Variable Outcomes After Metabolic Surgery:

Science or Selection?

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Disclosures

- Amgen (research grant)
- Amylyx (consulting)
- Eli Lilly (member of steering committee of a clinical trial)
- Ethicon (research grant, consulting)
- iRhythm (research grant)
- Medtronic (research grant, consulting)
- NIH (research grant)

“Individual” Response

Always

Varies

With Any Therapy

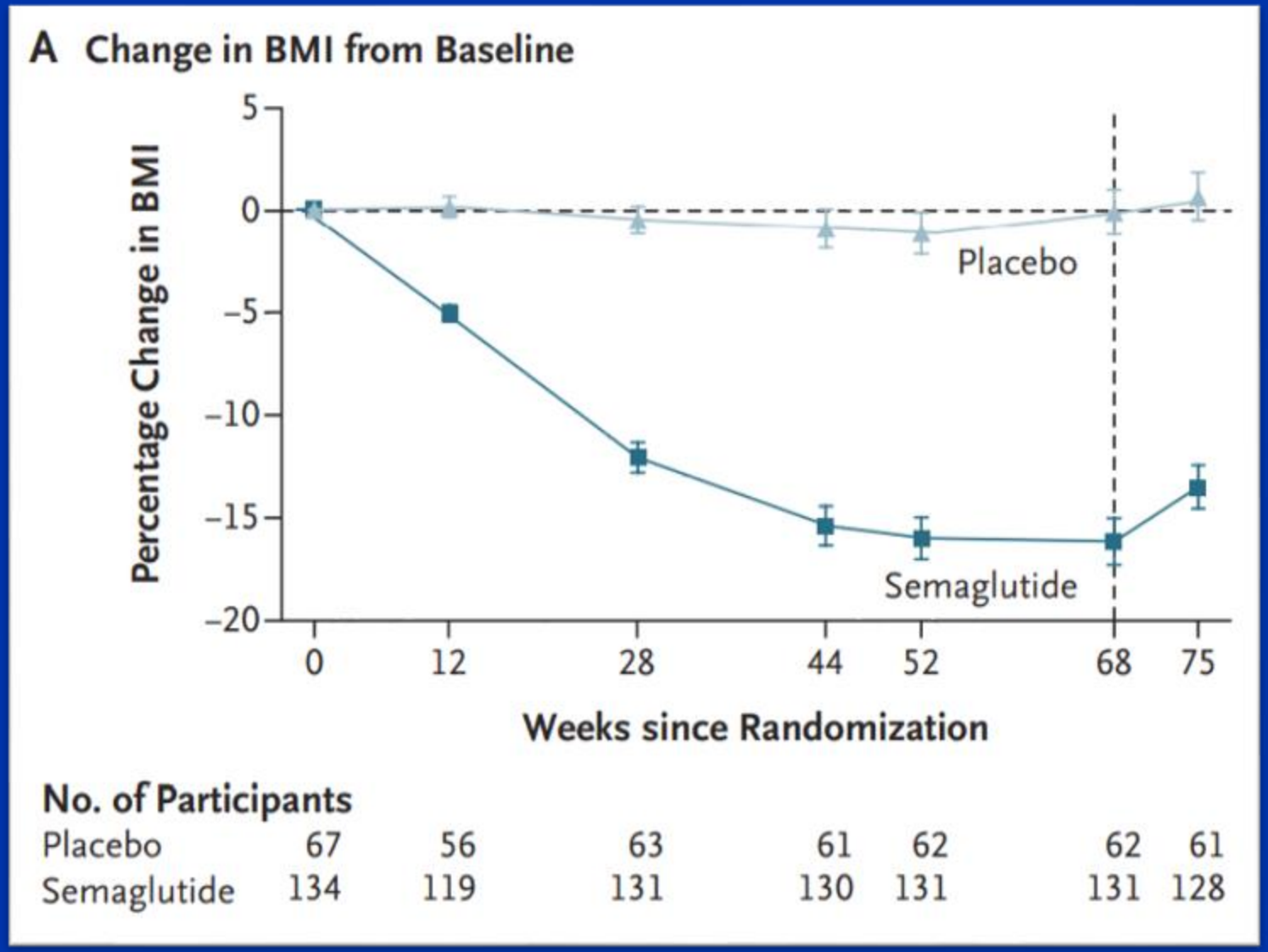
Response Varies All the Time

- **Cancer response to chemotherapy**
  - Cure vs Death

Response Varies All the Time

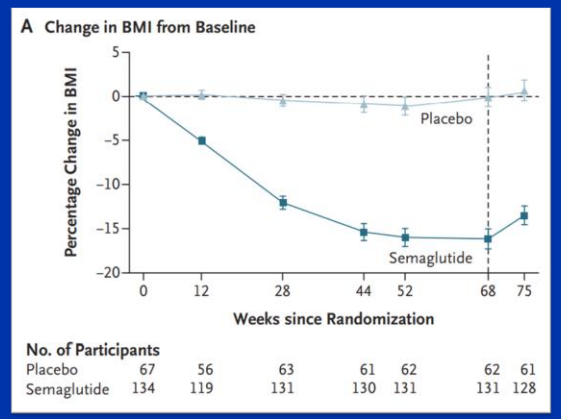
- **Cancer response to chemotherapy**
  - Cure vs Death
- **Lupus response to anti-inflammatory drugs**
  - Remission vs Progression

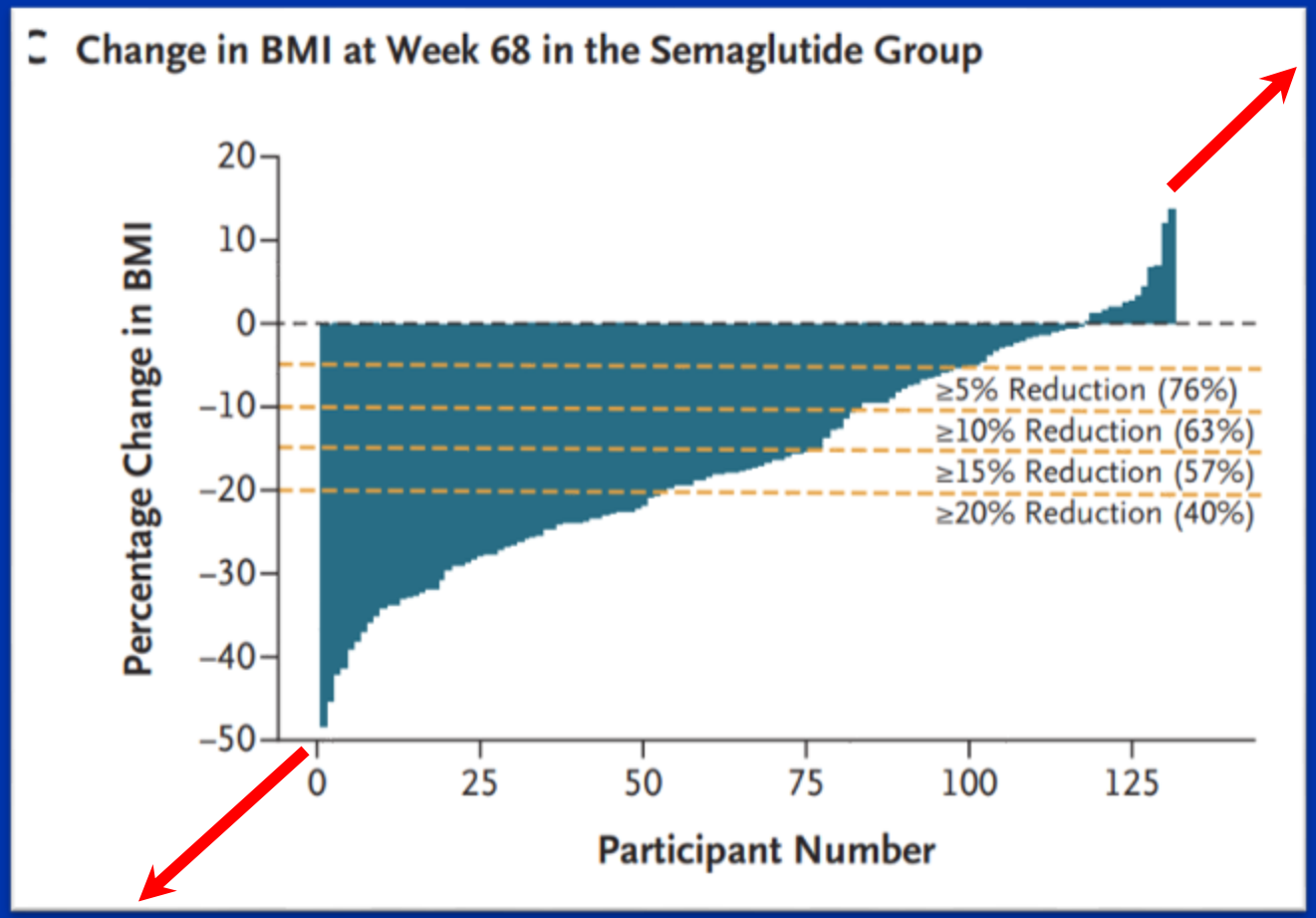
Once-Weekly Semaglutide in Adolescents with Obesity



STEP TEENS. NEJM 2022

Once-Weekly Semaglutide in Adolescents with Obesity





Gained 10%

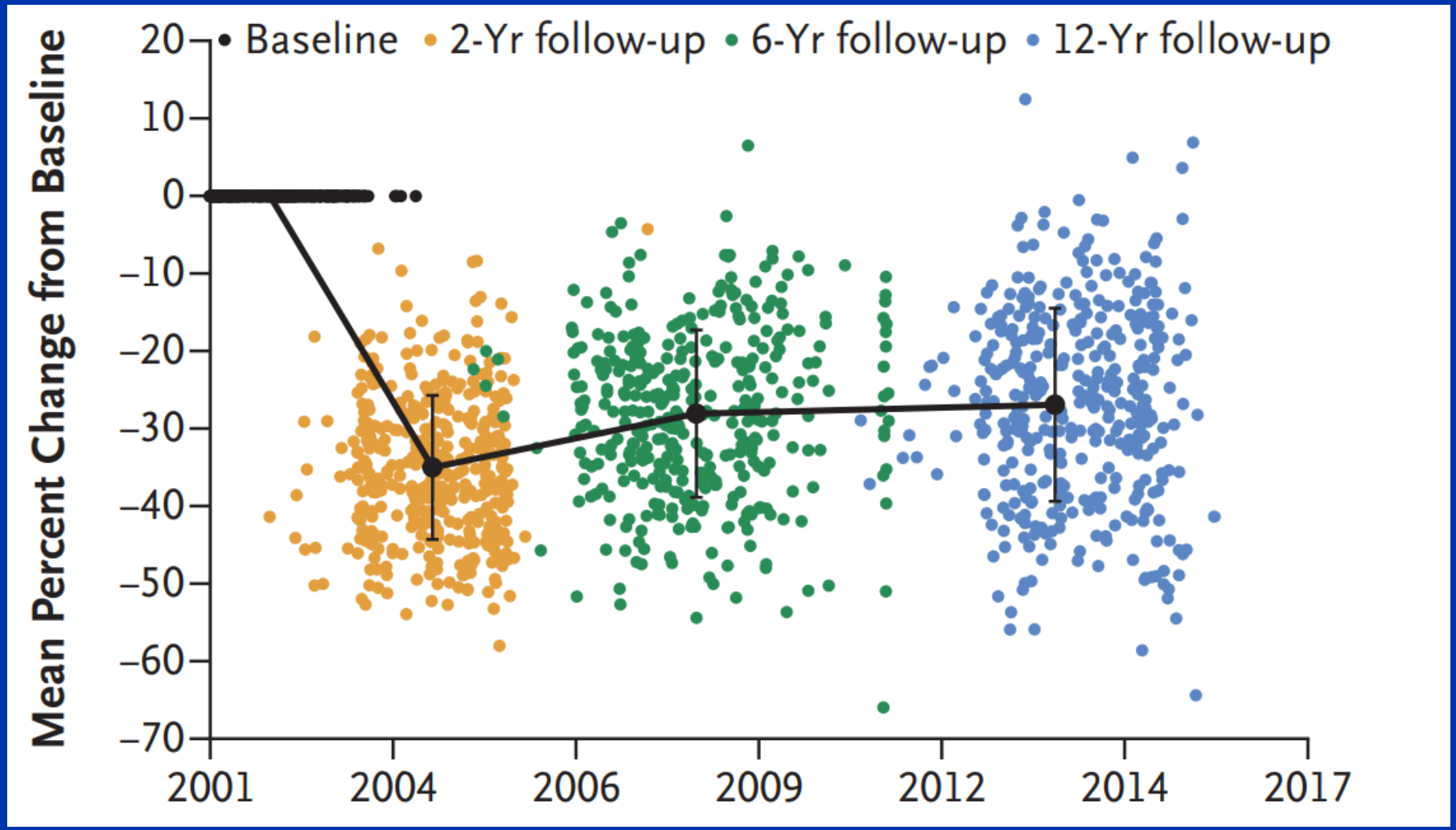
Lost 50%

STEP TEENS. NEJM 2022

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Weight and Metabolic Outcomes 12 Years after Gastric Bypass



NEJM 2017

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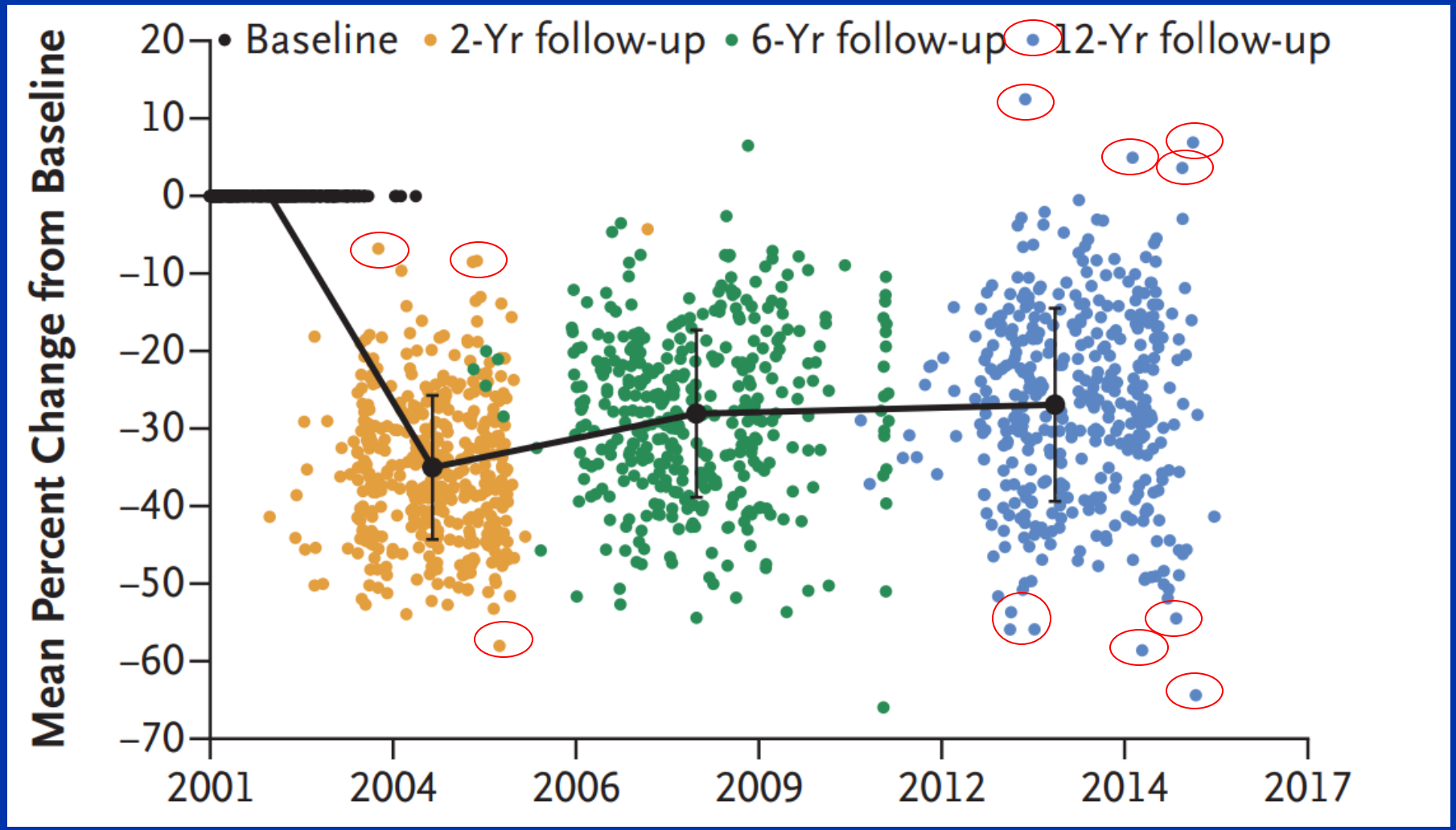
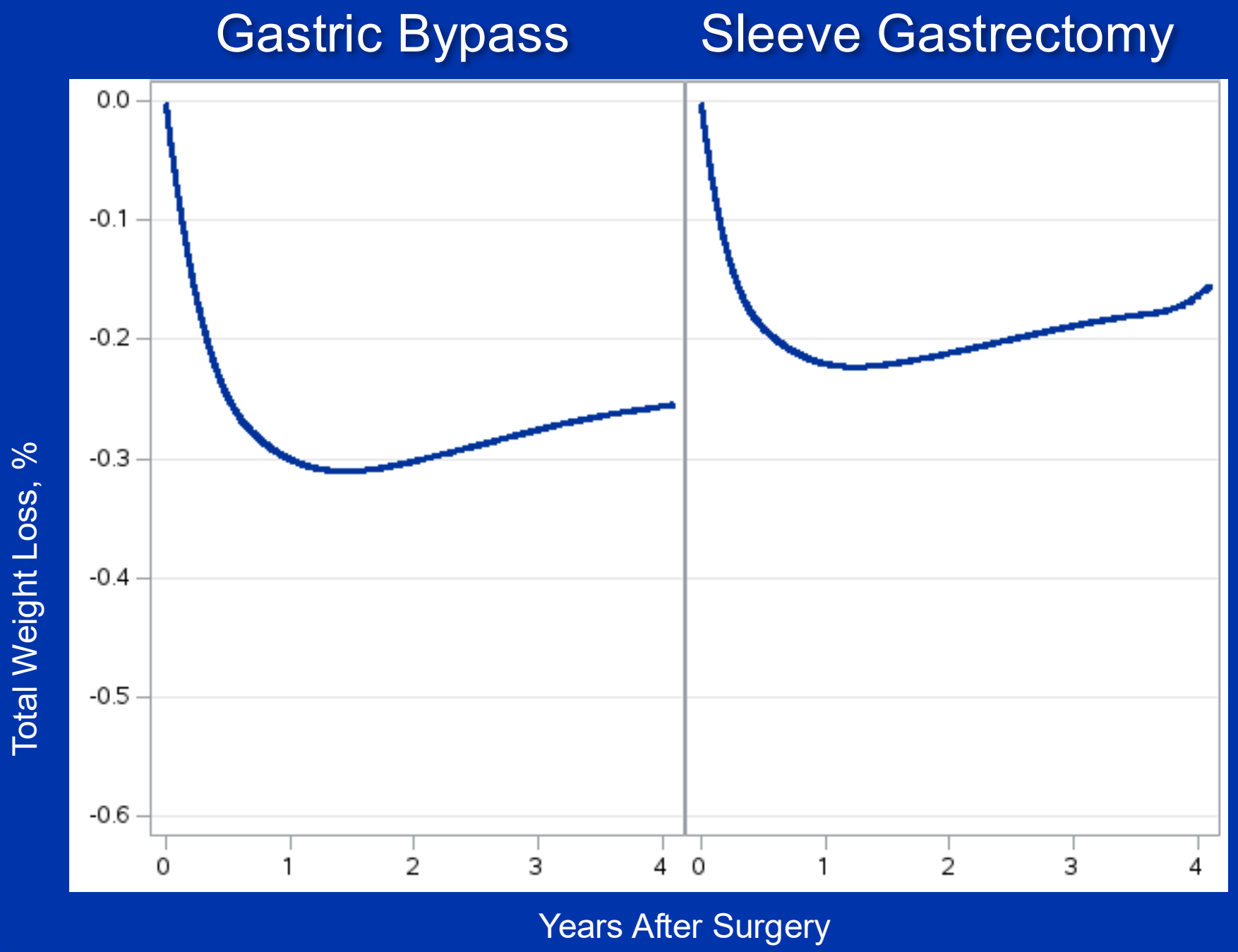


NEJM 2017

Individual Response to RYGB and SG



Aminian, Surg Endosc 2024

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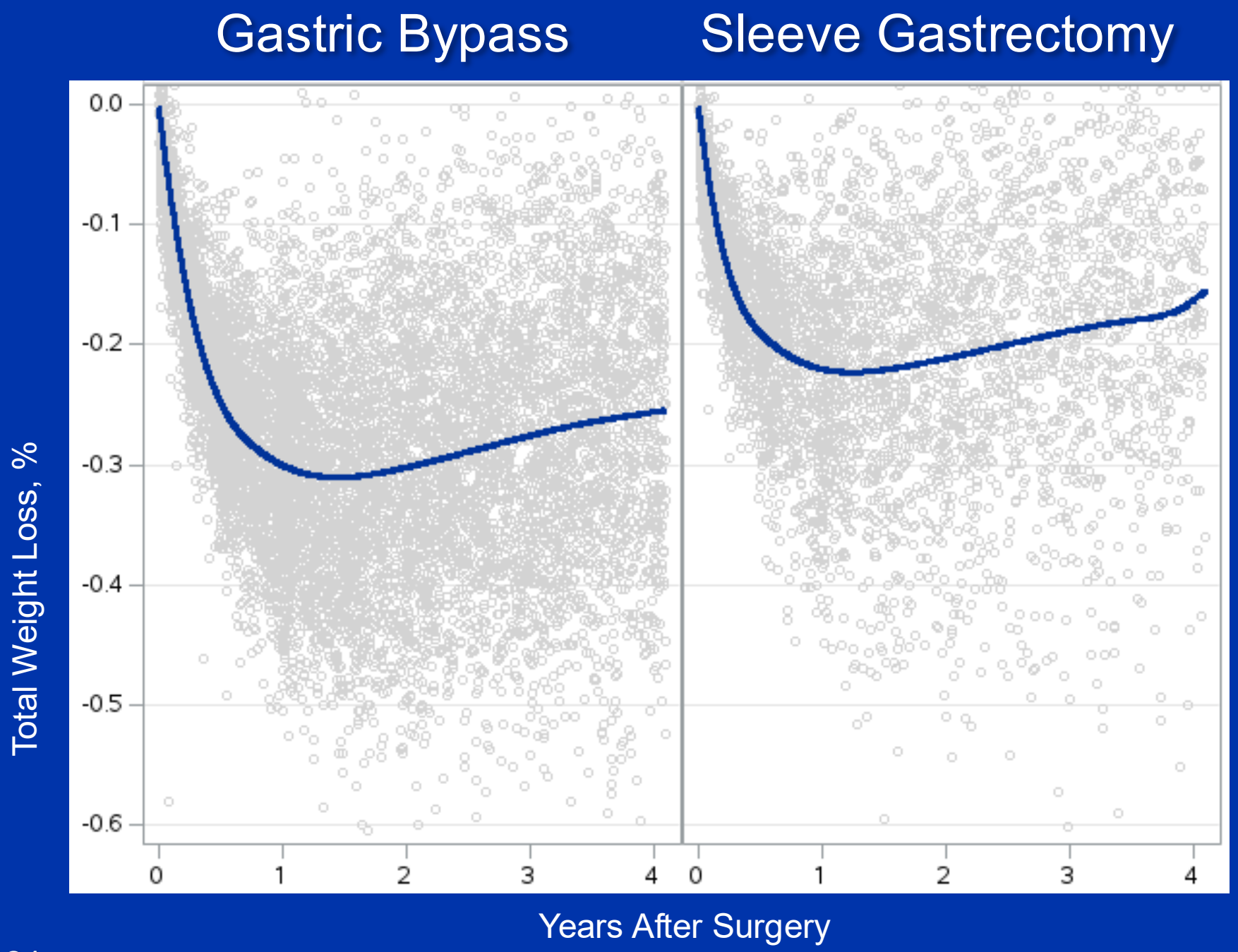

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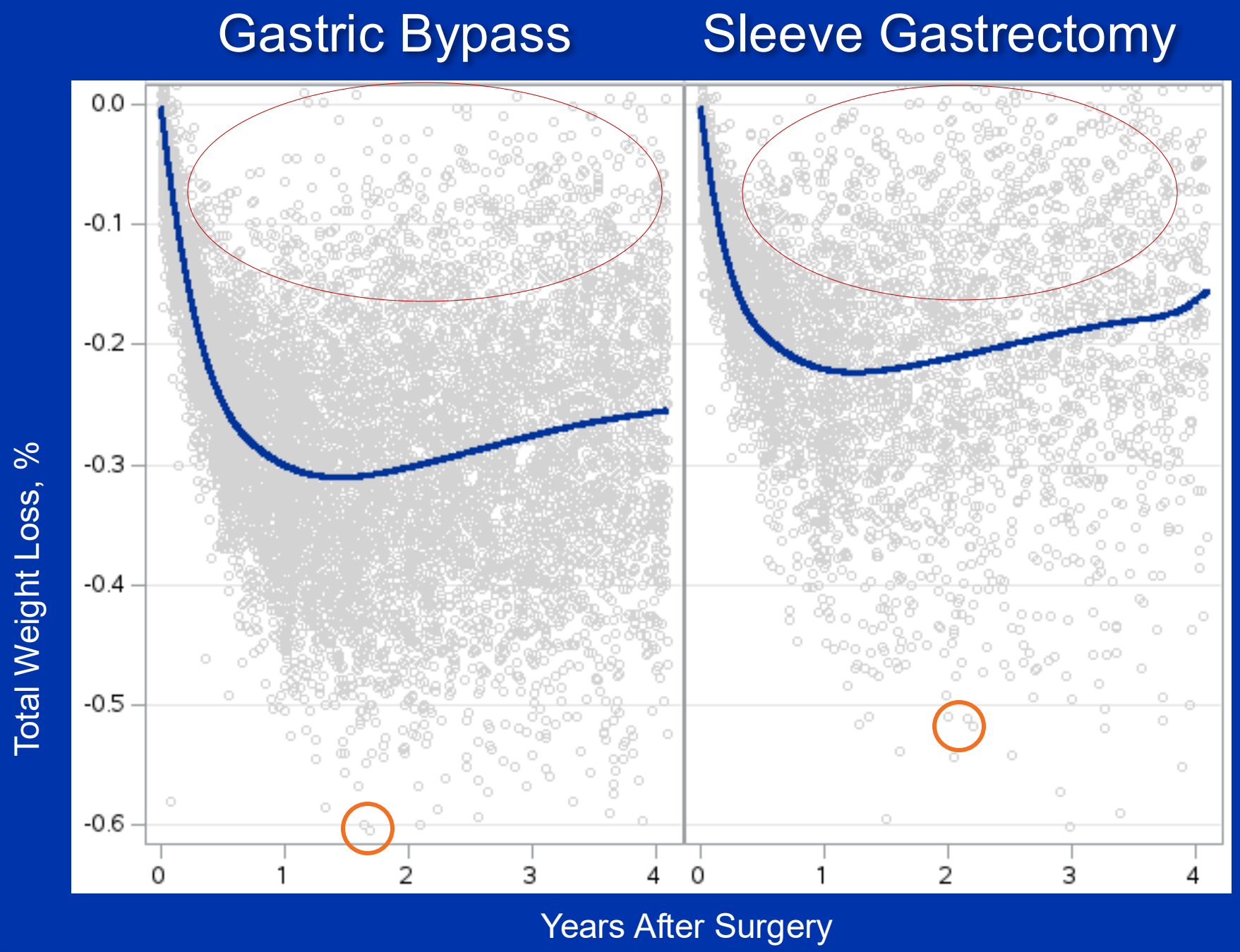


Aminian, Surg Endosc 2024

Why Variable Outcomes?

Whatever Dr Cummings Just Explained Applies Here Too

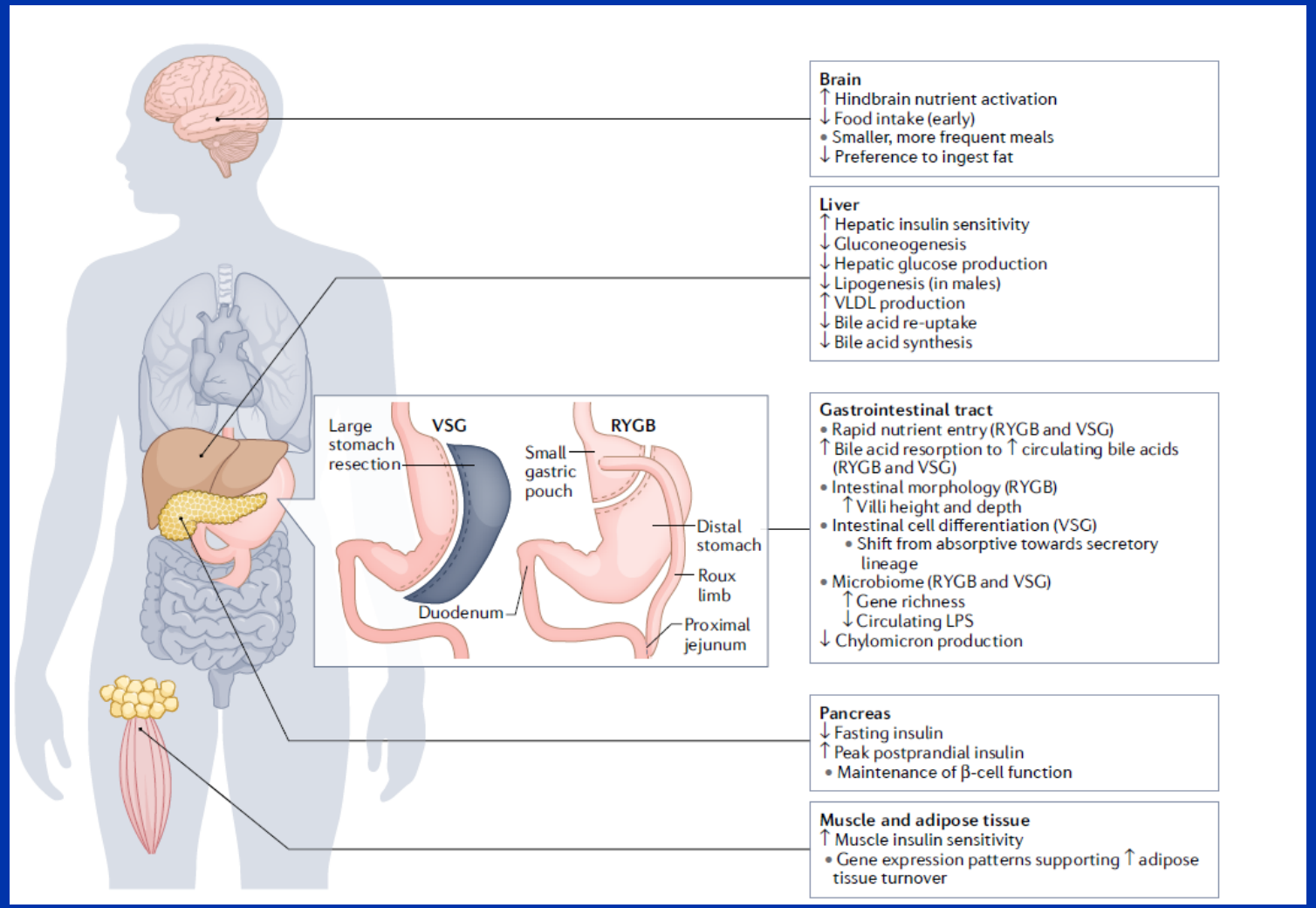
Selection Explains Some

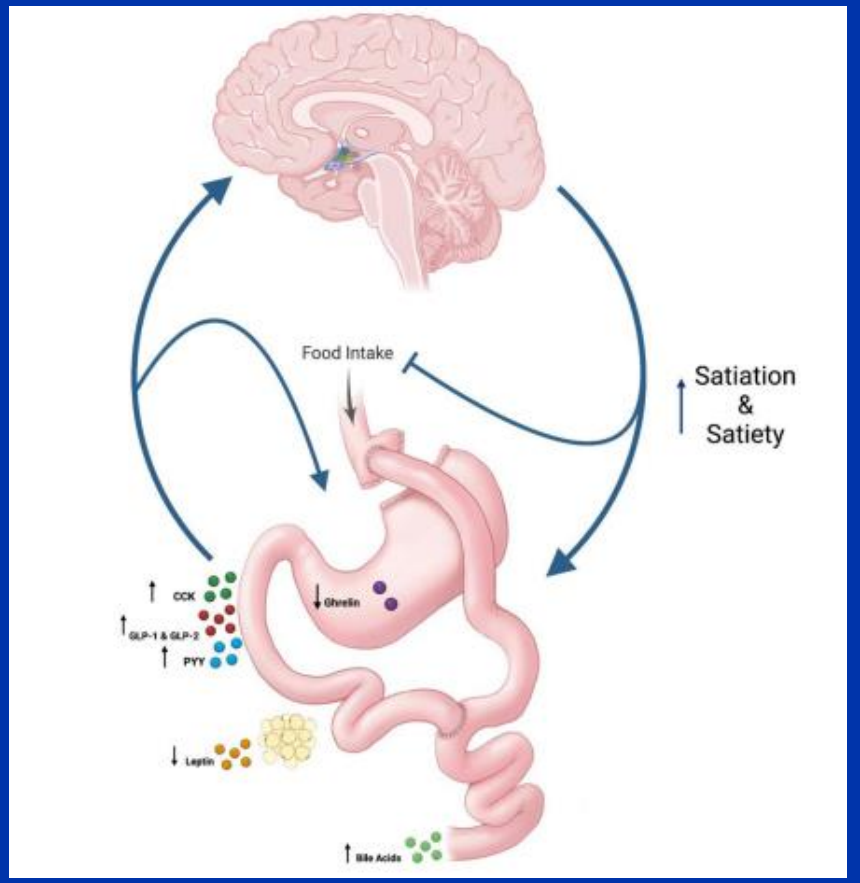
Behavior Explains Some

Biology Explains More

Multiple Mechanisms of Action Support Longterm Effect of Bariatric Surgery

Response is heterogeneous, not always sustained





Sandoval, Patti. Nat Rev Endocrinol 2023
Pucci, Batterham. Endotext 2020

Variable Outcomes After Metabolic Surgery

Multifactorial

1. ANATOMICAL

- Poorly constructed anatomy
- Pouch dilation
- Enlarged GJ anastomosis
- Gastro-gastric fistula
- Dilated sleeve

2. BEHAVIORAL

- Unhealthy diet pattern
- Loss-of-control eating
- Grazing
- Low physical activity
- Alcohol use / abuse

3. PSYCHOSOCIAL & CARE-RELATED

- Depression / anxiety
- Non-adherence
- Lack of follow-up
- Limited support
- Social determinants / environment

4. MEDICAL / PHARMACOLOGIC

- Weight gain–promoting medications
- Endocrine disorders
- Sleep deprivation
- Smoking cessation
- New medical comorbidities

5. RESISTANT BIOLOGY

- Adaptive thermogenesis
- Persistent hunger / hyperphagia
- Reduced satiety signaling
- Energy expenditure adaptation
- Neurohormonal compensation

6. GENETIC / GENOMIC FACTORS

- Polygenic susceptibility
- MC4R pathway variants
- Appetite / satiety pathway variants
- Reward pathway differences
- Pharmacogenomic variability

Outcomes after metabolic surgery result from a complex interplay of anatomical, behavioral, medical, biological, genetic, and psychosocial factors. A **comprehensive, personalized approach** is essential for long-term success.

Check for Weight Gain Promoting Medications

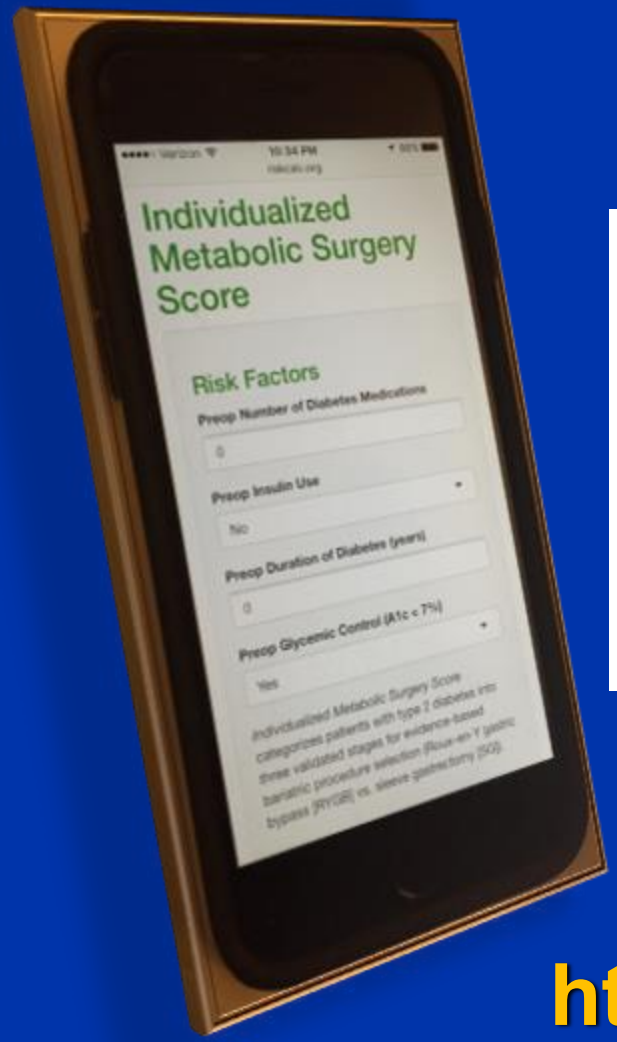
Depression Tricyclics eg. trazodone, nortriptyline, amitriptyline SSRIs eg paroxetine, citalopram, escitalopram Others eg mirtazipine, venlafaxine	**Diabetes** Insulin Sulfonylureas eg glipizide Thiazolidinediones eg pioglitazone
Atypical antipsychotics Clozapine, olanzapine, quetiapine, risperidone, aripiprazole	**Hypertenion** Betablockers, Propranolol, metoprolol, atenolol
Seizures Gabapentin, valproic acid	**Allergy** Diphenhydramine, hydroxyzine, cetrizine, fexofenadine
Miscellaneous Lithium	**Glucocorticoids** Prednisone, methylprednisone
Other Tamoxifen, HAART	**Contraception** Depoprovera

Preoperative Predictors: Useful, but Incomplete

- Age
- Baseline BMI
- Diabetes duration, insulin use, HbA1c
- Procedure type
- Eating behavior
- Depression/anxiety
- Sleep
- Medications

Diabetes as a Precision-Surgery Example

Individualized Metabolic Surgery (IMS) Score



ANNALS OF SURGERY
A Monthly Review of Surgical Science Since 1885

Individualized Metabolic Surgery Score: Procedure Selection Based on Diabetes Severity

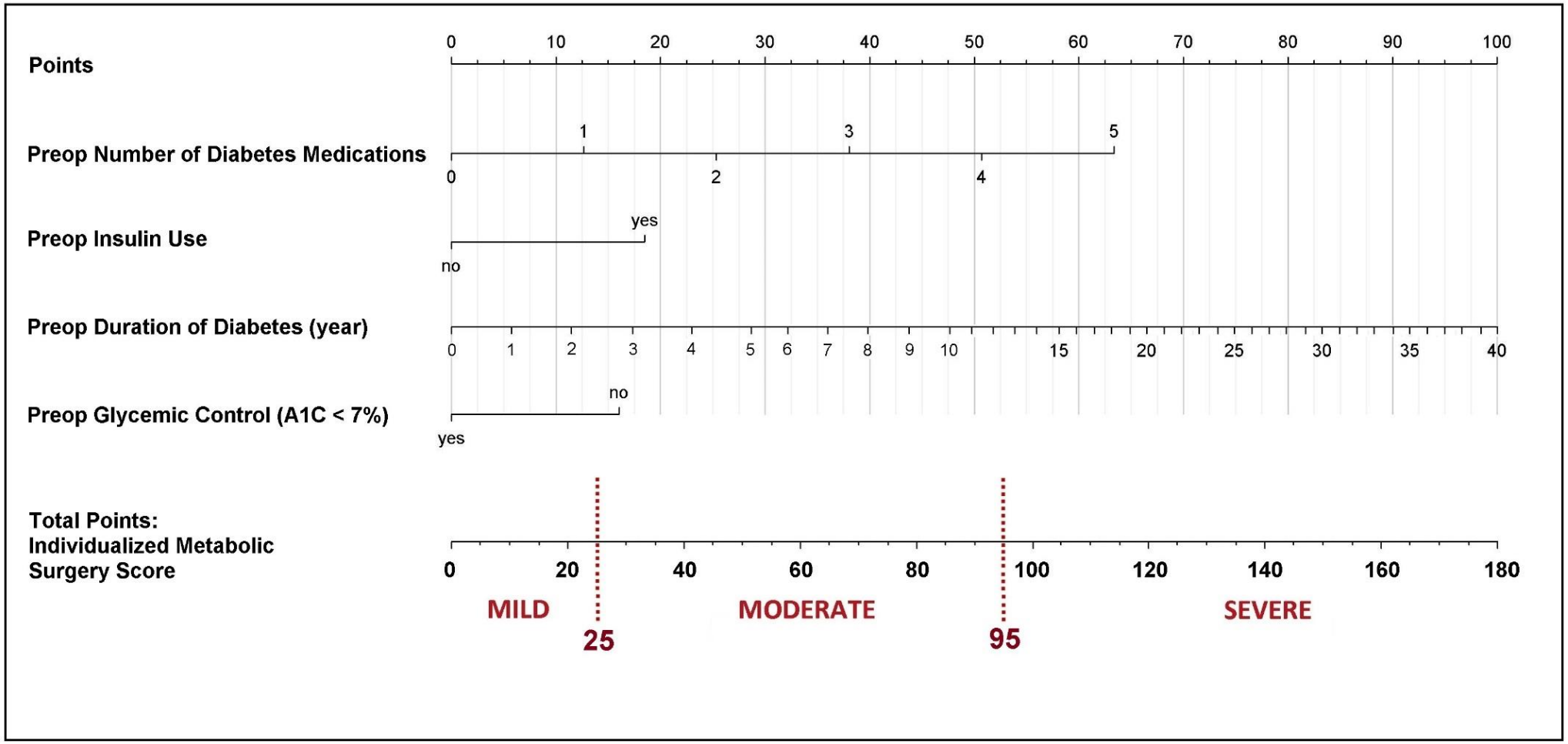
Ali Aminian, MD, Stacy A. Brethauer, MD,* Amin Andalib, MD, MSc,† Amy S. Nowacki, PhD,‡ Amanda Jimenez, MD, PhD,§ Ricard Corcelles, MD, PhD,§ Zubaidah Nor Hanipah, MD,*¶ Suriya Punchai, MD,*|| Deepak L. Bhatt, MD, MPH,** Sangeeta R. Kashyap, MD,†† Bartolome Burguera, MD, PhD,*†† Antonio M. Lacy, MD, PhD,§ Josep Vidal, MD, PhD,§‡‡ and Philip R. Schauer, MD**

BariatricCalc

Available on the App Store

Get it on Google play

http://riskcalc.org



Remission after RYGB vs. SG (Model Generating Data)	92% vs. 74%	60% vs. 25%	12% vs. 12%
Remission after RYGB vs. SG (Validation Data)	91% vs. 91%	70% vs. 56%	8% vs. 3%
Recommendation in Average Risk Patients	**RYGB is suggested.** Both procedures are highly effective.	**RYGB is recommended.** SG is less effective.	**SG is suggested.** Both procedures are less effective.

Individualized Metabolic Surgery (IMS) Score:

Bariatric Procedure Selection Based on Diabetes Severity

Surgery for Type 2 Diabetes:

Roux-en-Y Gastric Bypass

VS.

Sleeve Gastrectomy

4 Predictors of Diabetes Remission:

- Diabetes Duration
- Diabetes Med #
- Insulin Use
- Glycemic Control

NOMOGRAM

3 Stages of Diabetes Severity:

- **Mild** (IMS Score ≤25)
- **Moderate** (25< IMS ≤95)
- **Severe** (IMS score >95)

Procedure of Choice:

- ***Suggestion:*** 
- ***Recommendation:*** 
- ***Suggestion:*** 

BariatricCalc

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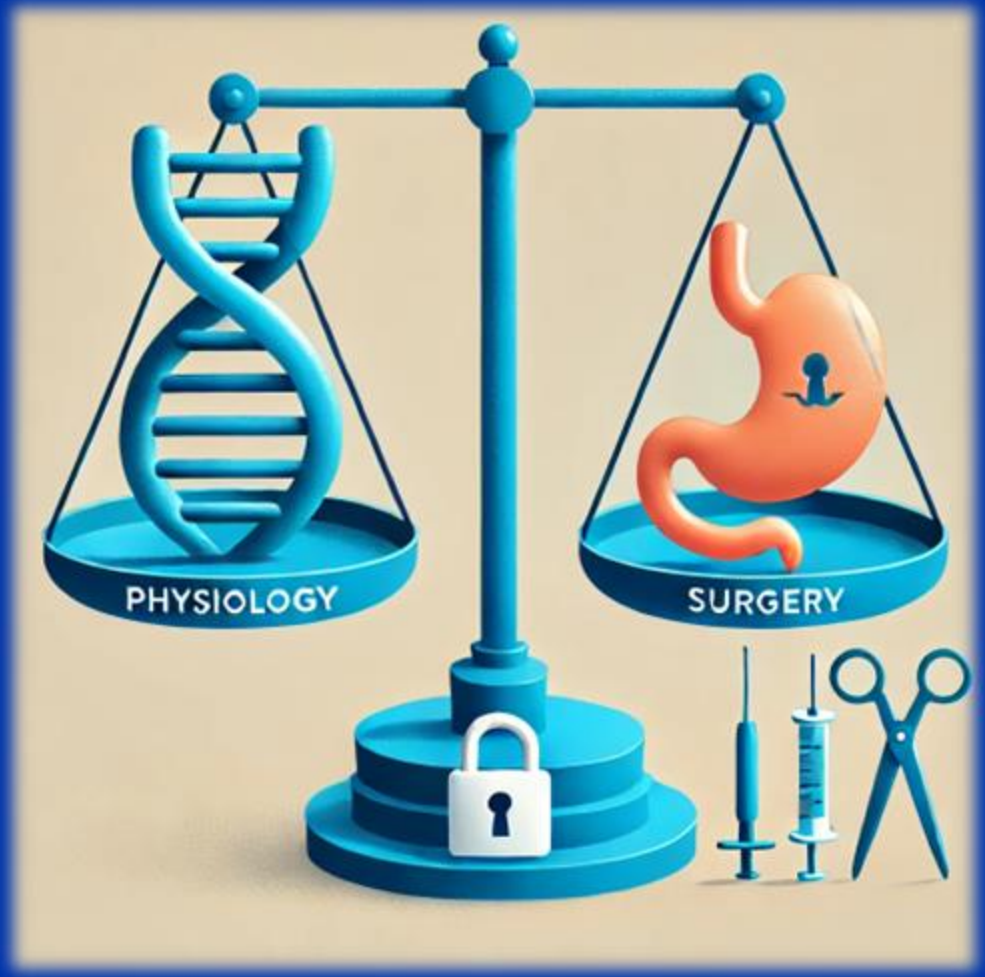
Aminian et al. *Ann Surg.* 2017

Surgery Can’t Fully Overcome Resistant Physiology



Genomic Predictors:
Promising but not ready for routine clinical use

- Polygenic scores show more promise than single genes.
- Single genes such as FTO and MC4R have inconsistent effects.
- Prediction is improving, but clinical utility and generalizability remain uncertain.
- Take-home: Genomics may eventually help personalize treatment, but cannot yet select the operation for an individual patient.

Gupta et al. Obes Surg. 2021

How to Improve Outcomes of Surgery?

- Patient selection
- Procedure selection
- Optimal surgical technique
- Postop behavioral interventions
  - Dietary
  - Physical activity
  - Sleep
  - Mental health
- Adjuvant pharmacotherapy
- 2nd bariatric surgery

Technical Aspects

- Perform good surgery!
- To the best of our scientific understanding:
  - Sleeve:
    - Bougie size 36-40
    - Don’t leave posterior fundus
  - RYGB:
    - Pouch should exclude funds
    - Stoma size ~15-25 mm
  - Anastomotic procedures:
    - Limb lengths

Future of Obesity Treatment

- Personalized therapy selection
- Genomic predictors of response
- Biomarker-guided treatment selection
- Multi-omics and AI decision support
- Tailored combination therapy (Medication +/- Surgery)

Summary

- Variable outcomes are expected in a chronic, heterogeneous disease.
- Selection, anatomy, behavior, and medical factors explain part of the variability.
- Biology and genetics may explain much of what remains.
- The future is adaptive precision obesity care: right patient, right procedure, right combination of therapies.
- **Science AND selection, followed by lifelong adaptive care.**

Thank You

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