Dr Ragini Agrawal MS,FICOG, FICMCH

- Fellow Clinical Gyne Endoscopy UK
- Functional ,Regenerative and Aesthetic Gynecologist
- Female Sexual Health Specialist
- **Director , AA Dermascience "Complete Clinic for Women Health“ Gurgaon**

Founder -NIGF 2022
President NIGF 2025

Lifetime aceivement Awards
ISAR (Haryana),InSARG

- **Founder Indian Society of Aesthetic and Regenerative Gynecology (InSARG)**
- **President InSARG 2022-2025**
- **President Indian Academy of Cosmetic dermatology& Gynecology (IACDG)**
- **General Secretary IMS 2025**
- **Vice President FOGSI 2020**
- **Founder President Association Of Obs & Gynecologists, Haryana (HARObGyn)**
- **Founder Chapter Convener AMWI Gurgaon**
- **WHO-GOI FOGSI Adolescent health trainer 2006**

- Best Committee Chairperson IMS 2022
- IMS President Appreciation Award 2022 & 2023
- C.L.Javeri ICOG Symposium Award 2024
- IMA NATIONAL PRESIDENT 2021 APPRECIATION AWARD
- IMA STATE PRESIDENT Appreciation Award2021
- National President IMA Appreciation Award 2022
- ORATION AWARDS & key Notes :GOGS, GGF ,InSARG,
- HAGE, HARObGyn, FOGSI,IMS
- APJ Abdul Kalam Award For Academic Excellence

Keen interest in
Community Medicine
Public Health educations
Women QOL
Medicolegal
Organised many national,international conferences, webinars and public forums
First national conference of IMLEA
4TH FOGSI National Medicolegal Conference

- Founder secretary IMS Gurgaon Chapter
- Founder Gurgaon Ob-Gyn Society
- Founder Chairperson IAGE Haryana Chapter
- Founder President ISOPARB Gurugram Chapter 2017
- National joint secretary IMS 2023
- National Convener Indian Menopause society(IMS) Projects 70+
- Patron Gurugram Menopause Society
- IMA Haryana Chairperson for Academics & Public Health Education 2021-2022
- Chairperson Public & Social Awareness IMA 2022-2023
- National Chairperson Public Awareness Committee ISCCP 2021
- Chairperson FOGSI, Food & Drug Committee (2009-2012)
- President Gurgaon Ob-Gyn Society (2010-2012)
- Nation Trainer adolescent health (FOGSI)
- Executive Founder member Gyne Endocrine society of India
- Past Executive member NARCHI Delhi
- Founder Executive Member Indian Society of Colposcopy & Cytopathology
- Past Peer reviewer JOGI
- Member IASR,ISOPARB, IMA, IAGE, IFS, IMLEA, AOGD, SELSI
- Member IASMPMM

President AaKRITI

Publications
Contributed chapters and articles in many books and Journals and Social awareness Magazines like Poise

Editor
IMS Clinical Updates 1.MHT 2.OSTEOPOROSIS
Vaginal Surgery Tips and Tricks
Poise magazine (North)in 2023
Author-Menopause- An Eternal Truth –Book for GPs and General Public
Manual of Aesthetic and regenerative gynecology
Authored Many short E books on different aspects of Menopause, Latest is “How to setup a menopause clinic”

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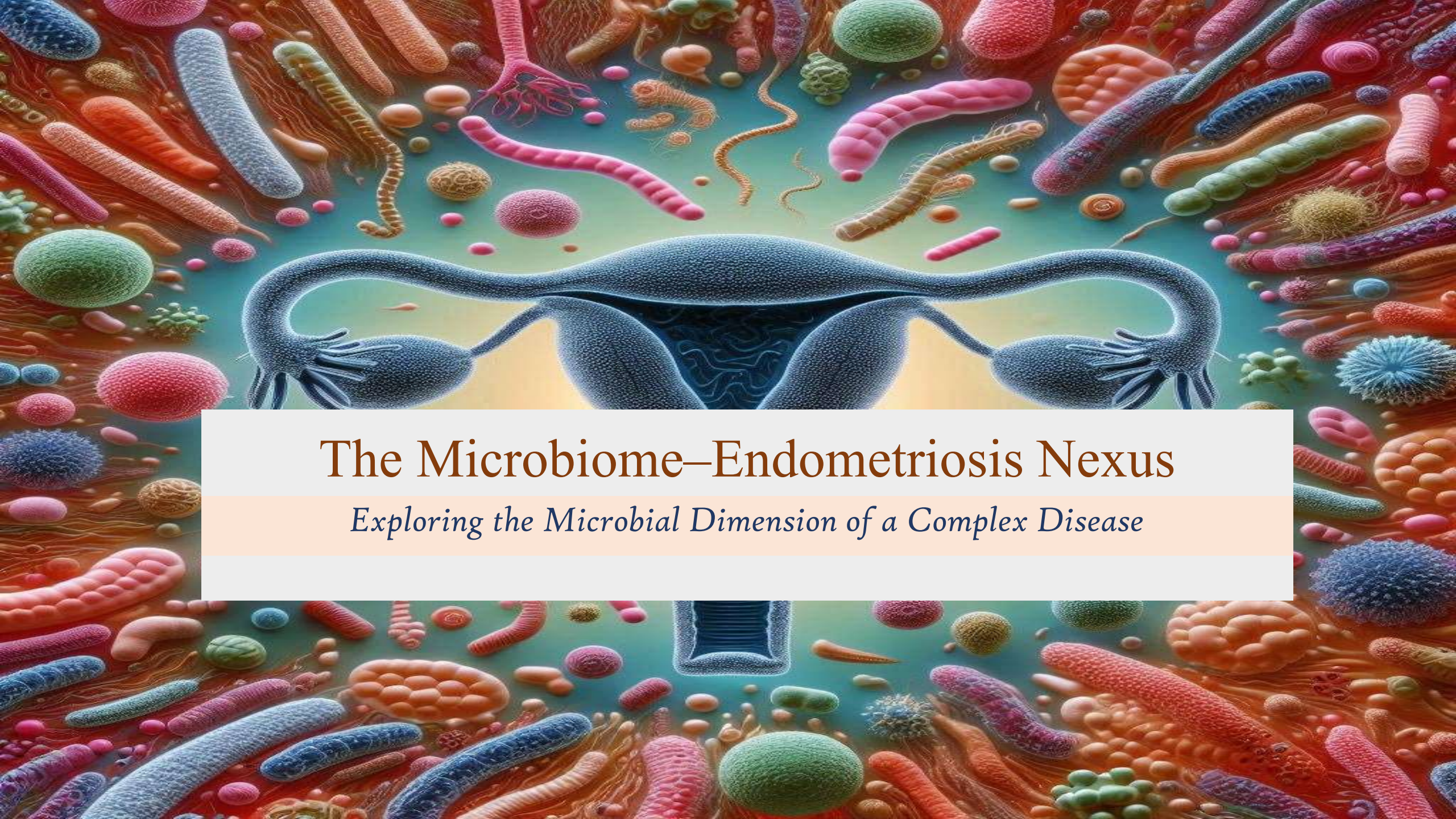


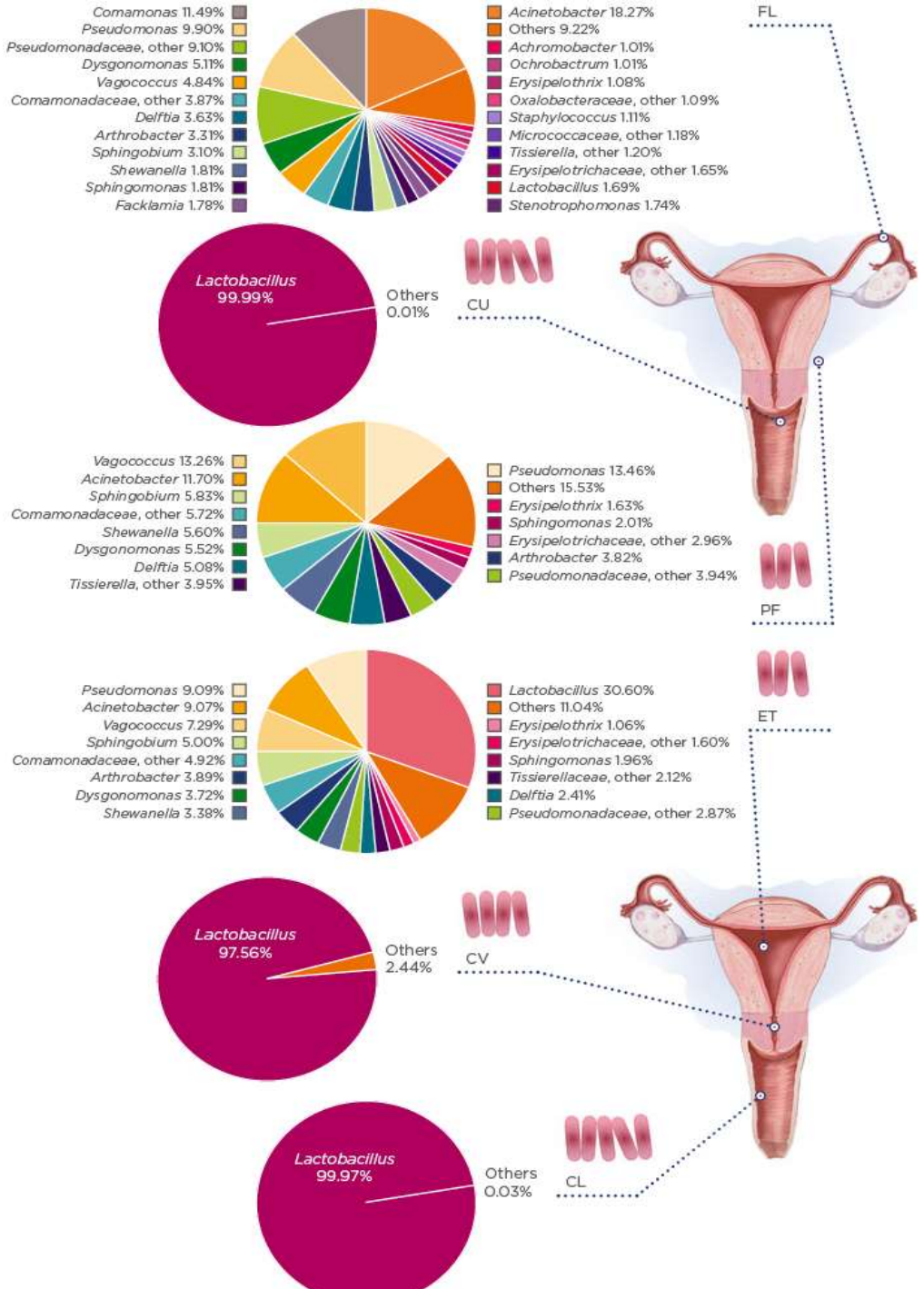
The Microbiome–Endometriosis Nexus

Exploring the Microbial Dimension of a Complex Disease

All science is subject to revision — but some shifts are revolutionary

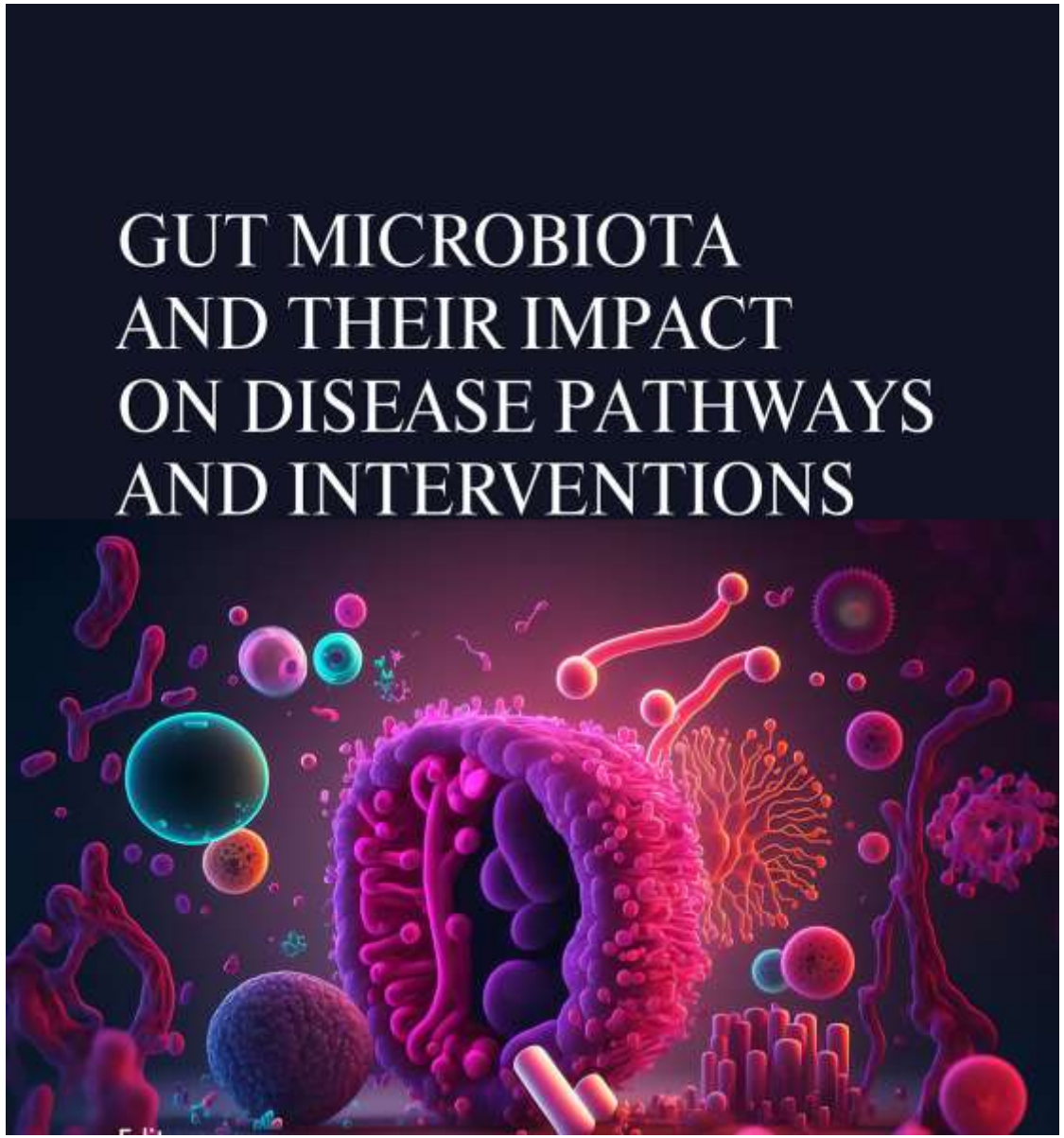
Introduction

- “Despite decades of research, we still lack definitive causes or universally effective treatments for endometriosis.
- The role of the microbiome is gaining attention as a possibly modifiable factor influencing immune activation and estrogen metabolism — two key components of this disease.”
- Microbial shifts might influence endometriosis development, symptom severity, and even therapeutic response.”



From Invisible Bugs to Clinical Burden

- Endometriosis affects ~10% of reproductive-age women.
- Pathophysiology is multifactorial — hormonal, immunologic, genetic.
- Growing interest in the **microbiome as a modifiable factor.**
- Is the microbiome a missing piece in the endometriosis puzzle



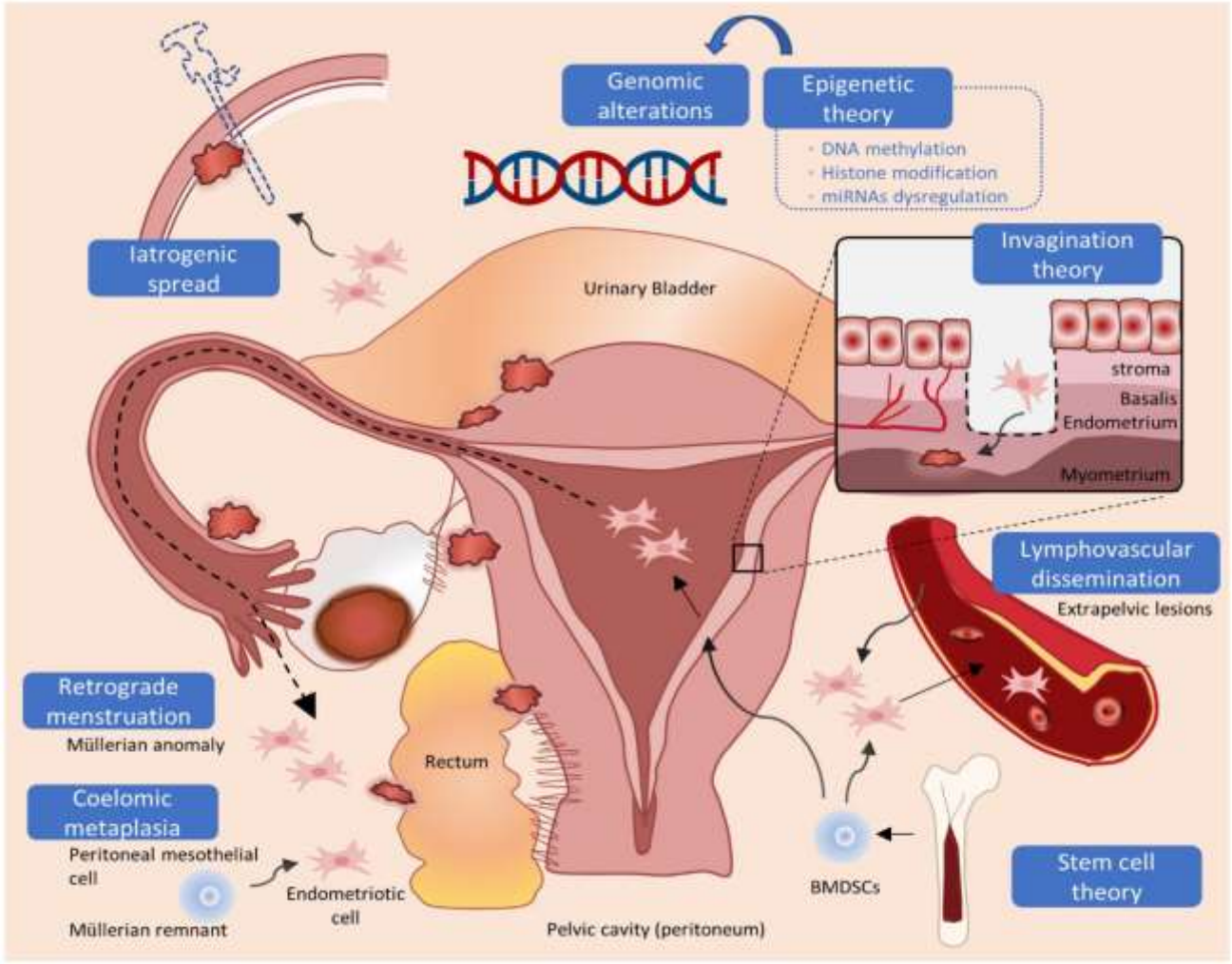
From Gut to Pelvis: A Systemic Connection

The Reproductive–Immune–Microbial Axis

- The gut and vaginal microbiota influence inflammation and immune tolerance by modulating **systemic inflammation.**

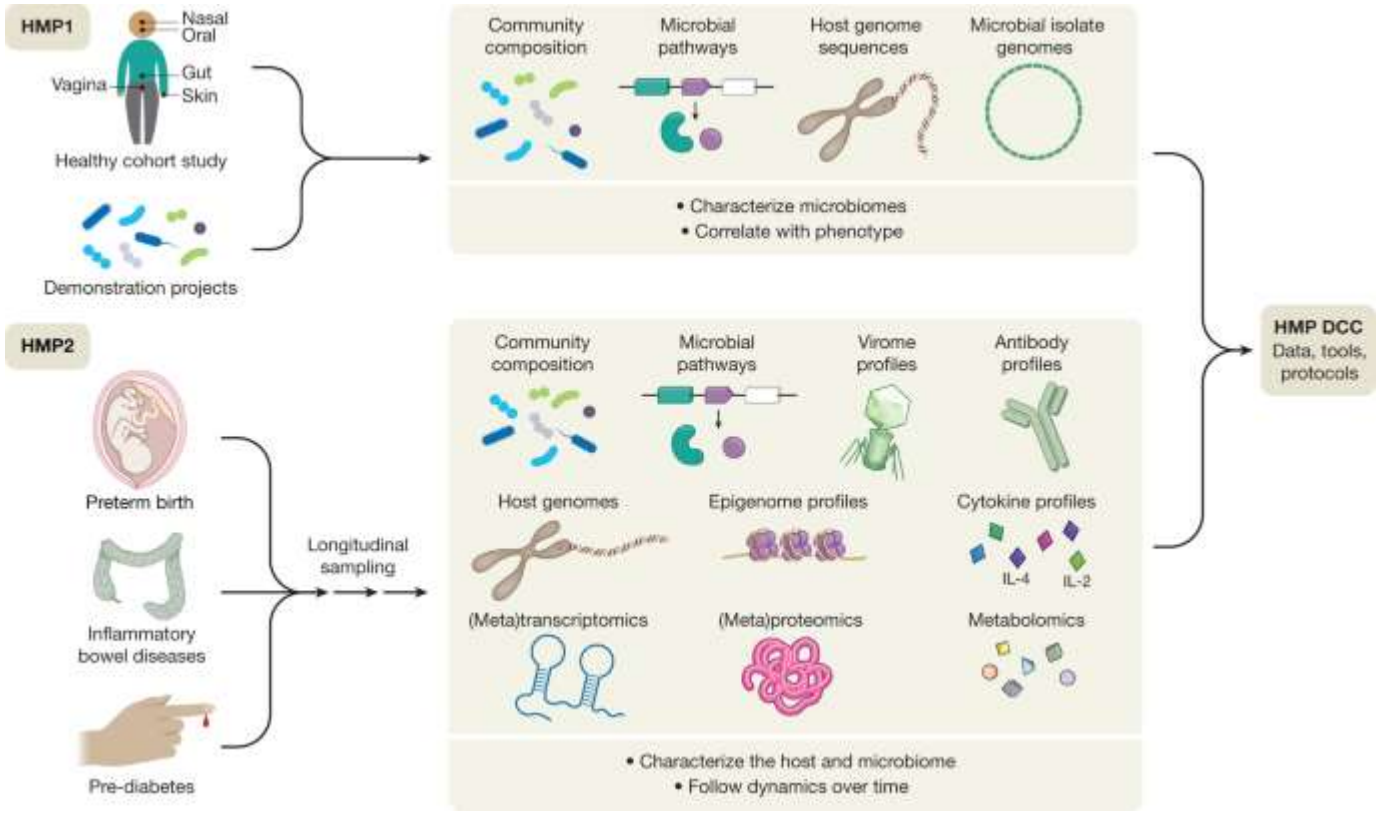
— both are central to the pathogenesis of endometriosis

- Emerging links between **gut permeability**, **endotoxins (LPS)**, and pelvic immune responses.
- Endometriosis is a **whole-body condition**, not just a pelvic disease.



Microbial Hype or Hormonal Truth?

- Exponential growth in microbiome research: >500 papers/year in gynecology.
- NIH launched a **Microbiome–Women's Health Initiative.**
- Critical to distinguish **correlation from causation.**
- Our goal: Identify actionable patterns without overinterpretation



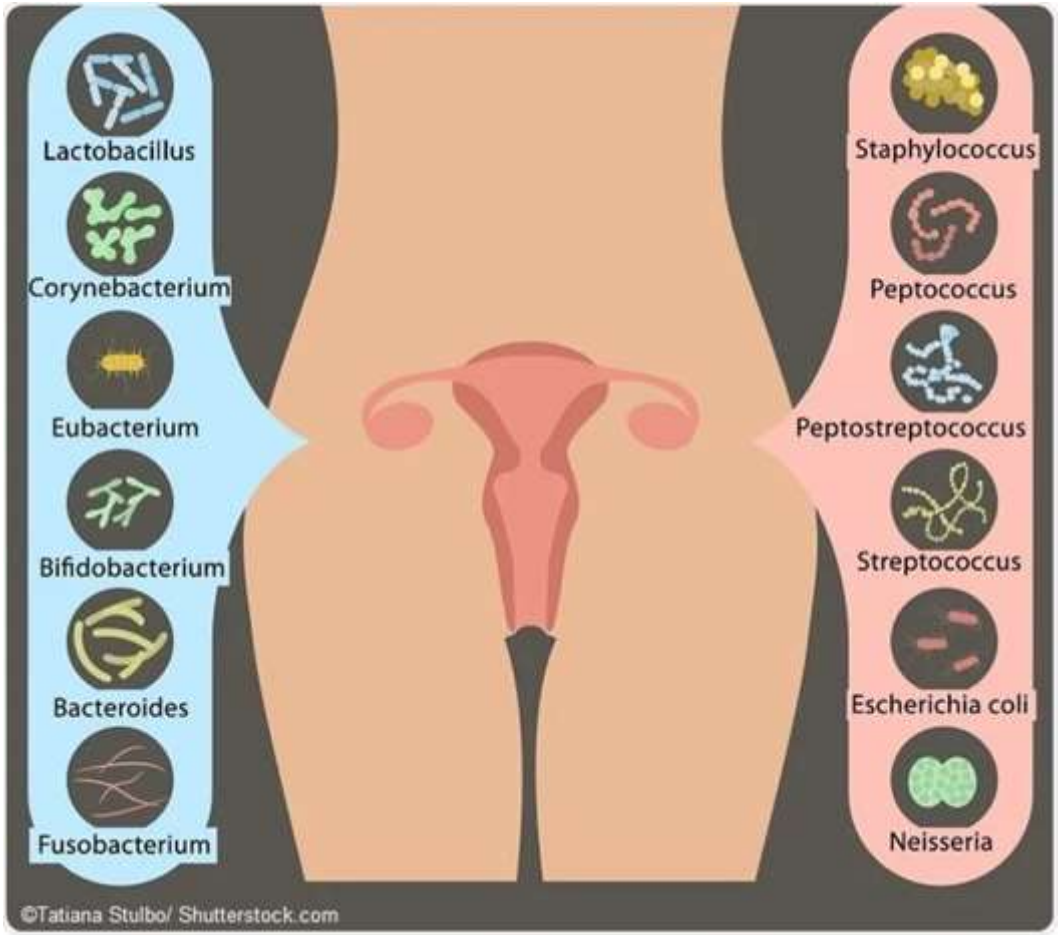
The Microbial Universe-

Not Just Passengers – They Drive Physiology

Human body harbors **over 100 trillion microbes**; most in the gut- A dynamic, symbiotic ecosystem living within us

- Vaginal and endometrial microbiota also have distinct roles. Their influence on metabolism, immune function, and even mood is profound.
- In endometriosis, even minor shifts in microbial diversity could matter.

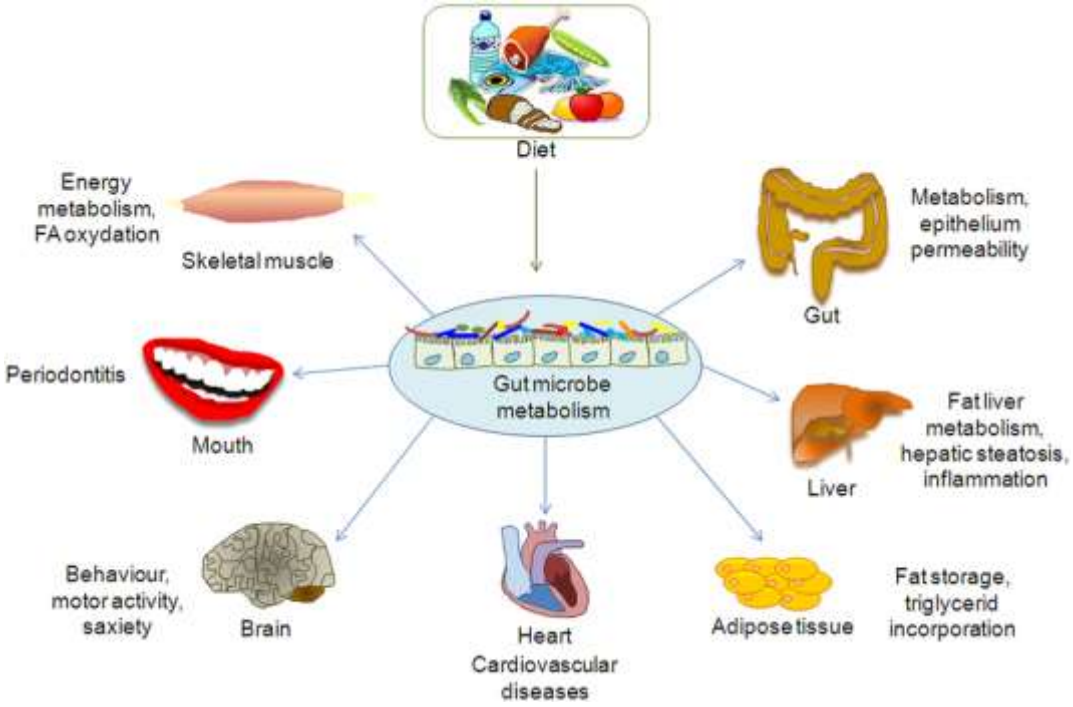
- Dominant phyla: **Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria**
- Microbial balance (eubiosis) vs. imbalance (dysbiosis)



Microbiome as a Metabolic Organ

-Your Second Genome, Working 24/7

- The microbiome as an invisible metabolic organ. It doesn't just digest fiber — it influences inflammation, immune activation, and hormone clearance.
- That's especially relevant in estrogen-driven conditions like endometriosis.
- Microbiota synthesize hormones, vitamins, and neurotransmitters.
- Play a major role in **estrogen metabolism (estrobolome)**
- Regulate **immune response** and epithelial barrier function
- Key outputs: **Short-chain fatty acids (SCFAs), LPS, bile acids**



The Vaginal Microbiota: A Guardian or a Gatecrasher?

When the Defense Turns Dysfunctional

- The vaginal microbiota serves as the gatekeeper to the upper reproductive tract.
- Healthy vagina: dominated by **Lactobacillus** (acidic pH, protection).
- Dysbiosis: reduced Lactobacilli, rise in **Gardnerella, Prevotella, Atopobium**
- Dysbiosis linked to:
  - Increased inflammation
  - Altered immune signaling

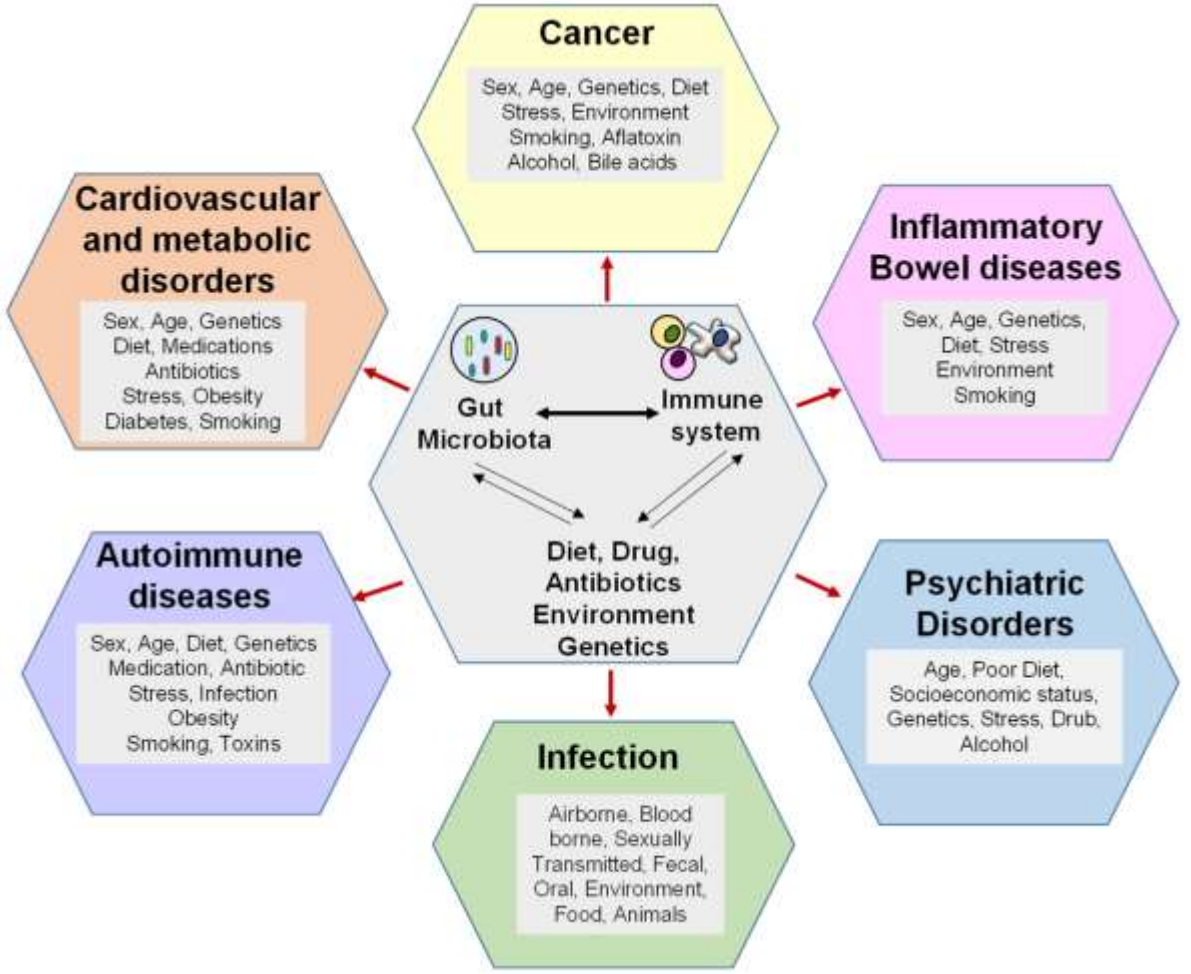
In dysbiotic states, pathogens and inflammatory mediators may ascend and contribute to chronic conditions, including endometriosis. This microbial shift is both a signal and a suspect

Cross-Talk: Gut–Repro–Immune Triangle

This ‘gut–immune–reproductive axis’ is not just a theoretical model.

There is evidence that microbial metabolites and immune responses originating in the gut can influence the uterine and peritoneal environment.

- Gut microbiota impacts **systemic inflammation**, which influences the pelvic immune milieu.
- **Leaky gut** → Endotoxin release (LPS) → Toll-like receptor activation → Chronic inflammation
- Immune dysregulation = a key player in endometriosis
- Vaginal and gut microbes communicate via immune and hormonal signals.



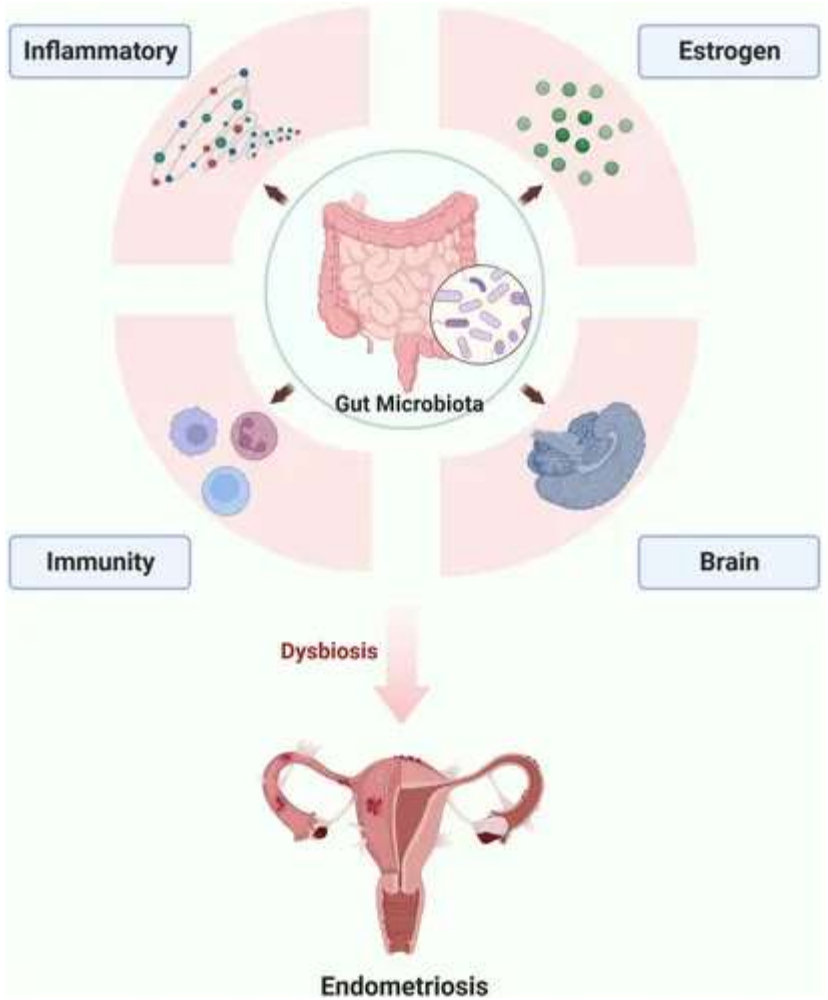
The Dysbiosis Fingerprint in Endometriosis

- Studies show altered microbial diversity in gut, vaginal, and endometrial samples from endometriosis patients.
- Patients with endometriosis often show a consistent microbial shift — less protective Lactobacillus and more pro-inflammatory or opportunistic bacteria.
- This ‘dysbiosis fingerprint’ may reflect both cause and consequence of the disease, especially its inflammatory nature
- **↓ Lactobacillus, ↑ Proteobacteria, Streptococcus, Gardnerella, Escherichia coli**
- Correlation with disease severity and pelvic pain.

Endometriosis Beyond Estrogen:

A Microbial Tale

- Certain bacteria in the gut produce enzymes that can ‘unpack’ estrogen after it’s processed by the liver, leading to its reabsorption.
- In endometriosis, where estrogen drives lesion growth, this microbial influence could be significant.
- The **estrobolome:** gut bacteria that modulate estrogen metabolism via β-glucuronidase activity.
- Dysbiosis → excessive estrogen recirculation → endometrial proliferation.
- Potential link to **estrogen dominance** observed in endometriosis.



The enterohepatic circulation and estrobolome of estrogens.

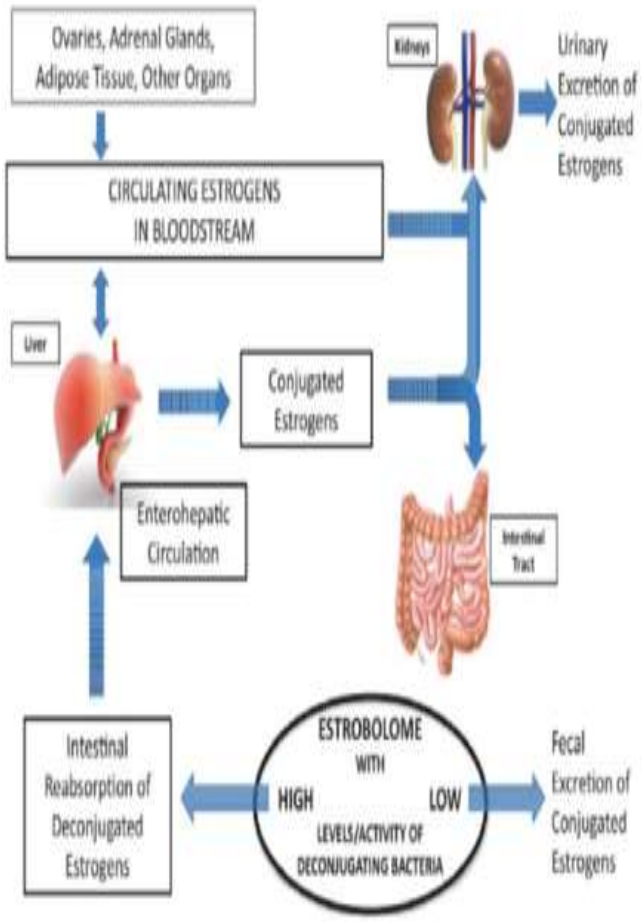
(A) Estrogens are primarily produced in the ovaries, adrenal glands, and adipose tissue and circulate in the bloodstream in free or protein-bound form and first undergo metabolism in the liver, where estrogens and their metabolites are conjugated.

Conjugated estrogens are eliminated from the body by metabolic conversion to water-soluble molecules, which are excreted in urine or in bile into the feces.

The conjugated estrogens excreted in the bile can be **deconjugated** by bacterial species in the gut with **beta-glucuronidase activity (constituents of the 'estrobolome'),** subsequently leading to **estrogen reabsorption** into the circulation.

(B) Several gut microbiota have beta-glucuronidase

A



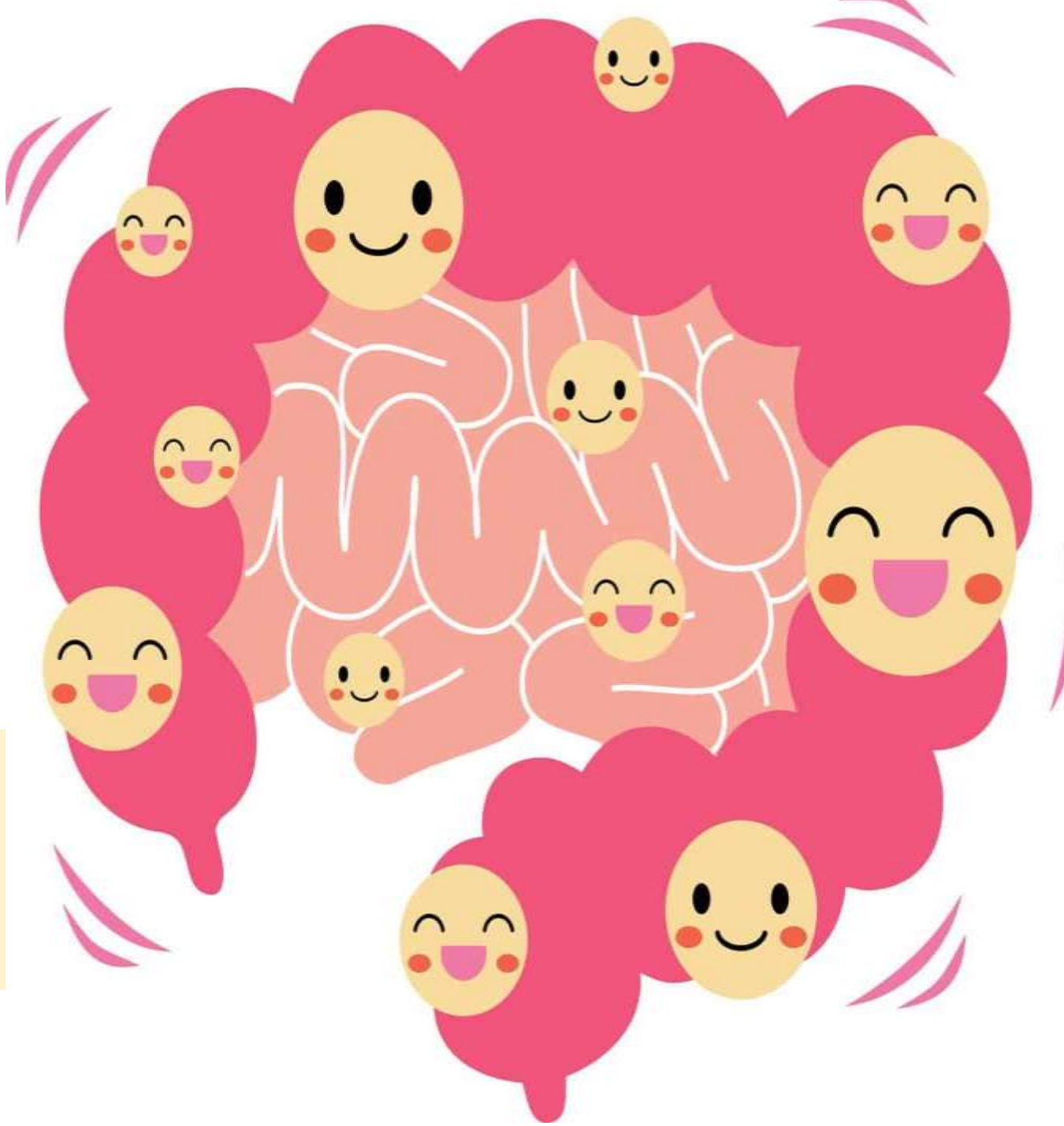
B

Genus	ß-glucuronidase	ß-galactosidase
Collinsella	+	–
Edwardsiella	+	–
Alistipes	+	+
Bacteroides	+	+
Bifidobacterium	+	+
Citrobacter	+	+
Clostridium	+	+
Dermabacter	+	+
Escherichia	+	+
Faecalibacterium	+	+
Lactobacillus	+	+
Marvinbryantia	+	+
Propionibacterium	+	+
Roseburia	+	+
Tannerella	+	+
Actinomyces	–	+
Alistipes	–	+

Enter the Estrobolome

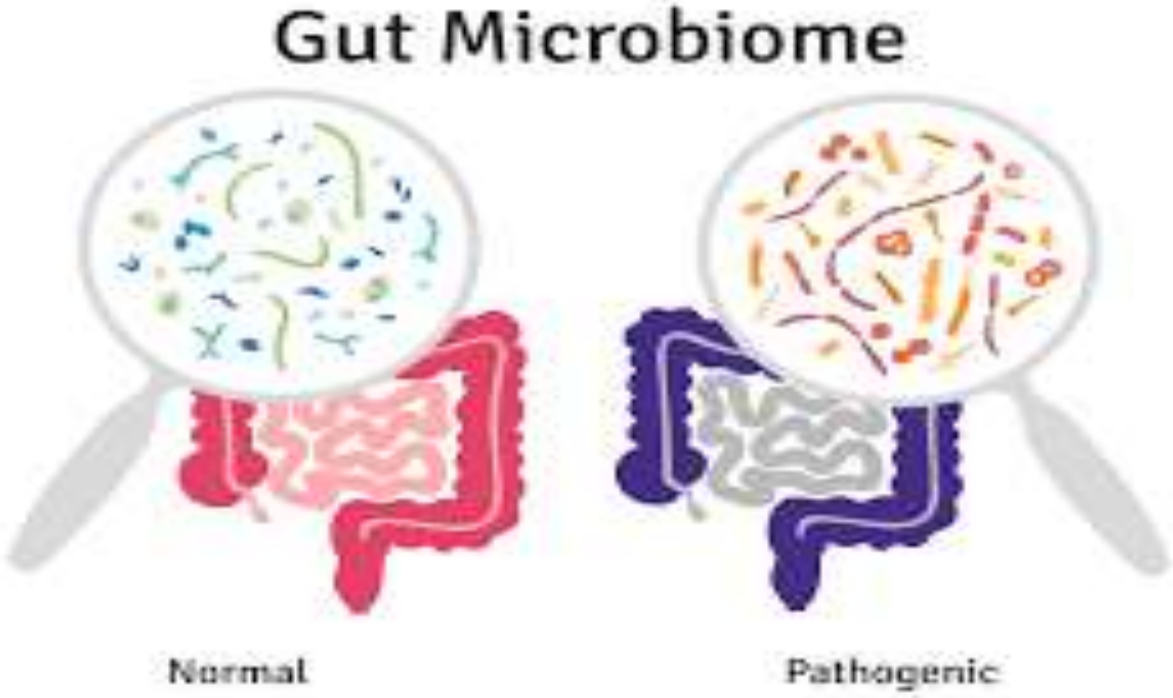
Estrobolome is the term for: "The collection of gut bacterial genes capable of metabolizing estrogens."

A **healthy estrobolome** maintains estrogen balance by **modulating reabsorption vs. excretion**



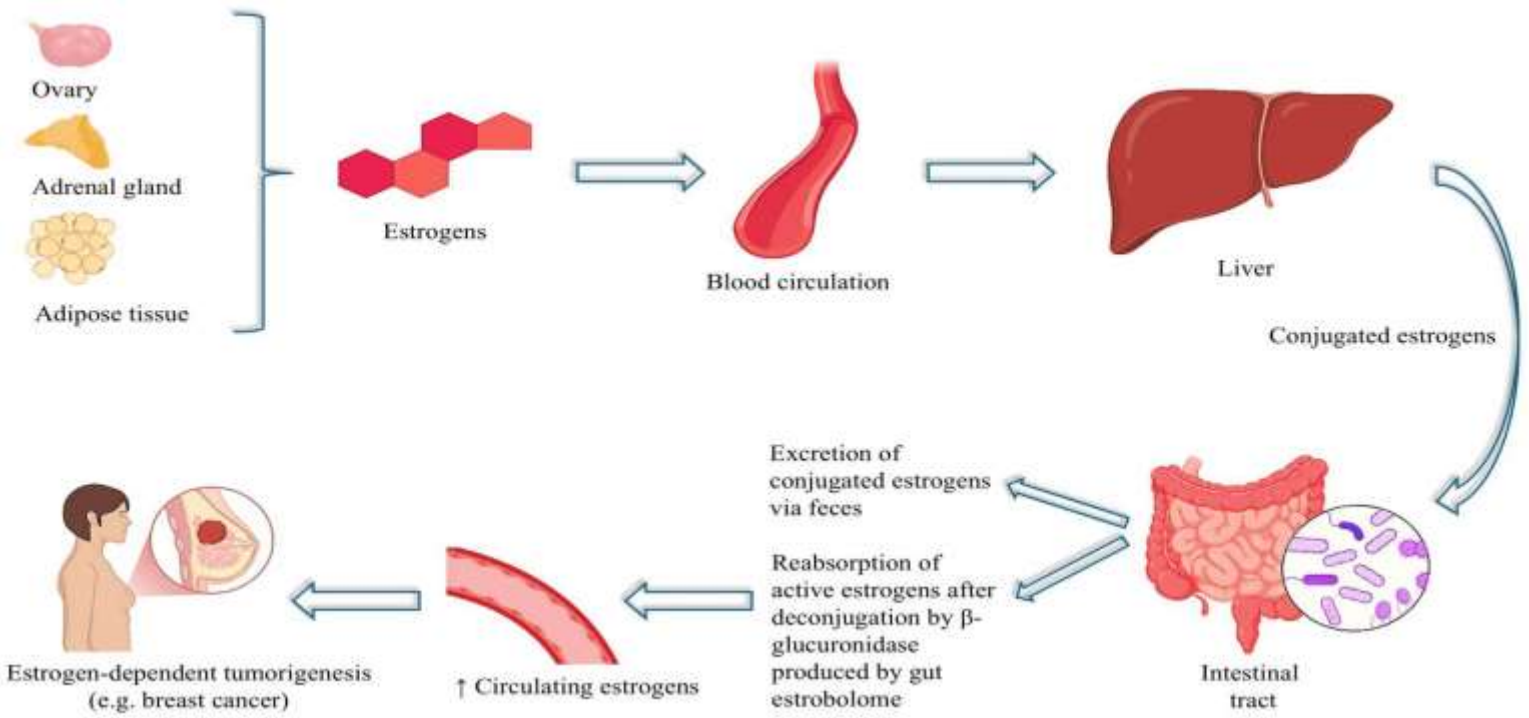
Dysbiosis

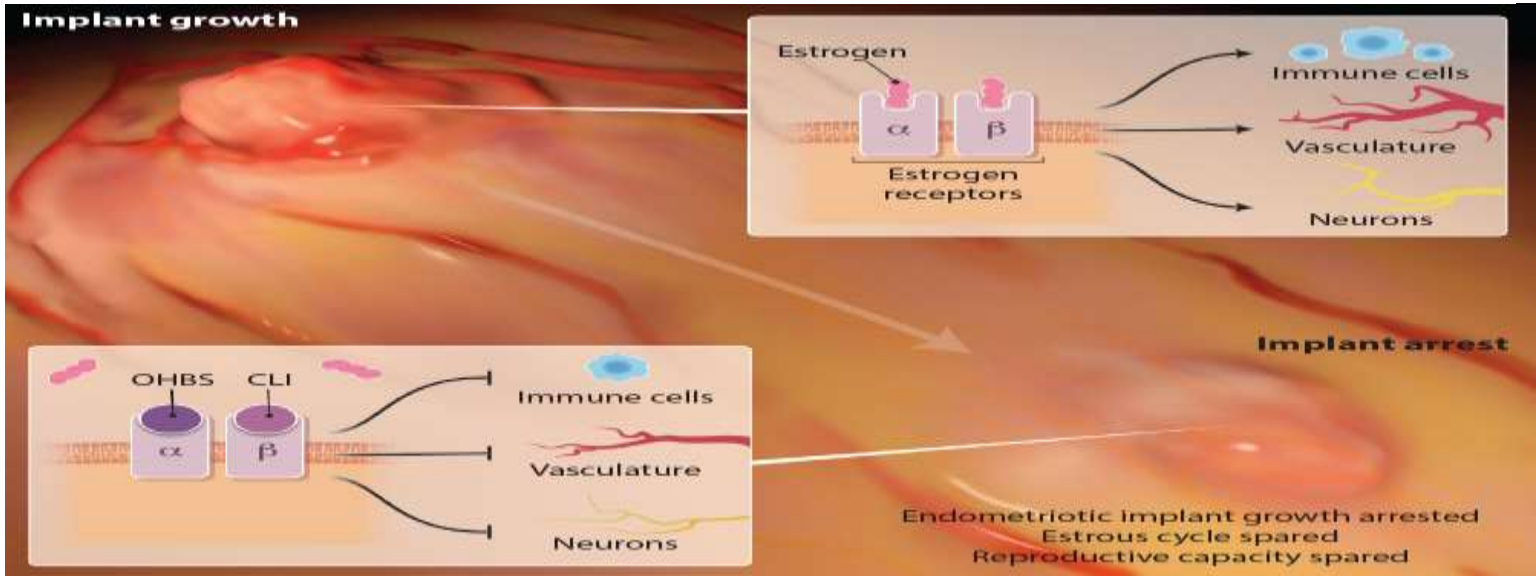
- **Dysbiosis** (imbalance in gut bacteria) can lead to:
  - **Low estrogen states** (if bacteria with β-glucuronidase activity are lacking)
  - Or **estrogen dominance** (if too much deconjugation and reabsorption occurs)



Why it matters:

- After estrogen is metabolized by the liver, it's excreted into the gut in an inactive, conjugated form.
- The **Estrobolome decides its fate:**
  - **Reabsorbed** → contributes to systemic estrogen levels
  - **Excreted** → cleared from the body





Inflammation: Microbial Ignition Switch?

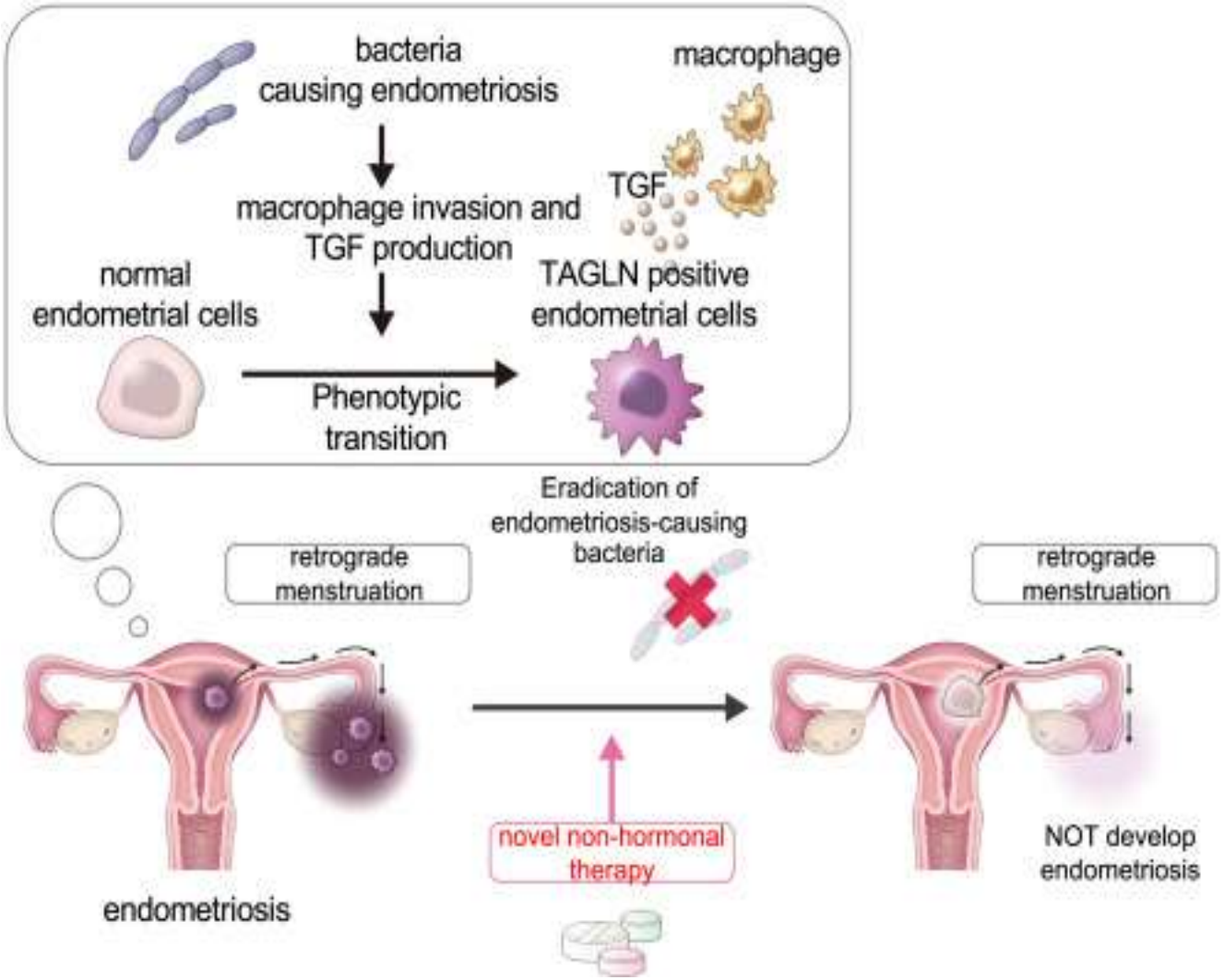
From Dysbiosis to Cytokine Storm

- Dysbiosis → ↑ permeability ("leaky gut") → LPS (endotoxin) enters circulation.
- LPS activates **TLR4**, increasing **IL-6, TNF-α, IL-1β** → chronic inflammation.
- Similar inflammatory signatures are seen in endometriotic tissue.

This supports the theory that microbial metabolites may act as an ignition switch for immune dysregulation in susceptible women."

Bacterial Contamination Theory – Revisited

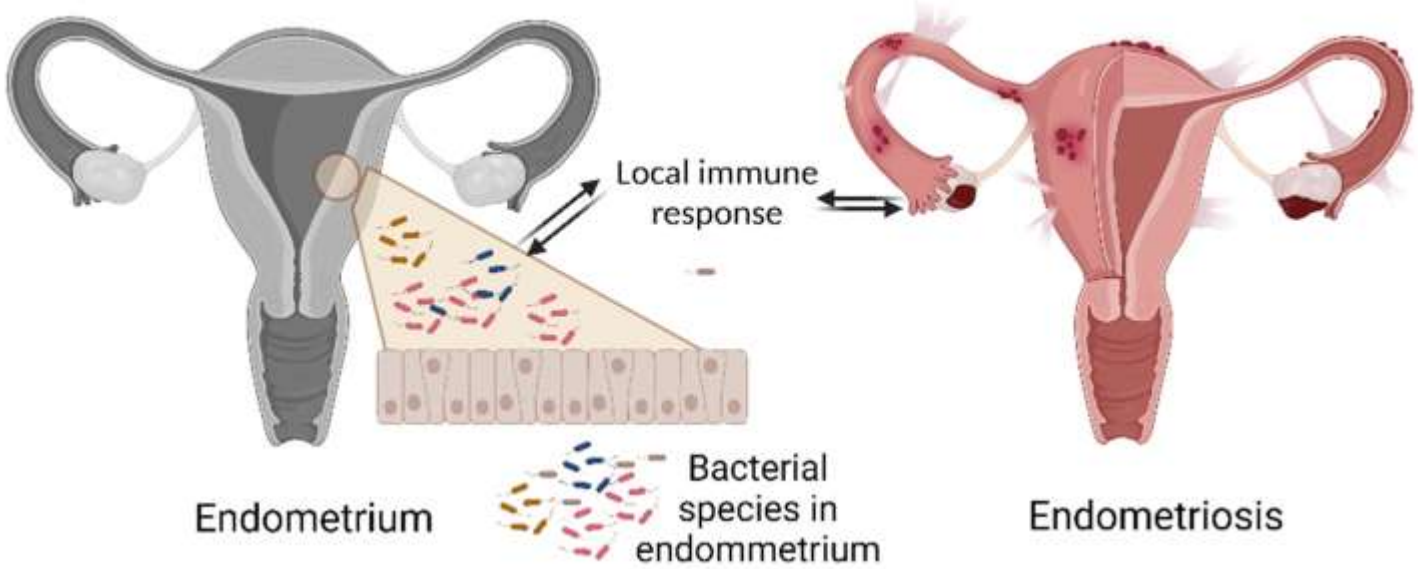
- Classic theory: Retrograde menstruation causes endometriosis.
- The bacterial contamination hypothesis suggests that it's not just endometrial cells moving upward — but also microbes that may inflame the peritoneal cavity. This combination could enhance lesion survival and immune evasion."
- Studies have found **E. coli**, anaerobes on lesions and in peritoneal fluid.
- May enhance local inflammation and adhesion formation.



Microbial Footprints on Lesions

Direct evidence of bacterial colonization on endometriotic lesions.

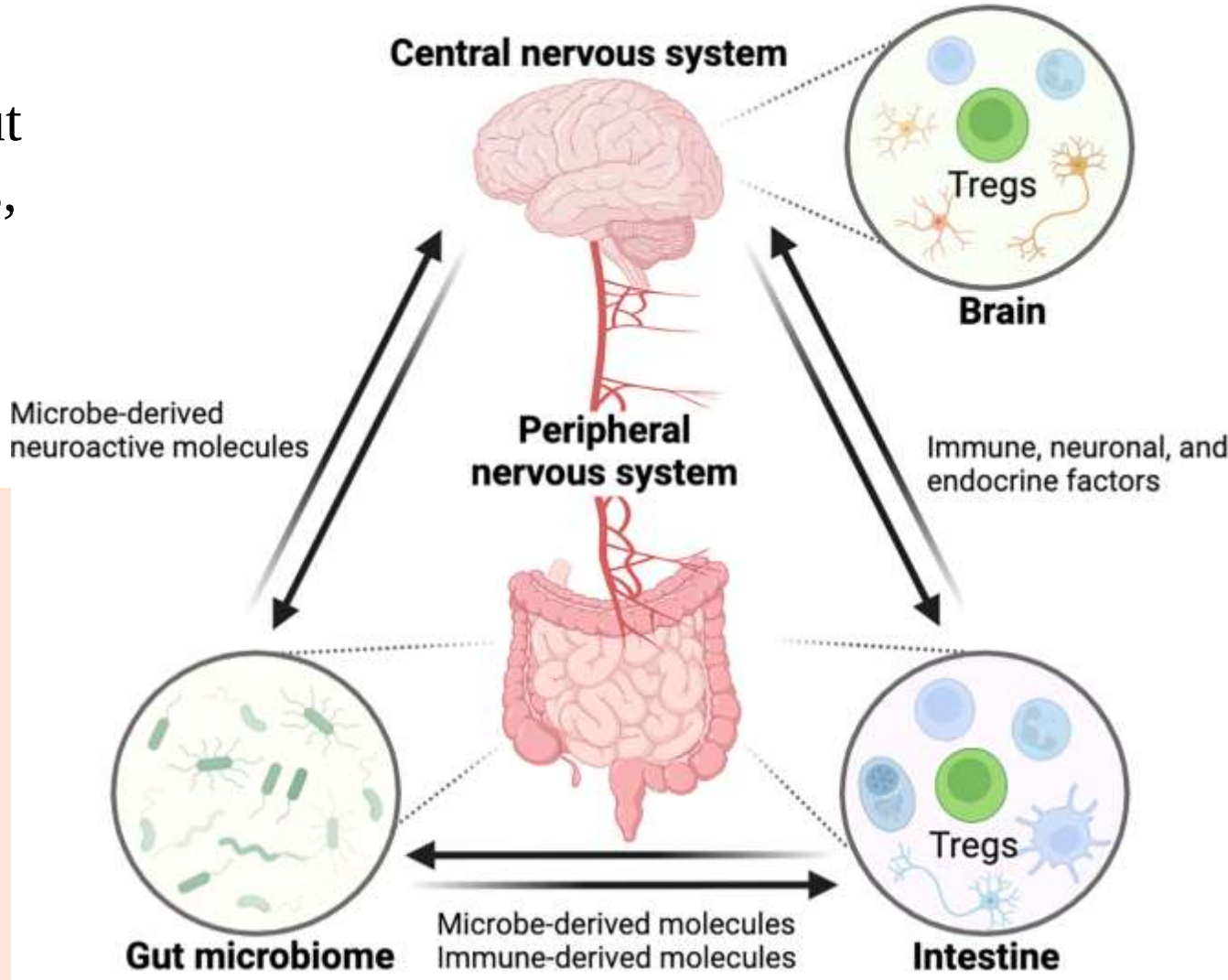
- Bacteria isolated from **ectopic endometrial lesions:**
  - *Streptococcus*, *Fusobacterium*, *Escherichia*, *Propionibacterium*
- Metagenomic analysis reveals unique lesion-specific microbiota.
- These microbial communities might create a localized biofilm, perpetuating inflammation and possibly even affecting therapeutic resistance & have a potential role in sustaining inflammation and angiogenesis



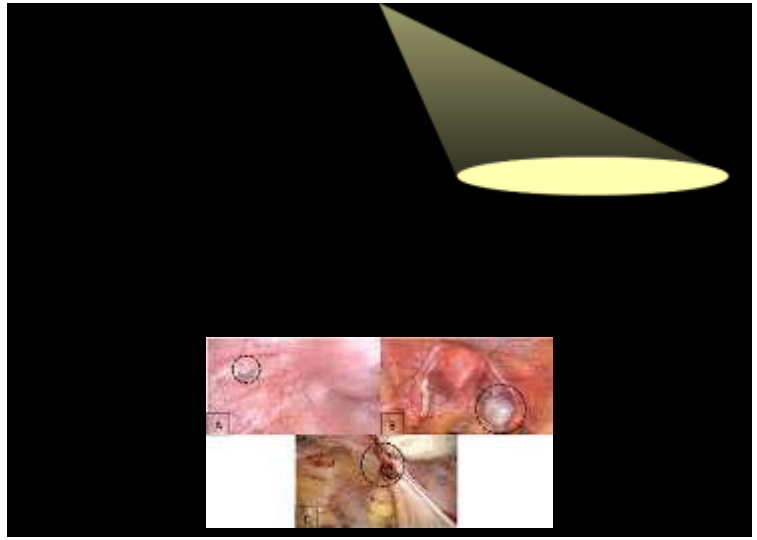
Gut Microbiota & Pain Sensitization

Chronic pain in endometriosis may not be purely anatomical. Microbial changes in the gut can influence central nervous system pathways, lowering pain thresholds and contributing to central sensitization — a hallmark of chronic pelvic pain."

- Gut dysbiosis → ↓ SCFAs → ↑ neuroinflammation
- Altered gut flora impacts **central pain processing** via vagus nerve, cytokines
- Links to **visceral hypersensitivity, central sensitization, fatigue**
- Emerging data connects microbiota to chronic pelvic pain syndromes.



Research Spotlight – The Microbiome in Endometriosis: 2020–2025



The research trajectory is clear — microbial shifts are consistently documented across anatomical sites. Interventional studies are now underway, and the next 5 years will likely shape our clinical approach

- **Wei et al., 2021 (Gut Microbes)**
  - Vaginal dysbiosis in endometriosis: ↓ *Lactobacillus crispatus*, ↑ *Gardnerella vaginalis*
- **Yamamoto et al., 2022 (Reproductive Biology)**
  - Endometrial microbiota in stage IV disease: ↑ *Streptococcus anginosus*
- **Cregger et al., 2023 (J Clin Microbiol)**
  - Gut microbial signatures linked to lesion burden and central sensitization
- **Ongoing Trials:**
  - Probiotic intervention in mild–moderate endometriosis (NCT04795852)
  - Vaginal microbiome restoration post-surgery (NCT05561194)

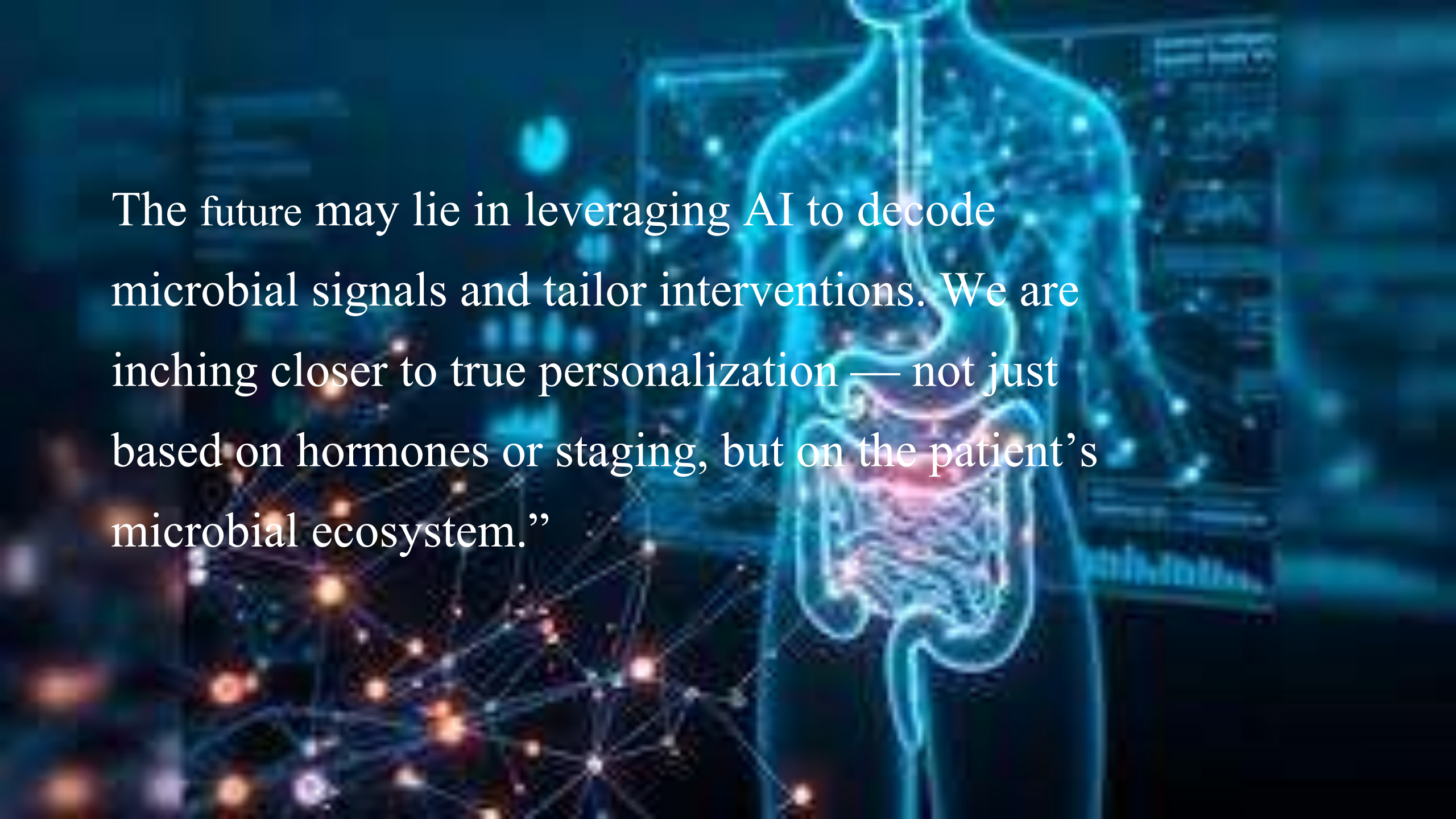
Microbiome–Endometriosis Trials: What's on the Horizon?

- **Promising Trial Designs:**
- **Microbiome-guided therapy arms** in RCTs
- Personalized probiotics based on sequencing
- FMT safety trials in recurrent cases
- Combination of hormonal therapy + microbiota-modulating agents
- Patient-reported outcomes tied to microbial profiles

Controversies in the Microbiome–Endometriosis Axis

Key Issues:

- **Causation vs. correlation:**
  Microbial shifts – primary drivers or consequence of inflammation?
- **Sample variability:**
  Vaginal, gut, peritoneal flora – influenced by collection method, cycle phase, and prior antibiotic use.
- **Small sample sizes & inconsistent controls:**
  Studies lack standardization; many findings not replicated.
- **Overinterpretation risk:**
  Is the microbiome a modifiable cofactor or a therapeutic target?

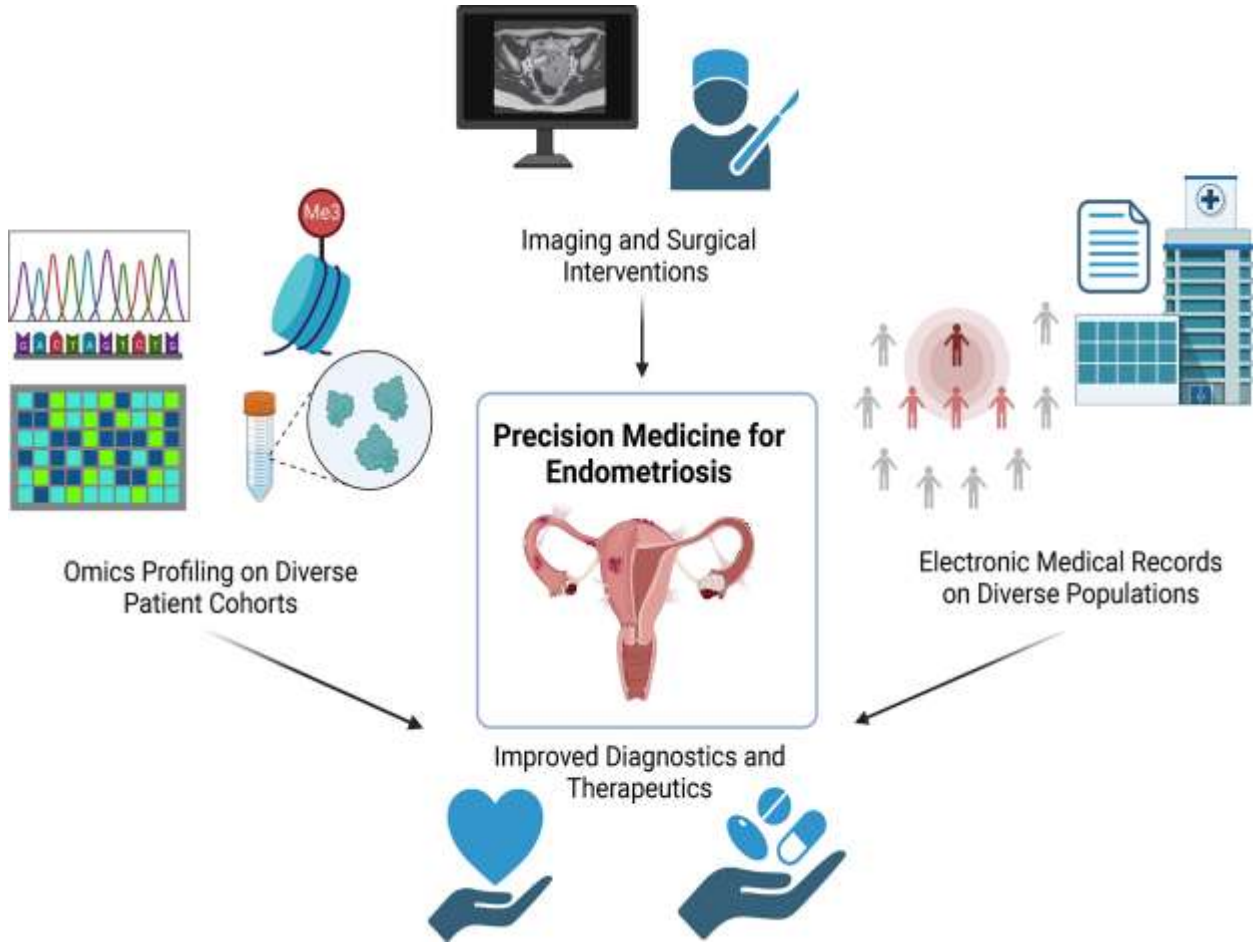


The future may lie in leveraging AI to decode microbial signals and tailor interventions. We are inching closer to true personalization — not just based on hormones or staging, but on the patient's microbial ecosystem."

Emerging Tools: Precision & Personalization

Future Frontiers:

- **Machine learning models** to predict endometriosis based on microbial profiles
- **Microbiome-based risk calculators** for early detection
- **Host–microbiome interaction mapping** (multi-omics: metagenomics + metabolomics + transcriptomics)
- **Individualized regimens**: Probiotic blends, dietary plans, microbial-derived therapies tailored per patient



Vision 2030: Ecosystem-Based Endometriosis Management

Conceptual Outlook:

- Endometriosis as a **multisystem disorder** – hormonal, immunologic, microbiotic
- Therapeutic shift from **lesion-focused** to **terrain-focused**
- Routine microbiome screening pre- and post-treatment
- Integration of gynecology, gastroenterology, immunology, and microbiome medicine
- Research imperative: Larger, multicenter longitudinal studies

Clinical Takeaways

- **Endometriosis is a systemic disorder** — not just pelvic and hormonal, but immunologic and microbial.
- **Microbial dysbiosis** is consistently documented across vaginal, gut, and peritoneal sites in affected women.
- **Microbiome modulation** (diet, probiotics, precision therapy) shows promise, especially in refractory cases.
- **Diagnostic advances** (metagenomics, microbial biomarkers) may reduce reliance on laparoscopy.
- **Future is personalized** — integrating microbial, hormonal, and immunologic profiles for tailored therapy.
- **Clinical humility is key** — while exciting, microbiome-based approaches must be evidence-driven, not hype-led.

Take Home Message

- The microbiome offers us a transformative lens — not just to view endometriosis differently, but to treat it holistically. As we move from symptom suppression to ecosystem restoration, the path ahead is both challenging and hopeful.”

"We must stop treating endometriosis as just a lesion — and start healing the whole system

Thank You