

Endoscopic Interventions in the Duodenum

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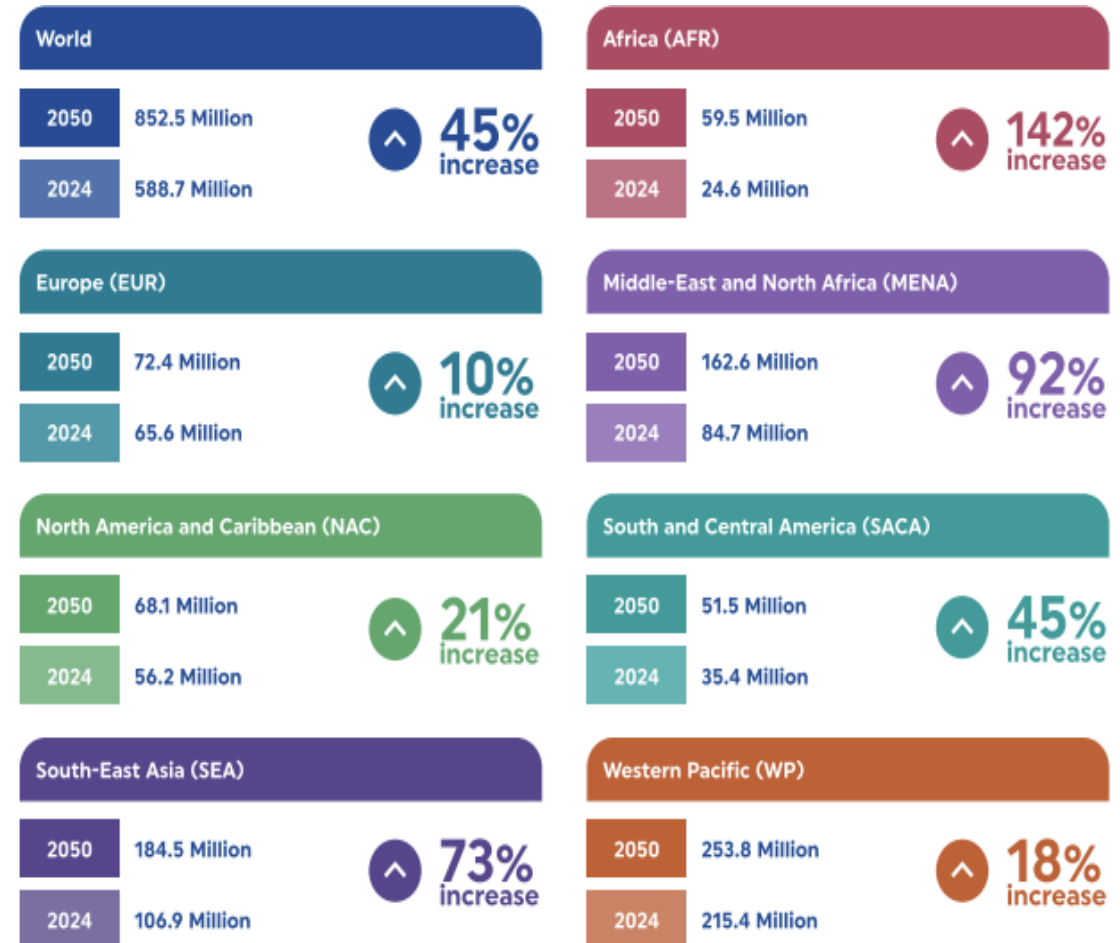
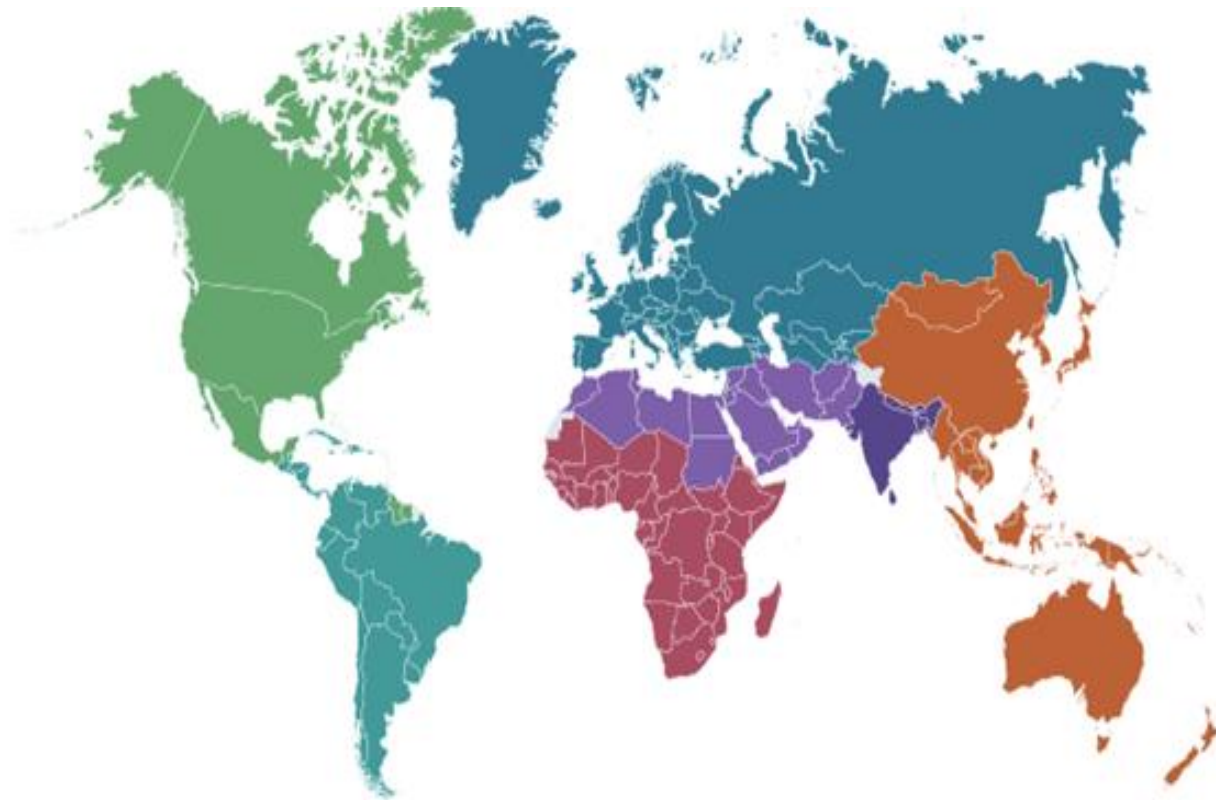
Disclosures

Consultant: Boston Scientific, Olympus, Intuitive

Co-inventor (Licensed Mayo Technology): Endogenex

Research Support: MERIT Medical

Type II Diabetes: 2024 Snapshot



The phenotype called “T2D” conceals divergent biology and risk

589M

adults living with diabetes worldwide
(2024 estimate)

1 in 4

develops macrovascular
complications

≈1 in 2

develops microvascular complications

We intensify glycemic therapy using a largely uniform disease label, while vascular, renal and mortality trajectories separate early.

Routine immune counts reveal four prognostically distinct T2D endotypes

Three routinely available circulating cell counts



NEUTROPHILS

innate inflammatory
tone



LYMPHOCYTES

adaptive immune
balance



MONOCYTES

myeloid inflammation

resolve into

SIND

**Severe
inflammation**
monocyte-driven

MIND

**Mild
inflammation**
intermediate

LYRD

Lymphocytes ↑
relative favorable

LYDD

Lymphocytes ↓
lymphocyte-low

HIGH-RISK TRAJECTORIES

SIND + LYDD

↑ **cardiovascular risk**

↑ **renal risk** · ↑ **mortality**

**Stable over time · reproducible across
cohorts · independent of age, sex, BMI and
HbA1c**

The Duodenum is the metabolic control center

The control center for sensing, signaling, and coordination

- Detects nutrients and gut environment
- Sends hormonal, immune, and neural signals
- Coordinates blood sugar, appetite, digestion, energy use, and immune function

Duodenal wall is composed of layers



Mucosa

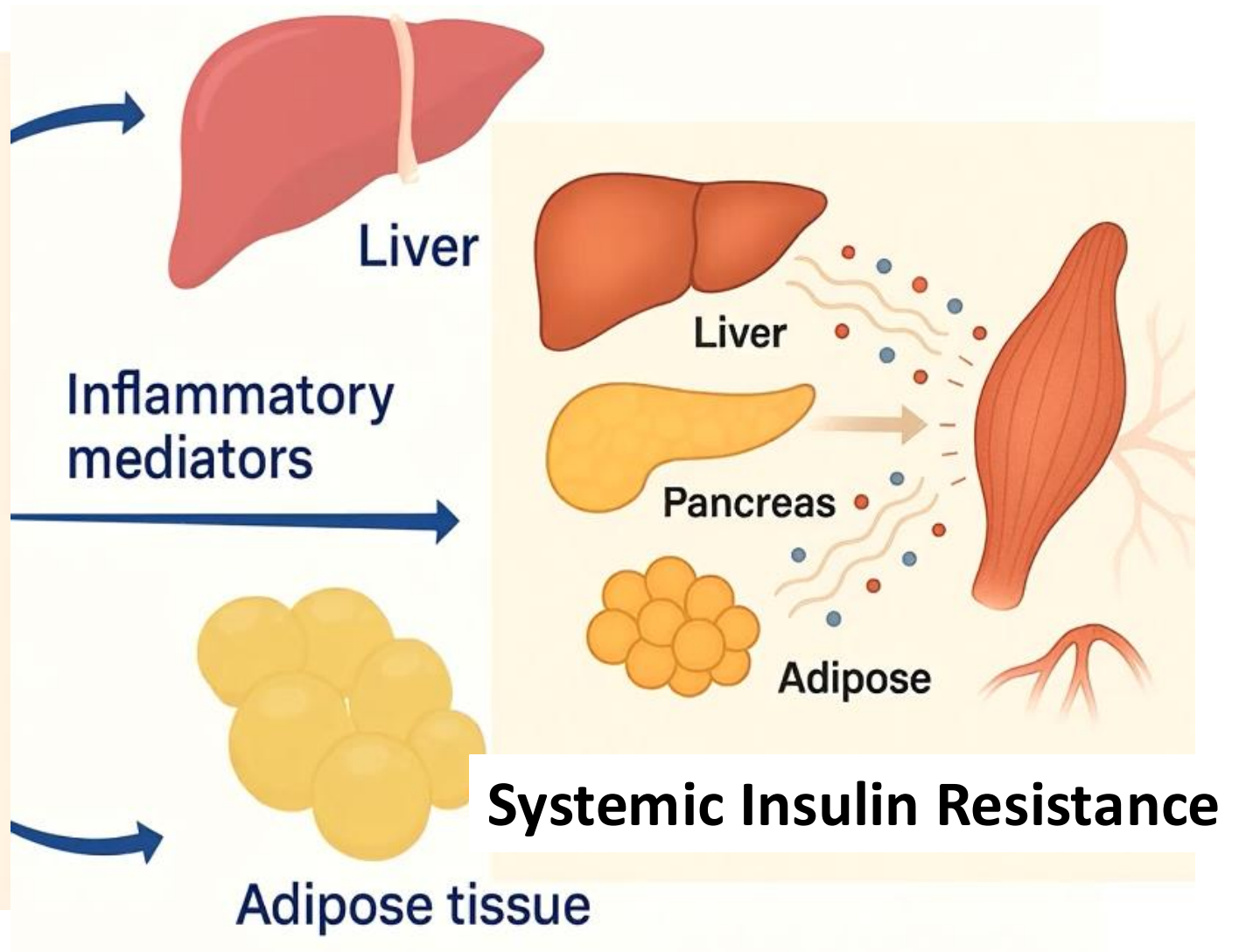
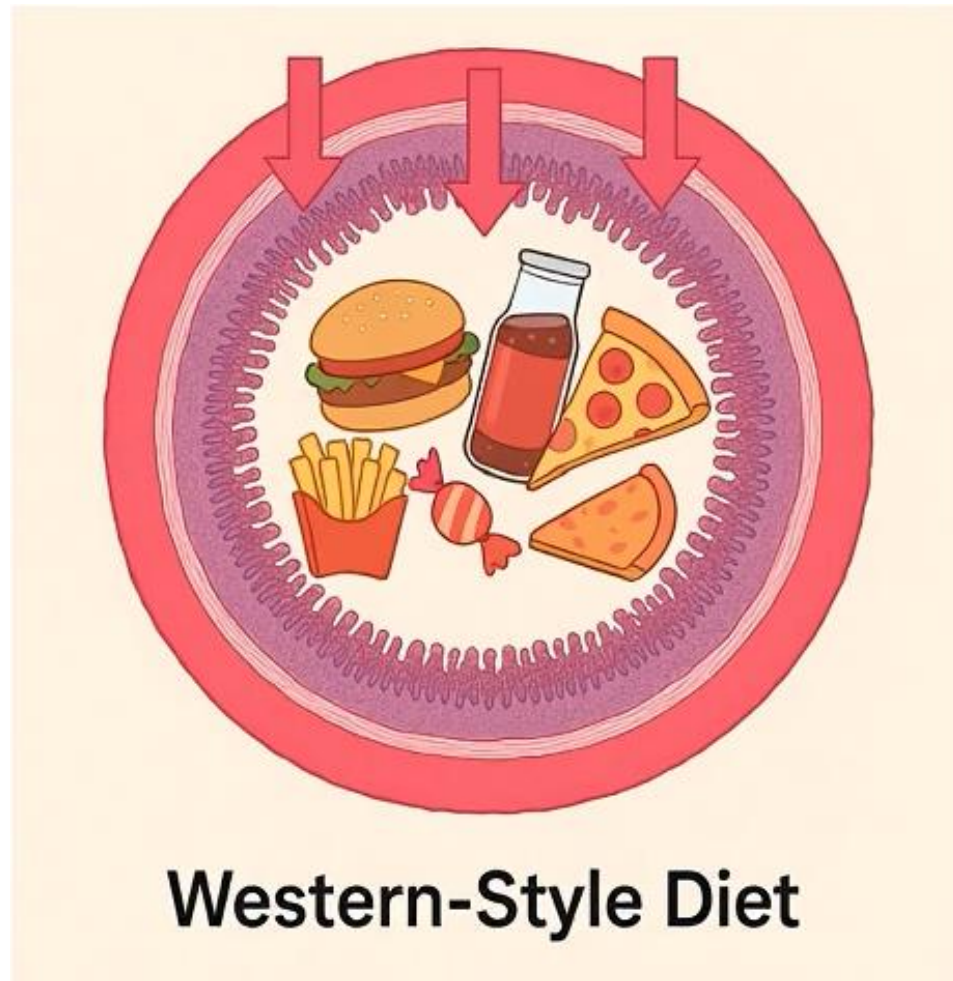
Nutrient sensing,
hormone release

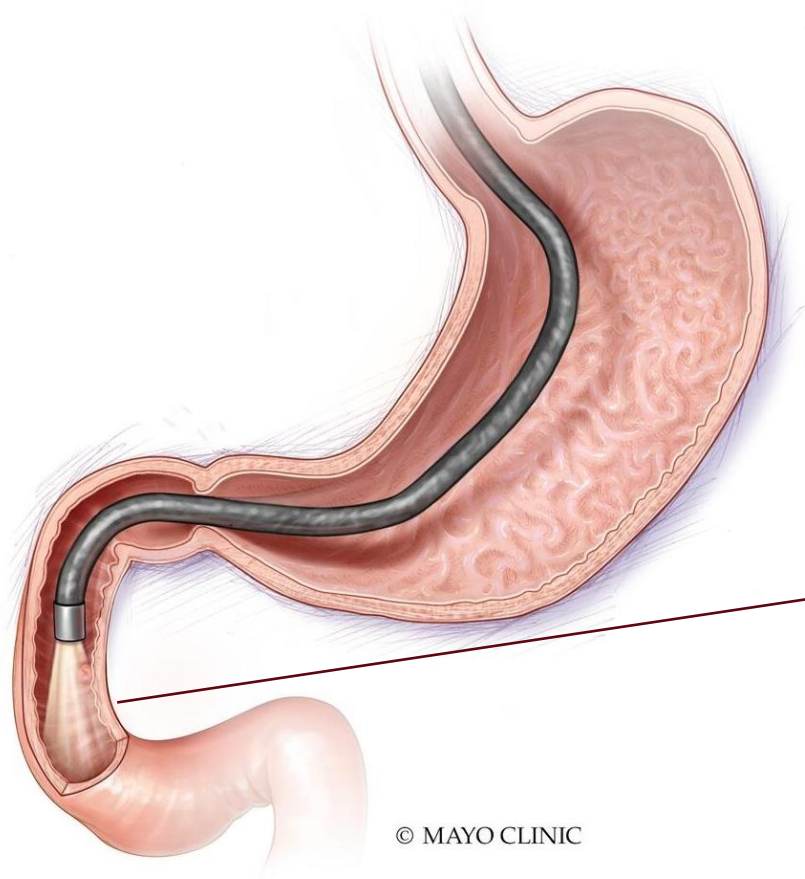
Submucosa

Neural and immune
signaling; link to Enteric
nervous system

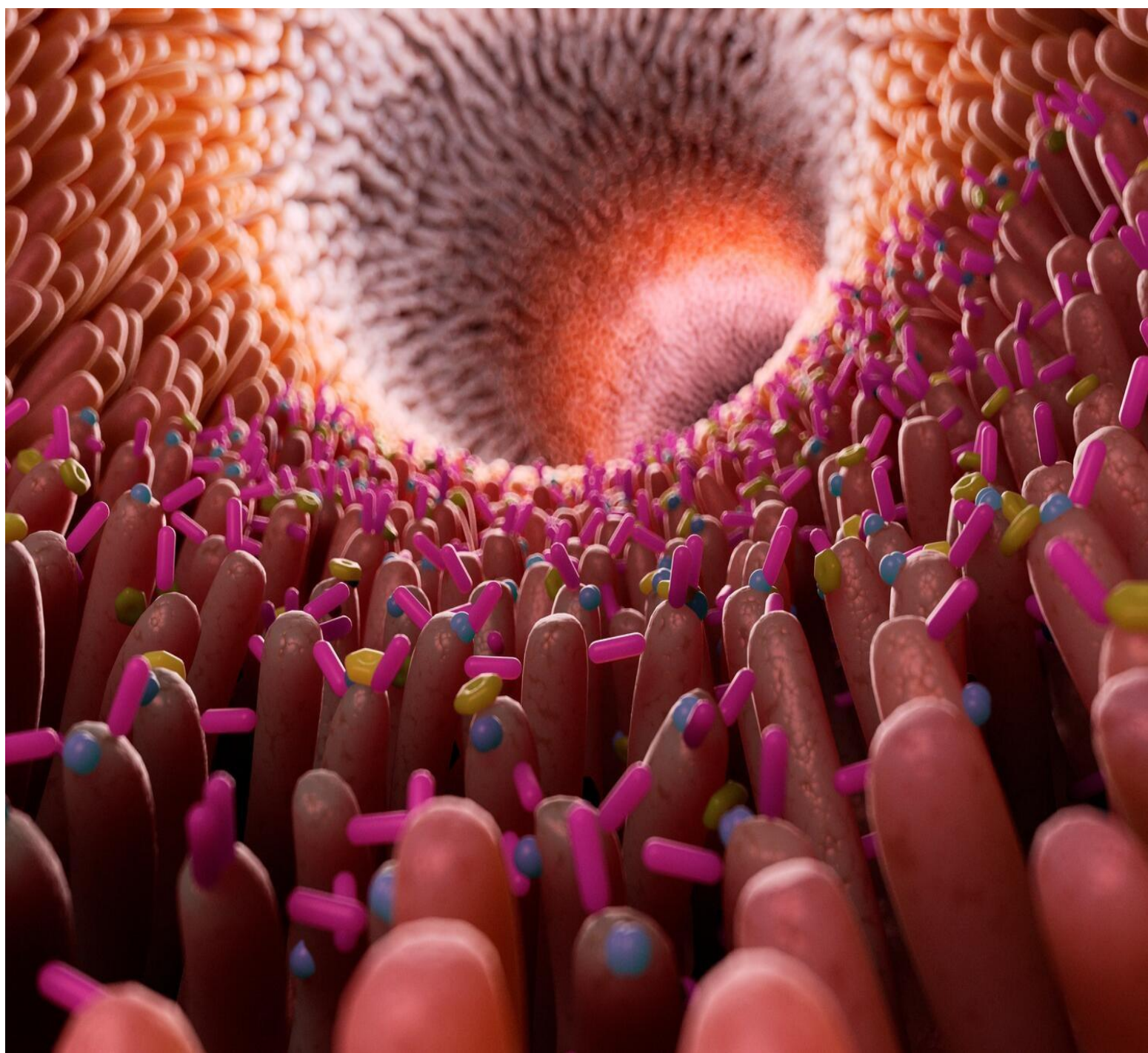
Muscularis

Supports movement and
coordination

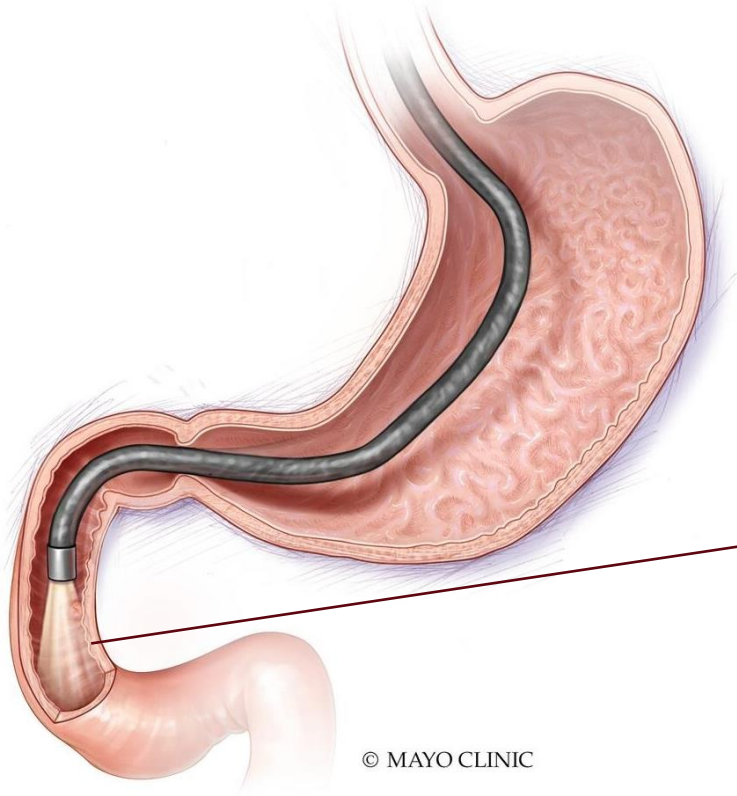




© MAYO CLINIC



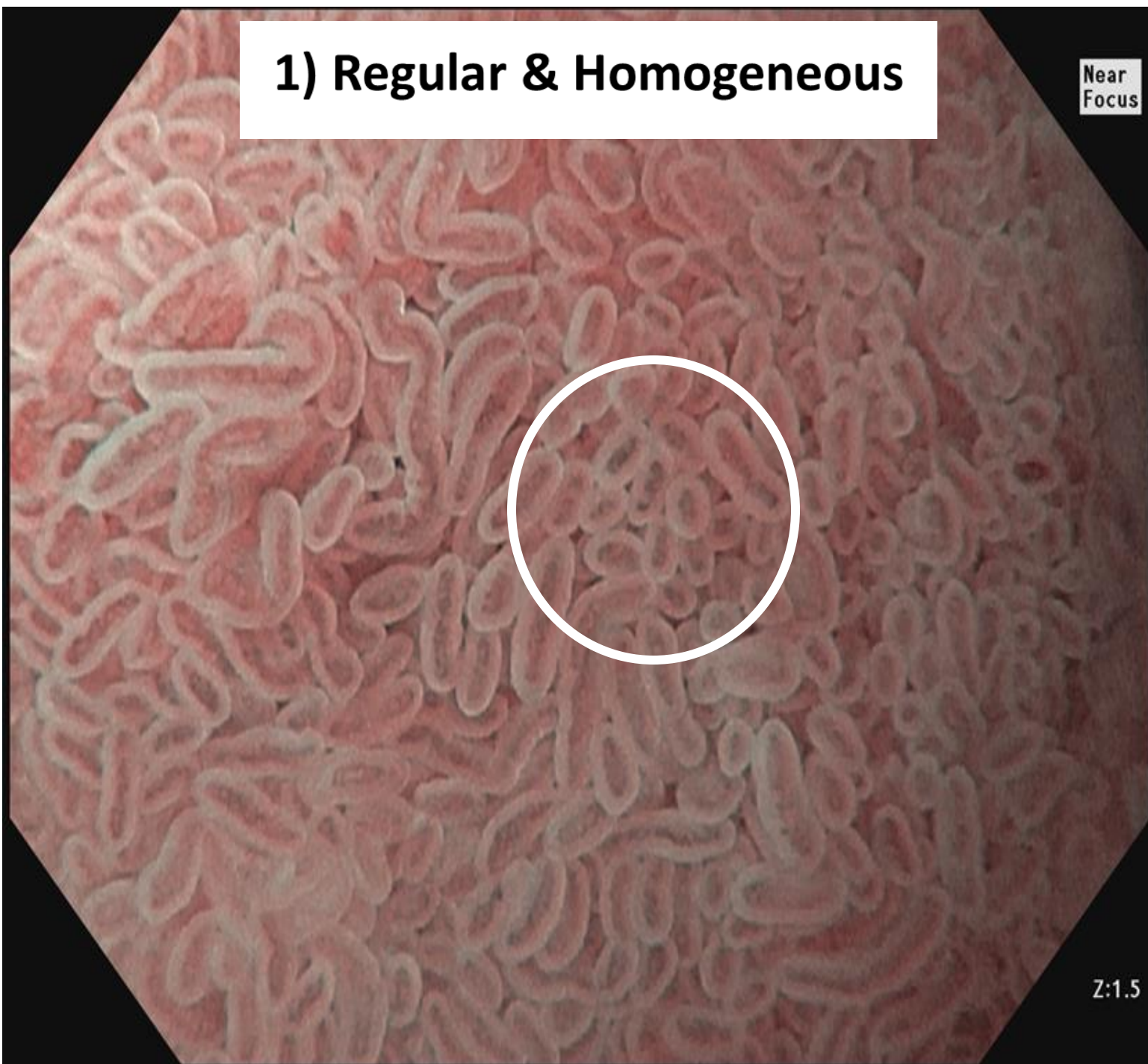
Normal Duodenum



© MAYO CLINIC

1) Regular & Homogeneous

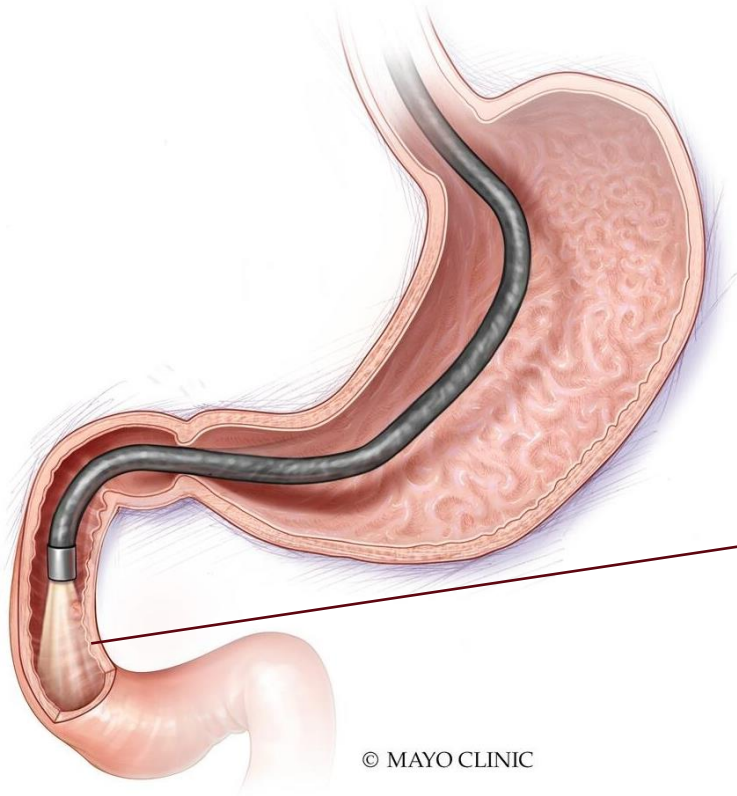
Near
Focus



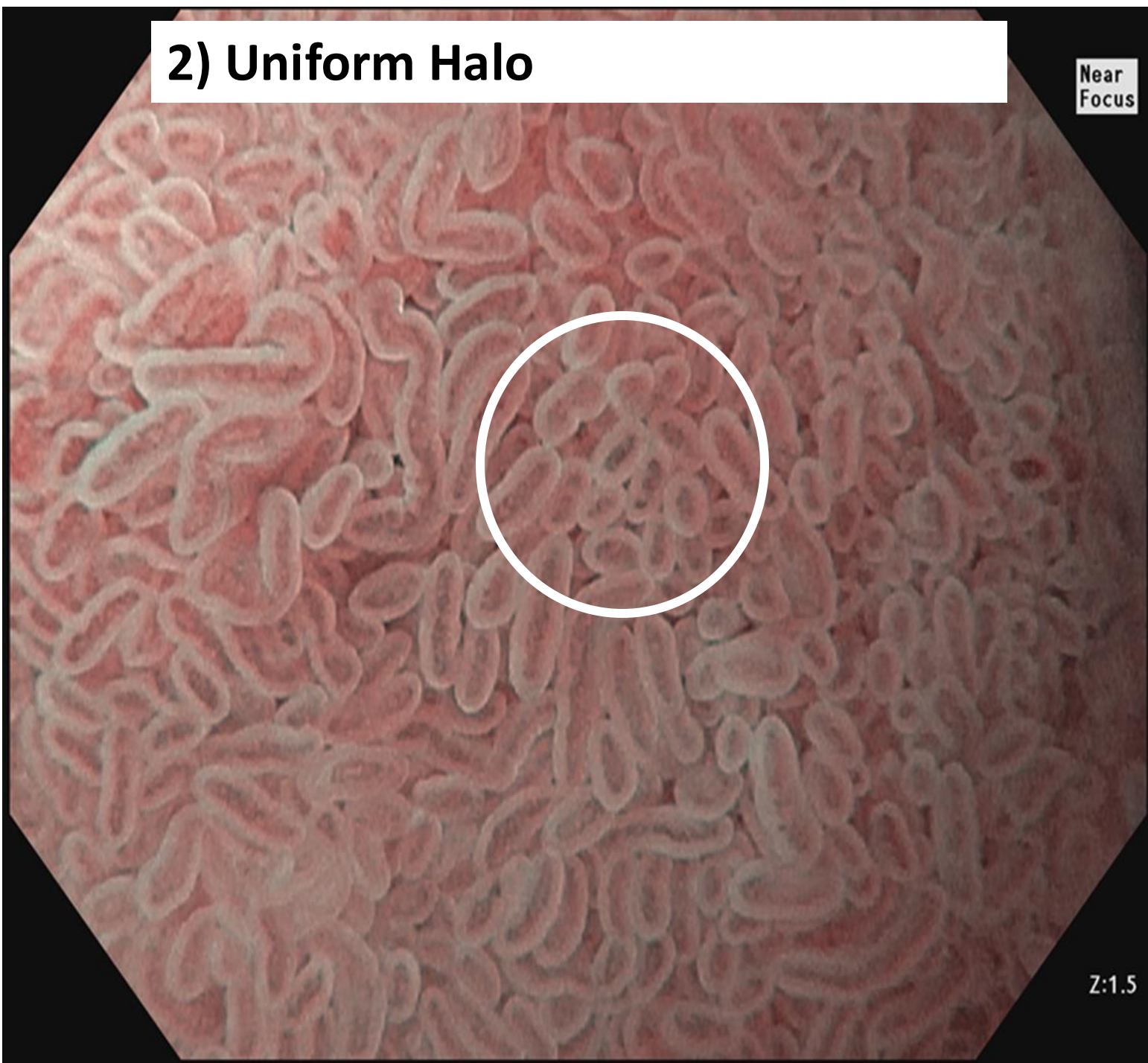
Z:1.5

2) Uniform Halo

Near
Focus

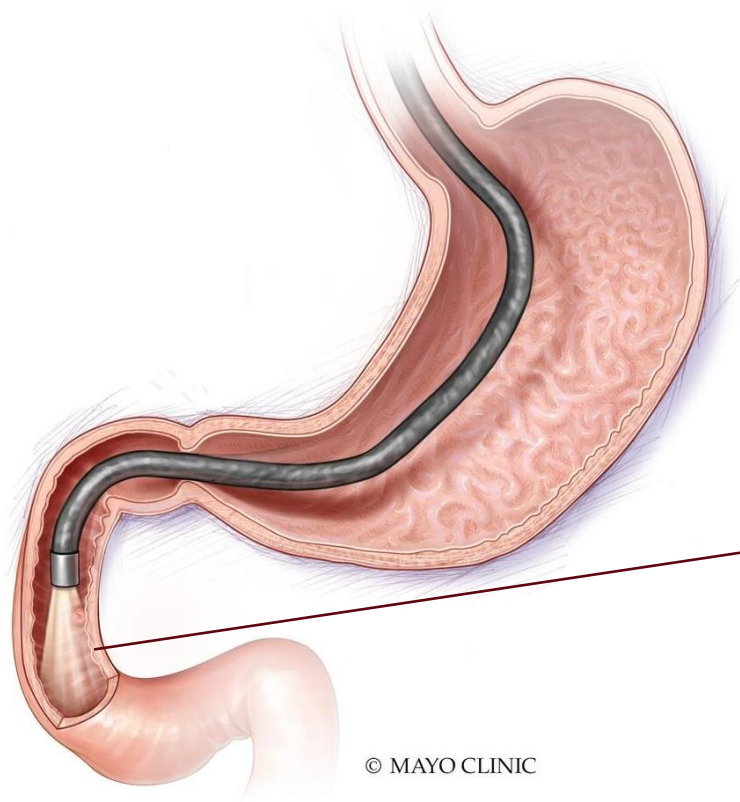


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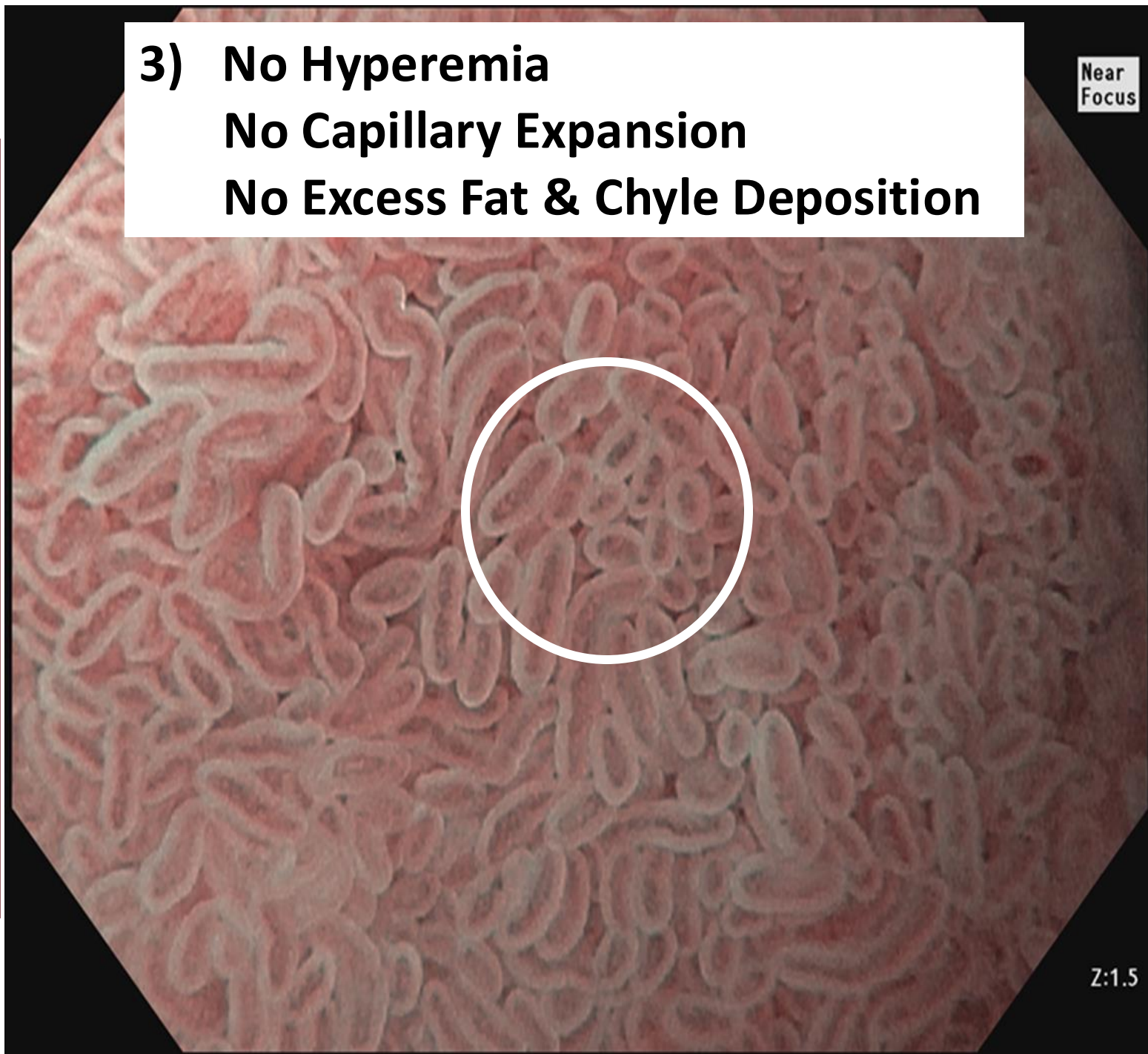


Z:1.5

- 3) No Hyperemia
No Capillary Expansion
No Excess Fat & Chyle Deposition**

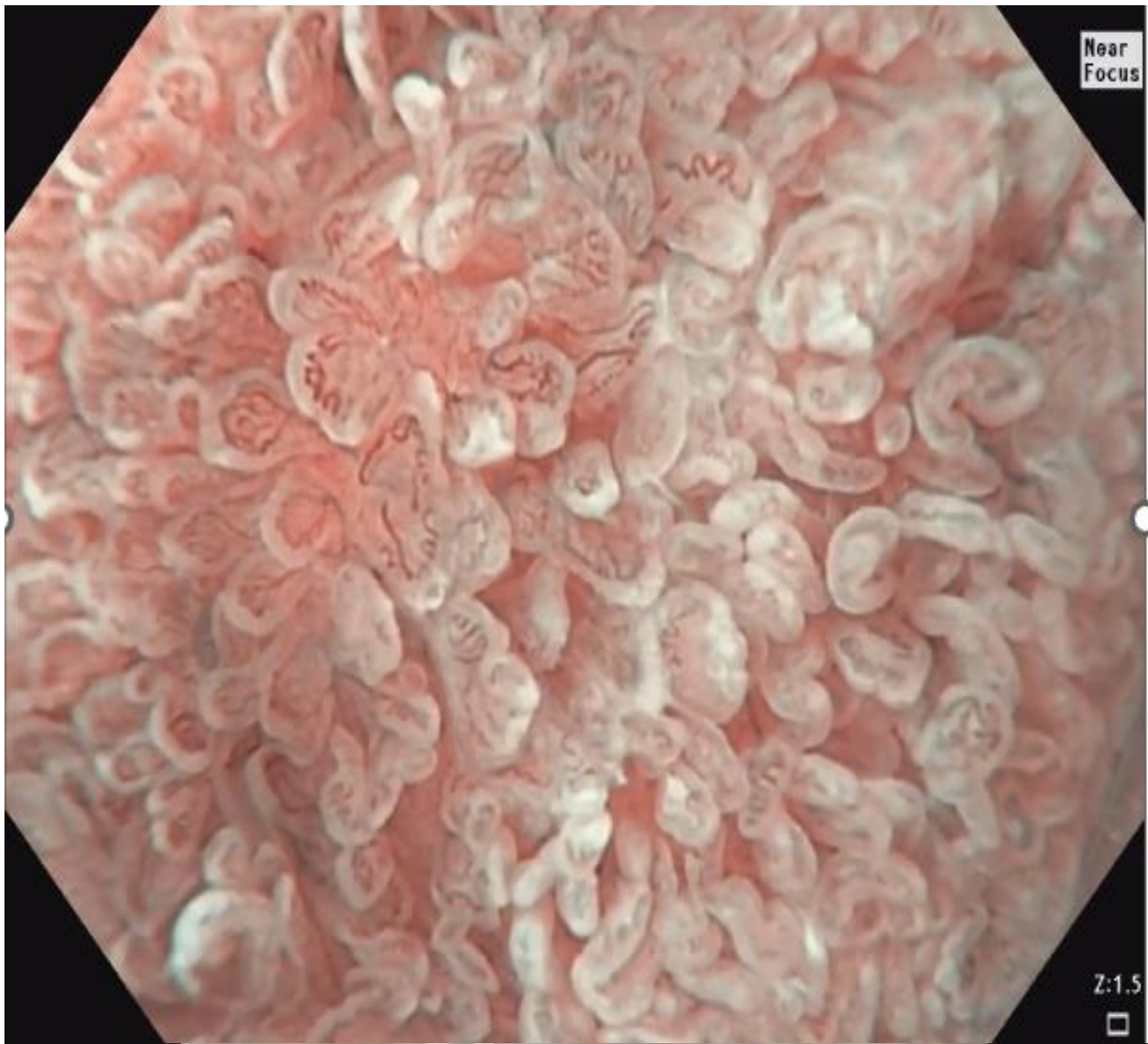
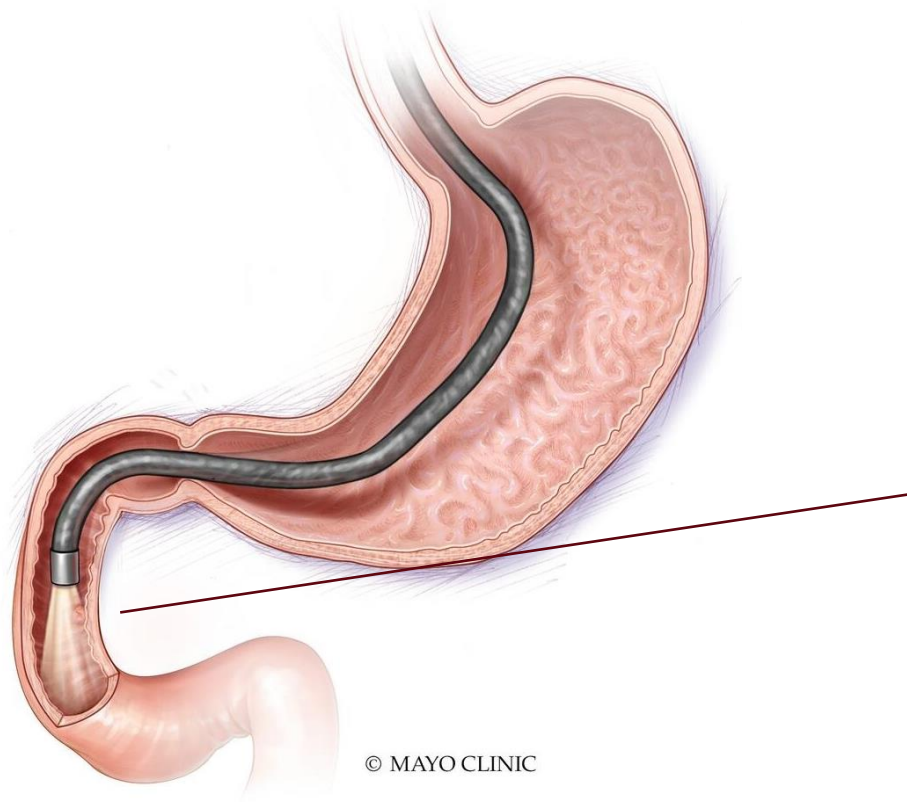


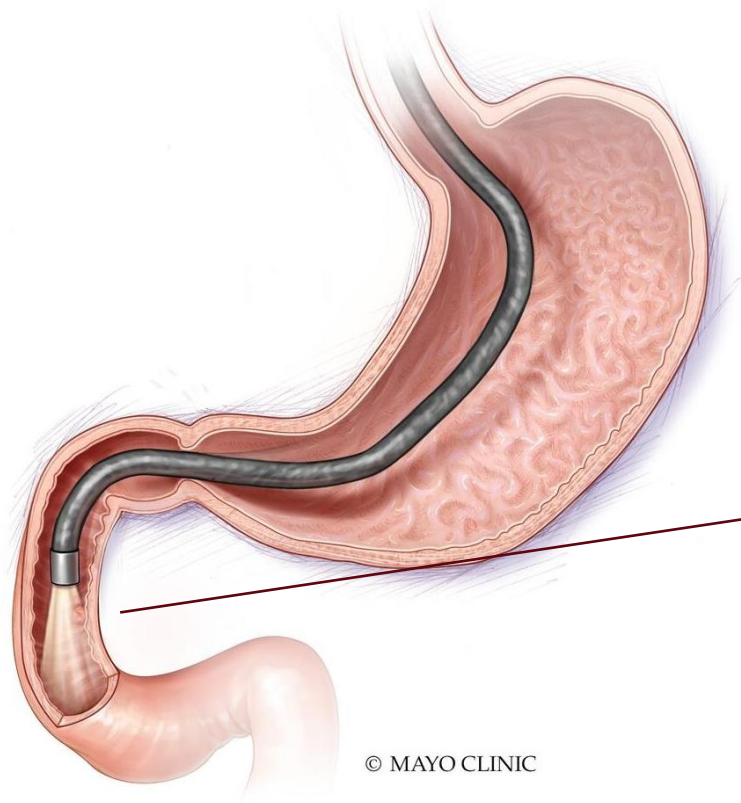
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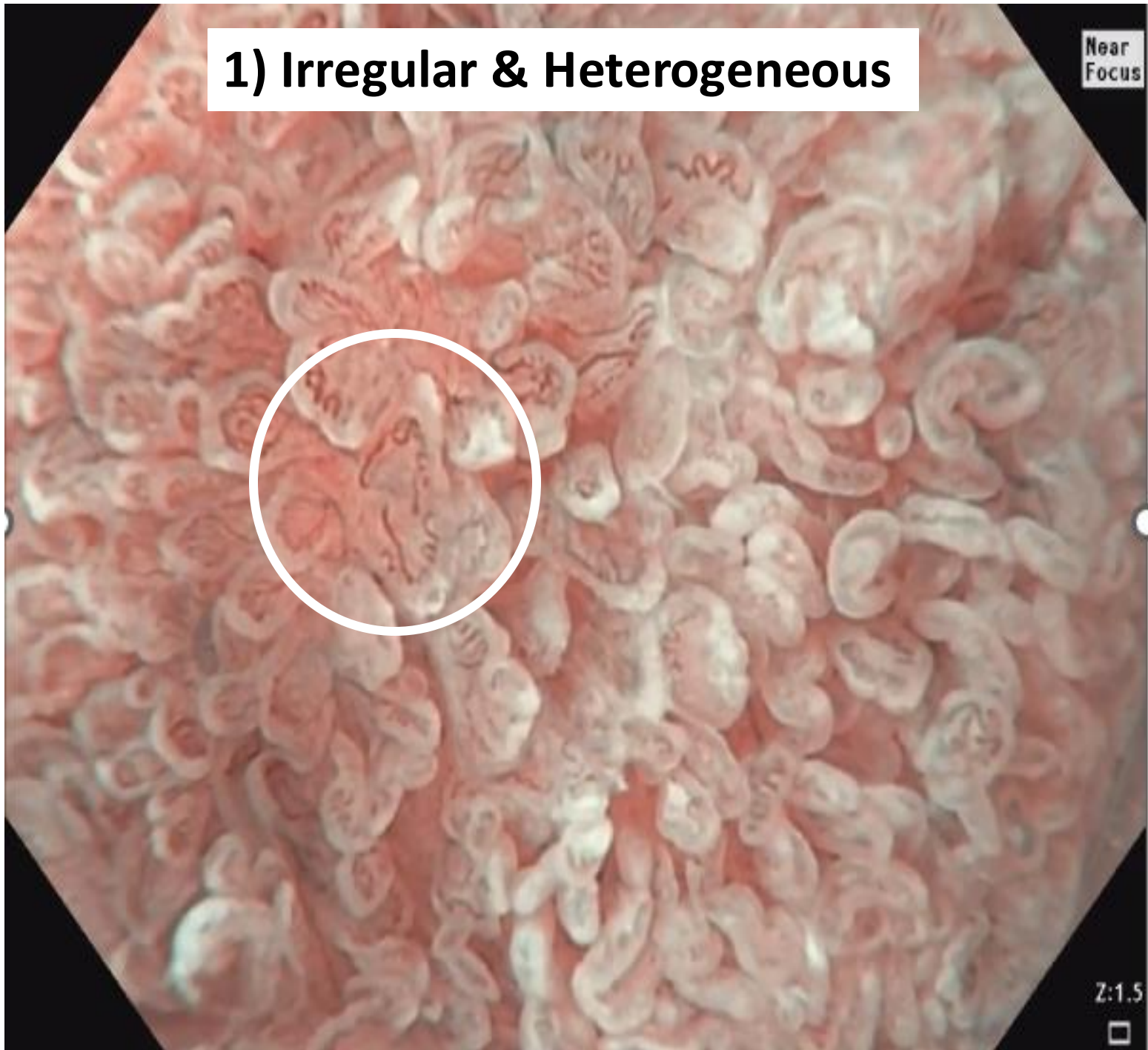
Z:1.5

Metabolic Duodenopathy (N = 231)

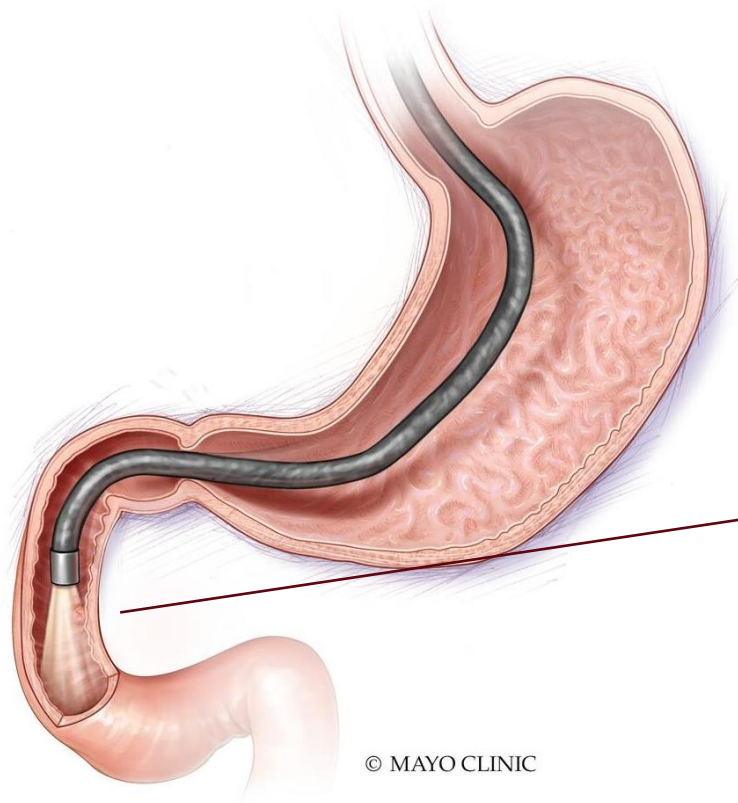


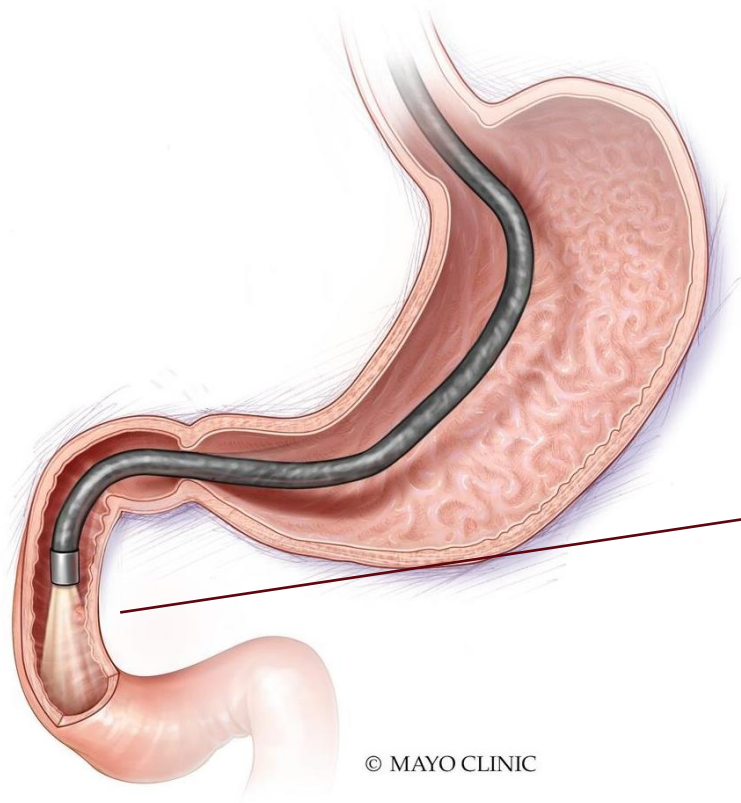


1) Irregular & Heterogeneous



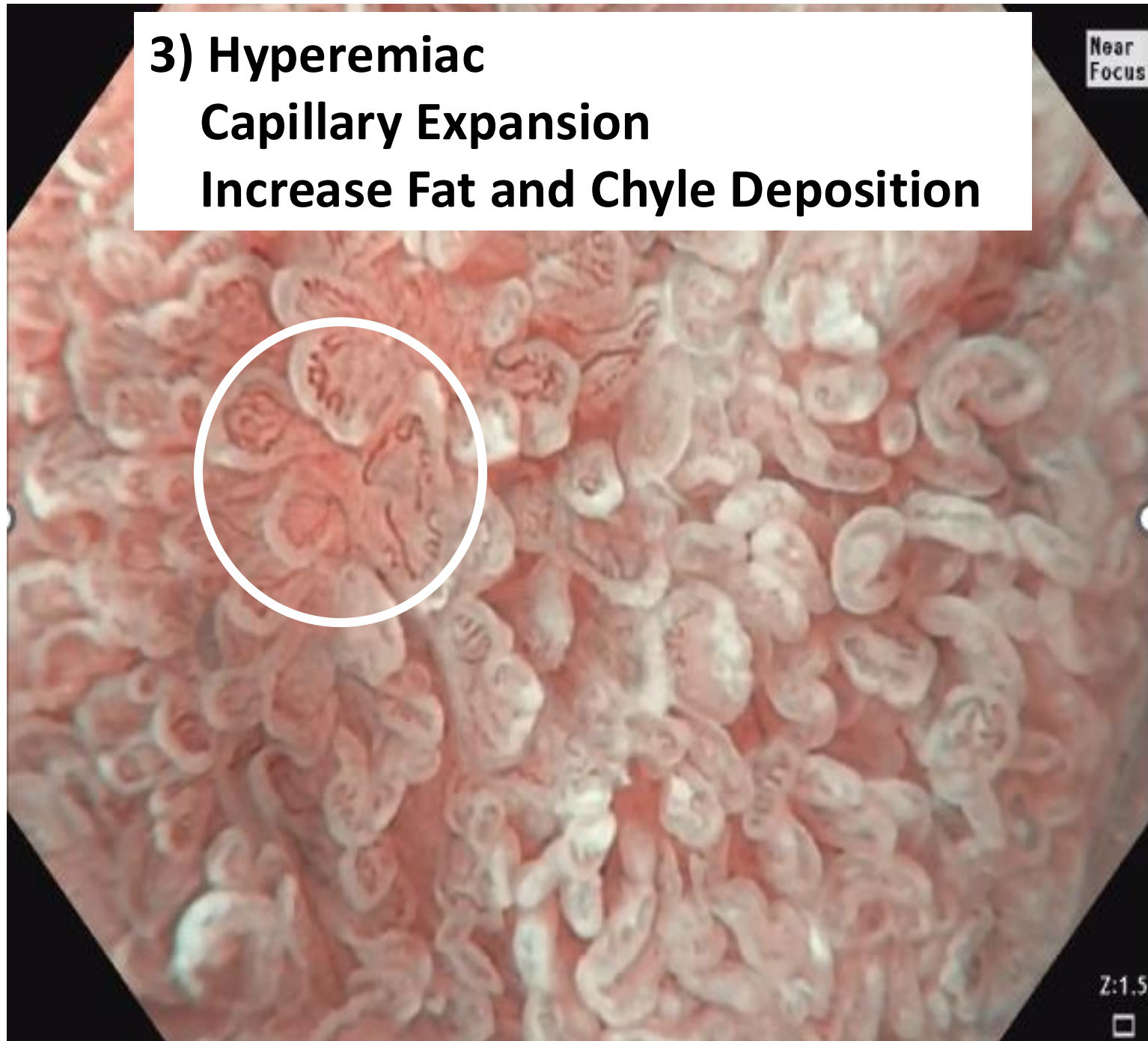
2) Blunting of the Halo





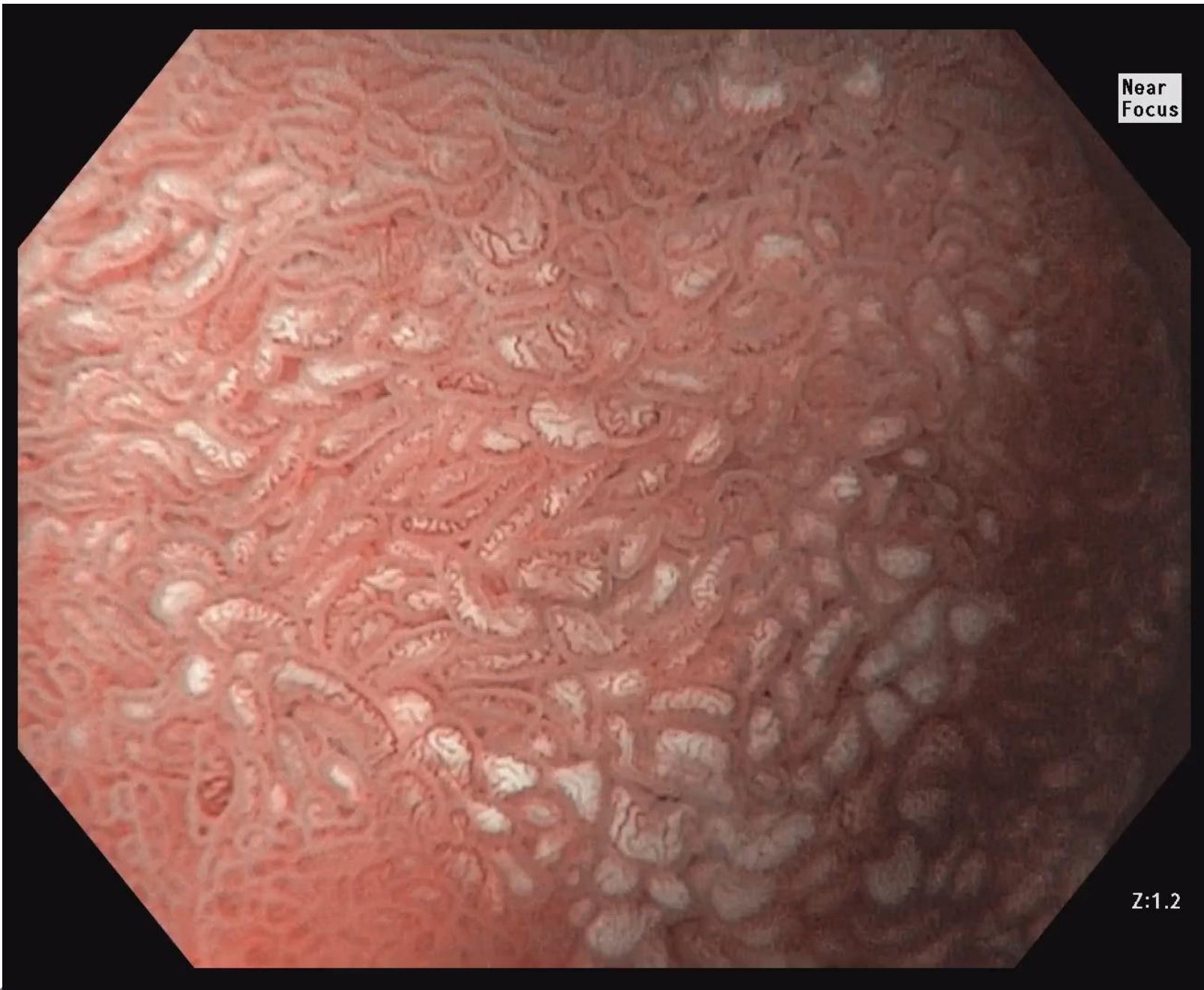
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3) Hyperemic Capillary Expansion Increase Fat and Chyle Deposition



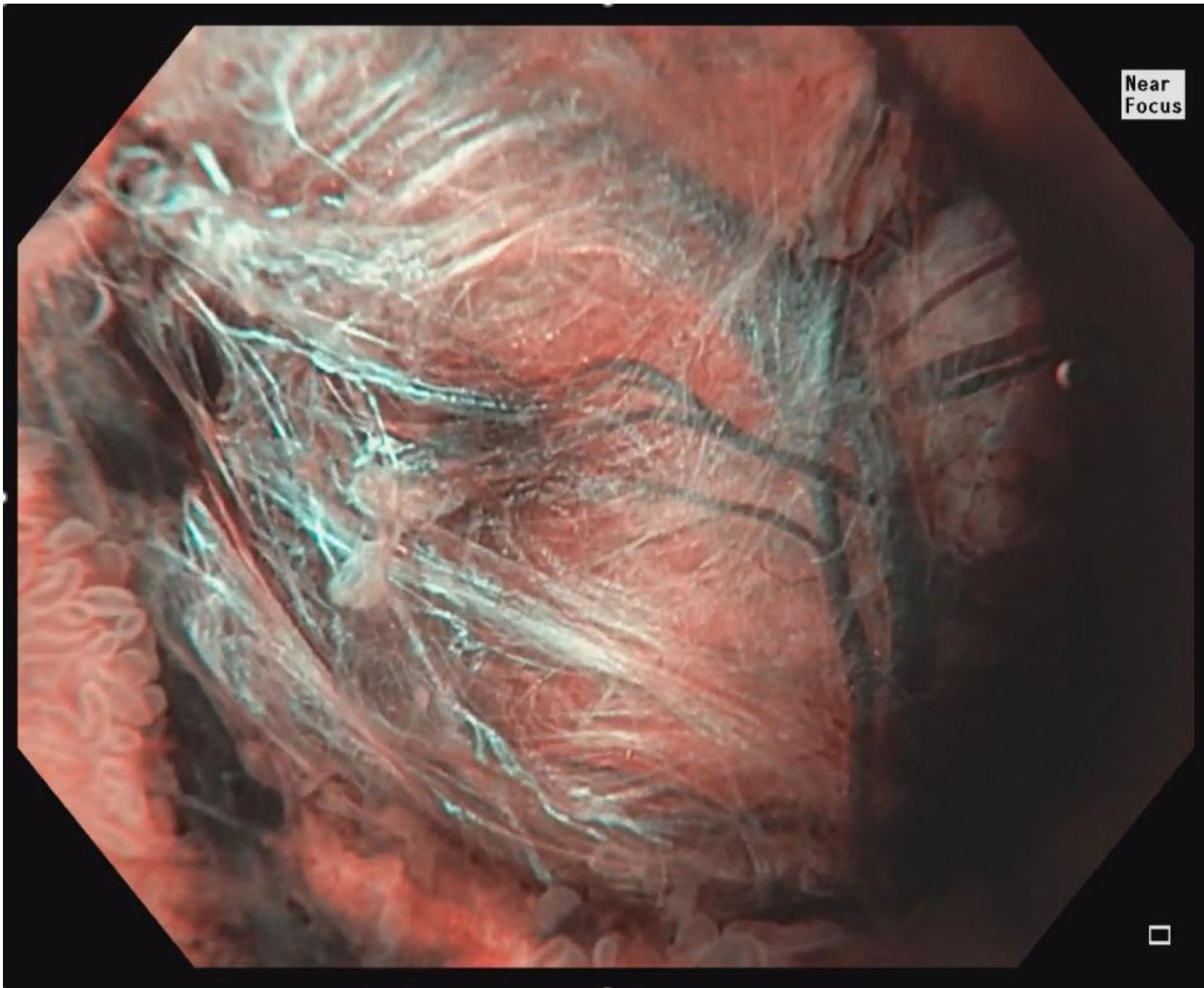
Near
Focus

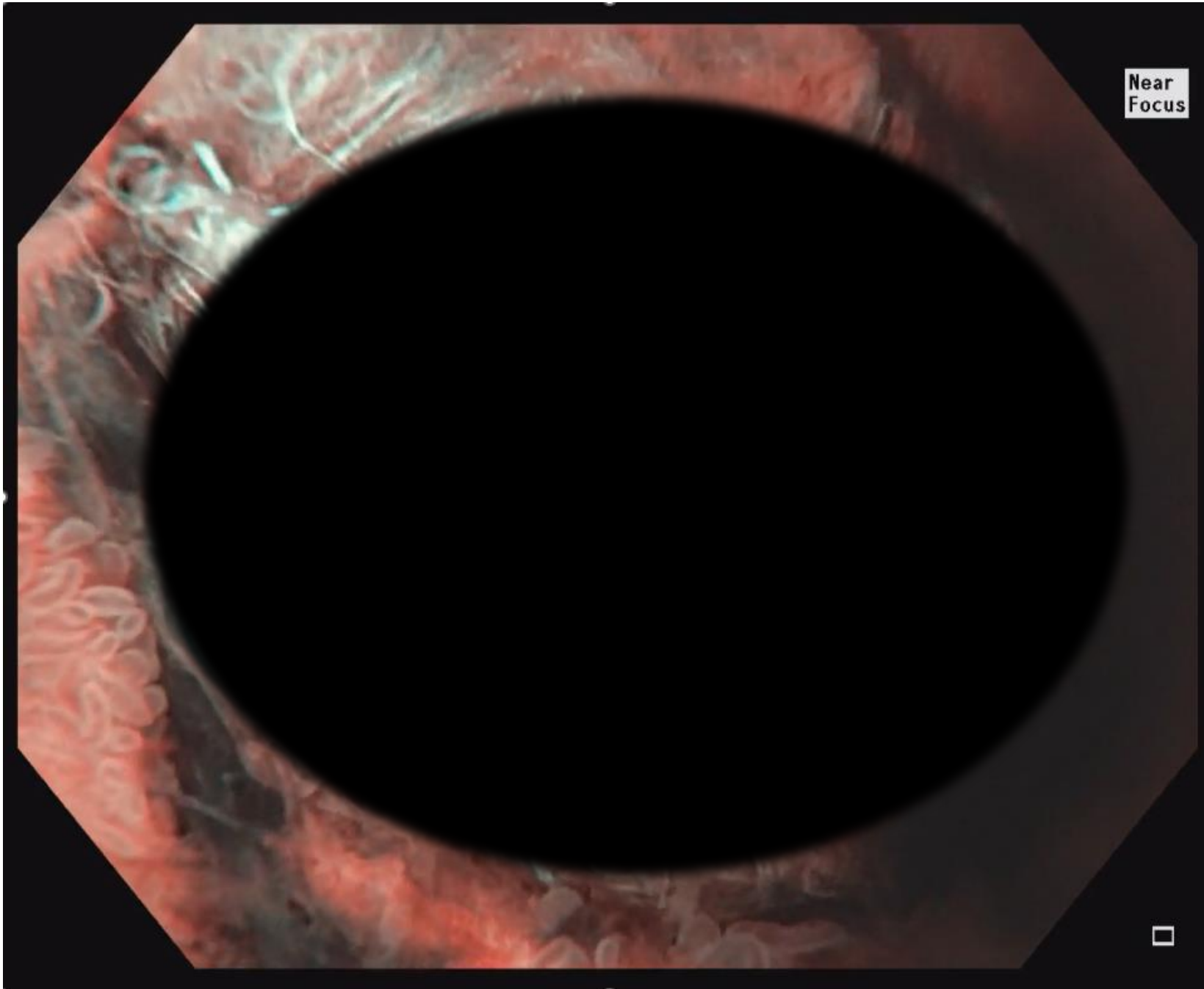
2:1.5



Near
Focus

Z:1.2



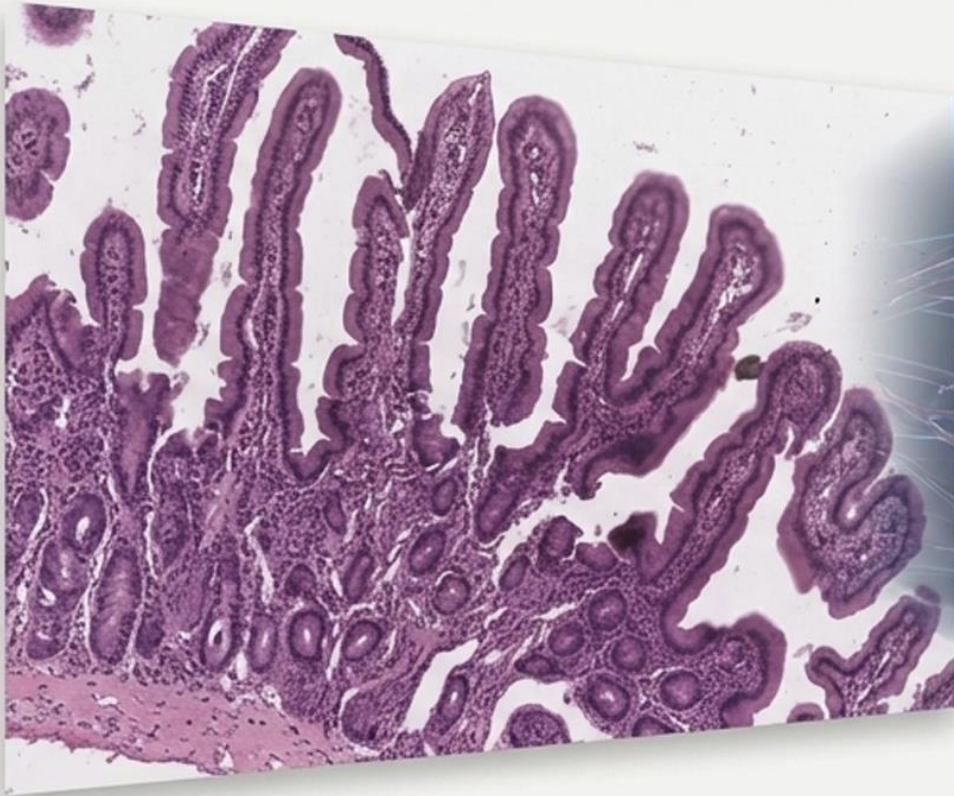


Near
Focus

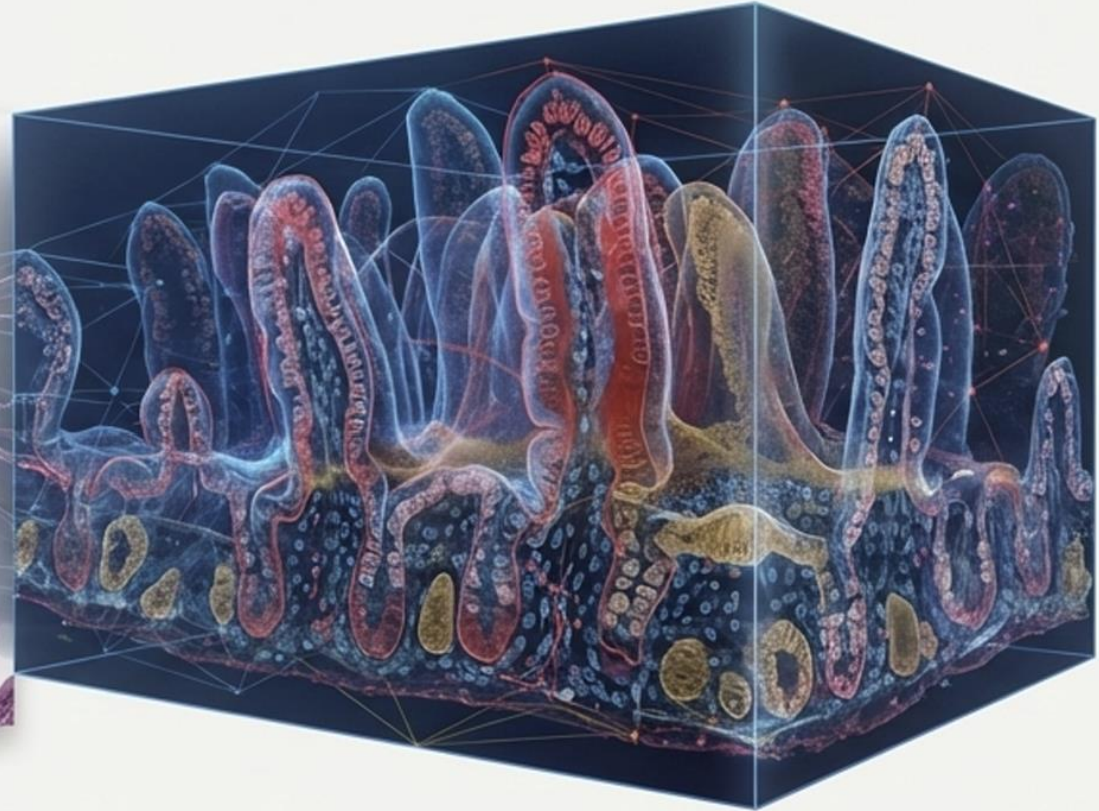
ENS (Second Brain)

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

Programmable Biology Happens in 5D



The "Flat Map": Traditional 2D Histology



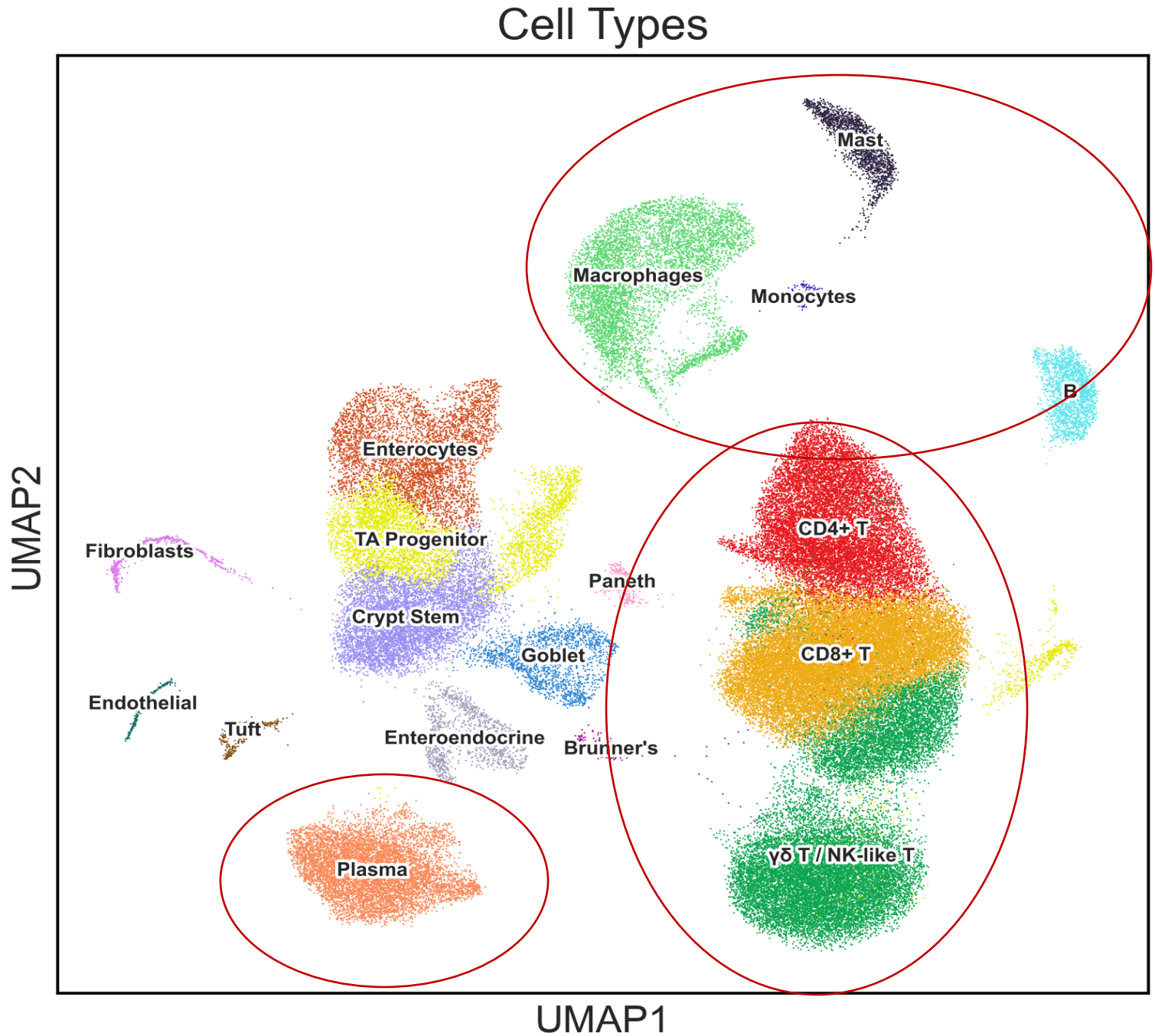
The "Glass Box": Our 4D Digital Twin

In-Situ Molecular Imaging (5 T2D vs 5 Control)

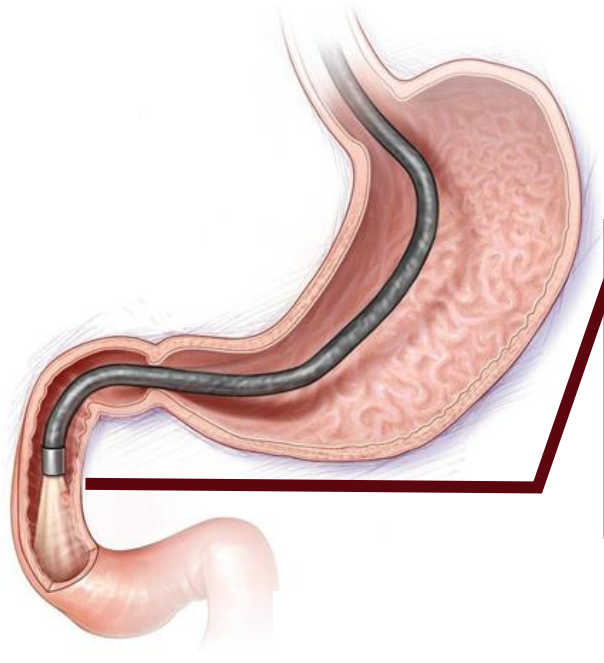


Cell Type Clusters

100K Cell RNA SEQ

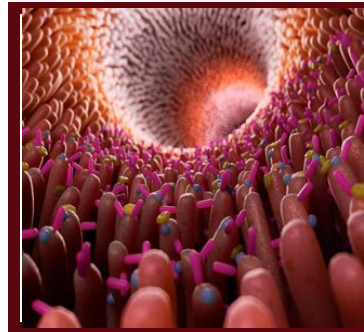


Metabolic Duodenopathy



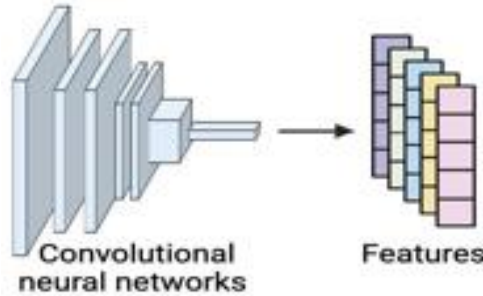
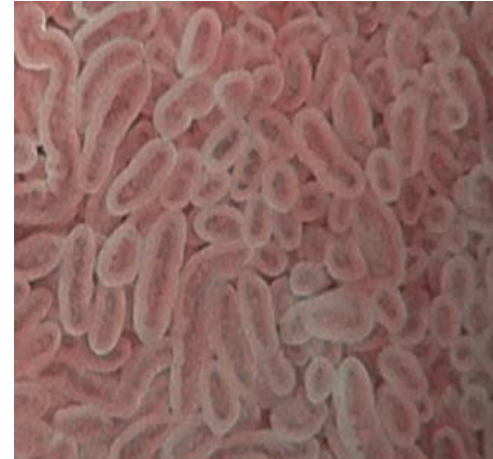
Non-Diabetic

Duodenum

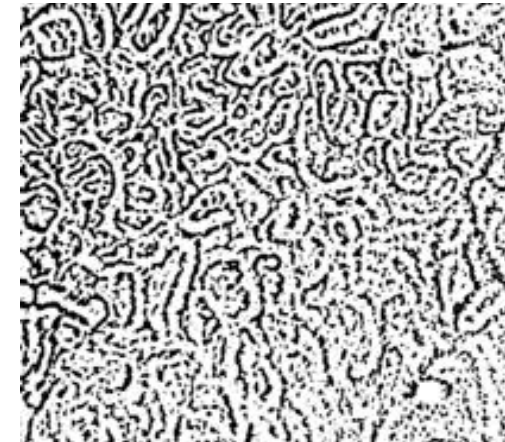
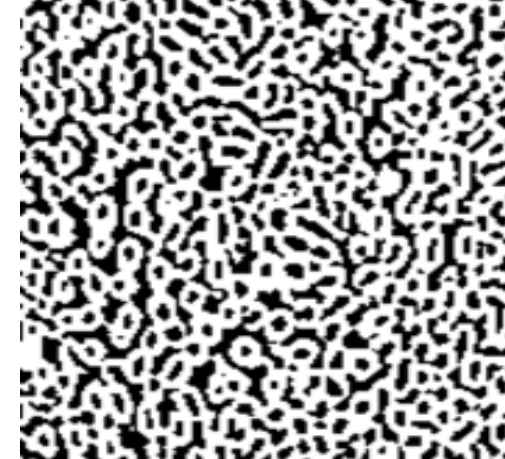


Type II Diabetes

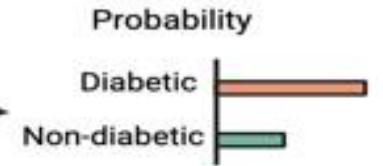
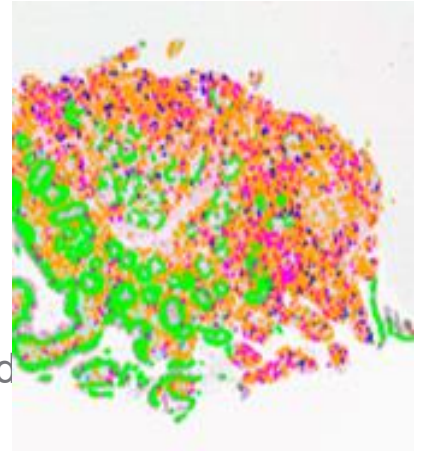
Endoscopy



AI Fingerprinting Analysis

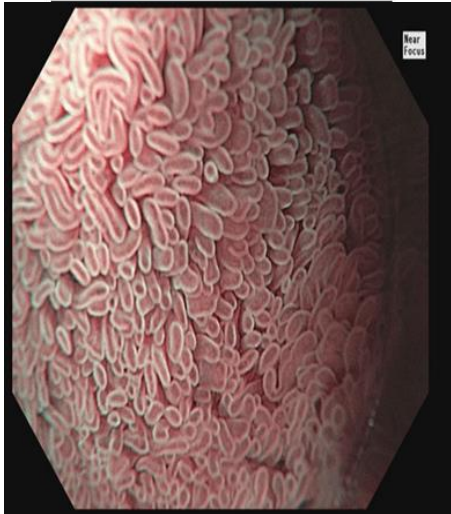


AI Cellular / Molecular

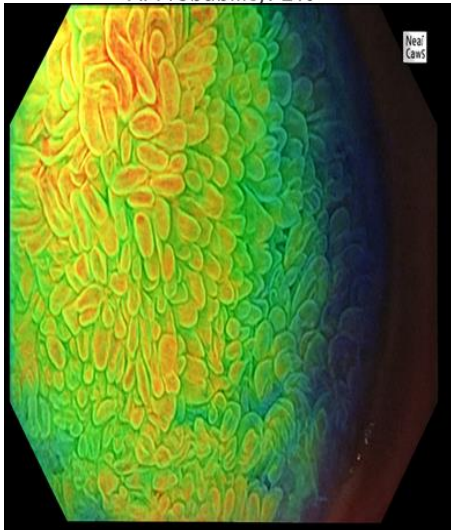


Raw NBI Images (Top) and AI Heatmaps (Bottom)

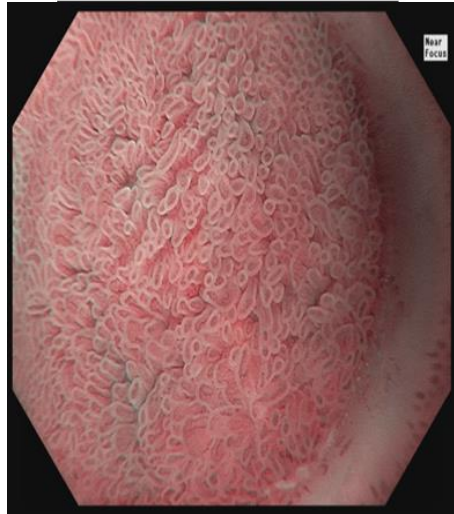
Normal



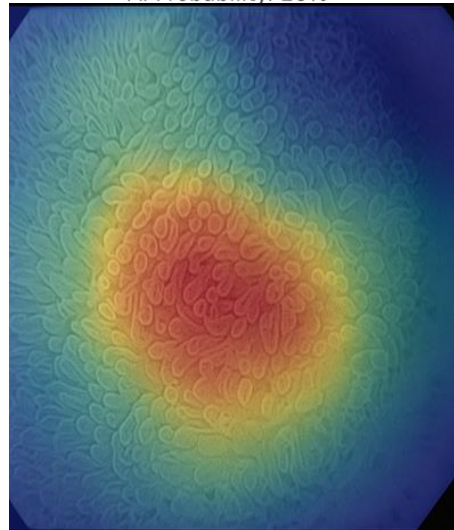
AI Probability: 2%



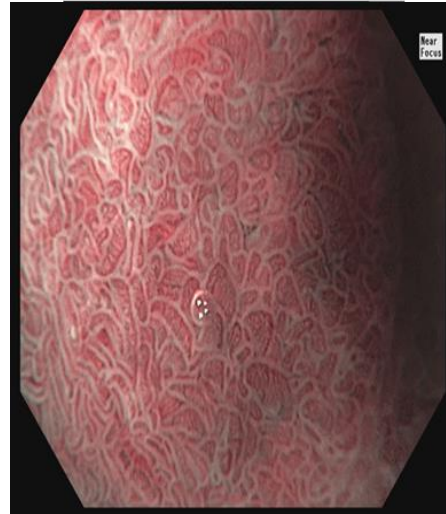
Mild



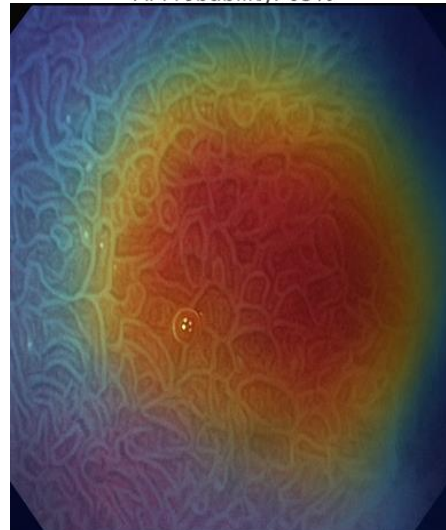
AI Probability: 28%



Moderate



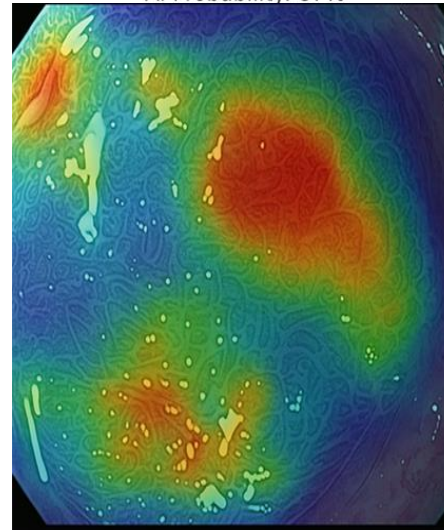
AI Probability: 65%



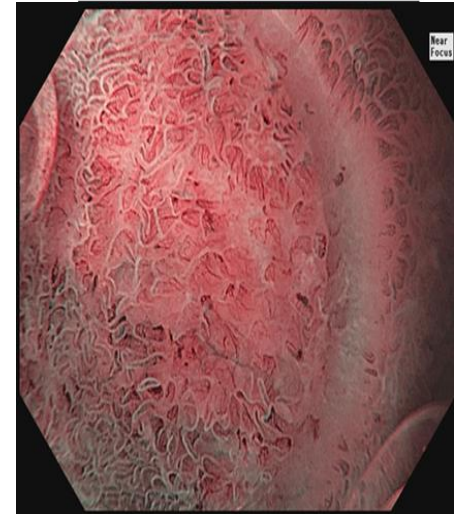
Advanced



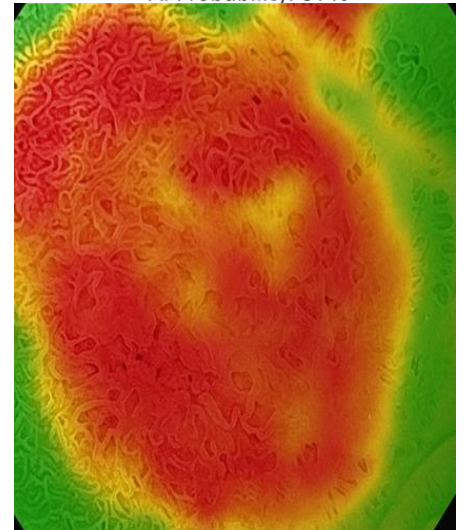
AI Probability: 87%



Severe

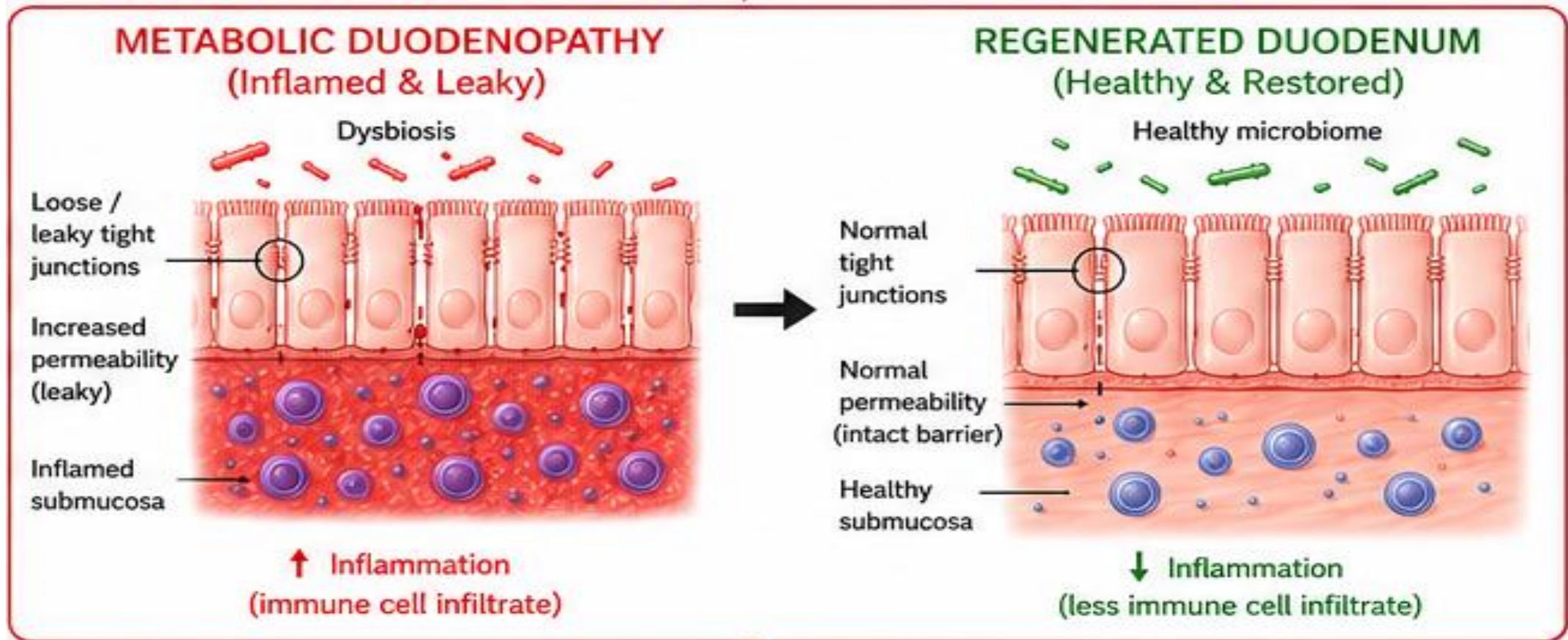


AI Probability: 97%



Spectrum of Metabolic Disease-Associated Duodenopathy

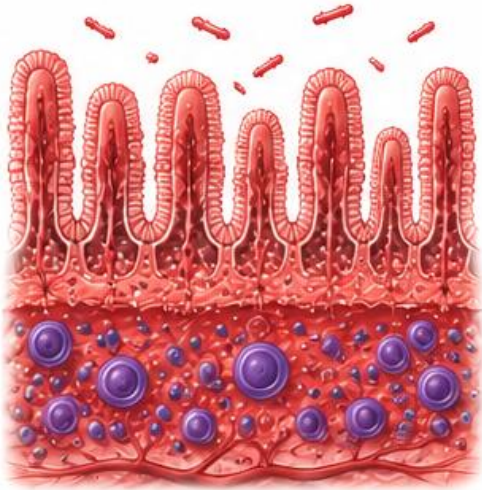
Reprogrammable Disease Modification Target



Reprogrammable Biology

1. DISEASE BEGINS IN TISSUE

Metabolic Duodenopathy



↑ INFLAMMATION

- Dysbiosis (imbalanced microbiome)
- Loose / leaky tight junctions
- Increased permeability (leaky barrier)
- Immune cell infiltration
- Inflamed submucosa

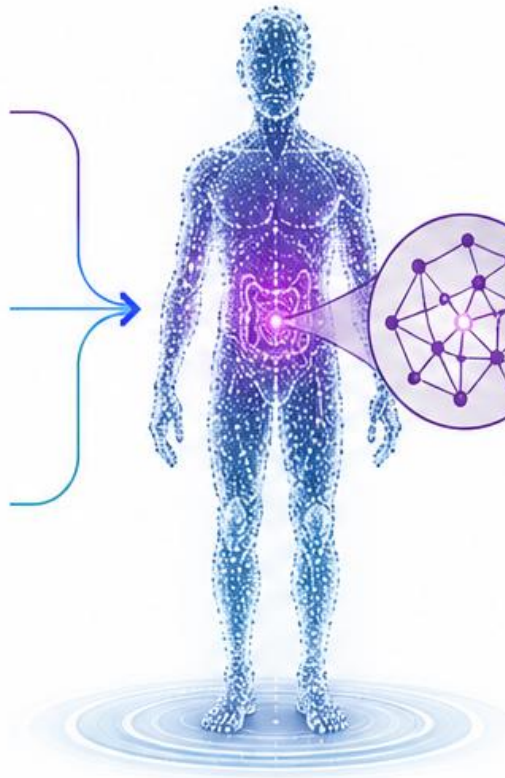
2. MULTIMODAL INTELLIGENCE

See What Matters



3. DIGITAL BIOLOGICAL TWIN

Your Avatar



4. PREDICTED DISEASE MECHANISM

Identify the Dominant Driver



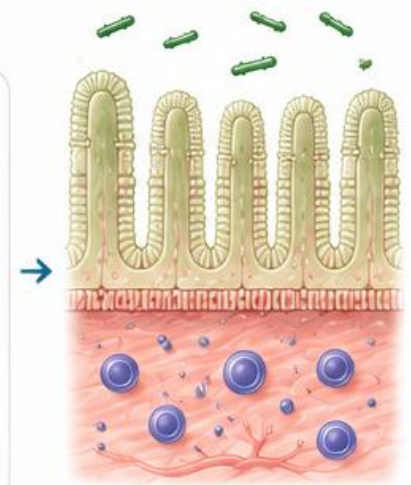
5. OPTIMAL THERAPY

Reprogram the Biology



6. TISSUE RESTORED

Metabolic Health



↓ INFLAMMATION RESOLVED

- Healthy microbiome
- Normal tight junctions
- Intact barrier (normal permeability)
- Reduced immune activation
- Healthy submucosa

THE OLD PARADIGM

Manage the Consequences

Measure Numbers → Treat Symptoms → Manage Disease

Temporary control. Disease persists.



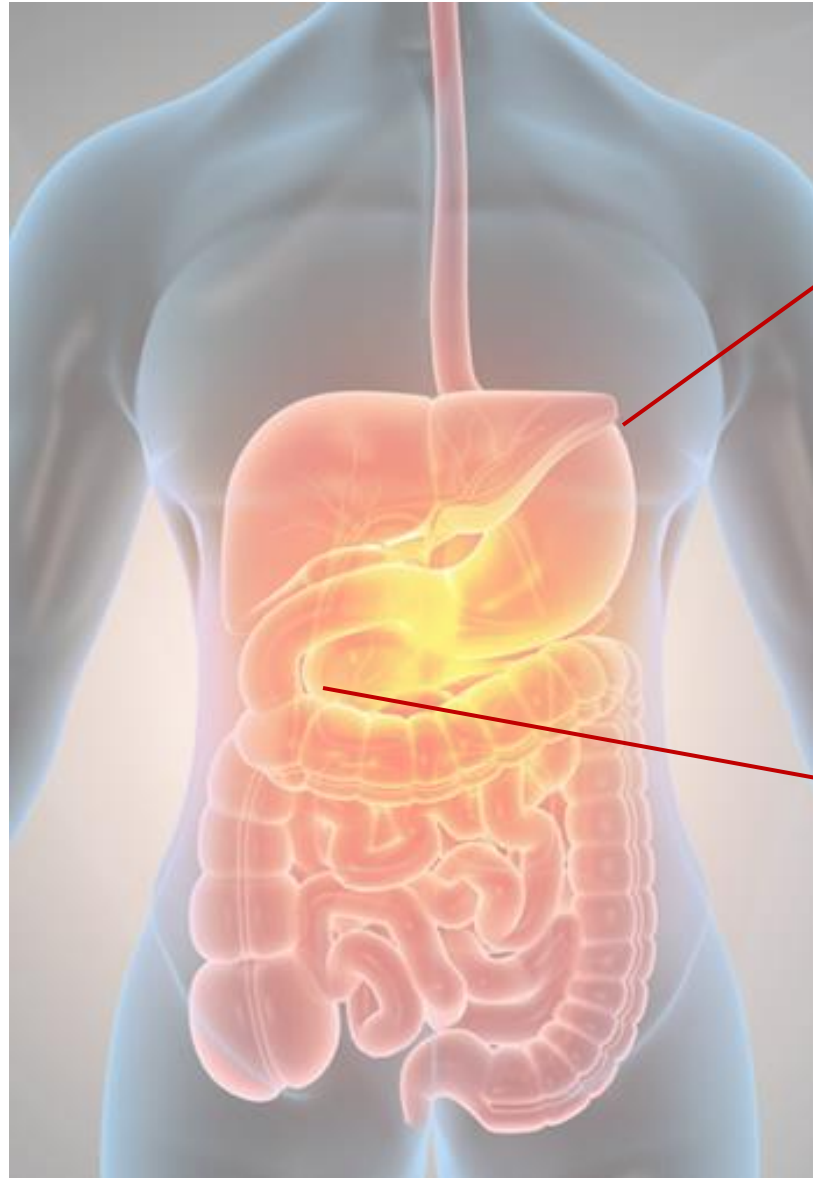
THE NEW HORIZON

Reprogram the Biology

Understand Tissue Biology → Identify Root Cause → Reprogram Biology → Reverse Disease

Address the cause. Restore health.

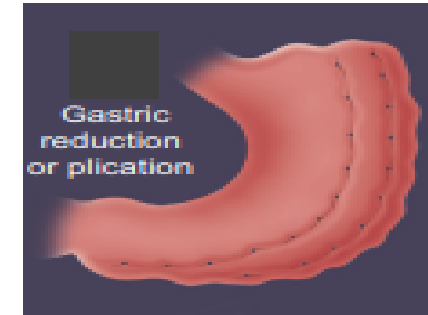
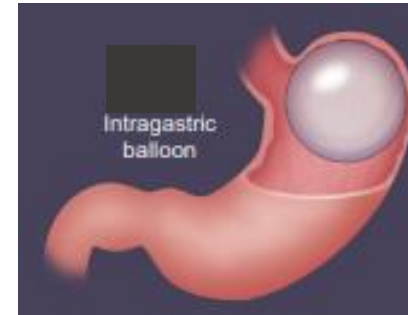
EBMTs



Gastric: Appetite Regulation

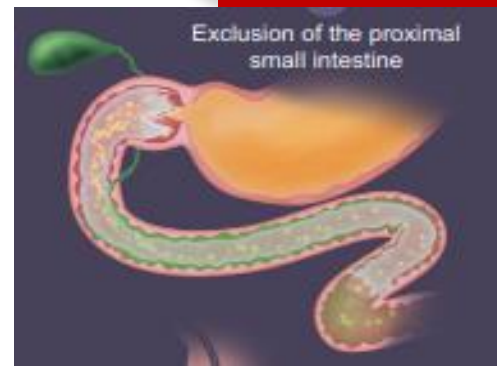
- Gastric Accommodation
- Gastric Emptying
- Ghrelin

ESG Delays Gastric Emptying Similar to GLP-1RA

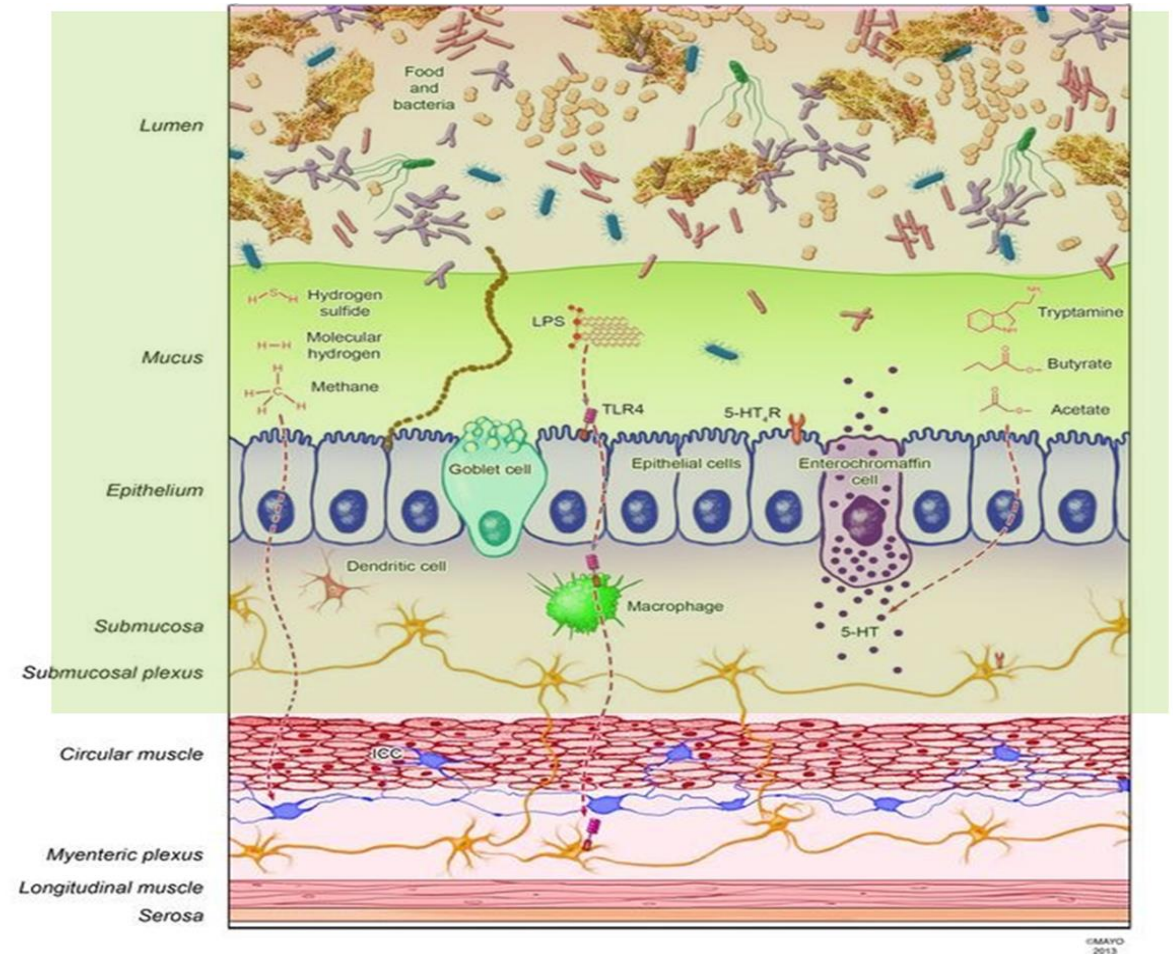
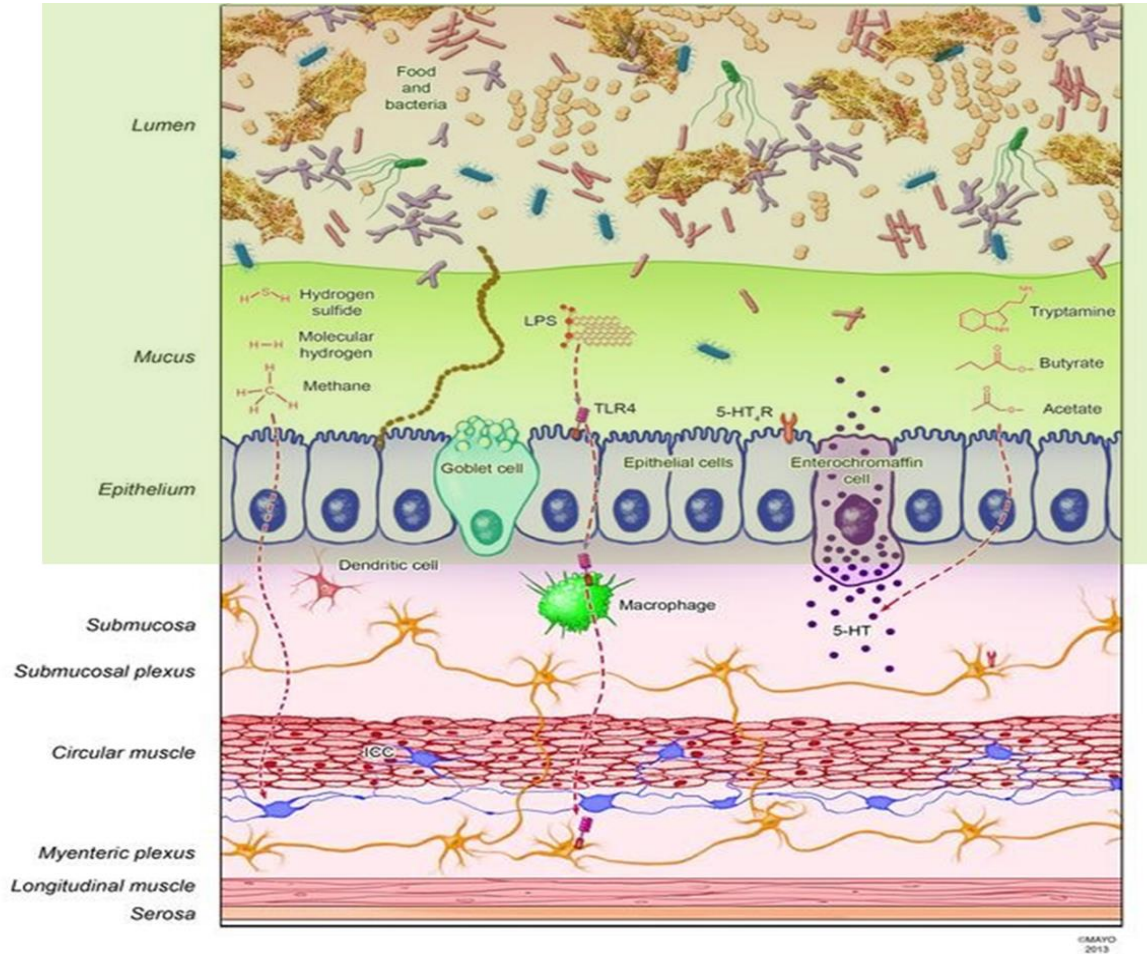


Small Intestinal: Metabolism Regulation

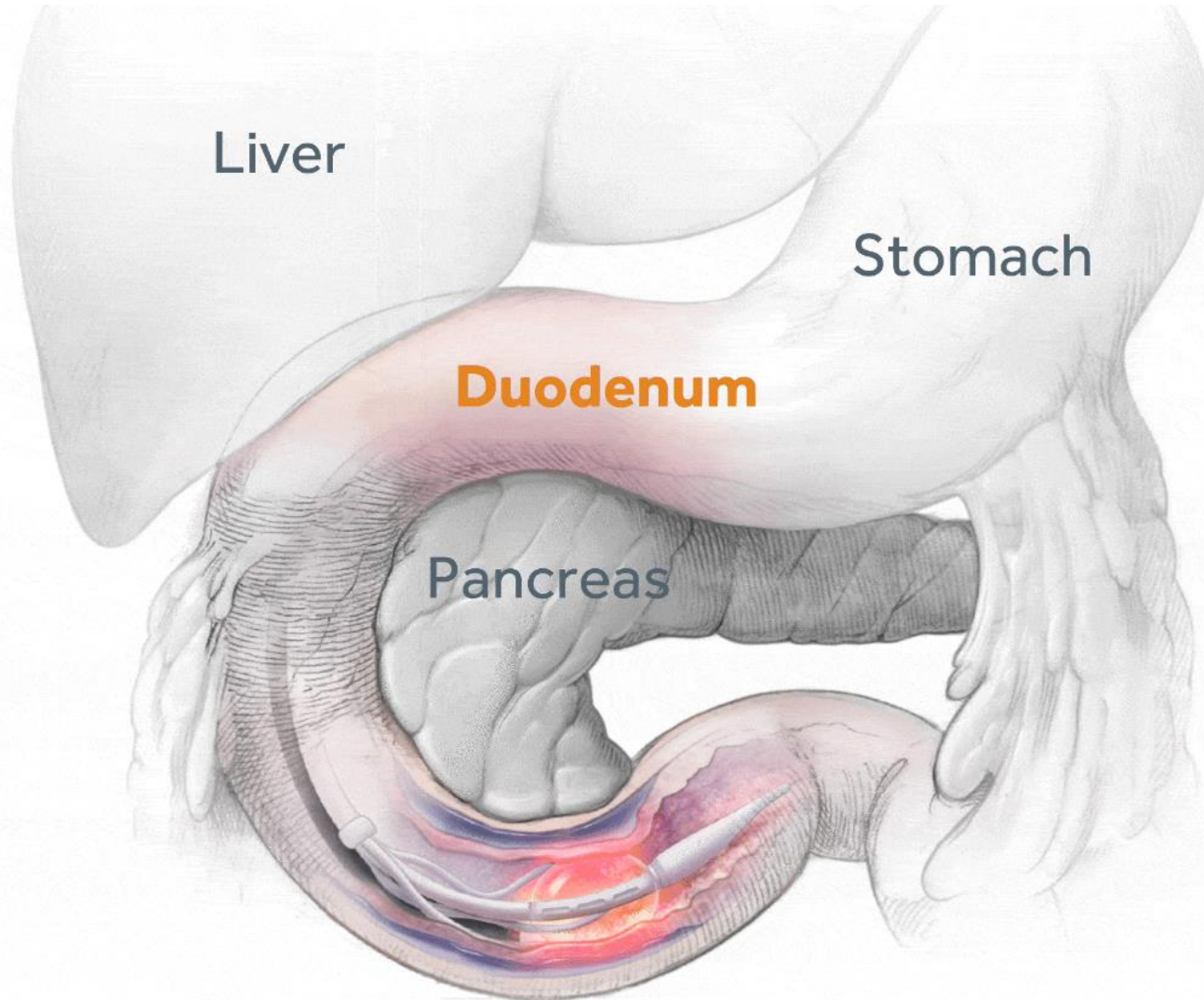
- Insulin Resistance
- Bile and Fat signaling
- Incretin and Microbiomes
- Inflammation



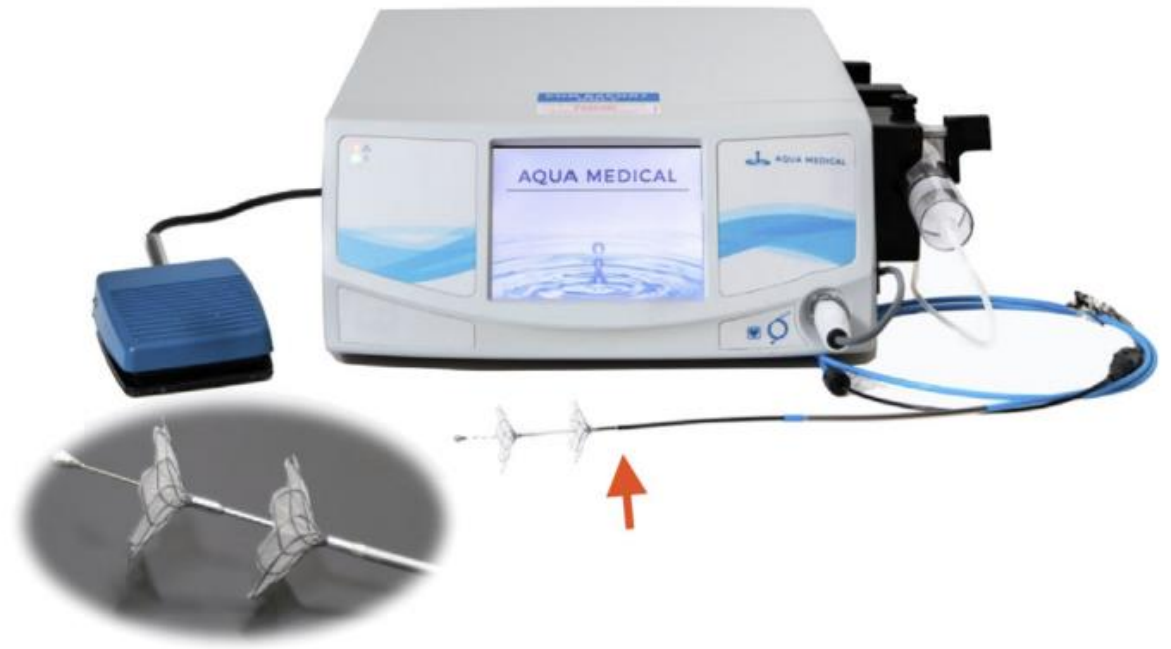
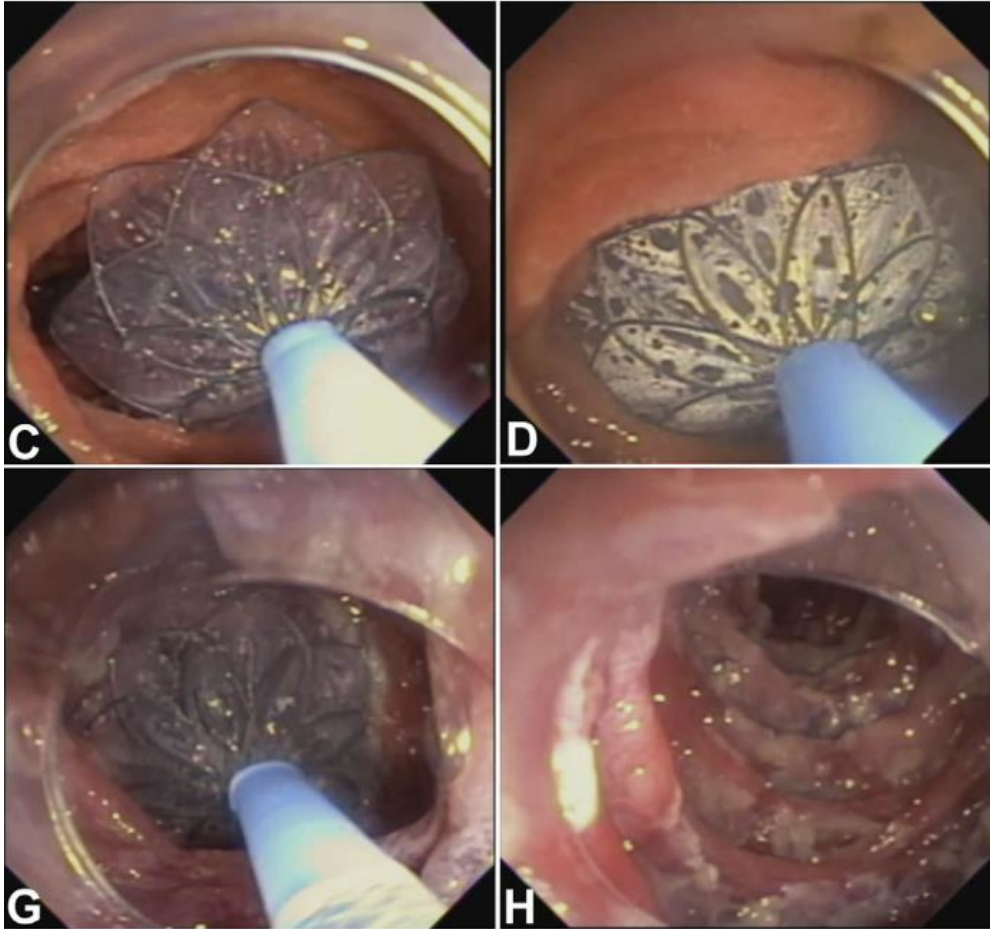
How to Reverse (Regenerative Medicine Paradigm for DMII)



Revita Fractyl Health Hydrothermal DMR (HEAT)

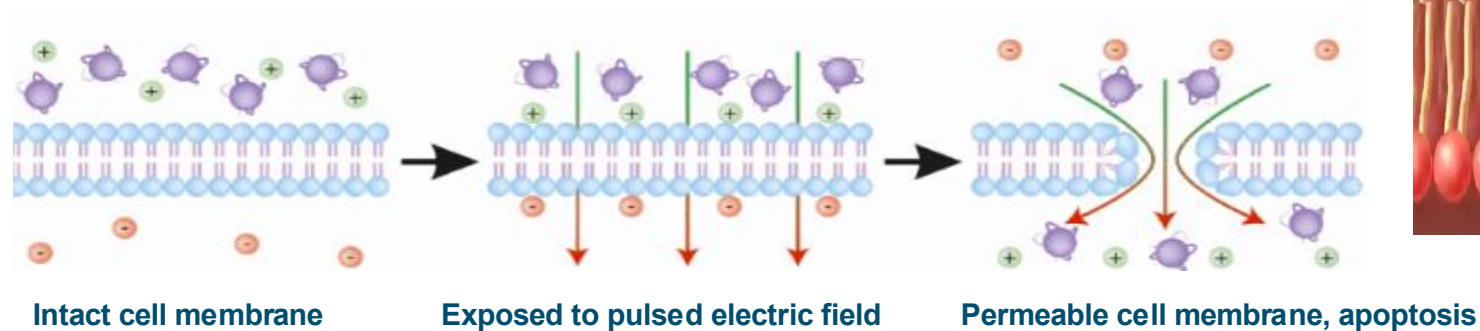
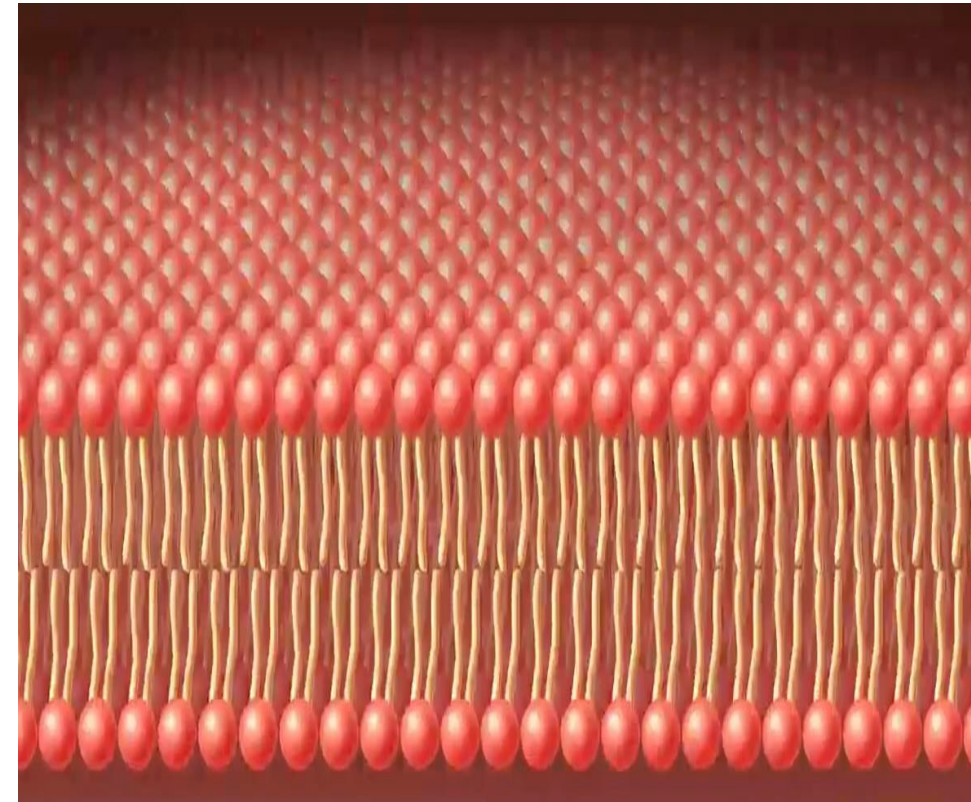


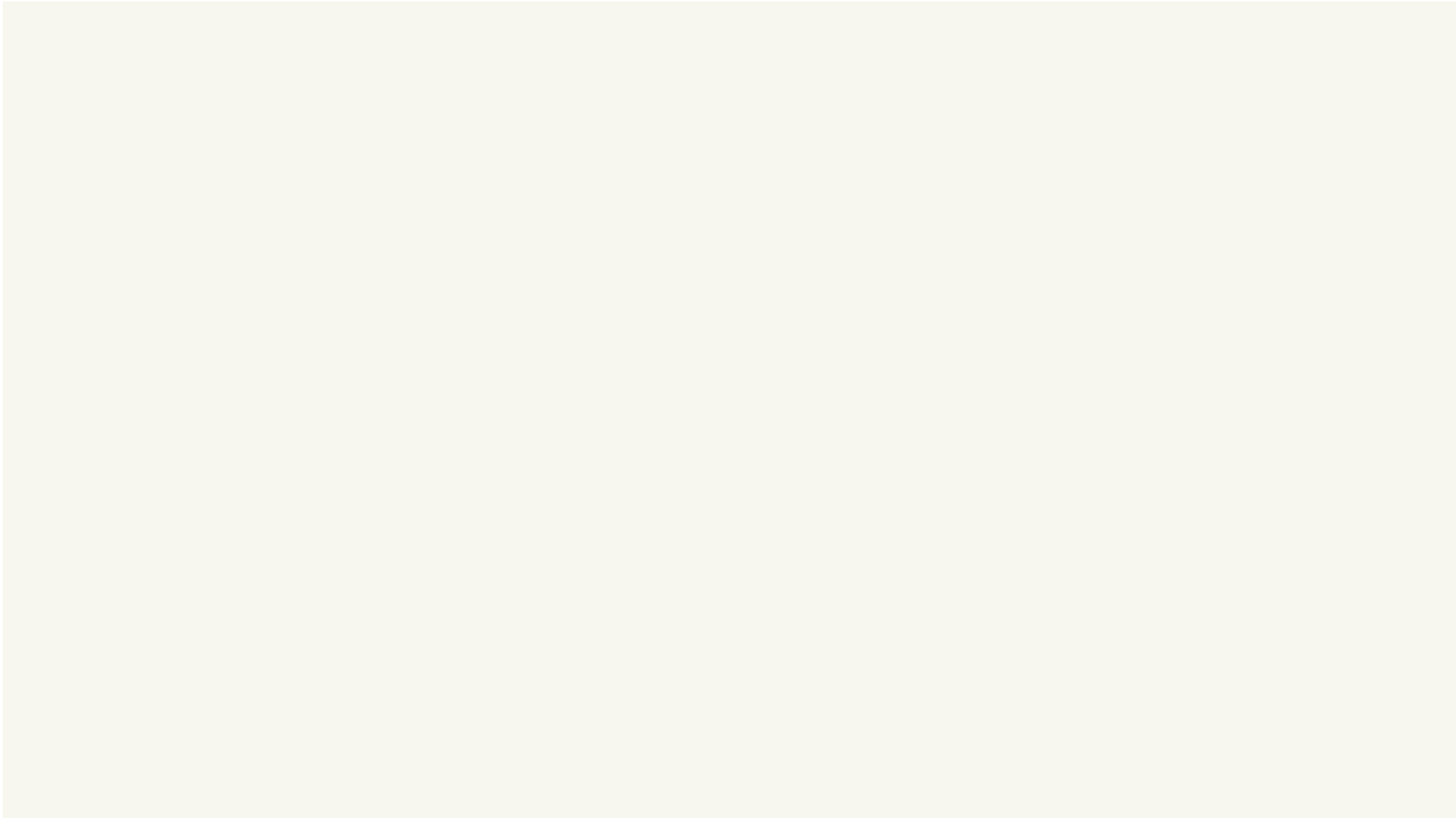
Radiofrequency Vapor Aqua (HEAT)



Electroporation or Pulsed Electric Field: The Era of None Thermal Depth Ablation

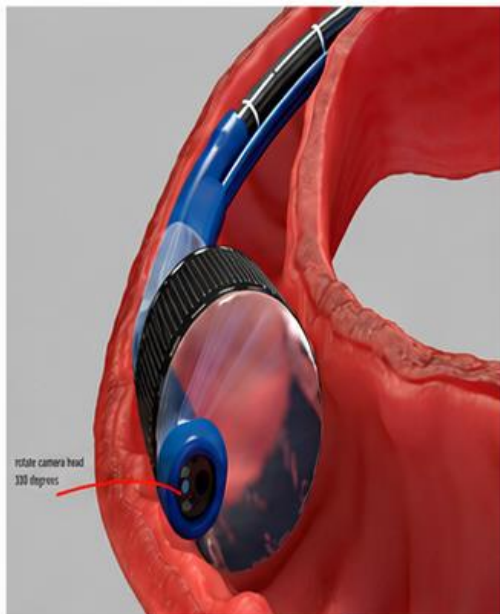
- High voltage, ultra short pulsed electric field
- Increases cell permeability resulting in cellular apoptosis
- Preserves extracellular matrix and myocytes
- Rapid re-epithelialization due to preserved tissue architecture
- Non-thermal ($< 4^{\circ}\text{C}$ average increase in probe temperature)
- Controlled depth of penetration (mucosa and submucosa)





OFFICIAL PROVIDER OF

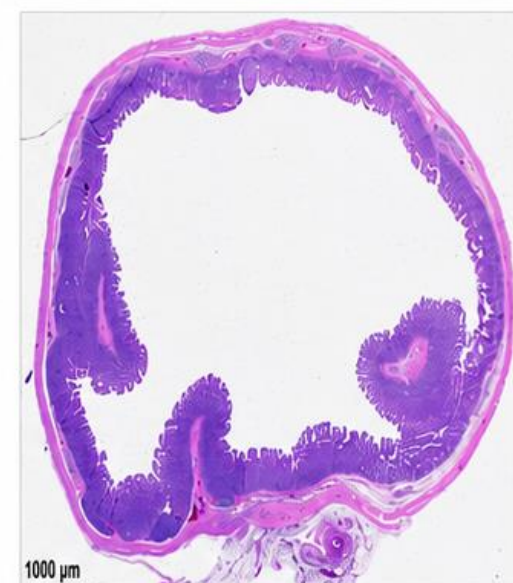
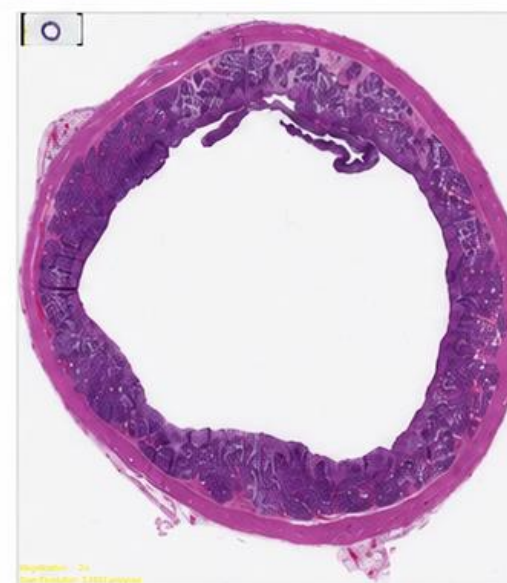
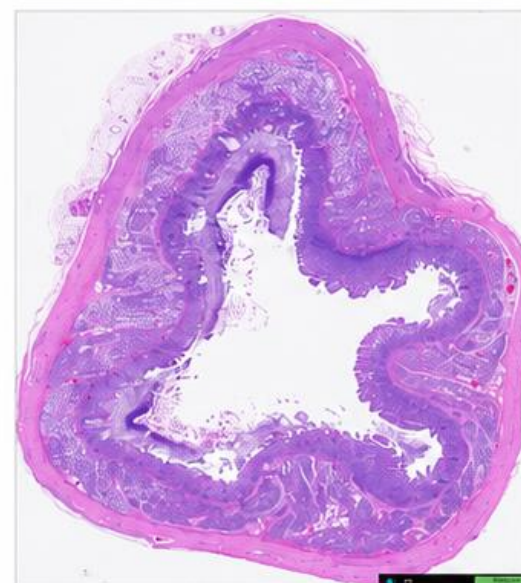




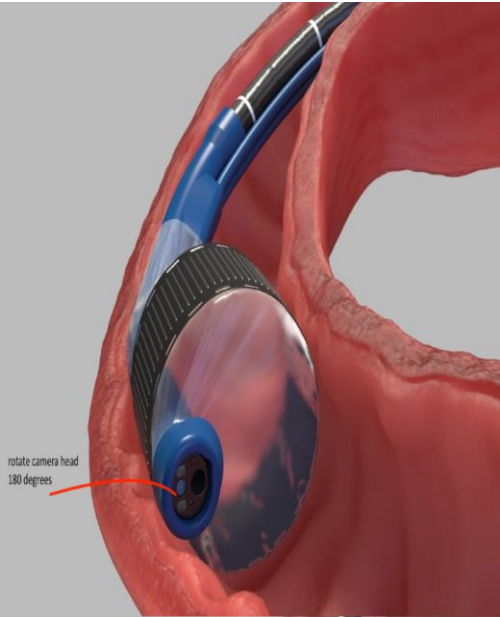
Untreated
Control



Treated

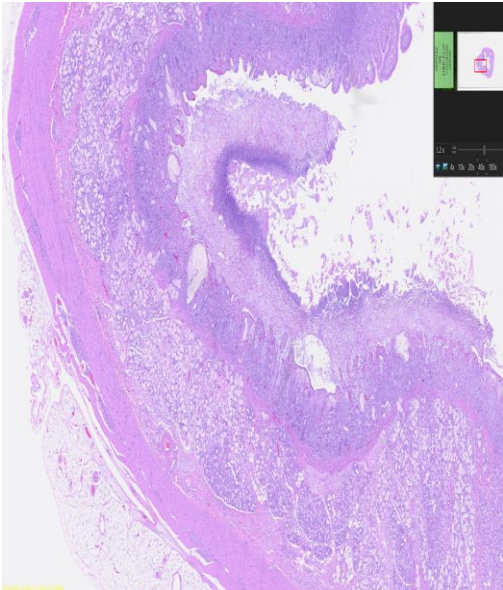
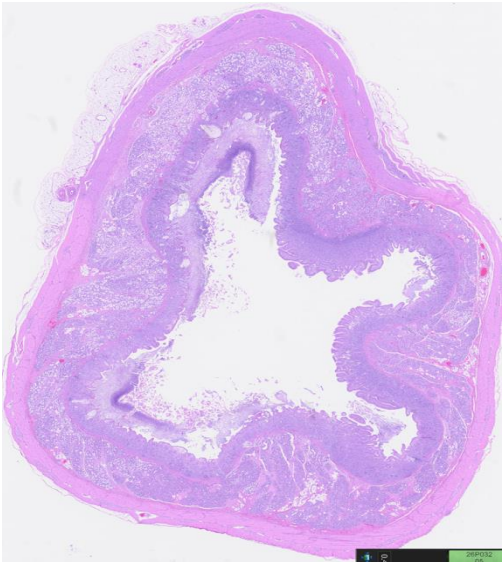


Gen 4 Catheter Histology

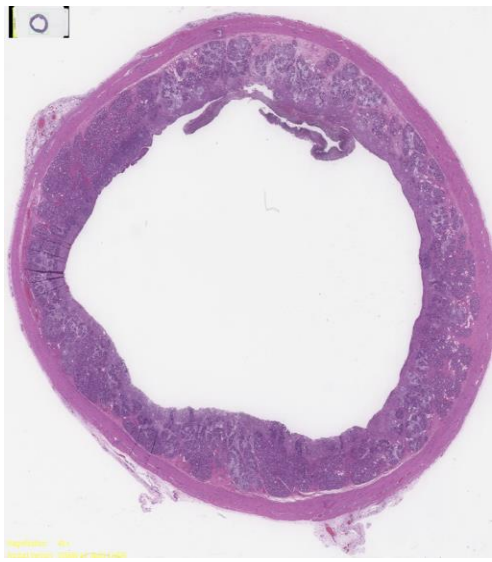


Regeneration
Sequence of
Mucosa and
Submucosa

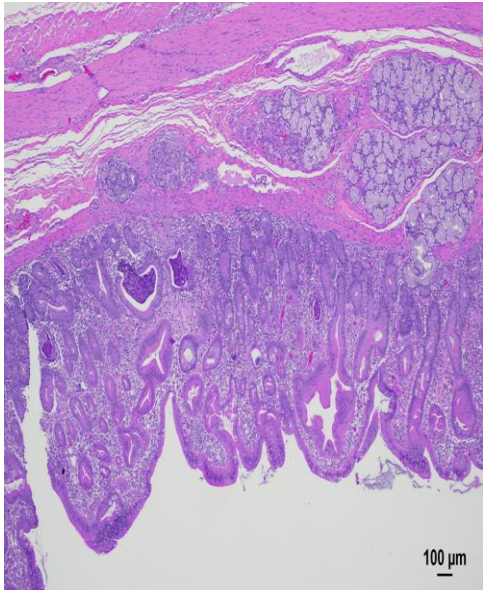
24hr



3 Days



5 Days



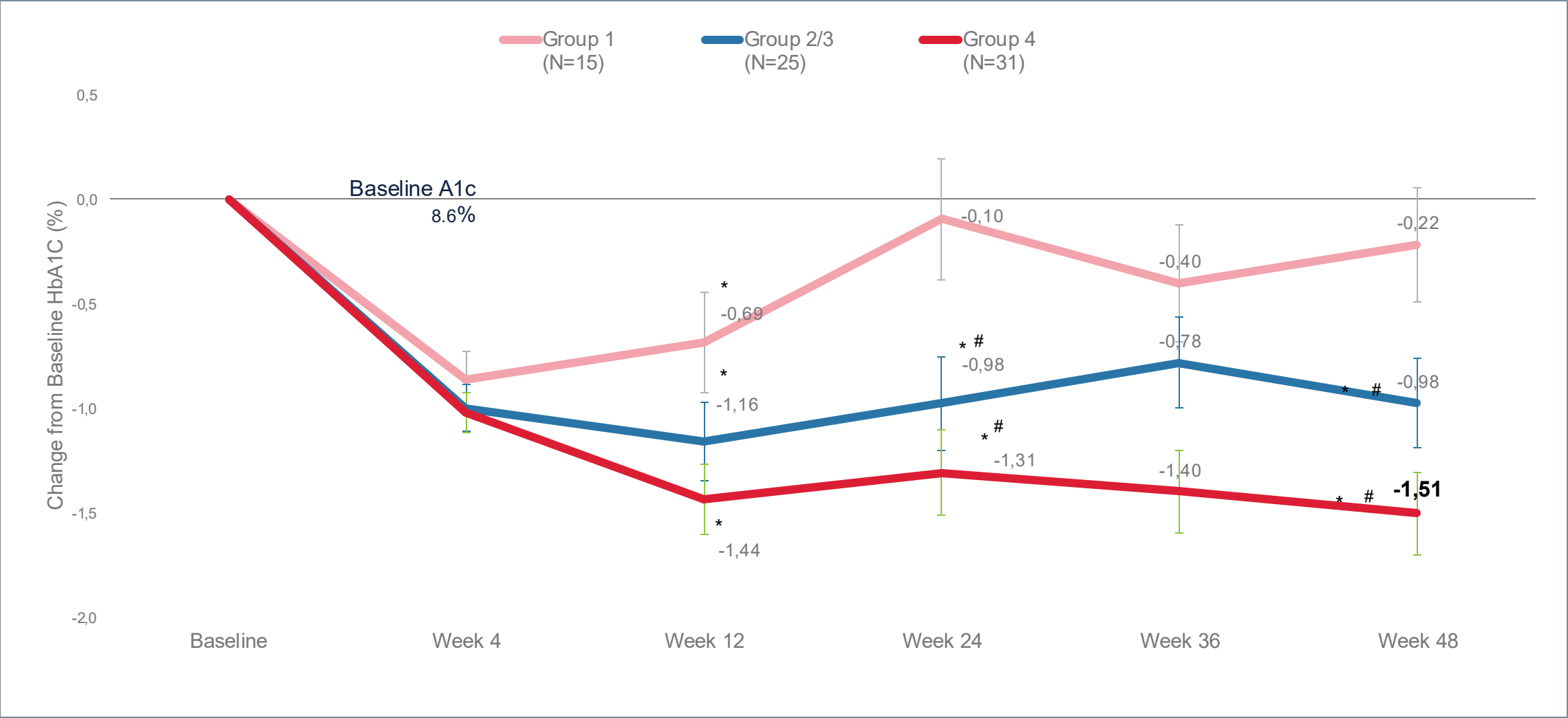
REGENT-1 Combined

Baseline Glycemic Parameters

Parameter	Group 1 Generation 1 600 Volts Single Treatment (N=15)	Group 2 & 3 Generation 1 600 or 750 Volts Double Treatment (N=25)	Group 4 Generation 2 750 Volts Double Treatment (N=31)	All Groups Combined (N=71)
HbA1c (%)				
Mean	8.7	8.5	8.6	8.6
Standard Deviation	0.87	0.87	0.84	0.84
Median	8.6	8.3	8.4	8.4
Minimum, Maximum	8, 11	8, 11	8, 10	8, 11
95% Confidence Interval	(8.2, 9.2)	(8.2, 8.9)	(8.3, 8.9)	(8.4, 8.8)
Fasting Plasma Glucose (mg/dL)				
Mean	169.1	178.4	179.7	176.9
Standard Deviation	24.29	40.87	41.88	38.09
Median	165.8	173.0	167.0	167.6
Minimum, Maximum	130, 209	123, 265	96, 261	96, 265
95% Confidence Interval	(155.6, 182.5)	(161.5, 195.2)	(163.8, 195.6)	(167.8, 186.1)

REGENT-1 Combined

Change from Baseline in HbA1C (%)



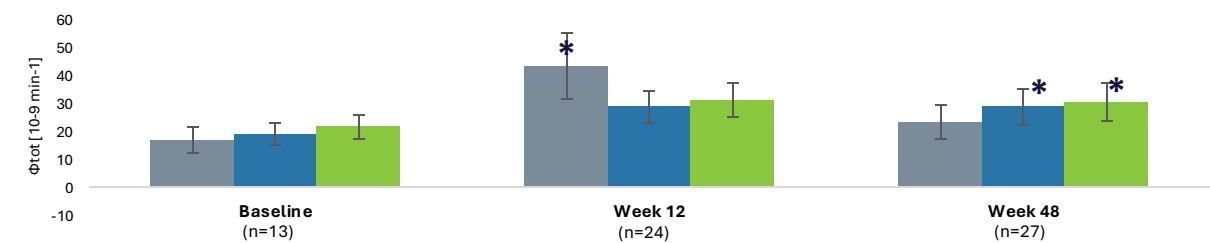
* $p \leq 0.05$ compared to baseline

$p \leq 0.05$ between groups (as compared to G1; no statistically significant differences between G2/3 vs. G4)

Disease modifying results

Based on Disposition index during the REGENT-1: Combined Prospective Cohort study follow-up N =71

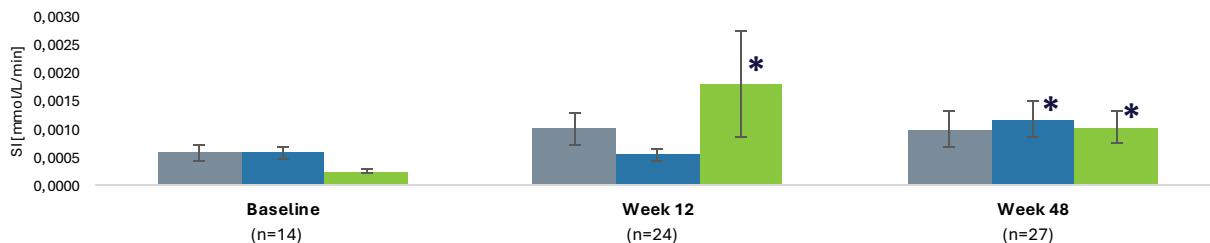
- β cell responsivity shows +42% with Generation 2 (REGENT-1: Combined Cohort)



	Baseline	Week 12	Week 48
Gen 1 600v Single	116.45	40.24 *	22.91
Gen 1 600v or 750v Double	18.84	28.59	28.68 *
Gen 2 750v Double	21.45	31.18	30.39 *

+42%

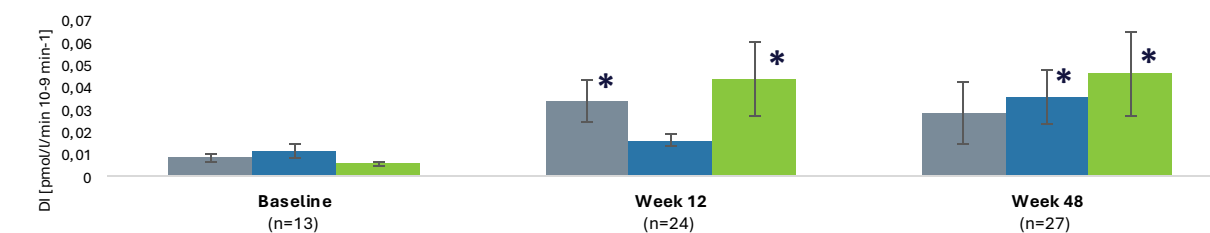
Insulin sensitivity (SI) results +340% with Generation 2 (REGENT-1: Combined Cohort)



Gen 1 600v Single	5.71E-04	9.86E-04	9.82E-04
Gen 1 600v or 750v Double	5.66E-04	5.27E-04	1.15E-03 *
Gen 2 750v Double	2.30E-04	1.79E-03 *	1.01E-03 *

+340%

Disposition Index shows +741% with Generation 2 (REGENT-1: Combined Cohort)



Gen 1 600v Single	8.1E-03	3.4E-02 *	2.8E-02
Gen 1 600v or 750v Double	1.1E-02	1.6E-02	3.5E-02 *
Gen 2 750v Double	5.4E-03	4.3E-02 *	4.6E-02 *

+741%

* P<0.05 vs. baseline

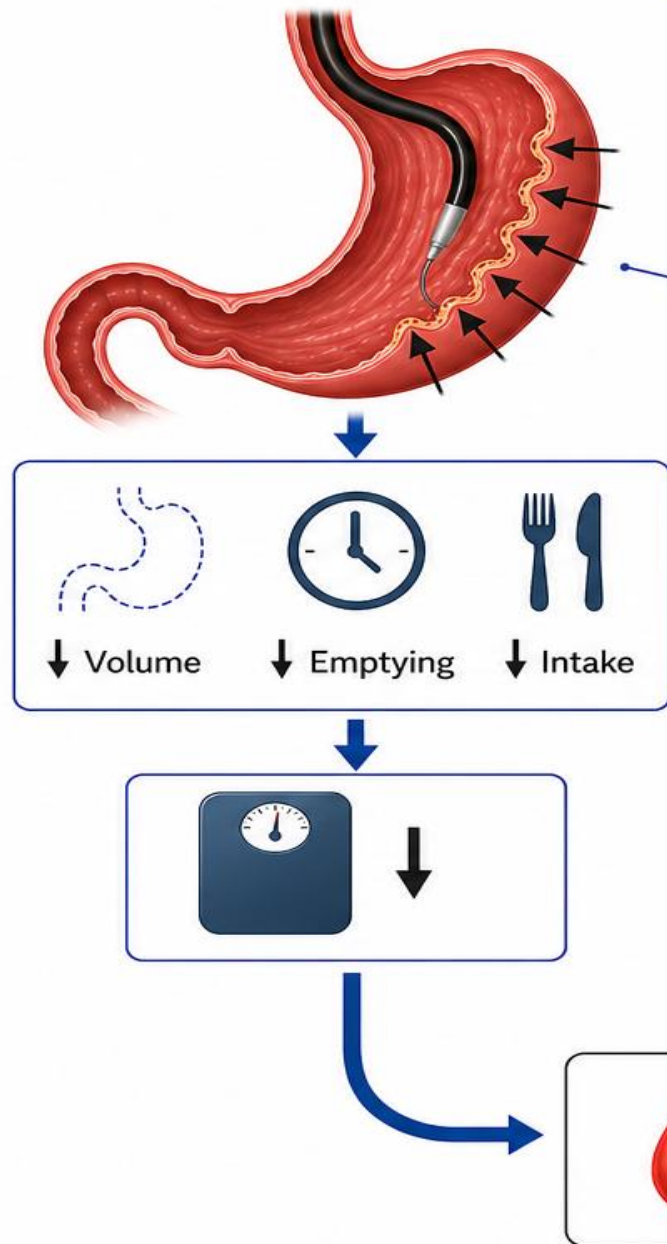


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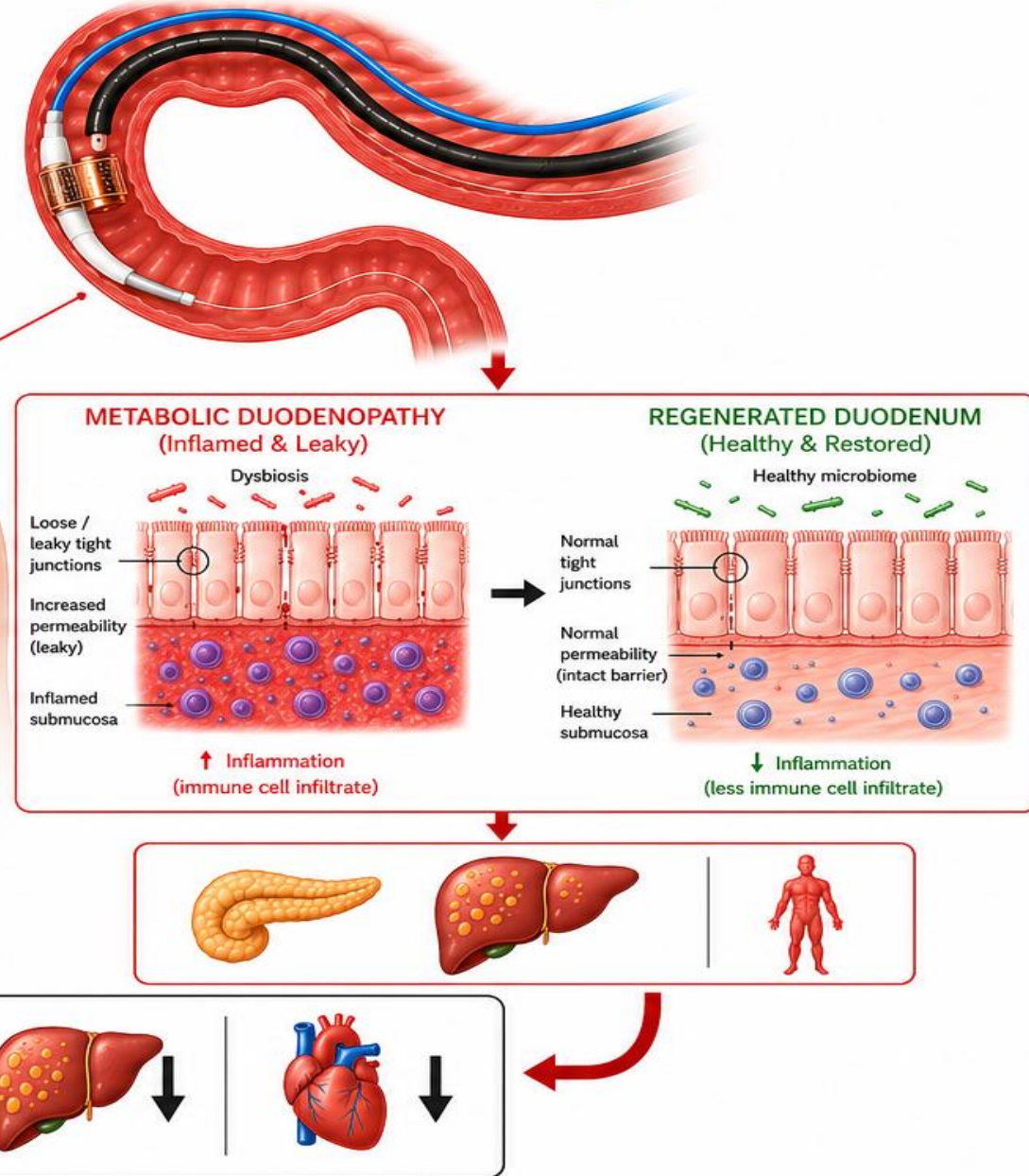
WEIGHT-DEPENDENT PATHWAY

ESG (Stomach Remodeling)



WEIGHT-INDEPENDENT PATHWAY

Duodenal PEF (Duodenal Regeneration)



Questions

