Il Microbiota intestinale

nella salute e nella malattia

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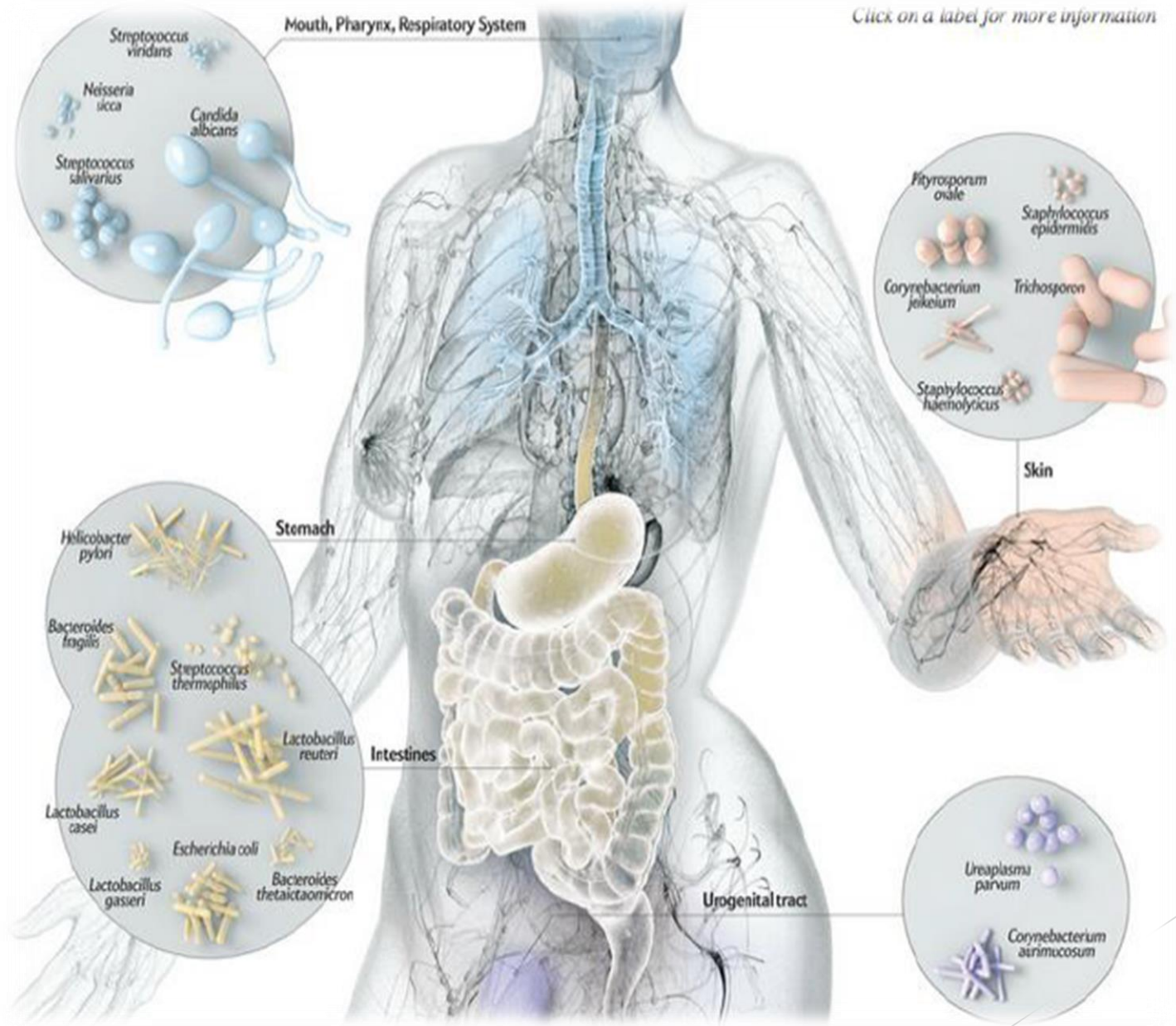
Unità di microbioma umano

Ospedale Pediatrico Bambino Gesù

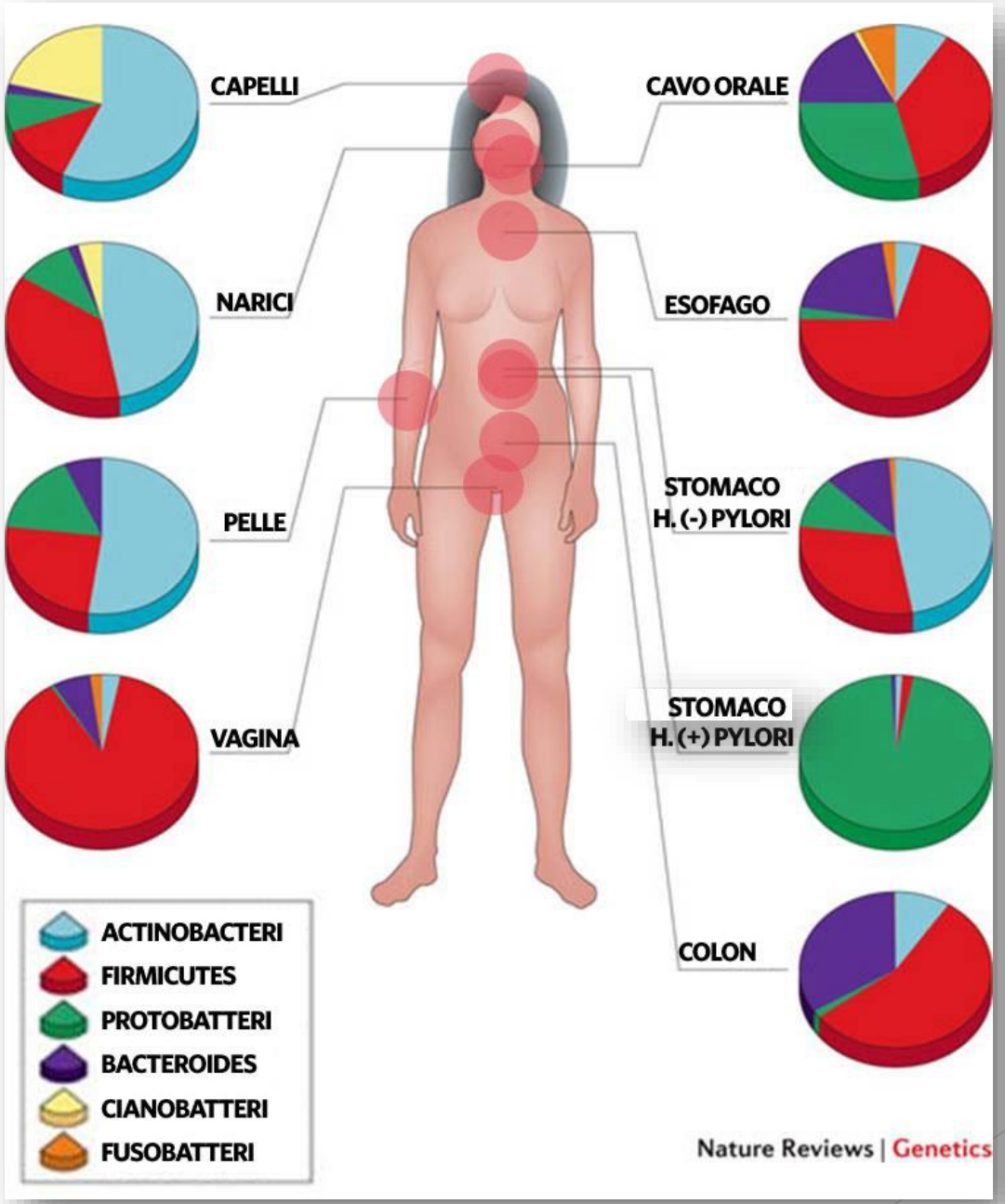
Tutte le malattie hanno origine nell’intestino…

Ippocrate 460 a.C. – 377 a.C.

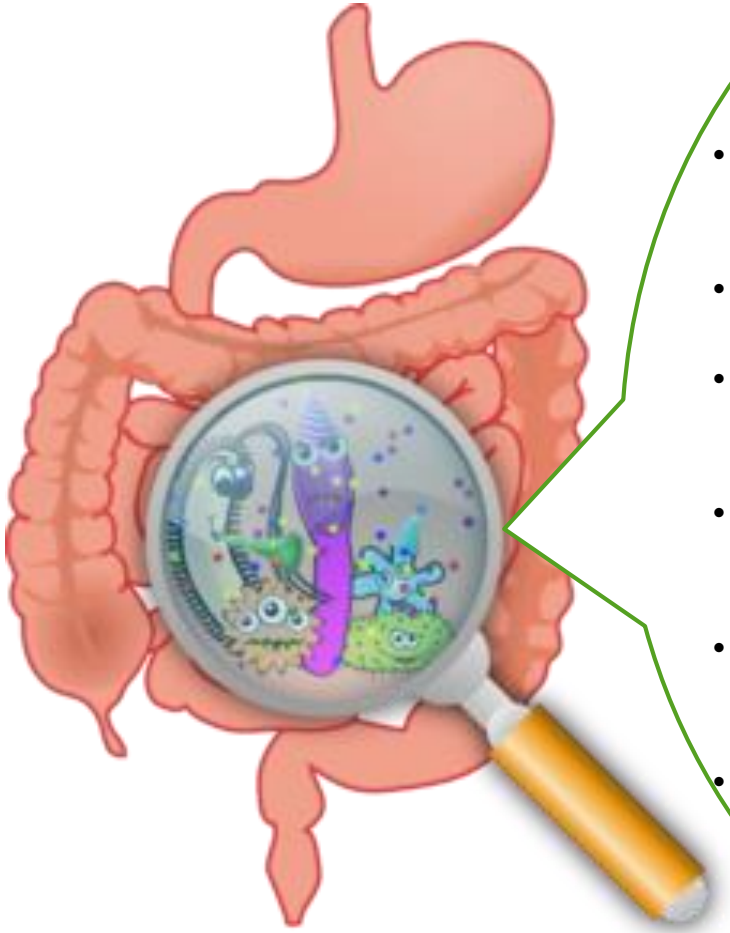
Il microbiota



Il microbiota



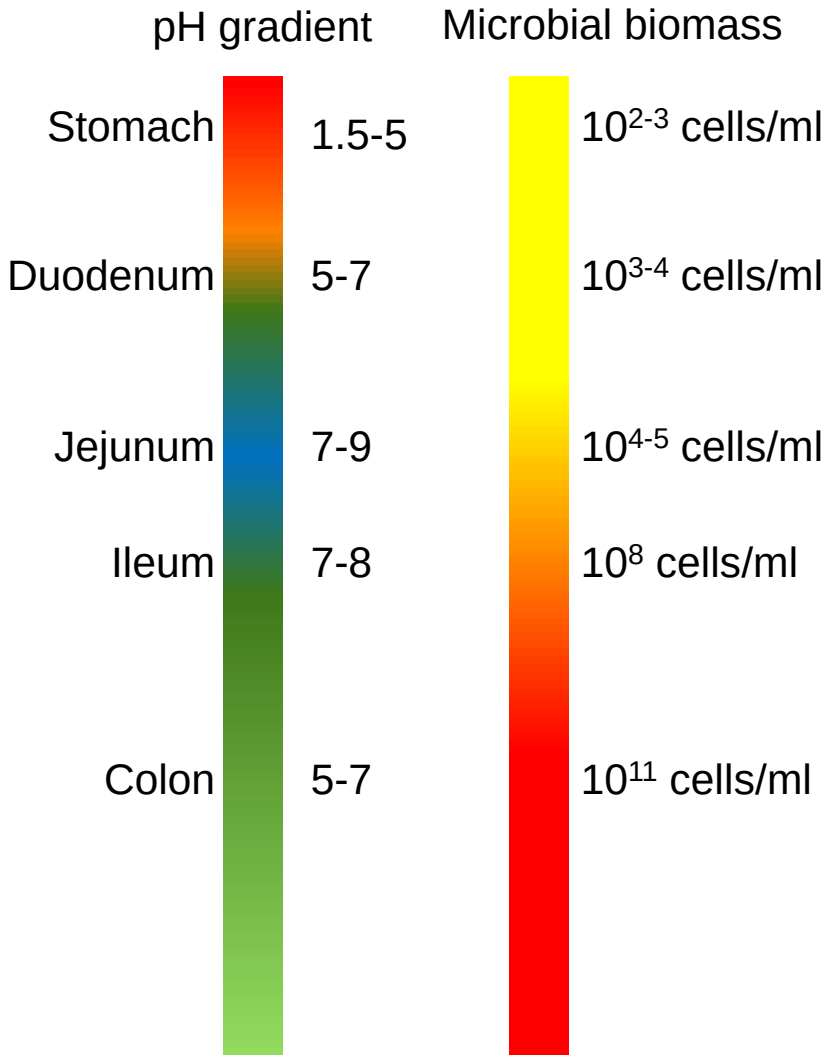
Il microbiota intestinale

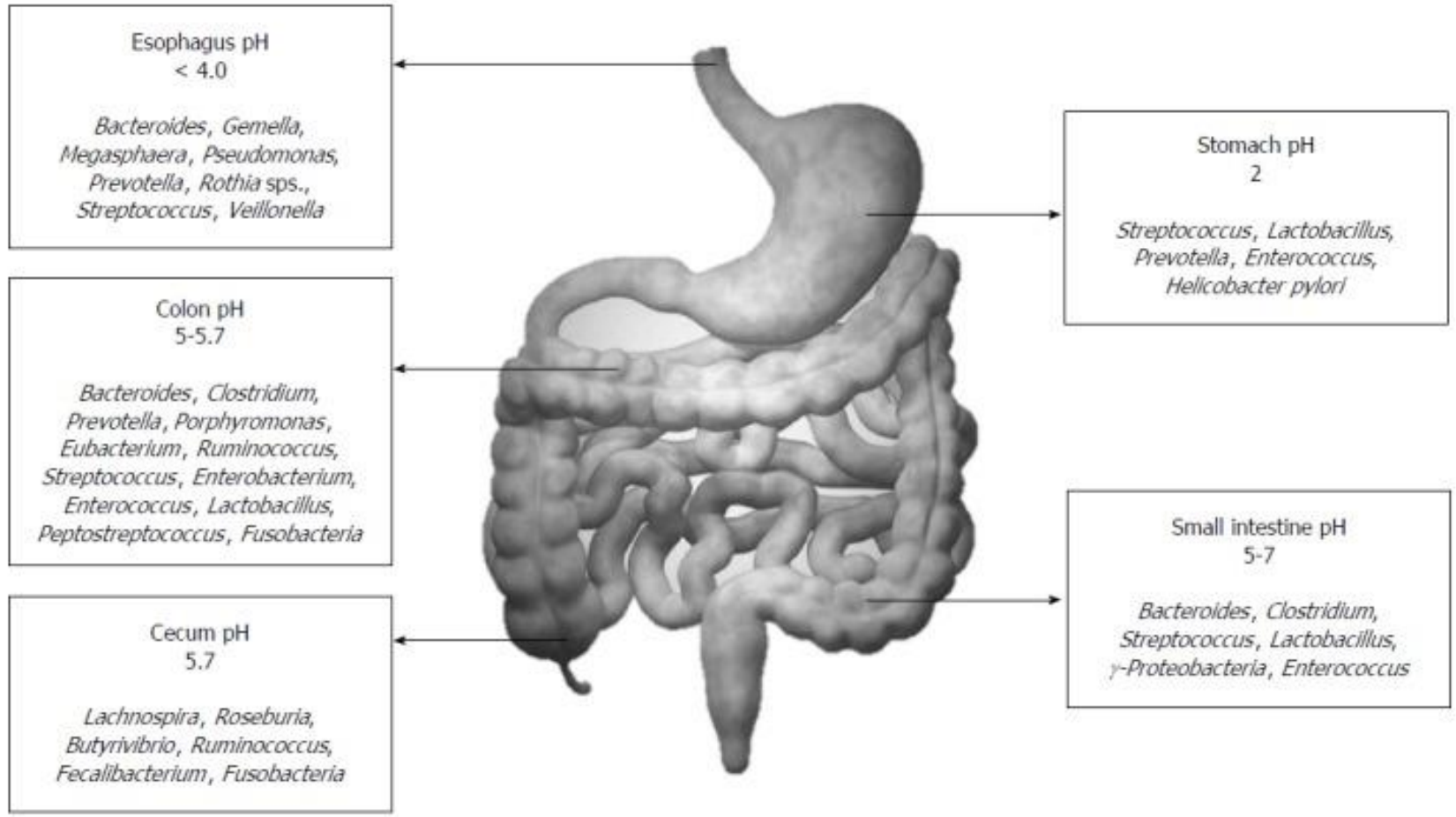


Human gut microbiota is:

- a complex community of 100 trillion archaeal and bacterial cells
- Composed by more than 1,000 bacterial species
- Composed by more than 90% from Firmicutes and Bacteroidetes.
- distinct and highly variable from person to person
- common among individuals (the core gut microbiota and the core microbiome)
- required for the correct functioning of the gut.

Il microbiota intestinale





Major Bacteria Phyla and Genera Predominating in Human Gut Microbiota

Phyla	Representative genera
Firmicutes (60-80%)	– Ruminococcus – Clostridium – Lactobacillus – Enterococcus
Bacteroidetes (20-30%)	– Bacteroides – *Prevotella*
Actinobacteria (< 10%)	– Bifidobacterium
Proteobacteria ((< 1%)	– *Escherichia* – *Enterobacteriaceae*

Fattori che influenzano la composizione del microbiota intestinale

ALLATTAMENTO

MODLITA' DI PARTO

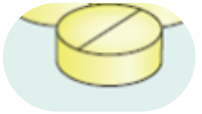
PROVENIENZA GEOGRAFICA

DIETA

ESERCIZIO FISICO

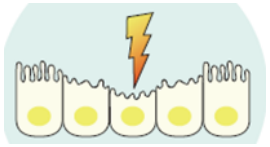
Composizione del microbiota intestinale umano

ANTIBIOTICI



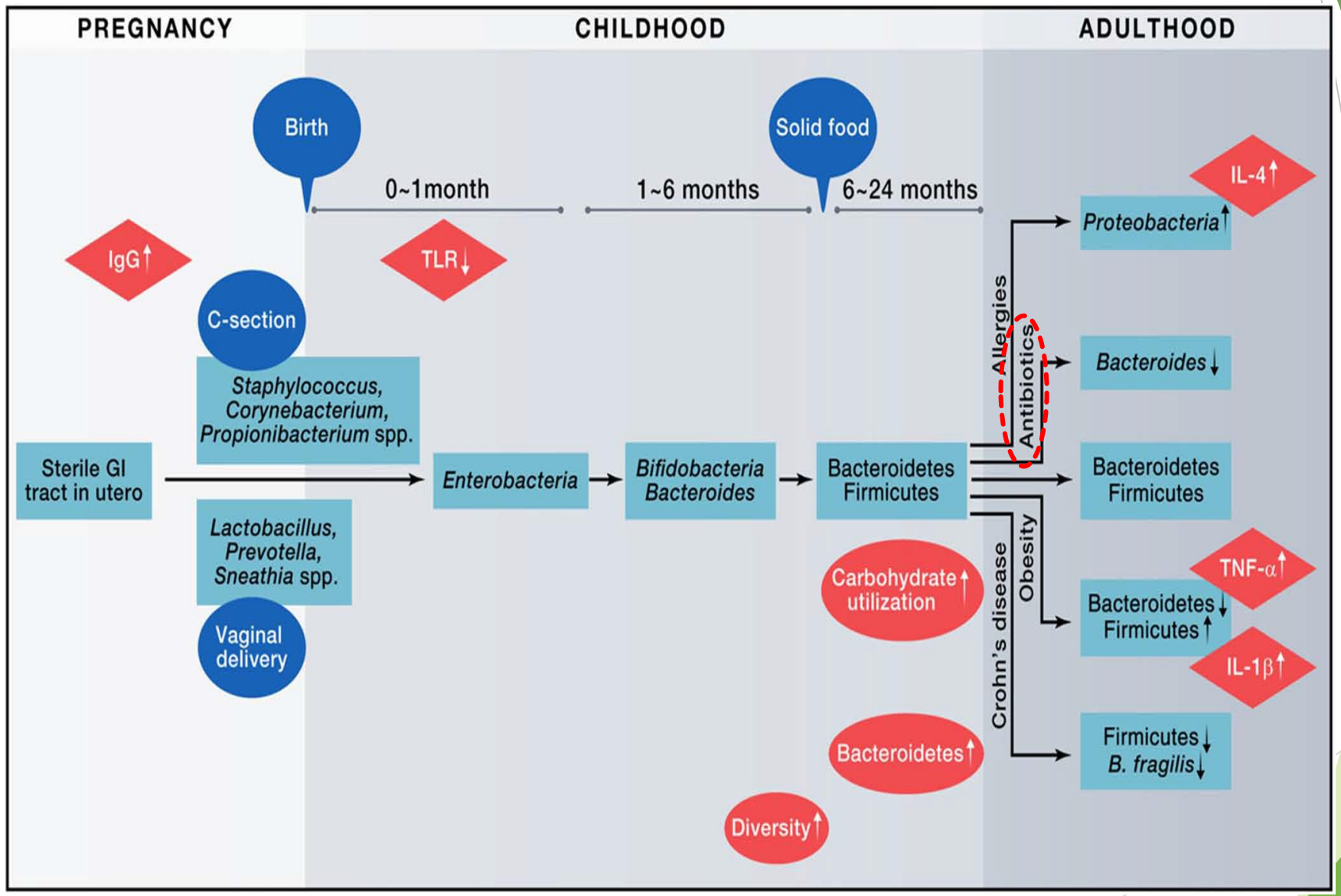
PRO/PREBIOTICI

AGING

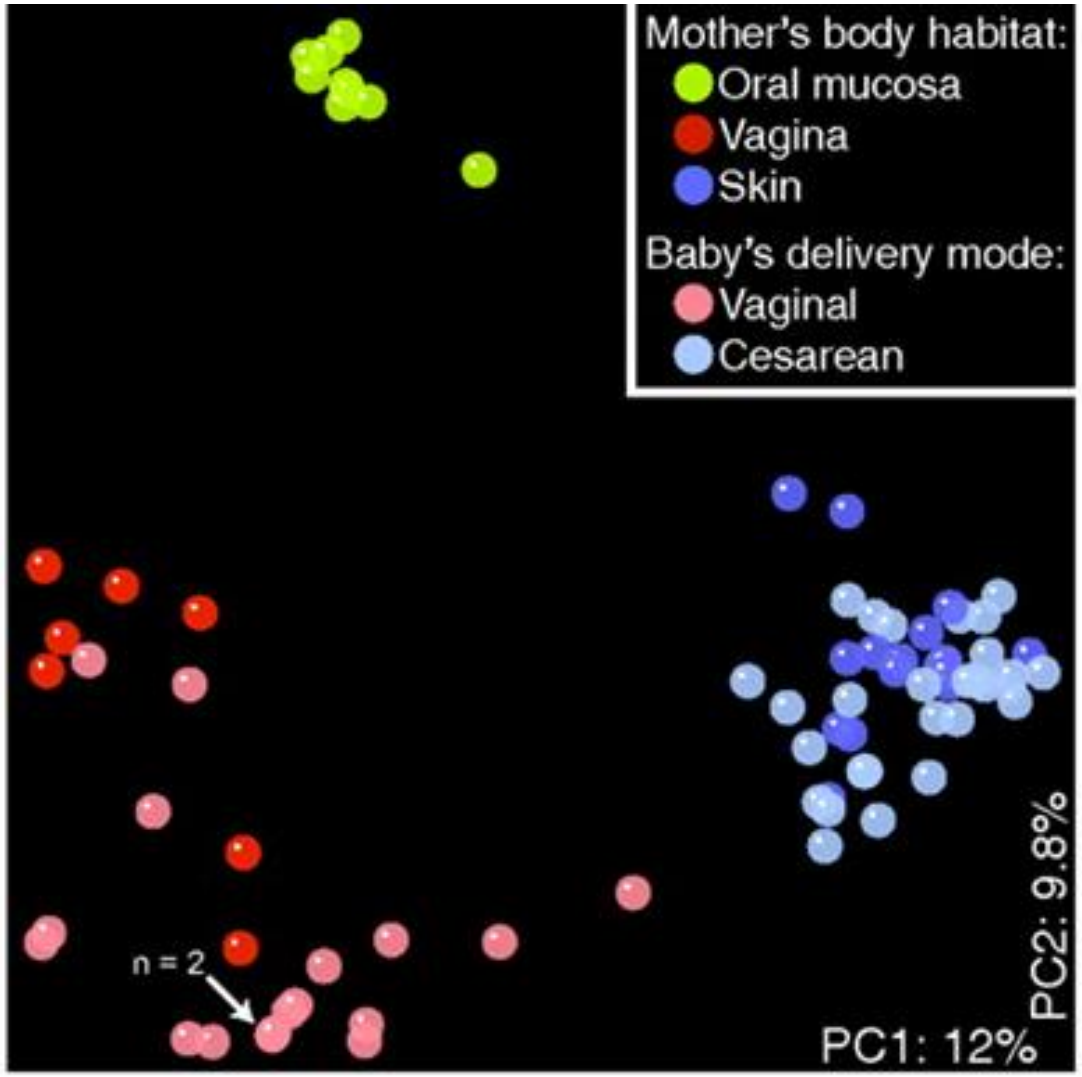


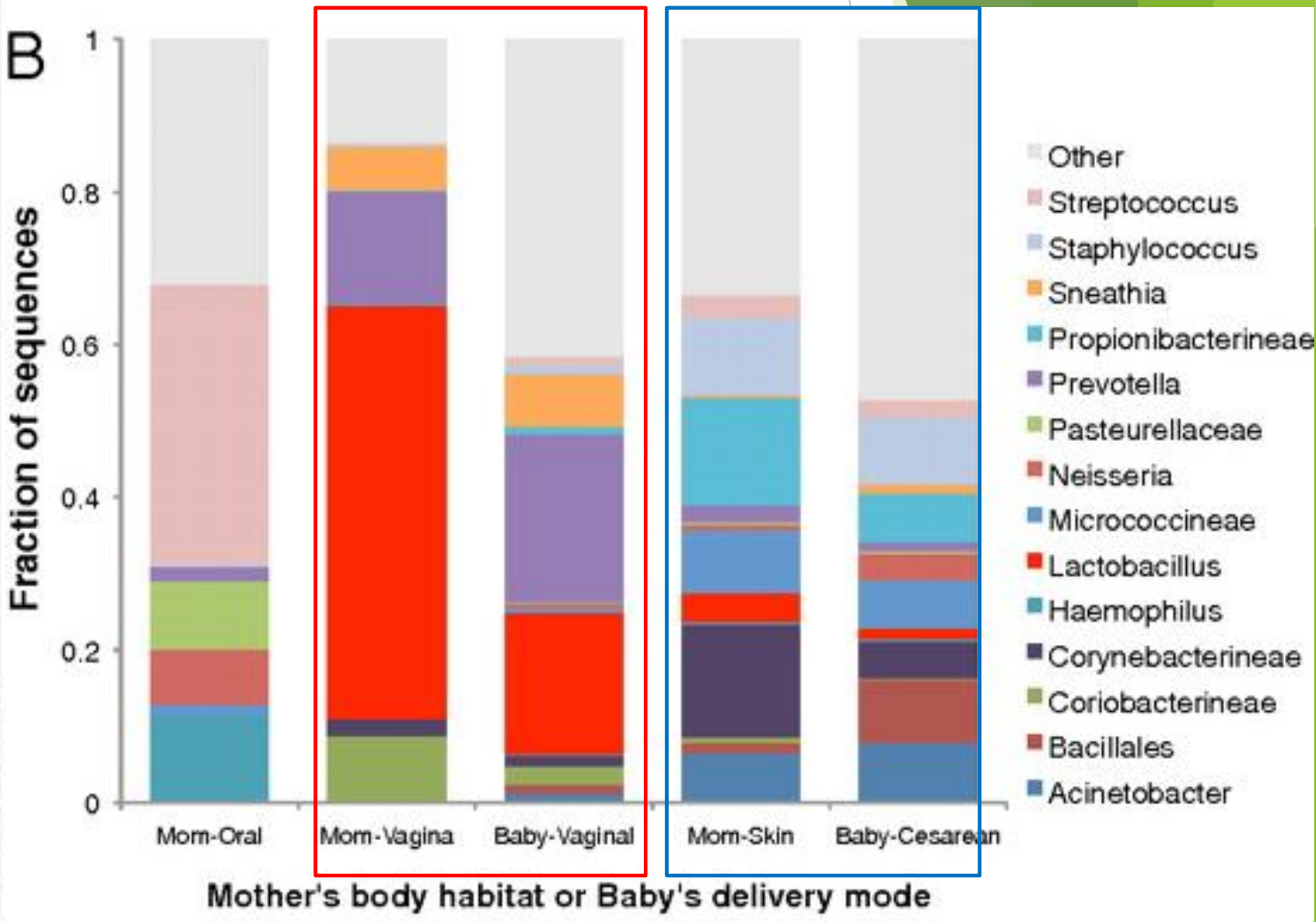
MALATTIE

Sviluppo del Microbiota

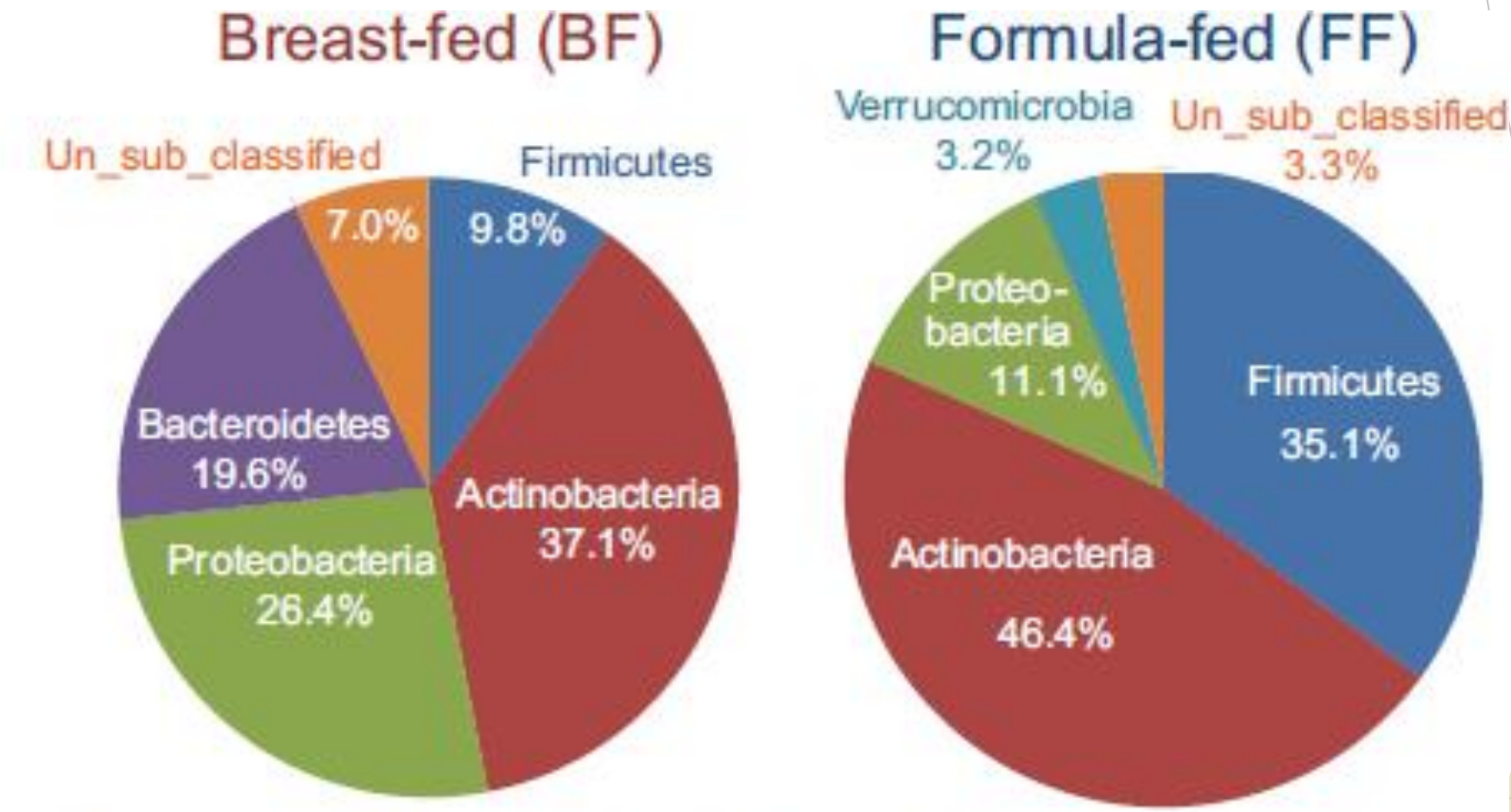


MODLITA' DI PARTO



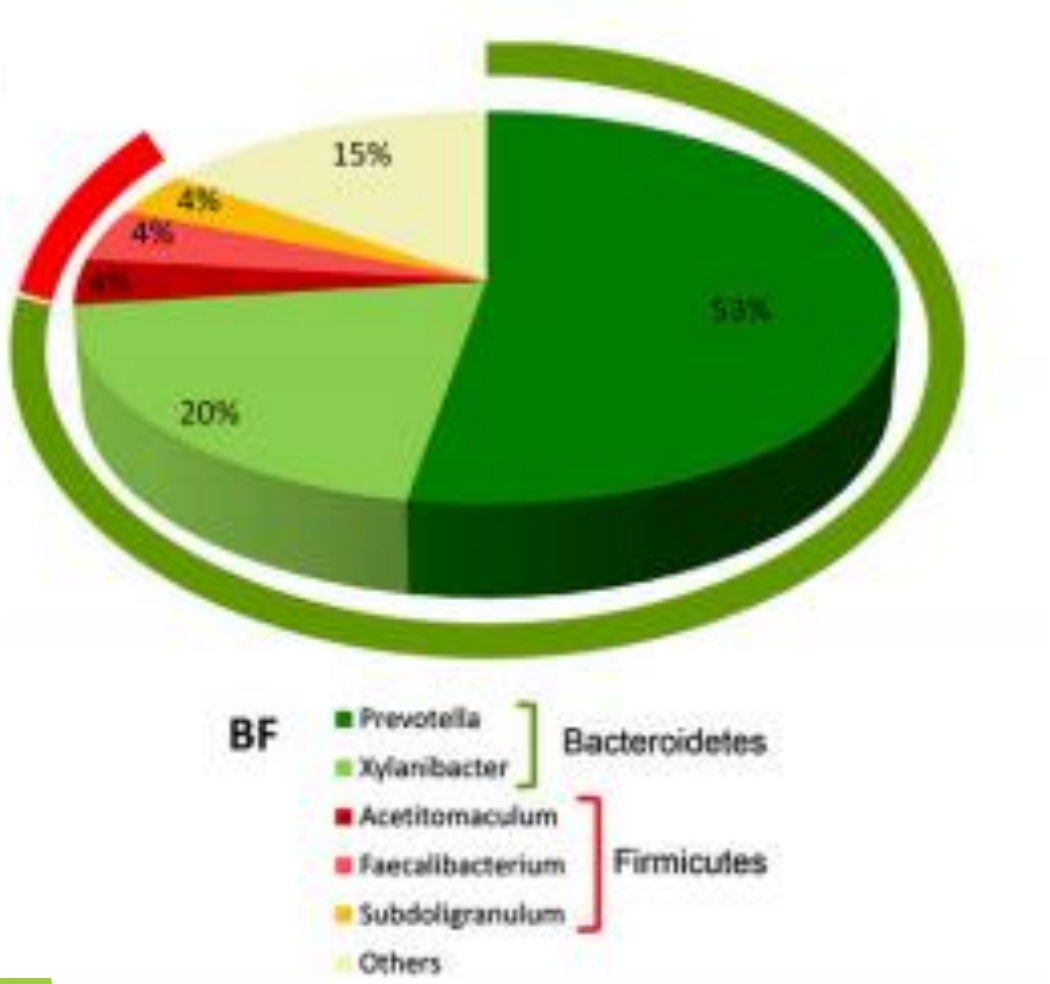


ALLATTAMENTO

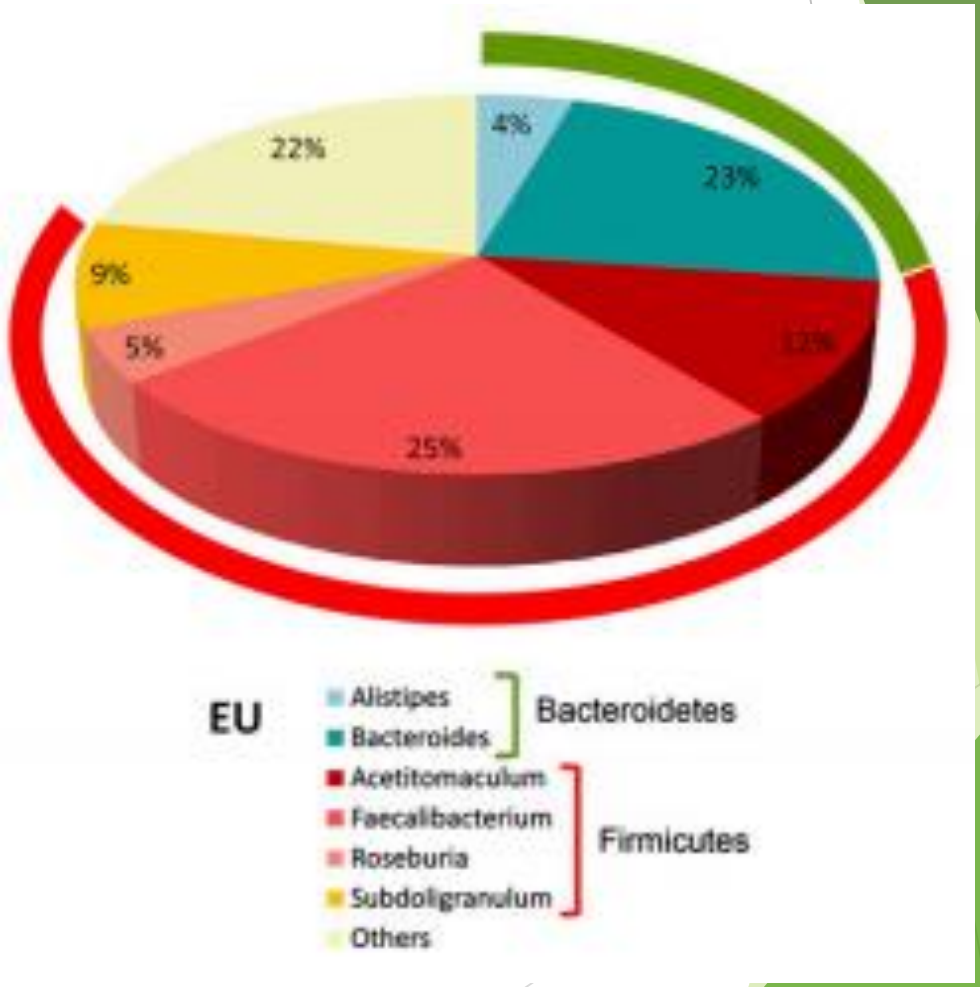


- BF had more total Proteobacteria and Bacteriodetes
- FF had more Firmicutes and no Bacteriodetes

ORIGINE GEOGRAFICA

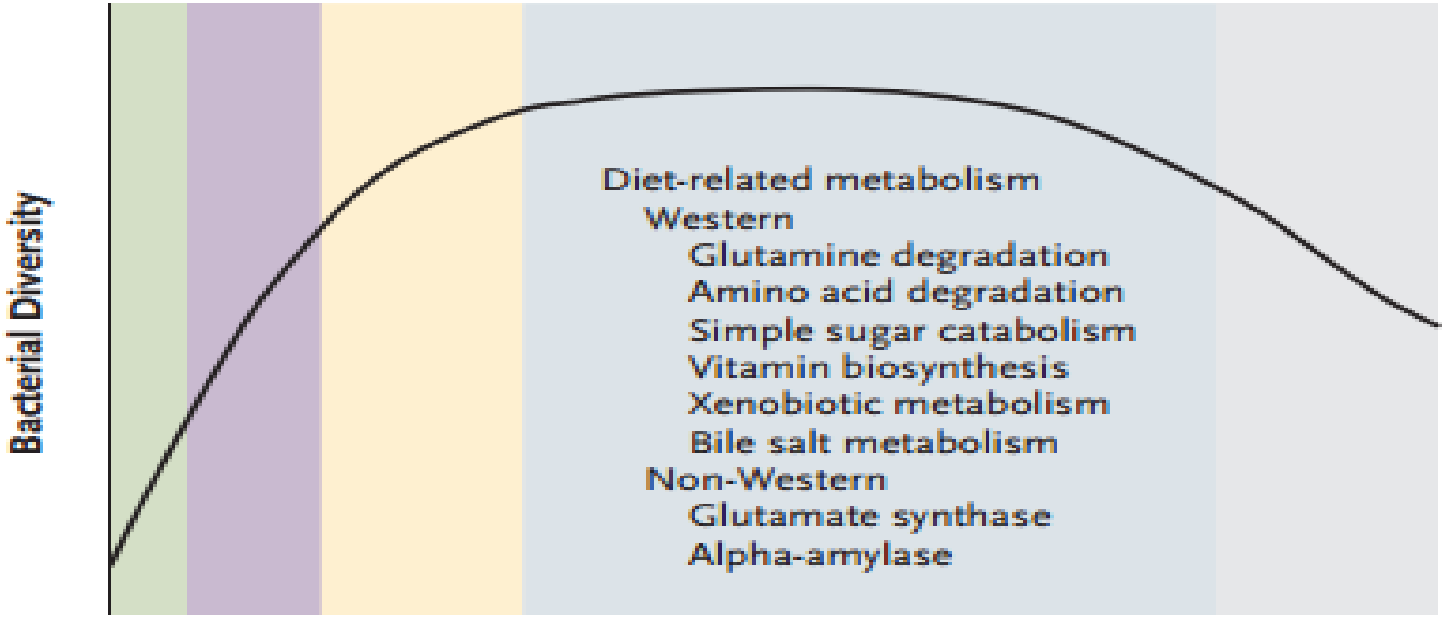


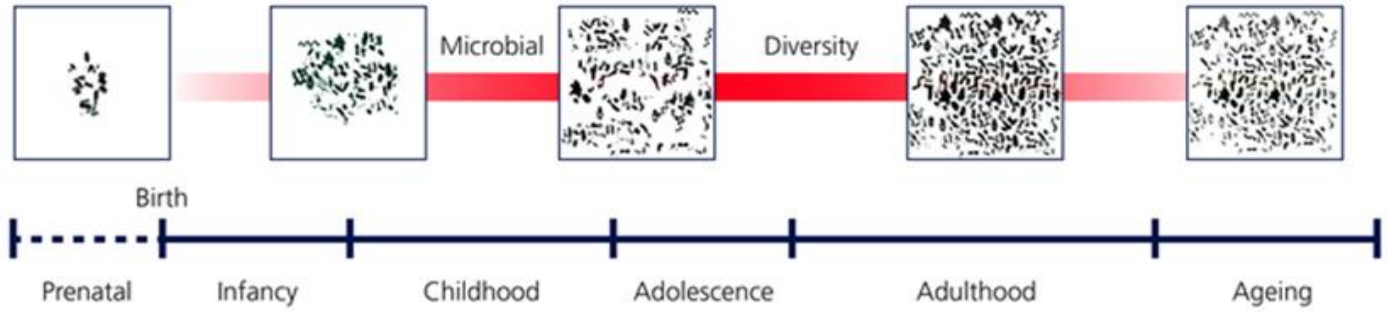
BURKINA FASO



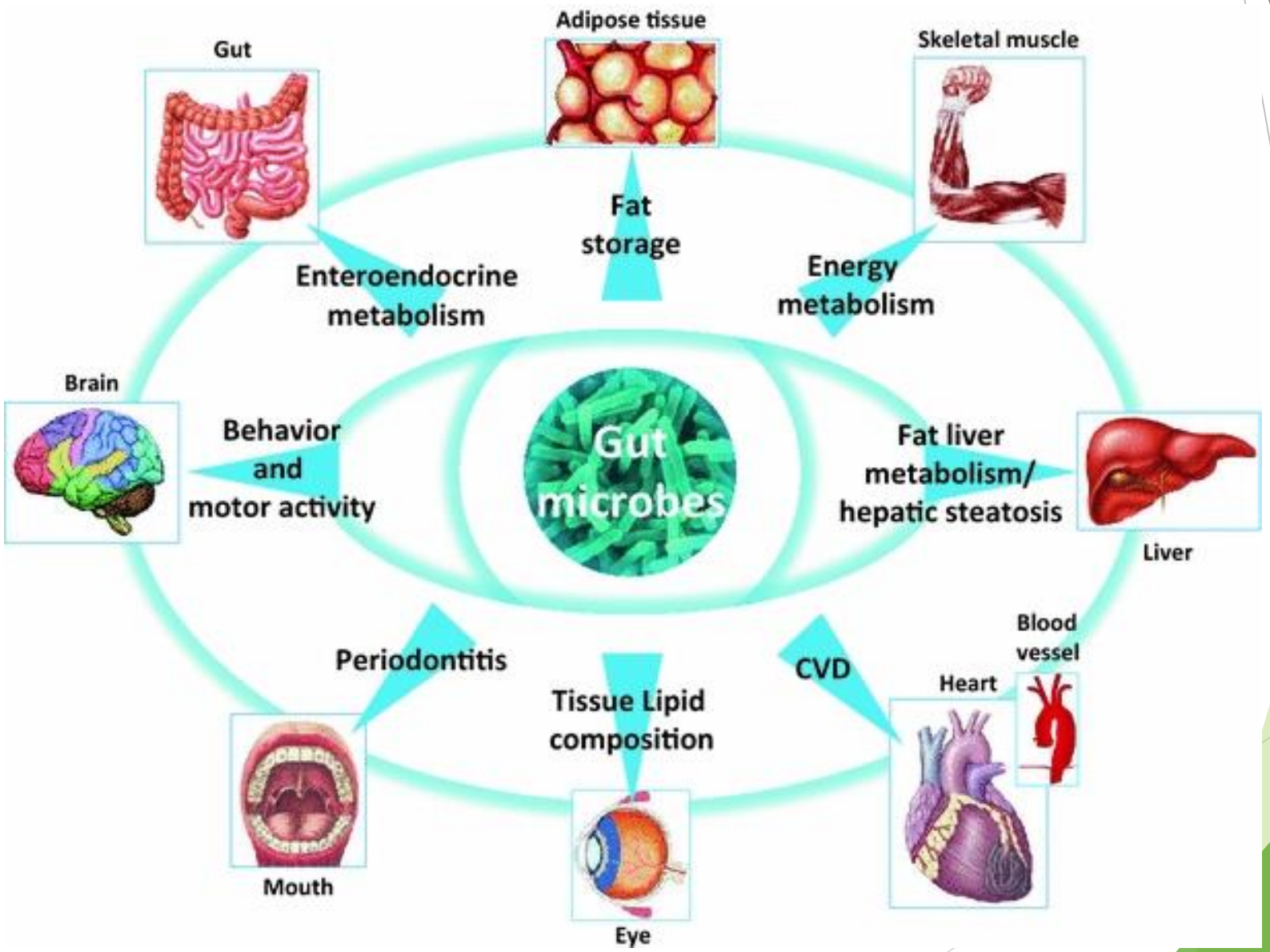
EUROPA

Il microbiota nelle diverse fasi della vita





IL RUOLO DEL MICROBIOTA NELLA SALUTE



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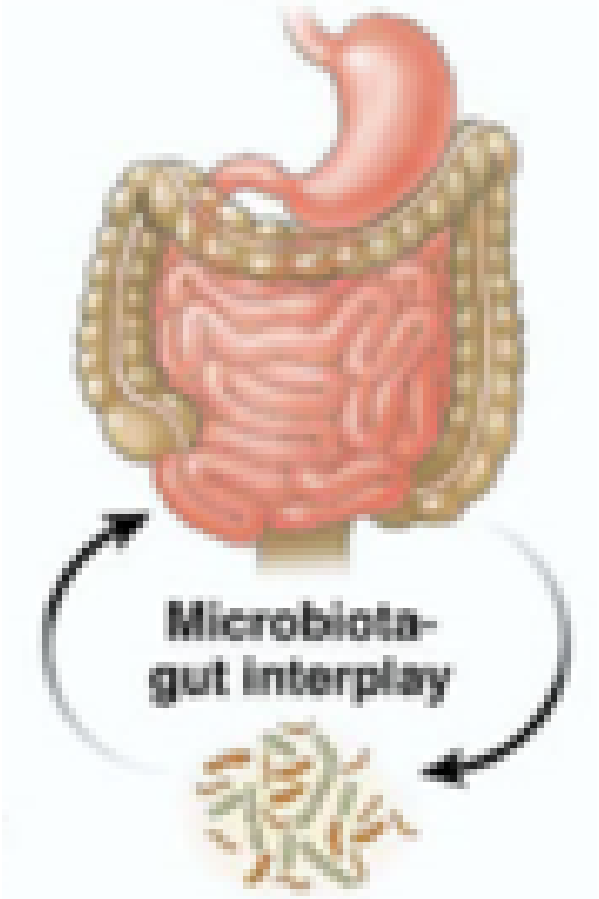


Metabolic

- Vitamines prouction
- Enterocytes differentiation
- Dietary carcinogenes digestion
- Non-digestible substrate fermantation
- SCFAs production

Antimicrobial secretion

Energy source

Sites and nutrients competition

Protective

- Colonization resistance
- Innate and adaptative immunity
- Inflammatory cytokine oversite

Immune system and barrier function

Structural

- IgA stimulation
- Intestinal villi and crypts stimulation
- Tight junction
- Mucous layer production

Ruolo **metabolico** del microbiota

Le diverse centinaia di specie presenti presentano un corredo enzimatico estremamente vario

Acidi grassi a corta catena

Acetato Propionato Butirrato

Gli acidi grassi a corta catena (SCFA) sono i principali prodotti della fermentazione batterica

Acidi grassi a corta catena

Attraverso il loro assorbimento e metabolismo, viene recuperata energia da alimenti, tra cui l'amido e le fibre, che non vengono digerite nella parte superiore del tratto gastrointestinale.

Gli SCFA influenzano:
il trasporto e il metabolismo delle cellule epiteliali,
la crescita e il differenziamento delle cellule epiteliali e il controllo epatico di lipidi e di carboidrati fornendo al contempo fonti di energia per muscoli e reni, nonché per il cuore e il cervello

Batteri che producono SCFA: Bacteroides, Bifidobacterium, Propionibacterium, Eubacterium, Lactobacillus, Clostridium, Roseburia e Prevotella

Ruolo **metabolico** del microbiota

I batteri producono molte altre sostanze

anidride carbonica

idrogeno

lattato

piruvato

metano

etanolo

succinato

acido solfidrico

Ruolo **endocrino** del microbiota

Bile acids: *Secondary bile acids* → produced by bacteria starting from primary bile acids;

Choline metabolites: *Trimethylamine* → produced by the gut microbiota from dietary quaternary amines (mainly choline and carnitine)

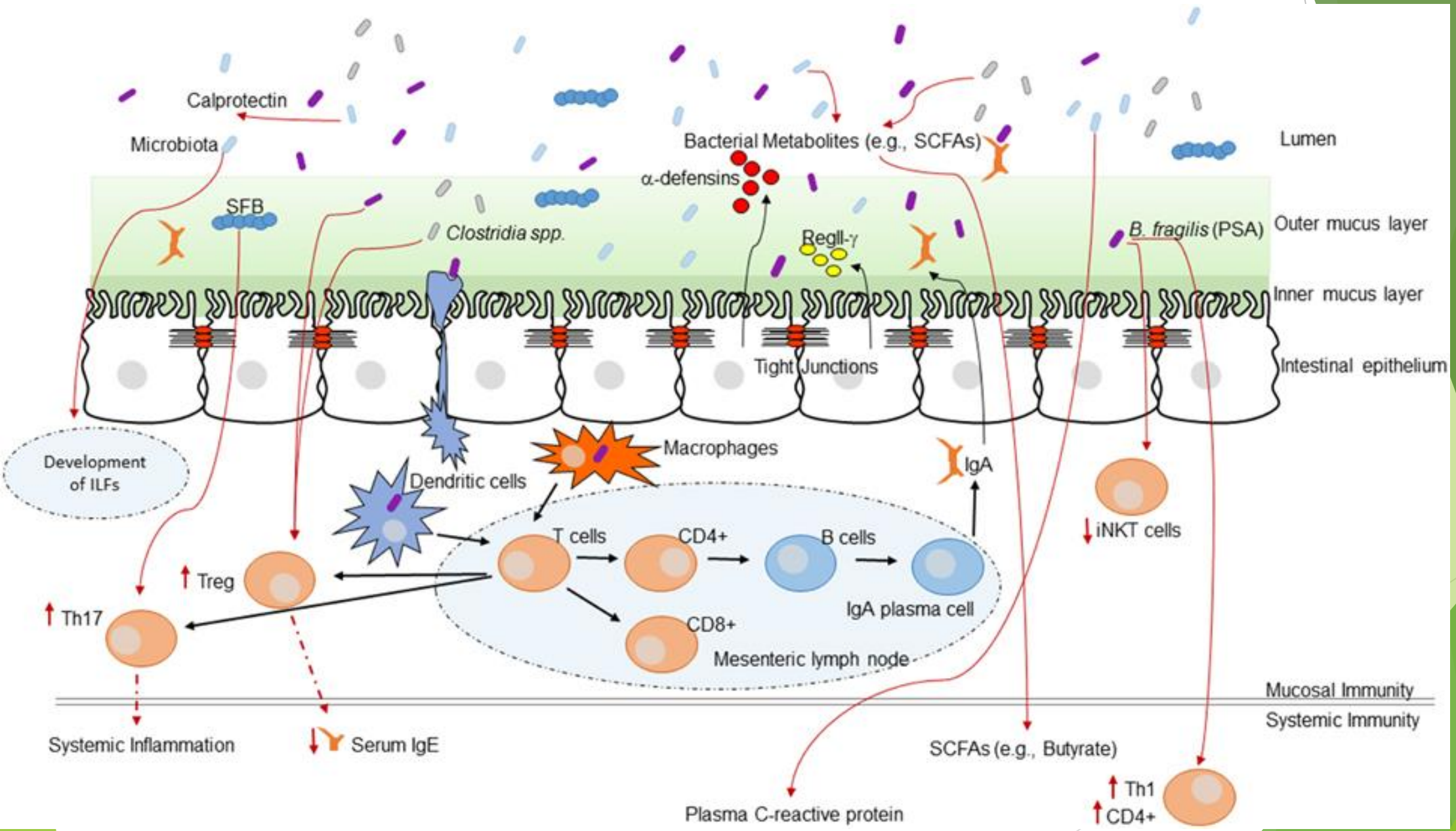
Neurotransmitters: *Serotonin, Dopamine, Noradrenaline, GABA* → directly produced by bacteria or indirectly regulated;

Precursors to neuroactive compounds: *Tryptophan, Kynurenine, l-Dopa* → production subject to regulation by microbiota;

hypothalamic-pituitary-adrenal (HPA) hormones: *Cortisol* → indirect regulation by bacteria

Gastrointestinal hormones: *Ghrelin, Leptin, Glucagon-like peptide-1, peptide YY* → Indirect regulation

IL RUOLO DEL MICROBIOTA NELL'IMMUNITA'

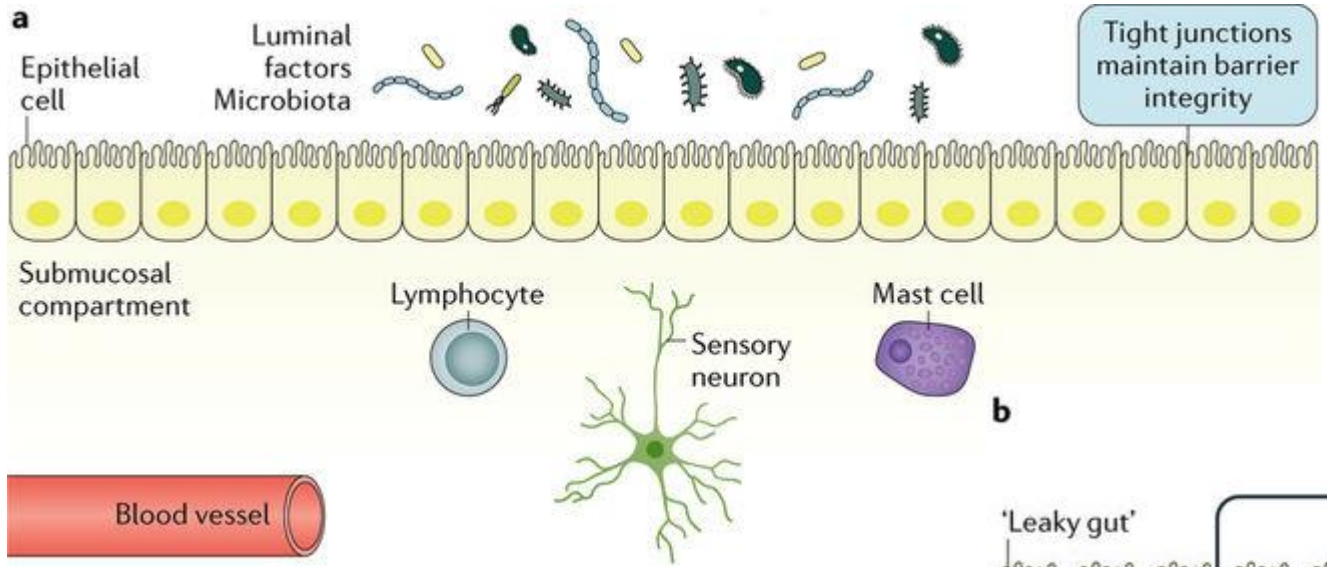


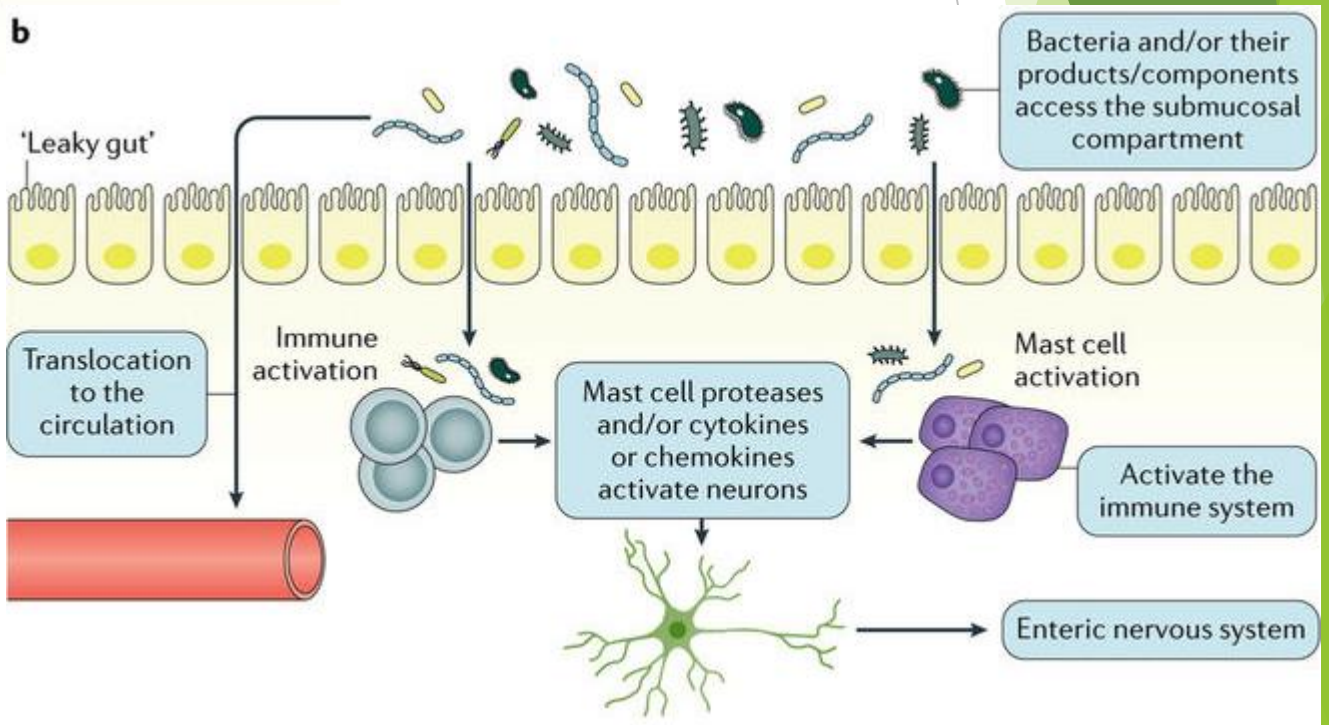
Ruolo **protettivo** del microbiota

- Competizione per i siti di adesione sull'orletto a spazzola dell'epitelio intestinale
- Competizione per i nutrienti disponibili
- Produzione di molecole antimicrobiche

Tutti questi meccanismi prevengono l'adesione di eventuali patogeni alle cellule epiteliali intestinali

The 'leaky gut' hypothesis

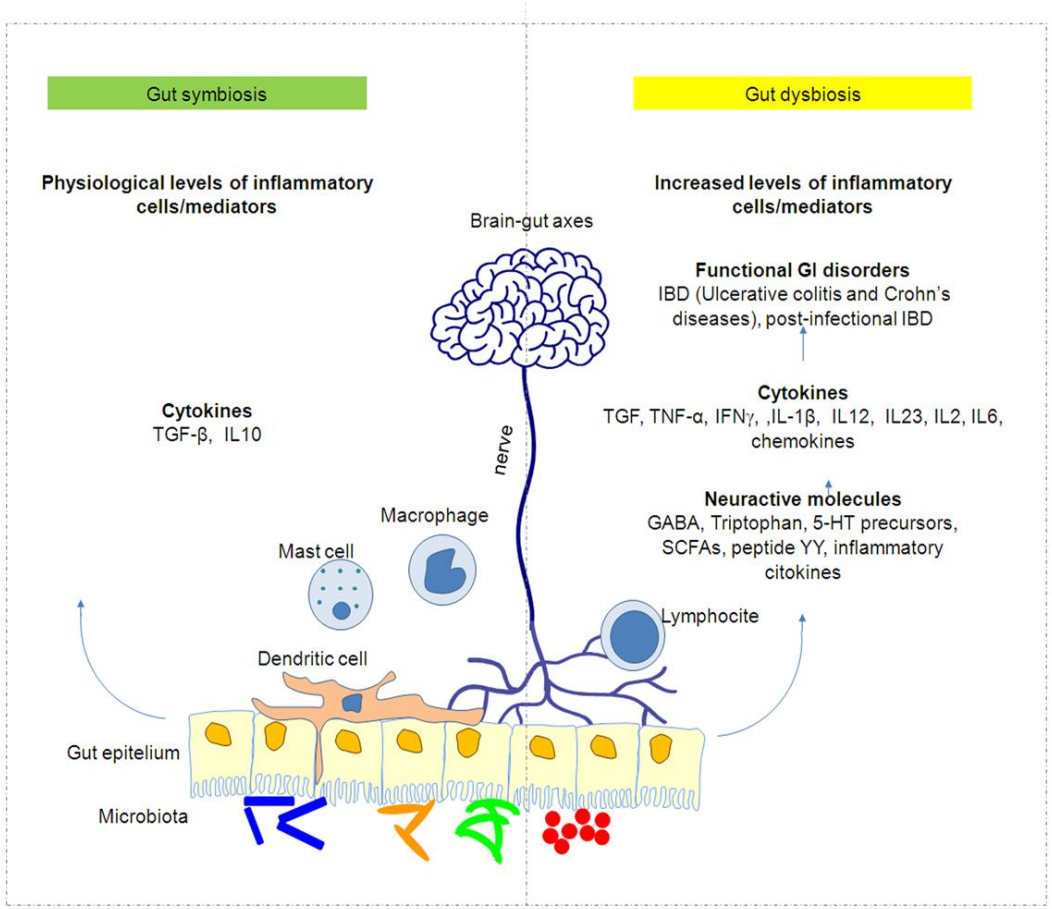




DISBIOSI

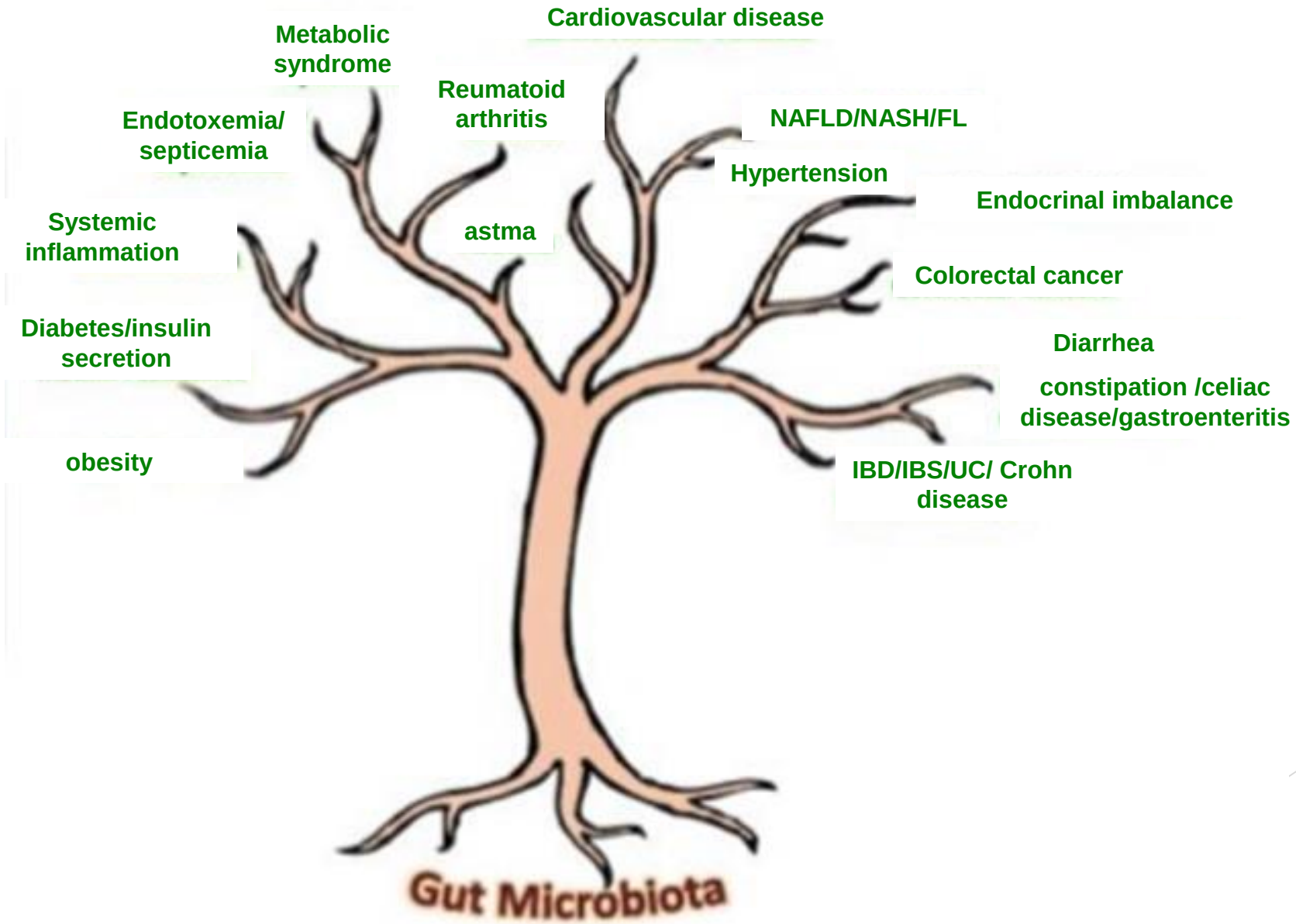
- Fattori genetici che possono alterare la barriera intestinale
- Crescita smisurata di batteri patogeni
- Traslocazione di batteri o prodotti batterici
- Attivazione immunitaria produzione di citochine pro-infiammatorie
- Infiammazione cronica che porta alla distruzione dei tessuti
- Leaky-gut

Gut microbiota symbiosis and dysbiosis



HEALTH ← HOMEOSTASIS — DYSFUNCTION → DISEASE

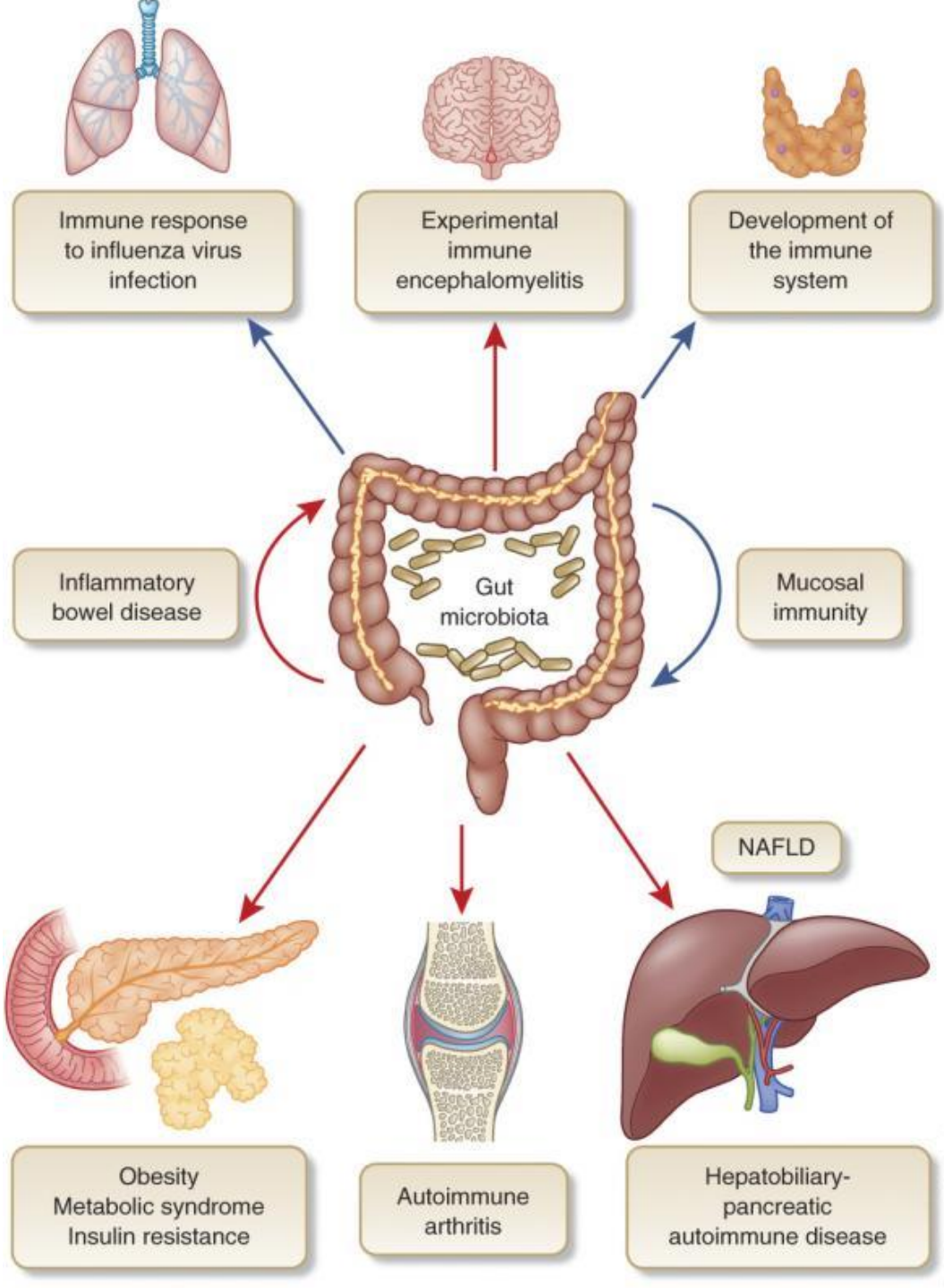
IL RUOLO DEL MICROBIOTA NELLE MALATTIE



PATOLOGIE CORRELATE AL MICROBIOTA

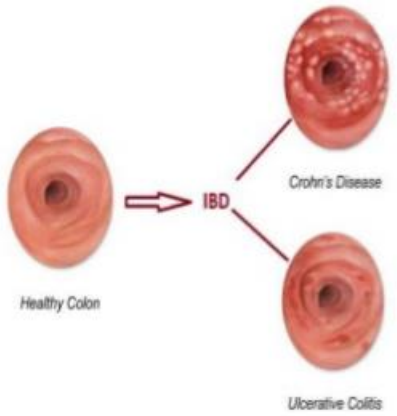
- **Diseases of the GUT**
  - Malabsorption syndrome
  - Malignancies: Colorectal cancer
  - Inflammatory Bowl disease (IBD)
  - Irritable Bowl syndrome
  - Diarrheal diseases
  - Clostridium Difficile Infection (CDI)

- **Non-mucosal diseases**
  - Obesity and metabolic syndrome
  - Malignancies: liver cancer, breast cancer
  - Complications of liver cirrhosis
  - Allergic conditions
  - Autoimmune disorders (T1DM, arthritis etc)
  - Abnormalities of the gut-brain axis- Autism an other neurological disorders
  - Obesity and other metabolic disorders
  - Chronic fatigue syndrome
  - Periodontal diseases



Inflammatory Bowl Disease (IBD)

A group of inflammatory and autoimmune conditions that affect the colon and small intestine, typically resulting in severe abdominal pain, weight loss, vomiting and diarrhea.



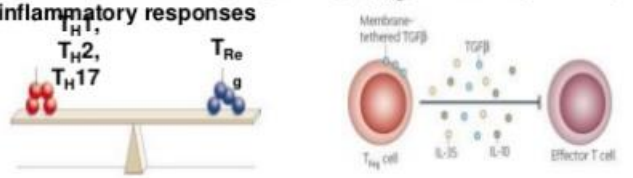
- Affects all layers of the bowel wall
- Granuloma formation in up to 60% of patients

- Affects superficial mucosal layers

IBD is driven by T cells

mucosal homeostasis

→ cytokine production by regulatory (T_{Reg}) T cells supresses pro-inflammatory responses



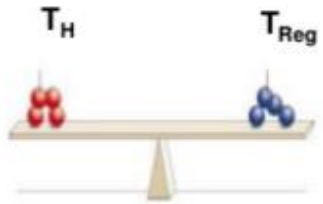
mucosal inflammation

→ increased production of pro-inflammatory cytokines by T helper (T_H) cells

TNF, IFNγ, IL-17

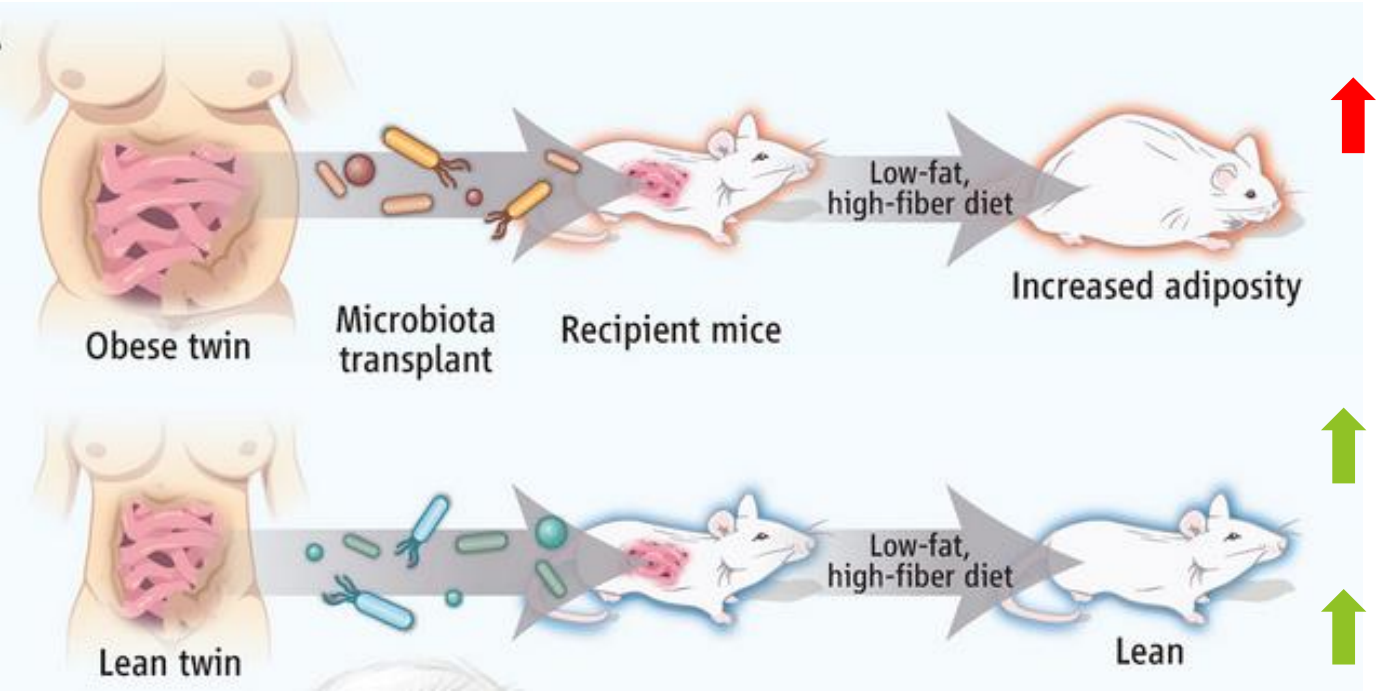
← T_{Reg} transfer can prevent the induction of experimental colitis

Involvement of the microbiota in regulating the balance between T_H and T_{Reg} cell subsets in the gut



→ Intestinal bacteria direct the differentiation of both pro- and anti-inflammatory T cell populations and may therefore play a crucial role in IBD

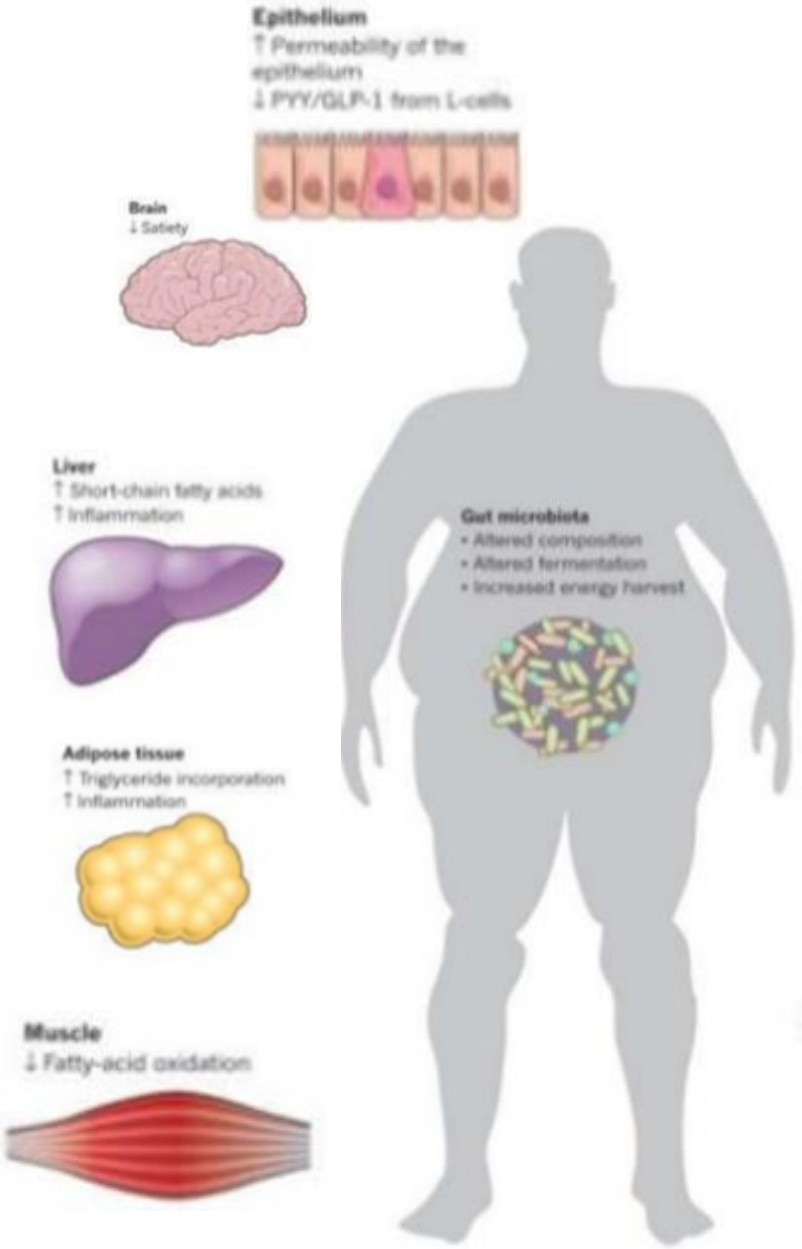
Gut microbiota and obesity: what is the link?



BCFA metabolism

SCFA fermentation

Bile acid microbial transformation



Oltre i batteri…..

Characteristic	Bacteria	Viruses	Eukaryotic microbes
Genome size	0.5–10 megabases	1–1,000 kilobases	10–50 megabases
Number of taxa in the human microbiome	At least thousands	Unknown, but could be as many as bacteria	Unknown, but may be fewer than bacteria
Relative abundances	Highly variable	Highly variable	Unknown
Targeted detection methods	Sequencing of genes such as 5S and 16S rRNA	No universal method for genes, but virus-specific polymerase chain reaction assays for some	Sequencing of 18S rRNA gene Spacer region in rRNA
Shotgun approach to analyses	Alignment to reference genomes or database comparison	Database comparison	Alignment to reference genomes or database comparison
Subspecies or strain diversity	Modest sequence variation Horizontal gene transfer also contributes	High sequence variation	Unknown

Disegno dello studio

Ipotesi dello studio

Studio longitudinale

cambiamenti nel microbiota (trattamenti farmacologici, stati di malattia)

Studio trasversale (cross sectional)

correlazione microbiota fenotipi clinici (relazione tra microbiota e patologie)

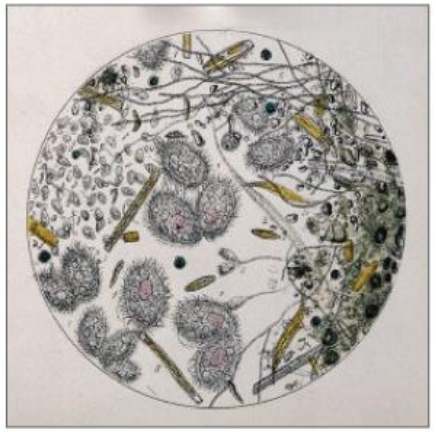
Scelta del campione

Table 1 | **Advantages and disadvantages of sample types for gut microbiome analysis**

Sample	Advantages	Disadvantages
Faecal sample	Noninvasive; no bleeding or discomfort; no bowel cleansing; easier to sample frequently	A proxy for the gut microbiome; might contain dead bacteria and/or bacteria from unspecified gastrointestinal tract compartments; less controlled sampling variables
Luminal brush	Captures host–microbe interactions; increased mucosal coverage; no bleeding; greater proportion of bacterial to host DNA than biopsies	Requires endoscopy; less biomass for host studies; affected by bowel cleansing
Rectal swab	No bleeding; greater proportion of bacterial to host DNA than biopsies; no bowel cleansing; can be administered at home; easier to sample frequently	No visual aid to pinpoint areas of interest; limited biomass for host studies; more discomfort than stool sampling; potential contamination with skin bacteria
Colonic lavage	Provides more DNA than biopsy samples; no bleeding	A proxy for the gut microbiome; requires endoscopy; affected by bowel cleansing
Pinch biopsy	Captures host–microbe interactions; can target exact areas of interest	Requires endoscopy; disrupts epithelium; affected by bowel cleansing
Sub-mucosal biopsy	Captures host–microbe interactions and bacterial translocations through epithelial layers; can target exact areas of interest	Requires endoscopy; disrupts epithelium; requires extensive sample processing; affected by bowel cleansing

Metodi di indagine del microbiota

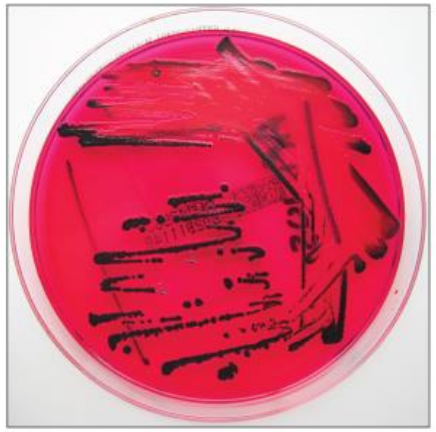
circa 1600:
Microscope invented

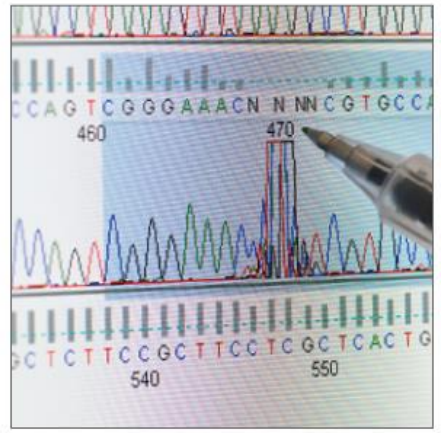


mid-1600s:
First microbes described

1800s:
Connection made between microbes and disease

1800s – Present:
Culture, staining, and microscopy used to study microbes that can be cultured

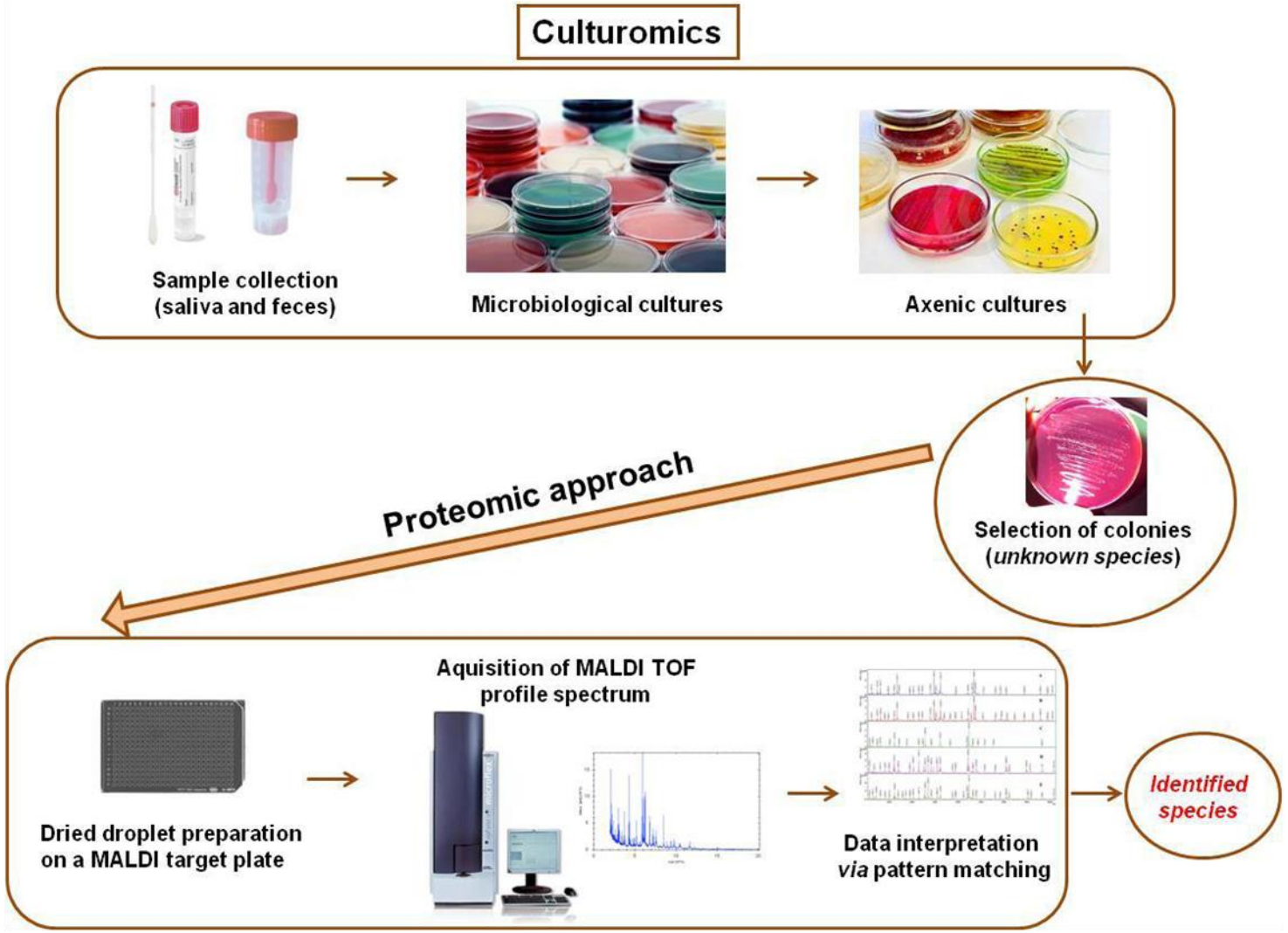




1990s:
DNA sequencing becomes available, allowing study of microbes that cannot be cultured

Metodi di indagine del microbiota

tecniche standard di microbiologia



99% of microbial species cannot currently be cultivated: Culturing: a few hundreds species per gram

Del Chierico, Gnani, Vernocchi et al., 2014. Meta-omic platforms to assist in the understanding of NAFLD gut microbiota alterations: tools and applications. ***Int J Mol Sci***. 2014 Jan 7;15(1):684-711

Metodi di indagine del microbiota

Tecnologie «OMICHE»

Quali microrganismi sono presenti?

ANALISI FILOGENETICA
Target: 16S rRNA

Qual è il potenziale genetico del microbiota?

ANALISI METAGENOMICA
Target: DNA

Quali attività stanno svolgendo?

ANALISI METAPROTEOMICA
Target: Proteine

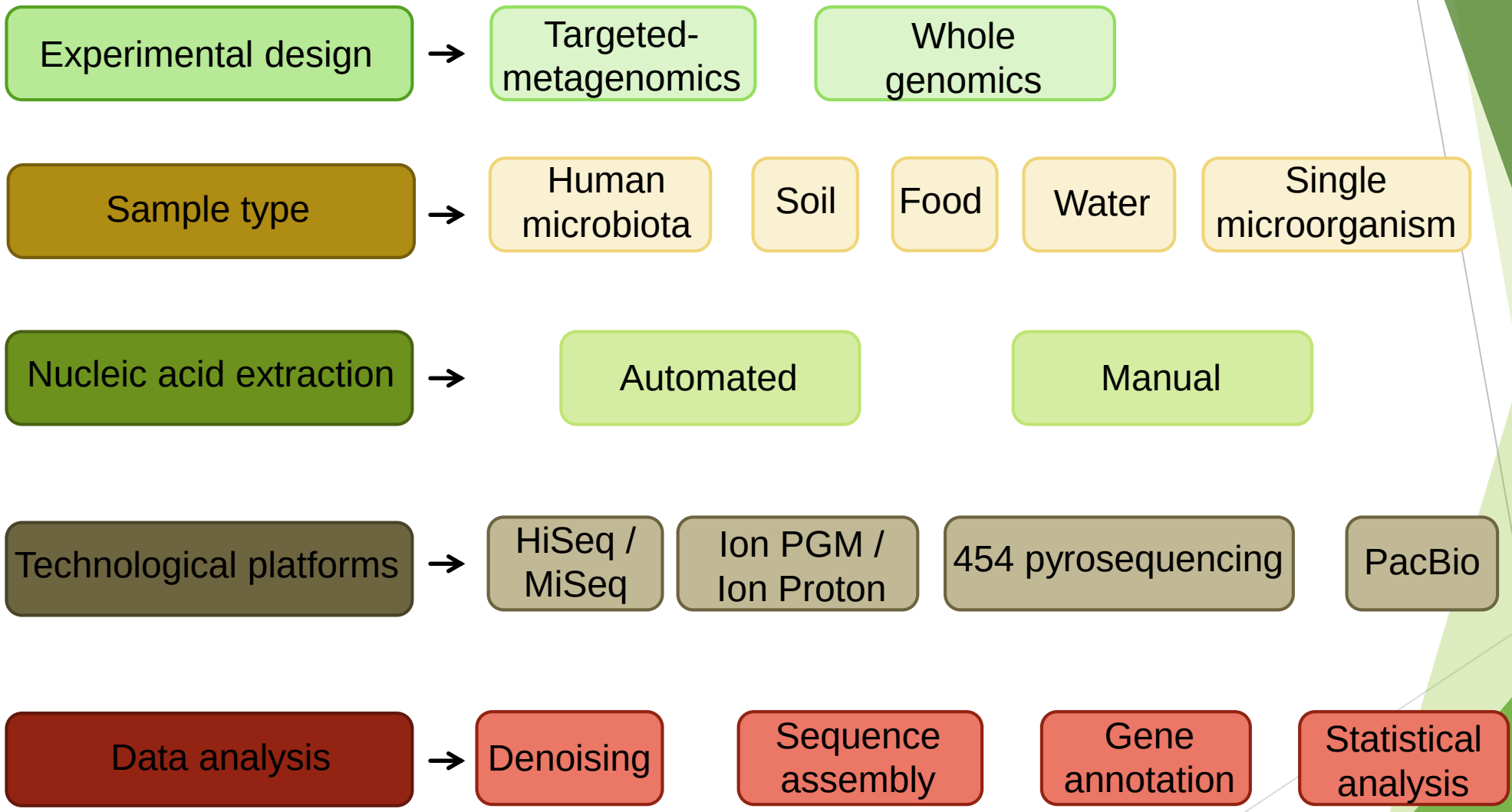
ANALISI METABOLOMICA
Target: Metaboliti

NGS sequencing

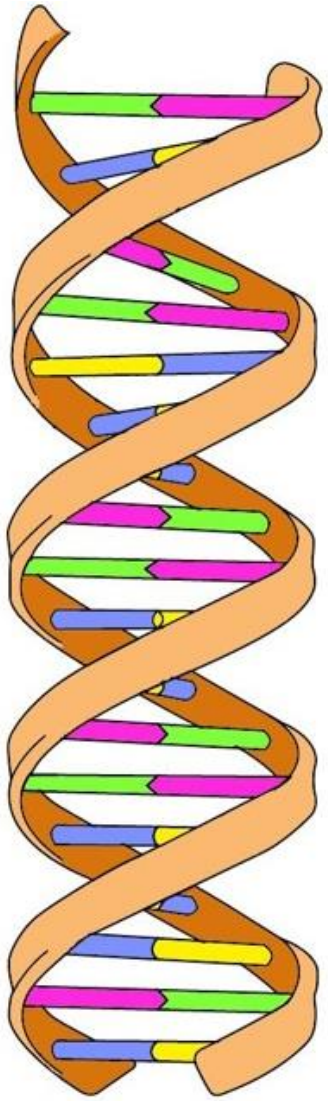
Culture-indipendent DNA-based methods

Platform	Method	Characteristics	16S rRNA	Shotgun	Comments
Established					
Sanger-based or capillary-based instrument	Fluorescent, dideoxy terminator	750-base reads High accuracy	Full length sequenced with 2–3 reads	Long reads help with database comparisons	Most costly method Relatively low throughput, so low coverage of 16S or shotgun
Roche–454	Pyrosequencing light emission	400-base reads	Up to 3 variable regions per read	Long reads help with database comparisons	Cost limits shotgun coverage but 16S coverage is good
Illumina	Fluorescent, stepwise sequencing	100–150- base reads	Only 1 variable region per read	Short reads do not seem to limit analysis	Very high coverage owing to high instrument output and very low cost
Not yet widely used					
Ion Torrent	Proton detection	More than 200-base reads	Like other NGS	Like Illumina	Expect high coverage, but longer reads than Illumina
PacBio	Fluorescent, single-molecule sequencing	Up to 10-kilobase reads Low accuracy	Accuracy an issue for correct taxon identification	Long reads could help assembly	Attractive for long reads, but lower accuracy limits applications
Oxford Nanopore*	Electronic signal as DNA passes through pore Single-molecule sequencing	Long reads	Unknown	Long reads could help assembly	Not yet available

Next generation sequencing



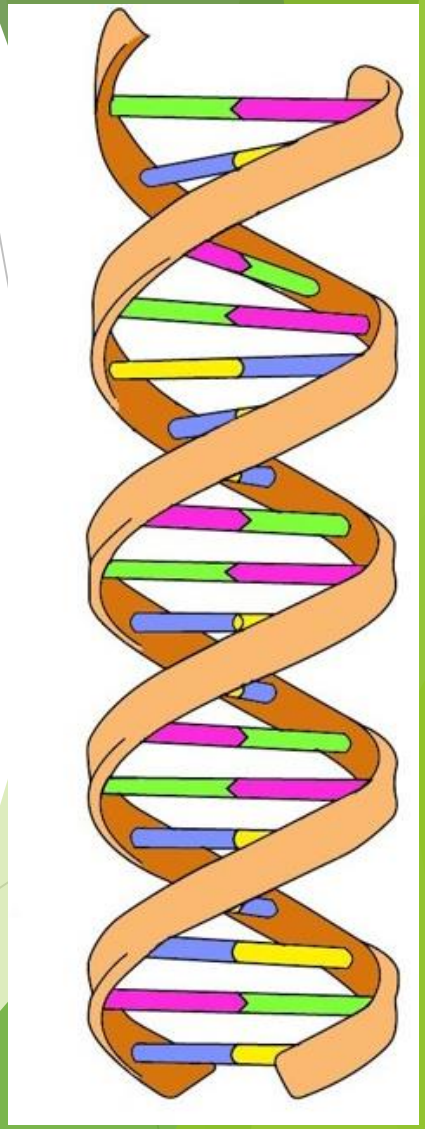
Il DNA è un ottimo strumento per la tassonomia



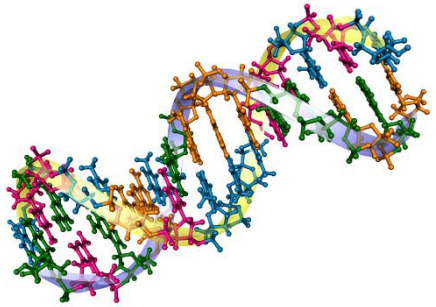
Le sequenze di DNA hanno numerosi vantaggi rispetto ai caratteri morfologici:

- Marcatori possono essere determinati in modo non ambiguo (variazioni di sequenza)

- Il DNA codificante per l'RNA ribosomale batterico è il miglior marcatore batterico

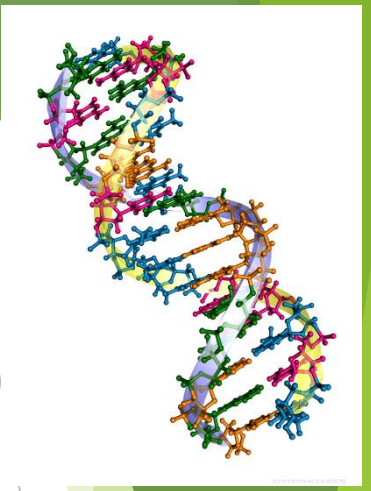


Estrazione del DNA

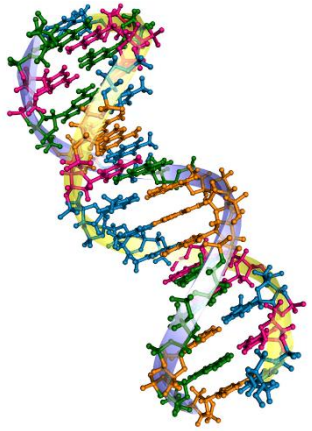


Requisiti fondamentali:

- quantità sufficiente
- alta qualità
- contenere una rappresentazione fedele della comunità microbica presente nel campione.

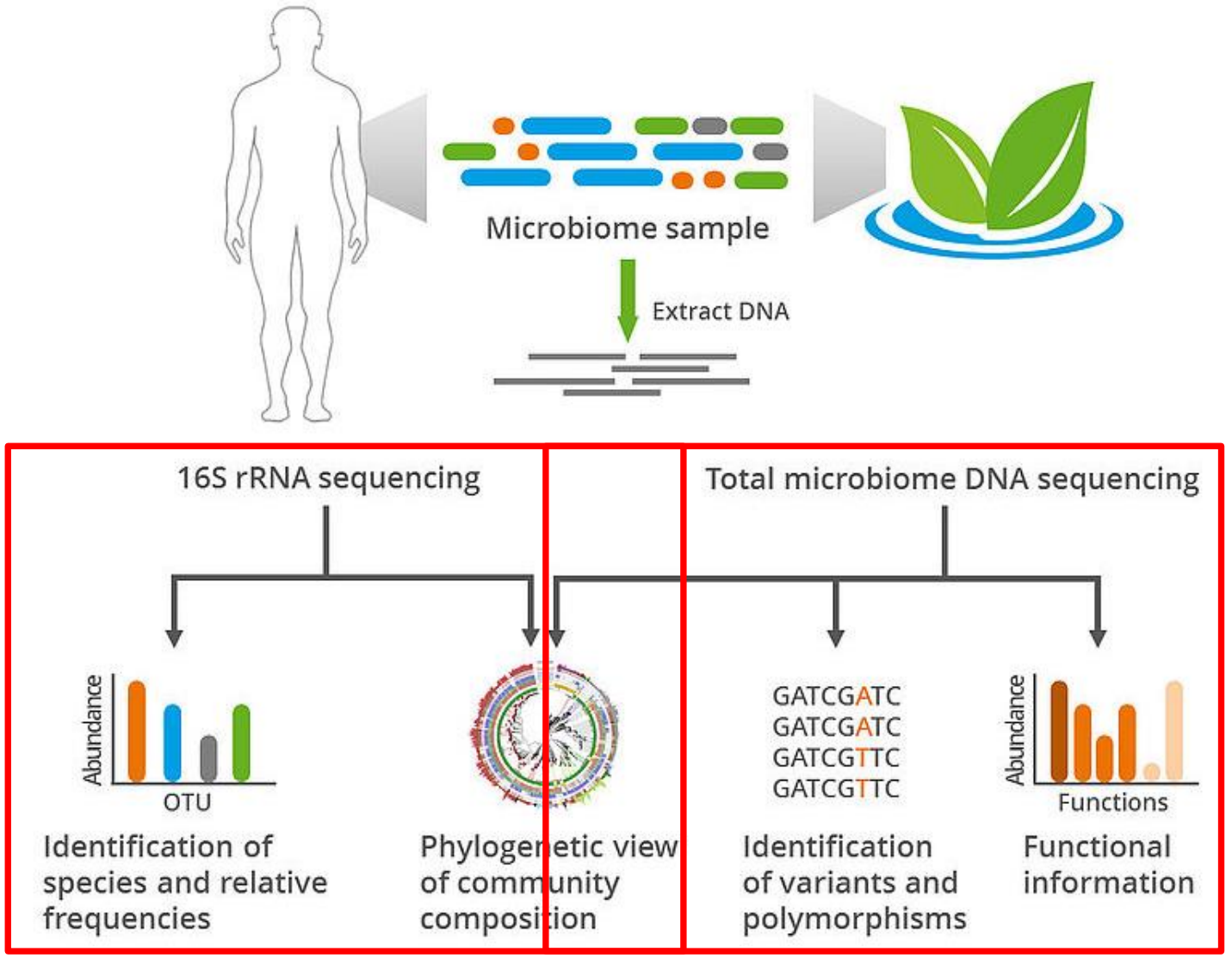


L’estrazione del DNA da campione fecale può risultare una procedura complessa a causa dell’elevata presenza di DNA proveniente da altre matrici come cellule umane e cibo, e da altri contaminanti come i metaboliti cellulari.



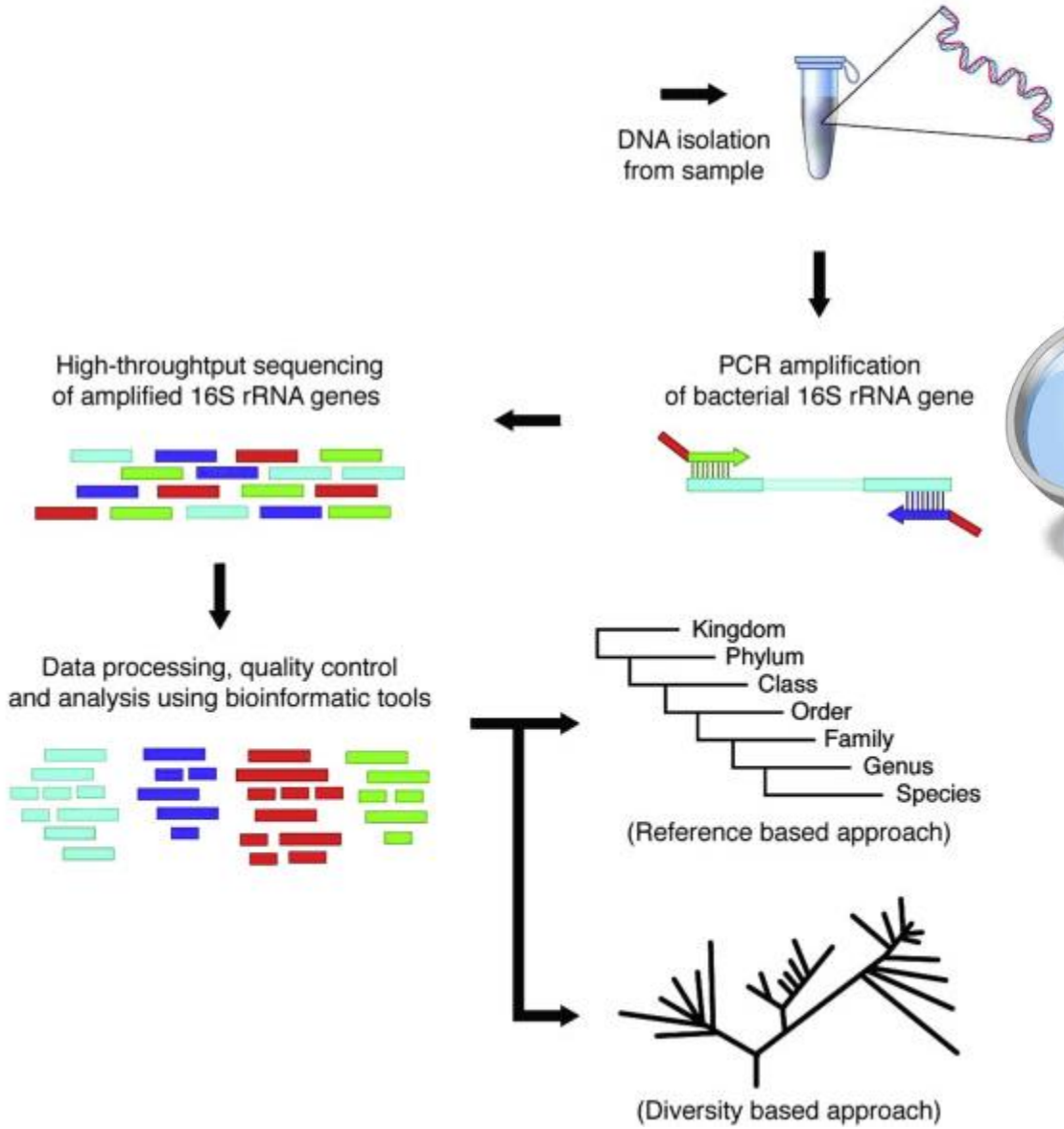
Metagenomica

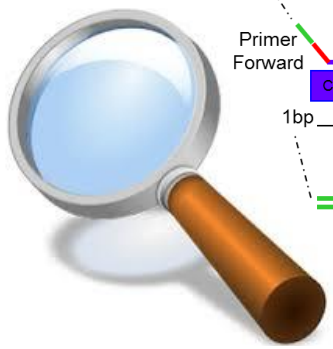
Analisi delle comunità microbiche mediante metodi indipendenti dalla cultura microbica

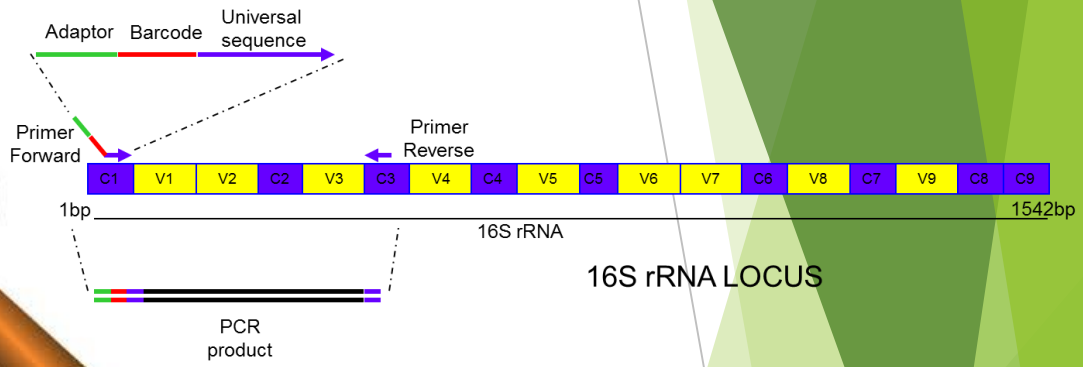


OTU = Operational Taxonomic Unit, a group of very similar 16S sequences

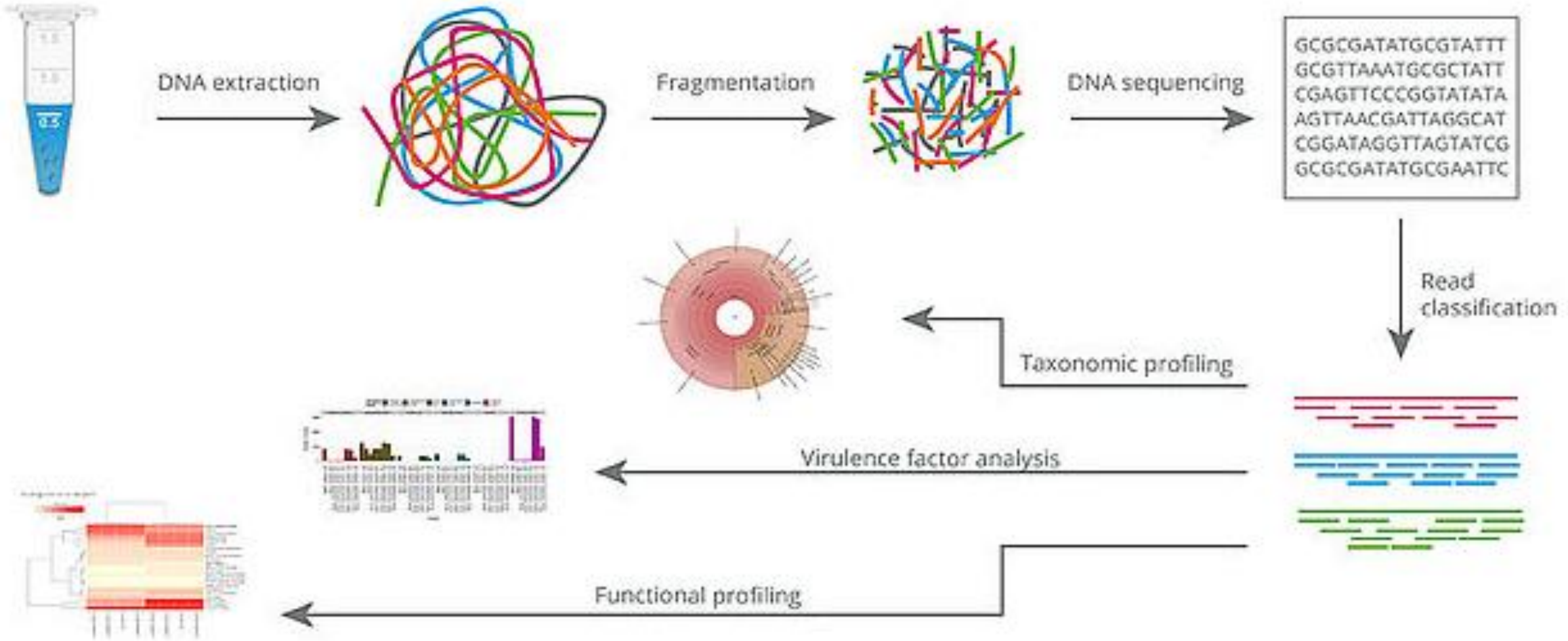
Metagenomica 16S-rRNA-based







Metagenomica Shotgun



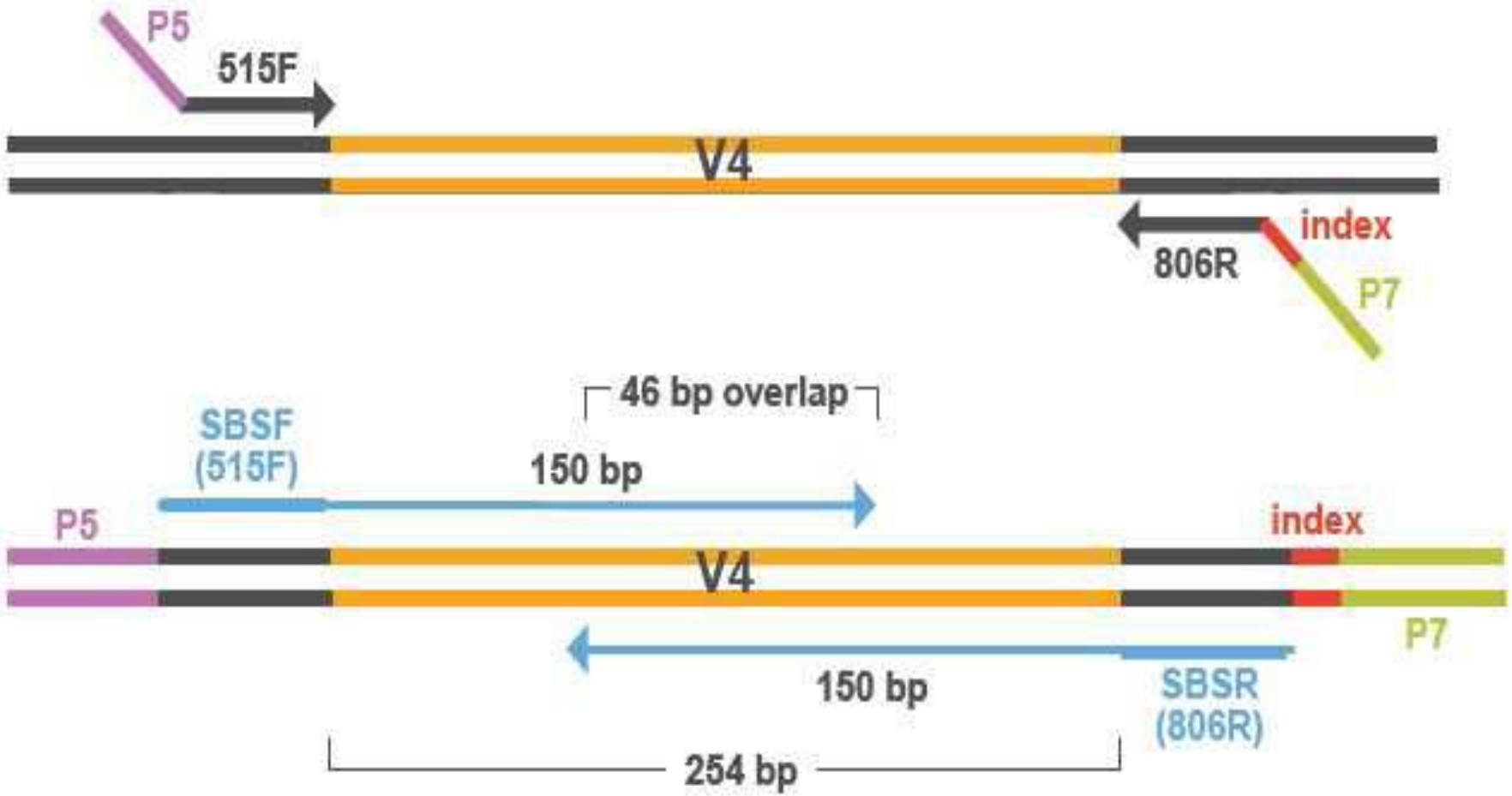
Metagenomica 16S-rRNA-based

- Pros
  - Well established
  - Sequencing costs are relatively cheap (~50,000 reads/sample)
  - Only amplifies what you want (no host contamination)
- Cons
  - Primer choice can bias results towards certain organisms
  - Usually not enough resolution to identify to the strain level
  - Different primers are needed for archaea & eukaryotes (18S)
  - Doesn't identify viruses

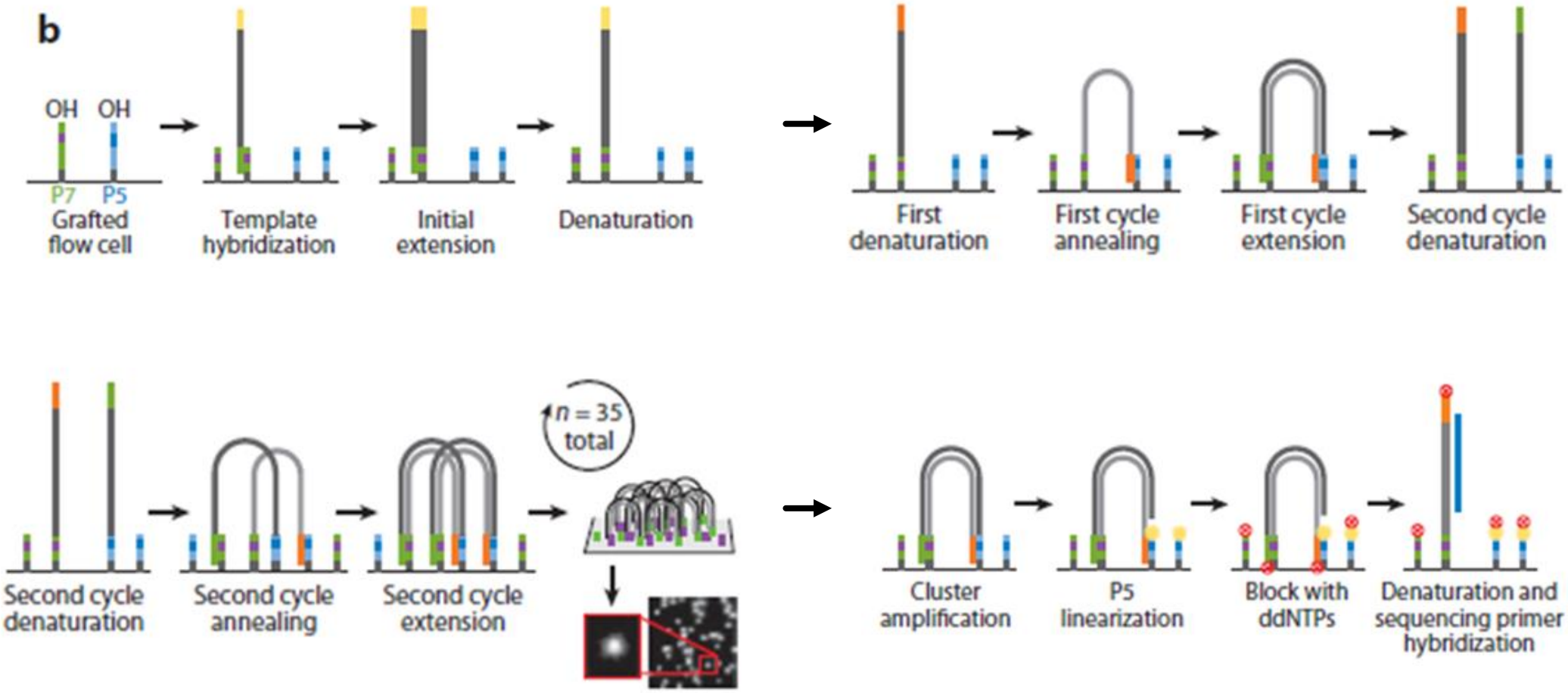
Metagenomica Shotgun

- Pros
  - No primer bias
  - Can identify all microbes (euks, viruses, etc.)
  - Provides functional information ("What are they doing?")
- Cons
  - More expensive (millions of sequences needed)
  - Host/site contamination can be significant
  - May not be able to sequence "rare" microbes
  - Complex bioinformatics

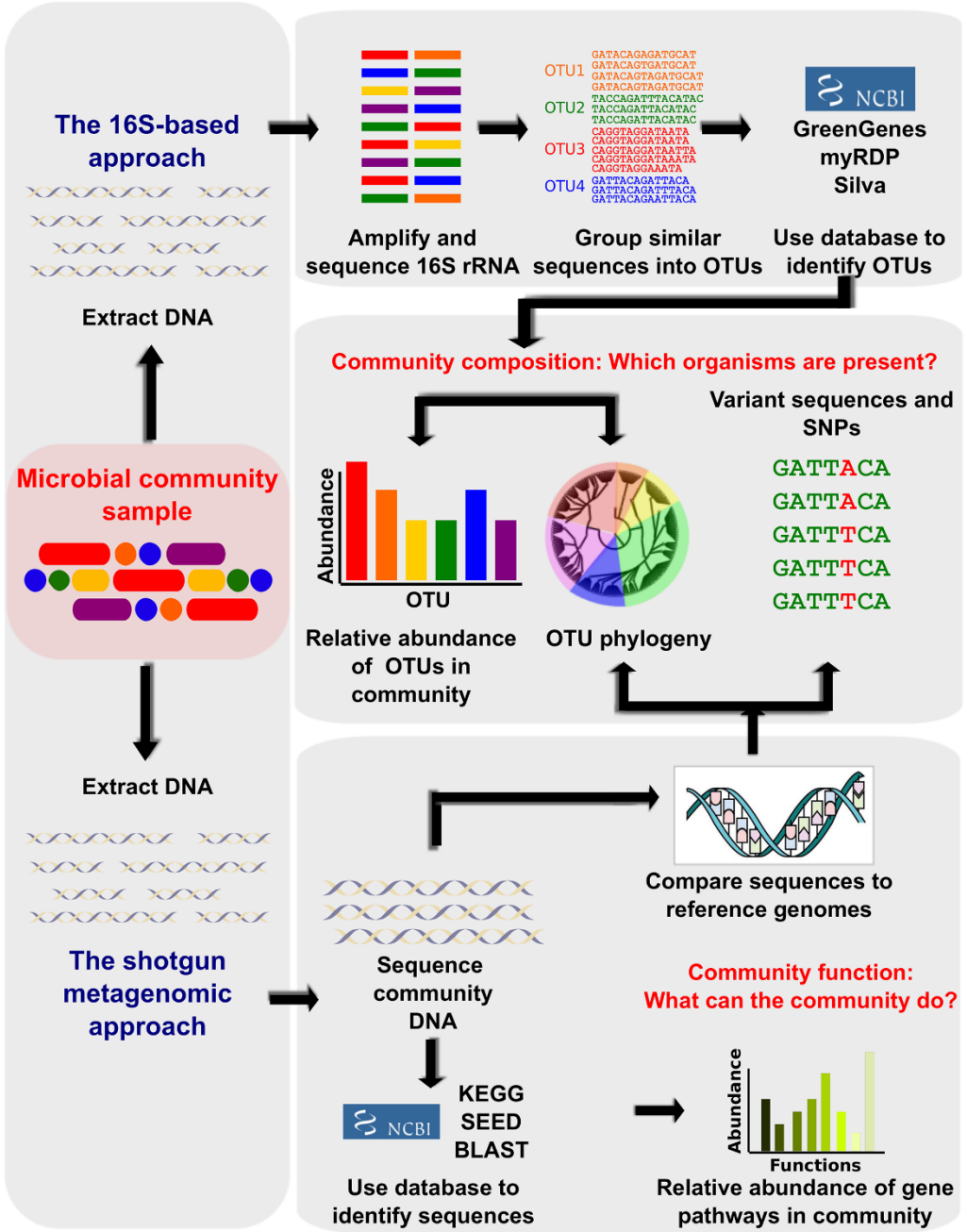
Illumina


P5
515F
V4
index
806R
P7
46 bp overlap
SBSF
(515F)
150 bp
P5
index
V4
P7
150 bp
SBSR
(806R)
254 bp

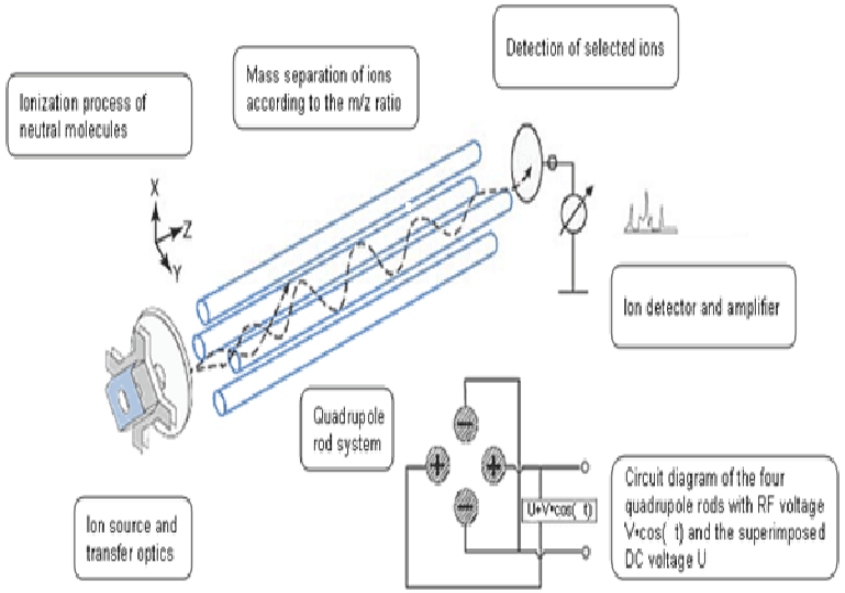
Illumina


b
OH OH
P7 P5
Grafted flow cell
Template hybridization
Initial extension
Denaturation
First denaturation
First cycle annealing
First cycle extension
Second cycle denaturation
Second cycle denaturation
Second cycle annealing
Second cycle extension
n = 35 total
Cluster amplification
P5 linearization
Block with ddNTPs
Denaturation and sequencing primer hybridization

Bioinformatic methods for metagenomics

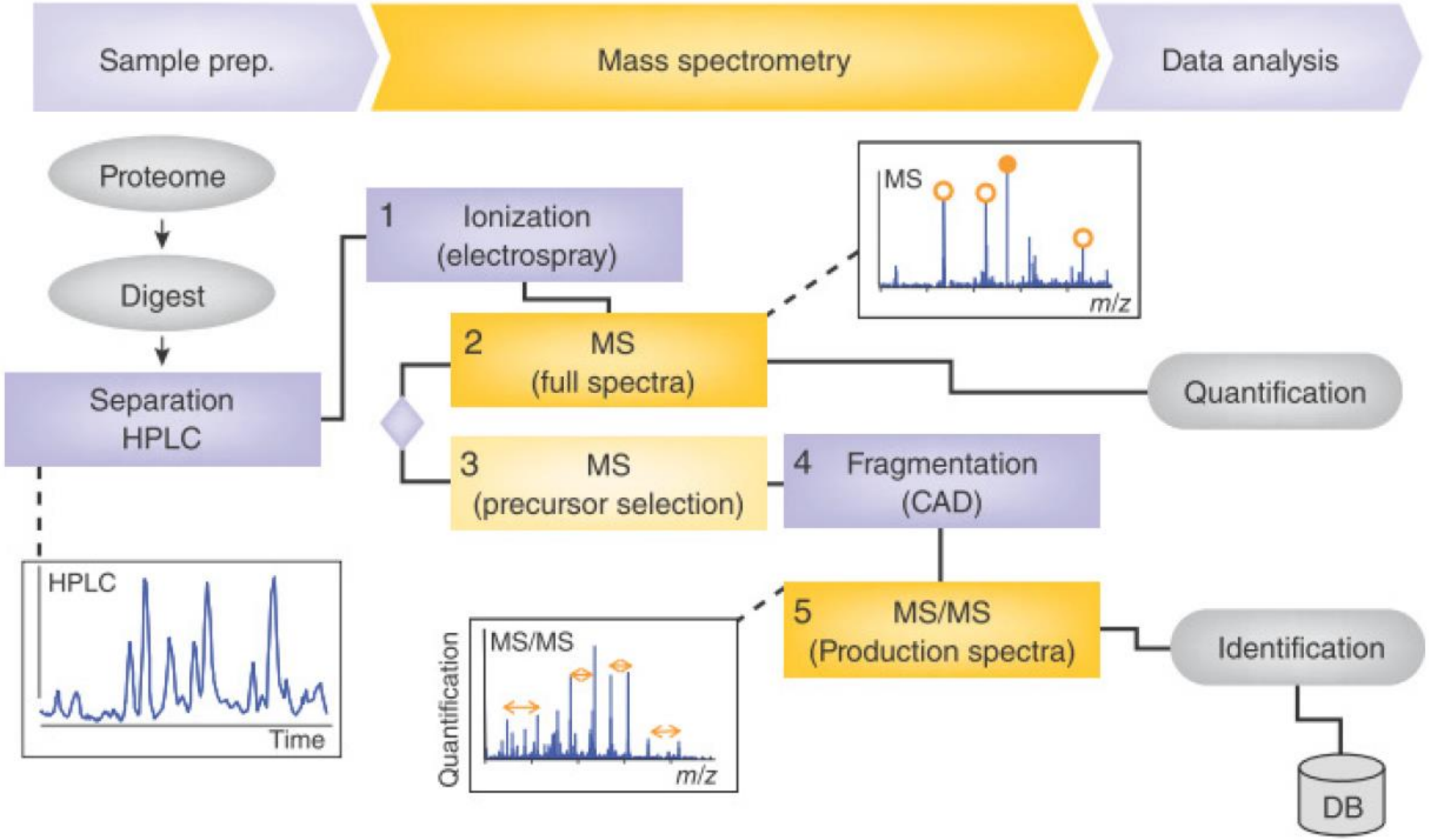


Mass Spectrometry



- Different compounds can be uniquely identified by their mass
  - For small organic molecules the MW can be determined to within 1 ppm or 0.0001% which is sufficiently accurate to confirm the molecular formula from mass alone
  - For large biomolecules the MW can be routinely determined within an accuracy of 0.002% (i.e. within 1 Da for a 40 kD protein)

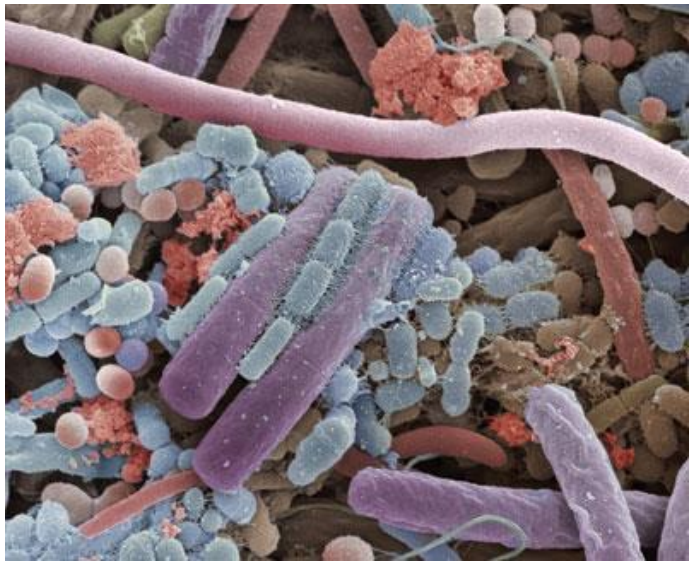
Proteomic



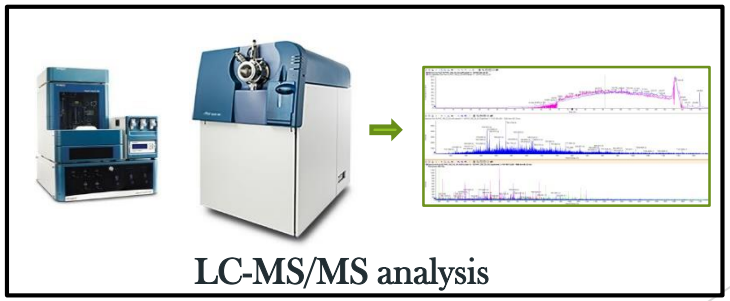
Domon and Aebersold, Nat Biotechnol 2010

From Proteomics to Metaproteomics

Microbiome



- ✓ How the population is composed
  - Operational Taxonomic Units (OTUs)
- ✓ What function does it accomplish
  - Protein Expression
  - Metabolism
- ✓ How does it react to external factors
  - Drugs
  - Diet
- ✓ How does the host respond to the community changes
  - Wellness
  - Disease



Metabolomics

Metabolomics has been defined as the identification and quantification of all metabolites (chemical fingerprints given by specific cellular processes) in a biological system.

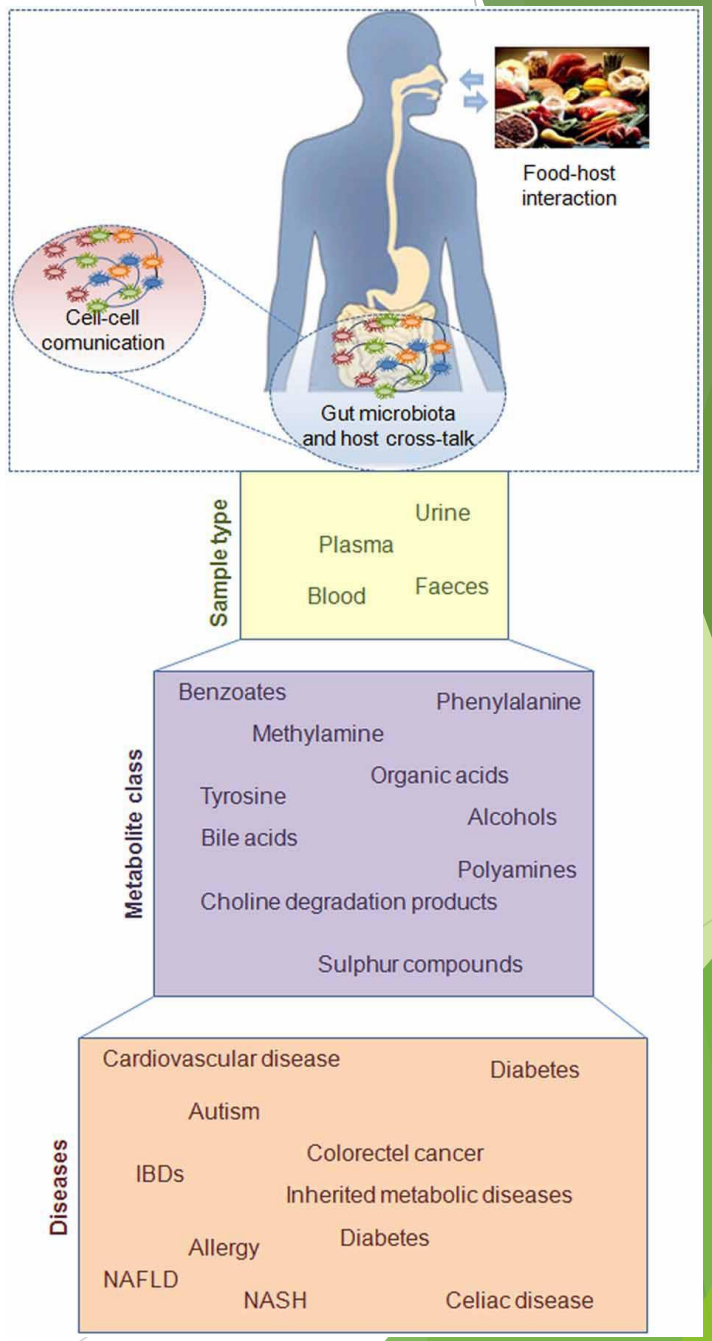
Metabolome refers to the complete set of small-molecules, metabolites (such as metabolic intermediates, hormones and other signaling molecules, and secondary metabolites) to be found within a biological sample, such as a single organism.

Host-microbiome metabolic interaction and cell-cell communication

Diet and caring (*i.e* probiotic consumption, antibiotic treatments, etc) has a key role in the gut microbiota modulation and shaping

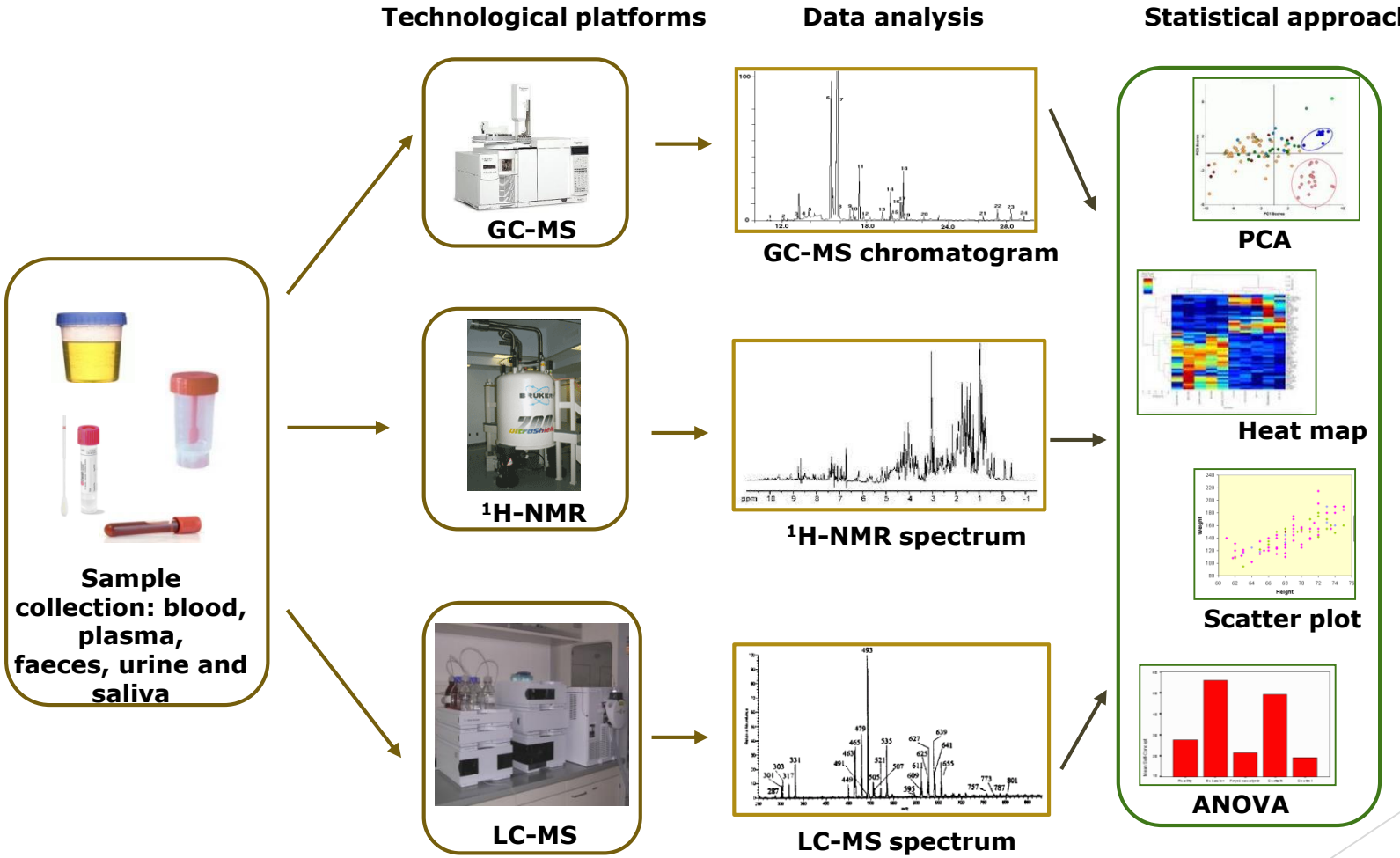
Foods or their ingredients and "drugs" play a crucial role in microbe selection and in a metabolic signaling network construction

The chemical dialogue via low molecular weight metabolites, peptides, and proteins between cell-cell and host-microbes leads to the *metabolite production* which may influence host healthy status ……and possibly represent disease biomarkers.



Vernocchi *et al.*, 2012. Front Cell Infect Microbiol. 2012;2:156

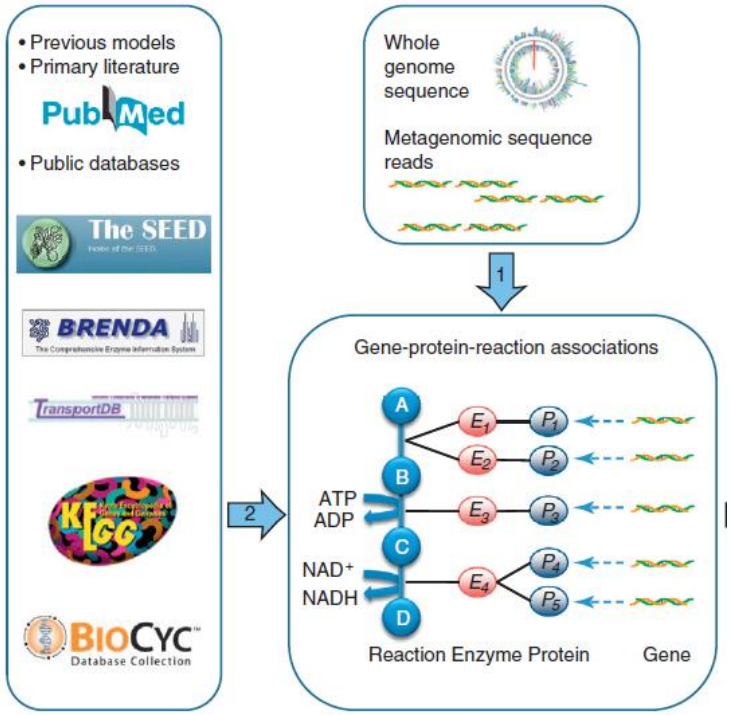
METABOLOMICS



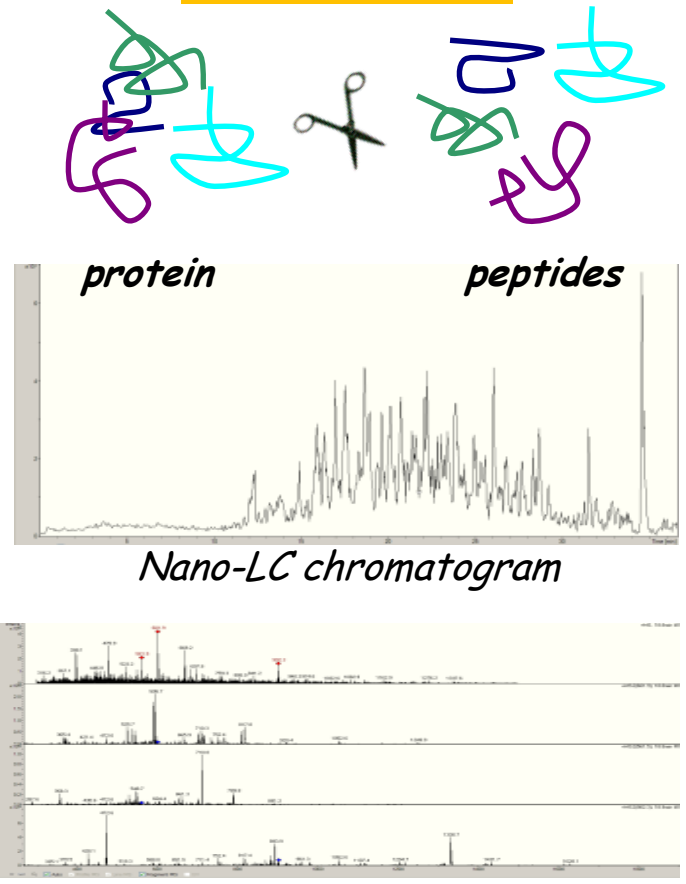
Del Chierico, Gnani, Vernocchi et al., 2014. Meta-omic platforms to assist in the understanding of NAFLD gut microbiota alterations: tools and applications. ***Int J Mol Sci***. 2014 Jan 7;15(1):684-711

INTEGRATED APPROACH: DEVELOPMENT OF ORIGINAL PIPELINES

METAGENOMICS



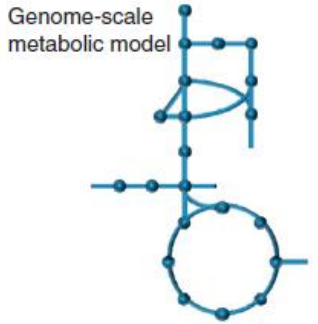
METAPROTEOMICS



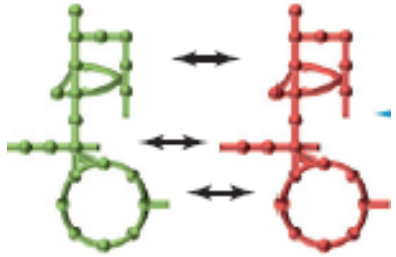
Nano-LC chromatogram

MS and MS² spectra

METABOLOMICS

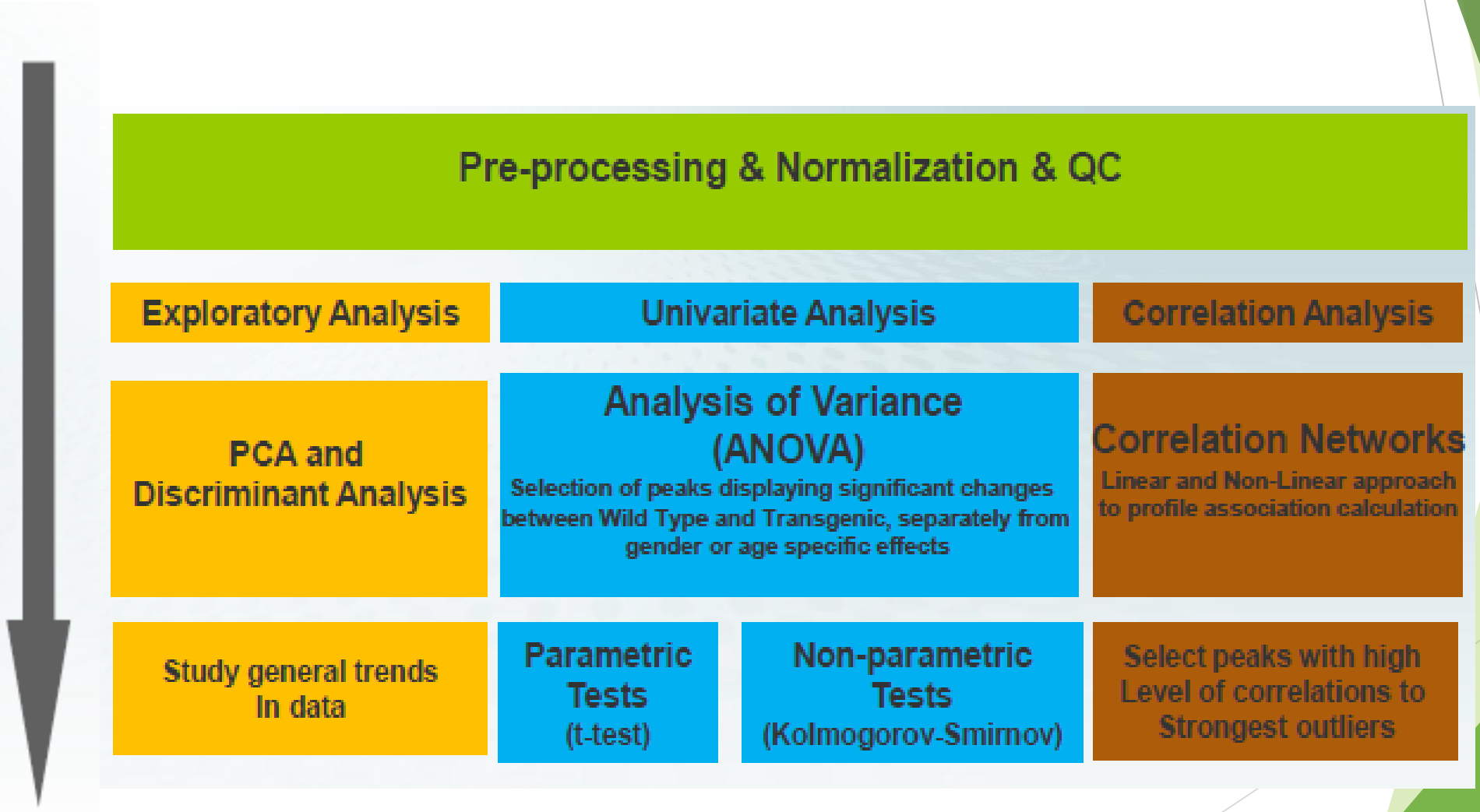


Inter-species metabolite exchange



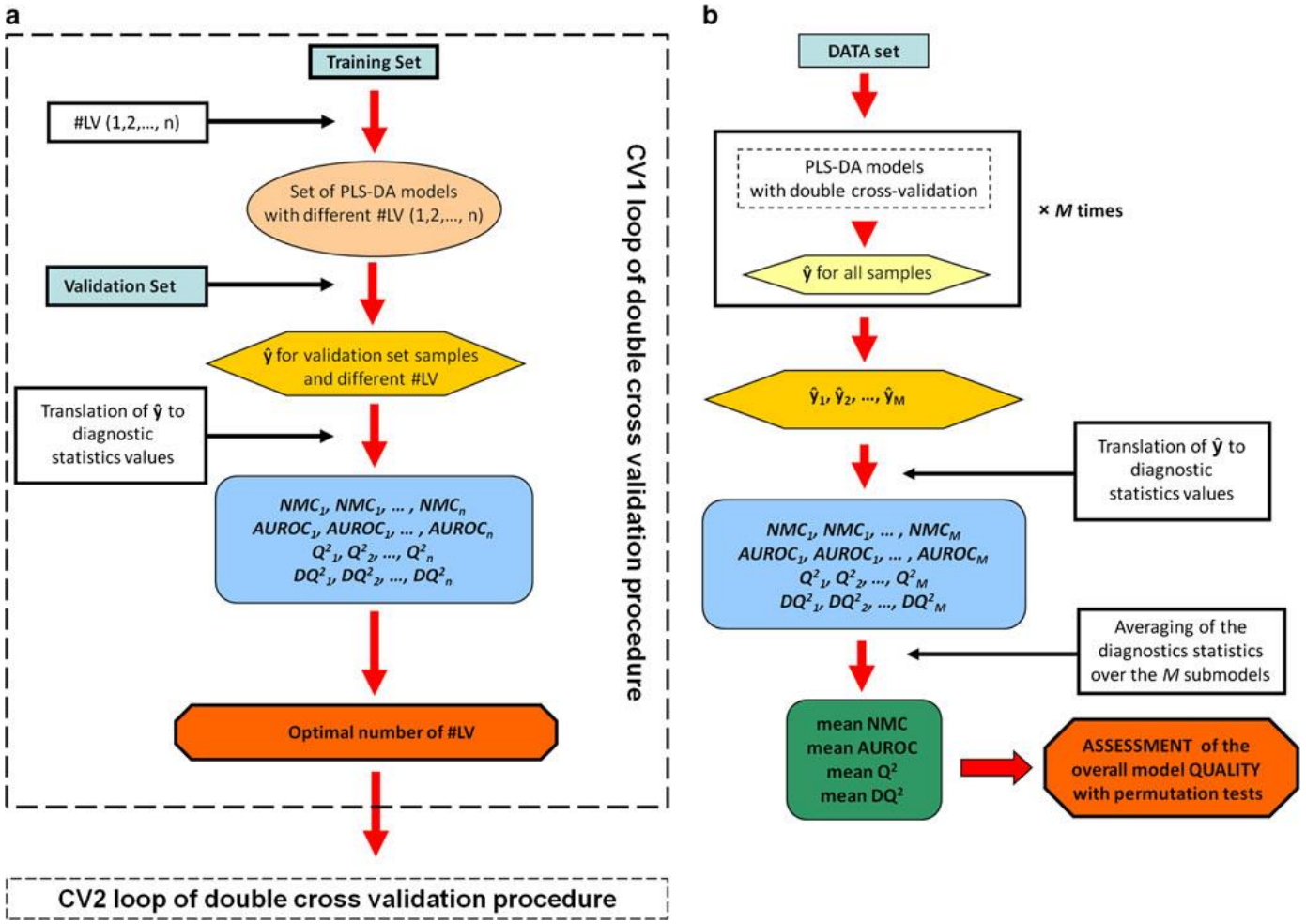
Del Chierico F, Vernocchi P, et al. Early-life gut microbiota under physiological and pathological conditions: the central role of combined meta-omics-based approaches. ***J Proteomics***. 2012 Aug 3;75(15):4580-7.

DATA ANALYSIS



Multivariated analysis methodologies

Graphical illustration of use of diagnostic statistics NMC, AUROC, and DQ2 in double cross validation procedure of PLS-Discriminant Analysis.
a) Use of diagnostics statistics in selection of optimal number of latent variables in CV1
b) use of diagnostics statistics in assessment of overall PLS-DA model quality after double cross validation procedure (CV2)



Szymanska E et al. Metabolomics 2012 Jun; 8(Suppl 1):3-16.

WHY WE STUDY THE MICROBIOTA BY SYSTEMS BIOLOGY APPROACH?

- Description of microbiota charts in physiological/pathological condition
- Discovery of microbial/molecular biomarkers in different diseases
- Discovery of the interplay between human and microbes
- how do microbial communities work and how are stable

Fecal Microbiota Transplantation

Definition

- Fecal microbiota transplantation (FMT) is the administration of a solution of fecal matter from a donor into the intestinal tract of a recipient in order to directly change the recipient's gut microbial composition and confer a health benefit.

[Bakken *et al.* 2011; Smits *et al.* 2013]

History

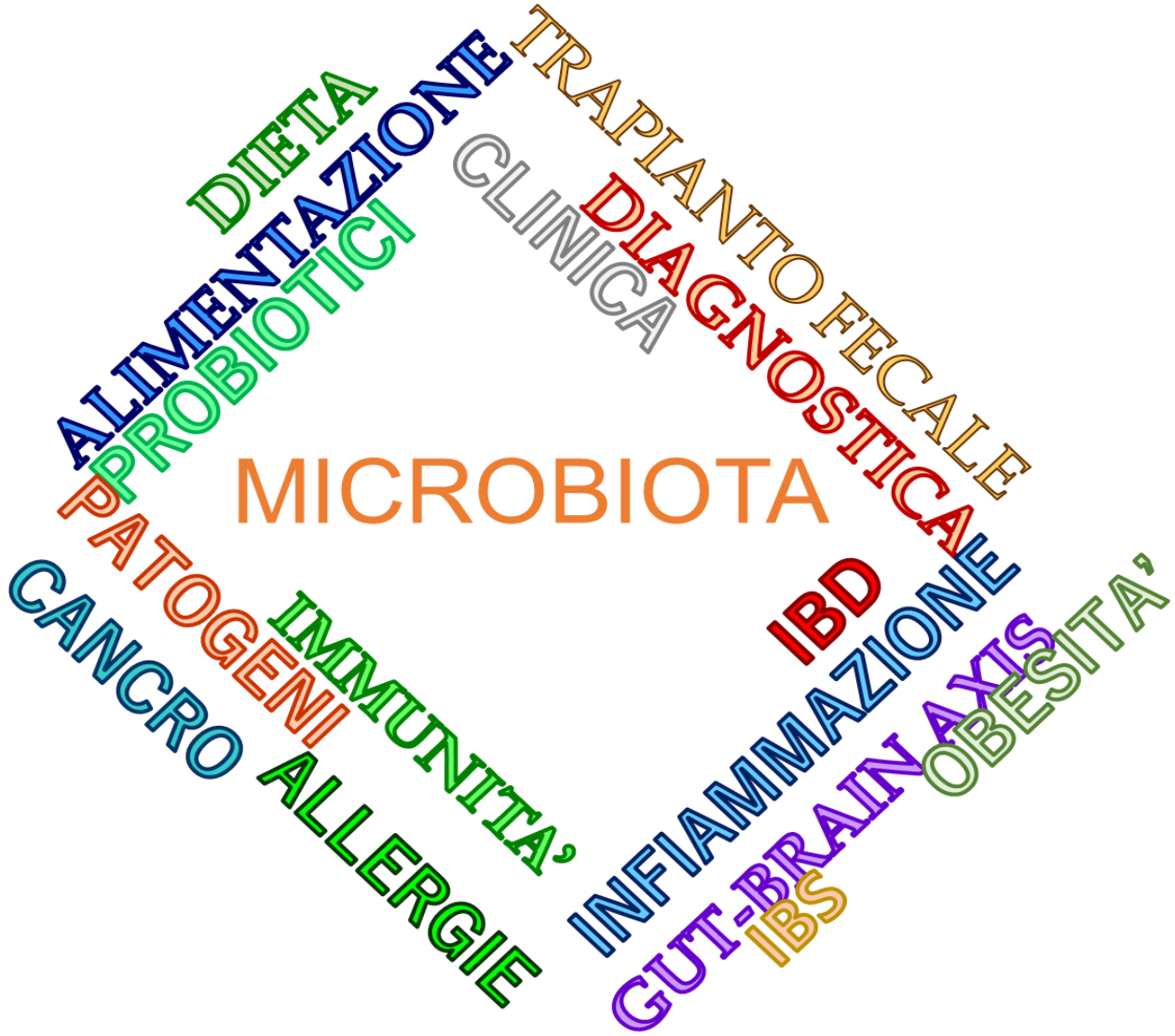
- First documented in 4th Century China as "Yellow Soup"
- In some countries, maternal feces is inserted into the newborn's mouth to "jumpstart" the colon
- June 17th, 2013: FDA approved the procedure for recurrent C. diff.
- 0 documented serious side effects
- 92% - 95% success rate

Potential Indications

- **GI Disorders:**
  - recurrent *Clostridium difficile* infection (RCDI).
  - inflammatory bowel disease (IBD),
  - irritable bowel syndrome (IBS), and
  - chronic constipation

The Procedure

- Carefully screened donor stool is mixed with a saline solution
- The solution is introduced into the GI tract via a NG tube, fecal enema, oral capsules, or during a colonoscopy
- The "good" bacteria multiply and help flush out the C. diff. bacteria
- 92% - 95% success rate



Grazie per l'attenzione

Per saperne di più…..

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Elizabeth G. Phimister, Ph.D., *Editor*

The Human Intestinal Microbiome in Health and Disease

Susan V. Lynch, Ph.D., and Oluf Pedersen, M.D., D.M.Sc.

HUMAN-ASSOCIATED MICROBES HAVE PRIMARILY BEEN VIEWED THROUGH the lens of a single species and its environment. Advances in culture-independent technologies have shown the enormous diversity, functional capacity, and age-associated dynamics of the human microbiome (see the Glossary). A large number of diverse microbial species reside in the distal gastrointestinal tract, and gut microbiota dysbiosis — imbalances in the composition and function of these intestinal microbes — is associated with diseases ranging from localized gastroenterologic disorders to neurologic, respiratory, metabolic, hepatic, and cardiovascular illnesses. Much effort is currently concentrated on exploring potential causality and related microbiota-mediated disease mechanisms, with the hope that an improved understanding will fuel the conception and realization of novel therapeutic and preventive strategies.

Until recently, our view of human microbiology was largely shaped by culture-based studies of single microbes (bacteria, archaea, fungi, and viruses), frequently isolated from patients who had acute infection or chronic disease. However, several decades ago, environmental microbial ecologists recognized that the diversity of microbes observed by microscopy far exceeded that of organisms recovered with the use of traditional culture-based approaches.[1] A variety of culture-independent molecular assays (Table 1) for detecting and classifying microorganisms (microbiota) and assessing their encoded genes (microbiome) and gene products showed

Biochemical Journal (2017) **474** 1823–1836
DOI: 10.1042/BCJ20160510

PORTLAND PRESS

Review Article

Introduction to the human gut microbiota

Elizabeth Thursby and Nathalie Juge

The Gut Health and Food Safety Programme, Institute of Food Research, Norwich Research Park, Norwich NR4 7UA, U.K.

Correspondence: Nathalie Juge (nathalie.juge@ifr.ac.uk)

OPEN ACCESS

The human gastrointestinal (GI) tract harbours a complex and dynamic population of microorganisms, the gut microbiota, which exert a marked influence on the host during homeostasis and disease. Multiple factors contribute to the establishment of the human gut microbiota during infancy. Diet is considered as one of the main drivers in shaping the gut microbiota across the life time. Intestinal bacteria play a crucial role in maintaining immune and metabolic homeostasis and protecting against pathogens. Altered gut bacterial composition (dysbiosis) has been associated with the pathogenesis of many inflammatory diseases and infections. The interpretation of these studies relies on a better understanding of inter-individual variations, heterogeneity of bacterial communities along and across the GI tract, functional redundancy and the need to distinguish cause from effect in states of dysbiosis. This review summarises our current understanding of the development and composition of the human GI microbiota, and its impact on gut integrity and host health, underlying the need for mechanistic studies focusing on host–microbe interactions.

Per saperne di più…..

INFLAMMATION REVIEW

nature immunology

Regulation of inflammation by microbiota interactions with the host

J Magarian Blander[1–3], Randy S Longman[1,2], Iliyan D Iliev[1,2], Gregory F Sonnenberg[1–3] & David Artis[1–3]

The study of the intestinal microbiota has begun to shift from cataloging individual members of the commensal community to understanding their contributions to the physiology of the host organism in health and disease. Here, we review the effects of the microbiome on innate and adaptive immunological players from epithelial cells and antigen-presenting cells to innate lymphoid cells and regulatory T cells. We discuss recent studies that have identified diverse microbiota-derived bioactive molecules and their effects on inflammation within the intestine and distally at sites as anatomically remote as the brain. Finally, we highlight new insights into how the microbiome influences the host response to infection, vaccination and cancer, as well as susceptibility to autoimmune and neurodegenerative disorders.

PERSPECTIVES

OPINION

The resilience of the intestinal microbiota influences health and disease

Felix Sommer, Jacqueline Moltzau Anderson, Richa Bharti, Jeroen Raes and Philip Rosenstiel

Abstract | The composition of the intestinal microbiota varies among individuals and throughout development, and is dependent on host and environmental factors. However, although the microbiota is constantly exposed to environmental challenges, its composition and function in an individual are stable against perturbations, as microbial communities are resilient and resistant to change. The maintenance of a beneficial microbiota requires a homeostatic equilibrium within microbial communities, and also between the microorganisms and the intestinal interface of the host. The resilience of the healthy microbiota protects us from dysbiosis-related diseases, such as inflammatory bowel disease (IBD) or metabolic disorder. By contrast, a resilient dysbiotic microbiota may cause disease. In this Opinion article, we propose that microbial resilience has a key role in health and disease. We will discuss the concepts and mechanisms of microbial resilience against dietary, antibiotic or bacteriotherapy-induced perturbations and the implications for human health.