Perspectum

Are We Capturing What Matters in MASLD?

A clinical perspective on decision-making

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This is not a talk about tests. It's about decisions.

AACE

Clinical Reality: What We See in Practice

From pre-event survey and discussions

- Variability in patient identification
- Uncertainty in interpreting non-invasive tests
- Limited confidence in assessing liver-specific response

Where uncertainty shows up

- Early disease that appears low risk
- Discordant test results
- Monitoring response to therapy

A patient you see every day

58-year-old male

- T2D × 8 years
- BMI 34
- HbA1c 7.8%
- ALT 42
- FIB-4 0.9
- VCTE 7.9 kPa

Not flagged as **high liver risk** by current pathways

What would you do?

- **Reassure?**
- **Refer?**
- **Escalate therapy?** e.g., intensify GLP-1?
- **Reassess / repeat labs in a year?**

The reality today:

- In reality, many of these patients are not being screened at all
- In primary care and endocrinology, liver risk often remains unassessed
- Even basic tests are inconsistently ordered or acted upon

This case assumes something important:

- That screening actually happened
- That labs were ordered, fibrosis was assessed, elastography was done

And even in this "best case"...

- We still don't have a clear, consistent answer on what to do next
- That's the problem we are trying to solve here

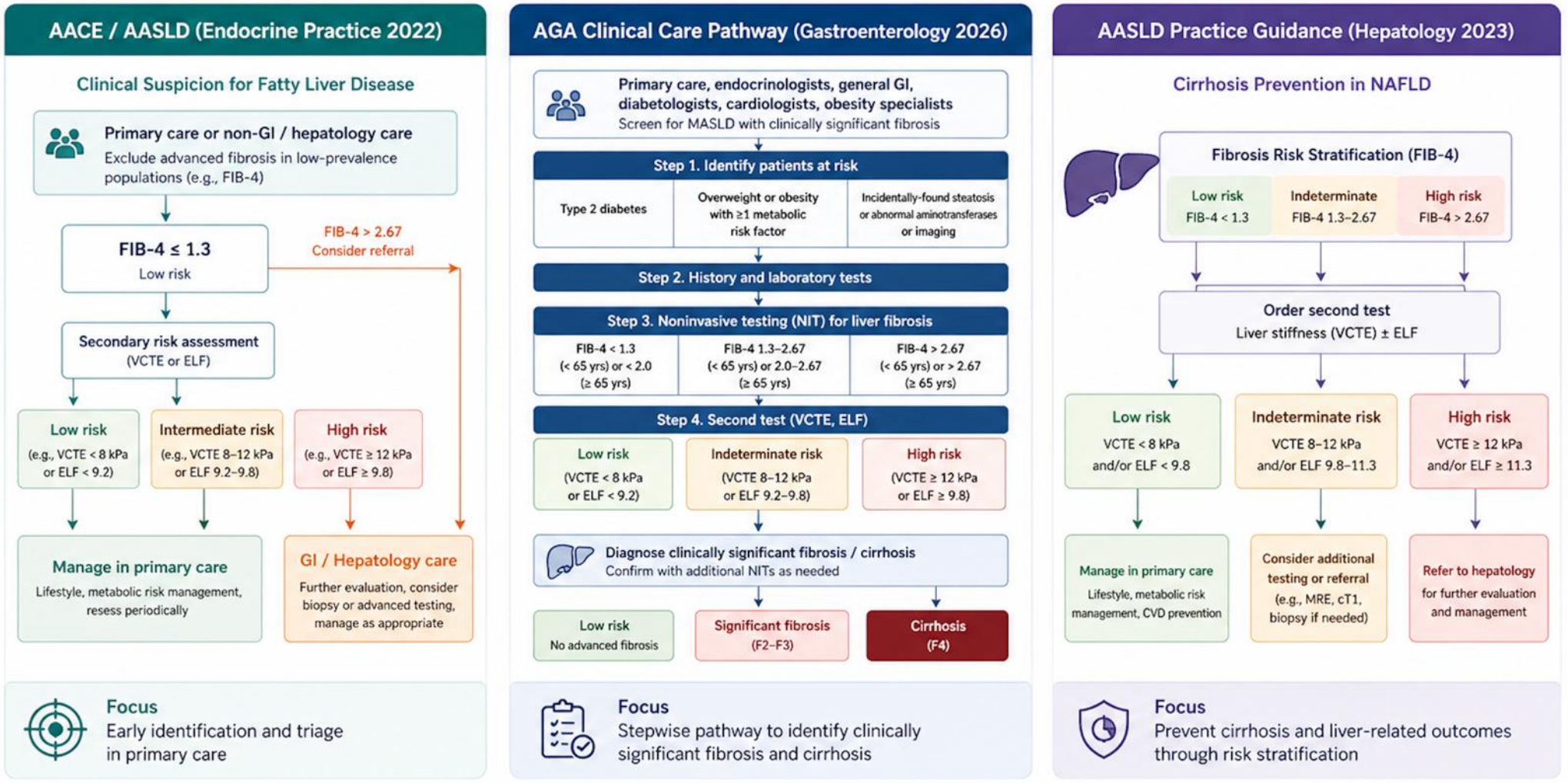
Why we are here: To build consensus that helps Endocrinologists and PCPs do two critical things:

1. Identify more patients through systematic screening
2. Know exactly what to do next — not watch and wait

Current guidelines focus on what tests measure. They do NOT provide clear, actionable next steps.

Current pathways

Fibrosis-based algorithms guide risk stratification and management



Adapted from: Cusi et al., Endocr Pract 2022 (AACE/AASLD); Kanwal et al., Gastroenterology 2026 (AGA Clinical Care Pathway); Rinella et al., Hepatology 2023 (AASLD Practice Guidance)

Clinical Reality: We Are Making Decisions with Incomplete Signals

What the data shows
(N 1,200)

- **Only ~40–55%** correctly identified
- **Up to 61%** false negatives
- **AUROC < 0.60**

Misclassification even after selection

F0:	F1:
17–20%	25–29%

What this means clinically

Performance Reality:
- Fibrosis pathways are necessary
- But performance remains modest

How Decisions are Actually Made:
- Threshold-driven
- Discordant signals
- Operational cutoffs (TE, ALT...)

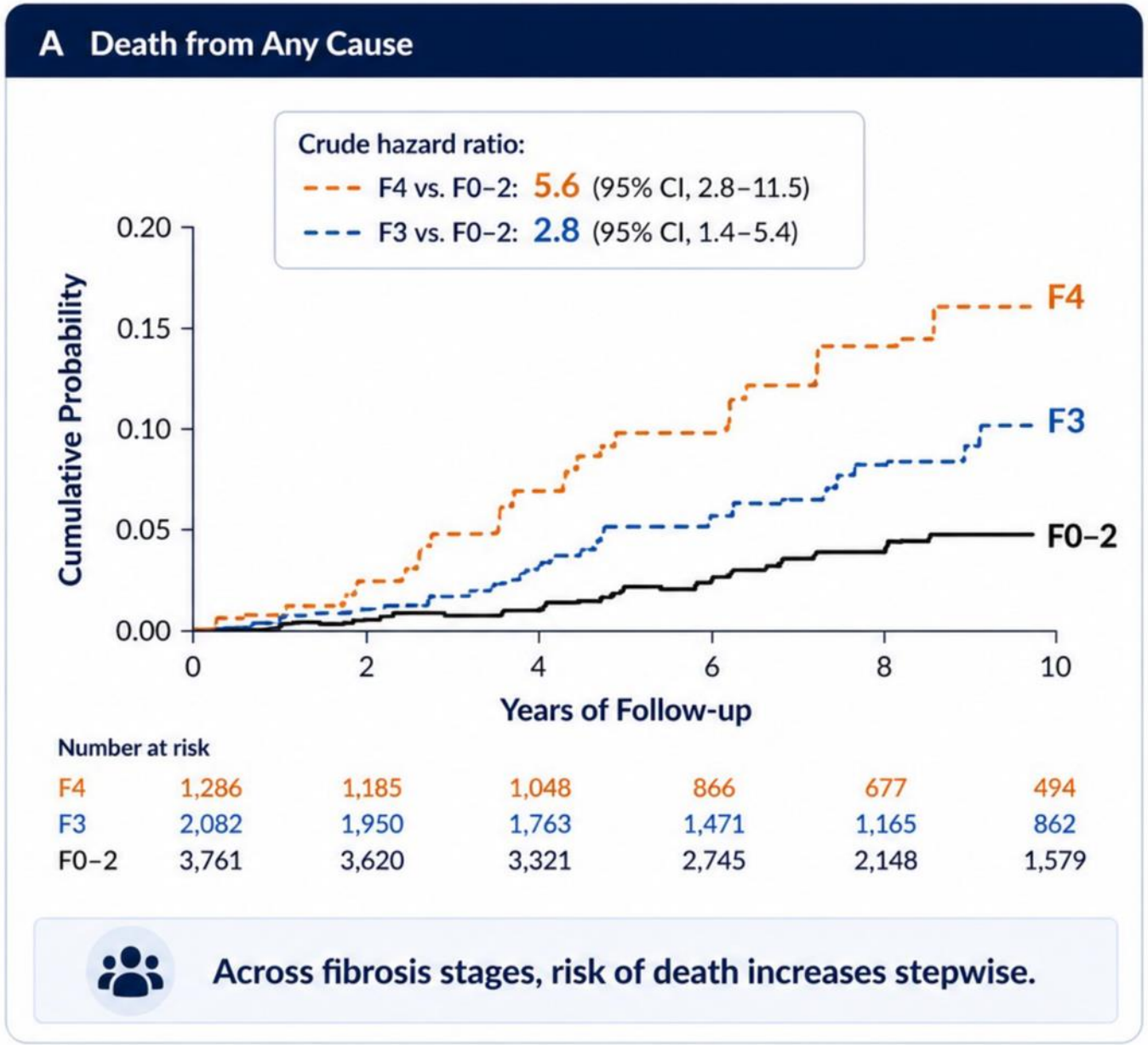
We are making treatment decisions without clarity on active liver disease

Olveira A, et al. Clinical Gastroenterology and Hepatology 2026

Fibrosis Predicts Long-Term Clinical Outcomes

Risk increases stepwise with fibrosis stage

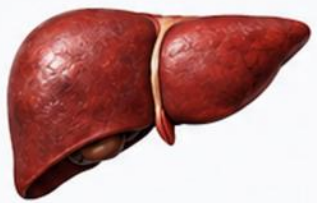
Stronger fibrosis, **worse outcomes.**



Sanyal A. et al. N Engl J Med 2021

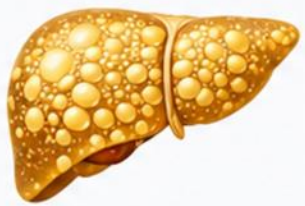
Where Progression Is Determined

Metabolic Stress



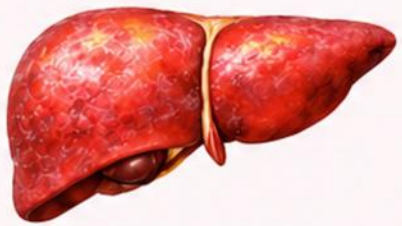
Insulin resistance, inflammation, metabolic dysregulation

Steatosis (PDFF)



Fat accumulation in the liver

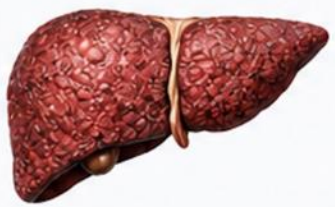
ACTIVE LIVER BIOLOGY
Dynamic
Potentially Reversible



Inflammation and injury with active fibrogenesis and repair

DECISION POINT

Fibrosis Structural Remodeling



Scar tissue accumulates; architecture disrupted

Cirrhosis Outcomes

Decompensation, HCC, liver-related mortality

The goal is to identify patients before fibrosis becomes structural and irreversible.

Evolving Framework - Persistent Gap

Consensus is advancing. The gap remains.

Across recent consensus pathways:

Standardized, NIT-driven approach to:

- Risk stratification
- Treatment initiation
- Response monitoring

Anchored in fibrosis-based tools

- Composite biomarkers
- Elastography
- Other clinical and laboratory data

Despite alignment on the framework, uncertainty remains in how we interpret results and make decisions.

Different Clinical Lenses: Hepatology vs Endocrinology

Same disease continuum. Different vantage point. Different questions. Different needs.

EARLIER DISEASE

ENDOCRINOLOGY / PRIMARY CARE

Where most patients are first seen

Is it active?
Detect current disease activity

Is it progressing?
Identify risk of progression

Is it responding?
Monitor response to treatment

EARLY DECISIONS REQUIRE UNDERSTANDING CURRENT DISEASE ACTIVITY
Biology today drives decisions today

EARLIER DISEASE
Entry into care

LATER DISEASE
Advanced disease

LATER DISEASE

HEPATOLOGY

Where patients are seen later

How much fibrosis?
Assess fibrosis stage

What is the risk?
Estimate risk of cirrhosis and adverse outcomes

Are there complications?
Identify and manage complications

DECISIONS ANCHORED IN STRUCTURAL SEVERITY
Fibrosis stage informs risk and management

EARLY DISEASE REQUIRES UNDERSTANDING ACTIVITY—NOT JUST FIBROSIS

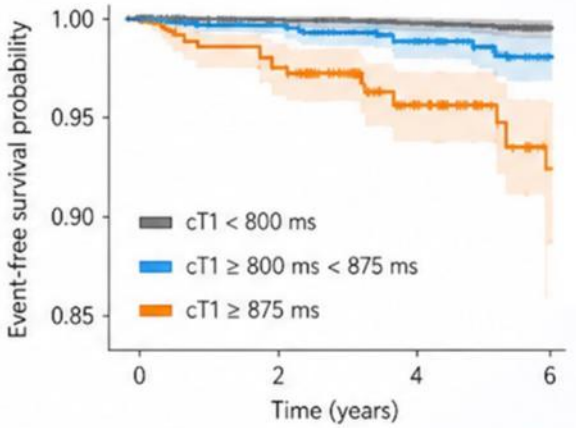
Aligning the right signal with the right clinical question improves decisions across the entire disease continuum.

Disease activity (cT1) is an early predictor of liver and CV risk

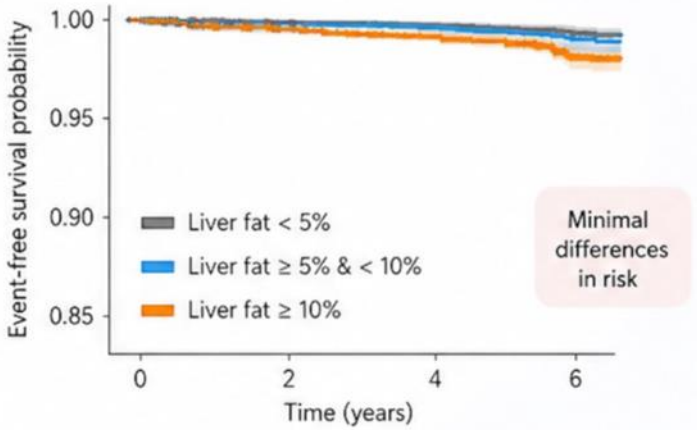
ACTIVITY
Captures what is happening now

OUTCOMES
Predicts clinical events

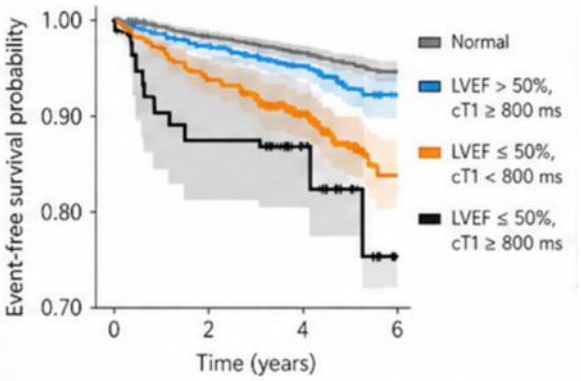
MAJOR LIVER EVENTS: cT1 LEVEL



MAJOR LIVER EVENTS: LFC LEVEL

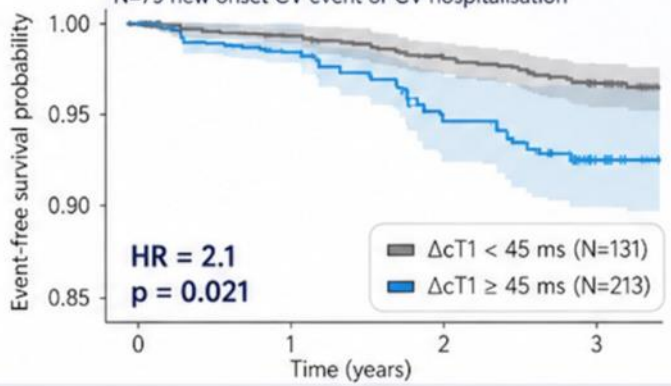


MAJOR CVD EVENTS: cT1 AND LVEF LEVEL



CHANGES IN cT1 AND CV OUTCOMES

2,325 with repeat scans, n at risk = 2,039
N=79 new onset CV event or CV hospitalisation



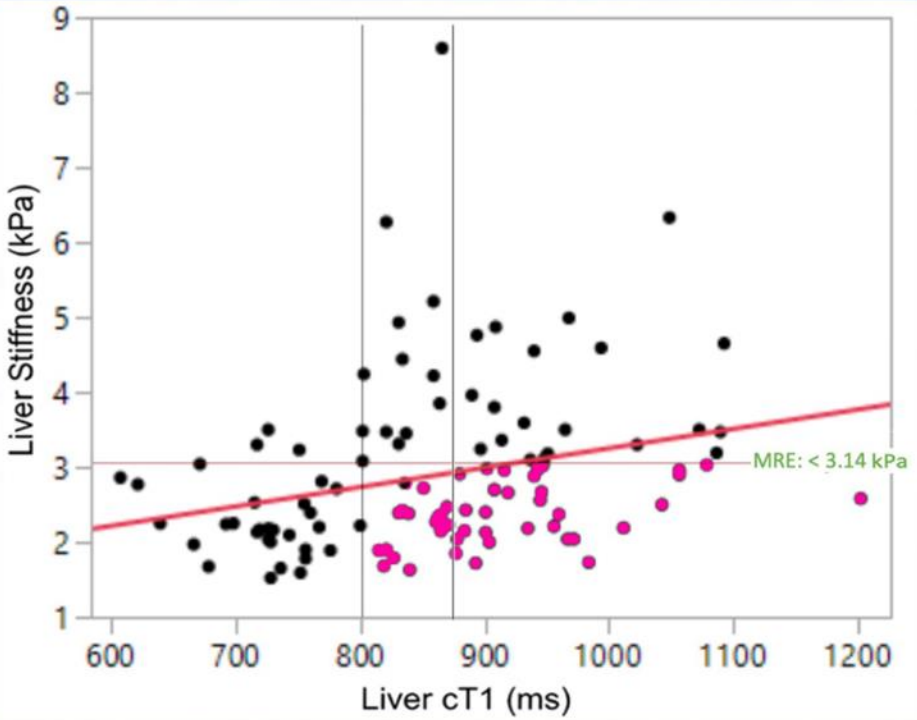
Measures of **disease activity** (cT1, LVEF change) identify **higher risk** that is **not captured** by fibrosis or fat alone.

Jackson, et al. Nat Med 2025

Fibrosis and disease activity do not always align

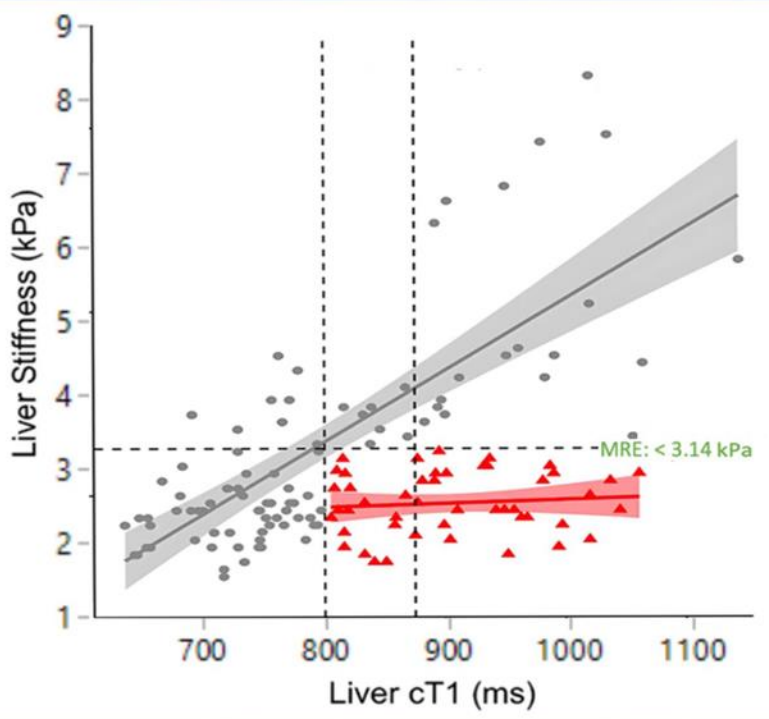
Some patients classified as low risk by stiffness show elevated cT1

Elevated cT1 despite low stiffness



Modified from Ortiz-Rocha A, et al. JCEM 2026

Elevated cT1 despite low stiffness



Corey K, et al. Liver International 2025

Stiffness (fibrosis) and disease activity (cT1) capture different biology.
Relying on stiffness alone may miss at-risk patients.

Clinical scenarios where current pathways fall short

Situations where structural measures alone may be insufficient

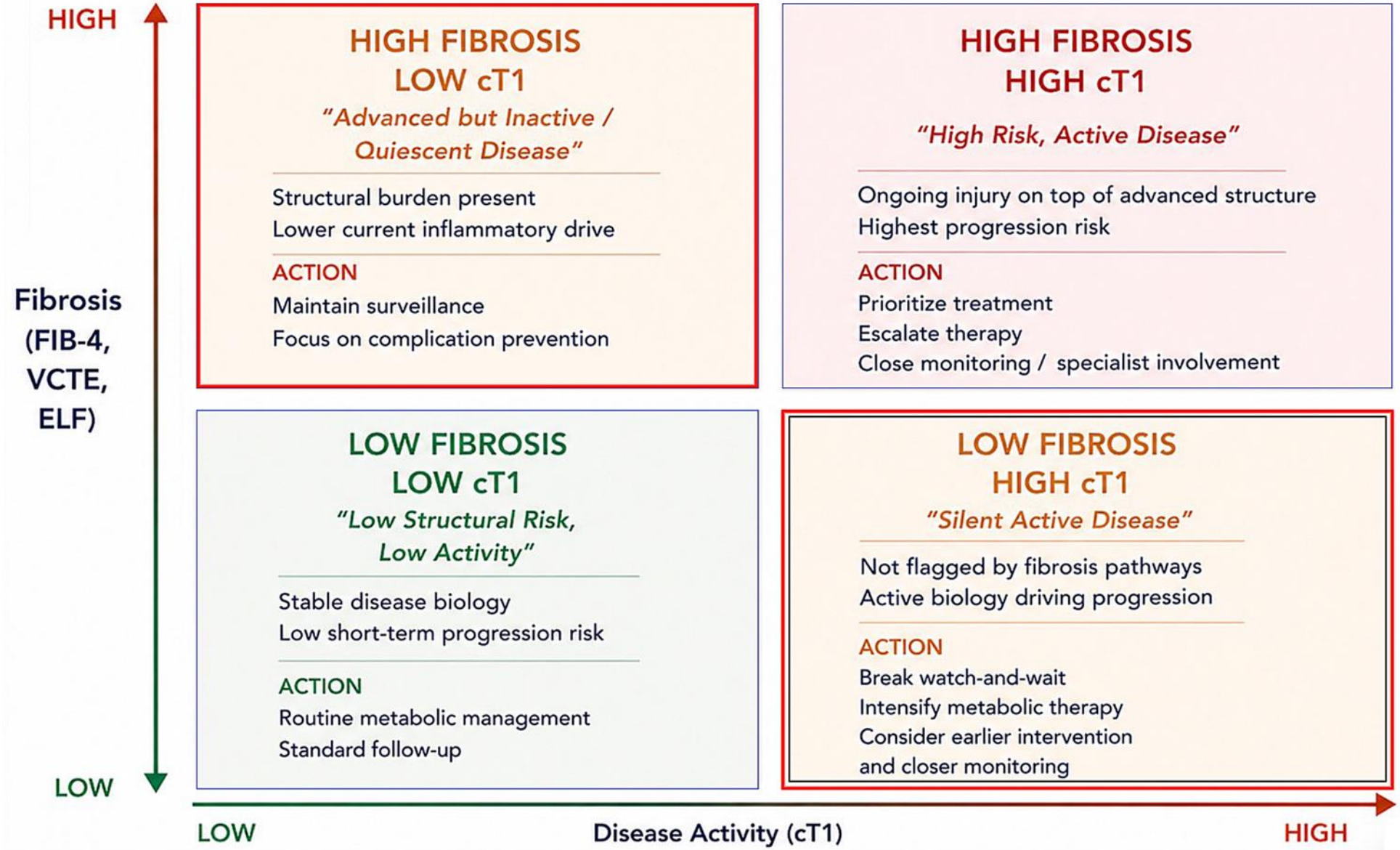
Normal labs, but high-risk phenotype

Refining risk within the same fibrosis stage

Discordant non-invasive tests

Assessing and monitoring treatment response

THE CLINICAL SHIFT: 4 PATTERNS, 4 DIFFERENT ACTIONS



Where Does cT1 Sit in the Clinical Pathway?

*cT1 adds a critical dimension—**active disease**—to guide better decisions*

1. Identify Risk

1

At-risk patients

T2D, obesity, metabolic syndrome, hypertension, dyslipidemia

2. Initial Assessment

2

Simple, noninvasive assessment

FIB-4
(lab-based score)

3. Further Evaluation

3

Fibrosis

Elastography (VCTE / MRE)

Captures accumulated damage

+

Active Disease (cT1)

Tissue-level disease activity

Captures what is happening now

4. Clinical Decisions

4

Informed decisions that impact care

- Reassure vs Escalate
- Refer vs Manage Locally
- Initiate / Adjust Therapy
- Monitor Response

Why both matter

Fibrosis tells us how much damage has occurred.
cT1 tells us how active the disease is right now.

Together, they provide the most complete picture to guide **better decisions.**

A strong foundation — but an incomplete picture for today's decisions

There is already a lot of alignment.

CURRENT FRAMEWORK
WHAT WORKS WELL

- Effective for fibrosis-based risk stratification
- Anchored in fibrosis and structural measures
- Widely adopted and aligned

But clinical needs are evolving

WHERE IT BECOMES INSUFFICIENT
LIMITATIONS OF THE CURRENT FRAMEWORK

- Does not capture current disease activity
- Limited for early decision-making
- Not designed for dynamic, treatment-driven care

The question is not whether fibrosis is useful — but whether it is sufficient for today's decisions.

This is where we need alignment as a group.

What we need alignment on next

From identification to action to monitoring — each step matters.

1 IDENTIFICATION
Find the right patients

We cannot manage what we are not consistently finding.

Screening in cardiometabolic patients has to improve.

But identification alone will not change outcomes if it does not lead to action.

2 ACTION
Know what to do next

Once a patient is identified, there needs to be clarity on what to do next.

Not variability — and not defaulting to "watch and wait."

This requires going beyond fibrosis alone to understand current disease biology.

3 MONITORING
Understand response over time

If we are making treatment decisions early, we need to understand response.

That requires capturing what is changing now — not just accumulated damage.

This means measuring disease activity — not just structure.

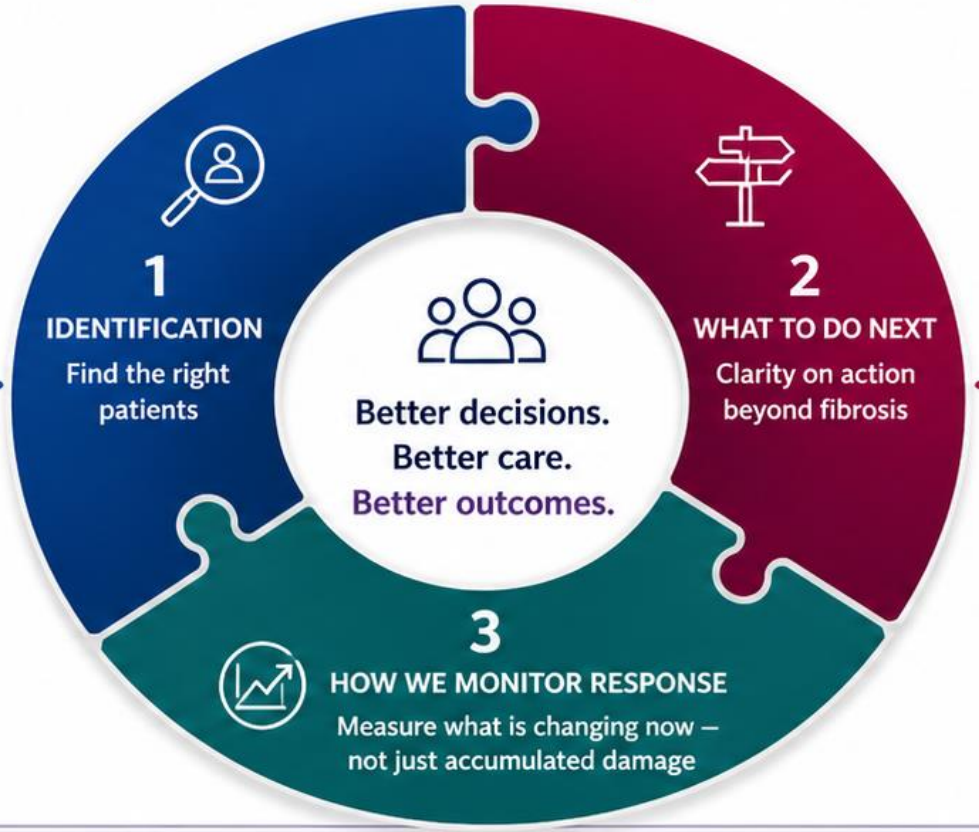
Our goal: consistently identify the right patients, take the right action, and monitor what matters to improve outcomes.

Three steps.
One shared purpose.

The opportunity is not to replace the framework— but to complete it.

Keep what works.

Our current framework is the right foundation for risk stratification.



Complete what's missing.

Add the insights we need for earlier, smarter, and more effective decisions.

Let's align to ensure that screening leads to meaningful action — not just classification.

- Find the right patients
- Act with clarity
- Monitor what matters