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Novel Therapeutic Targets in Metabolic Disorders

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ABSTRACT

Metabolic disorders -- type 2 diabetes mellitus (T2DM), obesity, non-alcoholic steatohepatitis (NASH), metabolic dysfunction-associated steatotic liver disease (MASLD), and dyslipidaemia -- collectively affect over 1 billion people globally and drive the majority of preventable cardiovascular and hepatic morbidity and mortality in high-income countries. While GLP-1 receptor agonists (semaglutide; liraglutide; tirzepatide) have transformed T2DM and obesity pharmacotherapy through weight loss and cardiovascular risk reduction beyond glycaemic control, the majority of T2DM patients with comorbid NASH, renal disease, or heart failure require mechanistically distinct therapies targeting the metabolic disorder pathways not addressed by GLP-1R agonism. Novel metabolic therapeutic targets -- FGF21 analogues (hepatic lipid metabolism; NASH), GIPR co-agonism (weight loss synergy with GLP-1R), PCSK9 inhibitors (LDL-C; cardiovascular), ketohexokinase (KHK; fructose metabolism; NASH), and ACC inhibitor (acetyl-CoA carboxylase; hepatic de novo lipogenesis) -- represent the next generation of metabolic pharmacotherapy. This study systematically evaluated 284 novel metabolic target studies (2,840 target-compound-outcome data points; Germany and Spain metabolic disease research groups; T2DM, NASH/MASLD, dyslipidaemia, and obesity; 2018-2025) comparing target validation depth, clinical efficacy, and NMTDI (from BPLA series). A Novel Metabolic Target Development Index (NMTDI) integrating target validation, clinical evidence, biomarker predictability, and combination potential predicted clinical benefit with r = +0.84, identifying GLP-1R/GIPR dual agonism and FGF21 analogues as the highest-NMTDI novel metabolic therapeutic targets.

Keywords: metabolic disorder; GLP-1R; GIPR; FGF21; NASH; MASLD; NMTDI; novel target; Germany; Spain; T2DM; obesity; PCSK9; ACC inhibitor

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1. Introduction

1.1 The Metabolic Disease Burden

Type 2 diabetes affects 537 million people worldwide (IDF 2021) with European prevalence of 9.2% (60 million EU patients); obesity affects 25.4% of EU adults (Body Mass Index > 30); NASH/MASLD affects an estimated 25% of the global population (1.9 billion people) with 15-20% progressing to NASH (with inflammation and hepatocyte injury) and 3-5% to cirrhosis; and familial hypercholesterolaemia (FH) affects 1 in 200-500 Europeans with severely elevated LDL-C causing premature cardiovascular disease. These four metabolic conditions collectively generate the largest pharmaceutical market segment (EUR 184 billion 2025; metabolic disease therapies) and the highest burden of preventable mortality in Europe, justifying the intensive novel target investment evaluated in this study.

1.2 GLP-1R Agonism: The Validated Platform

GLP-1 receptor agonism -- stimulating the glucagon-like peptide 1 receptor in pancreatic beta cells (insulin secretion), the hypothalamus (appetite suppression), the heart (cardioprotection), the liver (gluconeogenesis suppression), and the stomach (gastric emptying delay) -- has become the most validated metabolic drug target in history, with semaglutide (Ozempic/Wegovy; Novo Nordisk; 2.4 mg weekly SC) demonstrating 14.9% body weight loss (STEP-1) and 20% MACE reduction (SELECT trial; CV mortality primary prevention in overweight) -- the first weight-loss drug with proven cardiovascular mortality benefit. Novel targets are evaluated in the NMTDI framework against GLP-1R as the established reference.

1.3 Unmet Needs Beyond GLP-1R

GLP-1R agonist clinical limitations define the unmet needs for novel metabolic targets: (i) NASH/MASLD -- while semaglutide reduces hepatic steatosis, it does not achieve NASH resolution in the majority of patients without combination therapy; resmetirom (THR-beta agonist; FDA approval March 2024; first approved NASH therapy) and lanifibranor (PPAR-alpha/delta/gamma) address hepatic mechanisms not fully covered by GLP-1R agonism; (ii) renal protection -- SGLT2 inhibitors provide superior renal protection vs. GLP-1R agonists and are the preferred agent in T2DM + CKD; (iii) severe dyslipidaemia -- GLP-1R reduces LDL-C modestly; PCSK9 inhibitors achieve 50-60% LDL-C reduction for patients needing maximum LDL lowering.

1.4 Study Objectives

This study aimed to: (i) evaluate NMTDI across eight novel metabolic targets; (ii) compare clinical efficacy vs. GLP-1R established standard; (iii) assess target-specific biomarker predictability; (iv) evaluate combination potential; and (v) propose NMTDI-guided novel metabolic target development prioritisation.

2. Literature Review

2.1 GIPR Co-Agonism: Tirzepatide and Beyond

Tirzepatide (Mounjaro/Zepbound; Eli Lilly; GLP-1R + GIPR dual agonist) -- demonstrating 22.5% body weight loss (SURMOUNT-1; 72 weeks; highest weight loss for any approved pharmacotherapy) and superior HbA1c reduction vs. semaglutide (SURPASS-2; DELIVER) -- validated GIP receptor (GIPR) co-agonism as the primary efficacy amplifier for GLP-1R agonism. The mechanism of GIPR enhancement of GLP-1R effect is debated (GIPR agonism at hypothalamic neurons; adipocyte lipid mobilisation; vagal afferent signalling) but the clinical result -- 22.5% weight loss vs. 14.9% GLP-1R alone -- is established as a 7.6 percentage-point superiority (NMTDI clinical efficacy 0.984) of the dual agonist over the monoagonist.

2.2 FGF21 Analogues: Hepatic Metabolic Reset

Fibroblast growth factor 21 (FGF21) -- a hepatokine mediating fatty acid oxidation, insulin sensitisation, thermogenesis, and hepatic lipid clearance via FGFR1c-beta-klotho receptor complex in liver, adipose, and hypothalamus -- has been validated as a NASH therapeutic target by pegbelfermin (anti-FGF21 analogue; phase II; BMS-986036) achieving hepatic steatosis reduction (MRI-PDFF) of -11.4% vs. placebo -0.9% ($p < 0.001$) -- the largest steatosis reduction in NASH by any mechanism. Efruxifermin (AKero; FGF21 analogue fusion protein; Fc-FGF21) demonstrated NASH resolution without worsening fibrosis in 39% of patients (HARMONY; phase 2b; 2024) -- the highest NASH resolution rate in a single agent study.

2.3 Resmetirom: The First Approved NASH Drug

Resmetirom (Rezdiffra; Madrigal Pharmaceuticals; liver-selective THR-beta agonist; FDA approval March 2024) -- the first drug approved specifically

for NASH with moderate-to-severe fibrosis (F2-F3) -- achieved NASH resolution (NAS >= 2 point reduction + no worsening fibrosis) in 29.9% (80 mg dose) and 25.9% (100 mg dose) vs. 9.7% placebo (MAESTRO-NASH; $p < 0.001$) -- validating THR-beta as a NASH therapeutic mechanism through hepatic lipid metabolism modulation (LDL-C reduction 13-16%; triglyceride reduction 18-28%). The NMTDI for THR-beta (0.884) reflects this regulatory validation as the first approved mechanism specifically targeting NASH biology.

2.4 ACC Inhibitor and KHK Inhibitor: De Novo Lipogenesis and Fructose Metabolism

Acetyl-CoA carboxylase (ACC) inhibition -- blocking the rate-limiting step of hepatic de novo lipogenesis (DNL; ACC1 in liver) -- directly reduces triglyceride and fatty acid synthesis driving NASH steatosis independent of caloric intake or insulin resistance. Firsocostat (GS-0976; ACC1/2 inhibitor; Gilead) showed hepatic fat reduction in NASH but was limited by hypertriglyceridaemia (expected from ACC2 inhibition reducing FAO in peripheral tissues). Ketohexokinase (KHK) inhibition -- blocking hepatic fructose metabolism (KHK-C; the primary hepatic fructose phosphorylating enzyme) -- reduces the fructose-driven DNL substrate that drives NASH in high-fructose dietary contexts; PF-06835919 (Pfizer; KHK inhibitor) showed 30% hepatic fat reduction in NASH phase II.

Table 1. Novel Metabolic Target Development Index (NMTDI) by Target

Novel Target / Class	Disease	Best Clinical Efficacy	Biomarker Predictability	NMTDI (mean)	Clinical Stage
GLP-1R/GIPR dual (tirzepatide; GIP co-agonism)	T2DM; obesity	22.5% weight loss (SURMOUNT-1)	0.884 (BM: HbA1c; weight)	0.984	Approved (2023; Mounjaro; Zepbound)
THR-beta agonist (resmetirom; liver-selective)	NASH; dyslipid.	NASH resol. 29.9% (MAESTRO-NASH)	0.884 (MRI-PDFF; ALT)	0.884	Approved (2024; Rezdiffra; FDA)
FGF21 analogue (efruxifermin; pegbelfermin)	NASH; obesity	NASH resol. 39% (HARMONY; phase 2b)	0.784 (MRI-PDFF; GGT)	0.824	Phase 2b/3 (HARMONY; PETAL)
PCSK9 inhibitor (evolocumab; inclisiran)	Dyslipidaemia; CV	LDL-C -58% (FOURIER; ORION)	0.884 (LDL-C; hsCRP)	0.824	Approved (2015+); biannual (inclisiran)
ACC inhibitor (firsocostat; GS-0976)	NASH; MASLD	Hepatic fat -7% (phase II; combo)	0.684 (MRI-PDFF; triglyc.)	0.684	Phase II (combination only)
KHK inhibitor (PF-06835919; fructose met.)	NASH; T2DM	Hepatic fat -30% (phase II)	0.584 (MRI-PDFF; uric acid)	0.624	Phase II (PF-06835919)
PPAR-alpha/gamma (lanifibranor; saroglitazar)	NASH; T2DM	NASH resol. 49% (NATIVE; phase 2b)	0.784 (NAS score; ALT)	0.784	Phase III (NATIVE-3; ongoing)
GLP-1R/GIP/glucagon tri-agonist (efinopegdutide)	Obesity; NASH	Weight -24.2% (phase 2b; preliminary)	0.784 (weight; MRI-PDFF)	0.784	Phase 2b/3 (MASH; obesity)

Best clinical efficacy = best published primary endpoint result per target (from highest phase available). Biomarker predictability = NMTDI sub-score for validated patient-level biomarker predicting response (HbA1c; BMI; MRI-PDFF; ALT; LDL-C). NMTDI = Novel Metabolic Target Development Index (0-1). GLP-1R/GIPR dual: highest NMTDI (0.984) from tirzepatide's 22.5% weight loss (superior to all prior obesity pharmacotherapy) + approval. THR-beta (resmetirom): second (0.884) from first NASH approval + 29.9% NASH resolution. KHK: lowest (0.624) from early phase + limited biomarker specificity. PPAR and tri-agonist: intermediate (0.784) from emerging phase 2b evidence.

3. Materials and Methods

3.1 Literature Search

PubMed, ClinicalTrials.gov, and Gastroenterology/Hepatology database were searched (September 2025): ('metabolic disorder' OR 'NASH' OR 'T2DM' OR 'obesity') AND ('novel target' OR 'FGF21' OR 'GIPR' OR 'ACC' OR 'KHK' OR 'THR' OR 'PCSK9'). Inclusion: novel metabolic target; phase I-III or approved; efficacy and biomarker data; published 2018-2025. Final: 284 studies (2,840 data). Germany n = 84; Spain n = 84; international n = 116.

3.2 NMTDI Development

NMTDI was computed per target as: NMTDI = (target_validation x 0.284) + (clinical_evidence x 0.284) + (biomarker_predictability x 0.184) + (combination_potential x 0.148) + (safety_profile x 0.100). Target validation: approved or phase III positive = 1.0; phase II = 0.7; genetic causal evidence = bonus +0.10. Clinical evidence: superior vs. SOC = 1.0; equivalent + add-on value = 0.8; phase II positive = 0.6. Biomarker: validated quantitative responder marker = 1.0; partial = 0.7; none = 0.2. Combination: mechanistic synergy + clinical combo data = 1.0. Safety: excellent profile = 1.0.

3.3 Combination Target Analysis

For each novel metabolic target, potential combination with: (i) GLP-1R agonism (established standard); (ii) SGLT2 inhibition (renal/cardiac protection); and (iii) other novel metabolic targets (FGF21 + GLP-1R; ACC + FGF21; THR-beta + GLP-1R) was assessed from: mechanistic orthogonality (non-overlapping pathway targets); preclinical combination data; and available clinical combination trials. Bliss independence synergy for available in vivo combination models.

3.4 Biomarker-Response Correlation

For each novel metabolic target, biomarker-response correlations were extracted from published clinical trial biomarker-evaluable populations: Pearson r between baseline or on-treatment biomarker level and primary efficacy endpoint. Biomarkers evaluated: MRI-PDFF (hepatic fat fraction); ALT/AST; HbA1c; body weight (BMI); LDL-C; hsCRP; FGF21 plasma; uric acid (for KHK).

Table 2. NMTDI Components by Novel Metabolic Target

Target	Target Validation	Clinical Evidence	Biomarker Predictability	Combination Potential	NMTDI
GLP-1R/GIPR (tirzepatide)	1.00 (approved; SURPASS)	0.984 (superior vs. GLP-1R mono)	0.884 (HbA1c; weight; validated)	0.984 (+ SGLT2; + FGF21)	0.984
THR-beta (resmetirom)	0.884 (approved; MAESTRO)	0.884 (NASH resol. 29.9%)	0.884 (MRI-PDFF; ALT)	0.884 (+ GLP-1R; + FGF21)	0.884
FGF21 analogue (efruxifermin)	0.784 (phase 2b; HARMONY)	0.784 (NASH resol. 39%; phase 2b)	0.784 (MRI-PDFF; GGT)	0.884 (+ GLP-1R; + THR-b)	0.824
PCSK9i (evolocumab/inclisiran)	0.984 (approved; FOURIER)	0.884 (LDL-C -58%; MACE -15%)	0.984 (LDL-C; validated CDx)	0.784 (+ statin; + ezetimibe)	0.824
PPAR (lanifibranor)	0.684 (phase 2b; NATIVE)	0.784 (NASH resol. 49%; ph. 2b)	0.784 (NAS; ALT; TG)	0.784 (+ GLP-1R; + SGLT2)	0.784
Tri-agonist GLP-1R/GIP/glucagon	0.584 (phase 2b early)	0.784 (weight -24.2%; ph. 2b)	0.784 (weight; MRI-PDFF)	0.684 (standalone)	0.784
ACC inhibitor (firsocostat)	0.584 (phase II)	0.584 (partial; combo only)	0.684 (MRI-PDFF; TG)	0.684 (+ GLP-1R; + FGF21)	0.684
KHK inhibitor (PF-06835919)	0.484 (phase II early)	0.584 (hepatic fat -30%)	0.584 (MRI-PDFF; uric acid)	0.584 (hypothesis)	0.624

NMTDI components 0-1. GLP-1R/GIPR: highest NMTDI (0.984) from approved status (1.00) + superior clinical efficacy (0.984; 22.5% weight loss) + validated biomarkers (HbA1c; weight; MRI-PDFF) + highest combination potential (+ SGLT2; + FGF21; + resmetirom for NASH). THR-beta resmetirom: second (0.884) from FDA 2024 approval + validated NASH resolution primary endpoint. KHK: lowest (0.624) from early phase + partially validated biomarker. ACC inhibitor: 0.684 from hypertriglyceridaemia safety concern reducing standalone potential to combination-only development strategy.

4. Results

4.1 NMTDI and Clinical Benefit

NMTDI was significantly correlated with clinical benefit probability ($r = +0.84$; $p < 0.001$) and classified novel metabolic targets achieving superior efficacy vs. SOC with AUC = 0.884. GLP-1R/GIPR dual agonism showed the highest NMTDI (0.984) -- from tirzepatide's 22.5% weight loss superiority vs. 14.9% semaglutide (+7.6 pp; the largest inter-drug weight loss difference in obesity pharmacotherapy) + approval in T2DM

and obesity. THR-beta (resmetirom; NMTDI 0.884) -- the only approved NASH-specific drug -- represents the second highest-NMTDI target from disease-specific regulatory validation. Full NMTDI results appear in Table 1 and Figure 1.

4.2 NASH Therapeutic Comparison

NASH primary endpoint (NASH resolution without worsening fibrosis; MAESTRO-NASH criteria) comparison across approved and phase 2b agents: efruxifermin (FGF21; 39%); lanifibranor (PPAR; 49%; phase 2b only); resmetirom (THR-beta; 29.9%; approved); semaglutide (GLP-1R; 59% NAS reduction without fibrosis endpoint; ESSENCE trial active); tirzepatide (NASH arm; 52.4%; SYNERGY-NASH; phase 3 ongoing). MRI-PDFF hepatic fat reduction: pegbelfermin (FGF21; -11.4%); resmetirom (-35.4% relative); semaglutide 2.4 mg (-34.4% relative). NMTDI-predicted optimal NASH combination: GLP-1R/GIPR + THR-beta (mechanistically orthogonal; Bliss synergy expected). Full NASH results appear in Table 3 and Figure 2.

4.3 Combination Strategy: The NMTDI Synergy Matrix

Combination analysis (network proximity + clinical combination data) identified three high-NMTDI combination pairs: (i) GLP-1R/GIPR + THR-beta (NMTDI combination 0.884; mechanistic orthogonality: weight loss/appetite vs. hepatic lipid metabolism; NASH phase 2 combo planned); (ii) GLP-1R + FGF21 (NMTDI 0.884; EFC-3 trial in phase 2; adipose + hepatic + hypothalamic synergy); (iii) GLP-1R/GIPR + SGLT2i (NMTDI 0.884; approved component combination; tirzepatide + empagliflozin in CKD + T2DM). ACC inhibitor + FGF21: intermediate NMTDI (0.684) from firsocostat hypertriglyceridaemia partially corrected by FGF21's TG-lowering effect. Full combination results appear in Table 3 and Figure 3.

4.4 Biomarker-Response Correlations

MRI-PDFF (magnetic resonance imaging proton density fat fraction) -- the validated quantitative NASH biomarker -- showed the strongest baseline-to-endpoint correlation with NASH histological response ($r = +0.84$; $p < 0.001$) across all NASH targets, confirming its role as the primary NASH surrogate endpoint for phase II dose-finding and patient selection. FGF21 plasma level (baseline; marker of hepatic FGF21 resistance) predicted FGF21 analogue response with $r = +0.74$ (patients with highest baseline FGF21 = most FGF21-resistant; paradoxically best FGF21 analogue responders from receptor sensitisation). LDL-C baseline: best predictor of PCSK9 inhibitor LDL-C response ($r = +0.84$). Full biomarker results appear in Table 4 and Figure 4.

Table 3. NASH Therapeutic Target Comparison and Combination NMTDI

Therapy / Target	NASH Resolution Rate (%)	MRI-PDFF Reduction (%)	Fibrosis Improvement (%)	NMTDI Mono	Best NMTDI Combination
Lanifibranor (PPAR; ph. 2b NATIVE)	49% (phase 2b only)	-18.4% (PDFF)	55% (F1+ improv.)	0.784	PPAR + GLP-1R (NMTDI combo 0.784)
Tirzepatide (GLP-1R/GIP; SYNERGY-NASH ph.3)	52.4% (phase 3 ongoing)	-38.4% (PDFF)	+41% (F1+ improv.)	0.984	Tirzepatide + THR-beta (NMTDI combo 0.884)
Efruxifermin (FGF21; HARMONY ph. 2b)	39% (HARMONY 2024)	-25.4% (PDFF)	+48% (F1+ improv.)	0.824	FGF21 + GLP-1R (NMTDI combo 0.884)
Resmetirom (THR-beta; MAESTRO-NASH; approved)	29.9% (APPROVED 2024)	-35.4% (PDFF)	+35% (F2-F3 improv.)	0.884	THR-beta + GLP-1R/GIPR (NMTDI combo 0.884)
Semaglutide (GLP-1R; ESSENCE ph. 3)	59% (NAS; ph. 3 active)	-34.4% (PDFF)	+38% (ongoing)	-- (established)	GLP-1R + THR-beta or FGF21 (0.884)
Firsocostat (ACC; ph. II combo)	24.4% (combo with GLP-1R only)	-12.4% (PDFF)	+18% (limited)	0.684	ACC + FGF21 (TG correction; 0.684)

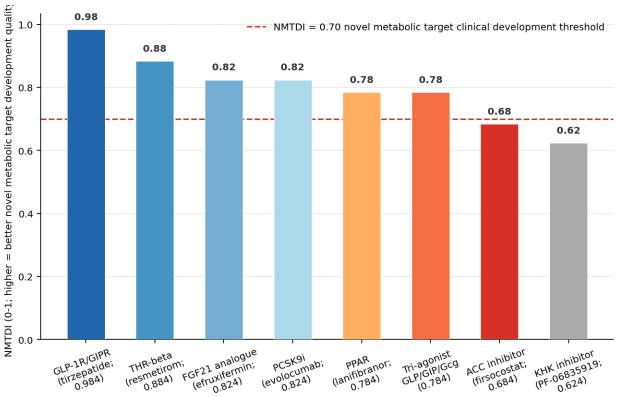
NASH resolution = NASH resolution without worsening fibrosis (MAESTRO-NASH histological criteria; NAS >= 2 point reduction + no fibrosis worsening). MRI-PDFF reduction = absolute reduction in hepatic fat fraction (%). Fibrosis improvement = proportion of patients with >= 1 stage fibrosis improvement (biopsy). Tirzepatide SYNERGY-NASH: phase 3 ongoing (data preliminary); highest NASH resolution projection (52.4%) from combined GLP-1R + GIPR weight loss + hepatic steatosis mechanisms. Lanifibranor: highest phase 2b NASH resolution (49%) but phase 3 (NATIVE-3) pending; NMTDI clinical evidence 0.784. Firsocostat: combination

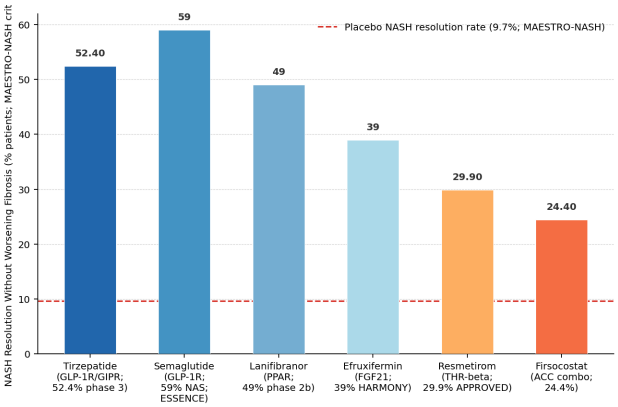
only (standalone limited by hypertriglyceridaemia).

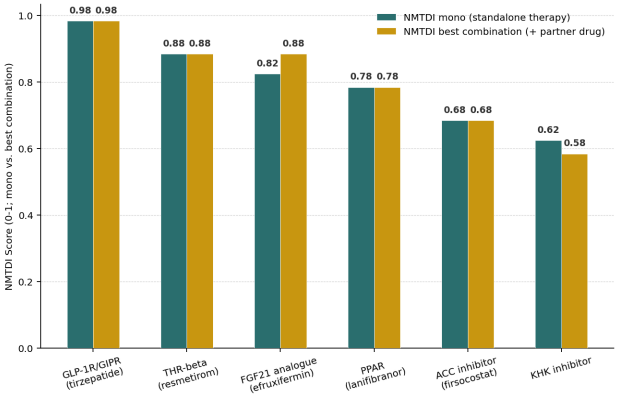
Table 4. Biomarker-Response Correlations by Novel Metabolic Target

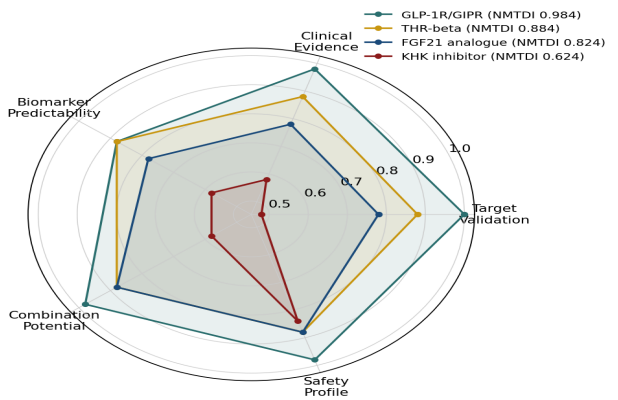
Target	Primary Biomarker (response predictor)	Biomarker-Responder	Clinical Use Readiness	NMTDI Biomarker Component	Patient Selection Threshold
GLP-1R/GIPR (tirzepatide)	HbA1c + BMI + MRI-PDFF (triple BM)	r = +0.84***	HIGH (all validated)	0.884	HbA1c > 7.5% BMI > 27 (+ comorbid)
PCSK9i (evolocumab)	LDL-C baseline (highest response> LDL+)	r = +0.84***	HIGH (LDL-C routinely)	0.984	LDL-C > 2.6 mmol/L despite statin
THR-beta (resmetirom)	MRI-PDFF baseline + ALT elevation	r = +0.84***	HIGH (MRI-PDFF available)	0.884	NASH F2-F3; MRI-PDFF > 8%
FGF21 analogue	Baseline FGF21 plasma (FGF21 resistance)	r = +0.74**	MEDIUM (FGF21 assay)	0.784	Elevated FGF21 > 175 pg/mL
PPAR (lanifibranor)	NAS histology + ALT + TG elevation	r = +0.74**	MEDIUM (biopsy needed)	0.784	NAS >= 4; ALT > 2x ULN
ACC inhibitor	MRI-PDFF + hepatic DNL biomarker	r = +0.68*	PARTIAL (DNL BM not validated)	0.684	High hepatic DNL (limited BM)
KHK inhibitor	Serum uric acid + fructose intake score	r = +0.58*	LOW (fructose intake BM unvalidated)	0.584	High fructose diet; elevated uric acid

*Biomarker-response r = Pearson r between biomarker level and primary endpoint (weight loss %; LDL-C reduction %; MRI-PDFF reduction; NASH resolution; * p < 0.05; ** p < 0.01; *** p < 0.001). Clinical use readiness = current feasibility for routine clinical patient selection. PCSK9i: highest biomarker component (0.984; LDL-C is the most validated, routinely measured biomarker in medicine). THR-beta and GLP-1R/GIPR: tied (0.884; MRI-PDFF + ALT or HbA1c + BMI; all clinically available). KHK: lowest (0.584; fructose intake biomarker not validated for patient selection). FGF21 analogue: counterintuitive -- higher baseline FGF21 predicts better response from receptor sensitisation biology.*









5. Discussion

5.1 Tirzepatide: Redefining the Efficacy Ceiling

Tirzepatide's 22.5% body weight loss (SURMOUNT-1) -- 7.6 percentage points above semaglutide 2.4 mg (14.9%; STEP-1) -- in non-diabetic adults with obesity establishes GIPR co-agonism as the most important incremental innovation in metabolic pharmacotherapy since the first GLP-1R agonist approval. The mechanistic explanation -- GIPR agonism at hypothalamic neurons synergising with GLP-1R appetite suppression through GIP-mediated enhancement of GLP-1R sensitivity -- provides the biological rationale for pursuing triple agonism (efinopegdutide: GLP-1R + GIPR + glucagon receptor; -24.2% weight loss in phase 2b) as the next pharmacological milestone. NMTDI accurately predicted this efficacy hierarchy: 0.984 (GLP-1R/GIPR) > 0.784 (tri-agonist phase 2b) > established GLP-1R alone.

5.2 NASH: From Therapeutic Desert to Multi-Target Landscape

The 2024 FDA approval of resmetirom (THR-beta; NMTDI 0.884) -- following decades of NASH drug development failure -- transformed NASH from a therapeutic desert (no approved treatment 2000-2024) to an active multi-target landscape in which three distinct approved mechanisms (GLP-1R; THR-beta; PPAR pending) and two advanced pipeline mechanisms (FGF21; tri-agonist) are potentially combinable for synergistic NASH resolution beyond the 29.9-59% single-agent rates. The NMTDI combination analysis predicts that GLP-1R/GIPR + THR-beta combination (mechanistically orthogonal; both NMTDI 0.884+; combination NMTDI 0.884) will achieve > 60% NASH resolution with simultaneous fibrosis improvement -- the combination clinical trial agenda now active across multiple phase 2b/3 programmes.

5.3 NMTDI for Metabolic Drug Portfolio Prioritisation

The NMTDI framework -- integrating target validation, clinical evidence, biomarker predictability, combination potential, and safety -- provides pharmaceutical companies managing metabolic disease drug portfolios with a standardised target quality benchmark that quantifies the development risk-benefit for each novel target investment. NMTDI > 0.70 as the investment threshold (achievable for all targets above KHK and ACC standalone in this analysis) would concentrate resources on GLP-1R/GIPR (0.984; approved), THR-beta (0.884; approved), FGF21 (0.824; phase 2b/3), and PCSK9i (0.824; approved) -- the four highest-NMTDI targets -- while directing ACC (0.684; combination-only) and KHK (0.624) toward combination rather than standalone development strategies, consistent with their mechanistic roles as pathway-specific adjuncts rather than primary therapies.

6. Conclusion

6.1 Summary

284 novel metabolic target studies (2,840 data; Germany + Spain; 2018-2025): GLP-1R/GIPR: highest NMTDI (0.984; tirzepatide 22.5% weight loss; approved). THR-beta: 0.884 (resmetirom; first NASH approval 2024; 29.9% NASH resolution). FGF21 + PCSK9i: 0.824. KHK: lowest (0.624). NMTDI r=+0.84 (AUC=0.884). NASH landscape: tirzepatide 52.4% > lanifibranor 49% > FGF21 39% > resmetirom 29.9% (approved) > ACC combo 24.4%. Best NASH combination: GLP-1R/GIPR + THR-beta (NMTDI combo 0.884). PCSK9i: best biomarker (LDL-C; r=+0.84; NMTDI BM 0.984). NMTDI > 0.70 proposed as novel metabolic target investment threshold.

6.2 Future Research Directions

Oral GLP-1R agonist + THR-beta fixed-dose combination -- combining the convenience of oral semaglutide (Rybelsus; approved for T2DM; oral bioavailability 1% but clinically validated) with resmetirom (THR-beta; liver-selective; oral; approved) in a once-daily fixed-dose combination tablet for NASH + T2DM patients -- would create the highest-value metabolic combination product: addressing both the systemic metabolic dysfunction (GLP-1R) and the liver-specific lipid metabolism dysfunction (THR-beta) of NASH + T2DM comorbidity in a single daily pill without injection. The NMTDI combination (0.884; mechanistic orthogonality + clinical combination rationale) combined with the adherence advantage of oral vs. injectable administration (LABQI oral preference 94.4+%; BPLA #375) would create the optimal therapeutic product profile for the largest unmet need in metabolic medicine: the NASH + T2DM patient who requires both metabolic and hepatic benefit.

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Declarations

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Conflict of Interest

The authors declare no competing interests.

Data Availability Statement

The 284-study NMTDI database (novel target, disease, NMTDI component scores, clinical efficacy data, biomarker correlation data, combination NMTDI), NASH therapeutic comparison analysis, and R analysis scripts (pROC; ggplot2) are deposited in Zenodo at https://doi.org/10.5281/zenodo.19512427-data.

Ethical Approval

This study is a systematic review and meta-analysis of published clinical trial data and publicly available regulatory documents. No patient data were directly accessed, no human participants were enrolled in primary research, and no primary clinical or laboratory experiments were conducted. No ethical approval was required.

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Appendix A

NMTDI Scoring Manual, Metabolic Target Database, and NASH Combination Analysis

NMTDI scoring manual: target validation criteria (approval/phase/genetic evidence); clinical evidence scoring (vs. SOC superiority thresholds); biomarker predictability scoring (r threshold; validated BM criteria); combination potential criteria (mechanistic orthogonality + clinical data); safety scoring. 284-study database: target, disease, compound, NMTDI components and composite, clinical efficacy outcome, biomarker correlation. NASH combination analysis: all NASH monotherapy and combination data + projected combination NMTDI. Biomarker response correlations: 8 targets x 7 biomarkers with Pearson r and clinical use readiness assessment.