What Does Personalized Obesity Treatment Look Like?

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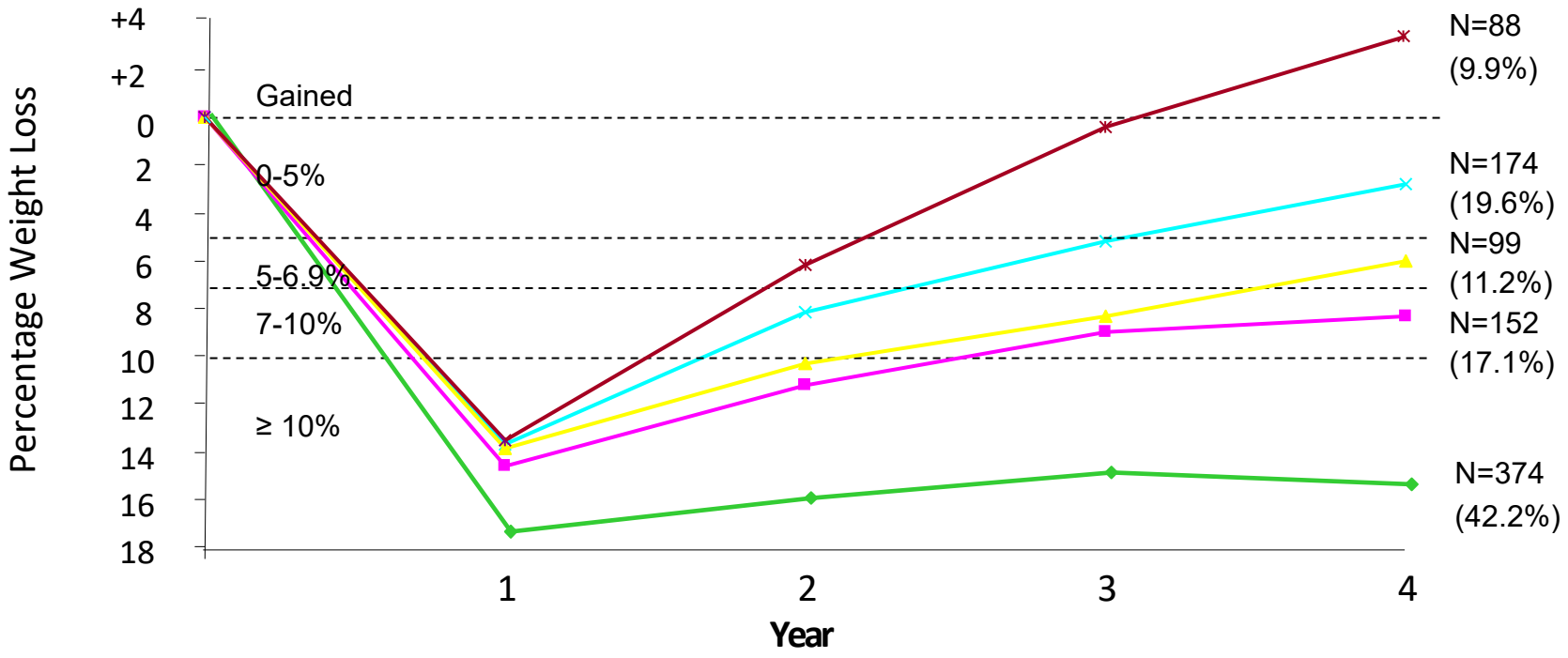
Obesity: One Size Does Not Fit All

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

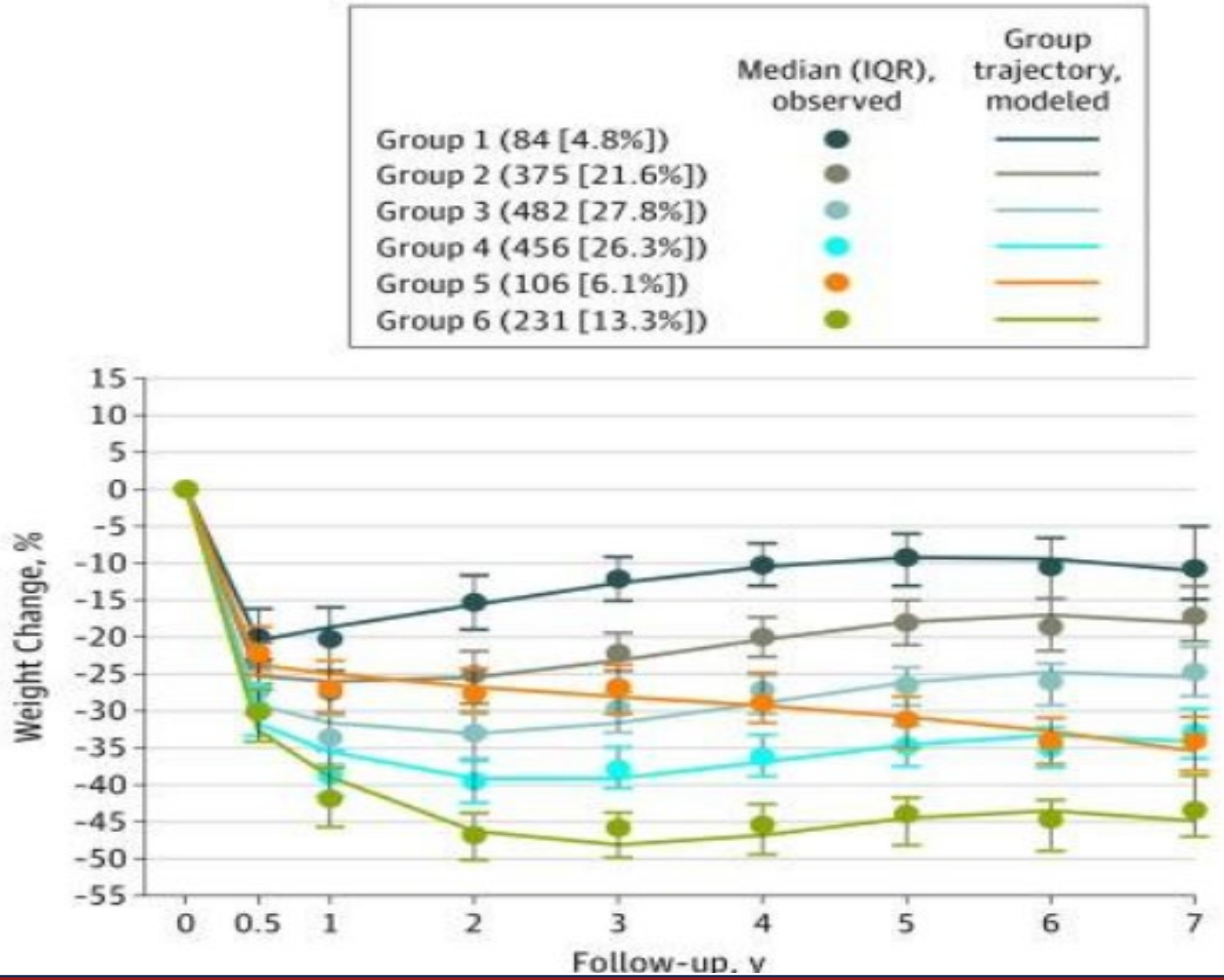
Individual Variability with Lifestyle Treatment

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.

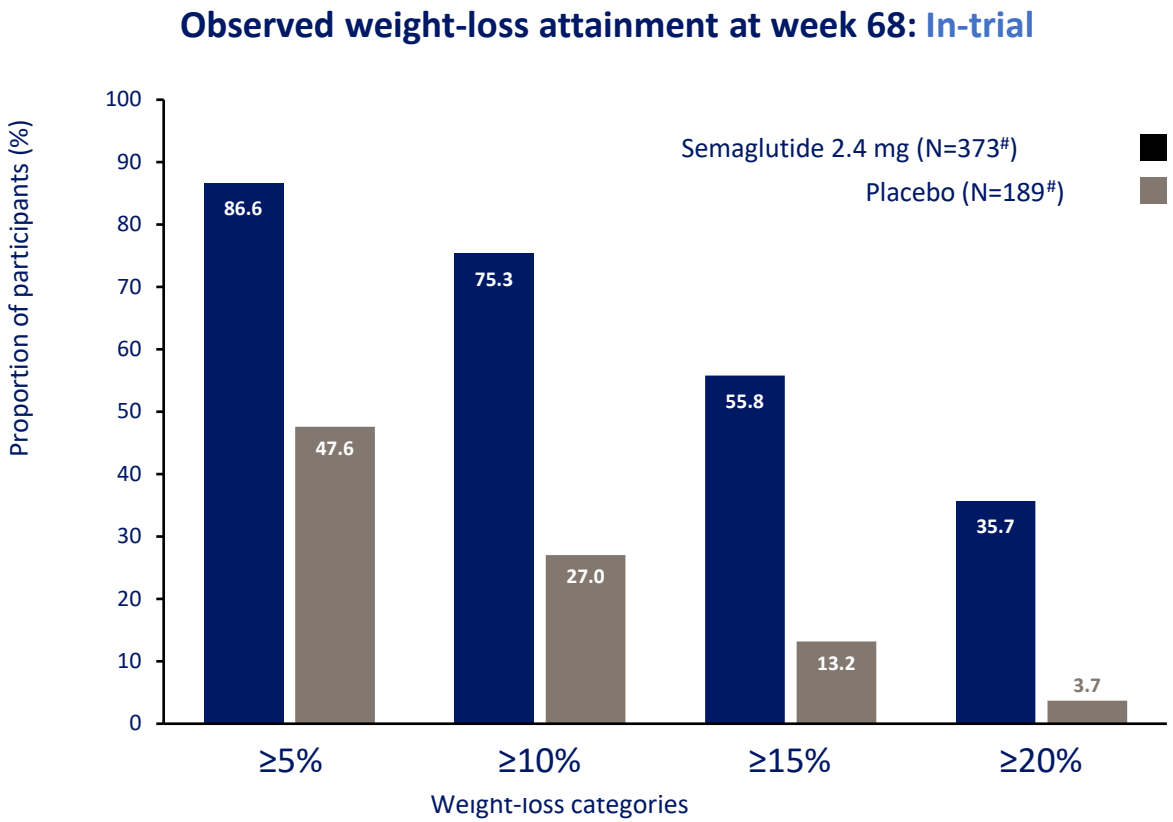
Seven-Year Weight Trajectories after Roux-en-Y gastric bypass in the Longitudinal Assessment of Bariatric Surgery Study



Six weight change trajectory groups were identified

From: Courcoulas et al. JAMA Surg 2018

Weight loss with semaglutide 2.4 mg plus intensive behavioral treatment



14% lost <5% Initial Weight

36% lost ≥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 ≥5% (co-primary endpoint), ≥10%, ≥15%, and ≥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*)

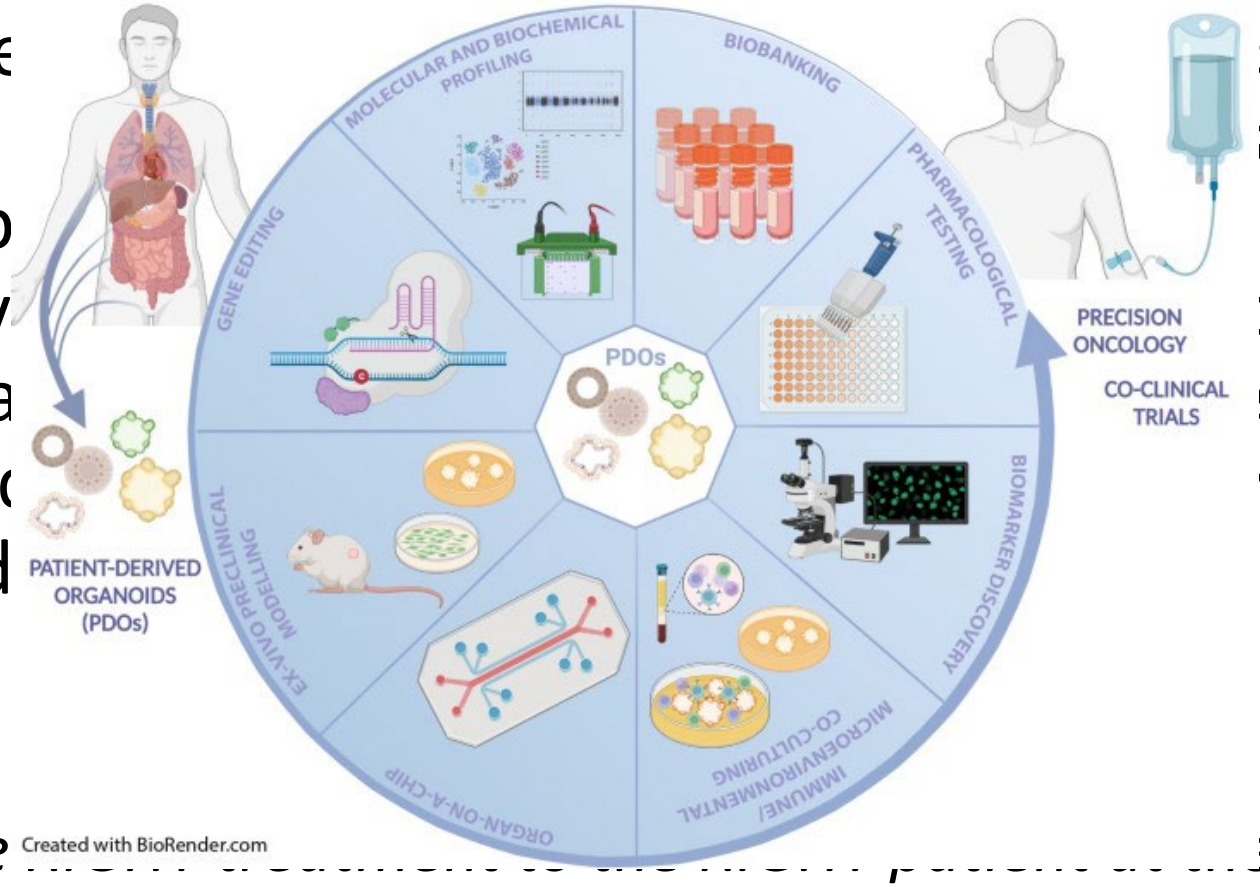
Anti-obesity medications (*Fujioka et al., Obesity, 2016, Mosenzon et al, J Endocri Soc, 2024*)

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

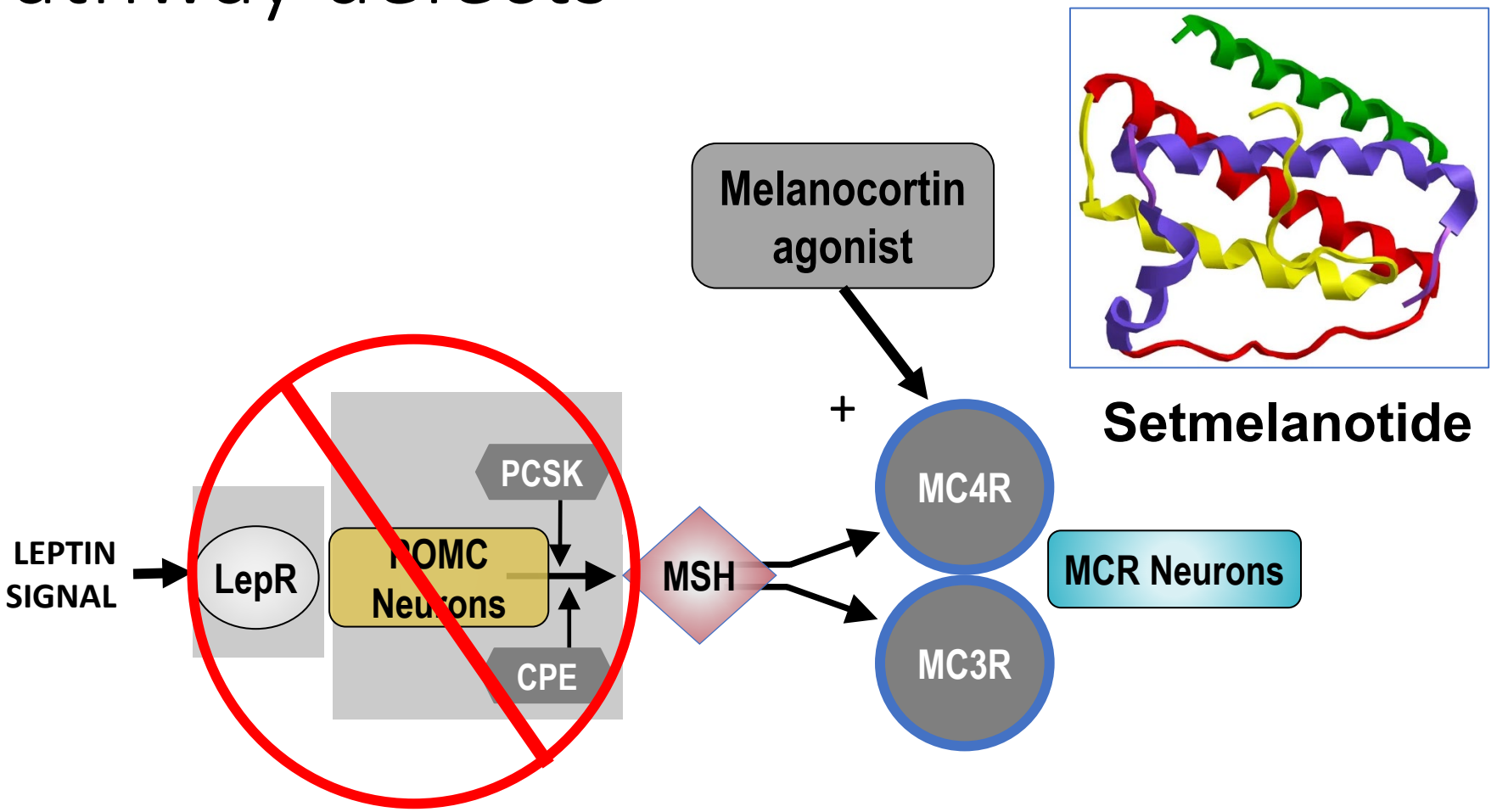
“Precision” = “Personalized” Medicine

- “Precision me s to personalized an innovative ap individual's genomic, env o guide decisions rela goal of precision me roach for the prevention, d
  - *NHGRI, NIH*



  - *“Getting the right treatment to the right patient at the RIGHT time”*

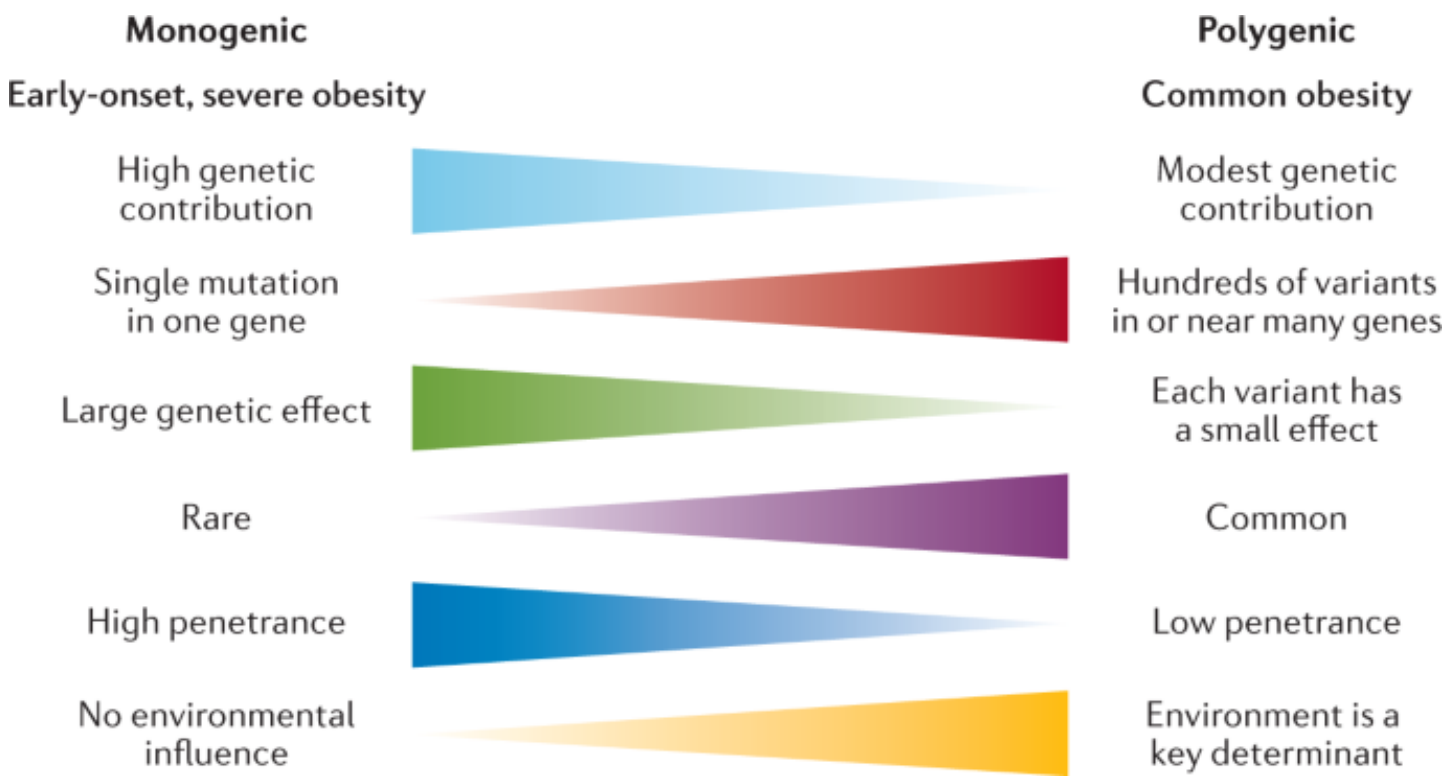
Specific treatments for leptin signaling pathway defects



Approved in 2020 for age ≥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…



Loos & Yeo, *Nature Reviews Genetics*, 2022

- 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

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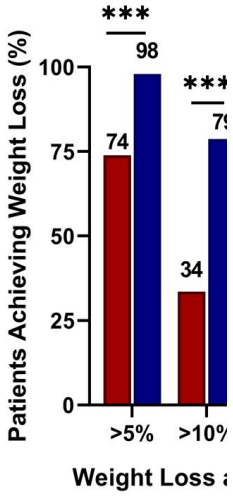

Summary

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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convenience

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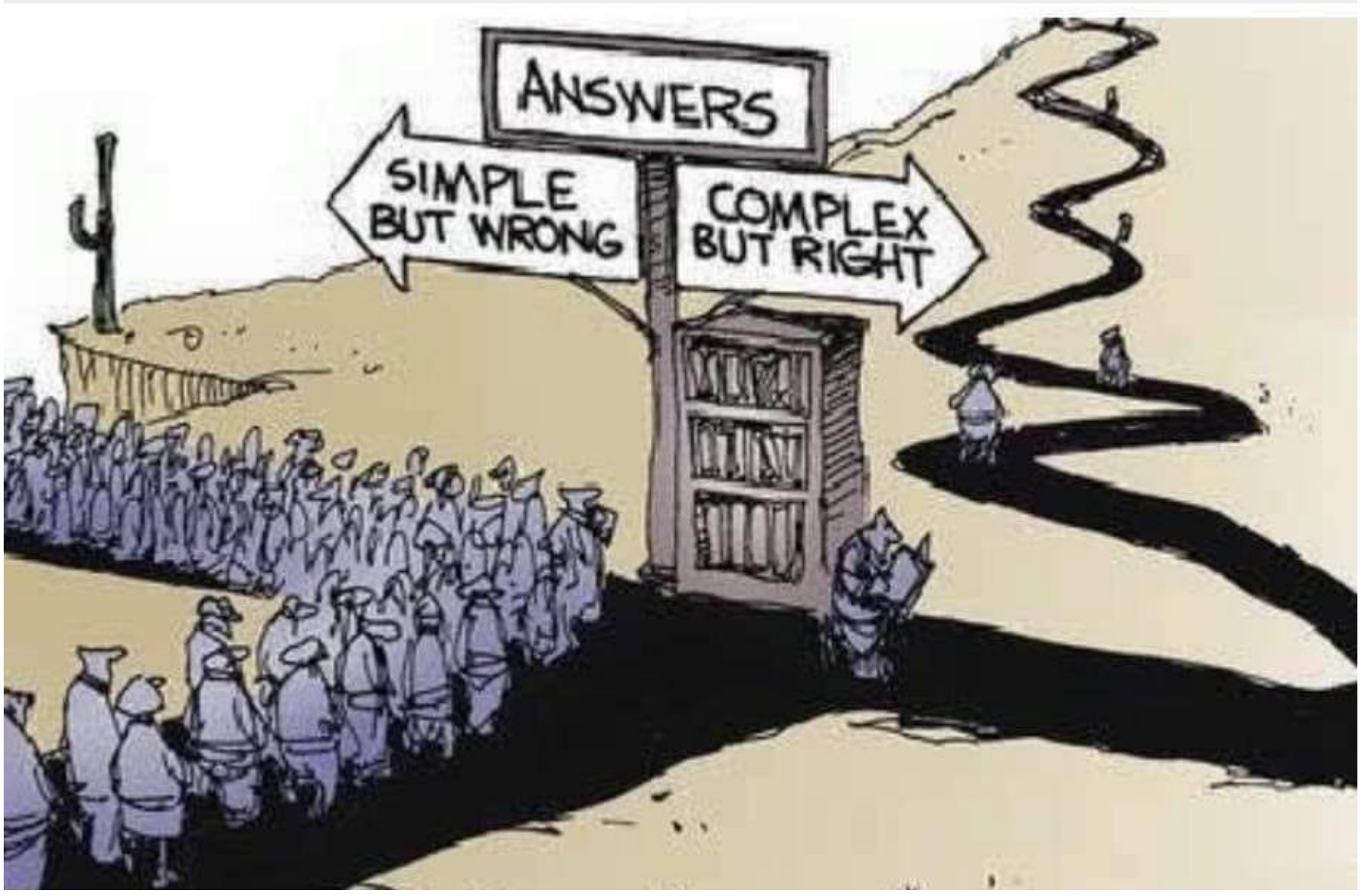
Are we there yet?



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

Endocr Pract. 2017 Mar;23(3):372-378. doi: 10.4158/EP161688.PS. Epub 2016 Dec 14.

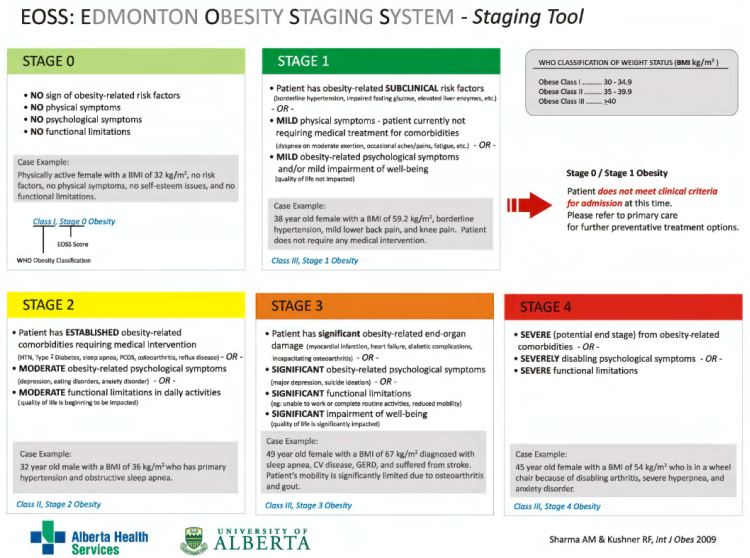
ADIPOSITY-BASED CHRONIC DISEASE AS A NEW DIAGNOSTIC TERM: THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY POSITION STATEMENT

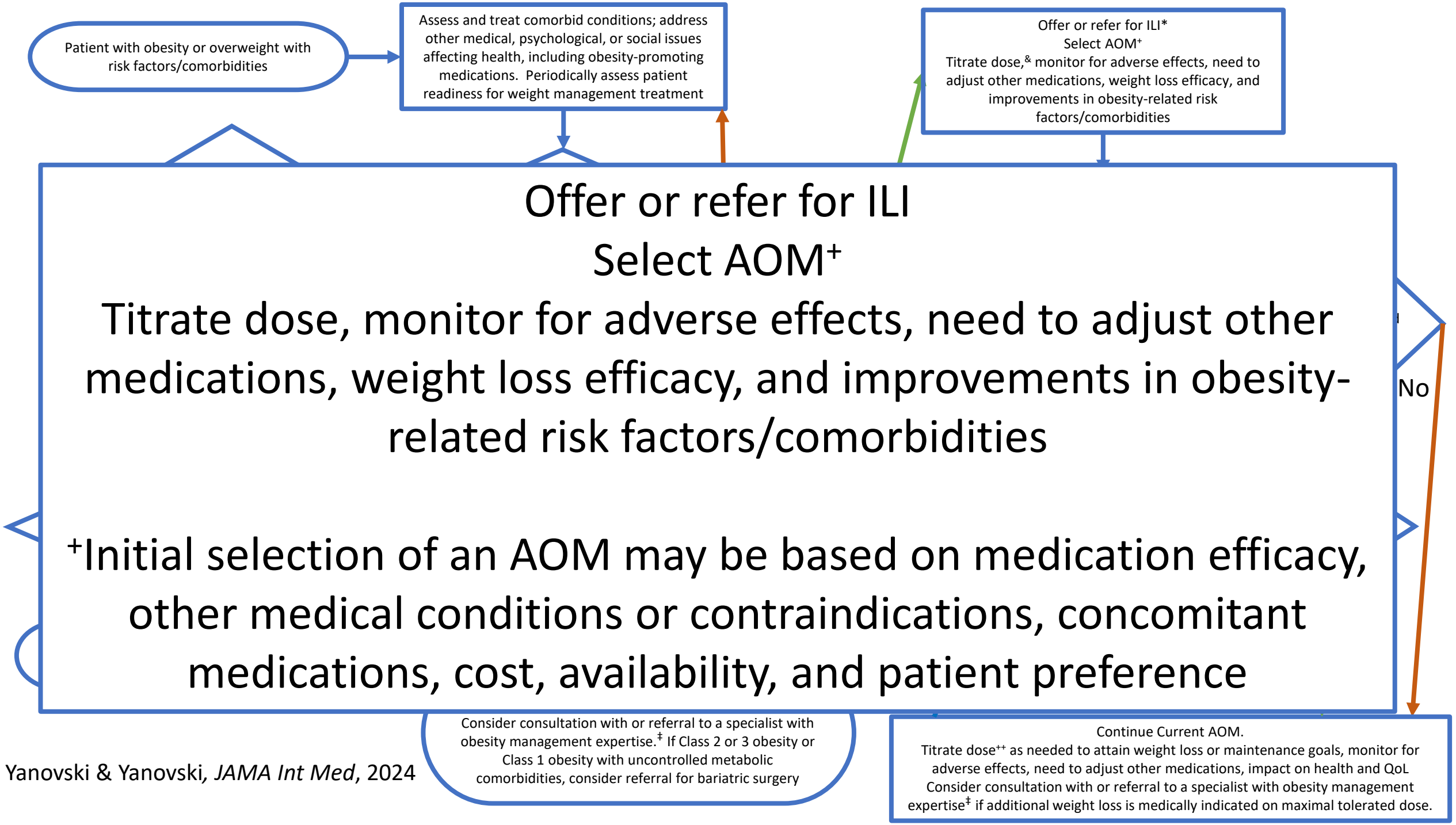
Jeffrey I Mechanick, Daniel L Hurley, W Timothy Garvey

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





Yanovski & Yanovski, *JAMA Int Med*, 2024

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!