Fatty Liver: When is it Benign and Who Needs to be Concerned?

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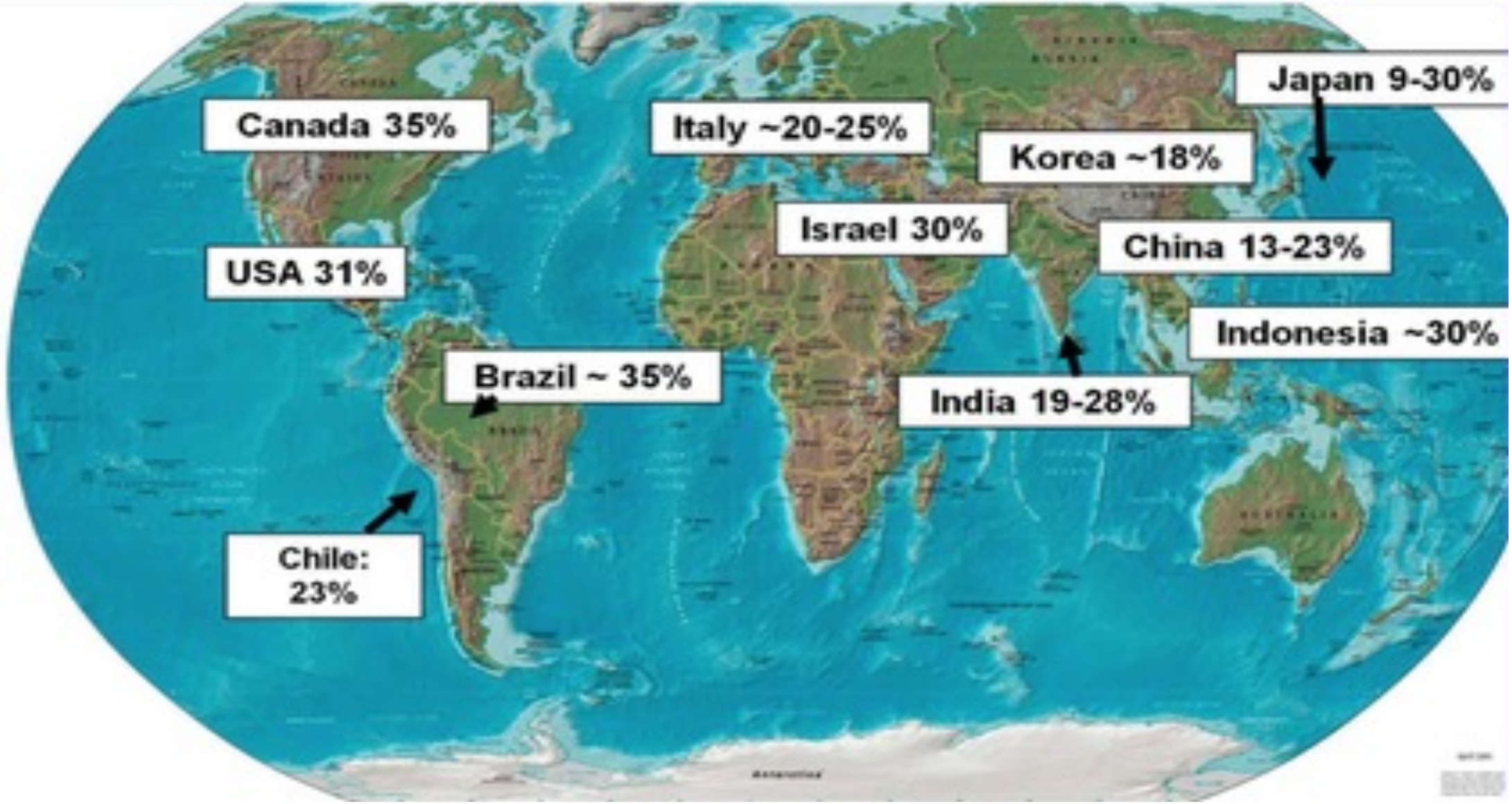
Definition of Non-Alcoholic Fatty Liver Disease (NAFLD)

- Presence of hepatic steatosis >5% AND
- No secondary causes AND
- Alcohol consumption
  - <21 standard drinks on average per week in men
  - <14 standard drinks on average per week in women
  - Considered the reasonable threshold for significant alcohol consumption when evaluating patients with suspected NAFLD.

AASLD Practice Guideline: Diagnosis & Management of NAFLD, *Hepatology* 2018; 67:328-357.

NAFLD Is Endemic



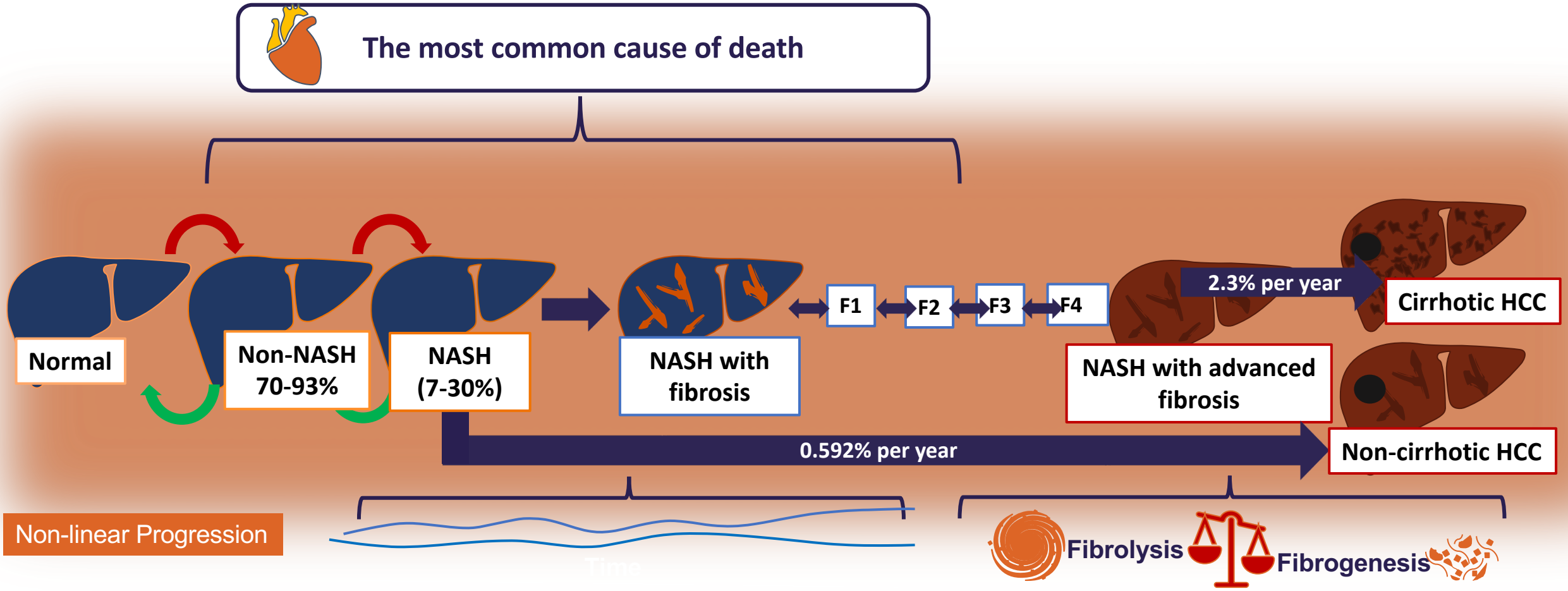
Clark J. *Clini Gastro* 2006; Bellentani et al. *Ann Intern Med* 2000; Browning et al. *Hepatology* 2004; Younossi et al. *Nature Reviews* 2017.

Epidemiology: Burden of NAFLD

- Globally, NAFLD is present in 1 in 4 people
- Ethnic predisposition
  - More common in Asian Indians>Hispanics>Caucasians>African Americans
- Risk factors include metabolic syndrome (MetS)
  - Obesity, hypertension, hypertriglyceridemia, insulin resistance and diabetes
  - PNPLA3, TM6SF2, MBOAT7 genotype
  - HSD17B13

Younossi et al. *Hepatology.* 2015;64:73–84.

The Clinical Outcomes of NAFLD

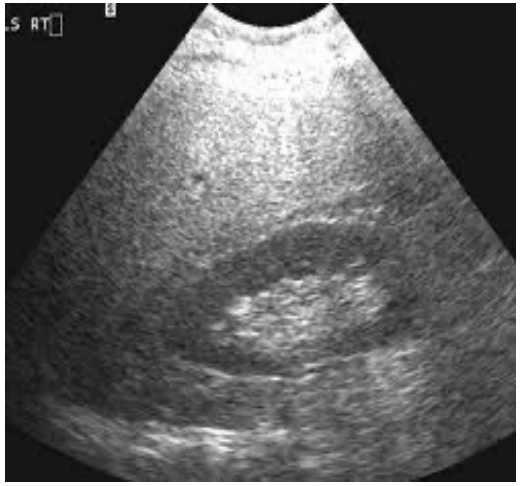


HCC, hepatocellular carcinoma.

Younossi ZM et al. *Hepatology*. 2018;68:349–360; Younossi ZM et al. *Hepatology*. 2018;68:361–371; Younossi ZM. *J Hepatol*. 2019;70:e17–e32; Jie Li et al. *Lancet Gastroenterol Hepatol*. May 2019

Incidental Discovery of NAFLD/NASH in Primary Care

- Vague right upper quadrant pain
- Hepatomegaly on exam
- Little (<20 gm/day) to no alcohol use
- “Bright” liver on ultrasound
- “Seronegative” chronic hepatitis (ALT>AST)
  - Viral serologies (HBsAb, HCV Ab)
  - Iron profile
  - Autoimmune markers (ANA, ASMA, AMA)
  - Ceruloplasmin
  - Alpha-1 antitrypsin
- Metabolic syndrome (3 or more features)
- *Caveat:* Recognition of elevated liver enzymes (normal F< 20 U/L; M< 30 U/L)



Clark JM, *Am J. Gastro* 2003

Case Finding Starts with Increased Awareness

- Among GPs, knowledge about NAFLD diagnosis and assessment is relatively inadequate, particularly for NAFLD pediatric patients
  - 60% GPs believe simple steatosis confers increased liver-related mortality
  - 4.7% GPs indicated a metabolic cause as the first determinant of an ‘‘undefined’’ persistently elevated ALT
  - 71% GPs make no referral to liver specialists for NASH
- PCPs and non-liver specialists under appreciate the overlap between NAFLD and metabolic risk factors
- Over-reliance on transaminases, even among liver specialists

Ratzui V, et al. *J Hepatol* 2012; Bergqvist CJ et al. *Int Med J* 2012; Loguercio C. et al. *Dig Dis Sci* 2011; Bertot G. et al. *Hepatol Commun* 2017.

How To Screen in Primary Care?

Laboratory Tests For Liver Fibrosis

- Simple (www.mdcalc.com)
  - Fibrosis-4 (FIB-4)
  - NAFLD fibrosis score (NFS)
  - AST/platelet ratio index (APRI)
- Proprietary
  - Enhanced Liver Fibrosis Test (ELF)
  - ADAPT/Pro-C3
  - FibroSure
  - Hepascore

Non-Invasive Tests: Fibrosis-4 (FIB-4) Index and NAFLD Fibrosis Score (www.mdcalc.com)

Fibrosis-4 (FIB-4) index

- **Predicts advanced fibrosis in the liver**
  - Age (years)
  - ALT (U/L)
  - AST (U/L)
  - Platelet count (x10^9/L)

Understanding the score:

Score <1.3 Rules out advanced fibrosis (Sn: 74%; Sp: 71%)	Indeterminate	Score >2.67 Predicts advanced fibrosis (Sn: 33%; Sp: 98%)

FIB-4<1.3 GOOD

NAFLD fibrosis score (NFS)

- **Predicts liver fibrosis in patients with NAFLD**
  - Age (years)
  - Albumin (g/dL)
  - ALT (U/L)
  - AST (U/L)
  - BMI (kg/m^2)
  - Hyperglycaemia
  - Platelet count (x10^9/L)

Understanding the score:

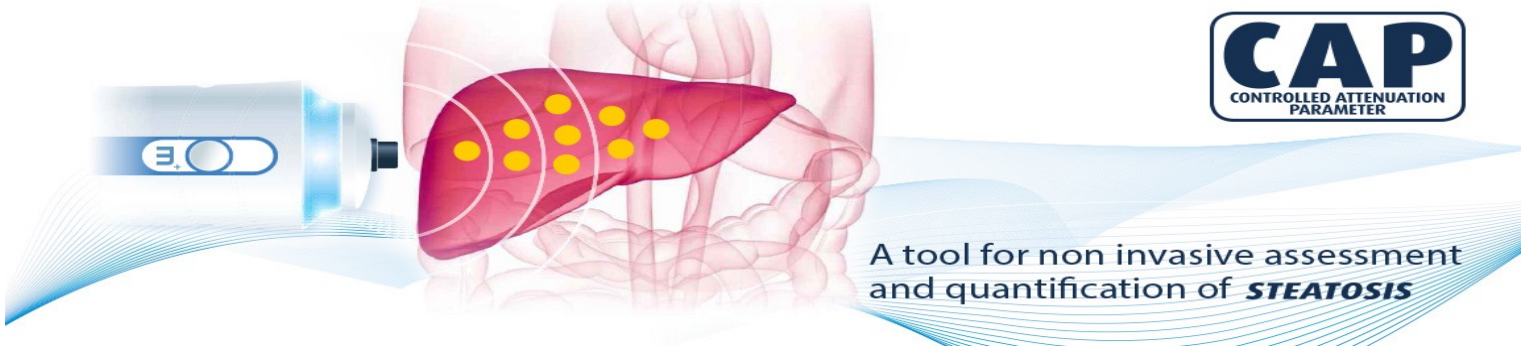
Score <-1.455 Rules out fibrosis (Sn: 82%; Sp: 77%)	Indeterminate	Score >0.676 Predicts fibrosis (Sn: 51%; Sp: 98%)

NFS<-1.455 GOOD

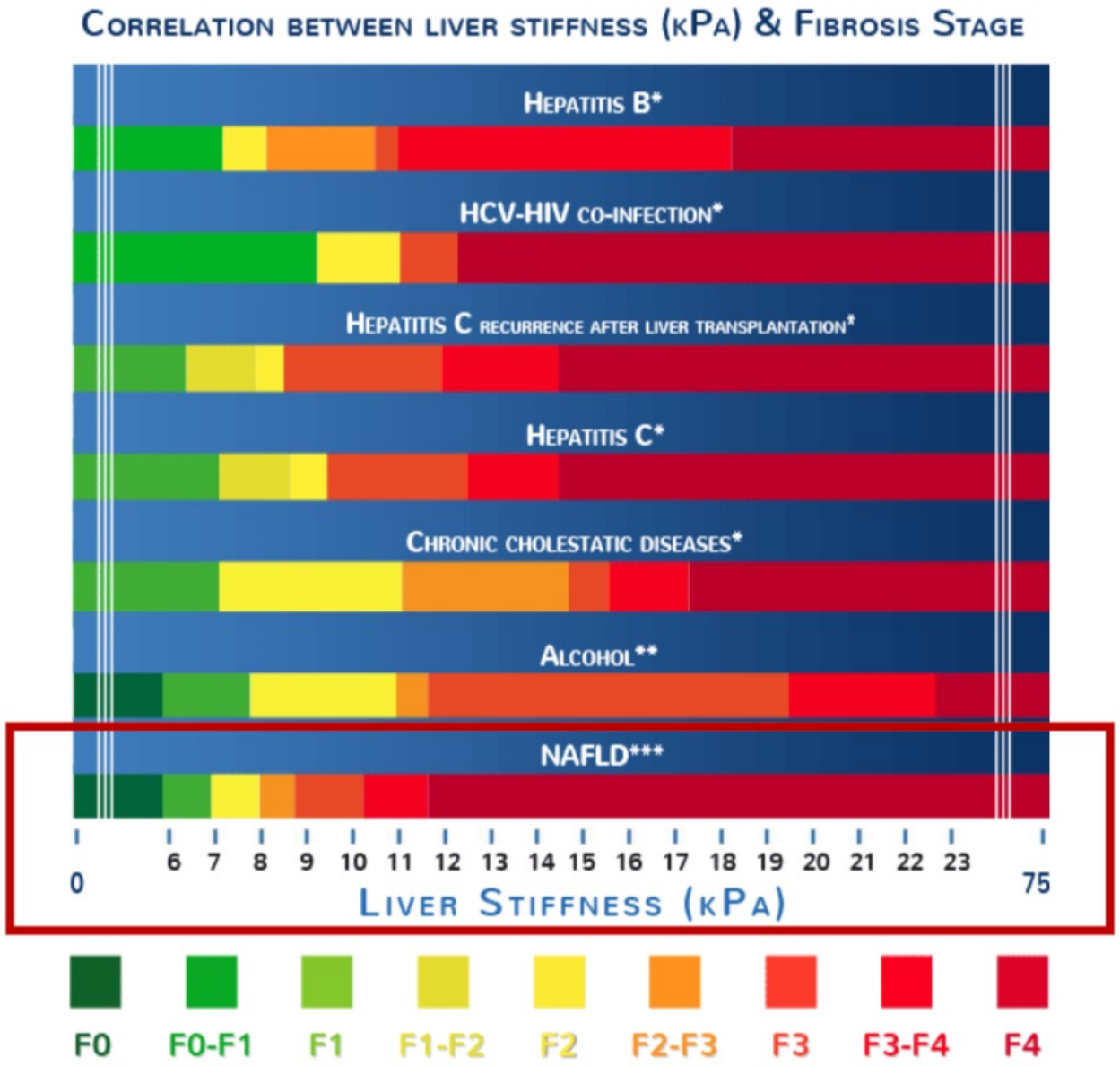
Sn: sensitivity; Sp: specificity.

Shah AG et al. *Clin Gastroenterol Hepatol*. 2009;7:1104–12; Angulo P et al. *Hepatology*. 2007;45:846–54.

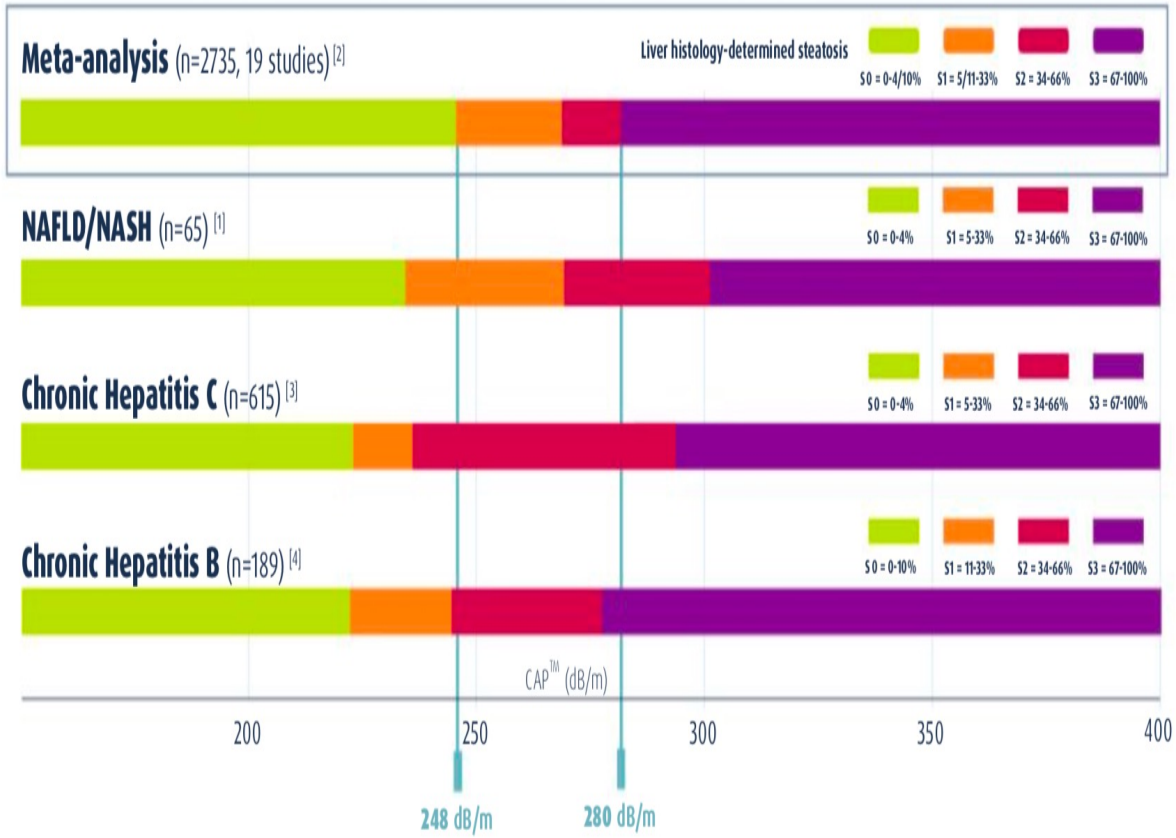
Staging the Severity of Steatosis and Fibrosis in NAFLD: VCTE + CAP (FibroScan)



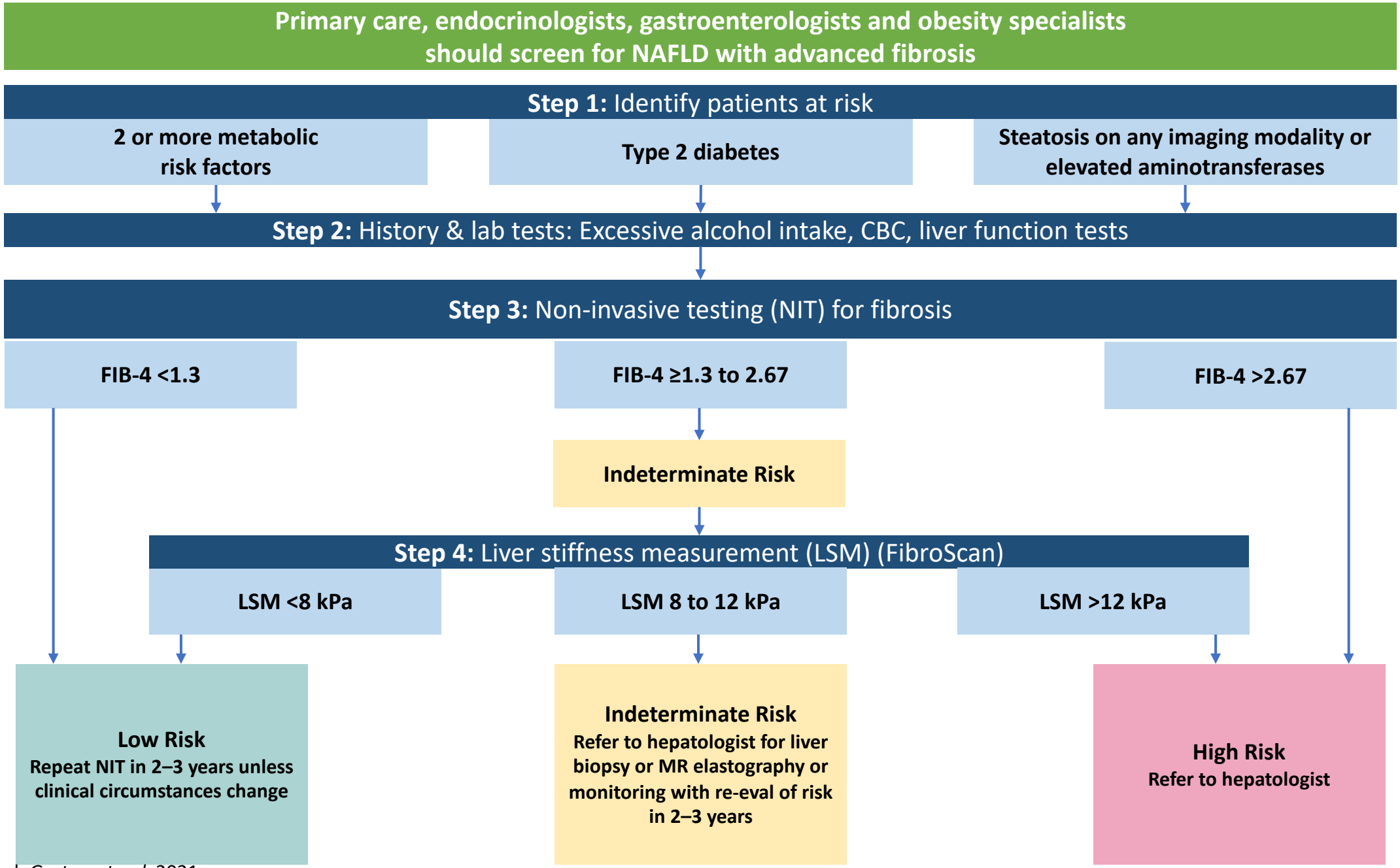
VCTE: Fibrosis



CAP: Steatosis



American College of Gastroenterology Algorithm



Kanwal F et al. *Gastroenterol.* 2021

Managing the Patient

Continue Management Under Primary Care

- Manage any features of metabolic syndrome, diabetes, hypertension, dyslipidemia → referral for specialty care as appropriate.
- Prescribe dietary intervention and physical activity supplemented with psychologic therapies.
- If patient overweight/obese, aim for 5-10% baseline weight loss.
- Continue regular follow-up (at least yearly) to encourage continued life-style change and monitor goals.
- Monitor anthropometrics, glucose control, liver biochemistry annually → referral as appropriate.
- Other preventative measures as required (e.g., smoking cessation, vaccination, cancer screening etc.)

Lifestyle Recommendations for Treating NASH

Caloric intake reduction

≥30% or
~750-1,000 kcal/day
improved insulin resistance
and hepatic steatosis

*Limit consumption of fructose-enriched beverages

Weight loss

of 3% to 5% can improve steatosis, but 6% to 10% is needed to improve NASH/fibrosis

Exercise

alone may reduce steatosis, but effect on other histologic features unknown

No heavy alcohol consumption

Insufficient data to guide recommendations regarding nonheavy alcohol consumption

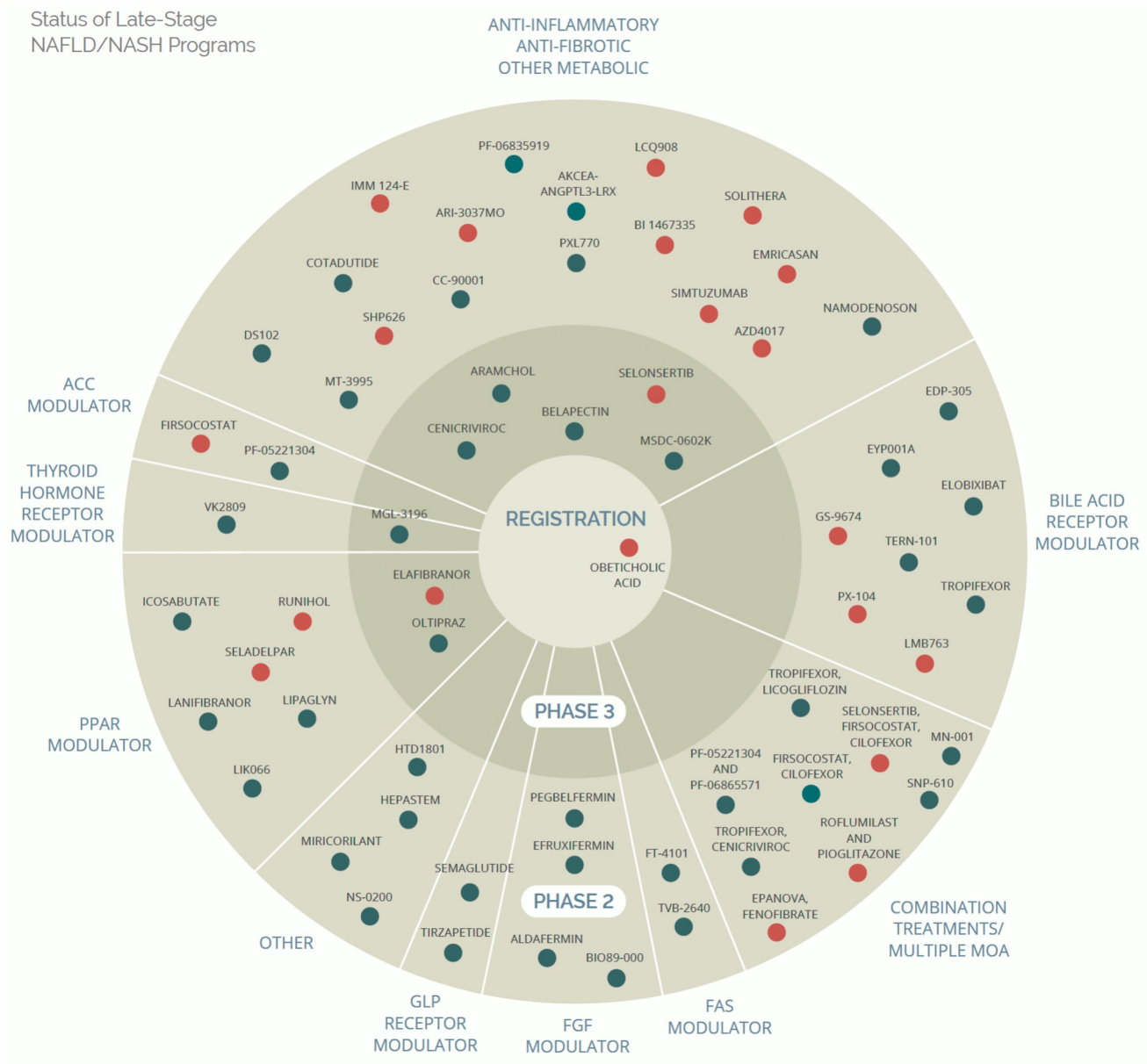
**Drink ≥2 cups of caffeinated coffee daily

*Fructose increases the odds of the development of NAFL in high-risk patients and of NASH and more advanced liver fibrosis in patients who already have NAFLD.

**Caffeinated coffee reduces the risk of liver fibrosis in several liver diseases, including NAFLD.

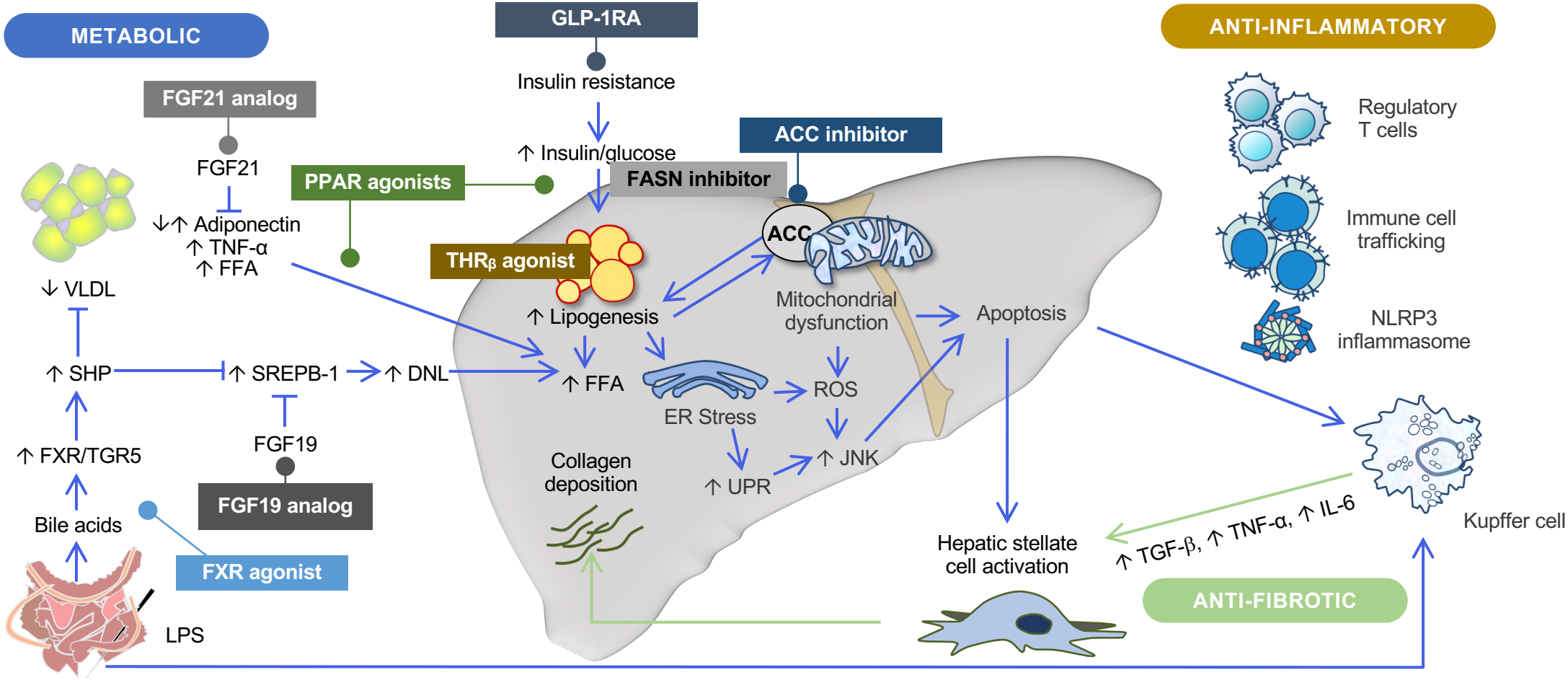
Chalasani N et al. *Hepatology*. 2018;67(1):328-357; Diehl AM, Day C. *New Engl J Med.* 2017; 377:2063-72.

By December 2020, >70 Agents Entered Phase 2/3



BackBay Life Science Advisors, Dec 2020.

NASH: Potential Therapeutic Targets



Adapted from: Konerman MA et al. *J Hepatol*. 2018;68:362–375.

Summary

- NASH is a major health crisis in the US and only getting worse.
- No approved therapies; however, lifestyle modifications very effective.
- Non-invasive tools are important for screening at risk patient populations (e.g., obese, T2DM, those with metabolic syndrome/high index of suspicion).
  - A combination of FIB-4, NFS and FibroScan are generally effective for most patients.
- Very active field of clinical research with numerous therapeutic targets.