Microbiota – The Role in Cancer Development and Progression

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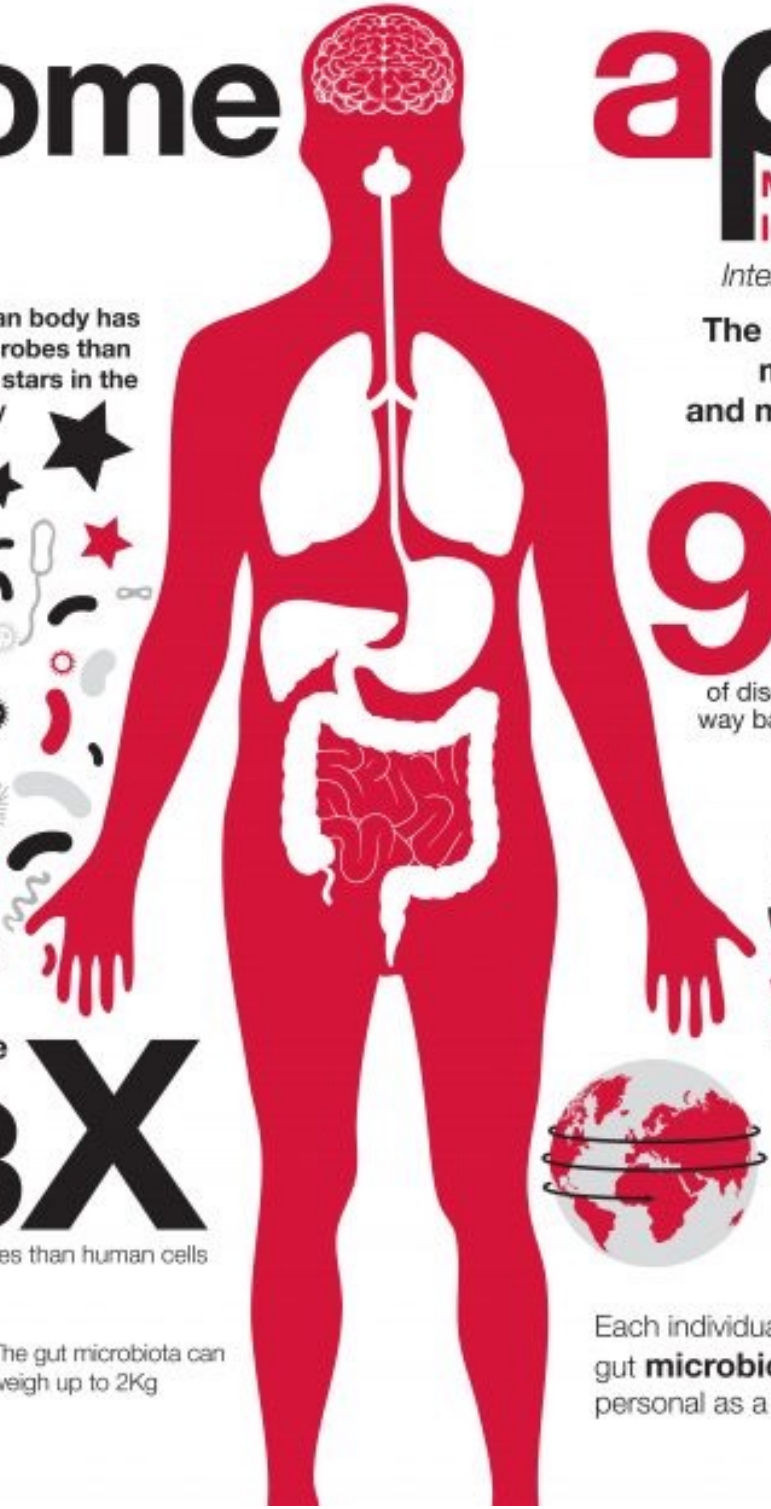
www.cgenomics.org

Microbiome

IN NUMBERS



100 Trillion

symbiotic microbes live in and on every person and make up the human microbiota

The human body has more microbes than there are stars in the milky way

95%

of our microbiota is located in the GI tract

150:1

The genes in your microbiome outnumber the genes in our genome by about 150 to one

The surface area of the **GI tract** is the same size as 2 tennis courts

You have 1.3X

more microbes than human cells

>10,000

Number of different microbial species that researchers have identified living in and on the human body

2kg

The gut microbiota can weigh up to 2Kg

Microbiome Ireland

Interfacing Food & Medicine

The microbiome is more medically accessible and manipulable than the human genome

It is thought that **90%** of disease can be linked in some way back to the gut and health of the microbiome

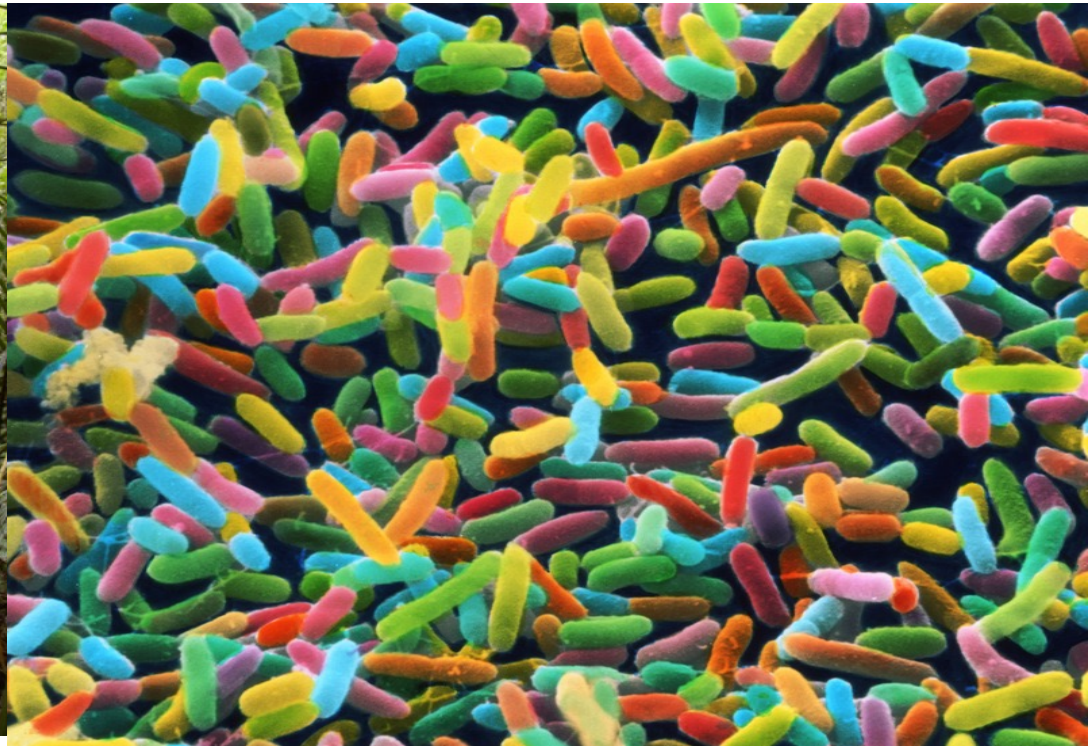
5:1

Viruses:Bacteria in the gut microbiota

2.5 The number of times your body's microbes would circle the earth if positioned end to end

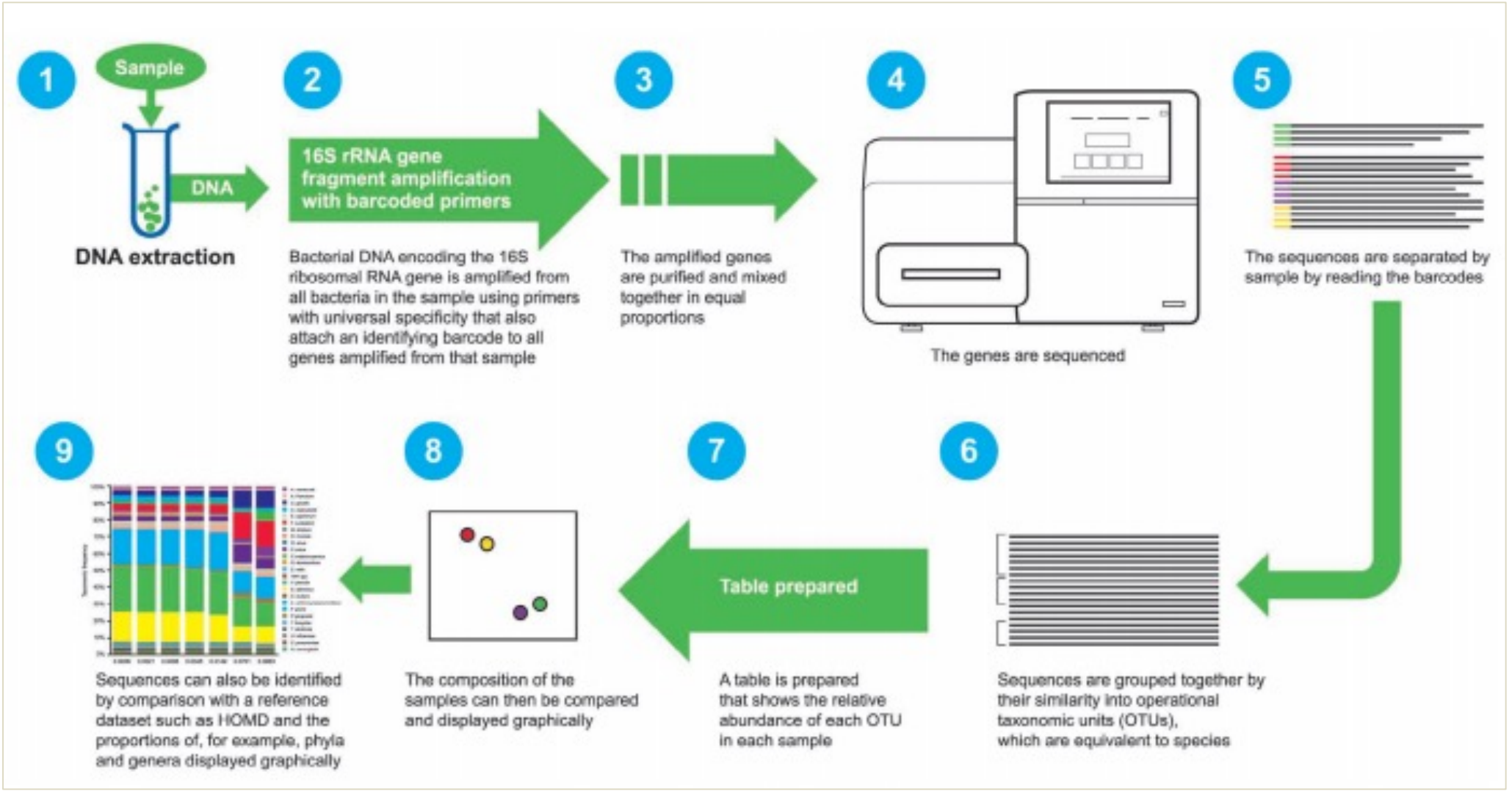
Each individual has a unique gut **microbiota**, as personal as a fingerprint

Microbiome as an ecosystem



How do we study the microbiome?


Welcome to MiSeq Control Software
MiSeq®
illumina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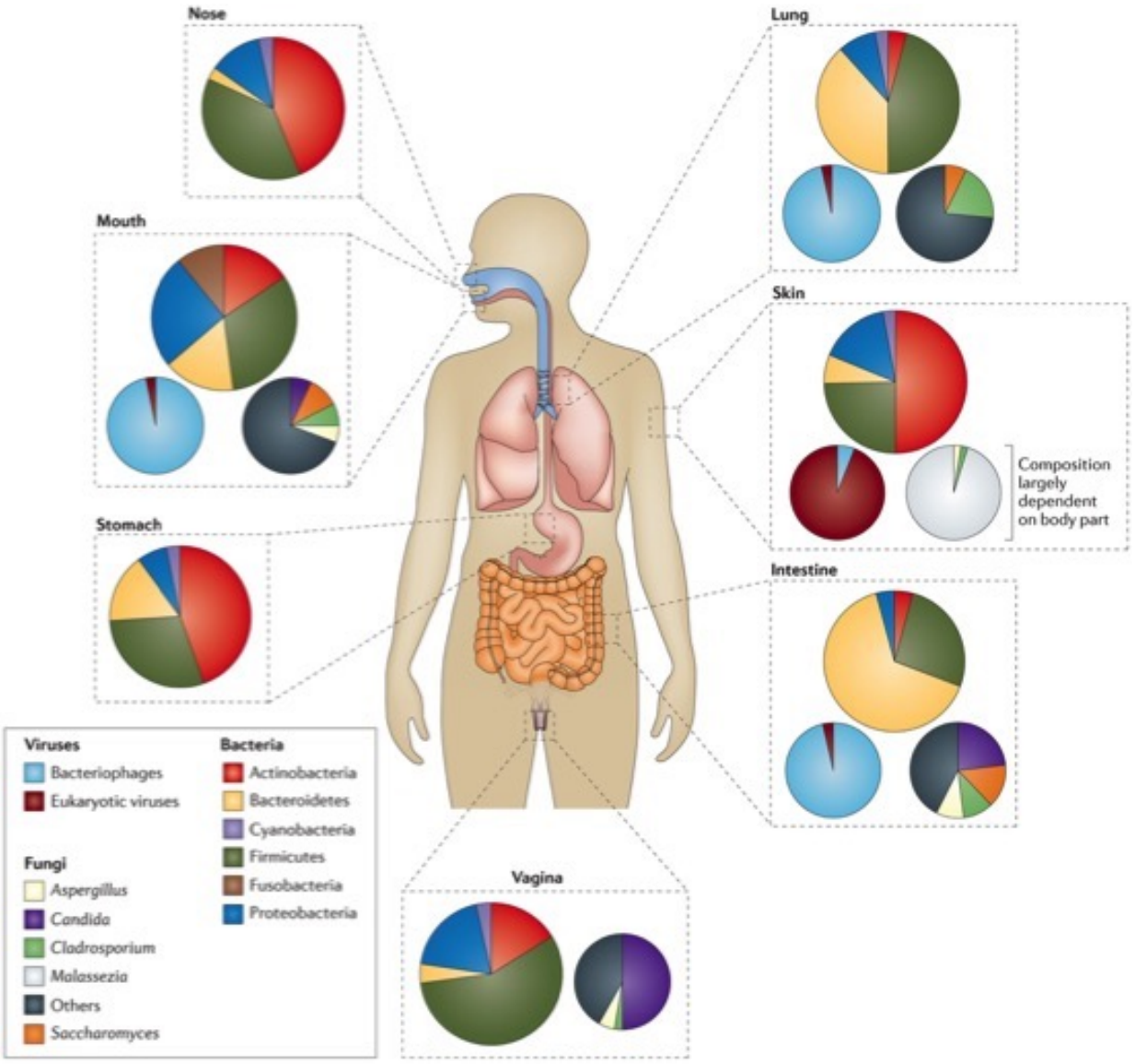
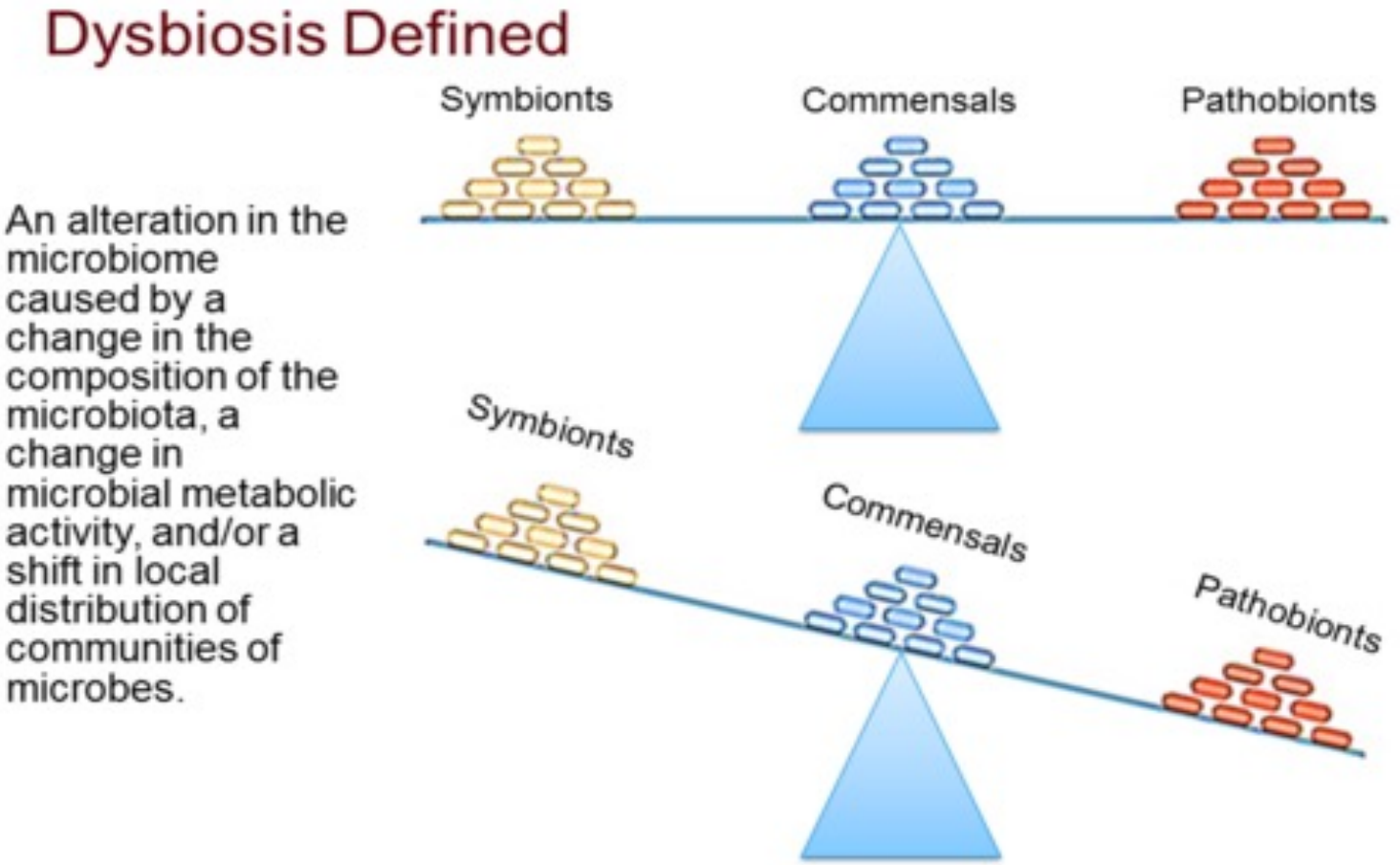
Different niches for the human microbiome

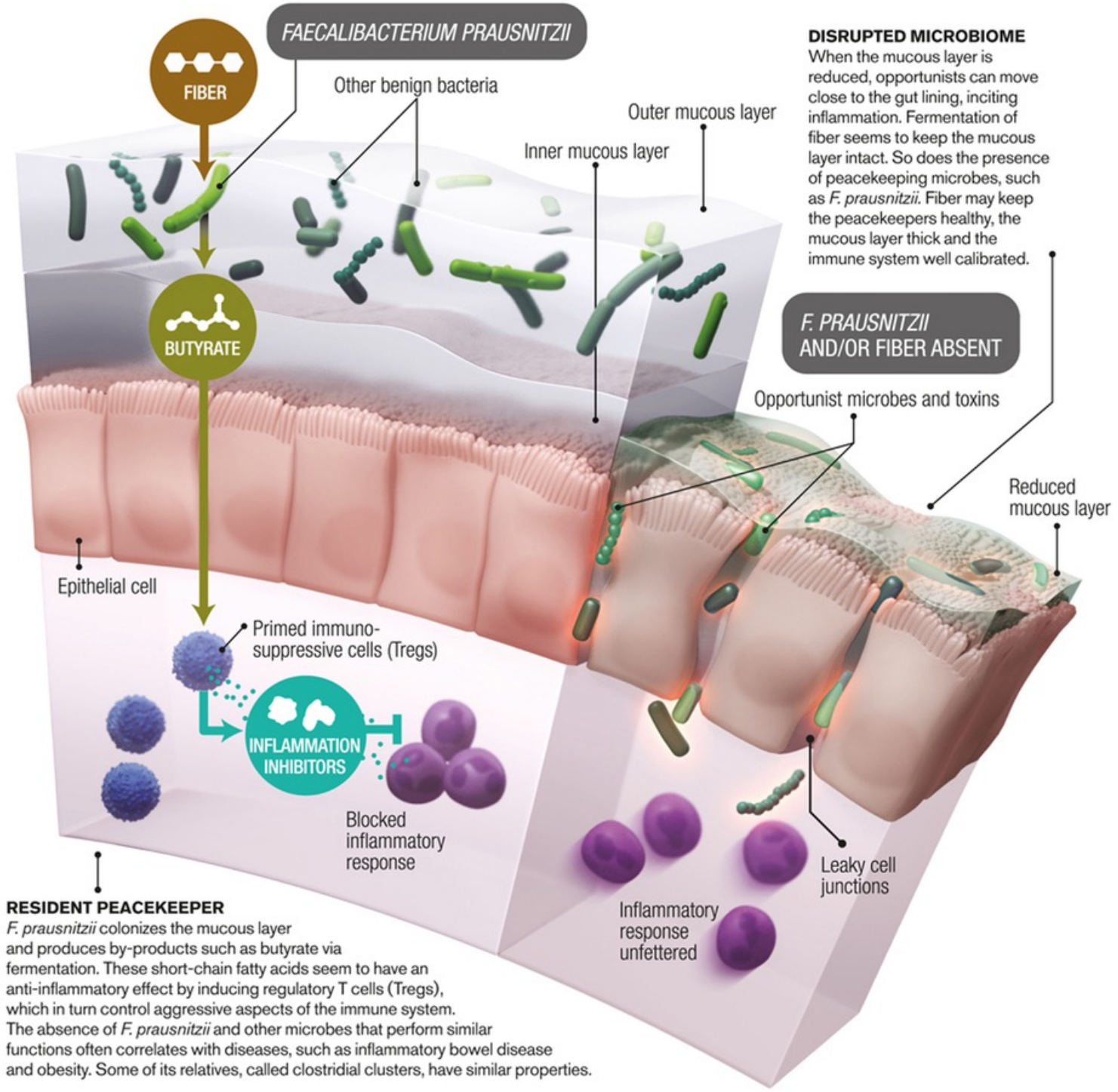


Alteration of the microbiome (dysbiosis) can be an important factor in disease

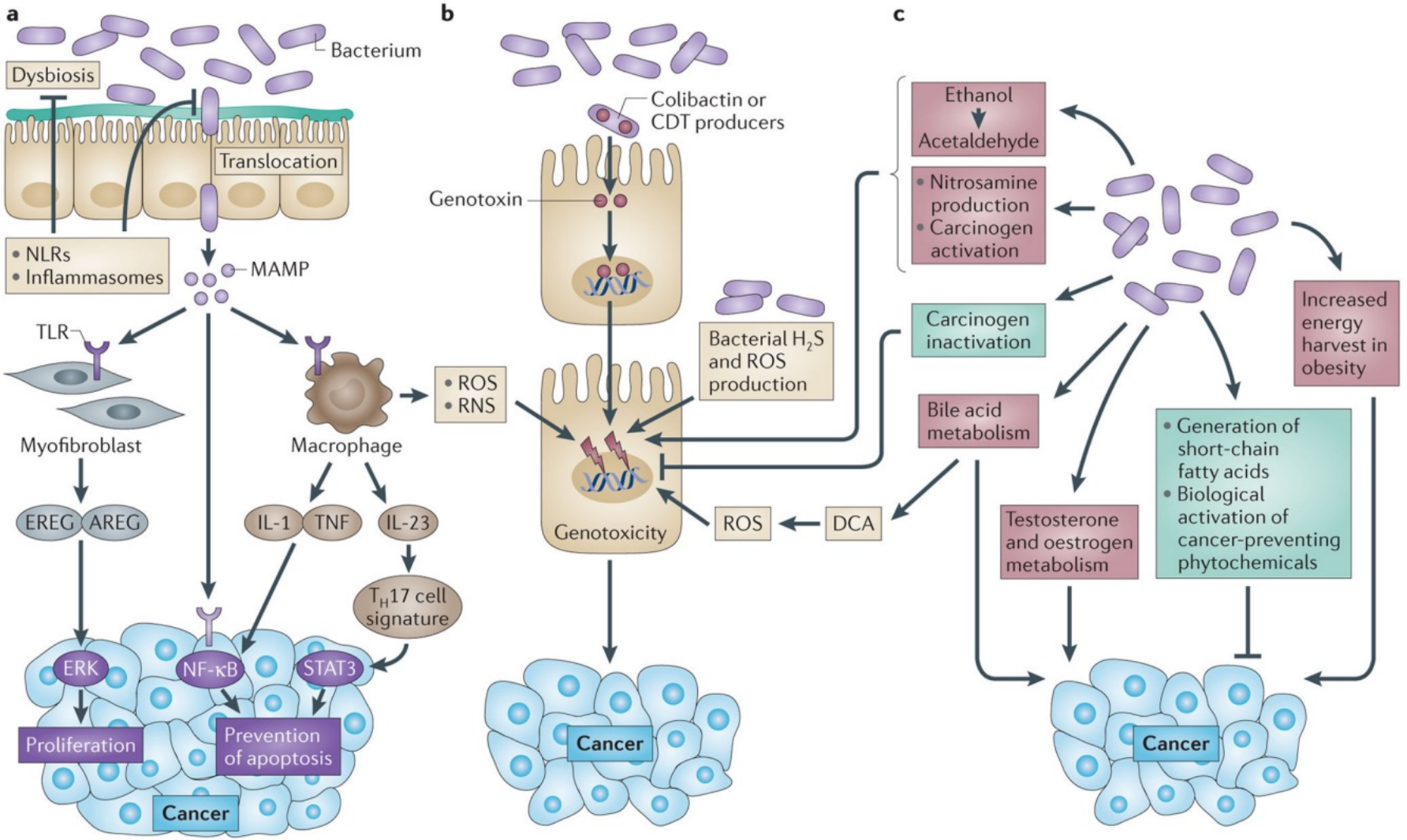


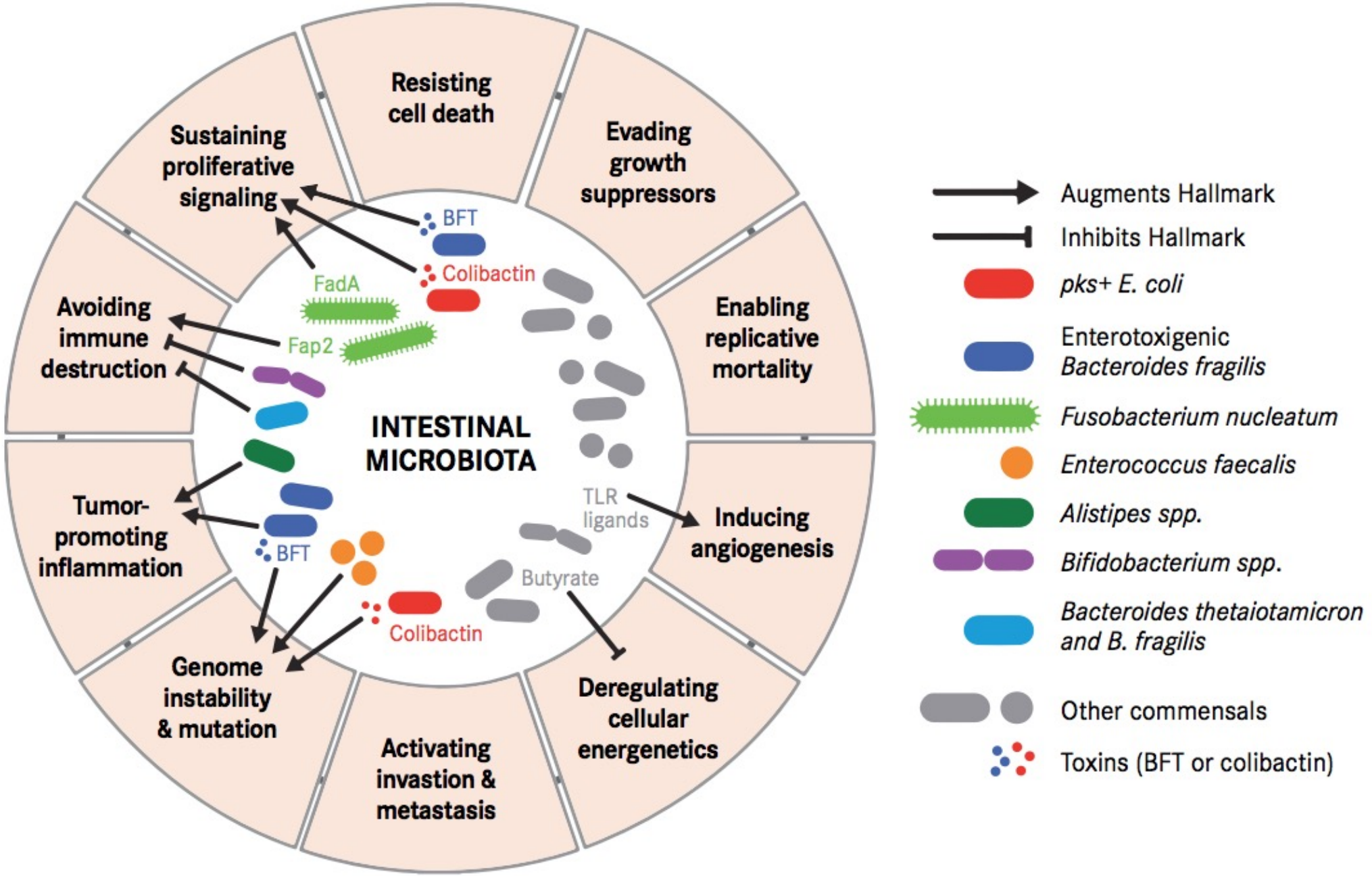
Round JL, Mazmanian SK. The gut microbiota shapes intestinal immune responses during health and disease. Nat Rev Immunol. 2009 May;9(5):313-23.

Microbiome and Cancer


FAECALIBACTERIUM PRAUSNITZII
FIBER
Other benign bacteria
Outer mucous layer
Inner mucous layer
BUTYRATE
DISRUPTED MICROBIOME
When the mucous layer is reduced, opportunists can move close to the gut lining, inciting inflammation. Fermentation of fiber seems to keep the mucous layer intact. So does the presence of peacekeeping microbes, such as F. prausnitzii. Fiber may keep the peacekeepers healthy, the mucous layer thick and the immune system well calibrated.
F. PRAUSNITZII AND/OR FIBER ABSENT
Opportunist microbes and toxins
Reduced mucous layer
Epithelial cell
Primed immuno-suppressive cells (Tregs)
INFLAMMATION INHIBITORS
Blocked inflammatory response
Leaky cell junctions
Inflammatory response unfettered
RESIDENT PEACEKEEPER
F. prausnitzii colonizes the mucous layer and produces by-products such as butyrate via fermentation. These short-chain fatty acids seem to have an anti-inflammatory effect by inducing regulatory T cells (Tregs), which in turn control aggressive aspects of the immune system. The absence of F. prausnitzii and other microbes that perform similar functions often correlates with diseases, such as inflammatory bowel disease and obesity. Some of its relatives, called clostridial clusters, have similar properties.

microbes may be involved in the origin and/or progression of other diseases, i.e. **cancer.**



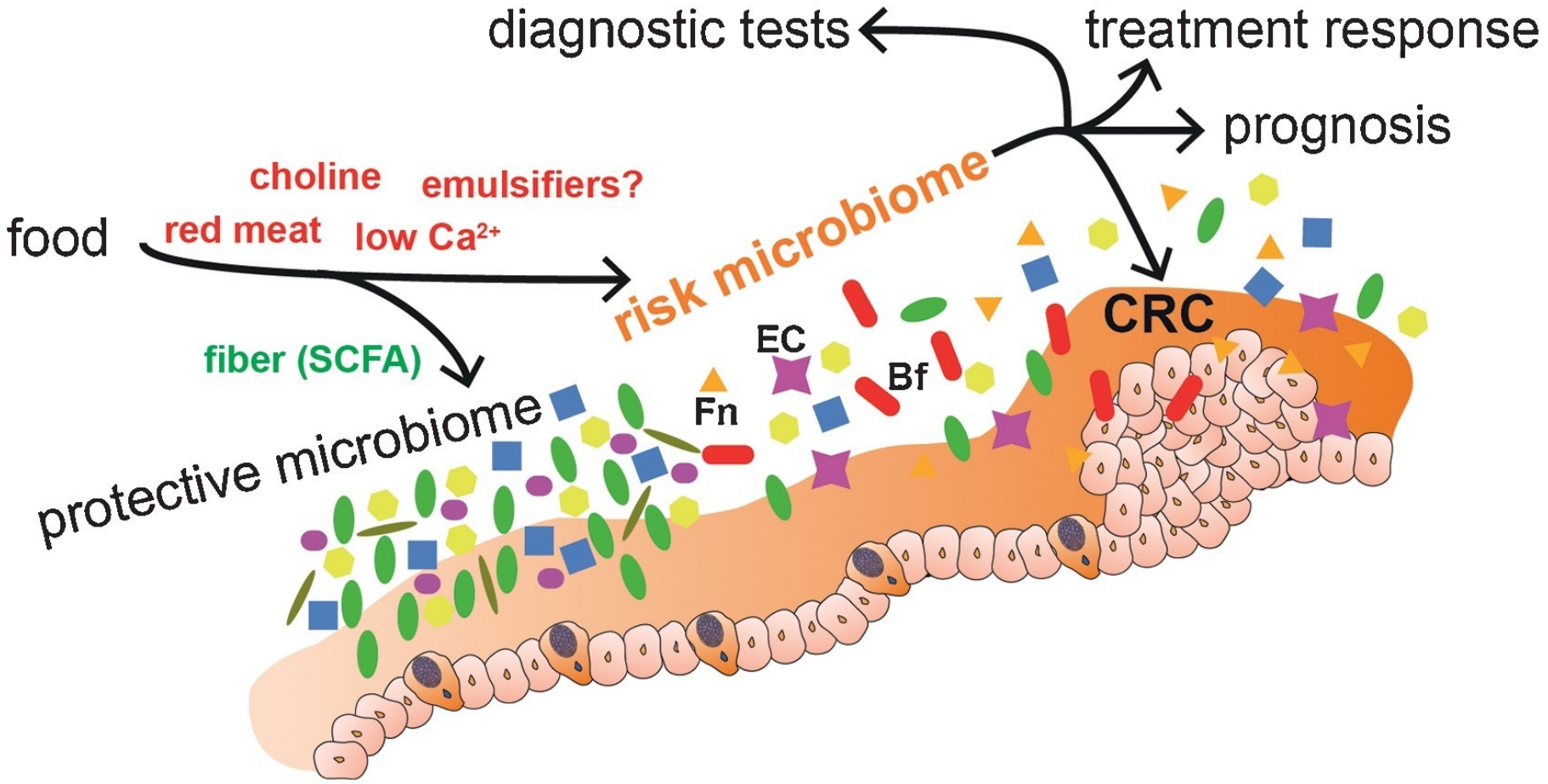


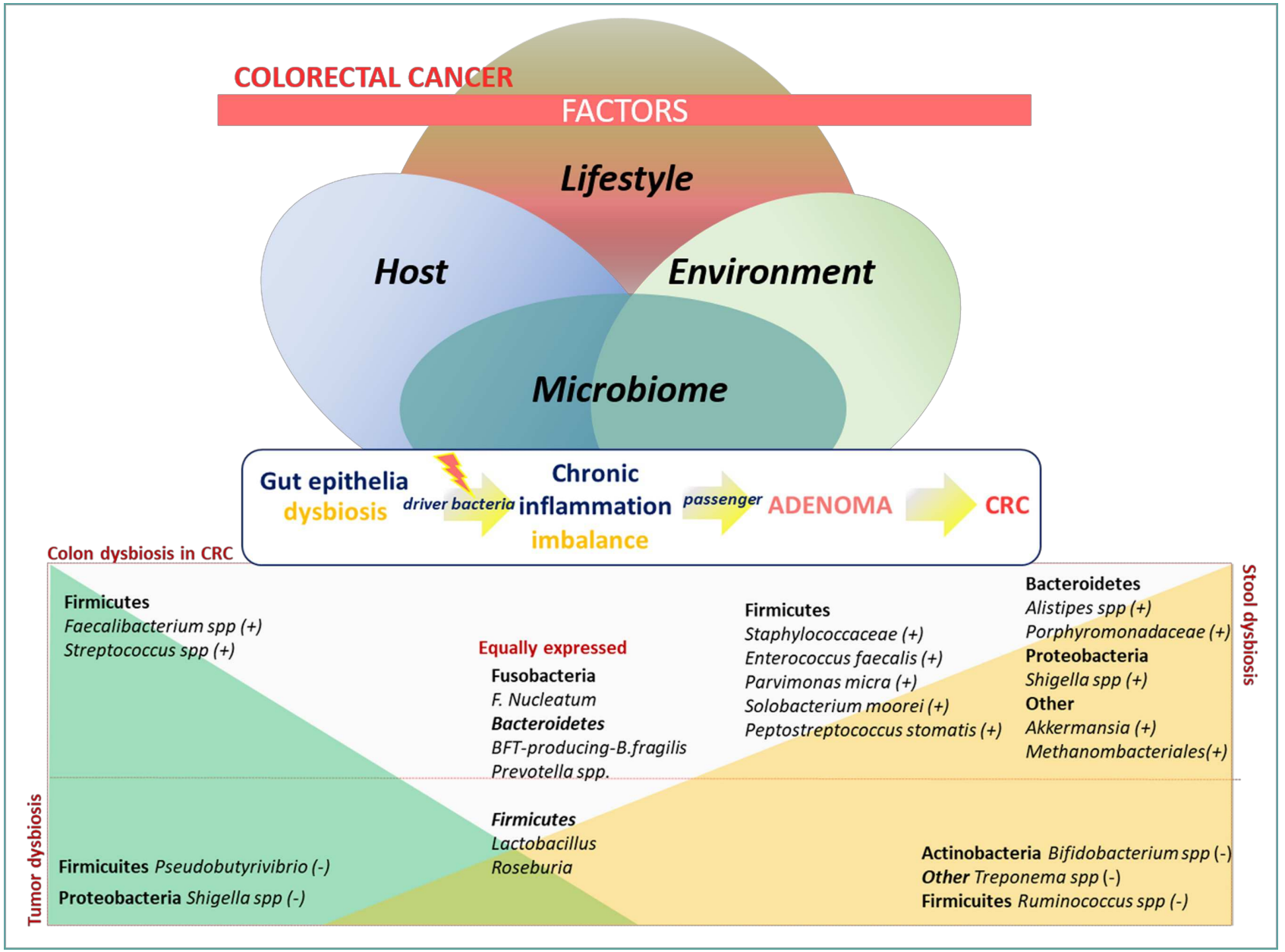
BFT indicates *Bacteroides fragilis* toxin; pks+, colibactin-producing; TLR, toll-like receptor.

A growing body of clinical evidence has uncovered links between the microbiota and the Hallmarks of Cancer. These include butyrate, a short-chain fatty acid; colibactin, a genotoxin; and FadA and Fap2, bacterial mechanisms of *Fusobacterium nucleatum*.

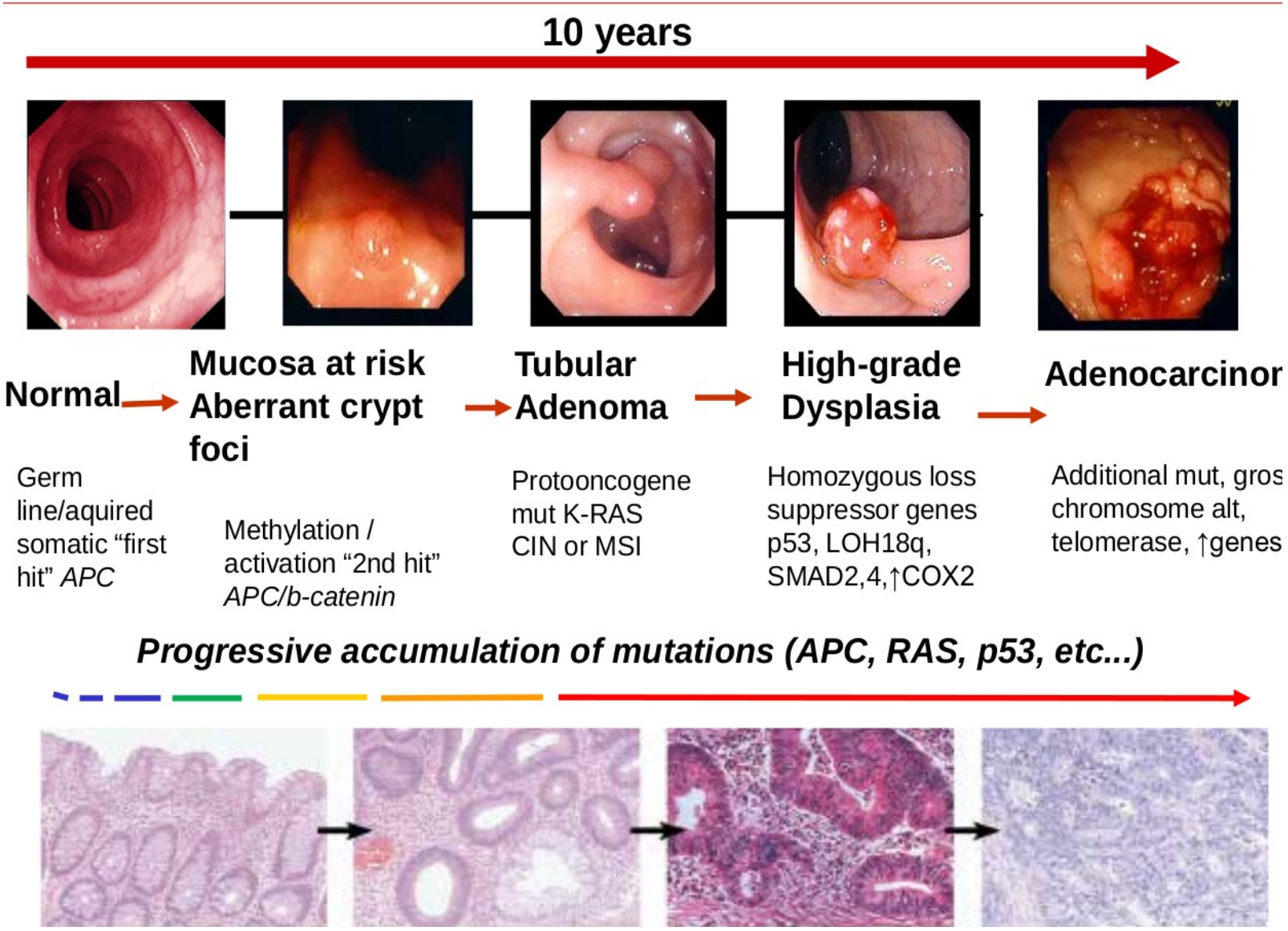
Fulbright LE, Ellermann M, Arthur JC. The microbiome and the hallmarks of cancer. *PLoS Pathog.* 2017;13(9):e1006480. doi :10.1371/journal.ppat.1006480.

Clinical applications of the microbiome

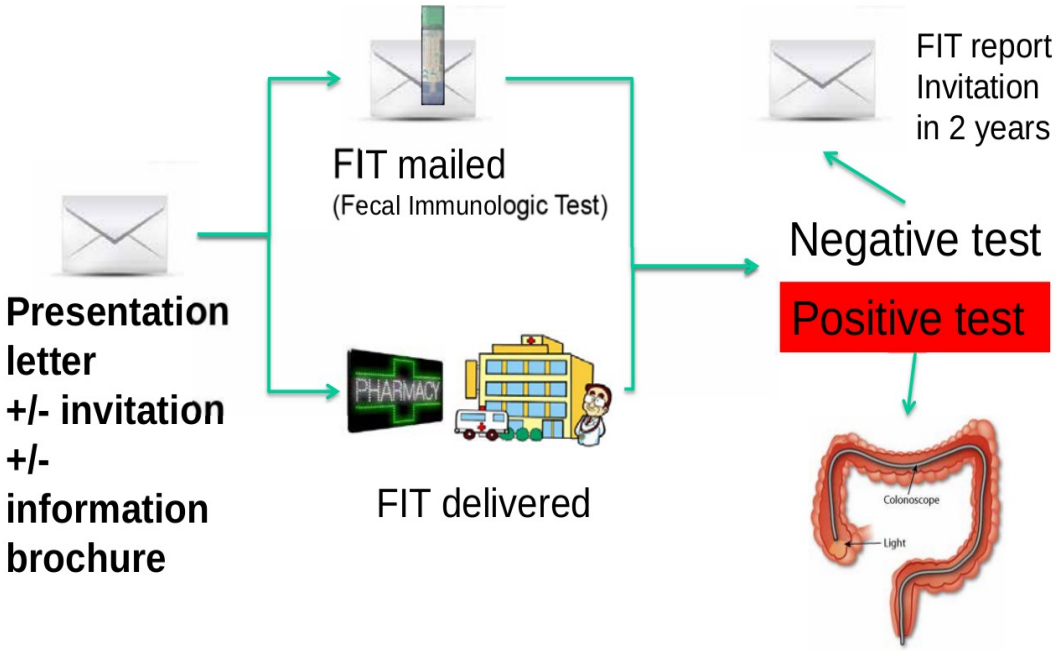




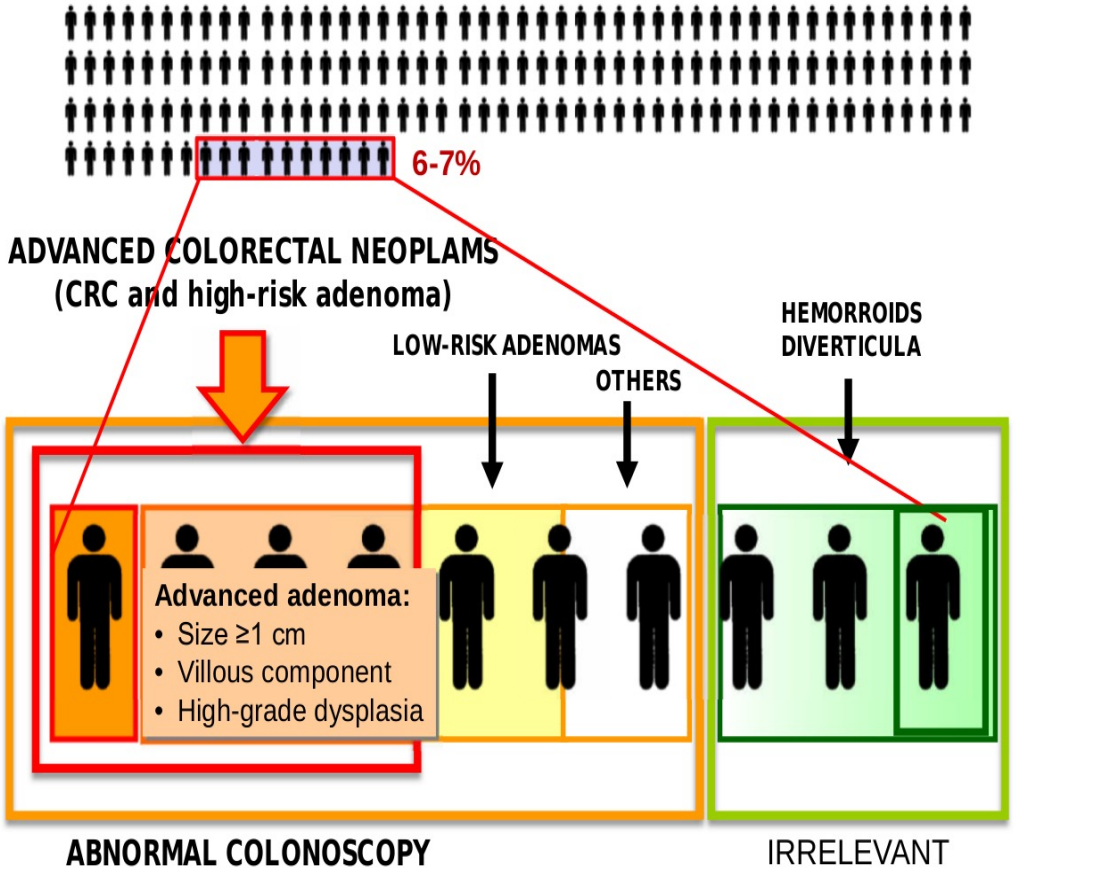
Saus E, et. al. Microbiome and colorectal cancer: Roles in carcinogenesis and clinical potential. Mol Aspects Med. 69:93-106. doi: 10.1016/j.mam.2019.05.001.


10 years
Normal
Mucosa at risk
Aberrant crypt foci
Tubular Adenoma
High-grade Dysplasia
Adenocarcinor
Germ line/aquired somatic "first hit" APC
Methylation / activation "2nd hit" APC/b-catenin
Protooncogene mut K-RAS CIN or MSI
Homozygous loss suppressor genes p53, LOH18q, SMAD2,4,↑COX2
Additional mut, gros chromosome alt, telomerase, ↑genes
Progressive accumulation of mutations (APC, RAS, p53, etc...)

Invitation procedure



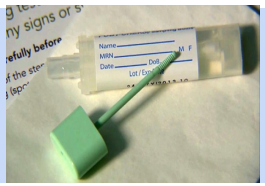
Endoscopic finding in FIT-positive participants



Courtesy of Dr. JM. Augé (H. Clínic)

Since 2000: Program of early detection of CRC implemented in Catalunya

Men / Women aged 50-69
Fecal Immunochemical Test (FIT)



FIT+

Colonoscopy

~5% CRC or clinically relevant

Microbiome profile

Germinal genetic variants

Environmental factors

RISK SCORE

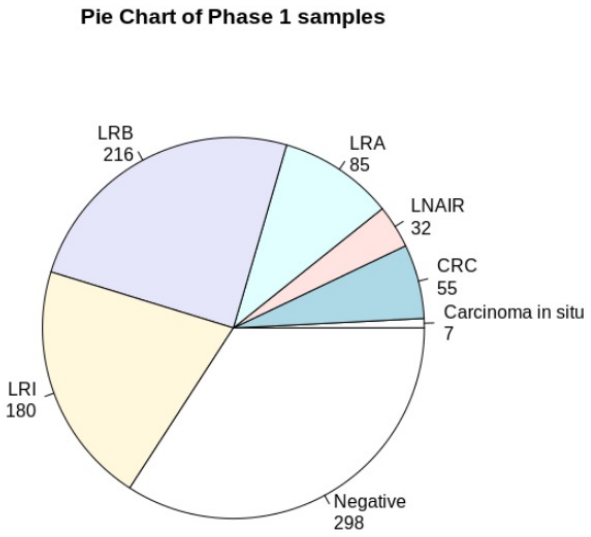
PERIS 2016 2020

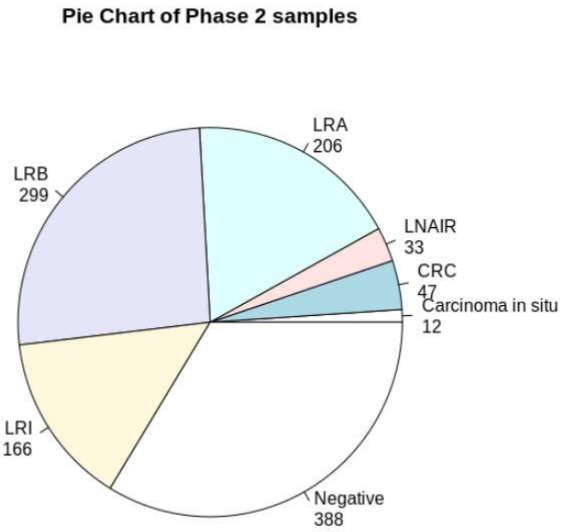
PHASE 1	PHASE 2
892 samples	2,072 samples

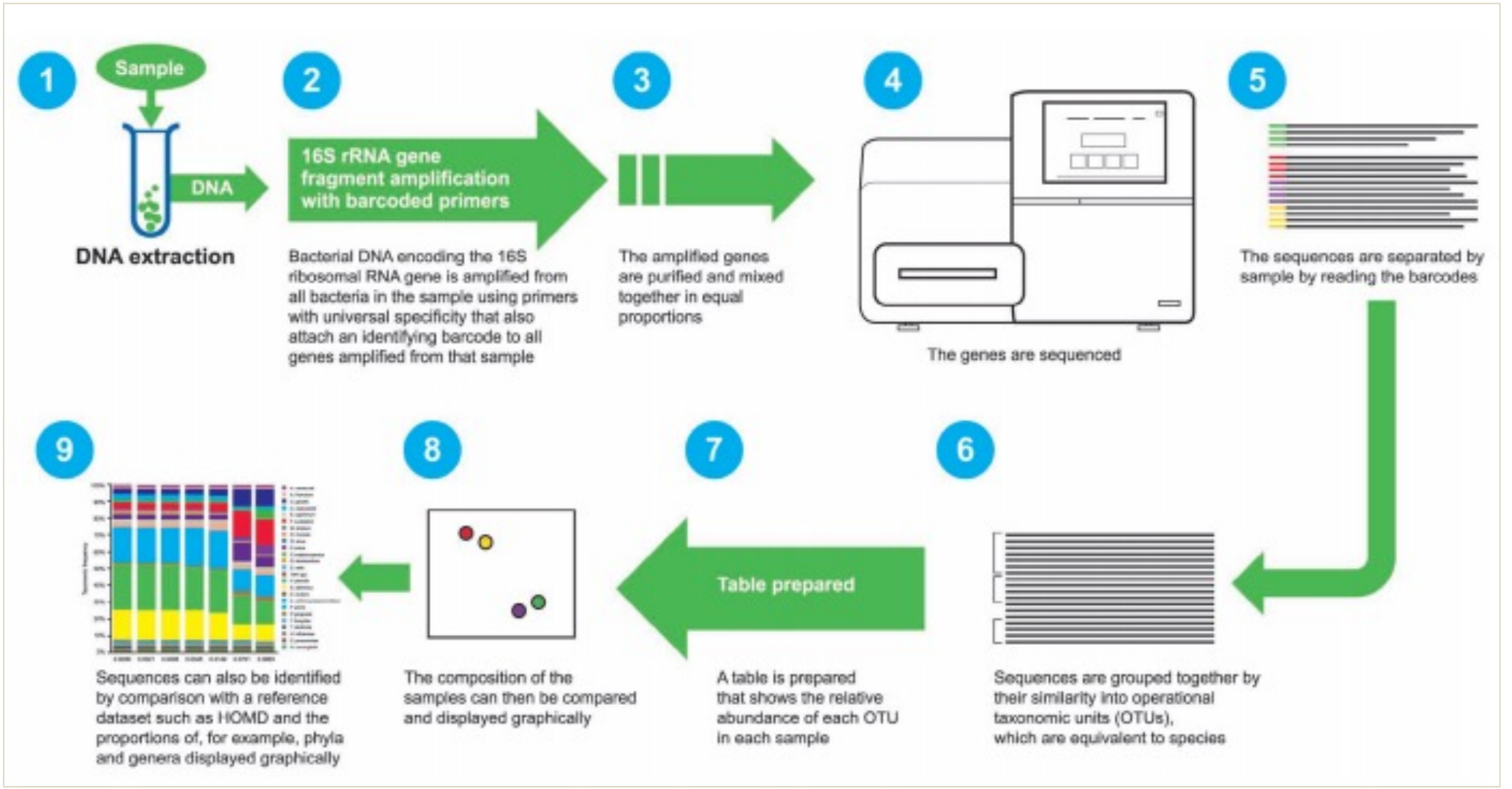
PHASE 1	PHASE 2
892 samples	2,072 samples

Colonoscopy results for FIT + samples:

LRA: High Risk Lesion
LNAIR: Lesion Not Associated to Risk
CRC: Colorectal cancer
Carcinoma in situ
Negative: Negative result in colonoscopy
LRI: Intermediate Risk Lesion
LRB: Low risk lesion



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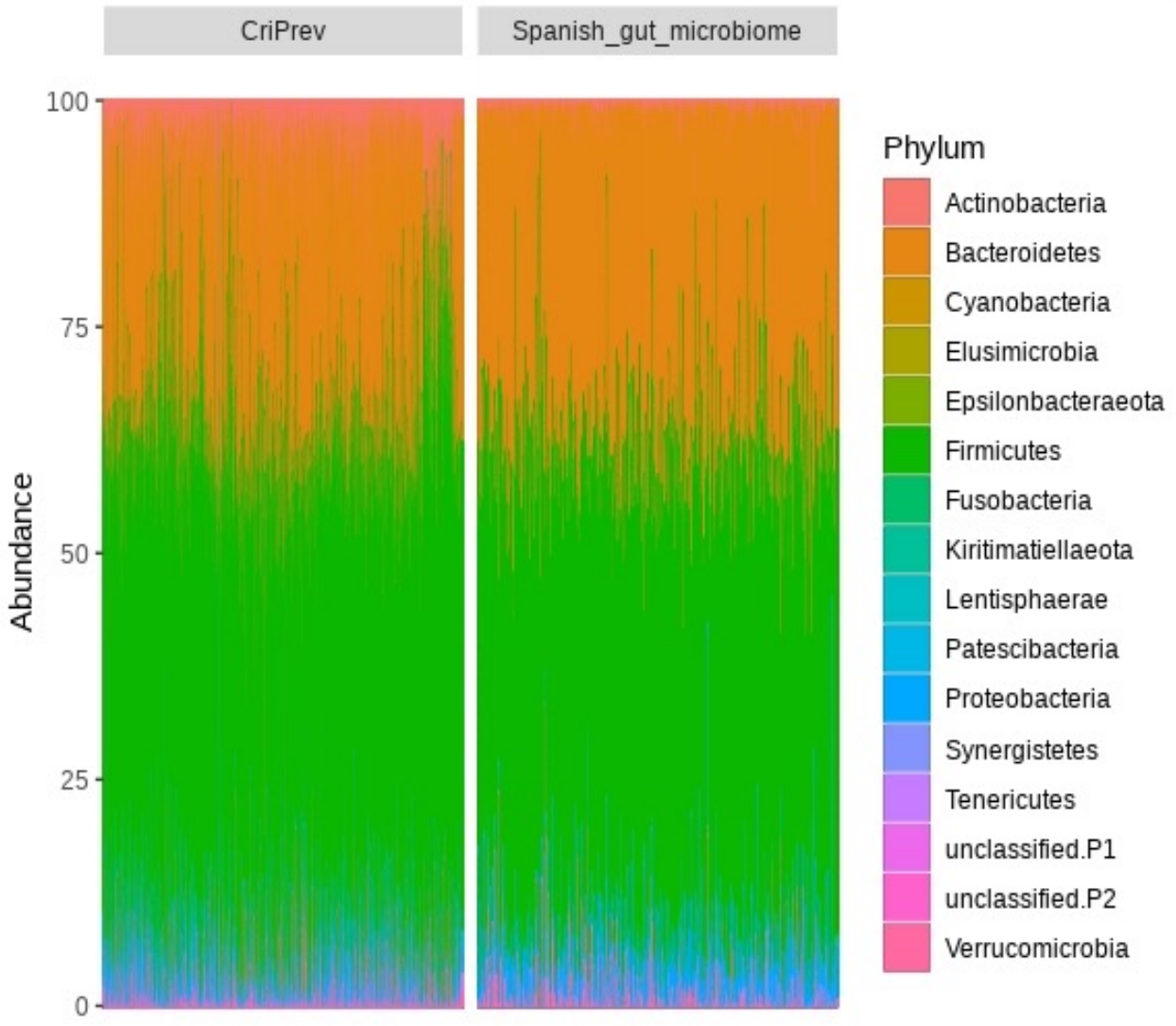
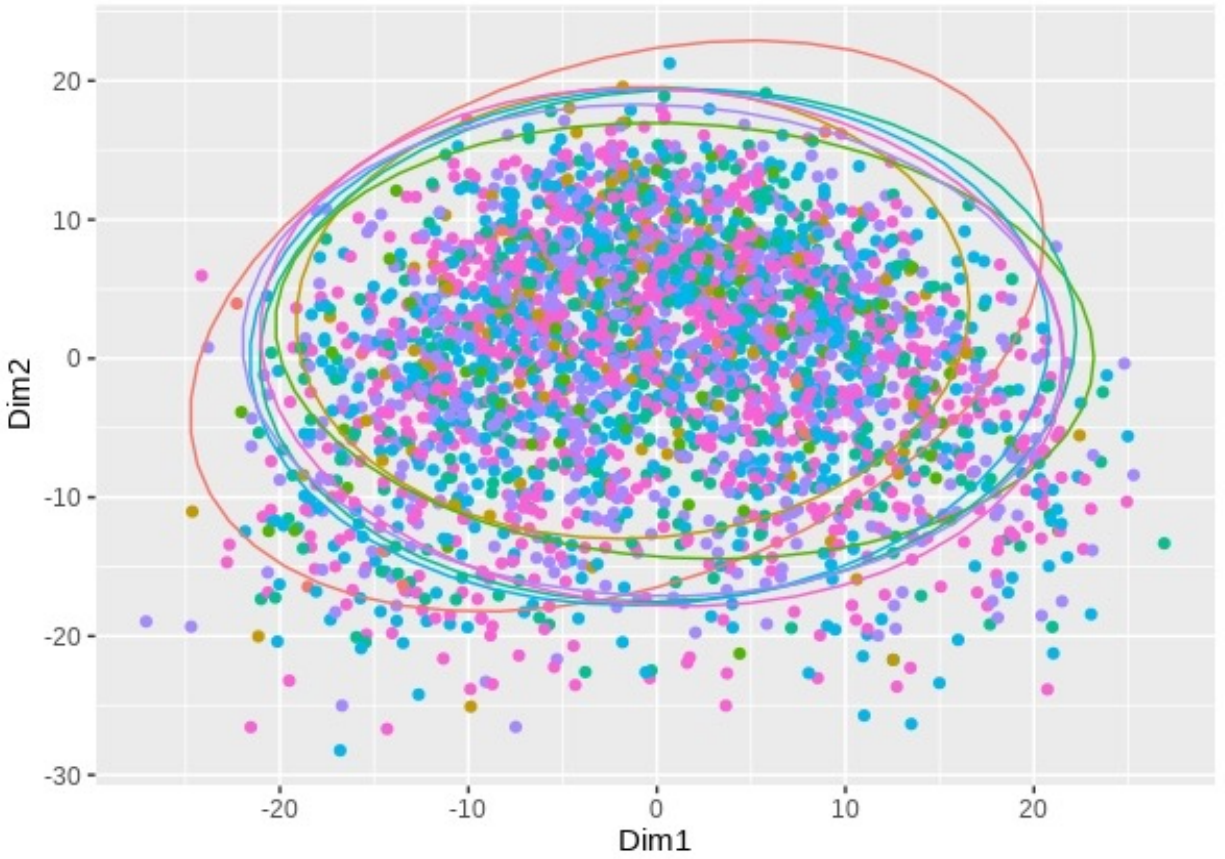
scientific reports



OPEN

The Spanish gut microbiome reveals links between microorganisms and Mediterranean diet

Adriel Latorre-Pérez[1✉], Marta Hernández[2✉], Jose Ramón Iglesias[2], Javier Morán[3], Javier Pascual[1], Manuel Porcar[1,4], Cristina Vilanova[1] & Luis Collado[5]



Adonis
Covariates: Sex and Age
(P = 0.001)

LRA: High Risk Lesion
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CRC: Colorectal cancer
Carcinoma in situ
Negative: Negative result in colonoscopy
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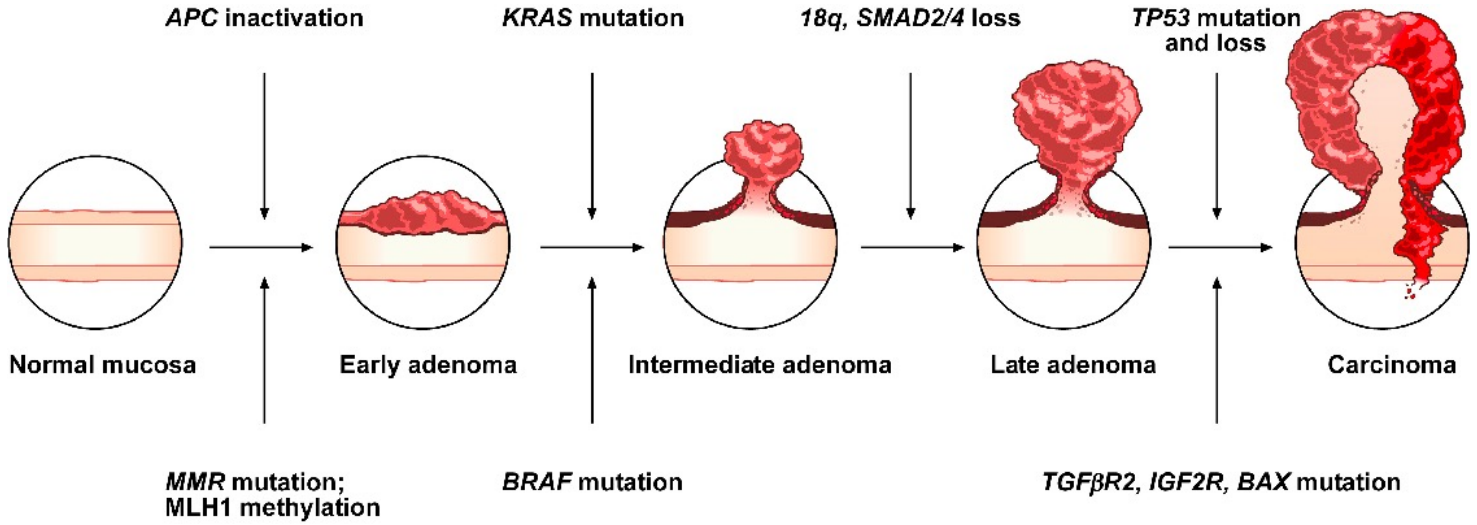
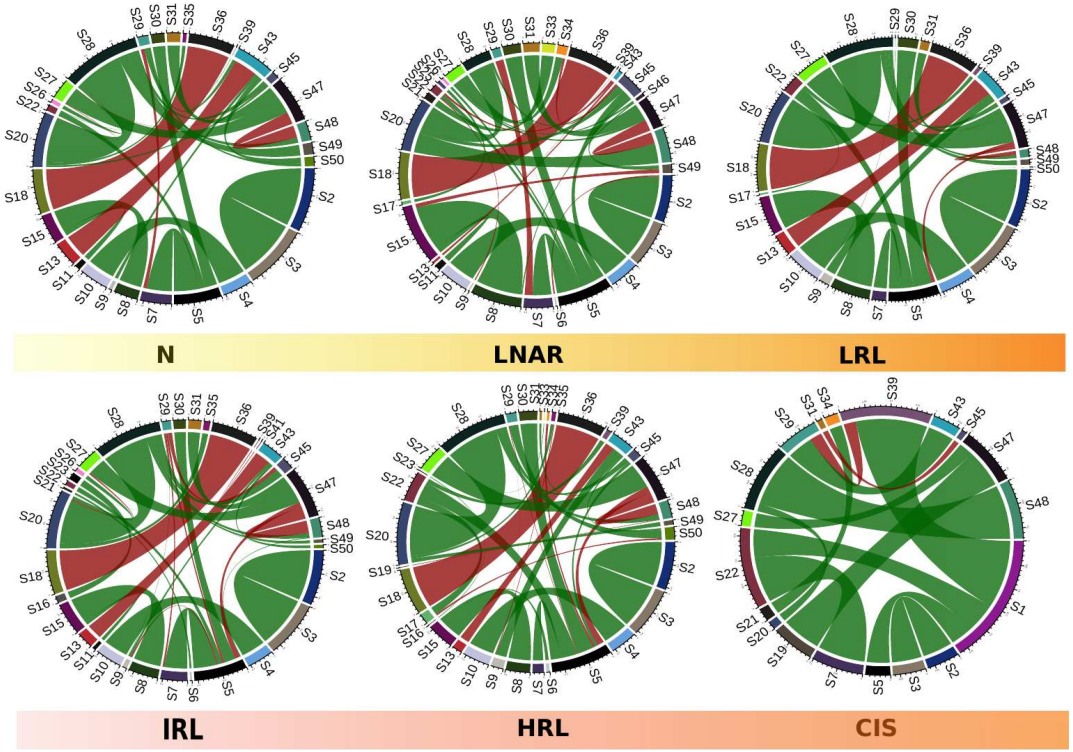
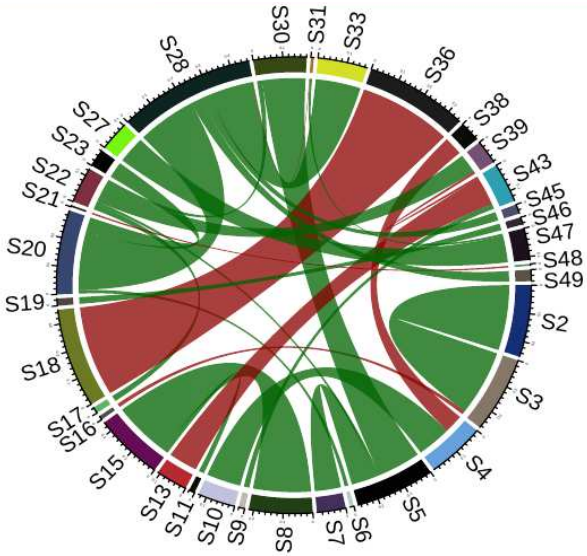


MSI - Microsatellite Instability pathway





CRC

50-69 age

FIT TEST
> 20 µg hemoglobin/g feces?

After 2 years

YES

NO

FIT POSITIVE

FIT NEGATIVE

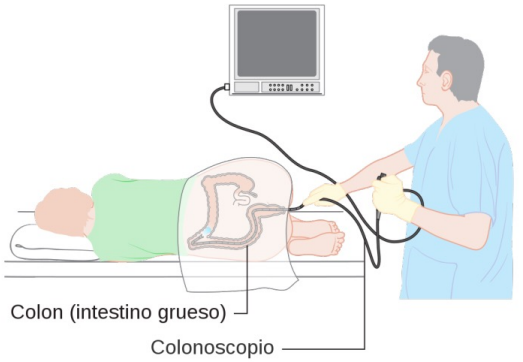
COLONOSCOPY
Is it a CR outcome?

YES

IRL
HRL
CIS
CRC

NO

N
LNAR
LRL



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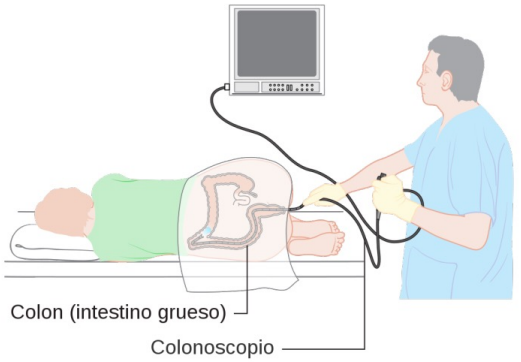

No clinical relevance (most outcomes)
False positives

50-69 age

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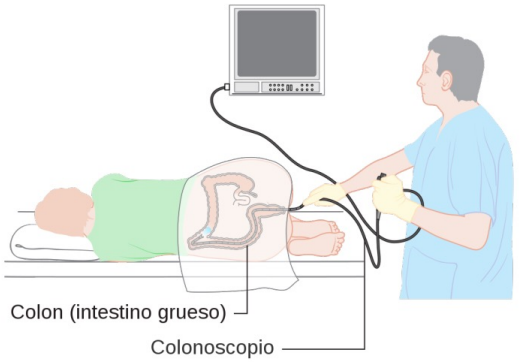
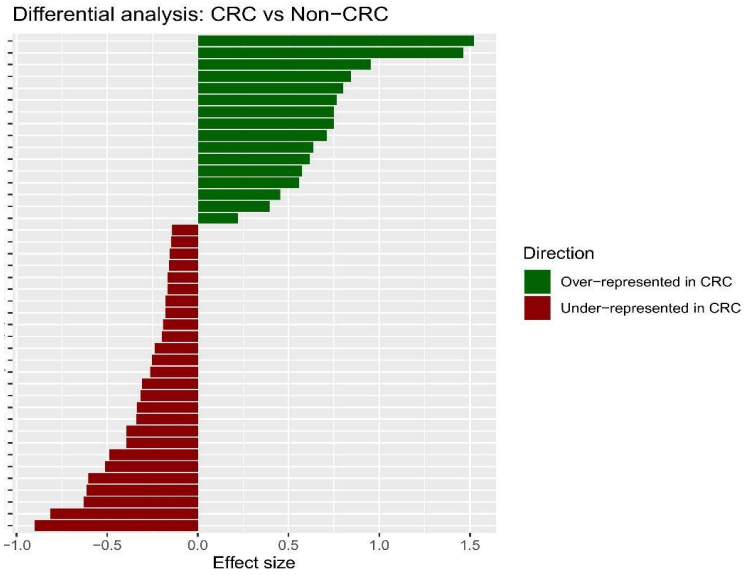


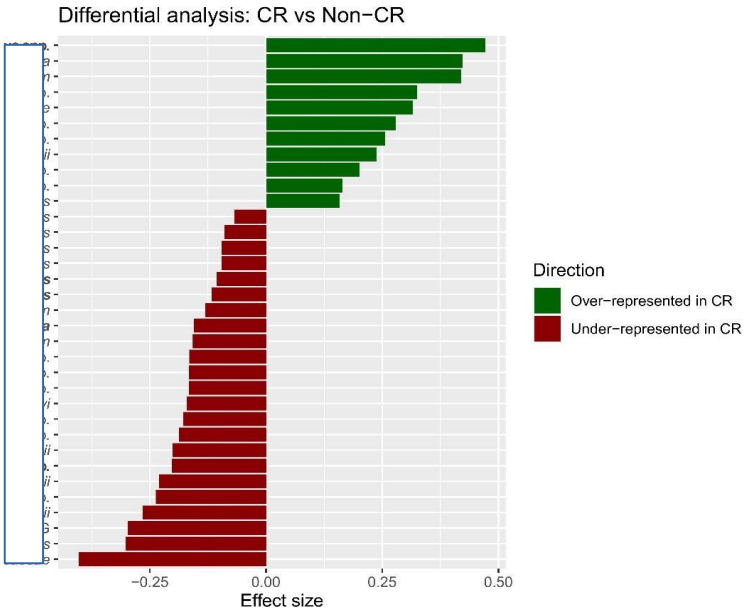
Is microbiome informative
Of colonoscopy outcome?

No clinical relevance (most outcomes)
False positives

41 taxa are significantly differentially abundant,
Between CRC / non-CRC samples

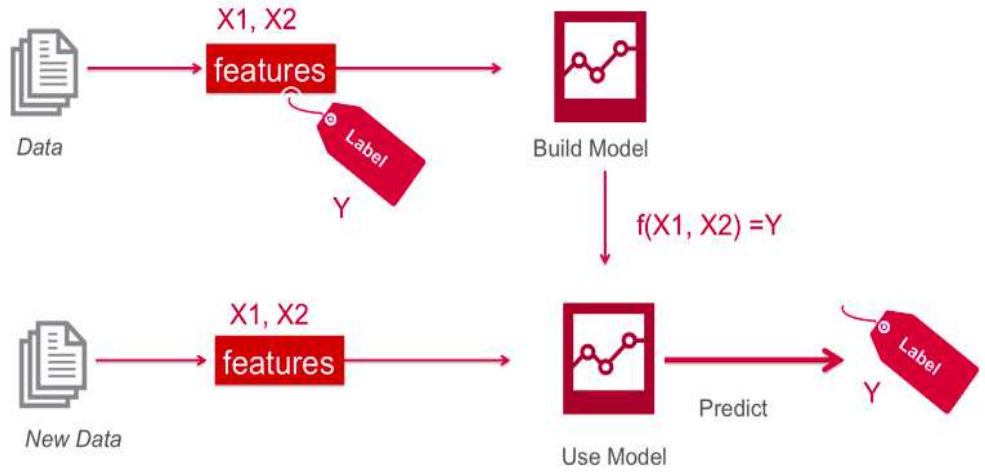


37 taxa are significantly differentially abundant,
Between Clinically relevant (CR) / non-CR samples



Features: Taxa clr + Clinical variables
Label: Diagnosis

➔ Machine Learning classification



$$\textit{Recall} = \frac{TP}{TP + FN}$$

FIT TEST
> 20 µg hemoglobin/g feces?

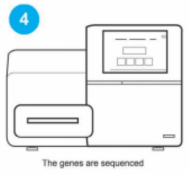
YES

NO

After 2 years

FIT POSITIVE

FIT NEGATIVE



16S rRNA seq

ASV TABLE

METADATA

NO COLONOSCOPY

ML Classifier
FS +
Clinical variables

SAVED COLONOSCOPIES

COLONOSCOPY

USA cohort

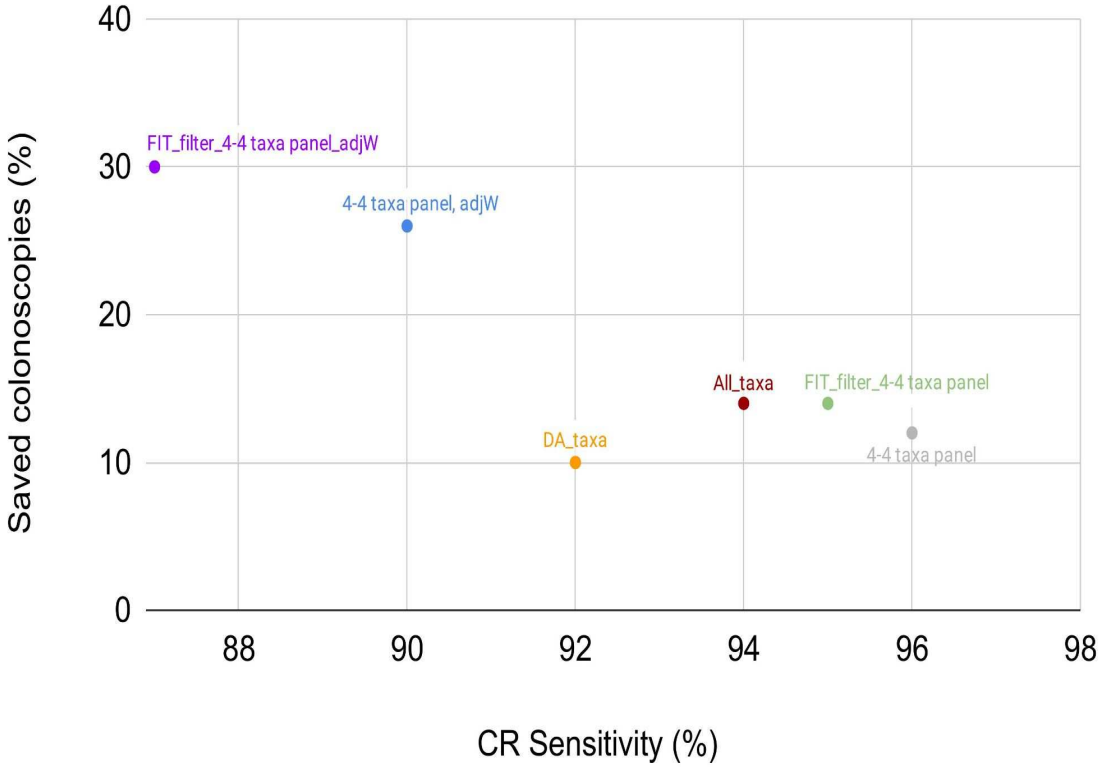
100 % CRCs classified
98.46 % CR classified
20 % saved colonoscopies

VALIDATION

100 extra participants

100 % CRCs classified
94 % CR classified
12 % saved colonoscopies

Different algorithm parameters balance sensitivity and saved colonoscopies differentially



Conclusions

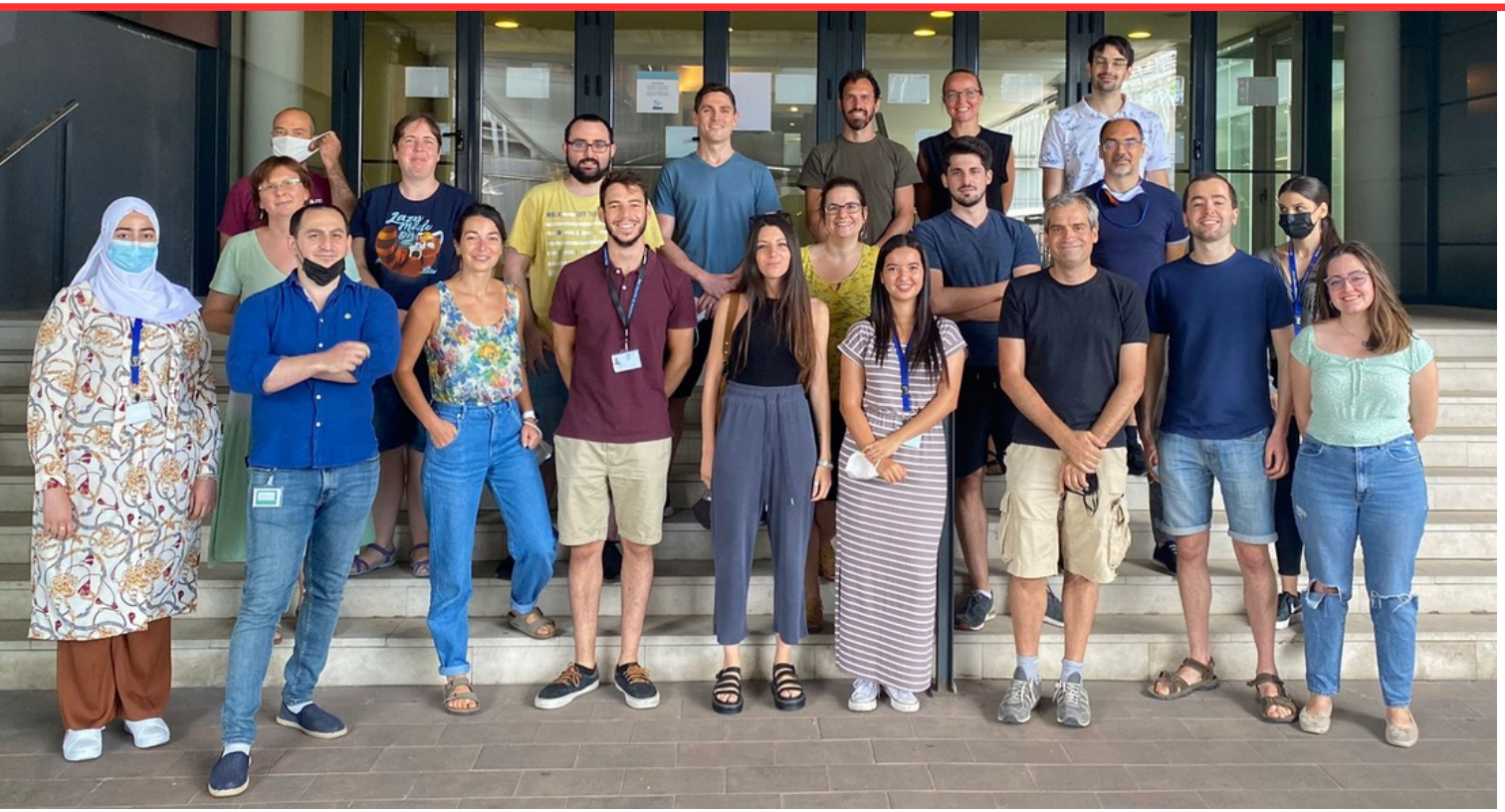
- Microbiome plays an important role in digestive cancers

- Microbiome-based diagnosis and therapeutic procedures are promising

- CRC population screening can be made cheaper and more efficient by exploiting this information

- Future vision: fecal (or salival) microbiome profiling as a general purpose routinary clinical test (i.e. as blood test)

THANKS



Thanks to all Gabaldón group, particularly

In this project:
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Olfat Khannous

Past members: Jesse Willis

Collaborators: COST action Transcoloncan, Sergi Castellvi, Hospitals in Barcelona

www.cgenomics.org

Funding:

GOBIERNO DE ESPAÑA MINISTERIO DE CIENCIA E INNOVACIÓN

European Research Council

Opathy

ciberinfec Centro de Investigación Biomédica en Red Enfermedades infecciosas

Fundació "la Caixa"