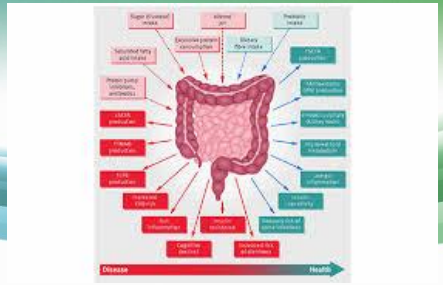

How Your Gastrointestinal Tract (Gut) Regulates Your Behavior

The Brain-Gut Connection

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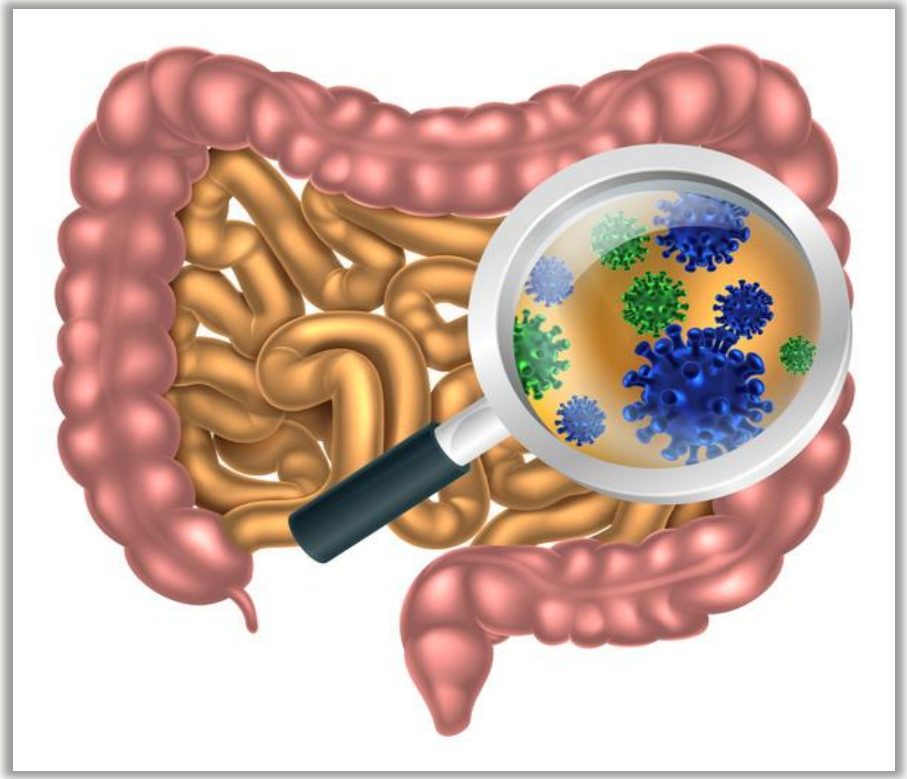
Objectives

- Review the importance of a balanced microbiota for a normal functioning immune system and health
- Discuss the science behind the relationship between the brain and the gastrointestinal tract and concept of dysbiosis
- Provide the evidence demonstrating the importance of the gastrointestinal tract microbiota and brain function in particular psychological/emotional health
- Describe the concept of functional gastrointestinal disease
- Outline the data supporting use of probiotics in functional GI disorders as well as manipulating the microbiota as a novel approach to functional GI disorders

Microbiome, Immune Development, and Dysbiosis

Role of Intestinal Microbiota in Immune Health

- **Gut microbiota help support gut barrier function:**
  - ↑ Mucin production
  - ↓ Permeability
- **Gut microbiota help support the adaptive immune response:**
  - Generate IgA activity (humoral)
  - Balance in T helper cell subclasses (cellular)
  - Enhances T regulatory cell function

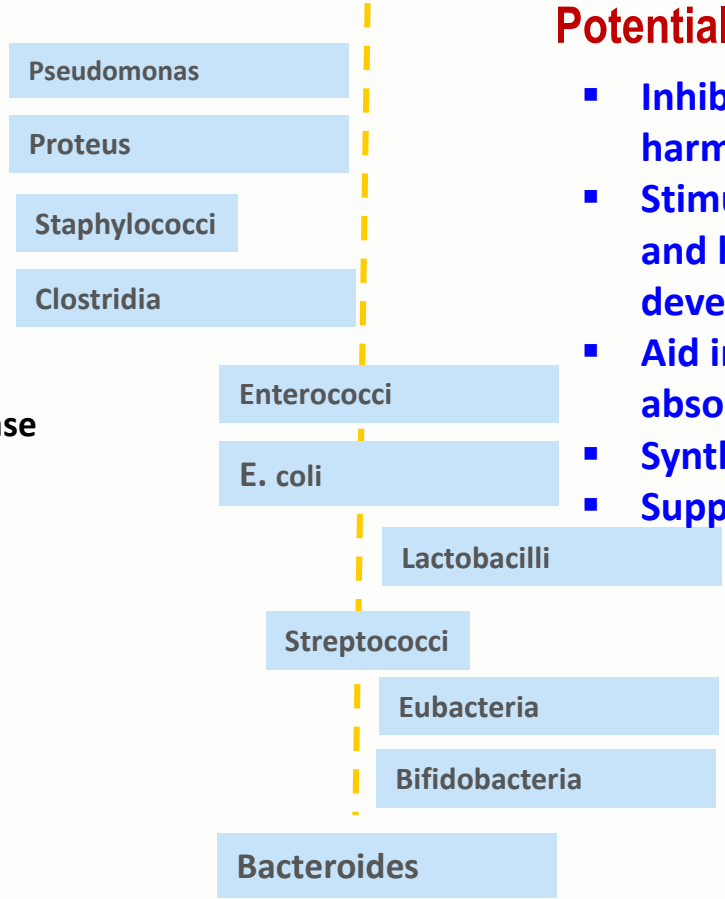


Li D et al. *Biotechnology Advances* 34 (2016) 1210–1224
Isolauri E., et al. *Am J Clin Nutr* 2001;73(suppl):444S-450S
Saavedra JM. *Nutr Clin Pract* 2007; 22:351-365

Microbiome: Microbiota and biofilm
A Balanced Ecosystem

Potentially Harmful Bacteria

- Diarrhea/constipation
- Altered Motility
- Decreased diversity with
  - Increased Allergy and
  - Increased Auto-immune disease
- Infections
- Production of Toxins



Potentially Helpful Bacteria

- Inhibition of exogeneous and/or harmful bacteria
- Stimulation of immune functions and healthy immune development
- Aid in digestion and/or absorption
- Synthesis of vitamins
- Supports the GI barrier

Microbiome and Dysbiosis

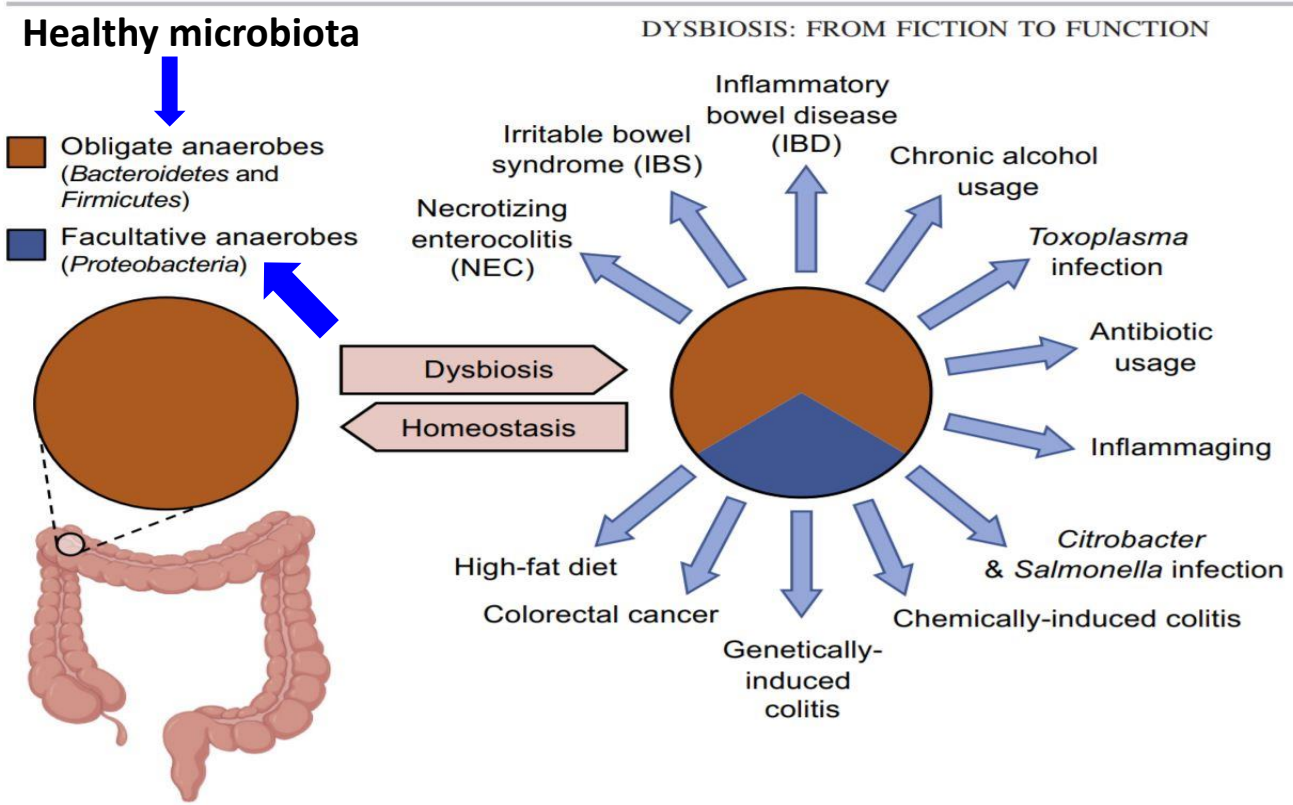
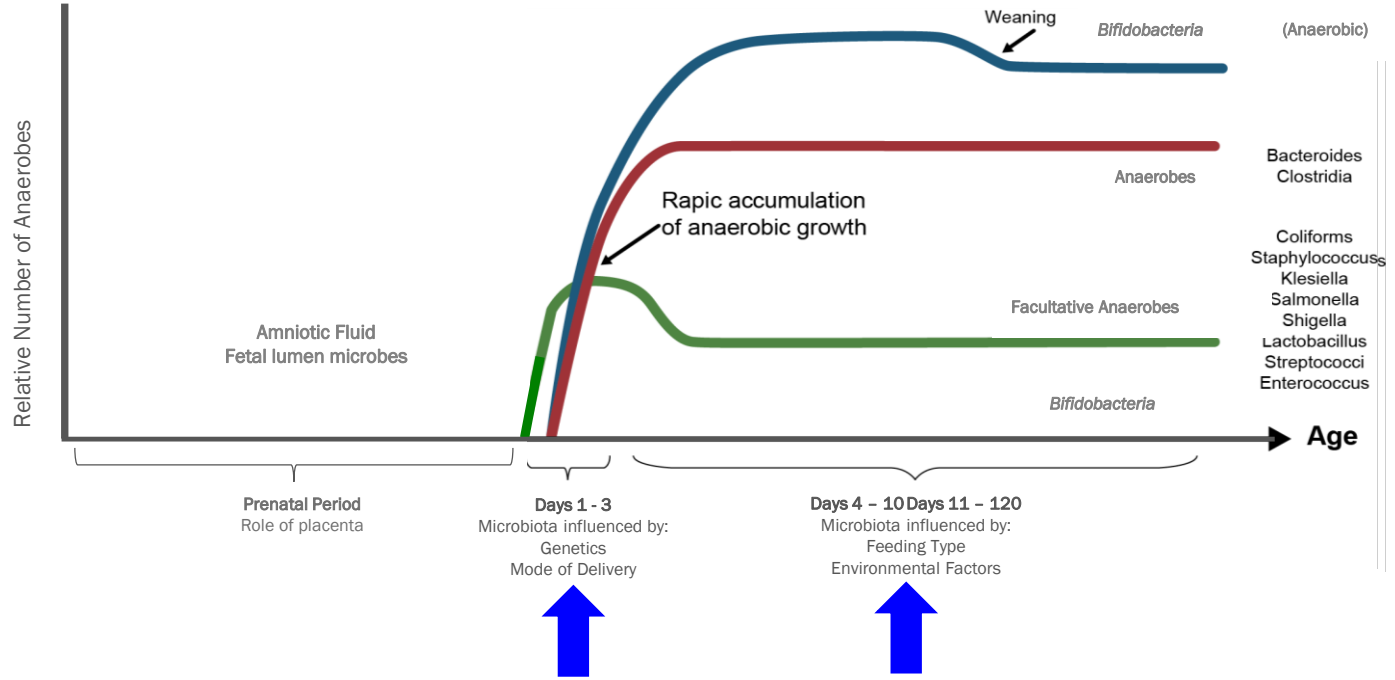


Fig. 3. An expansion of *Proteobacteria* is a microbial signature of dysbiosis in the fecal microbiota. The fecal microbiota of healthy individuals is dominated by obligate anaerobic bacteria belonging to the phyla *Firmicutes* and *Bacteroidetes* (30). A dysbiotic expansion in the fecal microbiota of facultative anaerobic bacteria of the phylum *Proteobacteria* is observed in patients with necrotizing enterocolitis (50), irritable bowel syndrome (12, 33), inflammatory bowel disease (18), colorectal cancer (3), or in individuals consuming a high-fat diet (46), with chronic alcohol usage (15), or undergoing inflammaging (48). A dysbiotic expansion of Proteobacteria in the large intestine is also observed in mouse models of chemically induced colitis (43), genetically induced colitis (23), antibiotic treatment (6, 59), and infection with *Salmonella enterica* (68), *Citrobacter rodentium* (43), or *Toxoplasma gondii* (27).

The Microbes and Infant is Exposed to Help Define their Intestinal Microbiota



Adapted from Rautava S. et al, JPGN 2004:38;378–388.

A Healthy Gut Microbiota Is Important For Maturation Of The Gut Barrier Function And Immune System Development

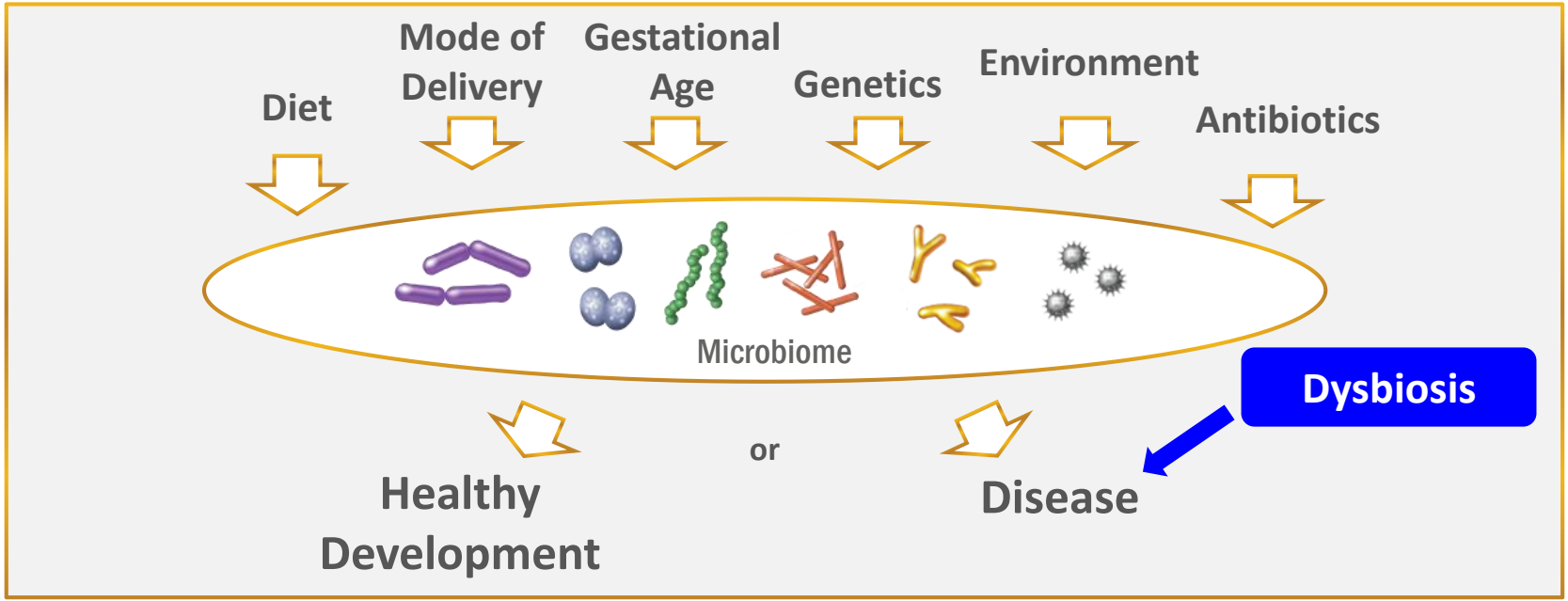
Important phases of gut microbiota development in early life

	In the womb	At birth	Introduction to oral feeding
Major influencing factors	*First inoculation* Potential exposure to the microbial communities in the placenta and amniotic fluid	*Initial colonisation* Mode of delivery influences exposure to the mother's vaginal and intestinal microbiota as well as skin microbiota	*Increasing diversity* Type of feeding, use of antimicrobials and the mother's skin microbiota

Arrieta et al., Front Immunol, 2014.
Rodrigruez et al., Microb Ecol Health Dis, 2015.
Collado et al., Sci Rep, 2016.
Collado et al., Gut Microbes, 2012; Bäckhed et al., Cell Host Microbe, 2015.

Each Person Develops a Unique GI Microbiome

Influenced by:



Martin R, Nauta AJ, Amor KB, Knippels LMJ, Knol J, Garssen J. *Benef Microbes*. 2010;1(4):367-82.

Stiemsma LT, Michels KB. *Pediatrics*. 2018;141(4):e20172437.

Yang I, Corwin EJ, Brennan PA, Jordan S, Murphy JR, Dunlop A. *Nurs Res*. 2016;65(1):76

Infant Exposures Help Define their Intestinal Microbiota

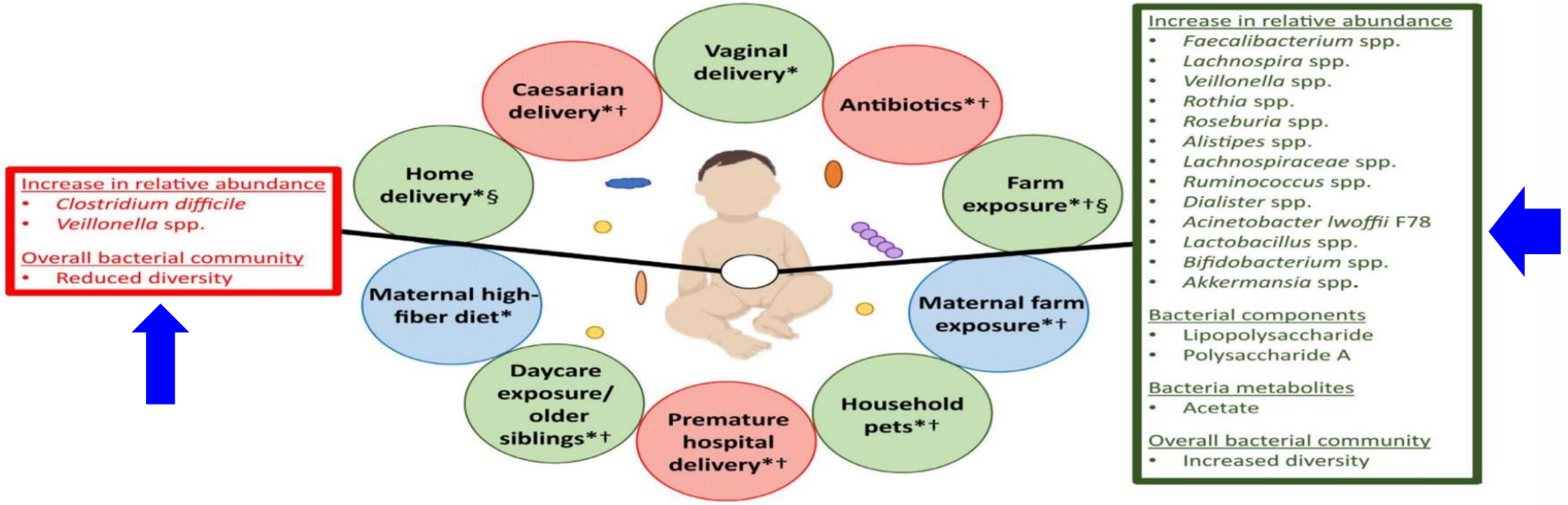


FIGURE 1 Early-life environmental factors affecting microbial exposures and demonstrated to be associated with gut microbiota composition and/or allergic diseases risk. Environmental and gut microbiota microbes **(bold font)** or features of the gut microbiota (plain font) associated with asthma*, sensitization or allergies†, atopic dermatitis§ risk or protection when present in infancy are shown in red and green boxes, respectively. Green circles denote protective environmental factors, red circles denote deleterious risk factors, and blue circles indicate maternal exposures that are protective against asthma/allergy in the offspring[20,24,26,30,32,33,39,41,42,45,46,48,52-55,59,117,134-138]

Microbiome

and the

Brain-Gut Axis (Connection)

Available online at www.sciencedirect.com

ScienceDirect

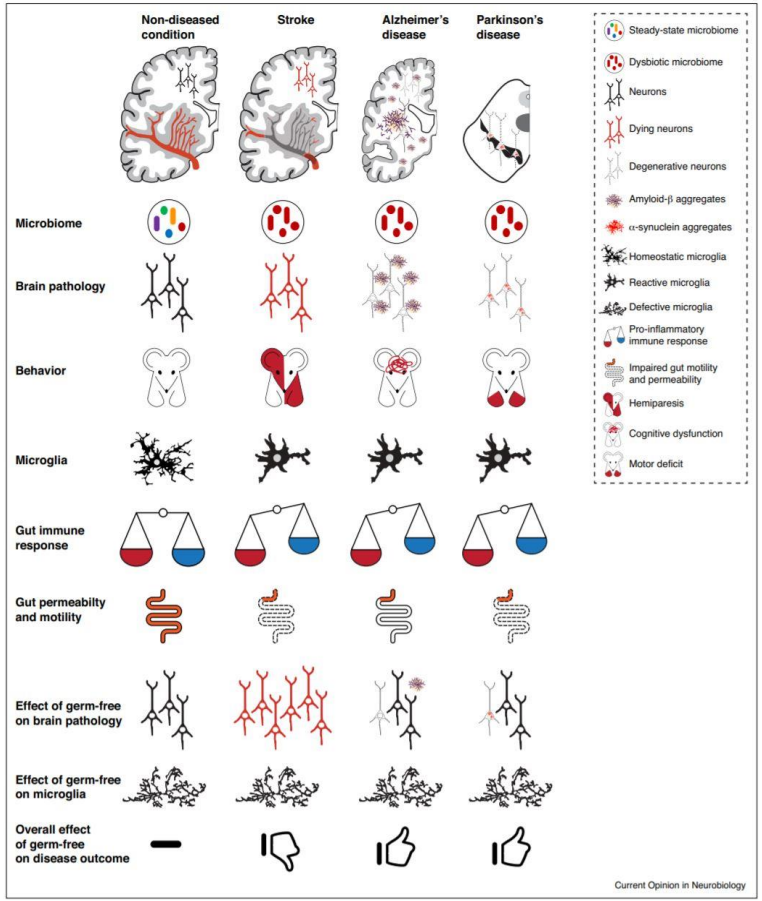
Current Opinion in Neurobiology

The microbiome-gut-brain axis in acute and chronic brain diseases

Corinne Benakis[1,†], Camille Martin-Gallausiaux[2,†], Jean-Pierre Trezzi[2,3], Philip Melton[1], Arthur Liesz[1,4,†] and Paul Wilmes[2,†]

The gut microbiome — the largest reservoir of microorganisms of the human body — is emerging as an important player in neurodevelopment and ageing as well as in brain diseases including stroke, Alzheimer's disease and Parkinson's disease. The growing knowledge on mediators and triggered pathways has advanced our understanding of the interactions along the gut-brain axis. Gut bacteria produce neuroactive compounds and can modulate neuronal function, plasticity and behavior. Furthermore, intestinal microorganisms impact the host's metabolism and immune status which in turn affect neuronal pathways in the enteric and central nervous systems. Here, we discuss the recent insights from human studies and animal models on the bi-directional communication along the microbiome-gut-brain axis in both acute and chronic brain diseases.

Figure 1



Effect of GF on brain pathology.
Major neuronal and inflammatory mechanisms implicated in stroke, AD and PD in comparison to non-diseased condition as demonstrated in animal models. All of the three diseases lead to gut microbiome dybiosis, neuronal death, behavioral deficits, microglia activation, pro-inflammatory milieu in the gut, intestinal motility impairment and/or increased gut permeability. In a context of GF condition, microglia showed an

Microbiota-Gut-Brain Axis cont'd

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ScienceDirect

Current Opinion in Pharmacology

Impact of gut microbiota on neurogenesis and neurological diseases during infancy

Tomás Cerdó[1,2,3,4], Estefanía Diéguez[1,2] and Cristina Campoy[1,2,3,4,5,6]

The first years of life constitute a crucial period for neurodevelopment and a window of opportunity to develop new strategies to prevent neurological and mental diseases. Different studies have shown the influence of gut bacteria in neurogenesis and a functional relationship between gut microbiota and the brain, known as 'gut–brain axis', in which the intestinal microbiota is proposed to play a key role in neurophysiological processes. It has been observed that certain microbiome metabolites could be related to the development of neurological disorders through mechanisms still unknown. Then, more studies are needed to broaden the knowledge regarding the relationship between the Central Nervous System and the gastrointestinal tract, which could help to develop new preventive and treatment protocols.

T Cerdo et al. Curr Opin Pharmacol 2020; 50:33-37

Can Gut Bacteria Shape Our Emotions?

By Shawn Radcliffe

People have long talked about trusting your 'gut instinct.' Or described nervousness as having 'butterflies in the stomach.' Recent research is finding that there may actually be some truth to these old sayings. Over the past decade, scientists have been investigating the link between the bacteria that live in our intestines—our microbiome—and our brain and mental health.

This avenue of research has been around since the early 1900s, when doctors and scientists wrote a lot about how the contents of the colon—and harmful bacteria living there—could **contribute to fatigue, depression and neuroses**. Based on this, they recommended treatments ranging from dairy-based beverages meant to change the bacterial ecology in the intestines to drastic surgical removal of parts of the colon—all with the goal of improving the patient's mental health.

Even more interesting, at least in terms of the role of the gut microbiome in shaping the brain, is a **study by researchers at McMaster University** in Ontario. When researchers transferred bacteria to germ-free mice from the intestines of another mouse strain, the personality of the recipient mice became more like the donor mice. Mice that were usually daring would become timid when they received bacteria from timid mice, and the other way around.

The influence of the gut bacteria on the brain goes beyond subtle effects on mood, thoughts and behavior. It may also affect the structure and function of the brain itself. In a study published this year in **Translational Psychiatry**, researchers found that germ-free mice had different active—upregulated—genes in the prefrontal cortex. This part of the brain is involved in planning and decision making. It also exerts control over other structures of the brain, including the amygdala, as part of the processing of emotional information.

Defining Functional Gi Disease and Probiotics Modulate Brain-Gut Interactions Influencing Gut-Brain Health

Breastfeeding is the Gold Standard of Infant Feeding

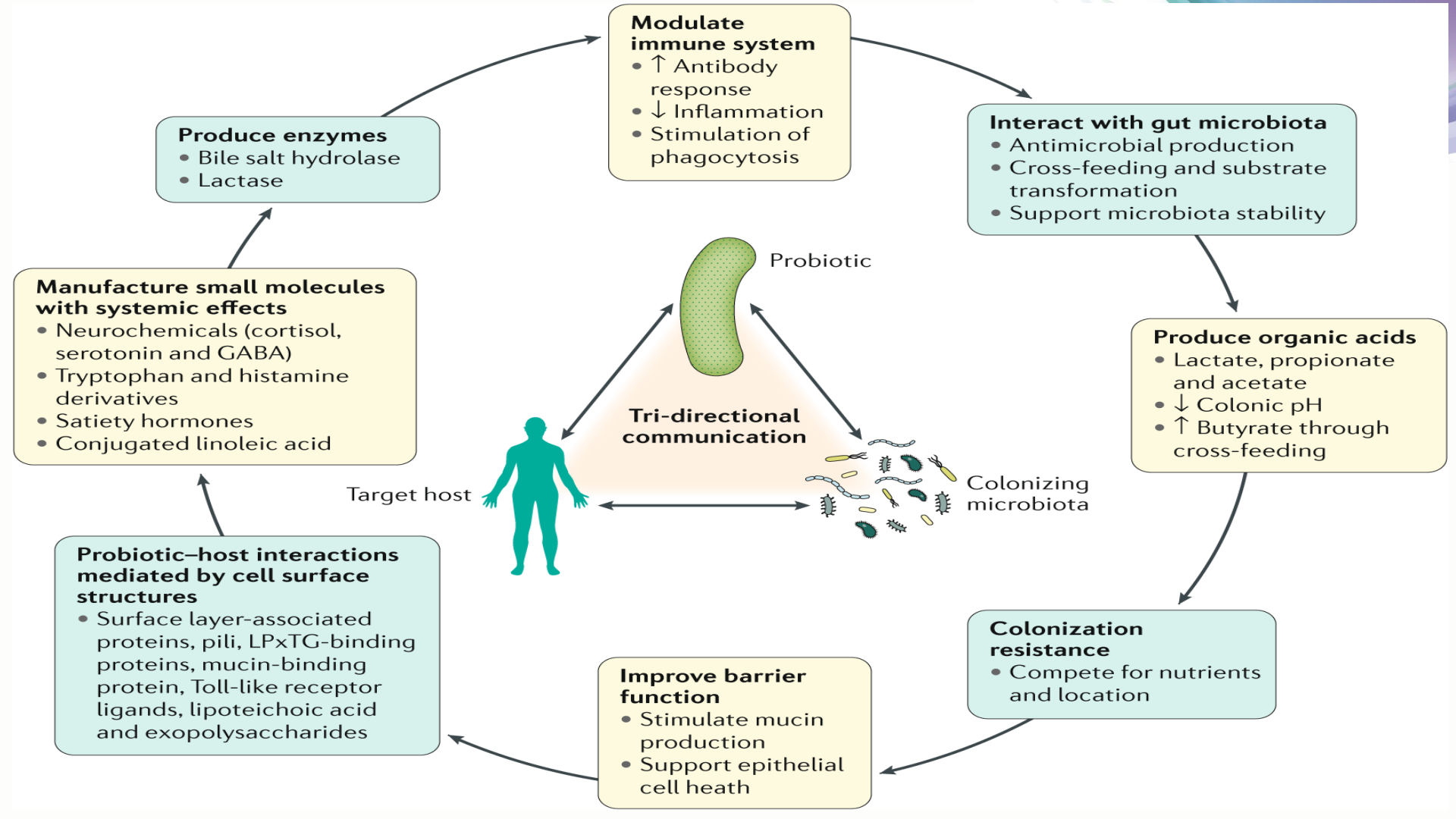
Breastmilk is the ideal way to nourish an infant, and it
the mother and the infant in the

Nutritional

Provides a critical foundation for the infant microbiome establishment and maturation

Immunologic

Maternity by Pablo Picasso, 1904/5


Modulate immune system
• ↑ Antibody response
• ↓ Inflammation
• Stimulation of phagocytosis
Interact with gut microbiota
• Antimicrobial production
• Cross-feeding and substrate transformation
• Support microbiota stability
Produce organic acids
• Lactate, propionate and acetate
• ↓ Colonic pH
• ↑ Butyrate through cross-feeding
Colonization resistance
• Compete for nutrients and location
Improve barrier function
• Stimulate mucin production
• Support epithelial cell heath
Probiotic–host interactions mediated by cell surface structures
• Surface layer-associated proteins, pili, LPxTG-binding proteins, mucin-binding protein, Toll-like receptor ligands, lipoteichoic acid and exopolysaccharides
Manufacture small molecules with systemic effects
• Neurochemicals (cortisol, serotonin and GABA)
• Tryptophan and histamine derivatives
• Satiety hormones
• Conjugated linoleic acid
Produce enzymes
• Bile salt hydrolase
• Lactase
Probiotic
Tri-directional communication
Target host
Colonizing microbiota

Clinical Gastroenterology and Hepatology 2019;17:809–817

NARRATIVE REVIEWS

Fasiha Kanwal, Section Editor

The Unregulated Probiotic Market

Claudio de Simone

University of L'Aquila, L'Aquila, Italy

No head-to-head clinical trials comparing one probiotic to another!

BACKGROUND & AIMS: This narrative review provides an overview of the current regulation of probiotics, with a focus on those used for the dietary management of medical conditions (Medical Foods).

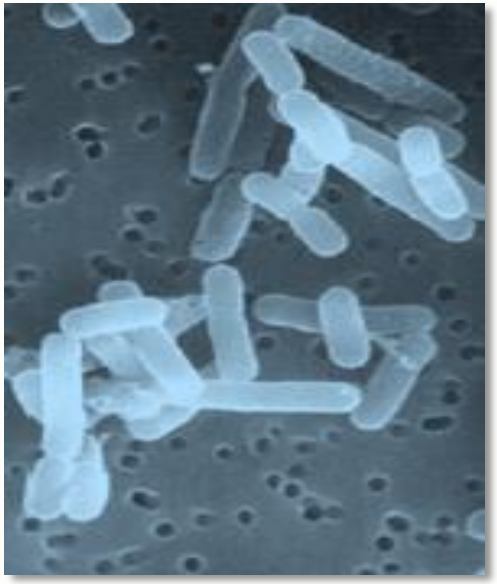
FINDINGS: The probiotic market has grown rapidly, both for foods and supplements intended to enhance wellness in healthy individuals, and for preparations for the dietary management of disease. Regulation of probiotics varies between regions. Unless they make specific disease-related health claims, probiotics are regulated as food supplements and regulation is focused on the legitimacy of any claims, rather than efficacy, safety and quality. Many properties of probiotics are strain-specific, and safety and efficacy findings associated to specific formulations should not be generalized to other probiotic products. Manufacturing processes, conditions and ingredients are important determinants of product characteristics and changes to manufacturing are likely to give rise to a product not identical to the "original" in efficacy and safety if proper measures and controls are not taken. Current trademark law and the lack of stringent regulation of probiotic manufacturing mean that the trademark owner can commercialize any formulation under the same brand, even if significantly different from the original. These regulatory deficits may have serious consequences for patients where probiotics are used as part of clinical guideline-recommended management of serious conditions such as inflammatory bowel diseases, and may make doctors liable for prescribing a formulation not previously tested for safety and efficacy.

CONCLUSIONS: Current regulation of probiotics is inadequate to protect consumers and doctors, especially when probiotics are aimed at the dietary management of serious conditions.

Keywords: Probiotics; Regulation; Manufacturing; Inflammatory Bowel Disease.

Lactobacillus reuteri

- ***L. reuteri*** **isolated from human breastmilk**
- **Most relevant areas of clinical research showing positive results:**
  - **Reduced infant colic and crying**
  - **Balanced microbiota**
  - **Reduced frequency of spit-ups**
  - **Improved GI motility**
  - **Reduced intensity of abdominal pain**
  - **Regulated bowel movements**
  - **GRAS status in term infant formula from day 1**



L. reuteri
Strain ATCC55730, DSM 17938

Nomenclature - *B. lactis* also: *B. animalis* sub-species *lactis, B. bifidum*

L. reuteri

- **Most studied probiotic in functional GI disorders**
- **Balances the microbiota**
- **Supports a healthy digestive tract and immune system**
- **Helps reduce occasional digestive upset**

Prophylactic use of probiotics for gastrointestinal disorders in children

Celine Perceval, Hania Szajewska, Flavia Indrio, Zvi Weizman, Yvan Vandenplas

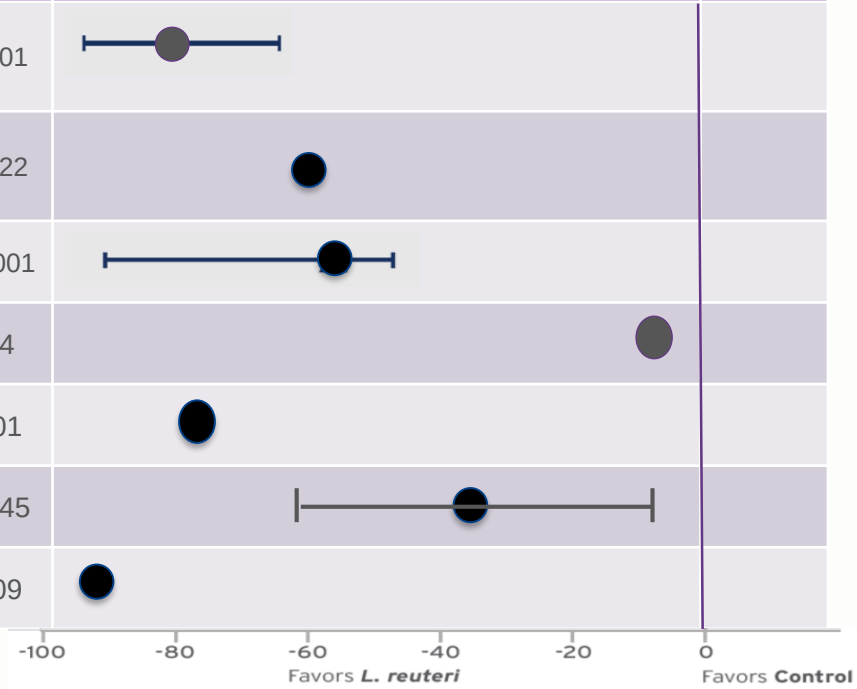
The gastrointestinal microbiome is a hot topic in clinical research. Beneficial effects of selected probiotics in the prevention of gastrointestinal disorders are mainly restricted to acute gastroenteritis, antibiotic-associated diarrhoea, infantile colic, and necrotising enterocolitis. However, no broad consensus exists to recommend the use of probiotics in the prevention of these conditions, mainly because of the different design of the studies done so far, resulting in little evidence for specific strains, dosages, and indications. More well designed studies are needed before recommendations can be proposed. At this stage, the evidence is insufficient to recommend the routine use of probiotics in infants and children for the prevention of gastrointestinal disorders.

Lancet Child Adolesc Health 2019
Published Online
July 3, 2019
http://dx.doi.org/10.1016/S2352-4642(19)30182-8

KidZ Health Castle, Universitair Ziekenhuis Brussel, Vrije Universiteit Brussel, Brussels,

L. reuteri Supplementation Reduced Crying Time In Colicky Infants In Multiple Clinical Studies

	Crying time min/day				
Source, Year	**L. reuteri**	**Control**	**Difference at day 21 (95 % CI)**	**P=**	
Savino et al, 2007	74	154	-80 (-95 to -60)	0.001	
Savino et al, 2010	35	90	-55* (N/A)	0.022	
Szajewska et al, 2013	75	128	-53 (-83 to -45)	0.0001	
Sung et al, 2014	56	63	-7*^ (N/A)	0.4	
Mi et al, 2015	82#	137#	-82# (N/A)	0.01	
Chau et al, 2015	60	102	-42 (-74 to -10)	0.045	
Savino et al. 2018	95#	188#	-93* (NA)	.009	



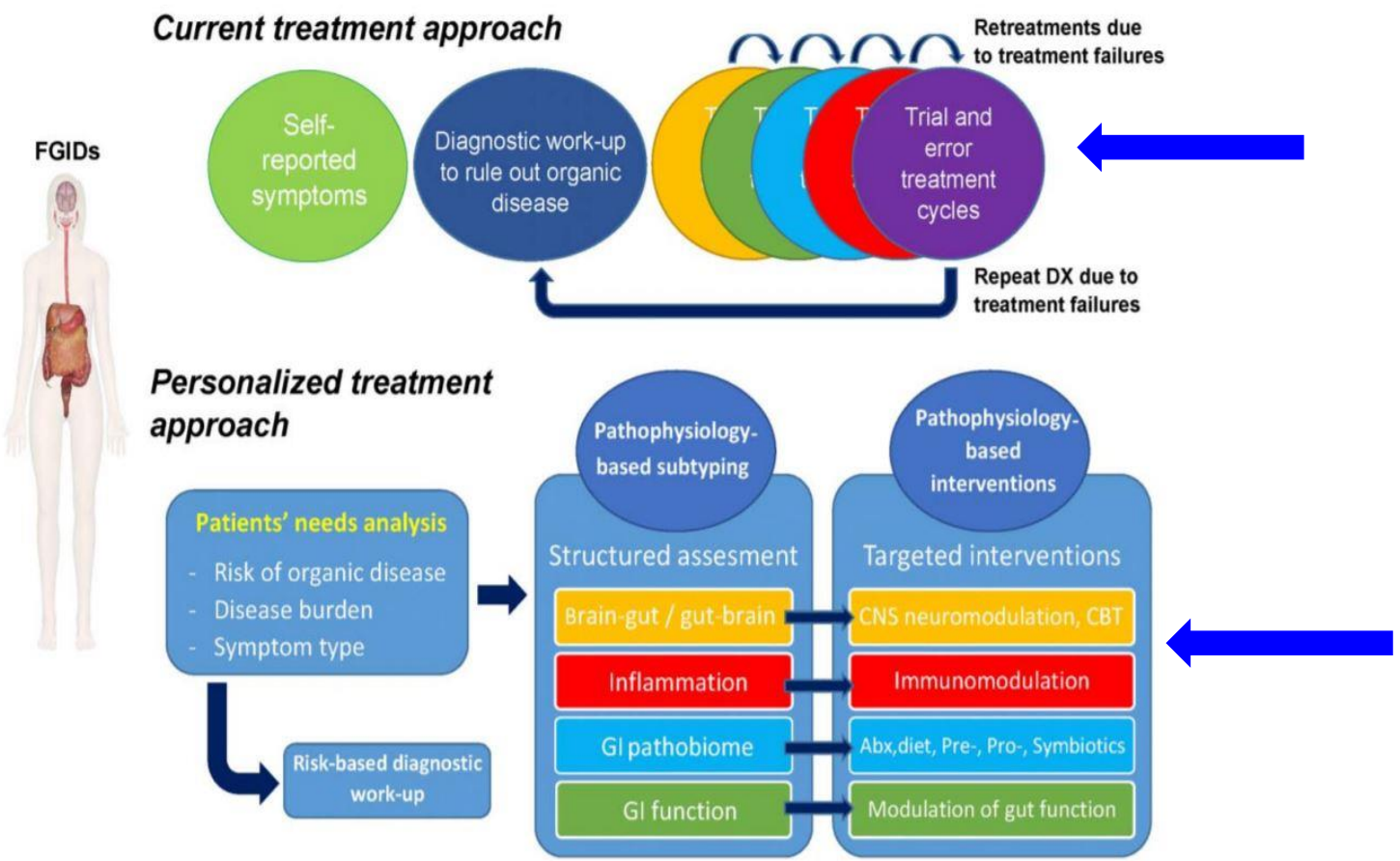


Figure 4. Current "trial and error" approach to diagnosing and treating unexplained. FGIDs (top) vs the envisioned future personalized, evidence-based approach. CBT, cognitive behavioral therapy; CNS, central nervous system; Dx, diagnostic; FGIDs, functional GI disorders, GI, gastrointestinal.

NJ Talley Am J Gastroenterol 2020;115:41-48

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Editorial

Eat Bacteria to Cure Mental Illness; The New Era "Psychobiotics" vs the Current Era Psychotropics

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