

A Patient with NAFLD: Does this Patient Need to be Referred for Further Workup?

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Goals of this Presentation

- What are the initial tests needed to determine the disposition of a person either at risk of NAFLD or has evidence of NAFLD on liver ultrasound?
- Which patients should have a test for liver fibrosis performed?
- If there is no evidence of liver fibrosis, how often should these patients be evaluated and with which tests?
- If there is evidence of fibrosis, which patients should have further imaging and what test and which need a liver biopsy?

Hypothetical Patient with Possible NAFLD

- A 28 y.o. Alaska Native female accountant has a history of obesity (BMI 36) and pre-diabetes. Her LFTs show an ALT of 40, AST 28, Alkaline Phosphates 85 and the rest of her CMP and CBC are all WNL.
- Family history of diabetes, HTN and dyslipidemia
- BP 140/84, LDL 120, HgA1C is 5.9
- You decide to order a liver US and the interpretation is a dense liver, liver span slightly increased with no other abnormalities
- What do you do next?

Epidemiology of NAFLD

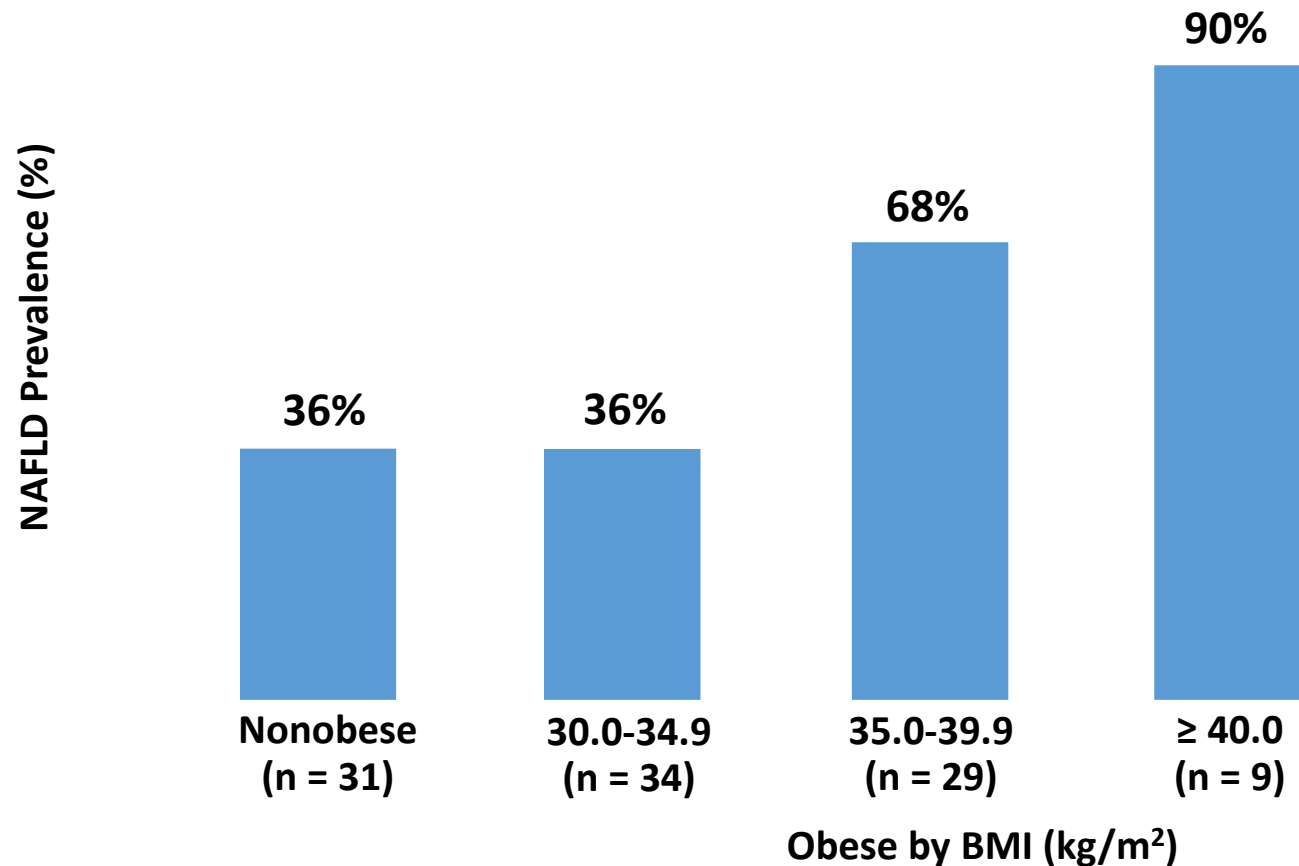
- The magnitude of NAFLD in the Alaska Native Population, estimation 25,000 to 30,000 persons
 - Estimated 7,000 to 7,500 persons may have NASH the form of NAFLD that is characterized by liver inflammation and progression of liver scarring that can lead to cirrhosis in 30% to 40% and hepatocellular carcinoma
- Which persons are at the highest risk of NAFLD in declining order: evidence
 - Adult and Pediatric persons with diabetes
 - Persons with pre-diabetes (metabolic syndrome, hyperlipidemia and mild glucose intolerance)
 - Persons with morbid obesity (BMI>40)
 - Persons with sleep apnea
 - Children and adults with obesity: BMI>30
 - Persons with BMI 25-30
 - Persons with BMI <25: this represents 5%-10% of persons with NAFLD

Obesity is the main risk factor for NAFLD

- 75–91% adults with obesity have NAFLD.
- A 2010–2014 report estimates 31% of Alaska Native adolescents (grades 9–12) are overweight or obese.
- The prevalence of obesity in Alaska Native 3-year old children ranges from 32–51%.
- Other research has reported **children with NAFL as early as 2 years old** and **with NASH-related cirrhosis as early as 8 years old**.

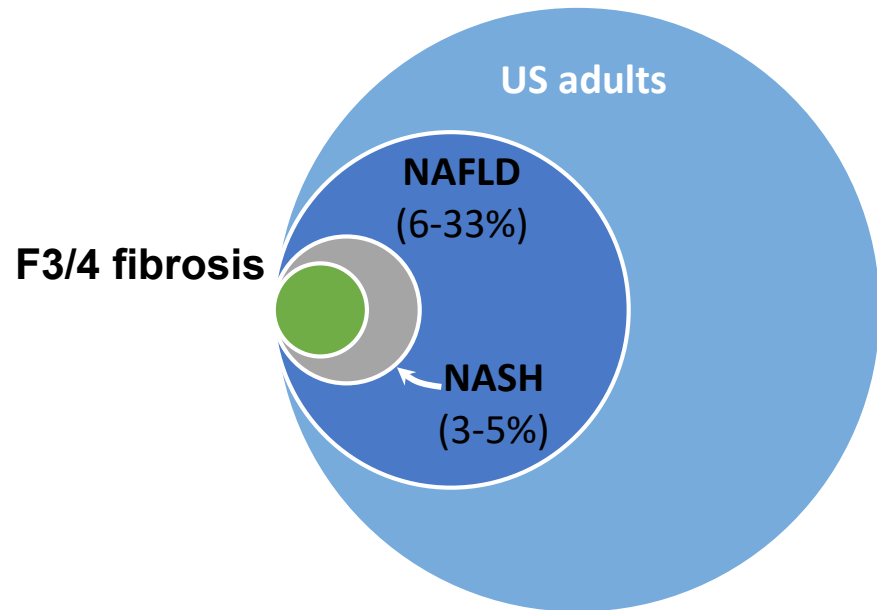
Prevalence of NAFLD and NASH in Patients With T2DM and Normal Plasma AST or ALT

- Patients with T2DM and normal AST or ALT evaluated for liver triglyceride content by H-MRS, insulin sensitivity, and adipose tissue insulin resistance (N = 103)

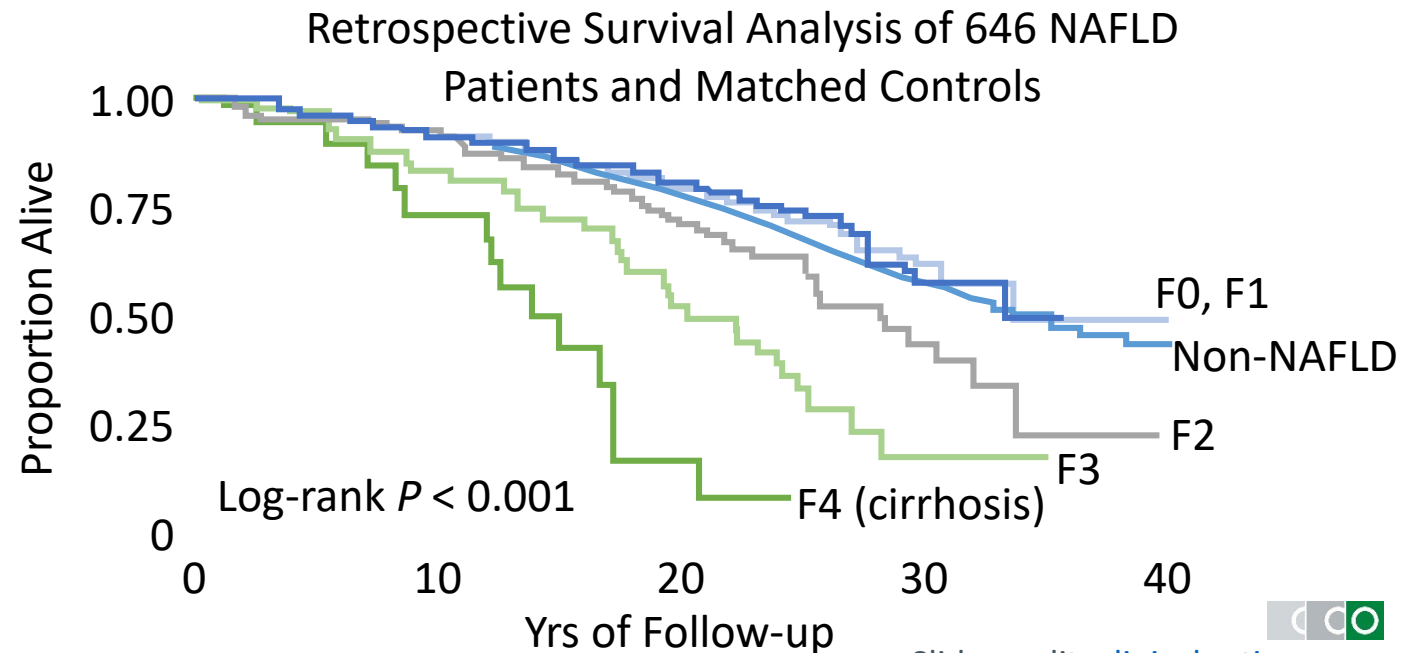


Diagnosis: Goals

- Goal 1: Identify those with NASH
 - Having NASH increases the risk of progression of fibrosis
 - Identify treatment candidates



- Goal 2: Identify those at risk for progressing to cirrhosis
 - Having advanced fibrosis is associated with increased mortality



Fibrosis stage is the most important predictor of liver mortality in NAFLD



Dulai et al. Hepatology, 2017

Progression of fibrosis in NASH

- Studies suggest fibrosis progression of 1 stage on average every 7 years
 - For example: Progression from stage 1 fibrosis (mild) to stage 4 (cirrhosis) would take on average about 20 years
 - However 20% of patients with NASH experience rapid progression: 1 stage every 2-5 years



'Simple Scores' for Predicting Presence of Advanced (F3/4) Fibrosis

NAFLD Fibrosis Score

$$= -1.675 + 0.037 \times \text{Age} + 0.094 \times \text{BMI} + 1.13 \times \text{IFG/diabetes} + 0.99 \times \text{AST/ALT ratio} - 0.013 \times \text{Platelets} - 0.66 \times \text{Albumin}.$$

- A score of less than -1.455 excludes fibrosis (NPV 88-93%).
- A score of greater than 0.676 predicts fibrosis (PPV 82-90%).

FIB-4 Score

$$= (\text{Age} * \text{AST}) / (\text{Platelets} * \text{Sqrt}(\text{ALT}))$$

- A score of less than 1.3 excludes fibrosis (NPV 95%)
- A score greater than 3.25 predicts fibrosis (PPV ~70%)



Transient Elastography

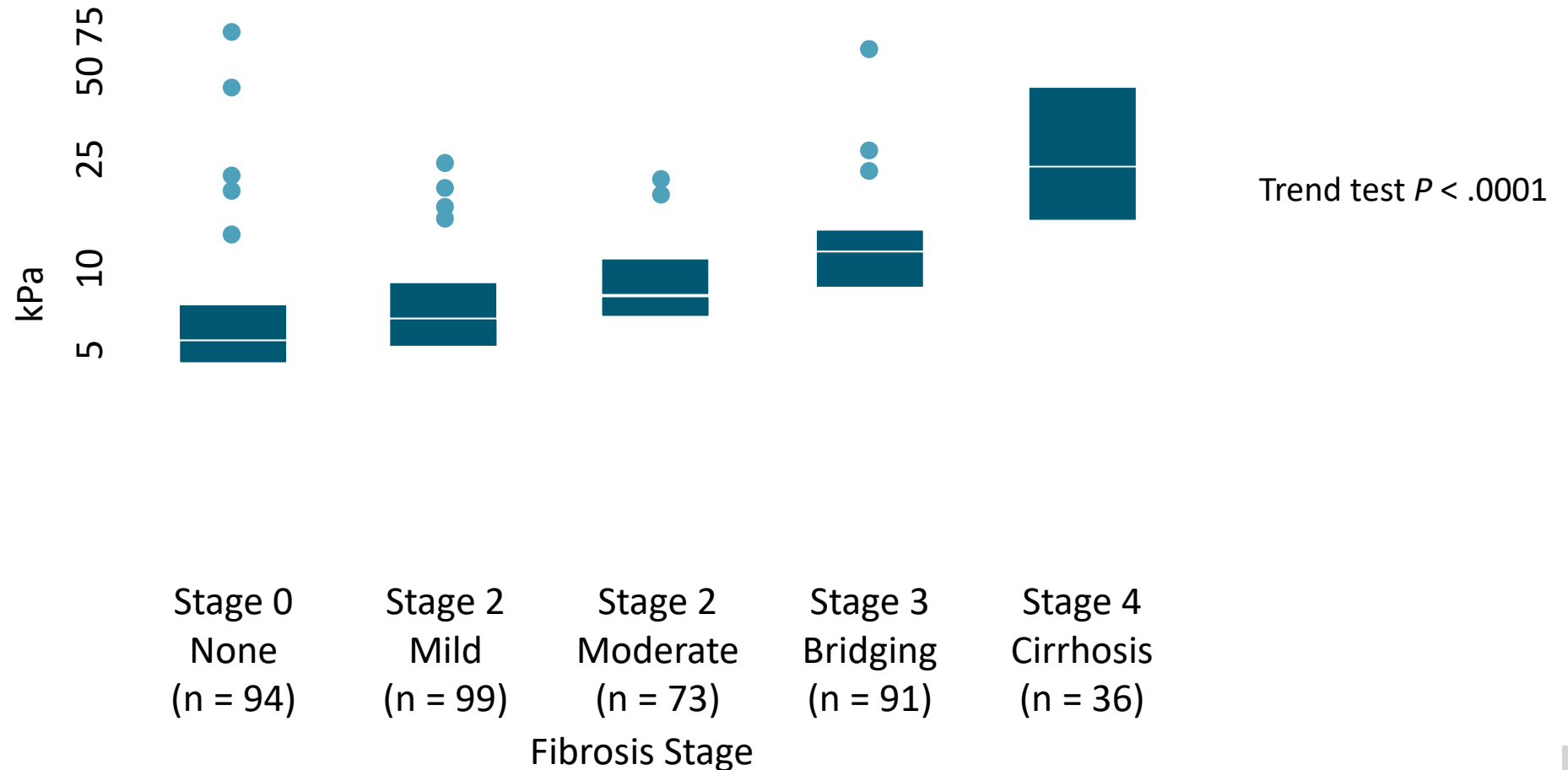
- Allows painless and simultaneous measurement of two quantitative parameters:
- Liver stiffness expressed in kPa
 - Correlated to liver fibrosis [1]
- Controlled Attenuation Parameter (CAP™) expressed in dB/meter
 - Correlated to liver steatosis [2]
- Both quantitative parameters are assessed on the same volume of liver tissue
- 100 times bigger than liver biopsy
- ANTHC has two FibroScan units: one at Int Med Clinic and one portable

1. Friedrich Rust, et al. *Gastroenterology*. 2008; 2. Sasso, et al. *Journal of Viral Hepatitis*. 2011.

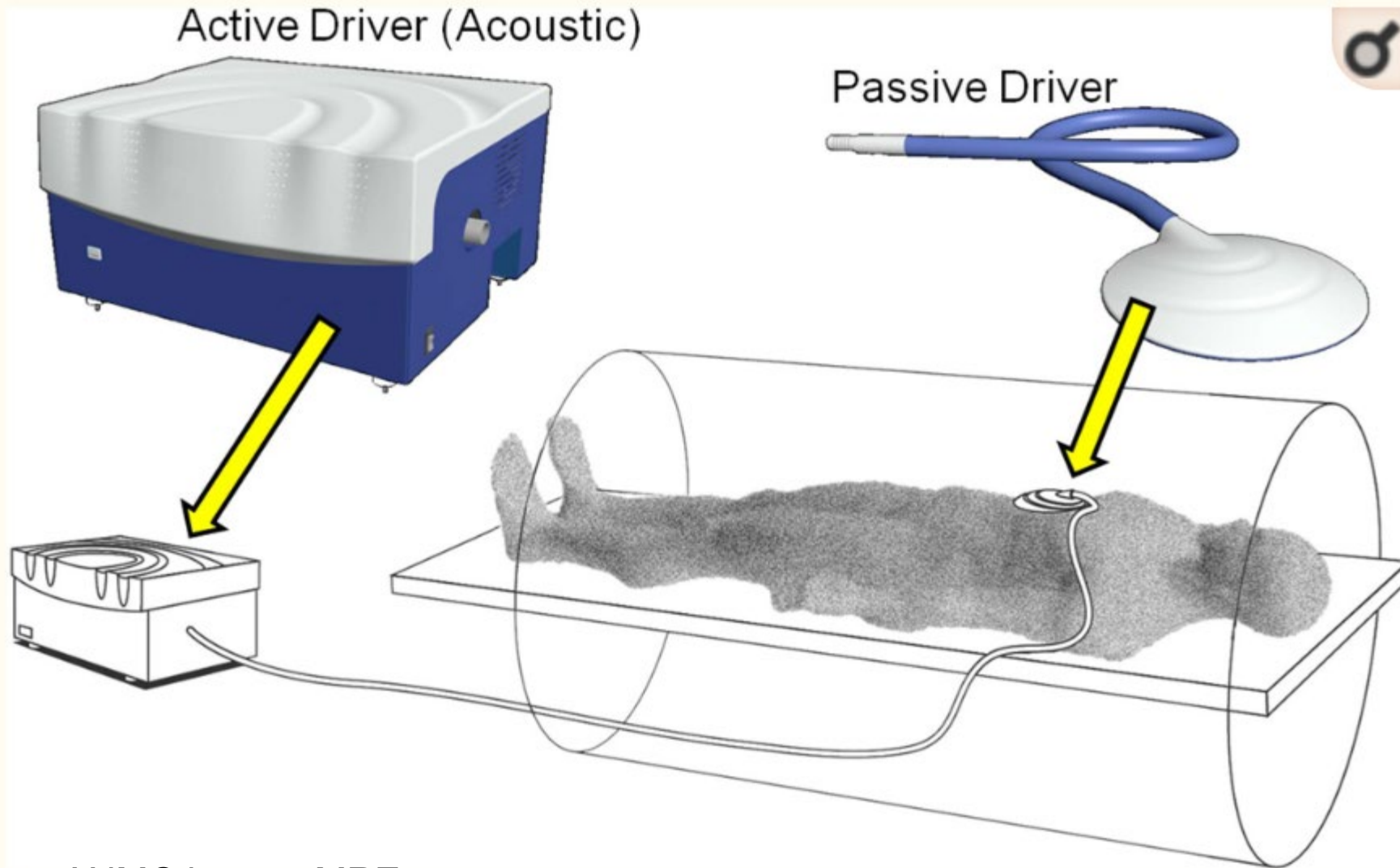


Detecting Liver Fibrosis With *FibroScan*

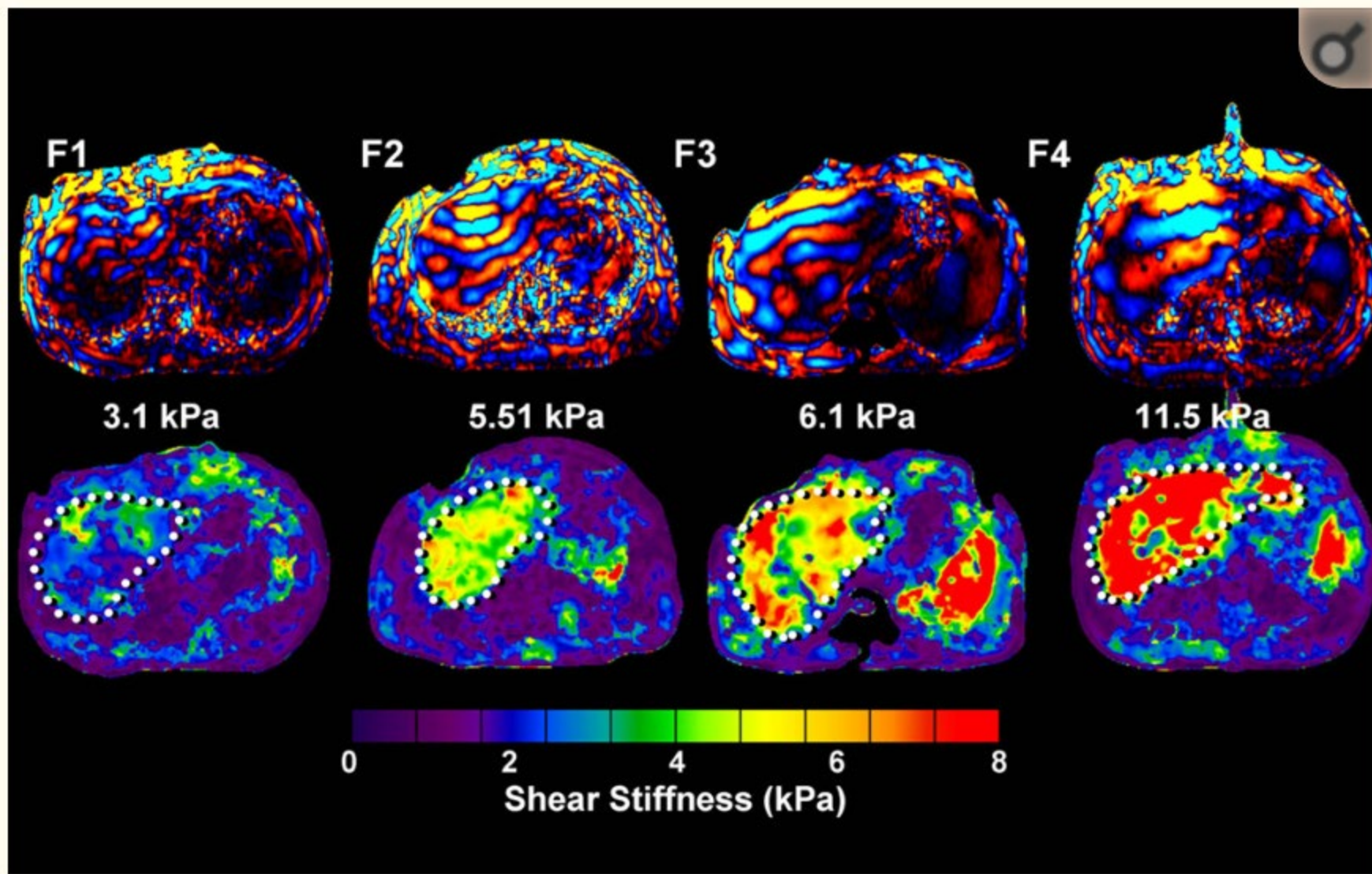
- NASH CRN: 393 patients with biopsies within 1 yr



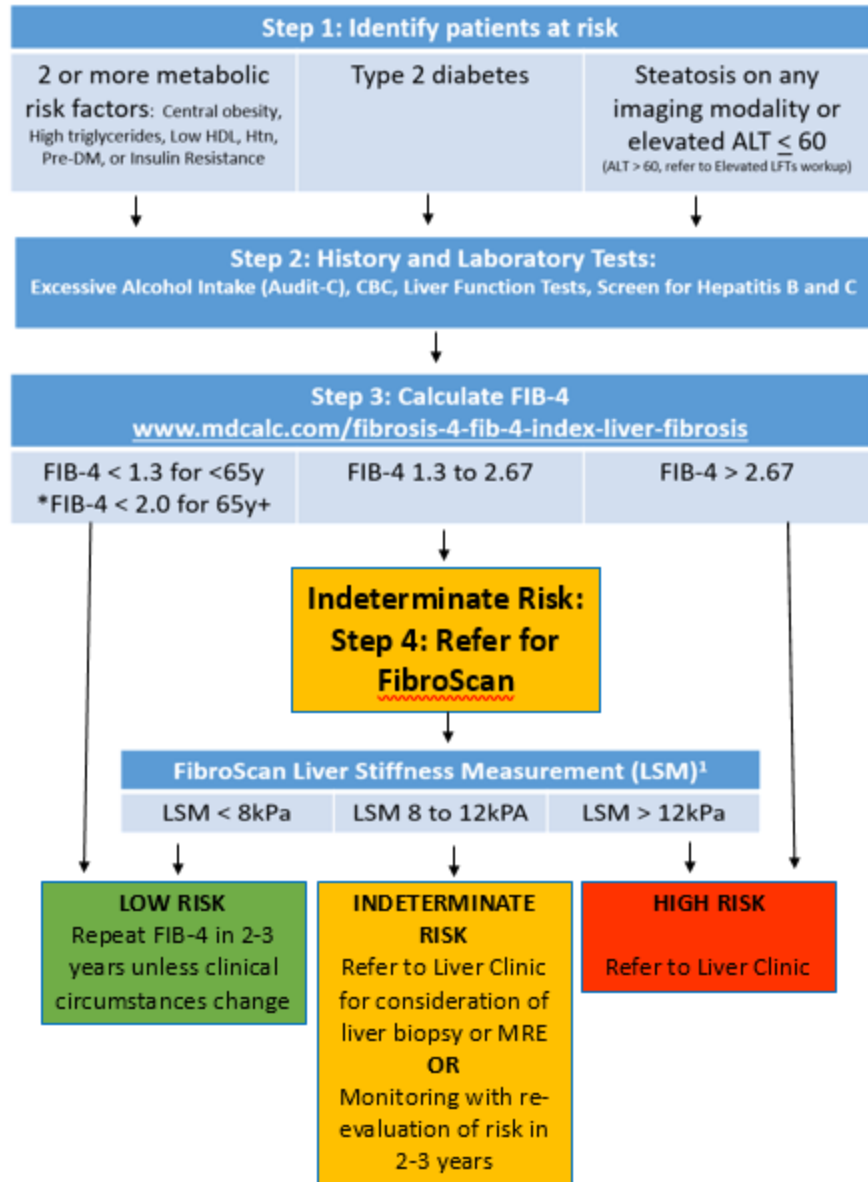
MRI Elastography to evaluate Liver Fibrosis



ANMC has an MRE
unit




Screening Patients with Possible Fatty Liver for Advanced Fibrosis



Footnotes: 1. Proprietary commercially available blood tests such as FibroScan™ or FibroTest™ may be considered for patients with indeterminate or high risk based on FIB-4 where FibroScan is unavailable.
Adapted from: Kanwal et. Al. Clinical Care Pathway for the Risk Stratification and Management of Patients with Nonalcoholic Fatty Liver Disease. Gastroenterology. 2021; <https://doi.org/10.1053/j.gastro.2021.07.049>

Histology of NAFLD

Clinical Assessment 

Caveats

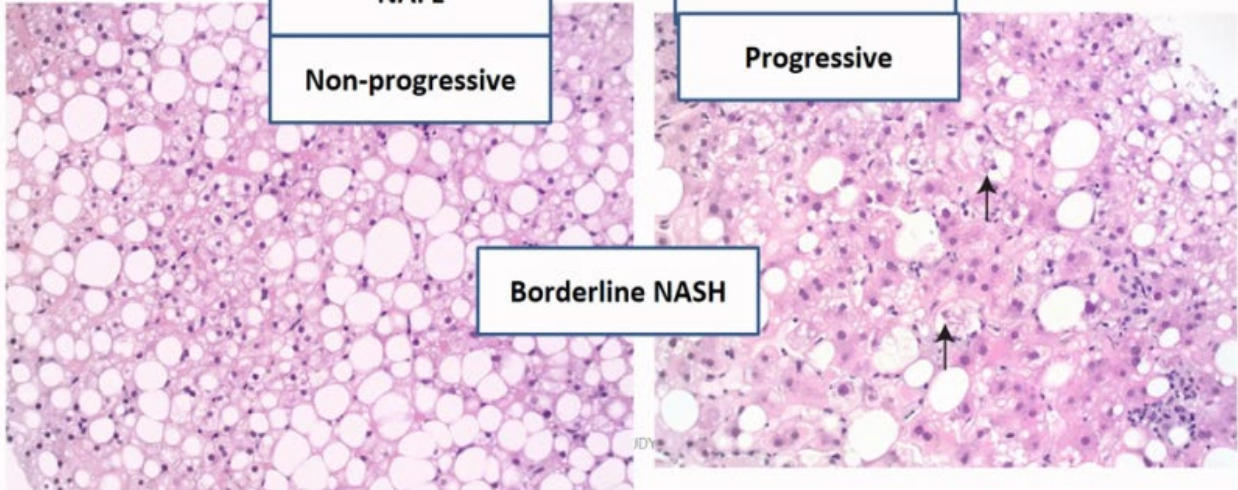
- Presence of steatosis in $\geq 5\%$ hepatocytes
- Minimal alcohol use
- Biopsy consistent with NAFLD
- No other etiology for liver disease
- No secondary causes of NAFLD
 - Medications
 - HIV
 - Lipodystrophy

NAFLD

NAFL
Non-progressive

NASH
Progressive

Borderline NASH



00:16/00:41

This Patient with NAFLD

- FIB4 score is 0.25: an indeterminate score needing further evaluation
- FibroScan score is 9.8 kPa which suggests at least moderate liver scarring
 - CAP score for liver steatosis is 295 dB/m consistent with moderate steatosis
- MRI Elastography (MRE) indicates moderate to advanced fibrosis
- Liver biopsy shows moderate steatosis with lobular inflammation, ballooning degeneration of hepatocytes, Mallory bodies and pericellular perisinusoidal liver fibrosis

Disposition and Plan

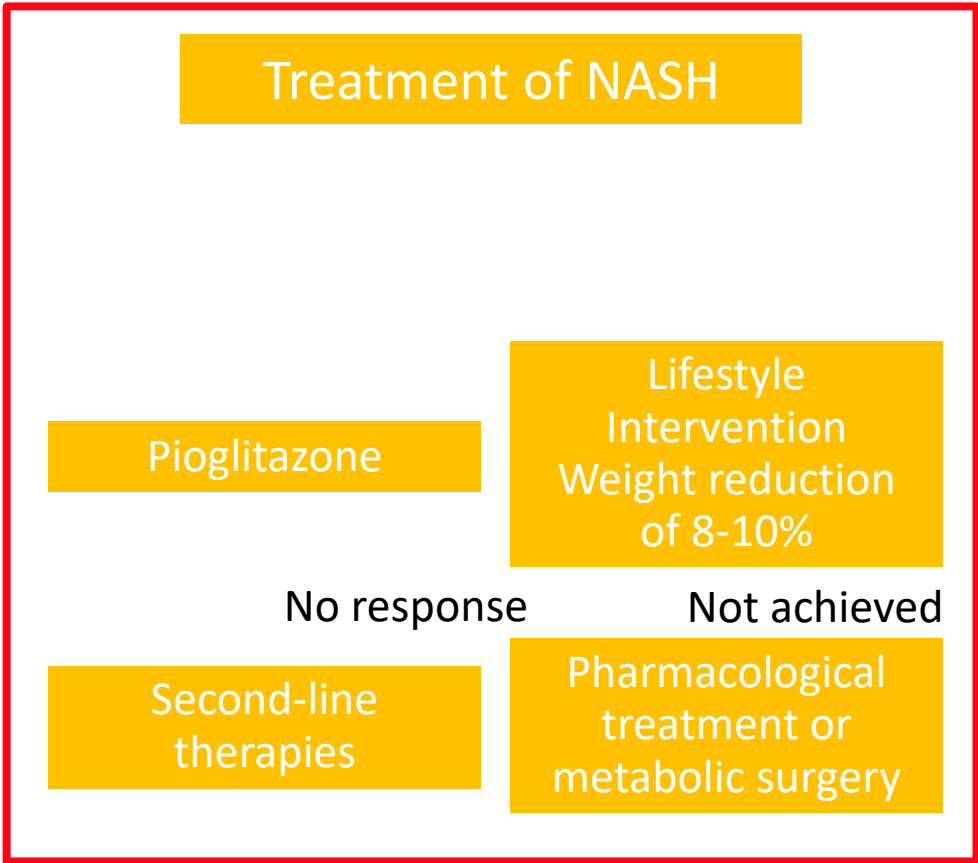
- Patient joins local gym and starts exercise program
- Patient gets a fit watch and walks or bikes to work
- Patient drinks 1 cup of coffee in am and no more as he gets jittery. Increases coffee to 2 additional cups of decaf Americano with non fat milk topping and Stevia for sweetener.
- Patient revises diet to combination of traditional Alaska Native diet with seal oil, salmon, she fish, caribou/moose and wild birds that he hunts and fishes for, traditional berries and greens supplemented by Mediterranean diet with olive oil and veggies/fruits

Returns to Liver Clinic 2-years Later

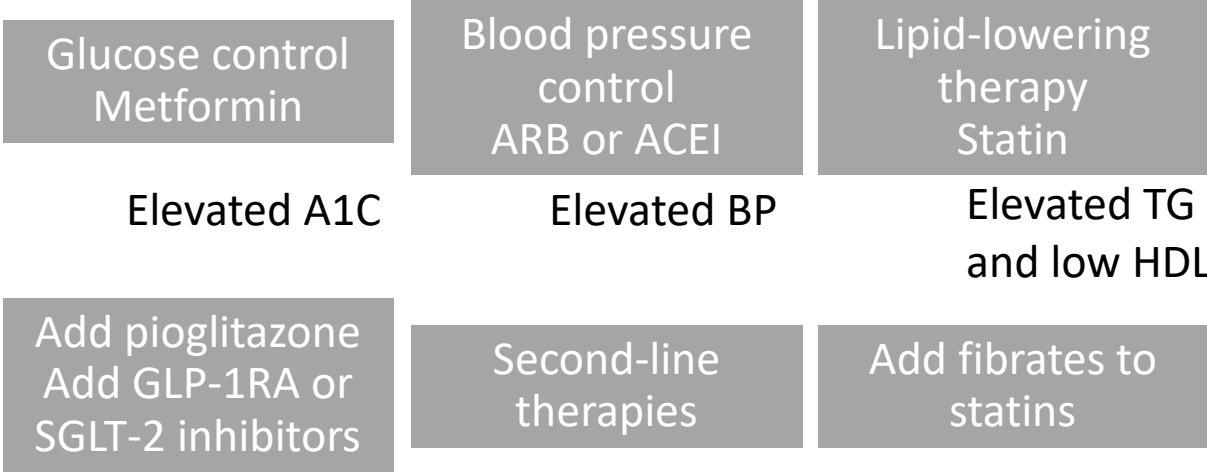
- Patient has lost 15 lbs., decreased fat and increased muscle mass
- Feels much better, less sluggish and enjoys life more
- Repeat FibroScan shows fibrosis score of 5.89 pKa consistent with no evidence of scarring and CAP score is now 280 dB/m, mild steatosis
- Primary care provider will follow patient and order FibroScan every 2-years to monitor any changes in liver fibrosis or steatosis
- LFTs are ALT 14, AST 18 and Hg A1C is now 4.2, HDL 70

Treatment of NASH

Prediabetes or T2DM and Definite NASH



Control of other CV risk factors



Conclusions

1. NAFLD is the leading cause of cirrhosis in US and #2 reason for Liver Transplant
2. Providers who care for patients with the metabolic syndrome need to evaluate them for liver fibrosis, even if LFTs are normal
3. Start with FIB4, if <1.3 (age < 65 , $<2.0 > 65+$), repeat every couple years
 - If $>$ minus 1.3 order FibroScan or Sheer wave elastography
 - If more than minimal fibrosis present but less than moderate to severe fibrosis, repeat FibroScan in 1-2 years and counsel for diet and exercise
4. If moderate to severe fibrosis suggested, order MRE and if confirmed, refer for consideration of liver biopsy