MAYO CLINIC

Phenotype-guided Obesity Management Enhances Weight Loss

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Disclosures

Stocks, Founder

- Gila Therapeutics
- **Phenomix Sciences**

Consultant

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- Rhythm Pharmaceuticals

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- Spatz Medical
- Rhythm Pharmaceuticals

OBESITY- The #1 Chronic Disease

40%

of US adults
are affected by obesity

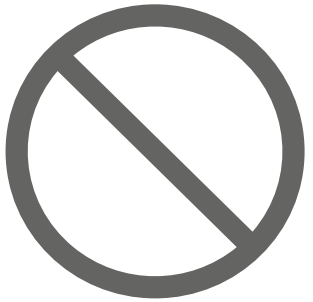
Obesity leads to heart disease, stroke, type 2 diabetes, cancer, and premature death

Obesity drives

$480B

of direct annual healthcare costs[1]

Existing obesity treatments are mostly



ineffective

[1] *Milken Institute: America's Obesity Crisis. 2018.*

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Challenges of Treating Obesity: Variable Response

One-size-fits-all is not working!

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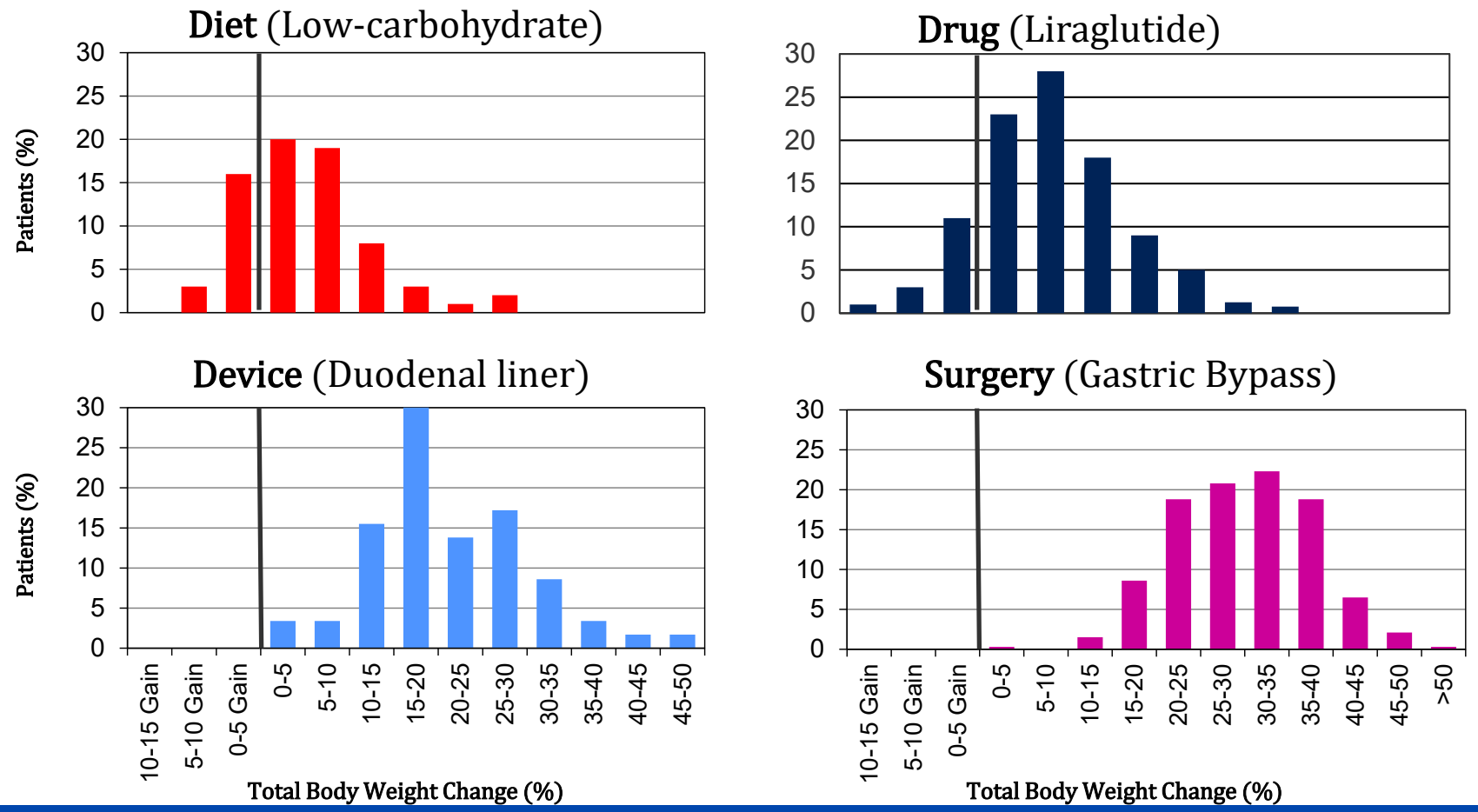
Obesity heterogeneity: One-treatment-fits-all does not work

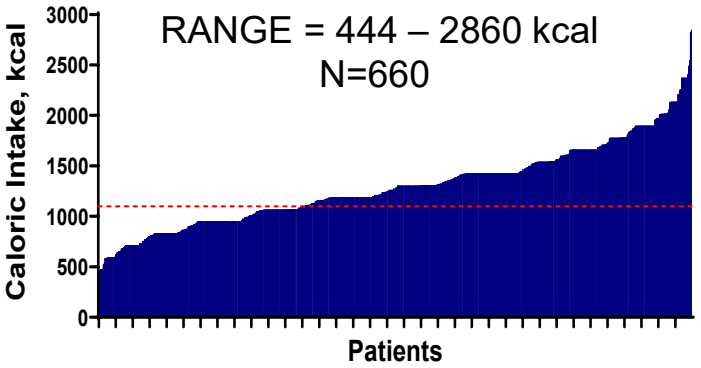
Weight loss varies widely among patients



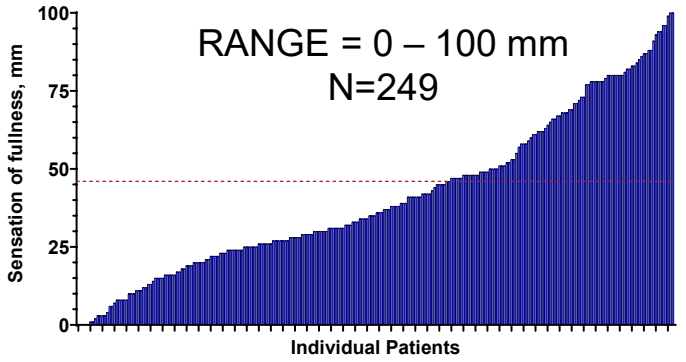
Courtesy of Dr. Lee Kaplan

Energy Balance Heterogeneity: Variability among traits

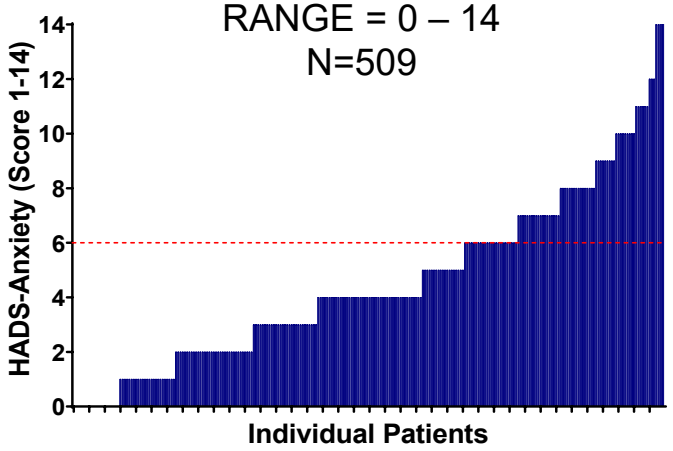
Satiation Test: Maximal Fullness



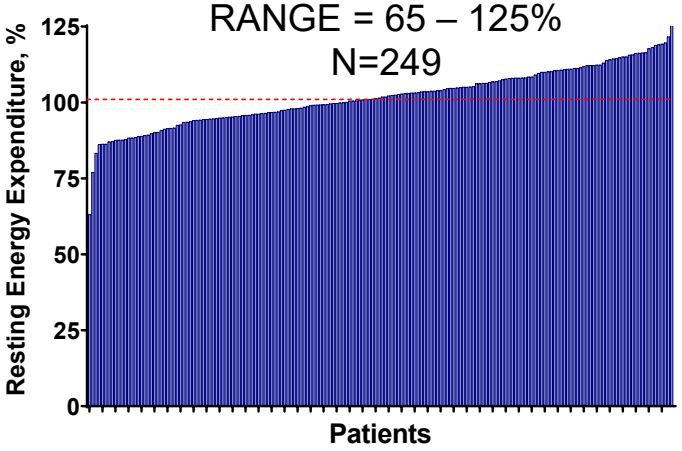
Satiety Test: Postprandial Fullness



Emotional Eating: Anxiety



Resting Energy Expenditure



Mean Value for Normal weight controls (n=138)

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Modified Acosta A, Camilleri M, et al, *Gastroenterology,* 2015

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Challenges of Treating Obesity: Current Classifications

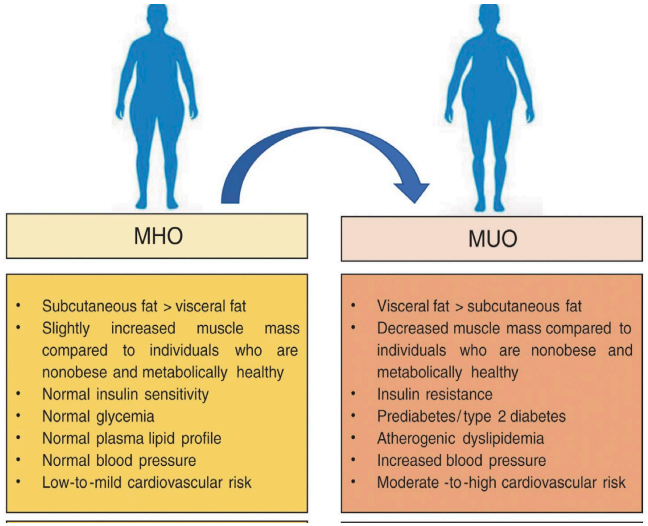
- "One-treatment-fits-all" strategy is not working
- Current obesity classification focus on obesity-cardiovascular or comorbidities risk ("severity") **not** on a real obesity stratification (segmentation).

Body Mass Index ± WC

	BMI, kg/m^2	Disease Risk Relative to Normal Weight and Waist Circumference	
		Men ≤102 cm, Women ≤88 cm	Men >102 cm, Women >88 cm
Underweight	<18.5	…	…
Normal	18.5–24.9	…	…
Overweight	25.0–29.9	Increased	High
Obesity	30.0–34.9	High	Very high
	35.0–39.9	Very high	Very high
Extreme obesity	≥40	Extremely high	Extremely high

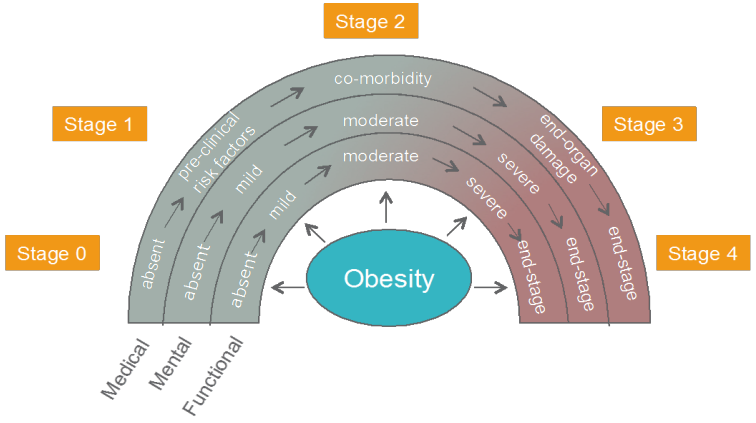
Lewis, Cora E., et al. Circulation 119.25. 2009

Metabolic Status



Lonardo, Amedeo, et al. 2020

Obesity Stages Comorbidities



Sharma AM et al. *Int J Obes*. 2009

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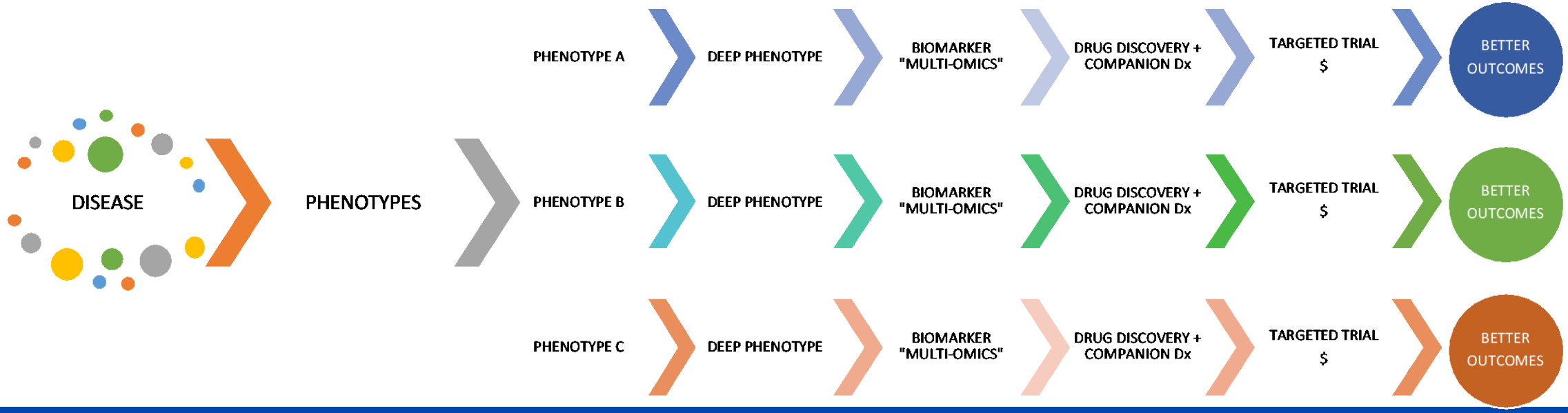
Precision Medicine for Obesity

TRADITIONAL APPROACH

PRECISION MEDICINE APPROACH



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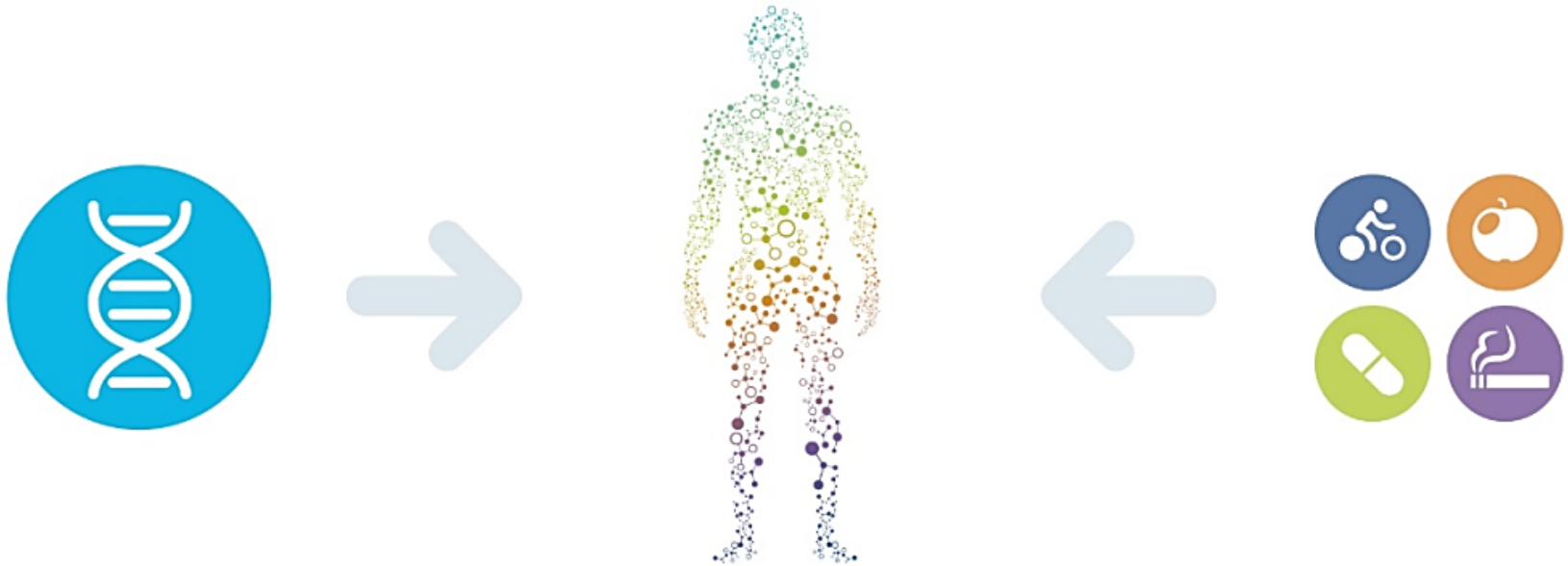
Phenotype: Interaction of our genes with our environment



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.

Adapted from Metabolon Report

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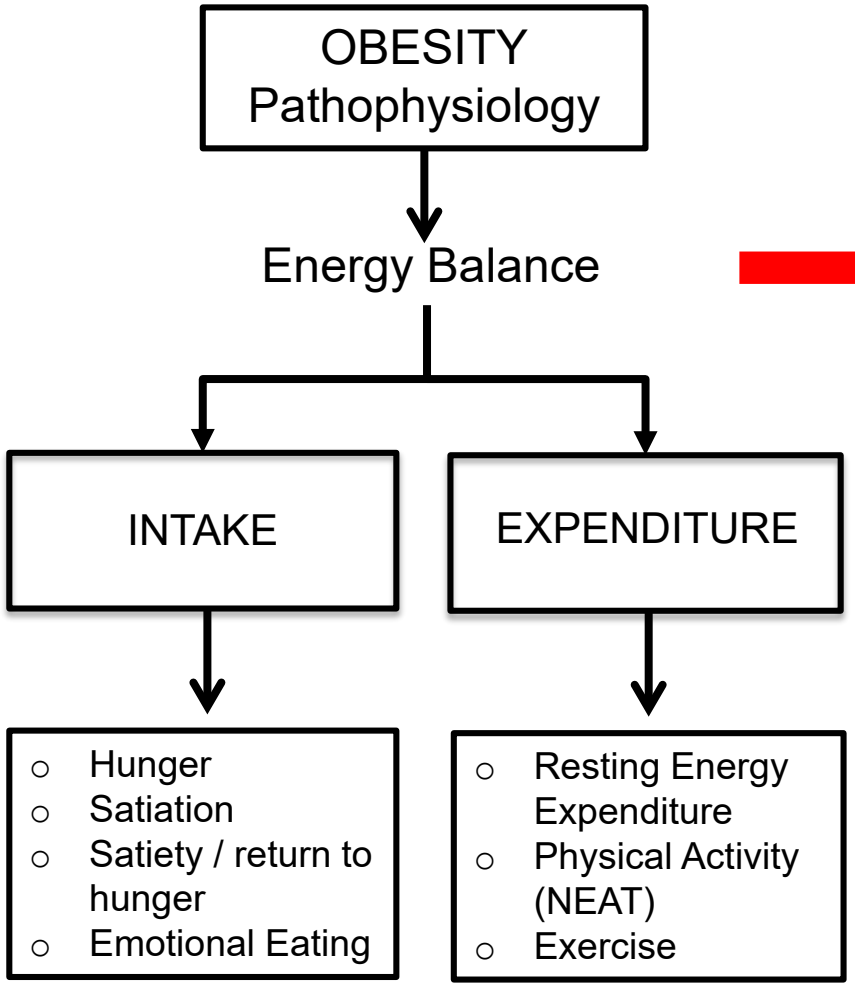
Obesity Phenotypes Based on their Pathophysiology



STORAGE

Adiposity toxicity
- Insulin resistance - Diabetes
- Inflammation
- Metabolic syndrome - CVD
- Cancer

Adiposity (excess)
- Joint disease
- Sleep apnea
- Depression
- GERD

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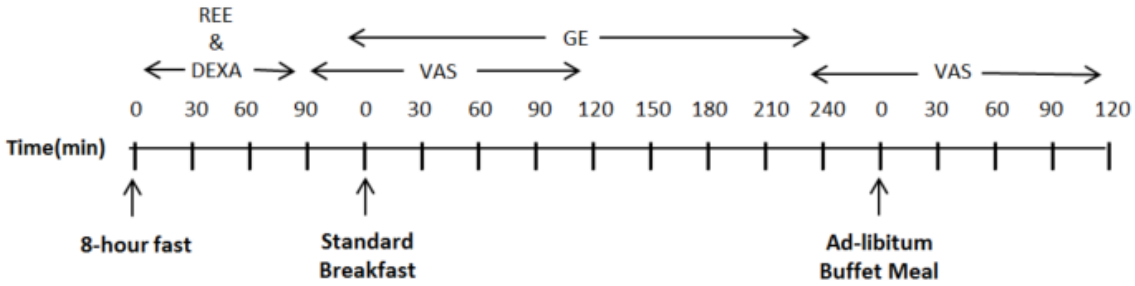
How we phenotype our patients?

Obesity Categories	Phenotype	Test
Food Intake – Homeostatic	Hunger	VAS – Hunger 240 min, 0-100 mm
	Satiation	*Ad Libitum* Buffett meal, Kcal
		VAS – Satisfaction 30 min postprandial, 0-100 mm
	Satiety / Return to hunger	VAS – Fullness 120 min postprandial, 0-100 mm
		Gastric Emptying T ½, min
Food Intake – Hedonic Eating	Emotional Eating	TEFQ – Emotional restraint (4-16 Scale)
		HADS-A (0-21 scale)
Energy Expenditure	Basal Metabolic rate	Predicted REE (HB) %
	Non-Exercise Physical Activity	Self-Reported Steps, #
	Exercise	Self-Reported Exercise (PASC), 0-8 scale

Typical Phenotyping Day:



Acosta A, Camilleri M, et al, *Obesity,* 2021

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Four Obesity Phenotypes

Machine-learning identified key phenotypes in 509-patient study at Mayo Clinic

1 HUNGRY BRAIN

Satiation
Knowing when the meal is over

2 HUNGRY GUT

Satiety
Ability to not eat in periods between meals

3 EMOTIONAL HUNGER

Emotional/Reward
Eating in response to negative and/or positive emotions

4 SLOW BURN

Energy Expenditure
Base metabolic rate plus overall activity level

Modified from Acosta A, Camilleri M, et al, *Gastroenterology,* 2015

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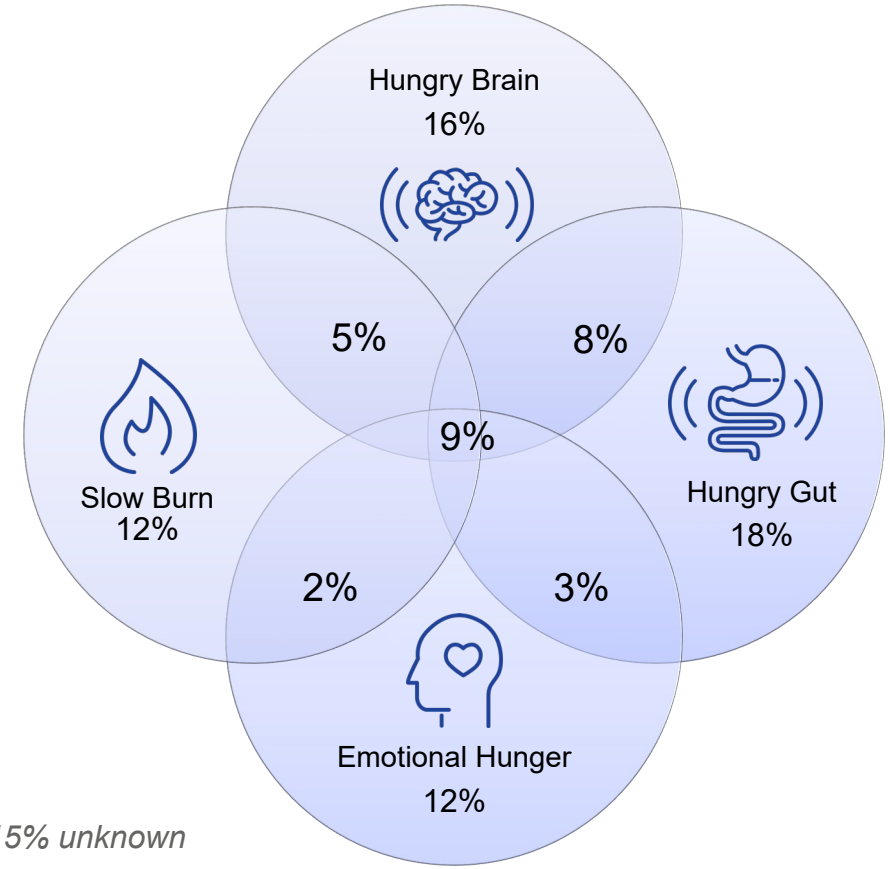
RESULTS: Obesity Phenotypes in 450 patients

Phenotypes were identified based on the 75th percentile from the median value in the population with obesity

N = 450 participants,
Obesity (defined as BMI >30 kg/m2) with the following demographics [mean ± SEM)]:
age 39 ± 0.5 years old,
BMI 37 ± 0.3 kg/m2,
72% females,
93% white,
waist circumference 105 ± 0.1 cm,
fasting glucose 103 ± 1.4 mg/dl



15% unknown

Acosta A, Camilleri M, et al, *Obesity,* 2021

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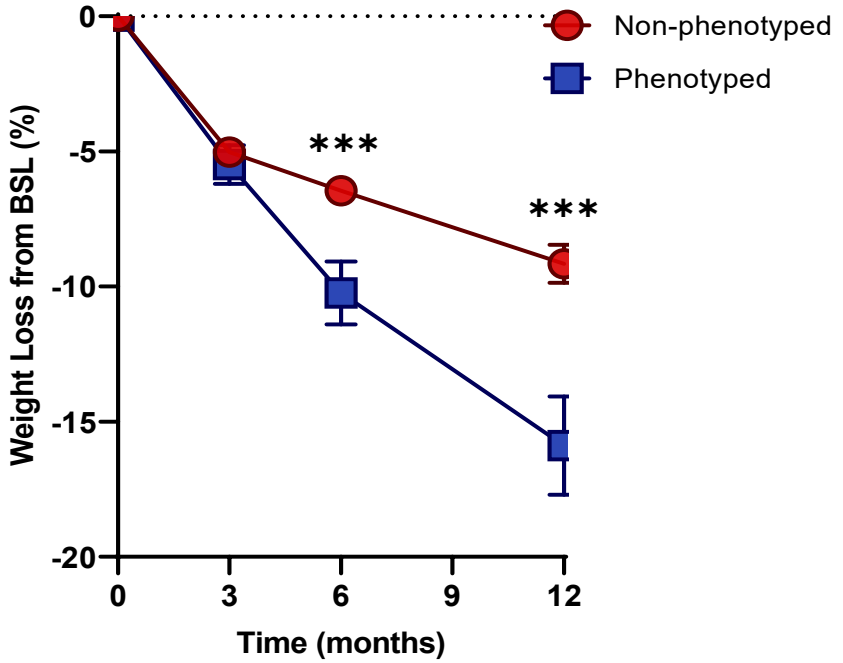
Proof of Concept Trials:

- Obesity-related Phenotypes predict response to obesity pharmacotherapy and endoscopic devices.
- Proof of Concept in a single-center, randomized, parallel-group, double-blind, placebo-controlled trial with:
  - Phentermine-topiramate-ER (7.5/46mg) [1]
  - Exenatide 5ug[2]
  - Liraglutide 3 mg[3]
  - Orbera Intragastric Balloon[4]
  - Endoscopic Sleeve Gastroplasty[5]
  - Aspire Assist Device[6]
  - Spatz Intragastric Balloon[7]
- Real-World Experience
  - Intragastric Balloon[8]
  - Phenotype-guided Pharmacotherapy[9]

Phenotype-guided Pharmacotherapy[9]



[1] Acosta A , Camilleri, et al., Gastroenterology. 2015
[2] Acosta A , et al., Physiology Reports, 2015
[3] Halawi H, Camilleri, et al., Lancet GI. 2017
[4] Gomez V, et al., Obesity. 2016
[5] Abu Dayyeh BK, et al., Clin Gastroenterol Hepatol. 2017
[6] Vargas EJ, et al., BMJ Open Gastroenterol. 2019
[7] Vargas EJ, et al., Clin Gastroenterol Hepatol. 2020
[8] Lopez Nava et al., Obesity Surgery 2020
[9] Acosta A., et al., Obesity 2021

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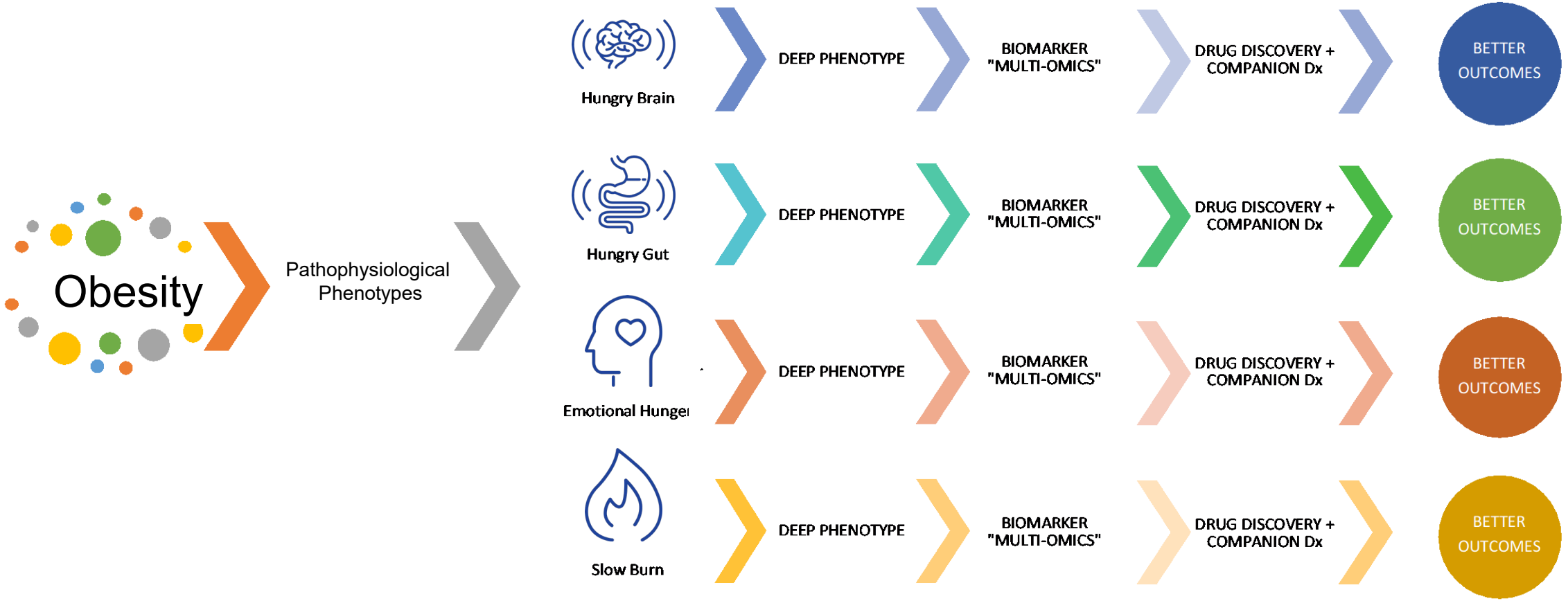
Personalized Approaches to Obesity



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Key Take Away

- “One-treatment-fits-all” is not working…
- Obesity is a complex disease with many different phenotypes
- Phenotype-guided intervention doubles (2x) weight loss
- Obesity phenotypes can be measured with a simple blood test

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Thank you for your attention!
Questions and Comments?

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