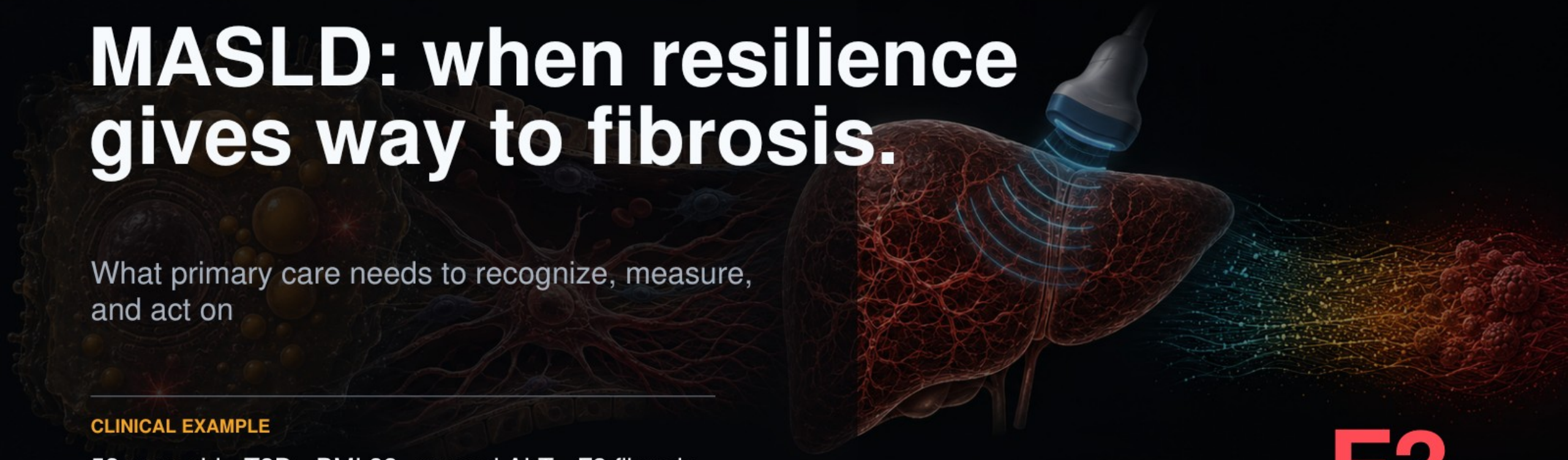
METABOLIC DYSFUNCTION–ASSOCIATED STEATOTIC LIVER DISEASE

MASLD: when resilience gives way to fibrosis.

What primary care needs to recognize, measure, and act on



CLINICAL EXAMPLE

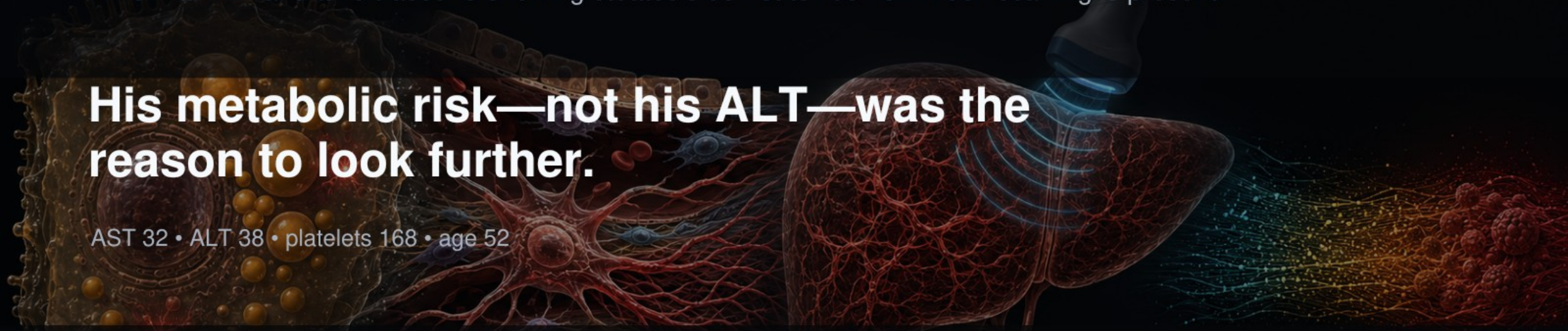
52-year-old • T2D • BMI 32 • normal ALT • F3 fibrosis

F3

at presentation

Fat is easy to find. Fibrosis is easy to miss.

A normal ALT and an ultrasound showing steatosis do not tell us how much scarring is present.



His metabolic risk—not his ALT—was the reason to look further.

AST 32 • ALT 38 • platelets 168 • age 52

1.61 → **12.6 kPa** → **F3**

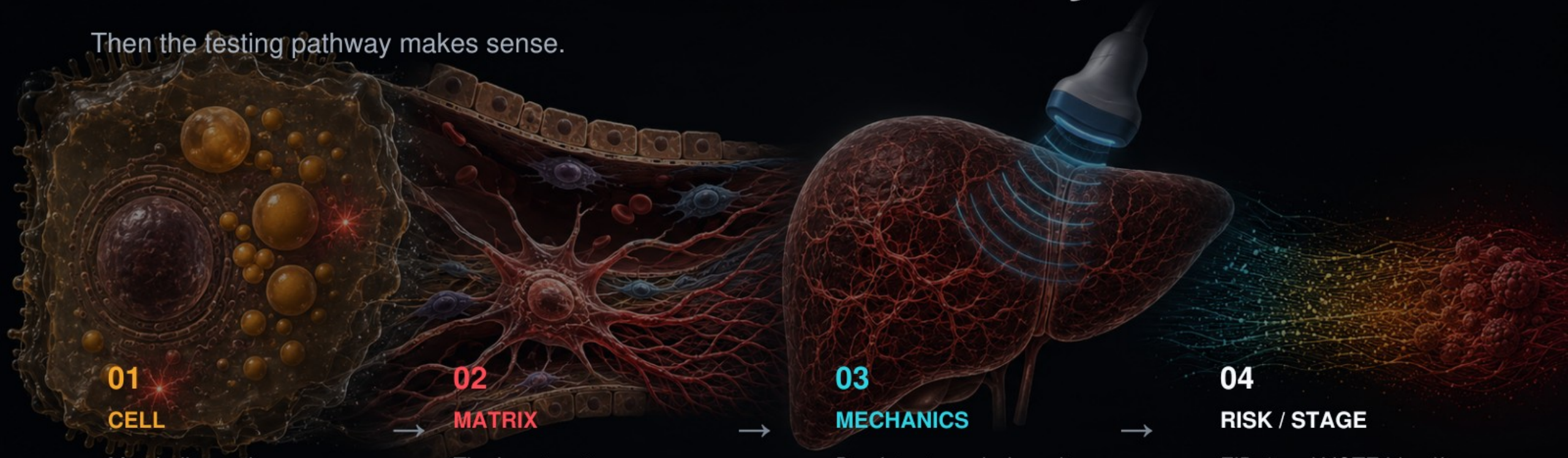
FIB-4
above rule-out threshold

VCTE
elevated liver stiffness

STAGE
F3 bridging fibrosis

Start with what the disease actually is.

Then the testing pathway makes sense.



01
CELL
Metabolic syndrome increases the liver's fat burden.

→

02
MATRIX
The hepatocyte compensates until storage no longer protects it.

→

03
MECHANICS
Persistent repair deposits collagen and reduces flexibility.

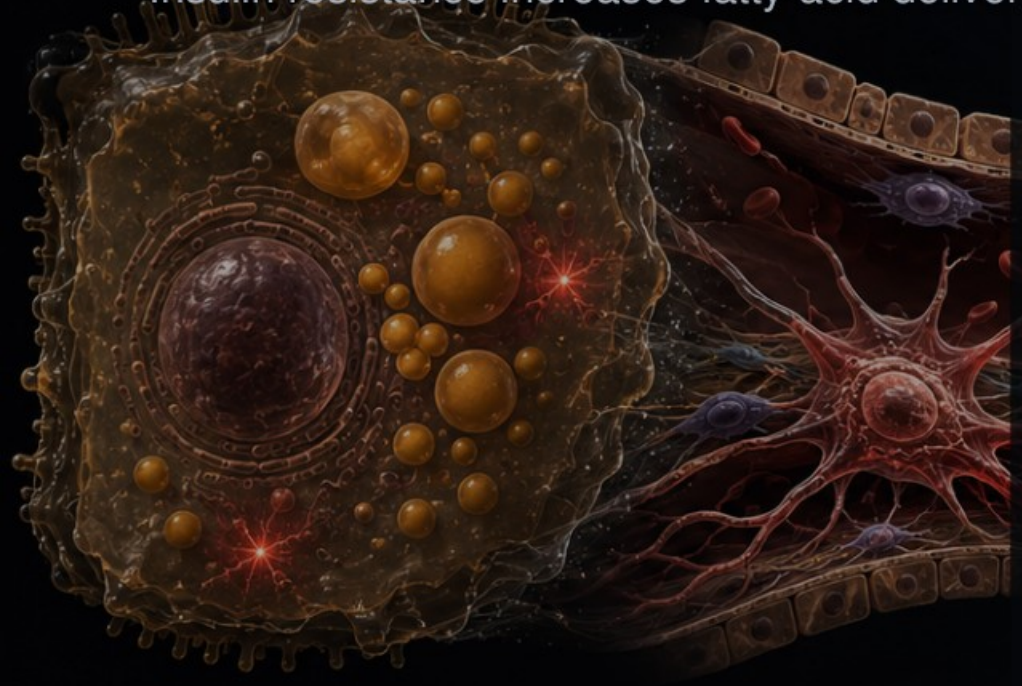
→

04
RISK / STAGE
FIB-4 and VCTE identify when management needs to change.

The pathophysiology tells us what to measure—and why.

MASLD is metabolic syndrome expressed in the liver.

Insulin resistance increases fatty-acid delivery, while the liver also makes new fat.



ADIPOSE-DERIVED FATTY ACIDS

59%

When insulin no longer suppresses lipolysis, more fatty acid reaches the liver.

DE NOVO LIPOGENESIS

26%

The liver also converts excess carbohydrate into fat; diet adds to the same burden.

The hepatocyte has four ways to handle excess fatty acid.

It can burn it, store it, export it, or leave it in a more toxic form.

01

OXIDIZE

The liver can burn only so much.

→

02

STORE / EXPORT

Triglyceride goes into droplets or leaves in VLDL.

→

03

REMAIN TOXIC

DAGs, ceramides, and free cholesterol remain biologically active.

→

04

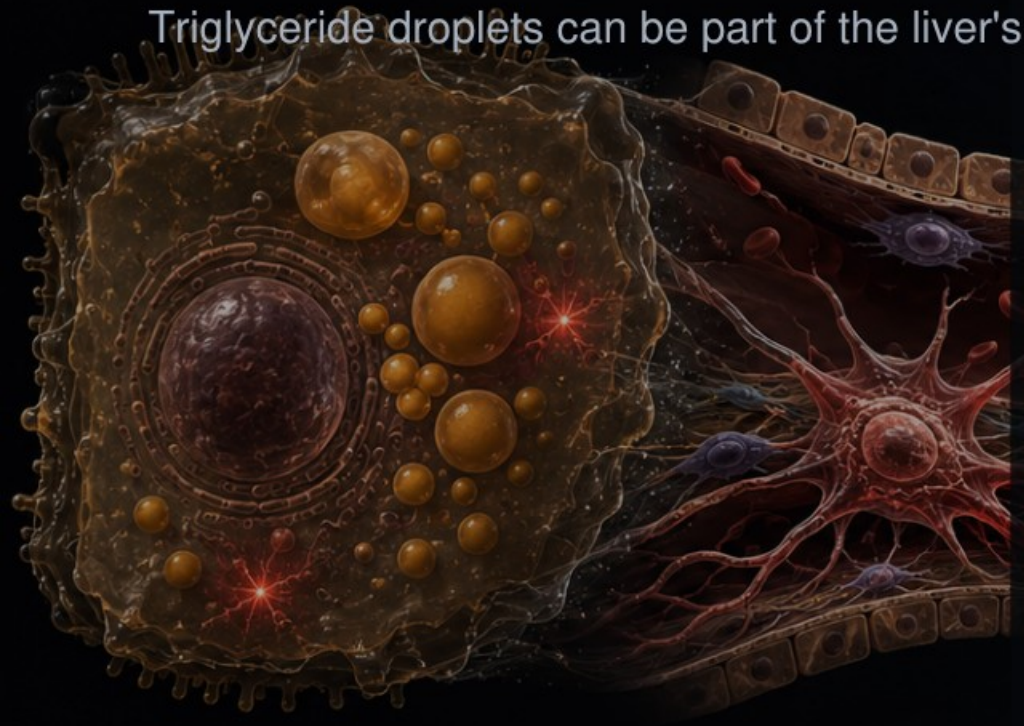
CELL INJURY

Cellular injury begins when these pathways are overwhelmed.

Storing fat as triglyceride can temporarily buffer more toxic lipid species.

Steatosis is evidence of storage—not proof of fibrosis.

Triglyceride droplets can be part of the liver's attempt to protect itself.



STORED TRIGLYCERIDE

VISIBLE ON IMAGING

This identifies steatosis; it does not tell us how much scarring is present.

LIPOTOXIC SPECIES

NOT SEEN ON ROUTINE IMAGING

DAGs, ceramides, free cholesterol, and saturated fatty acids injure organelles and activate inflammation.

When buffering fails, injury becomes persistent.

Lipid toxicity, organelle injury, immune signals, and host factors act together.

This is not a neat two-hit sequence.

The injury is overlapping, persistent, and difficult to see with one routine test.

LIPID STRESS
DAGs • ceramides

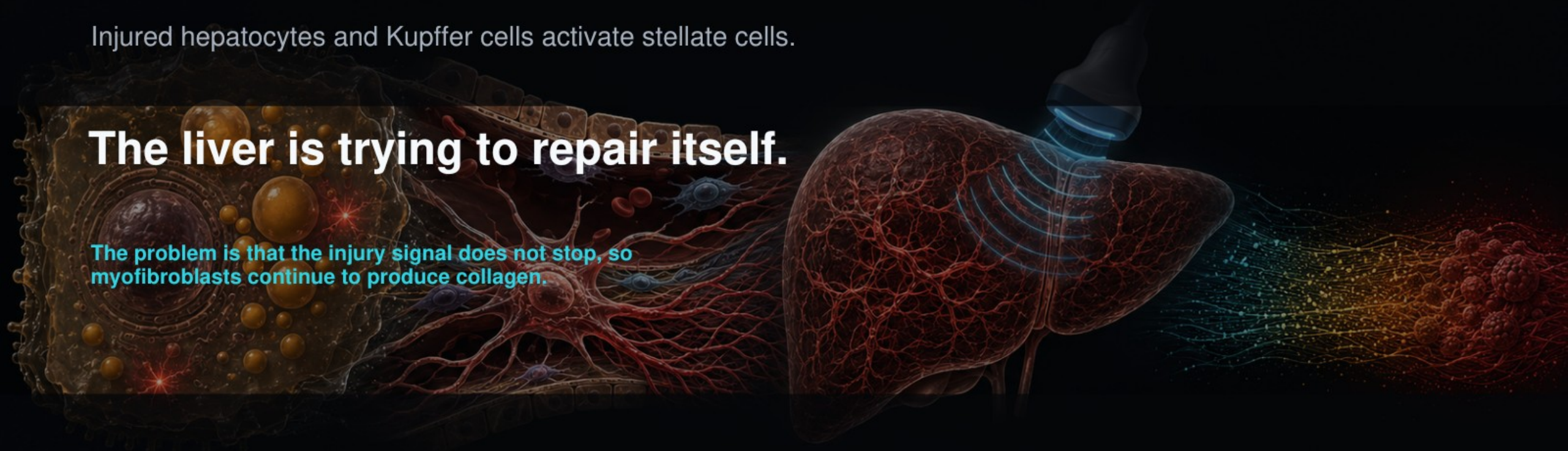
ORGANELLE STRESS
mitochondria • ER

IMMUNE / GUT
Kupffer cells • LPS

HOST FACTORS
adipokines • genotype

Persistent injury turns repair into fibrosis.

Injured hepatocytes and Kupffer cells activate stellate cells.



The liver is trying to repair itself.

The problem is that the injury signal does not stop, so myofibroblasts continue to produce collagen.

INJURED HEPATOCYTE
DAMPs • ROS

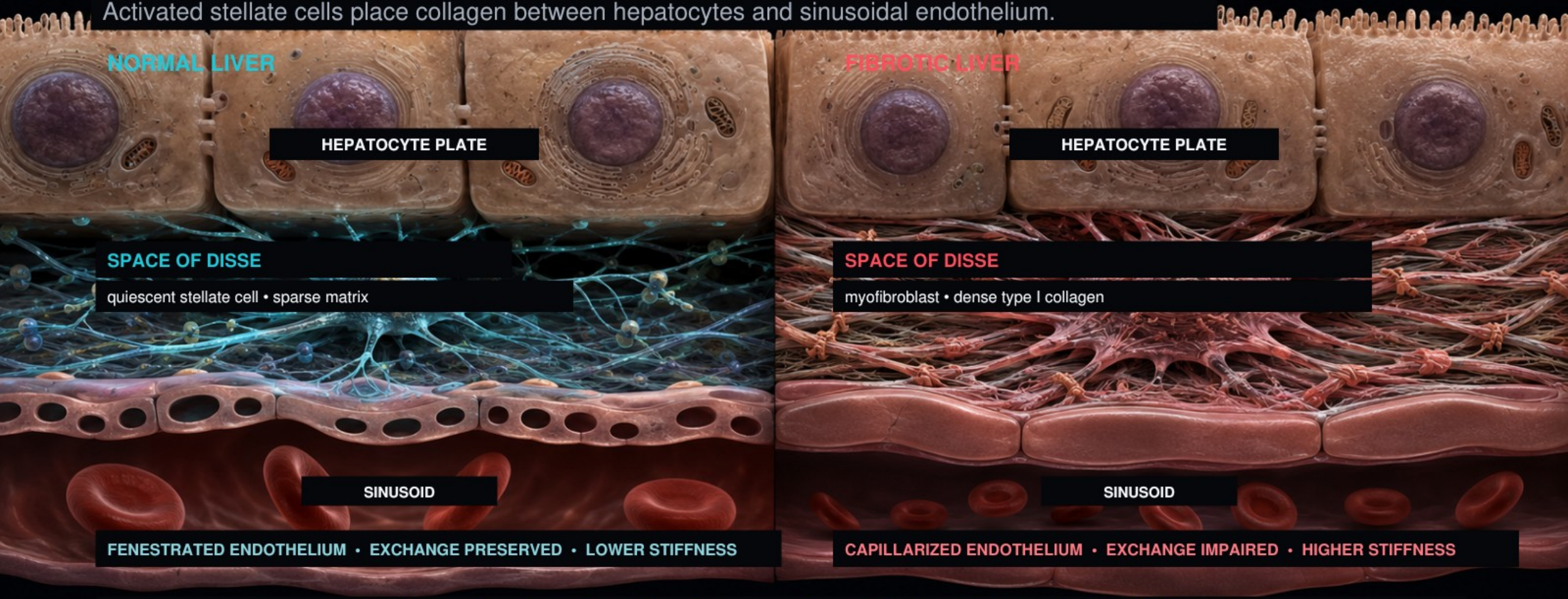
KUPFFER CELL
cytokines

STELLATE CELL
activation

MYOFIBROBLAST
collagen production

Fibrosis is laid down in the space of Disse.

Activated stellate cells place collagen between hepatocytes and sinusoidal endothelium.



The liver begins to lose the microscopic architecture that made it flexible.

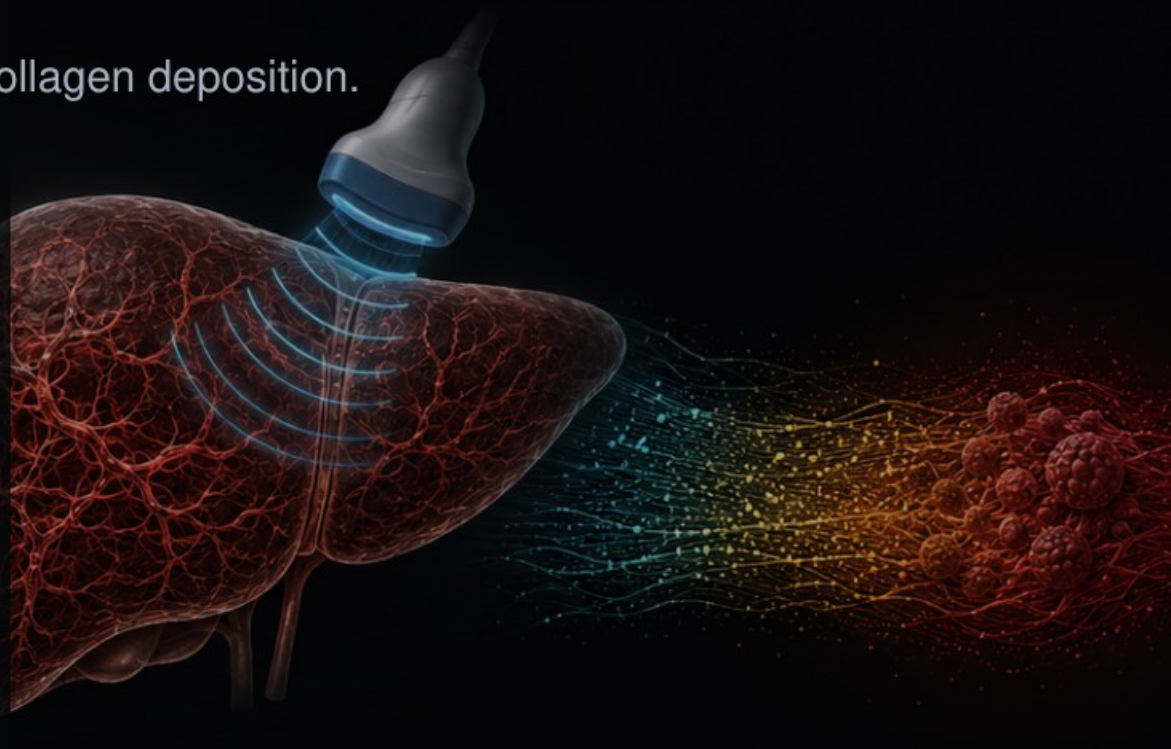
Collagen makes the liver less flexible.

A stiffer matrix can further activate myofibroblasts and sustain collagen deposition.

increased stiffness → **stellate-cell activation**

ongoing injury → collagen deposition

Fibrosis begins as a repair response and can become part of a self-reinforcing process.



This loss of flexibility is the bridge from fibrosis to elastography.

MECHANOTRANSDUCTION

tension → further activation

Steatosis identifies disease. Fibrosis identifies risk.

The presence of fat matters, but fibrosis stage best predicts liver-related outcomes.

Steatosis tells us metabolic liver disease is present.

Fibrosis tells us how far the disease has progressed.

Cardiovascular disease remains a major competing risk because the same metabolic syndrome affects the whole patient.

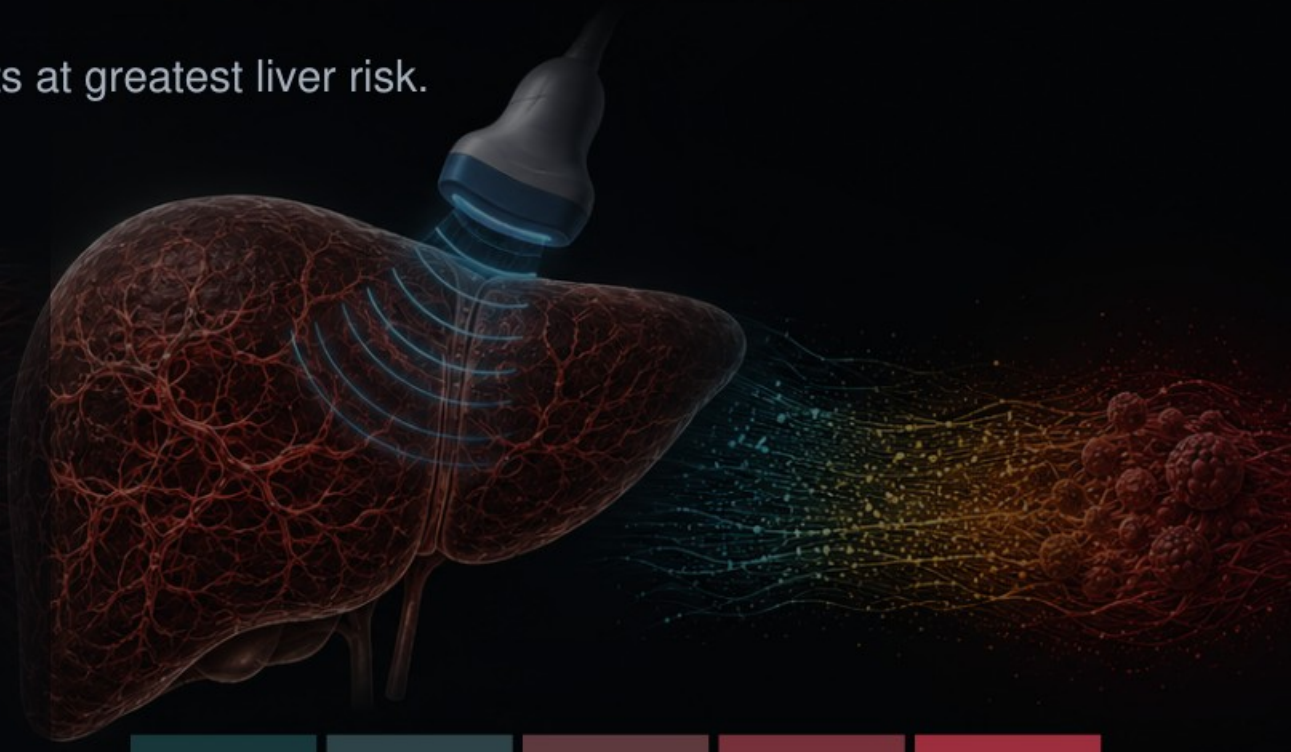
A minority progress. ALT cannot tell us who.

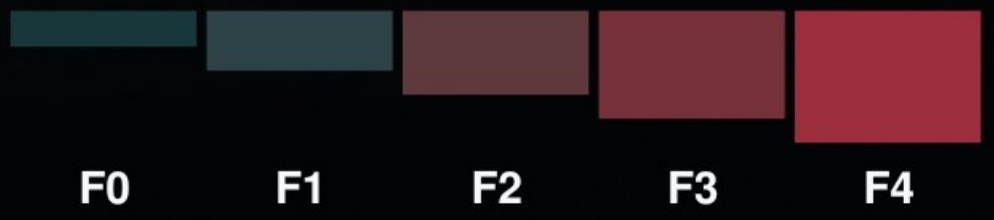
Progression varies. MASH and fibrosis identify the patients at greatest liver risk.

FAT CONTENT MAY STAY STABLE OR FALL

FIBROSIS MAY CONTINUE TO ACCUMULATE

Most patients will not reach cirrhosis. Our job is to find the patients who are moving in that direction.

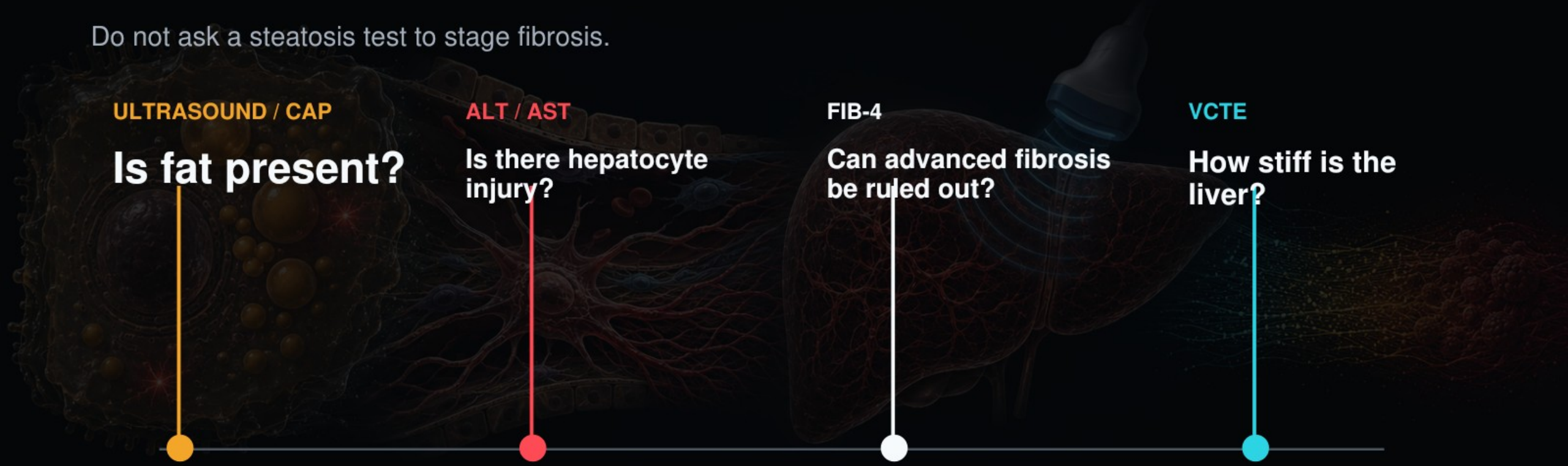




NORMAL ENZYMES DO NOT MEAN NORMAL LIVER ARCHITECTURE →

Every test answers a different question.

Do not ask a steatosis test to stage fibrosis.



ULTRASOUND / CAP

Is fat present?

Detects or estimates steatosis; does not stage fibrosis

ALT / AST

Is there hepatocyte injury?

May be normal even when advanced fibrosis is present

FIB-4

Can advanced fibrosis be ruled out?

Uses age and routine labs for first-line triage

VCTE

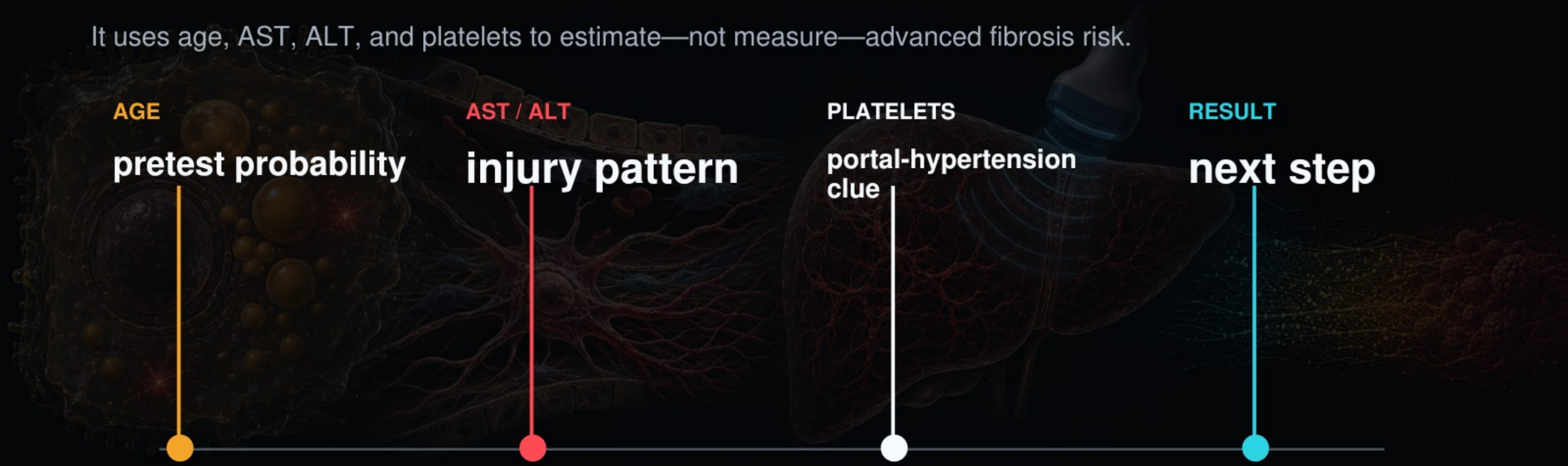
How stiff is the liver?

Estimates the probability of advanced fibrosis

$$\text{FIB-4} = \text{age} \times \text{AST} \div (\text{platelets} \times \sqrt{\text{ALT}})$$

FIB-4 tells you who needs another test.

It uses age, AST, ALT, and platelets to estimate—not measure—advanced fibrosis risk.



AGE

pretest probability

Age increases the probability of advanced fibrosis

AST / ALT

injury pattern

The AST-to-ALT relationship may change as disease advances

PLATELETS

portal-hypertension clue

A lower count may reflect portal hypertension and reduced thrombopoietin

RESULT

next step

FIB-4 1.61: obtain VCTE or ELF

$$\text{FIB-4} = \text{age} \times \text{AST} \div (\text{platelets} \times \sqrt{\text{ALT}})$$

FibroScan uses one probe to answer two questions.

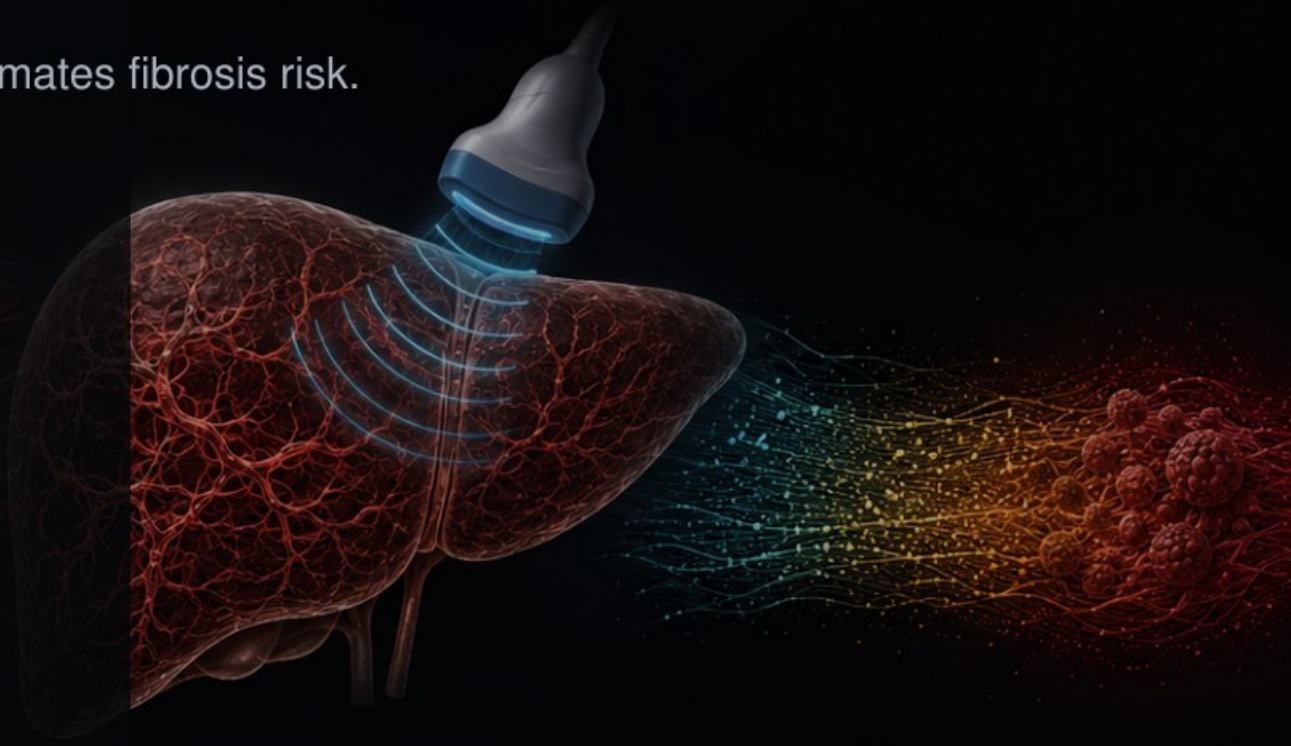
CAP estimates steatosis; liver stiffness measurement estimates fibrosis risk.

CAP → **steatosis**

CAP ≠ LSM

CAP uses ultrasound attenuation and is reported in dB/m. LSM uses shear-wave speed and is reported in kPa.

CAP and liver stiffness come from the same examination, but they are not the same measurement.



CAP • STEATOSIS

LSM • FIBROSIS RISK

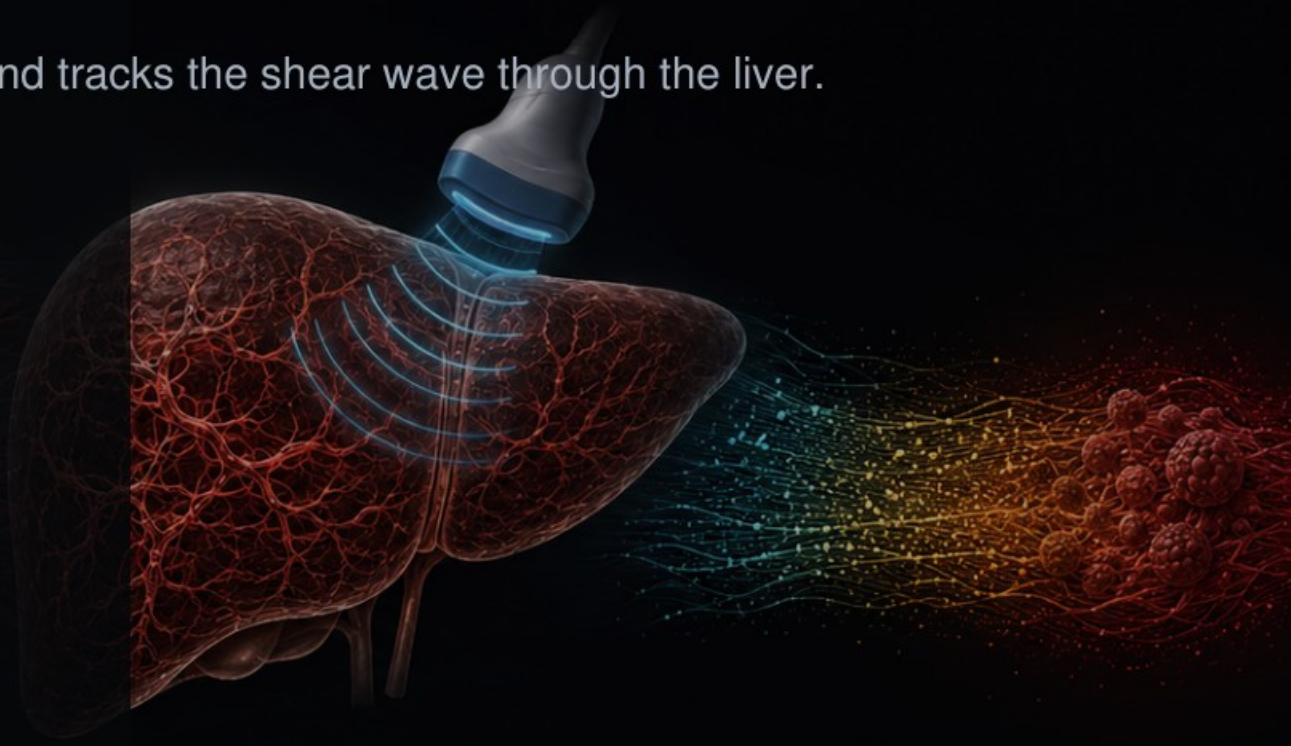
A stiffer liver carries a shear wave faster.

The probe creates a 50-Hz mechanical vibration; ultrasound tracks the shear wave through the liver.

faster shear wave → **greater apparent stiffness**

$$E \approx 3\rho v_s^2$$

The machine converts shear-wave speed into apparent stiffness reported in kPa.



Liver stiffness is a surrogate for fibrosis; it is not a collagen measurement.

FASTING • CORRECT PROBE • RELIABLE ACQUISITIONS

IQR/median ≤30%; repeat unexpected values

Stiffness estimates probability—not an exact stage.

The result changes the probability of advanced fibrosis; it does not replace histology.

<8

LOW RISK

Advanced fibrosis unlikely; follow in primary care

8–12

INTERMEDIATE RISK

Obtain additional assessment or hepatology review

≥12

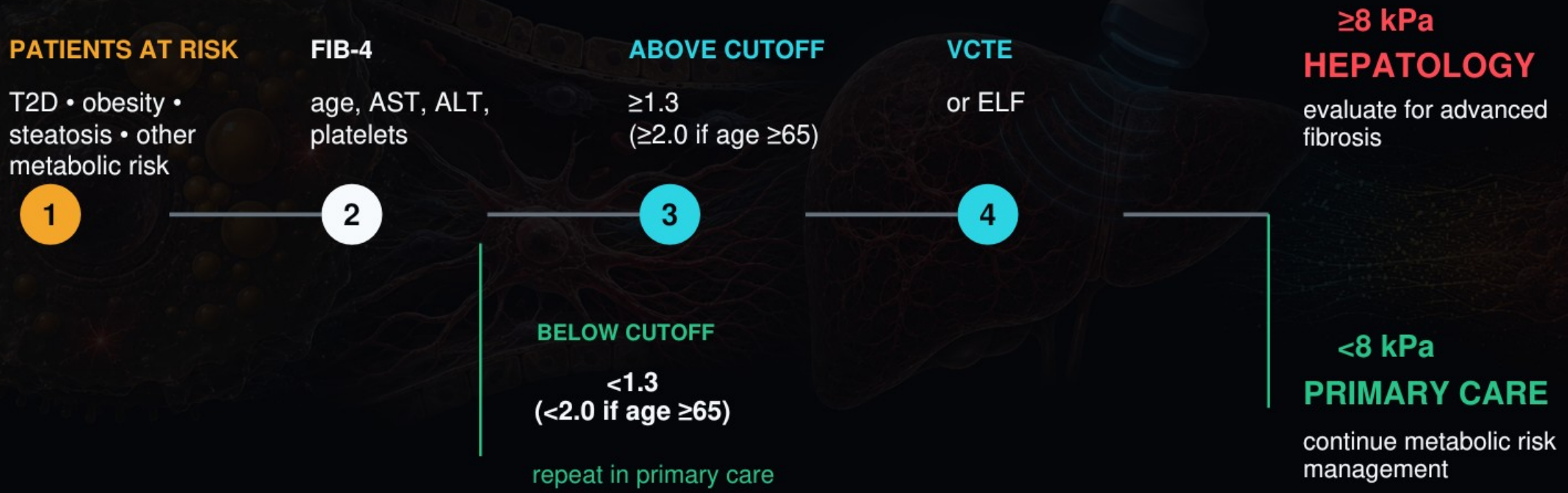
HIGH RISK

Advanced fibrosis likely; refer

Food intake, inflammation, cholestasis, congestion, and poor acquisition can increase stiffness. Repeat unexpected results.

Use FIB-4 first, then VCTE.

FIB-4 decides who needs a stiffness measurement. VCTE helps decide who needs hepatology.



Repeat FIB-4 every 1–2 years in T2D, prediabetes, or ≥2 metabolic risks; otherwise every 2–3 years.

Source: AASLD Practice Guidance, 2023

Fibrosis stage changes management.

This patient has F3 fibrosis despite a normal ALT.

F3 changes the plan: hepatology assessment, aggressive metabolic and cardiovascular treatment, and evaluation for MASH-directed therapy.

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VCTE
high fibrosis risk

STAGE
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