Big Data in Nursing Research: Frontiers in Microbiome and Metabolomics

Microbiome in Cancer Symptoms

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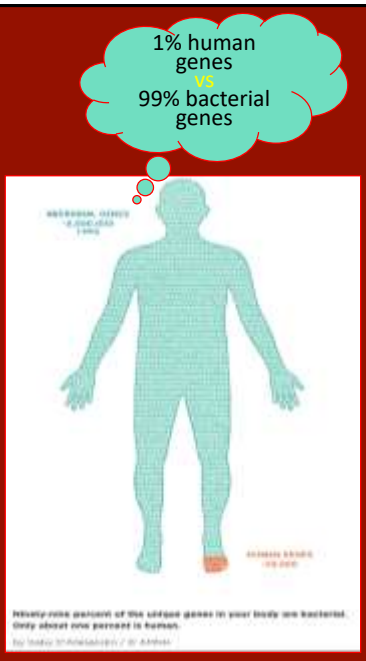
Content of Presentation

- Microbiome data in cancer treatment-related symptoms
- Processes to analyze big microbiome data

Human Microbiome

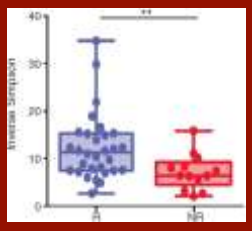
- **Human microbiome**
  The collection of microbes, their genes, genomes that exist in our body. It refers to all microbes including *bacteria, archaea, fungi, small eukaryotes* and *viruses*
- **Characteristics**
  Tens of trillions microbes, with hundreds if not thousands of different microbial species (>1000 species)
- **Functions**
  Digestion, metabolism, neurological, psychological functions, reproductive systems, immune system et al.



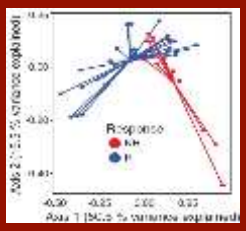
Knight & Buhler, 2015; Sender, Fuchs, & Milo, 2016

Microbiome in Cancer Treatment

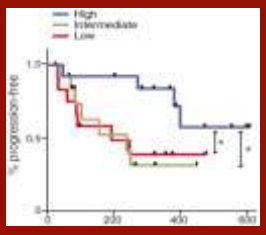
- **Treatment efficacy**: *Chemotherapy, radiotherapy immunotherapy*



N = 43 (30 VS 13)

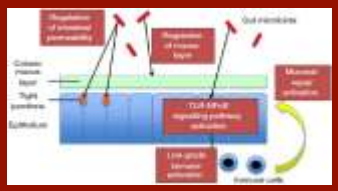


Weighted UniFrac



Kaplan-Meier (KM) plot

- **Treatment toxicities**: *Gastrointestinal toxicities and mucositis*



Alexander et al., Nature, 2017
Paulsen et al., Support Care in Cancer, 2017
Bai et al., Support Care in Cancer, 2018
Bhatt et al., CA Cancer Journal of Clinician, 2017
Gopalakrishnan et al., Science, 2018
Touchefeu, et al., Aliment Pharmacol Ther, 2014,

Microbiome in Cancer Treatment *cont'd*

- **Psychoneurological outcomes**: *distress, depression, fatigue, cognitive dysfunction*
  - *A few studies* focused on cancer survivors
  - *Unknown associations* between dysbiosis of the gut microbiome and psychoneurological symptoms in peds pts.

- ↑↑ of *Bacteroides and Ruminococcus* species in severe fatigue vs no fatigue
- ↓↓ abundance of *Streptococcus and Prevotella* species in severe fatigue vs no fatigue.
- Relative abundance of *Butyricimonas, Prevotella, Streptococcus, Bacillus, Lactobacillus and Megasphaera* species were found to correlate with neurocognitive ability of survivors

30 breast cancer survivors

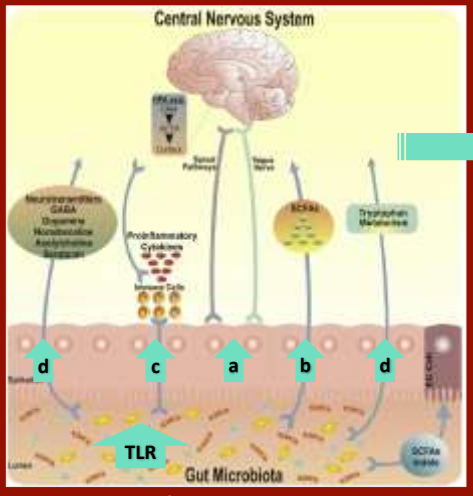
MGB Axis

- **Small sample;**
- **no adjustment of confounders**
- **Inconsistent findings**

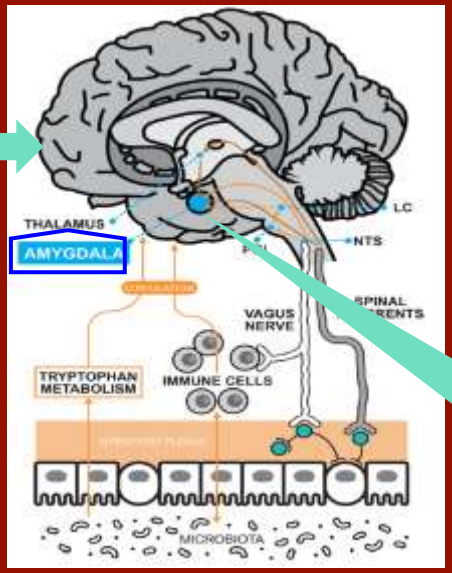
Gut microbiota composition associated with alterations in cardiorespiratory fitness and psychosocial outcomes among breast cancer survivors

Gut microbiome alterations in breast cancer survivors with cancer-related fatigue.

Microbial Signaling to Brain



Microbiome-Gut-Brain Axis

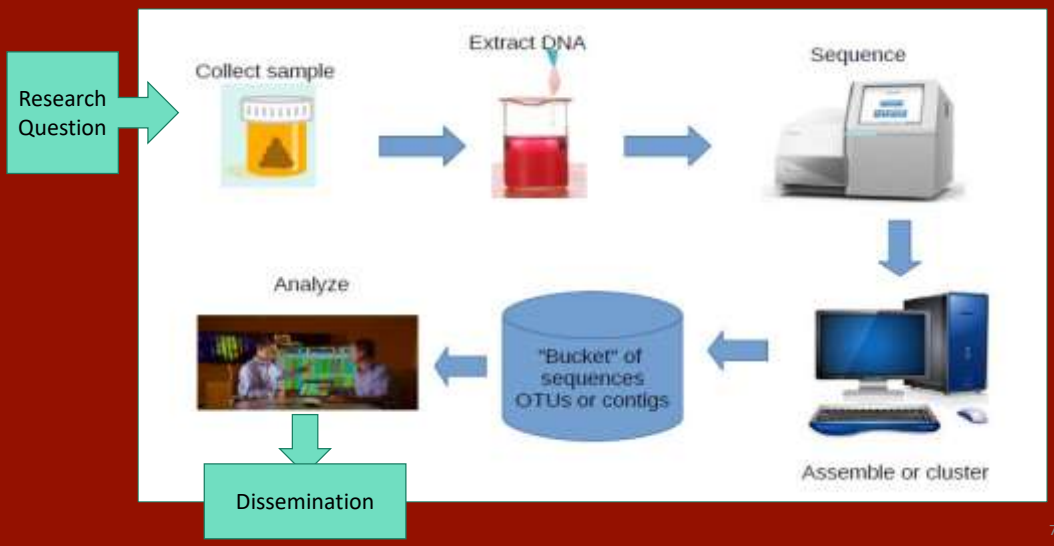


LC, locus coeruleus;
NTS, nucleus tractus solitarius;
PGi, nucleus paragigantocellularis.

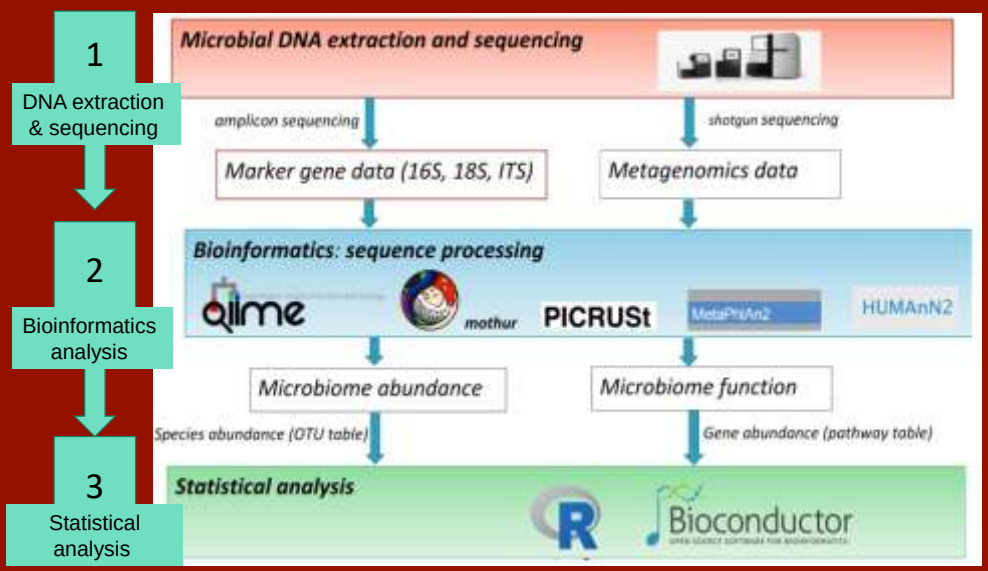
A key brain region critically involved in the processing and expression of anxiety, fear-related signals

Kennedy et al., Neuropharmacology, 2017
Dinan & Cryan, Gastroenterol Clin N Am, 2017
Cowan et al., BioEssays, 2017

A “Standard” Microbiome Project

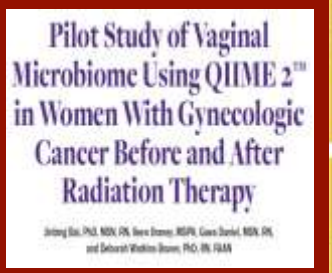


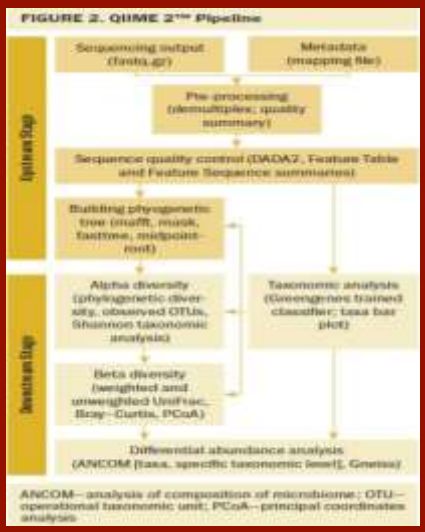
Microbiome Data Processing and Analysis



Calle, 2019

Microbiome Analysis Pipeline using QIIME

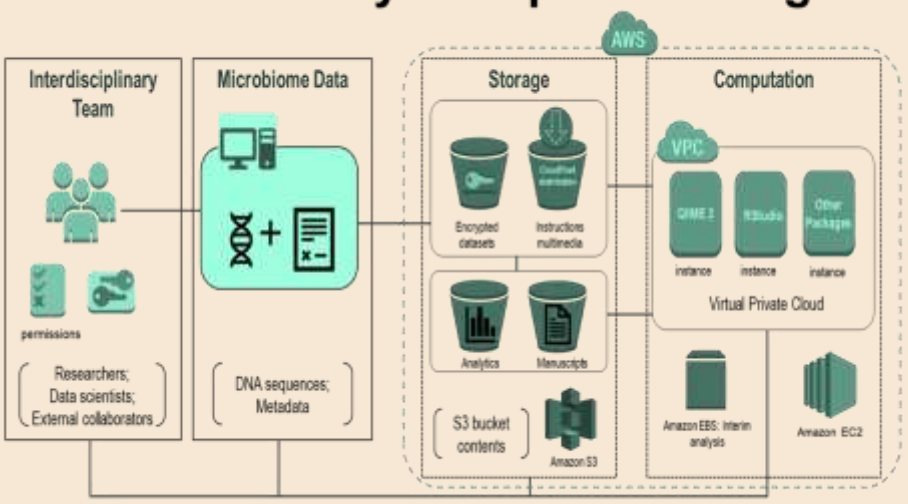




Upstream stage:
- import *16S rRNA sequences*
- sequence quality control
- build the phylogenetic tree

Downstream stage:
- taxonomic analysis
- diversity analysis
- abundance analysis

Microbiome Analysis Pipeline Using AWS



Bai, Jhaney & Wells, 2019, JMIR Medical Informatics

Profile the Gut Microbiota in 7-18 Years Old Children using the American Gut Project Dataset

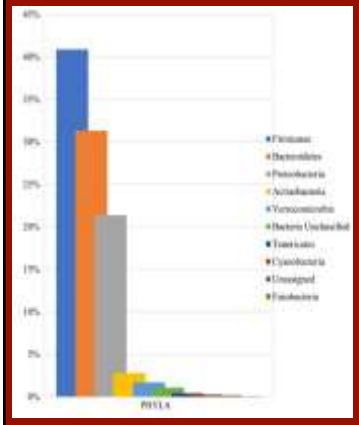
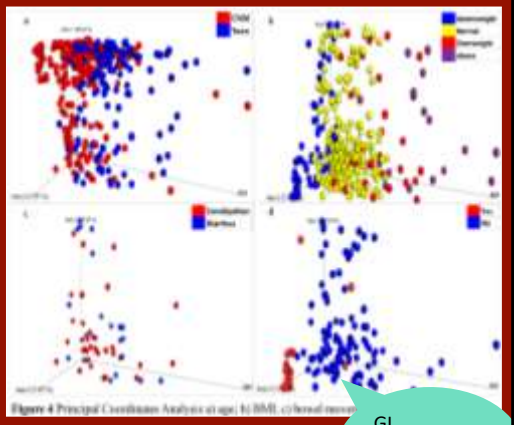


Table 1 Relationships of gut microbiota with study variables using LDM analysis after controlling for covariates (n = 267)

Model	p	N OTUs detected
1) Univariate analysis:		
Diet type	0.001	119
Exercise frequency	0.00007	63
BMI level	0.0002	127
Weight change	0.03	0
2) Multivariate analysis: Diet + Exercise frequency + BMI level + Weight change		
Diet type	0.001	122
Exercise frequency	0.00002	67
BMI level	0.0005	120
Weight change	0.04	0

Notes: The OTU table has 267 subjects and 416 OTUs at genus level after removing OTUs with a total frequency of 0 across all subjects (n = 45), subjects with a total frequency of 0 across all OTUs and subjects with missing values (n = 109). Both univariate and multivariate analyses adjusted for covariates: sex (male vs. female), age (child [7–12 years old] vs. teen [13–18 years old]), antibiotics use (yes vs. no) and probiotics use (never vs. rarely [a few times/month] vs. occasionally [1–2 times/week or more] vs. daily).
LDM, linear decomposition model; OTUs, operational taxonomic units.



GI symptoms matter

Significant associations were found between the gut microbiota composition and BMI level and lifestyles controlling for demographic and clinical factors in children aged 7–18 years

Bai, Hu, Bruner, 2019, Pediatric Obesity

Exploring the Microbiome-Gut-Brain Axis in Psychoneurological Symptoms in Children with Solid Tumors (MAPSS Study)

- **Aim 1 (K99 Phase):** to characterize profiles of the gut microbiome communities in 40 children with solid tumors aged 7-18 years pre-chemotherapy (T1), at the end of chemotherapy (T2), and at 3 months after the completion of chemotherapy (T3) as compared with 20 healthy siblings within 5 years of age from the children with cancer.

- **The R00 Phase** will include data from 100 cancer cases (40 from K99+60 from R00) at T1, T2, T3 and 50 siblings at T1:
- **Aim 2:** to screen specific microbial species and pathogens of the gut microbiome following the **16S rRNA gene sequencing** analysis using the whole-genome shotgun metagenomic sequencing among children with solid tumors and sibling controls
- **Aim 3:** to study whether the gut microbiome (e.g., genus identified from 16S rRNA analysis and species from **the whole-genome shotgun metagenomics**) is associated with GI symptoms (PRO-CTCAE) and PNS (pain, fatigue, anxiety, depression, cognitive dysfunction, assessed by the PROMIS®)

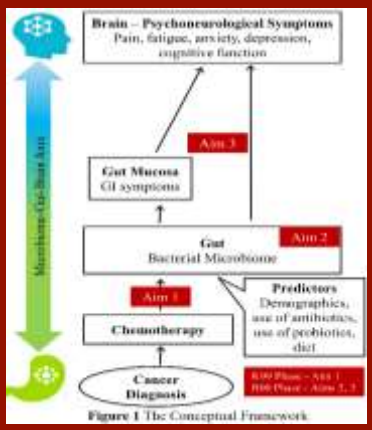


Figure 1 The Conceptual Framework

NIH 5K99NR017897-02, 2018-2023

Dynamics of the Skin Microbiome, Skin Inflammation, and Skin Toxicities and Symptoms during Breast RT

Emory Synergy Grant, Co-PIs: Bai & Lin

- **Aim 1:** Profile the skin microbiome in 40 women with breast cancer pre- (T0), during (week1, week2, week3 [T1-T3, respectively]), and 3 months post-RT (T4) and compare the skin microbiome of the RT involved breast with that of the control side (contralateral breast). Hypothesis: Women with breast cancer will have different skin microbiome pre-RT compared to post-RT and skin microbial communities will be different between the treated breast and control breast.
- **Aim 2:** Investigate the associations between the skin microbiome and clinician-scored dermatitis severity (assessed by the CTCAE) and patient-reported skin toxicities and symptoms (assessed by the Skindex-16 and Patient-Reported Outcomes version of the CTCAE [PRO-CTCAE™]). Hypothesis: Skin microbial communities' dysbiosis is associated with worse skin toxicities and more severe skin symptoms.
- **Aim 3:** Explore the associations between the skin microbiome and in situ protein markers of skin inflammation (e.g., IL-1α, IL-2, IL-4, IL-6, IL-8, IL-10, TNF-α, IFN-γ, and CRP) during the course of the RT and in association with the severity of the skin dermatitis. Hypothesis: Distinct microbial communities that are implicated in radiation-induced skin toxicities are associated with distinct profiles of skin inflammation markers.

Acknowledgements

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- NIH NINR K99/R00, 8/29/2018-8/28/2023
- Emory Synergy Grant, 9/1/2019-9/1/2020