Source: HepAPPtology

Predicting Prognosis

Image Source: Bitmoji

#5

- **All patient should have fibrosis assessed**
- **Serum markers**
  - AST:ALT >1, low platelets
  - APRI = AST to platelet ratio index
  - NAFLD Fibrosis score = age, BMI, DM, plts, albumin, AST, ALT
  - **FIB-4 score** = age, AST, ALT, plts
  - FibroTest™ = α2 macroglobulin, haptoglobin, apolipoprotein A1, bilirubin, age, gender
- **Elastography**
  - Transient elastography (FibroScan™)
  - **Sheer wave elastography** (2D US)
  - Magnetic resonance elastography

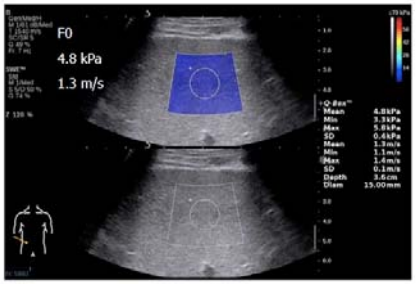

Image Source:
Xie LT, et al. *World J Gastroenterol* 2018; 24(9): 957-970.

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Non-invasive assessment of liver fibrosis using shear wave elastograpy (SWE)
*SWE is the gold standard for assessing liver fibrosis (stiffness) without a liver biopsy

LOW RISK for significant liver fibrosis based on SWE result SWE (ie. liver fibrosis) score < 8.0 KPa

Patient care within the medical home:

Lifestyle modification, exercise, wt loss (target 10% of BW), consider vitamin E (400-800 IU/d), consider omega 3 FA, consider vaccination for hepatitis A and B

HIGH RISK for significant liver fibrosis based on SWE result. SWE (ie. liver fibrosis) score > 8.0 KPa (or SWE test result reported as inconclusive)

REFER TO HEPATOLOGY CENTRAL ACCESS AND TRIAGE (CAT)

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Patient care within the medical home:

Lifestyle modification, exercise, wt loss (target 10% of BW), consider vitamin E (400-800 IU/d), consider omega 3 FA, consider vaccination for hepatitis A and B

- Monitor ALT yearly
- Screen for Type 2 DM (increased risk for developing NIDDM based on NAFLD diagnosis)
- Repeat U/S with Shear Wave Elastography (SWE) through EFW Radiology q3 years
  - If SWE results continue to be < 8 KPa then ongoing care within medical home.

If SWE > 8 KPa, then move to High Risk for significant liver fibrosis pathway

REFER TO HEPATOLOGY CENTRAL ACCESS AND TRIAGE (CAT)

- EFW Radiology will send a one time reminder letter to the primary care physician (on record from prior SWE test) 24 - 30 months after the previous LOW RISK SWE test result report. EFW Radiology will not contact patients directly unless requested by a primary care provider.

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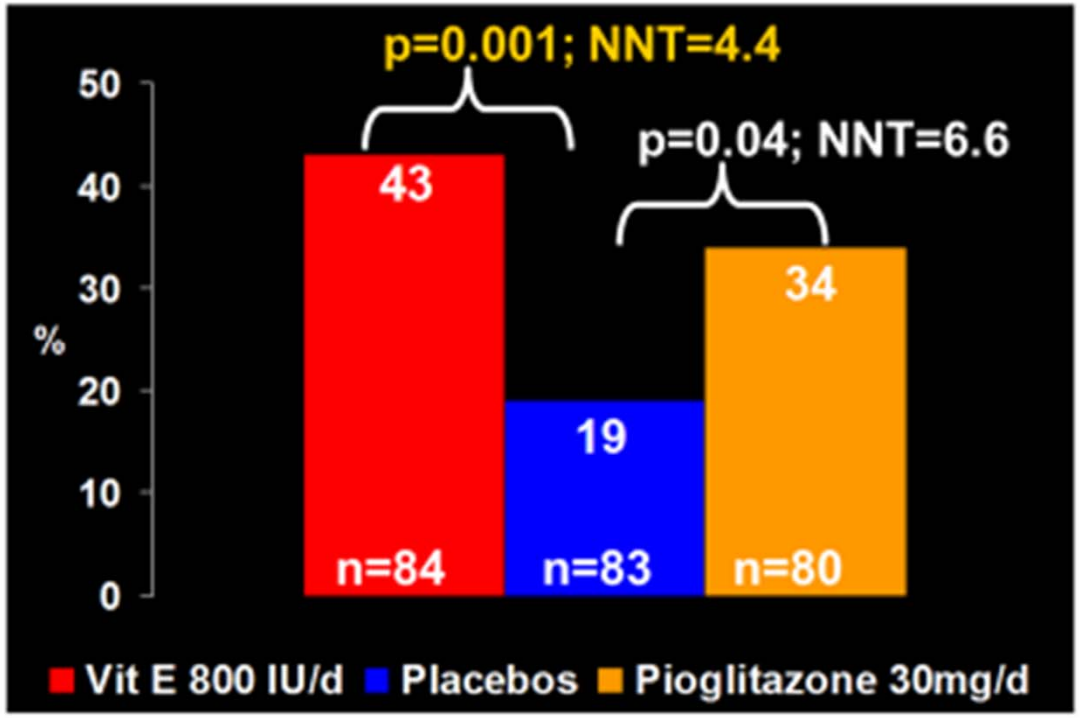
NAFLD Management

#6

- **Weight loss**
  - Diet & Exercise
- **DM management**
  - Metformin
  - Pioglitazone
- **Lipid ↓ therapy**
  - Statins
  - Fibrates
- **Vitamin E (400-800 U/d)**
- **Omega-3 fatty acids**
- **Bariatric surgery**
  - Morbidly obese
  - Safety in cirrhosis?
- **Alcohol use**
  - Avoid heavy use

Chalasani N, et al. AASLD, ACG, AGA Guidelines. Hepatology 2012; 55(6):2005-23.

PIVENS trial



Adapted from Sanyal AJ, et al.
N Engl J Med 2010; 363(18): 1675-85.

Natural History

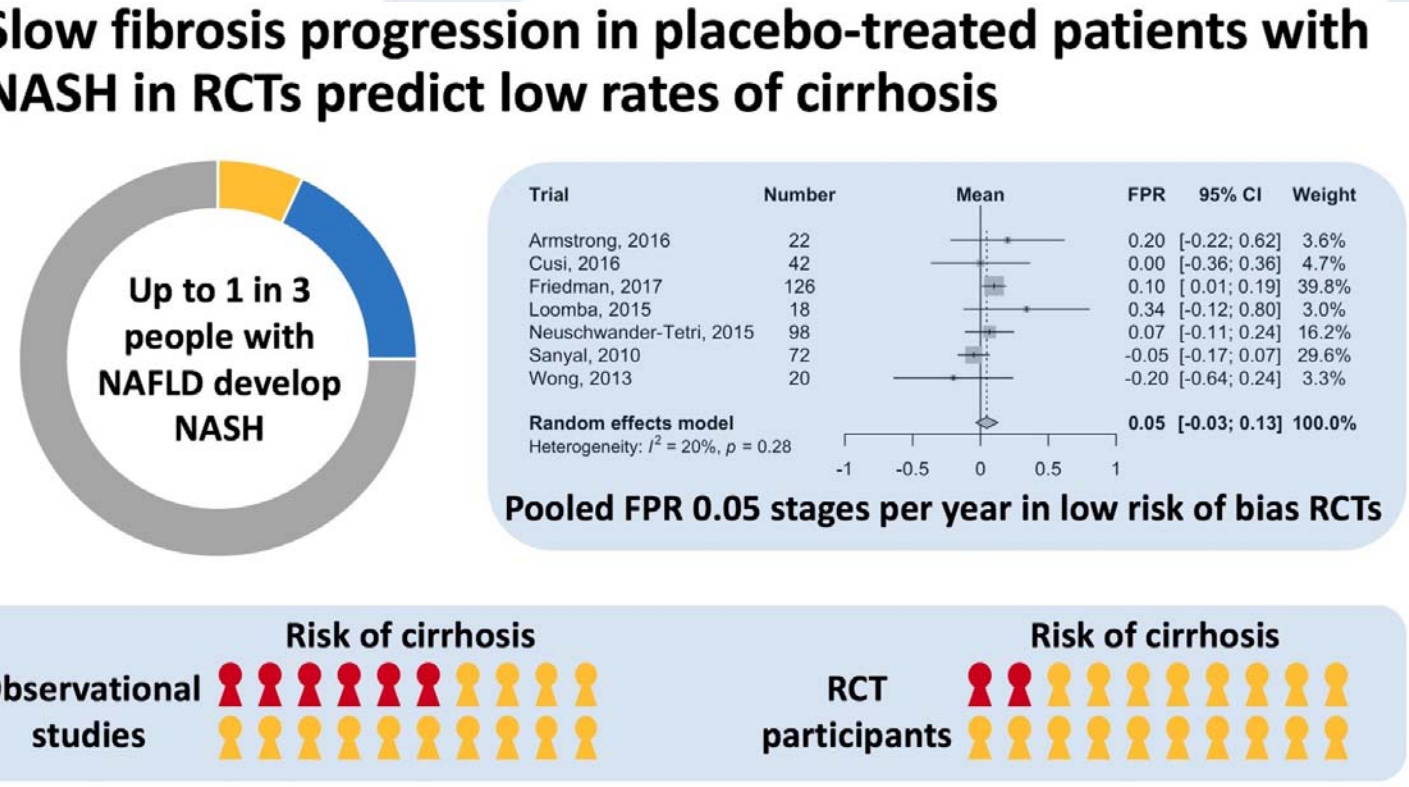
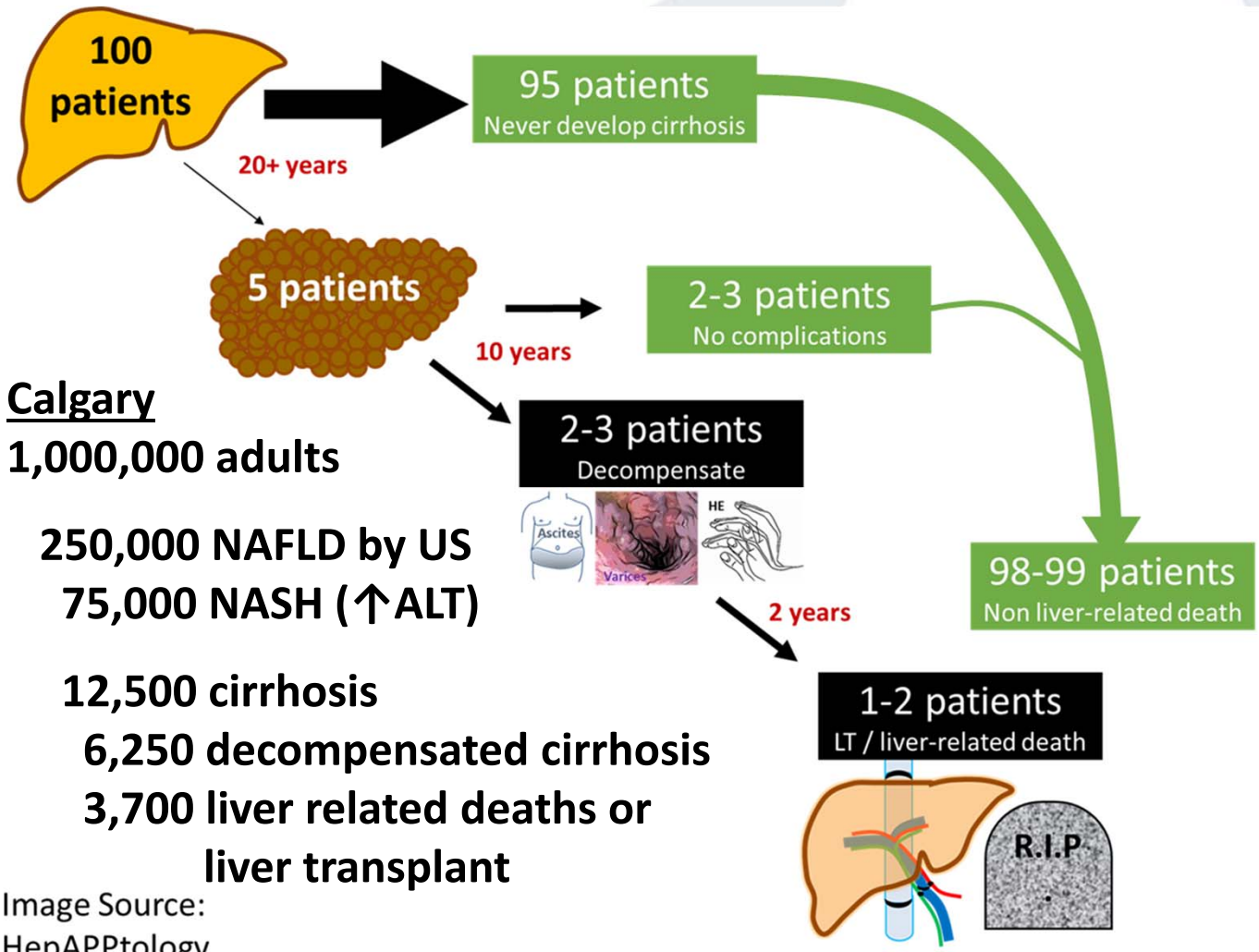


Image Source: Twitter @ianrowe

Roskilly Anna, et al. Hepatology 2018; Abstract 33



Calgary

1,000,000 adults

250,000 NAFLD by US

75,000 NASH (↑ALT)

12,500 cirrhosis

6,250 decompensated cirrhosis

3,700 liver related deaths or liver transplant

Image Source:
HepAPPtology

Adapted from Rinella M, Charlton C. Hepatology 2016; 64(1): 19-22.
an editorial on Younossi ZM et al. Hepatology 2016; 16(1): 73-84.

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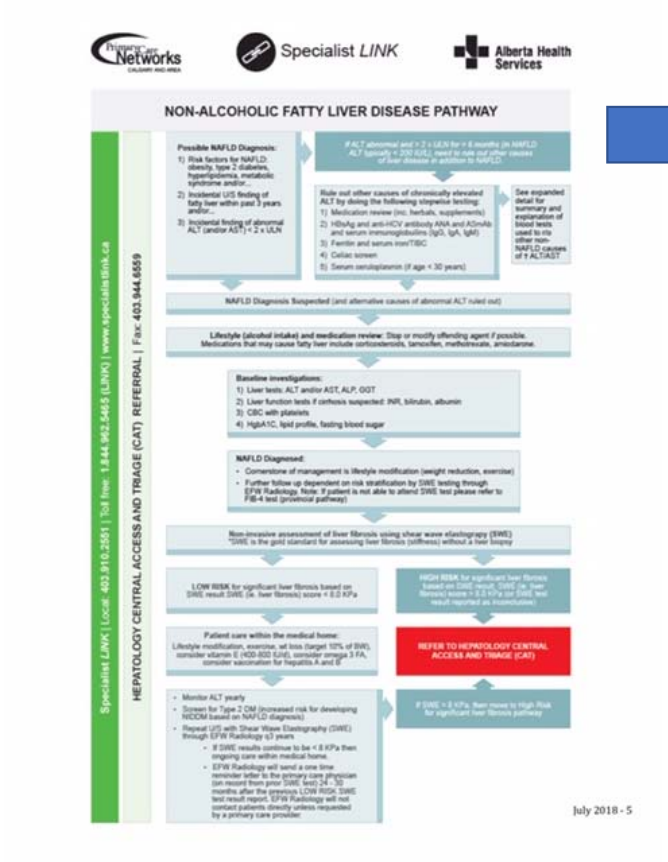
Coffee and the Liver

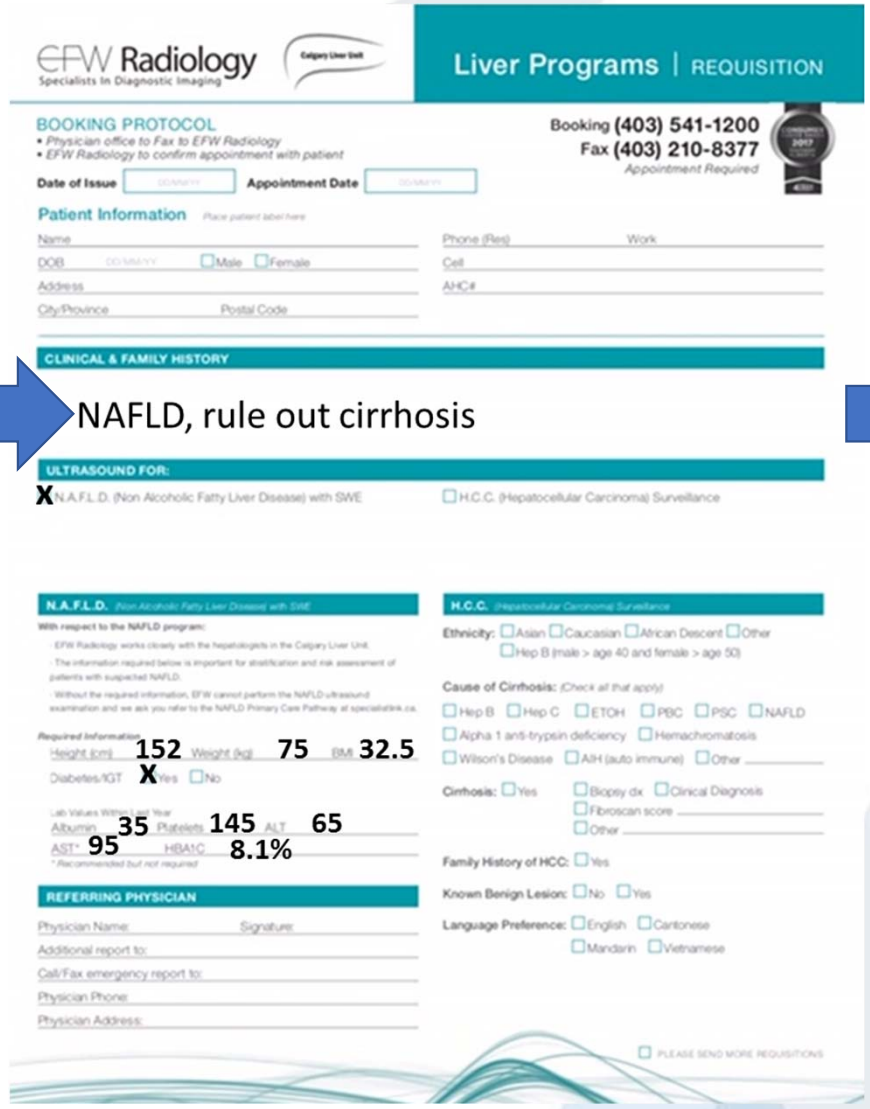
- Epidemiologic studies
  - ↓ ALT
  - ↓ DM
  - ↓ HCC
  - ↓ mortality
  - Dose response
  - Coffee > Tea

A Coffee a Day
Keeps the Hepatologist Away

Image Source: HepAPPtology

Case





NAFLD, rule out cirrhosis

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SWE score > 8.0kPa HIGH RISK for significant liver fibrosis based on SWE result.

REFER TO HEPATOLOGY CENTRAL ACCESS AND TRIAGE (CAT)

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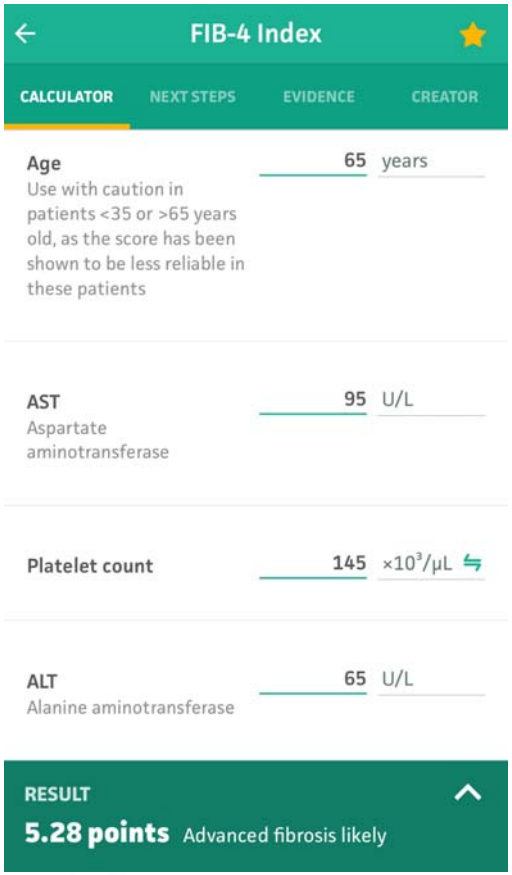

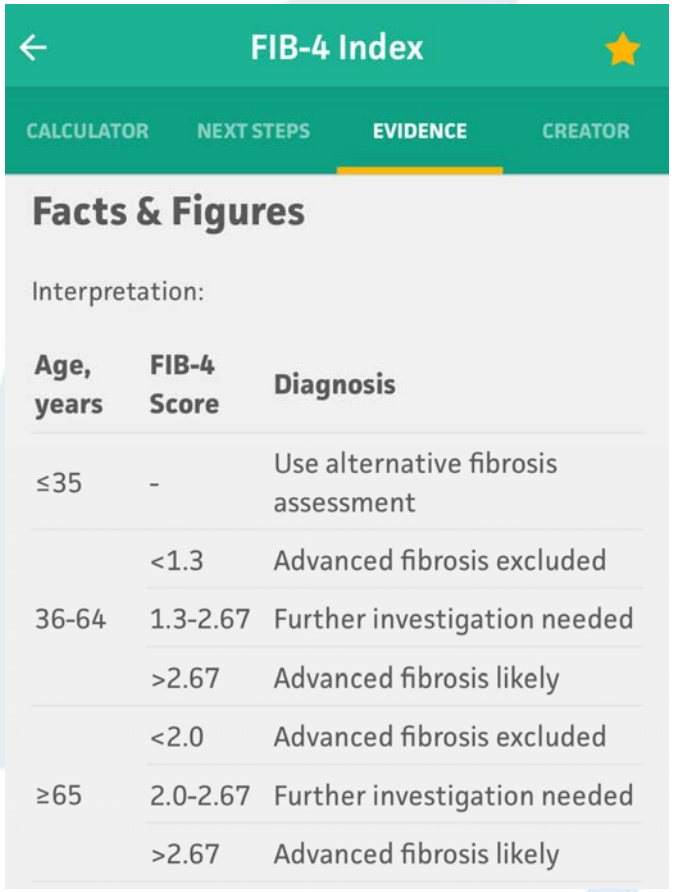

REFER TO HEPATOLOGY CENTRAL ACCESS AND TRIAGE (CAT)

Image Source: https://www.mdcalc.com/fibrosis-4-fib-4-index-liver-fibrosis

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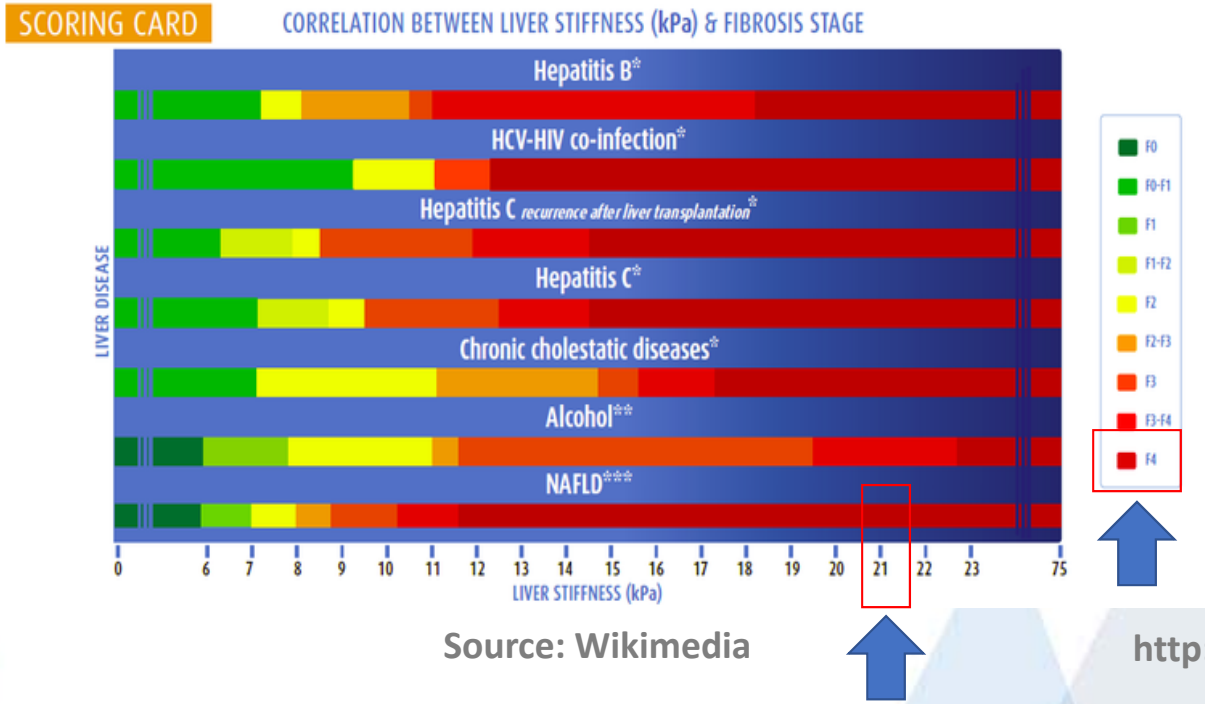
Hepatology Referral faxed to 403-944-6559
Triaged as Moderate (~6 months)



Source: Wikimedia

http://www.echosens.com

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Mrs DF - Management

- Weight loss through diet & exercise
- Manage diabetes
- Manage hyperlipidemia = CONTINUE STATIN
- Vitamin E ???
- Avoid alcohol
- AVOID NSAIDS = acetaminophen OK if NOT abusing alcohol
- Surveillance for varices and HCC
- Watch for ascites and encephalopathy

Primary Care Networks
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http://www.specialistlink.ca

Alberta Health Services

Specialist LINK Monthly Call Volume October 2018

Total Calls October 2018	Total Calls Previous Month	Total Calls since service start
531	491	8740

Top 3 Enhanced Pathway Downloads for October 2018

1. NAFLD (126)
2. Endocrinology Access Pathway (63)
3. IBS (60)

Source: Specialist Link Monthly Report, Nov 2018

Image Source: Bitmoji

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Conclusions

- NAFLD is the leading cause of abnormal liver tests
- Obesity, diabetes, and hyperlipidemia (metabolic syndrome) are major risk factors
- Most patients can be managed in their medical home
  - Rule out other causes of fatty liver or abnormal ALT
  - Diet, exercise, manage diabetes and lipids
  - Consider vitamin E and omega 3 fatty acids
  - Assess fibrosis (AST:ALT, platelets, SWE)
  - Refer patients with advanced fibrosis

References

- Kwo PY. ACG Clinical Guideline: Evaluation of Abnormal Liver Chemistries. *Am J Gastroenterol* 2017; 112: 18 -35.
- Chalasani N, et al. AASLD, ACG, AGA Guidelines. Hepatology 2012; 55(6):2005-23.
- https://www.specialistlink.ca/files/FINAL_UPDATED_-_Enhanced_Primary_Care_Pathway_NAFLD_Aug_7_2018.pdf

#7

Questions

Image Source: Bitmoji

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