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NIT-Based RLSE Framework In MASH Development

Liver Forum 21

September 9, 2026

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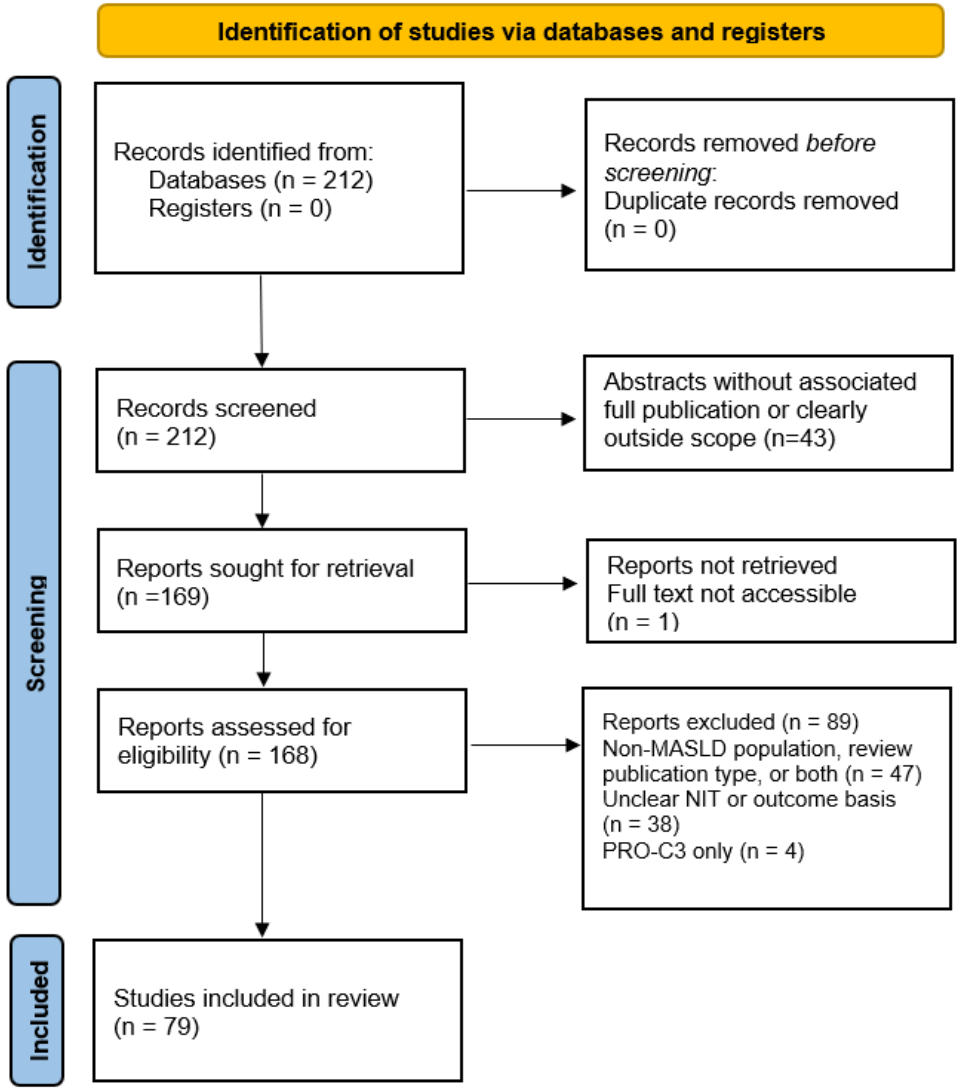
The Forum for Collaborative Research

UC Berkeley Public Health

Overview

1. Literature Review: Evidence across VCTE, ELF, MRE, and MRI-PDFF, covering both prognostic-monitoring and treatment response COUs
2. Emerging evidence
3. Proposed Framework: NIT-based treatment response in F2–F3 MASH trials
4. Discussion

Narrative Review



- PRISMA-guided systematic literature review prioritizing most recent studies (Jan 2015 – July 2026), screening 212 records down to 79 included studies covering 76,000 patient observations* focused specifically on four NITs: VCTE, ELF, MRE, and MRI-PDFF
- Databases: PubMed, EBSCOhost, ScienceDirect plus major hepatology journals, EASL/AASLD conference abstracts, and Google Scholar
- Search terms: disease, NIT, and outcome keywords, plus named MASH trials of interest (e.g., MAESTRO-NASH, ESSENCE, HARMONY, REGENERATE), across cohort and RCT study types

*Overlapping cohort size—not a unique n

Summary of Lit Review

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Topic	Total NIT papers	Prognosis: Baseline ± change	Treatment
VCTE	47	19	28
MRE	22	8	14
ELF	43	6	37
MRI-PDFF	35	0	35
ALL*	**79**	**30**	**49**
Patient Count†	**76,247**	**62,820**	**13,427**

Multiple NITs may be evaluated within a single study, therefore, counts across NIT rows are not mutually exclusive and should not be summed.
†Cohorts may overlap across separate studies.

COU: Prognostic and Monitoring

Prog & Monitoring: VCTE (Studies = 19, n = 55,846, LRE n = 2110)

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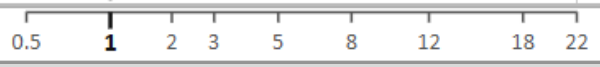
Reference	Drug / Design	Hazard Ratio (95% CI)	HR (95% CI)	P value
Zhang et al. (2026) *N=3,532*	Multicenter observational cohort *F/U: 56.6 mo*	**5-yr cumulative LRE incidence & discriminatory performance: LSM vs histology (head-to-head)**		
		LSM <10 kPa — 0.3% at 5 yr	—	<0.001
		LSM 10–20 kPa — 3.3% at 5 yr	—	<0.001
		LSM >20 kPa — 14.4% at 5 yr	—	<0.001
		5-yr AUROC: LSM vs Histology — *0.870 vs 0.869 (p=0.915)*	—	*NS*
		Integrated AUROC: LSM vs Histology — *0.878 vs 0.852 (p=0.159)*	—	*NS*
Loomba et al. (2023) *N=1,398*	Pooled cohort from 4 RCTs *F/U: 16.6 mo (F3); 16.2 mo (F4)*	**HR by VCTE threshold — progression to cirrhosis and time to LRE**		
		Baseline VCTE ≥16.6 kPa → cirrhosis	3.99 (2.66–5.98)	<0.001
		ΔVCTE ≥5 kPa and ≥20% → cirrhosis	1.98 (1.20–3.26)	0.008
		Baseline VCTE ≥30.7 kPa → LRE	10.13 (4.38–23.41)	<0.001
Sanyal et al. (2022) *N=1,135*	Simtuzumab + STELLAR-4 RCTs *F/U: 16.6 mo*	**HR per 2-kPa VCTE for time to LRE — compensated NASH cirrhosis**		
		Baseline VCTE (per 2 kPa)	1.13 (1.09–1.17)	<0.0001
		Change in VCTE (per 2 kPa)	1.07 (1.02–1.13)	0.0046
Younossi et al. (2021) *N=2,154*	Simtuzumab + Selonsertib RCTs *F/U: 16 mo*	**aHR per 1-kPa VCTE — time to adverse outcome (F3 and F4)**		
		F3 – Baseline VCTE	1.09 (1.06–1.11)	<0.0001
		F3 – Change in VCTE	1.05 (1.03–1.07)	<0.0001
		F4 – Baseline VCTE	1.07 (1.03–1.12)	0.0003
		F4 – Change in VCTE	1.06 (1.02–1.11)	0.0078
Petta et al. (2021) *N=1,039*	Retrospective cohort *F/U: 35 mo*	**HR for hepatic decompensation — baseline VCTE; change in VCTE, ≥20% increase (n=533 with repeat LSM)**		
		Baseline VCTE (per 1 kPa)	1.03 (1.02–1.04)	<0.001
		Change in VCTE (≥20% ↑)	1.56 (1.05–2.51)	0.04



VCTE (contd.)

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Reference	Design	AUROC / C-index (0.5–1.0 scale)	Estimate (95% CI)
Yip et al. (2025) *N=12,950*	Prospective, 16 centers; two-step FIB-4 → VCTE screening	**5-yr cumulative LRE incidence by LSM band: <8 kPa 0.4% · 8–12 kPa 1.3% · >12 kPa 12.2%**	
		Integrated tAUC — LRE	**0.866 (0.829–0.901)**
Lin et al. (2024) *N=16,603*	VCTE-Prognosis Study Group; prospective, 16 centers	**Largest prospective VCTE-prognosis cohort; LSM-only (Agile scores excluded); sens./spec. for 3-yr LRE**	
		Integrated tAUC — LRE	**0.85 (0.82–0.88)**
		AUROC — LRE (5-yr)	**0.86 (0.83–0.90)**
		AUROC — decomp. (5-yr)	**0.91 (0.87–0.94)**
		Sensitivity — rule-out (<8 kPa)	**0.84 (0.79–0.90)**
		Specificity — rule-in (≥12 kPa)	**0.88 (0.87–0.88)**
Mozes et al. (2023) *N=2,518*	IPD meta-analysis, 25 studies	**VCTE vs. histology, head-to-head discrimination for LRE (time-dependent AUC)**	
		VCTE tAUC — LRE (3-yr)	**0.74 (0.65–0.83)**
		VCTE tAUC — LRE (5-yr)	**0.76 (0.70–0.83)**
		VCTE tAUC — LRE (10-yr)	**0.79 (0.73–0.85)**
		Histology tAUC — LRE (10-yr)	*0.77 (0.71–0.85)*

Prog & Monitoring: MRE (Studies = 8, n = 5,010, LRE n = 412)

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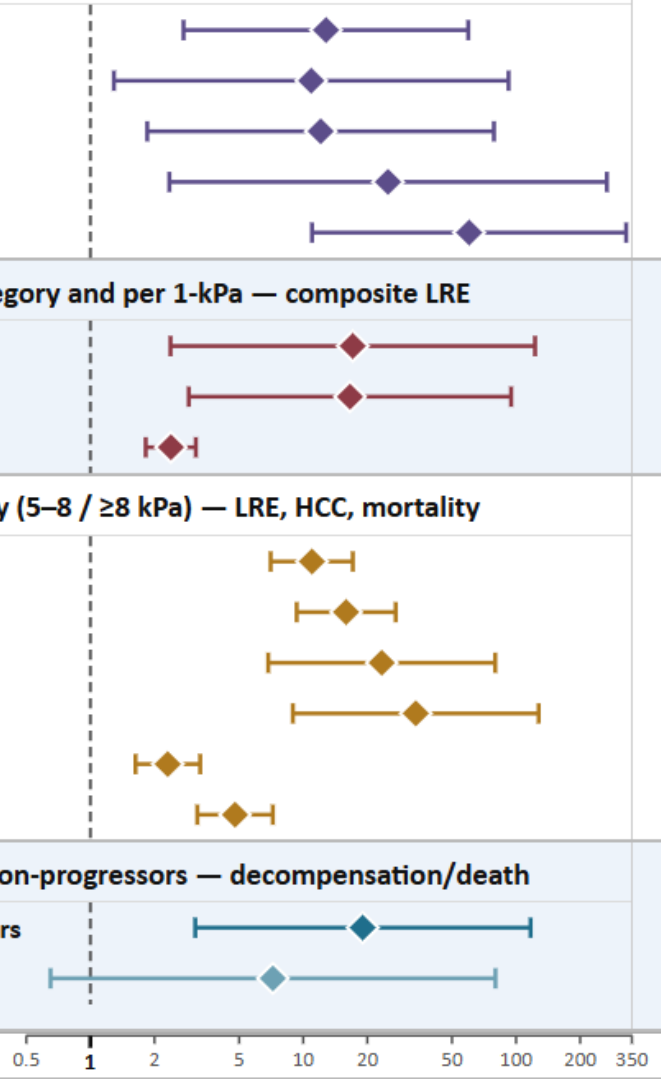
Reference	Drug / Design	Hazard Ratio (95% CI)	HR (95% CI)	P value
Kobayashi et al. (2023) *N=405*	Retrospective cohort, serial MRE ~24M apart *F/U: 72.6 mo*	**HR for MRE progressors (≥19% increase) vs non-progressors — LRE**		
		Overall	12.79 (2.74–59.6)	.001
		Low baseline subgroup	10.91 (1.29–92.18)	.028
		Decompensated cirrhosis	12.08 (1.85–78.7)	.009
		HCC	25.02 (2.35–267)	.008
		New-onset cirrhosis (n=386)	60.15 (11.0–329)	<.001
Ajmera et al. (2022) *N=265*	Retrospective cohort analysis, single center *F/U: 453 person-yrs*	**HR/OR by baseline MRE category and per 1-kPa — composite LRE**		
		MRE 3.63–5 kPa	17.09 (2.38–122.75)	.0048
		MRE ≥5 kPa	16.58 (2.90–94.79)	.0016
		Decompensation, OR (per 1 kPa)	2.39 (1.82–3.13)	<.001
Ajmera et al. (2022) *N=1,707*	6-cohort MEFIB IPD meta-analysis *F/U: 36 mo*	**HR by baseline MRE category (5–8 / ≥8 kPa) — LRE, HCC, mortality**		
		5–8 kPa	11.0 (7.03–17.1)	<.001
		≥8 kPa	15.9 (9.32–27.2)	<.001
		5–8 kPa	23.4 (6.85–79.8)	<.001
		≥8 kPa	33.8 (8.94–127.7)	<.001
		5–8 kPa	2.31 (1.63–3.28)	<.001
		≥8 kPa	4.78 (3.18–7.20)	<.001
Gidener et al. (2023) *N=128*	Retrospective cohort *F/U: 3.4 yr*	**HR for MRE progressors vs non-progressors — decompensation/death**		
		Progressors vs non-progressors	19.04 (3.11–117)	.001
		Non-cirrhotic subgroup	7.20 (0.65–80)	.059



Prog & Monitoring: ELF (Studies = 6, n = 5,496, LRE n = 821)

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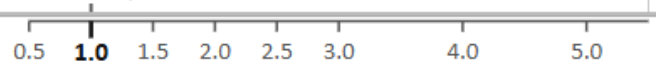
Reference	Drug / Design	Hazard Ratio (95% CI)	HR (95% CI)	P value
Pearson et al. (2024) *Observational cohort (N=1,327)*	Observational cohort (N=1,327) *F/U: 859 d*	**HR per 1-unit ELF — decompensation, liver-related and all-cause mortality**		
		Hepatic decompensation	**2.22 (1.93–2.54)**	**<0.001**
		Liver-related mortality	**2.02 (1.67–2.45)**	**<0.001**
		All-cause mortality	**1.86 (1.67–2.07)**	**<0.001**
Sanyal et al. (2022) *Simtuzumab + STELLAR-4 (N=1,135)*	Simtuzumab + STELLAR-4 RCTs (N=1,135) *F/U: 16.6 mo*	**HR per 0.5-unit ELF — time to LRE, compensated cirrhosis**		
		Baseline ELF (per 0.5 u)	**1.68 (1.50–1.88)**	**<0.0001**
		Change in ELF (per 0.5 u)	**1.09 (0.95–1.26)**	***0.23***
Younossi et al. (2021) *Sim + Selonsertib RCTs (N=2,154)*	Simtuzumab + Selonsertib RCTs (N=2,154) *F/U: 16 mo*	**aHR per 1-pt ELF — time to adverse outcome (F3 and F4)**		
		F3 – Baseline ELF	**2.48 (2.11–2.93)**	**<0.0001**
		F3 – Change in ELF	**1.47 (1.20–1.80)**	**0.0002**
		F4 – Baseline ELF	**2.83 (2.20–3.63)**	**<0.0001**
		F4 – Change in ELF	**1.68 (1.21–2.33)**	**0.0018**
Are et al. (2021) *Belapectin RCT (N=161)*	Belapectin RCT NASH cirrhosis (N=161) *F/U: 52 wk*	**HR by ELF threshold vs ELF <9.8 (reference) — time to LRE**		
		ELF <9.8 (reference)	*1.00 (reference)*	—
		ELF 9.8–11.2	**1.46 (0.45–4.65)**	***0.08***
		ELF ≥11.3	**4.81 (1.54–15.05)**	**<0.01**
Sanyal et al. (2019) *Simtuzumab RCT (N=475)*	Simtuzumab RCT (natural history) (N=475) *F/U: 29.0 mo (F3); 30.9 mo (F4)*	**HR per unit ELF — F3: progression to cirrhosis; F4: LRE**		
		F3 – Baseline ELF	**2.58 (1.96–3.38)**	**<0.001**
		F3 – Change in ELF	**1.64 (1.24–2.17)**	**<0.001**
		F4 – Baseline ELF	**2.11 (1.53–2.90)**	**<0.001**
		F4 – Change in ELF	**1.32 (0.96–1.82)**	***0.09***



COU: Treatment Response

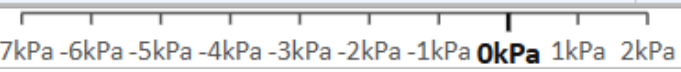
Treatment: VCTE Change (Studies = 28, Patients = 10,390) *(1 of 2)*

Reference	Drug studied	% Patients achieving liver stiffness (VCTE) reduction threshold	P value
Noureddin et al. (2025) *HARMONY · Phase 2b (N=126)*	Efruxifermin or placebo · 96 weeks	**Proportion of patients achieving ≥30% reduction in liver stiffness at Week 96 (%)** Placebo 18.2% **Efruxifermin 28 mg 48.1%** **Efruxifermin 50 mg 71.4%**	— -- --
Sanyal et al. (2025) *ESSENCE · Phase 3 (N=800)*	Semaglutide 2.4 mg or placebo	**Proportion of patients achieving ≥30% reduction in liver stiffness at Week 72 (%)** Placebo 30.3% **Semaglutide 2.4 mg 52.0%**	— —
Harrison et al. (2024) *MAESTRO-NASH · Phase 3 (N=966)*	Resmetirom or placebo	**Proportion of patients achieving ≥25% reduction in liver stiffness at Week 52 (%)** Placebo 29.0% **Resmetirom 80 mg 42.0%** **Resmetirom 100 mg 49.0%**	— -- --

0% 10% 20% 30% 40% 50% 60% 70% 80%

Treatment: VCTE Change *(2 of 2)*

Reference	Drug studied	Placebo-adjusted change in liver stiffness (VCTE, kPa)	Estimate (95% CI)	P value
Noureddin et al. (2026) *Phase 2 RCT (N=84)*	Efimosfermin 300 mg Q4W or placebo	**Week 28 (kPa) · Exploratory endpoint**		
		Placebo (ref)	—	—
		Efimosfermin 300 mg	**−0.4 (−2.1, 1.3)**	**0.64**
Harrison et al. (2023) *HARMONY · Phase 2b (N=128)*	Efruxifermin 50 mg or placebo	**Week 24 (kPa) · Secondary endpoint**		
		Placebo (ref)	—	—
		Efruxifermin 50 mg	**−3.6 (−6.1, −1.1)**	**0.005**
Rinella et al. (2022) *REGENERATE · Phase 3 (N=931)*	Obeticholic acid 25 mg or placebo	**Month 18 (kPa) · Exploratory endpoint**		
		Placebo (ref)	—	—
		OCA 25 mg	**−2.41 (−3.82, −1.00)**	—
Harrison et al. (2020) *STELLAR-3 · Phase 3 (N=802)*	Selonsertib 18 mg or placebo	**Week 48 (kPa) · Exploratory endpoint**		
		Placebo (ref)	—	—
		Selonsertib 18 mg	**−1.50 (−2.92, −0.09)**	**0.04**



Treatment: MRE Change (Studies=14, Patients=3,958) (1 of 2)

Reference	Drug studied	% Achieving MRE liver stiffness reduction threshold	P value
Harrison et al. (2024) *MAESTRO-NASH · Phase 3*	Resmetirom or placebo (F3 subgroup; n=250)	**% achieving ≥19% relative MRE reduction from baseline at Week 52 (F3 subgroup)** **Placebo** 12.5% **Resmetirom 80 mg** 26.2% **Resmetirom 100 mg** 31.4%	— -- --
Loomba et al. (2024) *FALCON-1 · Phase 2b*	Pegbelfermin or placebo (N=197; F2–F3)	**% achieving ≥15% relative MRE reduction from baseline at Week 48 (exploratory)** **Placebo** 30.3% **Pegbelfermin 10 mg** 41.2% **Pegbelfermin 20 mg** 28.6% **Pegbelfermin 40 mg** 41.2%	— **0.412** **0.853** **0.426**
Harrison et al. (2023) *MAESTRO-NAFLD-1 · Phase 3*	Resmetirom or placebo (paired MREs; n=192)	**% achieving ≥19% relative MRE reduction from baseline at Week 52** **Placebo** 11% **Resmetirom 80 mg DB** 22% **Resmetirom 100 mg DB & OL** 24%	— -- --

Treatment: MRE Change *(2 of 2)*

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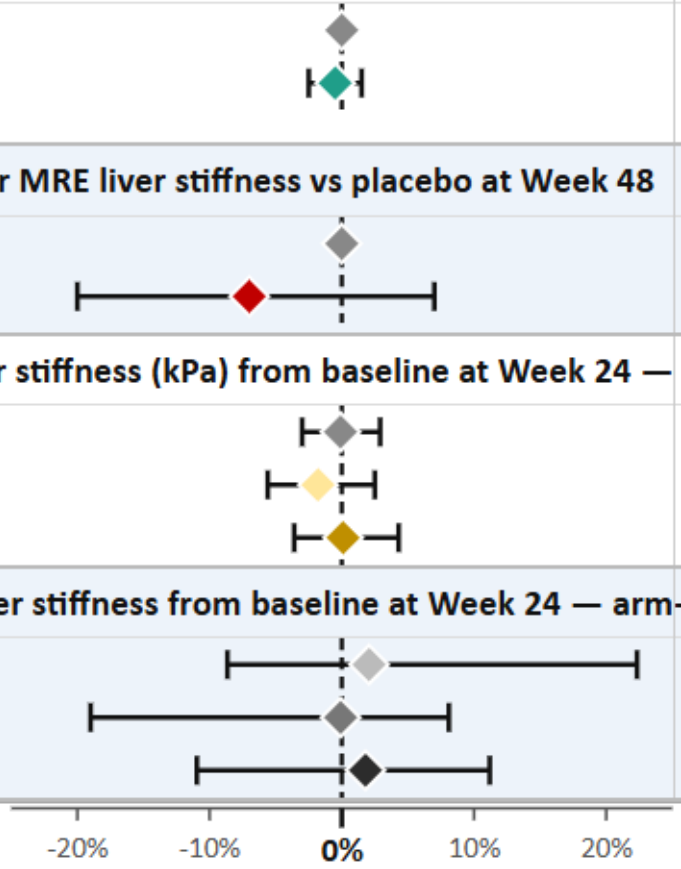
Reference	Drug studied	Change in MRE liver stiffness from baseline	Estimate (IQR or 95% CI)	P value
Kaplan et al. (2026) *SYNCHRONIZE-MASLD (N=216)*	Survodutide 6.0 mg or placebo	**Estimated treatment difference for MRE liver stiffness vs placebo at Week 48**		
		Placebo (ref)	—	—
		Survodutide 6.0 mg	**ETD −0.05 kPa [95% CI −0.25, 0.15]**	**0.62**
Loomba et al. (2023) *Phase 2b RCT (N=71, F4)*	Semaglutide 2.4 mg or placebo	**Estimated treatment ratio for MRE liver stiffness vs placebo at Week 48**		
		Placebo (ref)	—	—
		Semaglutide 2.4 mg	**ETR 0.93 [95% CI 0.80, 1.07]**	**0.30**
Patel et al. (2020) *Phase 2 RCT (F1–F3)*	Cilofexor or placebo (N=140)	**Absolute change in MRE liver stiffness (kPa) from baseline at Week 24 — arm-level estimates**		
		Placebo	−0.01 kPa [IQR −0.30, 0.29]	—
		Cilofexor 30 mg	**−0.18 kPa [IQR −0.56, 0.25]**	**0.47**
		Cilofexor 100 mg	**0.01 kPa [IQR −0.36, 0.43]**	**0.78**
Loomba et al. (2018) *Phase 2 RCT (F2–F3)*	Selonsertib ± Simtuzumab (N=72)	**Median % change in MRE liver stiffness from baseline at Week 24 — arm-level estimates**		
		Simtuzumab ±sim (ctrl)	2.1% [IQR −8.7, 22.3]	**NS**
		Selonsertib 6 mg ±sim	**−0.1% [IQR −19.0, 8.1]**	**NS**
		Selonsertib 18 mg ±sim	**1.8% [IQR −11.0, 11.2]**	**NS**



Treatment: ELF Change (Studies = 37, Patients = 11,543) *(1 of 2)*

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Reference	Drug studied	Change in ELF score from baseline	P value
Harrison et al. (2024) *MAESTRO-NASH · Phase 3 (N=966)*	Resmetirom or placebo	**LS mean change in ELF score from baseline at Week 52** Placebo -0.11 Resmetirom 80 mg -0.34 Resmetirom 100 mg -0.35	— -- --
Loomba et al. (2024) *SYNERGY-NASH · Phase 2 (N=190)*	Tirzepatide or placebo	**LS mean change in ELF score from baseline at Week 52** Placebo +0.16 Tirzepatide 5 mg -0.50 Tirzepatide 10 mg -0.47 Tirzepatide 15 mg -0.45	— -- -- --
Shankar et al. (2024) *Phase 2 RCT (N=74)*	Cotadutide or placebo (N=74)	**LS mean change in ELF score from baseline at Week 19** Placebo +0.05 Cotadutide 600 µg -0.15	— NS
Harrison et al. (2023) *HARMONY · Phase 2b (F2–F3, 24W)*	Efruxifermin or placebo (N=128)	**LS mean change in ELF score from baseline at Week 24** Placebo +0.10 Efruxifermin 28 mg -0.60 Efruxifermin 50 mg -0.70	— <0.001 <0.001
Harrison et al. (2022) *ALPINE 2/3 · Phase 2b (N=171)*	Aldafermin or placebo	**Absolute change in ELF score from baseline at Week 24** Placebo +0.10 Aldafermin 0.3 mg +0.10 Aldafermin 1.0 mg +0.00 Aldafermin 3.0 mg -0.20	— NS NS 0.033

Treatment: ELF Change *(2 of 2)*

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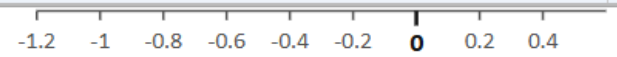
Reference	Drug studied	Change in ELF score (treatment difference vs placebo)	Estimate (95% CI)	P value
Kaplan et al. (2026) *SYNCHRONIZE-MASLD*	Survodutide or placebo (N=216)	**Treatment difference in ELF score vs placebo at Week 48 (95% CI)**		
		Placebo	—	—
		Survodutide 6.0 mg	**-0.28 [-0.50, -0.05]**	**0.0161**
Noureddin et al. (2026) *Phase 2 RCT*	Efimosfermin or placebo (N=84)	**Treatment difference in ELF score vs placebo at Week 24 (95% CI)**		
		Placebo	—	—
		Efimosfermin 300 mg	**-0.50 [-0.80, -0.20]**	**0.005**
Noureddin et al. (2025) *HARMONY · Phase 2b (96W)*	Efruxifermin or placebo (N=126)	**Treatment difference in ELF score vs placebo at Week 96 (95% CI)**		
		Placebo	—	—
		Efruxifermin 28 mg	**-0.60 [-1.00, -0.20]**	**0.0049**
		Efruxifermin 50 mg	**-0.70 [-1.10, -0.30]**	**0.0014**
Browne et al. (2025) *Phase 2b RCT (24W ext.)*	Pemvidutide or placebo (N=64)	**Treatment difference in ELF score vs placebo at Week 24 (95% CI)**		
		Placebo	—	—
		Pemvidutide 1.2 mg	**-0.20 [-0.60, 0.30]**	**0.451**
		Pemvidutide 1.8 mg	**-0.30 [-0.70, 0.20]**	**0.202**
		Pemvidutide 2.4 mg	**0.10 [-0.30, 0.60]**	**0.641**
Sanyal et al. (2025) *ESSENCE · Phase 3*	Semaglutide or placebo (N=800)	**ETD in ELF score vs placebo at Week 72 (95% CI)**		
		Placebo	—	—
		Semaglutide 2.4 mg	**-0.60 [-0.70, -0.50]**	**--**
Loomba et al. (2023) *ENLIVEN · Phase 2b*	Pegozafermin or placebo (N=222)	**Treatment difference in ELF score vs placebo at Week 24 (95% CI)**		
		Placebo	—	—
		Pegozafermin 15 mg QW	**-0.50 [-0.90, -0.20]**	**--**
		Pegozafermin 30 mg QW	**-0.50 [-0.70, -0.30]**	**--**
		Pegozafermin 44 mg Q2W	**-0.50 [-0.70, -0.30]**	**--**



Treatment: MRI-PDFF Change (Studies = 35, Patients = 6831) *(1 of 2)*

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Reference	Drug studied	% Change in hepatic fat (MRI-PDFF)	P value
Loomba et al. (2025) *Phase 2b RCT (N=160)*	ION224 or placebo	**Mean relative % change in MRI-PDFF from baseline at Week 51 (Day 351)** Placebo -20.9% ION224 60 mg -32.3% ION224 90 mg -42.2% ION224 120 mg -46.6%	— 0.068 <0.001 <0.001
Harrison et al. (2024) *MAESTRO-NASH · Phase 3 (N=966)*	Resmetirom or placebo	**LS mean % change in MRI-PDFF from baseline at Week 52** Placebo -8.7% Resmetirom 80 mg -35.4% Resmetirom 100 mg -46.6%	— -- --
Loomba et al. (2024) *SYNERGY-NASH · Phase 2 (N=190)*	Tirzepatide or placebo	**Mean % change in MRI-PDFF from baseline at Week 52** Placebo -9.8% Tirzepatide 5 mg -45.7% Tirzepatide 10 mg -41.3% Tirzepatide 15 mg -57.0%	— -- -- --
Harrison et al. (2023) *HARMONY · Phase 2b (24W)*	Efruxifermin or placebo	**LS mean % change in MRI-PDFF from baseline at Week 24** Placebo -6.0% Efruxifermin 28 mg -51.6% Efruxifermin 50 mg -63.7%	— <0.001 <0.001

-70% -60% -50% -40% -30% -20% -10% 0%

Treatment: MRI-PDFF Change *(2 of 2)*

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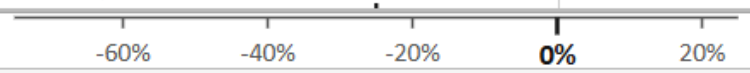
Reference	Drug studied	% Change in hepatic fat (MRI-PDFF)	Estimate (95% CI)	P value
Kaplan et al. (2026) *SYNCHRONIZE · Phase 3*	Survodutide or placebo (N=216)	**Relative % treatment difference vs placebo in MRI-PDFF at Week 48 (95% CI)**		
		Placebo	0.0%	--
		Survodutide 6.0 mg	**-49.2% [-61.7, -36.7]**	**<0.0001**
Noureddin et al. (2026) *Phase 2 RCT*	Efimosfermin or placebo (N=84)	**Absolute treatment difference (percentage points) vs placebo in MRI-PDFF at Week 28 (95% CI)**		
		Placebo	0.0%	--
		Efimosfermin 300 mg	**-8.1% [-11.0, -5.1]**	**< 0.001**
Noureddin et al. (2025) *HARMONY · Phase 2b (96W)*	Efruxifermin or placebo (N=126)	**Relative % treatment difference vs placebo in MRI-PDFF at Week 96 (95% CI)**		
		Placebo	0.0%	--
		Efruxifermin 28 mg	**-23.8% [-42.2, -5.5]**	**0.011**
		Efruxifermin 50 mg	**-30.9% [-48.9, -12.9]**	**0.0009**
Browne et al. (2025) *Phase 2b RCT (24W ext.)*	Pemvidutide or placebo (N=64)	**LS mean relative % change in MRI-PDFF from baseline, vs placebo (95% CI), Week 24**		
		Placebo	-14.0% [-32.2, 4.3]	--
		Pemvidutide 1.2 mg	**-56.3% [-78.2, -34.4]**	**<0.001**
		Pemvidutide 1.8 mg	**-75.2% [-93.8, -56.7]**	**<0.001**
		Pemvidutide 2.4 mg	**-76.4% [-99.7, -53.2]**	**<0.001**
Harrison et al. (2024) *MAESTRO-NASH · Phase 3*	Resmetirom or placebo (N=966)	**Relative % treatment difference vs placebo in MRI-PDFF at Week 52 (95% CI)**		
		Placebo	0.0%	--
		Resmetirom 80 mg	**-26.7% [-32.9, -20.6]**	**--**
		Resmetirom 100 mg	**-37.9% [-44.2, -31.7]**	**--**



Emerging Biomarker: PRO-C3

- Serum marker of type III collagen formation
- Primarily reflects active fibrogenesis and is associated with fibrosis severity
- Complements stiffness-based NITs by capturing extracellular-matrix formation
- Treatment-responsive, although assay harmonization and outcome-linked thresholds remain needed

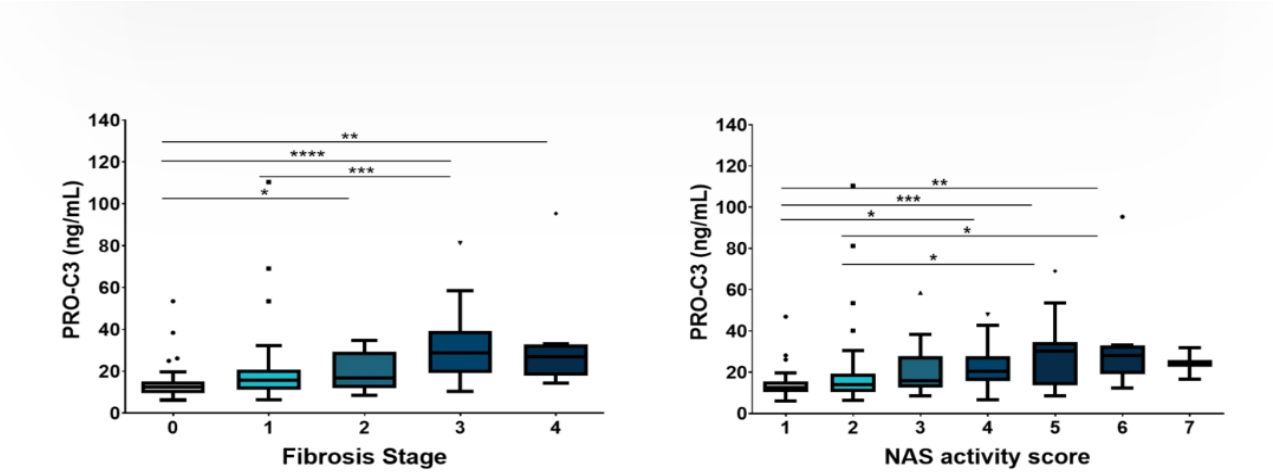


Figure 1. *NordicPRO-C3™ increases with increasing fibrosis and MASLD activity score (NAS).*

https://www.nordicbioscience.com/biomarker-solution/hepatic/masld-sld-and-mash/

Treatment Effect: PRO-C3 [reported estimate (95% CI)]

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Reference	Drug / Design	Change in Pro-C3 vs Comparator	Estimate (95% CI)	P value
Noureddin et al. (2026) *Phase 2 RCT (n=84)*	Efimosfermin 300mg SC Q4W vs placebo 24-week treatment	**Relative LS mean change from baseline, wk24 (treatment difference vs placebo)**		
		Efimosfermin 300mg	**−28.0% (−40.3, −15.7)**	**<0.001**
Sanyal et al. (2025) *Phase 3 RCT (n=800, interim)*	Semaglutide 2.4mg SC QW vs placebo 72-week treatment	**% relative difference (ETR) vs placebo, wk72**		
		Semaglutide 2.4mg	**−17.0% (−21.7, −12.1)**	**—**
Harrison et al. (2025) *Phase 2 RCT, parent trial (n=94)*	Pemvidutide 1.2/1.8/ 2.4mg SC QW vs placebo 12-week treatment	**LS mean change from baseline vs placebo, wk12 (ng/mL)**		
		Pemvidutide 1.2mg	**−2.5 (−6.0, 1.0)**	*0.156*
		Pemvidutide 1.8mg	**−3.7 (−7.2, −0.2)**	**0.038**
		Pemvidutide 2.4mg	**−3.0 (−6.6, 0.6)**	*0.099*
Harrison et al. (2023) *HARMONY, phase 2b RCT (n=128)*	Efruxifermin 28 or 50mg SC QW vs placebo 24-week treatment	**LS mean change vs placebo, wk24 (µg/L)**		
		Efruxifermin 28mg	**−5.2 (−7.1, −3.3)**	**<0.001**
		Efruxifermin 50mg	**−5.3 (−7.2, −3.3)**	**<0.001**
Harrison et al. (2022) *ALPINE 2/3, phase 2b RCT (n=171)*	Aldafermin 0.3/1.0/ 3.0mg SC QD vs placebo 24-week treatment	**Relative LS mean change from baseline vs placebo, wk24 (%; CI two-sided, P one-sided)**		
		Aldafermin 0.3mg	**−11.7% (−25.4, 2.0)**	**0.049**
		Aldafermin 1.0mg	**−13.8% (−28.1, 0.5)**	**0.030**
		Aldafermin 3.0mg	**−30.2% (−44.1, −16.3)**	**<0.0001**
Francque et al. (2021) *Phase 2b RCT (n=247)*	Lanifibranor 800 or 1200mg QD vs placebo 24-week treatment	**Within-arm change from baseline, wk24 (µg/L)**		
		Lanifibranor 800mg	**−3.93 (−5.26, −2.61)**	**—**
		Lanifibranor 1200mg	**−1.79 (−3.07, −0.52)**	**—**
		Placebo	*−1.01 (−2.30, 0.28)*	—

Treatment Effect: PRO-C3 (direction/p-value only)

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Reference	Drug / Design	Reported Finding		Value / Direction	P value
Bansal et al. (2025) *MAESTRO-NASH, phase 3 (n=966)*	Resmetirom 80/100mg vs placebo 52-week treatment	**Mean Δ from baseline, wk52 (ng/mL)**			
		Placebo	*–0.2 ng/mL*	—	*NR*
		Resmetirom 80mg	*–17.9 ng/mL*	—	*NR*
		Resmetirom 100mg	*–23.1 ng/mL*	—	*NR*
Mayorca-Guiliani et al. (2025) *EMMINENCE biomarker sub-analysis (n=392 randomised; 334 completed)*	MSDC-0602K 62.5/125/ 250mg vs placebo 12-month treatment	**Relative Pro-C3 diff vs placebo, LS-mean (adjusted), 12mo**			
		62.5mg	*no significant reduction*	—	*0.44*
		125mg	*reduction vs placebo*	—	**0.0274**
		250mg	*reduction vs placebo*	—	**0.0311**
Brown et al. (2023) *FALCON1, phase 2b (n=197)*	Pegbelfermin 10/20/ 40mg vs placebo 24-week treatment	**Pro-C3 trajectory by wk4+ vs placebo**			
		Pooled PGBF doses (rose in placebo, fell in all PGBF arms)	*pooled dose-response*	—	**6.5e-06**
Harrison et al. (2022) *Phase 2a RCT (n=107)*	Licogliflozin 30 or 150mg QD vs placebo 12-week treatment	**Geometric mean ratio vs placebo, wk6 / wk12**			
		30mg	*not significant*	—	*0.093 / 0.306*
		150mg	*not significant*	—	*0.084 / 0.251*

RLSE Framework: Guiding Principles

- Surrogate endpoints considered across all NIT types, with focus on the F2–F3 population
- Framework grounded in established surrogate endpoint criteria:
  - Biologic plausibility,
  - Epidemiologic evidence,
  - Sensitivity to change,
  - Defined test/retest variability (and analytical validation)
  - Drug MOA-agnostic, and
  - Threshold effect
- COU: The treatment-response context of use is evaluated separately from diagnostic or staging uses of the same NIT
- Considers both population-level performance and individual patient trajectory — including the direction and magnitude of change over time, not just a single threshold crossing

Proposed Framework: NIT Treatment Response

- No single NIT captures the full biology → requires careful consideration
- Proposed pairing for responder status:
  - **A measure of liver stiffness: VCTE (≥30% reduction) or MRE (≥25% reduction)**

    And/OR

  - **A measure of collagen formation: ELF (≥0.5 reduction) or PRO-C3**
- Open questions requiring discussion:

  - Categorical vs. continuous change-from-baseline

  - Threshold cut-offs: still need outcome-linkage data

Considerations — Methodologic Limitations

- Heterogeneity in LRE definitions across prognostic studies
- Basis for current NIT cut-offs varies by study and warrants explicit documentation
- Nonuniform follow-up durations across cohorts
- Platform/operator variability, especially for VCTE
- Discordance observed between histologic response and NIT response in some studies
- RCT evidence directly linking NIT change to later LRE reduction remains limited; most current evidence is prognostic/observational.

Considerations — Implementation Feasibility

- Central reading requirements and cross-platform standardization for imaging-based NITs
- MRI availability varies globally, with cost and access implications
- Operator dependence for VCTE
- Limited trial sample size
- Payer and access implications of embedding higher-cost imaging into entry or endpoint criteria
- Global trial site variability
- Framework applicability to patients already on approved therapy — placebo-controlled long-term trials face growing challenges from informative crossover, as seen previously in a PBC/OCA trial where placebo patients moved to commercial therapy

Key Takeaways

- Development of emerging framework: Two complementary domains — Liver stiffness and active fibrogenesis
- Key decisions: Responder definition and appropriate thresholds
- Critical evidence gap: Direct linkage between NIT change and hard clinical outcomes

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Thank You

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