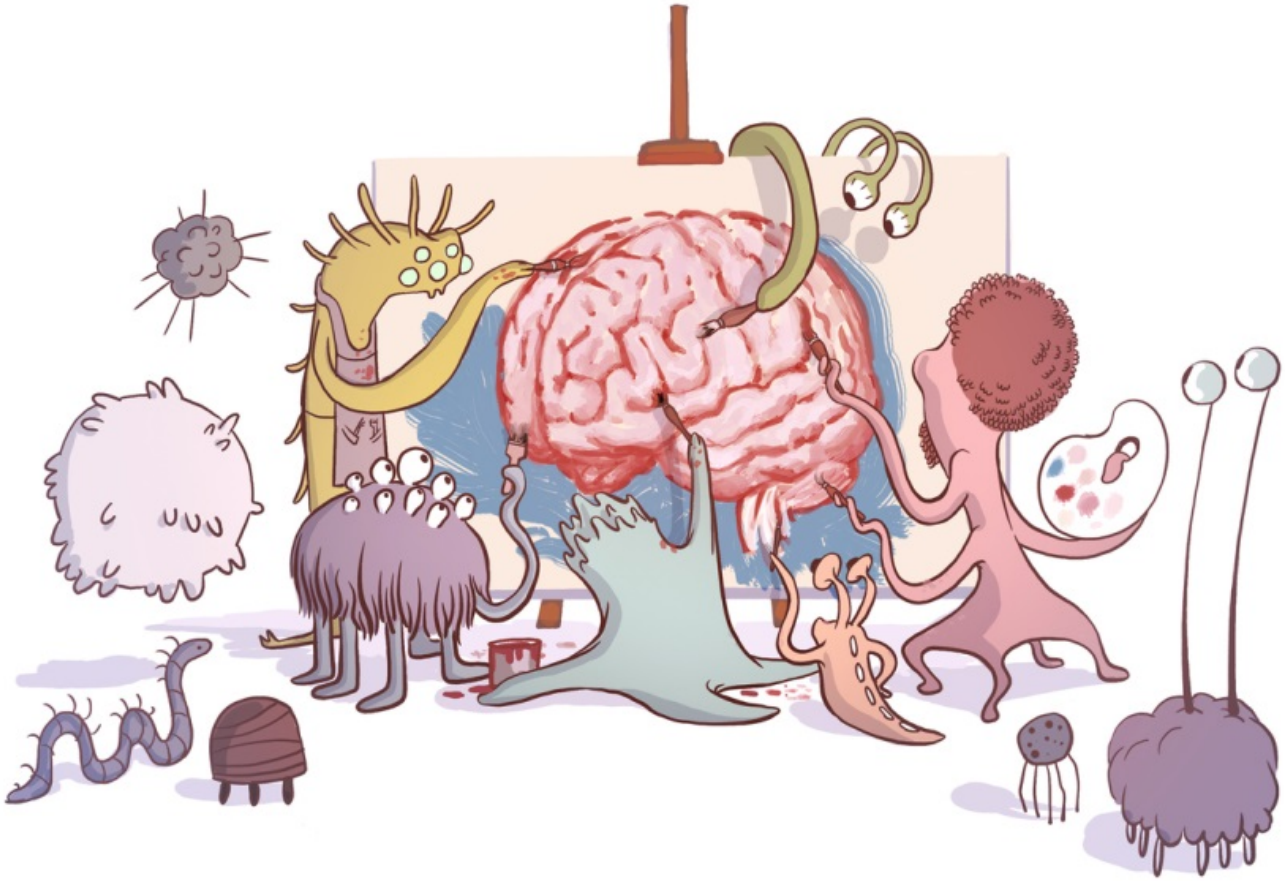
Identifying a microbiomic signature for colorectal cancer

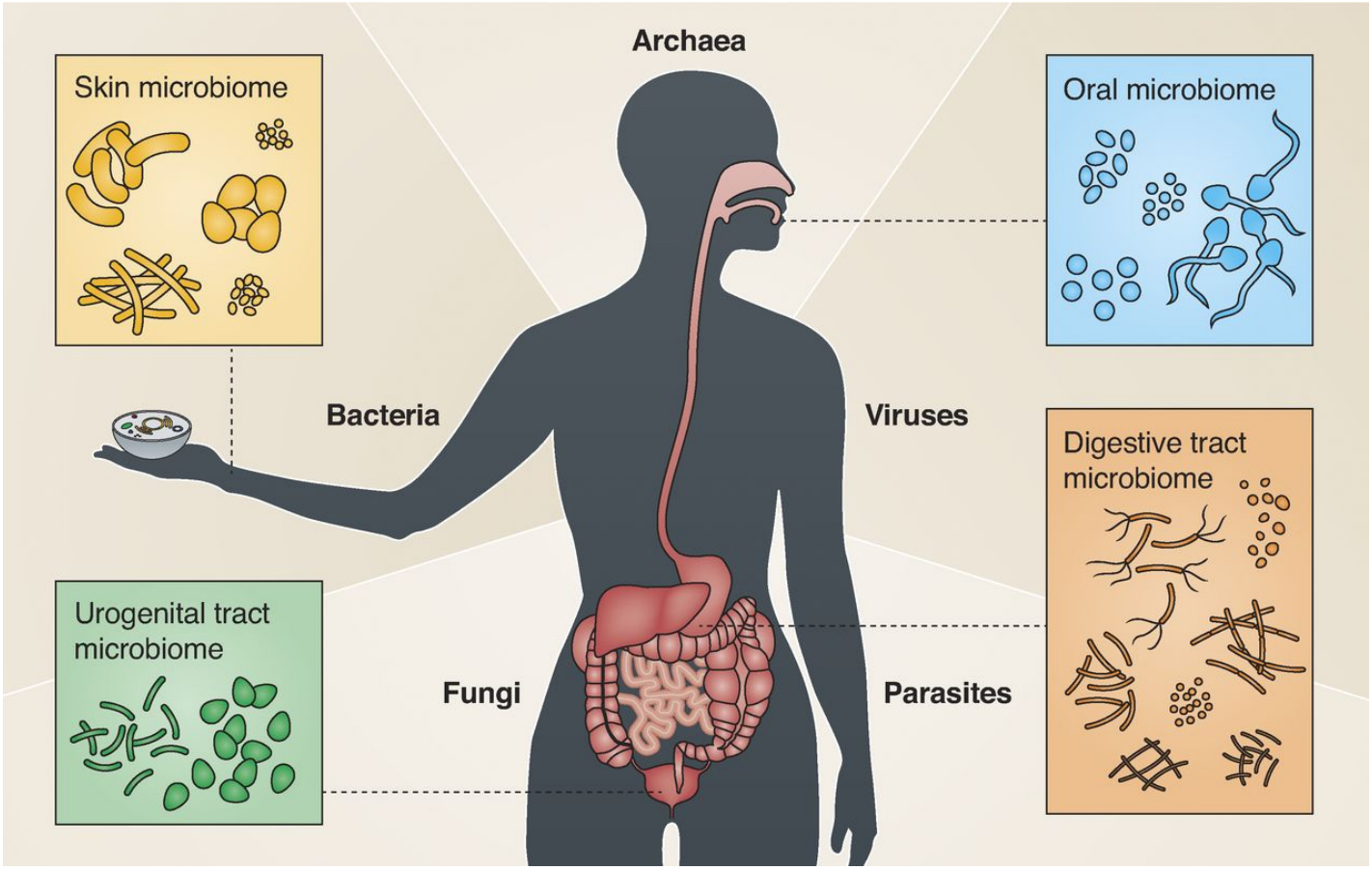
Identifying a microbial metagenomic signature for colorectal cancer

- Background
- Analytic approaches in microbiome studies
- Integrating microbiomic and metagenomic biomarker discovery in CRC research
- Summary
- References



BACKGROUND

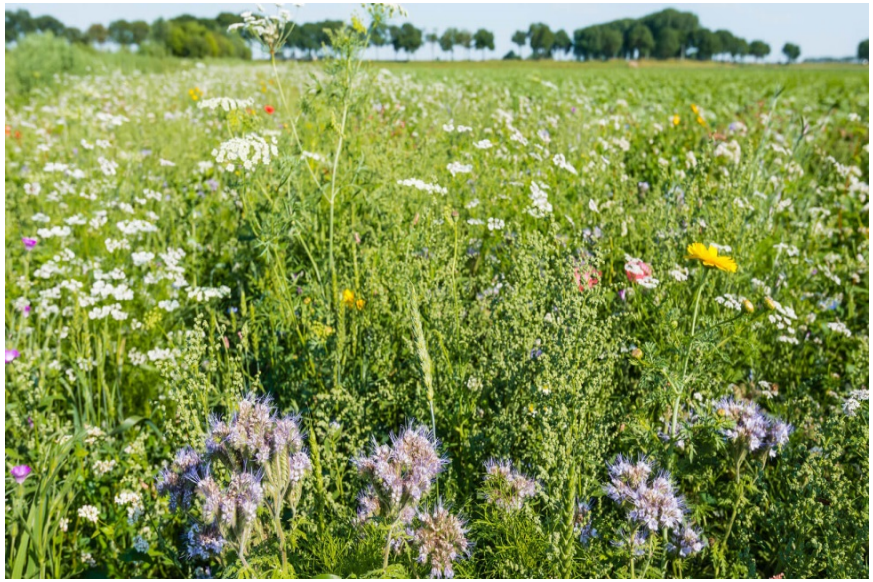
What is the human microbiome?



What is the human microbiome?

- Includes the collective genome of all **bacteria, archaea, fungi, protists, and viruses** found in and on the human body.
  - The microbiome is associated with diseases such as obesity, periodontal disease, inflammatory bowel disease, cardiovascular disease, and cancer.
  - Examples include:
    - Porphyromonas or Fusobacterium (Oral Microbiome)
    - C. difficile or H. Pylori (Gut microbiome)
    - HPV (Urogenital tract microbiome)

Gut Homeostasis



- This is a healthy and diverse gut
  - The gut microbiome has been shown to promote a healthy gut homeostasis
  - Functions of the gut microbiome include the metabolism complex polysaccharides and the biosynthesis of vitamins

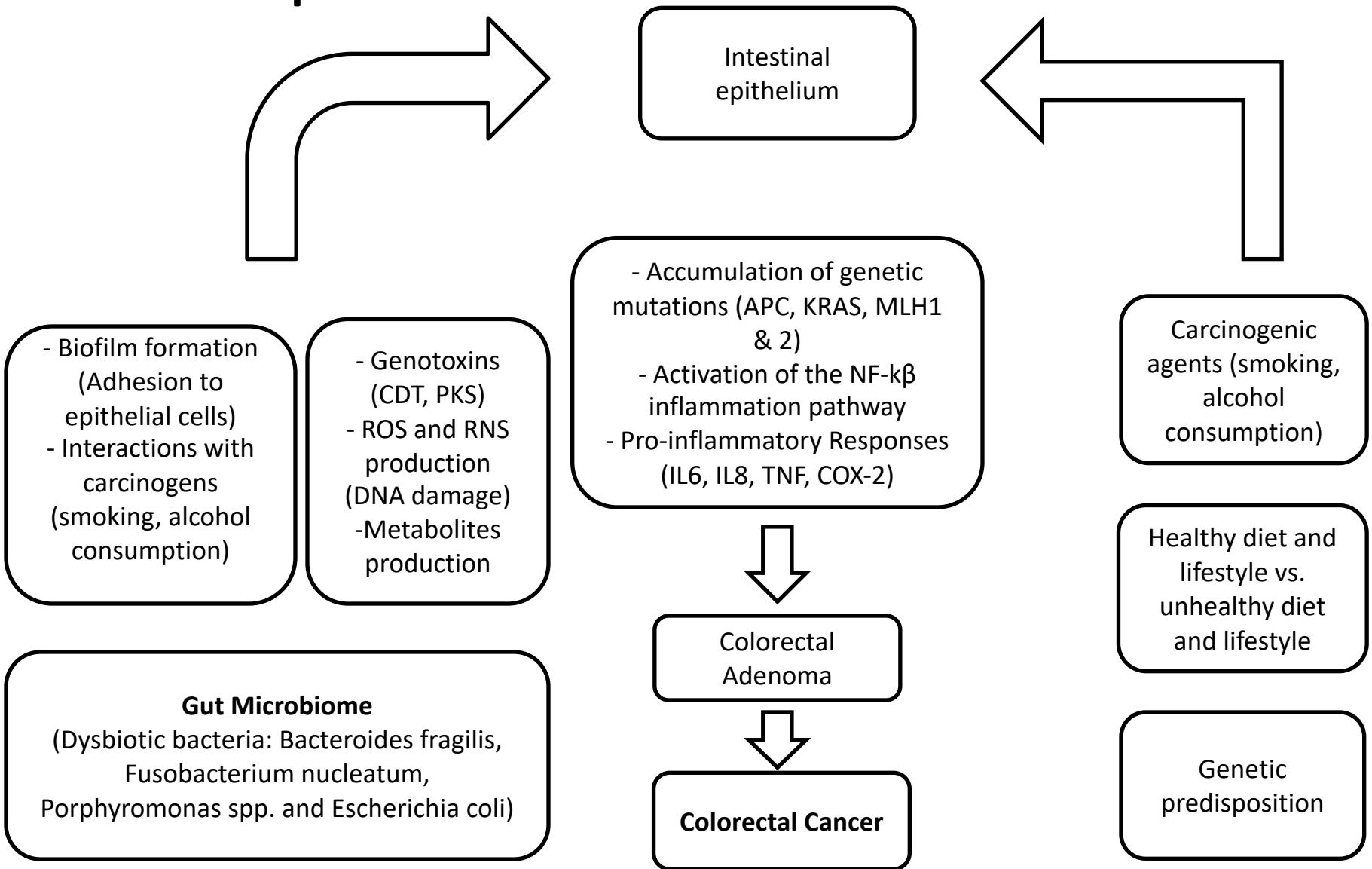
Gut Dysbiosis

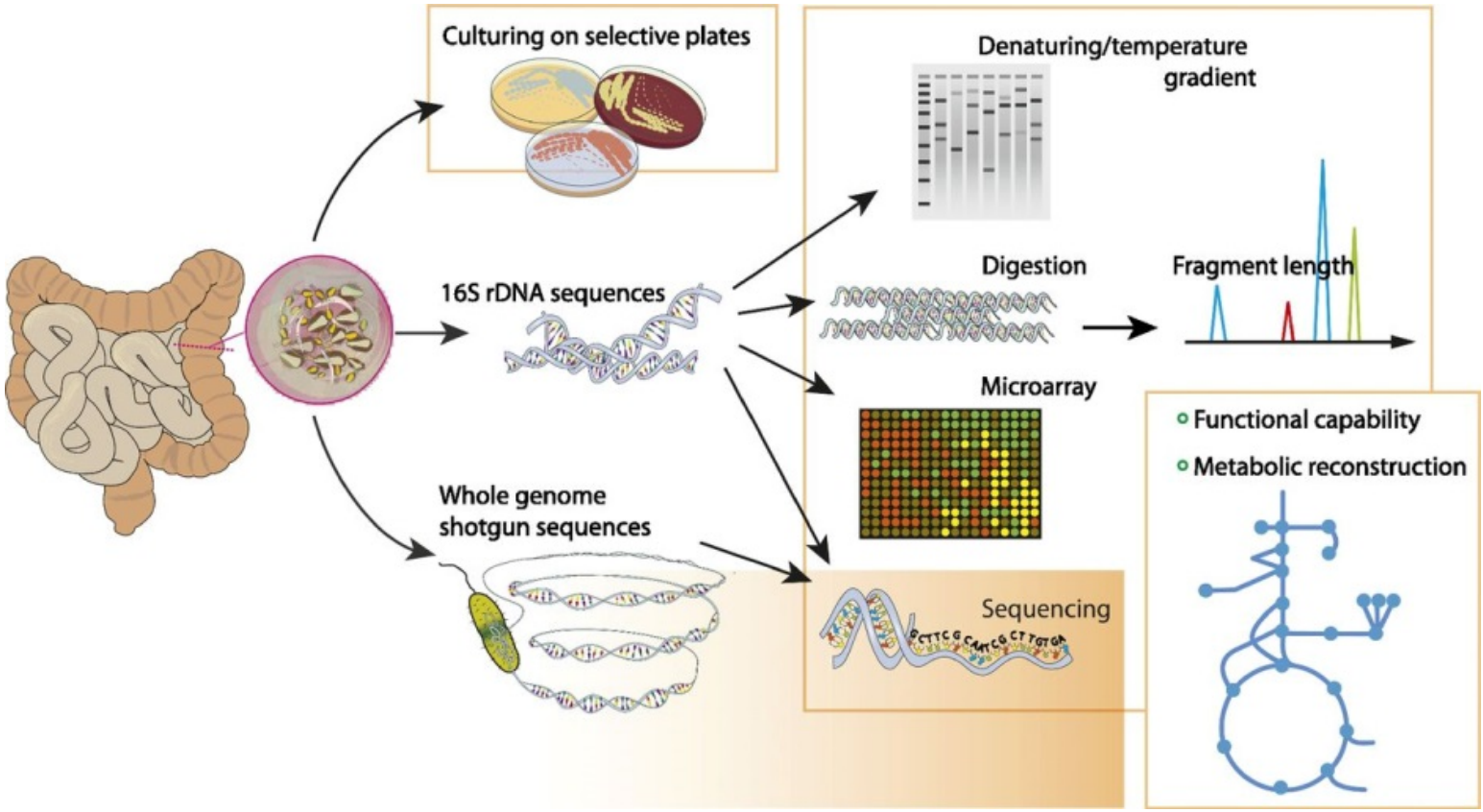
- This is an extreme example of dysbiosis (monoculture)
  - Such a microbiome can occur in conditions such as C. difficile infections, or as a result from excessive antibiotic use
  - Shifts in the composition of the resident microbiota associated with disease, ***or microbial dysbioses***, have been shown to lead to a variety of intestinal disorders (inflammatory bowel disease, CRC)

Why is the gutmicrobiome important in CRC research?

- The gut microbiome might be a candidate biomarker for early detection of CRC due to:
  - **Dysbiosis-related inflammation**
  - Generation of chemical carcinogens, including acetaldehyde and N-nitroso compounds
  - Release of **genotoxic virulence factors**.
  - Generation of protective metabolites (such as the **short chain fatty acid butyrate**)

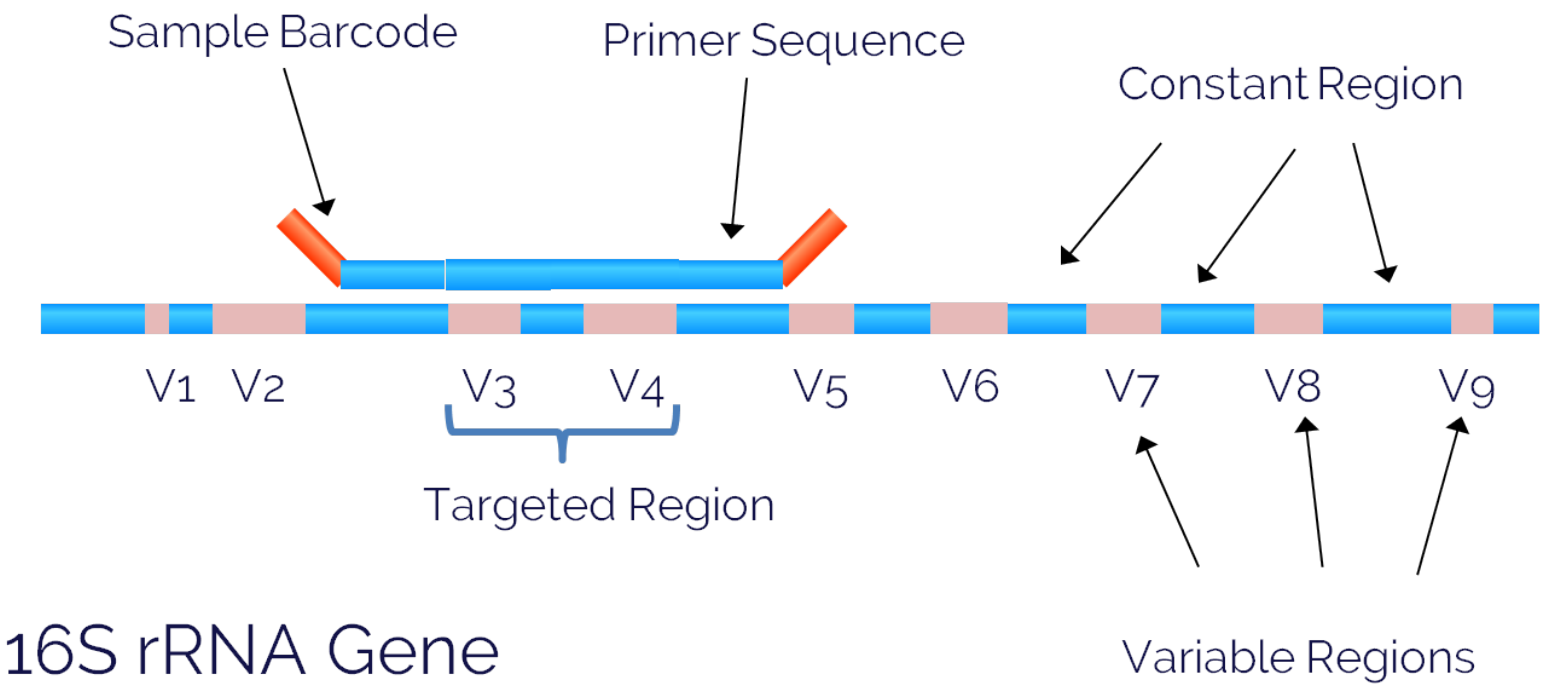
Why is the human microbiome important in cancer research?



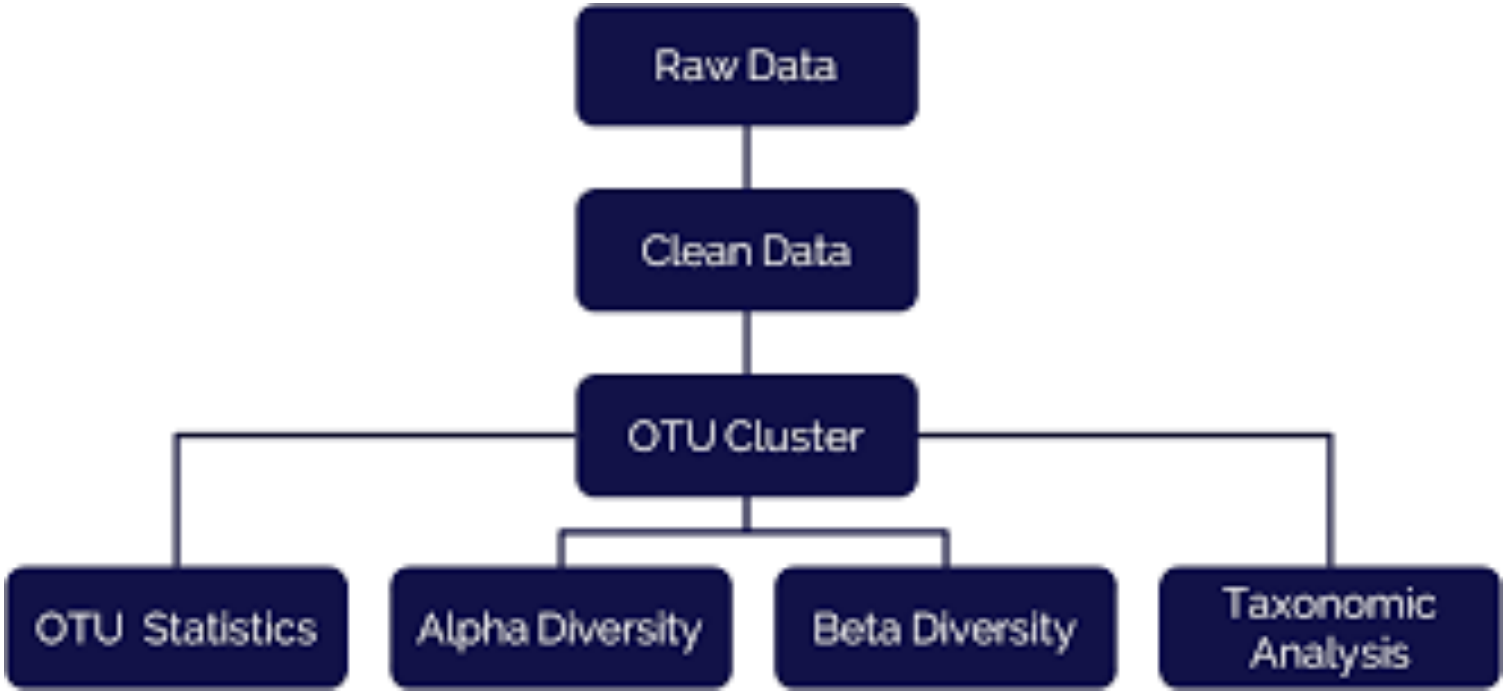


ANALYTIC APPROACHES IN MICROBIOME STUDIES

16S rRNA sequencing



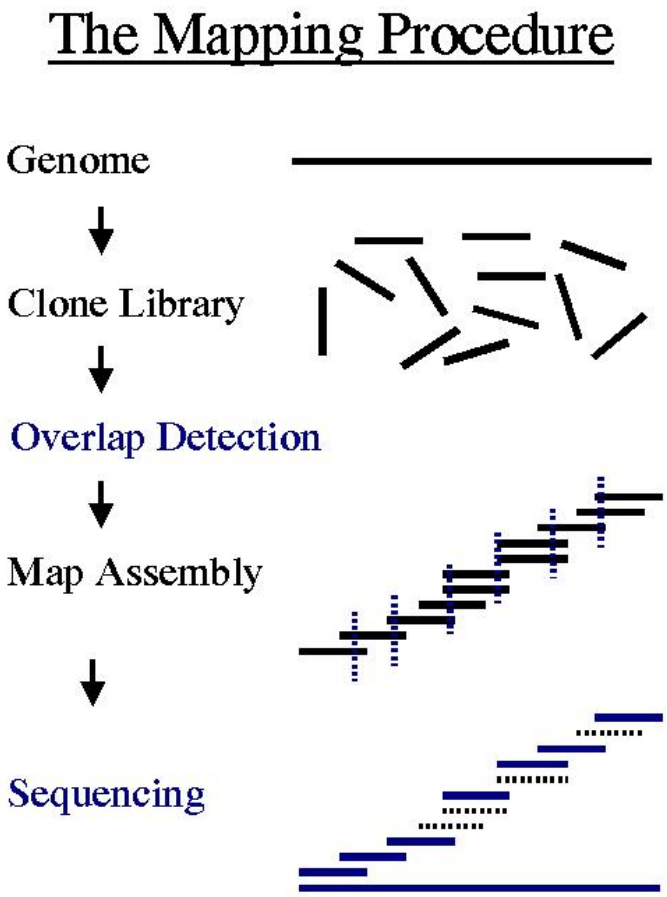
16S rRNA sequencing



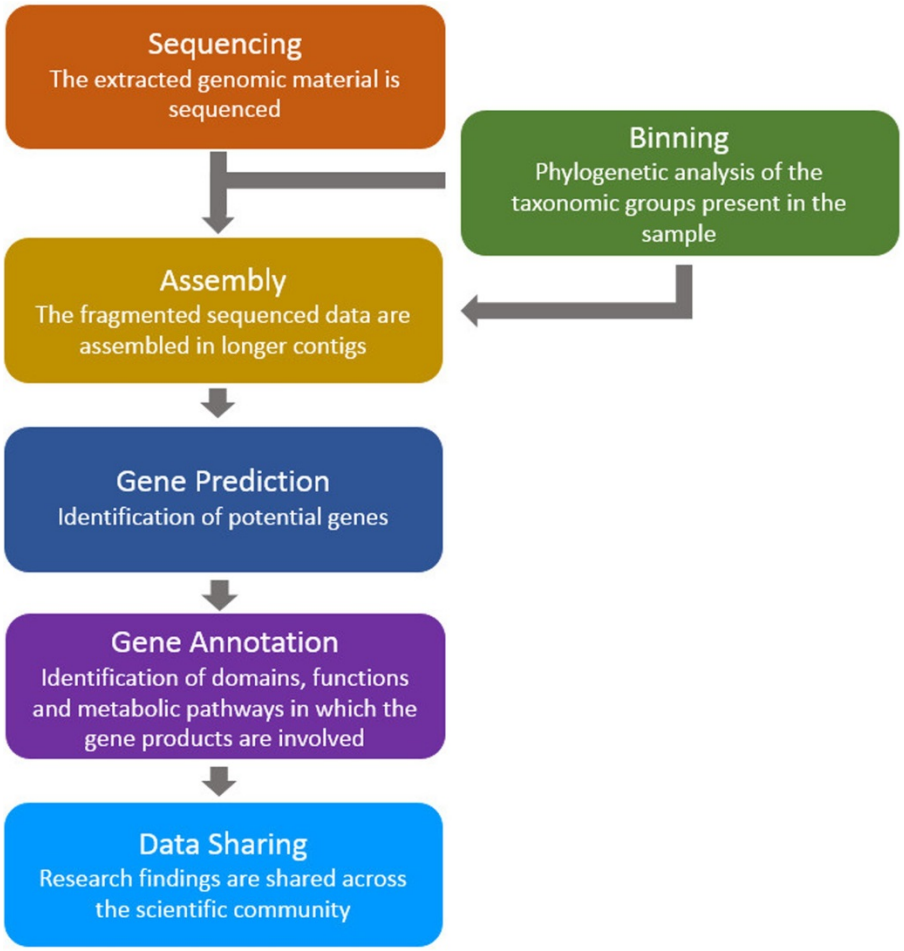
16S rRNA sequencing

	OTU 1 (Bacteroides)	OTU 2 (Firnicutes)	OTU 3 (Fusobacterium)	Age	Sex	treatment
Sample 1	1	1	0			
Sample 2	0	1	1			
Sample 3	0	1	1			
Total	1	3	2			

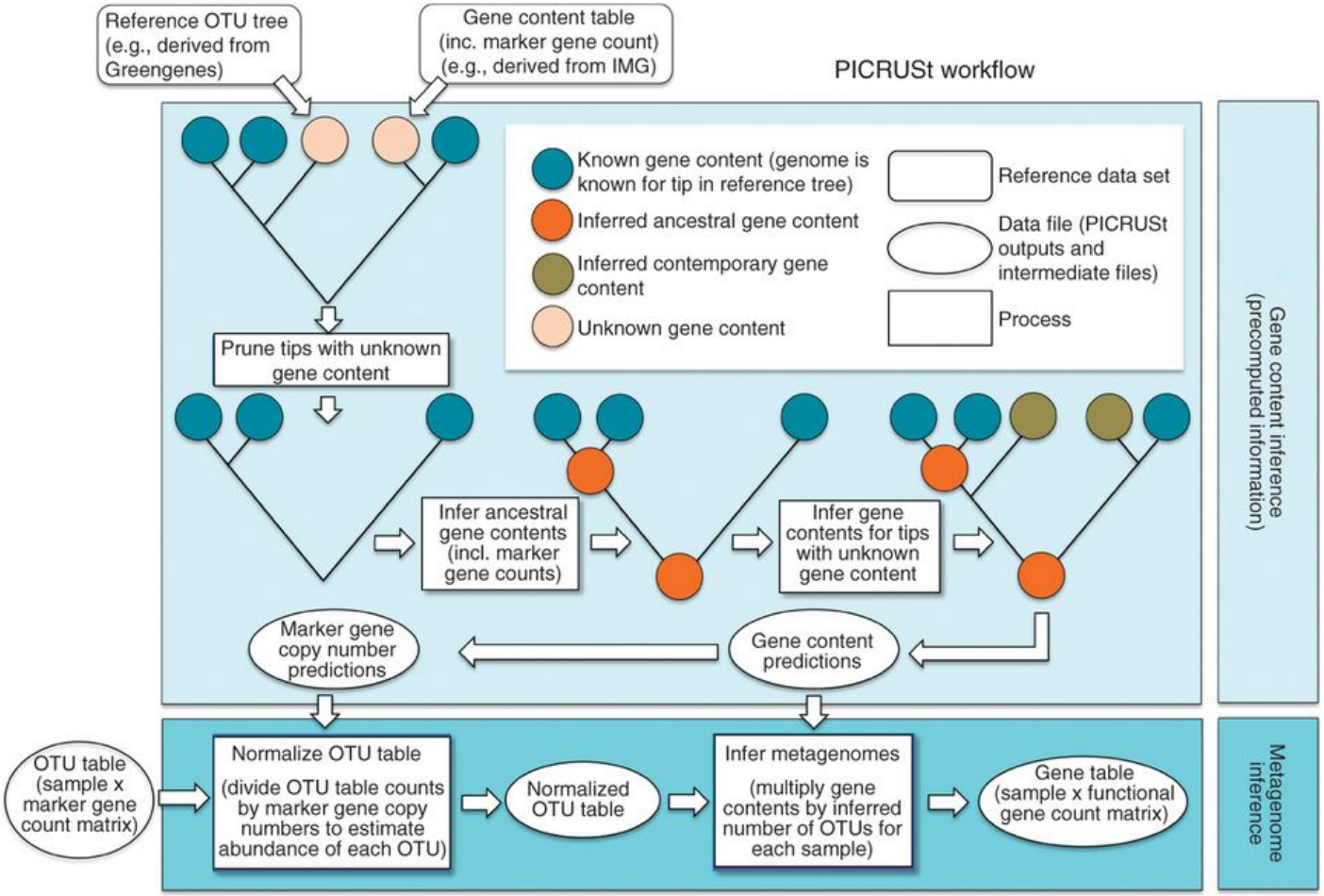
Shotgun Sequencing



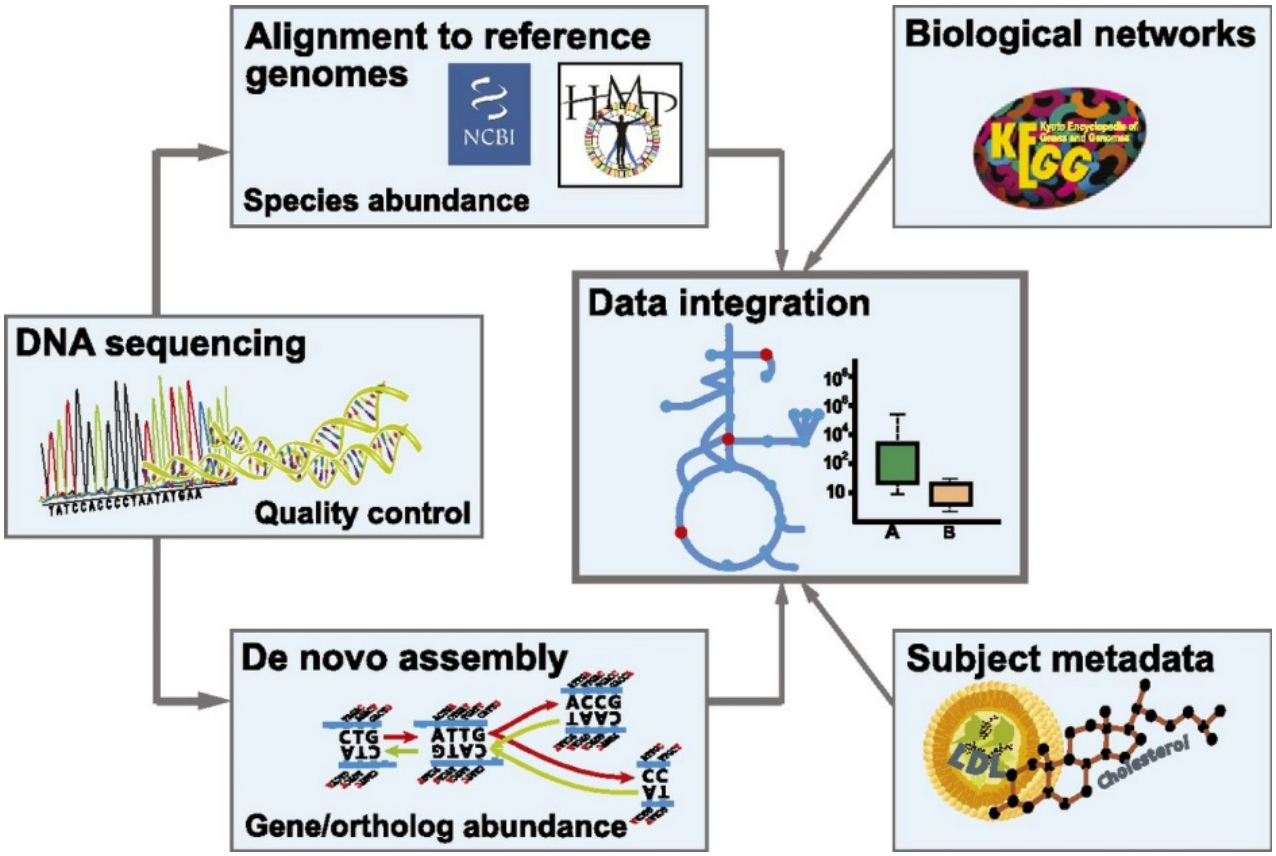
Shotgun Sequencing



Picrust Analysis

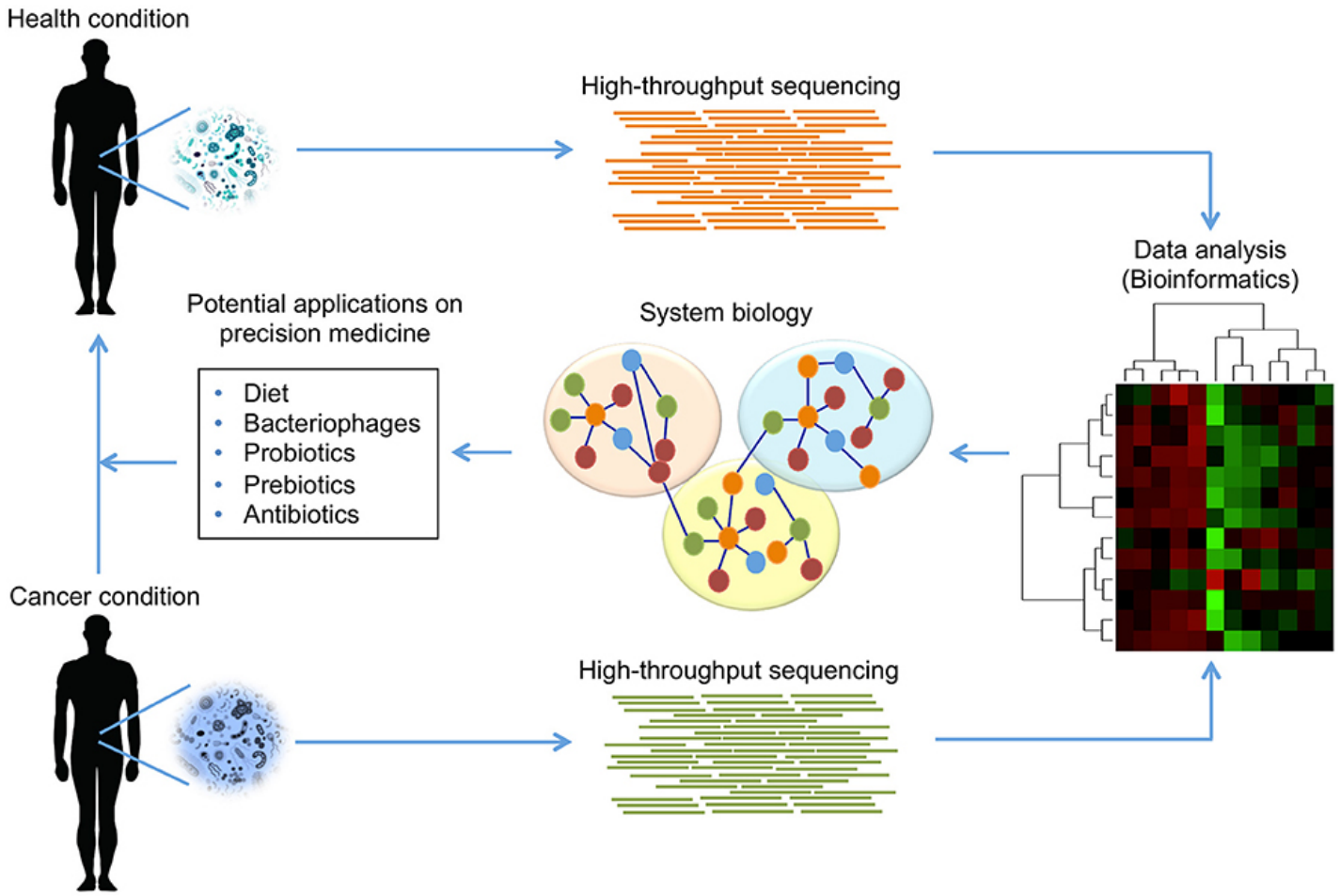


Predictive functional profiling of microbial communities using 16S rRNA marker gene sequences (Langille et al, 2013)



INTEGRATING MICROBIOMIC AND METAGENOMIC BIOMARKER DISCOVERY IN CRC RESEARCH

Microbiome signature in CRC



Bacterial Metagenome

- Concordance across studies with respect to CRC-associated bacteria taxa (Fusobacterium nucleatum, Peptostreptococcus spp., and Porphyromonas spp)
- Microbial association of the gut microbiome with CRC at the level of the bacterial **community's function**, rather than at the **compositional level** alone

Uses of taxonomic signatures in CRC

- Pro-inflammatory bacterial genes promote the colonization of the gut microbiome by specific strains of bacteria.

- **Hypothesis: We expect to see a higher prevalence of genes associated with biofilm formation, cell adherence, and inflammation in the metagenome of CRC cases, compared to controls.**

- These genes could include, but are not limited to:
  - The polyketide synthase multienzyme (pks island), which can induce DNA damage.
  - Pro-inflammatory gene products such as tcpC, (impairs toll-like receptor function)and cytotoxic necrotizing factor-1 (CNF-1)
  - Genes controlling the production of specific bacterial enzymes (such as β Glucoronidase, Lipopolysaccharides and mucinase)

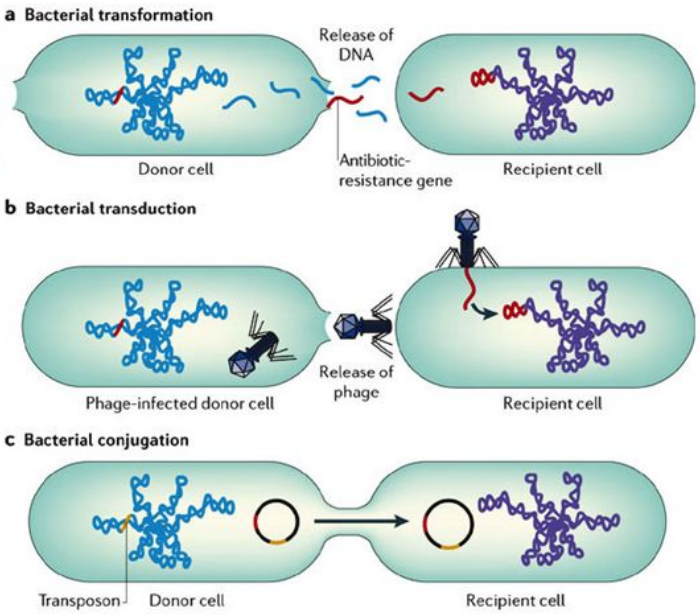
Bacterial Metagenome

Horizontal Gene Transfer: New Gene Acquisition

Transformation: naked DNA uptake by bacteria

Transduction: bacterial DNA transferred by viruses (phage)

Conjugation: DNA transfer between bacterial cells



Furuya EY and Lowy F (2006) *Nat Rev Microbiol.* **4**: 36–45.

SUMMARY/TAKE HOME MESSAGE

Summary/Take Home message

- The gut microbiome is well suited to influence CRC risk at multiple levels, and active research is being done to find a unique microbiomic signature in CRC
  - The bacterial metagenome may provide us additional data on defining features of the gut microbiome in CRC
  - Such findings may be use to improve CRC screening or future risk prediction
- Future work is not limited on integrating the bacterial metagenome in biomarker discover, but also involves exploring the impact of the gut virome and of the gut fungal genome in CRC

REFERENCES

References

- Great papers to start learning about the human microbiome in public health research
  - 1. Epidemiologic studies of the human microbiome and cancer (Vogtman et al, 2015)
  - 2. The human gut microbiome as a screening tool for colorectal cancer (Zackular et al, 2014)
  - 3. Oral Microbiome and history of smoking and colorectal cancer (Kato et al, 2016)
  - 4. Leveraging sequence-based faecal microbial community survey data to identify a composite biomarker for colorectal cancer (Shah et al, 2017)
  - 5. Predictive functional profiling of microbial communities using 16S rRNA marker gene sequences (Langille et al, 2013)