

Responders Vs. Non-Responders or How to Predict the Response to GLP-1 or GLP-1/GIP Receptor Agonist Therapy

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SECTION 1

INTRODUCTION



The GLP-1 Era in Obesity and Type 2 Diabetes

- GLP-1 receptor agonists have fundamentally transformed the treatment of obesity and type 2 diabetes (T2D).
- High-dose semaglutide 2.4 mg weekly produces clinically substantial and sustained weight loss.
Tirzepatide, a dual GIP/GLP-1 receptor agonist, has demonstrated even greater efficacy across multiple doses.
- In STEP 1, semaglutide 2.4 mg produced a mean total body weight loss (TBWL) of 14.9% in adults with obesity without T2D.
- SURMOUNT-1 demonstrated mean TBWL of 15.0%–20.9% with tirzepatide, reaching 20.9% with the 15-mg dose.
- These outcomes approach the magnitude of weight loss previously associated mainly with bariatric surgery.

Efficacy Varies Across Clinical Populations

- The magnitude of GLP-1-based treatment response differs substantially between individual patients and clinical populations.
- In STEP 2, semaglutide 2.4 mg produced 9.6% TBWL in patients with both obesity and T2D. This weight reduction was accompanied by robust improvements in glycated haemoglobin (HbA1c).
- Patients with T2D generally demonstrate different weight-loss responses from patients with obesity without T2D.
- The approval of **orforglipron**, the first oral **small-molecule GLP-1 receptor agonist**, further **expands the therapeutic landscape**.
- Despite impressive trial-level efficacy, individual treatment responses remain highly heterogeneous.

Why Do Some Patients Respond and Others Do Not?

- Approximately 10% of participants receiving high-dose semaglutide achieve less than 5% TBWL in controlled clinical trials.
- **Non-response may be** more frequent in routine practice because of **lower adherence, lower treatment doses, and greater comorbidity burden.**
- However, directly comparable real-world estimates remain limited, making the true prevalence of non-response uncertain.
- **Glycaemic non-response** occurs less frequently in T2D but is strongly influenced by **baseline glycaemic** burden and treatment context.
- Endogenous GLP-1 reserve and concomitant medications may also contribute to variability in glycaemic response.

Therefore, predictors of weight-loss response and glycaemic response should be considered as related but mechanistically distinct outcomes.

Emerging Pharmacogenomic Evidence

- Genetic variation has emerged as a potential contributor to interindividual variability in GLP-1-based treatment response.
- A landmark **pharmacogenomic genome-wide** association study was published in **Nature on 8 April 2026**. The study analysed self-reported data from nearly 28,000 GLP-1-treated users of the 23andMe platform.
- **Genome-wide-significant associations** were identified involving variation in the GLP1R and GIPR genes.
- These findings build on earlier genome-wide analyses by Dawed and colleagues using observational and randomized-trial data.
- However, the recent findings remain hypothesis-generating because they derive from a single self-reported cohort and require independent replication.

Rationale and Scope of the Review

- This review examines the determinants of heterogeneous response to GLP-1 and GLP-1/GIP receptor agonist therapy.
- The evidence is organized according to major biological and clinical domains.
- Three clinical contexts are considered separately: **obesity without T2D, T2D, and obesity with T2D.**
- The review integrates **pharmacogenomic, behavioural, neuroendocrine, microbiome, and early-response predictors.**
- Particular emphasis is placed on the strength and maturity of evidence supporting each proposed predictor.
- This framework aims to clarify which factors may ultimately support precision treatment with incretin-based therapies.

Suggested visual: Central concept diagram with the three clinical populations and major predictor domains surrounding them.

Domain	Positive predictors of response	Negative predictors of response	References
Baseline metabolic phenotype	Higher baseline HbA1c (T2D); preserved β -cell reserve (high fasting C-peptide); shorter diabetes duration; predominantly visceral adiposity	Severely diminished β -cell reserve (low C-peptide); longer diabetes duration; class III obesity (BMI ≥ 40 kg/m ²)	[1, 3]
Endocrine	Euthyroid status; higher endogenous oestrogen levels (premenopausal females)	Subclinical or overt hypothyroidism; markedly elevated leptin (severe leptin resistance)	[7–9]
Sex	Female sex (greater density of GLP-1-expressing hindbrain neurons; estrogenic potentiation of anorexigenic effects)	Male sex	[9–12]
Pharmacogenomic	<i>GLP1R</i> rs10305420 T allele (efficacy-enhancing variant)	<i>GIPR</i> risk alleles (tirzepatide-specific GI toxicity); combined <i>GLP1R</i> + <i>GIPR</i> high-risk genotype; <i>MC4R</i> loss-of-function variants; <i>FTO</i> rs9939609 A allele	[5, 13–15]
Neuroendocrine/hypothalamic	Intact hypothalamic integrity; high food-reward sensitivity (responsive to anti-reward effects of GLP-1RA)	Hypothalamic gliosis or inflammation; emotional eating driven by anxiety, depression, or trauma	[16–18]
Gut microbiome	Higher <i>Bacteroides</i> abundance (T2D glycaemic response); SCFA-producing taxa (<i>Akkermansia muciniphila</i> , <i>Faecalibacterium prausnitzii</i> , <i>Ruminococcaceae</i>); higher <i>Bacteroides/Firmicutes</i> ratio	<i>Prevotella copri</i> abundance; bacterial DPP-4-like activity (e.g., <i>Prevotella</i> , <i>Lactobacillus</i>)	[19–21]
Behavioural/lifestyle	Resistance training and physical activity; protein-rich, fibre-dense dietary adoption; behavioural readiness and self-efficacy	Sedentary lifestyle; highly processed, calorie-dense baseline diet; untreated depression, anxiety, or PTSD; weight-promoting psychotropic medications	[1, 7]
Comorbidities	Obstructive sleep apnea (cardiometabolic-responsive phenotype)	Pre-existing delayed gastric emptying (limits dose escalation)	[22–24]
Pharmacodynamic/GI tolerance	Moderate nausea or early satiety without dose reduction (marker of drug-target engagement)	Severe GI toxicity necessitating dose reduction or discontinuation; high-risk <i>GLP1R</i> + <i>GIPR</i> genotype on tirzepatide	[5, 25]
Early on-treatment response	$\geq 5\%$ TBWL by week 16; meaningful HbA1c reduction at weeks 12–16 (T2D); early reduction in leptin and rise in PYY	$< 5\%$ TBWL by week 16 on maximum tolerated dose	[1, 26–29]

TABLE 1 | Positive and negative predictors of response to GLP-1 receptor agonist therapy.

DEFINING RESPONSE: DIVERGENT ENDPOINTS ACROSS CLINICAL CONTEXTS



Clinical Definitions of Treatment Response

- The **definition of treatment** response differs fundamentally across obesity, T2D, and combined obesity–T2D populations.
- **For obesity without T2D**, the traditional threshold for clinically meaningful response is **at least 5% TBWL**.

Recent consensus increasingly considers 10% TBWL a threshold associated with more substantial metabolic benefit.

- **Super-response** is conventionally defined as at **least 20% TBWL** and may occasionally exceed 30%.
- In T2D, glycaemic response** is commonly defined as an HbA1c reduction of **approximately 0.5–1.0** percentage points.
- The clinical significance of HbA1c reduction depends on baseline glycaemia, treatment targets, and cardiovascular risk.

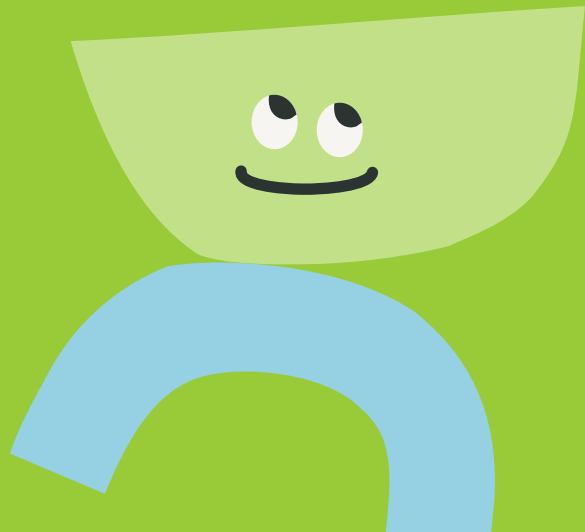
Early Versus Late Treatment Response

- Patients receiving GLP-1-based therapy can follow distinct response trajectories despite similar treatment exposure.
- **Early responders achieve** clinically meaningful weight or metabolic targets within approximately **the first 12 weeks**.
- **Late responders** initially show limited improvement but may achieve substantial benefit with continued treatment.
- Weight-loss trajectories at **weeks 4, 8, and 16 provide useful information** about subsequent long-term outcomes.
- STEP trial data indicate that patients achieving less than 5% weight loss by week 16 rarely reach meaningful endpoints by week 68.
- Week 16 may therefore represent an important clinical point for reassessing treatment response and considering therapeutic modification.

Weight-Loss and Glycaemic Response Are Distinct

- Weight loss and glycaemic improvement do not necessarily occur in parallel during GLP-1-based therapy.
- Some patients with T2D achieve near-normal HbA1c despite relatively modest weight loss.
- These patients represent **a distinct phenotype of glycaemic super-response.**
- Conversely, some patients achieve at least 20% TBWL while experiencing only modest improvement in glycaemic control.
- Patients with obesity and T2D may therefore obtain substantial benefit along one therapeutic axis without equivalent improvement along the other.
- Improvements **in hepatic steatosis, blood pressure, and sleep apnea** may also occur independently of the magnitude of weight loss.

MECHANISMS OF ACTION RELEVANT TO RESPONSE HETEROGENEITY



GLP-1 Signalling: Central and Peripheral Mechanisms

- GLP-1 was identified as a physiological incretin in humans in 1987 and subsequently became a major therapeutic target.
- Pharmacological GLP-1 receptor agonists amplify multiple receptor-mediated actions of endogenous GLP-1.
- **Central mechanisms** include **hypothalamic appetite suppression and reduced hedonic reward from highly palatable foods.**
- **Peripheral mechanisms** include **delayed gastric emptying** and enhanced satiety signalling through vagal afferents.
- The relative contribution of these mechanisms varies across obesity and T2D populations.
- This mechanistic heterogeneity partly explains why predictors of glycaemic and weight-loss response differ between clinical contexts.

Mechanisms Principally Relevant to Glycaemic Control in T2D

- In T2D, GLP-1RAs primarily reduce plasma glucose through glucose-dependent stimulation of pancreatic **β -cell insulin secretion**.
- They also suppress inappropriate glucagon secretion from **pancreatic α -cells**.
- **Delayed gastric emptying** further reduces postprandial glucose excursions.
- These effects depend on residual β -cell secretory capacity rather than replacement of lost β -cell function.
- In STEP 2, semaglutide 2.4 mg produced 9.6% TBWL together with a mean HbA1c reduction of 1.6 percentage points.
- Patients with T2D nevertheless achieve less weight loss than matched non-diabetic populations, potentially **reflecting hyperglycaemia-related impairment of hypothalamic insulin and GLP-1 signalling**.

Mechanisms Principally Relevant to Weight Loss

- In obesity without T2D, weight loss is mediated predominantly through central anorexigenic pathways.
- Hypothalamic GLP-1 receptors suppress neuropeptide Y/AgRP-driven hunger while enhancing proopiomelanocortin-mediated satiety.
- GLP-1RAs also modulate the mesolimbic dopamine system, including the nucleus accumbens, ventral tegmental area, and prefrontal cortex.
- These effects reduce the hedonic appeal of highly palatable foods and attenuate food-cue reactivity.
- Delayed gastric emptying and increased postprandial PYY and oxyntomodulin secretion further reinforce satiety.
- Tirzepatide produced greater mean weight loss than semaglutide in SURMOUNT-5, with 20.2% versus 13.7% TBWL at 72 weeks.

PREDICTORS OF GLYCAEMIC RESPONSE IN TYPE 2 DIABETES



Baseline Metabolic Predictors of Glycaemic Response

- Baseline metabolic phenotype strongly influences the magnitude of glycaemic response to GLP-1RA therapy.
- **Higher baseline HbA1c** consistently predicts a **greater absolute reduction in HbA1c**.
- This relationship reflects glucose-dependent amplification of insulin secretion by GLP-1 receptor activation.
- Conversely, **low fasting C-peptide** indicates diminished β -cell reserve and predicts a smaller achievable glycaemic response.
- **Longer diabetes duration** is associated with progressive β -cell loss and reduced glycaemic responsiveness.
- Weight-loss response may remain relatively preserved despite reduced glycaemic responsiveness in patients with advanced T2D.

Endogenous GLP-1 and Microbiome Effects in T2D

- **Endogenous GLP-1 secretion** is impaired in many patients with established **T2D**.
- Pharmacological GLP-1RA therapy can therefore provide important incretin activity beyond physiological GLP-1 exposure.
- However, **glucotoxicity** and impaired receptor-level or post-receptor signalling may partially limit this therapeutic advantage.
- **Gut microbiome** composition may also modify glycaemic response specifically in T2D.
- In a pilot study of 52 patients, microbial beta diversity differed significantly between glycaemic responders and non-responders ($p=0.004$).
- **Higher baseline Bacteroides** abundance correlated with greater HbA1c reduction, whereas **Prevotella copri** showed an inverse association.

PREDICTORS OF WEIGHT LOSS RESPONSE IN OVERWEIGHT/OBESITY WITHOUT T2D

Baseline Metabolic Phenotype and Body Fat Distribution

- **Baseline BMI** alone does not consistently predict the magnitude of percentage weight loss with GLP-1RA therapy.
- Patients with class III obesity may achieve lower percentage TBWL than patients with class I or II obesity.
- Potential **mechanisms** include greater hypothalamic leptin resistance, adipose inflammation, and altered gastrointestinal motility.
- Fat distribution may provide more useful information than BMI alone.
- Visceral adiposity, assessed by waist circumference or imaging, is metabolically active and may respond favourably to GLP-1RA-induced caloric restriction.
- Greater visceral fat may therefore be associated with greater cardiometabolic benefit for a given amount of weight loss.

Thyroid Function as a Potential Predictor

- **Subclinical and overt hypothyroidism** may negatively influence weight-loss response to GLP-1RA therapy.
- Thyroid hormone deficiency **reduces thermogenesis and basal metabolic rate** and may promote fluid retention.
- Altered gastrointestinal motility may also modify the pharmacodynamic effects of GLP-1RAs.
- Preclinical studies suggest that **triiodothyronine can increase GLP-1 production** and enhance its glucose-lowering effects.
- These findings provide a biological rationale for considering thyroid function when evaluating an apparently poor weight-loss response.
- Assessment of thyroid function before GLP-1RA initiation is reasonable, although prospective evidence linking hypothyroidism to treatment non-response remains limited.

Neuroendocrine and Hypothalamic Integrity

- The hypothalamus, **particularly the arcuate nucleus**, is a major anatomical substrate for GLP-1RA-mediated appetite suppression.
- **Severe obesity** is associated with **hypothalamic inflammation, including reactive gliosis and microglial activation**.
- Quantitative MRI studies have demonstrated hypothalamic gliosis in individuals with higher BMI and greater insulin resistance.
- **Neuroinflammation** may theoretically **impair** the response of hypothalamic circuits to anorexigenic GLP-1 signalling.
- However, the hypothesis that hypothalamic gliosis predicts GLP-1RA non-response has not been prospectively tested in humans.
- Neuroimaging-based hypothalamic integrity therefore remains a mechanistic research concept rather than a validated clinical predictor.

Hedonic Eating and the Food-Reward System

- GLP-1 receptors are expressed within the **mesolimbic dopamine reward system** and influence food reward independently of hypothalamic pathways.
- Individuals **with high food-reward sensitivity** may exhibit particularly **strong responses** to the anti-reward effects of GLP-1RAs..
- **Emotional eating** driven by psychological distress may **be less responsive** when behavioural drivers are not adequately addressed.
- **Tools such as the TFEQ, DEBQ,** and Binge Eating Scale can characterize baseline eating-behaviour phenotypes.

However, prospective validation of these behavioural phenotypes as GLP-1RA response predictors remains incomplete.

Physical Activity, Lean Mass, and Energy Expenditure

- **Lean body mass** and physical activity influence **resting metabolic rate and total energy** expenditure during GLP-1RA therapy.
- Resistance training can improve preservation of lean mass during pharmacological weight loss.
- Maintaining lean mass helps preserve resting metabolic rate and may reduce the impact of adaptive thermogenesis.
- Highly sedentary patients may experience greater relative loss of lean mass during treatment.
- **Excessive lean-mass loss** may compromise **long-term metabolic flexibility** and increase susceptibility to weight regain after treatment discontinuation.
- Physical activity and resistance exercise should therefore be considered integral components of weight-management therapy rather than secondary interventions.

PREDICTORS RELEVANT ACROSS BOTH DIABETES AND OBESITY CONTEXTS

Adipokines and Gut Hormone Profiles

- **Baseline leptin** concentrations reflect adipose mass and **play a central role in hypothalamic energy regulation.**
- Markedly elevated leptin may indicate leptin resistance and potentially reduced hypothalamic responsiveness to anorexigenic signalling.
- **PYY and oxyntomodulin** act synergistically with GLP-1 to promote satiety **and reduce energy intake.**
- Their baseline concentrations have been less extensively studied as predictors of GLP-1RA response.
- The functional reserve of the enteroendocrine system may influence the ability to augment satiety signalling after treatment.
- These hormonal profiles remain promising but insufficiently validated biomarkers for routine response prediction.

Gut Microbiome and GLP-1RA Response

- The gut microbiome influences energy homeostasis, nutrient absorption, gut hormone secretion, and systemic inflammation.
- Microbial metabolites such as butyrate, propionate, and acetate can stimulate intestinal L-cell GLP-1 secretion through free fatty acid receptors.
- **SCFA-producing organisms**, including *Akkermansia muciniphila* and *Faecalibacterium prausnitzii*, may therefore influence endogenous GLP-1 tone.
- In T2D, higher baseline **Bacteroides** abundance has been associated with superior glycaemic response, whereas **Prevotella copri** has shown inverse associations.
- In obesity without T2D, a higher Bacteroides-to-Firmicutes ratio has been associated with greater short-term weight loss in some studies.
- GLP-1RAs may themselves remodel the microbiome, raising the possibility that early microbial changes could become intermediate biomarkers of treatment response.

Gastrointestinal Tolerance as a Response Signal

- Nausea, vomiting, and early satiety are common during GLP-1RA dose escalation.
- **Moderate nausea** and early satiety that do not require treatment interruption have been associated **with greater early weight loss** and **improved glycaemic control**.
- These symptoms may reflect engagement of gastric-emptying and vagal satiety pathways rather than simply nonspecific toxicity.
- Conversely, pre-existing delayed gastric emptying may increase gastrointestinal adverse effects and restrict achievable therapeutic exposure.
- **Genetic variation** in both **GLP1R** and **GIPR** has been associated with nausea and vomiting in the 2026 GWAS.
- Gastrointestinal symptoms should nevertheless be managed as tolerability issues and should not be intentionally pursued to promote weight loss.

Genetic Contribution to Gastrointestinal Tolerability

- **The 2026 GWAS** identified associations between GLP1R and GIPR variants and treatment-related nausea and vomiting.
- The **GIPR association was specific to tirzepatide** and was not observed with pure GLP-1RAs such as semaglutide or liraglutide.
- Individuals homozygous for risk alleles at both loci had an estimated 14.8-fold higher odds of tirzepatide-associated vomiting.
- However, the confidence interval was very wide at 6.2–35.8, indicating substantial imprecision due to the small subgroup size.
- The finding has not yet been replicated and should not currently be used as a basis for individual drug selection.
- Absolute risk differences and prospective validation will be more informative for future clinical counselling.

Psychosocial, Behavioural, and Lifestyle Predictors

- GLP-1RA weight loss depends substantially on **appetite suppression** and the resulting reduction in caloric intake.
- Baseline **dietary patterns** and the ability to adapt to altered hunger and satiety signals can therefore influence treatment outcomes.
- Highly processed, **calorie-dense diets** may attenuate weight loss when reward-driven eating persists despite pharmacotherapy.
- **Protein-rich and fibre-dense dietary** patterns may improve lean-mass preservation and support sustained weight reduction.
- **Behavioural readiness, self-efficacy, motivation, and previous dieting experiences** may provide clinically relevant information about treatment response.
- Concurrent psychiatric medications with weight-promoting effects may also attenuate weight loss and should be considered during treatment planning.

Sleep Apnea and Chronobiology

- Obstructive sleep apnea affects a substantial proportion of individuals with obesity and has important metabolic consequences.
- Intermittent hypoxia can disrupt circadian regulation, impair leptin sensitivity, increase ghrelin, and promote insulin resistance.
- These pathways may influence the metabolic environment in which GLP-1RA therapy operates.
- Tirzepatide has demonstrated significant improvements in obstructive sleep apnea severity in the **SURMOUNT-OSA trial**.
- Treatment of sleep apnea may therefore modify the metabolic factors contributing to impaired treatment response.
- Whether OSA represents a validated predictive phenotype for superior GLP-1RA response remains uncertain.

Sex Differences in GLP-1RA Response

- Clinical studies have reported greater average weight loss and HbA1c reduction in females than in males receiving GLP-1RAs.
- This difference appears more pronounced as treatment potency and overall weight loss increase.
- One proposed mechanism is sex-specific variation in **central GLP-1 signalling within appetite-regulating neural circuits**.
- Preclinical and cross-species data suggest possible differences in GLP-1-expressing neurons within the nucleus tractus solitarius.
- estrogen signalling may also interact with GLP-1 pathways and **modulate mesolimbic food-seeking behaviour**.
- These mechanisms remain incompletely established in humans and should therefore be considered biological hypotheses rather than validated clinical predictors.

PHARMACOGENOMIC AND GENETIC PREDICTORS



GLP1R rs10305420: The Leading Pharmacogenomic Signal

- The 2026 Nature **GWAS** identified the **GLP1R missense variant rs10305420** as significantly **associated with GLP-1 medication efficacy**.
- The association reached genome-wide significance with **a p-value of 2.9×10^{-10}** .
- Each copy of the effect allele was associated with approximately 0.76 kg of additional weight loss.
- Homozygous carriers lost on average more than 1.5 kg more than individuals without the effect allele.
- The effect size was small compared with the approximately 11-kg mean weight loss observed in the study.
- Therefore, rs10305420 is biologically informative but currently insufficient to justify individual-level genotype-guided prescribing.

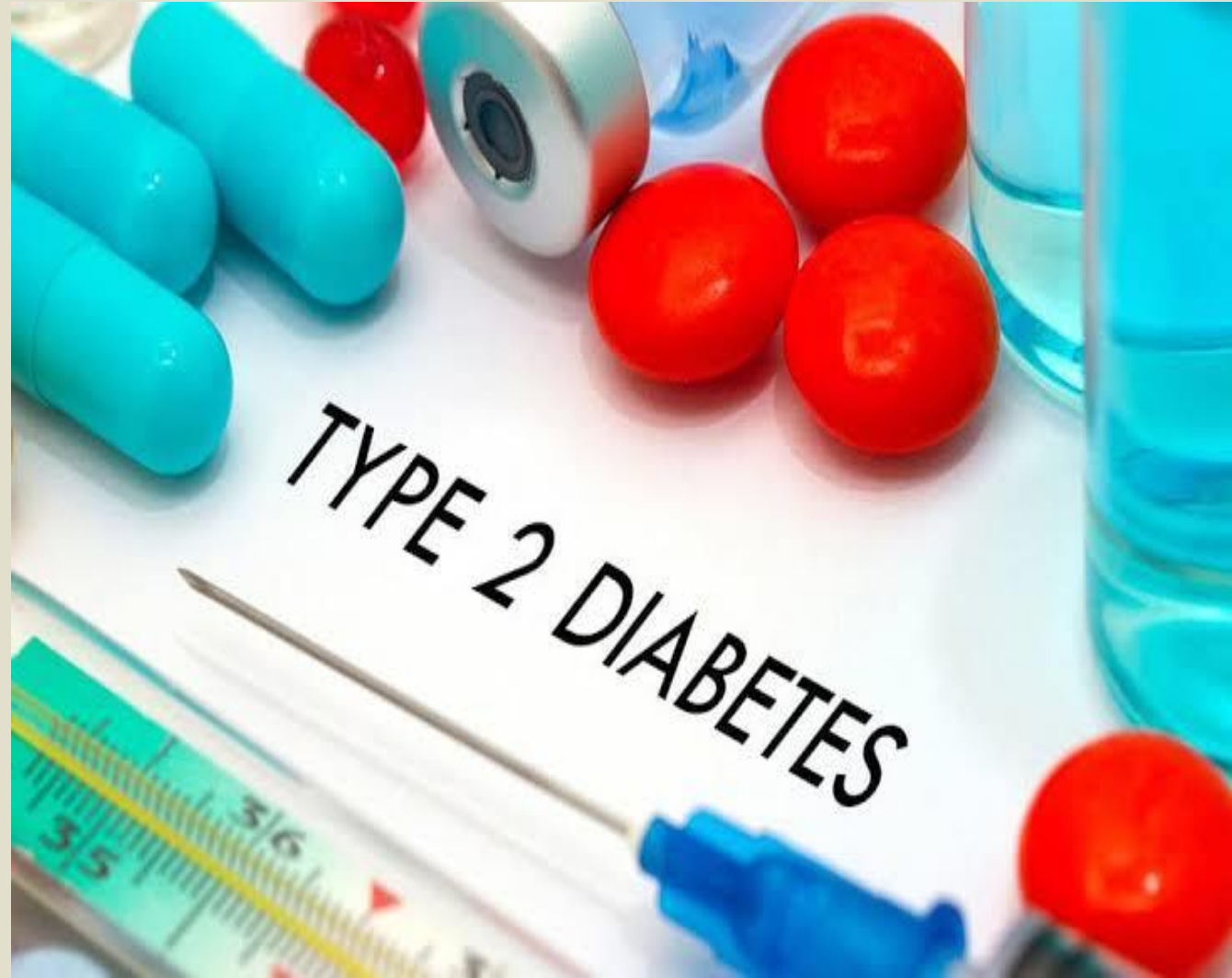
GLP1R and GIPR: Current Clinical Interpretation

- The **rs10305420** T allele occurs in approximately **40% of individuals** with European and Middle Eastern ancestry.
- The same allele has also been associated with lower T2D risk and lower fasting glucose in genetic studies.
- Earlier pharmacogenomic research focused mainly on the GLP1R rs6923761 (p.Gly168Ser) variant.
- The 2026 GWAS shifts current pharmacogenomic interest toward rs10305420 as a leading GLP1R candidate.
- Neither GLP1R nor GIPR genotyping is currently sufficiently validated for routine treatment selection.

FTO, MC4R, and Polygenic Risk

- Common obesity-associated variants in FTO and MC4R represent additional candidates for modifying GLP-1RA weight-loss response.
- **FTO variation** influences **food preference**, **reward-based eating**, and **hypothalamic energy regulation**.
- **MC4R** loss-of-function variants may partially disrupt **downstream hypothalamic anorexigenic** pathways targeted by GLP-1RAs.
- **Polygenic risk scores** may eventually provide **greater predictive information** than individual single-nucleotide variants.
- Future pharmacogenomic studies will require very large and ethnically diverse cohorts to improve generalizability.
- Separate genetic analyses of weight-loss and glycaemic endpoints will also be necessary because these represent biologically distinct response dimensions.

EARLY TREATMENT RESPONSE AS A COMPOSITE PREDICTOR



Early Response: The Most Actionable Predictor

- **Early change in weight or HbA1c** is currently among the most clinically actionable predictors of long-term GLP-1RA response.
- SCALE and STEP trial programmes consistently demonstrate strong associations between weeks 12–16 outcomes and later treatment response.
- Patients achieving at least 5% TBWL by week 16 are substantially more likely to achieve clinically meaningful long-term weight loss.
- Patients failing to reach this threshold have a low probability of eventually achieving at least 10% TBWL.
- In T2D, early HbA1c improvement at approximately weeks 12–16 similarly correlates with 52-week glycaemic outcomes.
- Early treatment response therefore functions as a practical composite marker of multiple underlying biological and behavioural determinants.

What Does Early Response Capture?

- Early treatment response may integrate **several biological mechanisms** that are difficult to measure individually.
- These include GLP-1 receptor expression and signalling capacity, genetic variation, microbiome composition, and hypothalamic integrity.
- **Behavioural adaptability** and adherence also contribute directly to the early response trajectory.
- **Circulating biomarkers** measured **during weeks 4–8** may provide additional information about pharmacodynamic drug engagement.
- Candidate biomarkers include **PYY, GLP-1, GIP, ghrelin, CRP, IL-6, leptin, and adiponectin.**
- Early leptin reduction and increased circulating PYY are promising signals but require prospective validation before routine clinical use.

DRUG-SPECIFIC PREDICTORS AND AGENT SELECTION

Response Differs Across Incretin-Based Agents

- GLP-1 receptor agonists are not pharmacologically equivalent, and treatment response varies across agents.
- In **SURMOUNT-5**, tirzepatide produced **20.2% TBWL compared with 13.7%** with semaglutide at 72 weeks in obesity without T2D.
- Semaglutide 2.4 mg has also demonstrated significantly greater weight loss than liraglutide 3.0 mg over 68 weeks.
- **Both** semaglutide and tirzepatide provide **substantial glycaemic improvement in T2D**.
- Tirzepatide's dual GIP/GLP-1 activity may contribute additional weight and glycaemic effects through complementary mechanisms.
- These differences highlight the importance of considering both agent-specific pharmacology and individual response characteristics.

Pharmacogenomics and Future Agent Selection

- The emerging pharmacogenomic framework remains exploratory because current genetic effect sizes are small and largely unreplicated.
- The **GLP1R rs10305420 efficacy** signal may **influence** response to both **semaglutide and tirzepatide**, but the magnitude is insufficient to select therapy for an individual patient.
- GIPR variants may eventually help explain differential gastrointestinal tolerability with tirzepatide.
- The April 2026 approval of **oral orforglipron** introduces an additional pharmacological context for studying receptor-specific genetic effects.
- It remains unknown whether the rs10305420 association will generalize to **small-molecule GLP-1R agonists**.
- Future therapies may further expand this landscape through GLP-1/GIP/glucagon triple agonism and combination approaches involving amylin or melanocortin pathways.

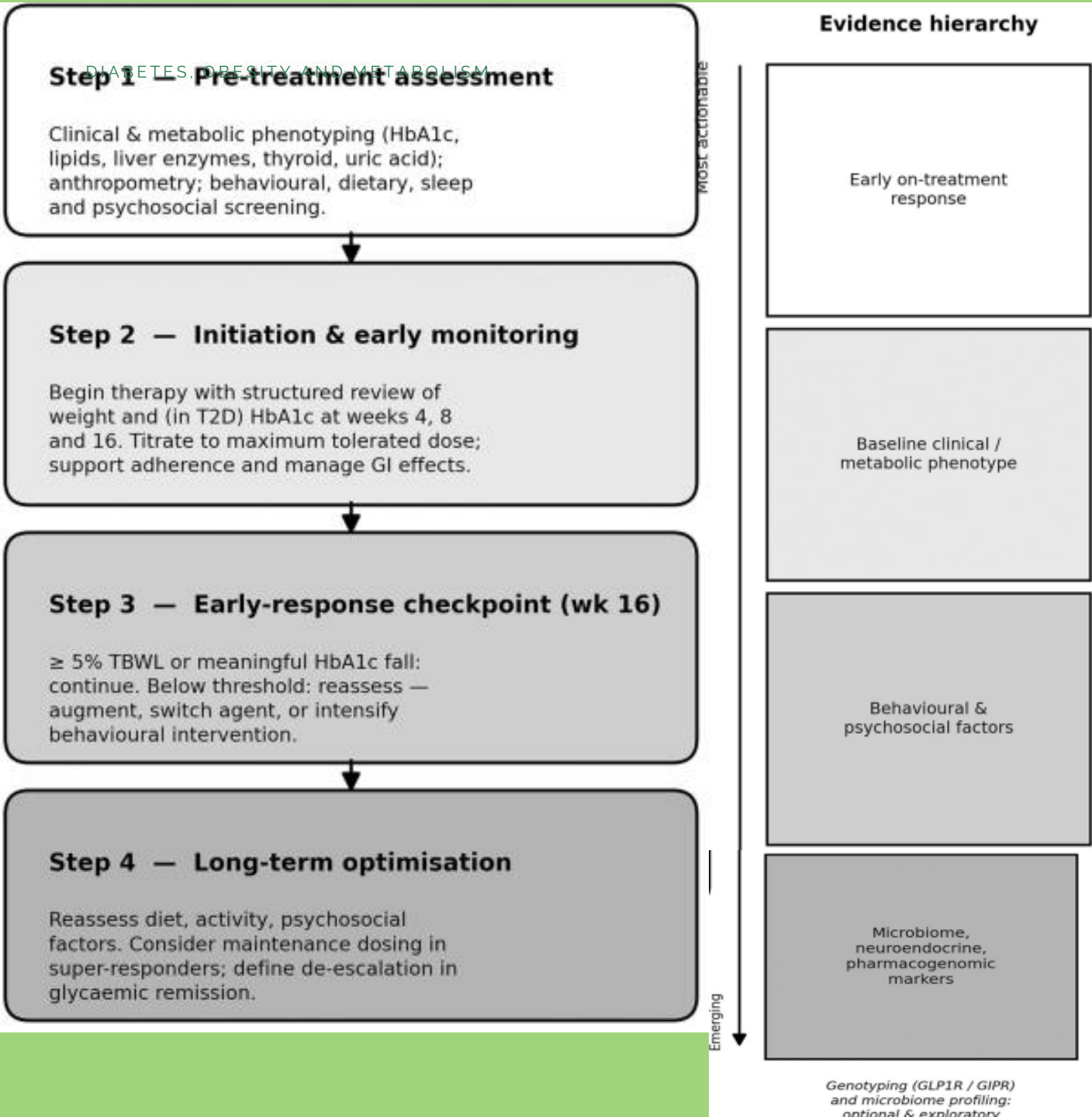
PROPOSED FRAMEWORK FOR CLINICAL APPLICATION

Structured Early Monitoring

- Treatment response should be **assessed** systematically during **the first 16 weeks** of therapy.
- **Weight and treatment tolerance** should be evaluated at approximately **weeks 4, 8, and 16**.
- In patients with T2D, HbA1c should be incorporated into the early-response assessment.
- Failure to achieve at least 5% TBWL or a clinically meaningful HbA1c reduction by week 16 on the maximum tolerated dose should prompt reassessment.
- Potential strategies include treatment optimization, agent switching, or intensification of multidisciplinary behavioural intervention.
- Genetic findings alone should not currently provide an independent indication for changing therapy.

Long-Term Optimization and Practical Limitations

- Long-term management requires periodic reassessment of **dietary quality, physical activity, psychosocial factors**, and **treatment response**.
- Patients achieving more than 20% TBWL or near-normal HbA1c may represent distinct phenotypes requiring individualized maintenance strategies.
- Pharmacogenomic testing is currently limited by accessibility, reimbursement, guideline adoption, and small predictive effect sizes.
- Microbiome-based prediction faces additional challenges involving **sampling, sequencing, analytical standardization**, and **population variability**.
- **Neuroimaging biomarkers remain research tools** rather than routine clinical assessments.
- At present, careful clinical phenotyping and structured early-response monitoring are the most readily implementable components of individualized therapy.



Proposed framework for individualised GLP-1RA therapy

Applicable across all three clinical contexts:

FIGURE 1 | Proposed framework for individualised GLP-1RA therapy across the three clinical contexts (type 2 diabetes, obesity without type 2 diabetes, and obesity with type 2 diabetes), shown in greyscale. The framework comprises pre-treatment clinical and metabolic phenotyping with behavioural and psychosocial screening (Step 1), treatment initiation with structured monitoring of weight and HbA1c at weeks 4, 8 and 16 (Step 2), an early-response checkpoint at week 16 (Step 3), and long-term optimisation (Step 4). The accompanying evidence hierarchy ranks predictors from those that are most readily actionable today (early on-treatment response and baseline clinical/metabolic phenotype) to those that remain emerging or research-grade (microbiome, neuroendocrine, and pharmacogenomic markers). Genotyping for GLP1R and GIPR variants and microbiome profiling are shown as optional and exploratory rather than routine, reflecting their small effect sizes, lack of replication, and limited accessibility and standardisation.

FUTURE DIRECTIONS



Toward Multimodal Response Prediction

- Future precision medicine approaches will likely integrate **genomic, metabolomic, microbiomic, and neuroimaging data**.
- These multimodal models could be developed separately for **diabetes, obesity, and combined metabolic disease**.
- Large-scale pharmacogenomic studies will be necessary to identify reproducible predictors of individual response.
- Future trials should distinguish genetic predictors of glycaemic response from those of weight-loss response.

Machine-learning models applied to real-world electronic health records may identify

- complex nonlinear interactions between biological and behavioural predictors.
- Development of validated clinical response-prediction tools remains a major priority for the field.

CONCLUSIONS

- Heterogeneous response to GLP-1-based therapy reflects the biological diversity of obesity, T2D, and their coexistence.
- Weight loss, glycaemic control, and broader metabolic benefits represent related but distinct treatment-response dimensions.
- **Non-responders and super-responders** may represent clinically meaningful **phenotypes** rather than simple statistical extremes.
- The 2026 Nature GWAS provides important proof-of-principle evidence linking GLP1R variation with treatment efficacy and treatment-limiting adverse effects.
- Current genetic findings remain insufficient for routine genotype-guided prescribing because effect sizes are small and replication is lacking.
- **Until stronger biomarkers become clinically validated, early on-treatment response remains the most practical tool for individualizing GLP-1-based therapy.**

Thank you

