This activity may include discussions of products or devices that are not currently labeled for use by the U.S. Food and Drug Administration (FDA).

The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational uses (any uses not approved by the FDA) of products or devices.

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#3 of 4 modules:

Riding the Waves of Obesity Science

The Phenotype Breakers: Heterogeneity, Signals, and Who Might Benefit From Which Biology

This activity is supported by an independent educational grant from Novo Nordisk, Inc.

CMEO Snack

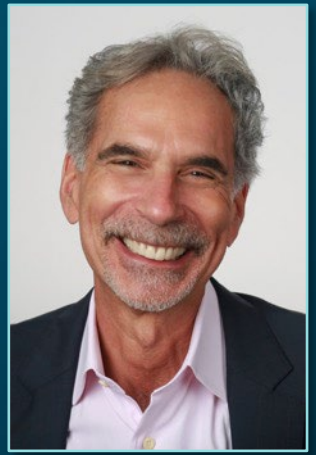
LEARNING OBJECTIVE 1

Identify obesity phenotypes relevant to mechanistically targeted pharmacotherapy

CMEO Snack

LEARNING OBJECTIVE 2

Anticipate how emerging amylin-based therapies may fit within a phenotype-guided framework



Robert F. Kushner, MD, MS, FACP, FTOS, DABOM

Professor Emeritus
Departments of Medicine and Medical Education
Northwestern University Feinberg School of Medicine
Chicago, IL



Andres Acosta, MD, PhD, DABOM

Professor of Medicine
Delaney Family Director, Nutrition Obesity Research Center
Director of Precision Medicine for Obesity Program
Consultant of Gastroenterology and Hepatology
Mayo Clinic
Rochester, MN

How do you define phenotype? How do phenotypes relate to response to therapy?

Phenotype: Interaction of Our Genes With Our Environment







GENOMICS

Our genes can suggest what diseases we *might* be predisposed to, but it's an incomplete picture of human health

PHENOTYPE

A snapshot of the current state of health that can be used to prevent, diagnose, and treat disease or improve health

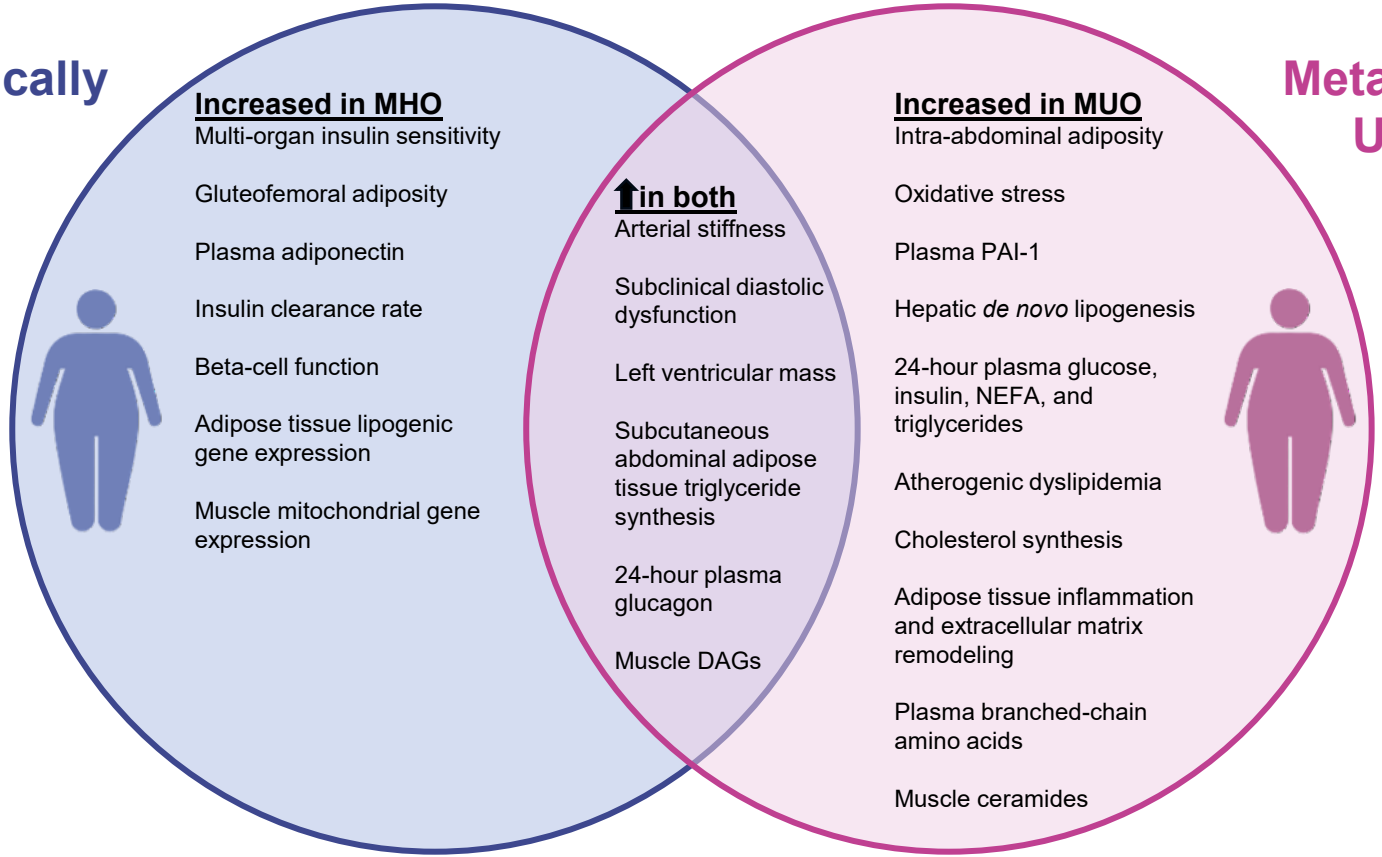
LIFESTYLE/ENVIRONMENT

External factors like diet, exercise, medications, microbiota, and even where we live influence our metabolic state

Tesfaye M, et al. *J Allergy Clin Immunol*. 2010;126(3):425-436. Rice JP, et al. *Adv Genet*. 2001;42:69-76.

CME OUTFITTERS

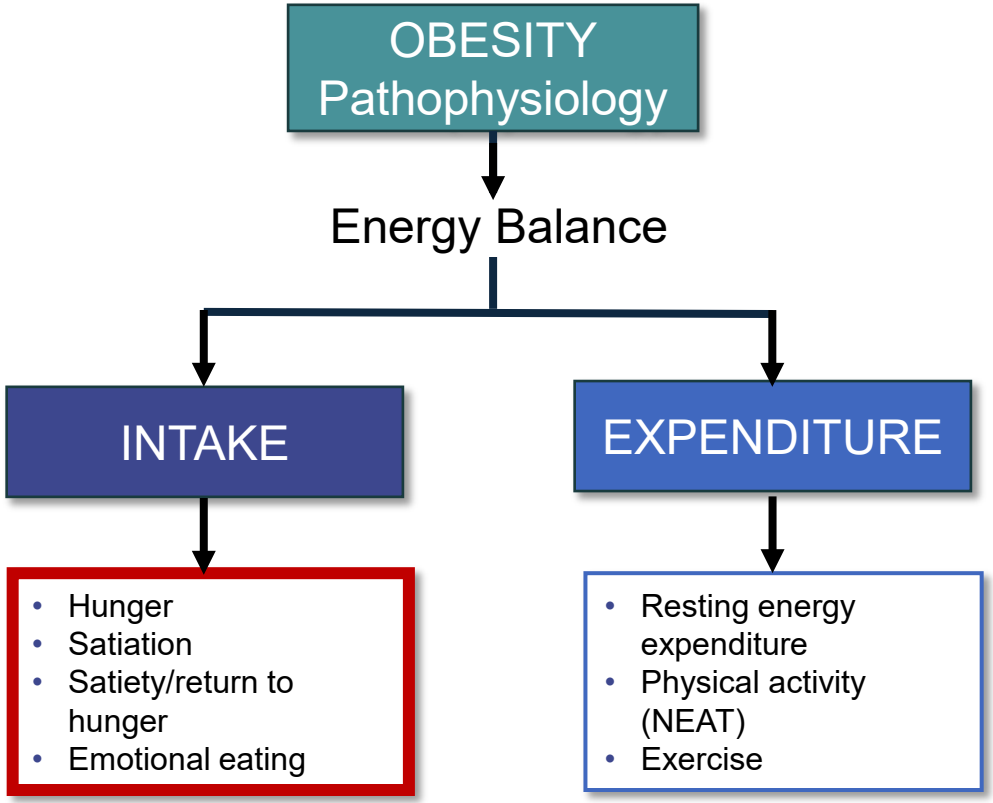
MHO vs MUO



DAGs = diacylglycerols; NEFA = non-esterified fatty acids; PAI-1 = plasminogen activator inhibitor-1.
Petersen MC, et al. *Cell Metab*. 2024;36:745-761.

CME OUTFITTERS

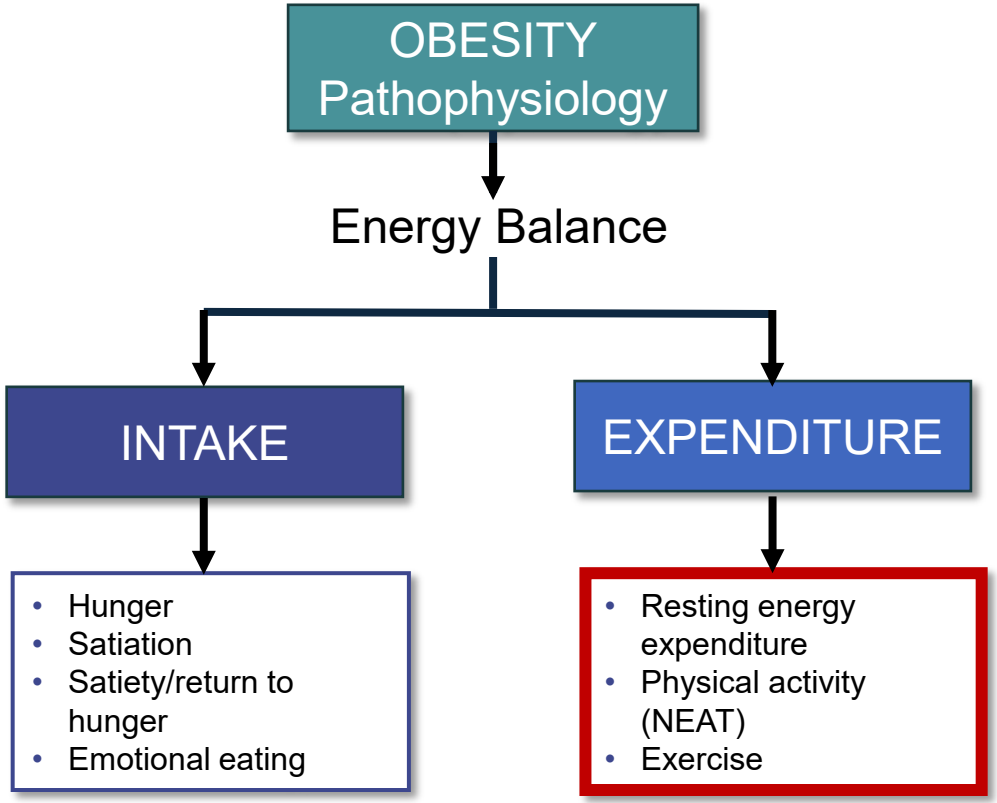
Obesity Phenotypes Based on Their Pathophysiology



NEAT = non-exercise activity thermogenesis.

CME OUTFITTERS

Obesity Phenotypes Based on Their Pathophysiology



NEAT = non-exercise activity thermogenesis.

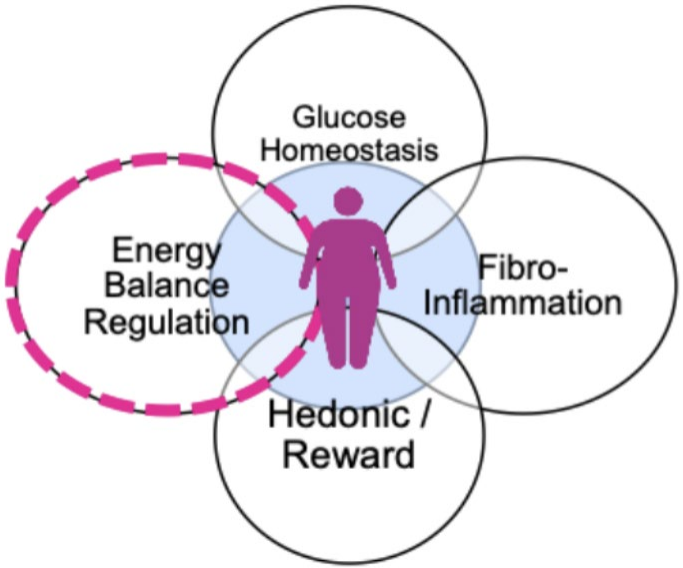
CME OUTFITTERS

Where does “reward eating” come in? Do you consider it part of the appetite or the satiety phenotypes?

Heterogeneity and Complexity of Obesity

Obesity-related Diseases

- Diabetes
- HTN
- CVD
- Cancer (some)
- +280 diseases



OMICS

- Exposomics
- Proteomics
- Metabolomics
- Epi-Genetics
- Genetics

Obesity Severity = BMI – Fat Mass

Social Determinants of Health

BMI = Body Mass Index; CVD = cardiovascular disease; HTN = hypertension; OMICS = fields of study.

Anazco D, Acosta A. *Int J Obes (Lond)*. 2025; 49:452-463.

CME OUTFITTERS

Heterogeneity of Obesity through Energy Balance Phenotypes



Acosta A, et al. *Gastroenterology*. 2015;148(3):537-546.e4. Anazco D, et al. *Int J Obes (Lond)*. 2025;49(3):452-463. Saba L, et al. *Nutrients*. 2026;18(2):303.

CME OUTFITTERS

How many of the patients you have seen have overlapping phenotypes?

Original Article
CLINICAL TRIALS AND INVESTIGATIONS

Obesity

Selection of Antiobesity Medications Based on Phenotypes Enhances Weight Loss: A Pragmatic Trial in an Obesity Clinic

Andres Acosta [1], *Michael Camilleri* [1], *Barham Abu Dayyeh*[1], *Gerardo Calderon*[1], *Daniel Gonzalez*[1], *Alison McRae*[1], *William Rossini*[1], *Sneha Singh*[1], *Duane Burton*[1], *and Matthew M. Clark*[2]

Objective: Little is known about the predictors of response to obesity interventions.

Methods: In 450 participants with obesity, body composition, resting energy expenditure, satiety, satiation, eating behavior, affect, and physical activity were measured by validated studies and questionnaires. These variables were used to classify obesity phenotypes. Subsequently, in a 12-month, pragmatic, real-world trial performed in a weight management center, 312 patients were randomly assigned to phenotype-guided treatment or non-phenotype-guided treatment with antiobesity medications: phentermine, phentermine/topiramate, bupropion/naltrexone, lorcaserin, and liraglutide. The primary outcome was weight loss at 12 months.

Study Importance

What is already known?

- Obesity is a chronic, relapsing, multifactorial disease, the prevalence of which continues to increase worldwide. Obesity is a remarkably heterogeneous disease, and sustained weight loss with current treatment paradigms remains a challenge in clinical practice.
- The heterogeneity among patients with obesity is particularly apparent in weight loss

Acosta A, et al. *Obesity (Silver Spring)*. 2021;29(4):662-671.

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Results: Four phenotypes of obesity were identified in 383 of 450 participants (85%): hungry brain (abnormal satiation), emotional hunger (hedonic eating), hungry gut (abnormal satiety), and slow burn (decreased metabolic rate). In 15% of participants, no phenotype was identified. Two or more phenotypes were identified in 27% of patients. In the pragmatic clinical trial, the phenotype-guided approach was associated with 1.75-fold greater weight loss after 12 months with mean weight loss of 15.9% compared with 9.0% in the non-phenotype-guided group (difference –6.9% [95% CI –9.4% to –4.5%], $P<0.001$), and the proportion of patients who lost >10% at 12 months was 79% in the phenotype-guided group compared with 34% with non-phenotype-guided treatment group.

Conclusions: Biological and behavioral phenotypes elucidate human

Study Importance

What is already known?

- Obesity is a chronic, relapsing, multifactorial disease, the prevalence of which continues to increase worldwide. Obesity is a remarkably heterogeneous disease, and sustained weight loss with current treatment paradigms remains a challenge in clinical practice.
- The heterogeneity among patients with obesity is particularly apparent in weight loss response to obesity interventions, such as diets, medications, devices, and surgery.
- Little is currently known about the predictors of response to obesity interventions.

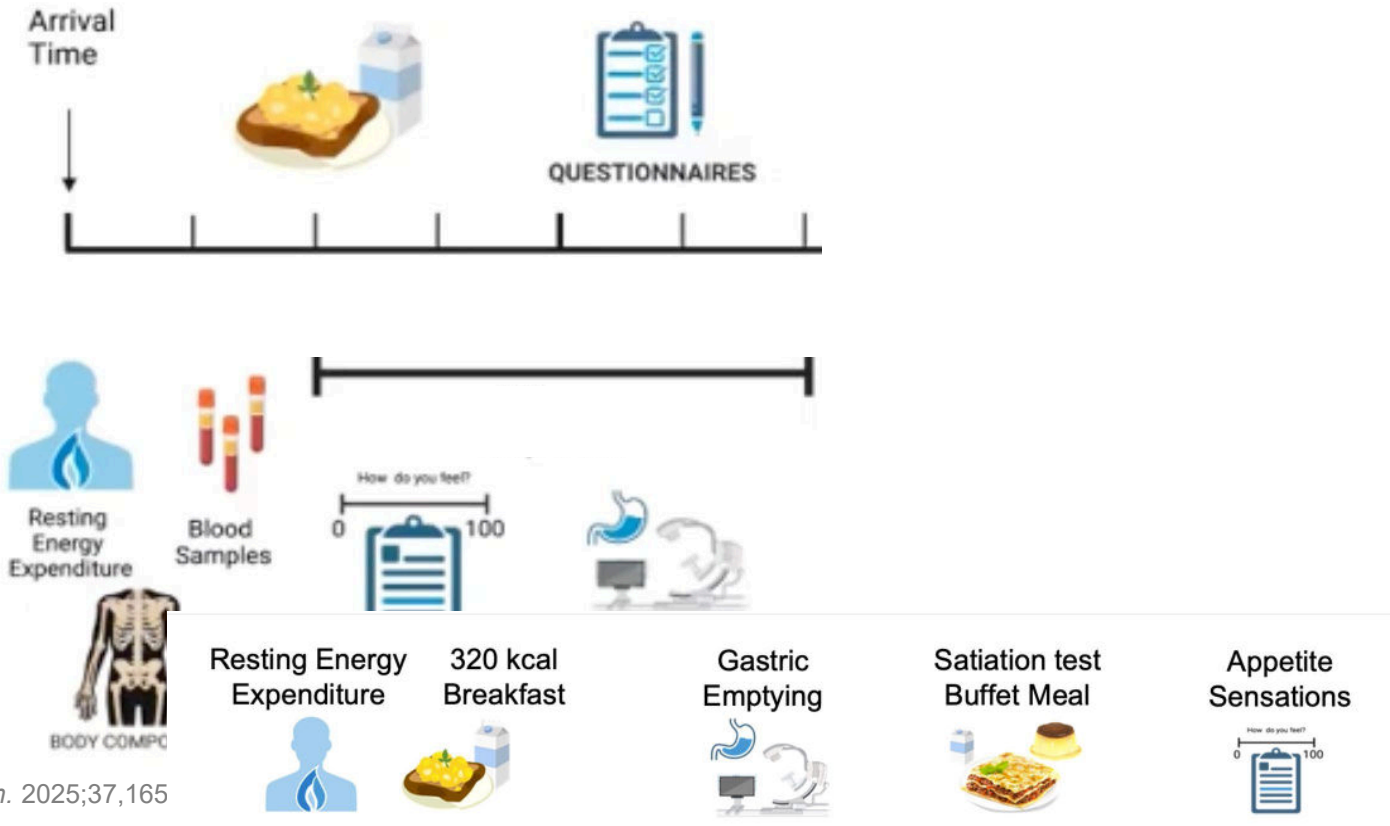
What does this study add?

- We stratified obesity into four phenotypes: hungry brain (abnormal satiation), emotional hunger (hedonic eating), hungry gut (abnormal satiety), and slow burn (decreased metabolic rate).
- In a clinical cohort prescribed antiobesity medication, the phenotype-guided

Acosta A, et al. *Obesity (Silver Spring)*. 2021;29(4):662-671.

Have you developed simplified methods to identify phenotypes versus those used in the scientific laboratory?

How Do We Phenotype Our Patients?



Cifuentes L, et al. *Cell Metabolism.* 2025;37,165

How can the practicing clinician identify these four phenotypes ?

How do results from phenotypic testing help tailor therapy for individual patients?

Precision Obesity: Cost-Effective-Phenotype Based Obesity Solution

LIFESTYLE INTERVENTION	• **Hungry brain diet**	• **Hungry gut diet**	• **Behavioral therapy** • **Hungry feelings diet**	• **Intense exercise plan** • **Slow burn diet**
MEDICATION	• Phentermine-topiramate ER	• Liraglutide • Semaglutide • Tirzepatide	• Bupropion-naltrexone SR	
ENDOSCOPY	• Vagal nerve block	• Intragastric balloons • Endoscopy sleeve gastroplasty		
SURGERY	• Laparoscopic sleeve gastrectomy	• Roux-en-Y gastric bypass		

ER = extended release; SR = sustained release.

Anazco D, Acosta A. *Int J Obes (Lond).* 2025; 49:452-463. Saba L, et al. *Nutrients.* 2026;18(2):303.

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Is it correct that by doing phenotypic selection, a patient is likely to lose more weight versus standard of care selection? Is this true across the other phenotypes, not just “hungry gut”?

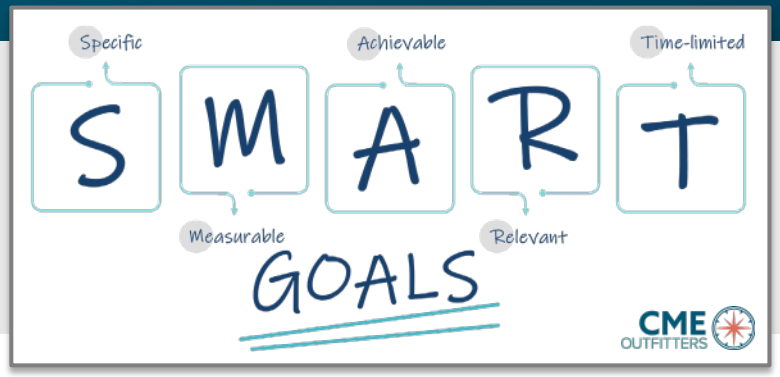
In your studies, have you seen females more responsive than males even using your phenotypic designations?

Can you comment on how amylin and other nutrient-stimulated gut hormones may play out in your phenotypic framework?

Key Takeways

- Consider phenotypes when assessing individual patients to target therapies
  - Hungry brain
  - Hungry gut
  - Emotional hunger
  - Slow burn
- New therapies and combinations are in development
- There will be heterogeneity regarding individual outcomes
  - Poor responders are not to be blamed!
  - The biology of a poor responder may not have been a good match for the medication
- Obesity is a recurrent, dynamic disease – phenotypes can evolve over time and as a result of metabolic adaptations

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Put information into action!

Takeaways from this program can be implemented into your practice to improve patient care.

- [example goal] *Incorporate latest clinical trial data* regarding ADCs into the care of your patients with HR+/HER2-neg mBC, as documented by treatment selection in electronic health record (EHR) patient charts.
- [example goal] *Provide ideal patient care* by taking the time focus on your patients to get to know them as a person and understand their unique needs while they receive therapy.

CMEO Snack

Other programs in this series include:

1. Riding the Waves of Obesity Science: A Multi-Pathway Rationale for the Next Therapeutic Current

2. The Satiety Current: Amylin Biology as a Systems Signal

4. Reaching the Shoreline: Emerging Amylin-Based Therapies and Trial Signals

To Receive Credit

To receive CME/CE credit for this activity, participants must complete the post-test and evaluation online.

Participants will be able to download and print their certificate immediately upon completion.