The Epidemic of Nonalcoholic Fatty Liver Disease (NAFLD)

Michelle Lai, MD, MPH
Associate Professor of Medicine, Harvard Medical School
Director of Non-Alcoholic Fatty Liver Disease Center
at Beth Israel Deaconess Medical Center

BETH ISRAEL DEACONESS MEDICAL CENTER

HARVARD MEDICAL SCHOOL

Learning Objectives

- Understand risk factors for NAFLD
- Evaluation of NAFLD
- Management of NAFLD

Case #1: RR

- 62M presents for his annual exam
- DM2, hypertriglyceridemia, obesity
- One glass of wine a week.
- BMI 34
- You get HgbA1c, BUN, Creatinine, urine albumin, order foot and eye exam.

Question #1: What other tests do you routinely check in a patient like this at an annual visit?

A. Lipid panel
B. Lipid panel, CBC
C. Lipid panel, CBC, Hepatic panel
D. CBC, Hepatic panel

Standards of Medical Care in Diabetes-2020 American Diabetes Association

- “Evaluation for nonalcoholic fatty liver disease should be done at diagnosis and annually thereafter.”

- “Patients with type 2 diabetes or prediabetes and elevated liver enzymes (ALT) or fatty liver on ultrasound should be evaluated for presence of nonalcoholic steatohepatitis and liver fibrosis”

American Diabetes Association. Diabetes Care 2020;43:S37-S47.

RR- Lab Data

- Hgb A1C 9.6%, Creatinine 0.8
- ALT 62, AST 44
- Review of historic labs showed ALT 48-63, AST 38-51 x at least several years.
- Normal platelet count

Question #2: What is your next step? (no right or wrong answer)

A. refer to GI/Hepatology
B. Advise on Weight loss and monitor
C. Send a work up for abnormal liver enzymes
D. Order a Fibroscan

RR’s work-up / data

- Neg Viral serologies
- Ferritin 1000, TS 42%
- US 11 years ago showing fatty infiltration of the liver.
- Last abdominal imaging 3 years ago –MRI –fatty infiltration of the liver. Normal spleen

RR- Summary

62M with DM2, obesity, metabolic syndrome

and chronically elevated liver enzymes and high ferritin with

fatty infiltration seen on liver imaging.

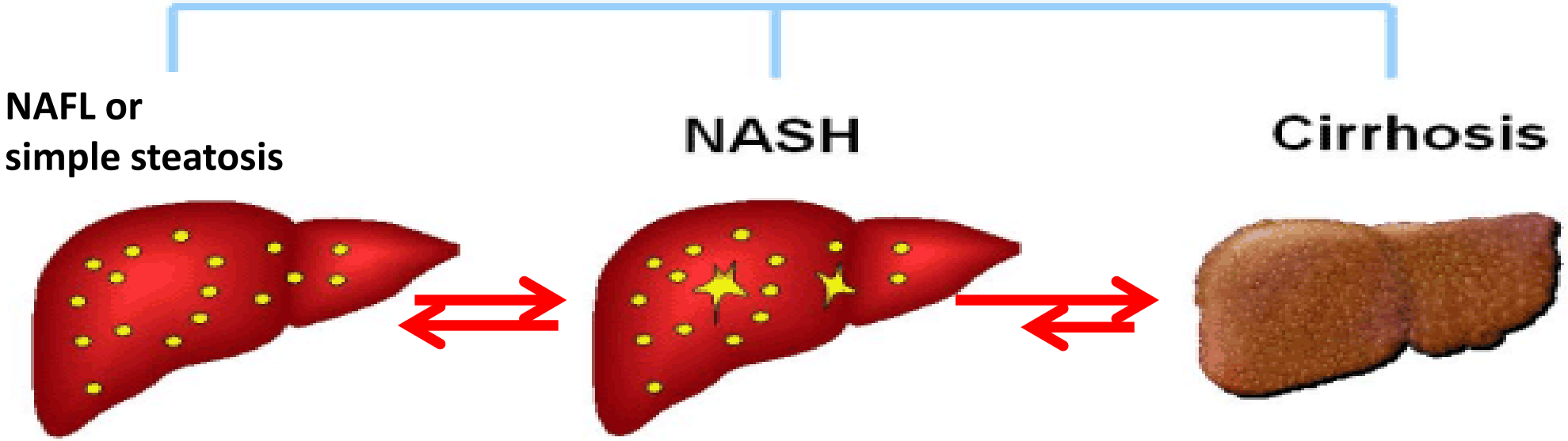
Outline

- Definitions and Epidemiology
- Risk factors for NAFLD
- Fibroscan
- Counseling patients

Definition: NAFLD and NASH

- **Nonalcoholic Fatty Liver Disease (NAFLD)** = Spectrum of disorders characterized by hepatic steatosis in the absence of alcohol consumption (<20g/day)
- **Nonalcoholic Steatohepatitis (NASH)** = more severe end of the spectrum characterized by steatosis, inflammation and fibrosis
- Some propose calling it MAFLD- metabolic associated fatty liver disease.

The Spectrum of NAFLD



70%

Relatively benign

30%

Can progress to cirrhosis and HCC

Summary of terminology

- **NAFLD**- all fatty liver disease (exclude significant alcohol intake)
- **NASH** –more severe disease (biopsy proven)
- **NAFL** or simple steatosis- NAFLD that is not NASH
- Liver biopsy gives two components:
  - **NAS score-** necroinflammatory component (defines whether NASH or not)
  - **Fibrosis score-** how much damage has accumulated

Epidemiology

- Most common cause of abnormal LFTs and cryptogenic cirrhosis in the U.S.
- Most common hepatic disorder seen in pediatric hepatology practice.
- ↑ prevalence in the U.S. and developed countries due to epidemic of obesity and metabolic syndrome

80 Million affected in the U.S.

~24.8 million

~37 million

80 million

Late diagnosis= high mortality

- ~50% of cases of advanced fibrosis from NAFLD are not discovered until presentation for first episode of decompensated cirrhosis
- at which point their five year transplant-free mortality rate is as high as 85%
- Across the world, NASH has emerged as one of the leading indication for liver transplantation.

Tanajewski et al. *BMJ Open*. 2017.
Ratib S et al. *J Hepatol*. 2014.
Schuppan D, NH A. *Lancet*. 2008;371(9615):838-851.

NASH and Liver–related Complications

- Second leading indication for LT (projected to be #1 by this year)
- Between 2004 and 2009, # of adults with NASH awaiting LTs has almost tripled.

Hepatocellular carcinoma (HCC)

- NASH-2nd most common cause of HCC
- Incidence in the US has increased over threefold in the past few decades
- Most present at an advanced stage and receive either no treatment or only palliative treatment
- One of the most lethal cancer with an overall 5-year survival of ~15%

Stepanova M, Younossi ZM. Clin Gastroenterol Hepatol 2012; 10:646.

NAFLD and HCC

- NAFLD patients less likely to receive surveillance for HCC.
- NAFLD HCC present at more advanced stages (less treatable)
- No reliable serologic biomarkers to diagnose

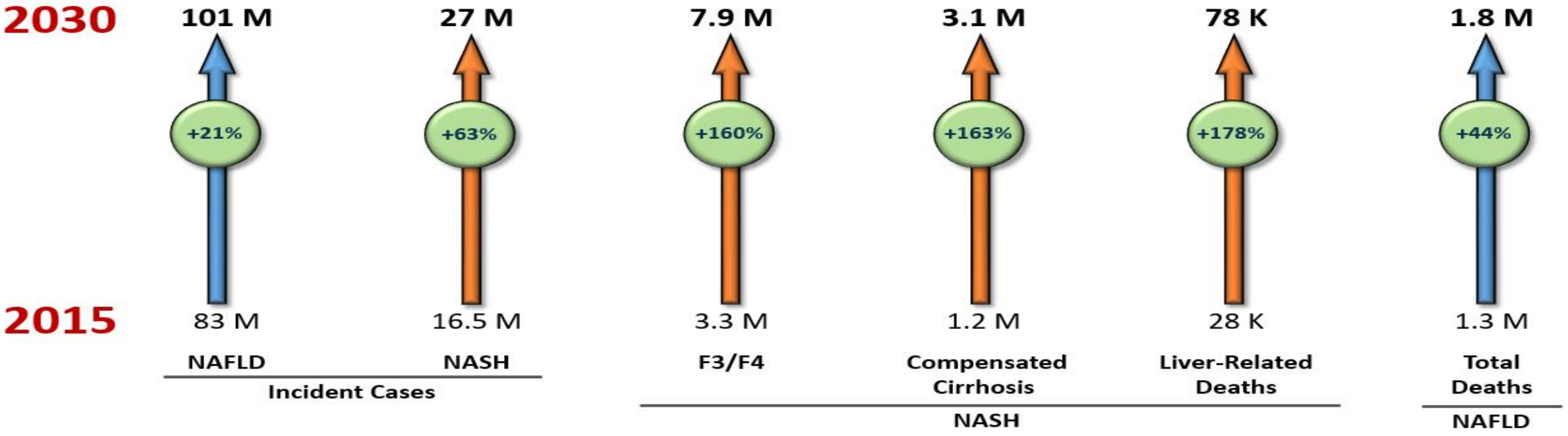
+ perception that NAFLD is a benign and indolent disease = less surveillance

- HCC might develop in non cirrhosis NAFLD
  - obesity and diabetes mellitus are independent risk factors of HCC
  - Surveillance for HCC in non cirrhotic NAFLD is not indicated

Mittal et al. *Clin Gastroenterol Hepatol*. 2015; 13(3): 594–601

Projected growth of NAFLD Disease Burden

For context- compare to a disease we screen for:
Colorectal cancer: ~ 150K cases annually



Estes et al; Hepatology. 2018;67:123-133.

Summary of Epidemiology

- NAFLD is the most common liver disease in adults and children in the U.S.
- **NASH with advanced fibrosis**-increased liver-related morbidity and mortality
- Liver related morbidity and mortality include HCC and liver failure.

Summary of Epi cont…

- NASH is contributing to the rising incidence of HCC
- There is underscreening of HCC from NASH.
- NASH will be the most common indication for liver transplant within the next few years.
- This epidemic is not going away any time soon.

Risk factors for NAFLD/NASH

- Obesity, metabolic syndrome (Type 2 diabetes), PCOS, medications, malnutrition, celiac disease, Wilson's, mitochondrial disorders, TPN, cystic fibrosis
- What were the risk factors for our patient, RR?
  - Type 2 diabetes mellitus (metabolic syndrome)
  - Obesity

DM2: Strongest Risk Predictor

- strongest risk factor for the development of NASH, advanced fibrosis/cirrhosis, HCC and mortality.
- ~70% of T2DM patients have underlying NAFLD
  - Among those, 37% have NASH and 17% will develop advanced fibrosis.
- NAFLD associated with more retinopathy and nephropathy
- Higher hgb A1C associated with more liver fibrosis
- NASH associated with more nephropathy and retinopathy

Koehler et al. Hepatology 2016;63:138-147
McPherson et al. J Hepatol 2015;62:1148-1155
Younossi et al. Hepatology 2015;62:1723-1730
Stepanova M et al. Dig Dis Sci 2013;58:3017-3023

Anstee et al. Nat Rev Gastroenterol Hepatol 2013;10:330-344
Williamson et al. Diabetes Care 2011;34:1139-1144
Targher et al. Diabetes Care 2007;30:1212-1218
Younossi ZM et al. J Hepatol 2019;71:793-801

NHANES Study 2017-2018

- Fibroscan of US adults with DM2 in NHANES
- 825 patients with reliable TE results
- 73.8% had liver steatosis
- 15.4% had advanced fibrosis (≥9.7 kPa)
- 7.7% had cirrhosis (≥13.6 kPa)

23.1% should be screened for HCC and varices

Ciardullo et al. *Diabetes Care*. 2020. epub ahead

NHANES Study- Conclusion

- Prevalence of both liver steatosis and fibrosis is high in patients with T2DM from the United States
- “Our results support the screening of these conditions among patients with diabetes.”

“Advanced Liver Fibrosis Is Common in Patients With Type 2 Diabetes Followed in the Outpatient Setting: The Need for Systematic Screening”

- Lomonaco et al. *Diabetes Care*. 2021 Feb; 44(2): 399-406.

Cross sectional study

- 561 patients with DM2 attending primary care or endocrinology outpatient clinics **without known NAFLD**
- Underwent TE
- Secondary causes of liver disease were ruled out.

Results

- Steatosis present in 70%
- Fibrosis: 21%
  - Moderate fibrosis (F2: LSM ≥8.2 kPa) 6%
  - severe fibrosis or cirrhosis (F3-4: LSM ≥9.7 kPa) 9%
- ↑ AST or ALT (≥40 units/L) in **only a minority** of patients with steatosis (8% and 13%) or with liver fibrosis (18% and 28%, respectively).

Conclusion

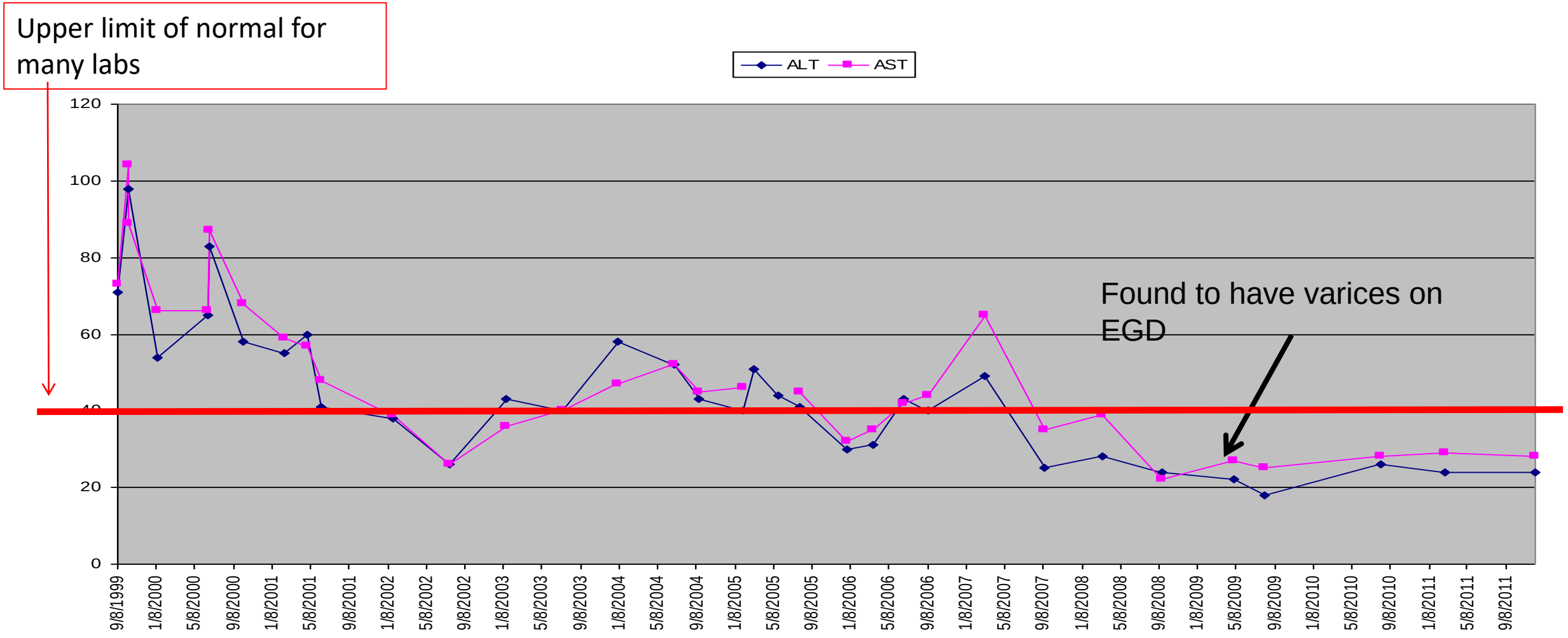
- Moderate-to-advanced fibrosis (F2 or higher), an established risk factor for cirrhosis and overall mortality, affects at least one out of six (15%) patients with T2DM.
- AST/ALT alone are insufficient as initial screening.
- These results support the American Diabetes Association guidelines to screen for clinically significant fibrosis in patients with T2DM

Problem with ALT

- Most lab “normal” ALT range inaccurate
- True normal ALT≤19 for women, ≤30 for men
- “Normal” ALT does NOT preclude NAFLD or severe disease (as we showed above)
- Also, ALT can normalize after progression to cirrhosis (“burnt out” liver)
- Look at trend over time

Portillo-Sanchez et al. J Clin Endocrinol Metab, June 2015, 100(6):2231–2238

O.A.- 60F with DM2



Ekstedt et al. Hepatology 2015;61:1547-1554.

Another Patient DB

- 57F with DM2 and obesity, previously with elevated liver enzymes, but now with “normal liver enzymes.”
- A1C 8.9%
- PCP heard talk about screening patients with DM2 for liver fibrosis

Patient DB

and there may be kidney disease in those over 65.

ENZYMES & BILIRUBIN	ALT	AST	LD(LDH)	CK(CPK)	AlkPhos	Amylase	TotBili	DirBili	IndBili
07/02/2018 17:44	24	27			83		0.2		
05/25/2018 14:07	23	26			91		0.3		
03/20/2018 12:06	21	27							
08/07/2017 16:02	27	22							
02/04/2016 12:16	22	19			85		0.3		
04/01/2015 14:10	31	27			98		0.3		
12/01/2011 15:23				44_1					
02/09/2011 12:40				80_1					
11/17/2010 06:05	51*	35			97		0.4		
11/16/2010 06:00	47*	24	145		89		0.2		
11/15/2									
04/28/2									
12/30/2									
08/24/2									
08/16/2									
03/20/2									
07/24/2									
11/05/2									
02/12/2									
10/05/2									
10/14/2004 17:45	15	16	229		77	50			

Fibroscan = 14.4kPa

Liver biopsy performed: showed NASH and stage 3-4 fibrosis.

How to screen patients with DM2?

- Want to identify those with **significant fibrosis** (not those with mild disease)
- Fibrosis staging- many commercially available non-invasive markers of fibrosis
  - Serum (usually combined with some clinical variables)
  - Elastography (ultrasound, vibration-controlled transient elastography, MR)
  - These markers do not make biopsies obsolete but does save a lot of patients from biopsies

Clinical Scoring Systems

- Free formulas using readily available variables (clinical variables and labs such as AST, ALT, platelets)
  - NFS, FIB-4, APRI
- Give you a low risk cut off, high risk cut off and indeterminate range
- Can be used as a first step in the algorithm, but lower negative predictive value in high risk populations like DM2

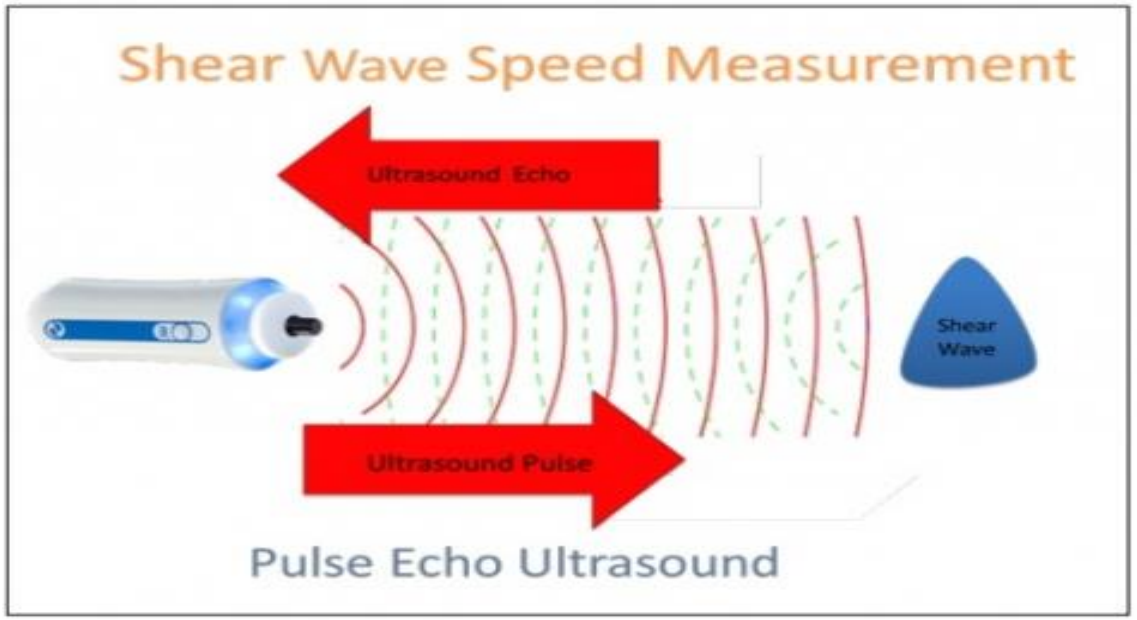
Elastography (Ultrasound, MRI, vibration controlled

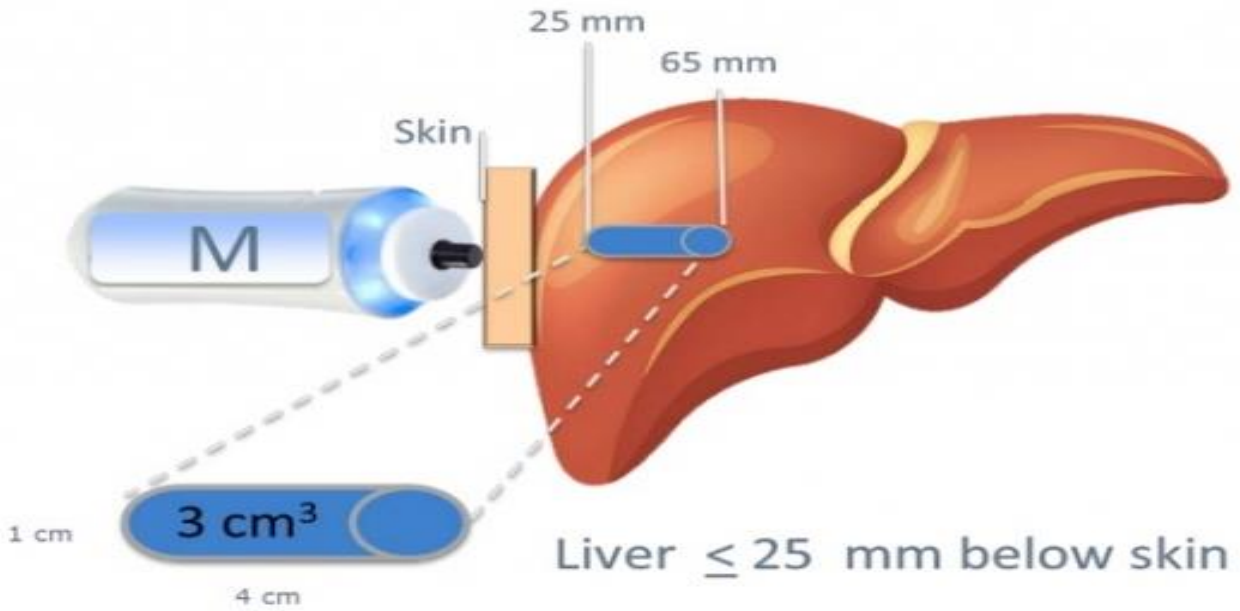
- Many different modalities- MRI, ultrasound, vibrations controlled (Fibroscan), Velacur, etc.
- All assess liver stiffness as a marker of liver fibrosis
- Some are point of care- to aid same day clinical management
- Which one depends on what's readily available to you

Vibration Controlled Transient Elastography (Fibroscan)

- Assesses liver stiffness by measuring shear wave velocity
- Liver stiffness measurement (LSM) as a marker of liver fibrosis
- Point of care
- At BIDMC, Open Access to primary care and endocrinologists to risk stratify who to send to GI

Transient elastography (TE)





Diagrams from Echosens

TE Result

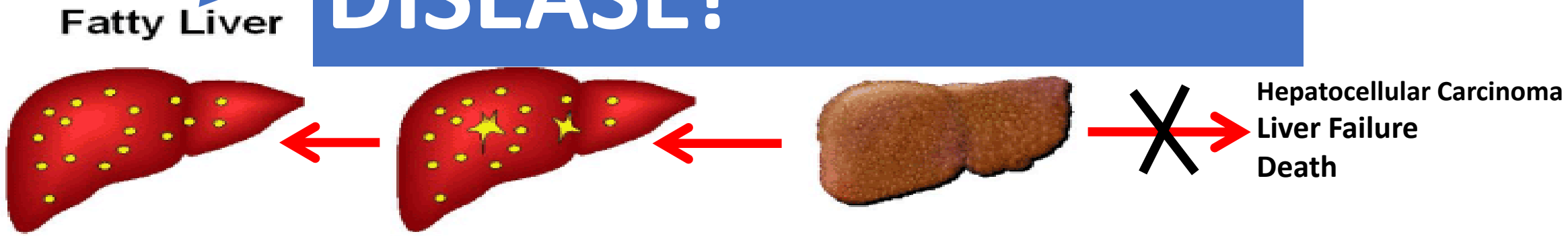
- Liver stiffness in kPa
- Low risk for advanced fibrosis <7.9kPa
- High risk for advanced fibrosis >9.9kPa
- CAP- fat quantification
- Refer patients with liver stiffness >7.9kPA
- For those less than that, repeat in 1-2 years if no weight loss or improvement in A1C. If rising liver stiffness, refer.

Tapper et al. Am J Gastroenterol 2016;111:677-684.

Early Diagnosis and Intervention

- To reverse dise
- To prevent pro
- Ideally we war

Message to patient: IT IS A REVERSIBLE DISEASE!



Back to
our patient, R.R.

Interventions

- Screen for HCC and varices in patients with advanced fibrosis (Stage 3-4)
  - to identify HCC at earlier, curable stages
  - Beta blockers to prophylax against variceal hemorrhage
- Weight loss leads to reversal of NASH, NAFLD and fibrosis regression
- More aggressive cardiovascular risk reduction (e.g. statin)
- Tighter glycemic control

RR

- No physical, laboratory, or radiologic signs of advanced fibrosis
- But risk factors: older age, obesity, DM and metabolic syndrome.
- TE (14kPa) was high indicating high risk for advanced fibrosis

Cirrhosis and Liver Cancer

- During ultrasound guided biopsy, 2.5cm focal mass found
- F/U MRI confirmed HCC
- Liver biopsy showed cirrhosis

Liver Transplantation

- EGD negative for varices
- RFA of HCC
- 16 months after initial presentation to Liver Clinic, RR underwent liver transplantation

Management of NAFLD

- Sustained weight loss- very effective but hard to achieve
  - Holy grail for metabolic syndrome
- Tighter glycemic and lipid control
- Multiple agents in clinical trial.

Sustained Weight loss

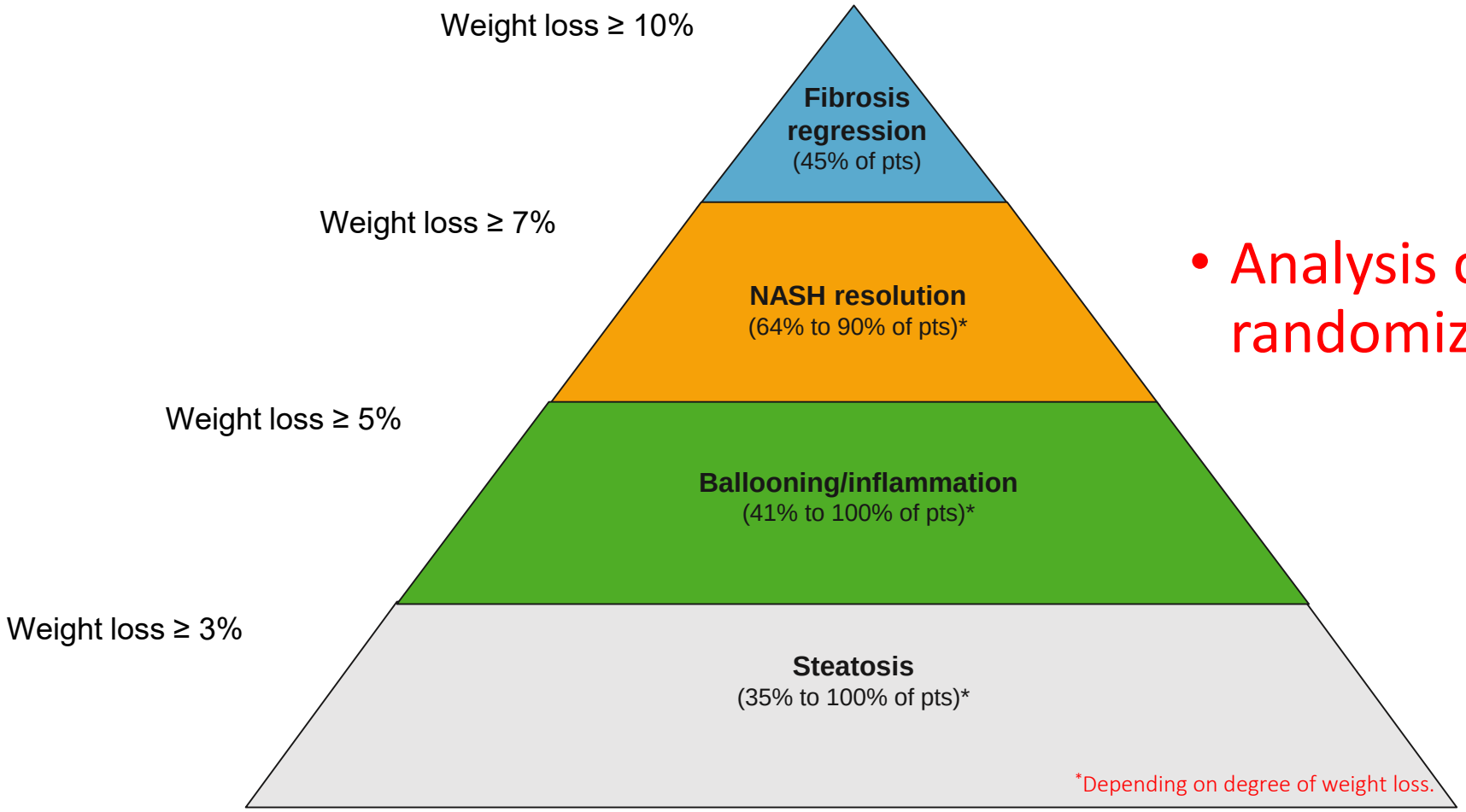
- Weight loss leads to reversal of NASH, NAFLD and fibrosis regression
- Also leads to improvement or resolution of the rest of metabolic syndrome
- Decrease cardiovascular risk.
- Number 1 cause of mortality for all patients with NASH is cardiovascular disease

Question #3
How much weight loss is needed to reverse NASH?

A. <2%
B. 5-10%
C. 10-20%
D. 15-25%

Weight Loss

leads to reversal of NASH, NAFLD and fibrosis regression



- Analysis of data from 4 randomized studies

Hannah WN, et al. Clin Liver Dis. 2016;20:339-350.

Sustained Weight loss

- Lifestyle Modifications
- Medical Weight Loss
- Surgical Weight Loss

Lifestyle Modification

- In-depth interview of patients on barriers to weight loss
  - Nutritional knowledge
  - emotional eating (untreated anxiety, depression, stress coping)
  - convenience eating (take-out, eating out, fast food)
  - resource limitations
- “Sustained changes in lifestyle”
- Avoid “diets” and “cleanses” – temporary

Medical and Surgical Weight Loss

- Many medical agents available
- Both medical and surgical weight loss methods should be use **in conjunction with lifestyle modifications**
- If the patient is not working on making the lifestyle modifications, they will regain weight once off of medical therapy or after surgery

Key Learning Points

- There is a pandemic of NAFLD with 1 in every 4 people affected worldwide. It goes up to 2 out of every 3 people with DM2
- Patients with DM2 are at high risk of NAFLD, NASH and cirrhosis.
- NASH is associated with higher cardiovascular and liver-related morbidity and mortality such as liver failure and liver cancer
- Early diagnosis and intervention can result in reversal of NAFLD, NASH and resulting liver fibrosis.

Key Learning Points

- All patients with DM2 should be screened for NASH and advanced fibrosis (regardless of ALT)
- Fibroscan is a useful tool for screening and for monitoring
- **This is a reversible disease!**
- Best treatment is still weight loss.