

Metabolic dysfunction–associated steatotic liver disease

From metabolic disturbance to steatohepatitis, fibrosis and clinical consequences

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Learning outcomes

- Define MASLD and distinguish it from MASH and isolated steatosis.
- Link insulin resistance and adipose dysfunction to hepatocellular lipid accumulation.
- Recognize the key histologic features and characteristic fibrosis pattern.
- Integrate morphology, clinical history and complications in diagnosis.

Terminology identifies two different disease states

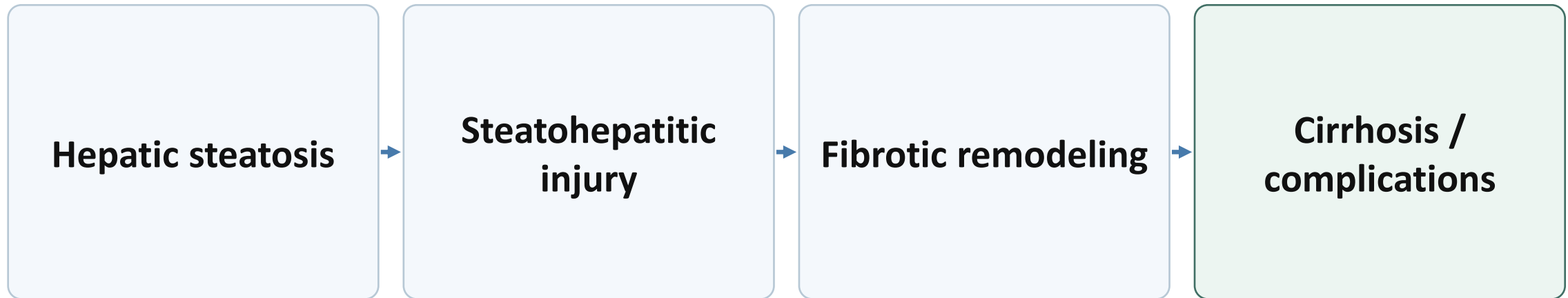
MASLD

Hepatic steatosis associated with cardiometabolic dysfunction, within the clinical exclusions.

MASH

The subset with steatohepatitic injury: Steatosis, lobular inflammation and hepatocyte ballooning.

Steatotic liver disease is a morphologic spectrum



This is a conceptual range, not an inevitable sequence for every patient.

MASLD diagnosis requires clinical context

Hepatic fat

Evidence of steatosis in the liver

Metabolic setting

At least one cardiometabolic risk factor

Etiologic assessment

Alcohol exposure and competing causes evaluated

The defining clinical assessment is more than detecting a fatty liver.

Steatosis alone is not etiologically specific

- Hepatic fat may arise in several different liver diseases.
- Hepatitis C, Wilson disease and medications among alternate causes to consider.
- Alcohol history and potential coexisting insults must be assessed.
- Do not label the cause from steatosis on imaging alone.

The burden of MASLD is substantial

- MASLD as the most common chronic liver disease in the United States.
- Its projected prevalence in the source exceeds 30% of U.S. Adults by 2030.
- Increasing MASLD is expected to increase the burden of MASH, cirrhosis and hepatocellular carcinoma.

The prevalence statement is a textbook projection, not a measured 2030 result.

Cardiometabolic associations dominate the phenotype

Obesity

Expanded, metabolically dysfunctional adipose tissue

Insulin resistance

Central contributor to abnormal lipid flux

Type 2 diabetes

Frequent associated metabolic disorder

Hyperlipidemia

Associated dysregulation of lipid metabolism

Insulin resistance does not fully determine severity

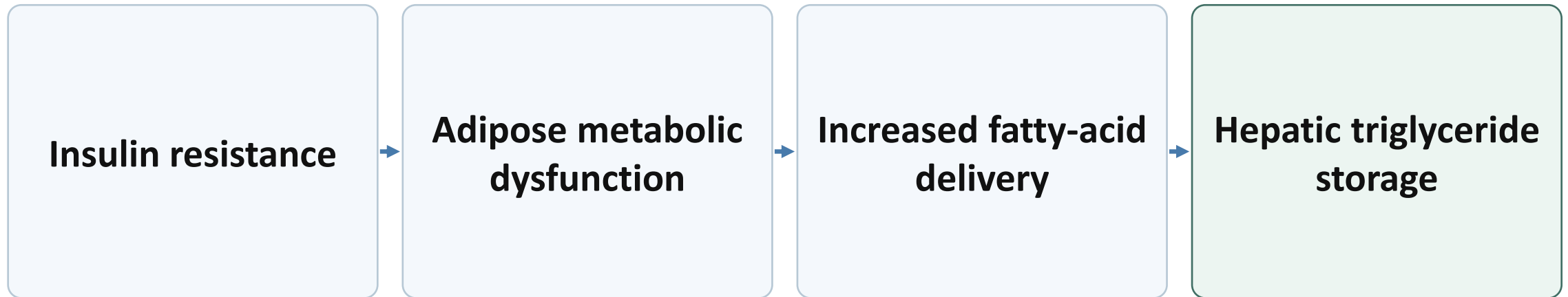
Shared background

Insulin resistance occurs in many affected individuals.

Variable outcome

Even with insulin resistance, disease severity varies substantially.

Insulin resistance links adipose tissue to liver

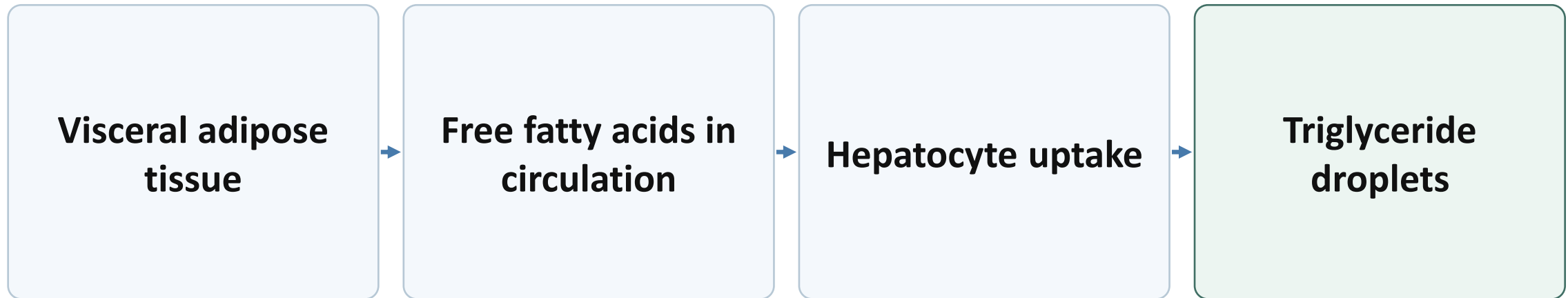


Metabolic dysregulation alters the influx and handling of fatty acids.

Visceral adipose tissue becomes dysfunctional

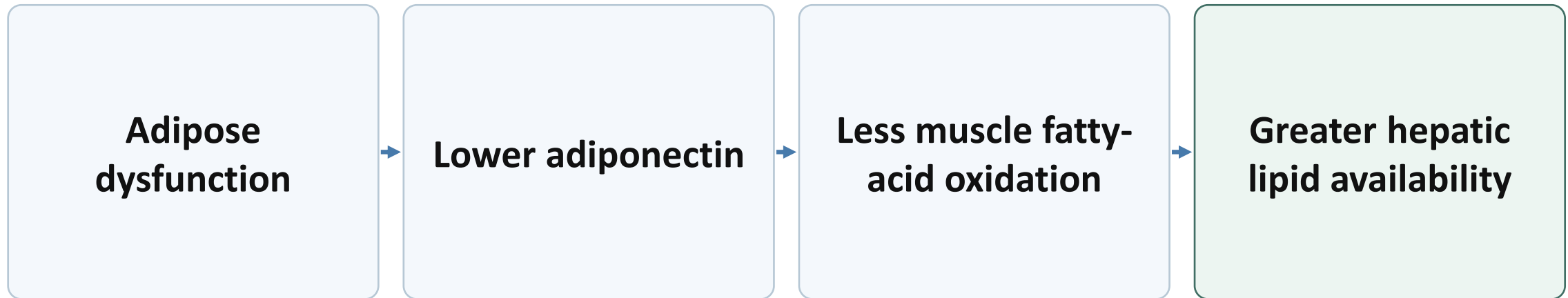
- With insulin resistance, visceral fat expands and acquires abnormal endocrine functions.
- The adipose compartment releases increased circulating free fatty acids.
- Dysfunctional adipocytes also produce proinflammatory mediators.

Circulating fatty acids feed hepatic steatosis



A key substrate supply route in MASLD pathogenesis.

Reduced adiponectin promotes lipid accumulation



The source connects altered adipokine signaling with tissue lipid redistribution.

Lipophagy normally helps clear stored lipid

Functional lipophagy

Selective autophagic processing of lipid droplets contributes to cellular lipid turnover.

Reduced lipophagy

Down-regulated lipid turnover can favor further hepatocyte fat accumulation.

Steatosis reflects a net excess of stored lipid

1

More delivery

Free-fatty-acid influx into hepatocytes rises.

2

Altered disposal

Metabolic handling and lipophagy are impaired.

3

Net storage

Triglyceride accumulates in cytoplasmic droplets.

Multiple inputs modify MASLD severity

Genetic variation

Diet composition

Variable MASLD severity

Intestinal microbiome

Obstructive sleep apnea

Other liver insults

These are contributory associations, not a single proven causal pathway.

Dietary exposures may influence progression

High-fructose diets

Associated with increased MASLD-related fibrosis risk.

Dietary trans-fats

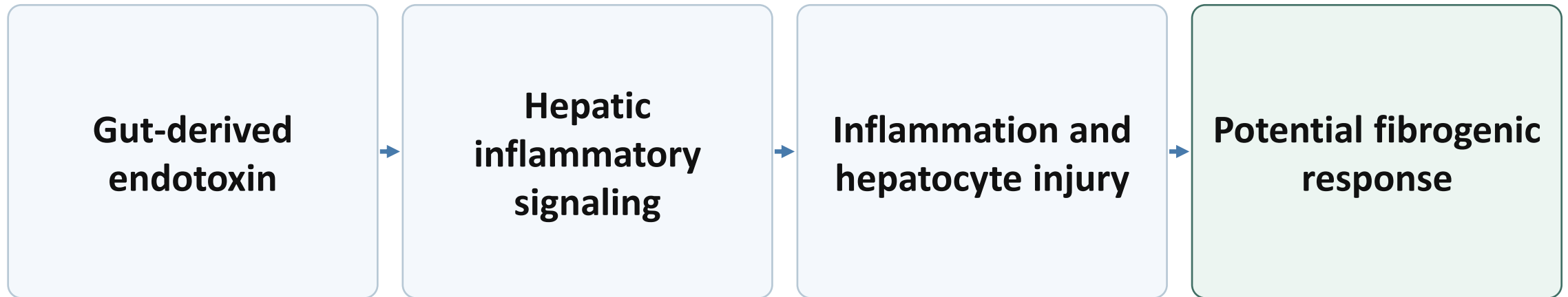
May contribute to hepatocellular injury.

Associations do not establish that either exposure independently explains every case.

The microbiome is a plausible disease modifier

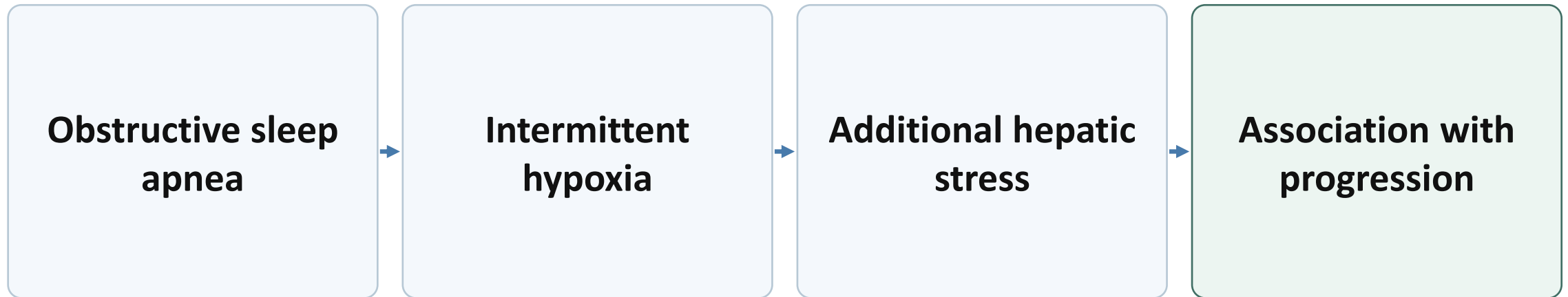
- The source describes complex associations between intestinal microbes and MASLD.
- Variation in intestinal products may contribute to between-patient differences.
- An association with liver inflammation does not identify one specific responsible microbial species.

Gut-derived endotoxin is linked to liver injury



An established association; The diagram does not imply a single sufficient cause.

Sleep apnea may amplify chronic injury

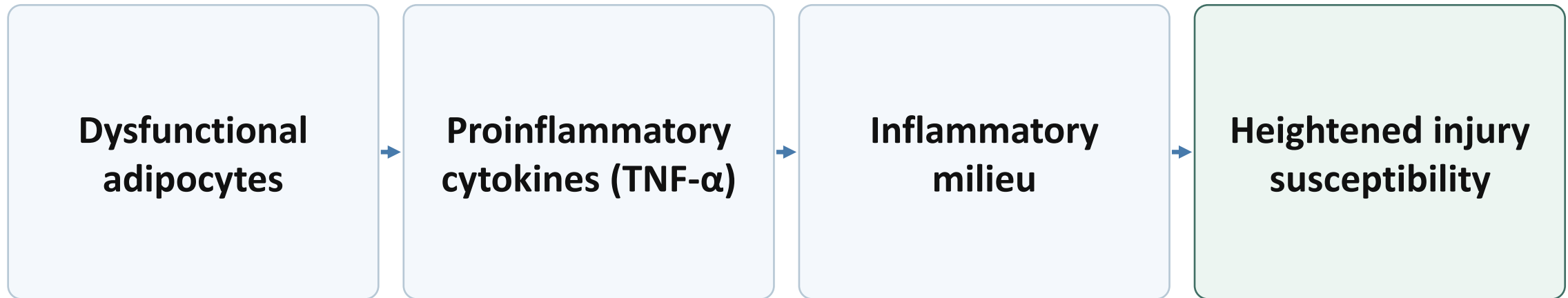


The hypoxia-mediated mechanism is suggested, not definitively established.

An additional liver insult can accelerate fibrosis

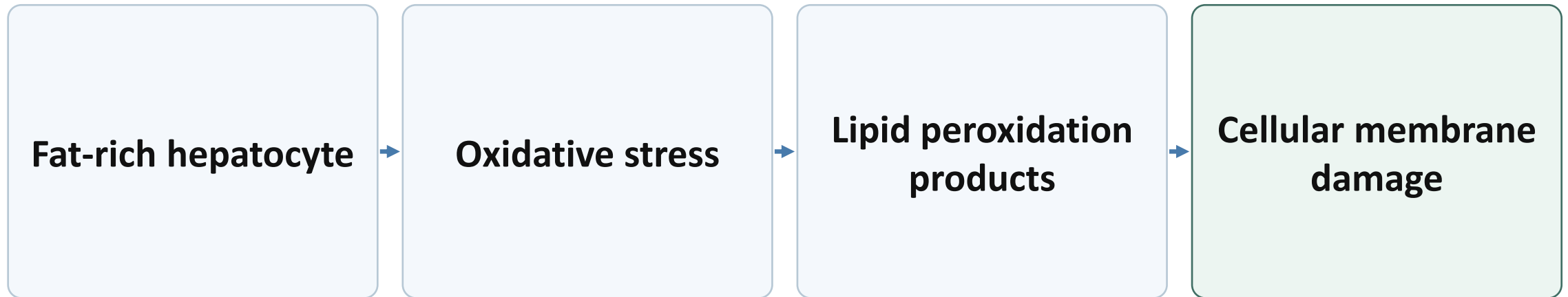
- MASLD can coexist with a second chronic liver disease.
- Hemochromatosis as an example of a superimposed injury.
- The combined insults may accelerate scarring and complicate attribution of liver damage.

Adipose cytokines prime an inflammatory state



The metabolic and inflammatory arms of disease are interrelated.

Oxidative stress links steatosis to injury



Fat storage alone and the response to lipid-associated injury are distinct processes.

Lipid peroxidation targets cellular membranes

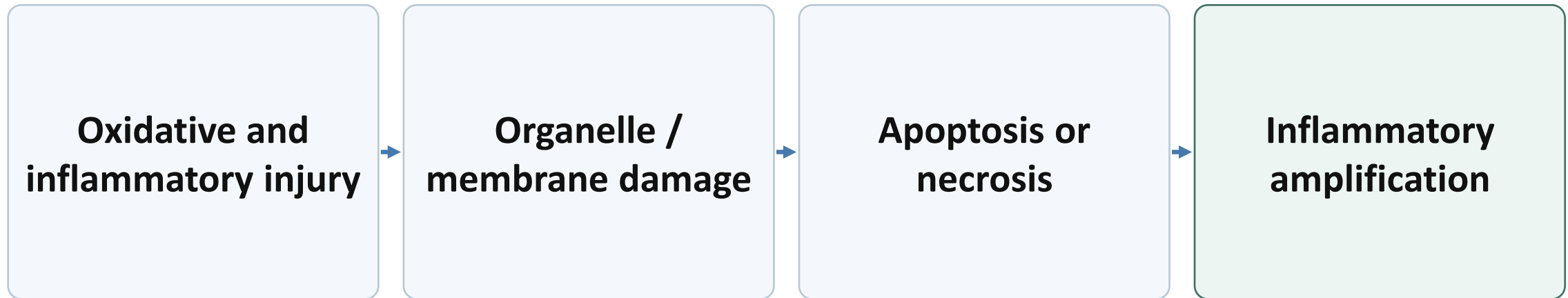
Mitochondrial membranes

Oxidative damage contributes to mitochondrial dysfunction and hepatocyte injury.

Plasma membrane

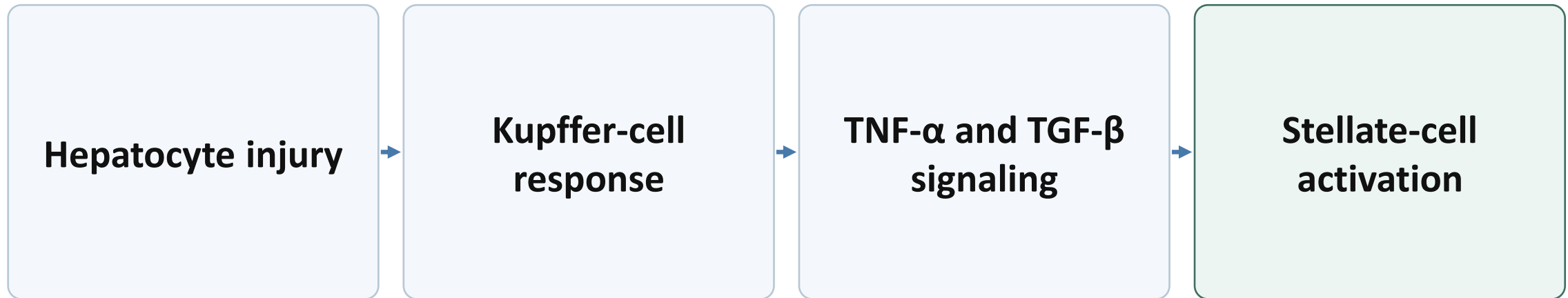
Peroxidation can impair cellular integrity and survival.

Hepatocyte injury can culminate in cell death



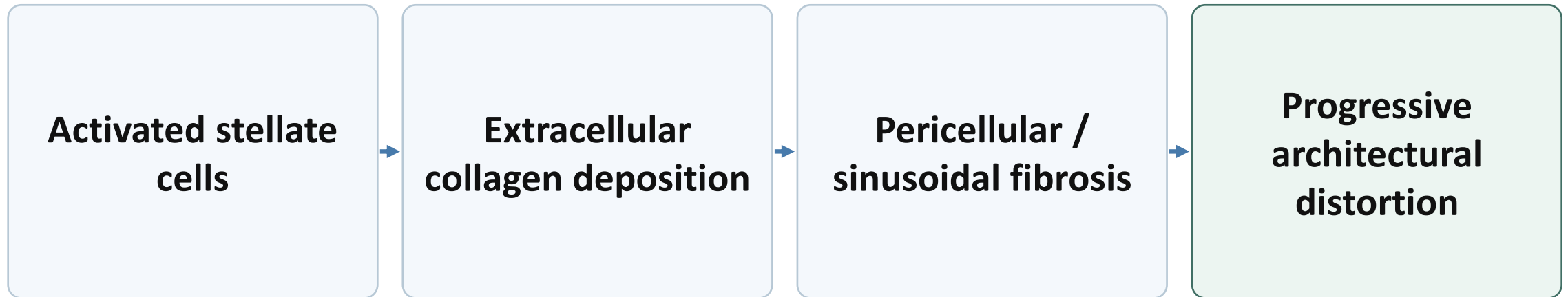
Different pathways of hepatocellular death can contribute to tissue damage.

Kupffer-cell signaling connects injury to fibrosis



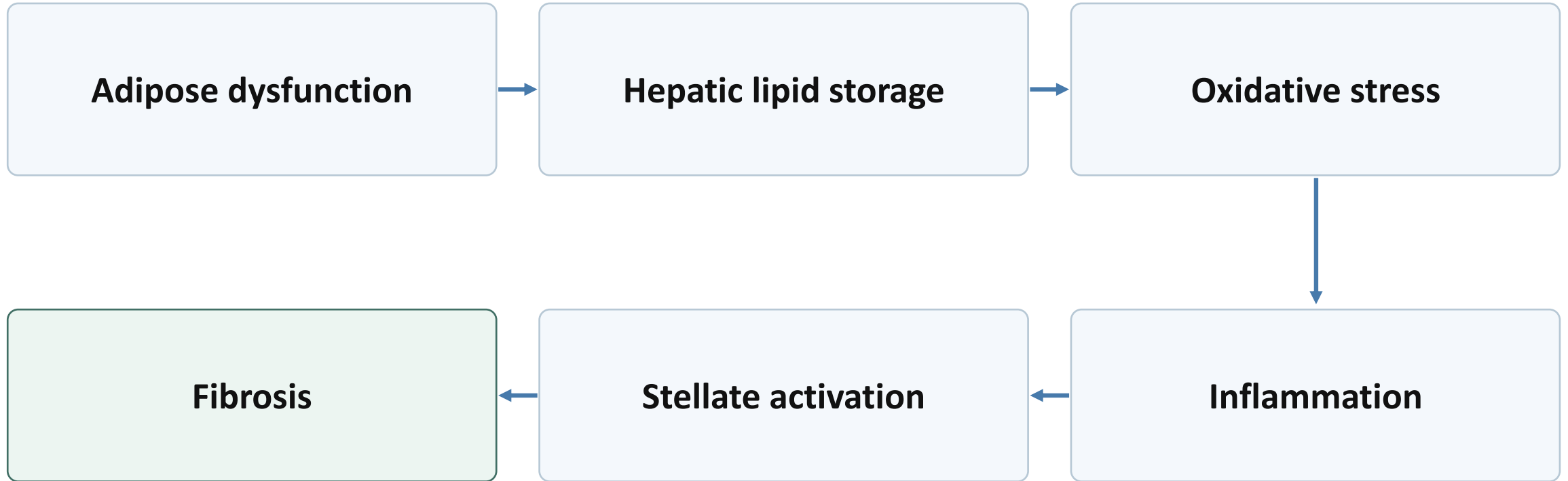
The source identifies local cytokine release as a driver of scarring.

Hepatic stellate cells deposit scar collagen



A cellular injury response becomes a sustained tissue-remodeling program.

MASLD is a network, not a single-hit disease



Causal model simplified from the source; Multiple modifiers affect each link.

MASH is defined by a morphologic triad

Steatosis

Fat in $\geq 5\%$ of hepatocytes

Lobular inflammation

Inflammatory cells within the parenchyma

Ballooning

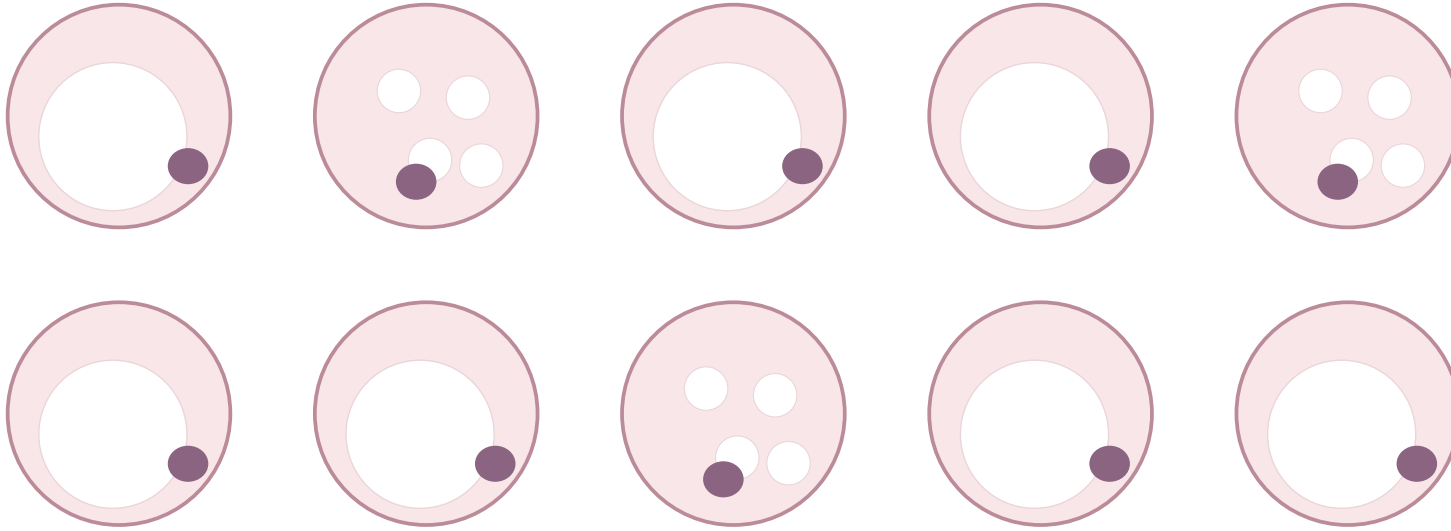
Swollen hepatocytes showing injury

All three are required in the Robbins description of MASH.

The steatosis threshold has a clear meaning

- Robbins specifies steatosis involving at least 5% of hepatocytes for MASH morphology.
- This is a histologic proportion of hepatocytes—not a percentage of liver volume or a blood biomarker.
- Steatosis is necessary but not sufficient for MASH in the described triad.

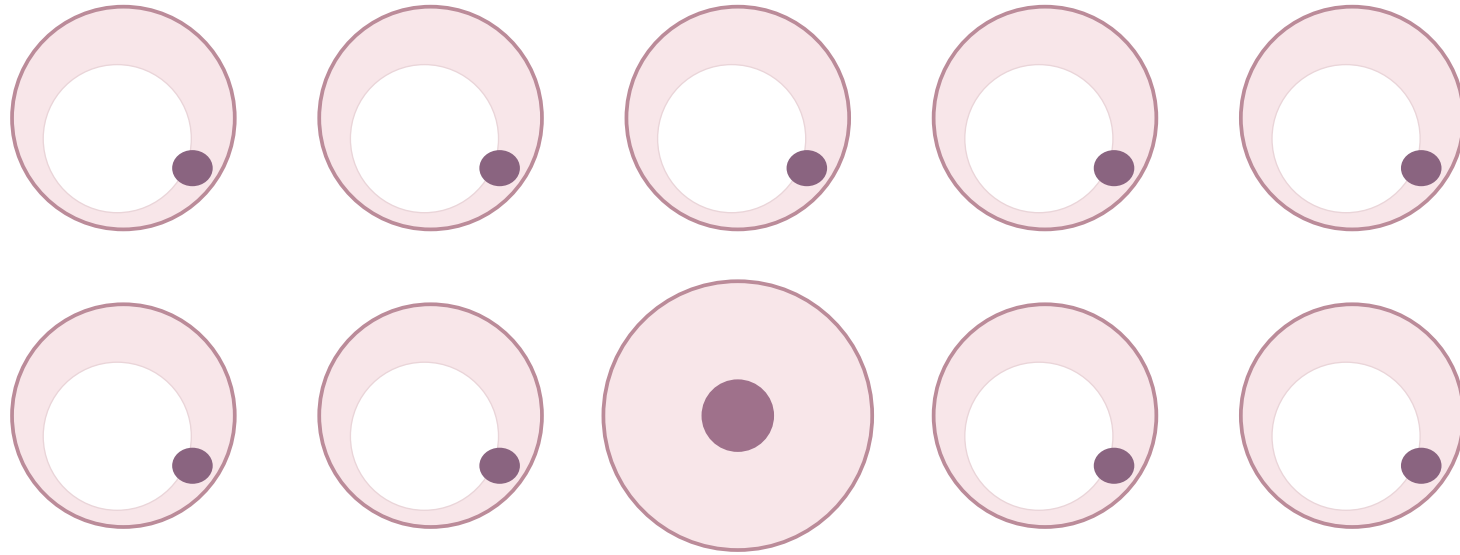
Fat droplets vary within hepatocytes



Schematic · not a histologic specimen

Mixed small and large cytoplasmic lipid droplets may appear; This is an editable schematic, not a tissue image.

Ballooned hepatocytes signify cellular injury

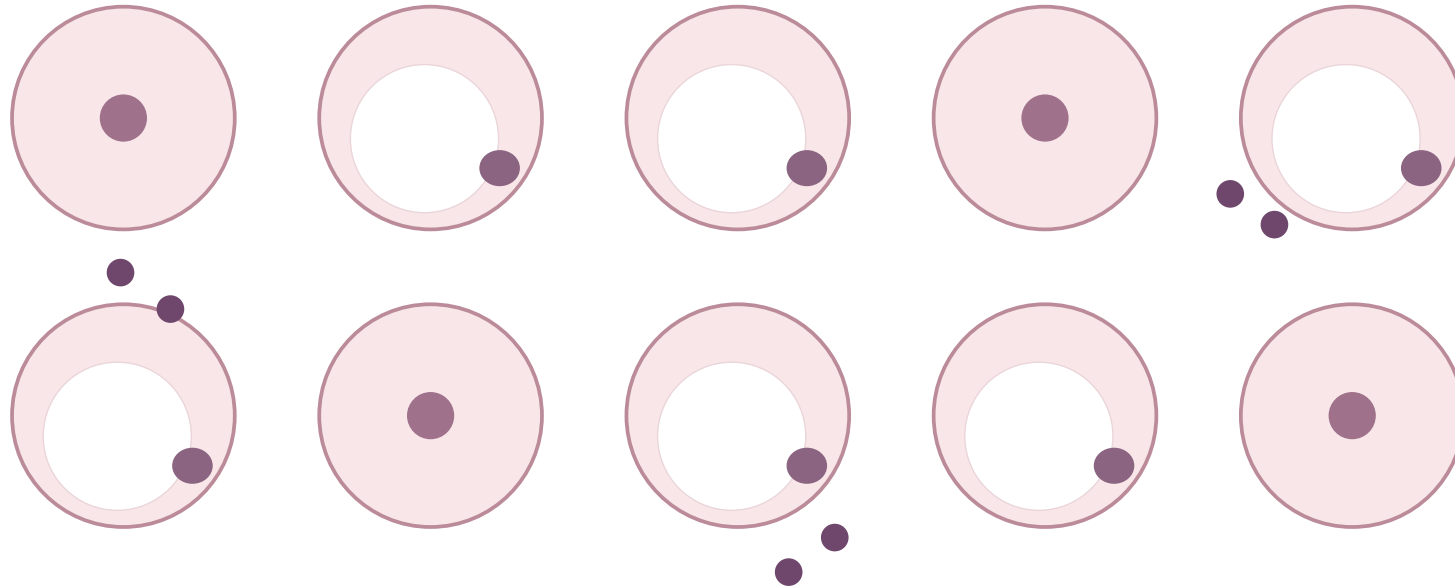


**Injured, enlarged
hepatocyte**

Schematic · not a histologic specimen

The swollen, pale-appearing hepatocyte is a component of the steatohepatitis diagnosis.

Lobular inflammation completes the injury pattern



Schematic · not a histologic specimen

Inflammatory foci should be interpreted together with steatosis and ballooning.

A triad-based reading prevents overdiagnosis

Is steatosis present in $\geq 5\%$ of hepatocytes?



Is lobular inflammation present?



Are ballooned hepatocytes present?

Interpretation

If absent: The Robbins MASH triad is not met.

Interpretation

If absent: Do not equate steatosis with steatohepatitis.

Interpretation

If present with the above: MASH morphology is supported.

Simple steatosis and MASH are not equivalent

Feature	Steatosis only	MASH
Hepatocellular fat	Present	Present
Lobular inflammation	Not part of isolated steatosis	Required by source
Ballooning	Not part of isolated steatosis	Required by source
Fibrosis risk	Variable	Higher risk of advanced fibrosis

Alcoholic and metabolic steatohepatitis overlap

- Both can exhibit steatosis, inflammation, hepatocyte ballooning and fibrosis.
- That routine morphology cannot reliably determine the etiology.
- Alcohol exposure, metabolic context and alternative causes must be evaluated together.

Histologic differences are tendencies, not rules

Feature	Alcohol-associated pattern (on average)	MASH
Steatosis	Often less marked	Can be prominent
Ballooning / inflammation	Often more prominent	Part of required triad
Mallory hyaline / neutrophils	Often more prominent	May overlap
Cholestasis / central venous injury	More often emphasized	Less characteristic

Group-level trends; No one feature reliably assigns the cause.

Etiology remains a clinicopathologic diagnosis

Clinical history

Characterize alcohol exposure and metabolic risks.

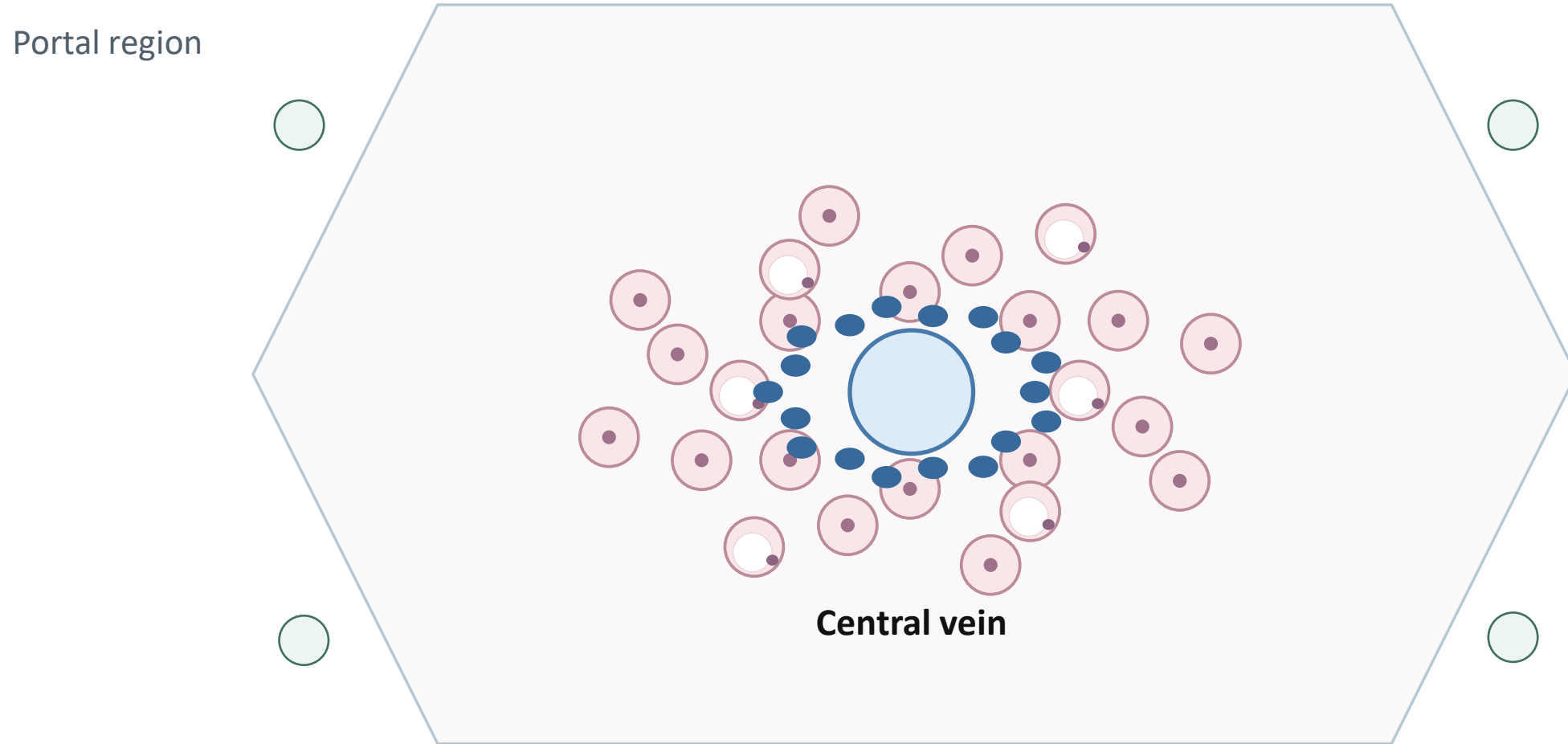
Pathology

Determine steatosis, injury and fibrosis pattern.

Exclusions

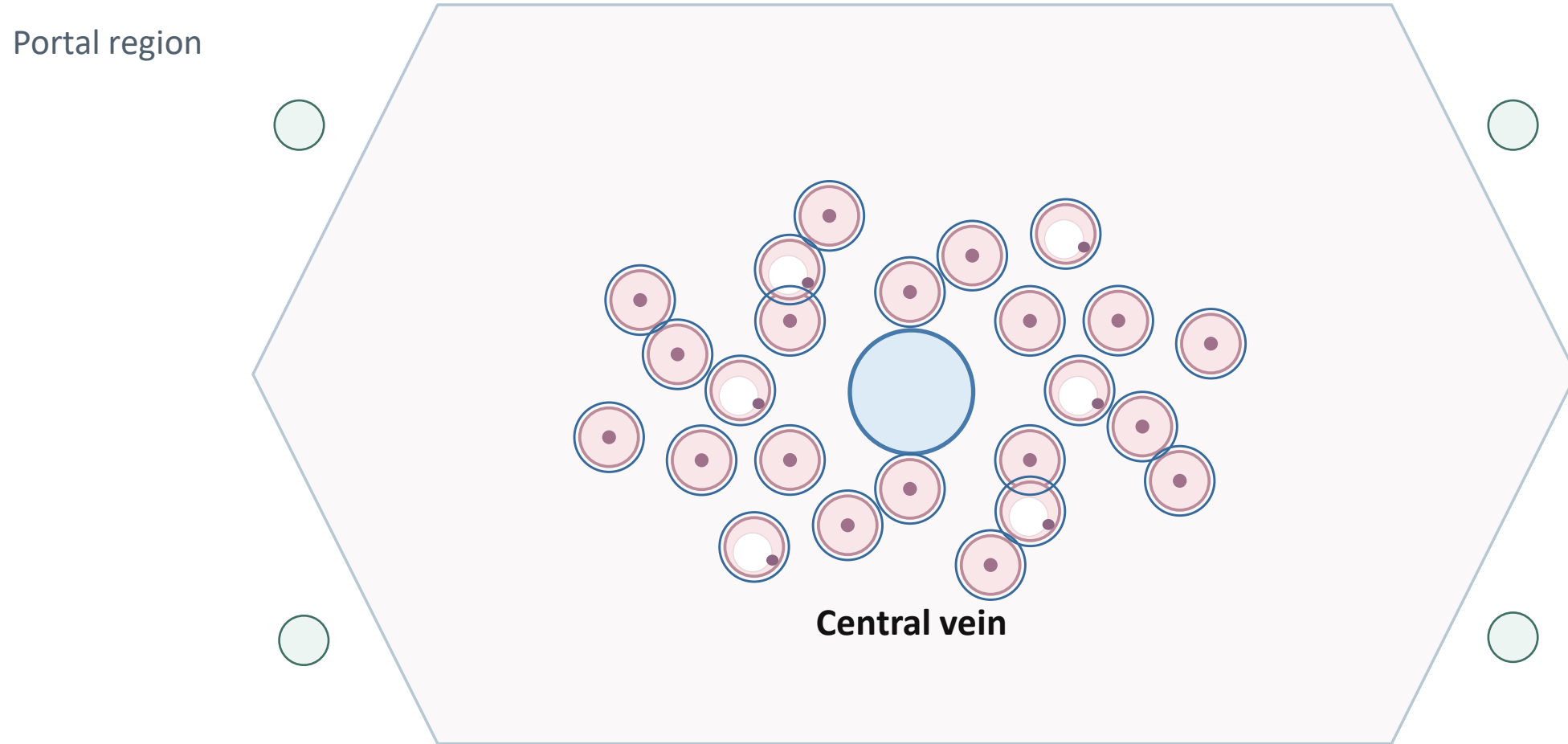
Consider viral, autoimmune and other metabolic causes.

Early fibrosis favors a pericentral location



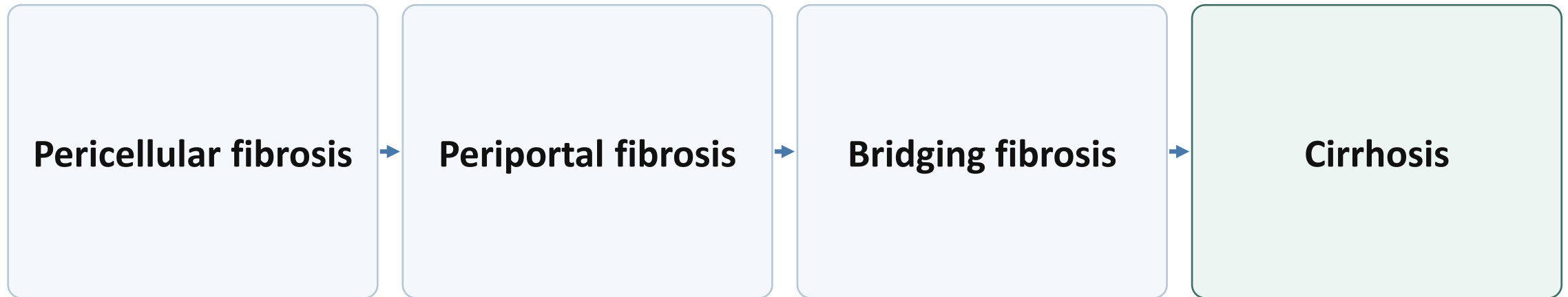
Schematic—not a photomicrograph. Early scarring arises near the central vein and surrounding hepatocytes.

Pericellular fibrosis forms a chicken-wire pattern



Schematic—not a photomicrograph. Pericellular collagen outlines hepatocytes; Trichrome can aid detection.

Fibrosis spreads beyond the pericentral region



A usual sequence; Individual patterns and rates vary.

Pericentral and portal fibrosis are distinct

Pericentral pattern

Fine pericellular collagen near central veins is typical in adult MASH.

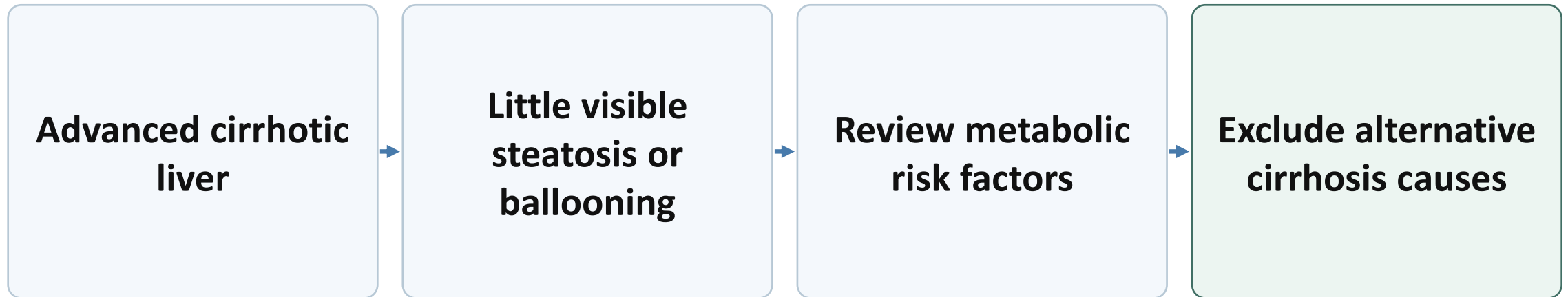
Portal pattern

Portal-area fibrosis is emphasized in many pediatric cases.

Cirrhosis can obscure the original steatohepatitis

- Established cirrhosis may persist after obvious fat accumulation diminishes.
- Ballooned hepatocytes can also be reduced or absent in the cirrhotic liver.
- The absence of current steatosis therefore does not exclude prior MASH.

“Burned-out” MASH is a diagnostic pitfall



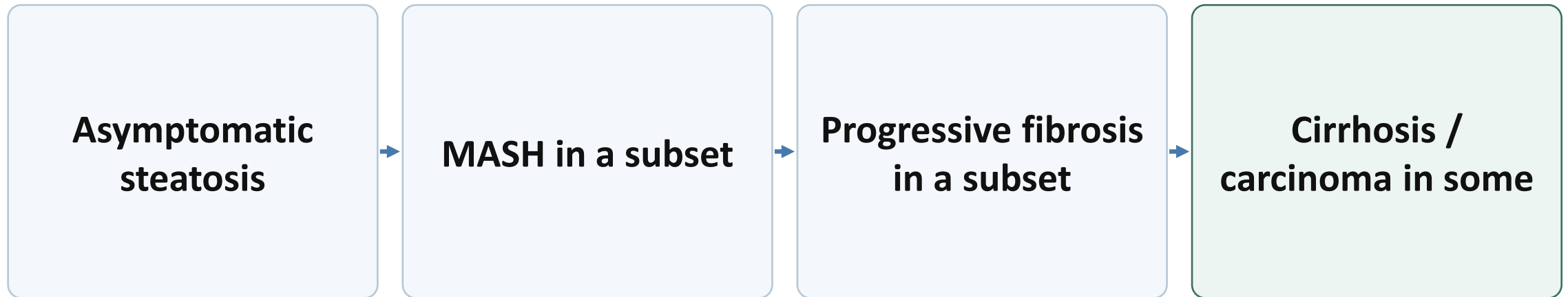
The source discusses this pathway among cases labeled cryptogenic cirrhosis.

Pediatric MASLD is morphologically different

Morphologic feature	Typical adult pattern	Pediatric pattern
Steatosis	Variable distribution	Often more diffuse
Fibrosis	Often central / pericellular initially	Often portal
Ballooning	Characteristic for MASH triad	May be absent

Adult diagnostic expectations should not be imposed without qualification on children.

Clinical trajectories vary substantially



The schematic is a range of potential outcomes, not a deterministic patient timeline.

Isolated steatosis is frequently silent

- Individuals with steatosis alone are generally asymptomatic.
- Fat accumulation may be detected incidentally on imaging.
- Absence of symptoms does not establish absence of histologic injury.

Presentation often reflects metabolic comorbidity

- Clinical encounters may be driven by insulin resistance or type 2 diabetes.
- Obesity and lipid abnormalities commonly coexist.
- The liver abnormality may be secondary in the clinical presentation yet prognostically important.

Symptoms, when present, are often nonspecific

Fatigue

May occur without severe or distinctive liver symptoms.

Right upper abdominal discomfort

May reflect hepatic enlargement.

Neither symptom identifies MASH or grades fibrosis.

Aminotransferase elevation does not define MASH

- AST and ALT are elevated in many patients with MASH.
- Patients may remain asymptomatic despite abnormal enzymes.
- Biochemistry alone cannot establish the requisite histologic triad or stage fibrosis.

Imaging reveals fat but not the full injury pattern

Imaging

Can show hepatic fat accumulation.

Liver biopsy

Characterizes steatohepatitis and contributes to fibrosis assessment.

The Robbins source specifically requires biopsy for definitive MASH diagnosis.

Histology answers questions imaging cannot

Inflammation

Is lobular inflammatory injury present?

Ballooning

Are damaged, enlarged hepatocytes demonstrable?

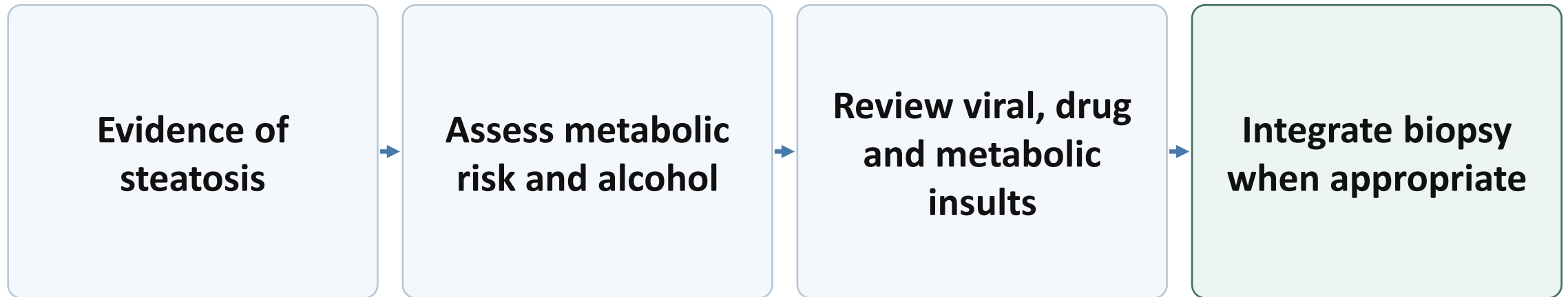
Fibrosis

How extensive is scar deposition and what pattern is present?

The differential diagnosis must remain open

- Viral hepatitides can coexist with or mimic elements of chronic liver injury.
- Autoimmune liver disease and metabolic conditions require consideration.
- Medication and alcohol histories help identify alternative or combined etiologies.

Mixed etiologies require explicit evaluation



A patient can have more than one contributor to liver injury.

An integrated diagnostic synthesis has four layers

Metabolic milieu

Obesity, insulin resistance, type 2 diabetes, lipids

Hepatic phenotype

Steatosis versus steatohepatitic injury

Fibrotic burden

Pericellular, periportal, bridging or cirrhotic

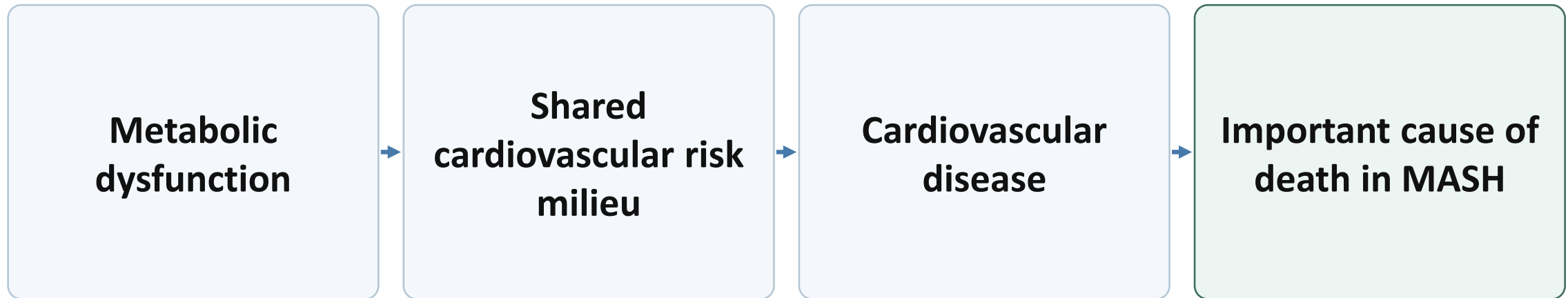
Competing insults

Alcohol, viral, drug-induced, inherited disease

Fibrosis assessment changes clinical priorities

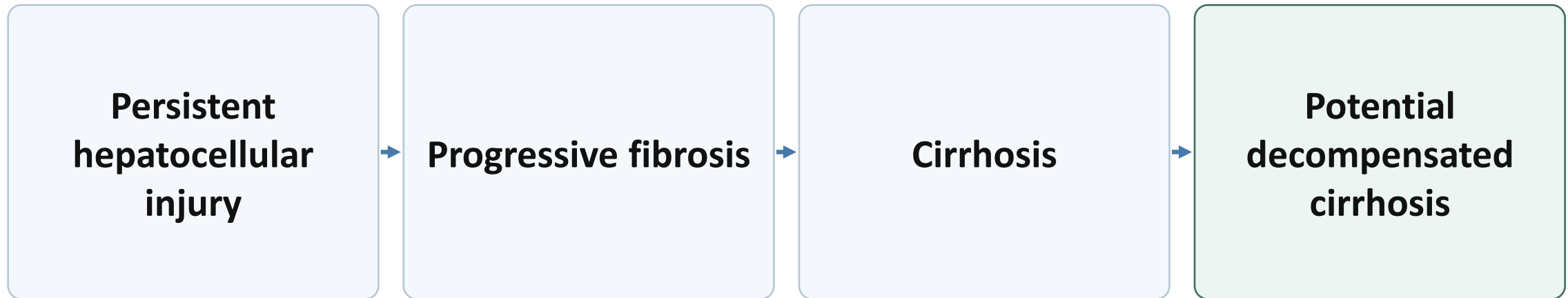
- MASH is associated with increased risk of advanced fibrotic disease.
- Assessment of the extent of fibrosis for management.
- Scar progression—not merely the presence of fat—drives major liver-related complications.

Cardiovascular disease is a major clinical outcome



Clinical risk extends beyond the liver.

Progressive liver injury can decompensate



Decompensated cirrhosis among serious complications.

MASH increases hepatocellular carcinoma risk

- MASH is associated with greater hepatocellular carcinoma risk.
- Advanced chronic liver disease is one pathway to liver-related morbidity.
- Cancer risk must be interpreted alongside other underlying metabolic and hepatic conditions.

Management targets the underlying metabolic disorder

Obesity

Correct excess adiposity and associated metabolic dysfunction.

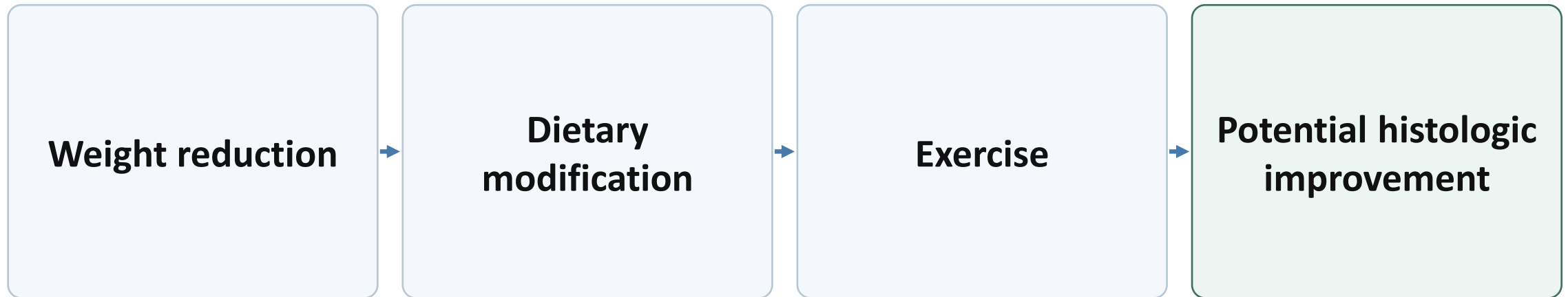
Hyperlipidemia

Address the abnormal lipid-metabolic milieu.

Insulin resistance

Treat the metabolic condition sustaining hepatic injury.

Lifestyle change can improve histologic injury



Lifestyle interventions can potentially reverse MASH abnormalities; No unverified effect sizes are presented.

Therapeutic claims must match the source

- The source prioritizes reducing hepatic injury and preventing or reversing fibrosis.
- It notes active pharmacologic research but supplies no drug-specific trial results.
- No current drug approvals, efficacy rates or treatment thresholds are inferred from this source extract.

Case 1 · Fatty liver discovered incidentally

Clinical vignette

- An asymptomatic adult with obesity and type 2 diabetes has hepatic steatosis on imaging.
- AST and ALT are not provided; No biopsy has been performed.
- Question: What can be concluded—and what remains unproven?

Case 1 · Separate steatosis from steatohepatitis

Supported

Hepatic fat plus relevant metabolic risk.

Not yet established

Ballooning, lobular inflammation and fibrosis stage.

Next interpretive task

Evaluate alcohol and competing hepatic causes.

Case 2 · Histologic features converge

Clinical vignette

- A liver biopsy shows steatosis in $\geq 5\%$ of hepatocytes, lobular inflammation and ballooning.
- Pericellular collagen is highlighted by trichrome.
- Question: What does pathology establish, and what does it not?

Case 2 · Morphology requires etiologic correlation

Pathology establishes

Steatohepatitis and
pericellular fibrotic change.

Clinical history establishes

Exposure and metabolic
setting relevant to etiology.

Avoid

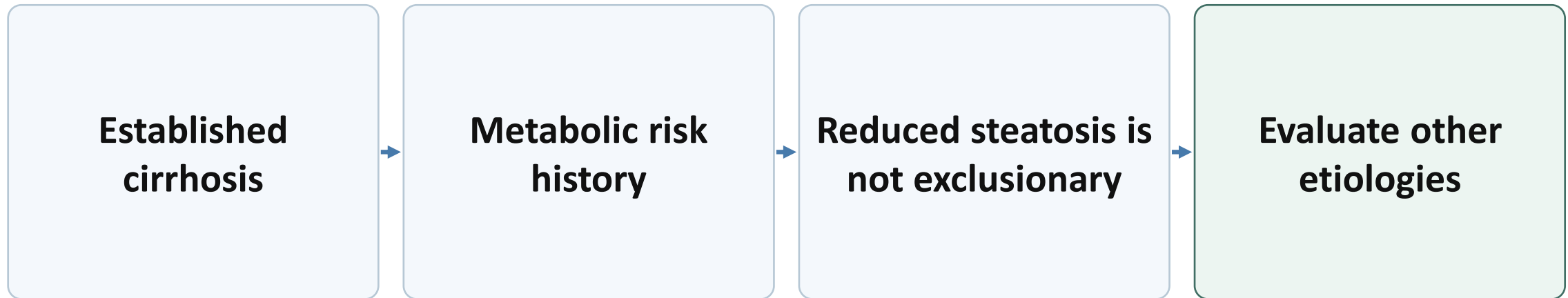
Calling MASH solely from a
microscopic pattern.

Case 3 · Cirrhosis with little current steatosis

Clinical vignette

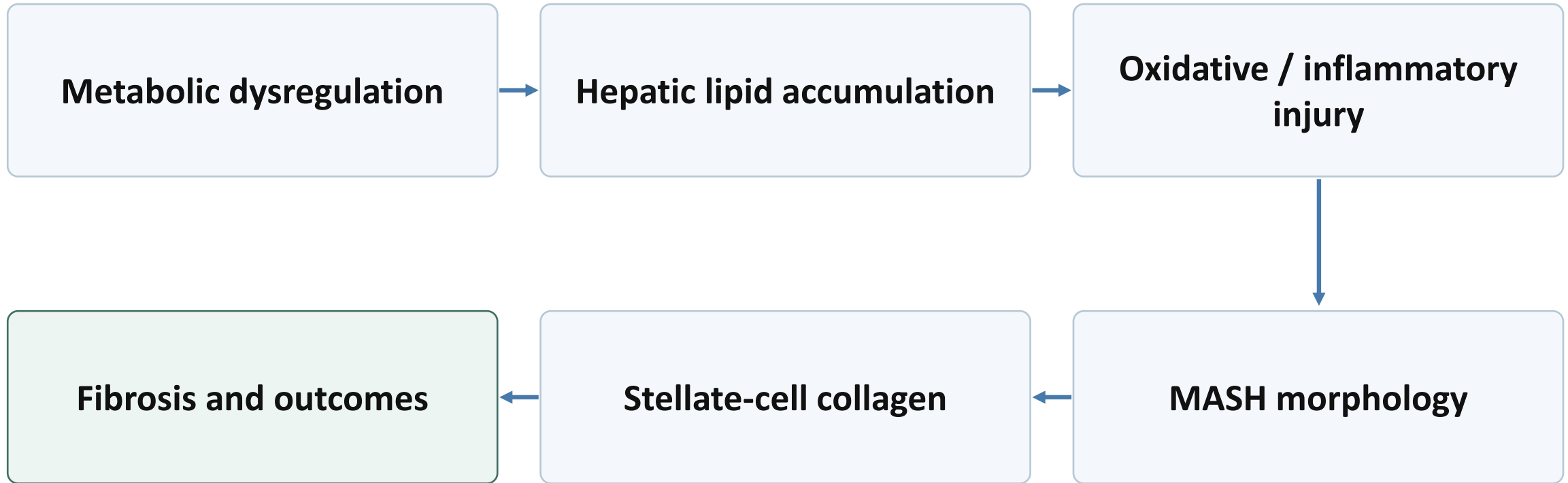
- A patient has established cirrhosis and longstanding type 2 diabetes and obesity.
- Current biopsy shows little fat and few ballooned hepatocytes.
- Question: Does the morphology rule out a prior MASH pathway?

Case 3 · Recognize burned-out disease carefully



Retrospective attribution remains clinicopathologic, not based on a single absent lesion.

Synthesis · The causal sequence to remember



Genetic, dietary, intestinal and comorbid factors modify progression.

The diagnostic synthesis in one frame

Fat

Recognize and assess the hepatic steatosis.

Injury

Find ballooning and lobular inflammation.

Scar

Determine fibrosis distribution and extent.

Cause

Use metabolic, alcohol and alternative etiologic history.

Source and interpretation notes

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. Chapter 18, “Liver and Gallbladder,” pp. 766–771.
- Primary source section: “Metabolic Dysfunction–Associated Steatotic Liver Disease,” beginning p. 769.
- Morphologic schematics are original editable PowerPoint drawings—not specimens or reproductions of textbook figures.
- The extracted source contains no reusable figure files. No external treatment algorithms were added.