M5.1 — Phenotype to Peptide Decision Matrix

Phenotype to Peptide Decision Matrix

Use: Point-of-care selection tool for matching weight-management peptide class to patient phenotype. **Companion to:** the M5.1 video lesson (Patient Phenotyping for Protocol Selection) + M5.2–M5.10 compound-specific lessons + Doc 1 (Baseline Labs Checklist) + Doc 5 (Hormone-Optimization Peptide Reference Card). **Print:** Two pages, clinician reference. Phenotype self-report + lab pattern → mechanism class → specific agent.

How to use this document

1. Phenotype the patient using the M5.1 phenotype framework — lab pattern + hunger/satiety self-report + family history + body composition.
2. Find the patient's row in **View A** (the matrix) and read across the columns for the strength of fit per peptide class.
3. Open **View B** for the matching phenotype card — first-line agent, second-line, adjuncts, parallel interventions, pitfalls.
4. Cross-check the **Special Considerations** rows for population-level modifiers (pre-conception, CVD, MASH, sarcopenia, post-bariatric, compounded access).
5. Document phenotype assignment, agent rationale, and shared decision-making in the chart.

> ***Calibration note.*** *This matrix presents facts that map to peer-reviewed evidence and current guideline consensus (AACE 2025 ABCD per Nadolsky 2025 PMID: 40956256; Acosta 2021 phenotype-guided trial PMID: 33759389). It is a starting frame for clinical reasoning, not a substitute for it. Mixed phenotypes are the rule; first-line agents address the dominant driver, then adjuncts layer for secondary drivers as response shape emerges.*

VIEW A — The Matrix

Legend: - ★★★ first-line (evidence + guideline consensus support) - ★★ reasonable (mechanism-aligned; second-line or co-equal option) - ★ caution (use only with specific co-conditions; not the dominant lever for this phenotype) - — avoid / not the right class for this phenotype - — (n/a) reserved cells where source material does not define a clear position

Peptide-class columns: - **SC GLP-1 RA** — single GLP-1 receptor agonist, subcutaneous (semaglutide 2.4 mg / liraglutide 3.0 mg) - **Oral GLP-1** — oral semaglutide (Rybelsus) / orforglipron

(pre-FDA-approval; FDA NDA anticipated end-2025 obesity) - **GLP-1/GIP** — dual incretin coagonist (tirzepatide) - **GLP-1/glucagon** — dual agonist (survodutide; pre-FDA-approval; FDA Breakthrough Therapy for MASH) - **Triagonist** — GLP-1/GIP/glucagon (retatrutide; pre-FDA-approval; TRIUMPH Phase 3 active) - **Amylin** — cagrilintide / CagriSema (pre-FDA-approval; Novo regulatory dossier submitted) - **GH-axis** — CJC-1295/Ipamorelin / Tesamorelin (Egrifta SV / WR, FDA-approved HIV-lipodystrophy on-label; off-label for visceral fat in non-HIV) - **Adjuncts** — AOD-9604 / MOTS-c / GHK-Cu (skin laxity, M5.7)

Phenotype	SC GLP-1 RA	Oral GLP-1	GLP-1/GIP	GLP-1/glucagon	Triagonist	Amylin	GH-axis	Adjuncts
1. Appetite-Driven (Hyperphagic)	★★★	★★	★★★	★★	★★	★★	—	★
2. Metabolic / Insulin-Resistant	★★	★	★★★	★★★	★★★	★★	★	★
3. Hormonal / Age-Related	★★	★★	★★	★	★	★	★★★	★★
4. Stubborn-Fat / Plateau	★	★	★★	★★	★★	★★	★★	★★★
5. Mixed (most common)	★★★	★★	★★★	★★	★★	★★	★★	★★

Reading guide. Rows 1, 2, 3, 4 trace directly to the four-phenotype framework taught in M5.1. Row 5 reflects the Clinical Pearl that “most patients present as mixed phenotypes” — the default first-line for adults meeting guideline BMI/WRC thresholds with ambiguous labs is a GLP-1 RA (semaglutide 2.4 mg or tirzepatide titrated to tolerance) per ADA 2025/2026 + AACE 2025.

Pre-FDA-approval columns (GLP-1/glucagon, triagonist, amylin/CagriSema, oral non-peptide orforglipron). Regulatory-status precision: these stars represent the mechanism-class fit for the phenotype where Phase 3 evidence supports the direction; they are NOT a recommendation to prescribe a pre-approval compound today. They are tracking decisions for when FDA approval lands. For prescribing today, follow first-line in the FDA-approved columns (SC GLP-1 RA, GLP-1/GIP, GH-axis where on-label/off-label fit applies).

VIEW B — Per-Phenotype Detail Cards

Phenotype 1 — Appetite-Driven (Hyperphagic) Obesity

- **Primary driver.** Excessive caloric intake plus blunted satiety signaling at the hypothalamic/brainstem integration point.
- **Typical presentation.** Constant hunger, difficulty with portion control, emotional eating, food preoccupation between meals. "I'm always hungry / I never feel full / I think about food constantly" self-report is clinically actionable even when labs are normal.
- **Lab markers.** Elevated fasting insulin, elevated ghrelin-to-leptin ratio, otherwise unremarkable lipid panel at presentation.
- **First-line pharmacotherapy.** Semaglutide 2.4 mg SC weekly (Wegovy); titrate 0.25 → 0.5 → 1.0 → 1.7 → 2.4 mg/wk over ≥16 wk per label. Anchored to STEP 1 –14.9% at 68 wk (PMID: 33567185).
- **Second-line or higher-magnitude alternative.** Tirzepatide 2.5 → 5 → 7.5 → 10 → 12.5 → 15 mg SC weekly (Zepbound); SURMOUNT-5 head-to-head –20.2% vs sema –13.7% at 72 wk (PMID: 40353578). Wegovy HD 7.2 mg post-2.4 mg tolerance (FDA-approved March 2026) where additional magnitude is the goal.
- **Adjuncts to layer.** Amylin axis where central appetite suppression remains incomplete on GLP-1 alone (cagrilintide or CagriSema when FDA-approved; mechanism is additive — REDEFINE-1 CagriSema 22.7% vs sema-alone 16.1% vs cagrilintide-alone 11.8% per PMID: 40544433).
- **Parallel interventions.** Foundation nutrition with adequate protein (1.2–1.6 g/kg reference body weight) + resistance training (see M5.6 + Mozaffarian 2025 multi-society advisory PMID: 40445127). Behavioral / emotional-eating support where the food-preoccupation pattern is psychosocially mediated. Sleep + cortisol assessment (Doc 1 inflammation/adrenal add-ons).
- **Pitfalls / caveats.** MTC/MEN2 family history → absolute contraindication. NAION counseling for semaglutide (EMA "very rare" classification). Pancreatitis history → relative contraindication. Pre-conception planning → see Special Considerations row. Lean-mass loss fraction during weight loss (~20–30% of total loss; per Beavers 2025 PMID: 39996356) is universal across this phenotype; protein + resistance training is the foundation.

Phenotype 2 — Metabolic / Insulin-Resistant Obesity

- **Primary driver.** Insulin resistance, impaired glucose disposal, visceral adiposity, often with concurrent MASLD/MASH.
- **Typical presentation.** Central obesity, metabolic syndrome features, elevated HbA1c (5.7–6.4%), elevated triglycerides, low HDL, fatty liver on imaging.
- **Lab markers.** HOMA-IR > 2.5, triglycerides > 150, fasting glucose > 100, MASLD on imaging or elevated transaminases with NAFLD pattern.

- **First-line pharmacotherapy.** Tirzepatide 2.5 → 15 mg SC weekly (Mounjaro for T2D / Zepbound for CWM). SURPASS-2 T2D HbA1c superiority vs semaglutide 1 mg; SURMOUNT-1 −20.9% at 15 mg / 72 wk (PMID: 35658024). GIPR component adds weight-loss magnitude and adipose-metabolic effect beyond GLP-1R-only.
- **Second-line or contraindication alternative.** Semaglutide 2.4 mg SC where tirzepatide is contraindicated or access is constrained (still effective; lower magnitude). For T2D + ASCVD: semaglutide carries SELECT (HR 0.80 MACE; PMID: 37952131) and SUSTAIN-6 (HR 0.74; PMID: 27633186) — CV-evidence-base advantage today. For T2D + CKD: semaglutide FLOW. For MASH F2/F3: semaglutide ESSENCE FDA-approved Aug 2025 (PMID: 40305708) is the FDA-labeled option (tirzepatide MASH Phase 3 pending).
- **Phase-3-active tracking compounds for this phenotype.** Survodutide (GLP-1/glucagon; FDA Breakthrough for MASH; hepatic GCGR engagement drives fatty-acid β-oxidation; SYNCHRONIZE-1 topline ~16.6% at 6 mg / 76 wk per Boehringer disclosure April 2026; LIVERAGE F2/F3 + F4 Phase 3 recruiting). Retatrutide (triagonist; TRIUMPH-4 topline −28.7% at 12 mg / 68 wk per Lilly disclosure Dec 2025; Sanyal 2024 *Nat Med* Phase 2a MASLD substudy ~82% MRI-PDFF reduction at 12 mg per PMID: 38858523). Both pre-FDA-approval.
- **Adjuncts to layer.** MOTS-c as metabolic-flexibility adjunct (see M5.6; preclinical-strong + clinical-translation-thin). Tesamorelin off-label for visceral-fat-specific component where central adiposity persists post-GLP-1 (see M5.5 — note FDA label "weight neutral effect"; VAT redistribution mechanism, not total-weight reduction).
- **Parallel interventions.** Hepatology co-management for F2/F3 MASH on off-label tirzepatide. Non-invasive fibrosis assessment (Fibroscan / MRE / ELF) at clinically appropriate intervals. Lipid optimization. Glucose monitoring + HbA1c reassessment q3 mo (Doc 1 reorder cadence).
- **Pitfalls / caveats.** Tirzepatide MASH is off-label (Phase 3 in development per SYNERGY-NASH); semaglutide is the FDA-labeled MASH F2/F3 option. F4 cirrhosis: semaglutide Phase 2 (Loomba 2023 PMID: 36934740) did NOT meet primary fibrosis endpoint — direct hepatic GCGR engagement (survodutide, retatrutide) is the mechanism-rationale alternative pending Phase 3. Diabetic retinopathy: Buckley 2025 baseline-stratified retinopathy progression signal warrants ophthalmology baseline + co-management in patients with R1M1 retinopathy on rapid HbA1c improvement.

Phenotype 3 — Hormonal / Age-Related Obesity

- **Primary driver.** Declining GH/IGF-1, declining gonadal hormones (testosterone in men; estradiol in postmenopausal women), suboptimal thyroid signaling.
- **Typical presentation.** Gradual weight gain with age, loss of lean mass, fatigue, reduced exercise capacity, sarcopenia features on body composition.
- **Lab markers.** Low IGF-1, low free testosterone (men) or symptomatic perimenopausal/postmenopausal hormonal profile (women), suboptimal TSH/free T3, reduced lean mass on DEXA.

- **First-line pharmacotherapy.** GH-axis support — CJC-1295 (without DAC; Mod-GRF 1-29) + Ipamorelin (see M5.6). Both not FDA-approved; 503A compounding pathway with FDA Category 2 listing imposing jurisdictional variation. Tesamorelin (Egrifta SV 1.4 mg SC daily / Egrifta WR 2 mg SC daily) off-label for visceral-fat component in non-HIV populations (see M5.5; Falutz 2007 NEJM PMID: 18057338; Stanley 2014 JAMA PMID: 25038357). Integrate with hormonal optimization (TRT or HRT where clinically indicated and within scope — see Doc 5).
- **Second-line.** Sermorelin (older GHRH agonist; FDA approval as Geref withdrawn 2008 for manufacturing reasons; currently 503A compounding) where CJC/Ipamorelin access is constrained. GLP-1 RA layered for the weight-management indication with explicit lean-mass-preservation discipline.
- **Adjuncts to layer.** MOTS-c (see M5.6) for mitochondrial/metabolic-flexibility support. GLP-1 RA (semaglutide 2.4 mg or tirzepatide; tirzepatide's fat-to-lean ratio is modestly more favorable per Look 2025 pooled DEXA per PMID: 39996356) where weight-management indication coexists.
- **Parallel interventions.** Hormone-optimization workup per Doc 1 sex hormones panel + Doc 5 — TRT evaluation for hypogonadal men; perimenopause/postmenopause HRT discussion for women. Thyroid optimization if TSH/free T3 suboptimal. Resistance training + protein 1.2–1.6 g/kg as foundation against further lean-mass loss (per Mozaffarian 2025 PMID: 40445127) — particular attention to older adults and post-menopausal women per multi-society advisory. Cross-reference to Doc 5 for HPG-axis peptides (Kisspeptin-10, Gonadorelin) and inflammation/recovery peptides (BPC-157, Thymosin alpha-1) where chronic inflammation or post-injury recovery limits exercise capacity.
- **Pitfalls / caveats.** CJC-1295 *with DAC* (~8-day half-life, sustained tonic GH) vs CJC-1295 *without DAC* / Mod-GRF 1-29 (~30-min half-life, pulsatile) are not interchangeable — the lean-mass-preservation protocol uses the without-DAC pulsatile form. Tesamorelin contraindications: active malignancy, pregnancy (Category X), hypopituitarism. Tesamorelin label has explicit "weight neutral effect" Limitation of Use — counsel as VAT redistribution with cardiometabolic benefit, NOT total-weight reduction. CJC/Ipamorelin and MOTS-c clinical evidence for lean-mass preservation during GLP-1 weight loss is mechanism-strong but RCT-thin; Phase 3 RCT specifically testing these as GLP-1 adjuncts does not exist.

Phenotype 4 — Stubborn-Fat / Plateau Obesity

- **Primary driver.** Metabolic adaptation after prior weight loss; localized resistant adipose; reduced resting metabolic rate; defended set point post-induction-phase response.
- **Typical presentation.** Patient can't lose "the last 10–20 lb," history of yo-yo dieting, often already on GLP-1 RA with attenuated response, may be in maintenance phase post-induction loss.
- **Lab markers.** Often normal glucose / insulin / lipids but reduced RMR on indirect calorimetry where measured; lean-mass loss on DEXA where preservation has been incomplete.

- **First-line approach.** Mechanism-class escalation where induction-phase response on single GLP-1 is inadequate: single GLP-1 → dual GLP-1/GIP (tirzepatide) → triagonist (retatrutide when FDA-approved). Layer AOD-9604 as localized-lipolysis adjunct (see M5.5; Phase 2b development discontinued by sponsor 2007 — regulatory-status precision is *development-discontinued*, not "emerging"; clinical-translation evidence is limited).
- **Second-line.** Tesamorelin off-label for visceral-fat-specific stubborn-component (see M5.5) where central adiposity persists. Cycling protocols (12–16 wk on / 4–8 wk off) used in some off-label off-HIV contexts have NOT been demonstrated to sustain VAT-reduction effect through washout per Falutz 2008 AIDS extension (PMID: 18690162) — chronic therapy is the evidence-supported approach if VAT reduction is the goal.
- **Adjuncts to layer.** MOTS-c (see M5.6) for metabolic-flexibility / mitochondrial support. GHK-Cu topical-leading or topical-plus-injectable protocol for post-loss skin laxity that drives discontinuation in real practice (see M5.7 — lightest-evidence lesson in Module 5; mechanism-moderate + RCT-thin for the specific post-loss skin-laxity indication).
- **Parallel interventions.** Re-evaluate foundation interventions — protein adequacy, resistance-training adherence, sleep, cortisol, alcohol — many "plateaus" reflect drift in foundation discipline rather than true mechanism saturation. Lean-mass assessment via DEXA + functional measures (grip strength, 5-STS, SPPB per EWGSOP2 / AWGS). Body-contouring surgical referral for Grade 3–4 skin laxity (peptide protocols are cosmetic-adjunct layer, not substitute for surgical contouring at high laxity grade).
- **Pitfalls / caveats.** "Plateau" is often premature pattern-naming at 6–12 wk; true mechanism-saturation plateau is a >6 mo phenomenon on max-tolerated dose. AOD-9604 evidence base is preclinical (Level V) + Wilding 2004 narrative review (PMID: 15134286) noting Phase IIa trials were underway in 2002; no Phase 2b human obesity trial published in peer-reviewed indexed literature — counsel patients accordingly. STEP 4 extension (PMID: 33755728) + STEP 1 extension (PMID: 35441470) document substantial regain after discontinuation; plateau on continued therapy is qualitatively different from plateau-then-discontinue.

Phenotype 5 — Mixed (most common)

- **Primary driver.** Multiple drivers overlapping — most often appetite-driven + metabolic, or metabolic + age-related, or post-induction with residual appetite component.
- **Typical presentation.** Variable. Patients rarely present as a clean single-phenotype textbook case.
- **Lab markers.** Often partial signals across multiple panels — elevated fasting insulin AND low IGF-1 AND borderline TSH, etc. Family history of obesity / T2D / bariatric surgery raises pre-test probability of set-point-defended biology that responds to incretin first-line.
- **First-line pharmacotherapy.** Default for adults meeting guideline BMI/WRC thresholds = GLP-1 RA (semaglutide 2.4 mg or tirzepatide titrated to tolerance) with explicit acknowledgment that you are starting with the broadest-effect agent and will refine based on response shape over 6–12 mo (per ADA 2025/2026 + AACE 2025 PMID: 40956256).

- **Second-line.** Mechanism-class escalation (single GLP-1 → dual GLP-1/GIP → dual GLP-1/glucagon or triagonist when FDA-approved) based on response shape. Switch class rather than dose-escalate beyond max-tolerated when response stalls.
- **Adjuncts to layer.** Sequenced over 6–12 mo as secondary drivers emerge: GH-axis adjunct (CJC/Ipamorelin) for lean-mass-loss fraction; tesamorelin for residual visceral-fat component; MOTS-c for metabolic flexibility; AOD-9604 for stubborn-fat plateau; GHK-Cu for post-loss skin laxity. Amylin (cagrilintide/CagriSema) when FDA-approved for incomplete appetite suppression.
- **Parallel interventions.** Full Doc 1 baseline panel — thyroid + sex hormones + metabolic + inflammation — to identify rate-limiters that should be addressed in parallel. See Doc 5 for hormone-optimization peptide integration.
- **Pitfalls / caveats.** Don't over-promise. Don't layer adjuncts at initiation — let the GLP-1 backbone establish response shape first, then layer secondary mechanisms against the residual phenotype features. Document phenotype reasoning and shared decision-making explicitly — the 2025 multi-society advisory (PMID: 40445127) frames pharmacotherapy + lifestyle as the evidence-based standard, with the medication making the lifestyle change biologically achievable and the lifestyle change determining the quality of the loss (lean-to-fat ratio).

Special Considerations (Population-Level Modifiers)

These rows modify the matrix selection across all phenotypes for the specified population.

Pre-conception / reproductive-age women

- **GLP-1 RA washout intervals.** Semaglutide elimination t½ ~7 d → ~5 half-lives = ~35 d for substantial clearance; planned pregnancy → ≥2-month washout. Tirzepatide t½ ~5 d → similar washout discipline. **Liraglutide** t½ ~13 h → substantial clearance in ~2 d — the shortest washout in the class, operationally relevant for patients planning pregnancy in the next 3–6 months.
- **Pregnancy / lactation.** Parker 2025 pooled review (PMID: 40329607) of unplanned pregnancies in GLP-1 RA regulatory clinical trials reports relatively low congenital-abnormality incidence in a limited dataset; authors call for prospective pregnancy registries. Discontinue upon pregnancy awareness; semaglutide is not used during breastfeeding per current manufacturer labels.
- **Oral contraceptive interaction.** Tirzepatide's gastric-emptying delay can reduce OC absorption efficacy during titration. Counsel on backup contraception (non-oral methods) at initiation and during titration.
- **Tesamorelin.** Pregnancy = absolute contraindication (Category X).
- **Selection guidance.** For reproductive-age women planning pregnancy within 6 months: **liraglutide 3.0 mg SC daily (Saxenda)** is the GLP-1 RA option with the operationally shortest

washout. Plan ≥2-mo washout for semaglutide/tirzepatide before conception attempts.

Diabetic + cardiovascular disease (SELECT-eligible)

- **First-line.** Semaglutide carries the established CVOT evidence base — SELECT in obesity + CVD without T2D (HR 0.80 MACE; PMID: 37952131); SUSTAIN-6 in T2D + high CV risk (HR 0.74; PMID: 27633186); SOUL in T2D + ASCVD/CKD for oral 14 mg (HR 0.86; PMID: 40162642).
- **Tirzepatide CV evidence.** SUMMIT in HFpEF + obesity (HR 0.62 for CV death or worsening HF events; PMID: 39555826). SURMOUNT-MMO MACE outcomes trial active (NCT05556512); primary completion ~2027-10. Semaglutide remains the FDA-labeled MACE-reduction option for obesity + established CVD without diabetes (Wegovy MACE indication March 2024).
- **PAD.** Semaglutide 1 mg per STRIDE in T2D + PAD (PMID: 40169145) — claudication-walking-capacity indication.
- **Selection guidance.** SELECT-eligible patients → semaglutide 2.4 mg SC weekly as first-line; HFpEF + obesity → either tirzepatide (SUMMIT) or semaglutide (STEP-HFpEF program + 4-trial pooled HR 0.69 per PMID: 39222642) is supportable.

MASH / NAFLD

- **F2/F3 fibrosis (non-cirrhotic). Semaglutide 2.4 mg** is the FDA-labeled option (ESSENCE Phase 3; FDA approval Aug 15, 2025; 62.9% MASH resolution + 36.8% fibrosis improvement at 72 wk per PMID: 40305708). Resmetirom (Madrigal; thyroid hormone receptor-β agonist; FDA-approved 2024) is the non-GLP-1 FDA-labeled MASH option.
- **Tirzepatide MASH.** SYNERGY-NASH Phase 2 (62% MASH resolution at 15 mg per PMID: 38856224) supports off-label use with hepatology co-management; Phase 3 in development; NOT FDA-labeled for MASH as of 2026-05-12.
- **F4 cirrhosis.** Semaglutide Loomba 2023 Phase 2 (PMID: 36934740) did NOT meet primary fibrosis endpoint (directionally toward placebo) — semaglutide is FDA-labeled F2/F3 only. Survodutide LIVERAGE-Cirrhosis F4 Phase 3 (recruiting) is the mechanism-rationale alternative pending readout; retatrutide TRIUMPH-MASH likewise pending.
- **Selection guidance.** F2/F3 → semaglutide 2.4 mg first-line (FDA-labeled); tirzepatide reasonable off-label where co-existing T2D/obesity indication anchors on-label prescribing and hepatology co-manages. F4 → track survodutide and retatrutide; current GLP-1 RA options do not have demonstrated fibrosis benefit in F4.

Older / sarcopenic patients (lean-mass preservation priority)

- **Lean-mass loss fraction during GLP-1 weight loss.** Look 2025 pooled DEXA: ~20–30% of total weight loss is lean mass (M5.6 §1.1; PMID: 39996356). Tirzepatide's fat-to-lean ratio is

modestly more favorable than semaglutide at equivalent total weight loss per the same pooled analysis — a consideration in sarcopenia-prone patient selection.

- **Functional assessment.** EWGSOP2 / AWGS prioritize muscle strength and physical performance over mass alone — grip strength, 5-STS chair-stand, SPPB (M5.6 §1.2). DEXA mass alone is necessary but not sufficient for sarcopenia diagnosis.
- **Foundation protocol.** Resistance training + protein 1.2–1.6 g/kg reference body weight + RDN nutrition referral per Mozaffarian 2025 multi-society advisory (PMID: 40445127) — load-bearing intervention against lean-mass loss. Particular attention to older adults and post-menopausal women per the advisory.
- **Peptide-adjunct layer.** CJC-1295 (without DAC; Mod-GRF 1-29) + Ipamorelin (M5.6 §2) on mechanism-rationale + practitioner-observation basis (research-state-incomplete per Pattern R; no Phase 3 RCT specifically tests these as GLP-1 adjuncts for lean-mass preservation). MOTS-c (M5.6 §3) for metabolic-flexibility / mitochondrial support.
- **Selection guidance.** Lower-magnitude GLP-1 (semaglutide 2.4 mg or tirzepatide titrated to tolerance, not necessarily to max 15 mg) with explicit lean-mass-preservation discipline. Slower titration pace. Functional re-assessment q3 mo (grip, 5-STS). Consider tirzepatide over semaglutide where fat-to-lean ratio advantage matters. Avoid pure caloric restriction without resistance-training foundation.

Post-bariatric / regain

- **Pattern.** Patients with prior bariatric surgery presenting with regain — set-point biology has reasserted; the surgical anatomic restriction is now insufficient to defend the reduced set point against metabolic adaptation.
- **First-line.** GLP-1 RA (semaglutide 2.4 mg or tirzepatide) titrated to tolerance — same first-line as non-bariatric patients meeting BMI/WRC thresholds. GI tolerability may differ from non-bariatric patients depending on anatomy (RYGB vs sleeve gastrectomy vs duodenal switch); titrate slowly.
- **Selection guidance.** Mechanism-class escalation logic same as Phenotype 4 (Stubborn-Fat / Plateau) — single GLP-1 → dual GLP-1/GIP → triagonist when FDA-approved. AACE 2025 ABCD Stage 2 framework supports bariatric-surgery evaluation as a co-equal intervention with high-effective-dose pharmacotherapy (PMID: 40956256). Coordinate with bariatric surgeon; assess for nutritional deficiencies (B12, iron, fat-soluble vitamins) before peptide initiation.
- **Pitfall.** Compounded GLP-1 use in this population without surgical-team coordination — unit-confusion + concentration-variance dosing errors carry higher AKI/dehydration risk in patients with altered GI anatomy. Per FDA Safety Alert MedWatch July 2024 / updated Dec 2024.

Compounded vs branded access

- **Post-shortage regulatory landscape.** Tirzepatide removed from shortage Oct 3, 2024; 503A enforcement discretion ended Feb 18, 2025; 503B ended Mar 19, 2025. Semaglutide

removed from shortage Feb 21, 2025; 503A ended Apr 22, 2025; 503B ended May 22, 2025. Compounding outside patient-specific clinical-need scenarios (e.g., excipient allergy, established clinical need the FDA-approved product cannot satisfy) is no longer in FDA enforcement discretion.

- **Pre-FDA-approval compounds (retatrutide, survodutide, orforglipron, CagriSema, IcoSema).** FDA-shortage-pathway 503A/503B routes are not available for pre-approval compounds. "Compounded retatrutide" preparations operate under different (research-use-only / non-FDA-regulated) pathways and are outside the operational framework developed for FDA-approved drug compounding.
- **Quality criteria** (see Doc 3 Compounding Pharmacy Quality Audit Checklist): sterility per USP <797>/<800>, per-batch certificate of analysis (peptide content, purity, residual solvents, endotoxin, salt-form), cold-chain shipping verification, state licensure or FDA 503B registration, PCAB or equivalent accreditation.
- **FDA Safety Alert — Dosing Errors in Compounded Semaglutide** (MedWatch July 2024 / updated Dec 2024). Unit-confusion (units vs mL vs mg), concentration variance (2.5 / 5 / 10 mg/mL in circulation), salt-form confusion (sodium/acetate mislabeled as base). Operational counseling: prescribe in mg not units; confirm concentration per dispensing pharmacy; counsel patients explicitly on concentration, volume, syringe type.
- **Selection guidance.** Branded FDA-approved formulation = default where insurance / cost / access permit. Patient-specific 503A compounding with documented medical necessity remains a legitimate clinical option in the post-shortage framework; document medical necessity, evaluate pharmacy quality, walk through reconstitution and dosing math at every prescription. Compliant patient-counseling phrasing: present operational facts neutrally for shared decision-making; do not lead with deficit framing about compounded preparations.

References

- M5.1 — Patient Phenotyping for Protocol Selection (the 4-phenotype framework + Clinical Pearls on mixed phenotypes + normal-labs default)
- M5.2 — Semaglutide deep dive
- M5.3 — Tirzepatide deep dive
- M5.4 — Liraglutide + comparator landscape (retatrutide, survodutide, orforglipron, cagrilintide, CagriSema, IcoSema)
- M5.5 — Tesamorelin + AOD-9604 visceral/adipose protocols
- M5.6 — Lean-mass preservation with CJC-1295/Ipamorelin + MOTS-c
- M5.7 — GHK-Cu post-loss skin laxity
- Acosta A et al. *Obesity (Silver Spring)* 2021;29:662-671. PMID: 33759389 — phenotype-guided AOM selection (15.9% vs 9.0% at 12 mo)
- Nadolsky K, Garvey WT et al. AACE 2025 ABCD Algorithm. *Endocr Pract* 2025;31(11):1351-1394. PMID: 40956256

- McGowan B, Ciudin A et al. EASO 2025 Framework. *Nat Med* 2025;31(10):3229-3232. PMID: 41039115
- Mozaffarian D et al. ACLM/ASN/OMA/TOS joint advisory. *Obesity (Silver Spring)* 2025;33(8):1475-1503. PMID: 40445127