



National Institute of  
Diabetes and Digestive  
and Kidney Diseases

# What Does Personalized Obesity Treatment Look Like?

Susan Z. Yanovski, MD

Co-Director, Office of Obesity Research

National Institute of Diabetes and Digestive and Kidney Diseases

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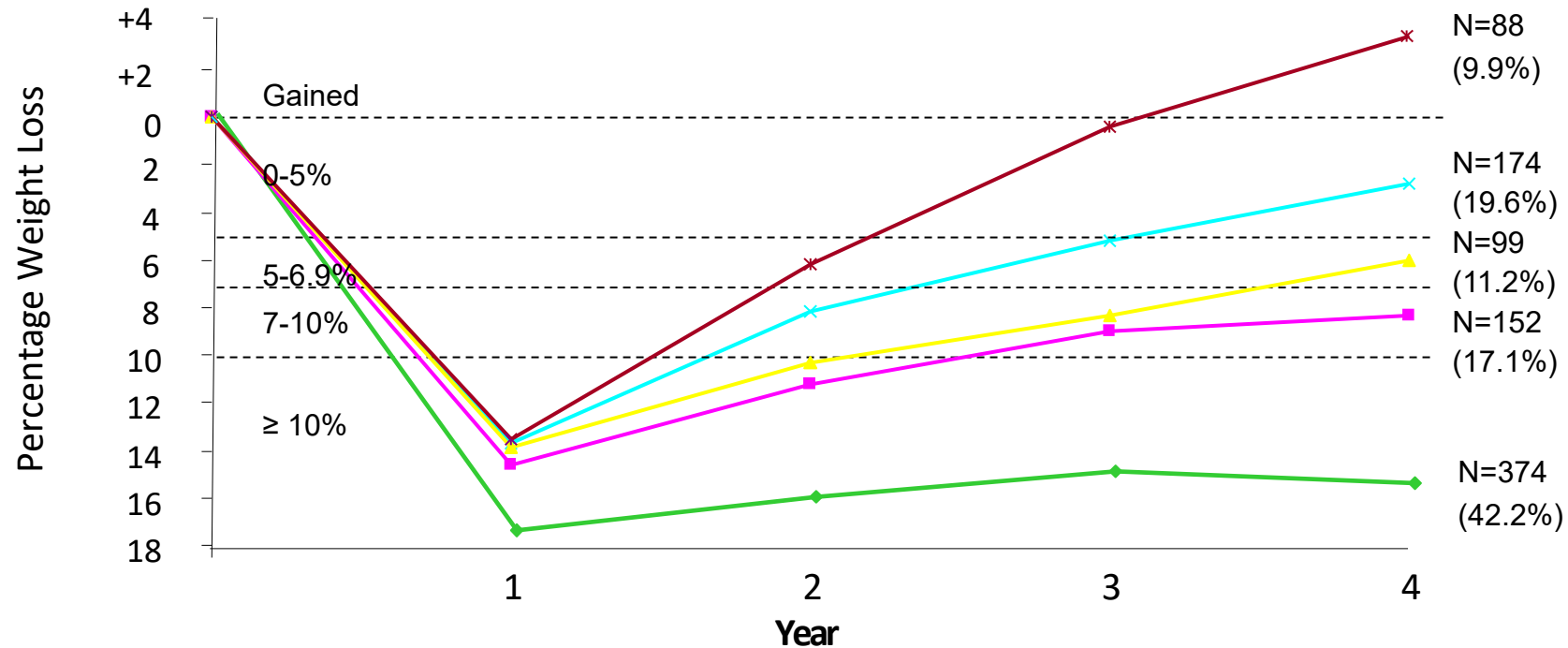
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# Obesity: One Size Does Not Fit All

- Heterogeneity in:
  - Risk for obesity development (across the lifespan)
  - Risk for development of complications of obesity
  - Response to treatment

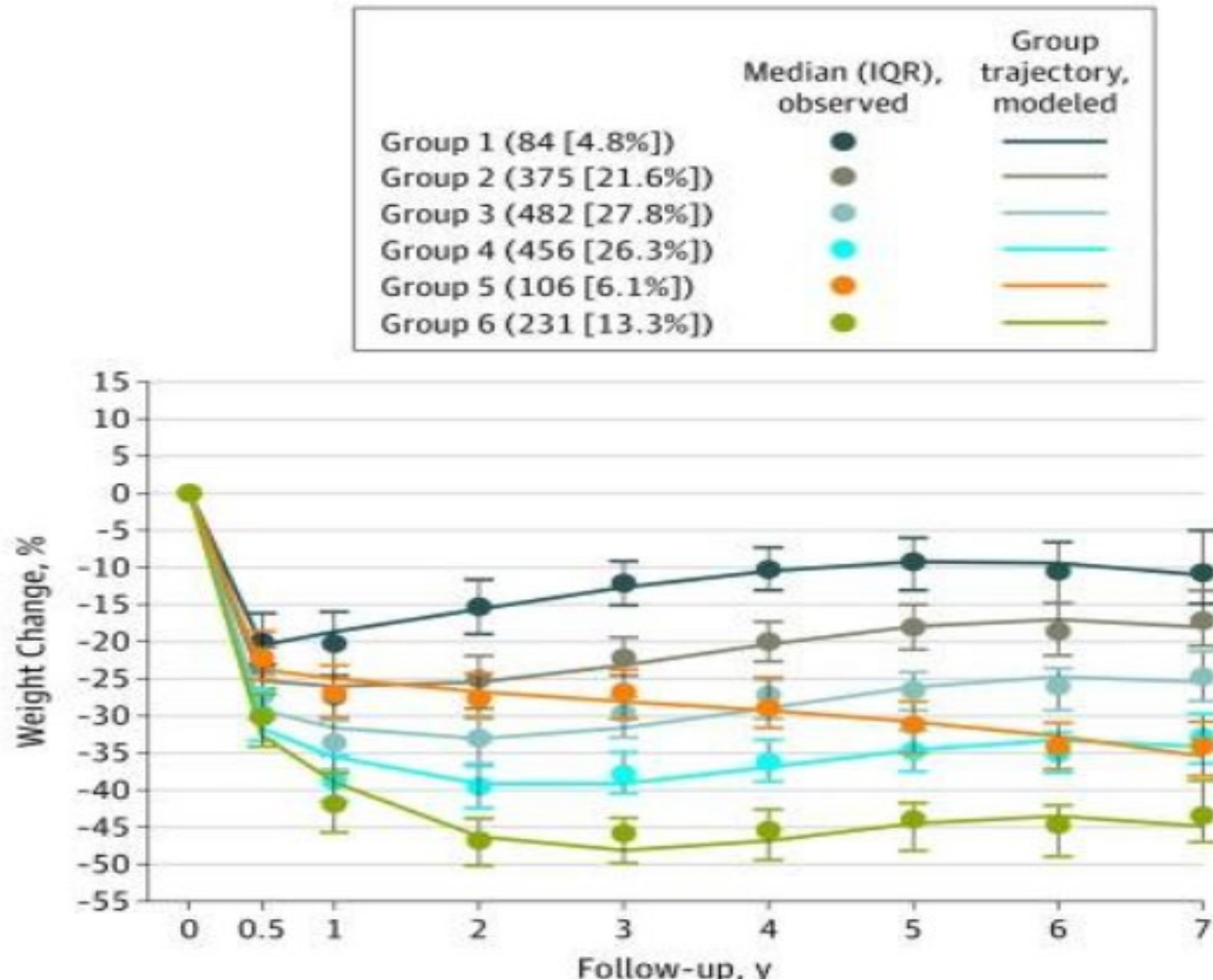
# Individual Variability with Lifestyle Treatment

4-Year Weight Loss Trajectories of 887 Intensive Lifestyle Intervention Participants Who Had  
Lost  
≥ 10% Initial Weight at Year 1



Data from Look AHEAD clinical trial. Wadden et al. Obesity. 2011.

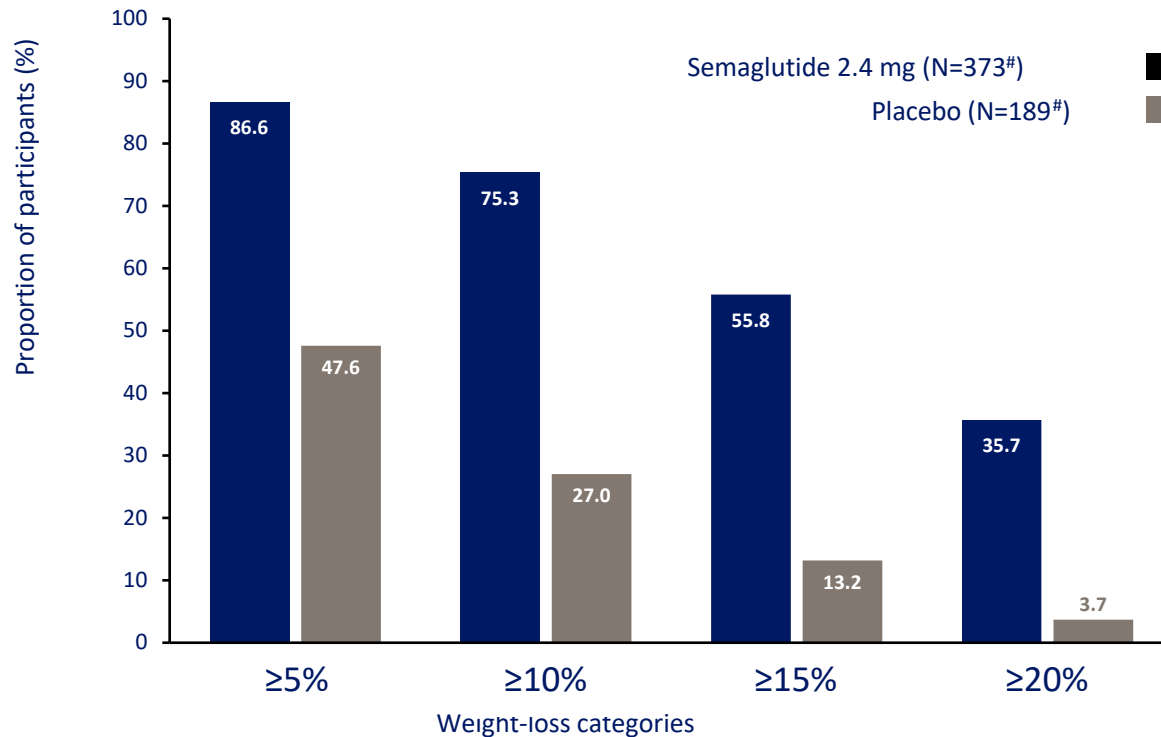
# Seven-Year Weight Trajectories after Roux-en-Y gastric bypass in the Longitudinal Assessment of Bariatric Surgery Study



*Six weight change trajectory groups were identified*

# Weight loss with semaglutide 2.4 mg plus intensive behavioral treatment

Observed weight-loss attainment at week 68: In-trial

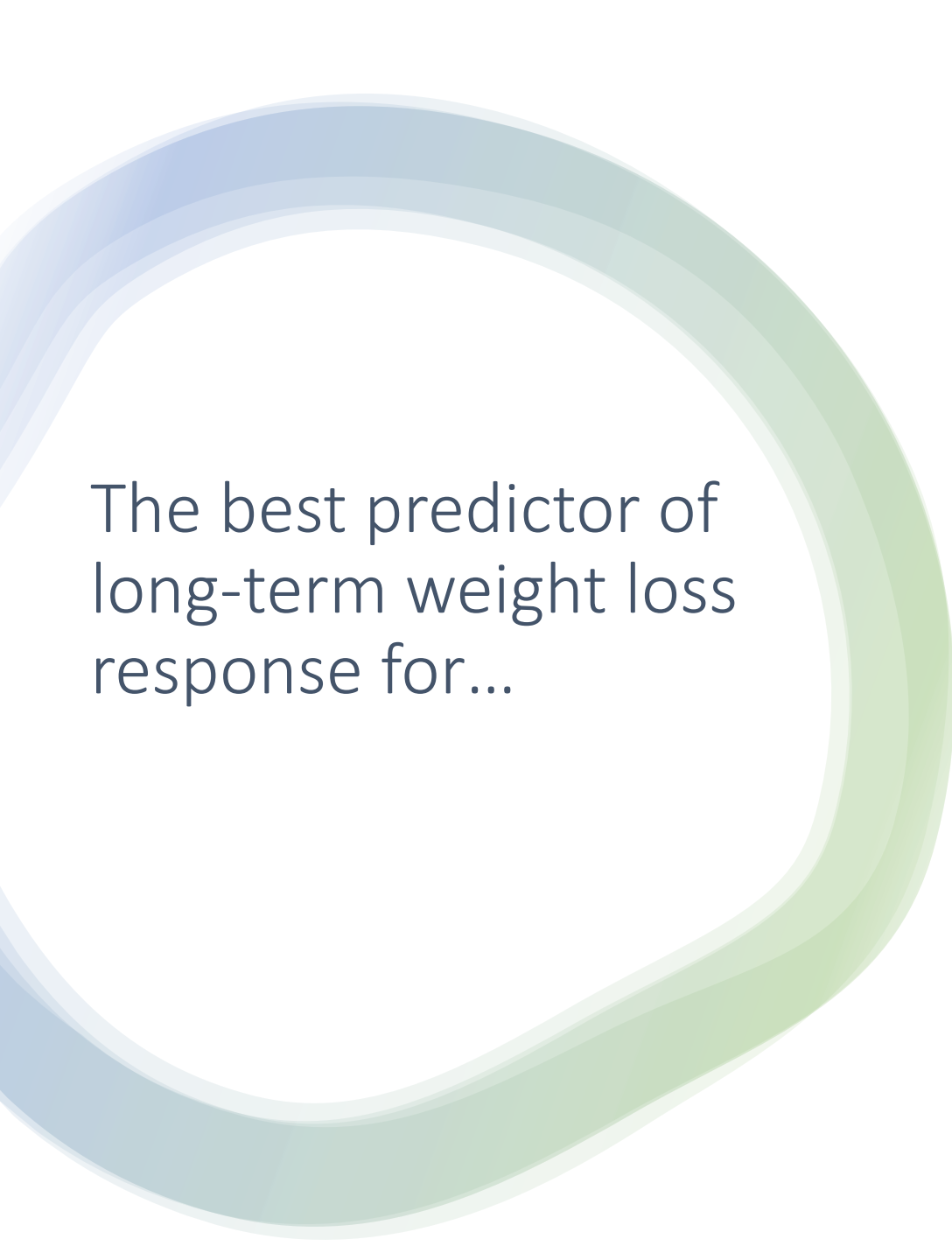


14% lost <5% Initial Weight

36% lost  $\geq 20\%$  Initial Weight

STEP3 Trial, Wadden et al. *JAMA*. 2021

Compared with placebo, participants in the semaglutide 2.4 mg group were more likely to achieve body weight reductions of  $\geq 5\%$  (co-primary endpoint),  $\geq 10\%$ ,  $\geq 15\%$ , and  $\geq 20\%$  (all  $p < 0.0001$ )



The best predictor of  
long-term weight loss  
response for...

**Lifestyle intervention** (*Unick et al., Curr Diab Rep, 2017; Gross et al., Obesity, 2019*)

**Bariatric surgery** (*Hindle et al., Obesity Reviews, 2017*)

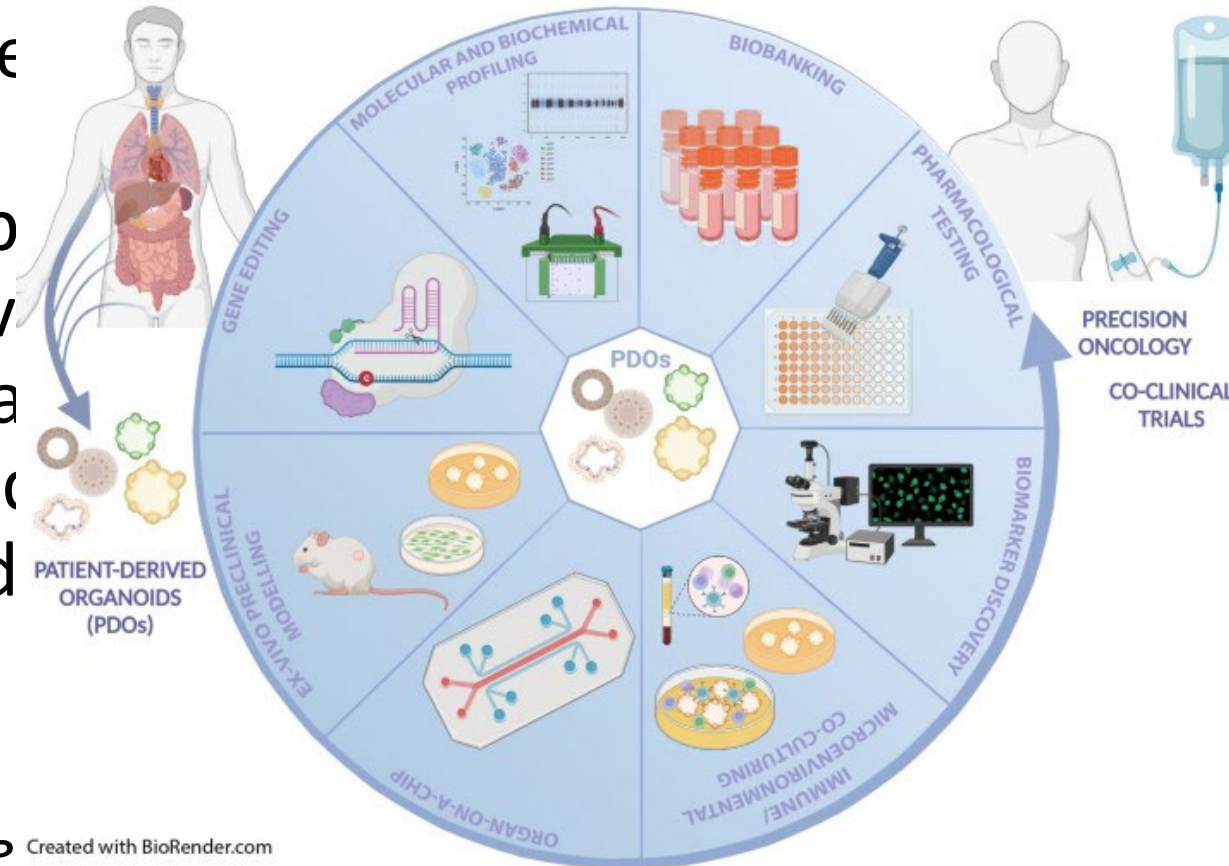
**Anti-obesity medications** (*Fujioka et al., Obesity, 2016, Mosenzon et al., J Endocri Soc, 2024*)

Is **early** weight loss (initial 2-3 months)

In polygenic obesity, no **baseline** behavioral, metabolic, genetic or other phenotypic characteristics can **consistently** predict response to a specific treatment

# “Precision” = “Personalized” Medicine

- “Precision medicine is personalized innovative approaches using genomic, environmental, and clinical data to guide decisions related to prevention, diagnosis, and treatment.”
  - NHGRI, NIH

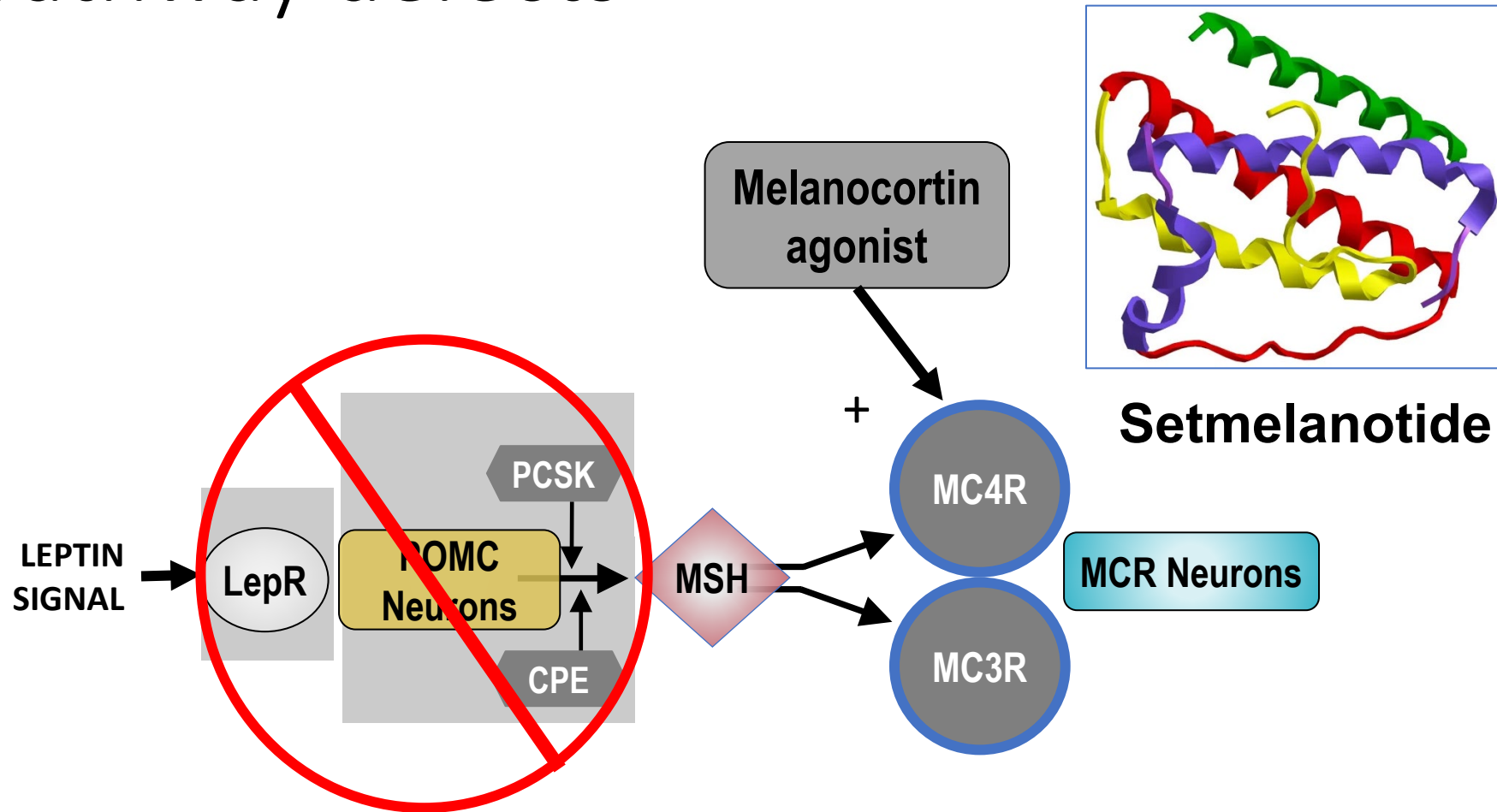


leads to an individual's guide to the goal of precision medicine approach for the

– “Getting the

RIGHT time”

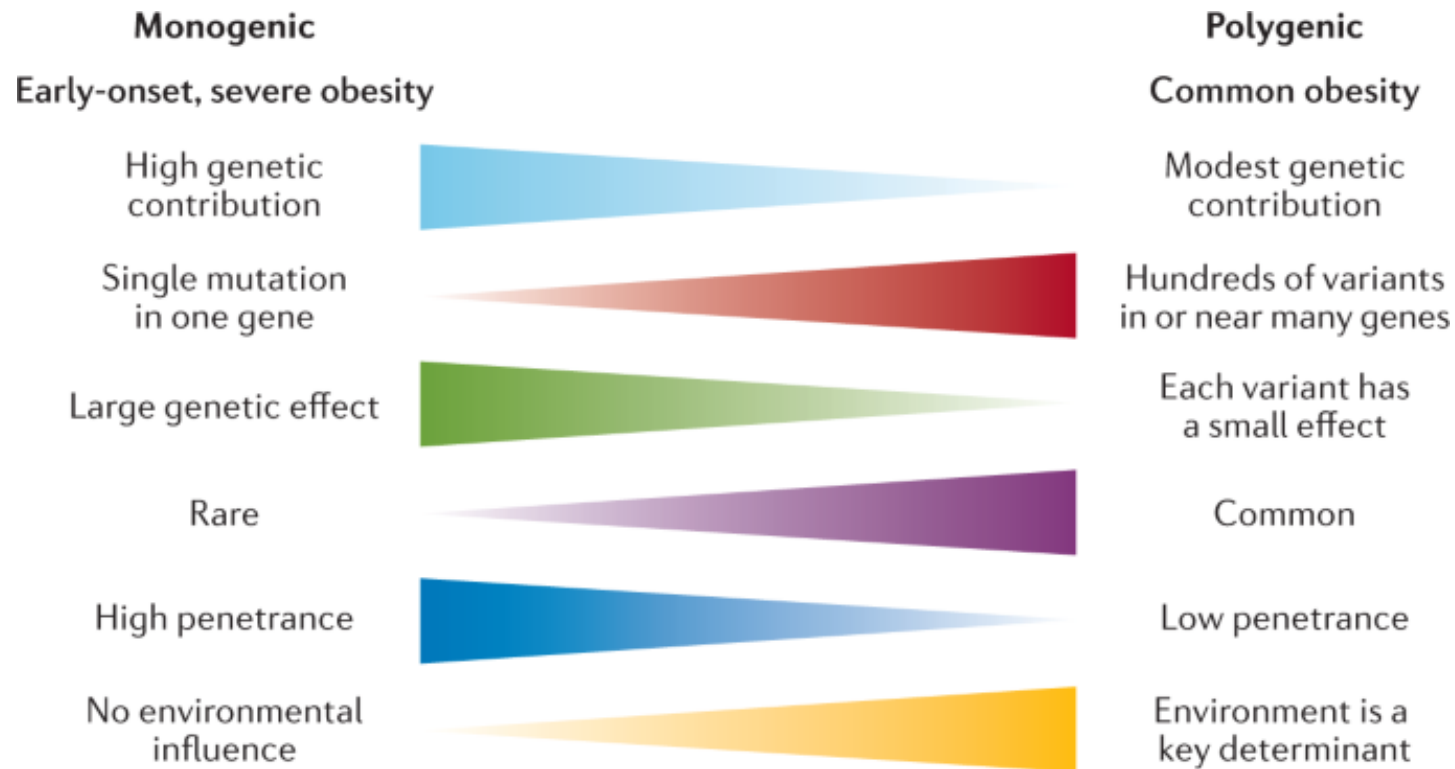
# Specific treatments for leptin signaling pathway defects



Approved in 2020 for age  $\geq 6$  with leptin receptor deficiency, POMC or PCSK1 deficiency, and Bardet Biedl Syndrome

**Disorders affecting leptin receptor action might respond to a melanocortin agonist**

# Most human obesity is polygenic...



Polygenic risk scores provides estimation of risk

>1000 loci identified

Environment critical, even with similar genetic risk

# Phenotype tailored lifestyle intervention on weight loss and cardiometabolic risk factors in adults with obesity: a single-centre, non-randomised, proof-of-concept study



Lizeth Cifuentes,<sup>a</sup> Wissam Ghusn,<sup>a</sup> Fauzi Feris,<sup>a</sup> Alejandro Campos,<sup>a</sup> Daniel Sacoto,<sup>a</sup> Alan De la Rosa,<sup>a</sup> Alison McRae,<sup>a</sup> Thom Rieck,<sup>b</sup> Sara Mansfield,<sup>b</sup> Jason Ewoldt,<sup>b</sup> Jamie Friend,<sup>b</sup> Karen Grothe,<sup>c,d</sup> Ryan J. Lennon,<sup>e</sup> Maria D. Hurtado,<sup>a,c</sup> Matthew M. Clark,<sup>a,c,f</sup> Michael Camilleri,<sup>a</sup> Donald D. Hensrud,<sup>a,b,f,\*\*</sup> and Andres Acosta<sup>a,\*</sup>



<sup>a</sup>Precision Medicine for Obesity Program, Division of Gastroenterology and Hepatology, Department of Medicine, Mayo Clinic and Mayo Foundation, Rochester, MN, USA

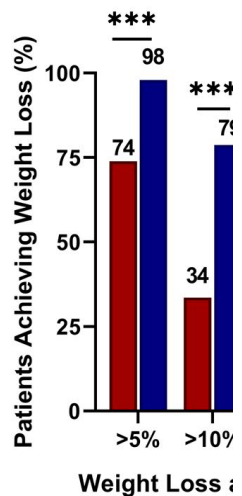
<sup>b</sup>Dan Abraham Healthy Living Center, Mayo Clinic and Mayo Foundation, Rochester, MN, USA

<sup>c</sup>Division of Endocrinology, Diabetes, Metabolism, and Nutrition; Department of Medicine, Mayo Clinic and Mayo Foundation, Rochester, MN, USA

<sup>d</sup>Department of Psychiatry & Psychology, Mayo Clinic and Mayo Foundation, Rochester, MN, USA

<sup>e</sup>Department of Quantitative Health Sciences, Mayo Clinic and Mayo Foundation, Rochester, MN, USA

<sup>f</sup>Division of General Internal Medicine, Mayo Clinic and Mayo Foundation, Rochester, MN, USA



## Summary

**Background** Lifestyle interventions for weight loss are currently not individualised to underlying pathophysiology and behavioral traits in obesity. We aim to compare the outcome of a standard lifestyle intervention (SLI) to phenotype-tailored lifestyle interventions (PLI) on weight loss, cardiometabolic risk factors and physiologic variables contributing to obesity.

**Methods** This 12-week, single-centre non-randomised proof-of-concept clinical trial including men and women aged 18–65 years with a body mass index (BMI) greater than 30 without history of any bariatric procedure, and current use of any medication known to affect weight. Participants lived anywhere in the United States, and underwent in-person testing in Rochester, MN at a teaching hospital. All participants completed in-person phenotype testing at baseline and after 12 weeks. Participants were assigned to their intervention based on their period of enrollment. In the first phase, participants were assigned to SLI with a low-calorie diet (LCD), moderate physical activity, and weekly

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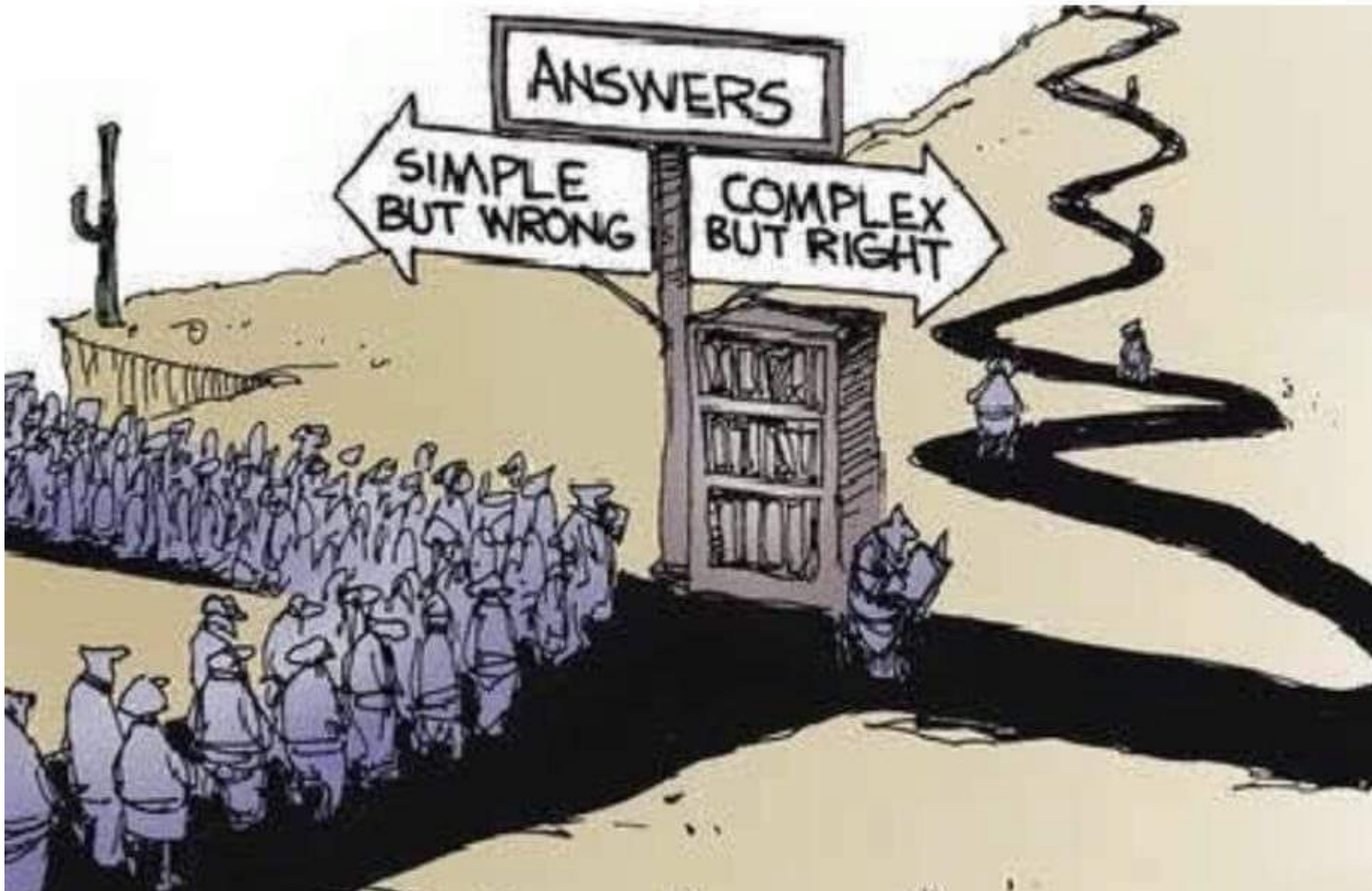
<https://doi.org/10.1016/j.edinm.2023.101923>

convenience

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Are we there yet?



# How do we provide personalized treatment for the patient in front of us?

- Moving beyond BMI to assess health risk
- Shared decision-making
- Assessing other health conditions/medications that may contribute to obesity development or complications or that may influence treatment
- Guidelines, algorithm-based approaches

## ADIPOSIITY-BASED CHRONIC DISEASE AS A NEW DIAGNOSTIC TERM: THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY POSITION STATEMENT

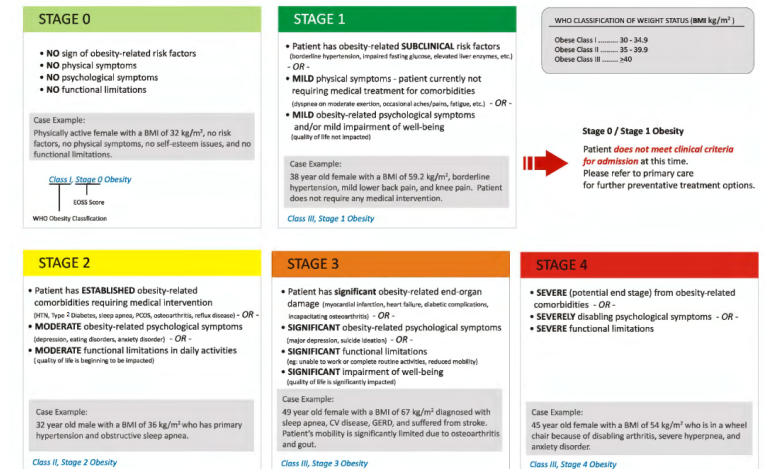
Jeffrey I Mechanick, Daniel L Hurley, W Timothy Garvey

PMID: 27967229 DOI: 10.4158/EP161688.PS

### Abstract

The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) have created a chronic care model, advanced diagnostic framework, clinical practice guidelines, and clinical practice algorithm for the comprehensive management of obesity. This coordinated effort is not solely based on body mass index as in previous models, but emphasizes a complications-centric approach that primarily determines therapeutic decisions and desired outcomes. Adiposity-Based Chronic Disease (ABCD) is a new diagnostic term for obesity that explicitly identifies a chronic disease, alludes to a precise pathophysiologic basis, and avoids the stigmata and confusion related to the differential use and multiple meanings of the term "obesity." Key elements to further the care of patients using this new ABCD term are: (1) positioning lifestyle medicine in the promotion of overall

### EOSS: EDMONTON OBESITY STAGING SYSTEM - Staging Tool



Patient with obesity or overweight with risk factors/comorbidities

Assess and treat comorbid conditions; address other medical, psychological, or social issues affecting health, including obesity-promoting medications. Periodically assess patient readiness for weight management treatment

Offer or refer for ILI\*  
Select AOM+  
Titrate dose,<sup>&</sup> monitor for adverse effects, need to adjust other medications, weight loss efficacy, and improvements in obesity-related risk factors/comorbidities

Offer or refer for ILI  
Select AOM+

Titrate dose, monitor for adverse effects, need to adjust other medications, weight loss efficacy, and improvements in obesity-related risk factors/comorbidities

+Initial selection of an AOM may be based on medication efficacy, other medical conditions or contraindications, concomitant medications, cost, availability, and patient preference

Consider consultation with or referral to a specialist with obesity management expertise.<sup>‡</sup> If Class 2 or 3 obesity or Class 1 obesity with uncontrolled metabolic comorbidities, consider referral for bariatric surgery

Continue Current AOM.  
Titrate dose<sup>\*\*</sup> as needed to attain weight loss or maintenance goals, monitor for adverse effects, need to adjust other medications, impact on health and QoL  
Consider consultation with or referral to a specialist with obesity management expertise<sup>‡</sup> if additional weight loss is medically indicated on maximal tolerated dose.

No

# Research Gaps and Opportunities

- How can we use real-world data (EHRs, prescriber databases) to answer important clinical questions about heterogeneity of response to treatment
  - Embed pragmatic trials to test validity of proposed phenotypes/biomarkers)
  - May need to collect additional types of information (biosamples, questionnaires)
- Promote use of common data elements across studies
- Leverage approaches being used to explore heterogeneity in other complex diseases (asthma, schizophrenia, hypertension) to better understand mechanism
- Using advances in data science/ML/AI to accelerate development of precision approaches

**MORE TO COME!**



The NIH Obesity Research Task Force presents  
**Moving Beyond BMI: Exploring the  
Heterogeneity of Obesity**

Obesity is a chronic disease with harmful effects on health and well-being. Body mass index (BMI) has long been used as a measure of obesity and a proxy for health risk, but evolving science shows it is an imperfect tool for a diverse, variable condition. This virtual event will feature renowned extramural investigators who will explore the heterogeneity of obesity, including its risk factors, development and complications, pathophysiology, and treatments. Presenters will also discuss implications for obesity prevention and treatments.

NIH Obesity Research Task Force Seminar Series

## Moving Toward Precision Obesity Treatment

September 6, 2018 | Lister Hill Auditorium  
NIH Campus, Bethesda, MD

**Morning Session**  
9:15 a.m. – 12:00 p.m.

**Accelerating Precision Health for All of Us**  
Eric Dishman  
*All of Us Research Program, NIH*

**Integrated Omics Profiling During Weight Gain and Loss: Implications for Obesity Treatment**  
Michael Snyder, Ph.D.  
*Stanford University*

**New Medical Insights from the Genetics of Body Fat Distribution in Humans**  
Elizabeth Spellates, M.D., Ph.D., M.P.H.  
*University of Michigan*

**Afternoon Session**  
1:00 p.m. – 2:30 p.m.

**A SMART Approach to Personalizing Obesity Treatment**  
Nancy Sherwood, Ph.D.  
*University of Minnesota*

**Panel Discussion**  
Penny Gordon-Larsen, Ph.D.  
*The University of North Carolina at Chapel Hill*  
(Moderator)

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