Obesity Biology: What's Trending?

Lee M. Kaplan, MD, PhD

Professor of Medicine and Chief, Section of Obesity Medicine
Director, Dartmouth Weight and Wellness Center
Geisel School of Medicine at Dartmouth

LMKaplan0@gmail.com

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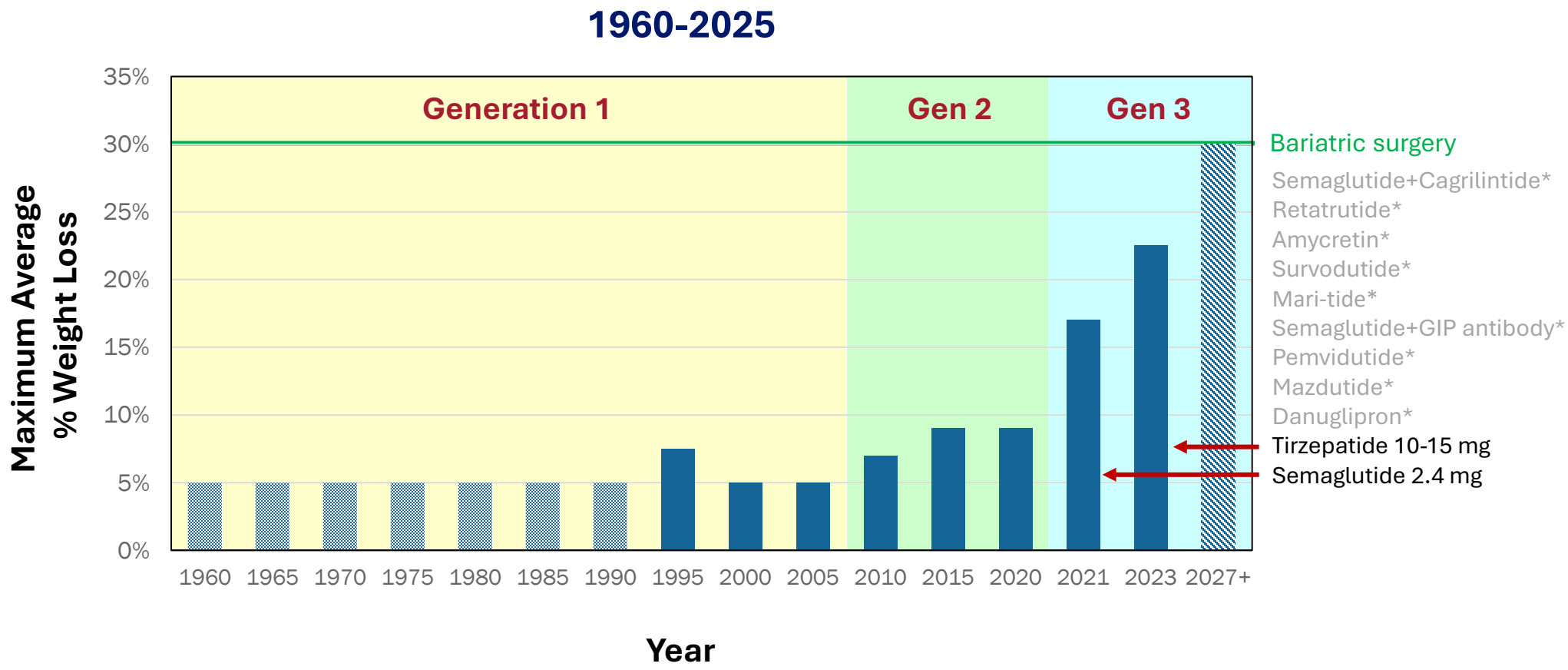
We have entered a rapidly expanding 3rd generation of anti-obesity medications



*These medications are not approved for the treatment of obesity

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There is a growing list of diseases that have now been demonstrated to benefit from effective treatment of the underlying obesity

- Type 2 diabetes (T2D) – 2007
- Atherosclerotic cardiovascular disease (ASCVD) – 2023
- Heart failure with preserved ejection fraction (HFpEF) – 2023
- Chronic kidney disease (CKD) – 2024
- Metabolic dysfunction-associated steatotic liver disease (MASLD/MASH) – 2021
- Obstructive sleep apnea (OSA) – 2024
- Obesity-associated cancers – 2022
- Osteoarthritis – 2024
- Polycystic ovary syndrome (PCOS) – a major cause of infertility in women - 2024

… and with the new, highly effective medications like semaglutide, **this list is growing very rapidly**

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The magnitude of weight loss is important …

Obesity complication	Weight loss for improvement (%)	More weight loss is better
Type 2 diabetes	5-15	✓
Hypertension	15	✓
Dyslipidemia	10-15	✓
Fatty liver disease (NAFLD)	10	✓
Sleep apnea	10	✓
Osteoarthritis	5-15	✓
Stress incontinence	5-10	✓
Gastroesophageal reflux	10-15	✓
Polycystic ovary syndrome	10-15	✓

… but some of the most important benefits of metabolic surgery and obesity medications have a large weight-independent component

What are the mechanisms of these weight-independent effects?

Are they the same for all obesity complications?

Can they be targeted to generate new treatments?

Adapted from Cefalu WT *et al.*, *Diab Care* 2015

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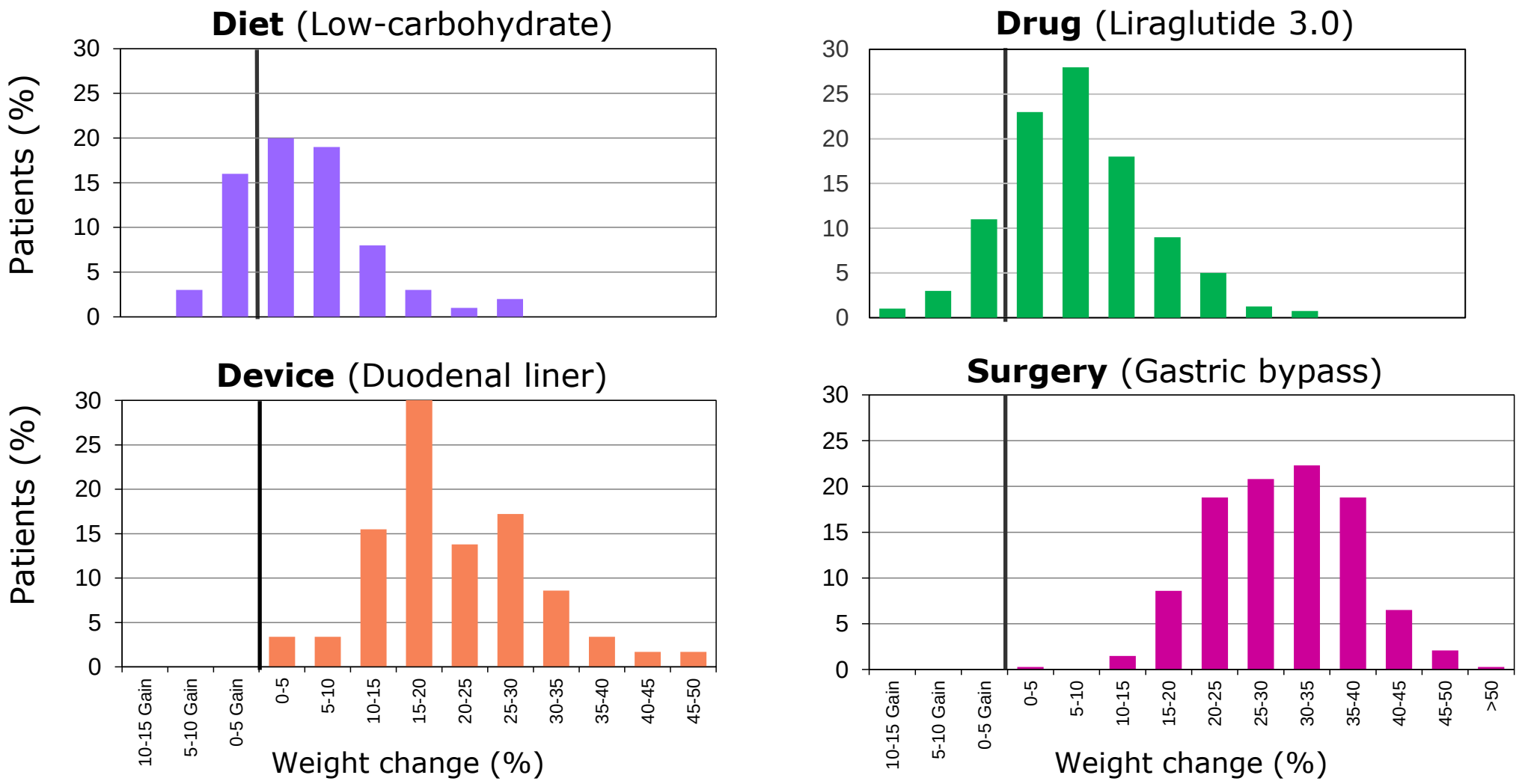
Weight loss varies widely among patients



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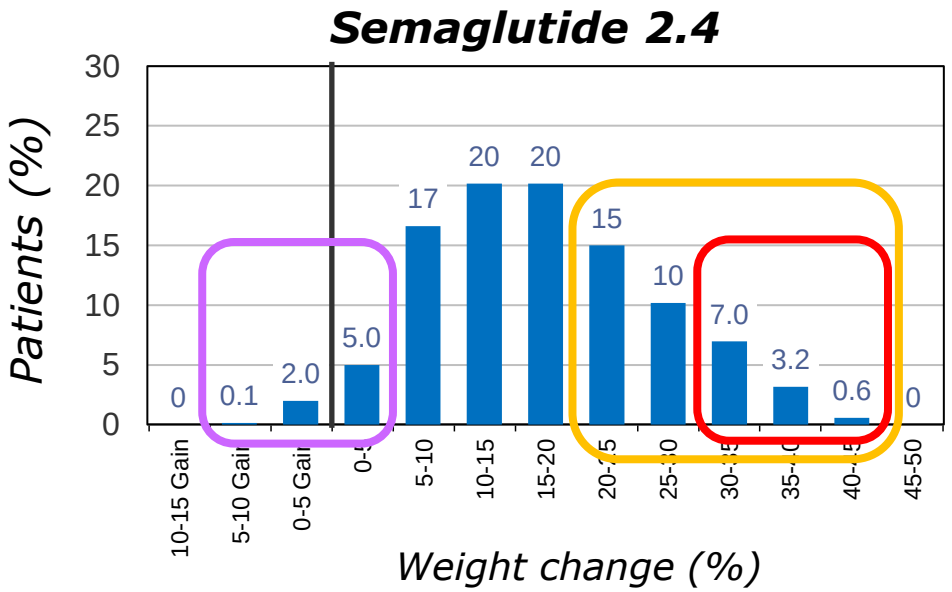
Future care will address the heterogeneity of obesity

10 MM people (US)

35 MM people (US)

11 MM people (US)



7-13% of patients lose less than 5% body weight (31% if have T2D)

35% of patients lose more than 20% body weight

11% of patients lose **>30% body weight**

Adapted from Wilding JPH *et al.*, *NEJM* 2021
STEP 1 Obesity Trial

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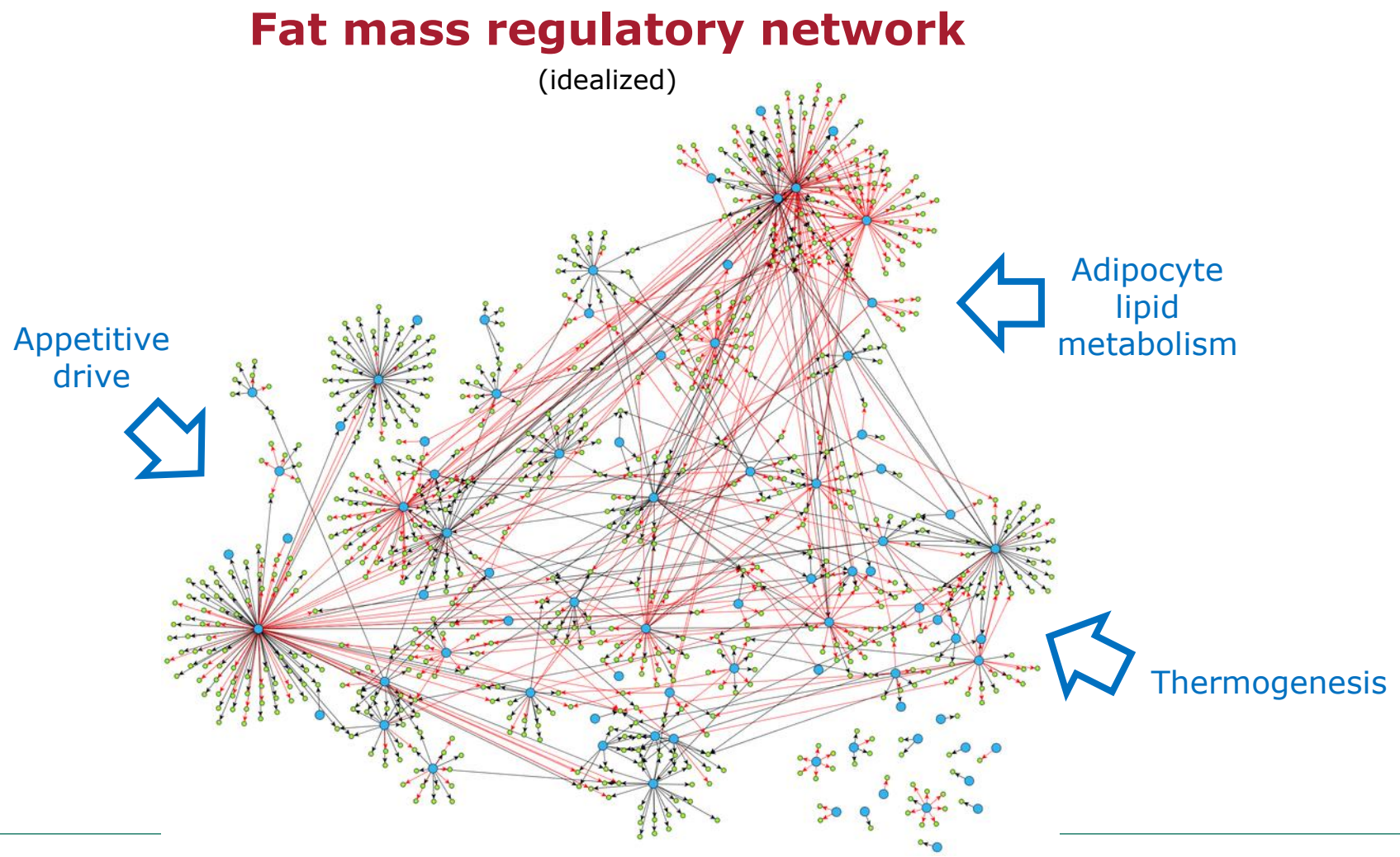
Fat mass and body weight are regulated by a complex network



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Is GLP-1 a unicorn?

- Are there **mechanisms other than GLP-1** that can exert **widespread, beneficial influence** on fat mass regulation?
- Amylin? PYY? Other targets?
- Do the mechanisms of metabolic surgery still hold the promise of identifying new, valuable targets?

How does the body determine how much fat to store?

How does the body determine **where** to store fat?

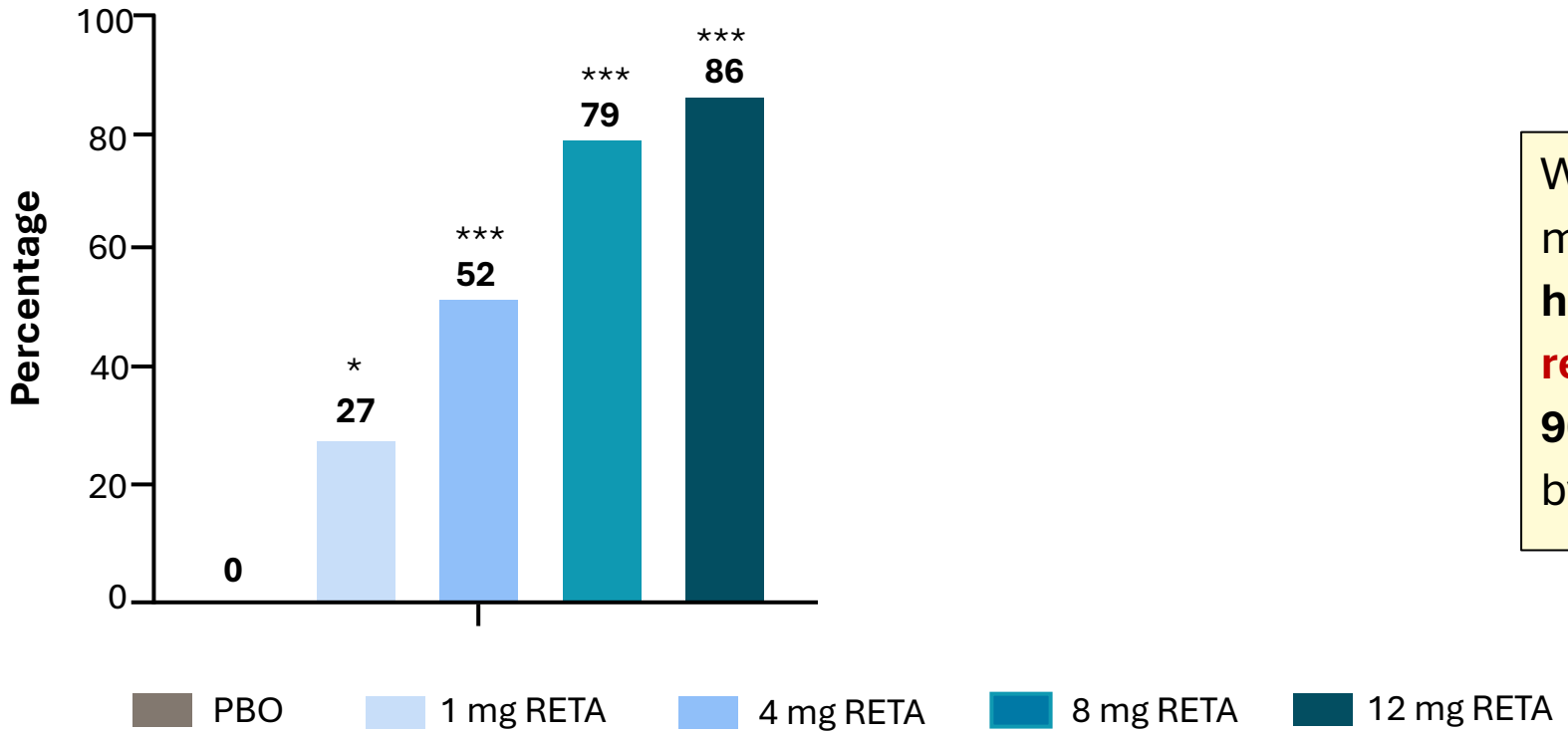
Knowledge of these mechanisms will likely reveal new, valuable treatment targets?

Retatrutide fully normalizes liver fat content in up to 90% of participants

Phase 2 substudy of obesity without T2D with 10% liver fat

(N=98)

Participants achieving liver fat content <5%



With retatrutide at 8 mg and 12 mg, **hepatic steatosis resolved in up to 90%** of participants by week 48

Sanyal AM *et al.*, ADA Annual Meeting, San Diego, CA, June 2023

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Drugs with glucagon receptor agonist activity appear particularly well-suited to clear liver fat?

Are there parallel mechanisms for other ectopic fat?

Cardiac

Pancreatic

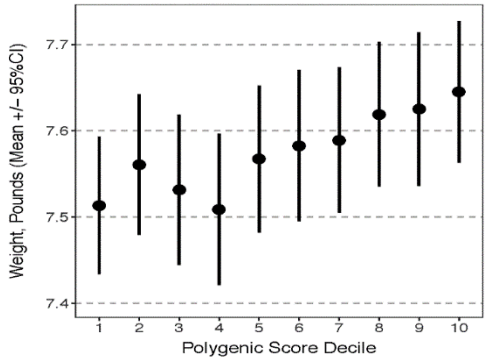
Renal

Muscle

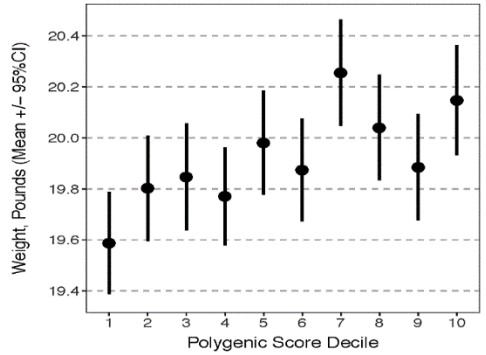
Will this allow targeting of obesity treatment depending on its complications?

Obesity polygenic score predicts later obesity development

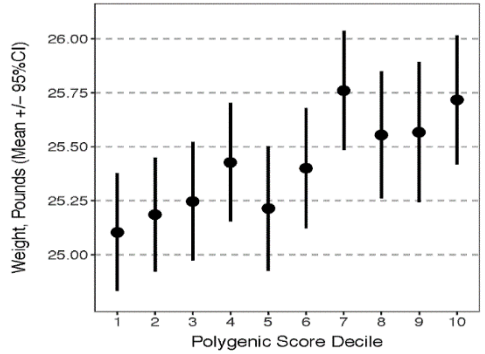
Birth



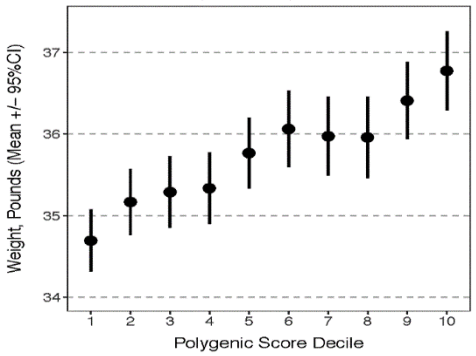
8 Months



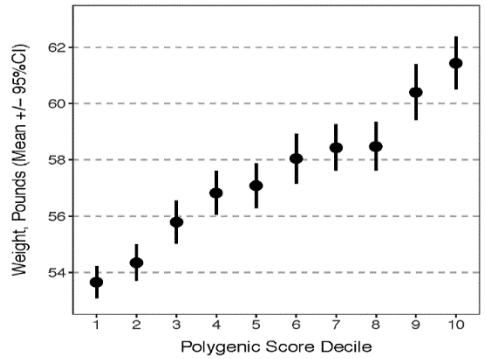
18 Months



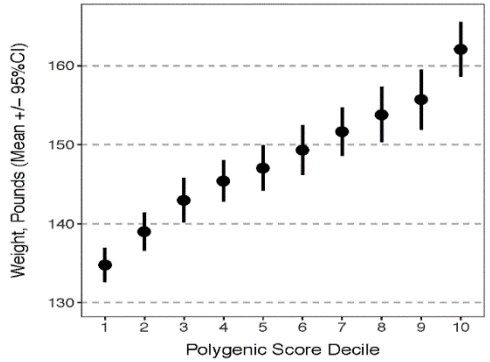
3.5 Years



8 Years



18 Years



Khera A … Kaplan LM, Kathiresan S, *Cell* 2019

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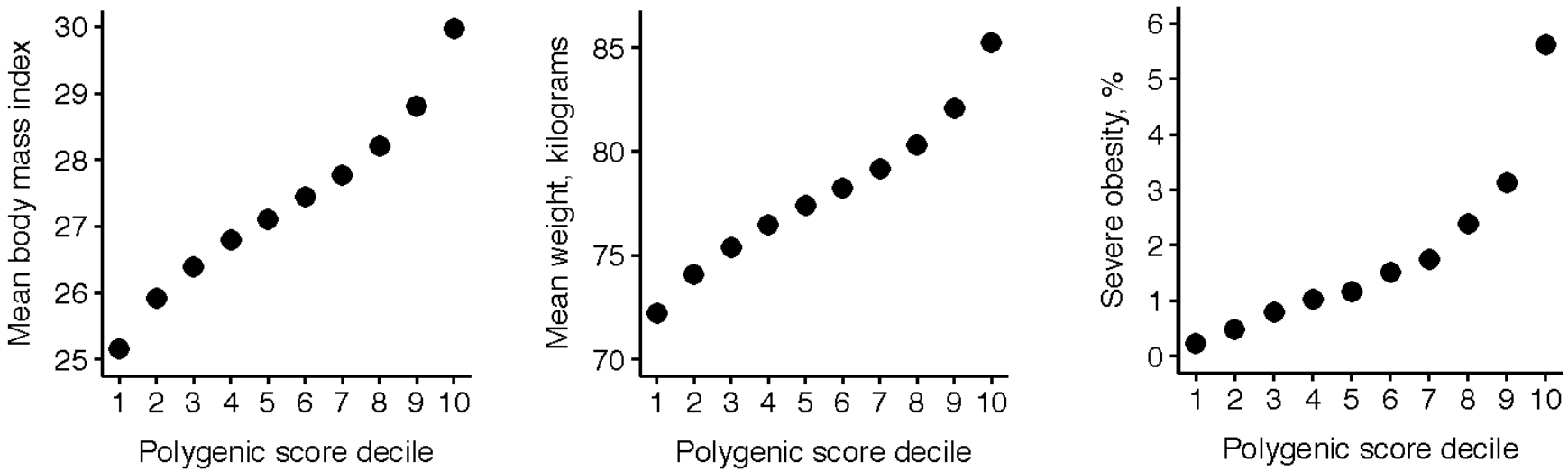
Obesity GPS predicts severe obesity



Khera A … Kaplan LM, Kathiresan S, under review

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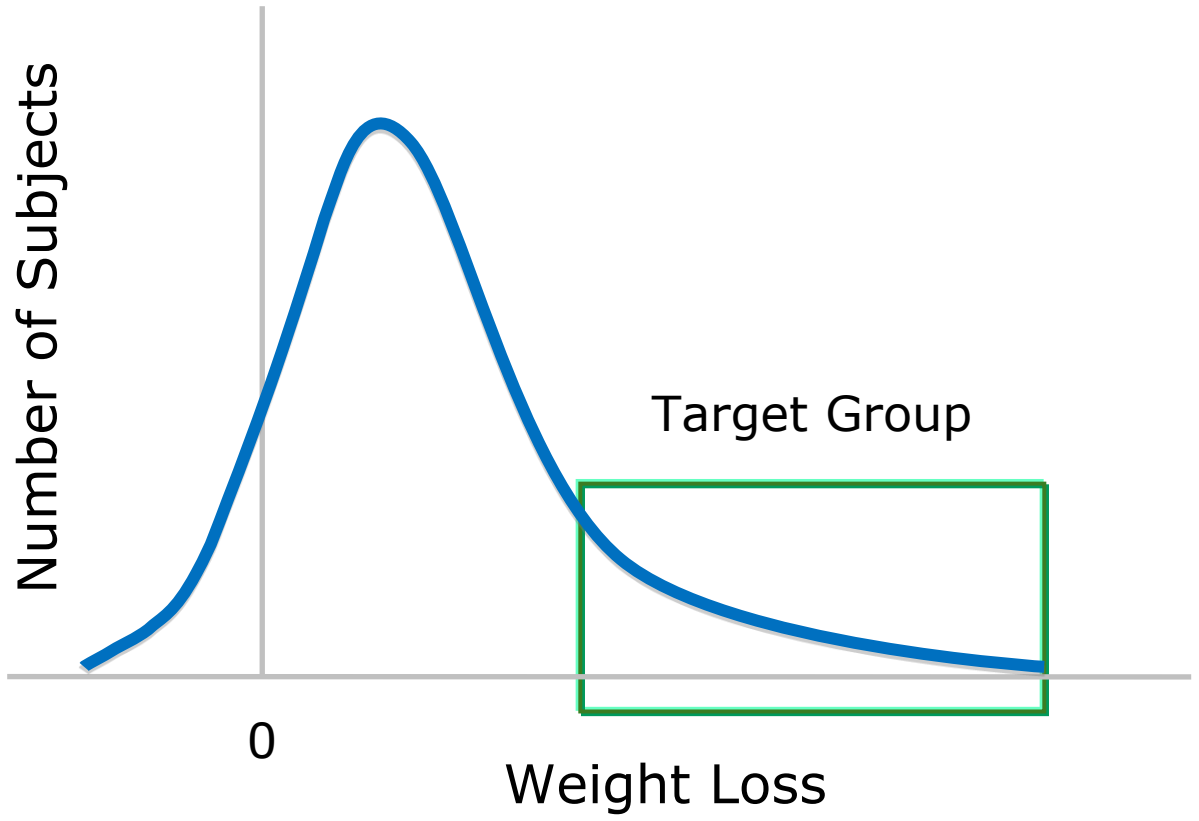
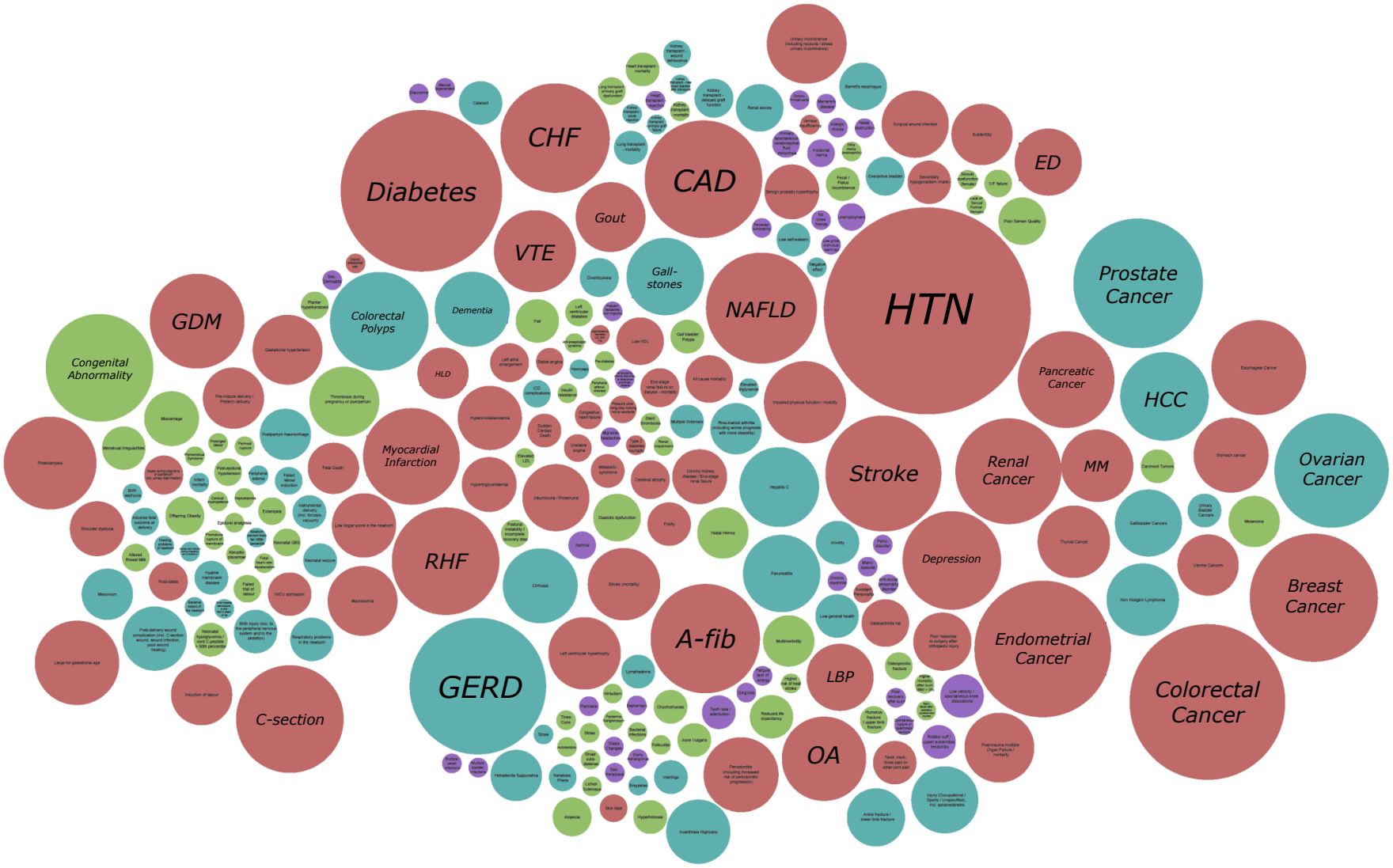
Heterogeneity of treatment response



The price of obesity

Color	GRADE	Strength of evidence
	4	Very strong
	3	Strong
	2	Moderate
	1	Weak

Size of circle reflects number of articles



Yuen M... Kaplan LM, *Obesity* 2016

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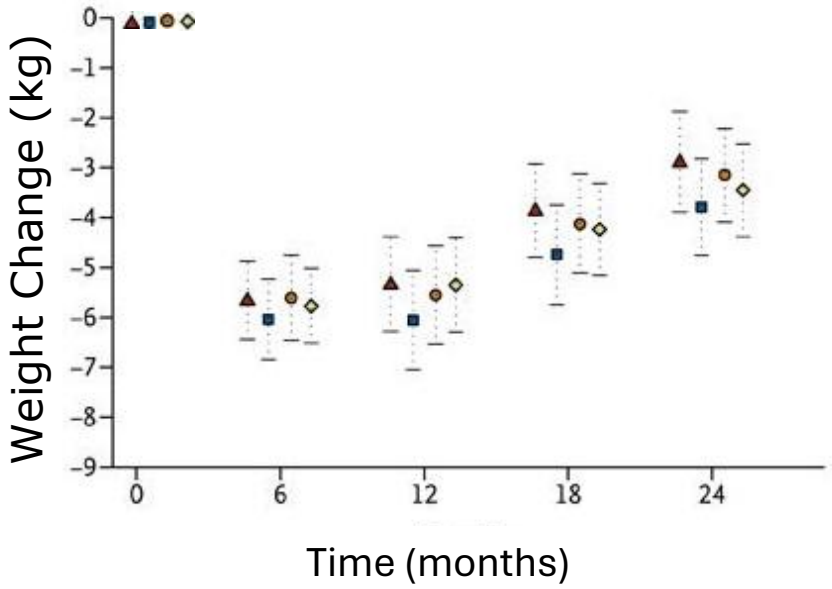
POUNDS Lost study

- Randomized controlled trial of 4 diets
- Diets varied widely in carbohydrate, fat and protein content
- Initial intensive calorie restriction followed by “maintenance” phase

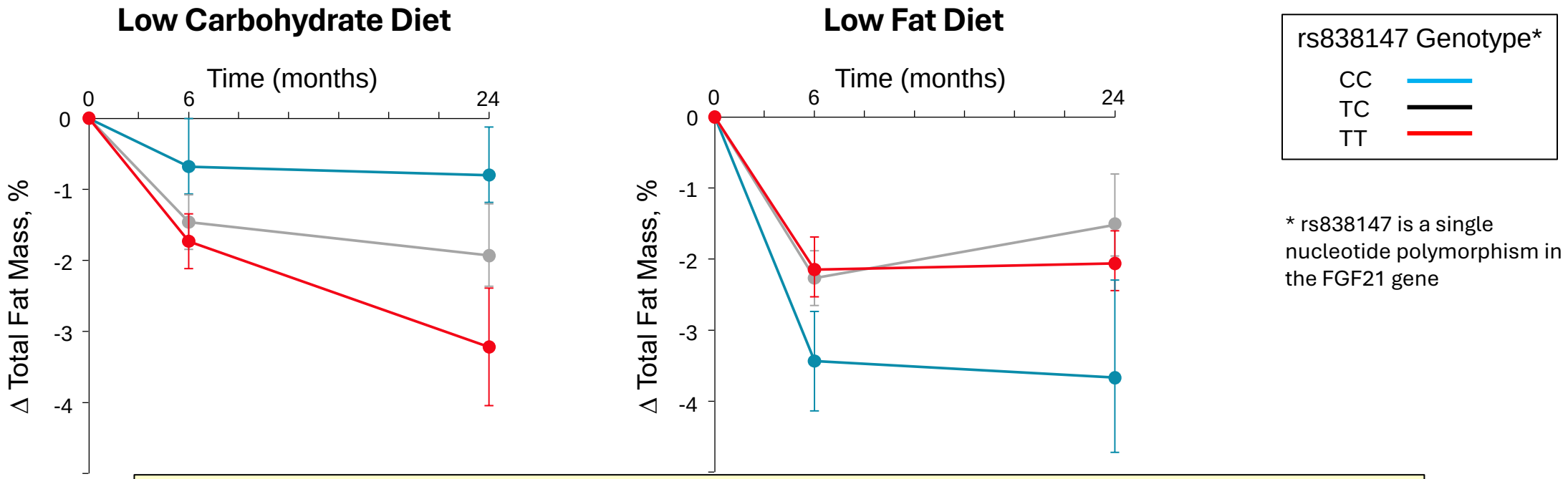


Conclusion: Nutrient content doesn’t matter – a calorie is a calorie

Sacks F *et al*. *NEJM* 2009

An FGF21 gene polymorphism is associated with differential response to specific diets

POUNDS Lost Study (2009)
Genome-wide Association (2016)



* rs838147 is a single nucleotide polymorphism in the FGF21 gene

Same study, NEW conclusion: Dietary composition is critical

Heianza *et al.*, *Diab Care* 2016

Variable response to obesogenic environmental influences

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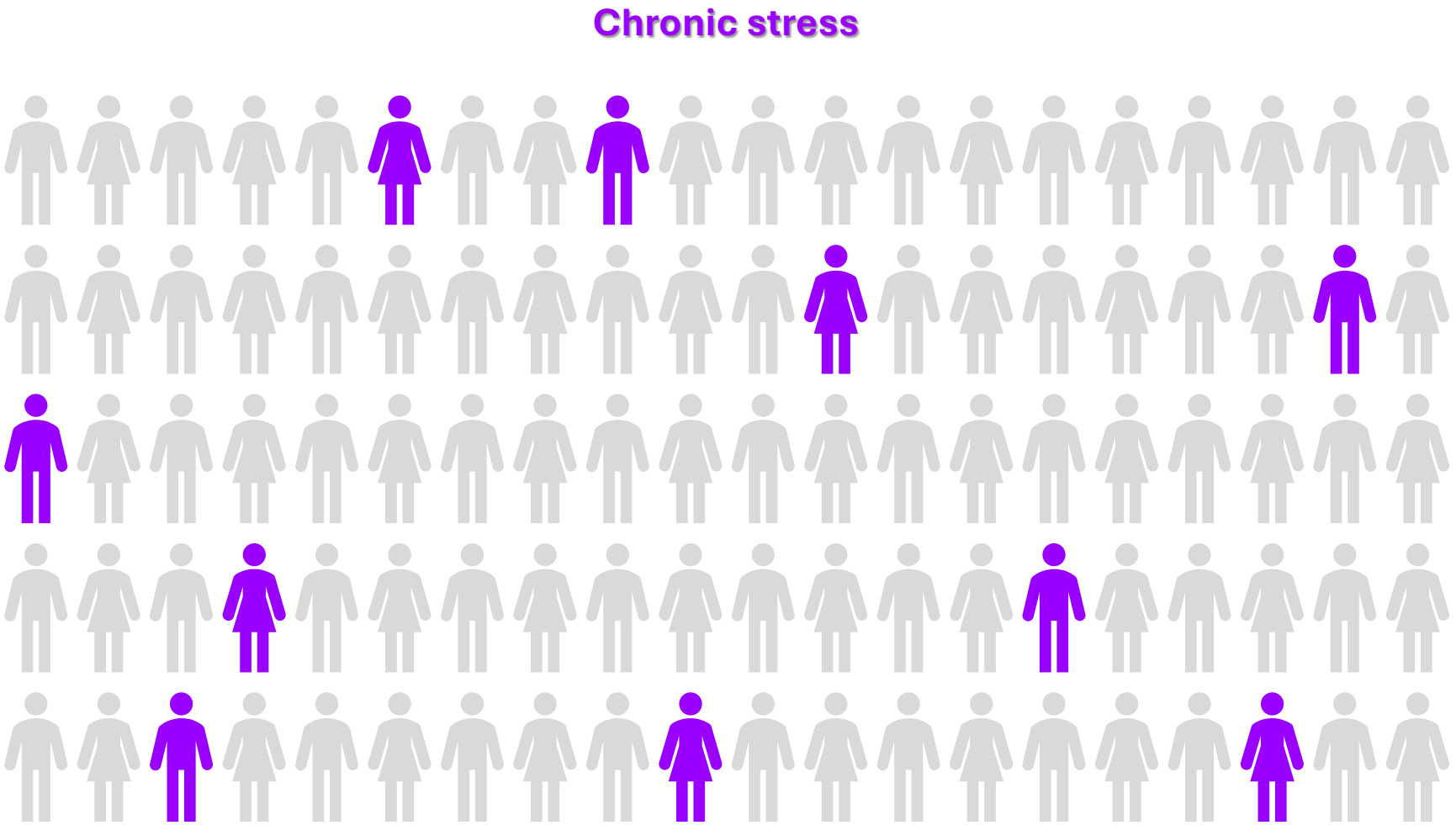
Variable response to obesogenic environmental influences



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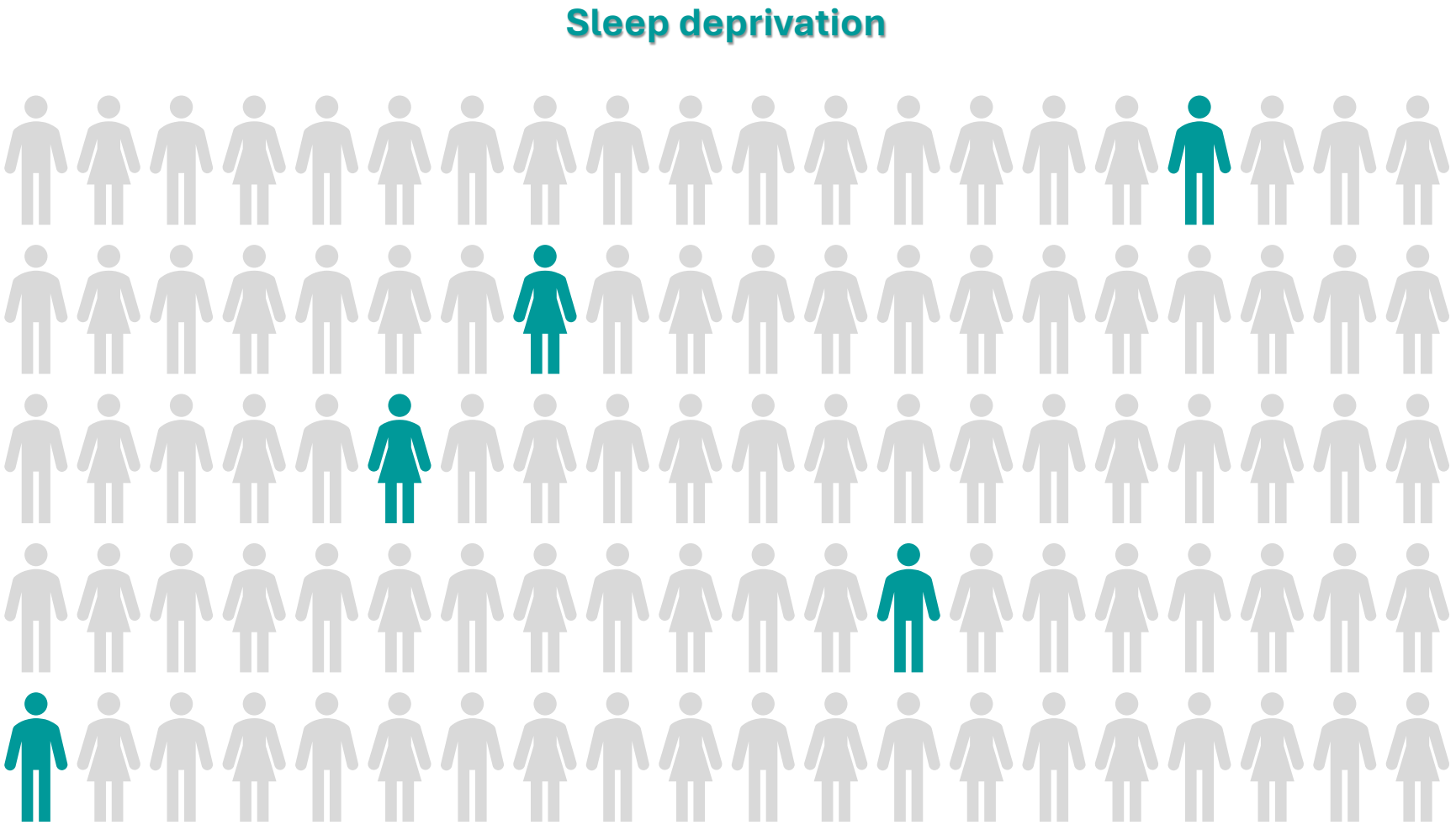
Variable response to obesogenic environmental influences



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How do environmental influences cause the disease of obesity?

Could this knowledge reveal new treatment targets?

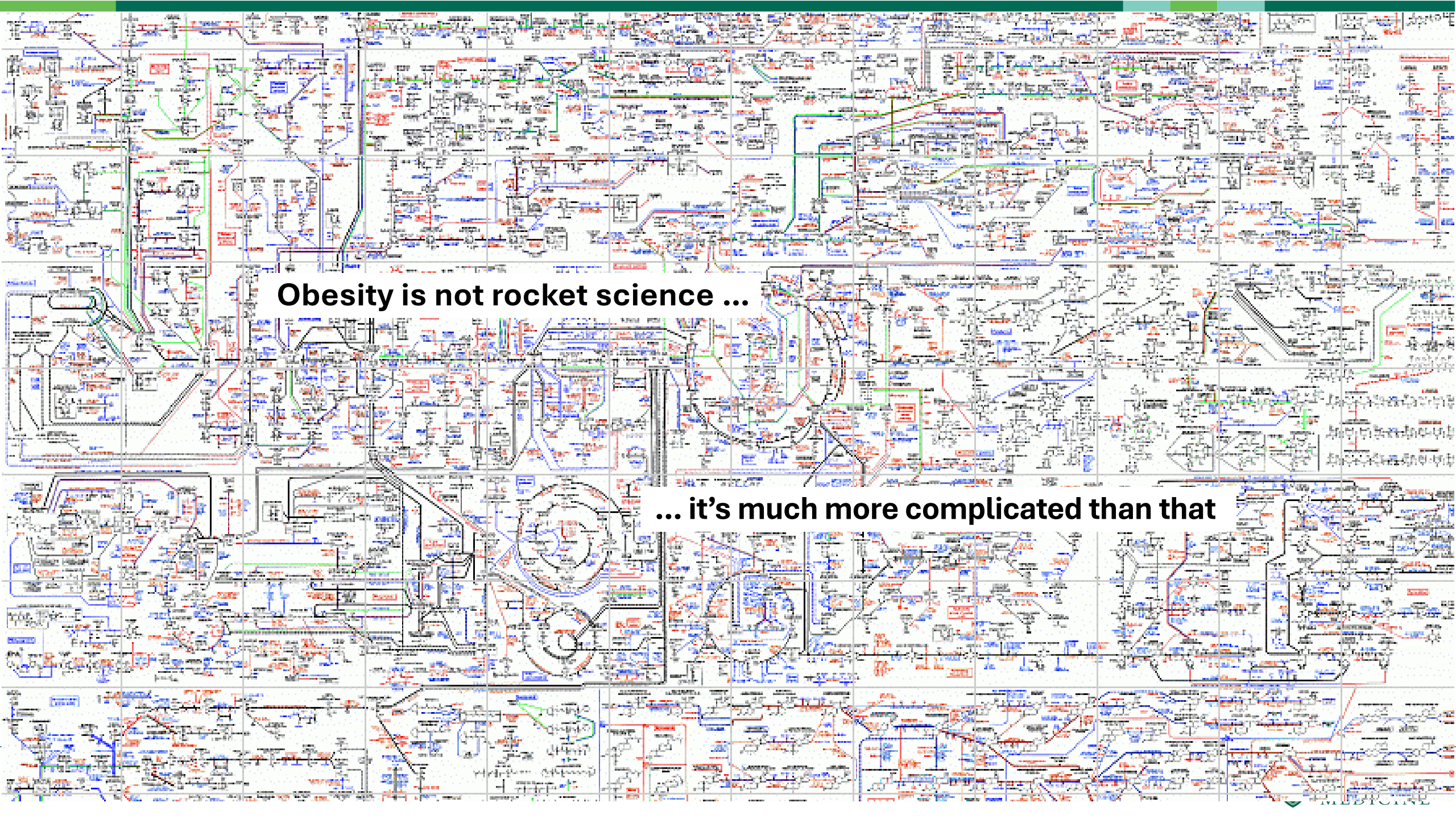
How do we **protect other tissues** during effective obesity treatment?

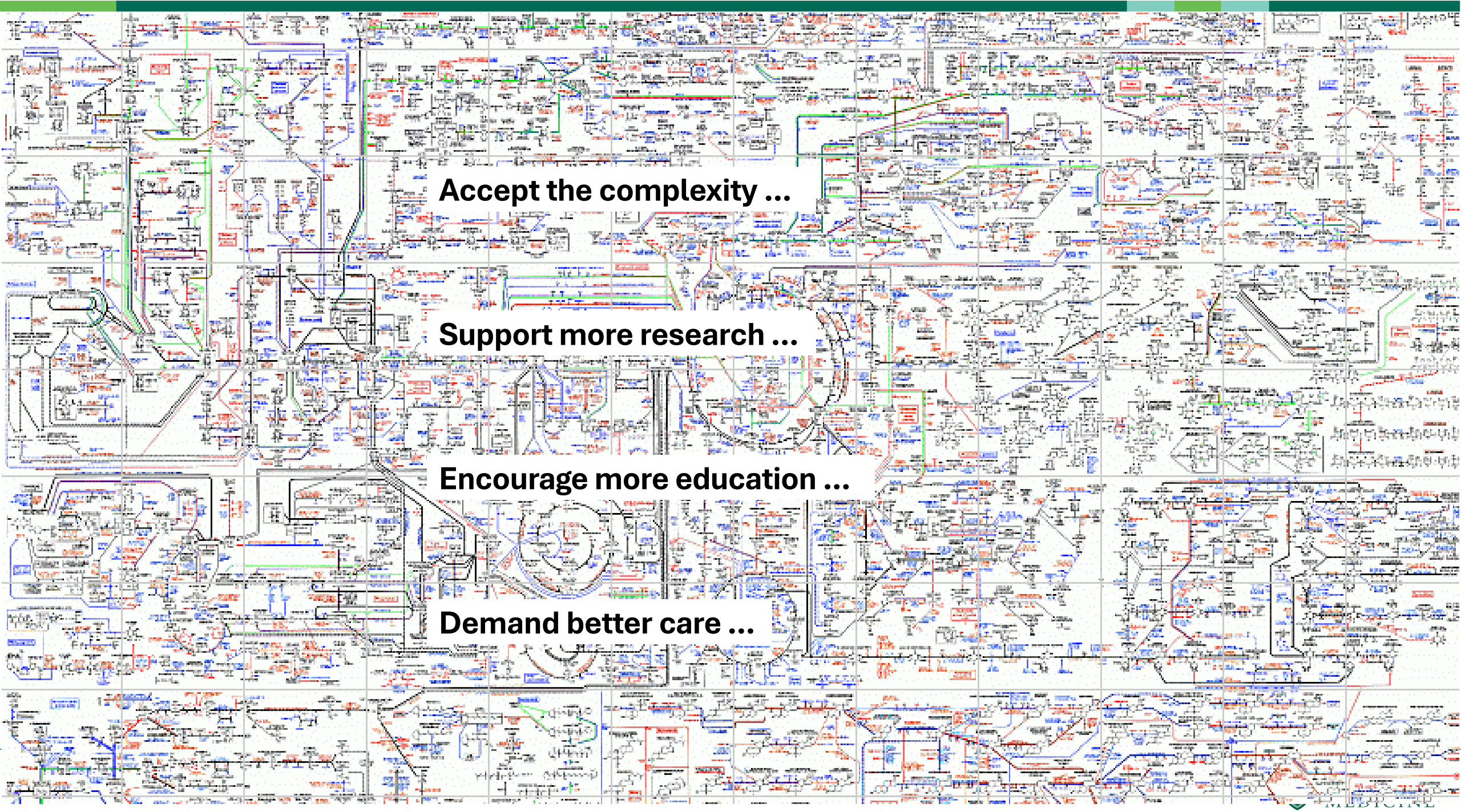
Muscle

Bone

Brain

What are the mechanisms governing growth and function of these tissues, **independent of fat regulation**?


Obesity is not rocket science ...
... it's much more complicated than that


Accept the complexity ...
Support more research ...
Encourage more education ...
Demand better care ...

> The greatest enemy of knowledge is not ignorance.
>
> It is the illusion of knowledge.
>
> Prof. Stephen Hawking

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