The Gut Microbiome and Inflammation

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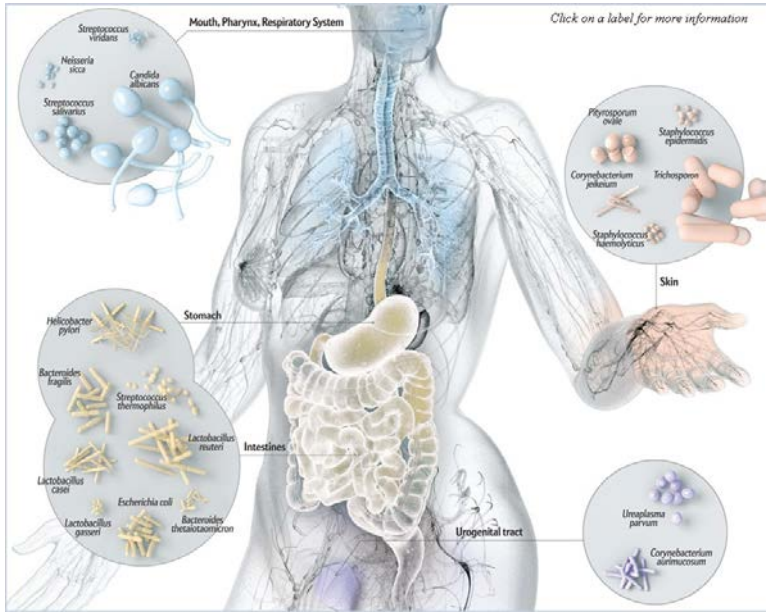
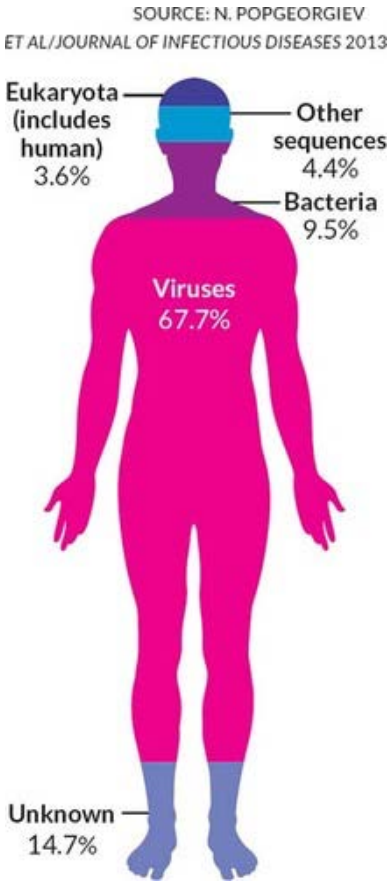
What is the Microbiome

- Collective genomes of **microbial flora** harbored by humans
- Microflora is the community of microorganisms, including algae, fungi, and bacteria that live in or on another living organism or in a particular habitat

The Microbiome

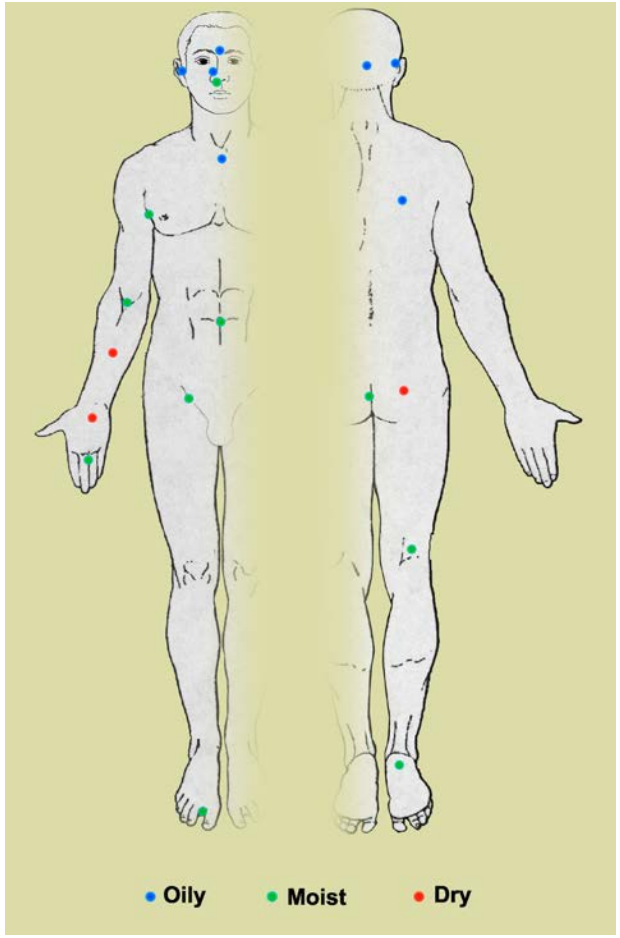


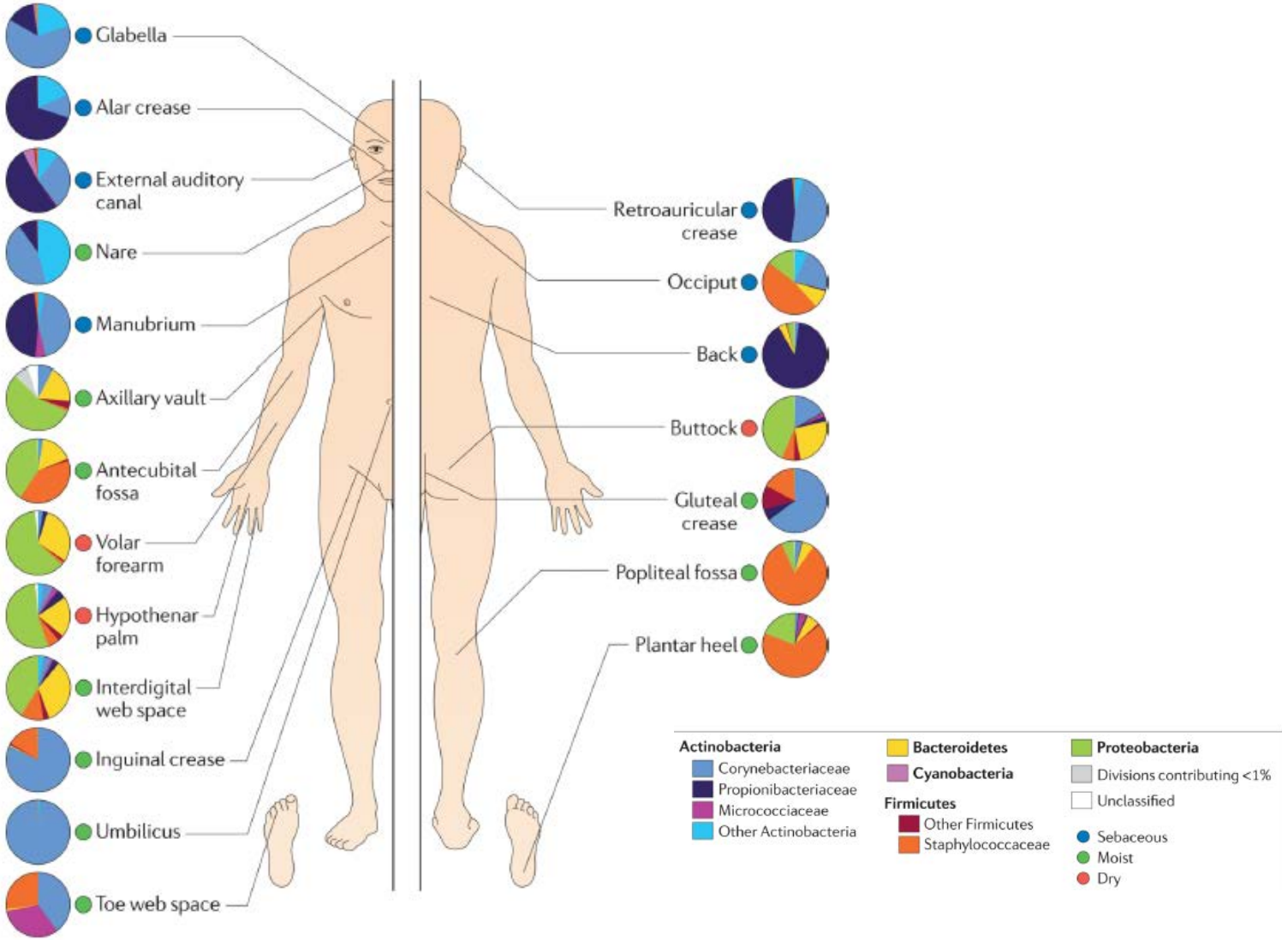


- The ratio of the amount of microbes to cells in our bodies is 10:1
- Most identified DNA sequences floating in our blood plasma belong to viruses
- We are more them than we are us

http://linxc10.wixsite.com/microbes/the-microbiome

Depiction of the human body and bacteria that predominate





Grice and Serge 2011

Ecosystem: Skin histology with microorganisms

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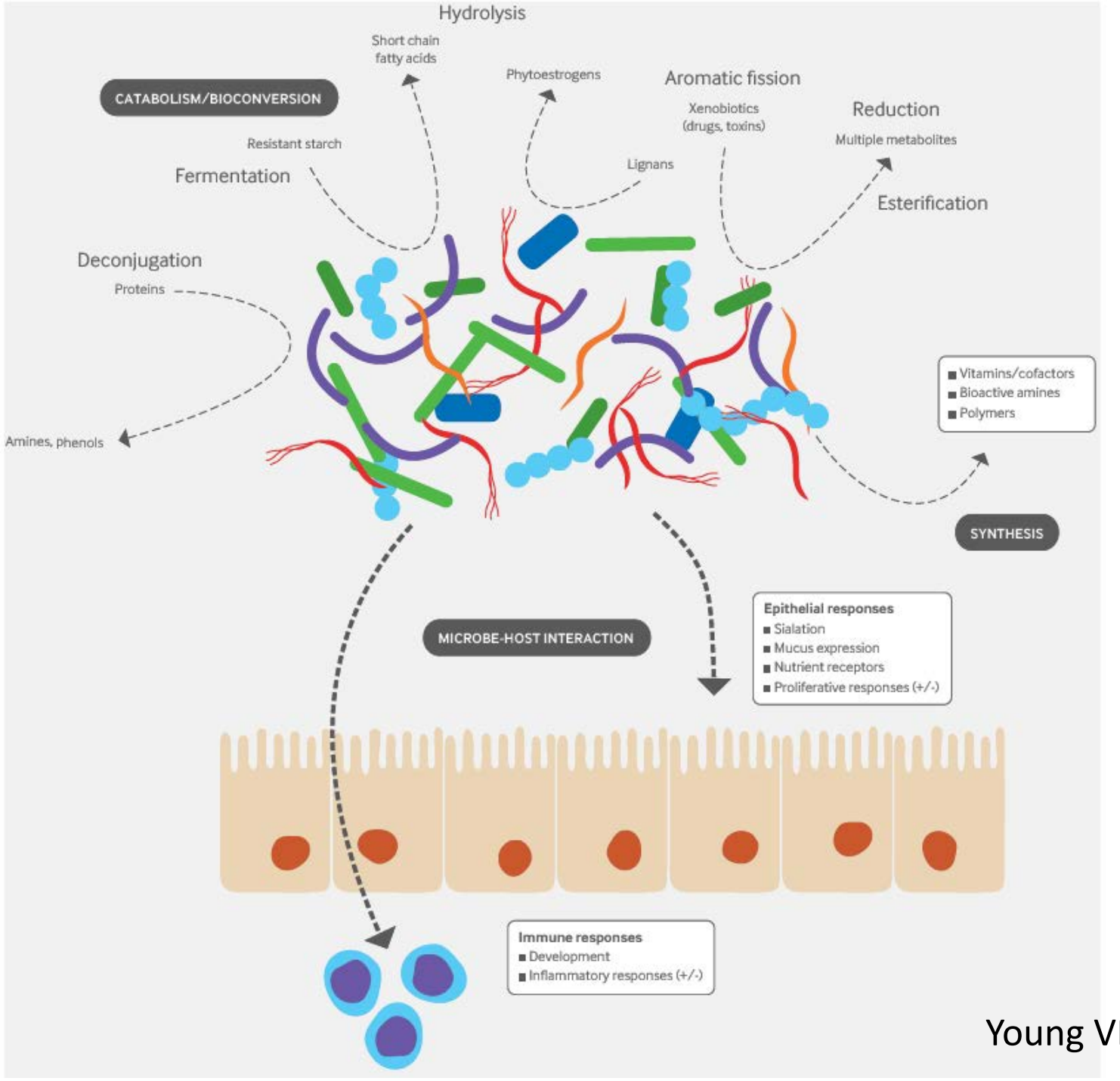
Grice and Serge 2011

Functions of microbiota



Young VB 2017

Prebiotic

Nutrients that favor the growth and predominance of beneficial microbes and their inherent functions. Most of these have been carbohydrates that cannot be broken down by the human digestive machinery but are metabolized by specific members of the microbiota

Probiotic

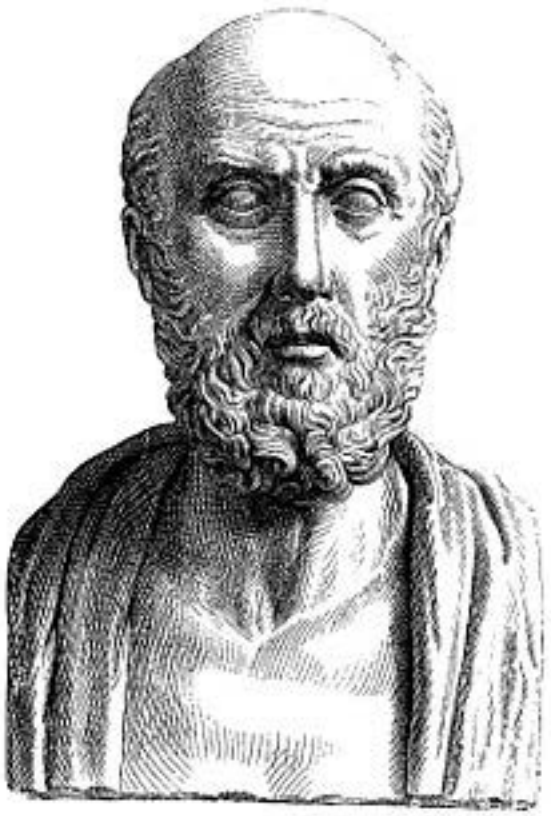
Commonly defined as “live micro-organisms which, when administered in adequate amounts, confer a health benefit on the host.” In the past, these were often organisms that were first recognized in fermented food products. Currently, there is interest in identifying potential probiotics that are members of the microbiota of healthy people

Young VB 2017

All diseases begin in the gut

The bacterial cells harbored within the human gastrointestinal tract (GIT) outnumber the host's cells by a factor of 10 and the genes encoded by the bacteria resident within the GIT outnumber their host's genes by more than 100 times.

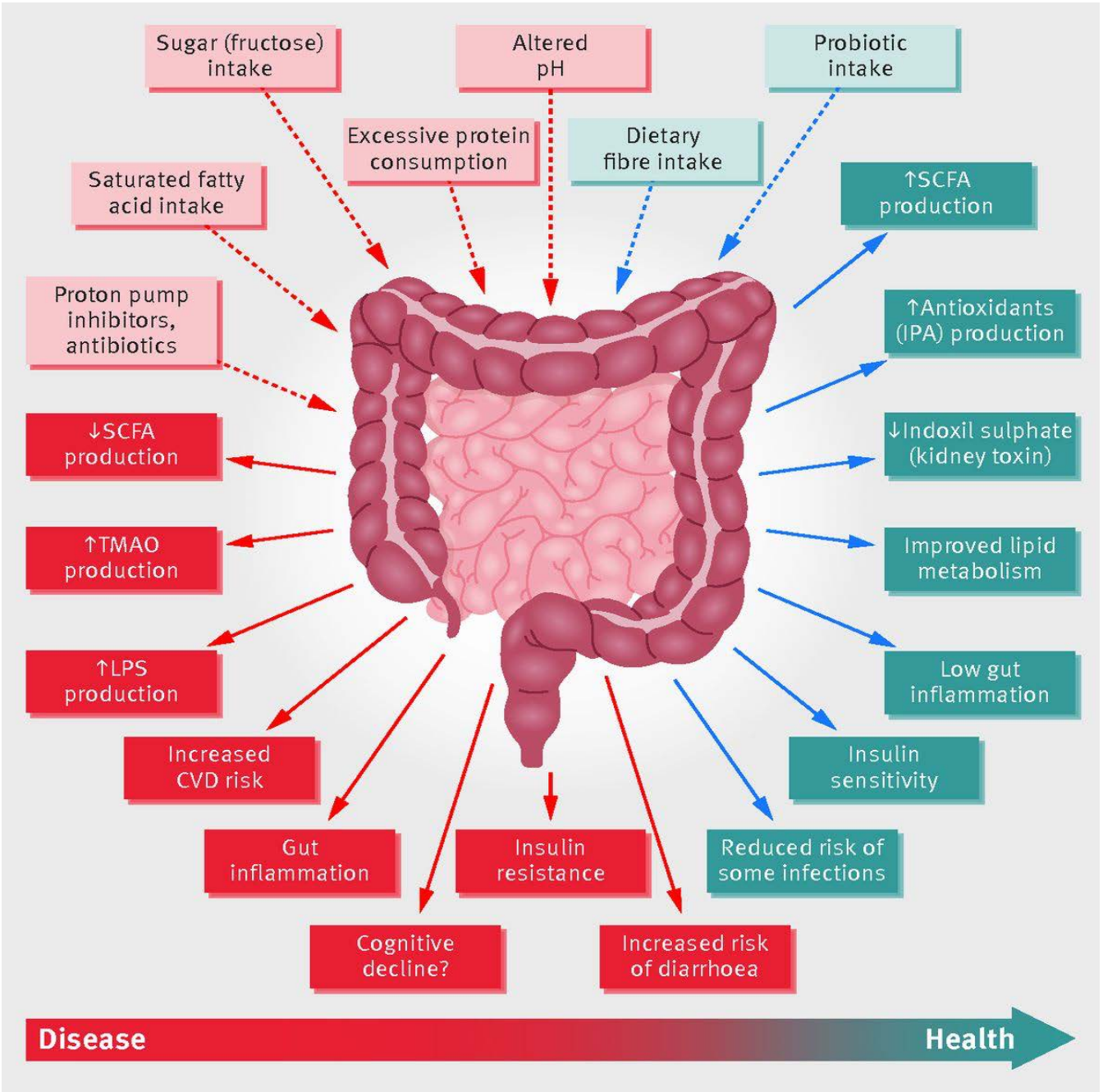
Approximately 100 trillion micro-organisms in the gut



Hippocrates
The Father of Western Medicine
460 BC-370 BC

Bull and Plummer 2014

Role of the gut microbiota in health and disease



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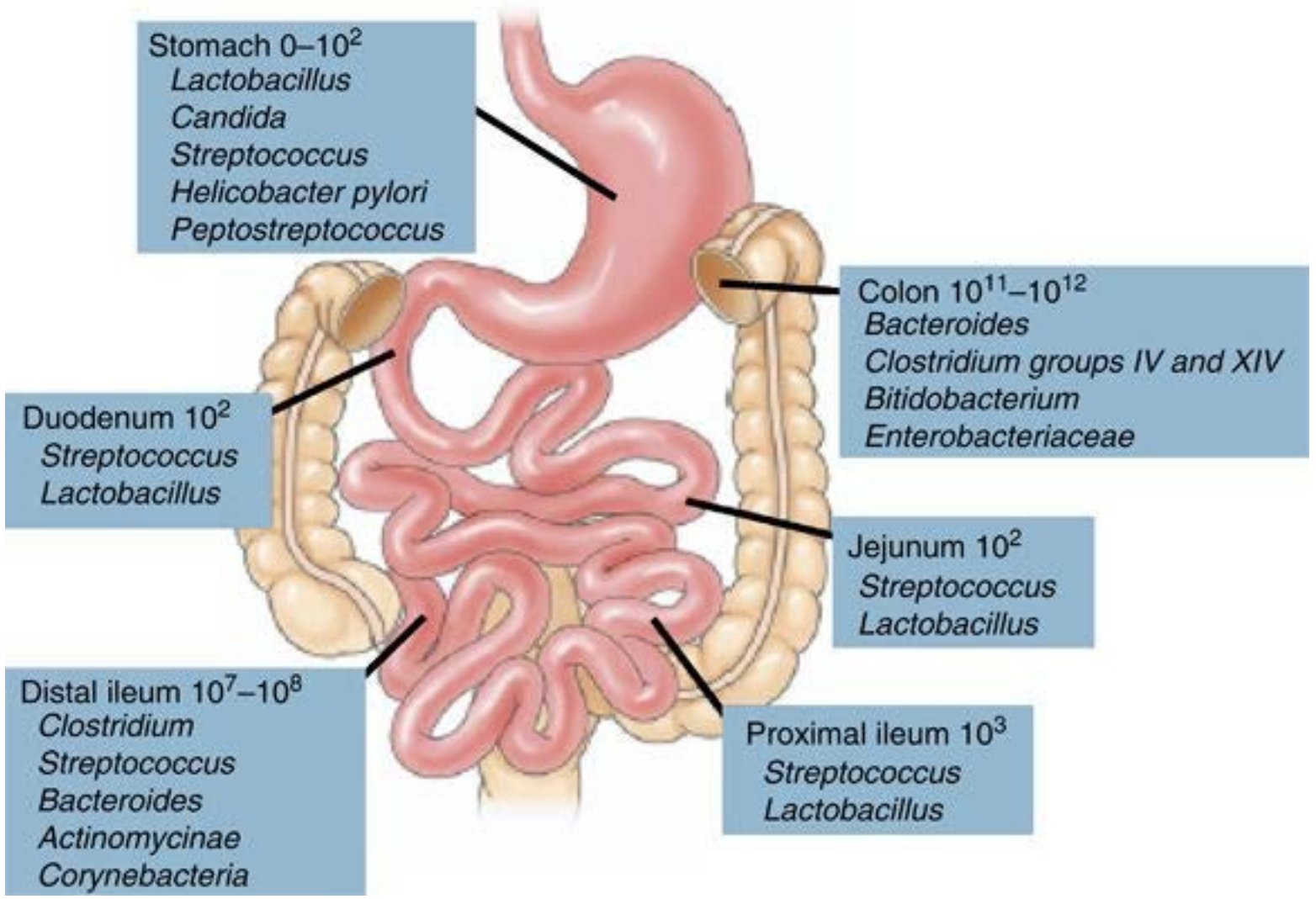
Composition and luminal numbers of dominant microbial species in the human gastrointestinal tract.



Sartor and Mazmanian 2012

The gut microbiota and diseases

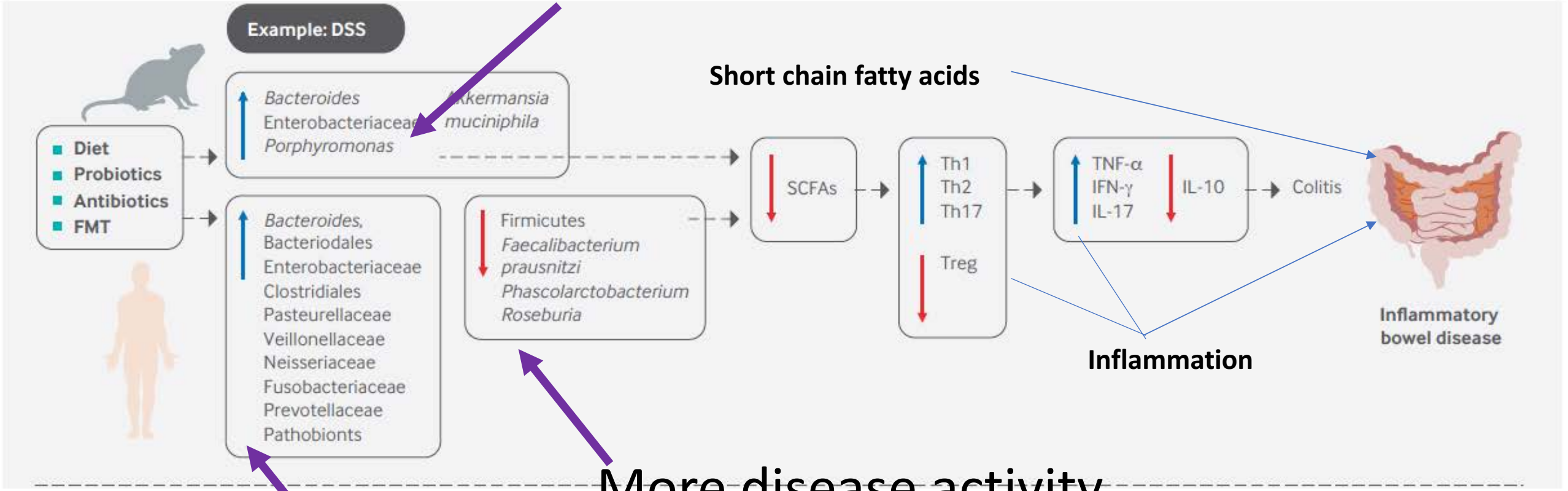
- Lower bacterial diversity has been reproducibly observed in people with inflammatory bowel disease, psoriatic arthritis, type 1 diabetes, atopic eczema, coeliac disease, **obesity,** type 2 diabetes, and arterial stiffness, than in healthy controls.

- Germ-free mice that receive faecal microbes from obese humans gain more weight than mice that receive microbes from healthy weight humans

IBD: Ulcerative Colitis and Crohn's disease

Colitis is reduced or absent in germ free animals and those treated with antibiotics

More inflammation



More disease activity

Shift in composition-perpetuation of the disease

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Arthritis is reduced or absent in germ free animals

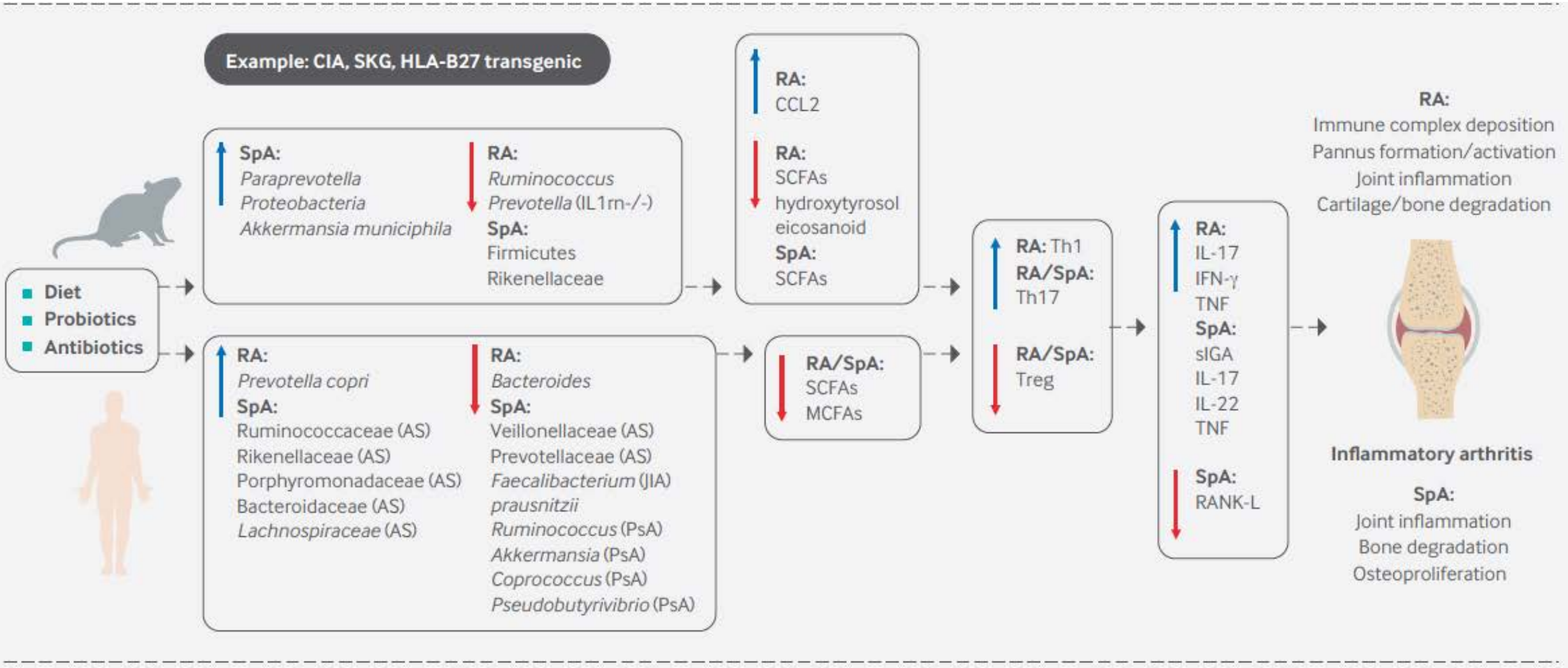

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Table 1 | Examples of foods, nutrients, and dietary patterns that influence human health linked to their effect on the gut microbiota

Dietary element	Effect on gut microbiome	Effect on health outcomes mediated by gut microbiome	Human observational studies	Human interventional studies
Low FODMAP diet	Low FODMAP diet increased Actinobacteria; high FODMAP diet decreased abundance of bacteria involved in gas consumption[58]	Reduced symptoms of irritable bowel syndrome[56]	Yes	Yes
Cheese	Increased *Bifidobacteria*,[97 98] which are known for their positive health benefits to their host through their metabolic activities.[99] Decrease in *Bacteroides* and *Clostridia*, some strains of which are associated with intestinal infections[98]	Potential protection against pathogens.[100] Increased production of SCFA and reduced production of TMAO[99]	Yes	Yes
Fibre and prebiotics	Increased microbiota diversity and SCFA production[22 101 102]	Reduced type 2 diabetes[22] and cardiovascular disease[103]	Yes	Yes
Artificial sweeteners	Overgrowth of Proteobacteria and *Escherichia coli*.[104] *Bacteroides*, *Clostridia*, and total aerobic bacteria were significantly lower, and faecal pH was significantly higher[47]	Induced glucose intolerance[105]	No	No
Polyphenols (eg, from tea, coffee, berries, and vegetables such as artichokes, olives, and asparagus)	Increased intestinal barrier protectors (*Bifidobacteria* and *Lactobacillus*), butyrate producing bacteria (*Faecalibacterium prausnitzii* and *Roseburia*) and *Bacteroides vulgatus* and *Akkermansia muciniphila*.[107] Decreased lipopolysaccharide producers (*E coli* and *Enterobacter cloacae*)[106]	Gut micro-organisms alter polyphenol bioavailability resulting in reduction of metabolic syndrome markers and cardiovascular risk markers[108]	Yes	Yes
Vegan	Very modest differences in composition and diversity in humans and strong differences in metabolomic profile compared with omnivore diet in humans[50]	Some studies show benefit of vegetarian over omnivore diet,[109] others fail to find a difference[110]	Yes	Yes

FODMAP=fermentable oligosaccharides, disaccharides, monosaccharides and polyols; SCFA=small chain fatty acids; TMAO= trimethylamine N-oxide

Valdes et al., 2018

Table 2 | Summary of systematic reviews analysing the role of probiotics on clinical outcomes

Outcome	Reference	No of studies/ participants	Evidence of benefit?	Results/conclusions
Clostridium difficile associated diarrhoea in adults and children	Goldenberg et al (2017)[111]	39/9955	Yes	Moderate quality evidence that probiotics are safe and effective for preventing *C difficile* associated diarrhoea. (RR 0.30, 95% CI 0.21 to 0.42)
Necrotising enterocolitis	Al Faleh et al (2014)[112] Rees et al (2017)[113]	17/5338	Yes	Enteral supplementation of probiotics prevents severe necrotising enterocolitis (RR 0.43, 95%CI 0.33 to 0.56) and all cause mortality in preterm infants (RR 0.65, 95% CI 0.25 to 0.81)
Antibiotic associated diarrhoea in children	Goldenberg et al (2015)[114]	26/3898	Yes	Moderate evidence of a fall in the incidence of antibiotic associated diarrhoea in the probiotic *v* control group (RR 0.46, 95% CI 0.35 to 0.61; I^2=55%, 3898 participants)
Probiotics for preventing acute upper respiratory tract infections	Hao et al (2015)[115]	12/3720	Yes	Probiotics were better than placebo in reducing the number of participants experiencing episodes of acute upper respiratory tract infections, the mean duration of an episode, antibiotic use, and related school absence (12 trials, 3720 participants including children, adults, and older people)
Urinary tract infections	Schwenger et al (2015)[116]	9/735	No	No significant benefit for probiotics compared with placebo or no treatment
Prevention of asthma and wheeze in infants	Azad et al (2013)[117]	6/1364	No	No evidence to support a protective association between perinatal use of probiotics and doctor diagnosed asthma or childhood wheeze
Prevention of eczema in infants and children	Mansfield et al (2014)	16/2797	Yes	Probiotic supplementation in the first several years of life did have a significant impact on development of eczema (RR 0.74, 95% CI 0.67 to 0.82)

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Prevention of invasive fungal infections in preterm neonates	Agrawal et al (2015)[119]	19/4912	Unclear	Probiotic supplementation reduced the risk of invasive fungal infections (RR 0.50, 95% CI 0.34 to 0.73, I^2=39%) but there was high heterogeneity between studies. Analysis after excluding the study with a high baseline incidence (75%) showed that probiotic supplementation had no significant benefits (RR 0.89, 95% CI 0.44 to 1.78)
Prevention of nosocomial infections	Manzanares et al (2015)[120]	30/2972	Yes	Probiotics were associated with a significant reduction in infections (RR 0.80, 95%CI 0.68 to 0.95, P=0.009; I^2=36%, P=0.09). A significant reduction in the incidence of ventilator associated pneumonia was found (RR 0.74, 95% CI 0.61 to 0. 90, P=0.002; I^2=19%)
Treatment of rotavirus diarrhoea in infants and children	Ahmadi et al (2015)[121]	14/1149	Yes	Probiotic supplementation resulted in a mean difference of −0.41 (CI 95% −0.56 to −0.25; P<0.001) in the duration of diarrhoea. Probiotics exert positive effect on reducing the duration of acute rotavirus diarrhoea compared with control
Prevention and treatment of Crohn's disease and ulcerative colitis	Saez Lara et al (2015)[122]	14/821 ulcerative colitis 8/374 Crohn's disease	Yes	The use of probiotics and/or synbiotics has positive effects in the treatment and maintenance of ulcerative colitis, whereas in Crohn's disease clear effectiveness has only been shown for synbiotics (no meta- analysis was performed)
Pulmonary exacerbations in children with cystic fibrosis	Ananathan et al (2016)[123]	9/275	Yes	Significant reduction in the rate of pulmonary exacerbation (two parallel group randomised controlled trials and one crossover trial: RR 0.25, 95% CI 0.15 to 0.41; P< 0.00001)
Type 2 diabetes (fasting glucose, glycated haemoglobin test)	Akbari et al (2016)[124]	13/805	Yes	Probiotics significantly reduced fasting blood glucose compared with placebo (8 studies; standardised mean difference −1.583; 95% CI −4.18 to 4.18; P=0.000). Significant reduction in HbA_{1c} was also seen (6 studies; SMD −1.779; 95% CI, −2.657 to −0.901; P=0.000)
Type 2 diabetes (insulin resistance, insulin levels)	Zhang et al (2016)[125]	7/425	Yes	Probiotic therapy significantly decreased homeostasis model assessment of insulin resistance (HOMA-IR) and insulin concentration (WMD: −1.08, 95% CI −1.88 to −0.28; and weighted mean difference −1.35mIU/L, 95% CI −2.38 to −0.31, respectively

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Necrotising enterocolitis in pre-term neonates with focus on *Lactobacillus reuteri*	Athalye-Jape et al (2016)[126]	6/1778	Yes	Probiotic reduced duration of hospitalisation (mean difference = −10.77 days, 95% CI −13.67 to −7.86; in 3 randomised controlled trials), and late onset sepsis (RR 0.66; 95% CI, 0.52 to 0.83; 4 RCTs) were reduced in the
Reduction of serum concentration of C reactive protein	Mazidi et al (2017)[127]	19/935	Yes	Significant reduction in serum C reactive protein after probiotic administration with a WMD −1.35 mg/L, (95% CI −2.15 to −0.55, I^2 65.1%)
Cardiovascular risk factors in patients with type 2 diabetes	Hendijani et al (2017)[128]	11/641	Yes	Probiotic consumption significantly decreased systolic blood pressure (−3.28 mm Hg; 95% CI −5.38 to −1.18), diastolic (WMD −2.13 mm Hg; 95% CI −4.5 to 0.24), low density lipoprotein cholesterol (WMD 8.32 mg/dL; 95% CI −15.24 to −1.4), total cholesterol (WMD −12.19 mg/dL; 95% CI −17.62 to −6.75) and triglycerides(WMD −24.48 mg/dL; 95% CI −33.77 to −11.18) compared with placebo
Reduction of total cholesterol and low density lipoprotein cholesterol	Wu et al (2017)[129]	15/976	Yes	*Lactobacillus* consumption significantly reduced total cholesterol by 0.26 mmol/L (95% CI −0.40 to −0.12) and LDL-C by 0.23 mmol/L (95% CI, −0.36 to −0.10)
Depressive symptoms	Wallace and Milev (2017)[79,130]	6/1080	Yes	No quantitative analysis was performed. Most studies found positive results, and the authors conclude that compelling evidence shows that probiotics alleviate depressive symptoms
Vulvovaginal candidiasis in non-pregnant women	Xie et al (2018)[131]	10/1656	Yes	Probiotics increased the rate of short term clinical cure (RR 1.14, 95% CI 1.05 to 1.24, low quality evidence) and mycological cure (RR 1.06, 95% CI 1.02 to 1.10, low quality evidence) and decreased relapse rate at one month (RR 0.34, 95% CI 0.17 to 0.68, low quality evidence)
Chronic periodontitis	Ikram et al (2018)[132]	7/220	Yes	The overall mean difference for gaining clinical attachment level gain between probiotics and placebo was significant (weighted mean difference 1.41, 95% CI 0.15 to 2.67, P=0.028)

RR=risk ratio, SBP systolic blood pressure, DBP= diastolic blood pressure, TC= total cholesterol, TG=serum triglycerides, SMD=standardised mean difference, WMD=weighted mean difference' CI=confidence interval

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Consensus and uncertainties

What we know

- Probiotic supplementation has several beneficial effects on human health
- The microbes in our gut influence and human energy metabolism[22-45]
- Diet and medication have a strong influence on gut microbiota composition
- Microbiota composition influences response to chemotherapy and immunotherapy[96]
- Microbiome composition defines glucose response to foods and can be used to personalise diet[94]
- Dietary fibre intake influences gut microbiota composition and is related to better health[86 87 104]

What we don't know

- Are natural probiotics in food better than probiotic supplements? Should we take them preventively?
- Can microbes influence food choices and appetite?
- Do low dose antibiotics in food affect human health?
- What is the effect of pesticides in food on the gut microbiome? Is organic food better for the gut microbiota?
- Should all new drugs and food chemicals be tested on the gut microbiota?

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Potential strategies for therapeutic microbiome manipulation

Approach	Rational	Example
Antibiotics	Target specific members or groups of the microbiota and suppress them, allowing expansion of desirable species	Small intestinal bacterial overgrowth Hepatic encephalopathy
Bacteriophages	Use naturally occurring bacterial viruses to target specific members of a community that are disruptive or are carrying out pathogenic processes	Pathogen targeted therapy to spare the microbiota from collateral damage
Probiotics (single species)	Replace a presumably missing organism and thus a missing function in the form of an organism	*Sacchromyces boulardii* for prevention of antibiotic associated diarrhea
Multispecies/designer communities	As with single species probiotics, use a collection of organisms to replace a missing function in the microbiome	Feces derived communities, multispecies
Prebiotics	Supply a complex food product (often carbohydrates) that is not digestible by the host to stimulate specific members of the microbiota. The prebiotic is meant to be metabolized by the microbiota to compounds beneficial to the host	Inulin, resistant starch
Synbiotics	Supply a complex of a microbe or microbes along with a prebiotic that is meant to be used by these organisms replace a missing function in a microbiome	
Nutritional therapy	Complete redesign of a diet to promote beneficial microbial communities and function	Low FODMAP diet for IBS. Exclusive enteral nutritional therapy for IBD
Community replacement, "microbiota restoration"	To restore a "deficient" microbiota, harvest a presumably normal microbiota from a healthy person and administer it to a patient	Fecal transplantation

FODMAP=fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; IBS=irritable bowel syndrome; IBD=inflammatory bowel disease.

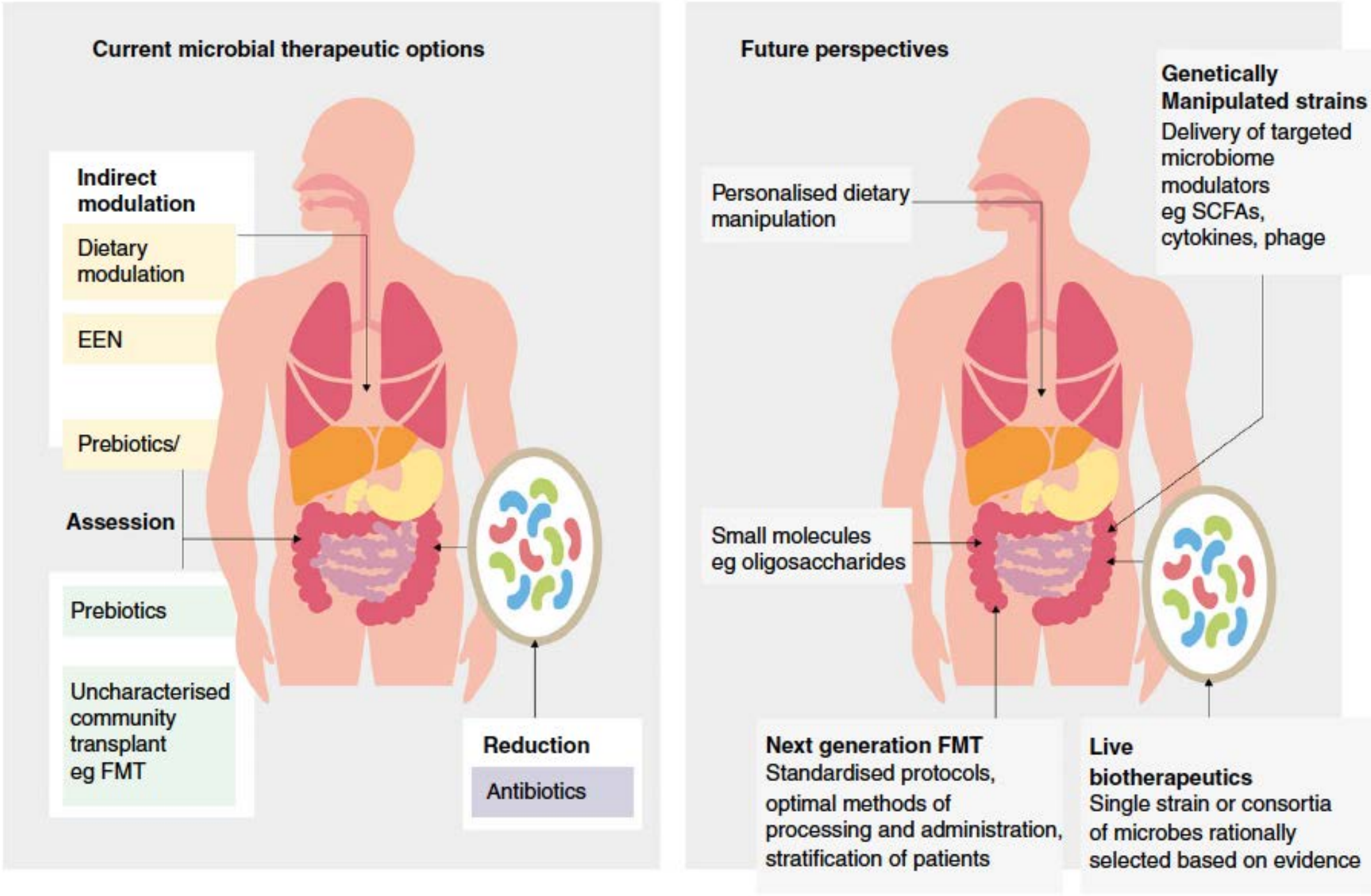
Current microbial therapeutic options
Indirect modulation
Dietary modulation
EEN
Prebiotics/
Assession
Prebiotics
Uncharacterised community transplant eg FMT
Reduction
Antibiotics
Future perspectives
Genetically Manipulated strains
Delivery of targeted microbiome modulators eg SCFAs, cytokines, phage
Personalised dietary manipulation
Small molecules eg oligosaccharides
Next generation FMT
Standardised protocols, optimal methods of processing and administration, stratification of patients
Live biotherapeutics
Single strain or consortia of microbes rationally selected based on evidence

Table 2 | Pipeline on microbiome derived therapeutics in inflammatory bowel disease and systemic autoimmunity

Company	Microbiota product and indication	Development stage	Pharmaceutical partner/s
AvidBiotics	Targeted antibacterial bacteriocins (Avidocin/Purocin)	Preclinical	DuPont Nutrition & Health
CIPAC	Standardized approach to FMT for CDI and IBD (Full-Spectrum Microbiota)	Undisclosed	–
Enterome	Anti-*Escherichia coli* small molecule for IBD (EB-8018; EB110)	Phase I	Takeda, Janssen, Bristol-Myers Squibb, Nestlé
4D Pharma	Therapies from microbiome based molecules for IBS and IBD indication (Blautix; Thetanix)	Phase I	Publicly traded
Rebiotix Inc	Prescreened stool offered to health providers for FMT (microbiota restoration therapy for recurrent CDI; RBX2660)	Phase III (FDA breakthrough therapy designation for CDI); phase I (pediatric UC)	Private
Osel Inc	Single strains of native and genetically engineered bacteria for urogenital and gastrointestinal disease indications (Lactin V; CBM588)	Phase II	Private
Second Genome	Application of microbiome science for discovery of new therapies (eg, IBD; SGM-1019)	Phase I	Janssen, Pfizer, Roche, Monsanto
Seres Health	Therapeutics to catalyze restoration of healthy microbiome in CDI (SER-109) and UC (SER-287)	Phase III (FDA orphan drug designation for SER-109); phase I (SER-287)	Nestlé Health Science, publicly traded
Symbiotix	*Bacteroides fragilis* derived polysaccharide A for IBD and multiple sclerosis	Preclinical	
Vedanta Biosciences	Human microbiome consortia (Clostridia cocktail for IBD/allergy indications; VE-202)	Phase I/II	Janssen

CDI=*Clostridium difficile* infection; FDA=Food and Drug Administration; FMT=fecal microbiota transplant; IBD=inflammatory bowel disease; IBS=irritable bowel syndrome; UC=ulcerative colitis.

Clemente et al., 2018

"THERE ARE MILLIONS OF BACTERIA IN YOUR INTESTINES, ANYWAY. WHAT HARM COULD ONE OR TWO MORE DO?"