MAYO CLINIC

IFSO 2024

SMALL BOWEL EBMT

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DISCLOSURES

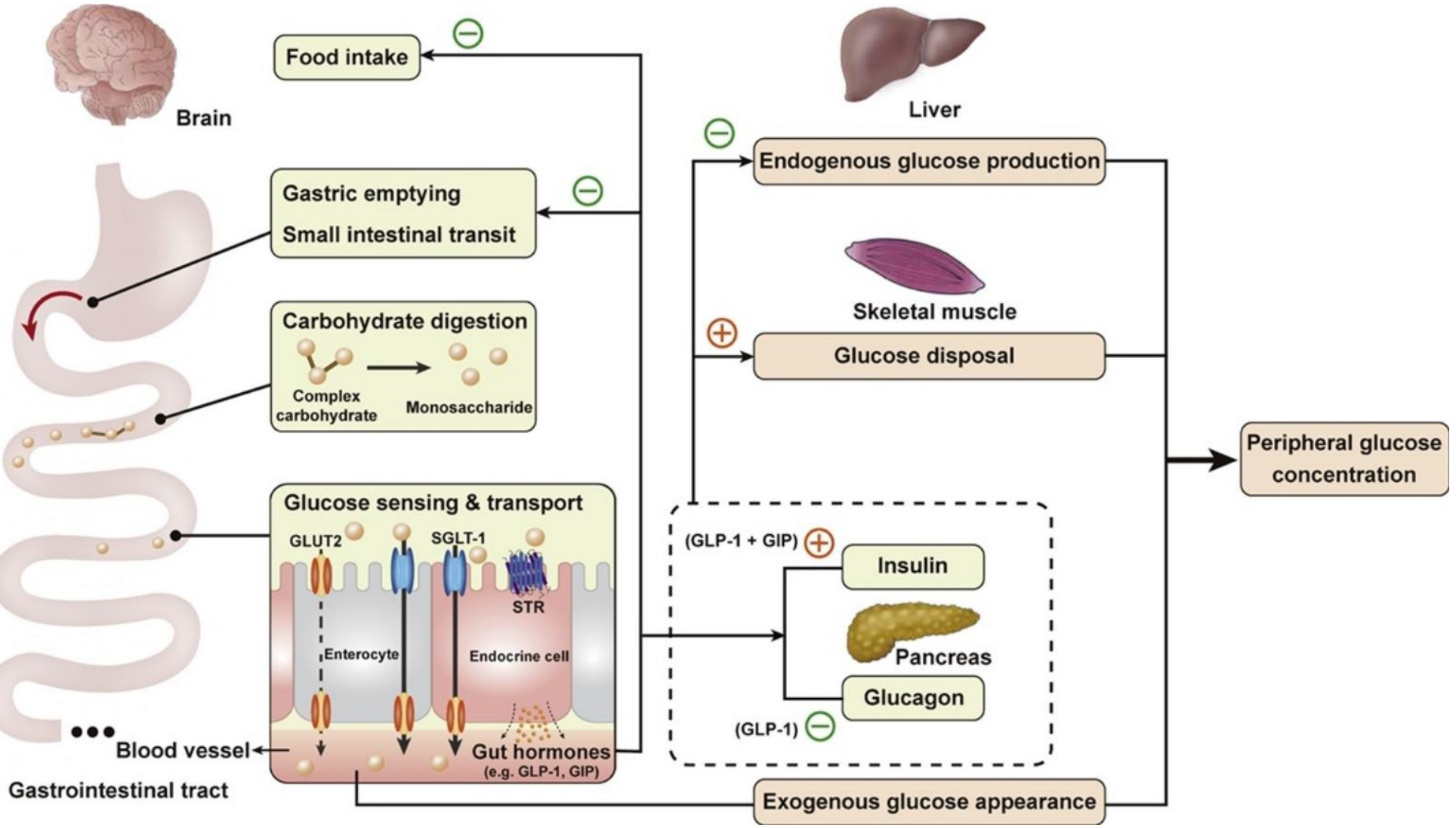
- **Consultant:** Boston Scientific, Olympus, Medtronic, Metamodix, BFKW, Apollo Endosurgery
- **Co-inventor:** Endogenex (licensed technology by Mayo Clinic)
- **Research Support:** Apollo Endosurgery, USGI, Endogastric Solutions, Boston Scientific, Medtronic, Spatz, Cairn.
- **Speaker:** Johnson & Johnson, Olympus, Endogastric Solutions

THE UNMET NEEDS

Scaling the benefits of metabolic surgery using the GI tract as therapeutic target

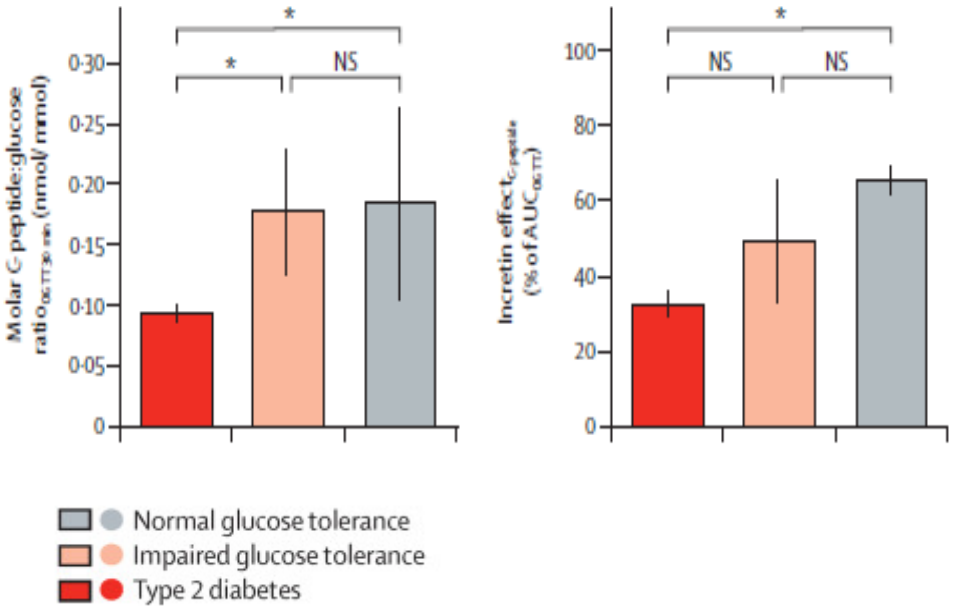
(The answer is in the GUT)

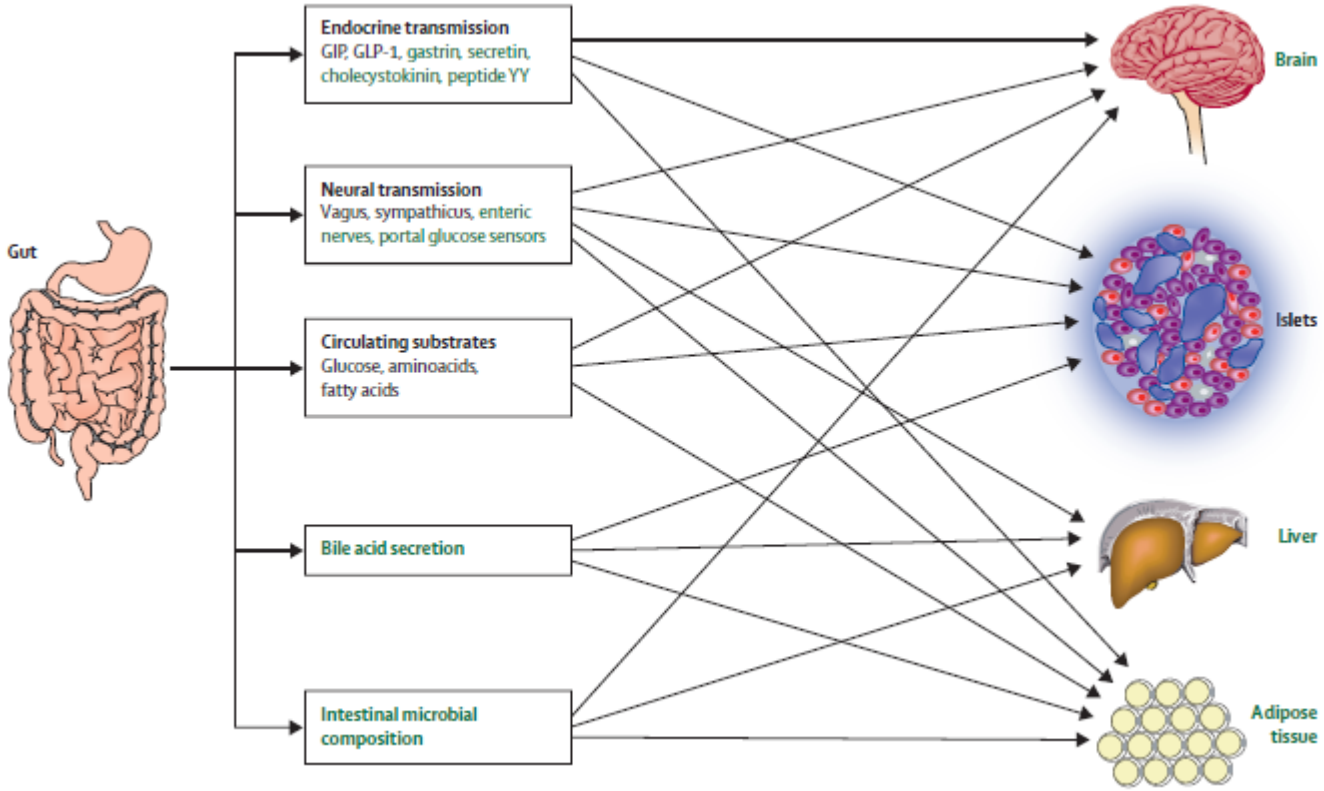
Metabolic Disease Starts in the Gut



The incretin effect in healthy individuals and those with type 2 diabetes: physiology, pathophysiology, and response to therapeutic interventions

Lancet Diabetes Endocrinol 2016; 4: 525–36





Giving the substrate (GLP-1 or GIP) without addressing the disease state has limitations

1) Dose-response relation between β-cell responsiveness to glucose and GLP-1 is severely impaired in patients with type 2 diabetes

Diabetes 2003;52(2):380–386

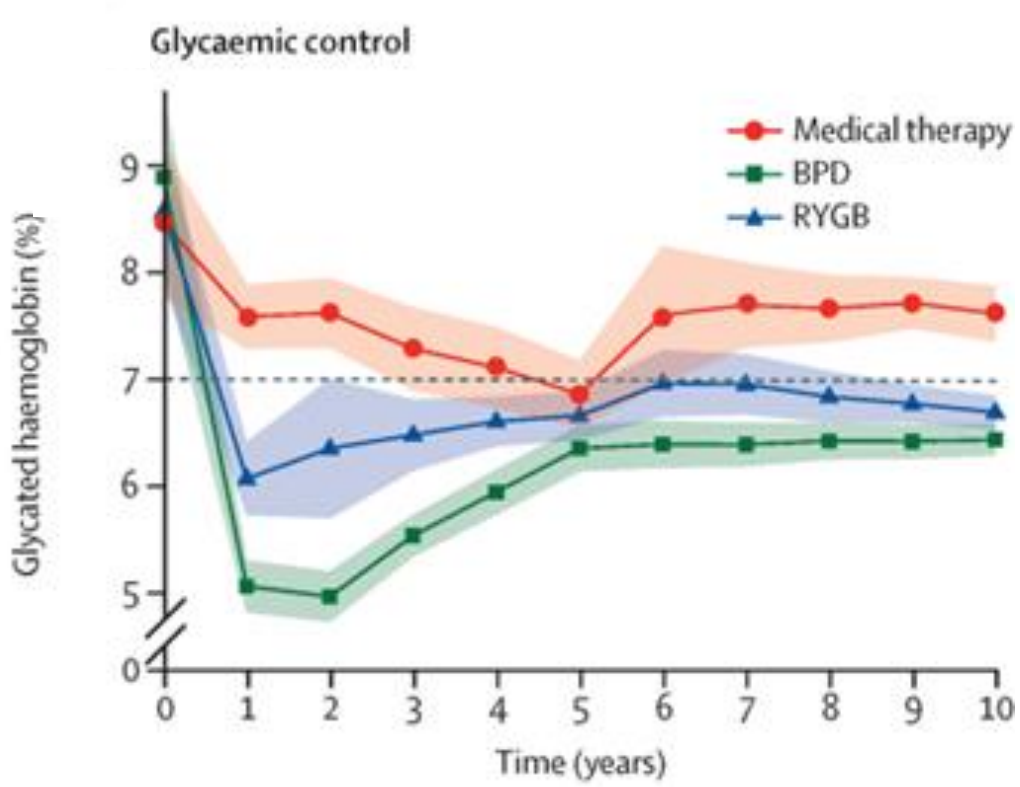
2) Defective amplification of the late phase insulin response to glucose by GIP in obese type 2 diabetic patients

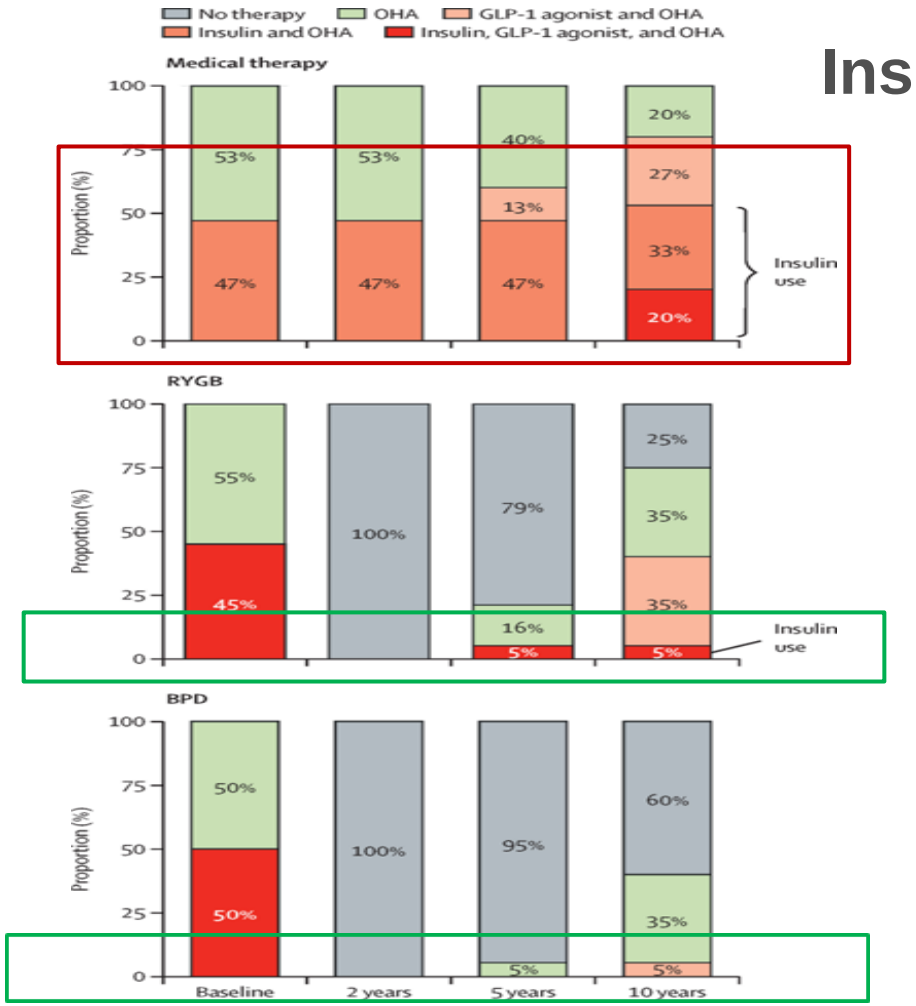
Diabetologia 2002 Aug;45(8):1111-9

THE LANCET

Metabolic surgery versus conventional medical therapy in patients with type 2 diabetes: 10-year follow-up of an open-label, single-centre, randomised controlled trial

The Lancet Volume 397 Issue 10271 Pages 293-304 (January 2021)





Insulin Use

50%

5%

0%

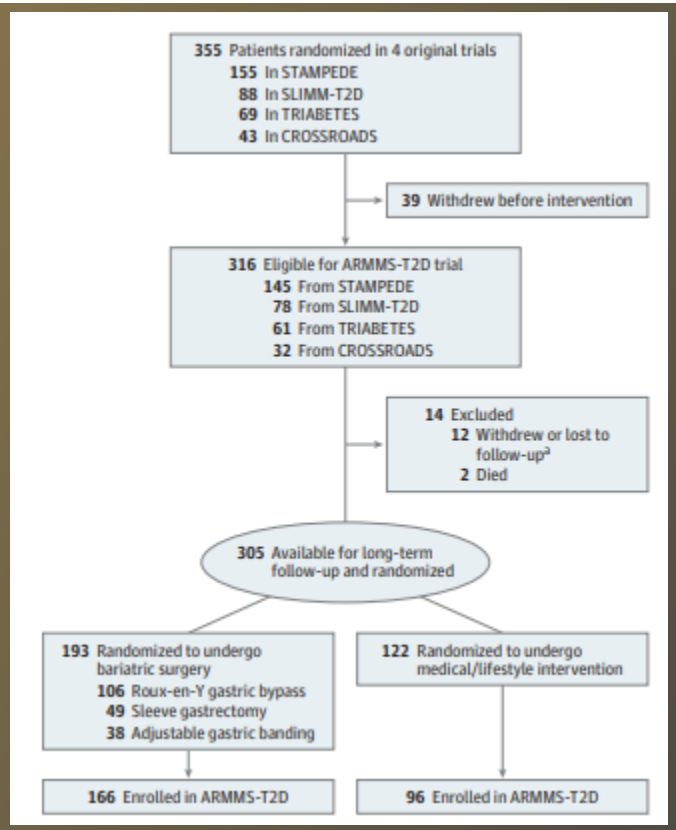
Research

JAMA | Original Investigation

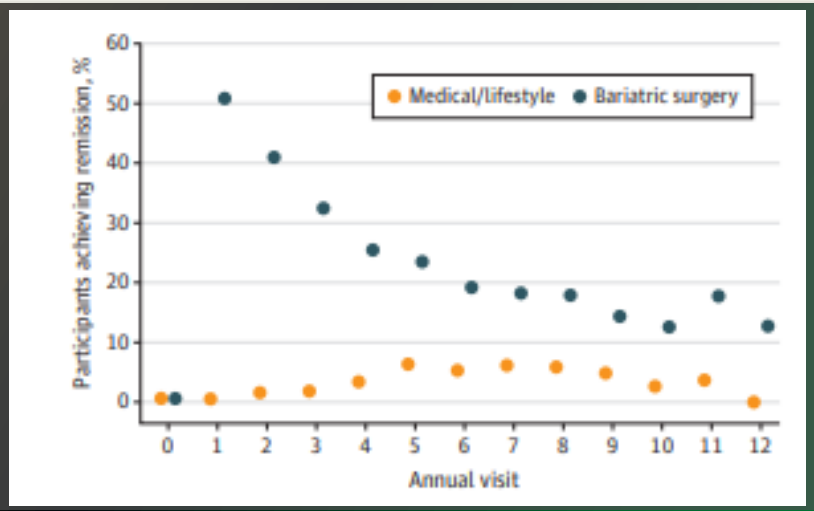
Long-Term Outcomes of Medical Management vs Bariatric Surgery in Type 2 Diabetes

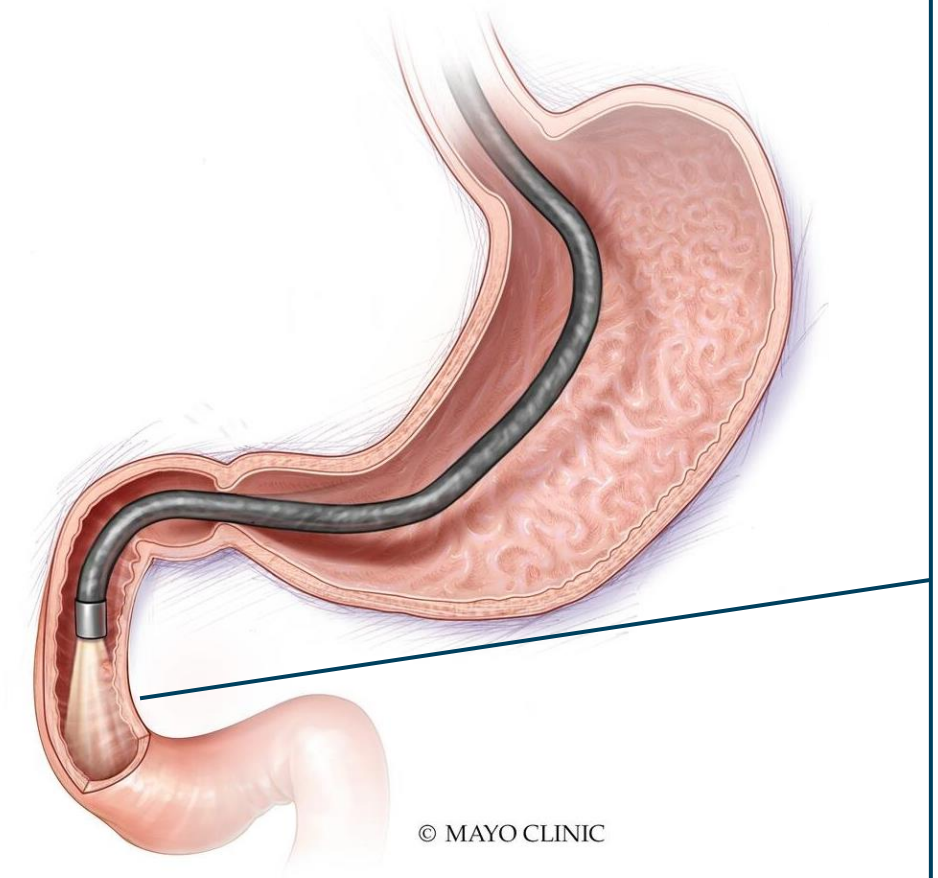
Anita P. Courcoulas, MD; Mary Elizabeth Patti, MD; Bo Hu, PhD; David E. Arterburn, MD; Donald C. Simonson, MD, ScD; William F. Gourash, PhD; John M. Jakicic, PhD; Ashley H. Vernon, MD; Gerald J. Beck, PhD; Philip R. Schauer, MD; Sangeeta R. Kashyap, MD; Ali Aminian, MD; David E. Cummings, MD; John P. Kirwan, PhD

Key Point:
Gut-based therapeutic interventions, particularly metabolic surgery, exhibit a potential disease-modifying effect on Type II diabetes mellitus. This is evidenced by a substantial reduction in insulin usage over a 7-year period (16% versus 56%), alongside improved glycemic control.



Outcome	Medical/lifestyle Baseline (n = 96)	Year 7 (n = 82)	Change (95% CI)[b]	Bariatric surgery Baseline (n = 166)	Year 7 (n = 136)	Change (95% CI)	Group comparison Difference in change[c]	*P* value
Primary outcome								
HbA_{1c}, mean (SD), %	8.2 (1.2)	8.0 (1.8)	−0.2 (−0.5 to 0.2)	8.7 (1.7)	7.2 (1.4)	−1.6 (−1.8 to −1.3)	−1.4 (−1.8 to −1.0)	<.001
HbA_{1c} <7.0%, %	11.7	26.7	2.77 (1.38 to 5.54)	15.5	54.1	6.42 (3.63 to 11.4)	3.22 (1.76 to 5.88)	<.001
Insulin and/or oral/GLP1	41.7	56.0	1.93 (1.07 to 3.46)	50.6	16.0	0.18 (0.11 to 0.31)	0.13 (0.06 to 0.29)	<.001

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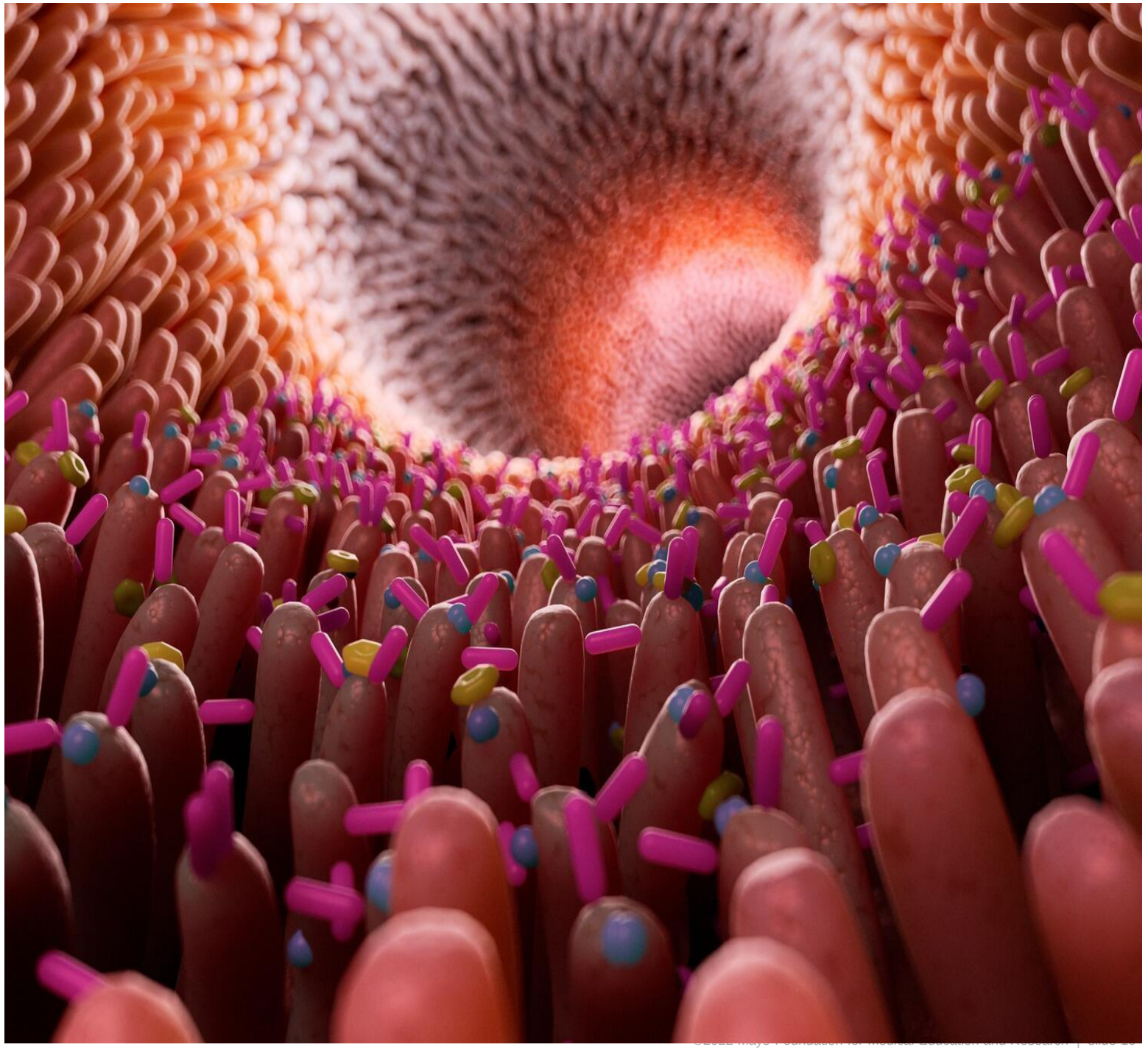
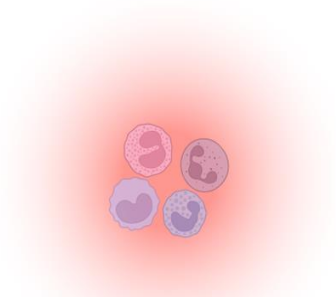


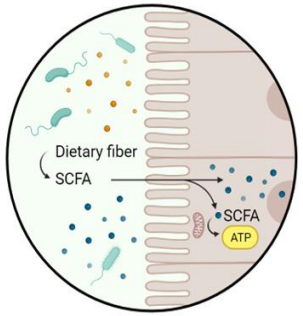


Gut
Inflammation

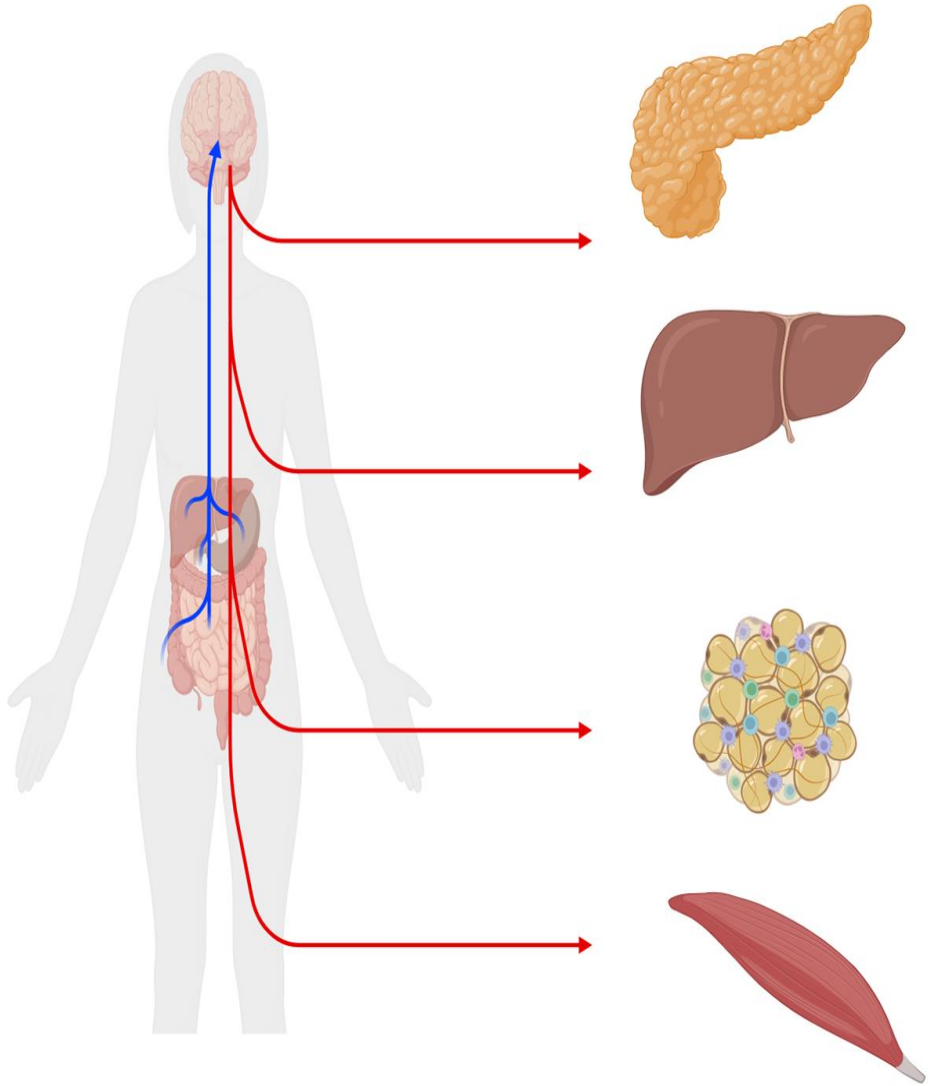
Nutrients

GLP-1

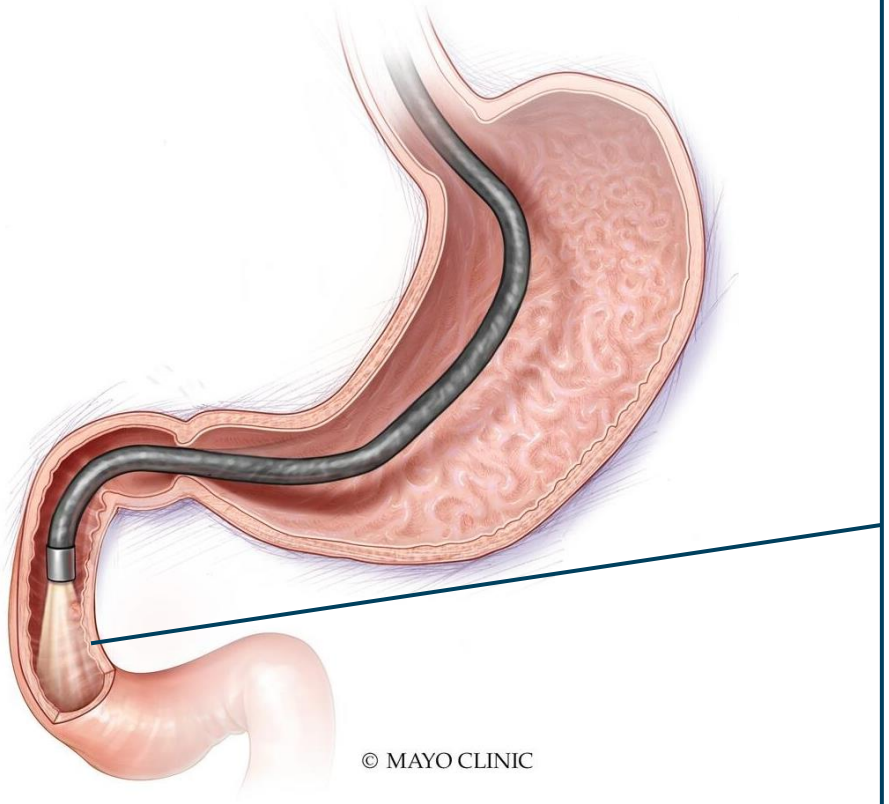
Gut
Hormones

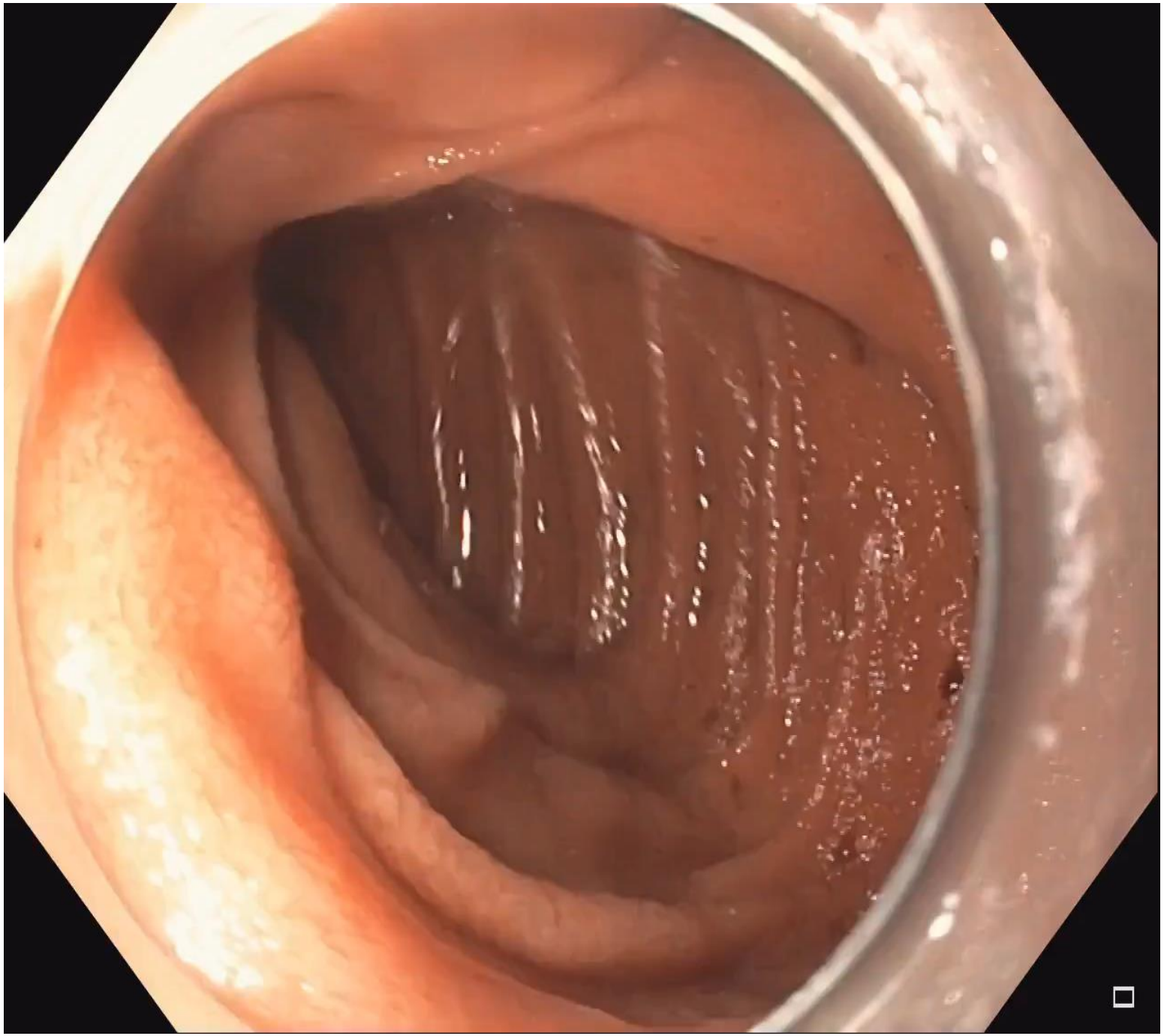


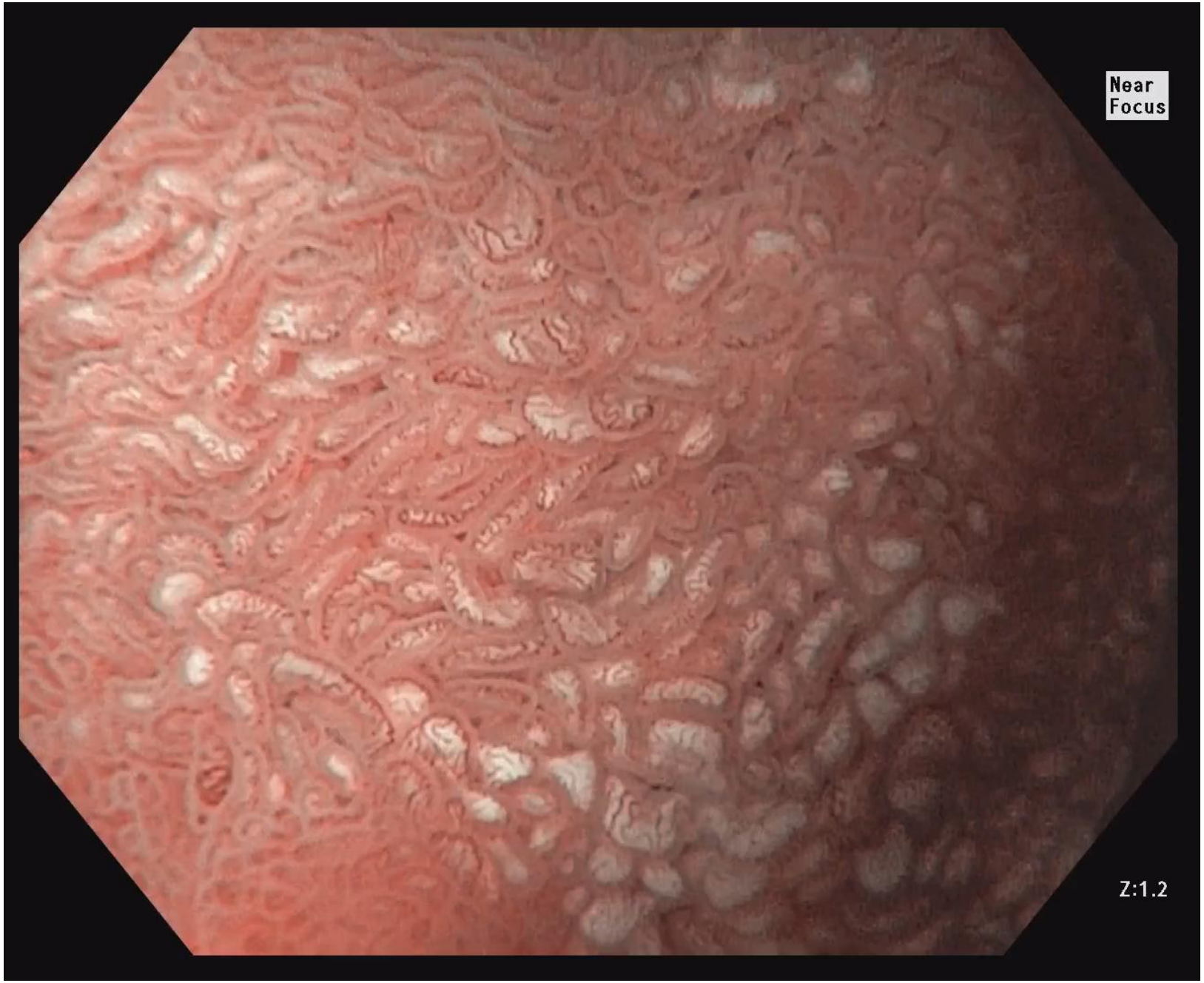
Microbiome

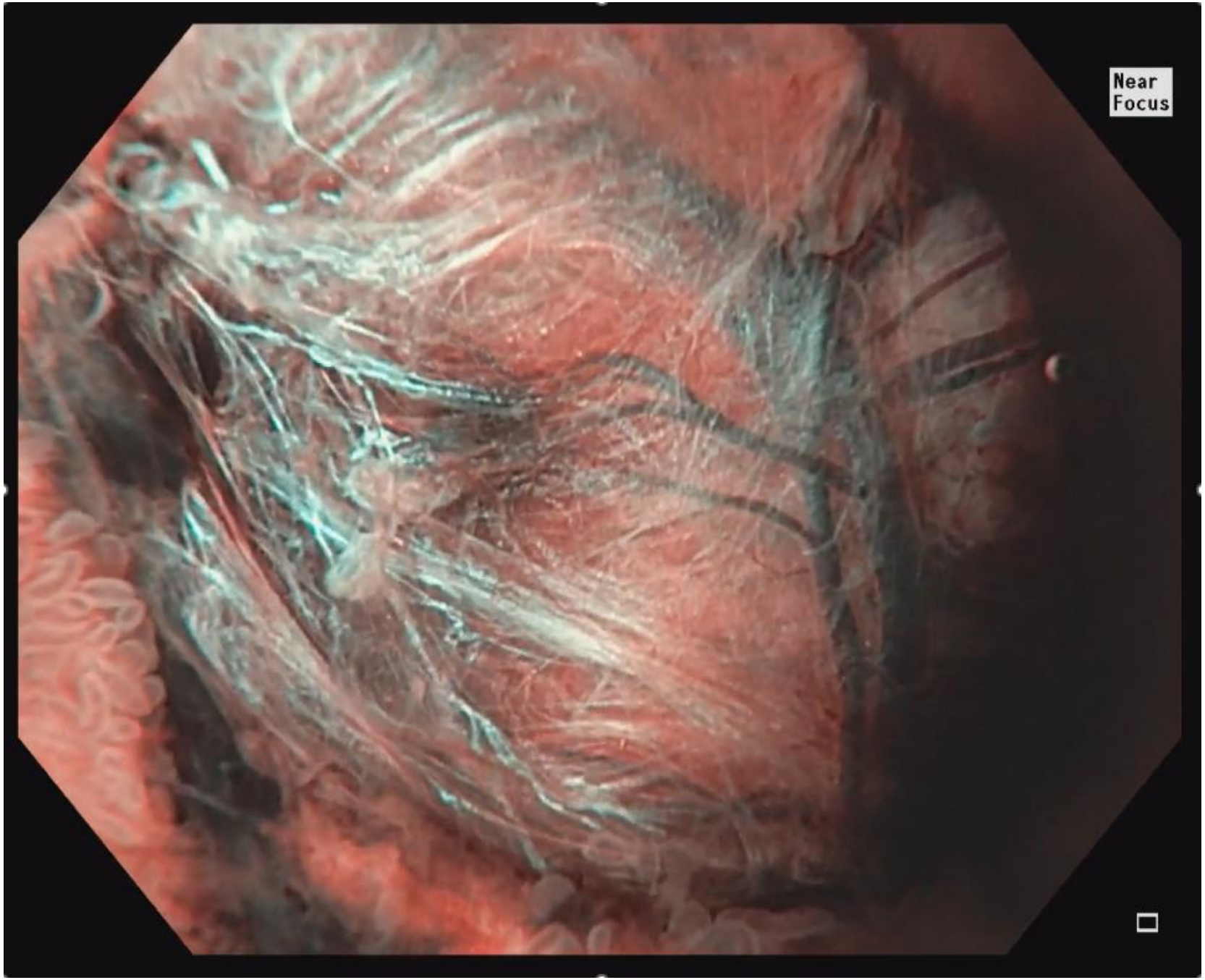


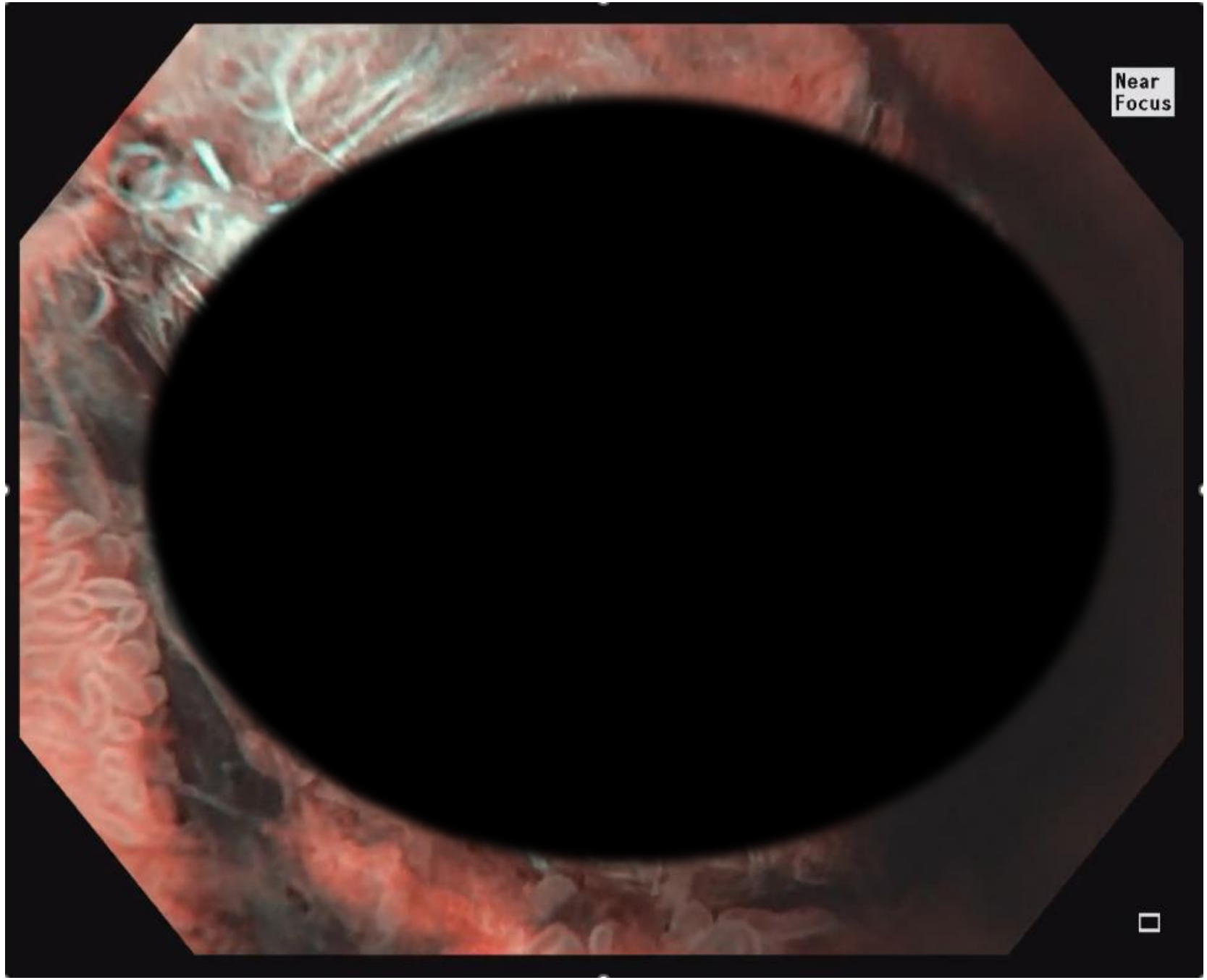
Normal Duodenum





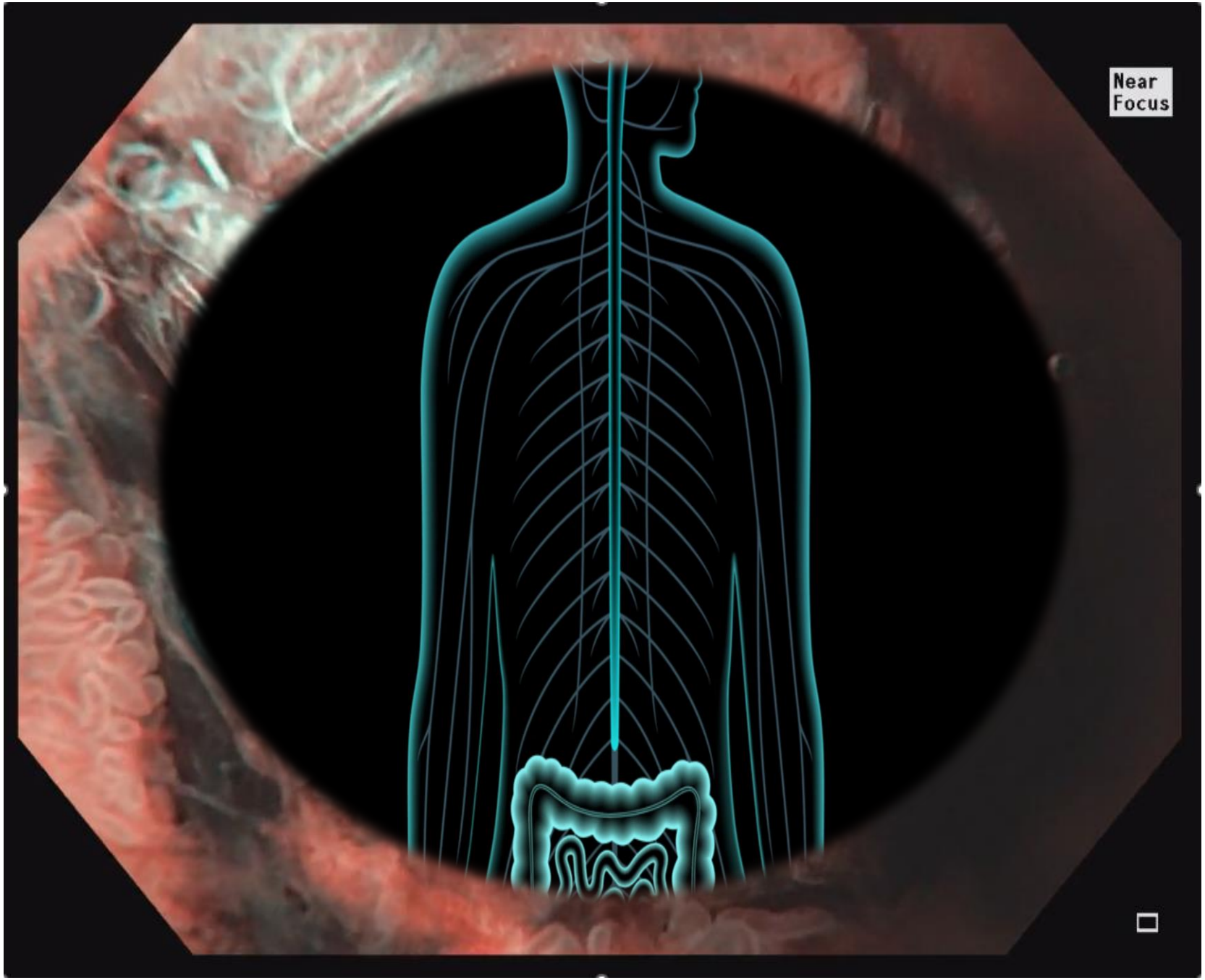


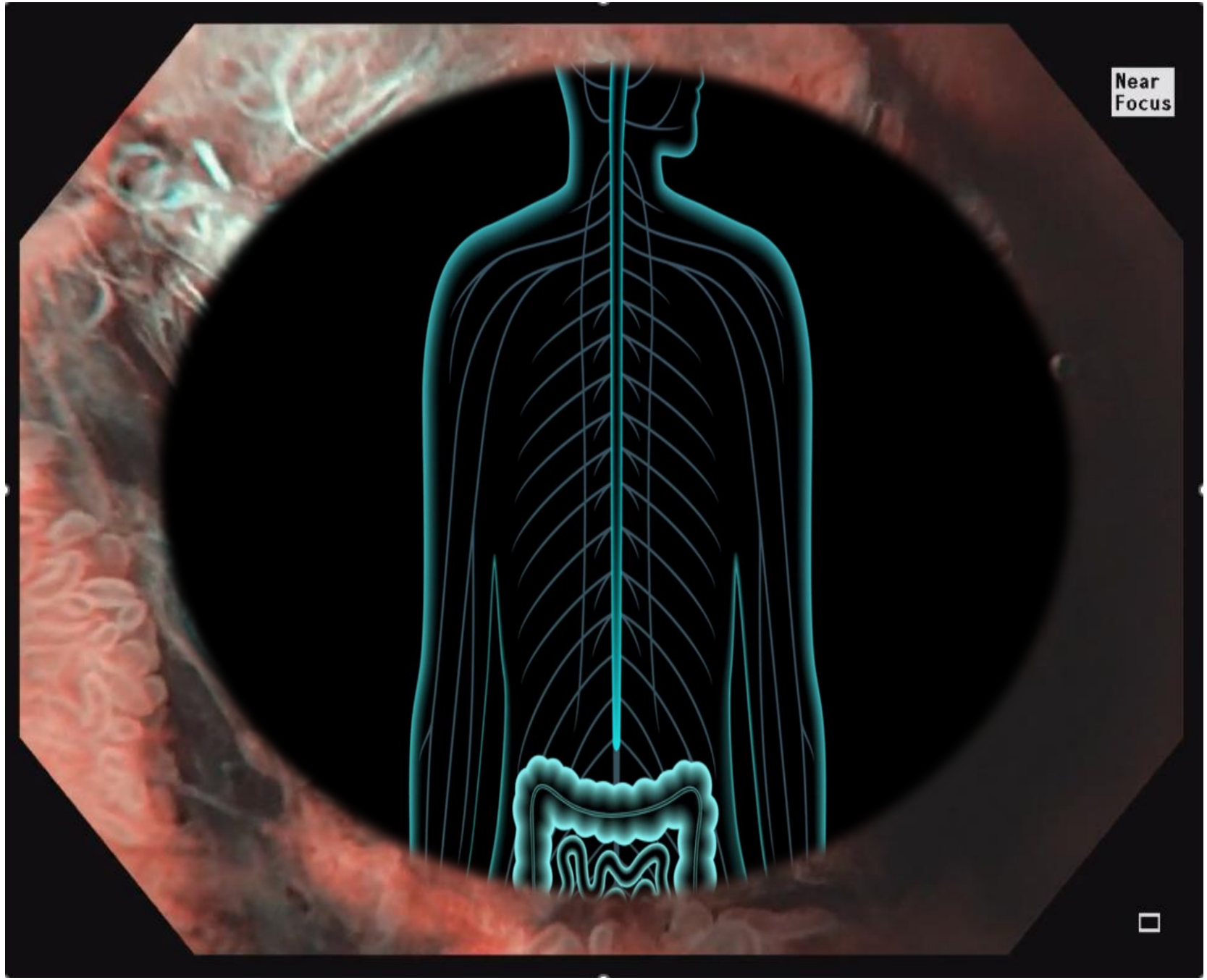




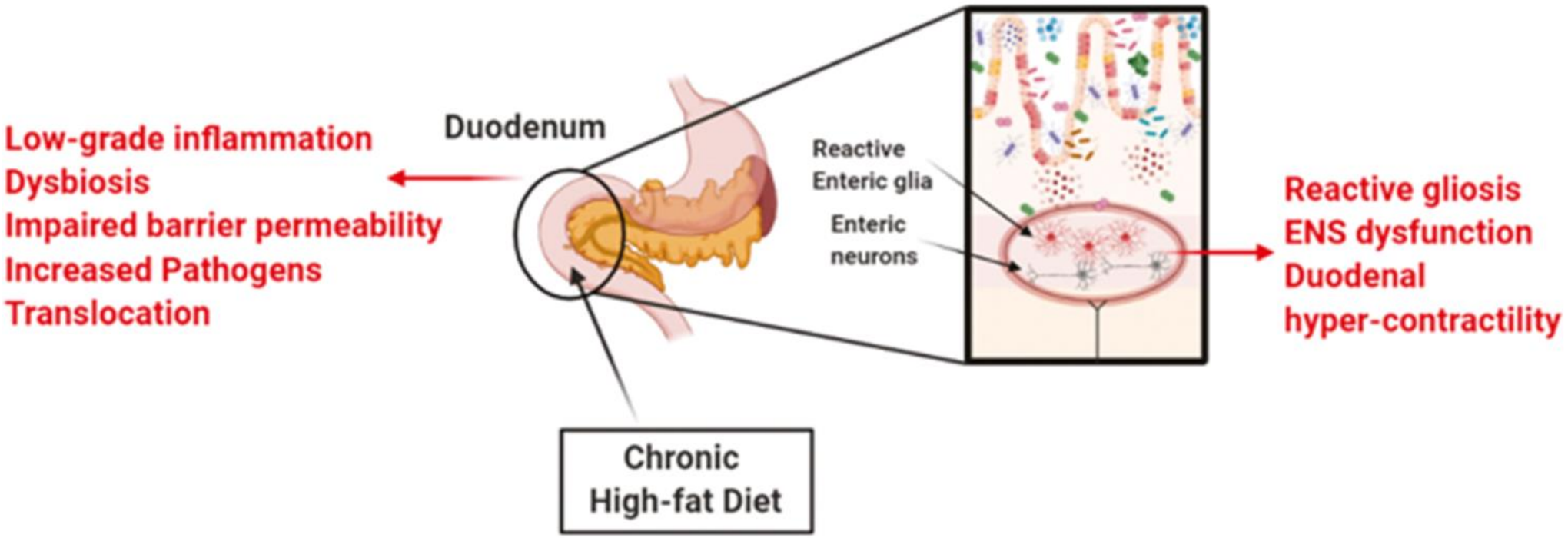
ENS (Second Brain)

40 Neurotransmitters identified
500 Million neurons
Produces 50% of all dopamine
Produces 95% of all serotonin
Barrier restricts blood flow

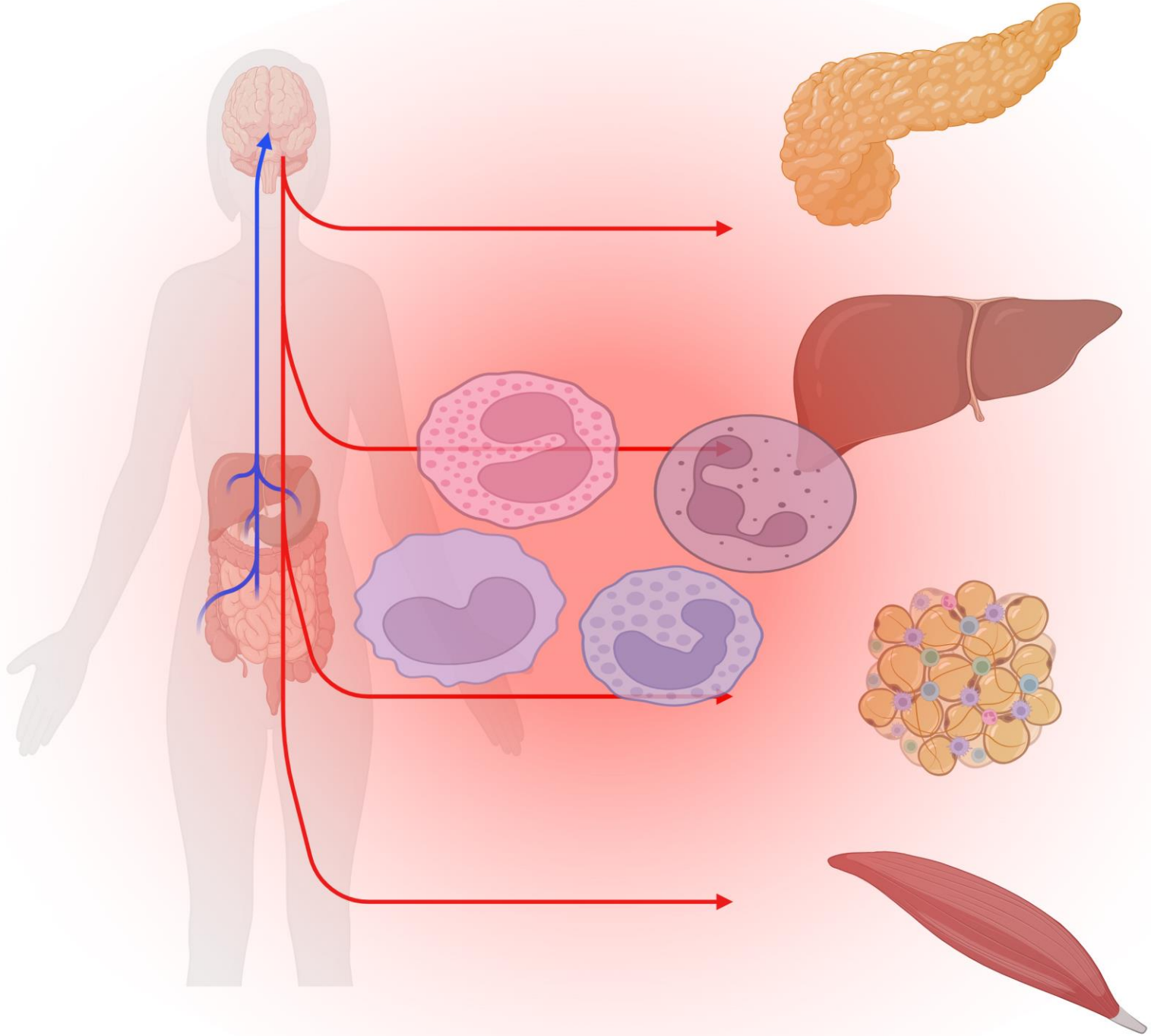




Gut Inflammation is an Important Target



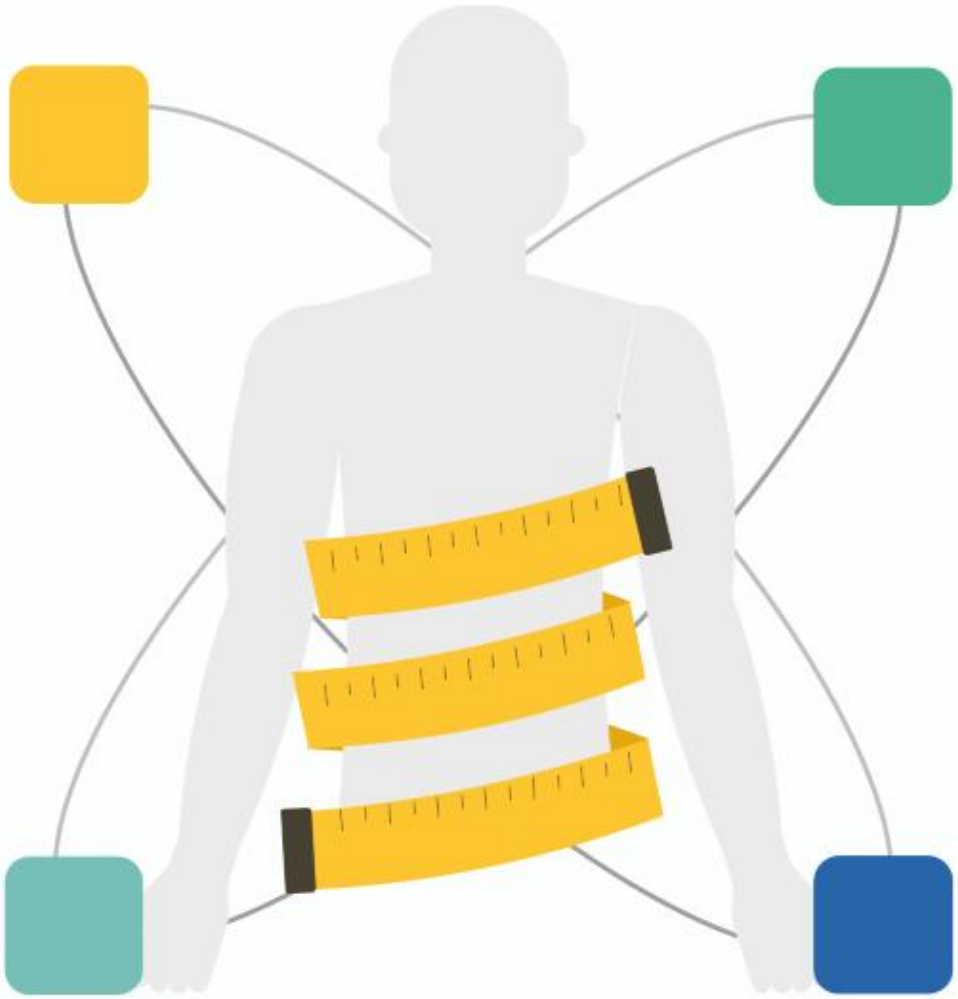
Nature 2021 Sep;597(7875):263-267
N Engl J Med 1996; 334:1106-1115
Mucosal Immunology (2022) 15:27–39



EBMTs

Organ Sparing

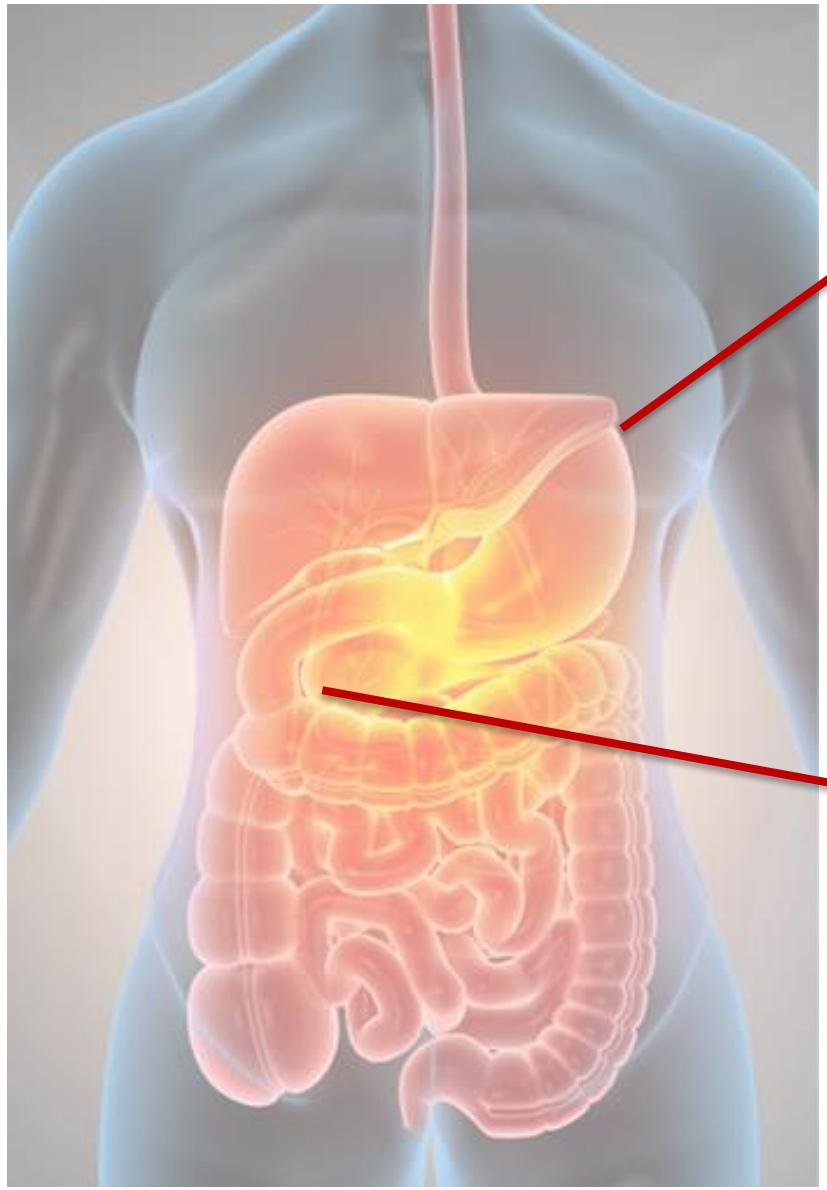
Safe Effective



No Long-Term Consequences

Minimal Disruption

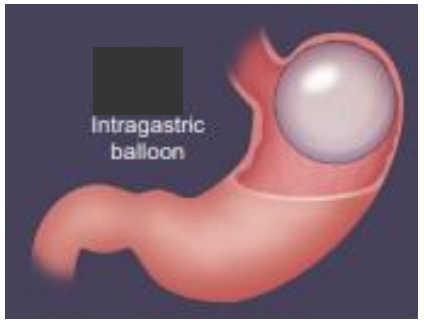
EBMTs

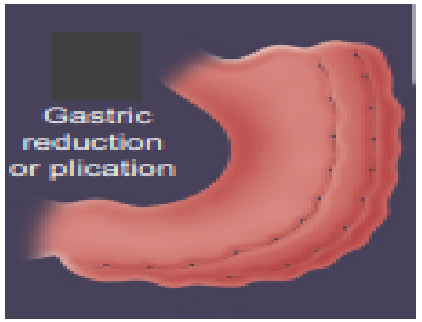


Gastric: Appetite Regulation

- Gastric Accommodation
- Gastric Emptying
- Ghrelin

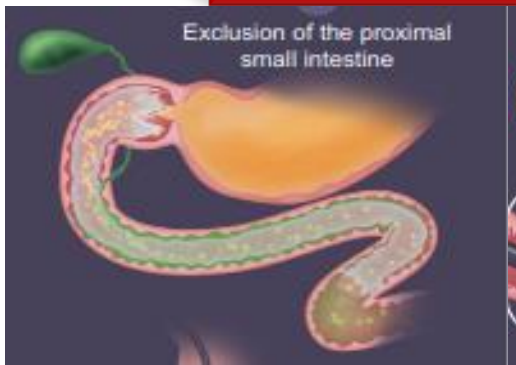
ESG Delays Gastric Emptying Similar to GLP-1RA

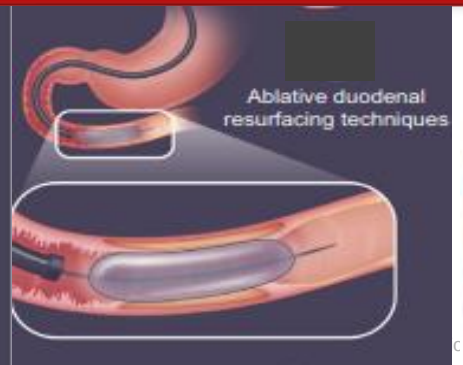




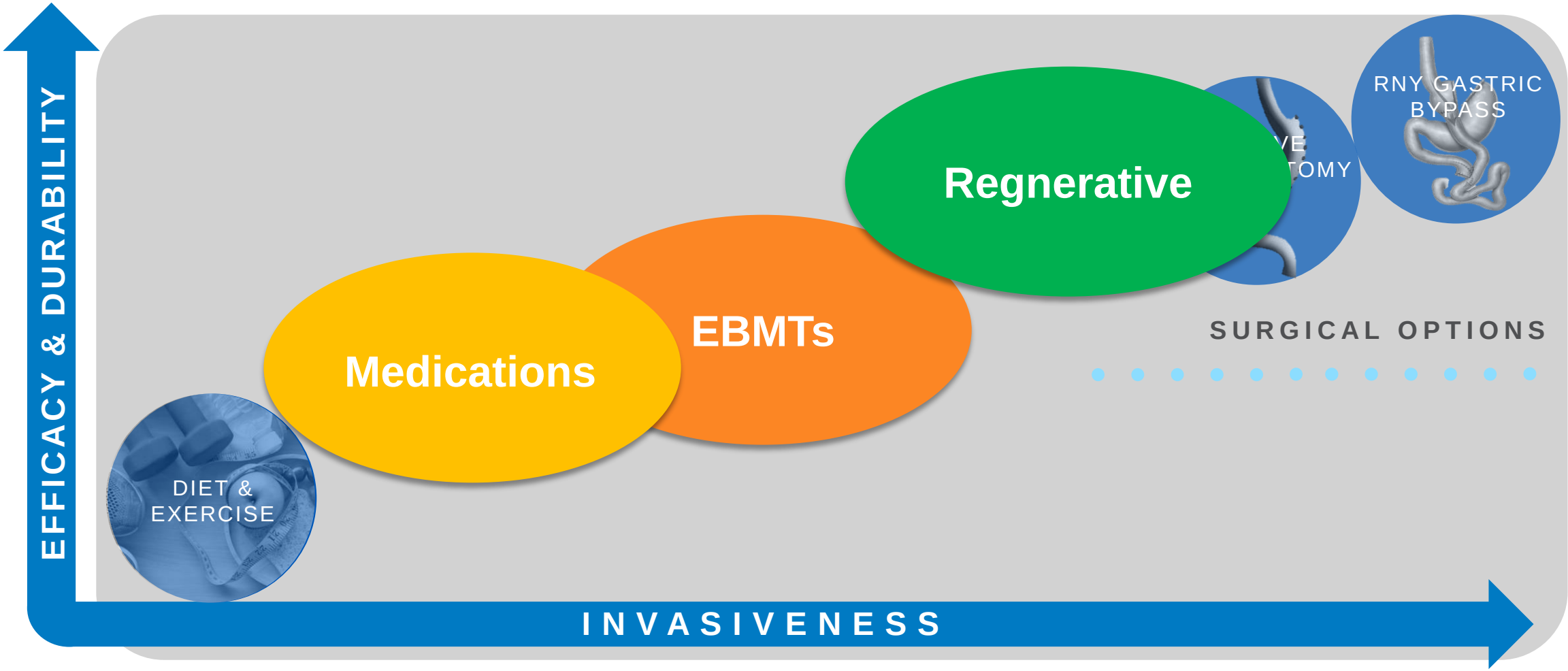
Small Intestinal: Metabolism Regulation

- Insulin Resistance
- Bile and Fat signaling
- Incretin and Microbiomes
- Inflammation



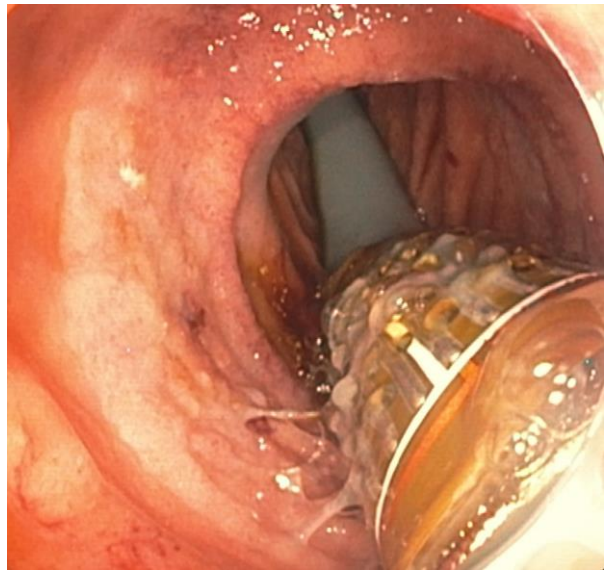


#Pushing the Boundaries (Regenerative)

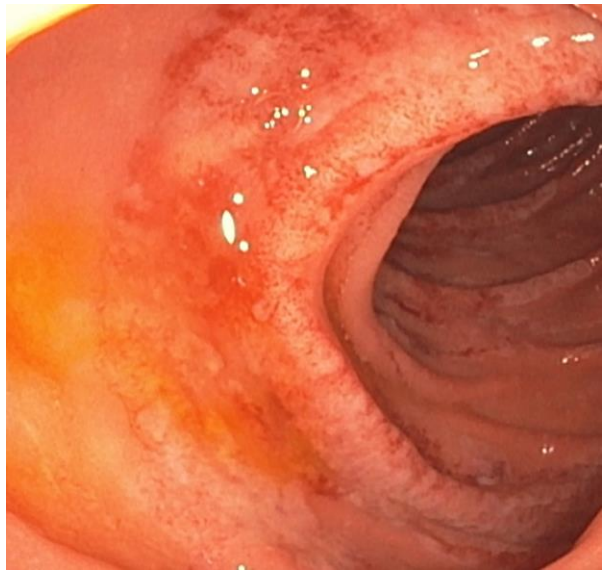


INTESTINAL RE-CELLULARIZATION INDUCED BY PULSED ELECTRIC FIELD (IN CLINICAL TRIALS ONLY) (NON-THERMAL REGENERATION)

Before ReCET



60 sec



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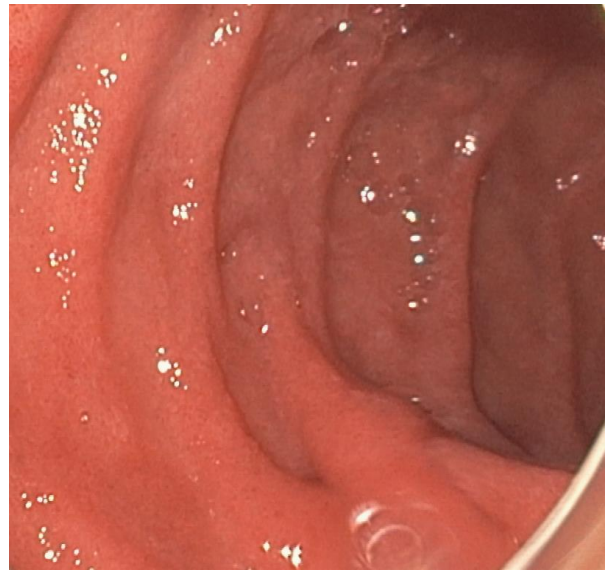
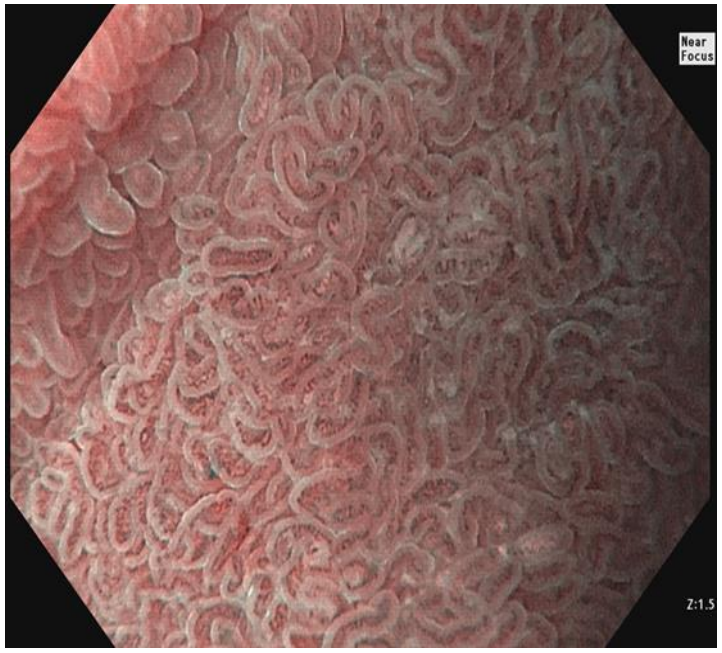
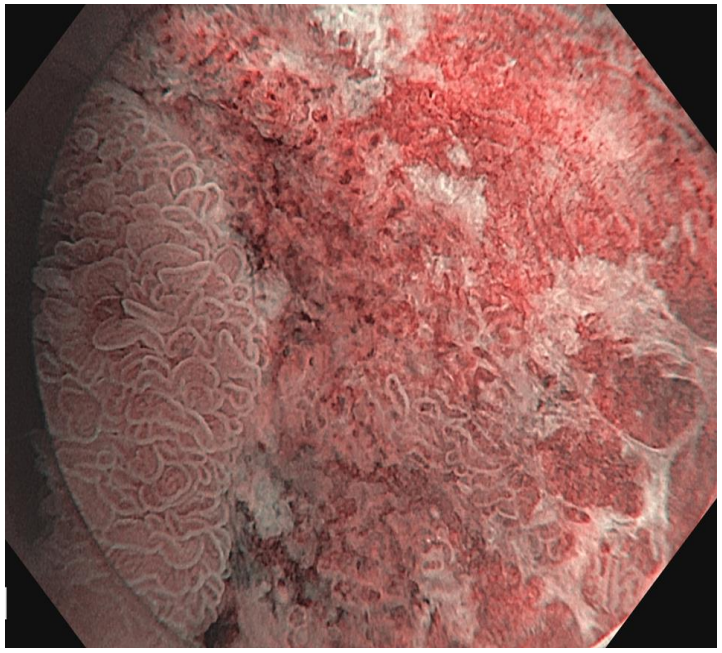


4weeks after ReCE



Before ReCET



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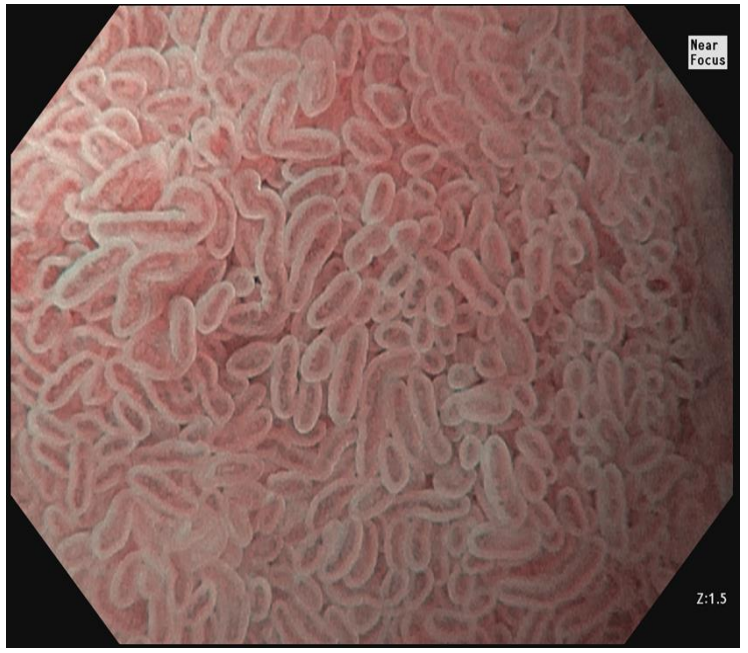
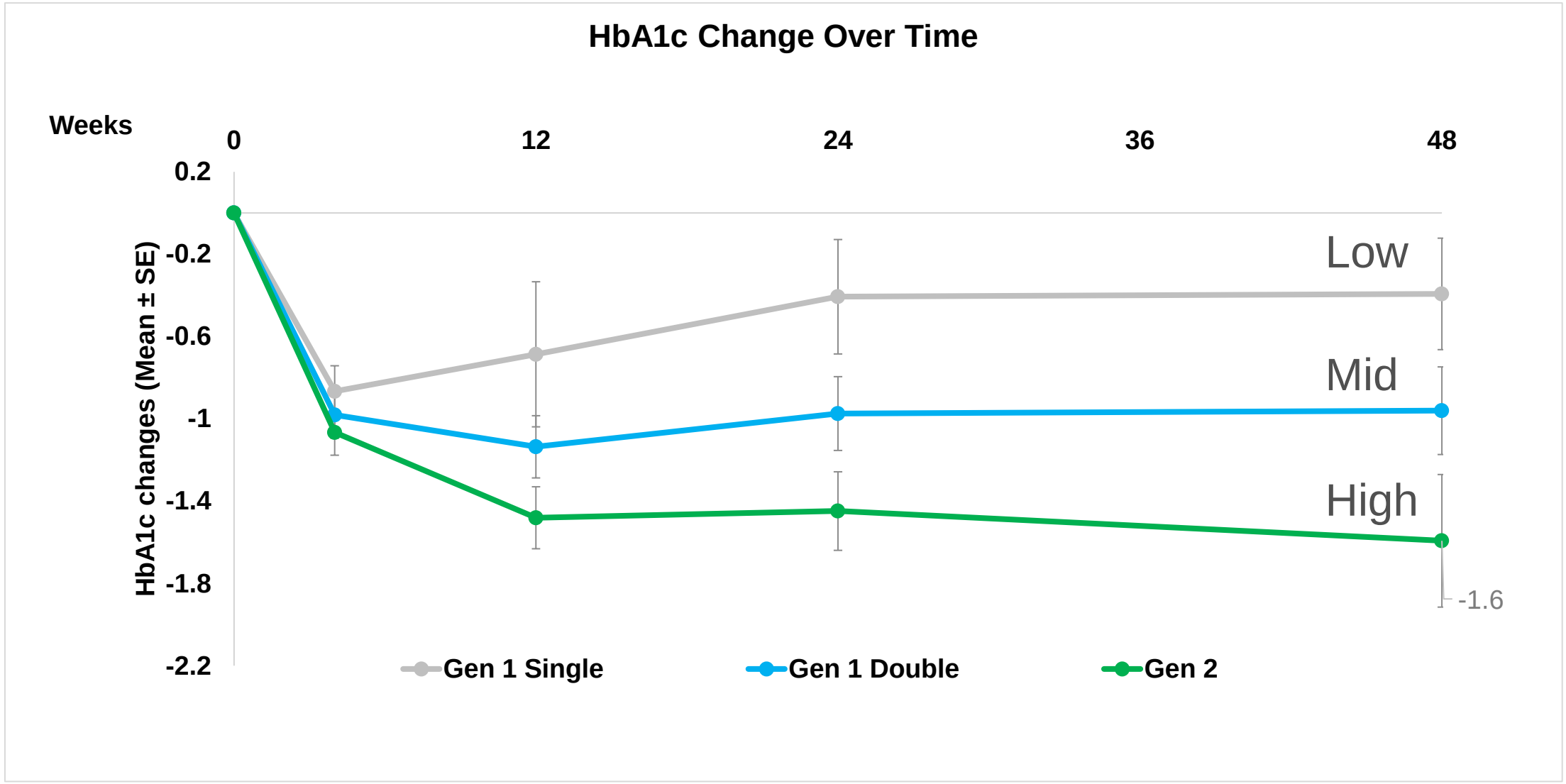


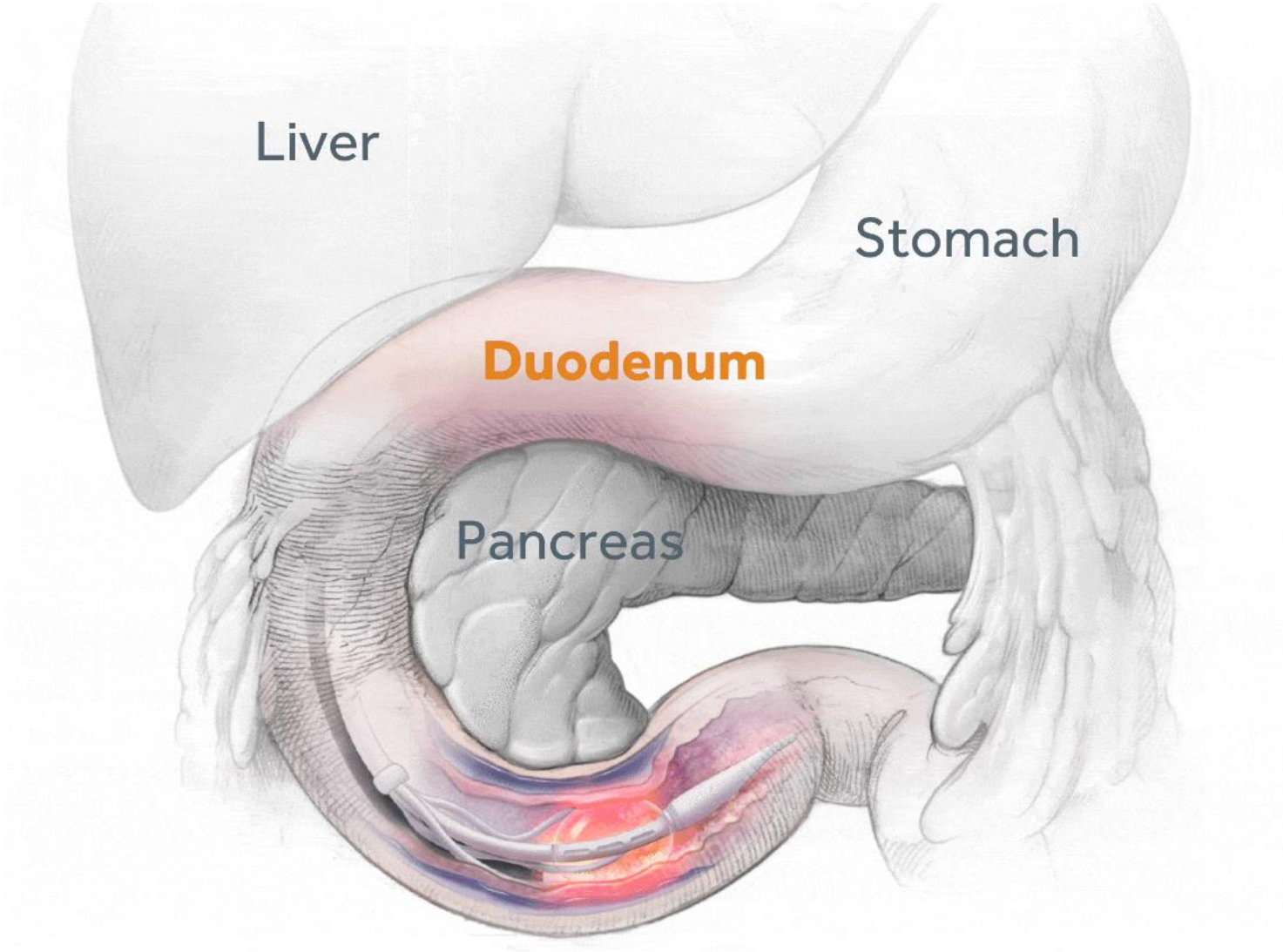
4weeks after

IMPROVEMENT IN GLYCEMIC CONTROL (DOSE TITRATION) (N=71)

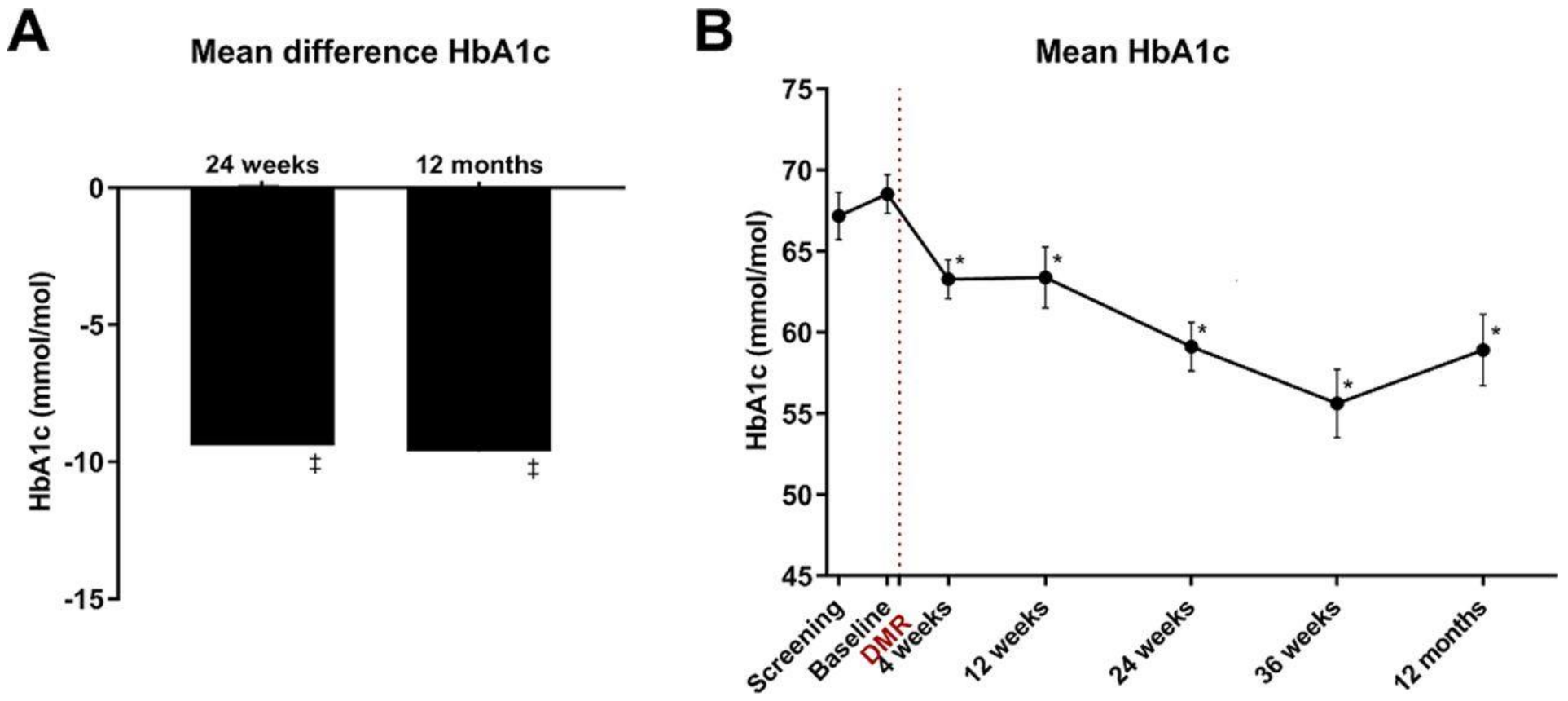


REGENT-1 & REGENT-1-US Combined

REVITA FRACTYL HEALTH HYDROTHERMAL DMR

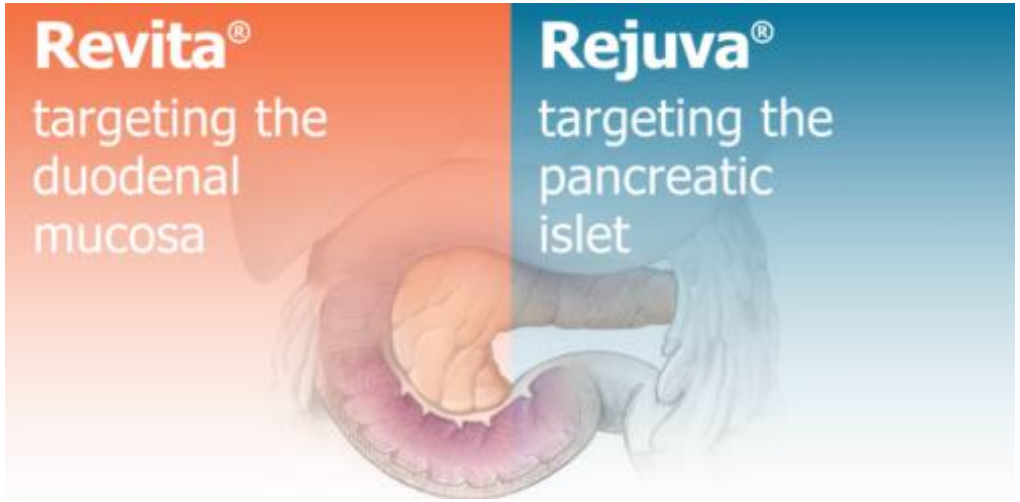


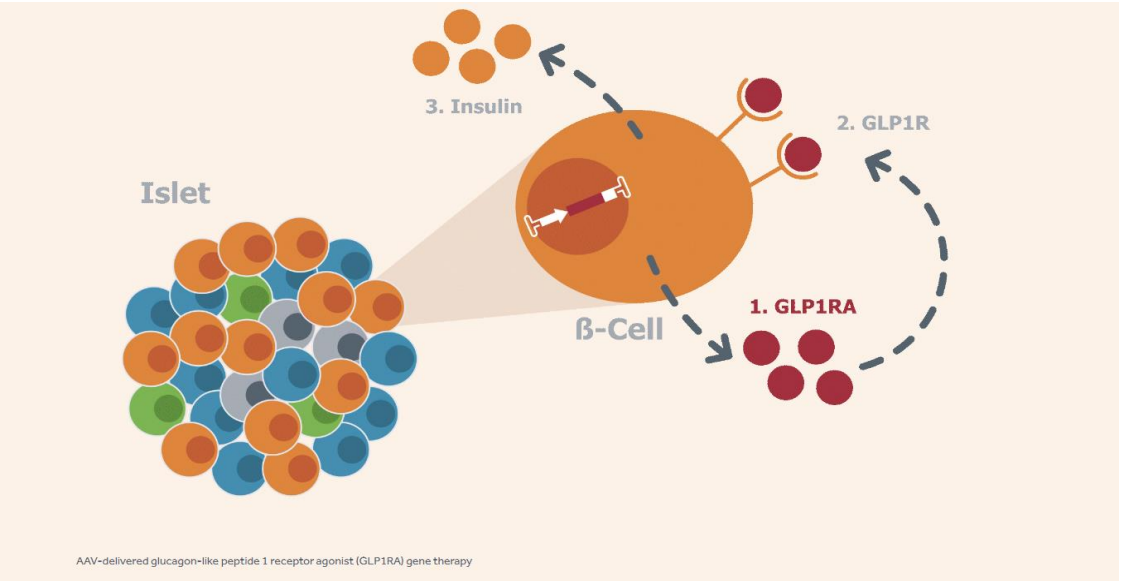
Change in HbA1c after DMR over 12 months follow-up.



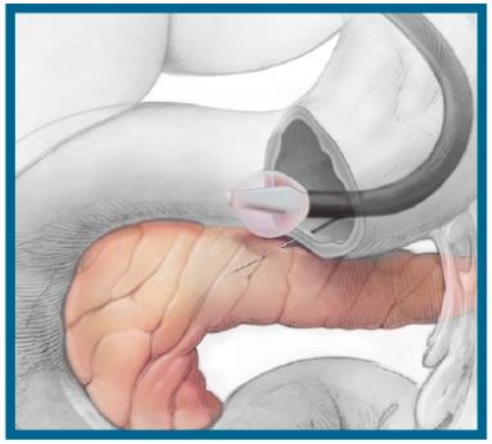
Annieke C G van Baar et al. Gut 2020;69:295-303

GUT

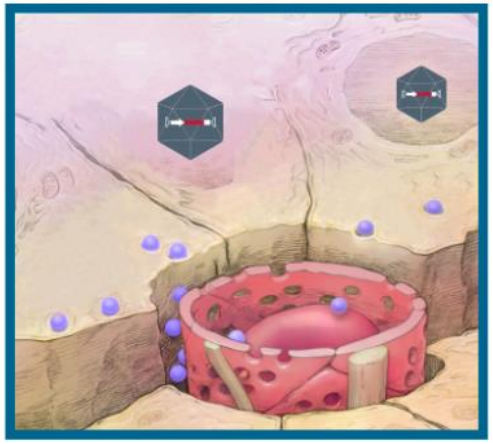




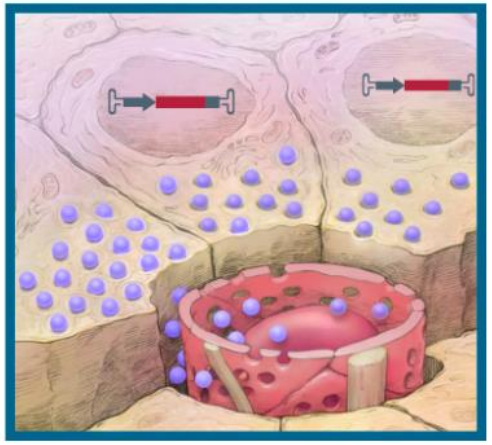
REJUVA IS A MODULAR PHYSIOLOGIC GENE THERAPY WITH 3 KEY ELEMENTS



Leverage our proprietary system to enable local, low dose virus delivery directly to pancreas



Vectors with high transduction efficiency and limited systemic biodistribution



Durable alteration of metabolic hormone response in the islets with tissue-restricted transgenes

https://www.fractyl.com/rejuva/

CONCLUSION

- Therapies targeting the GUT for correcting metabolic maladaptation in T2D represents a new frontier in Type 2 Diabetes management
- Potential for disease modification and decreasing the burden of disease

QUESTIONS

THANK YOU

