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Presented by Heather Hydzik, ND
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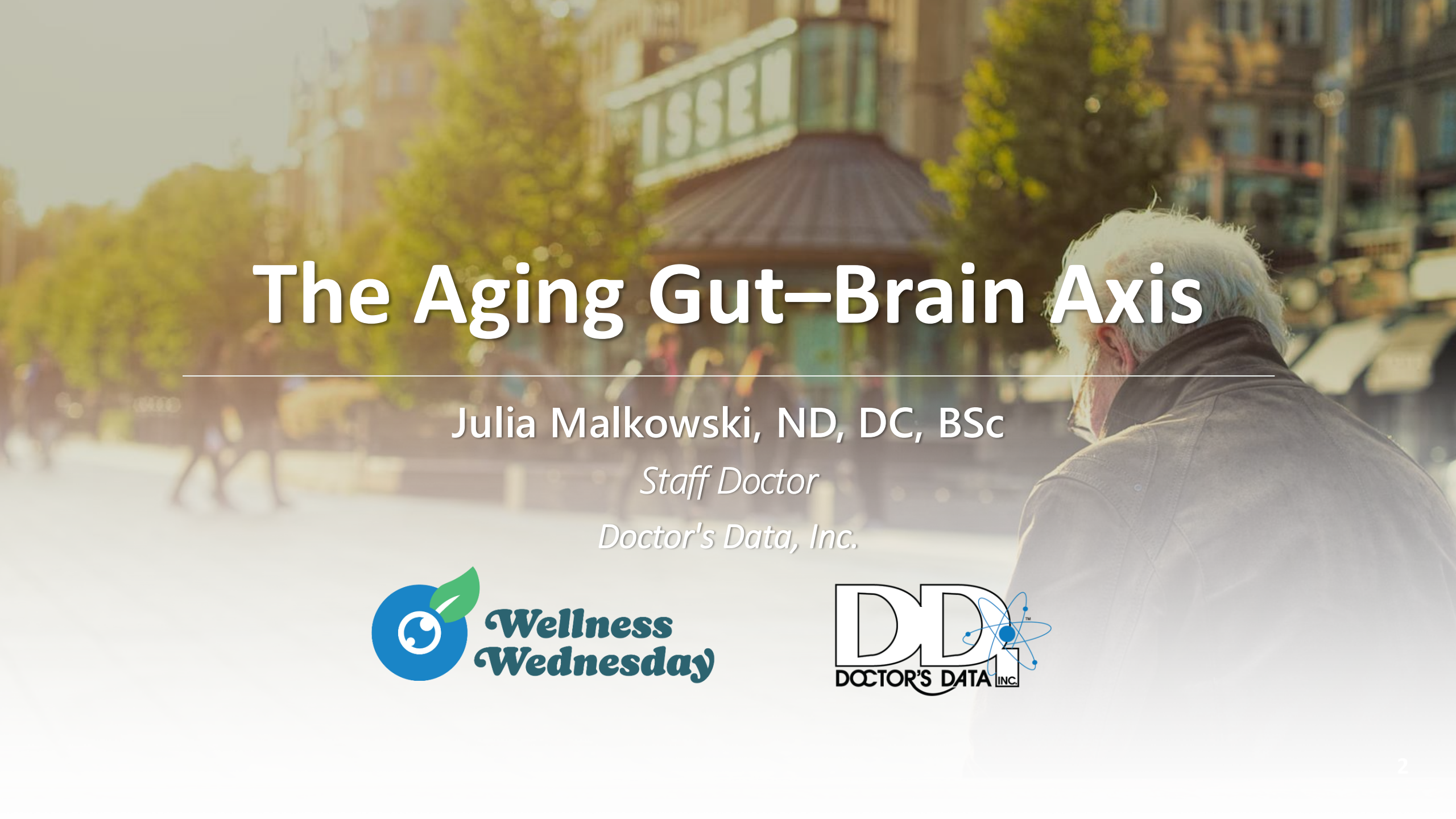
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Wellness Wednesday

WILL BEGIN SHORTLY



The Aging Gut–Brain Axis

Julia Malkowski, ND, DC, BSc

Staff Doctor

Doctor's Data, Inc.

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Learning Objectives

At the conclusion of this session, participants will be able to:

1. **Describe** age-associated changes in gut microbiome composition and diversity, including loss of butyrate producers, and how they relate to biological age.
2. **Explain** how intestinal barrier dysfunction, zonulin, and LPS translocation contribute to inflammaging, neuroinflammation, and cognitive decline.
3. **Interpret** stool microbiome diversity and dysbiosis profiles, zonulin, and hs-CRP in a patient with cognitive or functional decline, and recognize the limits of these tests.
4. **Apply** evidence-based dietary, nutraceutical, and medication-review strategies to restore microbial diversity and barrier integrity, including sequencing, dosing limits, and reassessment.



Patient A · Age 71

- No prescription medications
- MoCA: 29/30
- "I feel fifty."
- CBC, CMP, TSH, B12: normal



Patient B · Age 71

- PPI + statin, 11-year duration
- MoCA: 24/30
- "I can’t find words anymore."
- CBC, CMP, TSH, B12: normal

Same Chronological Age, yet different Biology

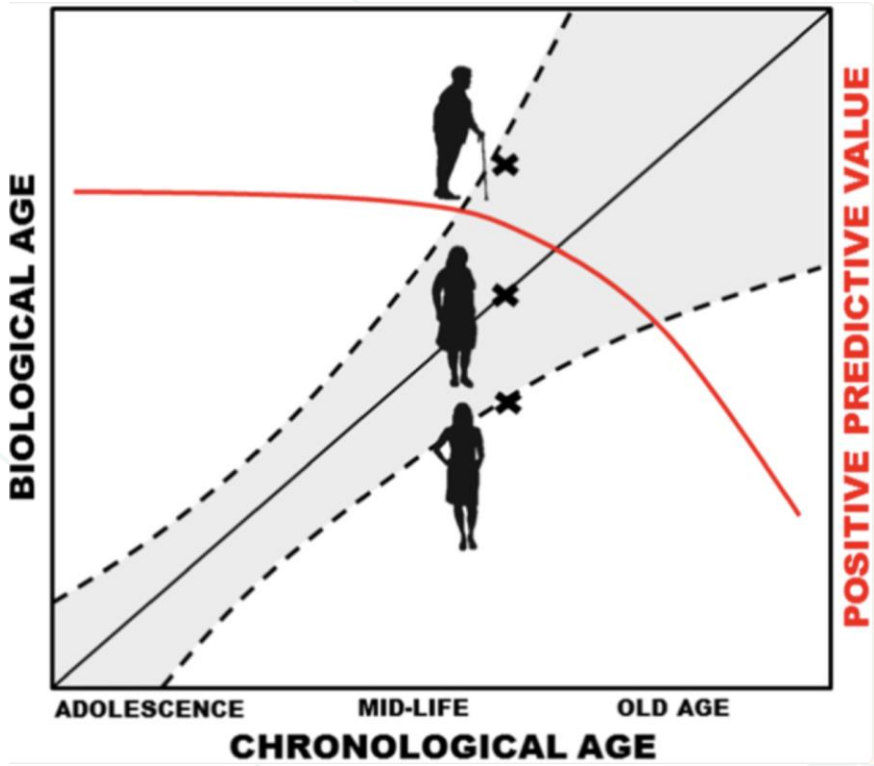
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What Standard Labs Miss

- Biological age, distinct from chronological age, is now independently measurable.
- Independent cohorts across countries and platforms converge on the same aging signature.
- **The clocks are not equal**
  - The epigenetic clock predicts mortality best; telomere length is the most-studied and the weakest predictor.
- **Age acceleration is the signal**
  - Each extra year of epigenetic Δage carries ~6% higher 3-year cancer incidence and ~17% higher 5-year cancer mortality.
- The gut microbiome is among the most reproducible tissues for estimating biological age
  - Gut microbiome diversity may be a better clinical biomarker of biological age than telomere length.



References: Jylhävä J, Pedersen NL, Hägg S. Biological age predictors. EBioMedicine. 2017;21:29–36 (PMCID: PMC5514388). · Wilmanski T, et al. Nat Metab. 2021;3(2):274–286. · Kunihiro BP, et al. Sci Rep. 2026;16:21903.

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Where We’re Headed

1. **Part 1**
   The Aging Gut Microbiome
2. **Part 2**
   Intestinal Permeability & Inflammaging
3. **Part 3**
   The Gut–Brain–Inflammaging Loop
4. **Part 4**
   Clinical Assessment & Case Study
5. **Part 5**
   Evidence-Based Interventions

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PART 1

The Aging Gut Microbiome



Your Microbiome Has an Age

- Machine-learning "microbiome aging clocks" predict chronological age from taxonomic profiles with strong accuracy.
- The clinically relevant number is the gap: microbiome age exceeding chronological age predicts frailty and mortality risk.
- Youth-associated taxa (e.g., *Akkermansia, Faecalibacterium*) are enriched in centenarians, suggesting resilience-linked microbial patterns
- Large longitudinal cohorts link increasing microbiome "uniqueness" in healthy aging to improved survival outcomes.
- Directly analogous to epigenetic clocks
    - Longevity data derived from a non-invasive, low-cost stool samples

References: Wilmanski T, et al. Nat Metab. 2021;3(2):274–286. · Kunihiro BP, et al. Sci Rep. 2026;16:21903.
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Gut Microbiome Diversity as a Biomarker of Biological Age

- Gut microbiome is akin to any ecological system in that diversity is associated with health
- Increased diversity associated with longevity, immune response, extroverted behavior, improved insulin sensitivity, response to sepsis, sleep behavior, and much more
- Microbiota diversity increases from infancy through adolescence, stabilizes in adulthood, and slightly declines after age 70.
- Loss of diversity is linked to frailty, cognitive decline, and metabolic dysfunction
  - Sharpest declines occur with frailty and advanced age, not chronological age alone.
  - Diversity loss correlates tightly with rising inflammatory markers and incident frailty.
- Functions as an early, sensitive signal, often shifting *before* conventional disease markers change.
- Gut-microbiome diversity is maintained in Blue Zone centenarians

References: Tseng CH, Wu CY. J Biomed Sci. 2025;32:93. · Wilmanski T, et al. Nat Metab. 2021;3(2):274–286. · Gruzdys, V., Malkowski, J., & Mortensen, J. (2025). Gut Microbiota Differences with Age and among North American, European, and Australian Regions. Journal of Restorative Medicine, 15(1), 34–53.

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Losing Our Butyrate Producers

BUTYRATE PRODUCERS DECLINE WITH AGE

- *Faecalibacterium prausnitzii,* Roseburia, *Eubacterium rectale*
- Bifidobacterium and *Akkermansia muciniphila* fall alongside them
- **What expands instead:** Proteobacteria and Enterobacteriaceae

WHY IT COMPOUNDS

- **Fuel:** butyrate is the colonocyte's primary substrate, burned by β-oxidation
- **That keeps the lumen anaerobic:** oxygen is consumed at the epithelium
- **Lose it:** colonocytes switch to glycolysis, oxygen and nitrate leak in, favoring organisms that make no butyrate

DYSBIOSIS BECOMES SELF-PERPETUATING

- Falling dietary fiber
- **Medications:** antibiotics, PPIs, metformin, opioids
- Dentition, chewing capacity, enzyme output, institutional diets

References: Byndloss MX, Olsan EE, Rivera-Chávez F, et al. Microbiota-activated PPAR-γ signaling inhibits dysbiotic Enterobacteriaceae expansion. Science. 2017;357(6351):570–575. · Donohoe DR, et al. Cell Metab. 2011;13(5):517–526. · Du Y, et al. Int J Mol Sci. 2024;25(13):7379. · Tseng CH, Wu CY. J Biomed Sci. 2025;32:93.

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How SCFAs Protect the Barrier

STRUCTURE

- **Tight junctions:** butyrate upregulates occludin and the claudins
- **Mucus layer:** SCFAs drive goblet-cell mucin production
- Two actions from one metabolite

IMMUNE TONE

- Signals through GPR43/FFAR2 (a G-protein-coupled receptor on the cell surface) and GPR109A(G protein-coupled receptor) on immune cells
- Intracellular histone deacetylase (HDAC) inhibition drives colonic regulatory T cells and IL-10
- Restraint rather than suppression

BEYOND THE GUT

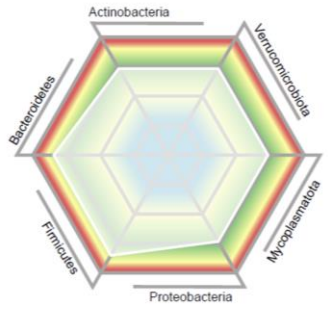
- Reaches the brain and signal through FFAR2 on brain endothelium
- Raise brain derived neurotrophic factor (BDNF)
  - Required for microglial maturation
- The fiber conversation is the neuroinflammation conversation

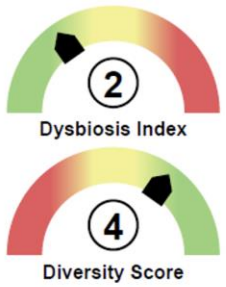
References: Du Y, et al. Int J Mol Sci. 2024;25(13):7379. · Furusawa Y, et al. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. Nature. 2013;504(7480):446–450. · Erny D, et al. Host microbiota constantly control maturation and function of microglia in the CNS. Nat Neurosci. 2015;18(7):965–977. · Więckowska-Gacek A, et al. Ageing Res Rev. 2021;70:101397.



Patient A — Normobiotic Gut Microbiome

- High diversity, low dysbiosis
- Robust *Faecalibacterium &* Bifidobacteria
- Robust *Akkermansia*
- Low dysbiosis index

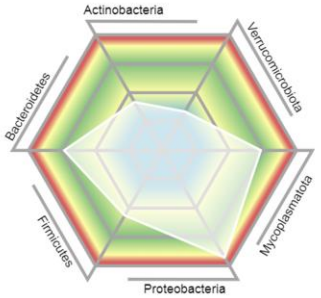


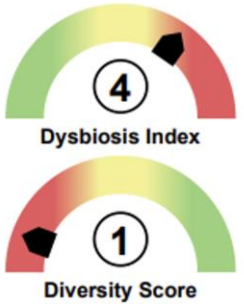




Patient B — Gut Microbiome Dysbiosis

- Reduced diversity
- Depleted SCFA producers
- Elevated Proteobacteria
- Low *Akkermansia*





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PART 2

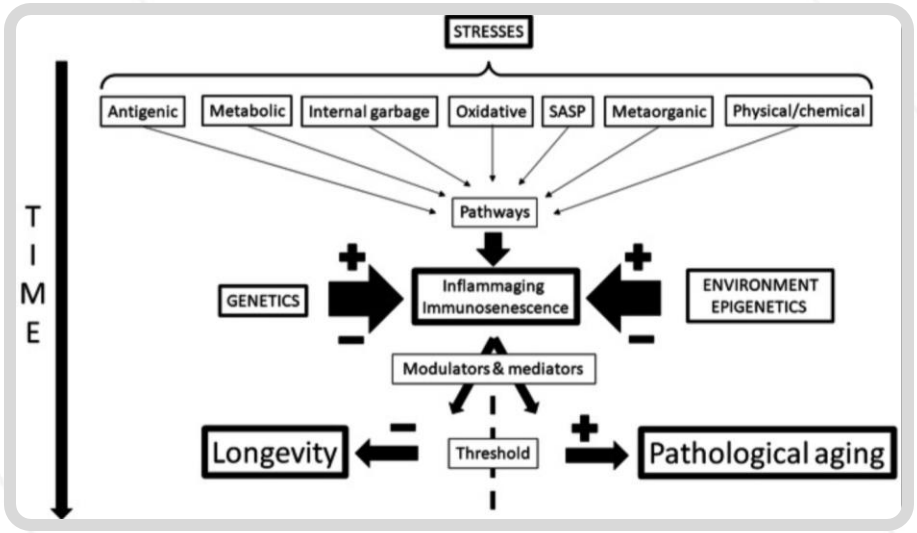
Intestinal Permeability & Inflammaging

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What Is Inflammaging?

- **Sterile and self-sustaining**
  - Driven by endogenous molecules released by stressed of dying cells that trigger immune activation (DAMPs)
    - Not by pathogens, so it does not resolve on its own.
- **Immunosenescence is the same process**
  - Thymic involution and lifelong antigen load remodel adaptive immunity while innate signaling stays switched on.
- **Mitochondria are a primary DAMP source**
  - Released mtDNA and ROS activate NLRP3 and cGAS–STING
    - Mitochondrial support is one upstream lever
- **The gut amplifies it**
  - Dysbiosis and barrier loss permit LPS translocation, sustaining systemic IL-6 and TNF-α tone.



- **Inflammaging predicts hard outcomes**
  - IL-6 and hs-CRP track frailty, sarcopenia, cardiovascular disease, dementia and all-cause mortality.
- **It is modifiable…and measurable**
  - Barrier repair, fiber and polyphenols, activity and mitochondrial support hit upstream drivers

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Reference: Fulop, T., Larbi, A., Pawelec, G., Khalil, A., Cohen, A. A., Hirokawa, K., & Franceschi, C. (2023). Immunology of aging: the birth of inflammaging. Clinical Reviews in Allergy & Immunology, 64(2), 109–122. PMCID: PMC8449217.

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The Intestinal Mucosal Barrier: Layers of Defense

KEY PROTEINS
MUC5AC · sIgA

THICKNESS
~150 µm

TURNOVER
3–5 Days

KEY RISK
Inflammaging

IMMUNE LOAD
70% of body IgA

Layer 1: Mucus Layer (Outer) — Lumen Interface

- Rich in glycoprotein & secretory IgA
  - *1st immunological checkpoint*

Layer 2: Mucus Layer (Inner) — Dense Exclusion Zone

- Dense, largely physical exclusion zone; MUC2-based, renewed by SCFA-producing bacteria
  - *Thins with age-related dysbiosis and SCFA-producer loss, not just overt disease*

Layer 3: Intestinal Epithelial Cell (IEC) Layer

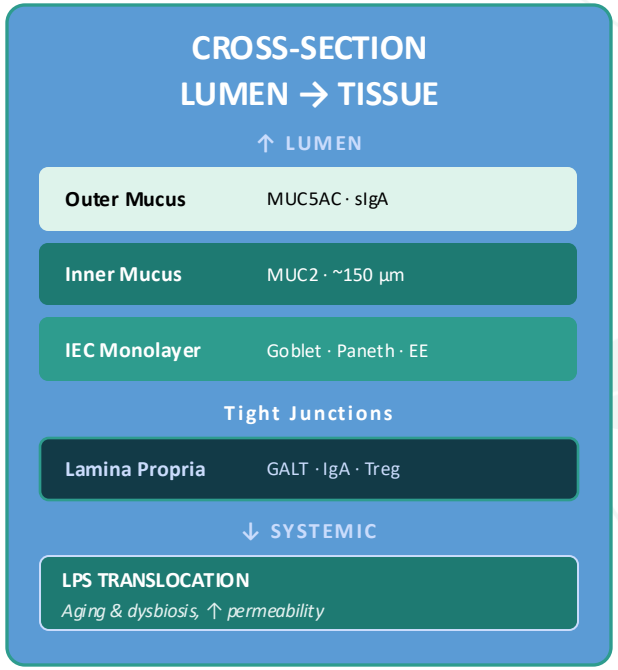
- Single cell layer
  - *Cell types: Enterocytes, Paneth cells, Enteroendocrine cells*

Layer 4: Tight Junction Complex

- Molecular gates — inflammation- and zonulin-sensitive
  - *Chronic LPS/cytokine exposure & zonulin release → ZO-1/claudin loss*

Layer 5: Lamina Propria & Gut-Associated Lymphatic Tissue (GALT)

- Immune cells
  - *70% of body's immune tissue resides here (GALT)*



References: Martini E, et al. Cell Mol Gastroenterol Hepatol. 2017;4(1):33-46. · Du Y, et al. Int J Mol Sci. 2024;25(13):7379. · Qi Y, et al. J Am Med Dir Assoc. 2017;18(9):810.e1-810.e4.

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Zonulin: The Gatekeeper Protein

- Zonulin Family Protein (ZFP)
  - Zonulin, an ~47-kDa protein, regulates intestinal permeability reversibly by modulating intercellular tight junctions
  - Elevated fecal levels of ZFP have been associated with metabolic syndrome, obesity, and apparently healthy cigarette smokers
  - High serum levels of ZFP (antigen) are correlated with abnormal results of the Lactulose Mannitol test
  - Higher zonulin levels are also associated with higher waist circumference, diastolic blood pressure, and fasting glucose and increased risk of metabolic diseases
  - Impaired fasting blood glucose is associated with increased serum LPS and zonulin levels
  - Excessive intake of simple sugars, sodium, emulsifiers, microbial transglutaminase (food additive) and nanoparticles may also be triggers for increased fecal ZFP and intestinal permeability

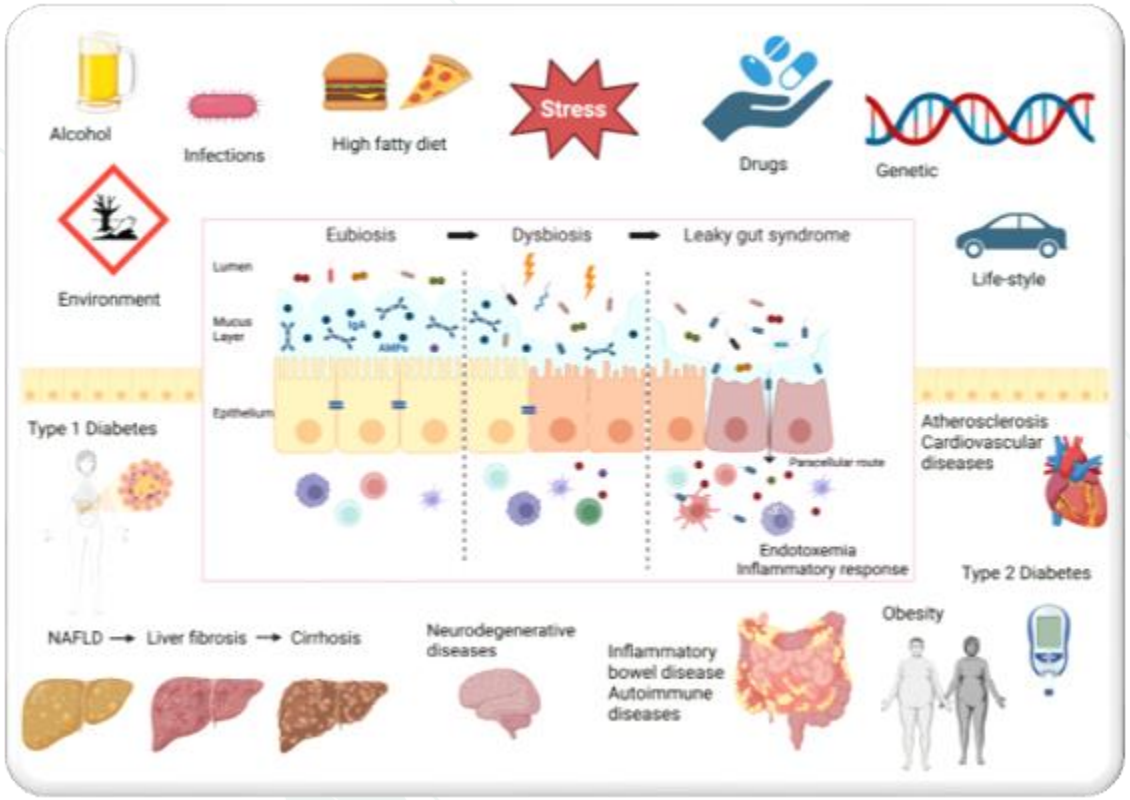
References: Qi Y, et al. J Am Med Dir Assoc. 2017;18(9):810.e1–810.e4. · Gargari G, et al. Sci Rep. 2021;11:11054. · Fasano A. Clin Gastroenterol Hepatol. 2012;10(10):1096–1100.

Intestinal Permeability Rises With Age

Elevated serum zonulin

In healthy older adults vs. younger controls
***NO** GI disease in either group*

- Healthy adults
  - ≥ 70 y (n = 18) vs. 18–30 y (n = 19)
- Serum zonulin +22%
- Zonulin correlated with TNF-α and IL-6
- Both markers inversely correlated with muscle strength and daily step count



References: *Qi Y, Goel R, Kim S, et al. Intestinal permeability biomarker zonulin is elevated in healthy aging. J Am Med Dir Assoc. 2017;18(9):810.e1–810.e4. · Di Vincenzo F, Del Gaudio A, Petito V, Lopetuso LR, Scaldaferri F. Gut microbiota, intestinal permeability, and systemic inflammation: a narrative review. Intern Emerg Med. 2024;19(2):275–293. doi:10.1007/s11739-023-03374-w*

When Bacteria Cross the Wall

LIPOPOLYSACCHARIDE

- **LPS** is a major component of the outer-membrane of gram-negative bacteria, like Proteobacteria and Enterobacteriaceae.
  - Hexa-acylated & strongly inflammatory.
- **Lipid A** is a conserved acyl core of LPS
  - Detected by immune receptors TLR4/MD-2.
- The lumen = grams of LPS
- The innate immune system reacts to *picograms* of Lipid A

TRANSLOCATION

- **Paracellular:** loosened tight junctions let LPS pass between cells
  - Intestinal permeability is key.
- **Transcellular:** dietary fat, particularly saturated fat, packages LPS into chylomicrons and carries it across with the meal.
- Endotoxin exposure is not constant
  - It spikes after eating, which is why fasting and postprandial samples differ.

PERSISTENT

- **Metabolic endotoxemia**
  - Chronic low-grade elevation of circulating LPS, first named by Cani and colleagues in 2007.
- In mice, that low-grade elevation alone was enough to initiate obesity and insulin resistance.
- Persistent exposure
  - No infection, no fever, no positive culture.

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References: Cani PD, Amar J, Iglesias MA, et al. Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes. 2007;56(7):1761–1772. · Ghosh SS, et al. J Endocr Soc. 2020;4(2):bvz039. · Gargari G, et al. Sci Rep. 2021;11:11054. · Zhang R, Ding N, Feng X, Liao W. Front Immunol. 2025;16:1529958.

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Where the Endotoxin Lands

ADIPOSE	Macrophages switch from anti- to pro-inflammatory, rising from ~15% to ~50% of the tissue. Producing TNF-alpha, interleukin-6, interleukin-1-beta
LIVER	Takes the first hit from portal blood. A fatty liver also clears less circulating amyloid. A damaged liver clears less of it.
VESSELS	Insulin resistance, endothelial activation (ICAM-1 and E-selectin upregulation), & cholesterol converted to a form that crosses the BBB (27-hydroxycholesterol)

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References: Więckowska-Gacek A, Mietelska-Porowska A, Wydrych M, Wojda U. Ageing Res Rev. 2021;70:101397. · Ghosh SS, et al. J Endocr Soc. 2020;4(2):bvz039. · Cani PD, et al. Diabetes. 2007;56(7):1761–1772. · Zhang R, Ding N, Feng X, Liao W. Front Immunol. 2025;16:1529958.

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Making Intestinal Permeability Measurable

Test	What it tells you	Considerations
Fecal calprotectin	Mucosal inflammation	Useful beyond IBD, but not specific
Stool testing	Diversity and dysbiosis index	Read the pattern, not one organism
hs-CRP and IL-6	Systemic inflammatory tone	Non-specific; track the trend
Serum zonulin	Barrier proxy	Serum correlates with LM drink test, venipuncture

Measure a *pattern,* not a marker

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References: Qi Y, et al. J Am Med Dir Assoc. 2017;18(9):810.e1–810.e4. · Du Y, et al. Int J Mol Sci. 2024;25(13):7379. · Ajamian M, Steer D, Rosella G, Gibson PR. Serum zonulin as a marker of intestinal mucosal barrier function: may not be what it seems. PLoS One. 2019;14(1):e0210728. · Scheffler L, et al. Front Endocrinol (Lausanne). 2018;9:22.

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Patient A — Microbiome

- High diversity
- Robust *Faecalibacterium*
- Robust Bifidobacteria
- Low dysbiosis index

Low	Mod	High	Reference Interval
			< 80

	Result	Unit
Zonulin*	30.4	ng/mL



Patient B — Microbiome

- Reduced diversity
- Depleted SCFA producers
- Elevated Proteobacteria
- **Intestinal permeability**

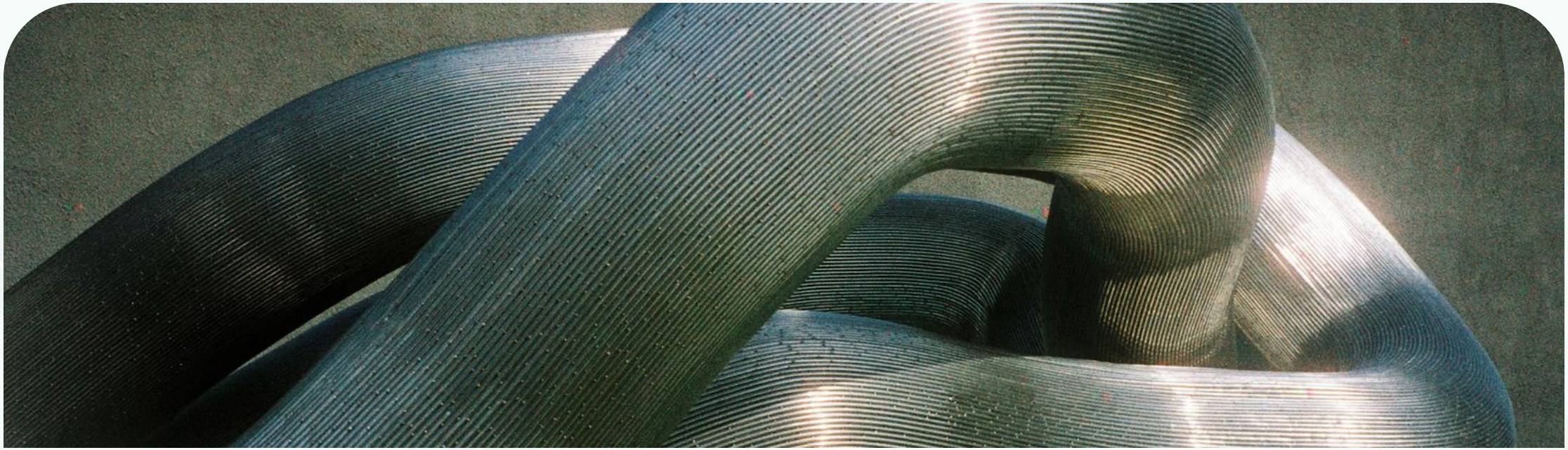
REFERENCE INTERVAL	LOW	MOD	HIGH
< 45.0			

	RESULT / UNIT
Zonulin Family Protein*	**50.0 ng/mL**

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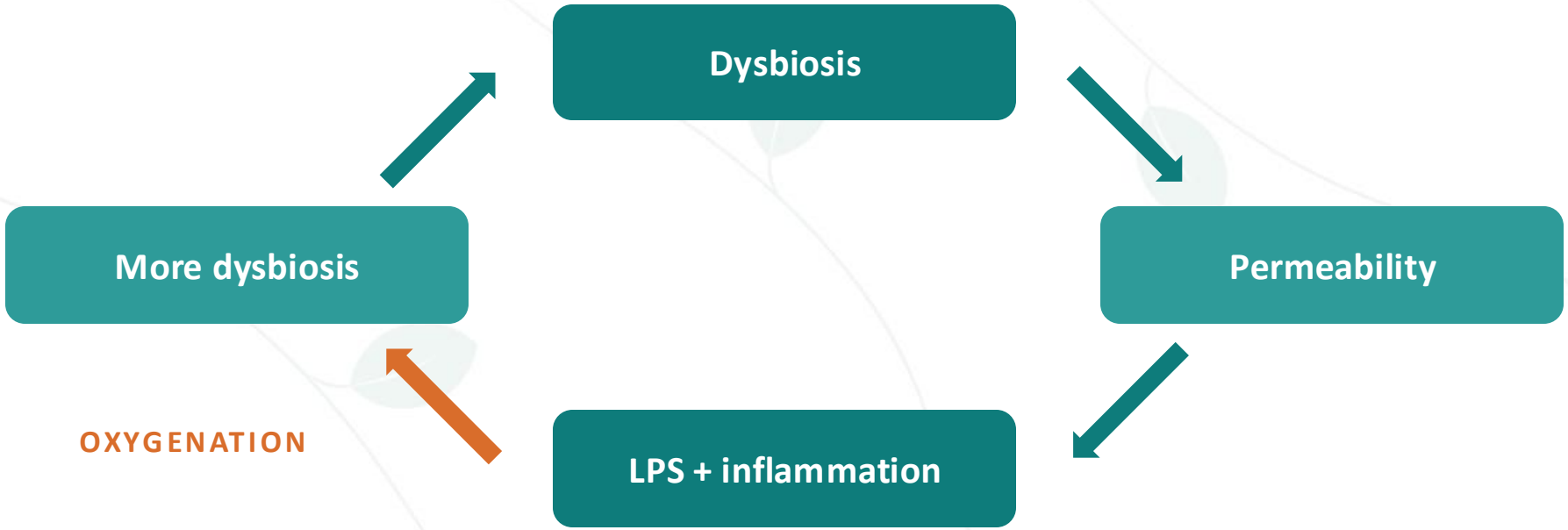
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PART 3

The Gut–Brain–Inflammaging Loop

The Inflammaging Feedback Loop



Associated with: Frailty · Sarcopenia · Insulin resistance · Cognitive decline

References: Tseng CH, Wu CY. J Biomed Sci. 2025;32:93. · Zhang R, Ding N, Feng X, Liao W. Front Immunol. 2025;16:1529958. · Fulop T, et al. Immunology of aging: the birth of inflammaging. Clin Rev Allergy Immunol. 2023;64(2):109–122.

The Blood-Brain Barrier Is Not a Wall



- Blood-brain barrier permeability also increases with age and systemic inflammation.
- Circulating cytokines signal centrally via direct crossing, circumventricular organs, and vagal afferents.
- **Same junction proteins, both barriers**
  - ZO-1/-2, occludin and claudins-3/-5/-12 seal brain endothelium
  - The gut epithelium uses the same family. Western-diet feeding lowers ZO-2, claudin-5 and claudin-12 and the barrier leaks.
- **LPS is the courier**
  - Endotoxin from a permeable gut modifies tight junctions, damages endothelium and degrades the glycocalyx via prostanoids and nitric oxide.
- **Failure is gradual and dose-dependent**
  - In rodents BBB leak appears only after ~90 days of Western diet (7-9 yrs), and obesity-prone animals break down first
    - This is a midlife exposure problem.

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References: Więckowska-Gacek A, Mietelska-Porowska A, Wydrych M, Wojda U. Ageing Res Rev. 2021;70:101397. · Zhang R, Ding N, Feng X, Liao W. Front Immunol. 2025;16:1529958.

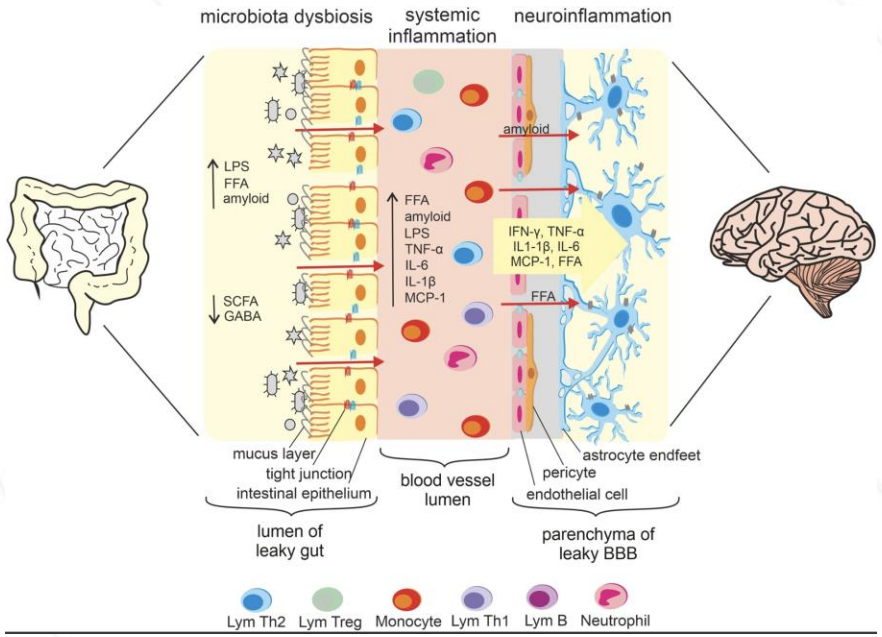
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From Gut Dysbiosis to Neuroinflammation

One defect, two barriers

1. **Western diet → dysbiosis**
   - High saturated fat and sugar, low fiber
   - *Bacteroides* fall ~50%,
   - Firmicutes and Proteobacteria rise
   - Bifidobacteria drop
   - Tight-junction genes (ZO, occludin) are downregulated = intestinal permeability
2. **Endotoxemia**
   - LPS leaks into circulation and activates CD14/TLR4
     - → TNF-α, IL-6, IL-1β, MCP-1
3. **BBB deterioration**
   - Cytokines, LPS and adhesion molecules (ICAM-1, E-selectin) open the barrier
   - ~90 days of Western diet lowered ZO-2 and claudin-5/-12 and impaired hippocampal memory.

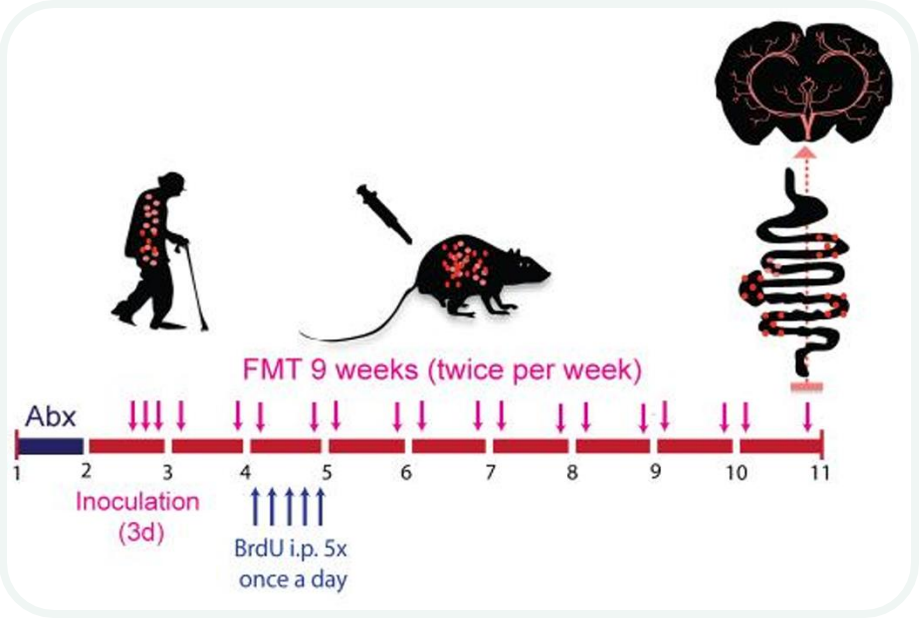


4. **Neuroinflammation before plaques**
   - Microglia and astrocytes activate months before amyloid deposits; RAGE influx rises as LRP1 efflux falls, and bacterial amyloid can cross-seed Aβ and tau.

Figure and data: Więckowska-Gacek A, Mietelska-Porowska A, Wydrych M, Wojda U. Western diet as a trigger of Alzheimer's disease: from metabolic syndrome and systemic inflammation to neuroinflammation and neurodegeneration. Ageing Res Rev. 2021;70:101397 (Fig. 4). CC BY.

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Why the Hippocampus Is Especially Vulnerable

- High metabolic demand and continuous synaptic plasticity make the hippocampus sensitive to inflammatory disruption.
- Pro-inflammatory cytokines directly interfere with long-term potentiation, the substrate of memory encoding.
- Transplanting gut microbiota from Alzheimer's patients into healthy rodents produced cognitive deficits and impaired hippocampal neurogenesis
  - No genetic model, no amyloid injection.
- Transferring aged microbiota into young mice alone caused hippocampal synapse loss and cognitive impairment.

References: Grabrucker S, et al. Brain. 2023;146(12):4916-4934. · Li X, Bao Y, et al. Aging Cell. 2025;24:e70064.

The Axis Runs Both Ways & It Is Modifiable

Dysbiosis → permeability → endotoxemia → neuroinflammation → altered motility and barrier function → dysbiosis

Forward arc

- Dysbiosis → permeability → LPS and cytokines → microglial priming → hippocampal injury.
- CD14- and TLR4-knockout mice are protected from the same diet, which makes this causal rather than correlative.

Reverse arc

- Central stress and inflammatory signaling (vagal and HPA-axis)

  Alter motility, secretion and barrier function.

Reverse arc *(continued)*

- Treating the gut without addressing stress physiology treats half the loop.
- Neuroinflammation precedes amyloid deposition, and barrier breakdown took ~1 decade (human years) of Western diet to appear.
- CD14- and TLR4-knockout mice are protected from the same diet, which makes this causal rather than correlative.

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References: Więckowska-Gacek A, et al. Ageing Res Rev. 2021;70:101397. · Zhang R, Ding N, Feng X, Liao W. Front Immunol. 2025;16:1529958. · Tseng CH, Wu CY. J Biomed Sci. 2025;32:93.

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Patient A — IP & Inflammaging Absent

- High diversity
- Robust *Faecalibacterium*
- Robust Bifidobacteria
- Low dysbiosis index
- **Low inflammation (hsCRP)**



Patient B — IP & Inflammaging Present

- Reduced diversity
- Depleted SCFA producers
- Elevated Proteobacteria
- Low *Akkermansia*
- Intestinal permeability
- **Inflammaging present**

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PART 4

Clinical Assessment & Case Study

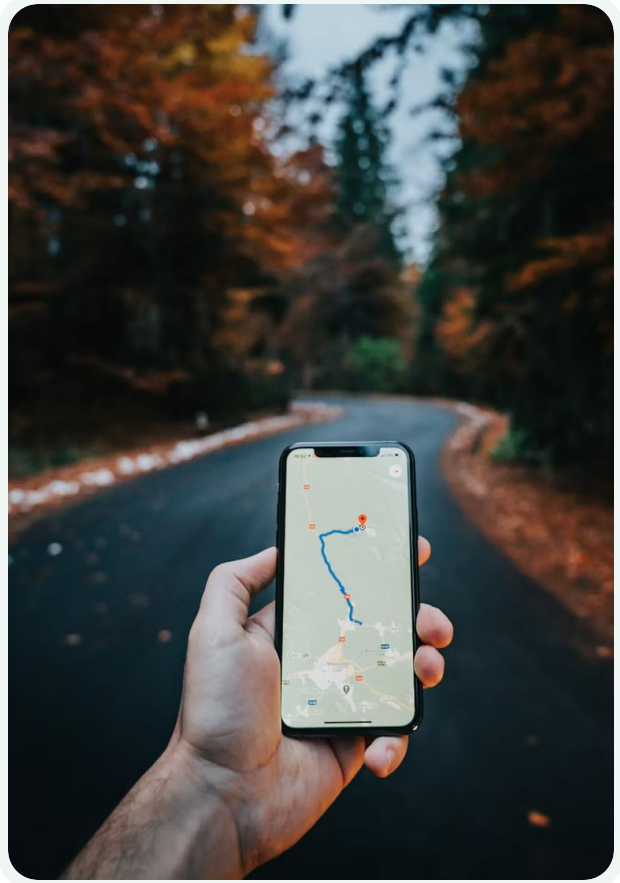
A Practical Assessment Panel

1. **Stool Microbiome Analysis**
   Alpha diversity, validated dysbiosis index, SCFA-producer abundance.

2. **Serum Zonulin**
   A measure of tight-junction integrity.

3. **hs-CRP**
   Downstream systemic inflammatory marker

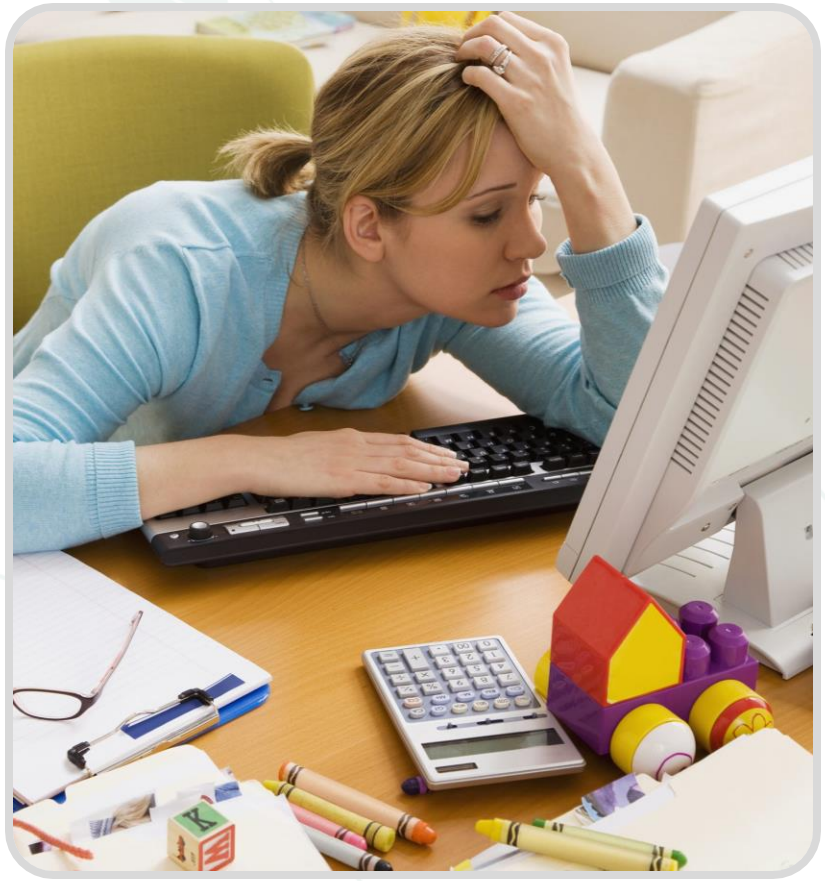
4. **Medication & Diet Review**
   PPIs, antibiotics and metformin; fiber, polyphenol and fermented-food intake.



References: Qi Y, et al. J Am Med Dir Assoc. 2017;18(9):810.e1-810.e4. · Du Y, et al. Int J Mol Sci. 2024;25(13):7379. · Wilmanski T, et al. Nat Metab. 2021;3(2):274-286.

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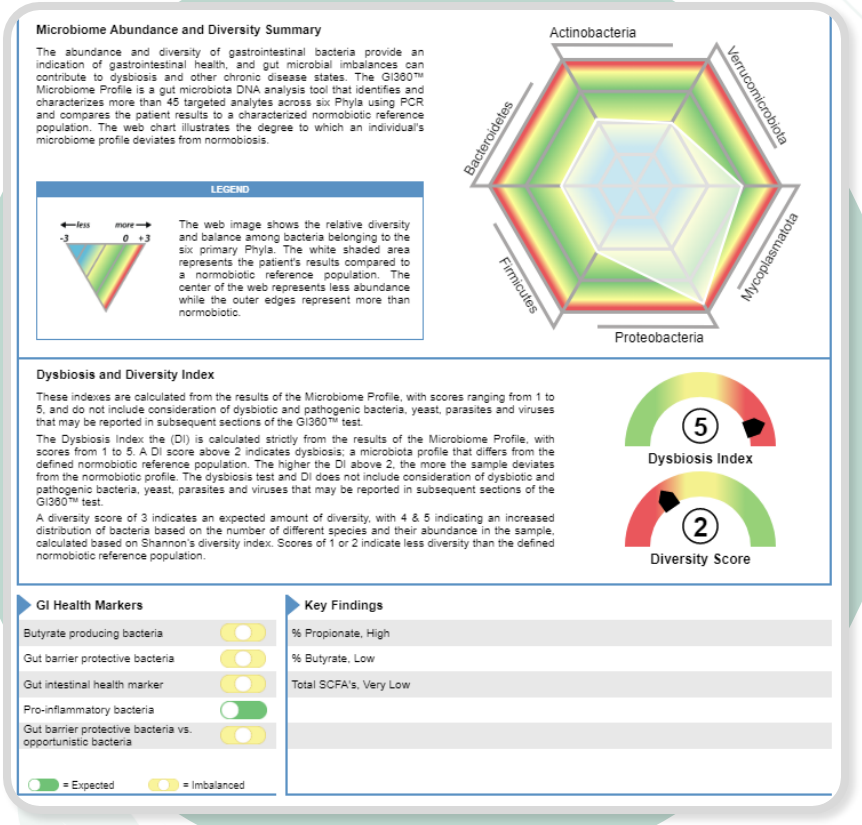
Will this person fare well in aging?

- 43 yof
- Typical daily intake:
  - Bfast: bagel with cream cheese, orange juice, coffee drink
  - Lunch: cheeseburger fries, apple, pop
  - Potato chips & chocolate cookie snack
  - Dinner: Frozen dinner, beer with ice cream dessert most days
- Rates job stress 9/10

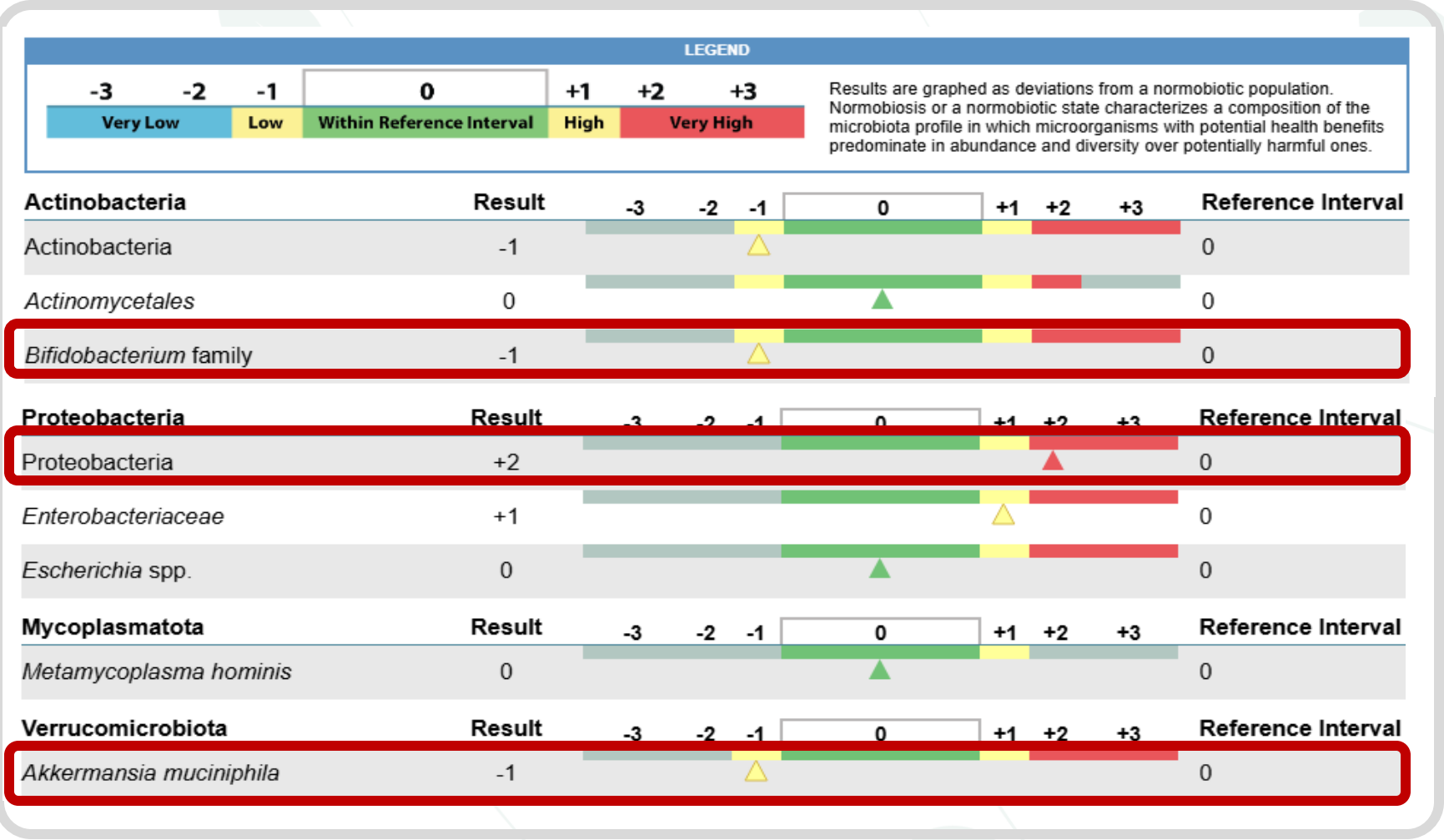
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Dysbiotic Microbiome

- Elevated Proteobacteria
  - Dysbiosis & Aging
- Dysbiosis
  - Inflammation & IP
  - Associated with IBS, IBD, obesity, diabetes, AI
- Low diversity
  - Inflammaging & IP
- Low butyrate producing bacteria
  - Inflammation & IP
  - Low butyrate
- Low gut barrier protective bacteria
  - Compromised mucosal barrier integrity
  - IP
- Low gut barrier protective bacteria & elevated opportunistic
  - Translocation & LPS



Associated with longevity



Elevated in dysbiosis, inflammation, poor health with aging

Associated with longevity, mucosal barrier, intestinal permeability, metabolic homeostasis

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Associated with longevity



Clostridium L2-50	-1		0
Dialister invisus	+2		0
Dialister invisus & Megasphaera micronuciformis	0		0
Dorea spp.	0		0
Holdemanella biformis	0		0
Anaerobutyricum hallii	-1		0
Agathobacter rectalis	0		0
Eubacterium siraeum	0		0
Faecalibacterium prausnitzii	-2		0
Lachnospiraceae	0		0
Ligilactobacillus ruminis & Pediococcus acidilactici	-1		0
Lactobacillus family	-2		0
Phascolarctobacterium spp.	0		0
Ruminococcus albus & R. bromii	0		0
Mediterraneibacter gnavus	-1		0

Associated with mucosal barrier, intestinal permeability

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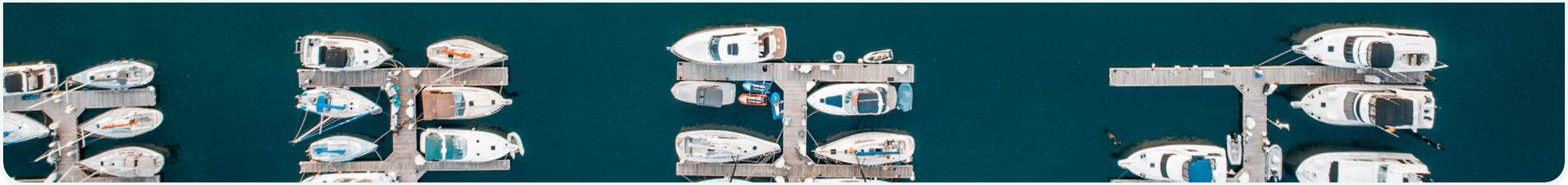
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Zonulin: Intestinal Permeability

Zonulin Family Protein; stool

	RESULT / UNIT	REFERENCE INTERVAL	LOW MOD HIGH
Zonulin Family Protein*	**90.5 ng/mL**	< 80.0	

- Higher zonulin levels are also associated with intestinal permeability, which is associated with aging.
- Higher zonulin associated with higher waist circumference, diastolic blood pressure, and fasting glucose and increased risk of metabolic diseases



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Foundational Protocol: Lifestyle and Supplements

LIFESTYLE

Stress reduction

- Meditation nightly
- At least 150 minutes of moderate-intensity aerobic activity per week, plus muscle-strengthening on 2 or more days

Remediate SAD

Modified Mediterranean diet

- 1 cup of olive oil per week
- Soluble fiber 8–15 g QD
- Polyphenols 1–2 g QD

SUPPLEMENTS · DAILY

- Soluble fiber & polyphenols: 6 g fiber with 25–40 mg polyphenols QD
- Vitamin D3/K2: 4,000 IU D QD
- Omega-3s (CLO): 2,200 mg QD
- NAC: 1 g QD
- L-glutamine: 1.5 g QD
- Quercetin: 100 mg QD
- Zinc carnosine: 17mg QD
- Curcumin: 1g QD

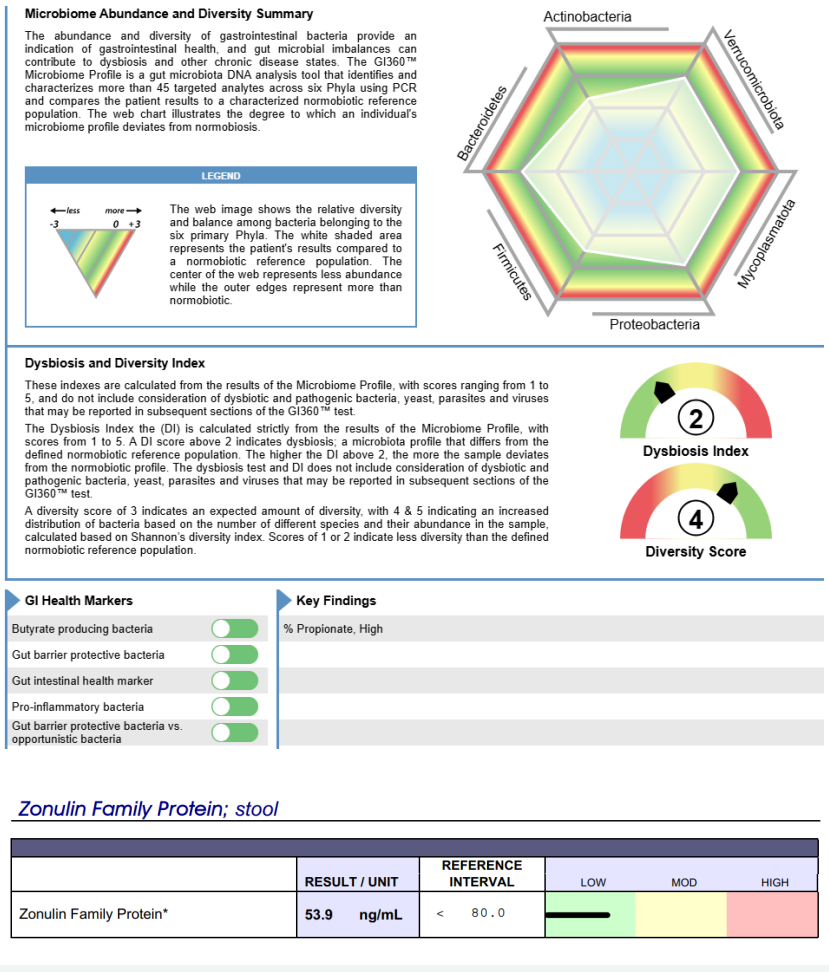
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References: Pirinen E, et al. Cell Metab. 2020;31(6):1078–1090. · Makki K, et al. Cell Host Microbe. 2018;23(6):705–715. · Shabbir U, et al. Nutrients. 2021;13(1):206. · Hill C, et al. Nat Rev Gastroenterol Hepatol. 2014;11(8):506–514.

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Re-test 6 months later

- Dysbiosis decreased
  - Decreased inflammation & IP
- Diversity improved
  - Anti-aging benefit
- Proteobacteria WNL
  - Anti-aging benefit
- WNL butyrate producing bacteria
  - Anti-inflammatory
- WNL Gut barrier protective bacteria
  - Restoring mucosal barrier integrity
- *Bifidobacterium* improved
  - Anti-aging benefit
- *Lactobacillus* improved
  - Anti-aging benefit
- *Akkermansia muciniphila* improved
  - Anti-aging benefit
- Zonulin WNL
  - Restored mucosal barrier
  - Anti-aging benefit



Microbiome Abundance and Diversity Summary

The abundance and diversity of gastrointestinal bacteria provide an indication of gastrointestinal health, and gut microbial imbalances can contribute to dysbiosis and other chronic disease states. The GI360™ Microbiome Profile is a gut microbiota DNA analysis tool that identifies and characterizes more than 45 targeted analytes across six Phyla using PCR and compares the patient results to a characterized normobiotic reference population. The web chart illustrates the degree to which an individual's microbiome profile deviates from normobiosis.

LEGEND

less -3 more 0 +3

The web image shows the relative diversity and balance among bacteria belonging to the six primary Phyla. The white shaded area represents the patient's results compared to a normobiotic reference population. The center of the web represents less abundance while the outer edges represent more than normobiotic.

Actinobacteria
Verrucomicrobiota
Mycoplasmatota
Proteobacteria
Firmicutes
Bacteroidetes

Dysbiosis and Diversity Index

These indexes are calculated from the results of the Microbiome Profile, with scores ranging from 1 to 5, and do not include consideration of dysbiotic and pathogenic bacteria, yeast, parasites and viruses that may be reported in subsequent sections of the GI360™ test.

The Dysbiosis Index the (DI) is calculated strictly from the results of the Microbiome Profile, with scores from 1 to 5. A DI score above 2 indicates dysbiosis, a microbiota profile that differs from the defined normobiotic reference population. The higher the DI above 2, the more the sample deviates from the normobiotic profile. The dysbiosis test and DI does not include consideration of dysbiotic and pathogenic bacteria, yeast, parasites and viruses that may be reported in subsequent sections of the GI360™ test.

A diversity score of 3 indicates an expected amount of diversity, with 4 & 5 indicating an increased distribution of bacteria based on the number of different species and their abundance in the sample, calculated based on Shannon's diversity index. Scores of 1 or 2 indicate less diversity than the defined normobiotic reference population.

2 Dysbiosis Index

4 Diversity Score

GI Health Markers	Key Findings
Butyrate producing bacteria	% Propionate, High
Gut barrier protective bacteria	
Gut intestinal health marker	
Pro-inflammatory bacteria	
Gut barrier protective bacteria vs. opportunistic bacteria	

Zonulin Family Protein; stool

	RESULT / UNIT	REFERENCE INTERVAL	LOW	MOD	HIGH
Zonulin Family Protein*	53.9 ng/mL	< 80.0			

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This is the follow-up report

Data Point	Initial Report	Follow-Up	Interpretation
Dysbiosis Index	5 (High dysbiosis)	2 (Low)	Marked improvement; microbiome rebalancing
Diversity Score	2 (Low diversity)	4 (High)	Significant increase; anti-aging and decreases inflammation
Butyrate-Producing Bacteria	Low	Expected	Protective
Gut Barrier Protective Bacteria	Low	Expected	Confers mucosal barrier integrity, anti-aging benefit
Microbiome Balance	Imbalanced	Balanced	Restored equilibrium across phyla
Barrier vs. Pro-inflammatory	Imbalanced	Balanced	Reduced inflammatory burden
% Propionate	Elevated	Elevated	Continue protocol
Bifidobacterium	Low	Balanced	Confers anti-aging benefit
Lactobacillus	Very Low	Balanced	Confers anti-aging benefit
Proteobacteria	Elevated	Balanced	Decreased inflammation, Confers anti-aging benefit
Zonulin	Elevated	WNL	Confers anti-aging benefit, metabolic and CVD benefit

Part 5: Evidence-Based Interventions

- Increasing Microbiome Diversity & Decreasing Inflammation
- Gut Barrier Restoration & Key Nutraceuticals
- Sequencing: Repair the Barrier Before You Seed It
- Medications & Other Modifiable Inputs

Increasing Microbiome Diversity & Decreasing Inflammation

THE FE-FI-FO STUDY

- **Ten weeks:** a 4-week ramp followed by 6 weeks of maintenance.
- **Fiber arm:** at least 20 g/day added to baseline
  - Fruits, vegetables, legumes, grains, nuts and seeds.
- **Fermented arm:** 6 servings/day (4–6 oz), low-sugar
  - Kimchi, plain yogurt, sauerkraut.
- People already eating >20 g fiber or >2 servings of fermented food daily were excluded.

FERMENTED FOODS & INFLAMMATION

- **Fiber:** no significant increase in microbiome diversity.
- **Fermented foods:** diversity increased.
- **And inflammation decreased:** 19 inflammatory proteins decreased, including IL-6.
- Gut microbiome diversity is anti-inflammatory
  - *Anti-inflammaging?.*

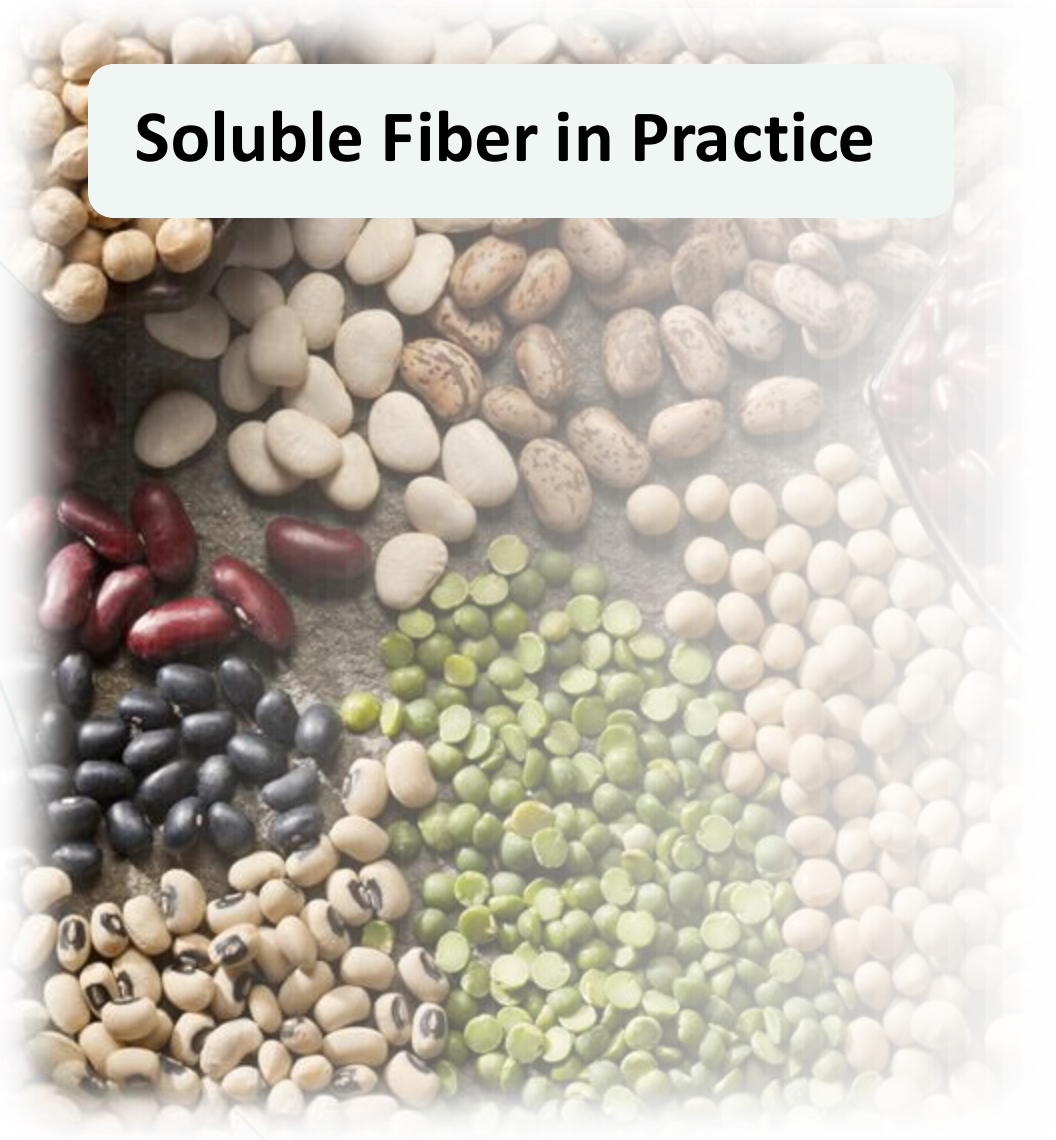
THE CONSIDERATION: the fiber arm was predominantly insoluble (whole grains, vegetable skins, nuts and seeds). Insoluble fiber adds bulk and speeds transit but is poorly fermented, it delivers little substrate to the organisms we are trying to feed.

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Reference: Wastyk HC, et al. Gut-microbiota-targeted diets modulate human immune status. Cell. 2021;184(16):4137–4153. doi:10.1016/j.cell.2021.06.019

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Soluble Fiber in Practice



- **Soluble · fermentable:** pectins, inulin, beta-glucan, acacia, guar, GOS and FOS — gels and ferments to short-chain fatty acids
  - Insoluble (cellulose, lignin — bran, skins, nuts) adds bulk and passes largely unfermented; whole produce runs ~30% of each, not one or the other.
- **Target:** 8–15 g of soluble fiber QD, titrated up over 4–6 weeks.
- **Food sources: red kidney beans**, lima beans, chickpeas, inulin, Jerusalem artichoke, garlic, onions, green bananas.
- **Complexity beats quantity:** the variety of fiber structures drives microbial diversity more than total grams.
- **Who responds:** butyrate producers in the *Firmicutes* phylum: class *Clostridia*, *Lactobacillus* spp., *Faecalibacterium prausnitzii*.
- **Why butyrate:** fuels enterocytes, tunes immune and inflammatory tone, and maintains mucosal barrier integrity.
- **The gap:** SAD, low-FODMAP, ketogenic and carnivore patterns are largely devoid of soluble fiber and drive dysbiosis.

References: Makki K, et al. Cell Host Microbe. 2018;23(6):705–715. · So D, et al. Am J Clin Nutr. 2018;107(6):965–983. · Halmos EP, et al. Gut. 2015;64(1):93–100.

Polyphenols: The Second Substrate

- **Sources:** berries, green tea, cocoa, red wine, cranberry, pomegranate, curcumin, grapeseed.
- **Who responds:** *Akkermansia muciniphila* and *Lactobacillus*
  - The **mucus-layer species,** expanded by polyphenol-rich extracts in controlled feeding studies.
- **Dose:** no RDA exists. Roughly 1–2 g QD of total polyphenols is the intake associated with chronic disease prevention.
- **Synergistic:** polyphenols plus daily soluble fiber is the practical combination
  - Fiber feeds the fermenters, polyphenols feed the mucus layer.



References: Anhê FF, et al. Gut. 2015;64(6):872–883. · Roopchand DE, et al. Diabetes. 2015;64(8):2847–2858. · Cardona F, et al. J Nutr Biochem. 2013;24(8):1415–1422.

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Gut Barrier Restoration & Key Nutraceuticals

MUCOSAL SUBSTRATES	• **N-acetyl glucosamine:** precursor for mucin synthesis; lowers permeability and tightens junctions.
	  ◦ Safe in shellfish allergy (IgE targets flesh, not shell)
	• **Phosphatidylcholine:** structural lipid of the mucus layer, delivered by vascular entry
	  ◦ Depleted by ectophospholipase-expressing E. coli and H. pylori
	• **Glutamine:** Primary enterocyte fuel; restores tight junction protein expression

JUNCTION & ANTI-INFLAMMATORY	• **Zinc carnosine:** chelated zinc-L-carnosine; reduces permeability and supports epithelial repair at the site of injury • **Curcumin:** organizes tight junction proteins and reduces bacterial translocation; <1% oral bioavailability is an advantage when the lumen is the target • **Quercetin:** flavonoid supporting tight junction assembly; pairs with vitamin D and retinol, which modulate junction gene expression
LIPID MEDIATORS	• **Omega-3s (EPA/DHA):** lower permeability and pro-inflammatory cytokines; raise pro-resolving mediators • **Palmitoylethanolamide (PEA):** reduces intestinal permeability within 72 hours of an inflammatory insult • **γ-linolenic acid:** anti-inflammatory fatty acid supporting epithelial membrane integrity

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References: Salvatore S, Heuschkel R, Tomlin S, et al. Aliment Pharmacol Ther. 2000;14(12):1567–1579. · Stremmel W, Weiskirchen R. Livers. 2024;4(3):479–494. · Durkin LA, Childs CE, Calder PC. Foods. 2021;10(1):199. · Kleessen B, Hartmann L, Blaut M. Fructans in the diet cause alterations of intestinal mucosal architecture, released mucins and mucosa-associated bifidobacteria in gnotobiotic rats. Br J Nutr. 2003;89(5):597–606. · Bischoff SC, Barbara G, Buurman W, et al. Intestinal permeability—a new target for disease prevention and therapy. BMC Gastroenterol. 2014;14:189. doi:10.1186/s12876-014-0189-7. · De Santis S, Cavalcanti E, Mastronardi M, Jirillo E, Chieppa M. Nutritional keys for intestinal barrier modulation. Front Immunol. 2015;6:612. doi:10.3389/fimmu.2015.00612. · Shabbir U, Rubab M, Daliri EB, et al. Nutrients. 2021;13(1):206.

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Dosing and Duration Guidelines

Compound	Maximum Dose	Duration
GlcNAc (NAG)	6 g QD	6 weeks (IBD)
PC	1,200 mg QD	Up to 1 year
Glutamine	1.5-30 g QD	Up to 1 year
Zinc carnosine	75 mg BID	8 weeks
Curcumin	3 mg/kg/day	Acceptable daily
Omega-3s	Up to 4,000 mg QD	≥12 weeks, reassess
Quercetin	250–1,000 mg QD	2–12 weeks
γ-linoleic acid	2.2 g QD	Up to 1 year
PEA	300–1,200 mg QD	2–12 weeks

These are *maximum* doses and *maximum* studied durations, not starting points. Individualize to the patient and reassess before continuing.

References: WebMD monographs for palmitoylethanolamide, curcumin, gamma-linolenic acid and glutamine. · Nutrients. 2021;13(12):4415. doi:10.3390/nu13124415. · Stremmel W, Merle U, Zahn A, Autschbach F, Hinz U, Ehehalt R. Retarded release phosphatidylcholine benefits patients with chronic active ulcerative colitis. Gut. 2005;54(7):966–971. doi:10.1136/gut.2004.052316. · Natural Medicine Journal. N-acetylglucosamine treatment for inflammatory bowel disease. Accessed 1 October 2024.

Inflammaging: The Modifiable Inputs

MEDICATION & MICROBIOME SHIFTS

- **Pro-inflammatory potential:** PPIs, corticosteroids, SSRIs, antipsychotics, beta-blockers, thiazides, hormone therapy.
- **Anti-inflammatory mechanisms:** metformin and GLP-1 receptor agonists.

NUTRACEUTICALS & BIOACTIVES

- **Evidence for:** cocoa flavanols, polyphenols, ALA, NAC, CoQ10, magnesium, vitamin D, omega-3s.
- **Shared mechanism:** omega-3s and polyphenols shift the community toward SCFA producers and lower LPS-driven signaling.

GUT MICROBIOME & AGING: higher diversity may mitigate inflammaging.
Holding that diversity into advanced age supports immune regulation and lowers chronic inflammatory tone.

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References: Maier L, et al. Nature. 2018;555(7698):623–628. · Imhann F, et al. Gut. 2016;65(5):740–748. · Forslund K, et al. Nature. 2015;528(7581):262–266. · Li et al. Biology. 2025;14(12):1705. · Zou et al. Front Nutr. 2025;12:1575323.

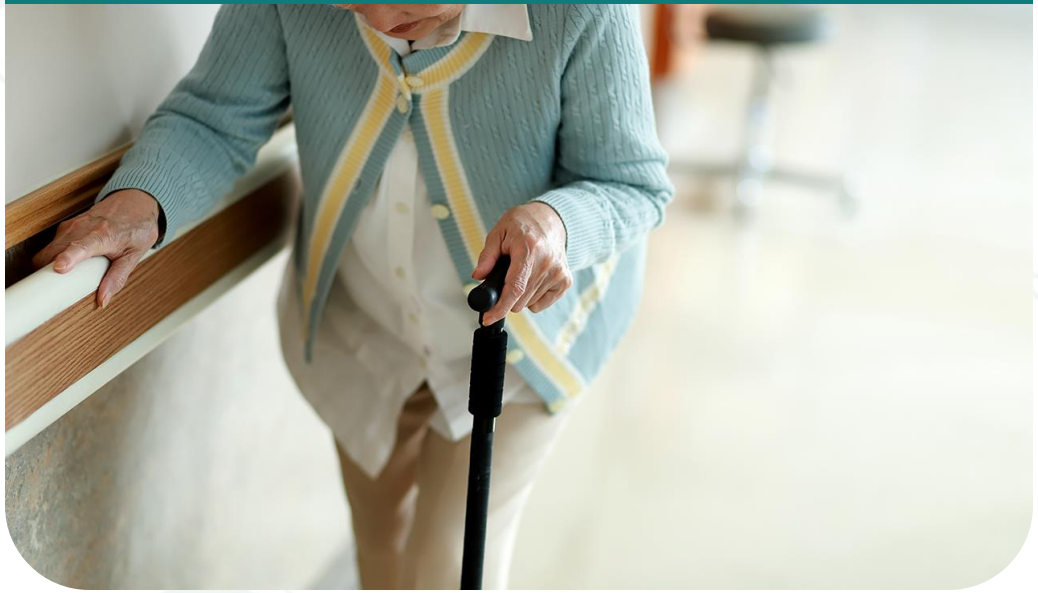
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Same lifespan, yet vastly different health-span.

Patient A · Age 71



Patient B · Age 71



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Key Takeaways

1. Biological gut age, not chronological age, predicts the inflammaging trajectory.
2. Diversity, dysbiosis and zonulin are measurable, actionable biomarkers today.
3. The gut-brain inflammatory loop is bidirectional
4. Diversity-supporting diet (soluble, fermentable fiber, polyphenols, fermented foods) is the foundation.
5. Sequence intervention: foundation → barrier repair → reassess (re-test at ~6 months).



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THANK YOU
QUESTIONS?
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