Non-alcoholic Fatty Liver Disease and Non-invasive Assessment of Liver Disease

Hellan Kwon, MD
Clinical Associate Professor
Division of Gastroenterology and Hepatology
Department of Internal Medicine
Michigan Medicine

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No disclosures

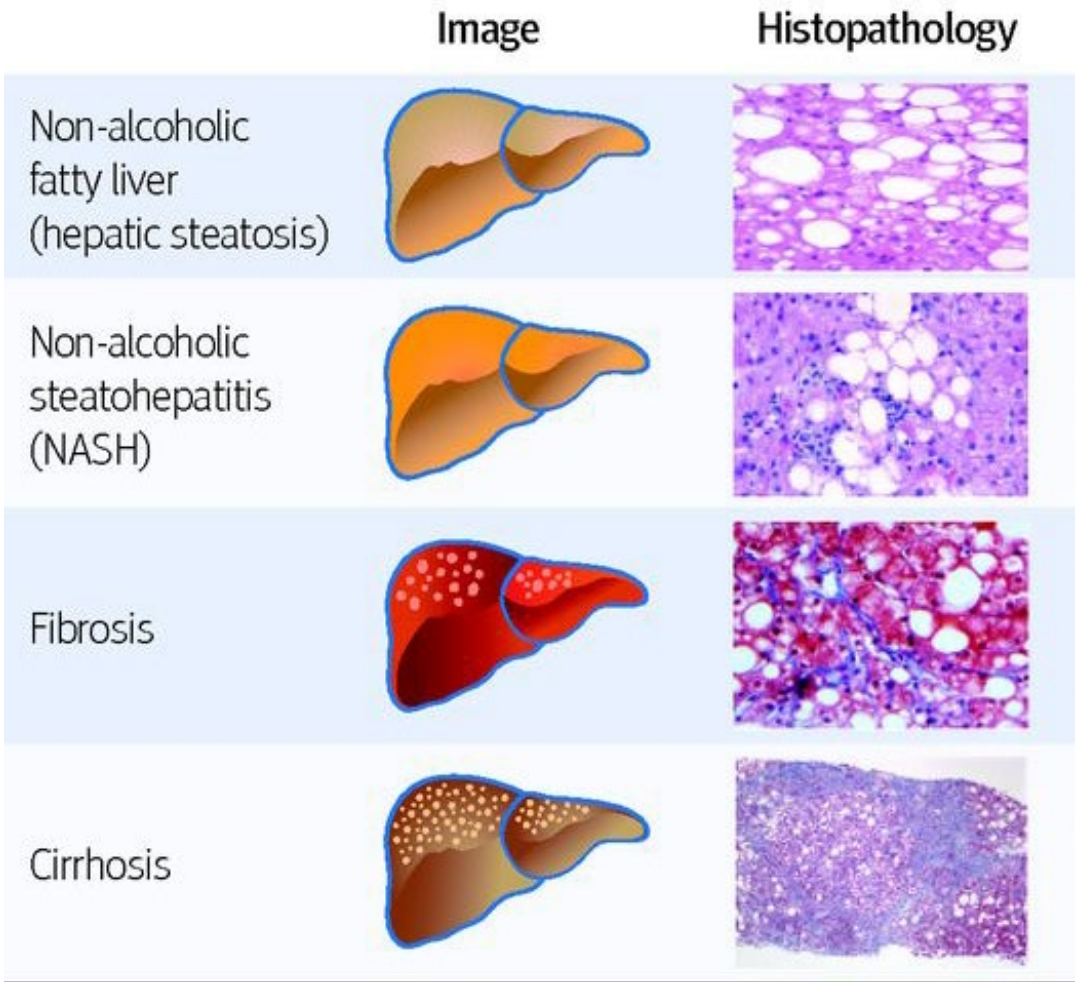
Outline

- What is NAFLD/MAFLD?
- Prevalence of NAFLD
- Outcome of NAFLD
- Noninvasive measurements of fat and fibrosis
- Management of NAFLD
- Approach to a pt with suspected NAFLD

What is NAFLD/MAFLD?

Metabolic Associated Fatty Liver Disease (MAFLD)

NAFLD: Spectrum of disease



Day C, et al BMJ 2016

NAFLD

1. Evidence of hepatic steatosis

   -- imaging or histology

2. No secondary etiology for hepatic steatosis
   - Alcohol < 14-21 drinks/wk (women vs. men) x2 yrs
   - HCV GT3, Wilsons ds, lipodystrophy, starvation, TPN
   - Amiodarone, methotrexate, tamoxifen, steroids, valproic acid, antiretroviral Rx
   - Reye's syn, HELLP syn, inborn errors of metabolism

3. Assess for causes of chronic liver disease

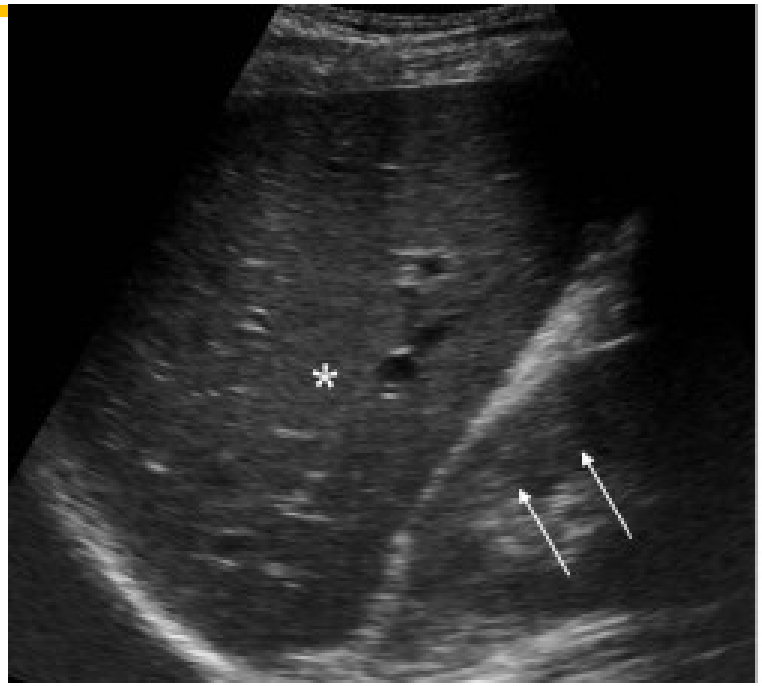
Chalasani et al. Hepatol 2012, 2018

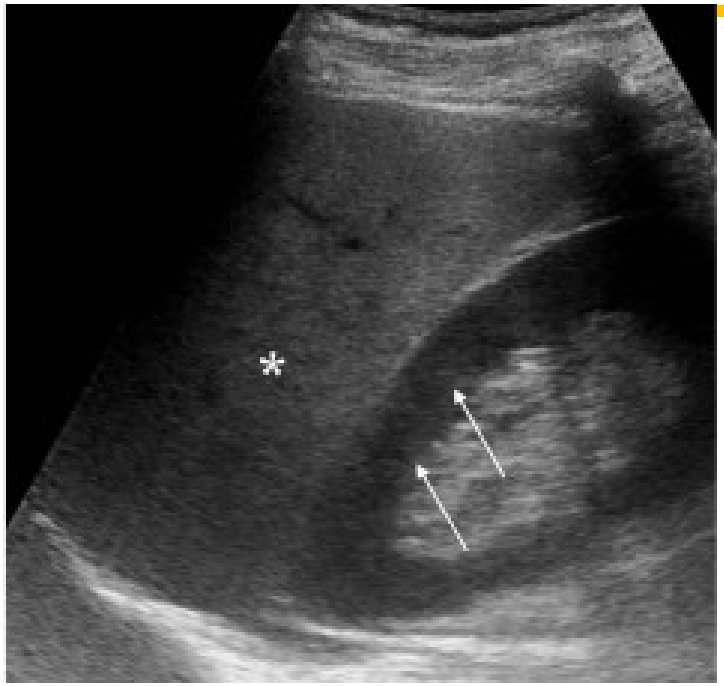
Imaging Modalities for Evaluating Hepatic Steatosis

Technique	Advantages	Disadvantages
US	Widely available, easy to perform, fast Inexpensive	Qualitative, not quantitative assessment Low sensitivity for mild steatosis Limited by patient habitus, presence of bowel gas Operator dependent
CT	Widely available, easy to perform, fast Moderate cost Quantitative assessment	Exposure to radiation Low sensitivity for mild steatosis
MRI basic (in/out of phase)	Available on all scanners Increased sensitivity for mild steatosis	Contraindication to metallic implants, pacemakers Limited by large body habitus (most scanners) Mainly qualitative assessment More costly and less available than US or CT
MRI complex (PDFF)	Quantitative assessment High accuracy and reproducibility Measurement independent of scanning parameters	Contraindication to metallic implants, pacemakers Limited by large body habitus (most scanners) High cost, limited availability
MRS	Most precise fat quantification Quantitative assessment High accuracy and reproducibility Measurement independent of scanning parameters	Contraindication to metallic implants, pacemakers Limited by large body habitus (most scanners) High cost, limited availability, expertise required Complex post processing Small portion of liver evaluated (sampling error)

Chartampilas et al Hormones 2018

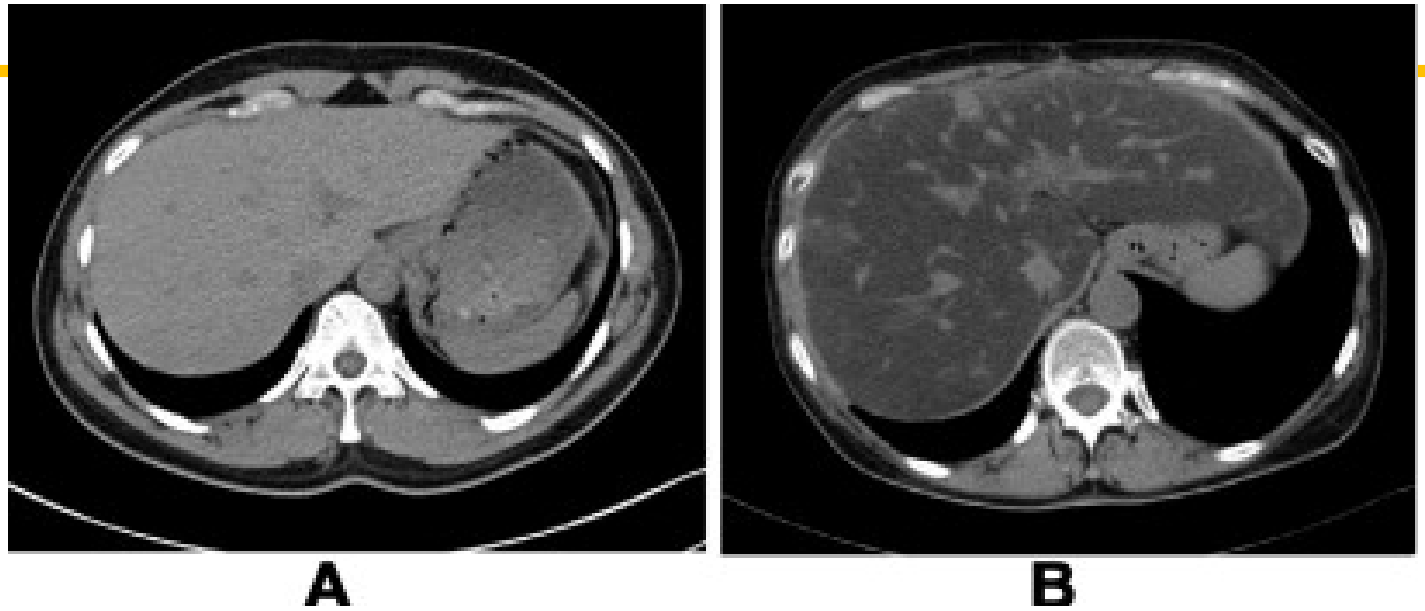
Ultrasound





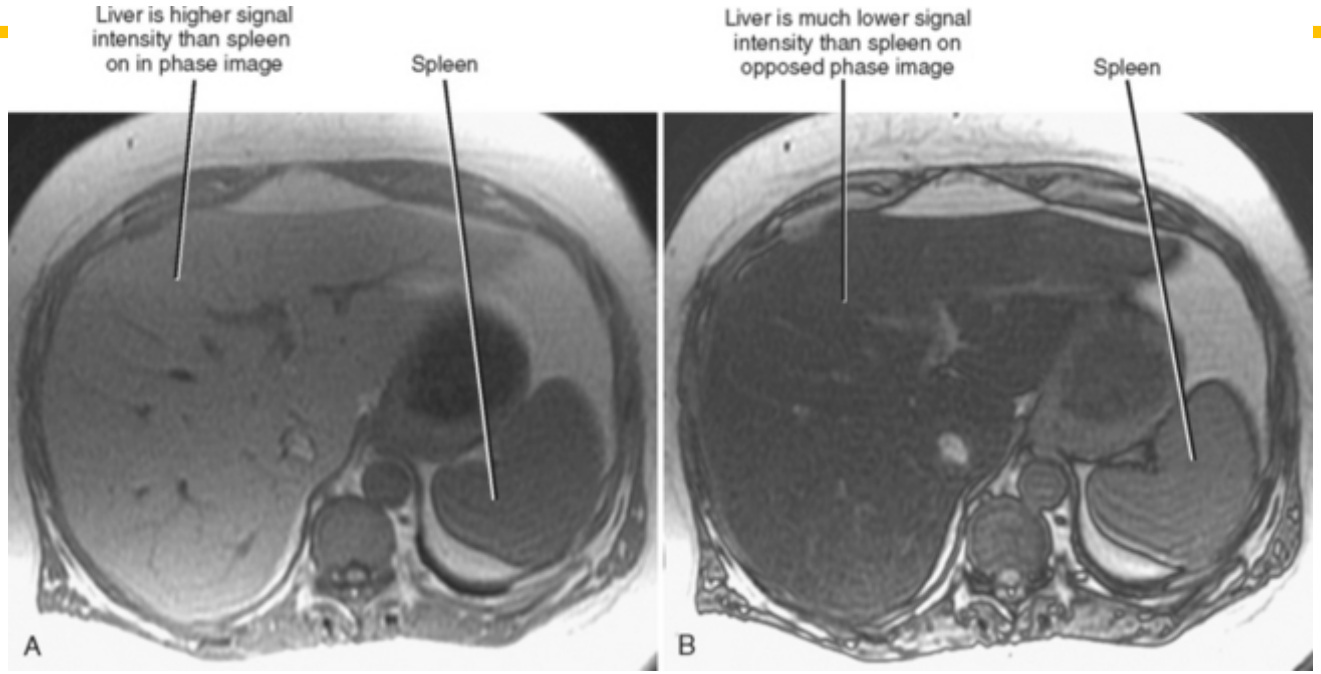
- ≥12% fat to detect fatty liver
- Sensitivity 85% specificity 93% (moderate to severe steatosis)

CT



- Quantitative measurement of hepatic steatosis by measuring liver attenuation
- Sensitivity and specificity for steatosis >30% are 73% and 91%
- CT density changes due to increased iron, copper, glycogen content, edema, inflammation and radiation

MRI



- Presently the most accurate imaging modality for evaluating hepatic steatosis
- Sensitivity and specificity are 82-90% and 89-91% for detecting all degrees of steatosis

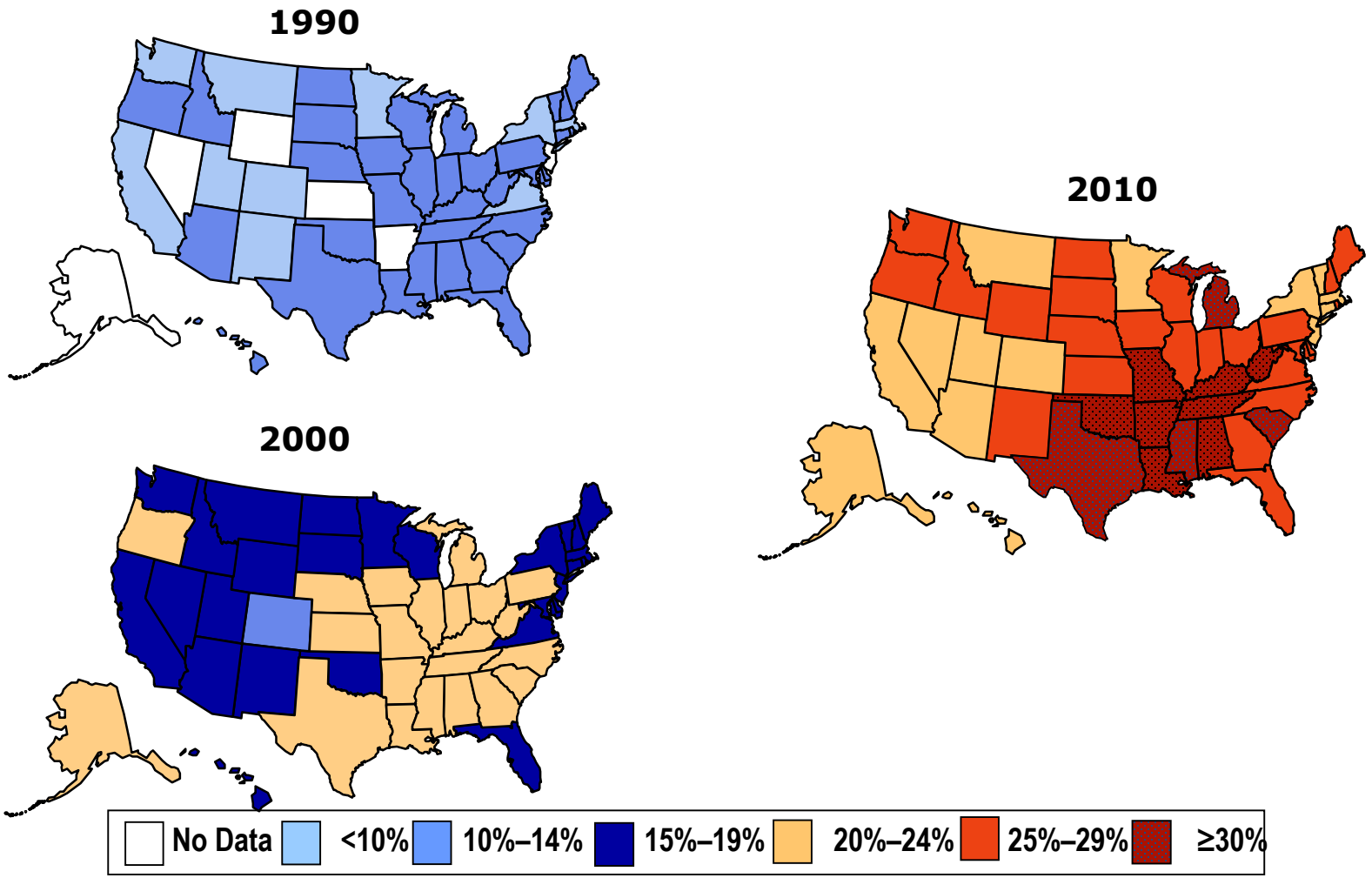
radiologykey.com

Associated Factors of NAFLD

- Obesity, T2DM, dyslipidemia
- Metabolic syndrome—bidirectional association
  - HDL <40/50, TG>150, glucose intolerance/DM, high blood pressure, abdominal girth >35/45 inches
- Increasing age, male, Hispanic white
- Emerging association
  - obstructive sleep apnea, colon cancer, osteoporosis, psoriasis, endocrinopathy, PCOS, hypothyroidism, hypopituitarism, hypogonadism, pancreato-duodenal resection

Obesity Trends* Among U.S. Adults
BRFSS, 1990, 2000, 2010

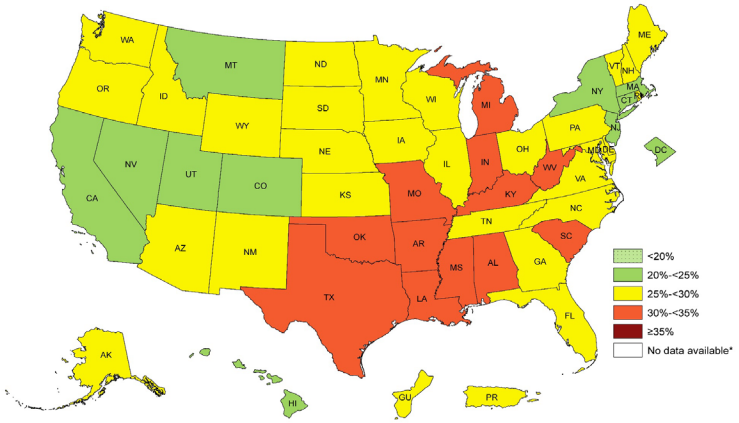
(*BMI ≥30, or about 30 lbs. overweight for 5'4" person)



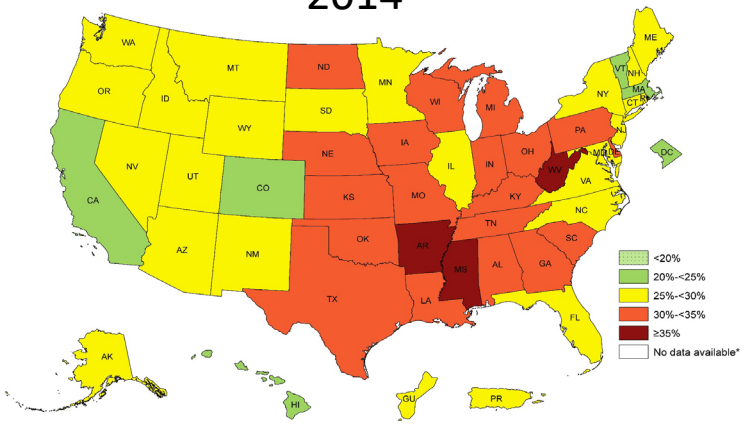
www.cdc.gov

Prevalence of Self-Reported Obesity BRFSS

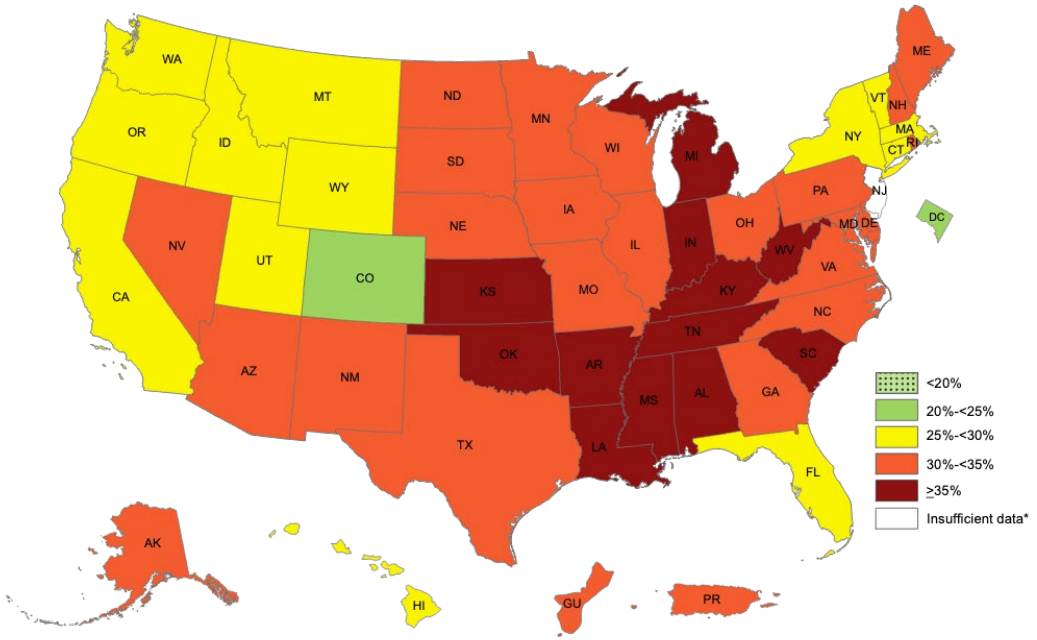
2011



2014



2019



Michigan
Adult obesity rate: 36%

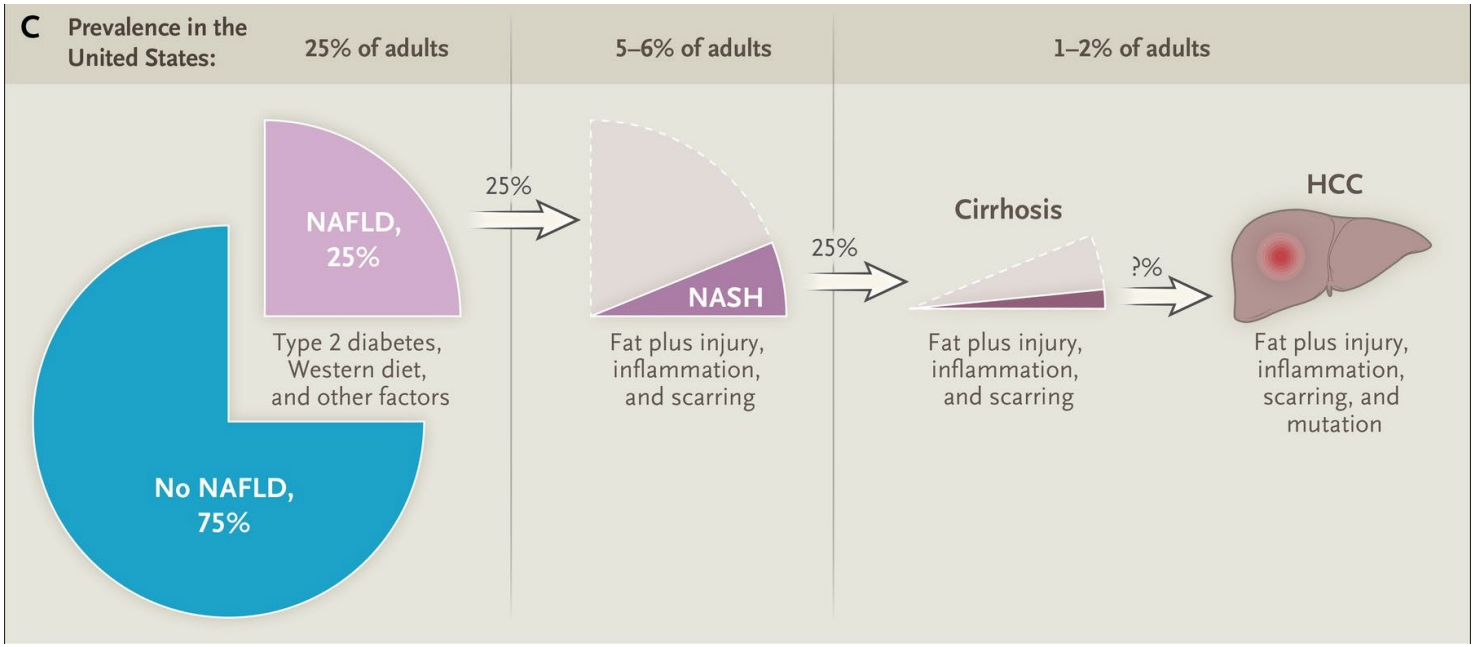
www.cdc.gov

Prevalence of NAFLD

- Overall global prevalence of NAFLD by imaging is 25% (meta-analysis, 95% CI, 22.10-28.65)
- Highest prevalence of NAFLD is from the Middle East 31.79% (95% CI, 13.48-58.23) and South America at 30.45% (95% CI, 22.74-39.44)
- Lowest prevalence rate is from Africa at 13.48% (95% CI, 5.69-28.69)

Younossi AM Hepatology 2016 Le MH PLoS One 2017 VanWagner Curr Hepatol Rep 2016

Prevalence of NAFLD--US



- Obese population –bariatric clinic: >95%
- T2DM: up to two third
- Lipid clinics: 50%

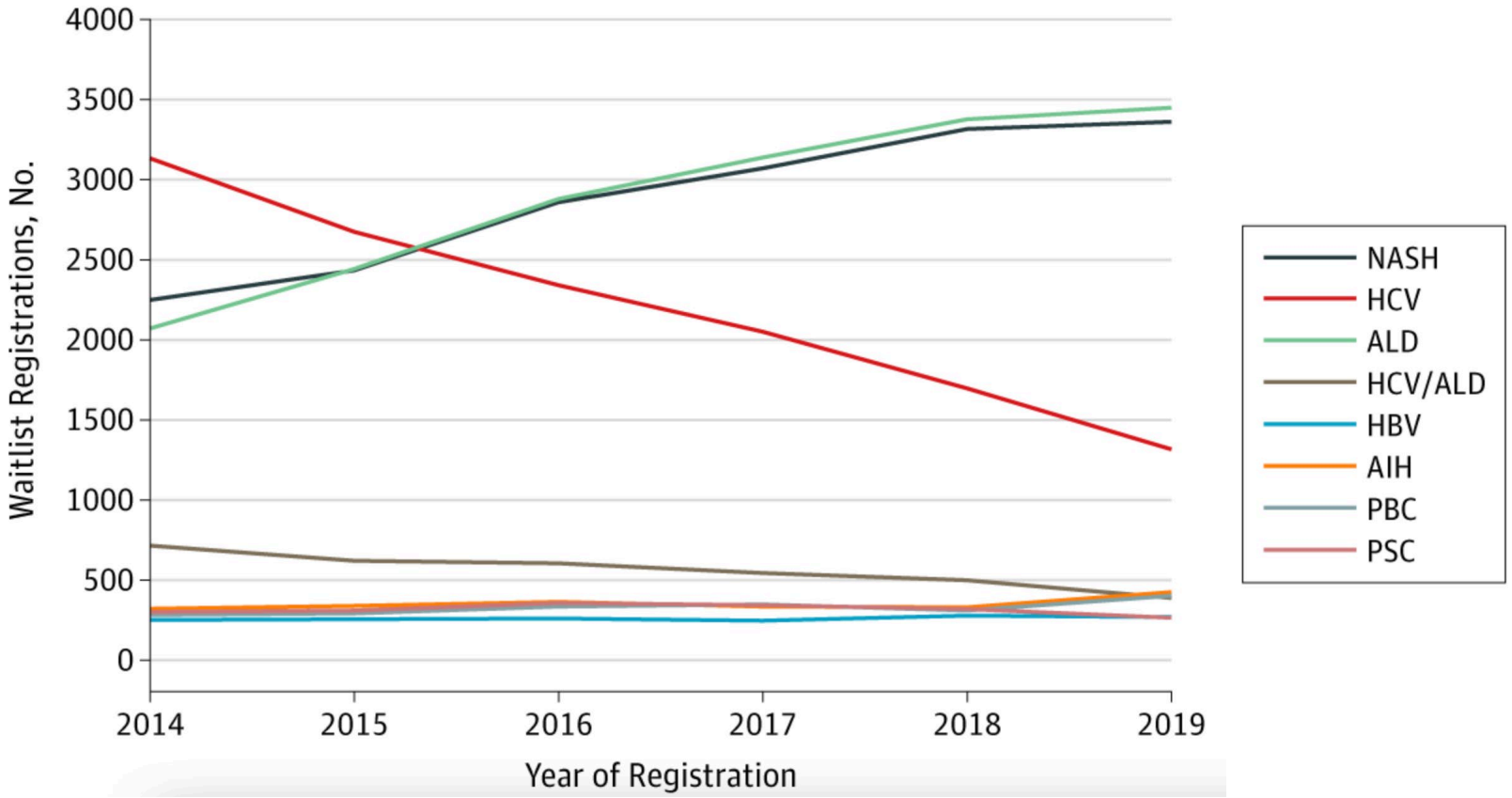
Diel et al, NEJM 2017 Williams et al, Gastroenterology 2011 Adams et al, Am J Gastroenterol 2010 Sasaki A Front Endocrinol 2014 Subichin M Surg Obes Relat Dis 2015 Byrne CD et al J Hepatol 2015 Wu KT J Clin Lipidol 2016

Outcomes of NAFLD

- Increased overall mortality compared to matched control population w/o NAFLD
- Liver-related mortality is the second or third cause of death (vs. 12th, esp NASH)

Ahmed A et al Clin Gastroenterol Hepatol 2015, Younossi ZM Hepatology 2016, Wong RJ et al Liver Transpl 2016

Liver disease etiology trend among adults awaiting LT in the US



Wong R, et al JAMA 2020

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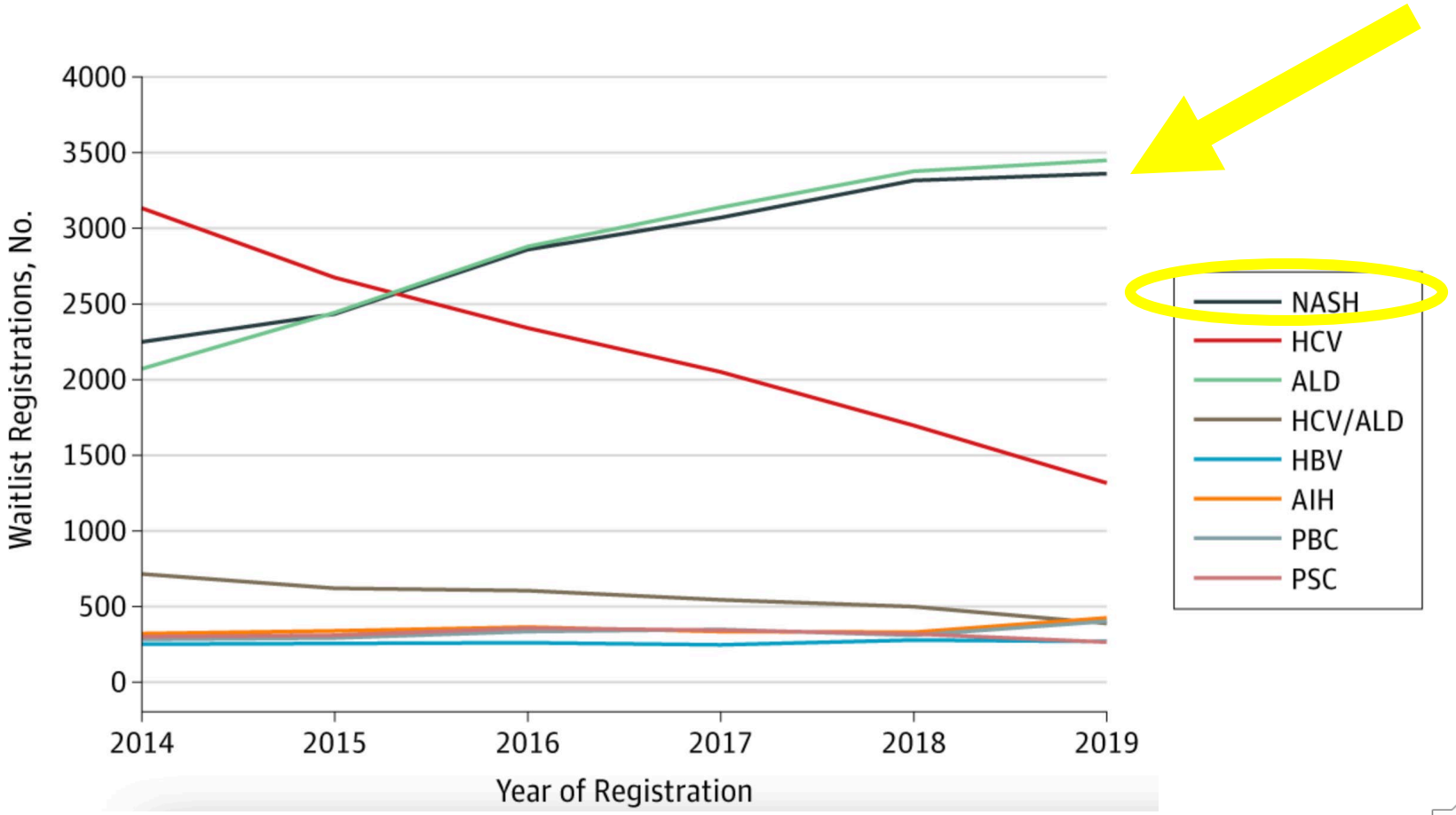


Wong R, et al JAMA 2020

Outcomes of NAFLD

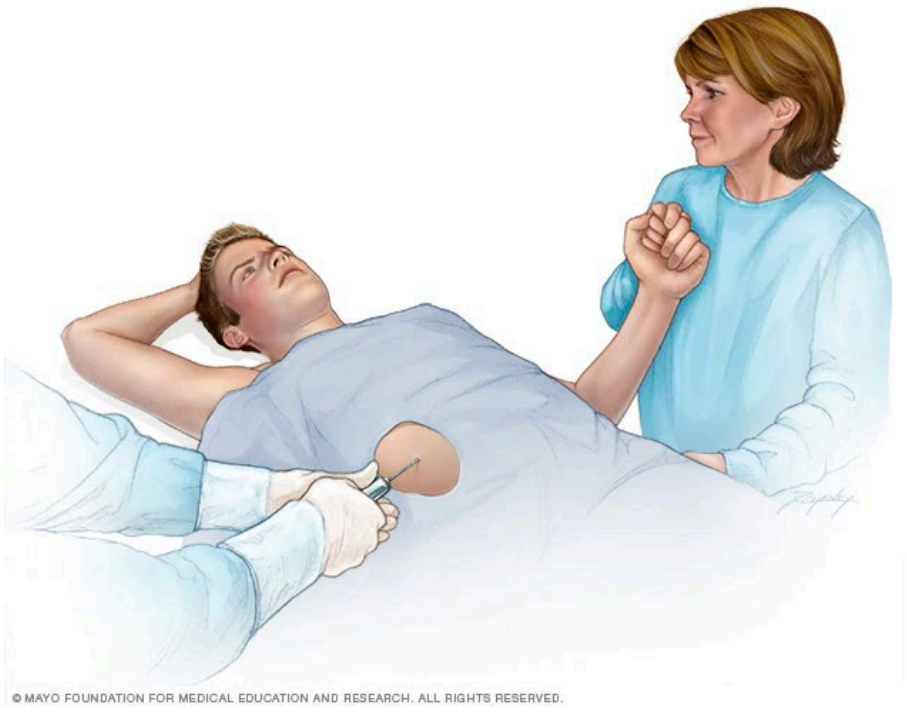
- Most common cause of death is cardiovascular disease, independent of other metabolic co-morbidities
- Cancer-related mortality is among the top three cause of death
- NAFLD is the 3rd most common cause of HCC in the US
- Fibrosis is the most important histological feature of NAFLD associated with long-term mortality

Ahmed A et al Clin Gastroenterol Hepatol 2015, Younossi ZM Hepatology 2016, Wong RJ et al Liver Transpl 2016

Noninvasive Assessment of Liver Disease

Why do we need non-invasive test?

- Liver biopsy is the most reliable approach to identify steatohepatitis and fibrosis
- Cost, sampling error, morbidity, mortality



Liver Biopsy - Complications

Table 9. Complications (Bleeding and Death) After Liver Biopsy

Author	Year	N	Bx	Mild (%) (No Blood Tx)	Moderate-Severe (%) (Transfusion or Intervention)	Mortality (%)	Needle Type
Knauer	1978	175	P	0	0.5	0	Cut
Perrault	1978	1000	P	5.9	5.3	0	Mix
Piccinino	1986	68,276	P	N/A	0.2	0.009	Mix
McGill	1990	9212	P	N/A	0.24	0.11	Mix
Janes	1993	405	P	3.2	0.49	0	Cut*
Stone	1996	168	P	2.3	1.7	0.5	Cut
Cadranel	2000	2084	P	3	0.05	0	15G; asp
Firpi	2006	3214	P	18	0.06	0.06	15G; asp
Pawa (non-ESRD)	2007	241	P	0.4	1.2	0.4	14-18G; cut
Pawa (ESRD)	2007	78	P	1.2	0	0	14-18G; cut
Huang	2007	3806	P	N/A	0.32	0	18G
Myers	2008	4275	P	N/A	0.75	0.14	Mix

Abbreviations: N, number; Bx, biopsy; P, percutaneous; Tx, transfusion; asp, aspiration; ESRD, end-stage renal disease; G, gauge. *A total of 92% of the procedures were with cutting needle.

Rockey, et al. Hepatol 2[illegible]9

Noninvasive Assessment of Advanced Fibrosis in NAFLD

- Clinical decision aids
  - NAFLD fibrosis score (NFS)
  - FIB-4 Index
  - APRI (AST to platelet ratio index)
  - Enhanced Liver Fibrosis (ELF) panel
  - Fibrometer
  - FibroTest
  - Hepascore
- Imaging
  - Transient Elastography
  - MR Elastography
  - Acoustic radiation force impulse imaging
  - Supersonic shear wave elastography
- PNPLA-3 variant genetic polymorphism
  - Associated with SH and advanced fibrosis in NAFLD
  - Not advocated for use in routine clinical care

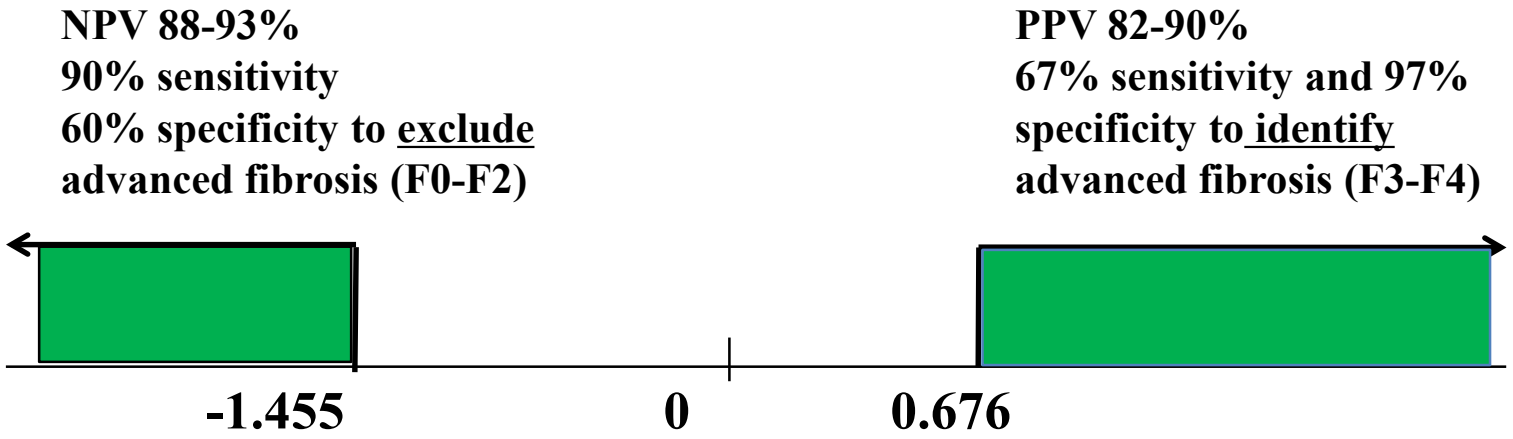
Noninvasive Assessment of Advanced Fibrosis

Author, year [ref]	Test/ score	Elements^	No. of cases	Cut-offs ^	AUROC	SENS %	SPEC %	PPV %	NPV %	Strengths/Limitations
Fibrosis										
Ratziu, 2006 [35]	Fibro-Test®	GGT, BIL, haptoglobin, apoA1°, α2macroglobulin	267	>0.30 >0.70	0.81	92 25	71 97	33 60	92 89	- Advanced fibrosis predicts overall mortality; progression to advanced fibrosis associated with CV mortality [21]
Angulo, 2007 [36]	NFS - NAFLD fibrosis score	Age, BG, BMI, platelets, albumin, AST/ALT	733	≥0.676	0.84	43	96	82	80	- Predicts liver-related events [37, 38], incident diabetes [39], all-cause and CV mortality [40] - Changes in NFS predict mortality [38]
Guha, 2008 [41]	ELF – Enhanced Liver Fibrosis	HA, TIMP1, PIIINP	192	>0.3576	0.90	80	90	71	94	- Predicts overall and CV mortality
Harrison, 2008 [42]	BARD	BMI, AST/ALT, DM	827	2-4	0.81	NA	NA	43	96	- Predicts liver-related events [37]
Cales, 2009 [43]	Fibrometer NAFLD	BG, AST, ALT, ferritin, weight, age	235	≥0.715	0.94	79	96	88	92	- Initially developed in hepatitis C [44]
Shah, 2009 [45]	FIB-4 index	Age, ALT, AST, platelets	541	≥2.67	0.80	33	98	80	83	- Predicts all-cause and CV mortality [40] and liver-related events [37]
Cales 2009 [43]	APRI – AST/platelet	AST, platelets	235	≥0.918	0.87	66	91	73	87	- Developed in hepatitis C [46]; predicts liver-

Journal of Hepatology 2015

NAFLD Fibrosis Score

- -1.675+0.037 x **age** + 0.094 x **BMI** + 1.13 x **hyperglycemia or DM** + 0.99 x **AST/ALT** - 0.013 x **platelet** -0.66 x **albumin**



  - Accuracy 90%
  - Liver bx can be avoided in 75% of pt
  - Meta-analysis of 13 studies, 3,064 pts: AUROC of 0.85 for predicting advanced fibrosis

Angulo, Hepatol 2007
Musso, et al Ann Med 2011

FIB-4 Index

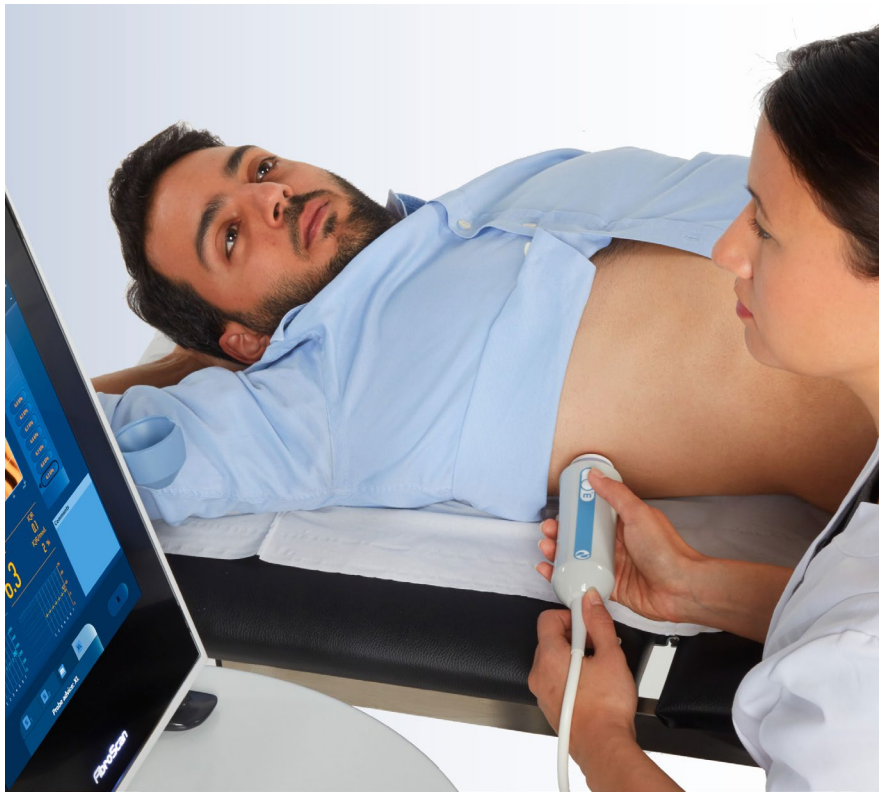
- (Age x AST)/(Platelets x square ALT)
- <1.45 are unlikely, >3.25 are likely to have advanced fibrosis

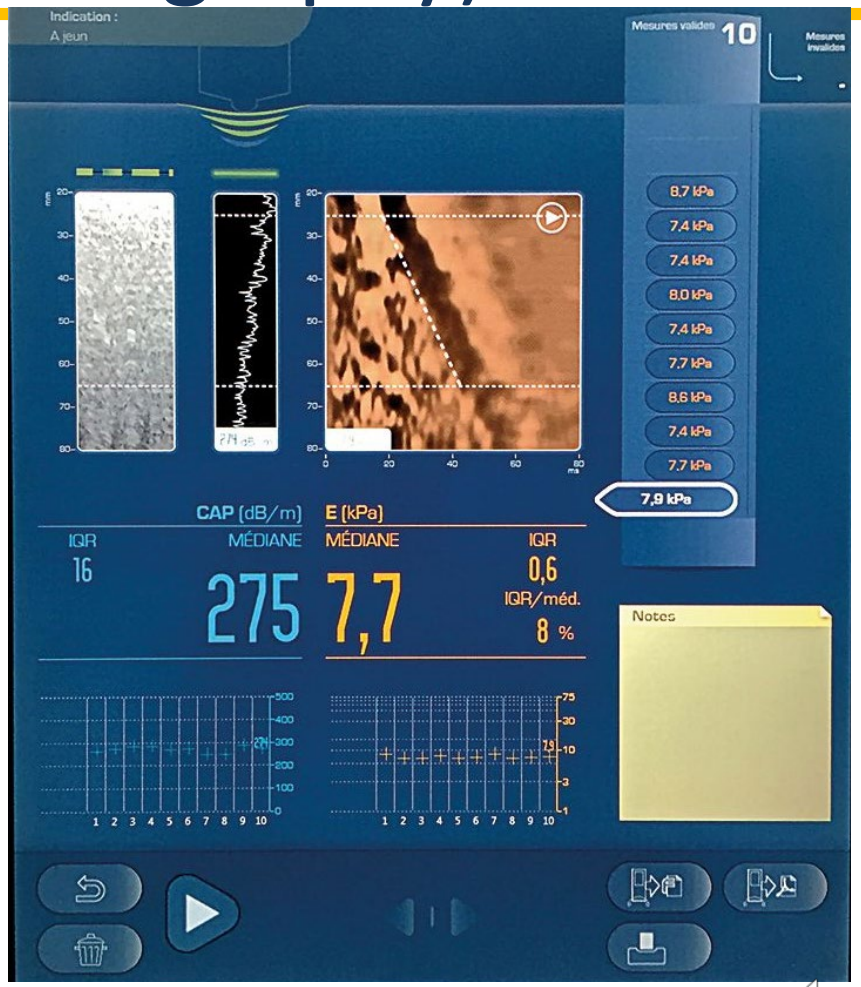
ELF Panel

- Plasma level of three matrix turnover proteins
  - Hyaluronic acid, tissue inhibitor of metalloproteinases 1, N-terminal procollagen III-peptide
  - AUROC of 0.90 with 80% sensitivity and 90% specificity for detecting advanced fibrosis
  - Approved for commercial use in Europe, not available in US

Angulo, Hepatology 2007

Fibroscan- VCTE (Vibration Controlled Transient Elastography)





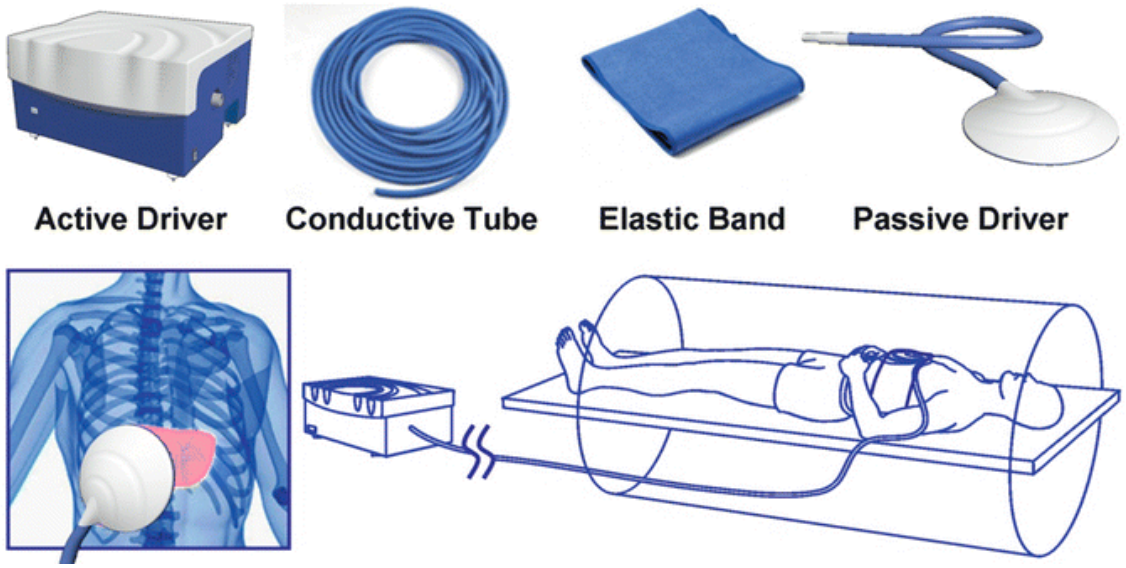
Fibroscan- VCTE (Vibration Controlled Transient Elastography)

- Optimal liver stiffness measurement cutoff for advanced fibrosis was 9.9kPa with 95% sensitivity and 77% specificity
- AUROC for detecting advanced fibrosis was 0.88-0.93 (95% CI, 0.79-0.97, 0.86-0.96)
- 2.6-27% of participants yielded unreliable results
  - Lower failure rate by using XL probe

Tapper et al, Gastro 2016, Imajo et al, BMC Gastroenterol 2015 Vuppalachi et al Hepatology 2015

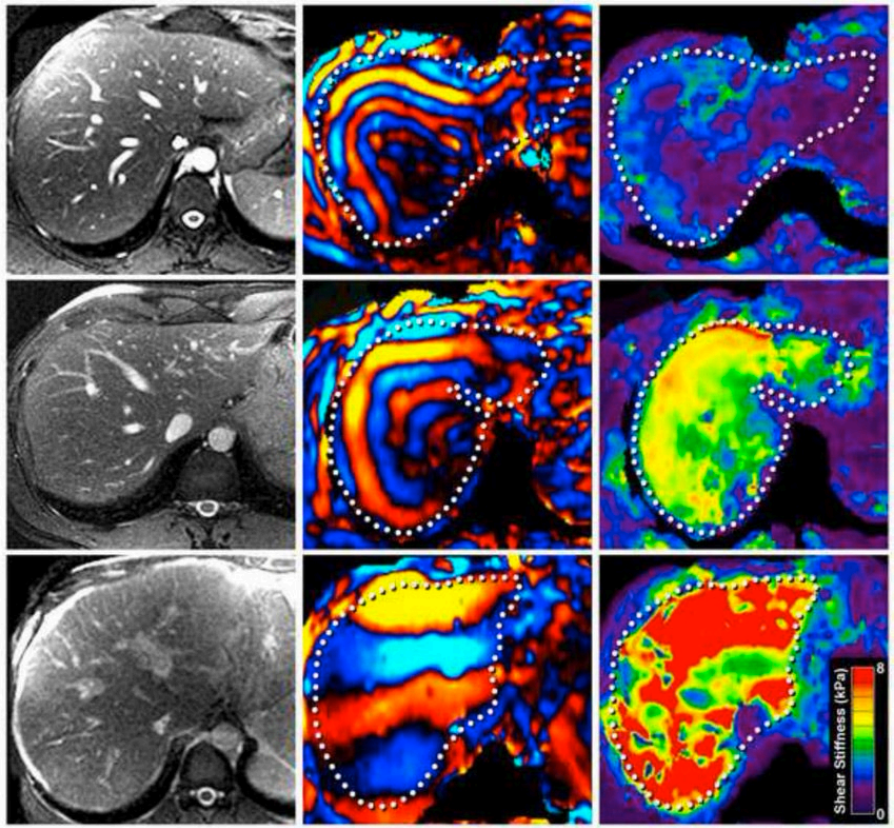
MRE

- MR Elastography (MRE)
  - Can be performed in obese, presence of ascites
  - Highly reproducible with excellent inter-observer agreement
  - Increased iron deposition leads to technical failure



Sudhakar et al. Magnetic Resonance Elastography 2014

MRE



Normal Liver: 2.1 kPa

Moderate hepatic fibrosis
Prolongation of the visualized shear waves
Mean stiffness 4.8kPa

Moderate to advanced fibrosis
Marked lengthening of the visualized shear waves
Median liver stiffness 8kPa

Comparing Noninvasive Test for Advanced Fibrosis in NAFLD

- NAFLD Fibrosis Score and FIB-4 are good predictors for advanced fibrosis when compared against liver histology in NAFLD
  - better than other indices (BARD, APRI, AST/ALT ratio)
  - As good as MRE
- MRE vs. VCTE (AUROC 0.88, 0.89 respectively)
  - MRE performs better for identifying fibrosis stage 2 or above
  - Performed equally for identifying fibrosis stage 3 or above

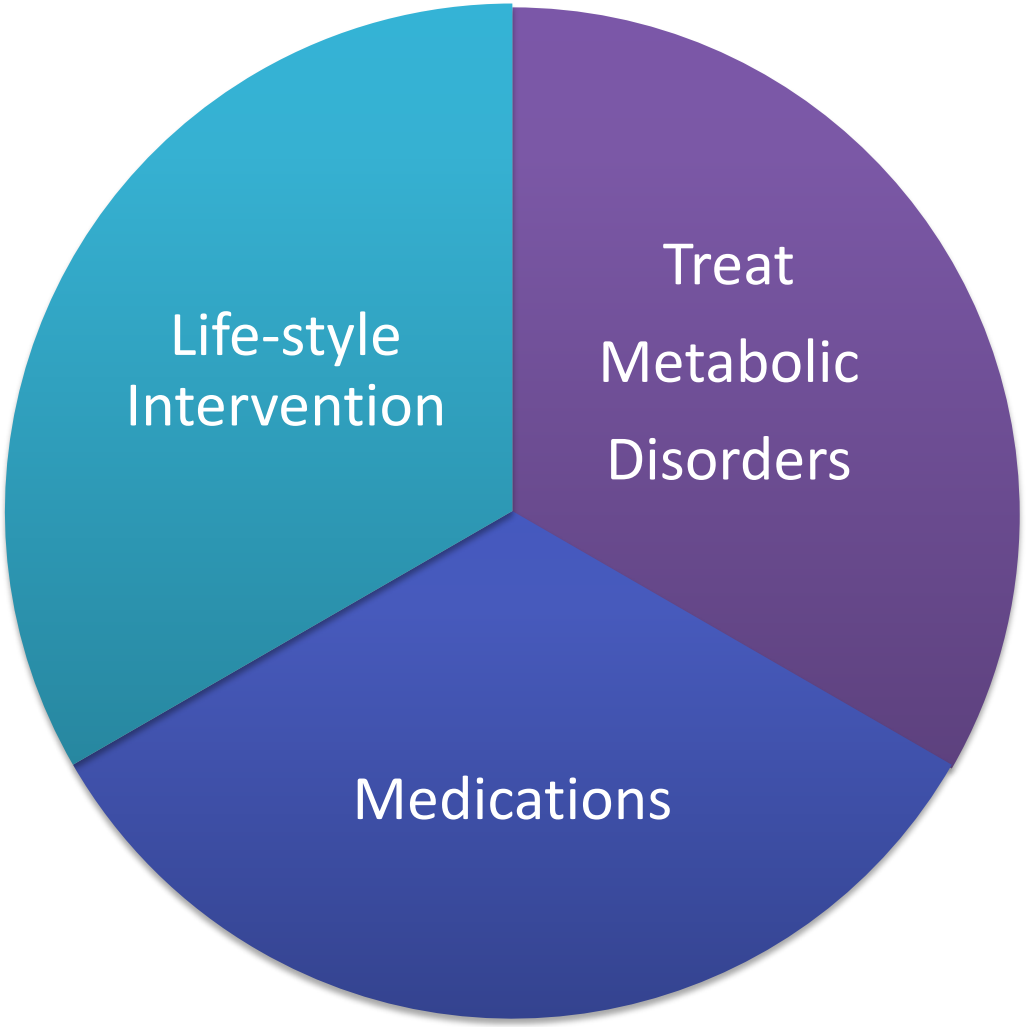
Imajo et al, Gastroenterology 2016

When should we consider a liver biopsy?

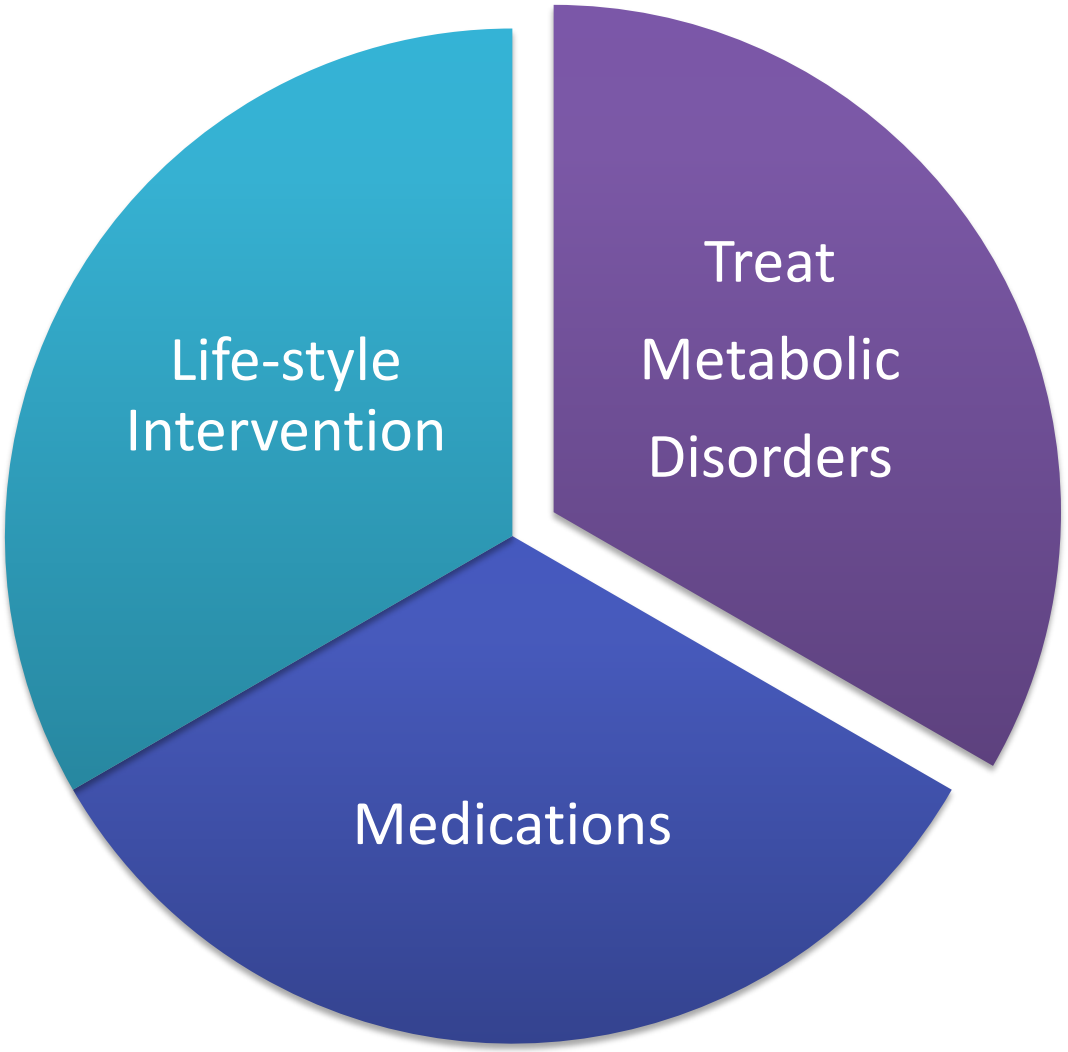
- NAFLD with increased risk of steatohepatitis or advanced fibrosis
- Pt with suspected NAFLD in whom competing etiology for hepatic steatosis and the presence /severity of coexisting chronic liver disease cannot be excluded without a liver biopsy

Management of NAFLD

Overview of Management



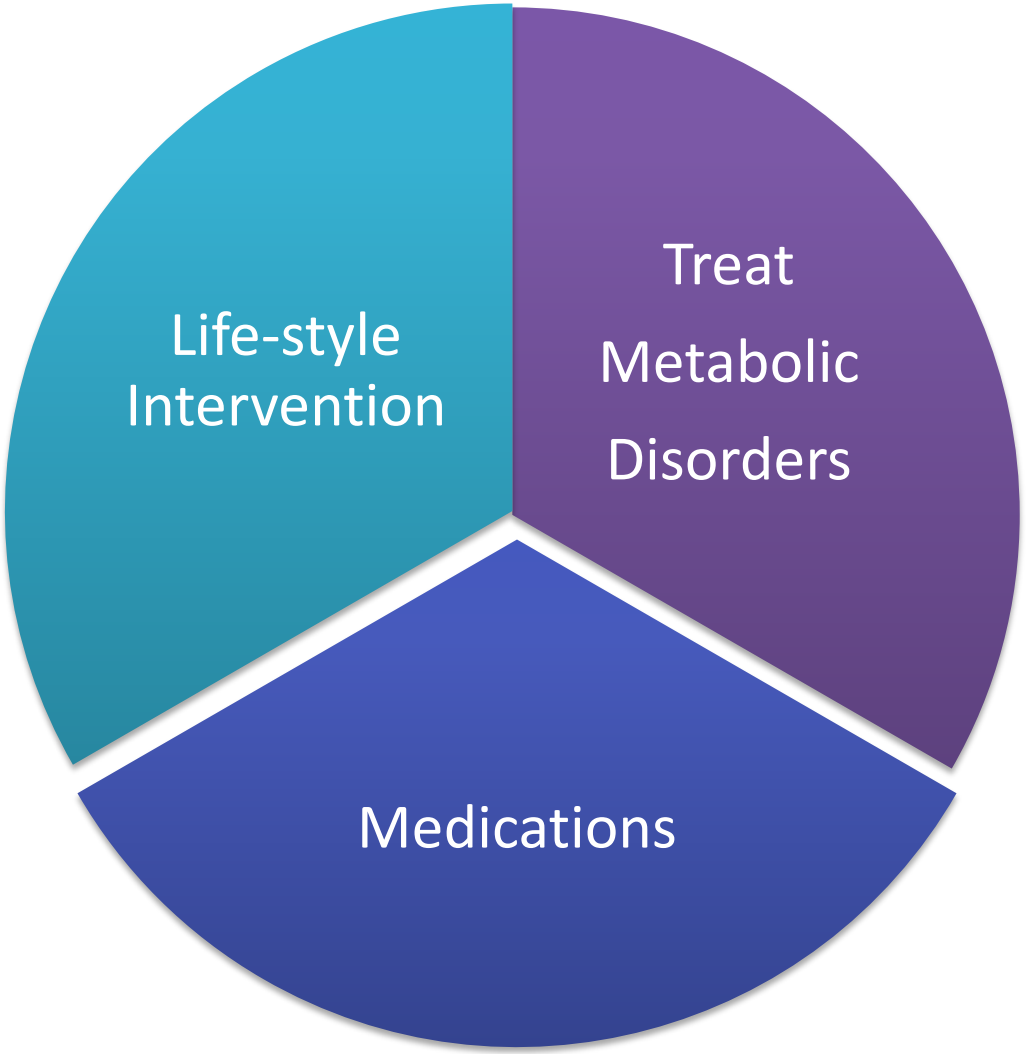
Overview of Management



*Aggressive modification of CVD risk factors

*Safe to use statins

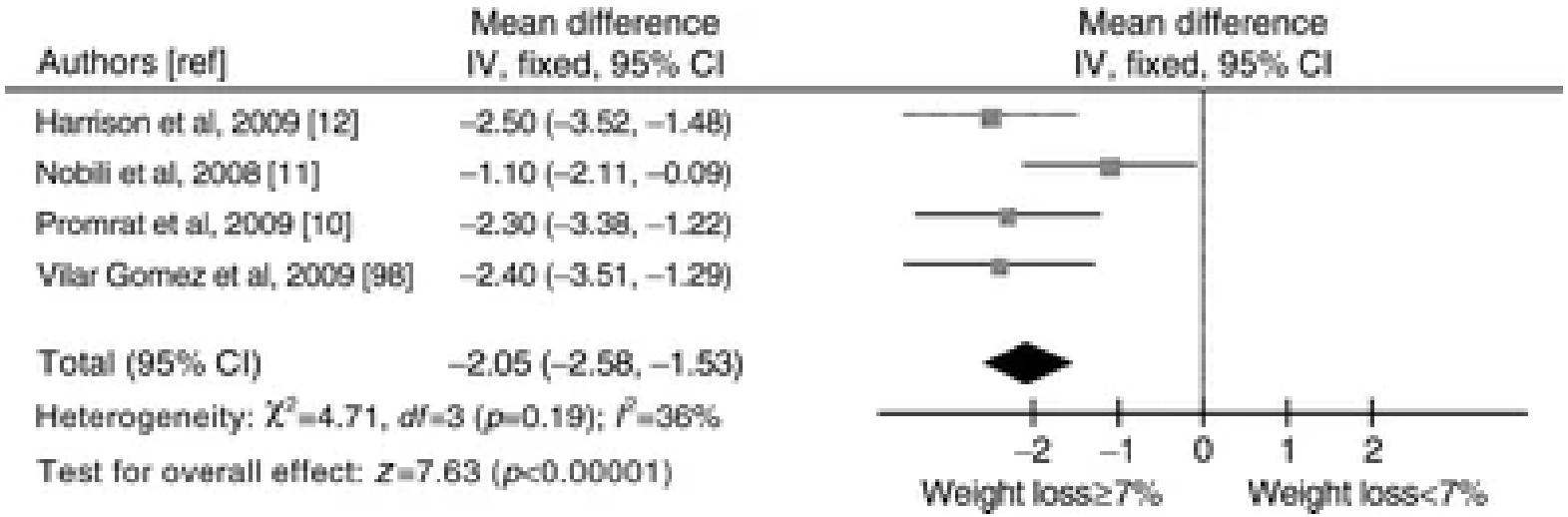
Overview of Management



Lifestyle Intervention

Lifestyle Intervention– Weight loss

- NAS change with 7% BW loss



- Improvement in fibrosis with ≥ 10% BW loss
  - Twelve month prospective paired liver biopsy study 260 pts
  - ≥ 5% BW loss stablized or improved fibrosis in 94% of cases

Musso G Diabetologia 2012 Vilar-Gomez Gastroenterology 2015

Diet

- Macronutrient composition is less important than sustained weight loss for improving cardiovascular risk
- Lack macronutrient trials in NAFLD
- Decrease caloric intake by at least 30% (750-1000kcal/d) → improves IR and steatosis
- Mediterranean diet (high monounsaturated FA) compared to high fat low carb showed improvement in steatosis (no weight change)

Exercise

- Optimal duration, intensity and type of exercise unknown
- More than 150 min/wk or increase activity by more than 60 min/wk have decreases transaminases, independent of weight loss
- Retrospective study
  - Moderate intensity exercise (MET 3-5.9) or total exercise did not improve NASH or fibrosis
  - Vigorous (≥6 METs) activity improved NASH, double had improvement on fibrosis

Lifestyle Intervention

- Combination of calorie reduction (500-1000 kcal/d) and moderate intensity exercise has best likelihood of sustaining weight loss over time
- 7-10% weight loss is needed to improve NASH and fibrosis
- Exercise alone may improve steatosis

Insulin sensitizers

- Metformin—not recommended
  - Improves transaminases and IR, no improvement in histology
- Thiazolidinediones– biopsy proven NASH can consider
  - PPAR-gamma Rc agonist
  - Pioglitazone improved NASH in DM and non-DM pts
  - Bone loss may occur in women
- Glucagon-like peptide-1 analogue-- premature for Rx
  - 48 wk randomized controlled trial
  - Improvement in steatosis and less fibrosis progression, weight loss, GI SE
  - meta-analysis shows improvement in fat and NASH

Mantovani A et al. Metabolites 2021, Cusi K Ann Intern Med 2016 Aithal GP Gastroenterology 2008 Sanyal AJ NEJM 2010

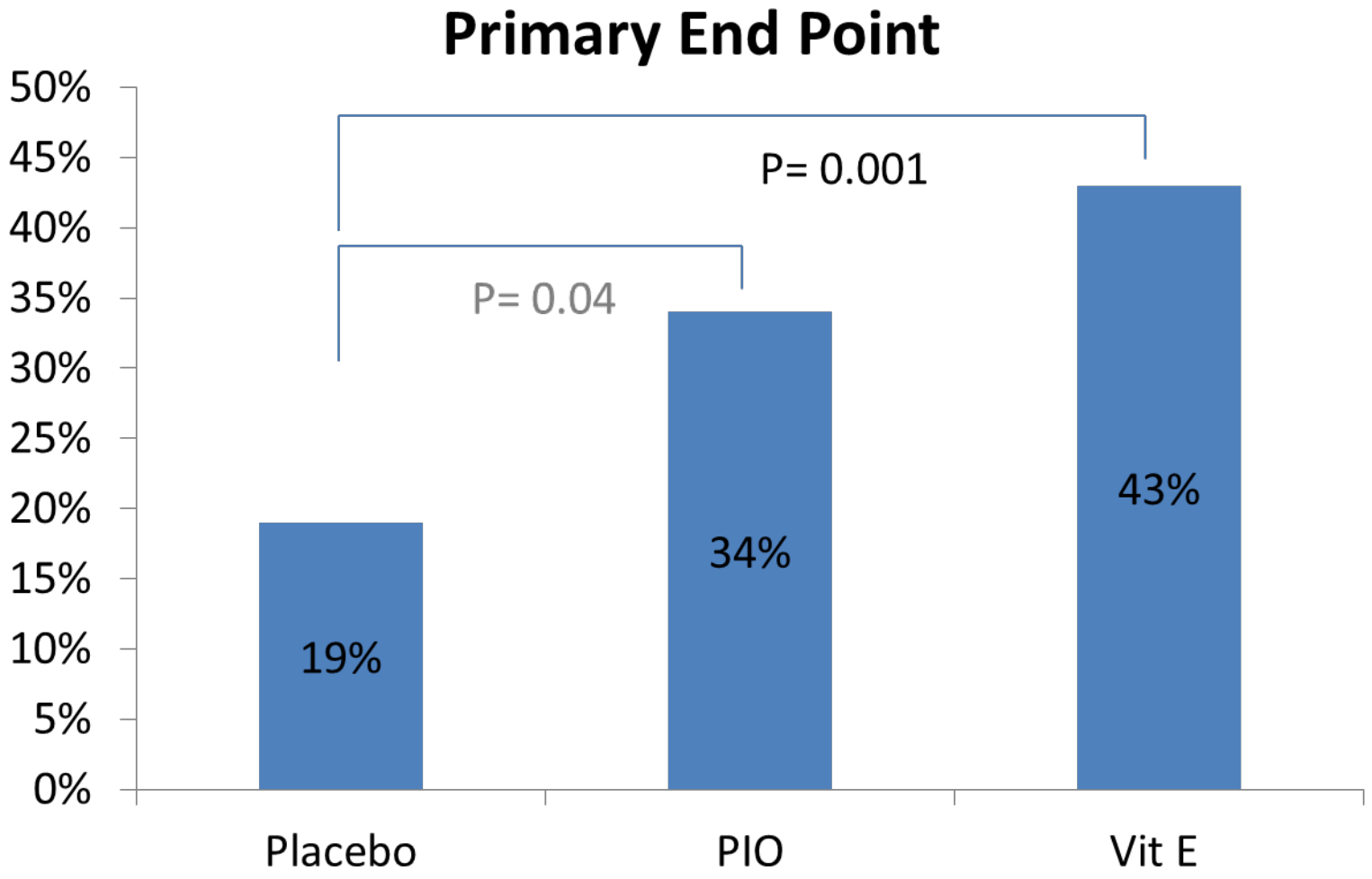
Vitamin E therapy

- Antioxidant, Limited studies, dose, histology, entry criteria, formulation of vit E, underpowered studies
- Associated with decrease in aminotransferases in NASH, steatosis, inflammation, ballooning
- PIVENS
  - nonDM pts, compared vit E, pioglitazone and placebo
  - Vit E improved histology (42 vs 19%, P<0.001)
- TONIC
  - Ped NAFLD, compared vit E, metformin and placebo
  - Vit E had resolution of NASH in greater number (58 vs 28%, P=0.006)
- Long-term safety questioned
  - Association with prostate cancer (absolute risk increase of 1.6 per 1000 person-years)

PIVENS

- **PI**oglitazone, **V**itamin **E**, or placebo for **N**on-alcoholic **S**teatohepatitis
- Multicenter RCT, 247 non-diabetic with NASH
- PIO (30mg/d) vs. Vit E (800 IU/d) vs. Placebo for 24 months, f/u 24 wks
- Primary end point: improvement in NAS ≥2 points with no increase in fibrosis

PIVENS


Primary End Point
50%
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
P= 0.001
P= 0.04
19%
34%
43%
Placebo
PIO
Vit E

PIVENS

- No significant improvement in fibrosis
- Pioglitazone associated with 4.7kg wt gain
- Insulin resistance improved with pioglitazone and returned to baseline when treatment discontinued

Vitamin E

Vitamin E (α-tocopherol) 800 IU/day improves histology in non-diabetic patients with biopsy-proven NASH

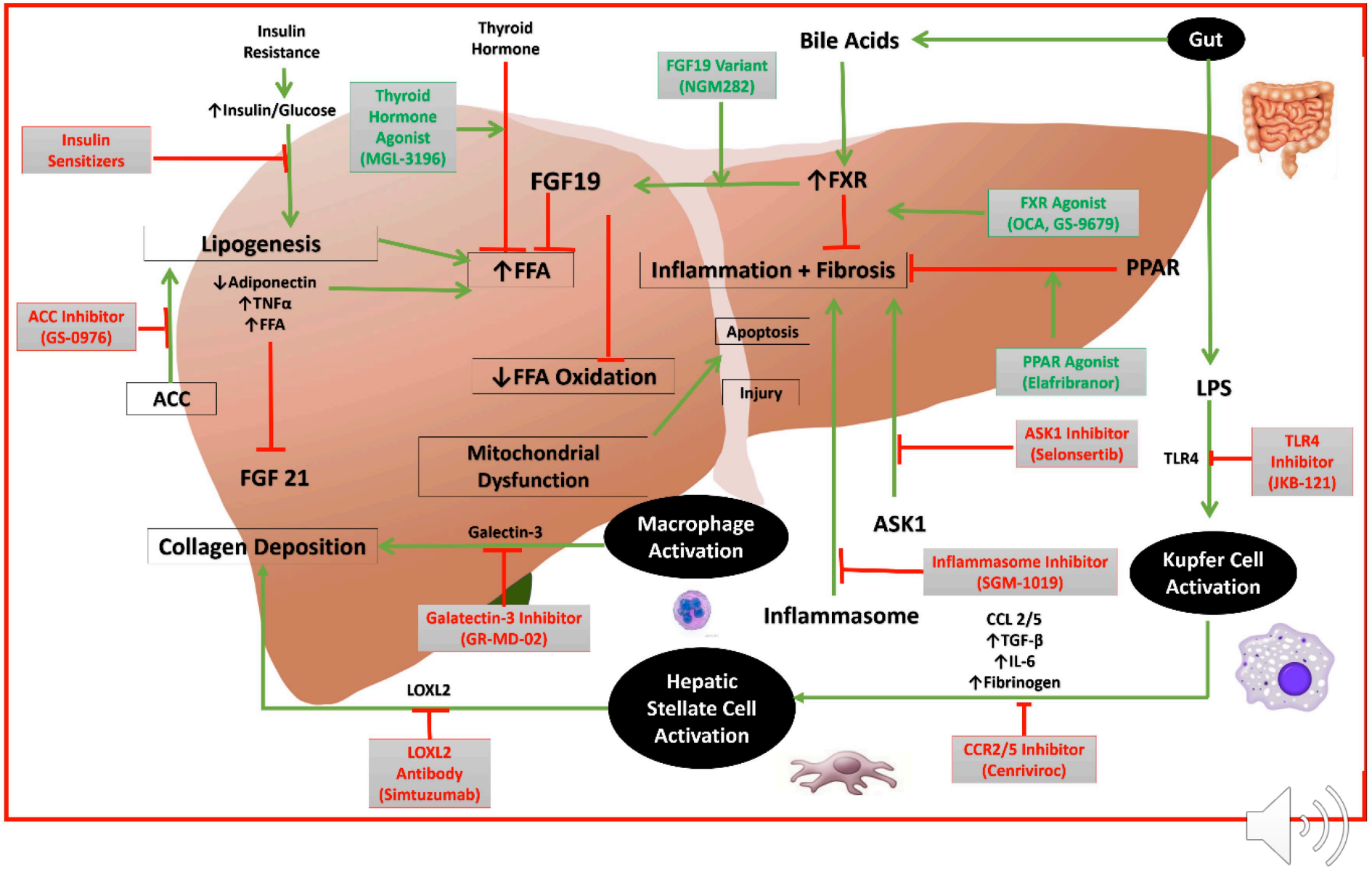
Long-term effect and safety is not established

Bariatric Surgery

- No RCT of bariatric surgery in NASH
- Prospective study of 381 bariatric surgery pt with biopsy at 1 and 5 yrs
  - Improves steatosis, ballooning and NASH within the first year
  - No difference in histology between 1 and 5 yrs
  - Minor increase in mean fibrosis score 5 years after bariatric surgery (0.27± 0.55 to 0.36± 0.59, P=0.001)
  - At 5 yrs 96% of pts fibrosis score ≤ 1 and 0.5% had bridging fibrosis
- Prospective study of 109 pts with NASH with 1 yr f/u bx
  - NASH resolution in 85% (95% CI, 75.8-92.2) in a year
  - Fibrosis improved in 33%

Mathurin P Gastroenterology 2009 Lassailly G Gastroenterology 2015

- Bariatric surgery can be considered in otherwise eligible NAFLD pts
- Premature to consider bariatric surgery as a treatment option for NASH
- Type, safety, efficacy of bariatric surgery in pt with cirrhosis due to NAFLD are not established



Dibba P et al, Diseases 2018

Drug(s)	Mechanism of action	Phase in clinical trial	Trial identification
Obeticholic acid	FXR agonist	III	NCT02548351
Elafibranor	PPAR-α/δ agonist	III	NCT02704403
Cenicriviroc	CCR2/CCR5 inhibitor	III	NCT03028740
MSDC-0602K	MPC inhibitor	IIb	NCT02784444
NGM282	FGF19 analogue	IIb	NCT03912532
Saroglitazar	PPAR-α/γ agonists	II	NCT03061721
Resmetirom	THR-ß agonist	III	NCT03900429
Tropifexor	FXR agonist	IIb	NCT02855164
Aramchol	SCD1 inhibitor	III	3rd quarter 2019
Selonsertib	ASK1 inhibitor	III	NCT03053050

Cardosa AC et al, liver International Feb 2020

Obeticholic acid

- Bile acid analogue synthetically derived from chenodeoxycholic acid
- Farnesoid X receptor agonist
- Improved fibrosis in NASH
- SE: atherogenic lipoprotein profile
  - coadministration of statin may mitigate effect

PPAR Agonist- Elafibranor

- PPAR (peroxisome proliferator-activated Rc) are nuclear Rc that regulate lipid and insulin metabolism

	Tissue	Regulates genes	Results	SE
PPAR α fibrates	liver, heart, kidney, ms	lipid and lipoprotein metabolism gluconeogensis	↓TG, ↑ HDL, VLDL lipolysis ↓ CVD risk factors, delay coronary atherosclerosis improves insulin sensitivity (animal study)	↑ cr and homocysteine, myopathy/rhabdomyolysis, lithogenicity
PPAR γ Thiazolidinediones	adipose, immune/inflammatory cells in colon, placenta	adipocyte differentiation and lipid metabolism modulate foam-cell formation	Improves insulin resistance removes cholesterol, prevents atherosclerosis development	wt gain, edema, CHF, osteoporosis, ? Bladder cancer
PPAR δ	adipocytes, small intestine, heart, skeletal ms, macrophage	lipid and lipoprotein metabolism	↑ HDL, ↓ LDL and VLDL-TG, normalize insulin level ↓ adiposity, improves insulin sensitivity	small intestinal tumor (animal), angiogenesis , ↑ intima-media thickness

Elafibranor

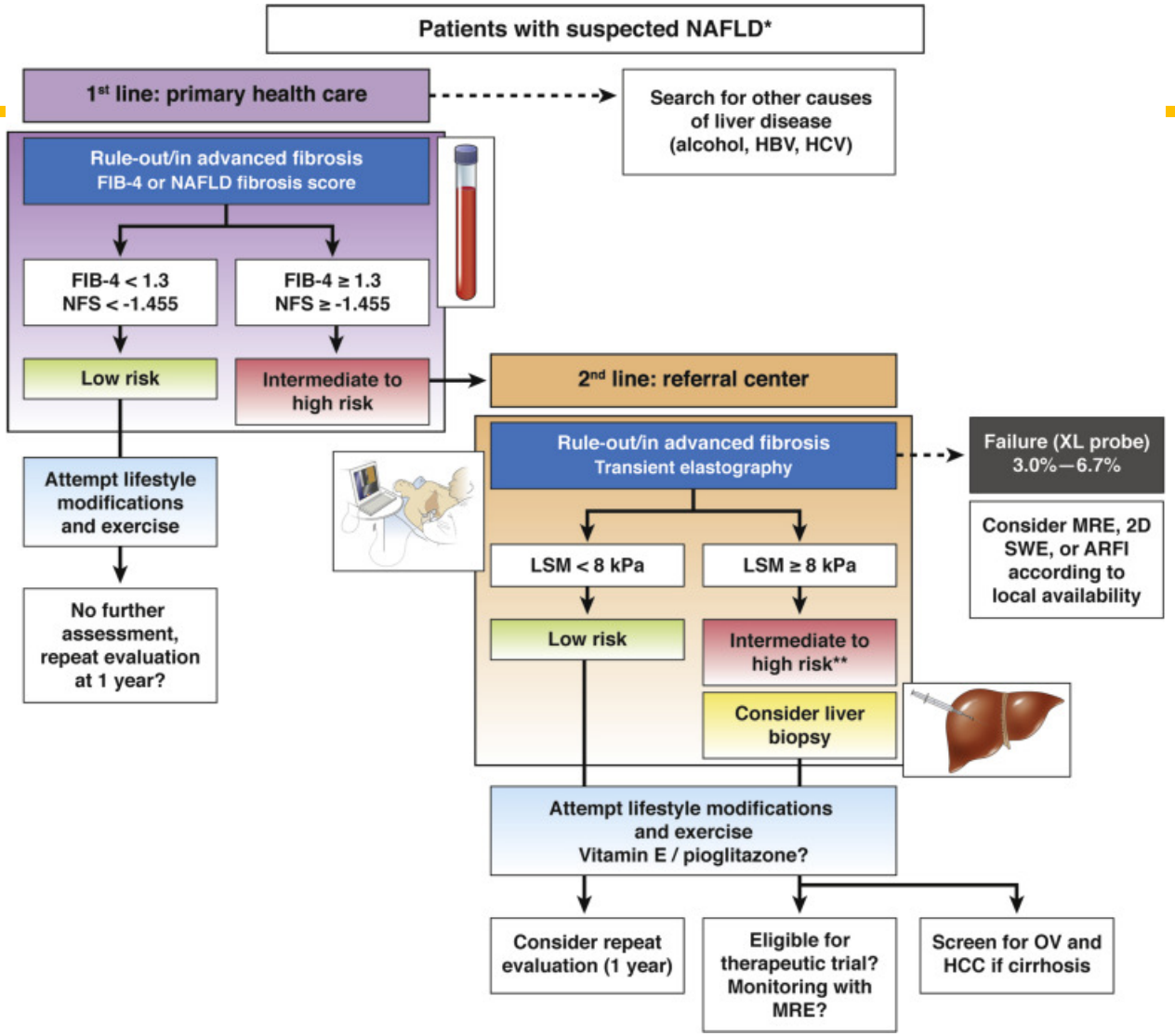
- Elafibranor acts on PPAR-alpha and PPAR-delta
- Resolution of NASH, improves IR and lipid
- SE: reversible Cr rise

Cenicriviroc

- chemokine 2 and 5 Rc antagonist that may block fat accumulation and Kupffer cell activation and hepatic stellate cell activation responsible for fibrogenesis
- Trend toward fibrosis regression

Approach to pt with suspected NAFLD

- Careful history taking
- Serologic evaluation to assess for chronic liver disease
  - Ferritin>1.5ULN was associated with more advanced fibrosis in a retrospective cohort
  - HFE gene testing, liver biopsy can be considered
  - Low titers of serum autoantibodies are common (anti-SM Ab, ANA)—21%, not associated with advanced disease



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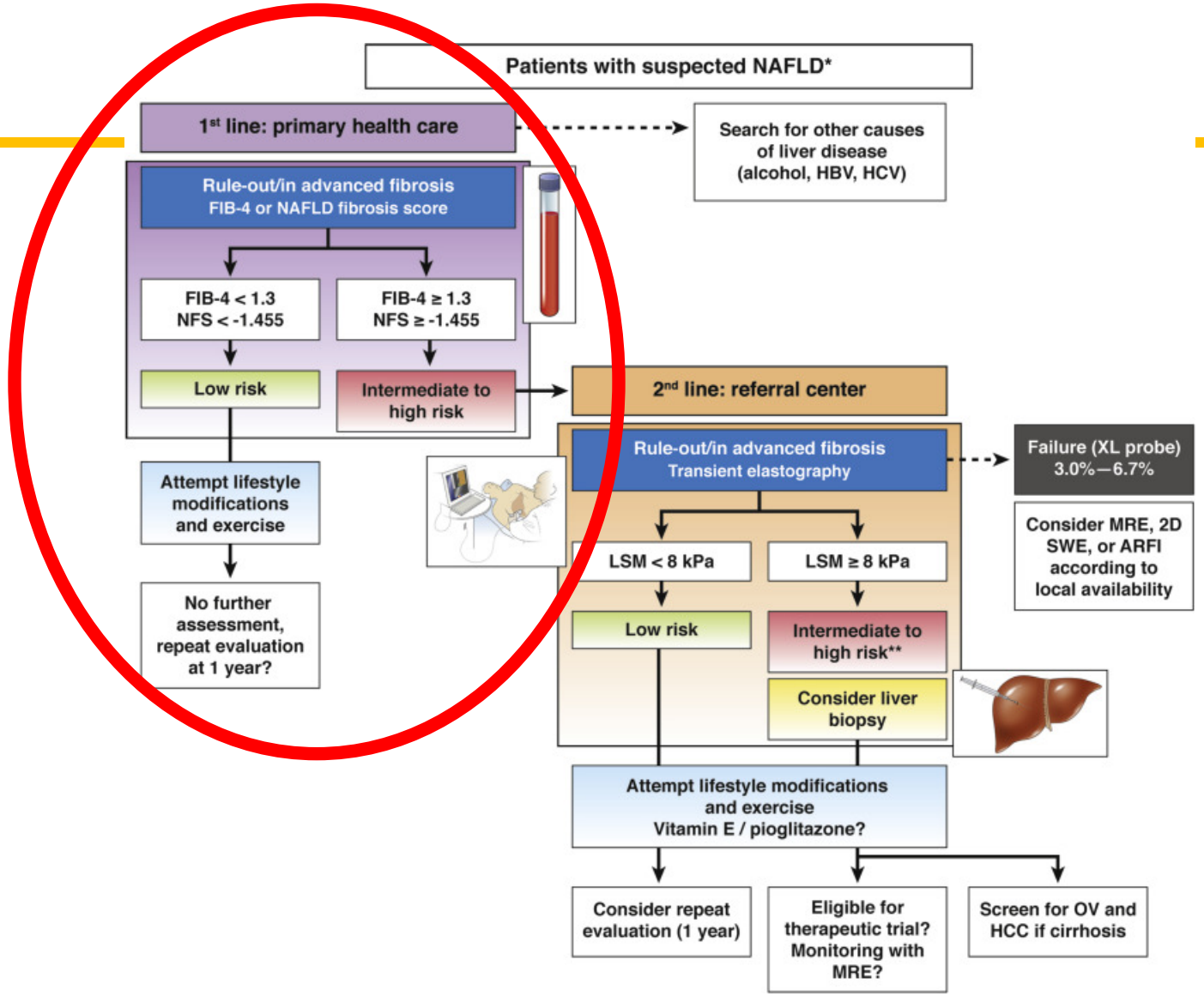

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Approach to pt with suspected NAFLD

- Routine screening for NAFLD in high risk pts is not recommended
- High index of suspicion for NAFLD in pts with T2DM
  - Consider clinical aids and VCTE can be used to identify those at low or high risk for advanced fibrosis.

Summary

- NAFLD→ MAFLD
- Diagnose by assessing for fatty liver and check for secondary causes of fatty liver
- Fibrosis is the most important histological feature of NAFLD associated with long-term mortality

Summary

- Encourage diet and exercise for 10% BW loss for improvement in histology
- Aggressive modification of CVD risk factors- statins safe
- Biopsy proven NASH
  - No DM can consider vit E therapy
  - Thiazolidinedione
- Bariatric surgery not standard of care for NAFLD
- GLP-1 agonists look promising

Thank you