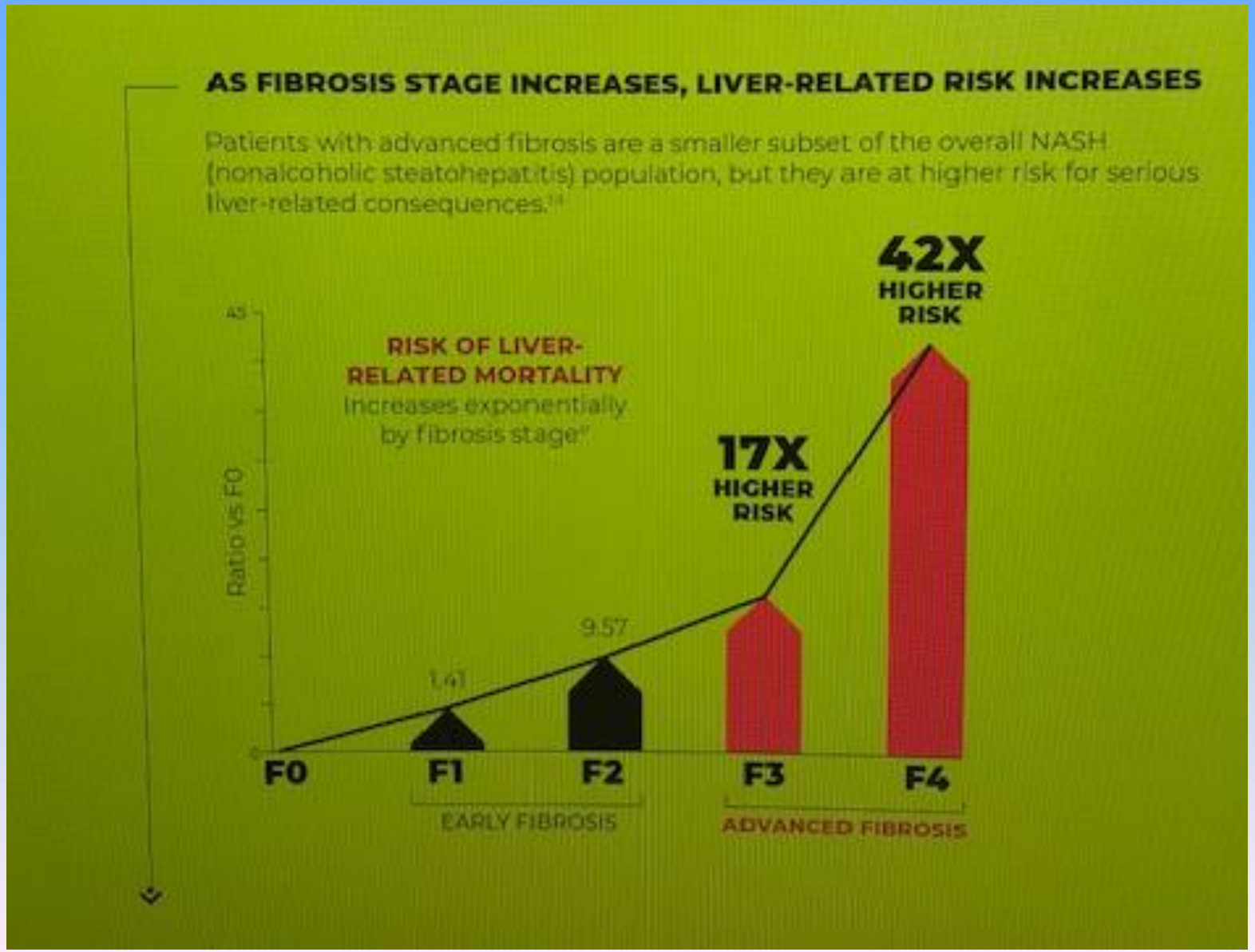
The NASH Epidemic

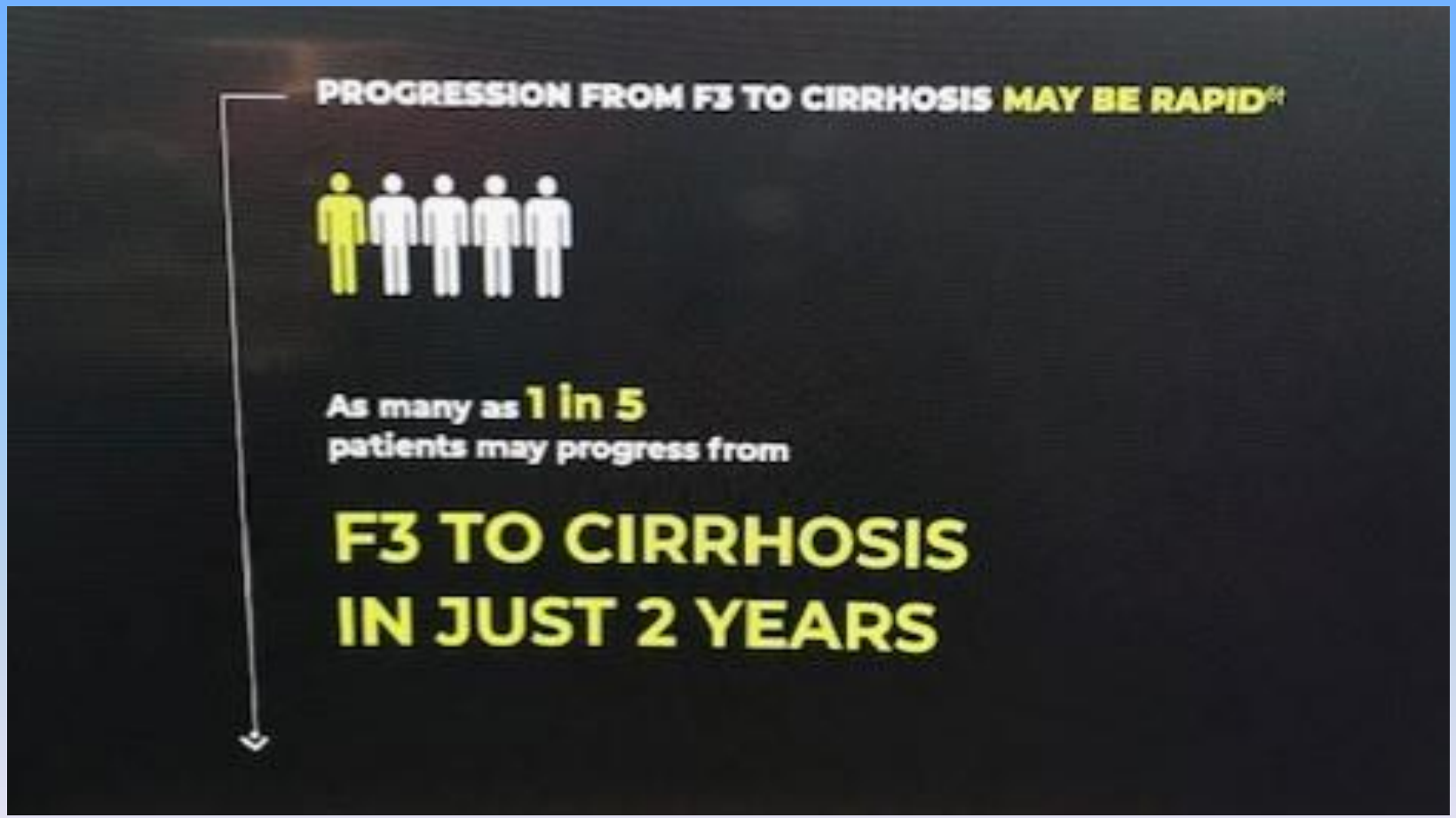
Angel E. Alsina MD, FACS, FAASLD
Director Liver Cancer Program
Tampa General Hospital
Collaborative Professor of Surgery,
University of South Florida, Morsani College of Medicine

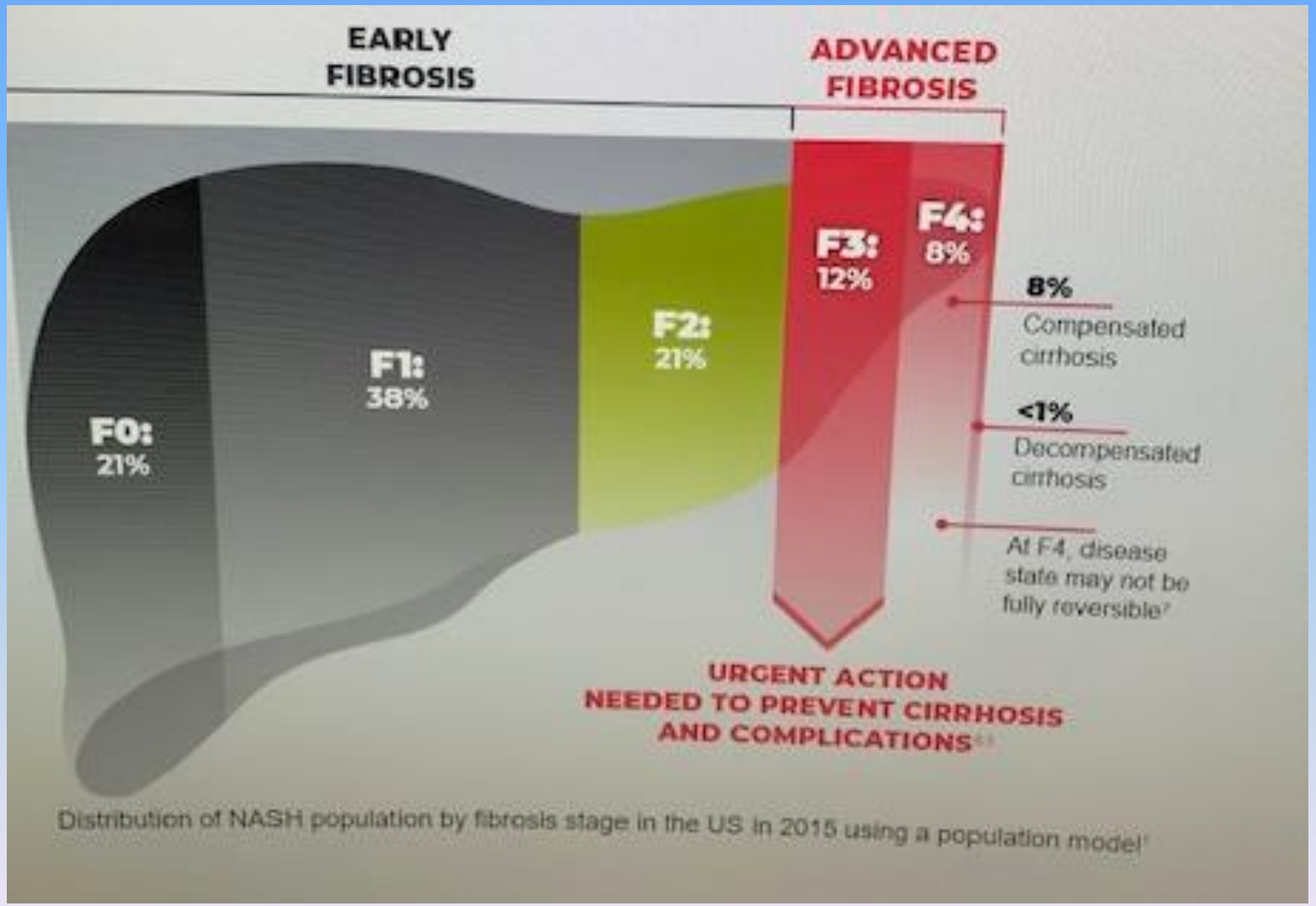
Disclosures

- None

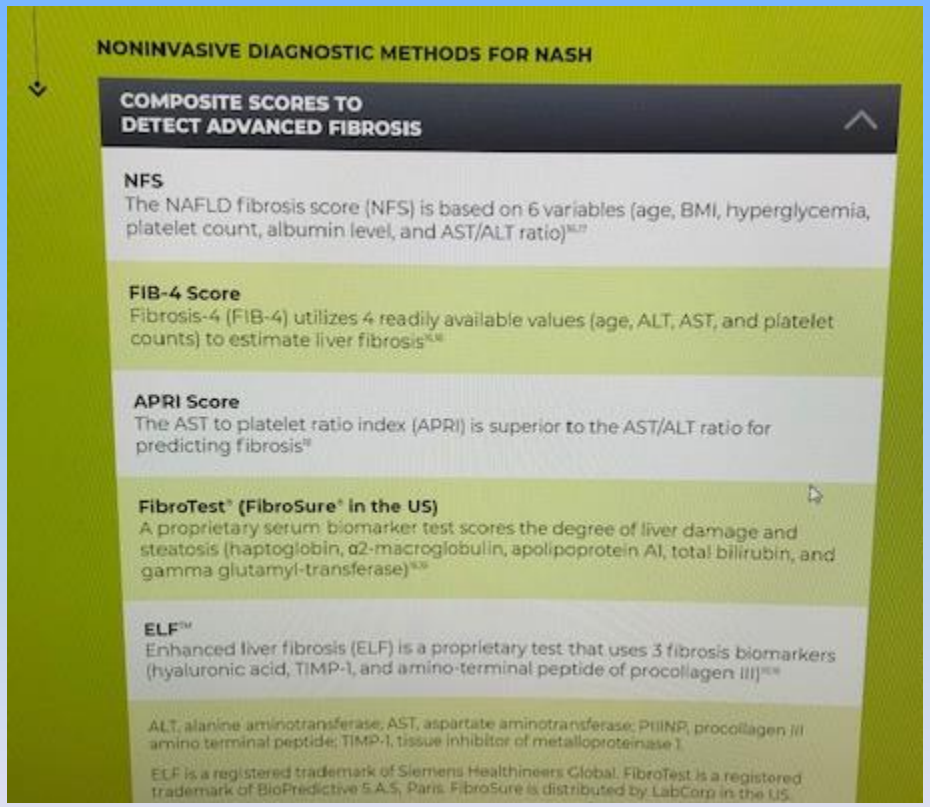
Fibrosis


AS FIBROSIS STAGE INCREASES, LIVER-RELATED RISK INCREASES
Patients with advanced fibrosis are a smaller subset of the overall NASH (nonalcoholic steatohepatitis) population, but they are at higher risk for serious liver-related consequences.[1]
RISK OF LIVER-RELATED MORTALITY
Increases exponentially by fibrosis stage[1]
Ratio vs F0
45
0
1.41
9.57
42X HIGHER RISK
17X HIGHER RISK
F0
F1
F2
F3
F4
EARLY FIBROSIS
ADVANCED FIBROSIS


PROGRESSION FROM F3 TO CIRRHOSIS MAY BE RAPID[4]
As many as 1 in 5
patients may progress from
F3 TO CIRRHOSIS
IN JUST 2 YEARS


EARLY FIBROSIS
ADVANCED FIBROSIS
F0: 21%
F1: 38%
F2: 21%
F3: 12%
F4: 8%
8% Compensated cirrhosis
<1% Decompensated cirrhosis
At F4, disease state may not be fully reversible
URGENT ACTION NEEDED TO PREVENT CIRRHOSIS AND COMPLICATIONS
Distribution of NASH population by fibrosis stage in the US in 2015 using a population model

Non- Invasive Tests



THERE IS ADDITIONAL BENEFIT IN ADDRESSING INFLAMMATION, AN UNDERLYING DRIVER OF FIBROSIS[2,3]

Growing evidence demonstrates that advanced fibrosis in patients with NASH is driven by inflammation.

PROGRESSION RATE (ON AVERAGE) BETWEEN FIBROSIS STAGES[2,4]

THE DIFFERENCE IS INFLAMMATION

NAFLD and NASH both have ≥5% hepatic steatosis. The difference is that there is also **inflammation with hepatocyte injury** present in NASH.[5]

A MODERN LIFESTYLE DISEASE

NASH is closely related to the triple epidemic of obesity, pre-diabetes, and diabetes, and can be defined as the liver manifestation of the metabolic syndrome. It is heavily influenced by lifestyle (e.g. chronic excessive calorie intake, sedentary activity) and is distinct from other fatty liver diseases caused by alcohol abuse or medication side effects.

A LIVER MANIFESTATION OF METABOLIC DISORDER

HYPERTENSION

HEART DISEASE

HIGH BLOOD LIPIDS

INSULIN RESISTANCE

TYPE 2 DIABETES

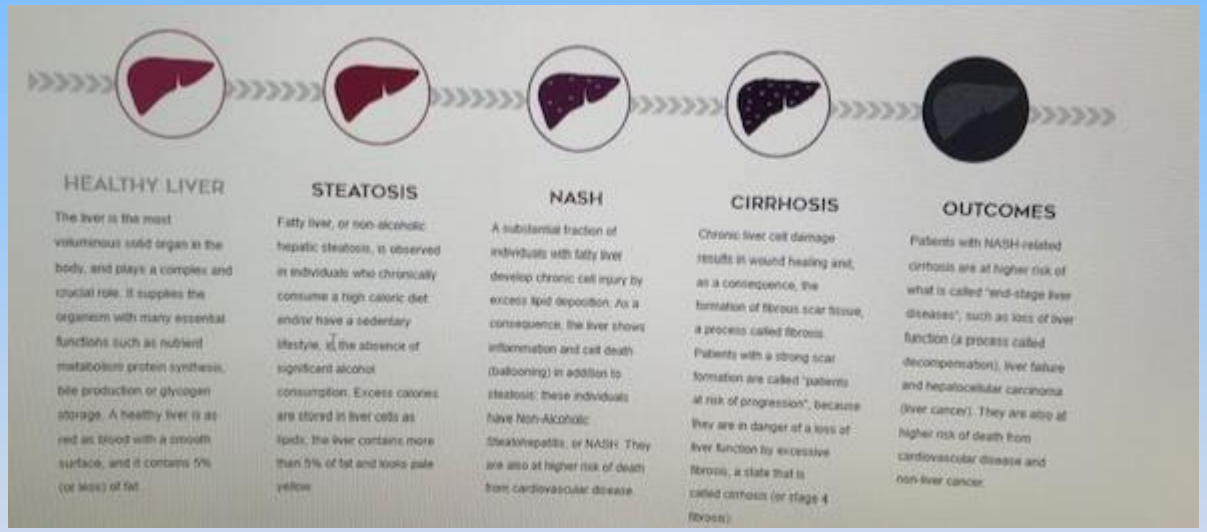
OVERWEIGHT AND OBESITY

A LIFE THREATENING DISEASE

NASH is a chronic yet silent disease, which means that most patients live with it for several years without experiencing any symptoms and are mostly unaware of their liver condition. NASH can progress to more serious disease stages, such as advanced fibrosis, cirrhosis, liver failure or liver cancer.

Liver transplant might then be required, but this is a risky surgical procedure associated with several types of complications, not to mention long waiting lists due to the lack of available healthy organs from donors, or eligibility issues related to patient condition.


CURRENT MANAGEMENT OPTIONS ARE LIMITED
LIFESTYLE MODIFICATION[10,11,27]
• Diet, weight loss, and exercise are recommended as a first-line treatment
• Lack of patient compliance is a key limitation of this approach
NONINDICATED PHARMACOLOGICAL TREATMENTS[10,11]
• Nonindicated treatments (such as vitamin E or pioglitazone) are used in selected patients
• However, supportive data are limited and risks/benefits should be discussed with each patient
There is an urgent need for options for patients with Advanced Fibrosis due to NASH[8]



HEALTHY LIVER

The liver is the most voluminous solid organ in the body, and plays a complex and crucial role. It supplies the organism with many essential functions such as nutrient metabolism protein synthesis, bile production or glycogen storage. A healthy liver is as red as blood with a smooth surface, and it contains 5% (or less) of fat.

STEATOSIS

Fatty liver, or non-alcoholic hepatic steatosis, is observed in individuals who chronically consume a high caloric diet and/or have a sedentary lifestyle, in the absence of significant alcohol consumption. Excess calories are stored in liver cells as lipids; the liver contains more than 5% of fat and looks pale yellow.

NASH

A substantial fraction of individuals with fatty liver develop chronic cell injury by excess lipid deposition. As a consequence, the liver shows inflammation and cell death (ballooning) in addition to steatosis; these individuals have Non-Alcoholic Steatohepatitis, or NASH. They are also at higher risk of death from cardiovascular disease.

CIRRHOSIS

Chronic liver cell damage results in wound healing and, as a consequence, the formation of fibrous scar tissue, a process called fibrosis. Patients with a strong scar formation are called "patients at risk of progression", because they are in danger of a loss of liver function by excessive fibrosis, a state that is called cirrhosis (or stage 4 fibrosis).

OUTCOMES

Patients with NASH-related cirrhosis are at higher risk of what is called "end-stage liver diseases", such as loss of liver function (a process called decompensation), liver failure and hepatocellular carcinoma (liver cancer). They are also at higher risk of death from cardiovascular disease and non-liver cancer.

Resources

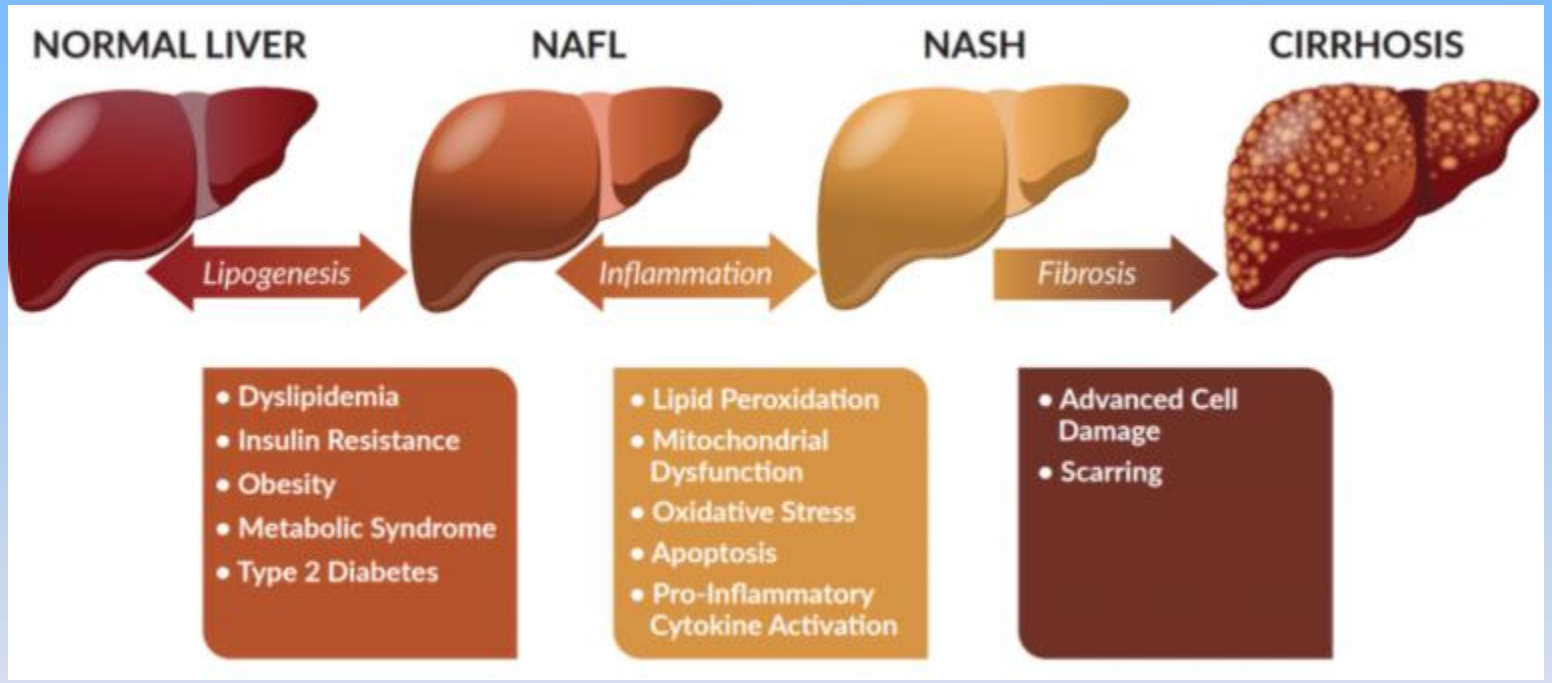

LEAFLETS ABOUT NAFLD & NASH
Find below some leaflets you can read if you want to know more about the disease.
THE NASH EDUCATION PROGRAM
NASH:
An Explanatory Guide for Patients and their Families
TO BETTER UNDERSTAND NONALCOHOLIC STEATOHEPATITIS (NASH)
THE NASH EDUCATION PROGRAM
NON-ALCOHOLIC STEATOHEPATITIS
UNDERSTANDING NASH, A MAJOR PUBLIC HEALTH ISSUE

NAFLD

- First described in 1980, nonalcoholic fatty liver disease (NAFLD) has become more common although the exact incidence and prevalence is unknown.
- While the exact prevalence varies from region to region, the overall trend shows an increased number of patients with NAFLD.
- Risk factors for the development of NAFLD includes advanced age, male gender, obesity, and having elements of the metabolic syndrome.
- There is also an association between the presence of NAFLD and coronary atherosclerosis.

NASH

- NASH Non-Alcoholic SteatoHepatitis.
- It is the most severe form of non-alcoholic fatty liver disease (NAFLD)
- Abnormal accumulation of fat in the liver, progress to liver cell injury in some.
- Hepatocellular ballooning and inflammation – *necroinflammation* – considered as the drivers of disease progression, or as the underlying causes of the disease.
- As NASH evolves, (fibrosis), a natural response to injury which can lead to liver cirrhosis or liver cancer.


NORMAL LIVER
NAFL
NASH
CIRRHOSIS
Lipogenesis
Inflammation
Fibrosis
• Dyslipidemia
• Insulin Resistance
• Obesity
• Metabolic Syndrome
• Type 2 Diabetes
• Lipid Peroxidation
• Mitochondrial Dysfunction
• Oxidative Stress
• Apoptosis
• Pro-Inflammatory Cytokine Activation
• Advanced Cell Damage
• Scarring

- About 25% of adults have the benign form of the disease (NAFL)
- 3-5% go on to develop NASH.
- It is estimated that the number of people with NASH will increase 63% by the year 2030.

Risk Factors for NASH

- Obesity and overweight
- High blood pressure
- Abnormal cholesterol (low high-density lipoprotein HDL)
- High Triglycerides
- Insulin resistance
- Type 2 diabetes
- Diet high in sugar (fructose)
- Certain medications
- Shift work
- Environmental toxins
- Certain genetic diseases

Lifestyle modifications to prevent NASH

- Lose 7 to 10% of body weight if overweight or obese
- Increase physical activity and exercise intensity
- Reduce saturated fats in diet
- Stop drinking sugary beverages
- Limit alcohol to ≤1 drink/day for women and ≤2 drinks/day for men
- Drink two or more cups of caffeinated coffee a day (reduces fibrosis)

Modeling the Disease

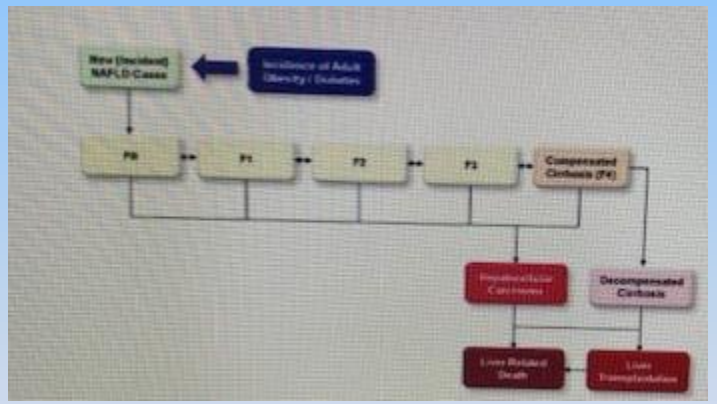
Modeling the Epidemic of Nonalcoholic Fatty Liver Disease Demonstrates an Exponential Increase in Burden of Disease

Estes C, et al. *HEPATOLOGY* 2018;67:123-133

Markov Model

A Markov model was used to forecast NAFLD disease progression.

Incidence of NAFLD was based on historical and projected changes in adult prevalence of obesity and type 2 diabetes mellitus (DM).



- Assumptions were derived from published literature where available and validated using national surveillance data for incidence of NAFLD related HCC.

- Projected changes in NAFLD-related cirrhosis, advanced liver disease, and liver-related mortality were quantified through 2030.

Results

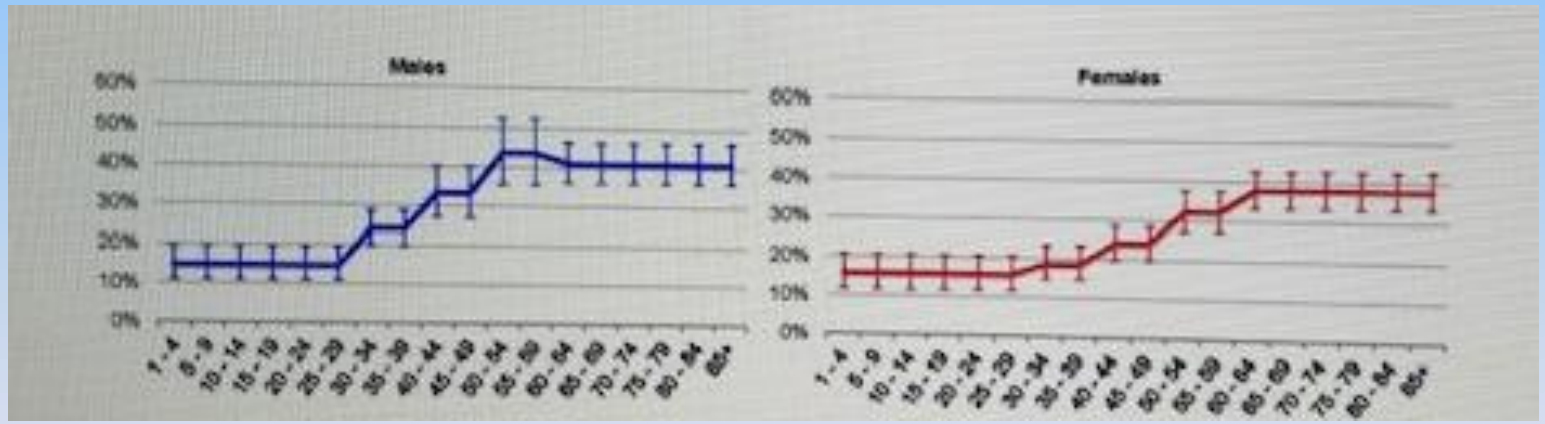
- Prevalent NAFLD cases are forecasted to increase 21%, from 83.1 million (2015) to 100.9 million (2030)
- Prevalent NASH cases will increase 63% from 16.52 million to 27.00 million cases.
- Overall NAFLD prevalence among the adult population (aged 15 years) is projected at 33.5% in 2030, and the median age of the NAFLD population will increase from 50 to 55 years during 2015-2030.
- In 2015, approximately 20% of NAFLD cases were classified as NASH, increasing to 27% by 2030, a reflection of both disease progression and an aging population.
- Incidence of decompensated cirrhosis will increase 168% to 105,430 cases by 2030, while incidence of HCC will increase by 137% to 12,240 cases.
- Liver deaths will increase 178% to an estimated 78,300 deaths in 2030.
- During 2015-2030, there are projected to be nearly 800,000 excess liver deaths.

Conclusion

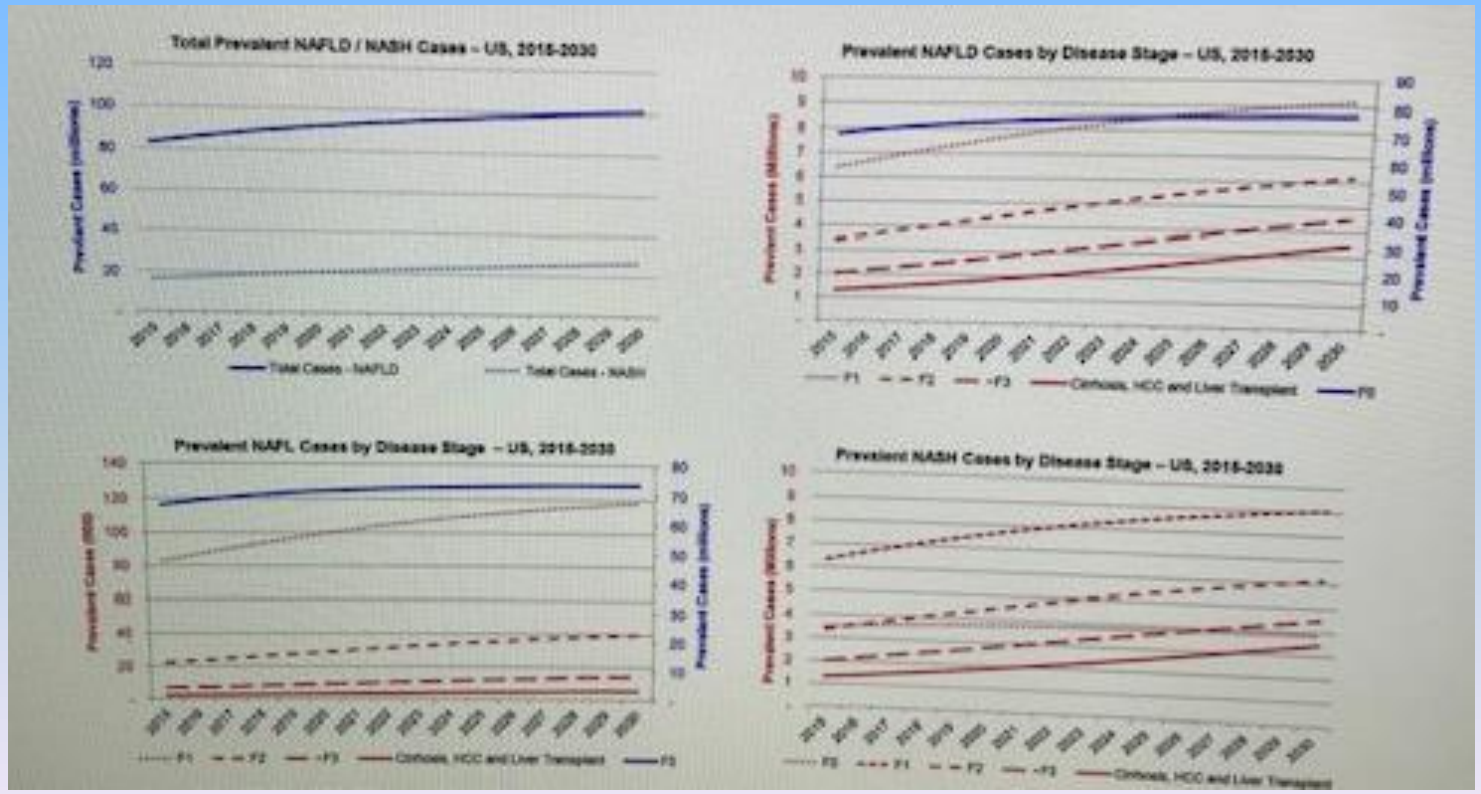
With continued high rates of adult obesity and DM along with an aging population, NAFLD related liver disease and mortality will increase in the United States. Strategies to slow the growth of NAFLD cases and therapeutic options are necessary to mitigate disease burden.

Prevalence

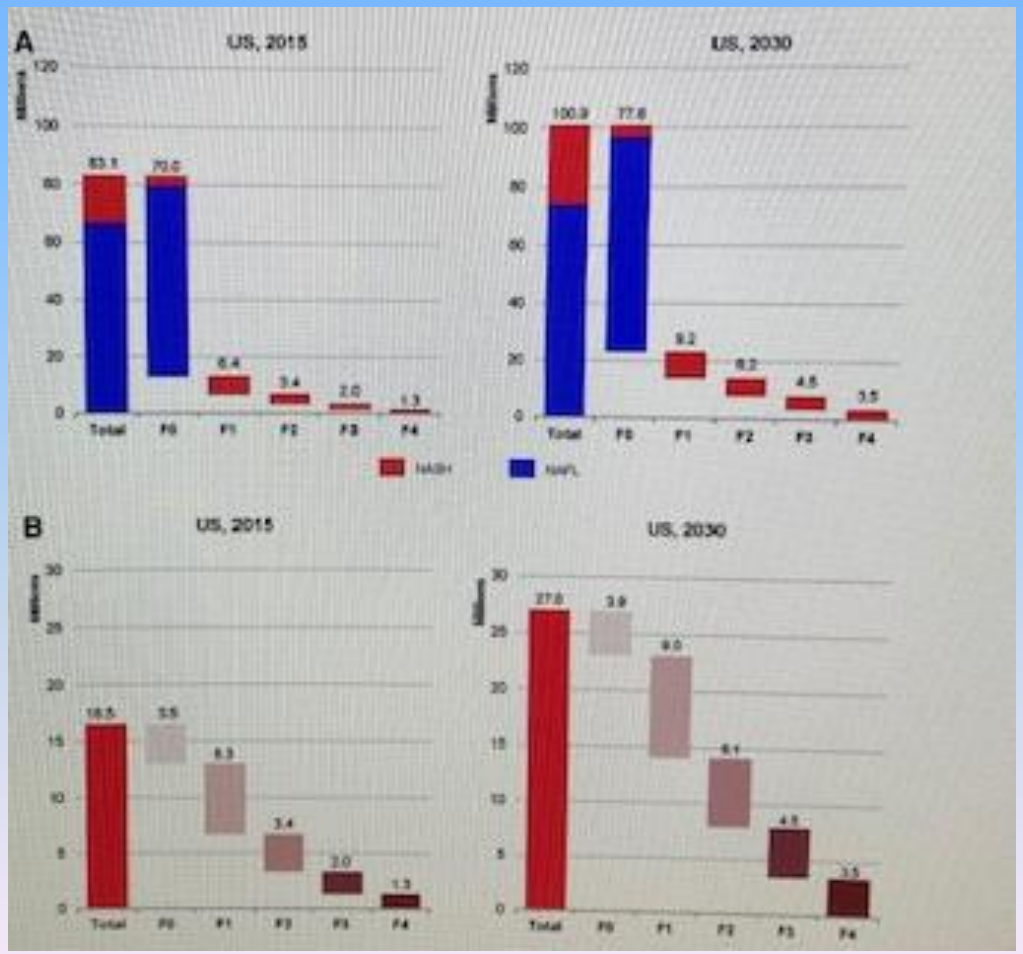
- The prevalence rates by age were adjusted proportionally to sum to 83.1 million NAFLD cases in 2015



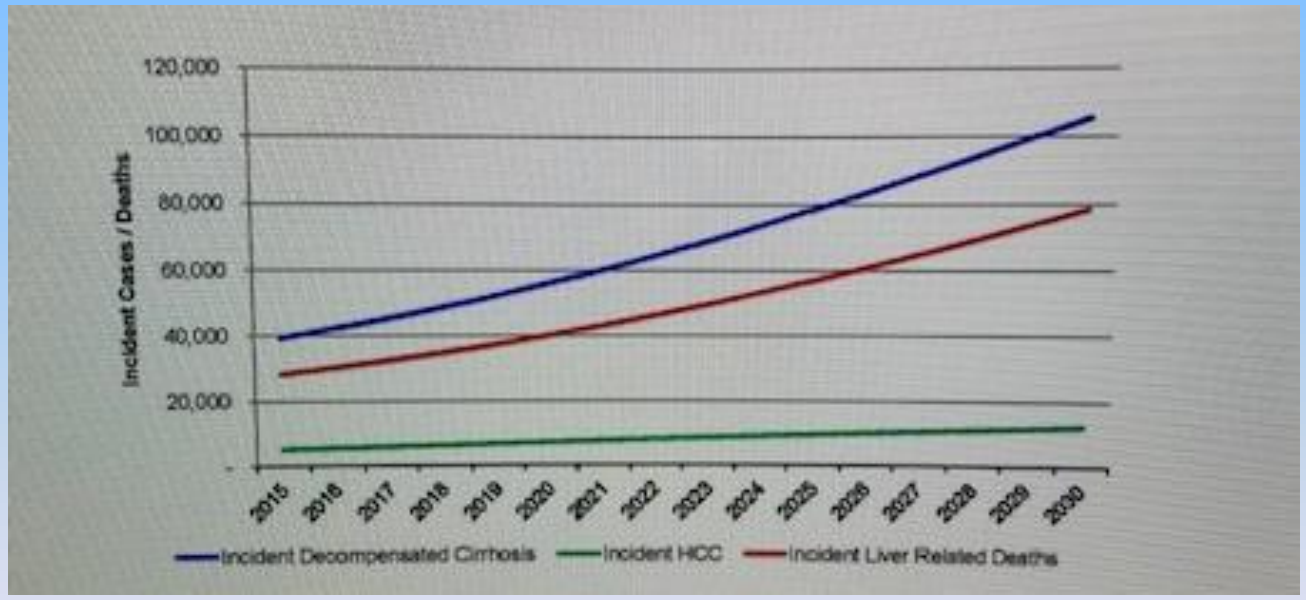
Distribution of the NAFLD and NASH population by fibrosis stage in the United States for 2015 and 2030. (A) NAFLD; (B) NASH.



Prevalent NAFLD, NAFL, and NASH cases in the United States, 2015-2030.



Incident decompensated cirrhosis, HCC, and liver-related deaths among the prevalent NAFLD population in the United States, 2015-2030.



Transplants

Siddique O, et al. J Clin Transl Hepatol 2017;5(3):193–196

Annual waitlist registrations for non-alcoholic steatohepatitis (NASH) and annual NASH-related liver transplants by birth cohorts from 2004–2014.