PRE-RELEASE RESOURCE FOR SNACK THREE OF FOUR
RELEASING [DATE TBD]

Thinking in Phenotypes

A Clinician Lens for Evaluating Emerging Data

THE PHENOTYPE BREAKERS: HETEROGENEITY, SIGNALS & WHO MIGHT BENEFIT FROM WHICH BIOLOGY

CME OUTFITTERS

Obesity isn't one disease with one response. In this third CME Snack in the series, **Andres Acosta, MD, PhD**, joins series chair **Robert F. Kushner, MD** to explore how energy-balance phenotypes may explain why patients respond so differently to the same drug — and point to which biology fits whom. Here's the lens, and early signals on emerging amylin data beyond percent total body weight loss (%TBWL).

FOUR PHENOTYPES, FOUR BIOLOGIES

("best match" examples do not include amylin therapies in trials or newer glucagon-like peptide-1 [GLP-1] or GLP-1/glucose-dependent insulinotropic polypeptide [GIP] agents)

Hungry Brain *abnormal satiation*

"I go back for seconds and thirds — I just don't feel full."

High calories to fullness. Genetic variants in hypothalamic & brainstem appetite control — the brain doesn't register "stop."

BEST MATCH Phentermine–topiramate ER • 9% → 17% TBWL

Hungry Gut *abnormal postprandial satiety*

"I eat a normal meal and I'm hungry again an hour later."

Rapid gastric emptying; short-lived fullness. Two flavors — too little GLP-1 (type 1) or GLP-1 that doesn't signal (type 2).

BEST MATCH GLP-1 receptor agonists • 12% → 18% TBWL

Emotional Hunger *hedonic / reward eating*

"Good day or bad day, I'm driving through for a treat."

Eating to cope — stress, anxiety, reward overriding homeostatic signals. Flagged by validated eating/anxiety questionnaires.

BEST MATCH Naltrexone–bupropion • reward pathway

Slow Burn *abnormal energy expenditure*

"I barely eat and still can't lose."

Resting energy expenditure ~10% below predicted, with low muscle mass (sarcopenic pattern).

BEST MATCH High intensity interval training (HIIT) + resistance training • no drug yet

~85%	30→80%	≥ ⅓	2×
of energy-balance variability captured by 4 phenotypes	response rate with phenotype-matched selection	of patients carry 2+ phenotypes — treat the predominant one	weight loss in hungry-brain on phentermine–topiramate

BEYOND %TBWL — A READING LENS FOR EMERGING DATA

Total body weight loss matters — but on its own it hides who is actually helped. Read the coming amylin data through four questions:

1. **Appetite & satiation.** Is the drug doing, mechanistically, what its biology predicts?
2. **Durability.** Does the effect persist? Obesity is a chronic, relapsing disease.
3. **Cardiometabolic parameters.** Glucose, A1c, lipids, inflammatory markers (c-reactive protein [CRP]) — not just the scale.
4. **Who responds.** Which phenotype — and which sex? Response is heterogeneous, not average.

Widen the lens: every phenotype travels with a metabolic-burden profile — hypertension, insulin resistance, visceral adiposity — that shapes cardiometabolic risk and what "benefit" really means.

THE AMYLIN BRIDGE · HYPOTHESIS

Because amylin drives meal-ending satiation, Dr. Acosta hypothesizes that **hungry-brain patients** — who over-eat to fullness — may under-respond to their own amylin and could be super-responders to amylin-based therapy.

HYPOTHESIS — not yet tested in humans or animals

ON THE RADAR · AMYLIN SIGNALS

Cagrilintide	~11–12% TBWL · monotherapy (~16 mo)
CagriSema	~20–23% mean · Ph 3 REDEFINE
Preserved lean-mass/muscle strength - Ph 3A REDEFINE 1 DXA substudy	
Petrelintide	~11% · Ph 2 · tolerability ≈ placebo

Phenotype signals: heterogeneous response (clear super-responders) • women lost more than men (Ph 2).

INVESTIGATIONAL • preliminary — fuller data in Snack Four

PROGRAM COMING YOUR WAY...

FORMAT	~30 min video CME "Snack" — a moderated expert conversation
FACULTY	Andres Acosta, MD, PhD, with chair Robert F. Kushner, MD
AUDIENCE	Obesity-medicine, endocrinology, primary care & cardiometabolic clinicians (MD, nurse practitioner [NP], physician associate [PA], PharmD)

LEARNING OBJECTIVES

- Identify obesity phenotypes relevant to mechanistically targeted
- Anticipate how emerging amylin-based therapies may fit within a phenotype-guided framework

THE SERIES AHEAD — FOUR SNACKS, ONE ARC

SNACK ONE
The multi-pathway rationale
Lee M. Kaplan, MD, PhD

SNACK THREE (NOW)
Phenotypes & who benefits
Andres Acosta, MD, PhD

SNACK TWO
The biology of amylin
Matthew R. Hayes, PhD

SNACK FOUR
Emerging therapies & the data
W. Timothy Garvey, MD

Chaired throughout by **Robert F. Kushner, MD** — *Northwestern University Feinberg School of Medicine. Emerging amylin agents are investigational.*

In support of improving patient care, CME Outfitters, LLC, is jointly accredited by the ACCME, ACPE, and ANCC to provide continuing education for the healthcare team. Supported by an independent educational grant from Novo Nordisk, Inc.

Key references: Acosta A, et al. *Gastroenterology*. 2015;148(3):537-564.e4. • Acosta A, et al. *Obesity*. 2021;29(4):662-671. • Cifuentes L, et al. *Cell Metab*. 2025;37(8):1655-1666.e5. • Ravussin E, et al. European Congress on Obesity. 2026. Abstract No. AD04.04. https://karger.com/ofa/article-pdf/19/Suppl.%201/1/4536238/000551826.pdf. • Saba L, et al. *Nutrients*. 2026;18(2):303.