

**There is more to Metabolic Associated Steatotic Liver Disease
(MASLD)
than Liver Mortality**

Sanjiv Chopra, M.D., MACP, FRCP (London)

Professor of Medicine

Harvard Medical School

Editor in Chief

Hepatology Section Up to Date

Disclosure Statement

The commercial entities with which I, Sanjiv Chopra, MD, MACP have relationships do not produce healthcare-related products or services relevant to the content I am planning, developing, or presenting for this activity.

The Emperor Has New Clothes

The Term Non-Alcoholic Fatty Liver Disease was felt to be stigmatizing and an International Group has proposed a name change to:

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD).

This change is expected to yield greater awareness, timely patient identification, more funding and even reductions in mortality.

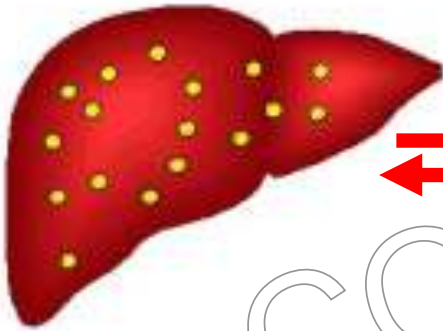
The Spectrum of MASLD



Fatty Liver

NASH

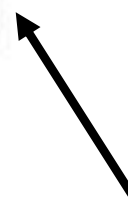
Cirrhosis



Fat accumulates in the liver

Fat plus inflammation and scarring

Scar tissue replaces liver cells



70%

Relatively benign

30%

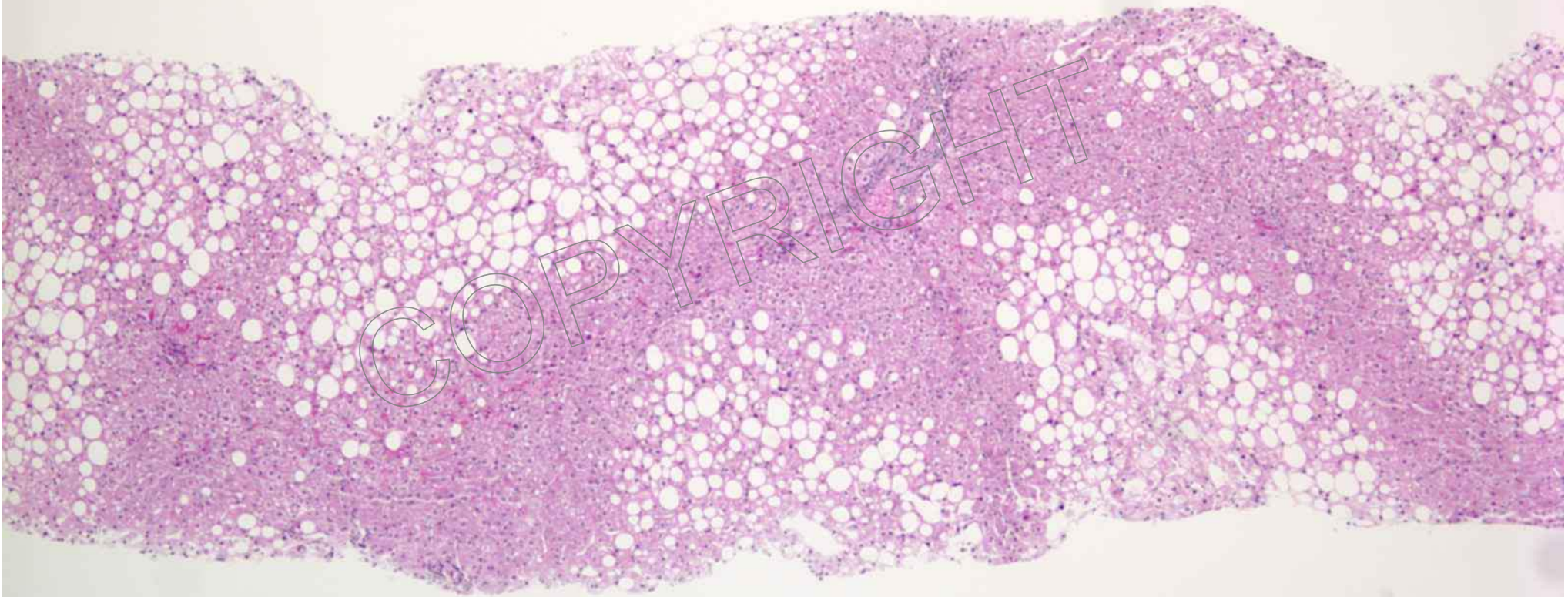
Can progress to cirrhosis and HCC

Ultrasound: Bright echogenic liver



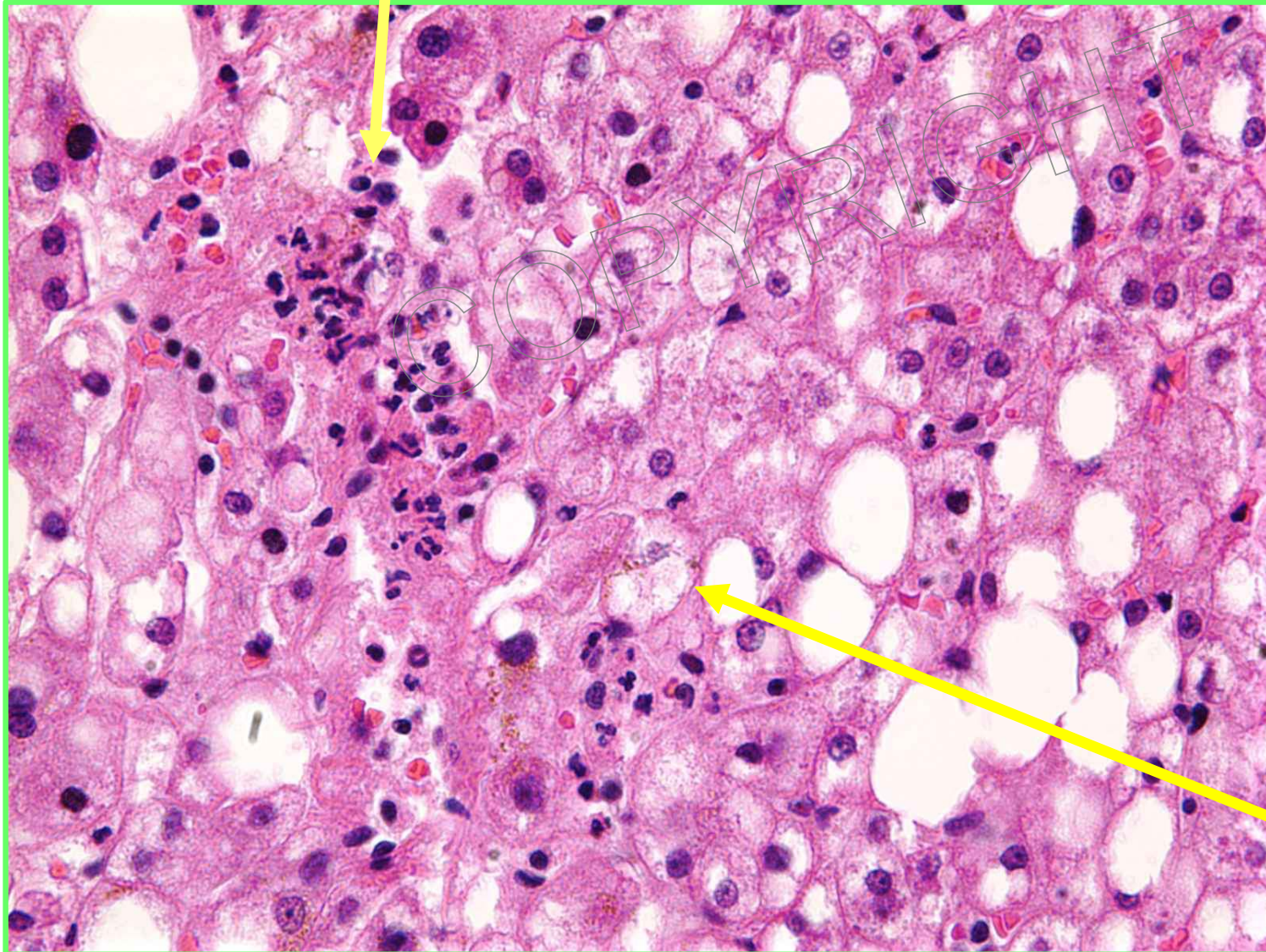
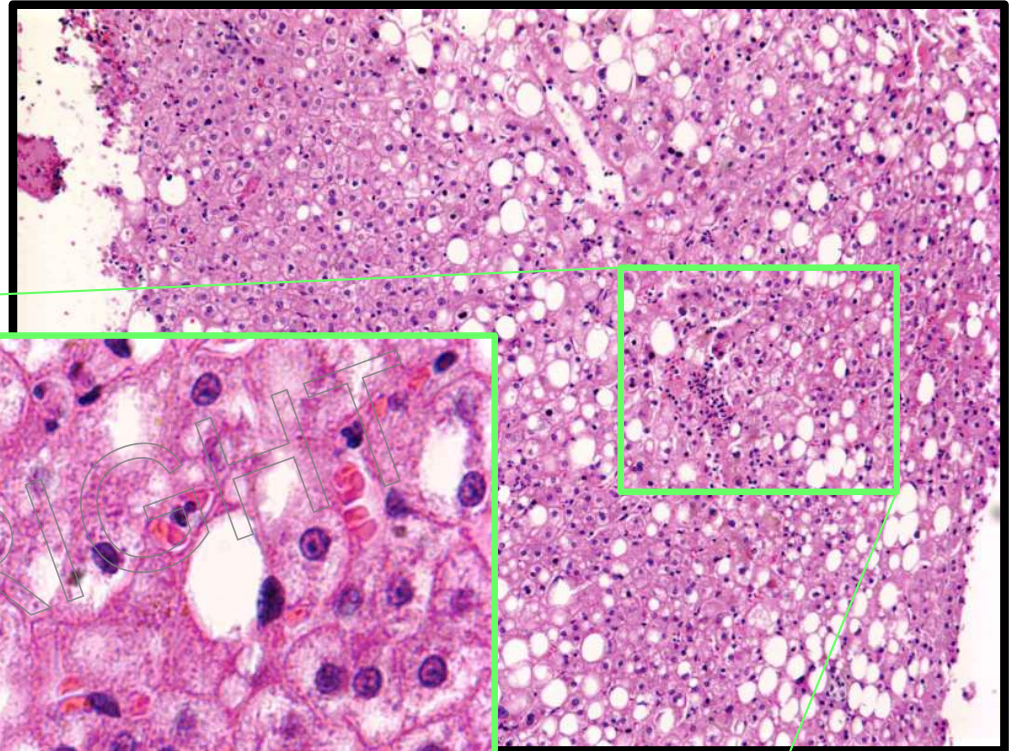
The liver is enlarged. It is diffusely echogenic consistent with fat infiltration of the liver. **Other forms of liver disease and more advanced liver disease including early cirrhosis cannot be excluded by this study.**

Biopsies

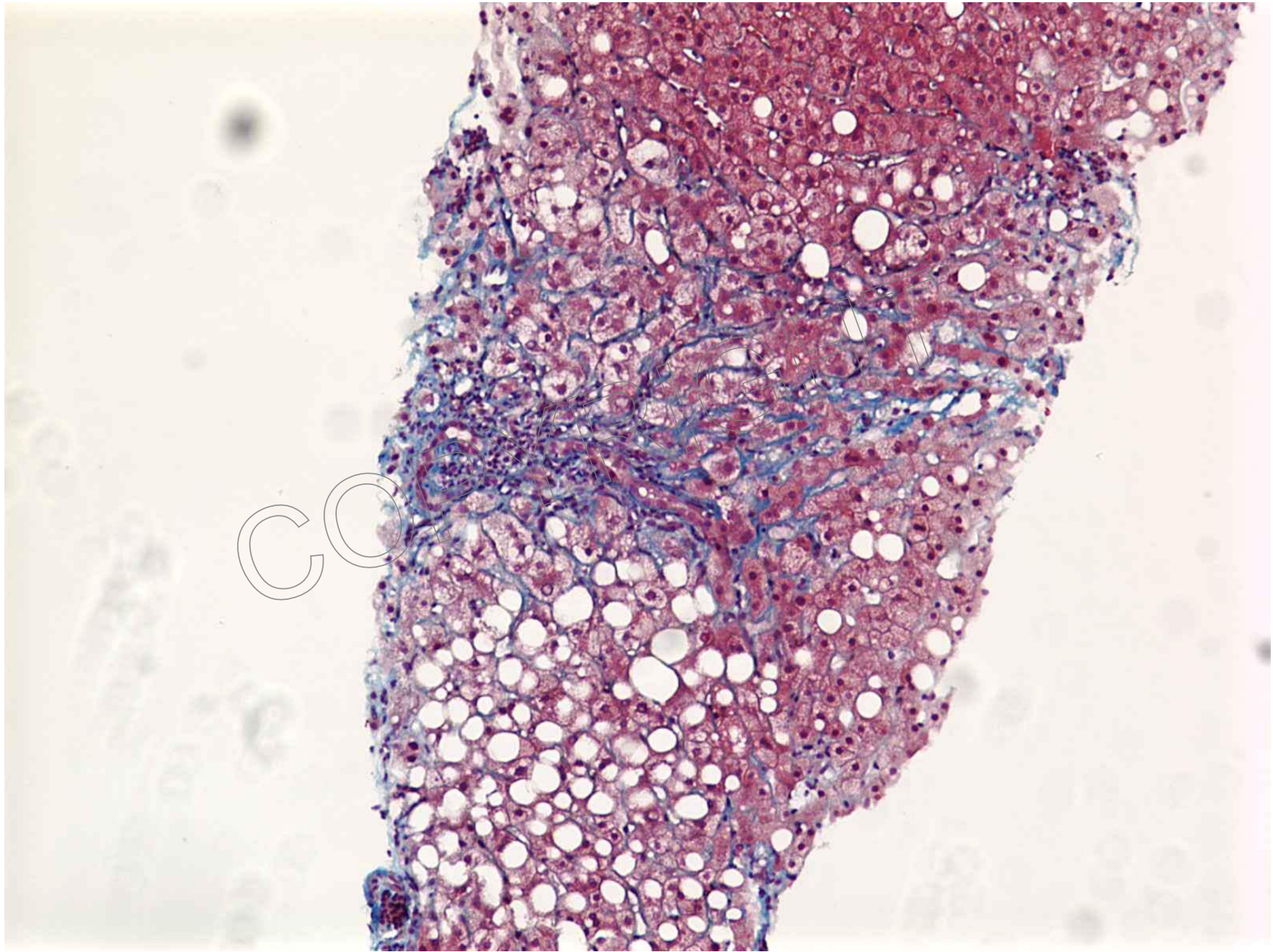


macrovesicular steatosis (zone III)

lobular sinusoidal
neutrophils

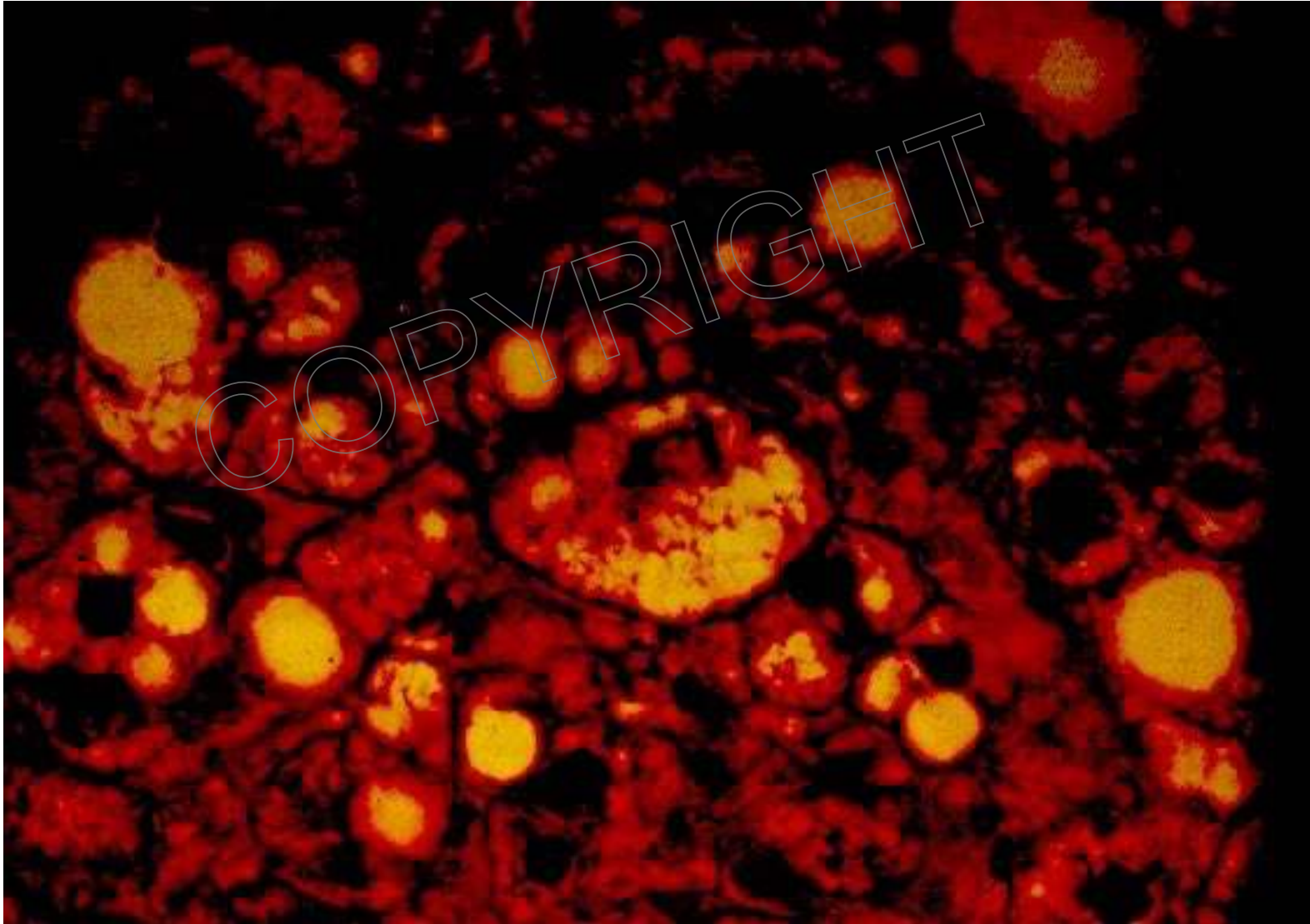


Ballooning
degeneration



Sinusoidal pericellular fibrosis, trichrome stain

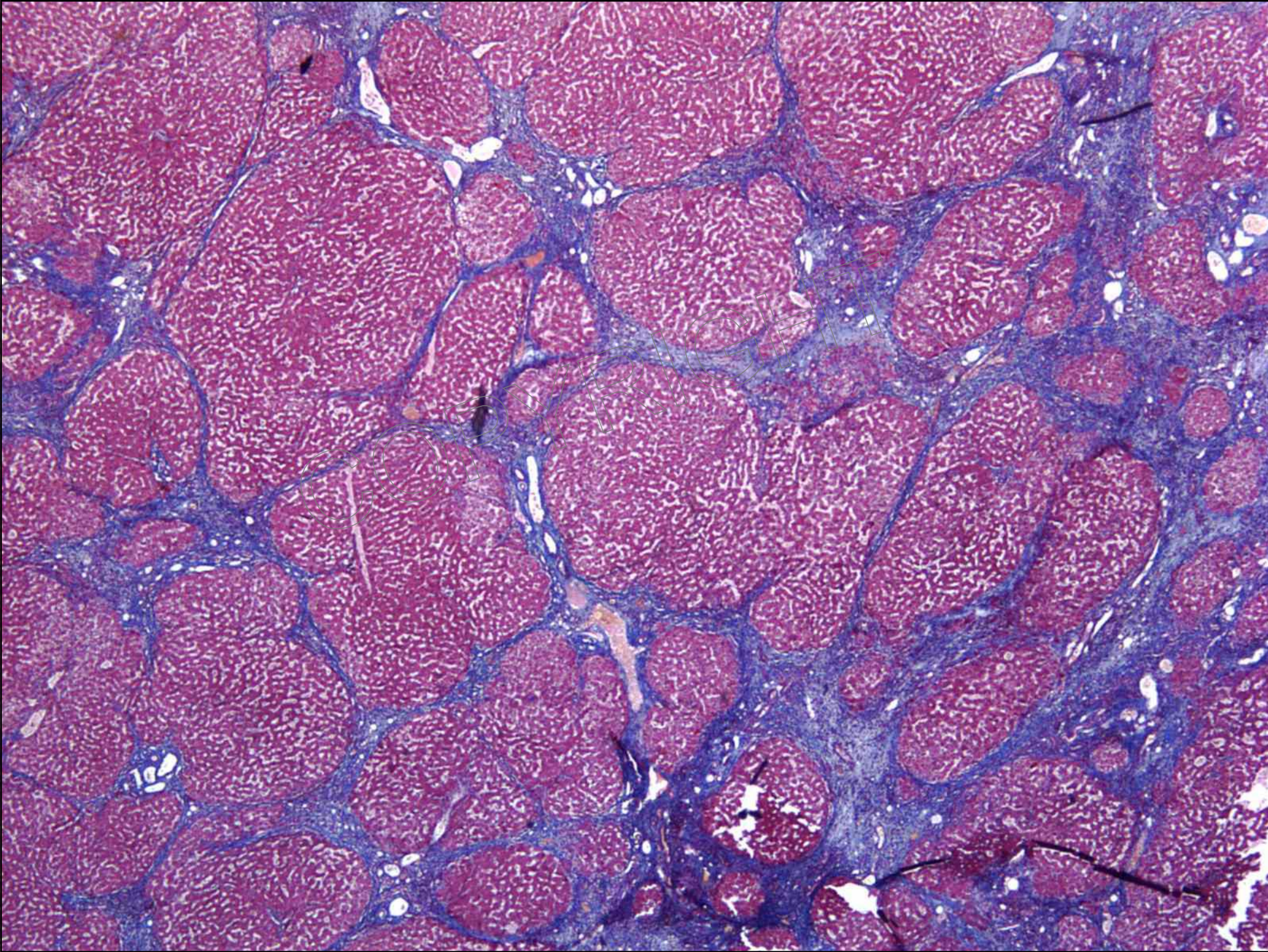
NASH: Liver Histology



Proper Interpretation of the Histology

...these features are consistent with a **Toxic Metabolic etiology.**

COPYRIGHT



Epidemiology of NAFLD

- Estimate: **70-100 million** Americans have **NAFLD**
More than **5 million** are **cirrhotic**
- Majority of Pts with NASH have metabolic syndrome
- Over age 60 years, 40% have metabolic syndrome

Patients with NASH

	Normal ALT	Increased ALT	p.value
Fibrosis Stage 2 or greater	22%	34%	NS

Fracanzani AL, et al.
Hepatology 2008;48;792

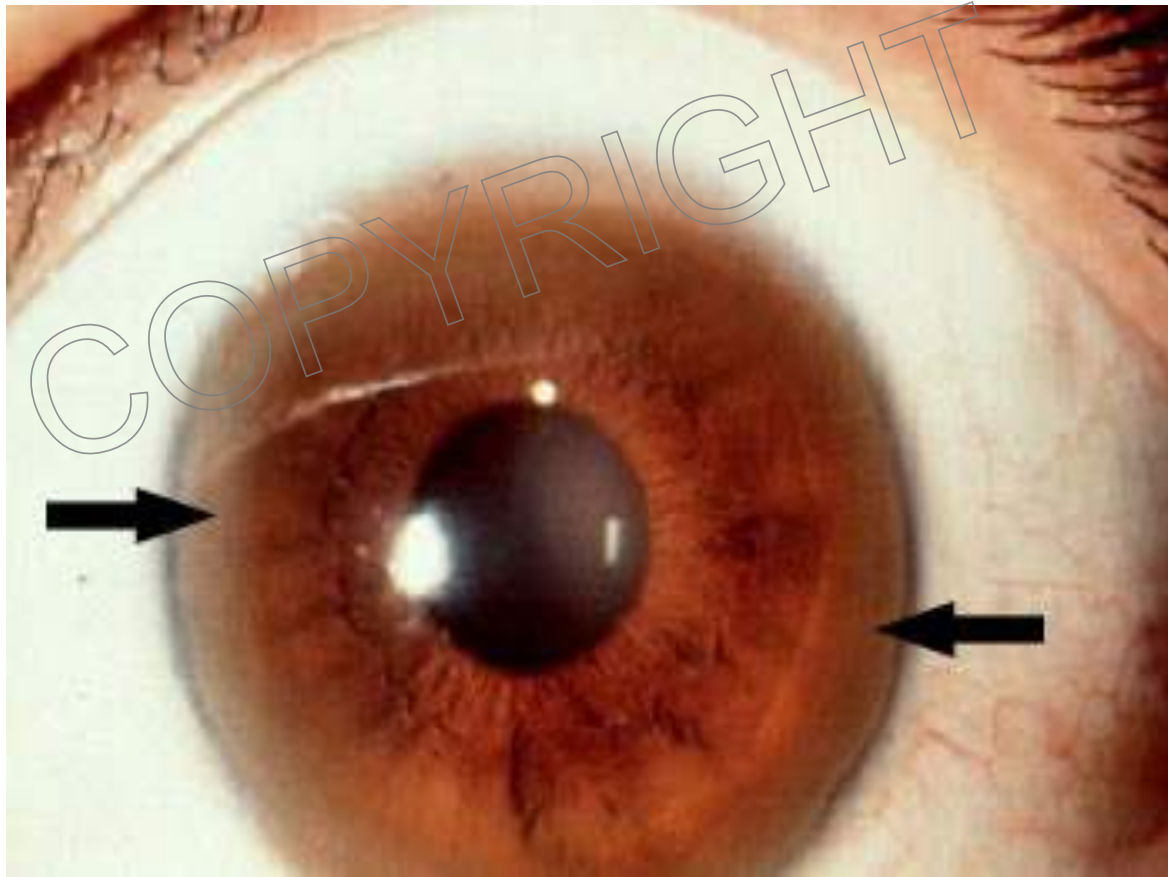
Other Conditions Associated with NASH

- Drugs or Toxins
- Abdominal Surgery
- Metabolic Disorders
- Miscellaneous

One disorder that is **critical** to exclude in young individuals is **Wilson's disease**

COPYRIGHT

K-F Ring



Drugs Associated with NASH

- **Glucocorticoids**
- **Tamoxifen**
- **Synthetic estrogens**
- **Perhexilene maleate**
- **Amiodarone**
- **Isoniazid**

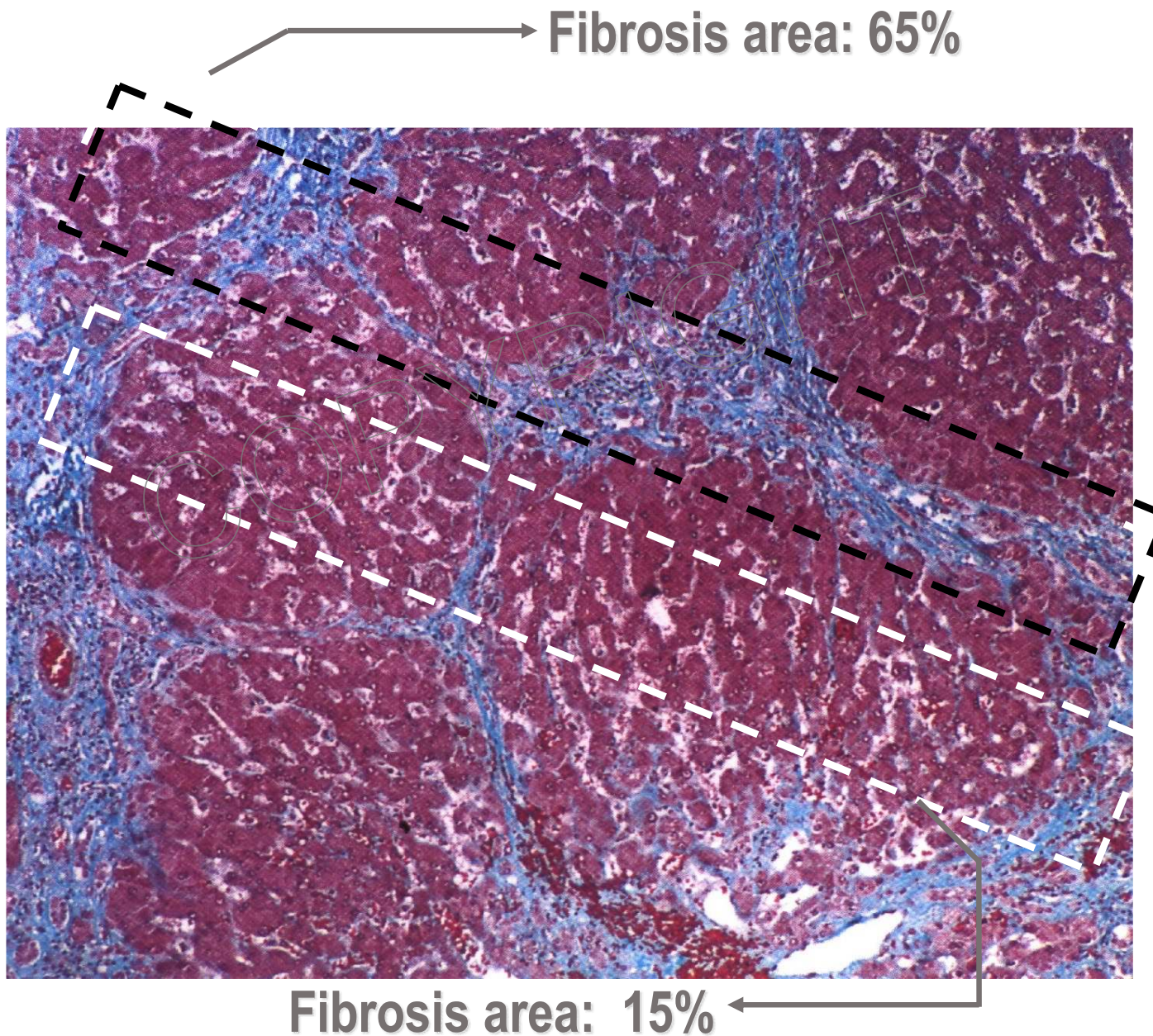
We need to Think Differently about the Upper Normal Limit of ALT

- True normal healthy ALT:
 - 19 to 25 IU/L in females
 - 29 to 33 IU/L in males
- Multiple studies: Elevated ALT associated with increased liver-related mortality.
- Likely, many of the newly identified patients using these parameters will have NAFLD.

Are there alternatives to liver biopsy?

COPYRIGHT

Sampling error of liver biopsy



Courtesy of M. Pinzani, Florence

Fibroscan



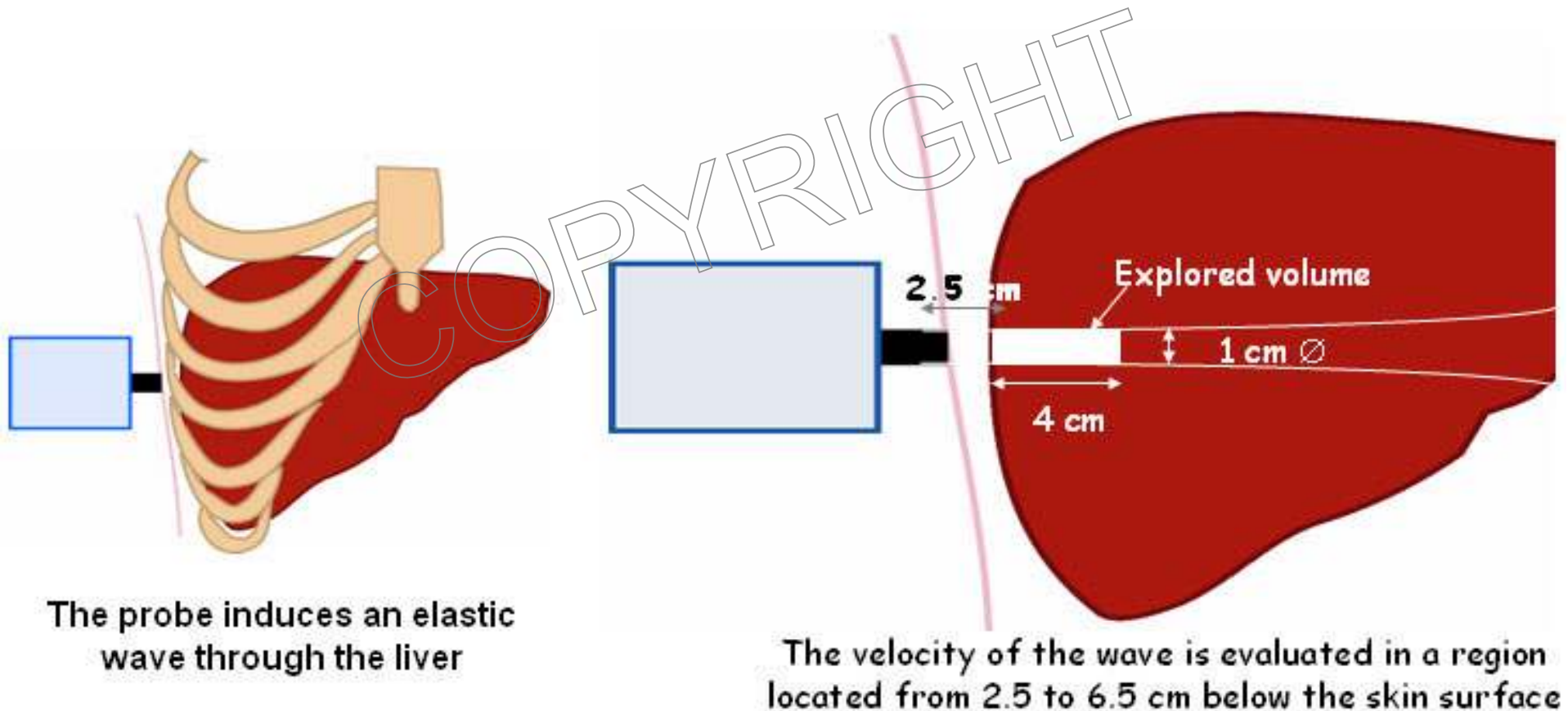
- Fasting
- Examination time < 5 minutes
- Median value of 10 successful acquisitions
- Sampling error
 - Biopsy – 1/50,000
 - Fibroscan – 1/500



Courtesy of N. Afdhal, MD

Hepatic Elastography

- Fibroscan is a rapid and non-invasive measure of hepatic stiffness
- Hepatic stiffness correlates with fibrosis



Sampled volume: 1: 500

Sampling

- Liver biopsy samples only $1/50,000^{\text{th}}$ of whole liver.
- Fibroscan samples $1/500^{\text{th}}$ of whole liver.

Noninvasive Methods as good as biopsy for NAFLD Prognosis

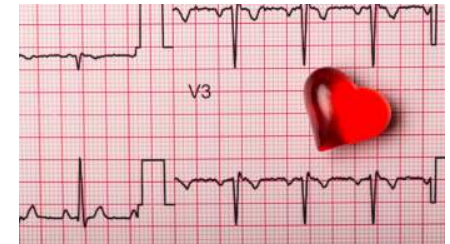
- Researchers conducted meta-analysis looking at the endpoint of all cause mortality, cirrhosis complications, HCC, and Liver Transplantation.
- Noninvasive tests – **transient elastography, FIB-4 and NAFLD Fibrosis Score** performed as well as histologically assessed fibrosis in predicting major clinical outcomes.

Mozes FE. Et al. The Lancet Gastroenterology & Hepatology. June 2023.

Fibroscan- pros

- Noninvasive
- Excellent negative predictive value to exclude advanced fibrosis
- Fast- 5 minute tests
- Point of care- results immediately available

Can the Good Old EKG Accurately Discriminate Patients with and without Cirrhosis?



- Cirrhosis is associated with cardiac dysfunction & distinct ECG abnormalities.
- Review of 5,212 patients with advanced cirrhosis at Mayo Clinic who underwent liver transplantation.
- An AI – Cirrhosis – ECG (ACE) score was generated
- Significant elevations in ACE score seen with increasing MELD – Na
- **The ACE score a deep learning model accurately discriminates ECGs from patients with and without cirrhosis.**

CIRRHOSIS



Liver Fibrosis Markers are Predictive of All Cause Mortality in Type 2 Diabetes

- FIB-4, Nonalcoholic Fatty Liver Disease Fibrosis Score (NFS), and aspartate aminotransferase to platelet ratio index (APRI) were assessed in 12,589 patients in a retrospective study.
- All three fibrosis risk scores positively correlated with all cause mortality in people with Type 2 Diabetes.

Collier A. et al. Diabetes Obes Metab. 2023 June.

Pathogenesis of NASH

- **Perturbation of fatty acid processing.**
- **Insulin resistance**
- **Lipid peroxidation and oxidative stress***

*** Potential oxidative stressors include:
hepatic iron, intestinal bacteria, leptin and states
characterized by anti-oxidant deficiencies**

The Gut Microbiota and NAFLD

- Microbiota in addition to regulating body fat gain and insulin resistance:
 - Change gene expression
 - Increase energy harvest from diet
 - Produce ethanol
 - Affect inflammation and immunity

Two notable references:

1. Lau E. *et al.* Gut Microbiota: Association with NAFLD and Metabolic Disturbances. Biomedical Research International. 2015.
2. Wisniewsky JA. *et al.* Gut Microbiota and human NAFLD: disentangling microbial signatures from metabolic disorders. Nature Reviews Gastroenterology and Hepatology. 2020.

Metagenome-based Gut Microbiome Panel Can Accurately Diagnose Advanced Fibrosis

- 86 patients with biopsy proven NAFLD (14 with Stage 3 or 4 Fibrosis) had their gut microbiome compositions characterized using whole genome shotgun DNA sequencing from stool samples.
- This study provides preliminary evidence for a fecal microbiome derived metagenomic signature that detects advanced fibrosis in patients with NAFLD.

Loomba R. et al. Cell Metabolism. 2017.

The Most Common Cause of Mortality in Patients with NASH...

1. Cardiovascular Disease
2. Extra-hepatic Cancer
3. Decompensated Cirrhosis and HCC
4. Mortality Related to Complications of Diabetes
5. Mortality in NAFLD is further influenced by mutations in the PNPLA3 gene, low thyroid function, and sarcopenia.

Prevention and Treatment of NASH

- **Prevention of obesity and metabolic syndrome**
- **Treatment of metabolic syndrome**
- **Coffee ?**
- **Weight loss regimens**
- **Bariatric Surgery if appropriate**

NASH: Weight Loss is Beneficial !

1. 9% or greater weight loss resulted in:

- Biochemical improvement
- Histologic improvement (steatosis, ballooning, inflammⁿ)
- Improvement in Insulin resistance
- Higher Adiponectin levels

Harrison SA, et al.

Hepatology 2009;49:80

2. Following bariatric surgery, Hepatic Fibrosis improved or was reversed in 66%.

Furuya CK Jr., et al.

J Gastro Hepatol 2007;22:510

Other Pharmacological Treatment Modalities

- Pic
- Mo
- Lir
- Or
- Pr
- Be



acid (UDCA)
ids

GIP/GLP-1 Receptor Agonist: A Game Changer?

- 72-week phase III SURMOUNT-1 clinical trial, people taking **15 mg** of the once-weekly injectable lost an average of **22.5% of body weight – mean loss of 52 pounds.**
- Those taking **5 mg** the average weight loss was **35 pounds.**
- Those taking **10 mg** the average weight loss was **49 pounds.**

It Is A Game Changer!

- 1 in 8 adults in the US has taken Semaglutide (Ozempic or Wegovy) or Mounjaro (tirzepatide).
- Wegovy- 25,000 new sign ups every week in the US.
- But be cognizant of the side effects. *

“The best time to use a new drug is right away while its still working”
-Sir William Osler

GLP-1 Drugs in MASLD Tied to Lower Risk of Cirrhosis, Death

- Matched cohort study of more than 30,000 patients.
- GLP-1 receptor agonist use was associated with a lower risk of progression to cirrhosis and mortality in patients with MASLD and Diabetes.
- Protective association not seen in patients with pre-existing cirrhosis.

Kanwal F. et al. JAMA Internal Medicine September 2024

Side Effects of GLP 1 Agonists

- Nausea, vomiting and diarrhea
- Gastroparesis, ileus and constipation
- Pancreatitis (?)
- Renal impairment
- Increased risk of thyroid cancer (?)
- Unexpected Pregnancy

A Tale of Caution

- Cost
- Repeated use may be necessary
- Children who have benefited, when they come off regain the weight and are subject to bullying.
- Fake drugs available on the Internet
- Vanity use

The Future Will Be Very Bright

Cost will come down

We will know about mechanisms of action

Interplay with gut microbiome
will be understood

AI will aid in drug development

Unexpected benefits – depression, anxiety, addiction will need to be studied and understood.

Estimated that there are **100 novel** drugs to address weight loss in the pipeline.

Two Seminal Articles NEJM June 2024

1. Survodutide superior to placebo with respect to improvement in MASH without worsening fibrosis.

Sanyal A. et al. A Phase 2 Randomized Trial of Survodutide in MASH and Fibrosis. NEJM June 2024.

2. Tirzepatide treatment for 52 weeks more effective than placebo in resolution of MASH without worsening of fibrosis.

Loomba R. et al. Tirzepatide for Metabolic Dysfunction- Associated Steatohepatitis with Liver Fibrosis. NEJM. June 2024.

Bariatric Surgery has many benefits!

- In adults with obesity Bariatric Surgery compared with no surgery led to a significantly lower incidence of **obesity associated cancer** and **cancer-related mortality**.

Aminian A. et al. JAMA June 2022

Bariatric Surgery Superior to Lifestyle Change for NASH

- 236 patients with obesity and biopsy confirmed NASH completed the trial.
- Sleeve gastrectomy and Roux-en-Y bypass were more effective than lifestyle modification.
- 56% and 57% of the surgical group achieved resolution compared to 16% of the lifestyle group.

Verrastro O. et al Bariatric-metabolic surgery versus lifestyle intervention plus best medical care in non-alcoholic steatohepatitis (BRAVES): a multicenter, open-label randomized trial. The Lancet. April 2023.

Weight Loss Has Myriad Benefits!

- Cardiovascular Benefit
- Blood Pressure
- Lipid Profile
- Arthritis
- Sleep Apnea
- Obesity related Cancer mortality

The Economist

Our election model: Trump ahead
Leads 18 months' forecasts
Pence's plan to defuse the deficit
Why liberal economists can't get drunk

COPYRIGHT

THE EVERYTHING DRUGS

New cure for obesity—but addiction, Alzheimer's and spring too!





1. Who is this person and how old was he when he died?

Voltaire (1694 – 1778) 83 years

2. How many cups of coffee did he drink every day?

50-72 !

Mechanism of Protective Effect of Coffee Unknown

- Caffeine, cafestol and kahweol protective in experimental studies
- Antioxidant effect
- Insulin sensitizing effect
- Coffee drinkers have lower levels of CRP, TNF-alpha and higher levels of plasma adiponectin

Patients with NAFLD who drink coffee have the least amount of Hepatic Fibrosis

1. Molloy JW, Calcagno CJ, Williams CD, Jones FJ, Torres DM, Harrison SA. Association of coffee and caffeine consumption with fatty liver disease, nonalcoholic steatohepatitis, and degree of hepatic fibrosis. *Hepatology*. 2012;55(2):429-36.
2. Dranoff JA. Coffee as chemoprotectant in fatty liver disease: caffeine-dependent and caffeine-independent effects. *American Journal of Physiology*. 2023.



Kaldi the shepherd from Kaffa

“Coffee is so good, the infidels should not have exclusive use of it.”

Pope Vincent III

Low Vitamin D May Increase Risk of NAFLD

- Vitamin D Deficiency may be more common in patients with NAFLD than controls.
- Patients with low Vitamin D appear to have higher risk of moderate-severe NAFLD compared with patients with normal levels.

Trahan L. Pharmacy Times July 2016.

Patients with Elevated Transaminases are not at Higher Risk for Statin Hepatotoxicity

	<u>Mild-Moderate Elevations</u>	<u>Severe Elevations</u>
• 1439 with normal transaminases prescribed a statin	1.9%	0.2%
• 342 with elevated transaminases prescribed a statin	4.7%	0.6 %
• 2245 with elevated transaminases <u>not</u> prescribed a statin	6.4%	0.4%

Chalasani et al: Gastroenterology 2004;126

*My Doctor Said I Could Have One Glass of
Wine per Day*



My Doctor Said I Could Have One Glass of Wine per Day

- How Much of That Bottle is in the Glass?
- A. 33%
- B. 50%
- C. 66%



Quiz Answer **True** or **False**

1. NAFLD is the most common hepatic disorder in the U.S.
2. Serum ferritin is elevated in 50% of pts with NASH.
3. NASH has been reported in children.
4. Progression to cirrhosis occurs in 15-20% of pts.
5. NASH is likely the leading cause of cryptogenic cirrhosis.

Quiz (Continued) Answer **True** or **False**

- 6. The histologic features of NASH maybe seen in Wilson's disease.**
- 7. Both Amiodarone and Tamoxifen can cause NASH.**
- 8. Primary hepatocellular carcinoma has been reported in patients with NASH and cirrhosis.**
- 9. Most Common Cause of Mortality is Cardiovascular followed by Obesity related cancers and then by Cirrhosis and HCC.**

Practical Management Tips

1. Motivate patients to lose weight.
2. Vitamin D3 2,000-4,000 IU per day.
3. Coffee 2-4 cups per day.
4. Vaccinate against Hepatitis A & B if needed.
5. Safe to use Statins if needed.
6. Encourage to enroll in clinical trials.

What did Big Ben say to the Leaning Tower of Pisa?



If you have the inclination, I have the time

COPYRIGHT

RESERVE SLIDES

COPYRIGHT

Initiative to Assess Prevalence of NAFLD (2024)

- First ever national study conducted by the Agency of Healthcare Research and Quality, in collaboration with other Federal Agency stakeholders to evaluate the prevalence, cost to patients and families, cost to the healthcare system, identification of barriers preventing, diagnosing and treating NAFLD and include an analysis of disparities and access to care.

Progression to Cirrhosis

10 Yr Survival

**Alcoholic
Hepatitis**

38 – 50%

20%

NASH

8 – 26%

60%

COPYRIGHT