Regional variation in the gut microbiome and its implications for colorectal cancer screening

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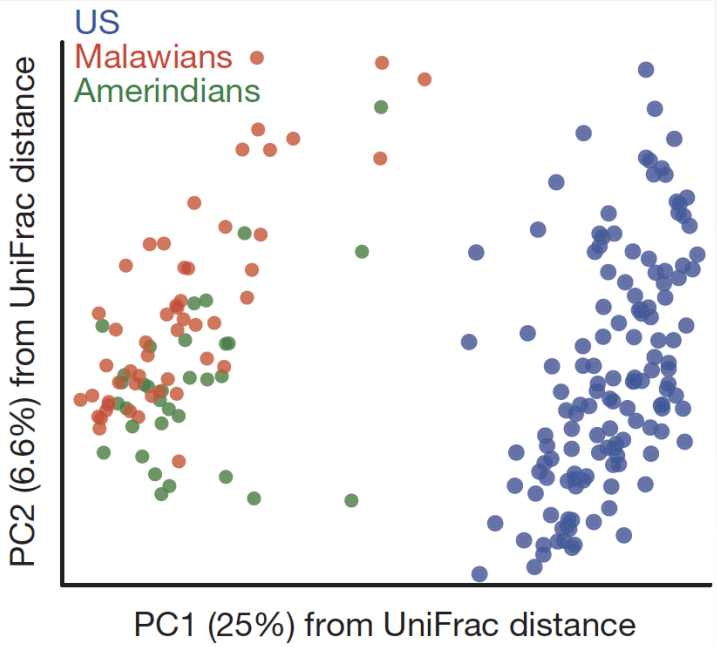
Key facts about the gut microbiome

- 10^{14} microbes residing in the human gut, with >2,000 unique species.
- Higher inter-individual variation than intra-individual variation.
- Function more conserved than taxonomy – *functional redundance*.
- Microbiome structure established by around age 3 years.
- Environment dominates over host genetics in shaping the microbiome.
- Diet can rapidly change the gut microbiome, but the core patterns and functions are shaped by long-term diet/lifestyle – *regional variation*.

Almeida A. Nature. 2019
Yassour M. Sci Transl Med. 2016
Olsson LM. Cell Host Microbe. 2022
Wu GD. Science. 2011
Bokulich NA. Sci Transl Med. 2016

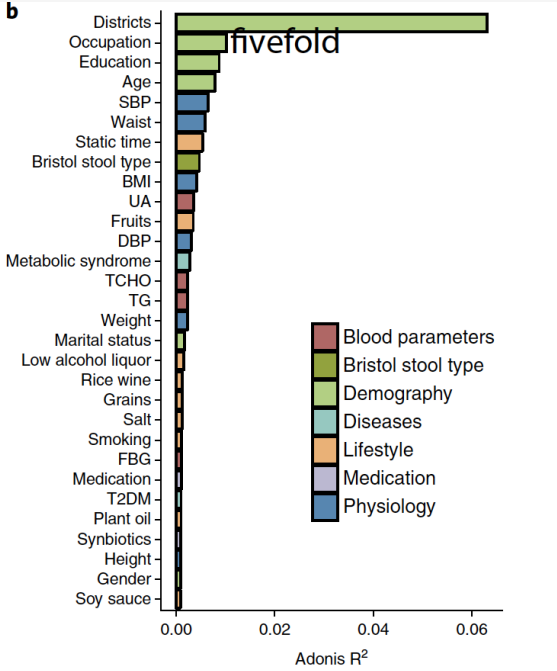
Regional variation of the gut microbiome

31 Malawians, 35 Amerindians, 136 US residents



Yatsunenko T. Nature. 2012

7,009 subjects from 14 districts in 1 province in China



He Y. Nat Med. 2018

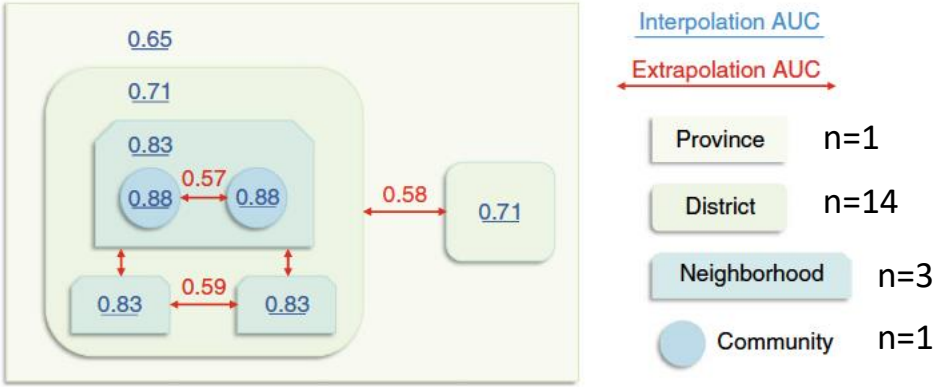
LETTERS
https://doi.org/10.1038/s41591-018-0164-x
nature medicine
Corrected: Author Correction

Regional variation limits applications of healthy gut microbiome reference ranges and disease models

Yan He[1,16], Wei Wu[2,3,16], Hui-Min Zheng[1,2,16], Pan Li[1,2,16], Daniel McDonald[4], Hua-Fang Sheng[1], Mu-Xuan Chen[1], Zi-Hui Chen[3], Gui-Yuan Ji[3], Zhong-Dai-Xi Zheng[2], Prabhakar Mujagond[5], Xiao-Jiao Chen[1], Zu-Hua Rong[1,2], Peng Chen[6], Li-Yi Lyu[7], Xian Wang[7], Chong-Bin Wu[7], Nan Yu[1], Yan-Jun Xu[8], Jia Yin[9], Jeroen Raes[10,11,12], Rob Knight[4,13,14], Wen-Jun Ma[3]* and Hong-Wei Zhou[1,2,15]*

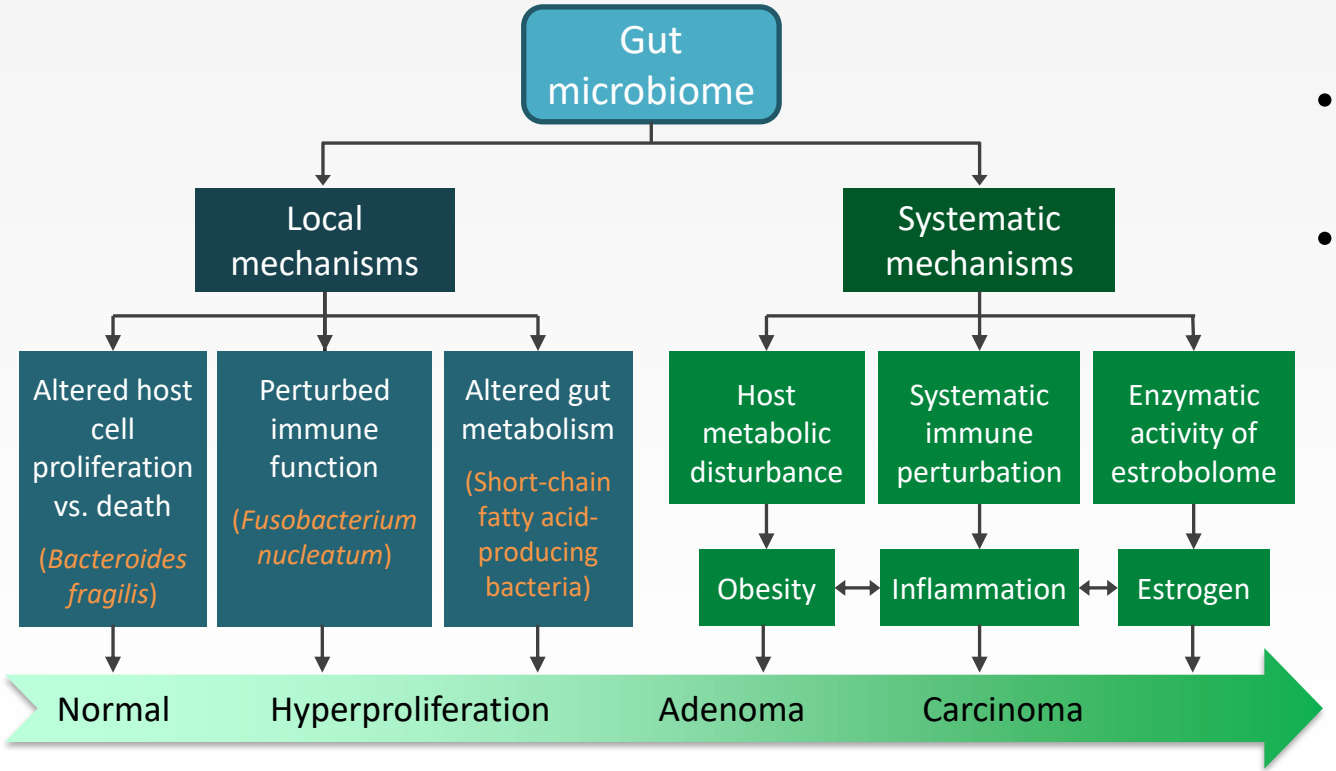
variations. Microbiota-based metabolic disease models developed in one location failed when used elsewhere, suggesting that such models cannot be extrapolated. Interpolated models performed much better, especially in diseases with obvious microbiota-related characteristics. Interpolation efficiency decreased as geographic scale increased, indicating a need to build localized baseline and disease models to predict metabolic risks.

Prediction accuracy for metabolic syndrome



He Y. Nat Med. 2018

Mechanisms and clinical implications for the link b/t gut microbiota and CRC



- Prediction
  - Screening tool
- Chemoprevention
  - Microbiota modification
  - Combinational approach

Song M. Gastroenterology. 2020
Tilg H, Cancer Cell. 2018

Microbiome as a screening tool for CRC

Study	microbes	Country	AUC for CRC	AUC for adenoma
Zeller, 2014	4 species (2 *Fusobacterium* species, *Porphyromonas asaccharolytica, Peptostreptococcus stomatis*)	France	0.84	
Zackular, 2014*	5 OTUs (*Clostridiales, Clostridium, Lachnospiraceae, Bacteroides*)	USA	0.80 (0.69-0.91)*	0.84 (0.74-0.94)*
Feng, 2015	10 metagenomic groups (*Bacteroides massiliensis, Bacteroides xylanisolvens, Bifidobacterium animalis, Paraprevotella clara, Streptococcus mutans*, 5 unclassified)	Austria	0.96 (0.88-1.00)	0.60 (0.38-0.82)
Baxter, 2016	34 OTUs (most belong to *Clostridales* order and some to *Bacteroides*)	USA	0.85	0.67
Wong, 2017	1 species (*F. nucleatum*)	China	0.89 (0.80-0.98)	0.58 (0.49-0.67)
Liang, 2017	4 species (*F. nucleatum, Bacteroides clarus, Roseburia intestinalis, Clostridium hathewayi*, and one undefined)	China	0.76	
Thomas, 2019	16 species (e.g., *Peptostreptococcus stomatis, F. nucleatum, Parvimonas spp., Porphyromonas asaccharolytica, Gemella morbillorum, Clostridium symbiosum and Parvimonas micra*)	Multi	0.81	0.54

*No validation was performed. The AUC was calculated in the training set.

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ARTICLES

https://doi.org/10.1038/s41591-019-0406-6

Meta-analysis of fecal metagenomes reveals global microbial signatures that are specific for colorectal cancer

Jakob Wirbel[1,31], Paul Theodor Pyl[2,3,31], Ece Kartal[1,4], Konrad
Alessio Milanese[1], Jonas S. Fleck[1], Anita Y. Voigt[1,5], Albert Pa
Shinichi Sunagawa[1,6], Luis Pedro Coelho[1,30], Petra Schrotz-Ki
Nina Habermann[9], Emma Niméus[3,10], Andrew M. Thomas[11,12],
Davide Serrano[13], Sayaka Mizutani[14,15], Hirotsugu Shiroma[14], Sa
Shinichi Yachida[16,18], Takuji Yamada[14,19], Levi Waldron[20,21], Ale
Rashmi Sinha[8], Cornelia M. Ulrich[24], Hermann Brenner[7,25,26], M
Peer Bork[1,4,28,29,32*] and Georg Zeller[1,32*]

Table 1 | Fecal metagenomic studies of CRC included in this meta-analysis

Country code	Reference	No. of cases	No. of controls
France	Zeller et al.[8]	53	61
Austria	Feng et al.[9]	46	63
China	Yu et al.[11]	74	54
United States	Vogtmann et al.[10]	52	52
Germany	The current study	60	60
External validation cohorts			
Italy 1	Thomas et al.[27]	29	24
Italy 2	Thomas et al.[27]	32	28
Japan	Courtesy of T. Yamada et al.	40	40

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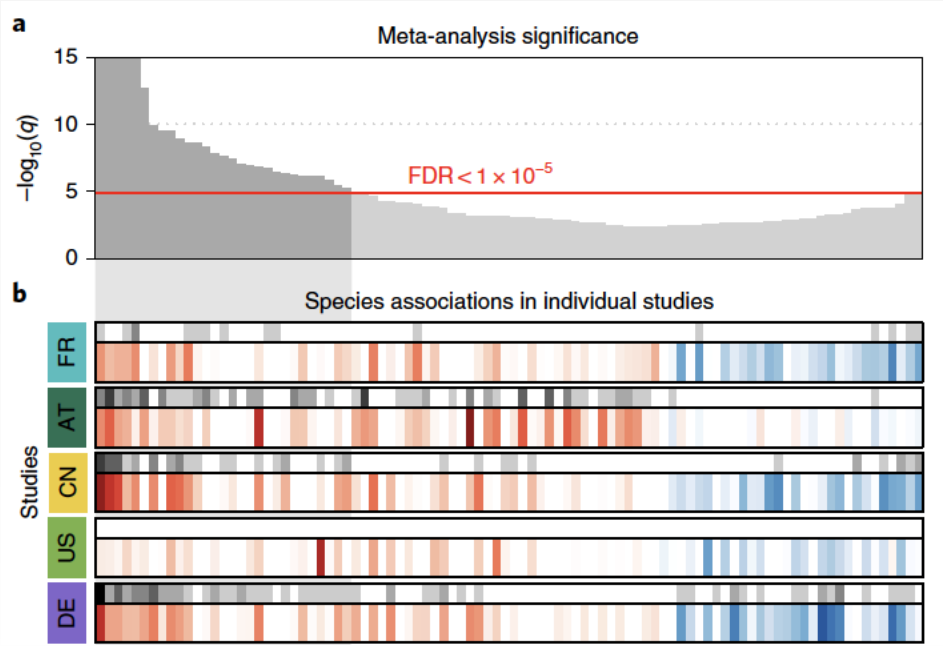
ARTICLES

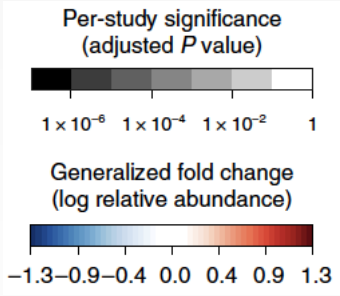
https://doi.org/10.1038/s41591-019-0405-7

Metagenomic analysis of colorectal cancer datasets identifies cross-cohort microbial diagnostic signatures and a link with choline degradation

Paolo Manghi[1,32], Francesco Asnicar[1], Edoardo Pasolli[1],
fo[1], Francesco Beghini[1], Serena Manara[1], Nicolai Karcher[1],
Davide Serrano[4], Sonia Tarallo[5], Antonio Francavilla[5],
betto[7], Giulio Ferrero[8], Sayaka Mizutani[9,10], Hirotsugu Shiroma[9],
ta[11,12], Shinichi Yachida[11,13], Takuji Yamada[9,14], Jakob Wirbel[15],
M. Ulrich[17], Hermann Brenner[16,18,19], Manimozhiyan Arumugam[20,21],
r[15], Francesca Cordero[8], Emmanuel Dias-Neto[3,25],
Tett[1], Barbara Pardini[5,27], Maria Rescigno[28], Levi Waldron[29,30,33],
cola Segata[1,33*]

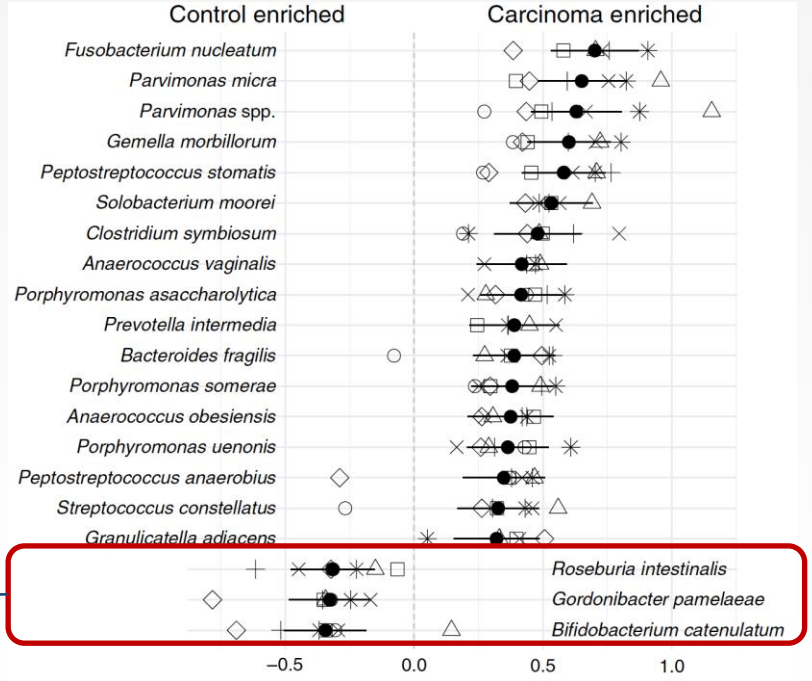
The core set of gut microbes associated with CRC is relatively consistent across studies





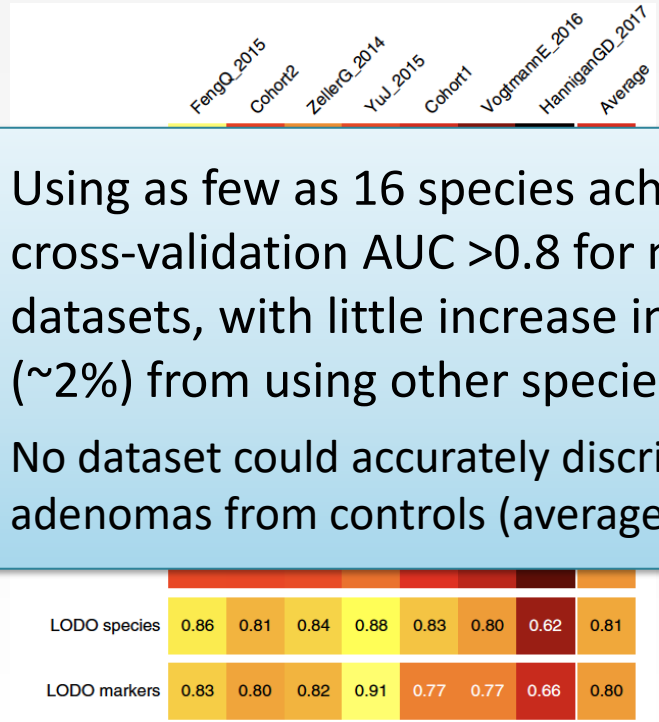
Wirbel J. Nat Med. 2019

Individual microbes consistently associated with CRC



Short-chain fatty acid-producing bacteria

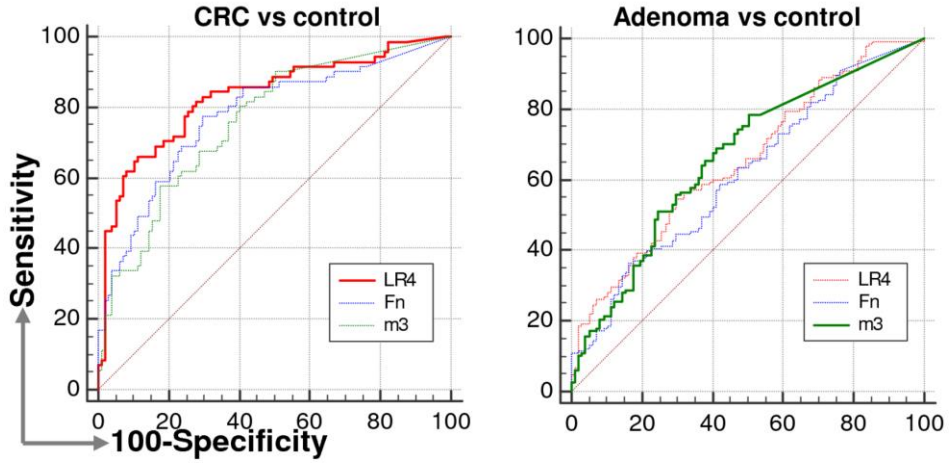
Validation set



- Using as few as 16 species achieved cross-validation AUC >0.8 for most of the datasets, with little increase in AUC (~2%) from using other species.
- No dataset could accurately discriminate adenomas from controls (average AUC=0.54).

Thomas AM. Nat Med. 2019

Microbiome improves the accuracy of FIT-based test for adenoma detection



Variables	CRC			Adenoma		
	Fn	*m3*	*LR4*	*Fn*	*m3*	*LR4*
AUROC	0.776	0.759	**0.830**	0.616	**0.662**	0.652

Fn: *Fusobacterium nucleatum*

m3: *Lachnoclostridium sp.*

LR4: Fn+m3+*Bacteroides clarus*

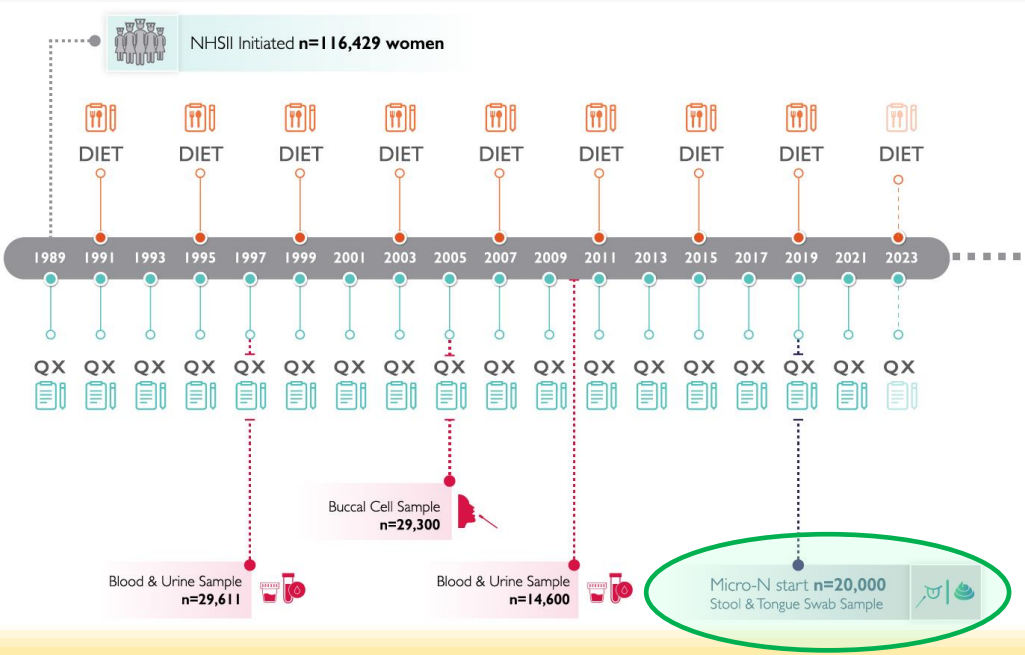
Remains to be validated in other populations

Liang JQ. Gut 2019.

A prospective microbiome study

Nurses' Health Study
Micro-N
Microbiome Among Nurses

- Microbiome among Nurses Study (Micro-N): n=20,000
  - To interrogate causes vs. consequences
  - To identify early changes in microbiome during carcinogenesis



nature protocols
PERSPECTIVE
https://doi.org/10.1038/s41596-021-00519-z
Check for updates

Overview of the Microbiome Among Nurses study (Micro-N) as an example of prospective characterization of the microbiome within cohort studies

Christine Everett[1,2,19], Chengchen Li[1,3,19], Jeremy E. Wilkinson[1,3,19], Long H. Nguyen[1,4,5], Lauren J. McIver[1,3], Kerry Ivey[6,7,8], Jacques Izard[9,10], Natalia Palacios[1,6,11], A. Heather Eliassen[1,2,12], Walter C. Willett[1,2,6,12], Alberto Ascherio[1,2,6,12], Qi Sun[1,2,6], Shelley S. Tworoger[12,13], Andrew T. Chan[1,2,4,5,14,15,19], Wendy S. Garrett[1,14,15,16,17,18,19], Curtis Huttenhower[1,3,14,15,19], Eric B. Rimm[1,2,6,12,19] and Mingyang Song[1,4,5,6,12,19]✉

U01CA261961: "The Gut Microbiome, Lifestyle, and Colorectal Neoplasia"

Everett C, et al. Nat Protoc, 2021.

Summary

- There is substantial regional variation in the gut microbiome.
- A consistent gut microbial signature has been identified across regions to differentiate CRC from non-CRC.
- Microbial features predict poorly for adenomas but may help improve the accuracy of FIT test.
- Prospective studies are needed to assess the potential of the gut microbiome for early detection of colorectal neoplasia.

Acknowledgements

- Lab members
  - Kai Wang
  - Scott Smith
  - Chun-Han Lo
  - Yang Hu
  - Markus Knudsen
  - Georgios Polychronidis
  - Mathew Vithayathil
  - Alaina Bever
  - Zhe (Gigi) Fang
  - Mingming He
  - Dong Hang
  - Liang Wang
- Collaborators
  - Mass General Hospital
    - Andrew Chan
    - David Drew
    - Long Nguyen
    - Wenjie Ma
    - Raaj Mehta
  - Harvard TH Chan School of Public Health
    - Curtis Huttenhower
    - Wendy Garrett
    - Eric Rimm
    - Edward Giovannucci
    - Kana Wu

Thank you!

Harvard Chan School Dean's Fund for Scientific Advancement: Activation Award

Thank you!