APPLICATIONS AND LESSONS LEARNED: WEARABLES

SENSORS, IMAGES AND AI FOR FOOD INTAKE MONITORING

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DISCLOSURES

Founder and partner in Bitwear Labs Inc

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Wearables: Now and Future

www.impactlab.com

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Wearables for Measurement of Food Intake: Detecting Eating Proxies

- Sucking
  - Pressure
  - Motion
- Swallowing
  - Acoustical
  - Mechanical (strain)
  - Electrical
  - Apnea detection
- Hand gestures
  - Inertial
  - Proximity
- Chewing
  - Acoustical
  - Mechanical (strain)

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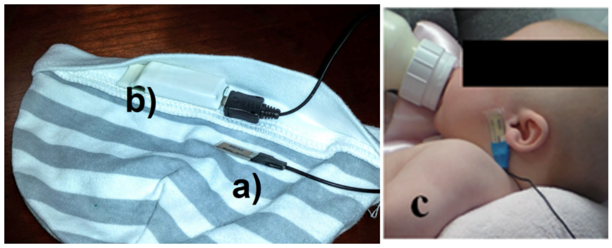
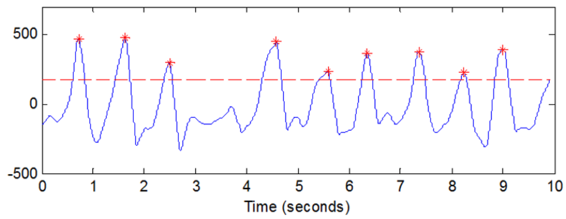
WEARABLES: SUCKING MONITORS



Sensor in the infant's hat. (a) jaw motion sensor, (b) wireless data acquisition module, and (c) a bottle-fed infant wearing the sensor.



Jaw motion sensor signal. Sucks are represented by *.

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Farooq M, Chandler-Laney PC, Hernandez-Reif M, Sazonov E. Monitoring of infant feeding behavior using a jaw motion sensor. J Healthc Eng 2015;6(1):23-40.

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WEARABLES: HAND-TO-MOUTH MONITORS

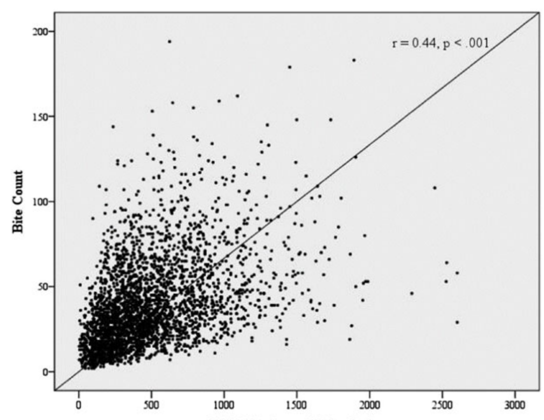

Figure 2. Scatterplot of the relationship between bite count and automated self-administered 24-hour dietary recall (ASA24) estimated kilocalories across all 2,975 eating activities (r=0.44; P<0.001).

- **High social acceptance**
- **Relatively low accuracy due to similarity of everyday gestures**
- **No insight into the type of foods consumed**

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Y. Dong, A. Hoover, J. Scisco, and E. Muth, "A New Method for Measuring Meal Intake in Humans via Automated Wrist Motion Tracking," Appl. Psychophysiol. Biofeedback, vol. 37, no. 3, pp. Sep. 2012.

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WEARABLES: SWALLOWING MONITORS

Acoustical

Magnetic

Electrical

Piezoelectric

- **A very reliable way to detect food and beverage consumption**
- **Very low social acceptance: people do not like “collars”**
- **No insight into the type of foods consumed**

O. Makeyev, P. Lopez-Meyer, S. Schuckers, W. Besio, and E. Sazonov, “Automatic food intake detection based on swallowing sounds,” Biomed. Signal Process. Control, vol. 7, no. 6, pp. 649–656, Nov. 2012.
A. Kandori, T. Yamamoto, Y. Sano, M. Oonuma, T. Miyashita, M. Murata, and S. Sakoda, “Simple Magnetic Swallowing Detection System,” IEEE Sens. J., vol. 12, no. 4, pp. 805–811, Apr. 2012.
M. Farooq, J. M. Fontana, and E. Sazonov, “A novel approach for food intake detection using electroglottography,” Physiol. Meas., vol. 35, no. 5, p. 739, May 2014.
H. Kalantarian, N. Alshurafa, T. Le, and M. Sarrafzadeh, “Monitoring eating habits using a piezoelectric sensor-based necklace,” Comput. Biol. Med., vol. 58, pp. 46–55, Mar. 2015.

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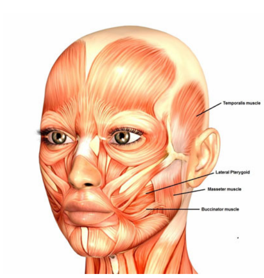
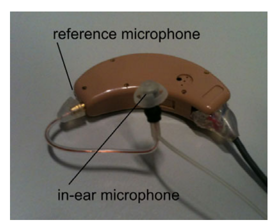
WEARABLES: CHEWING MONITORS



Temporalis muscle

Masseter muscle



Ear canal

- **Reliable way to detect food and beverage consumption. Sipping of beverages may generate false negatives and chewing gum/lip biting may generate false positives**
- **Moderate to high social acceptance**
- **No insight into the type of foods consumed**

S. Päßler, M. Wolff, and W.-J. Fischer, “Food intake monitoring: an acoustical approach to automated food intake activity detection and classification of consumed food,” Physiol. Meas., vol. 33, no. 6, pp. 1073–1093, 2012.
E. Sazonov and J. M. Fontana, “A Sensor System for Automatic Detection of Food Intake Through Non-Invasive Monitoring of Chewing,” IEEE Sens. J., vol. 12, no. 5, pp. 1340 –1348, 2012.
M. Farooq and E. Sazonov, Segmentation and Characterization of Chewing Bouts by Monitoring Temporalis Muscle Using Smart Glasses with Piezoelectric Sensor, IEEE J. Biomed. Health Inform., 2017
D. Hossain, T. Ghosh, M. Haider Imtiaz, and E. Sazonov, “Ear canal pressure sensor for food intake detection,” *Frontiers in Electronics*, vol. 4, 2023, Accessed: Jul. 18, 2023.

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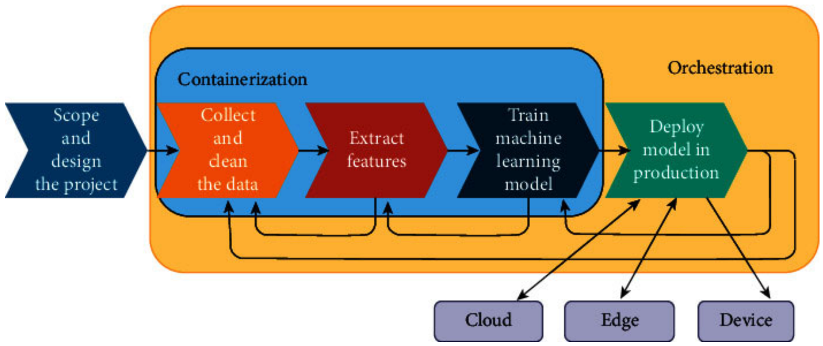
ML/AI in Wearables



- ML/AI is the driving force for data analysis in wearables
- Data collection, cleaning, labeling, feature extraction and model training/validation are critical steps
- Limitation: only simple, small models may be deployed on the device
- Sophisticated and computationally intensive models may only be deployed on the edge or in the cloud, requiring network connectivity

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Sabry F, Eltaras T, Labda W, Alzoubi K, Malluhi Q. Machine Learning for Healthcare Wearable Devices: The Big Picture. J Healthc Eng. 2022 Apr 18;2022:4653923. doi: 10.1155/2022/4653923. PMID: 35480146; PMCID: PMC9038375.

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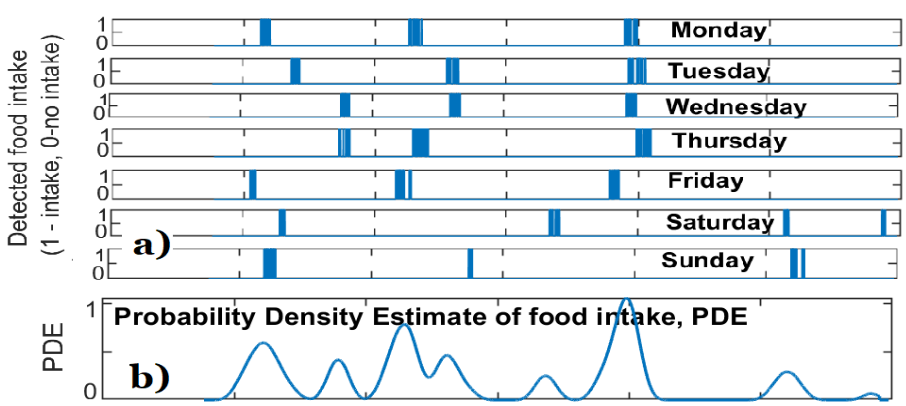
Wearables: Capabilities



Eating pattern of an individual over a week

- Detect eating events through “passive” detection
- Measure timing and duration
- Evaluate daily patterns

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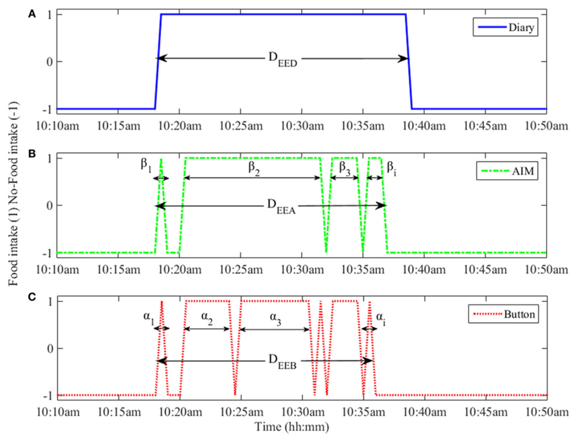
Wearables: Capabilities



- **Evaluate microstructure of eating: number of bouts, hand gesture rate, chewing rate, etc.**

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Meal microstructure characterization from sensor-based food intake detection, Abul Doulah, Muhammad Farooq, Xin Yang, Jason Parton, Megan A. McCrory, Janine A. Higgins, Edward Sazonov, Front. Nutr., 17 July 2017

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Wearables: Capabilities

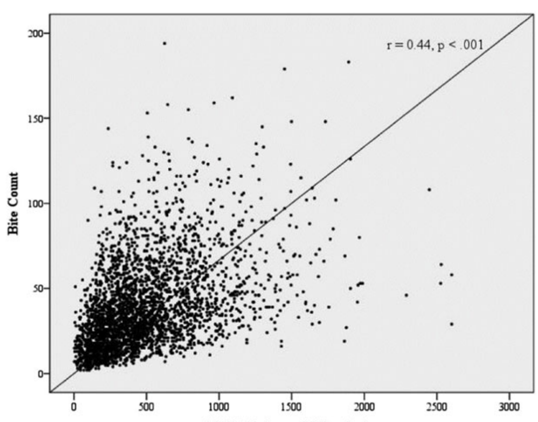

Figure 2. Scatterplot of the relationship between bite count and automated self-administered 24-hour dietary recall (ASA24) estimated kilocalories across all 2,975 eating activities (r=0.44; P<0.001).

	Relative reporting error		Mean estimation error		Lower LOA	Upper LOA
	Mean	SD	Mean	SD		
Full	0.252	0.189	−17.665	226.901	−462.391	427.061
Chew	0.291	0.282	−1.186	230.42	−452.808	450.437
Bite	0.292	0.221	−39.669	266.946	−562.884	483.546
Swallow	0.266	0.212	−0.698	210.725	−413.72	412.323
Sensor	0.342	0.42	−8.627	252.591	−503.706	486.452

- **Estimate the consumed amount.**

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Statistical models for meal-level estimation of mass and energy intake using features derived from video observation and a chewing sensor, Xin Yang, Abul Doulah, Muhammad Farooq, Jason Parton, Megan A. McCrory, Janine A Higgins, Edward Sazonov, Nature Scientific Reports, 9, 45. 2019.
Y. Dong, A. Hoover, J. Scisco, and E. Muth, “A New Method for Measuring Meal Intake in Humans via Automated Wrist Motion Tracking,” Appl. Psychophysiol. Biofeedback, vol. 37, no. 3, pp. 205–215, Sep. 2012.

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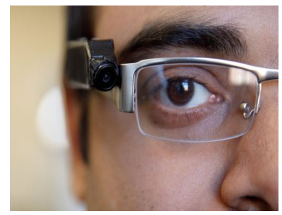
Wearbles + Images



J. Liu *et al.*, "An Intelligent Food-Intake Monitoring System Using Wearable Sensors," *2012 Ninth International Conference on Wearable and Implantable Body Sensor Networks*, London, UK, 2012, pp. 154-160, doi: 10.1109/BSN.2012.11.
M. Sun *et al.*, "eButton: A wearable computer for health monitoring and personal assistance," *2014 51st ACM/EDAC/IEEE Design Automation Conference (DAC)*, San Francisco, CA, USA, 2014, pp. 1-6, doi: 10.1145/2593069.2596678.
A. Doulah, T. Ghosh, D. Hossain, M. H. Imtiaz and E. Sazonov, ""Automatic Ingestion Monitor Version 2" – A Novel Wearable Device for Automatic Food Intake Detection and Passive Capture of Food Images," in *IEEE Journal of Biomedical and Health Informatics*, vol. 25, no. 2, pp. 568-576, Feb. 2021, doi: 10.1109/JBHI.2020.2995473.

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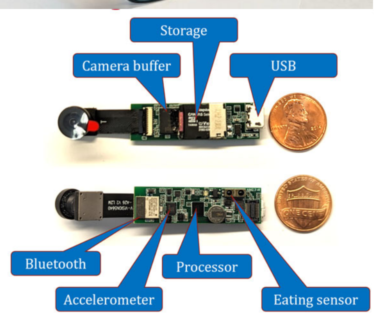
Wearables + Images

Automatic Ingestion Monitor v2

AIM-2 is a "passive" wearable device that is:
- Does not require user actions beyond wearing
- Captures egocentric images of food showing eating progression
- Automatically detects eating and captures images of food intake
- Captures eating in various environments (on the go, during transportation, etc.)
- Captures the dynamic process of eating, including any additions in servings
- Monitors compliance with wear regimen

The images may be analyzed by a nutritionist or by an image recognition system to identify type of food and portion size.



A. B. M. S. U. Doulah, T. Ghosh, and E. Sazonov, "Automatic Ingestion Monitor Version 2 – A Novel Wearable Device for Automatic Food Intake Detection and Passive Capture Of Food Images," J. Biomed. Health Inform. Rev., 2019

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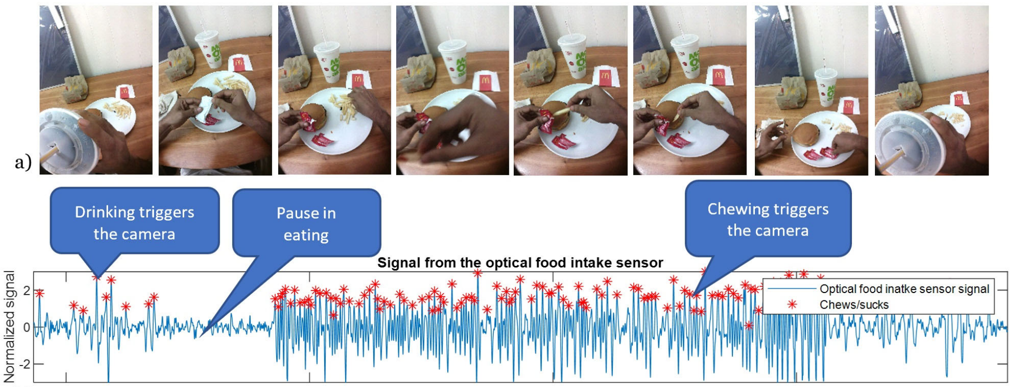
Wearables + Images

- Optical sensor monitors activations of temporalis muscle associated with eating and drinking.
- Images of the complete meal progression, including any foods introduced during the meal
- Sensor signals describing the eating process such as chewing rate, and chewing bouts



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Food Image Analysis by a Nutritionist

By a human: a nutritionist recognizing the images and estimating portion sizes

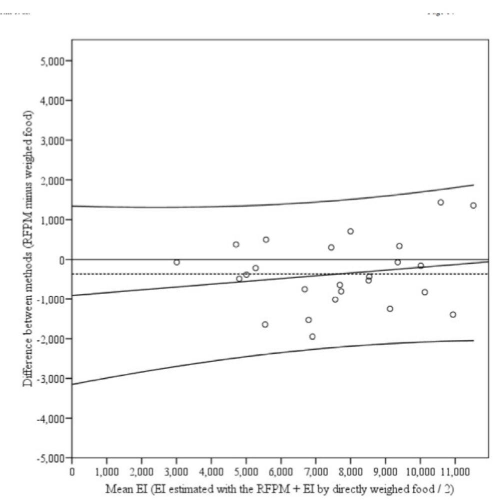

Figure 2.
Bland and Altman analysis comparing the RFPM to weighed EI in the laboratory. Lunch and dinner data from the dine-in group was included in these analyses. The RFPM bias in estimating EI was consistent over different levels of EI, $R^2 = .03$ (adjusted $R^2 = -.01$), $p = .39$.

C. K. Martin et al., "A novel method to remotely measure food intake of free-living individuals in real time: the remote food photography method," *Br. J. Nutr.*, vol. 2009

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FOOD IMAGE ANALYSIS BY A NUTRITIONIST

Table 3. Sources of error contributing to differences in EI assessment by image analysis compared with WFR ($n = 25$)[a].

	Line items, *n* (% of WFR)	WFR, MJ/d (% of WFR daily EI)	Image analysis, MJ/d (% of WFR daily EI)	Image analysis adjusted, MJ/d (% of WFR daily EI)
Food identification errors				
Nutritionist error	0.6 ± 1.0 (3.5)	0.47 ± 0.83 (5.3)	0.55 ± 1.37 (6.2)	0.41 ± 0.85 (4.7)
Ambiguity in image	0.9 ± 1.0 (5.8)	0.53 ± 0.73 (6.0)	0.79 ± 1.15 (8.9)	0.70 ± 0.80 (7.8)
No database match	0	0	0	0
Portion size errors				
Nutritionist error	5.5 ± 3.8 (34.5)	2.49 ± 1.75 (28.1)	3.94 ± 2.74 (44.4)	2.89 ± 2.00 (32.5)
Ambiguity in image	1.2 ± 2.2 (7.3)	0.42 ± 0.70 (4.7)	0.66 ± 1.11 (7.4)	0.60 ± 0.95 (6.8)
No database match	4.0 ± 2.2 (24.8)	2.85 ± 2.16 (32.1)	3.98 ± 2.61 (44.8)	3.47 ± 2.36 (39.1)
Other error types				
No database match in energy density	0.1 ± 0.3 (0.8)	0.04 ± 0.12 (0.4)	0.05 ± 0.16 (0.6)	0.05 ± 0.16 (0.6)
More than one type of error	0.5 ± 0.8 (3.0)	0.33 ± 0.60 (3.8)	0.39 ± 0.66 (4.4)	0.33 ± 0.64 (3.7)
Acceptable error (EI within ±10% of WFR daily EI)	3.2 ± 2.0 (20.3)	1.69 ± 1.06 (19.0)	1.75 ± 1.13 (19.8)	1.54 ± 0.98 (17.4)

EI energy intake, *WFR* weighed food record.
[a]Values are mean ± SD (% of mean WFR daily EI in parentheses).

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A. Doulah et al., "Energy intake estimation using a novel wearable sensor and food images in a laboratory (pseudo-free-living) meal setting: quantification and contribution of sources of error," Int J Obes (Lond), Oct. 2022, doi: 10.1038/s41366-022-01225-w.

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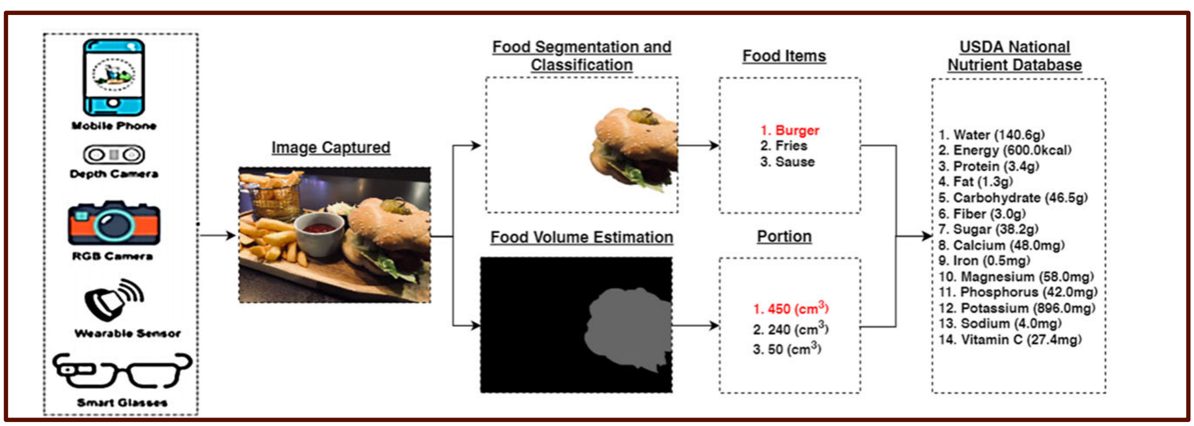
IMAGE-BASED DIETARY ASSESSMENT BY AI



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Lo, Frank Po Wen & Sun, Yingnan & Qiu, Jianing & Lo, Benny. (2020). Image-Based Food Classification and Volume Estimation for Dietary Assessment: A Review. IEEE Journal of Biomedical and Health Informatics. PP. 1-1. 10.1109/JBHI.2020.2987943

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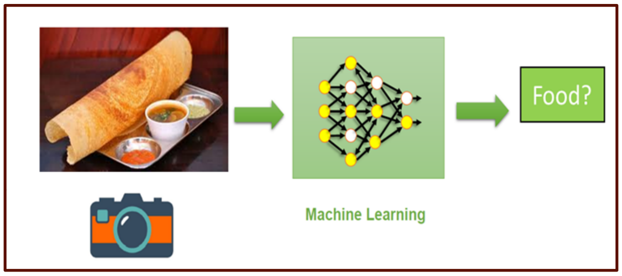
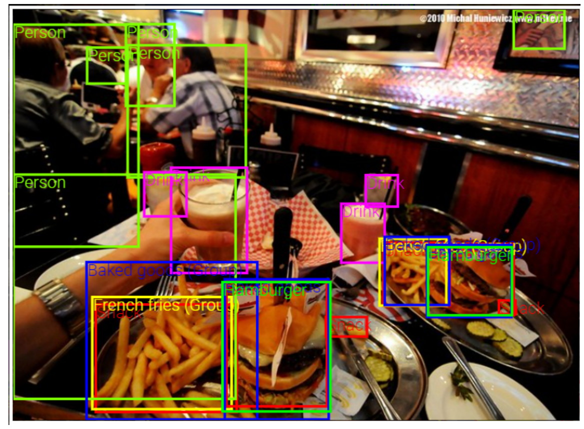
FOOD DETECTION AND RECOGNITION

Food detection can be achieved by :
1. Detection: Classifying images as food and non- food images.
2. Localization: Object detection (identify instances of food objects in the image)
3. Food recognition: Identify the type of food





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G. Chen et al., “Food/Non-Food Classification of Real-Life Egocentric Images in Low- and Middle-Income Countries Based on Image Tagging Features,” Frontiers in Artificial Intelligence, vol. 4, p. 28, 2021, doi: 10.3389/frai.2021.644712

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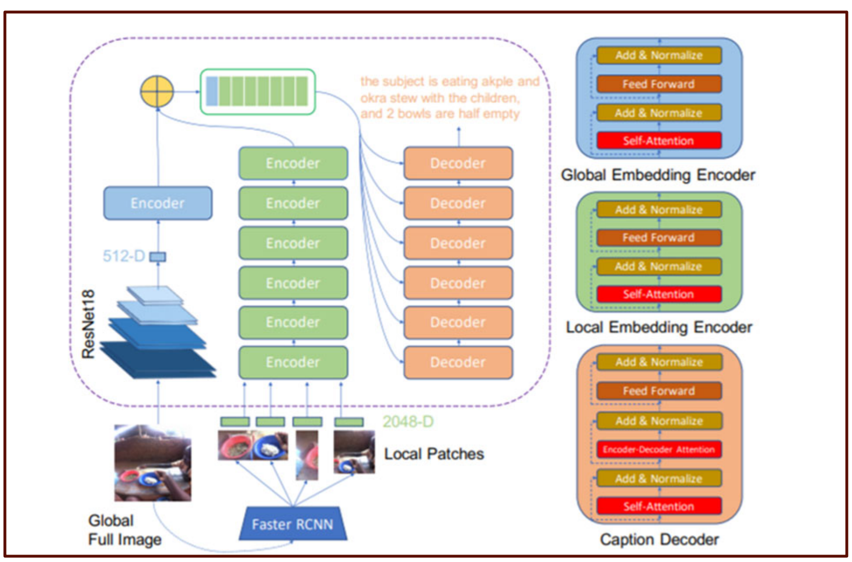
FOOD IMAGE TO TEXT DESCRIPTION



A Deep learning architecture for conversion of images into text captions

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Qiu et al., “Egocentric Image Captioning for Privacy-Preserved Passive Dietary Intake Monitoring,” arXiv:2107.00372 [cs], Jul. 2021, Accessed: Jul. 12, 2021. [Online]. Available: http://arxiv.org/abs/2107.00372

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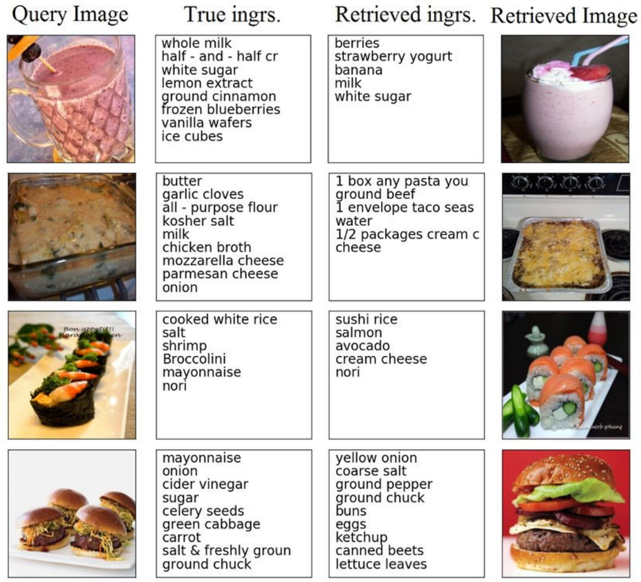
FOOD IMAGE TO RECEIPE



Im2Recipe: ingredients from an image

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J. Marín *et al.*, "Recipe1M+: A Dataset for Learning Cross-Modal Embeddings for Cooking Recipes and Food Images," in *IEEE Transactions on Pattern Analysis and Machine Intelligence*, vol. 43, no. 1, pp. 187-203, 1 Jan. 2021, doi: 10.1109/TPAMI.2019.2927476.

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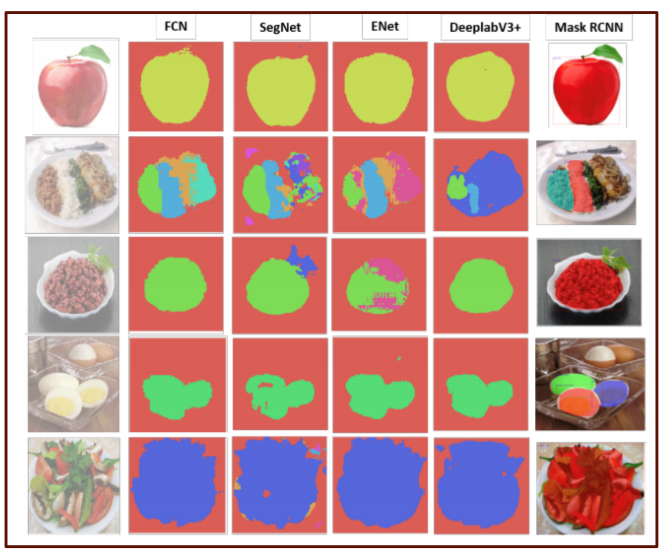
SEGMENTATION OF FOOD IMAGES



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He Y, Xu C, Khanna N, Boushey CJ, Delp EJ. FOOD IMAGE ANALYSIS: SEGMENTATION, IDENTIFICATION AND WEIGHT ESTIMATION. Proc (IEEE Int Conf Multimed Expo). 2013;2013:10.1109/ICME.2013.6607548. doi:10.1109/ICME.2013.6607548
X. Wu, X. Fu, Y. Liu, E.-P. Lim, S. C. H. Hoi, and Q. Sun, “A Large-Scale Benchmark for Food Image Segmentation,” arXiv:2105.05409 [cs], May 2021, Accessed: Jul. 12, 2021. [Online]. Available: http://arxiv.org/abs/2105.05409

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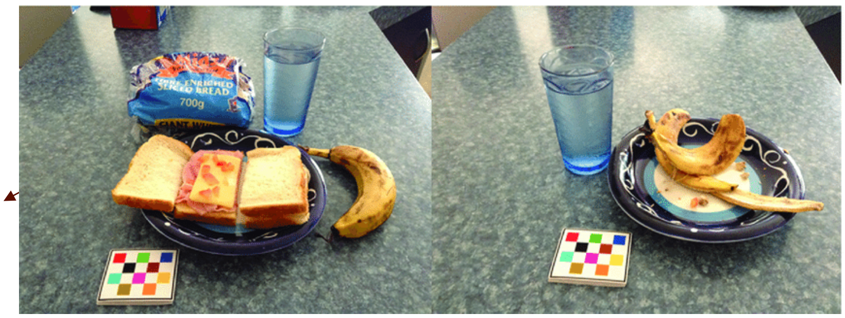
Portion Size Estimation from Food Images

- A dimensional reference is required for estimation of the portion size
- Frequently, participants are asked to place fiducial markers in the image
- Leftover images are taken to estimate consumed amounts



K. E. Bathgate *et al.*,
"Feasibility of Assessing Diet with a Mobile Food Record for Adolescents and Young Adults with Down Syndrome," *Nutrients*, vol. 9, no. 3, p. E273, Mar. 2017, doi: 10.3390/nu9030273

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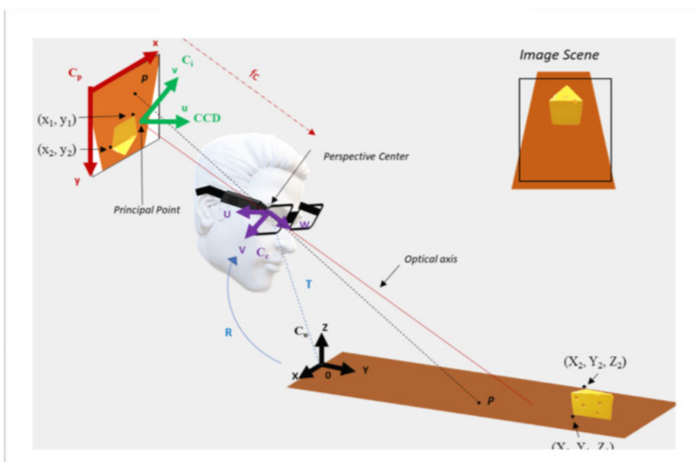
Portion Size Estimation from Food Images



Perspective transformation: an example of the geometric transformations for portion size estimation by the Automatic Ingestion Monitor

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PORTION SIZE ESTIMATION FROM FOOD IMAGES

Performance of recent methods

Table 8. Comparison with other methods. n/a means not applicable, '-' represents the value was not reported in the corresponding paper.

Method	Scale Reference	Input	Core Idea	Error
MuseFood [39]	Depth	RGB Image (Top + Side View)	Differential Modeling	−0.27~12.37% Test dataset: 3 food items
Eye-Measurement [39]	n/a	RGB Image	Visually Gauged by Human	−13.84~22.87% Test dataset: 3 food items
Hassannejad et al. [13]	Checkerboard	Multi-View (6) RGB Images	3D Modeling with Structure from Motion	1.70~19.10% Test dataset: 10 food items
im2calories [21]	Depth	RGB + Depth Image	3D Reconstruction with Deep Learning	- Test dataset NFood-3D dataset
Fang et al. [40]	Depth	Gray + Depth Image	3D Voxel Representation from depth	11.00~33.90% [38] Test dataset: 10 food objects
Lo et al. [18]	Depth	Depth Image (Front + Back View)	3D Reconstruction with Iterative Closest Point	3.30~9.40% Test dataset: 8 synthetic food objects
Point2Volume. [41]	Depth	RGB + Depth Image	3D Point Cloud Completion	15.32% Test dataset: 11 food items
VD Meter [42]	-	Multi-View (192) RGB Images	3D Reconstruction	0.83~5.23% Test dataset: 6 food items
Ours	Learned	Single RGB Image	Reference Volume Classification	11.60~20.10% Test dataset: 174~540 food images

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Z. Yang et al., "Human-Mimetic Estimation of Food Volume from a Single-View RGB Image Using an AI System," Electronics, vol. 10, no. 13, Art. no. 13, Jan. 2021, doi: 10.3390/electronics10131556

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COMPLEXITY OF REAL-LIFE BEHAVIOR

Natural food intake behavior is significantly more complex than commongly used staged food scenes:

- Foods are not staged. Food items may be occluded or consumed mixed.
- Foods are eaten in all kinds of environments (car, bed, etc.)
- Foods may be consumed from shared plates (e.g. appetizers)
- Dimensional refences may not be available

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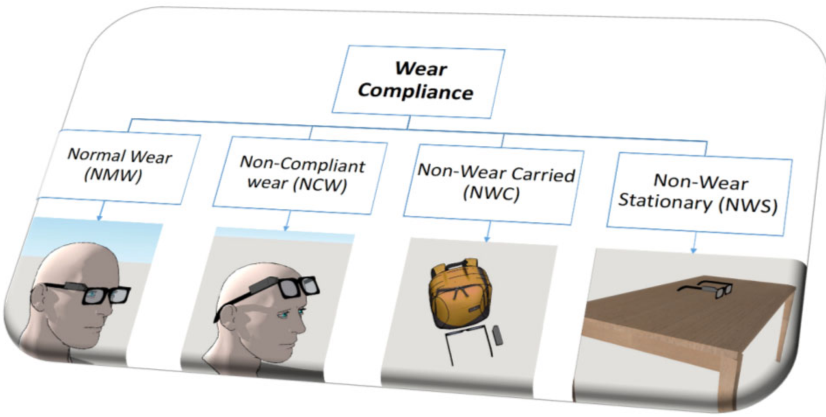
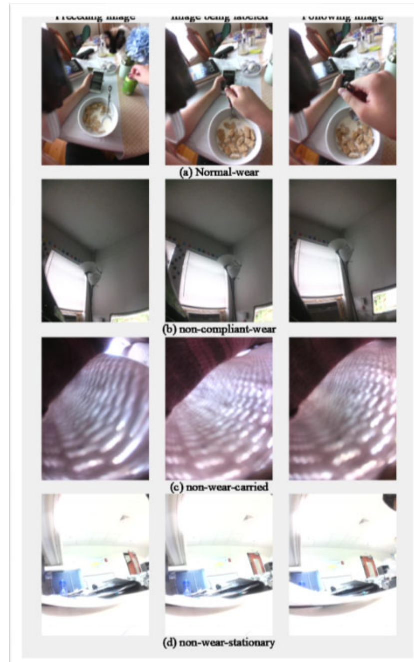
Compliance

- Compliance with use/wear is hard to establish
- Eating out of the protocol is frequent
- With wearable devices compliance may be assessed from image and sensor data





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T. Ghosh, D. Hossain and E. Sazonov, "Detection of Food Intake Sensor's Wear Compliance in Free-Living," in *IEEE Sensors Journal*, vol. 21, no. 24, pp. 27728-27735, 15 Dec.15, 2021, doi: 10.1109/JSEN.2021.3124203.

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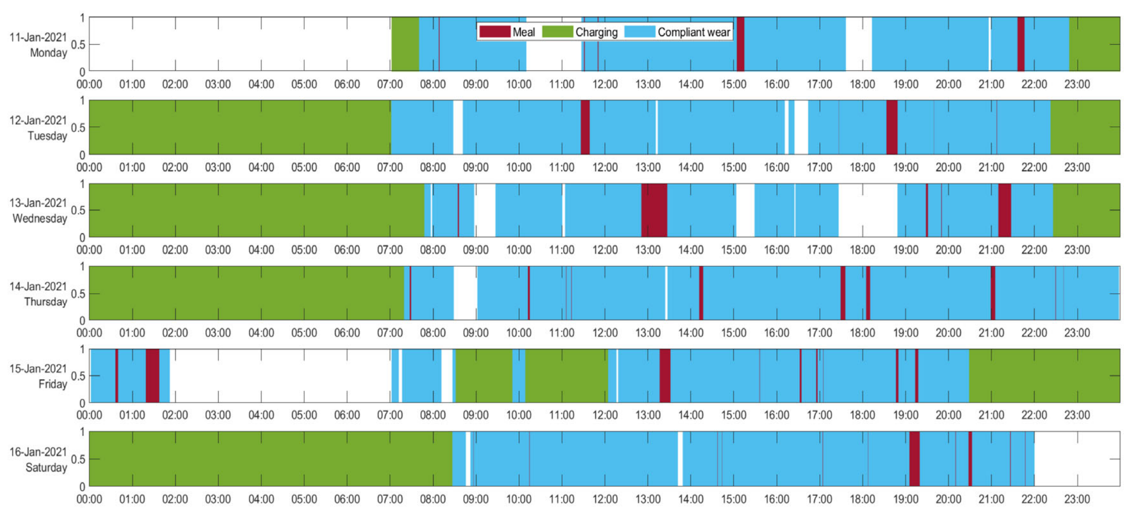
Compliance



Compliance report from an ongoing study

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PRIVACY

- Use of any image data raises privacy concerns
- Images may contain HIPAA-protected information
- Privacy issues are not inherent to personal cameras (e.g. in the US there is 1 surveillance camera per 6.5 people)

Potential issues:
- Inappropriate or Unwanted Images
- Confidentiality (capture of illegal activities)
- Third Parties (family members, co-workers, general public)

Potential solutions:
- Use of ethical guidelines in research
- Use of privacy-preserving techniques

P. Kelly et al., "An ethical framework for automated, wearable cameras in health behavior research," Am. J. Prev. Med., vol. 44, no. 3, pp. 314–319, Mar. 2013
M. A. Hassan and E. Sazonov, "Selective Content Removal for Egocentric Wearable Camera in Nutritional Studies," IEEE Access, vol. 8, pp. 198615–198623, 2020

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INHERENT LIMITATIONS OF IMAGING

- Similar-looking items may have different nutritional value

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SUMMARY

- Wearables allow for "passive" detection of eating events but do not provide insights of the foods being consumed

- Leveraging imaging capability allows to combine the best aspects of wearables and image –based methods

- AI/ML methods form the backbone of technology-based dietary and behavioral assessment, but many technical issues yet to be resolved

- All of the described methods are indirect measurements with inherent limitations

- Ethical and privacy issues need to be addressed along with technical aspects

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THANK YOU!

Thanks to all colleagues, postdocs and students with whom I had privilege to collaborate on these projects!

NIH support:

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- R21HL083052
- R21DK085462
- R01DK100796
- U24CA268228

BILL & MELINDA GATES foundation

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A Systematic Review of Sensor-Based Methodologies for Food Portion Size Estimation
(https://ieeexplore.ieee.org/document/9272773)

An Ethical Framework for Automated, Wearable Cameras in Health Behavior Research
(https://www.sciencedirect.com/science/article/pii/S0749379712008628?via%3Dihub)

Image-Based Food Classification and Volume Estimation for Dietary Assessment: A Review
https://ieeexplore.ieee.org/document/9082900

The Use of Mobile Devices in Aiding Dietary Assessment and Evaluation
https://ieeexplore.ieee.org/document/5473089

Vision-Based Approaches for Automatic Food Recognition and Dietary Assessment: A Survey
https://ieeexplore.ieee.org/document/8666636

College of Engineering

33

Applications and Lessons Learned: Microbiome

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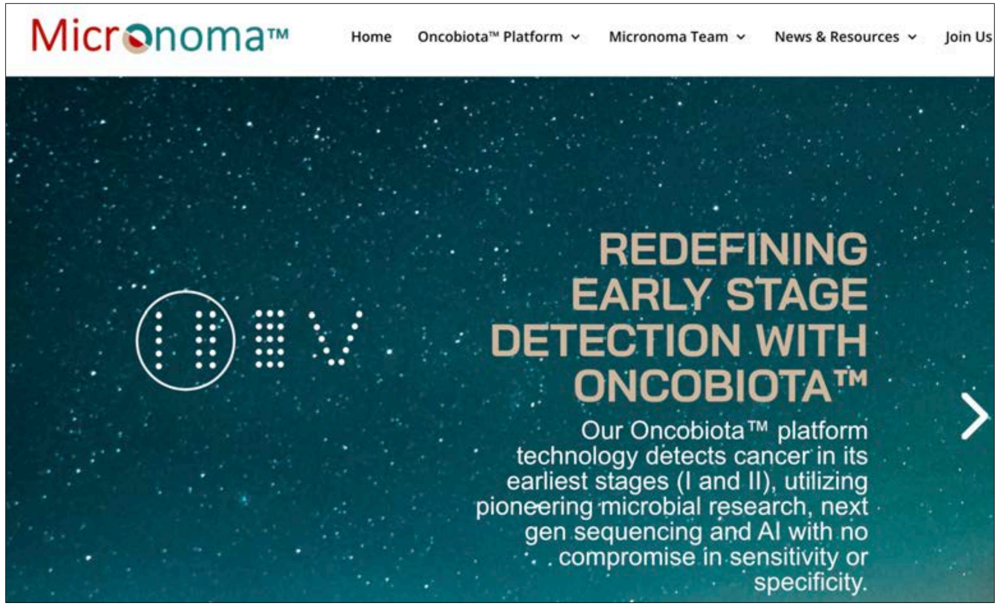
Wolfe Family Endowed Chair of Microbiome Research
at Rady Children's Hospital of San Diego
Professor, Pediatrics, Bioengineering CSE & HDSI at
University of California San Diego

Disclosures (Knight):

Micronoma™

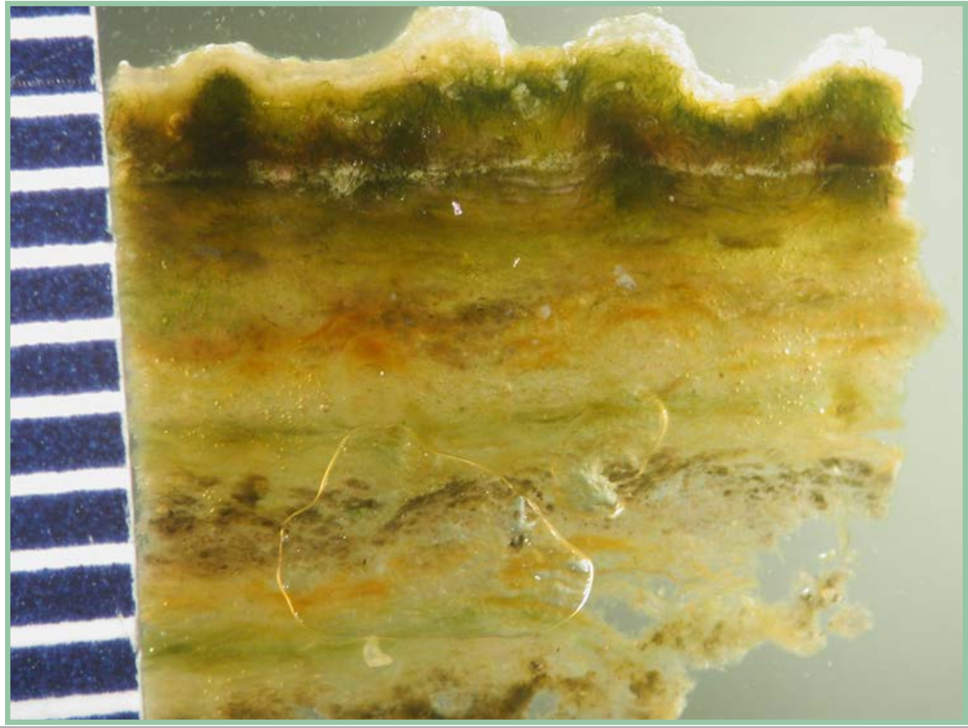
- Filed international patent applications:
  - PCT/US19/59647: Cancer microbiome tissue and blood diagnostics
  - PCT/US2021/051261: Metastatic cancer microbiome tissue and blood diagnostics
- Filed national patent applications:
  - U.S. Patent Application No. 62/754,696
  - U.S. Patent Application No. 63/081,075
  - U.S. Patent Application No. 63/105,624
  - U.S. Patent Application No. 63/221,504
- Pursuing commercialization of this work through a company (Micronoma) that has exclusively licensed the intellectual property from UC San Diego.
- Also: co-founder and shares, Biota; SAB and shares, BiomeSense, GenCirq; SAB, DayTwo; consultant and shares, Cybele

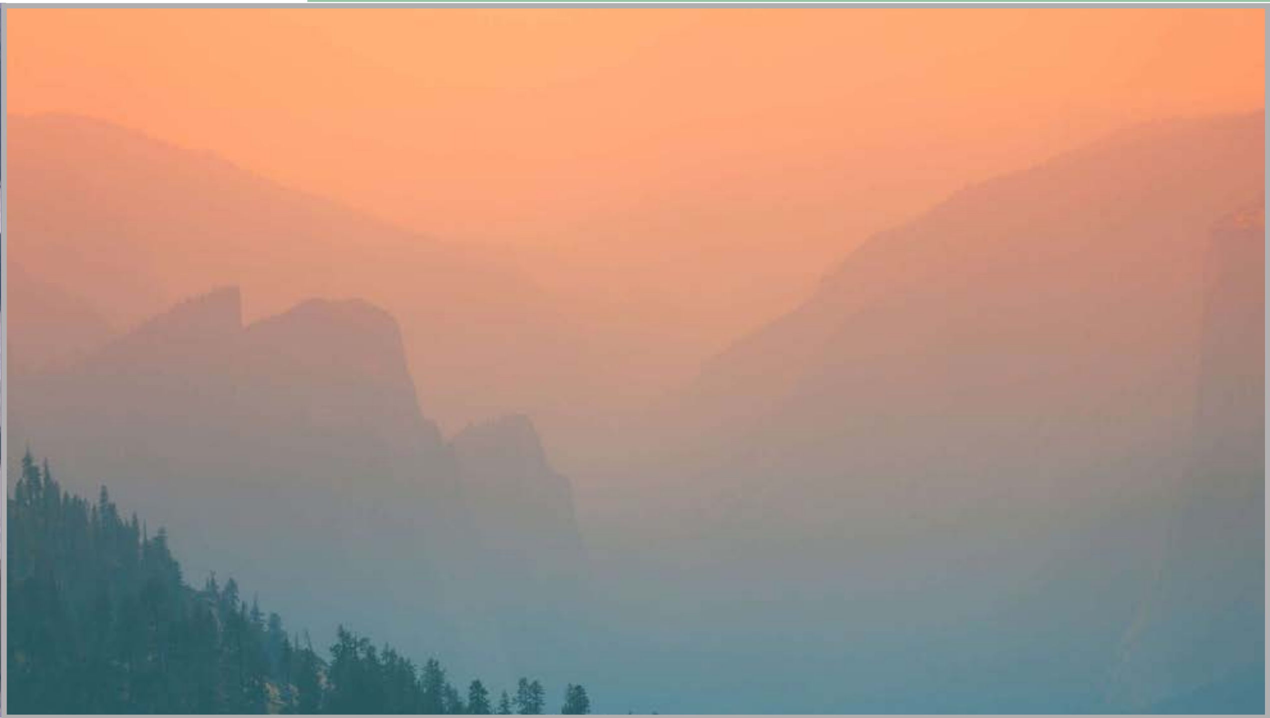


Error-correcting barcoded primers for pyrosequencing hundreds of samples in multiplex

Micah Hamady[1], Jeffrey J Walker[2], J Kirk Harris[3], Nicholas J Gold[2] & Rob Knight[4]

NATURE METHODS | VOL.5 NO.3 | MARCH 2008 | 235





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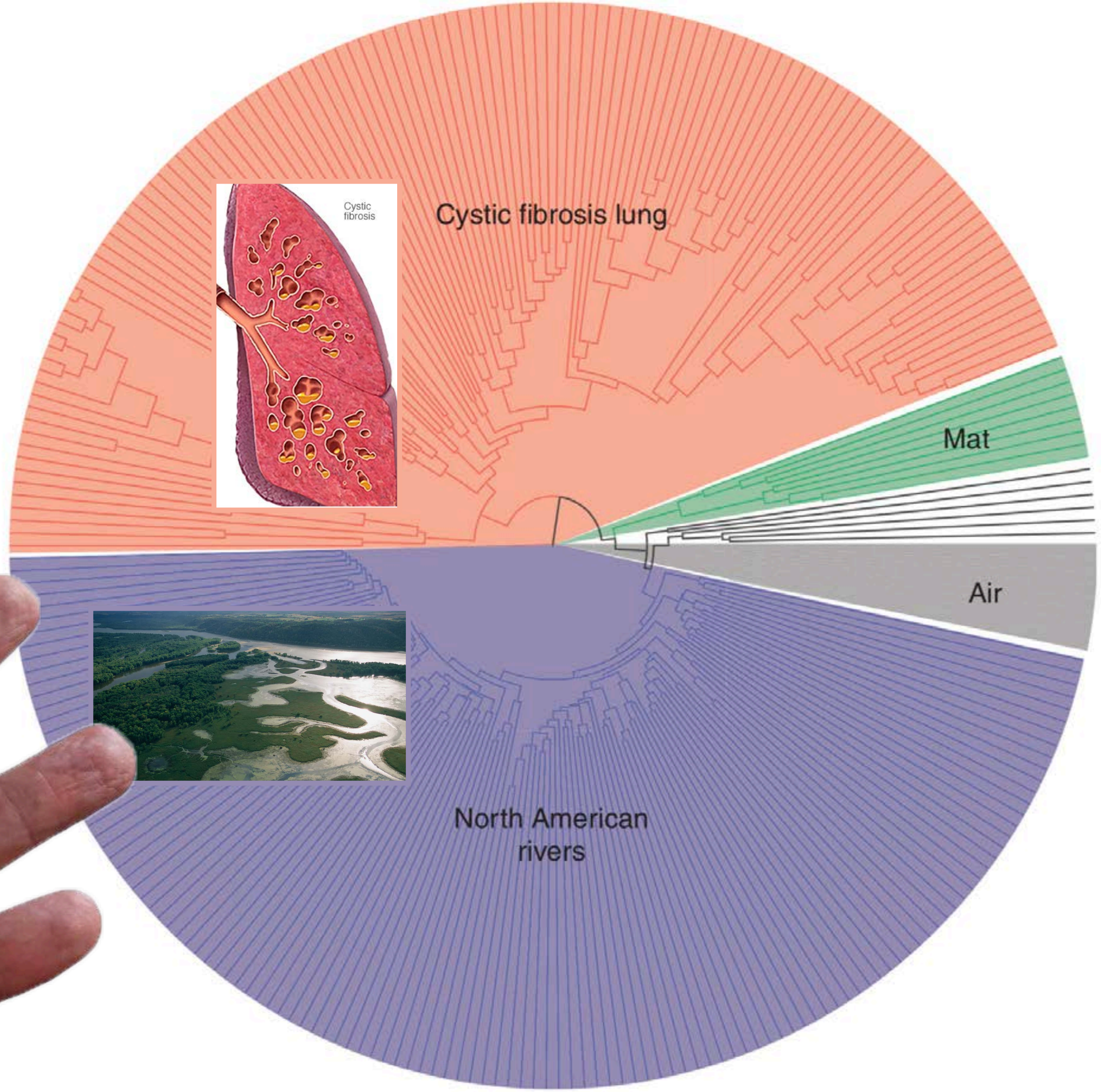
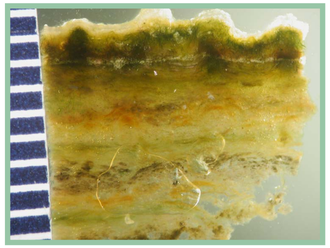
NATURE METHODS | VOL.5 NO.3 | MARCH 2008 | 235





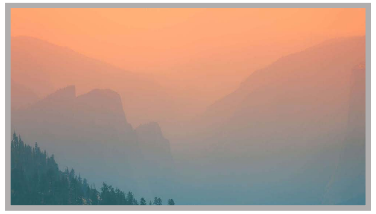


Figure 2 | UniFrac clustering by community was essentially perfect with sequences from pyrosequencing. Samples from cystic fibrosis lung, Guerrero Negro microbial mat, air and North American rivers cluster by environment type.

earth microbiome project

Thompson et al. 2017 *Nature*

We can now build **predictive models** for many traits related to health from the **microbiome**

Classifying lean/obese*:

57% accuracy from **human** genes

vs

90% accuracy from **microbial** genes

*Random Forests classifier

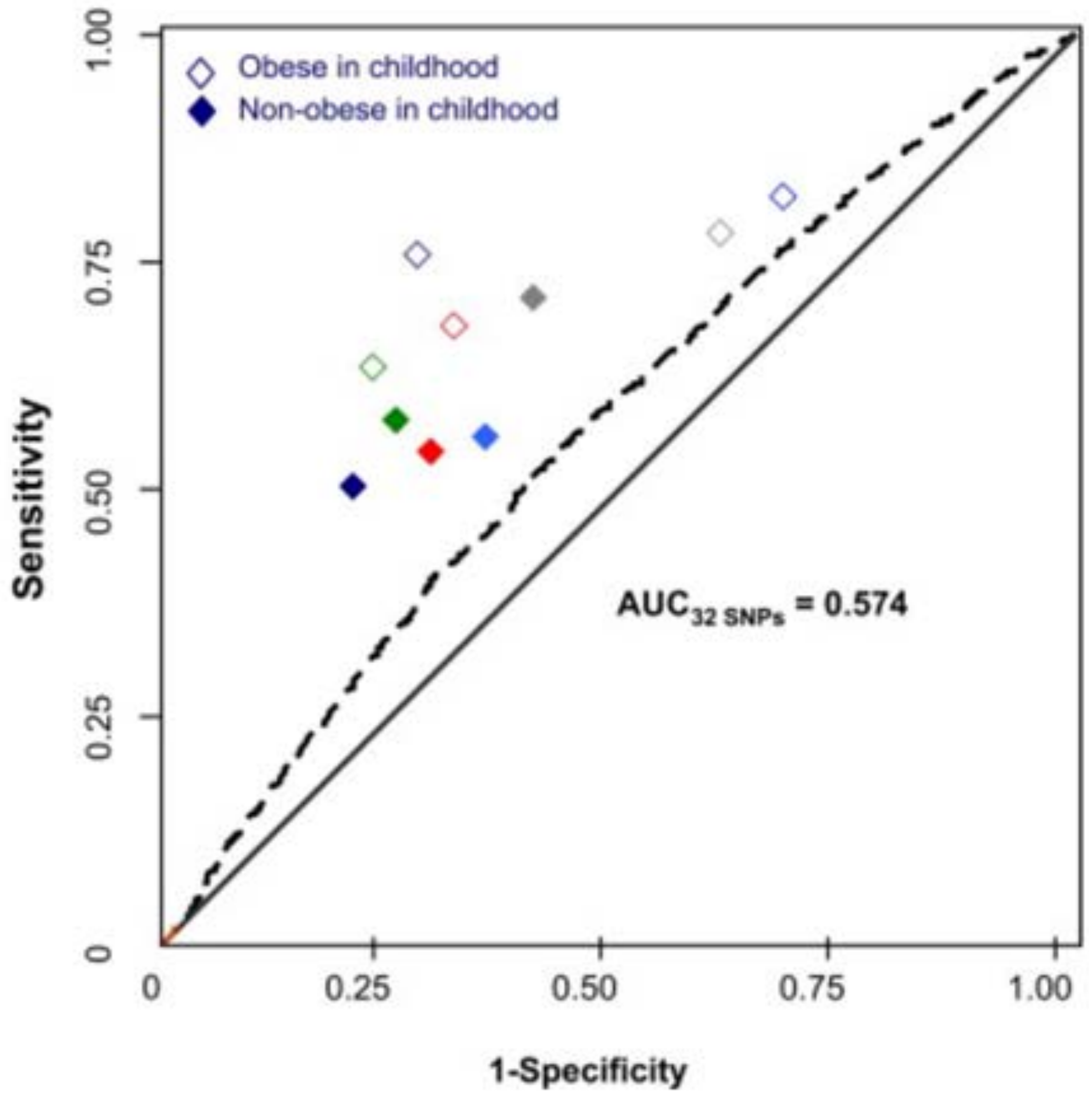
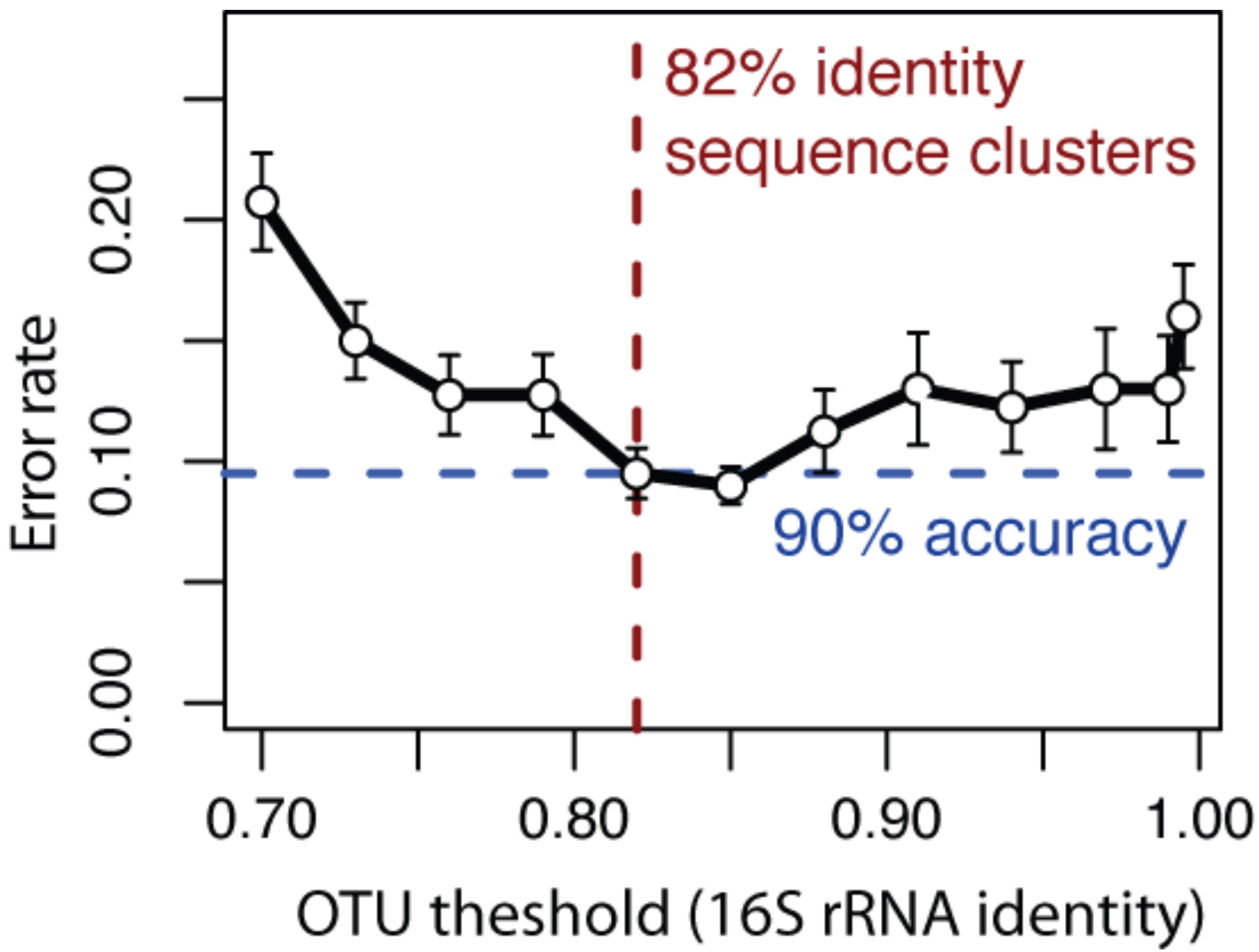
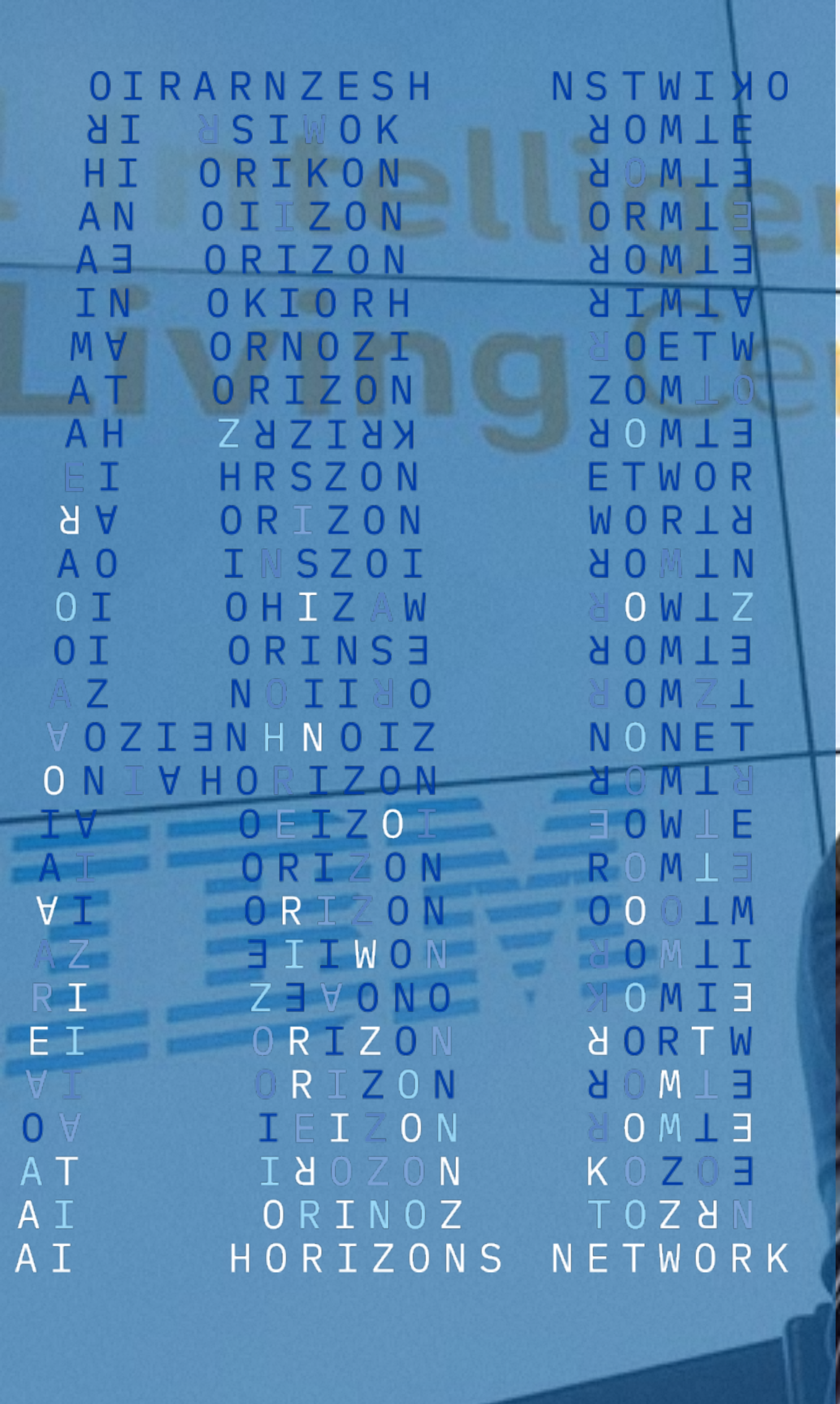


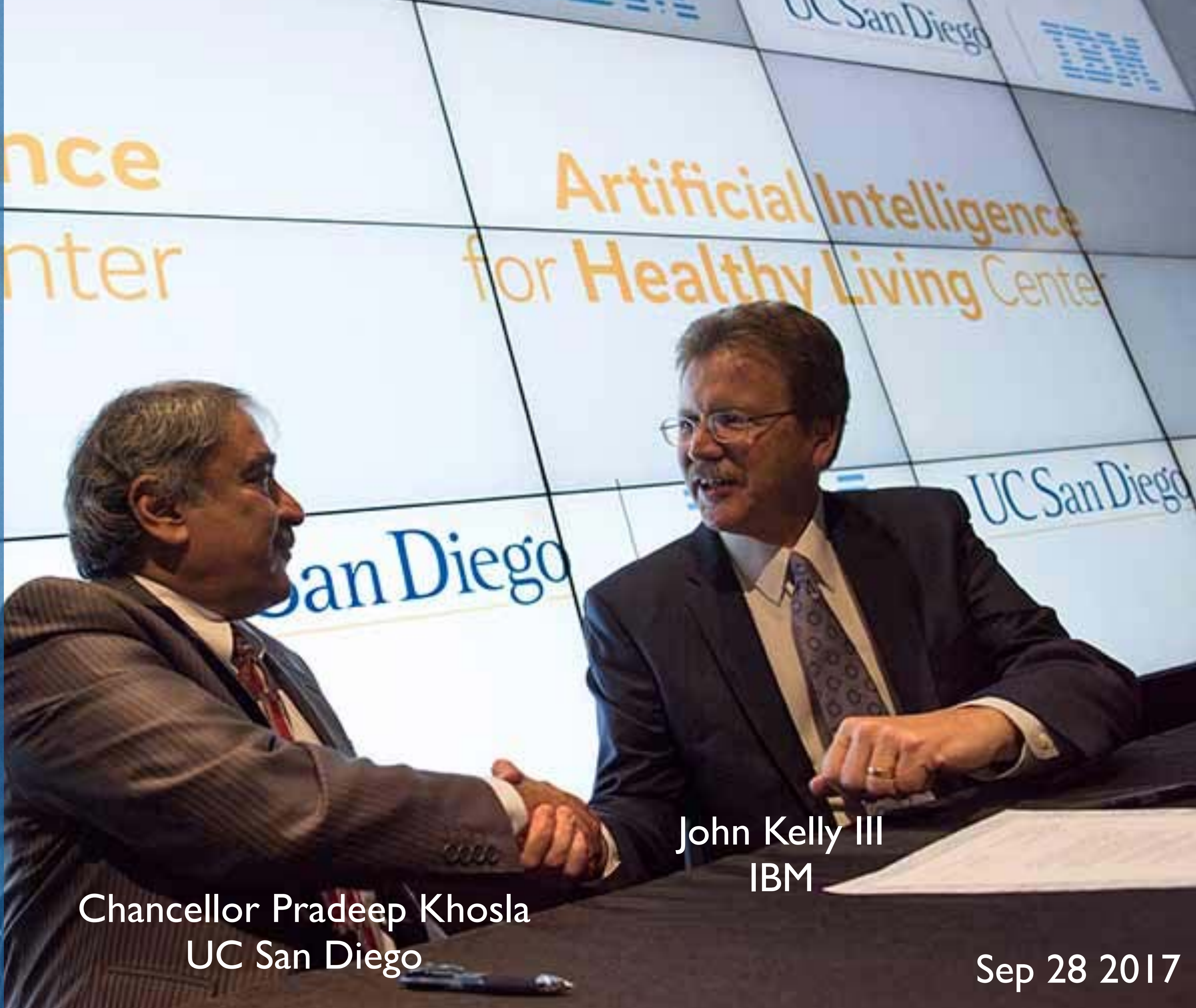
Fig. 5. The AUC$_{ROC}$ for the 32 BMI-associated loci to predict obesity in 8,120 individuals from the ARIC study.[48] For comparison, sensitivity and 1-specific are shown for 'parental obesity' as a test at various ages during childhood and adolescence (1–2 yrs in dark blue, 3–5 yrs in green, 6–9 yrs in red, 10–14 yrs in light blue, 15–17 yrs in grey) to predict obesity in adult life, with data derived from Whitaker et al.[71]



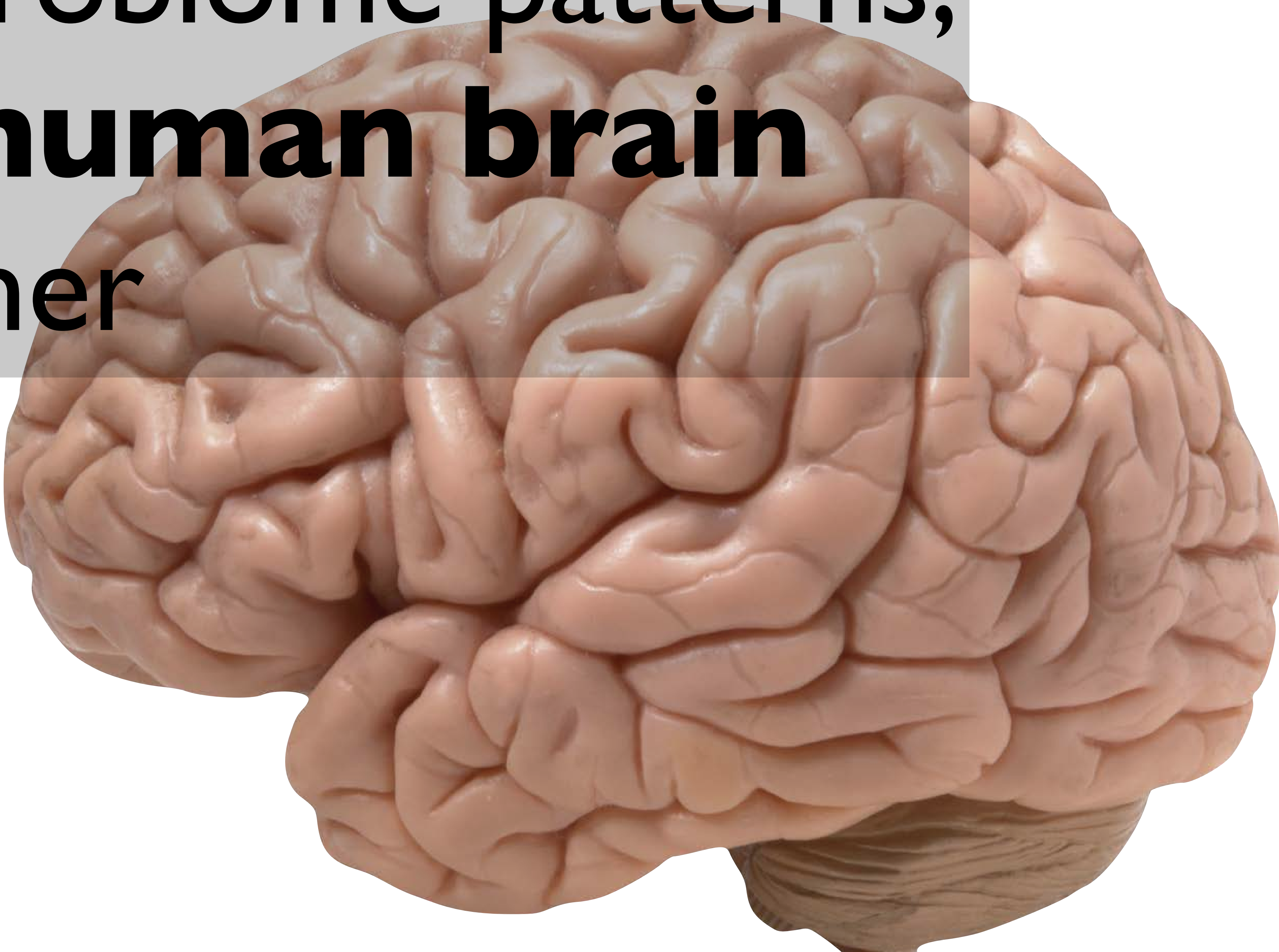
Loos 2012 Best Pract Res Clin Endocrinol Metab 26:211

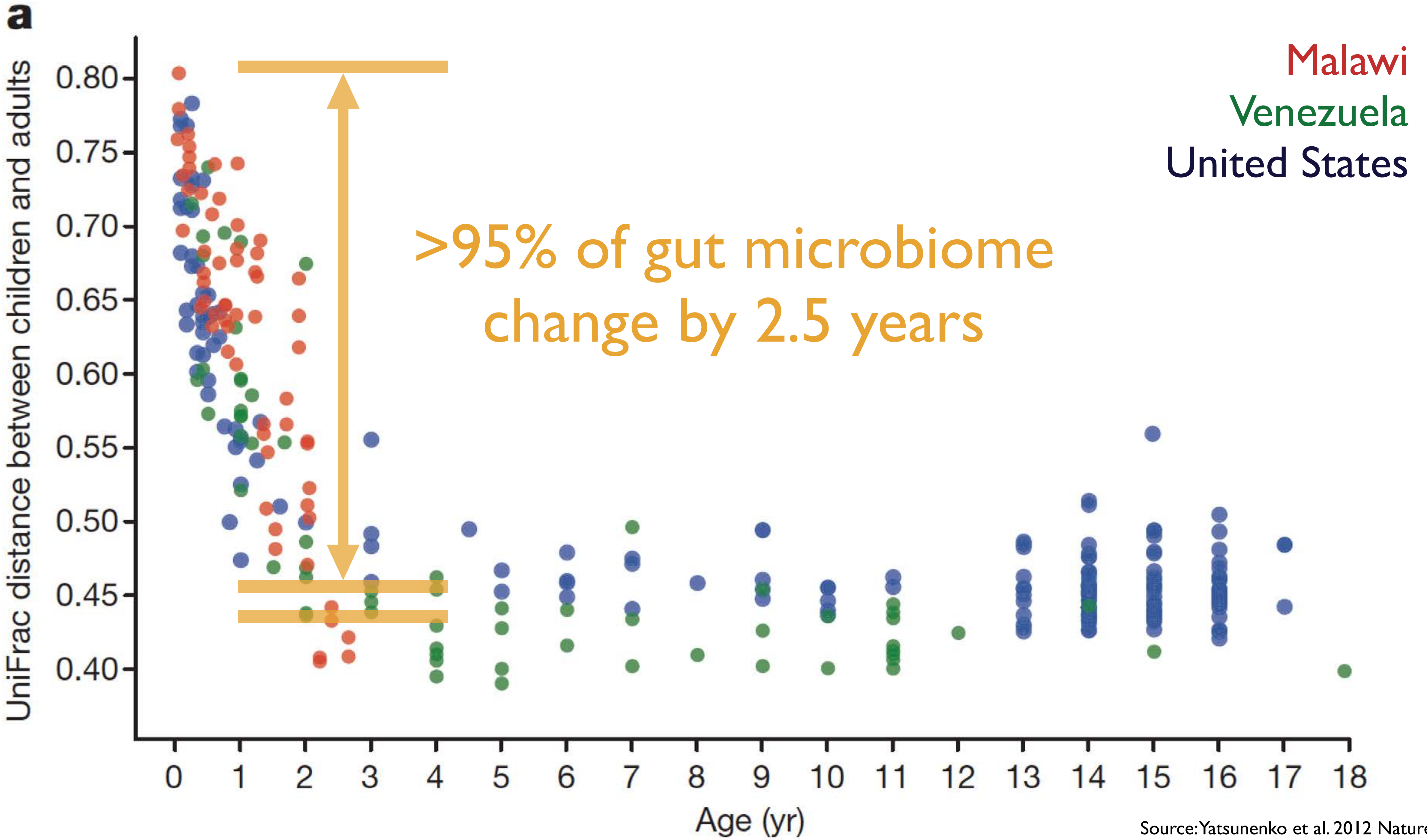
Knights et al. 2011 Cell Host & Microbe 10:292


AI HORIZONS NETWORK


Artificial Intelligence for Healthy Living Center
UC San Diego
IBM
John Kelly III
IBM
Chancellor Pradeep Khosla
UC San Diego
Sep 28 2017

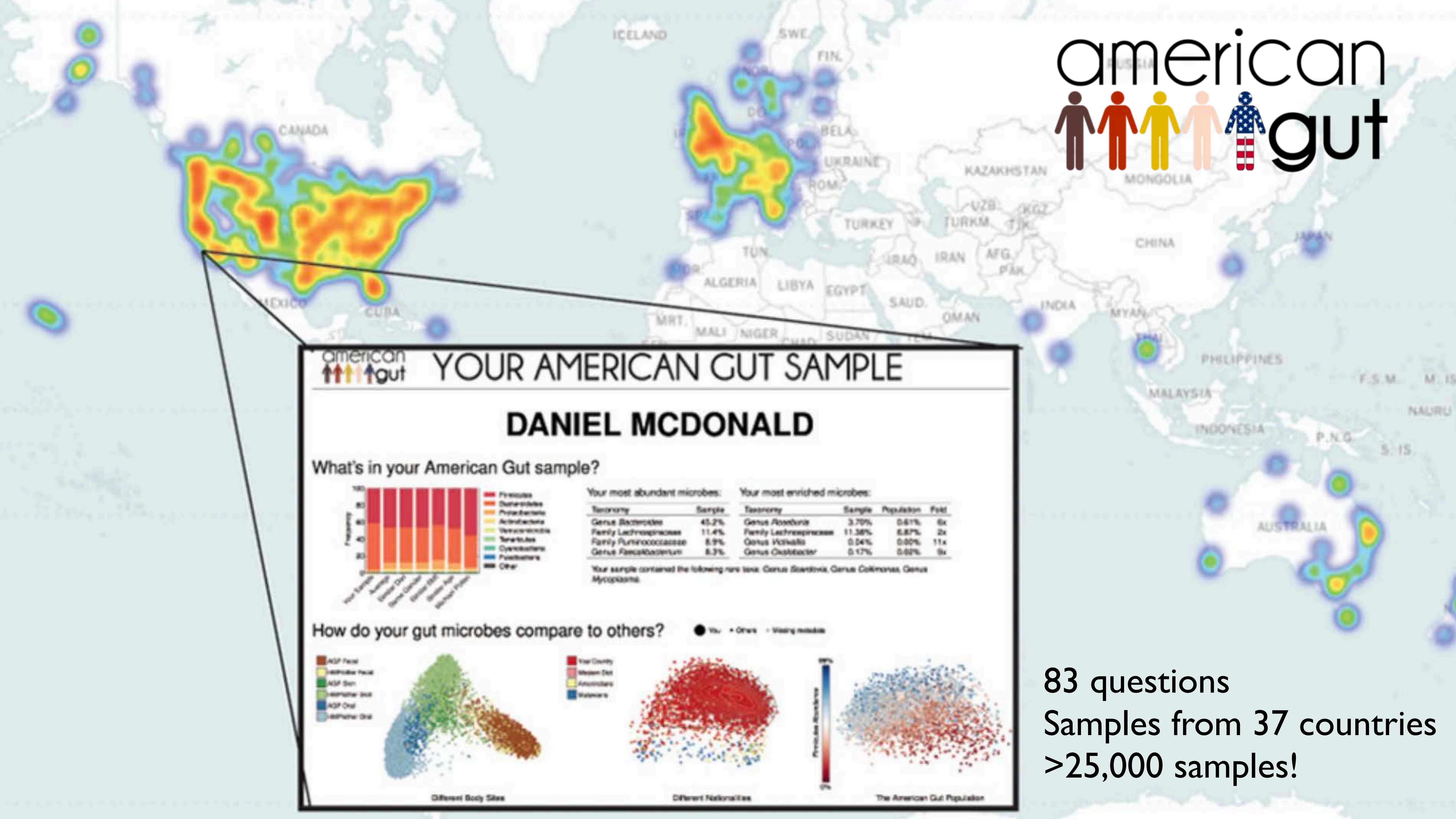
Some microbiome patterns, even the **human brain** can decipher





Source: Yatsunenko et al. 2012 Nature

So is your microbiome **doomed** by **age 3**?

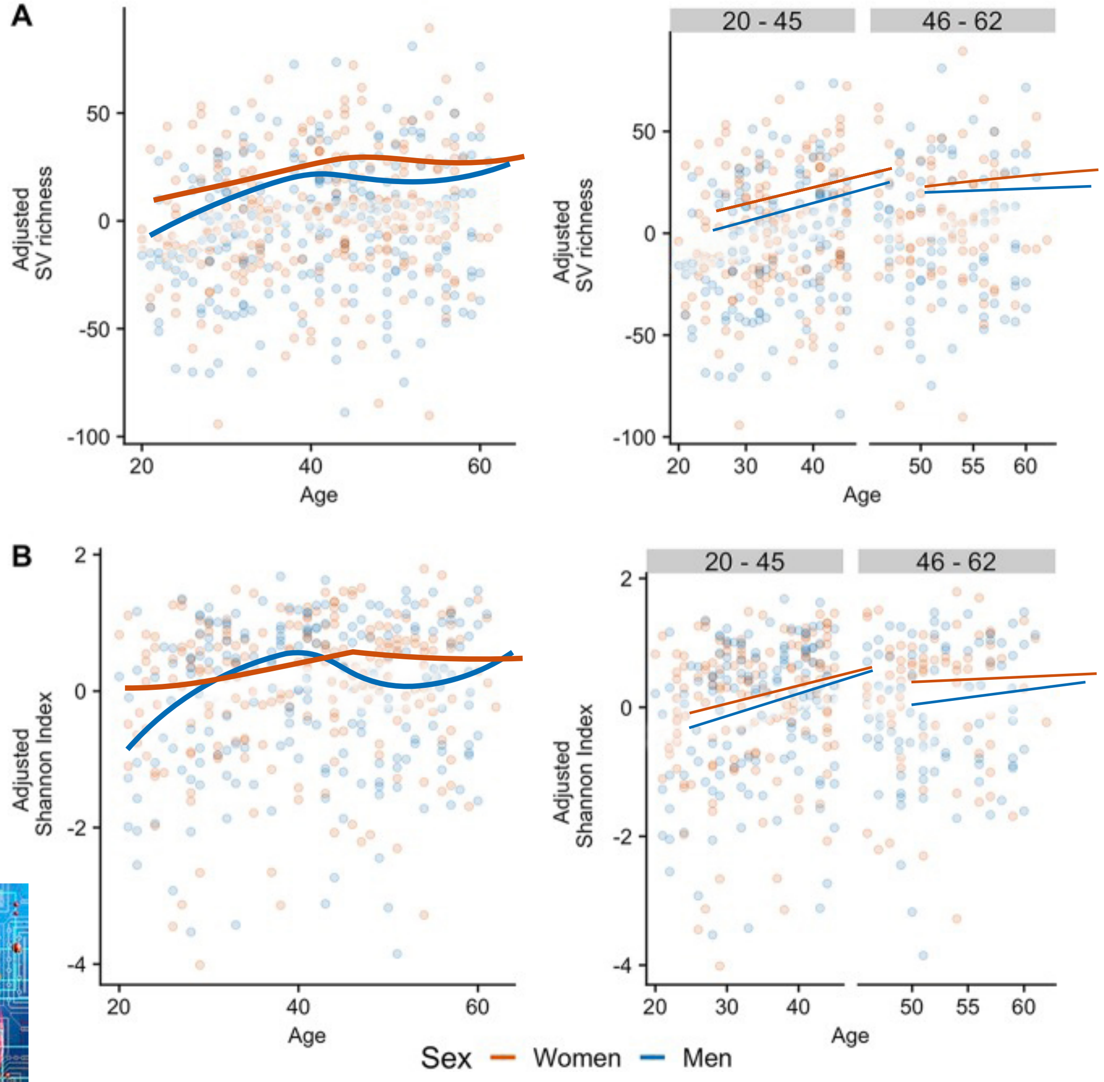


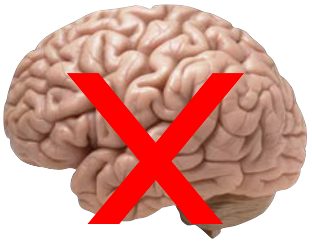
83 questions

Samples from 37 countries

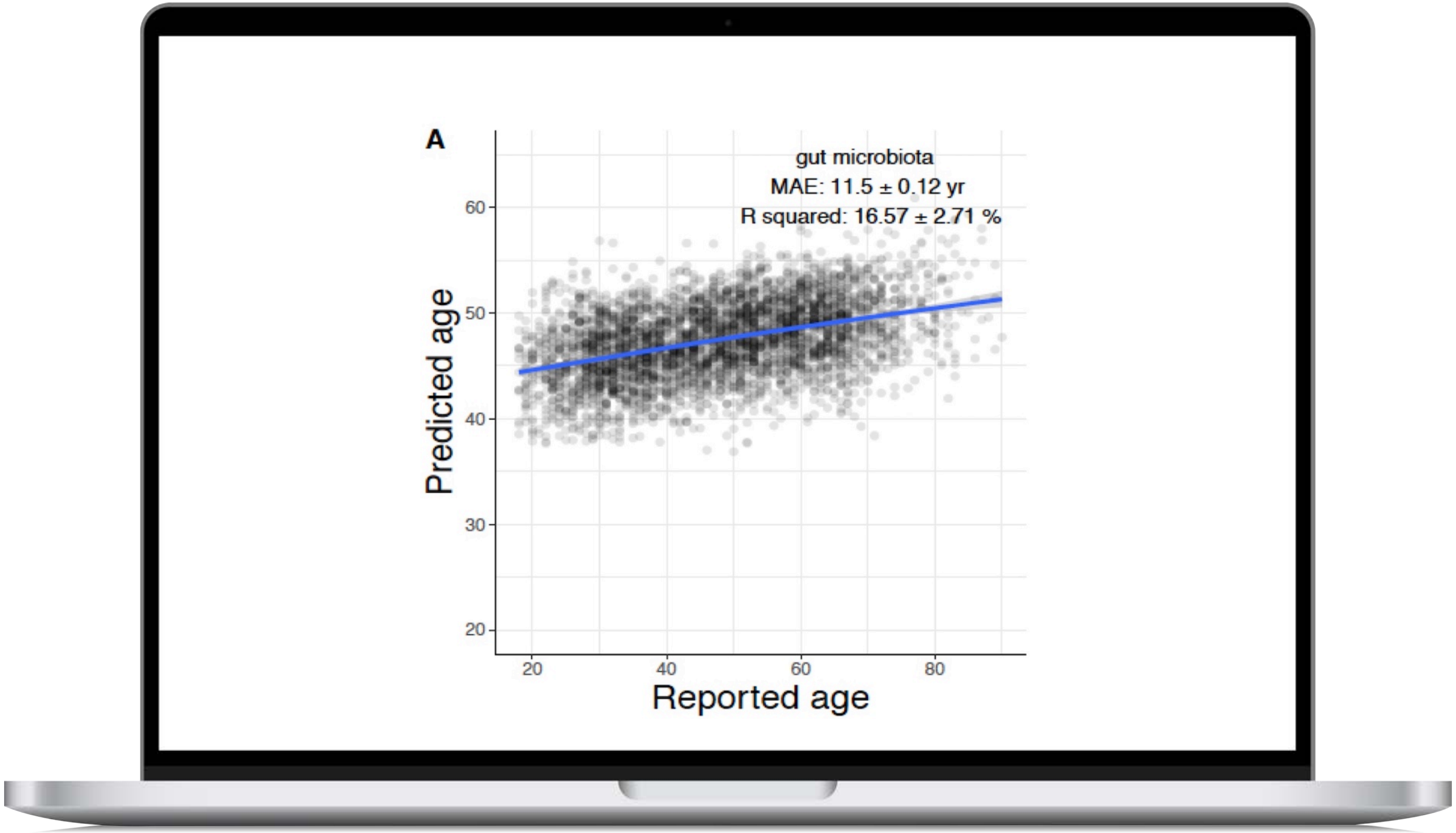
>25,000 samples!

Microbiome changes with age in adults are subtle…

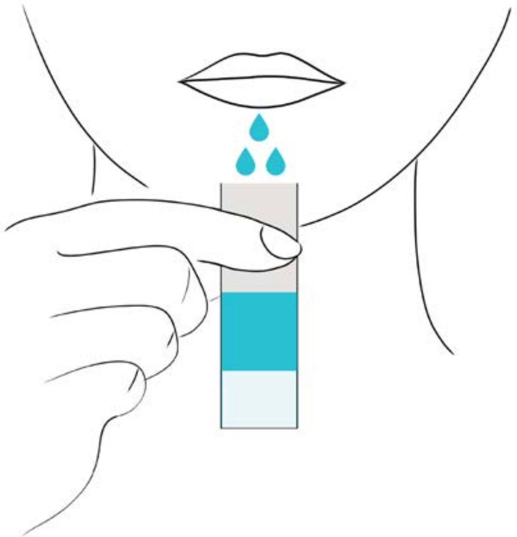


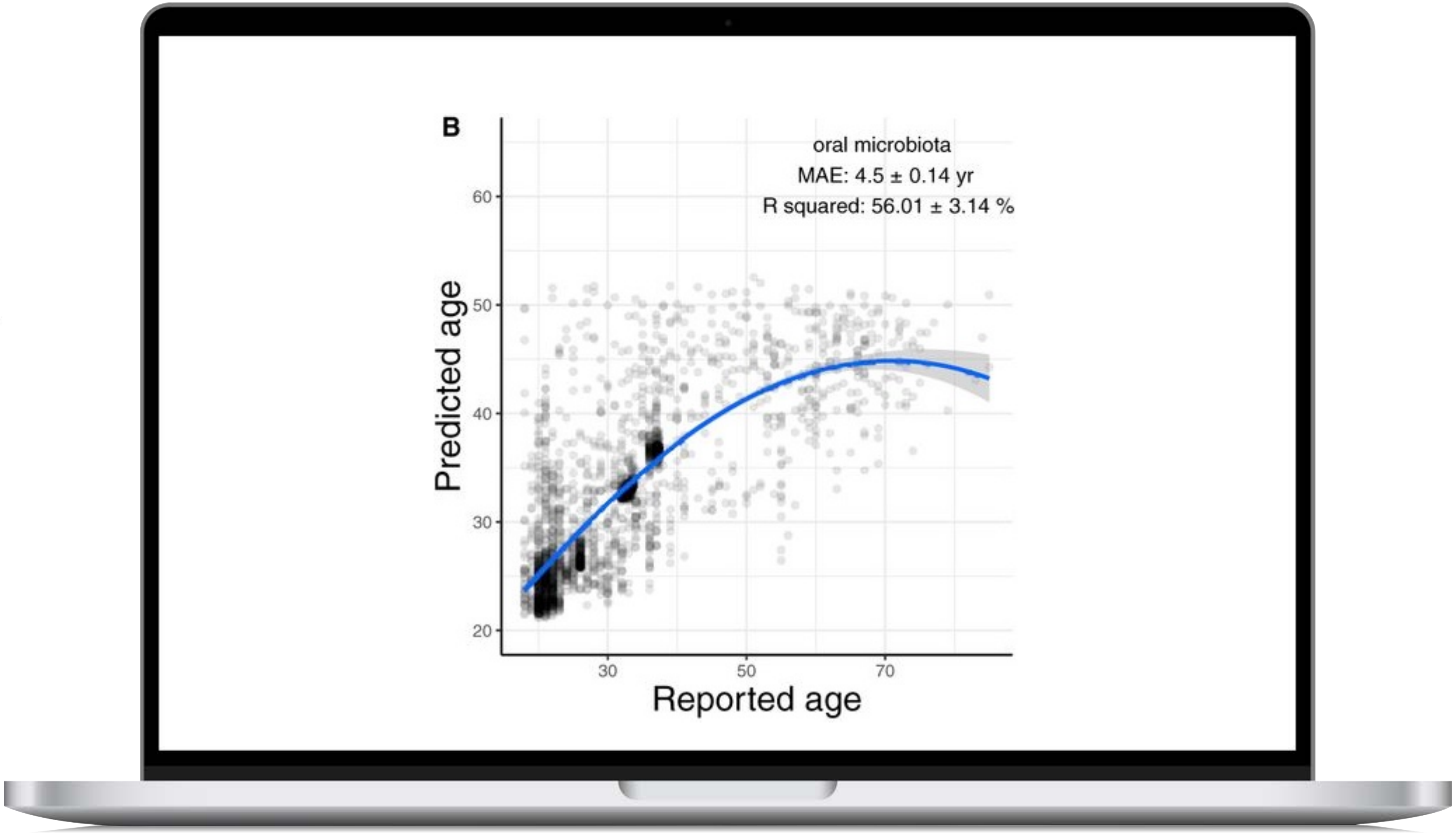


Source: de la Cuesta-Zuluagua et al. 2019 mSystems

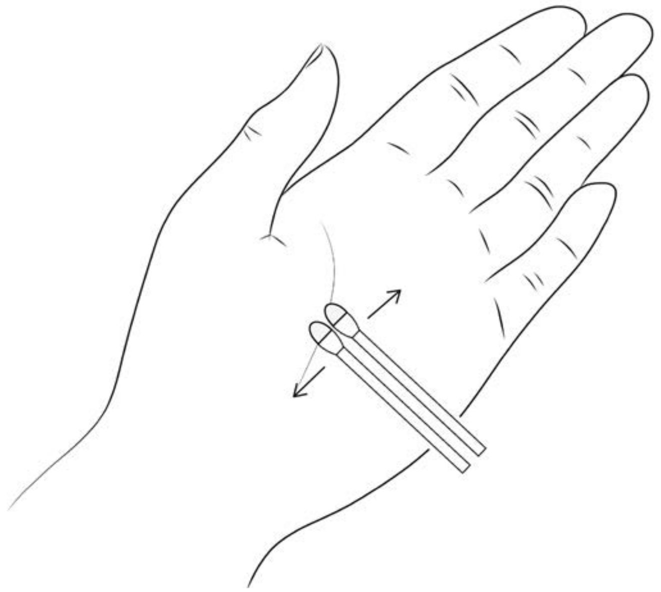


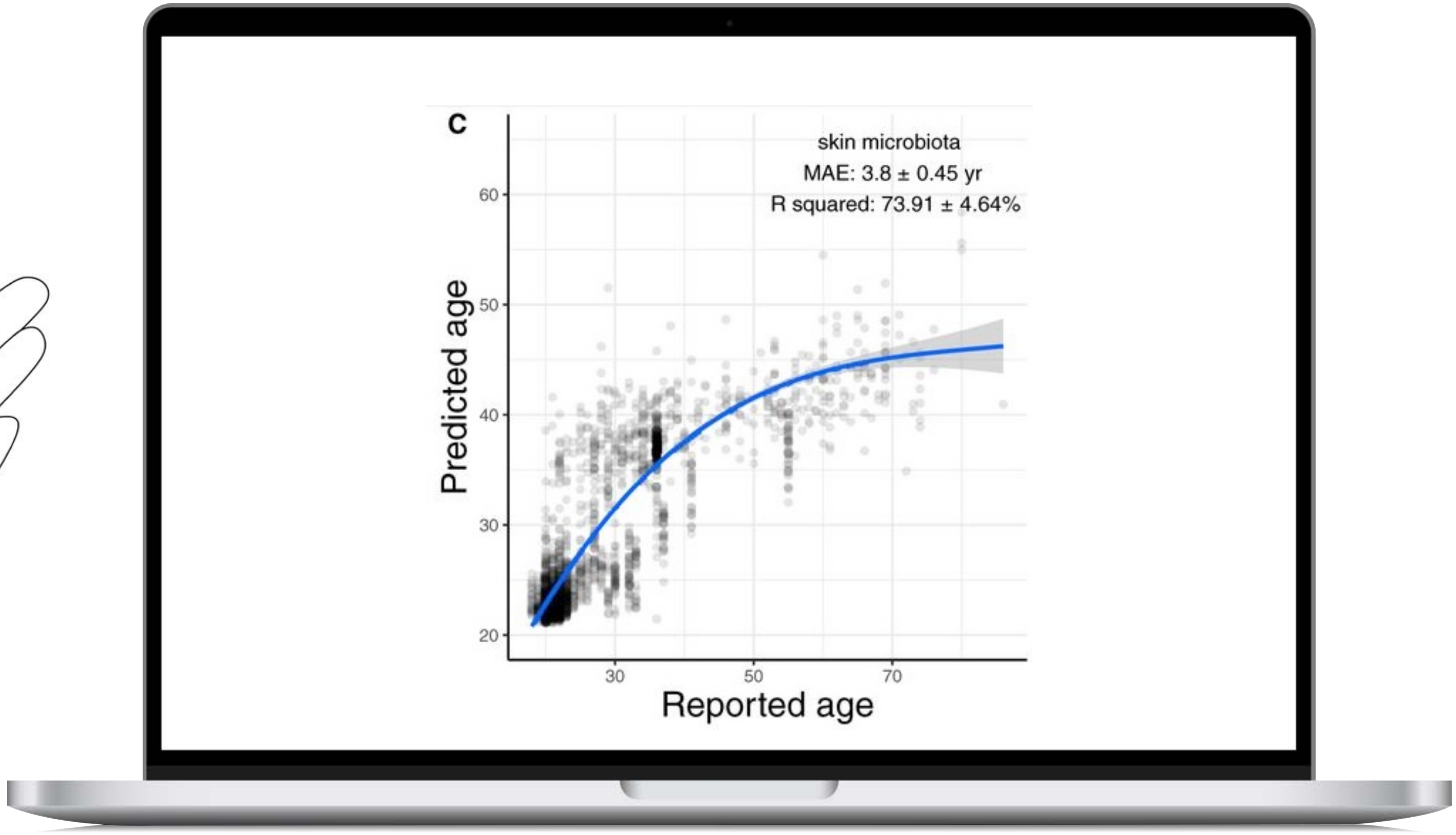
Stool Sample - Determines age within 12 years



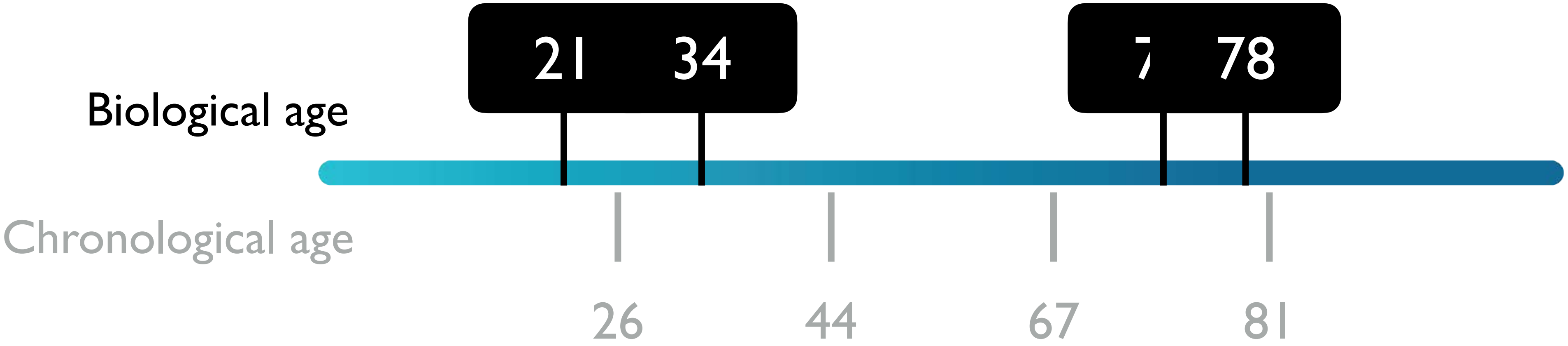


Saliva Sample - Determines age within 5 years





Skin Sample - Determines age within 4 years


21
34
78
Biological age
Chronological age
26
44
67
81

Lower
Actual Age

Higher
Bio Age

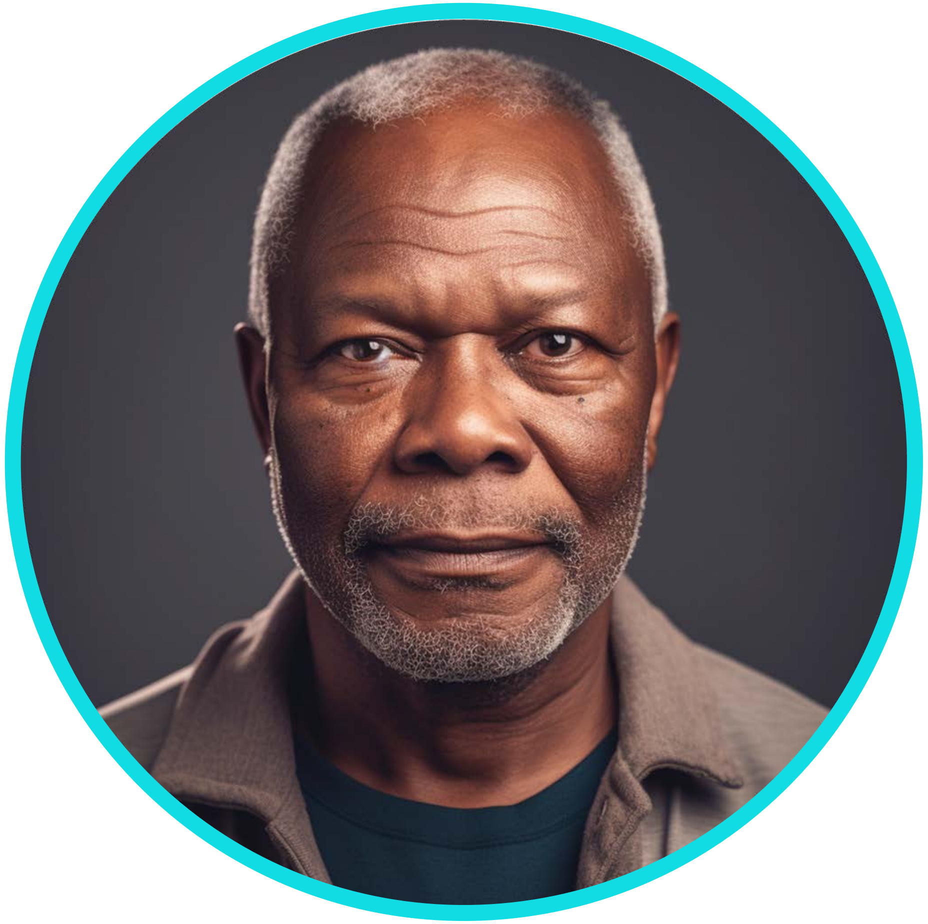
Less
Healthy?

Biological age

75

Chronological age

67



Higher
Actual Age

Lower
Bio Age

Extra
Healthy?

Biological age

78

Chronological age

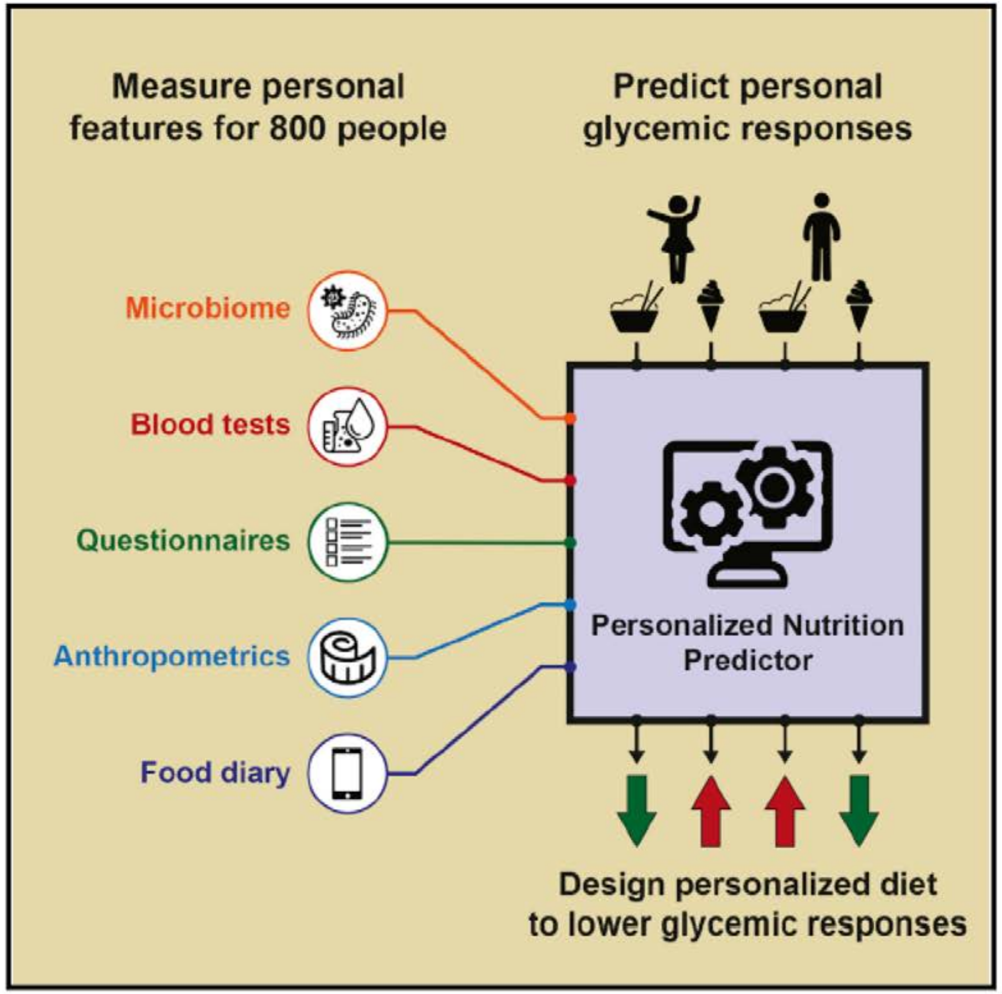
81

Cell

Article

Personalized Nutrition by Prediction of Glycemic Responses

Graphical Abstract



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Correspondence

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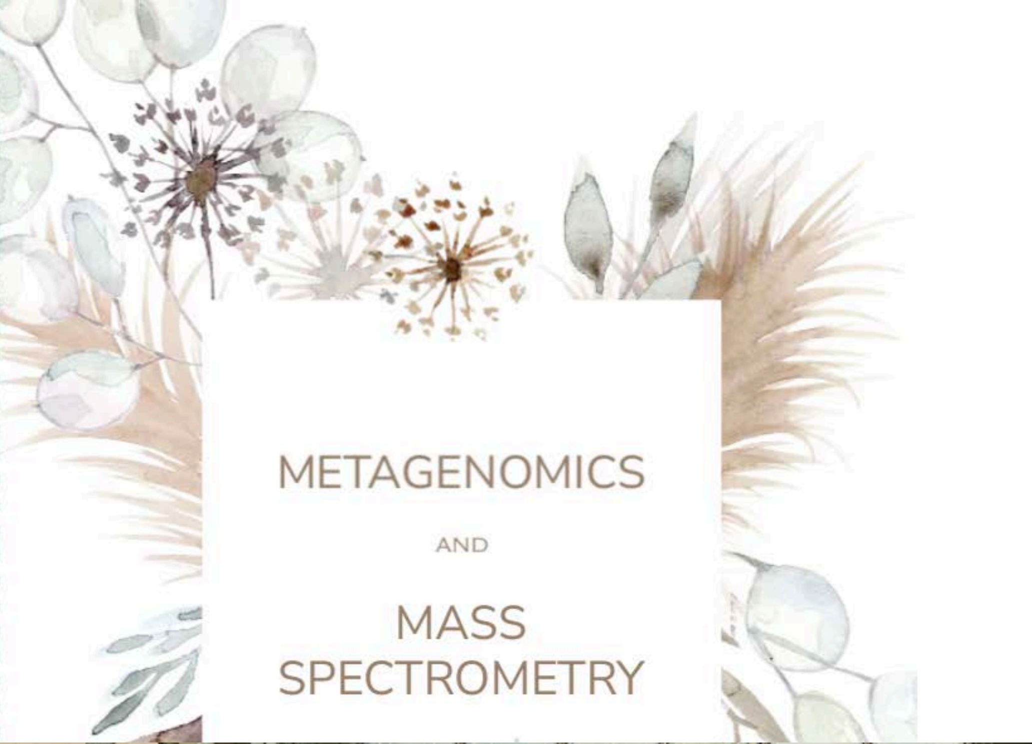
eran.segal@weizmann.ac.il (E.S.)

In Brief

People eating identical meals present high variability in post-meal blood glucose response. Personalized diets created with the help of an accurate predictor of blood glucose response that integrates parameters such as dietary habits, physical activity, and gut microbiota may successfully lower post-meal blood glucose and its long-term metabolic consequences.

or  ?

Your **microbes** decide!

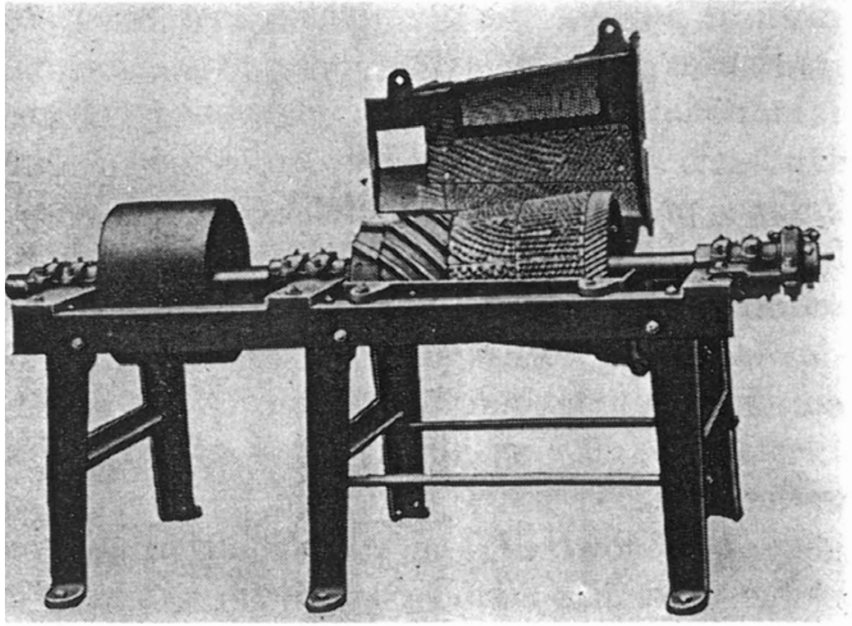

METAGENOMICS
AND
MASS
SPECTROMETRY


BIOMEDICAL RESEARCH


ical Sciences
Skaggs School of Pharmacy
& Pharmaceutical Science

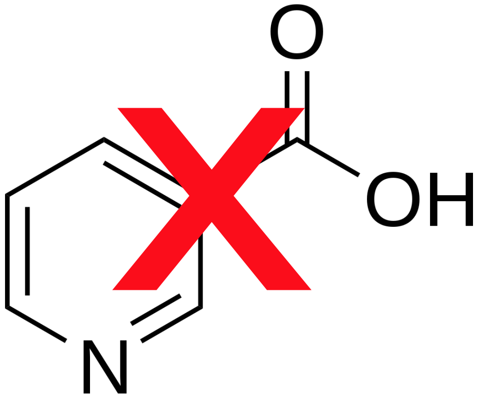
This happy event was motivated (in part) by a sad one…

…a murder…



Courtesy of The Beall Improvements Co.

FIG. 14.2. BEALL DEGERMINATOR AND CORN HULLER



STUDIES ON PELLAGRA. I. THE INFLUENCE OF THE MILLING OF MAIZE ON THE CHEMICAL COMPOSITION AND THE NUTRITIVE VALUE OF MAIZE-MEAL. BY CASIMIR FUNK.

(From the Department of Chemical Physiology, Cancer Hospital Research Institute, Brompton, London, S.W.)

J Physiol. 1913 Dec 19; 47(4-5): 389–392.

Arcimboldo 1591

“Der Mensch **ist**, was er **ißt**.”
— Feuerbach, 1863

"Food is a **language** that speaks to our **genes**"

— Jeff Bland, Personalized Medicine Lifestyle Institute

Our genes are fixed at conception, but
what they do
depends on **what we eat**

"Health consequences of ultraprocessed foods are **dire.**"

"The concerns include recent documentation of an increased risk of **type 2 diabetes**, **cardiovascular disease** and **dementia.**"

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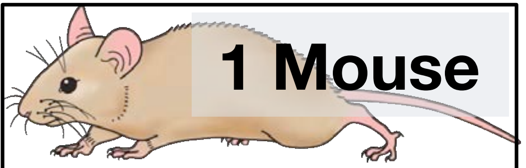
What doctors wish patients knew about ultraprocessed foods

DEC 16, 2022 · 8 MIN READ By Sara Berg, MS, Senior News Writer



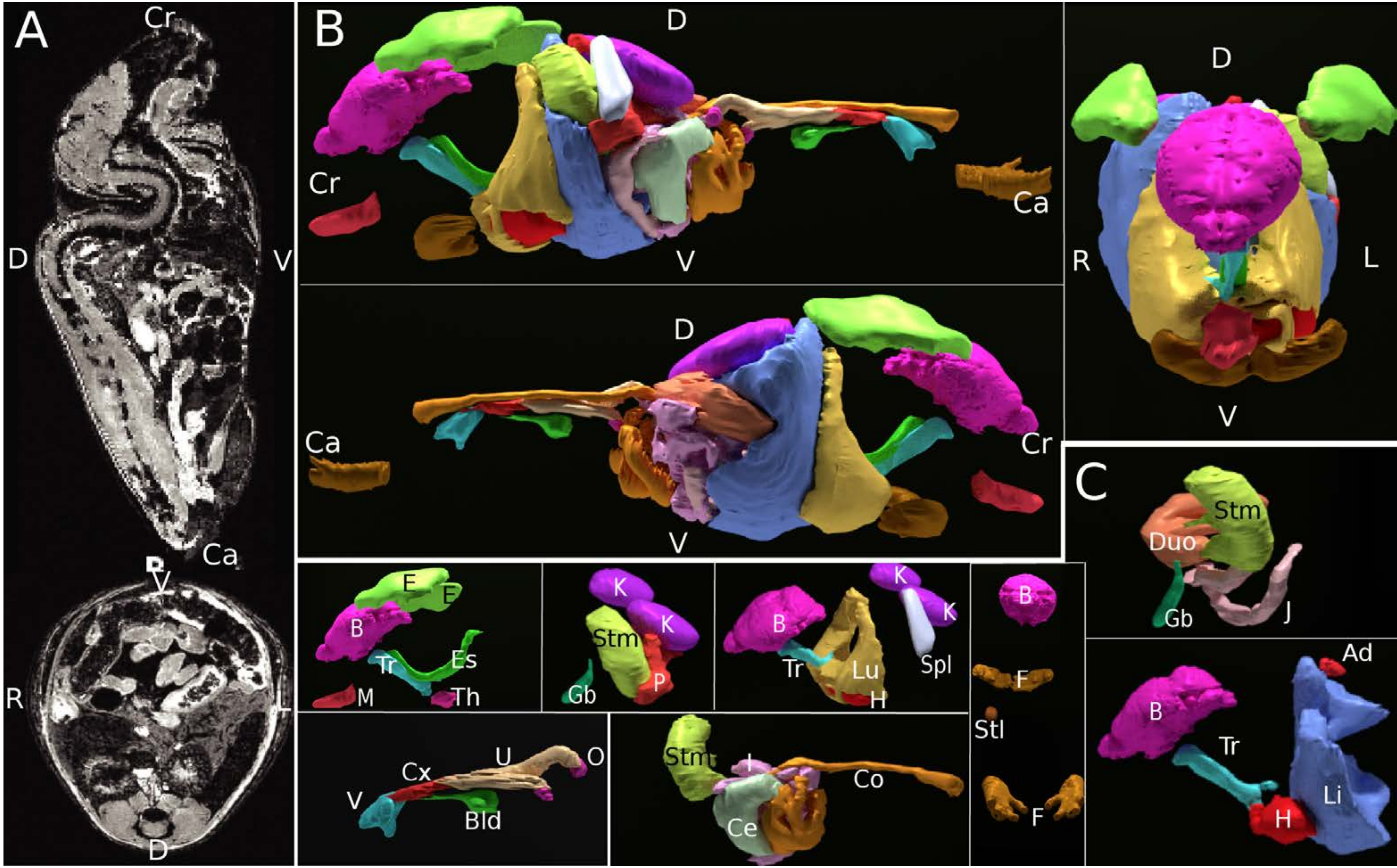
1 Mouse

26 organs
77 samples

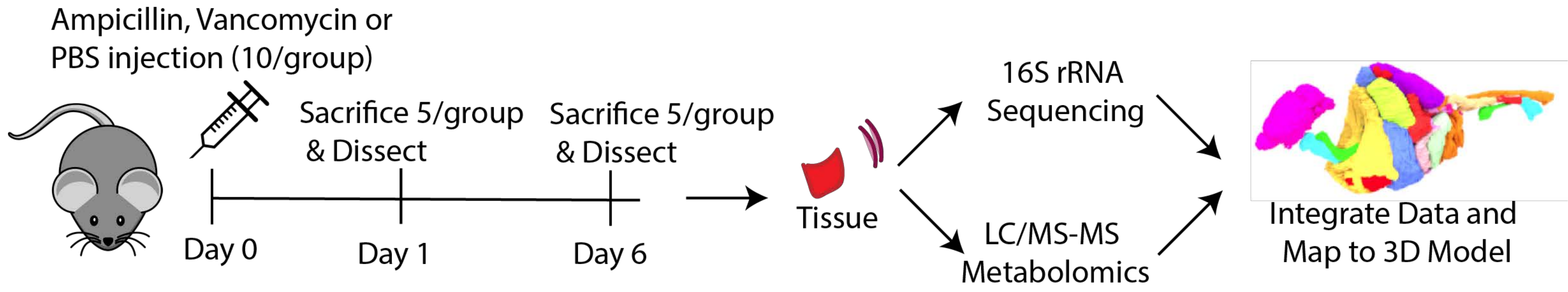
↓

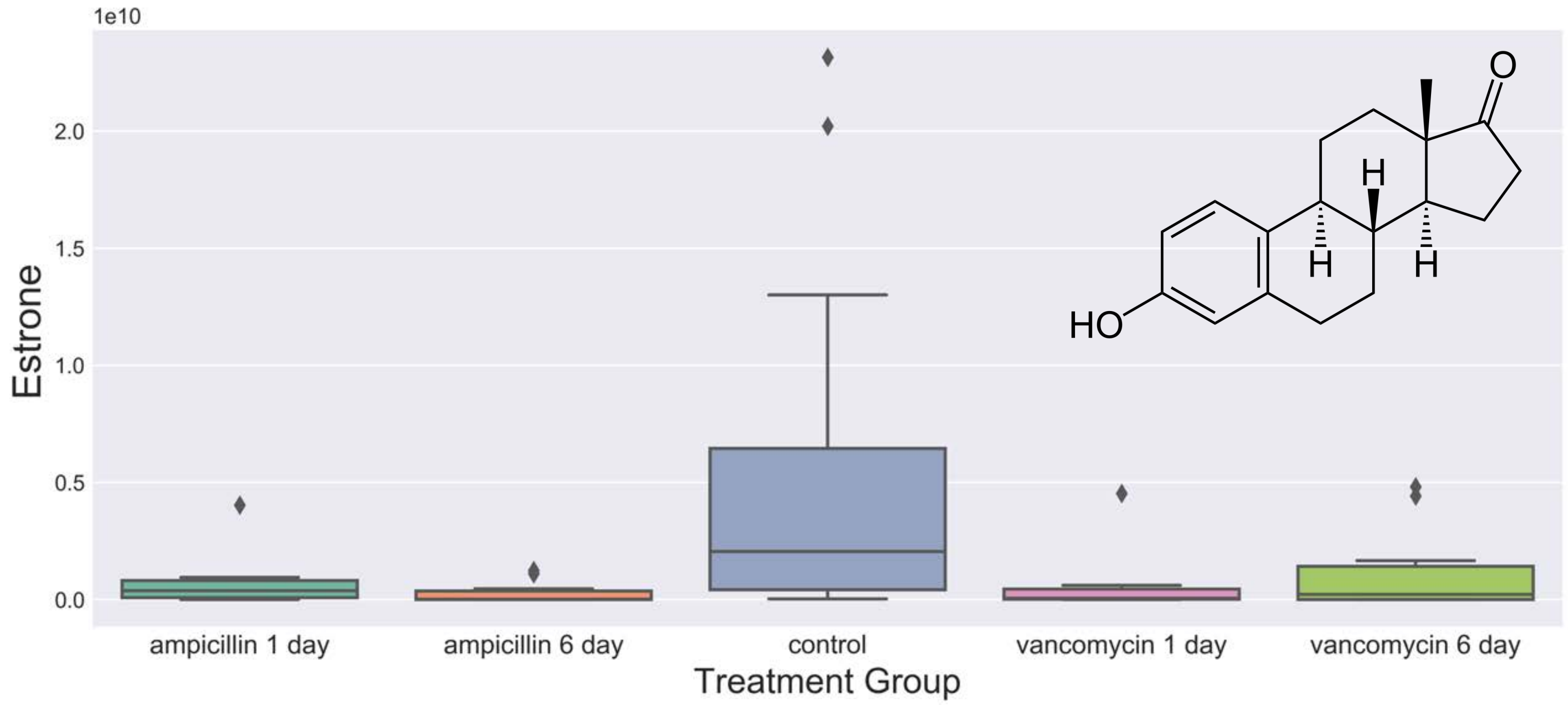
16S rRNA sequencing

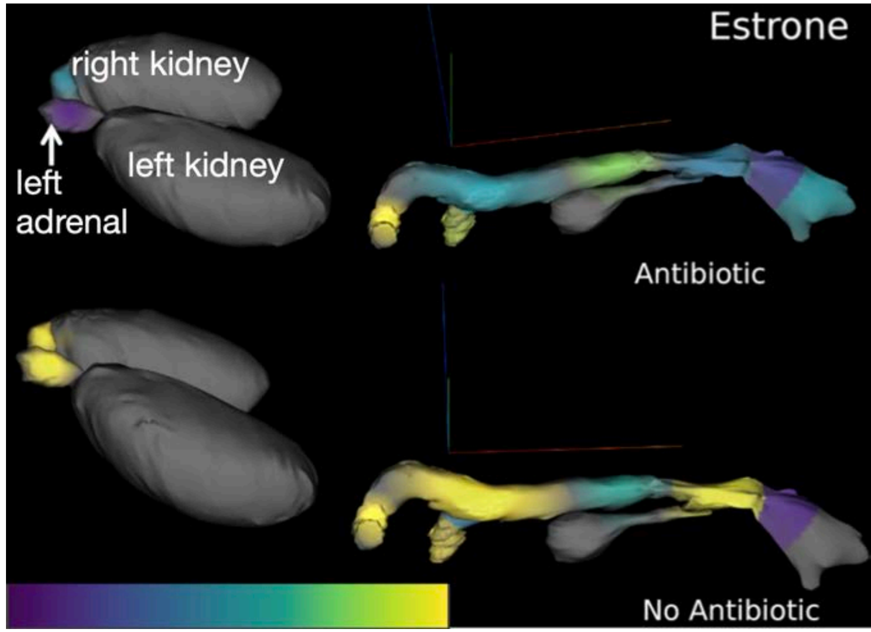
LC-MS/MS (untargeted)



Vrbanac et al. 2020 mSystems

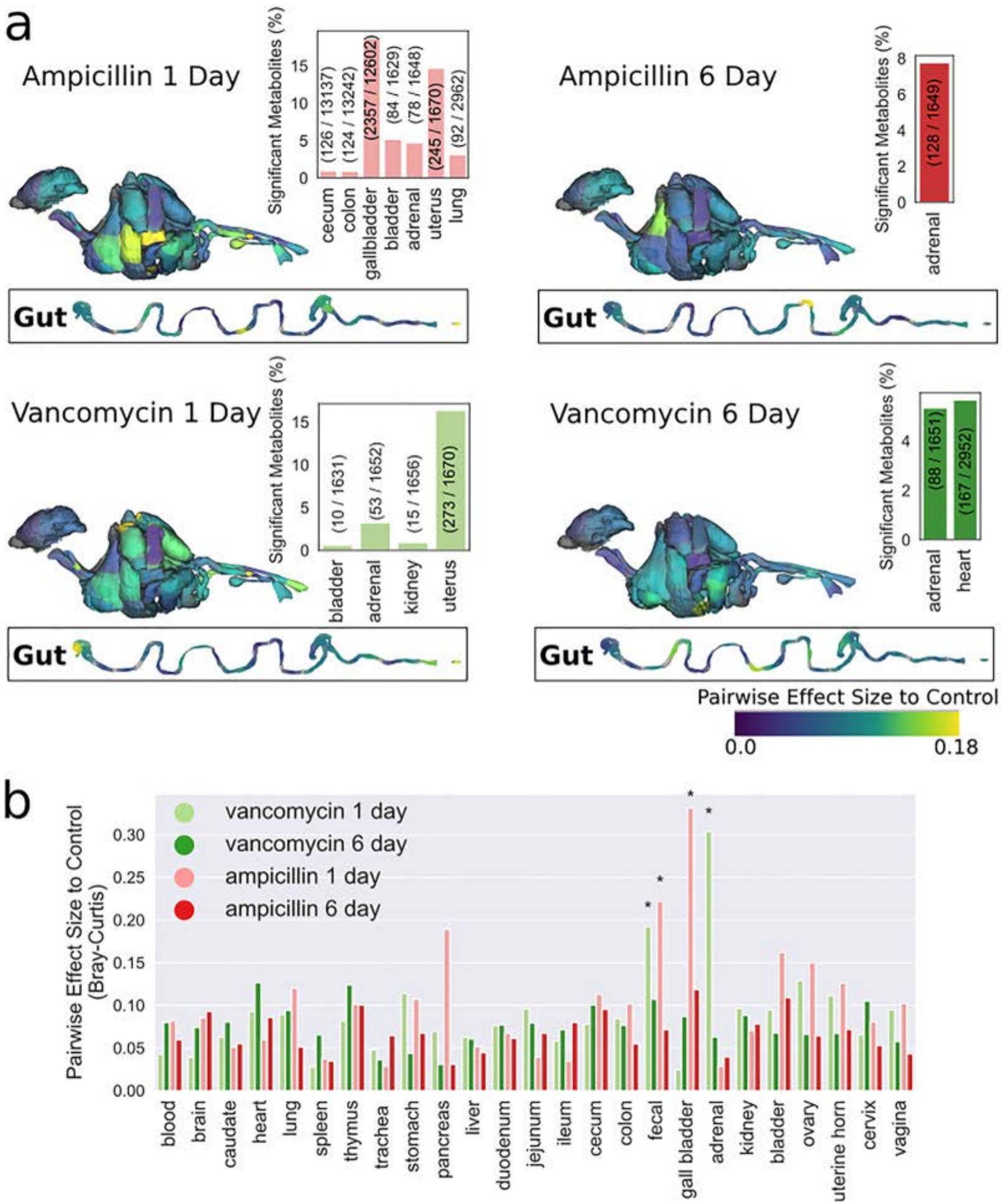






Vrbanac et al. 2020 mSystems

Alison Vrbanac
(BMS)



Antibiotics **change** molecules throughout the **body**

[1]**Graphic**: Vrbanac et al. mSystems 2020
Quinn et al. Nature 2020

UCSD to study centenarians in Italian village

Fruits and vegetables are a staple at open air markets in Acciaroli, Italy (Courtesy of Dr. Alan Maisel)

By **Gary Robbins . Contact Reporter**

AUGUST 25, 2016, 8:12 PM

Scientists from UC San Diego have begun to arrive in a small coastal village in southwestern Italy to study why a disproportionate number of its citizens live to be

Salvatore Di Somma ·
Professor of Medicine Md PhD at Sapienza Università di Roma

Cilento on Aging Outcomes Study

Example Community in the Cilento Region: Acciaroli

Is Rosemary The Secret To Longer Life? New Study Looks Into Lifestyle Of Italian Village With 300 Centenarians

1 April 2016, 6:46 am EDT By Deepthi B Tech Times

Rosemary | Centenarian | Italian Village | Longevity

A remote Italian village, home to 300 men who have crossed 100 years of age, might hold the secret to longevity. Researchers are studying the lifestyle behaviors of these centenarians and found the common factor among them is the use of rosemary herb. (Ajale | Pixabay)

The secret to longevity leave alone immortality, has been an age-old quest boggling the minds of curious mortal men. Statistically, the average lifespan worldwide is around 70 to 80 years of age, but yet a few miraculously live on until a ripe old age of 100.

Researchers from the San Diego School of Medicine, University of California along with University of Rome La Sapienza have delved into an interesting study on longevity. The study group consists of 300 senior citizens wherein each and every one of them have outlived a whopping century.

These centenarians are idealistically living together in peace and harmony not to forget good health, in a quaint little village in Acciaroli, Italy.

Over and beyond long life, this group of 300 is surprisingly free of the usual and common old-age diseases such as Alzheimer's and heart-related conditions. Mentally and physically they are found to be fit.

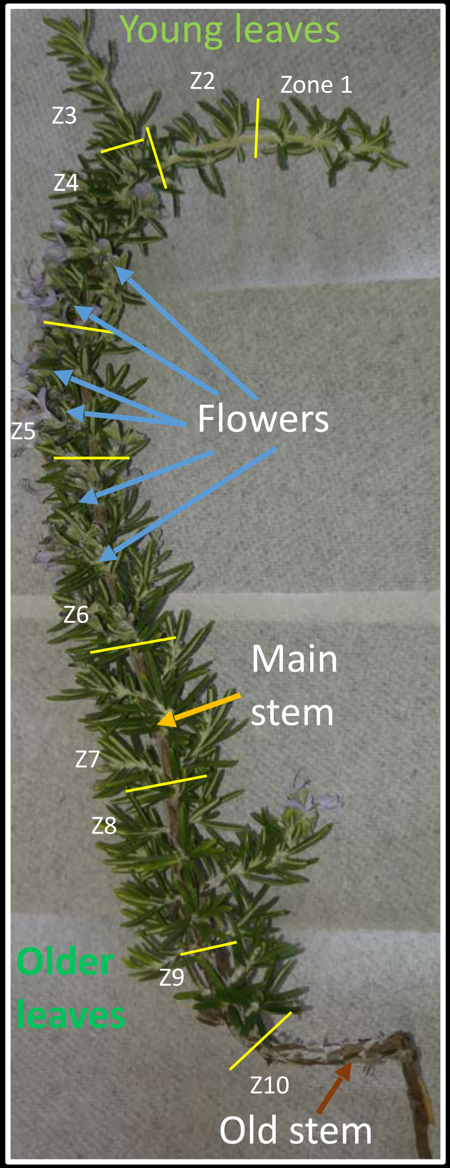
"The goal of this long-term study is to find out why this group of 300 is living so long by conducting a full genetic analysis and examining lifestyle behaviors, like diet and exercise. The results from studying the longevity of this group could be applied to our practice at UC San Diego and to patients all over the world." said Alan Maisel, investigator and professor at the San Diego School of Medicine.

MOST POPULAR

1 GOOGLE

Google I/O 2017 Date Confirmed In A Puzzle

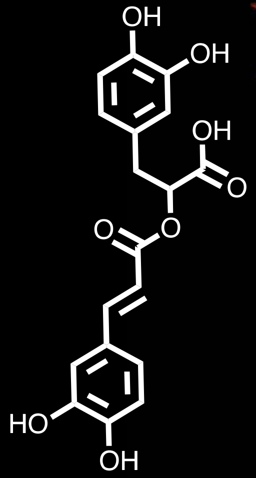
Molecular 3D cartography of Rosemary using LC-MS/MS



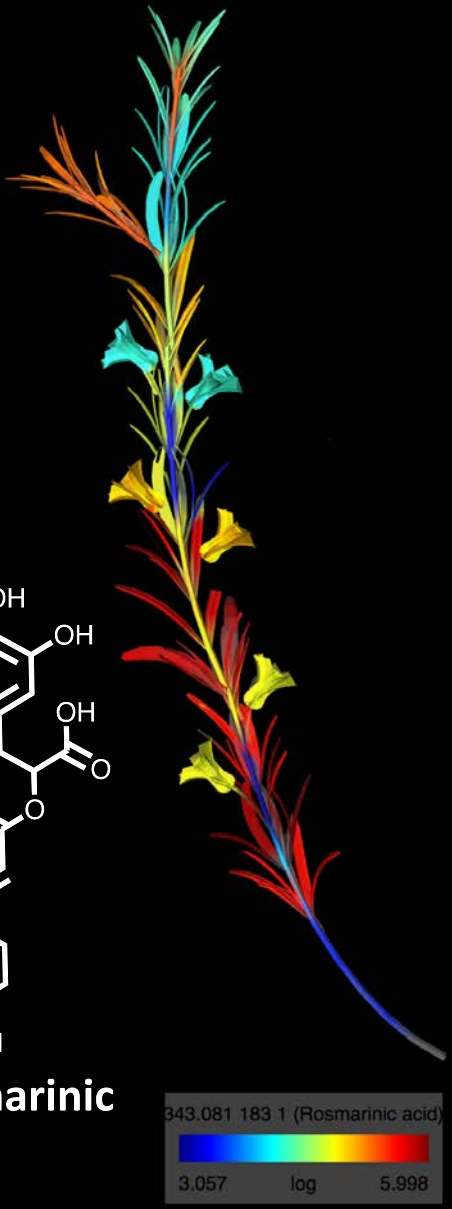
LC-MS/MS and Molecular 3D cartography

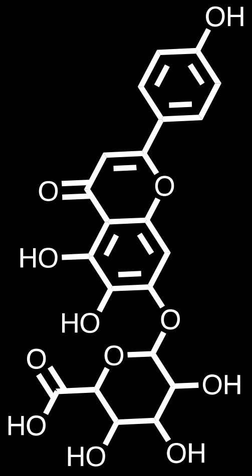
With Alexander Aksenov, Louis-Felix Nothias-Scaglia and Pieter Dorrestein

Distribution of some bioactive molecules from Rosemary

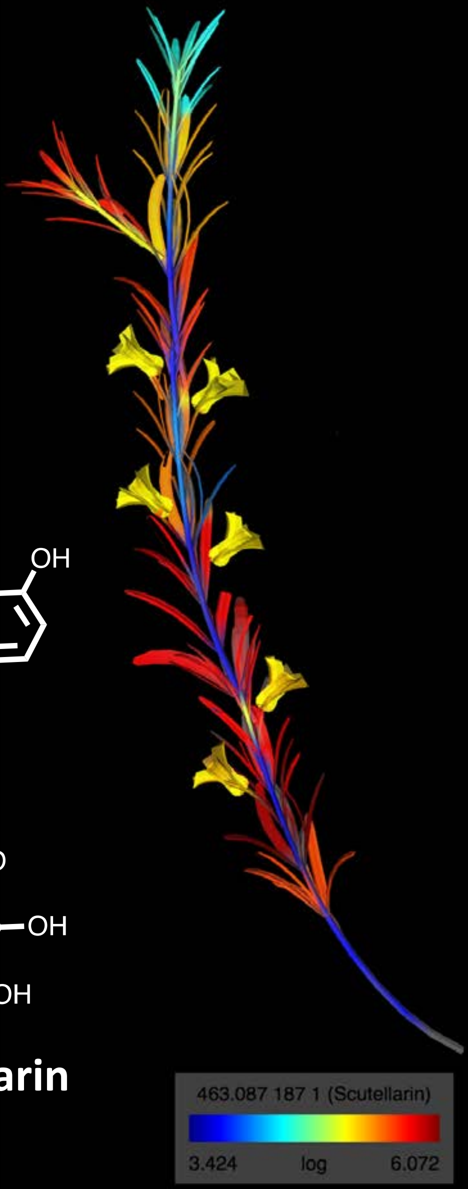


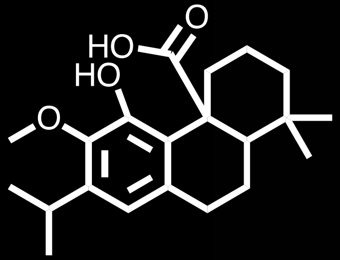
Rosmarinic acid



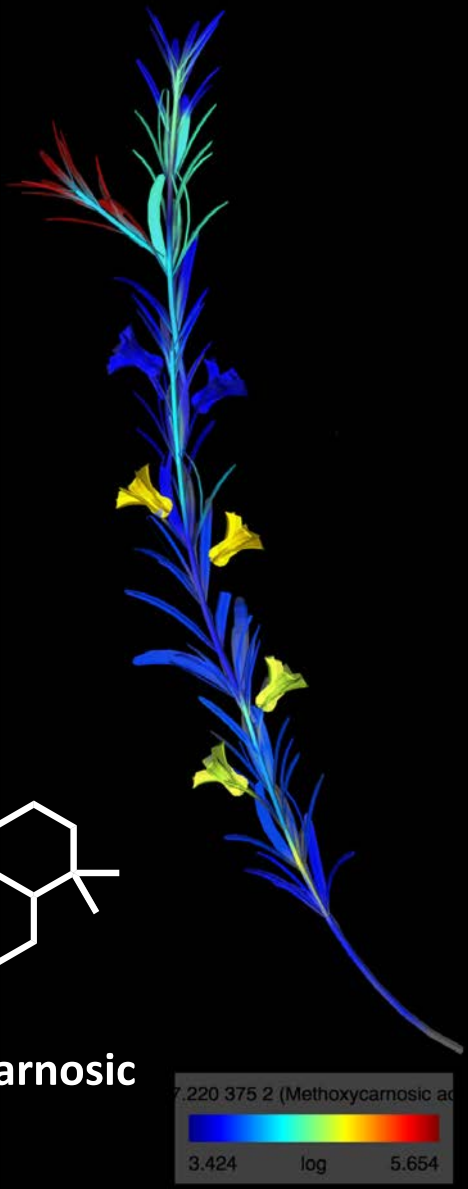


Scutellarin

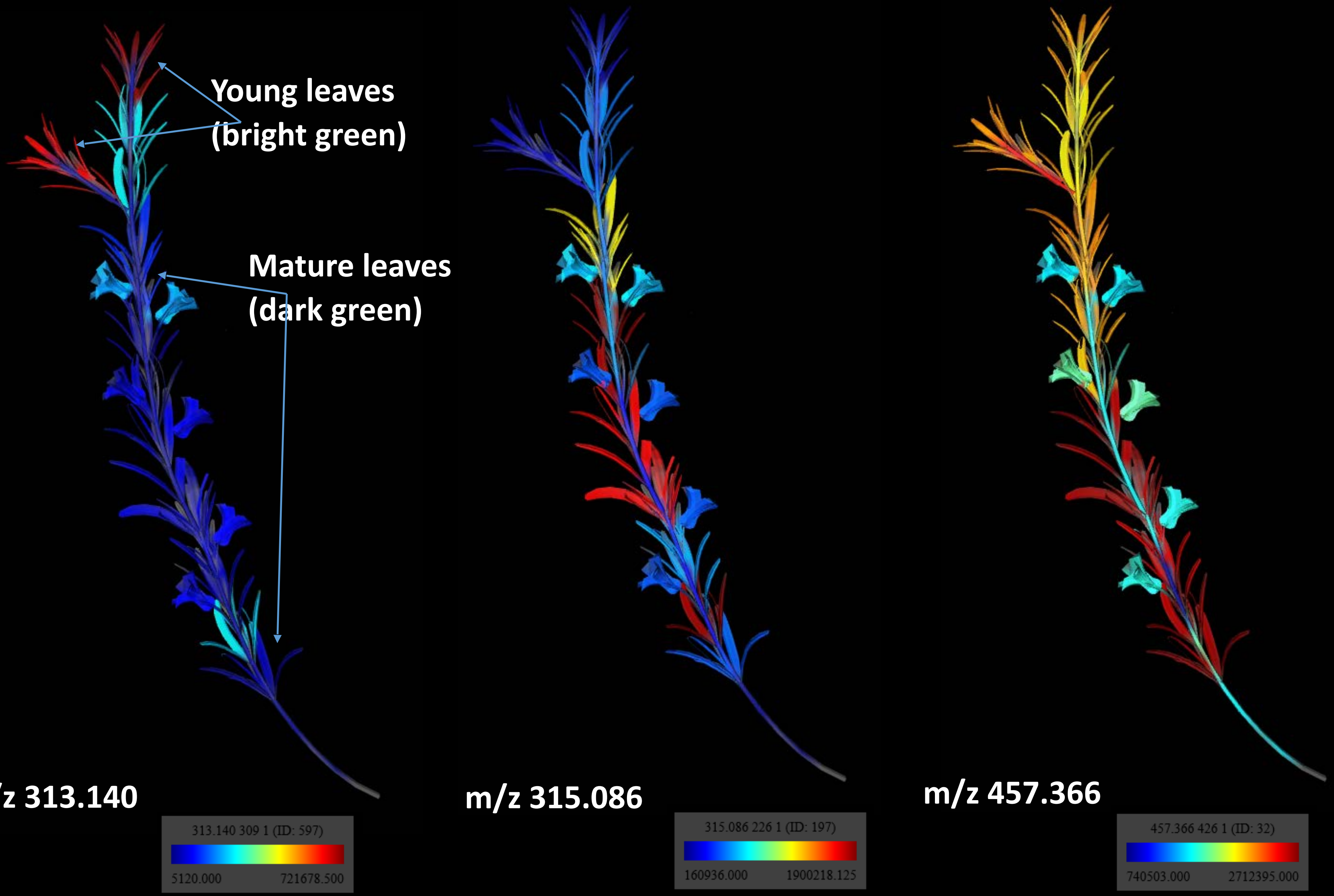




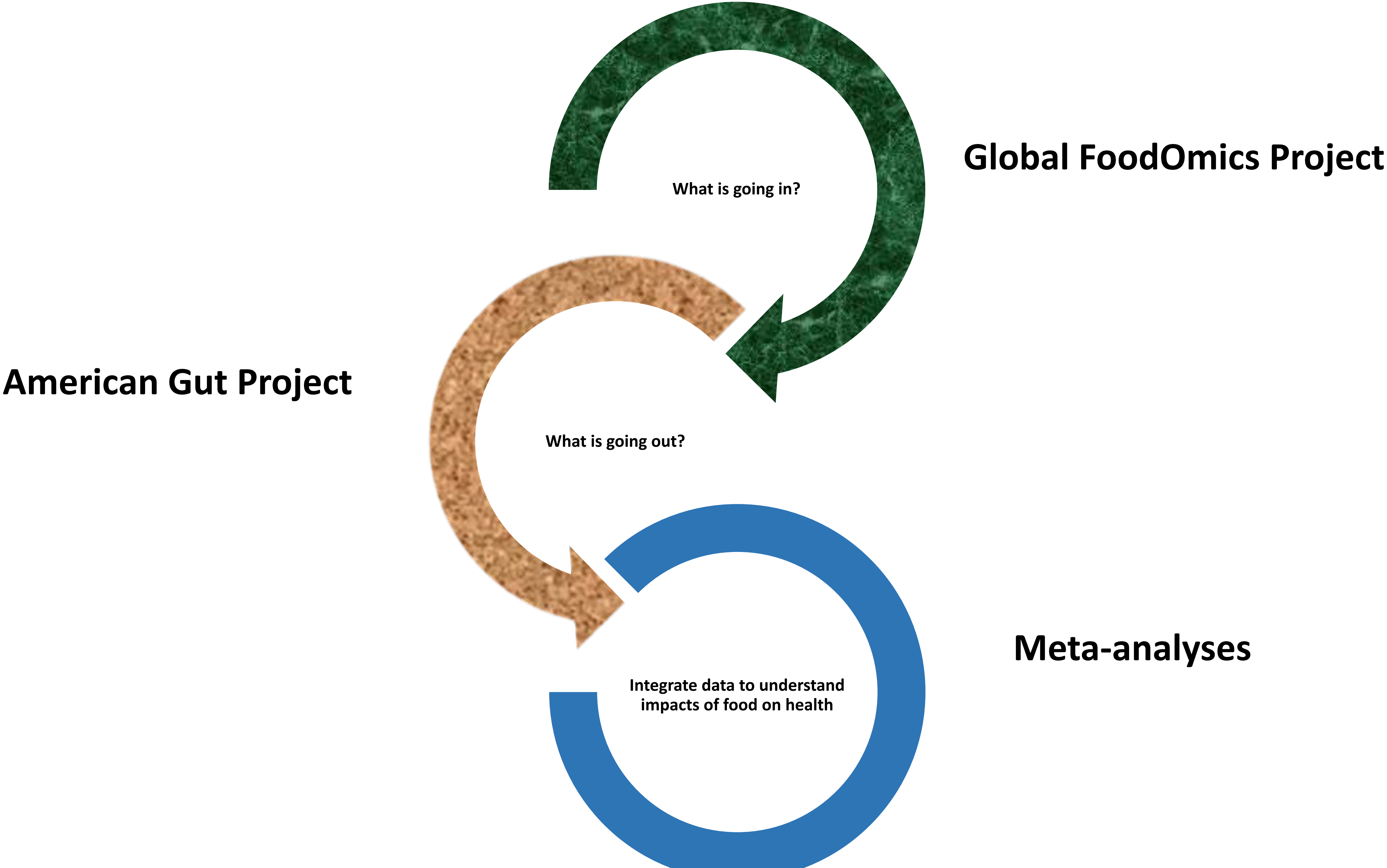
Methoxycarnosic acid

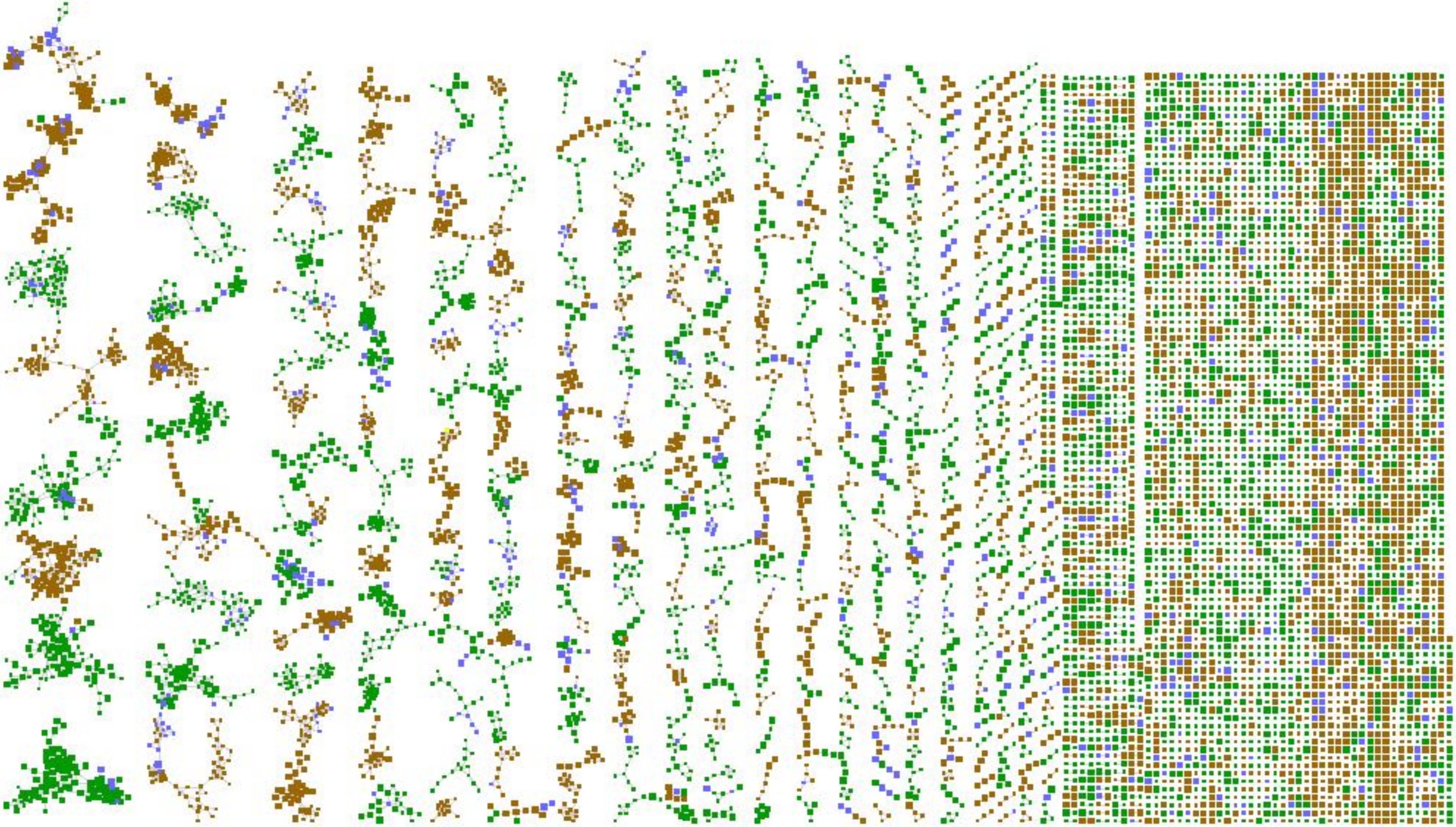


Unidentified metabolites unique to foliage

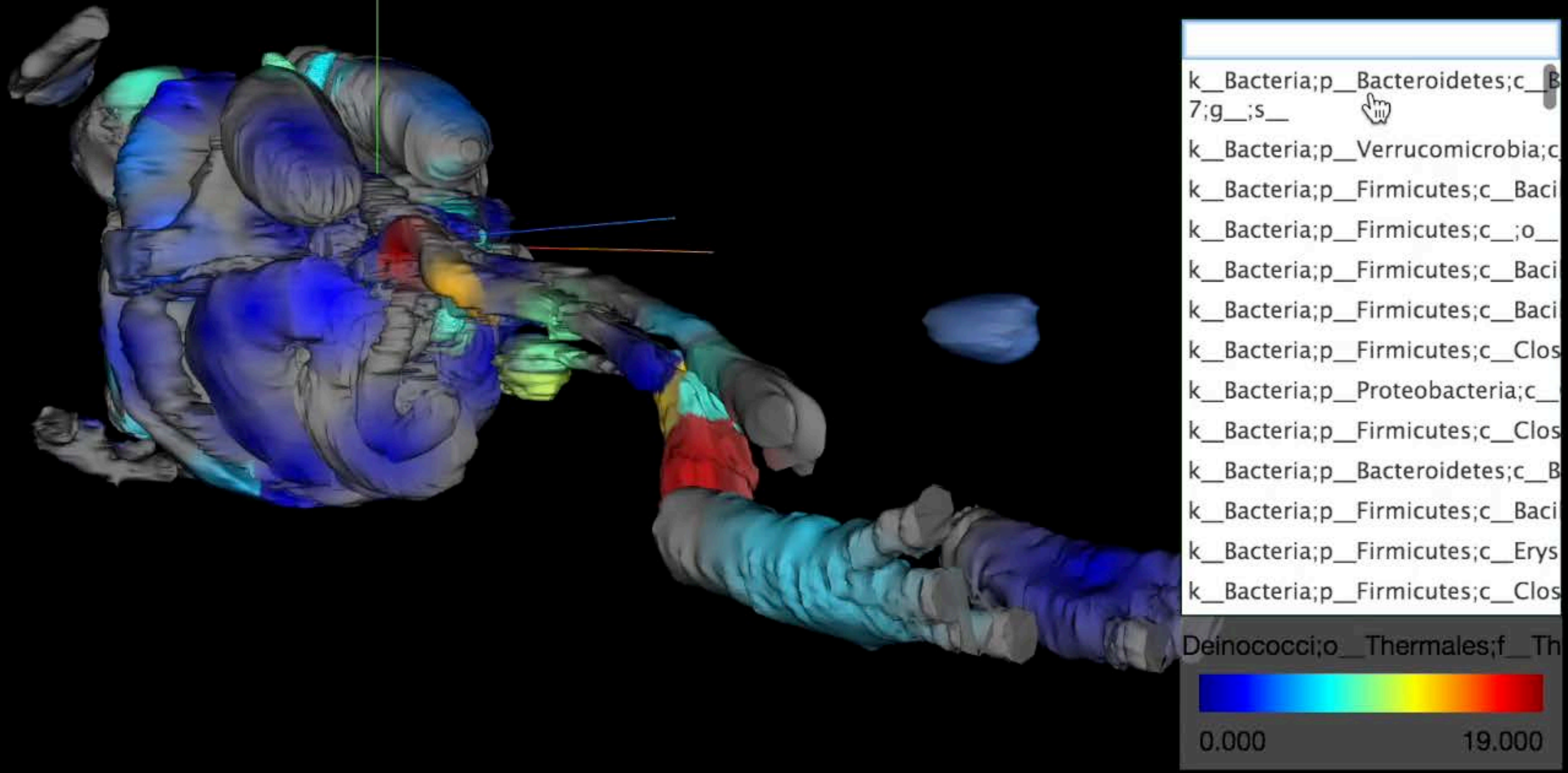


www.globalfoodomics.org

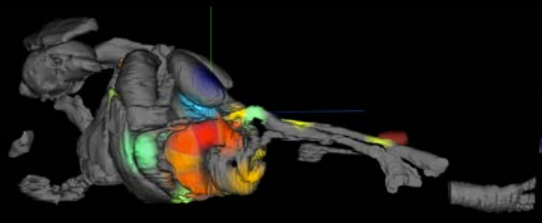

Global FoodOmics Project
What is going in?
American Gut Project
What is going out?
Meta-analyses
Integrate data to understand
impacts of food on health



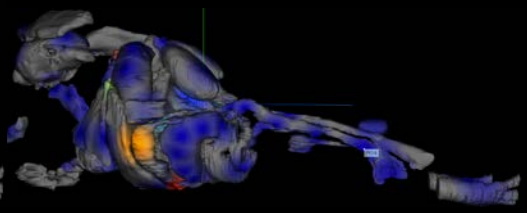
Imaging microbes and molecules throughout the mouse



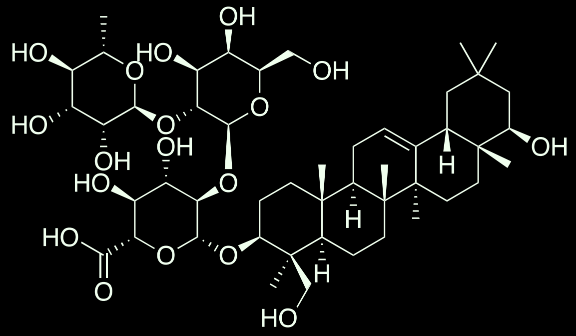
Microbiome-Mediated Metabolism of Food



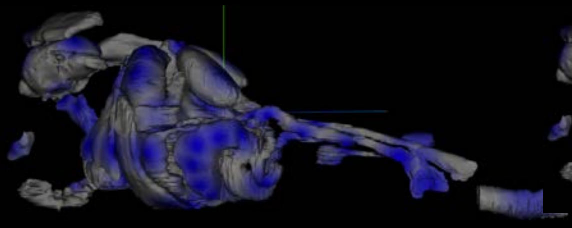
GF



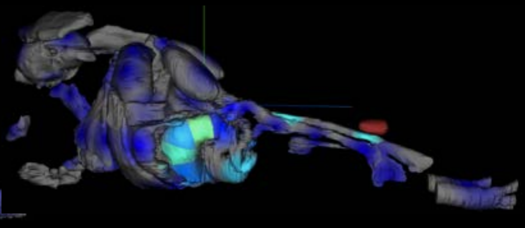
SPF



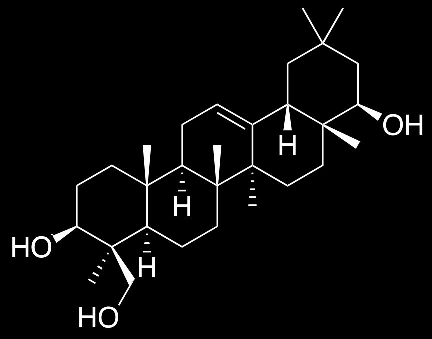
Soyasaponin



GF



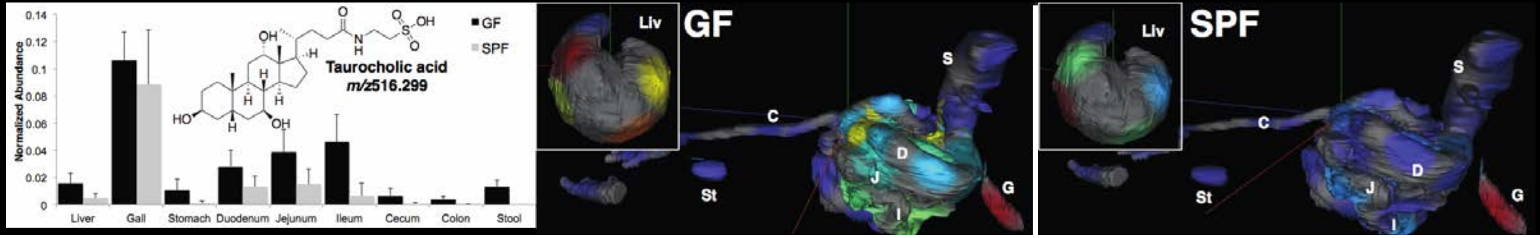
SPF



Soyasapogenol

0 max

Quinn et al. 2020 *Nature*



Article

Global chemical effects of the microbiome include new bile-acid conjugations

https://doi.org/10.1038/s41586-020-2047-9

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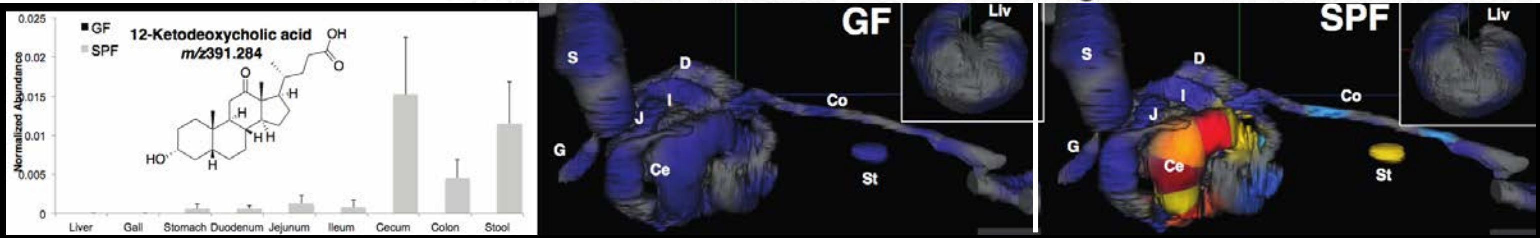
Published online: 26 February 2020

Check for updates

Robert A. Quinn[1,2], Alexey V. Melnik[1], Alison Vrbanac[3], Ting Fu[4], Kathryn A. Patras[3], Mitchell P. Christy[1], Zsolt Bodai[5], Pedro Belda-Ferre[3], Anupriya Tripathi[1,3], Lawton K. Chung[3], Michael Downes[4], Ryan D. Welch[4], Melissa Quinn[6], Greg Humphrey[3], Morgan Panitchpakdi[1], Kelly C. Weldon[1,19], Alexander Aksenov[1], Ricardo da Silva[1], Julian Avila-Pacheco[7], Clary Clish[7], Sena Bae[8,9], Himel Mallick[7,8], Eric A. Franzosa[7,8], Jason Lloyd-Price[7,8], Robert Bussell[10], Taren Thron[11], Andrew T. Nelson[1], Mingxun Wang[1], Eric Leszczynski[6], Fernando Vargas[1], Julia M. Gauglitz[1], Michael J. Meehan[1], Emily Gentry[1], Timothy D. Arthur[3,7], Alexis C. Komor[5], Orit Poulsen[3], Brigid S. Boland[12], John T. Chang[12], William J. Sandborn[12], Meerana Lim[3], Neha Garg[13,14], Julie C. Lumeng[15], Ramnik J. Xavier[7], Barbara I. Kazmierczak[16], Ruchi Jain[16], Marie Egan[17], Kyung E. Rhee[3], David Ferguson[6], Manuela Raffatellu[3], Hera Vlamakis[7], Gabriel G. Haddad[3], Dionicio Siegel[1], Curtis Huttenhower[7,8], Sarkis K. Mazmanian[11], Ronald M. Evans[4,18], Victor Nizet[1,3,19], Rob Knight[3,19,20,21] & Pieter C. Dorrestein[1,3,19] ✉

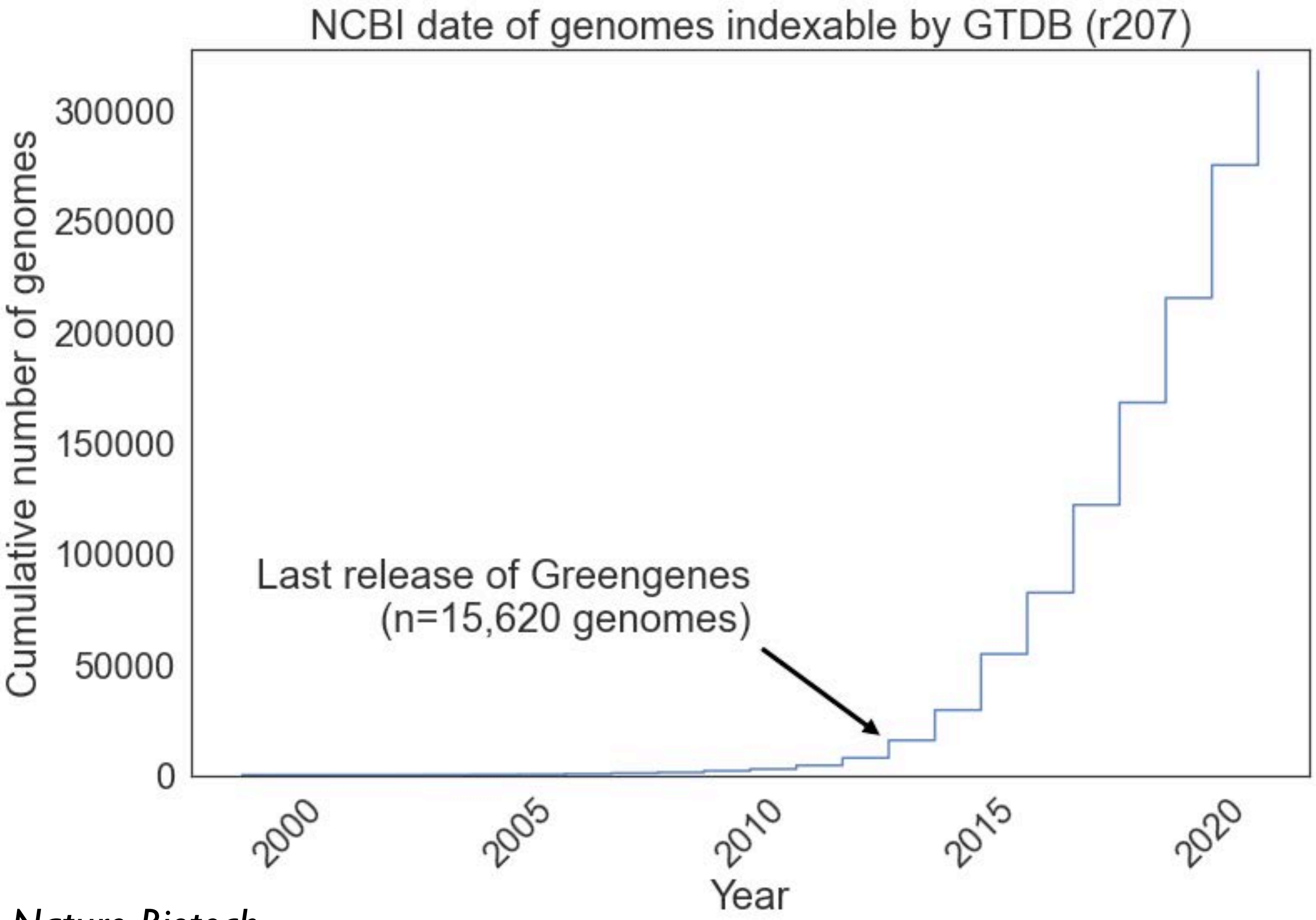


Problem: how to integrate 16S and shotgun data?

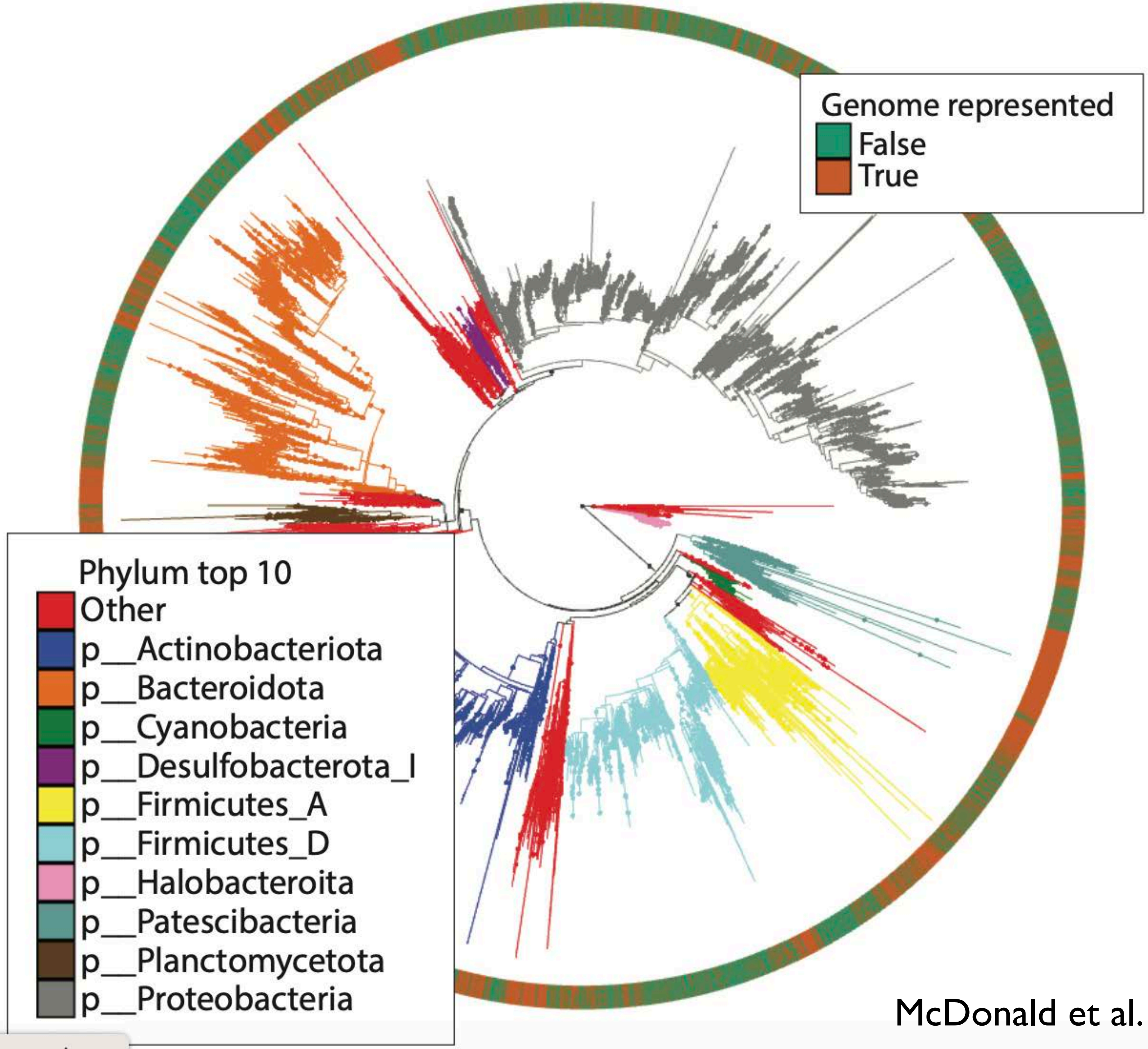
GG^2 | GREENGENES^2

Daniel McDonald

McDonald et al. 2023 *Nature Biotech*



McDonald et al. 2023 *Nature Biotech*

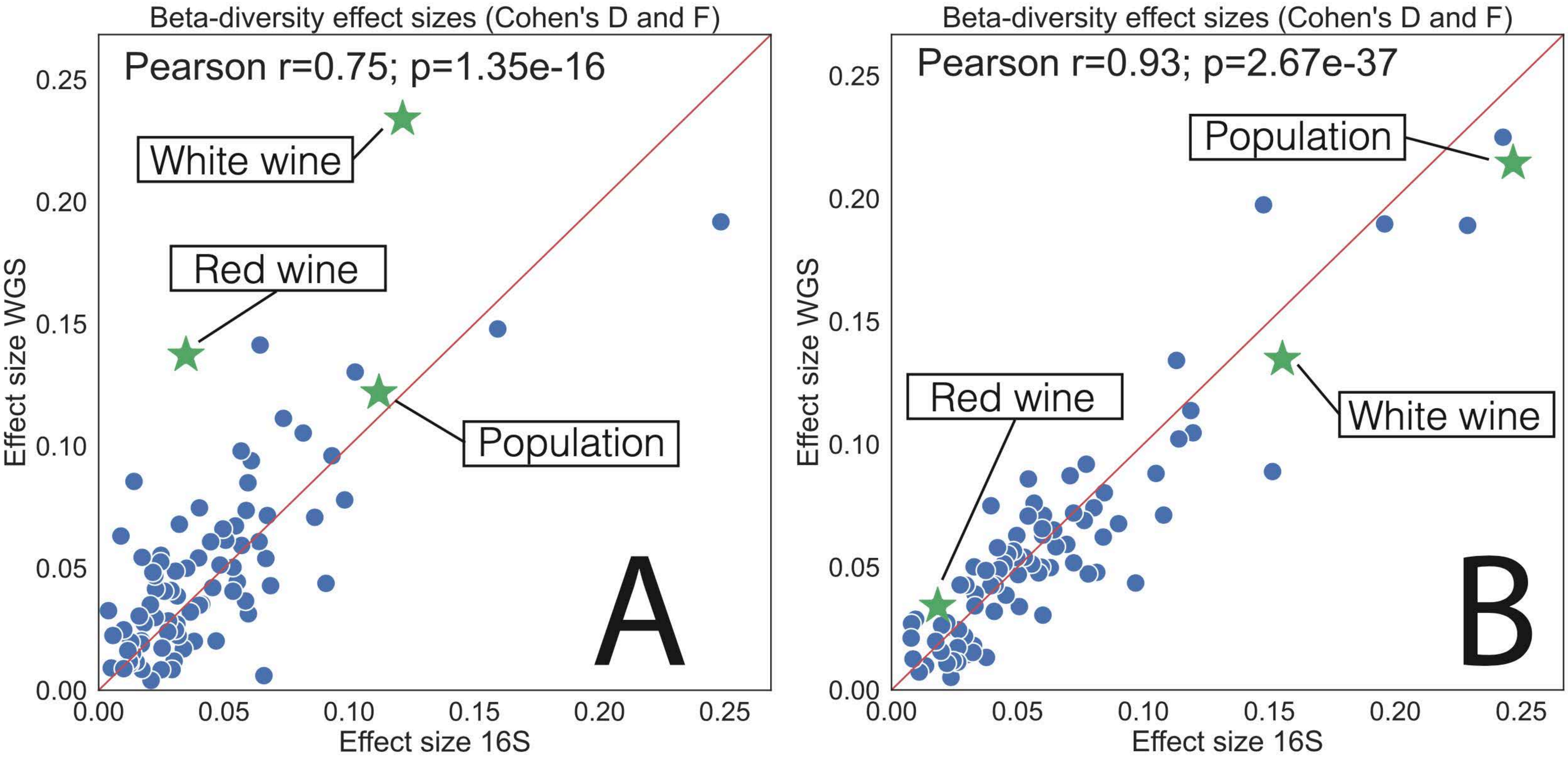


McDonald et al. 2023 *Nature Biotech*

Samples sequenced both for16S rRNA V4 and whole genome shotgun were characterized by Greengenes2. Beta diversity and principal coordinates were computed, plotted and colored by the preparation type. (A) Bray Curtis and (B) Weighted UniFrac.

McDonald et al. 2023 *Nature Biotech*

For the first time, see correlation in effect size



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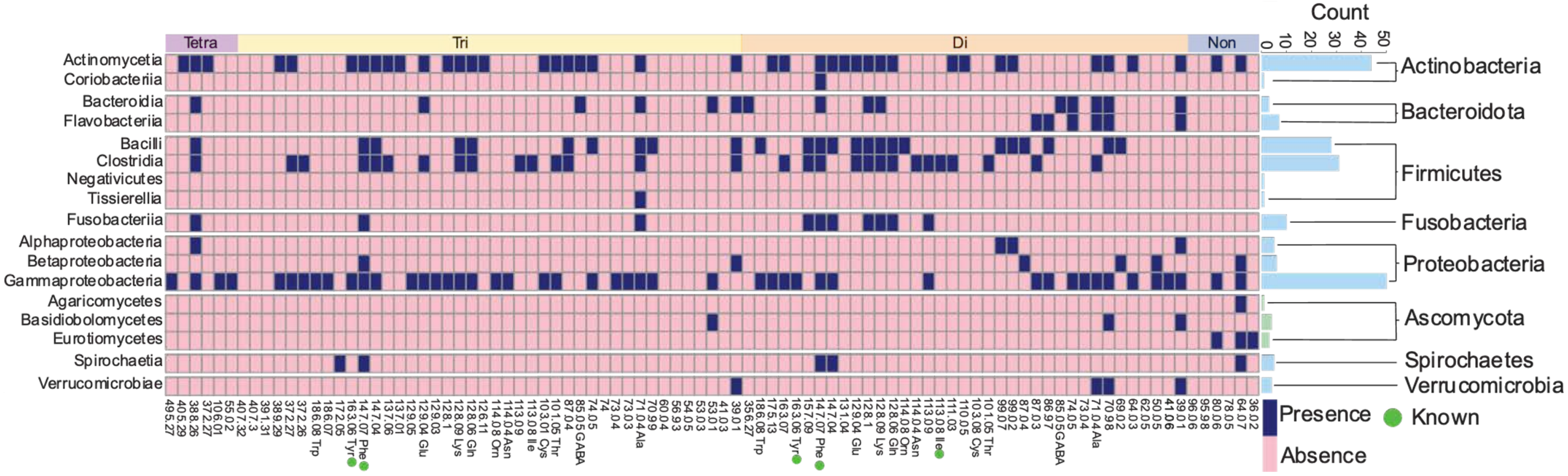
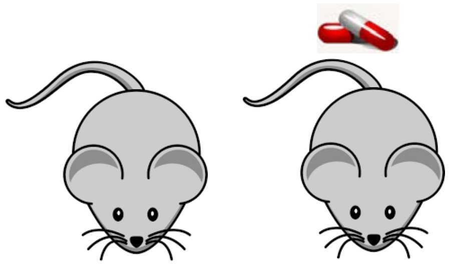
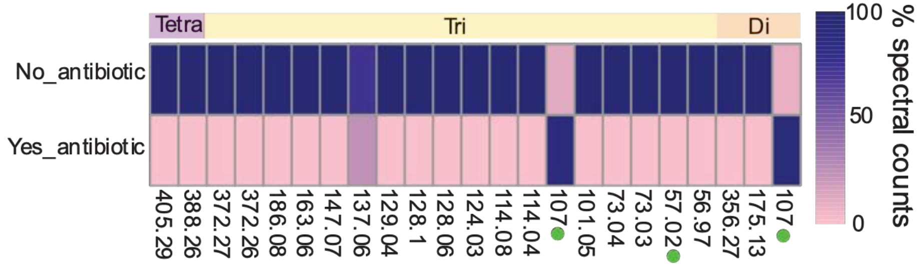
MicrobeMASST allows searches using MassQL to find microbe-specific molecules







Reanalysis of Shalapour, S. *et al*. Inflammation-induced IgA+ cells dismantle anti-liver cancer immunity. *Nature* 551, 340-345, 2017.

Zuffa et al. in revision *Nat Micro*

Exploring the Connection Between the Gut Microbiome & Alzheimer's Disease Pathogenesis

Alzheimer Gut Microbiome Project (AGMP)

Rima Kaddurah-Daouk
Duke University Medical Center

NIH National Institute on Aging

1U19AG063744
POs: Suzana Petanceska, Nandini Arunkumar

Duke University School of Medicine
UC San Diego School of Medicine
Caltech
Wake Forest School of Medicine
UCLA
ADMC
University of Oxford
Rush University
Universiteit Leiden
Indiana University
Weill Cornell Medicine
NCRAD
HelmholtzZentrum münchen German Research Center for Environmental Health
NACC National Alzheimer's Coordinating Center
NUI Galway OÉ Gaillimh

Caltech

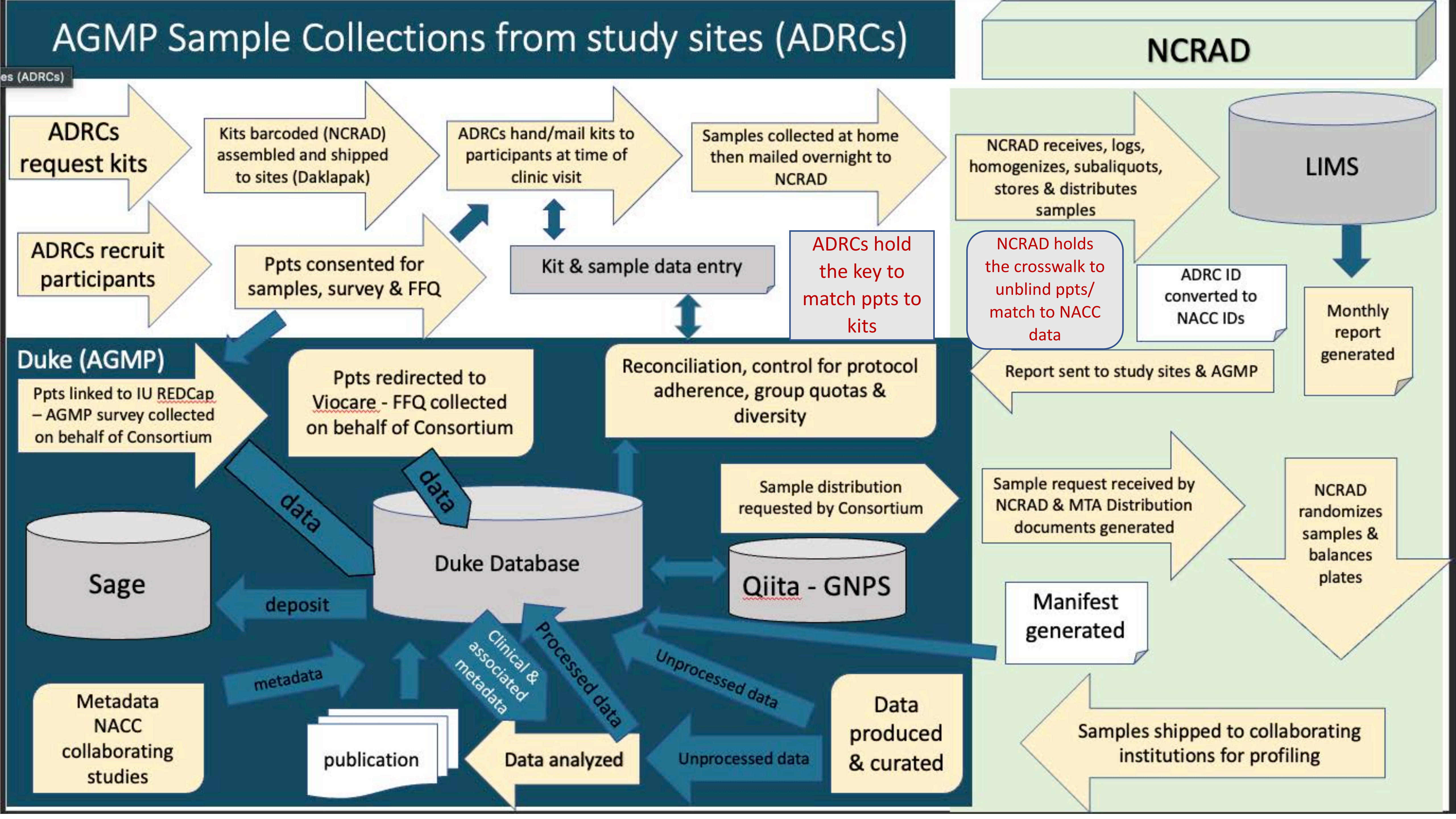
UC San Diego School of Medicine

Duke University School of Medicine

Multi PIs

ALZHEIMER GUT MICROBIOME PROJECT

Management Team


AGMP Sample Collections from study sites (ADRCs)
es (ADRCs)
NCRAD
ADRCs request kits
Kits barcoded (NCRAD) assembled and shipped to sites (Daklapak)
ADRCs hand/mail kits to participants at time of clinic visit
Samples collected at home then mailed overnight to NCRAD
NCRAD receives, logs, homogenizes, subaliquots, stores & distributes samples
LIMS
ADRCs recruit participants
Ppts consented for samples, survey & FFQ
Kit & sample data entry
ADRCs hold the key to match ppts to kits
NCRAD holds the crosswalk to unblind ppts/ match to NACC data
ADRC ID converted to NACC IDs
Monthly report generated
Duke (AGMP)
Ppts linked to IU REDCap – AGMP survey collected on behalf of Consortium
Ppts redirected to Viocare - FFQ collected on behalf of Consortium
Reconciliation, control for protocol adherence, group quotas & diversity
Report sent to study sites & AGMP
data
data
Sample distribution requested by Consortium
Sample request received by NCRAD & MTA Distribution documents generated
NCRAD randomizes samples & balances plates
Sage
Duke Database
Qiita - GNPS
deposit
Manifest generated
metadata
Clinical & associated metadata
Processed data
Unprocessed data
Metadata NACC collaborating studies
publication
Data analyzed
Unprocessed data
Data produced & curated
Samples shipped to collaborating institutions for profiling

ALZHEIMER GUT MICROBIOME PROJECT

Diet/Microbiome AD Studies

U19AG063744

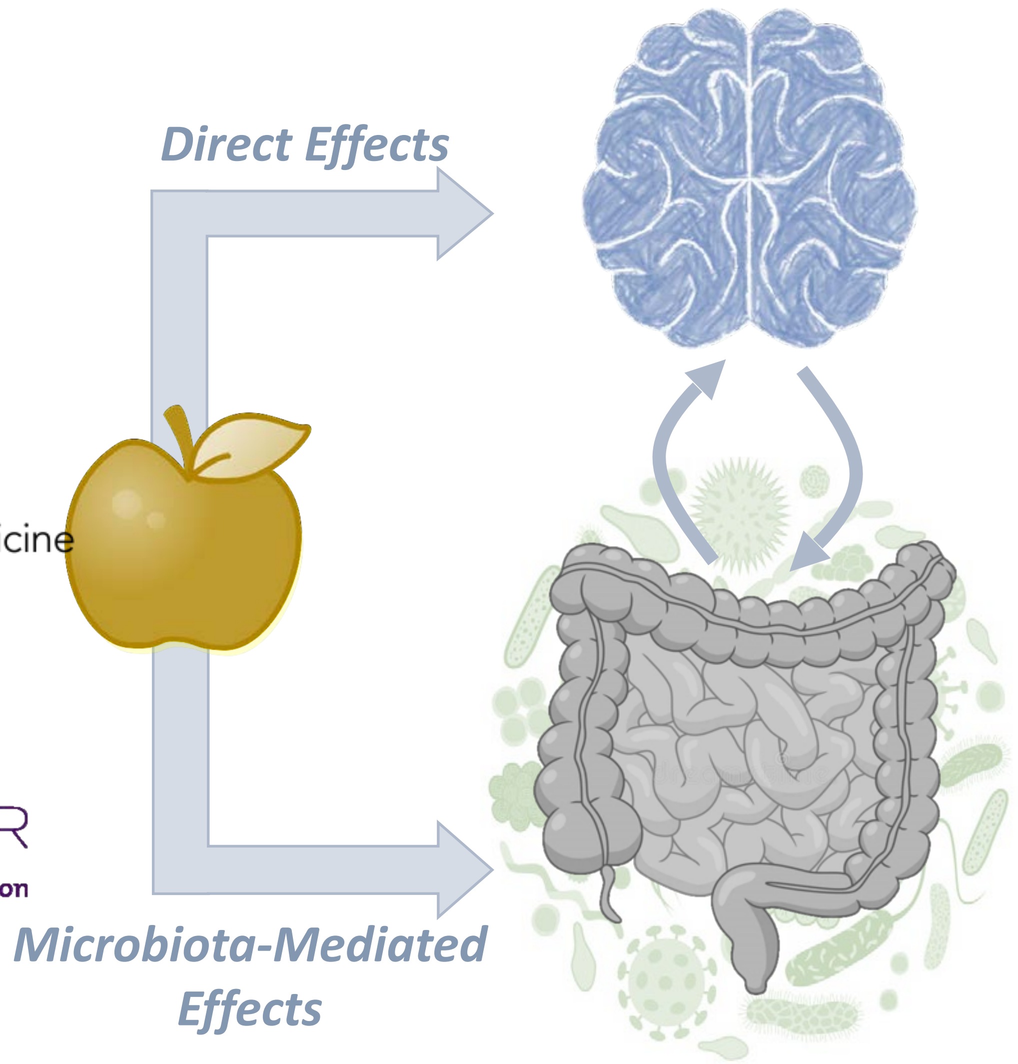
mind

Wake Forest School of Medicine

BEAT-AD

U.S. POINTER

alzheimer's association



MIND:
Mediterranean-DASH Diet **I**ntervention for **N**eurodegenerative **D**elay

BEAT:
Brain **E**nergy for **A**myloid **T**ransformation in Alzheimer's Disease Study

Influence of Controlled Diets on Gut Microbiome, Metabolome, and Cognitive Function

POINTER:
U.S. Study to Protect Brain Health Through Lifestyle Intervention to Reduce Risk

nature biotechnology

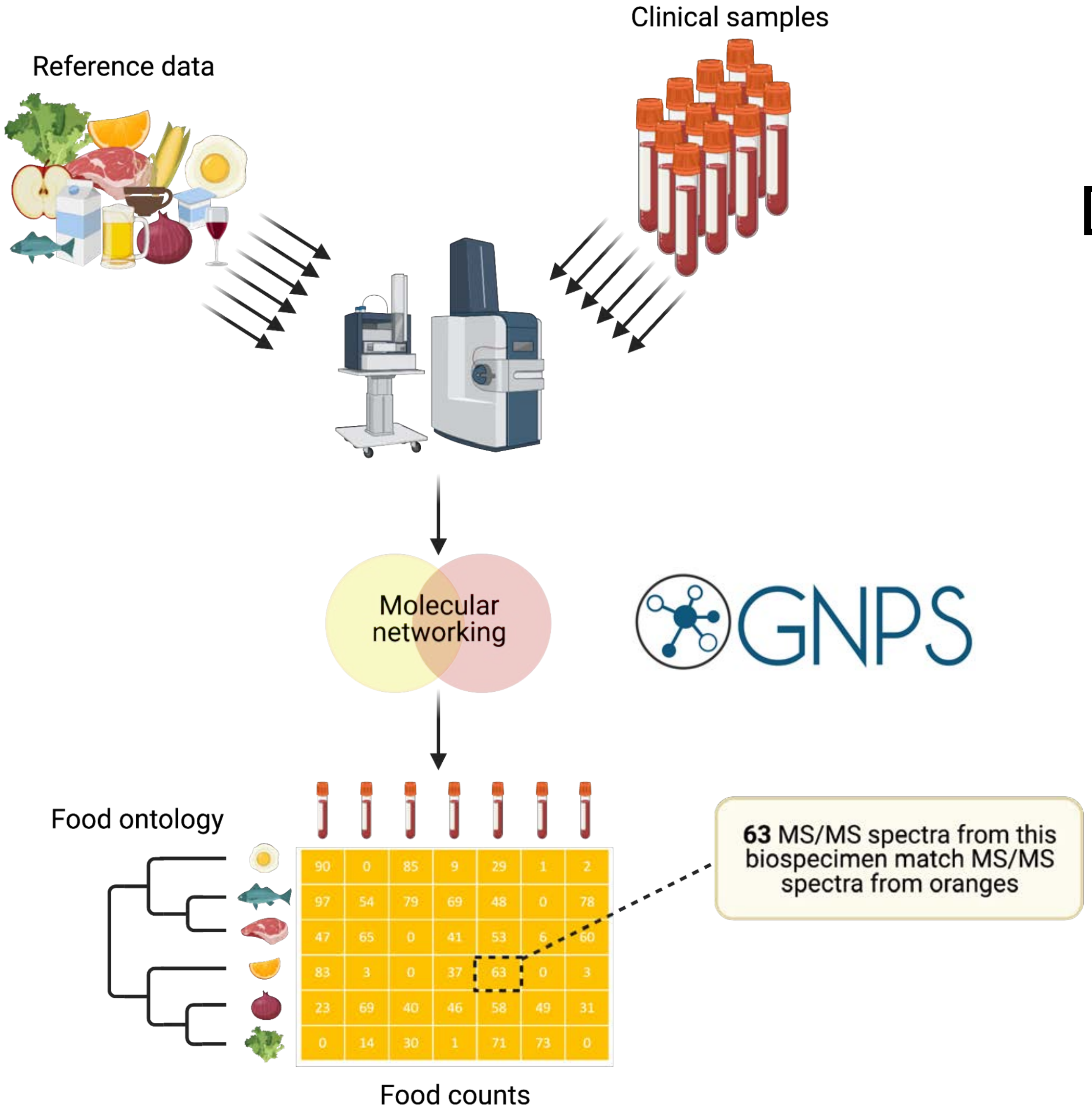
BRIEF COMMUNICATION

https://doi.org/10.1038/s41587-022-01368-1

Enhancing untargeted metabolomics using metadata-based source annotation

Julia M. Gauglitz[1,2,36], Kiana A. West[1,2,36], Wout Bittremieux[1,2,36], Candace L. Williams[3], Kelly C. Weldon[1,2,4], Morgan Panitchpakdi[1,2], Francesca Di Ottavio[1], Christine M. Aceves[1,2], Elizabeth Brown[2,5], Nicole C. Sikora[1,2], Alan K. Jarmusch[1,2], Cameron Martino[4,6,7], Anupriya Tripathi[2,5,6], Michael J. Meehan[1,2], Kathleen Dorrestein[1,2], Justin P. Shaffer[6], Roxana Coras[8], Fernando Vargas[1,2,5], Lindsay DeRight Goldasich[6], Tara Schwartz[6], MacKenzie Bryant[6], Gregory Humphrey[6], Abigail J. Johnson[9], Katharina Spengler[1], Pedro Belda-Ferre[4,6], Edgar Diaz[6], Daniel McDonald[6], Qiyun Zhu[6], Emmanuel O. Elijah[1,2], Mingxun Wang[1,2], Clarisse Marotz[6], Kate E. Sprecher[10,11], Daniela Vargas-Robles[12], Dana Withrow[10], Gail Ackermann[6], Lourdes Herrera[13], Barry J. Bradford[14], Lucas Maciel Mauriz Marques[15], Juliano Geraldo Amaral[16], Rodrigo Moreira Silva[17], Flavio Protasio Veras[15], Thiago Mattar Cunha[15], Rene Donizeti Ribeiro Oliveira[18], Paulo Louzada-Junior[18], Robert H. Mills[1,2,6,19], Paulina K. Piotrowski[20], Stephanie L. Servetas[20], Sandra M. Da Silva[20], Christina M. Jones[20], Nancy J. Lin[20], Katrice A. Lippa[20], Scott A. Jackson[20], Rima Kaddurah Daouk[21,22,23], Douglas Galasko[24], Parambir S. Dulai[25], Tatyana I. Kalashnikova[26], Curt Wittenberg[27], Robert Terkeltaub[8,28], Megan M. Doty[6,27], Jae H. Kim[29], Kyung E. Rhee[6], Julia Beauchamp-Walters[30], Kenneth P. Wright Jr[10], Maria Gloria Dominguez-Bello[30], Mark Manary[31], Michelli F. Oliveira[32], Brigid S. Boland[21], Norberto Peporine Lopes[17], Monica Guma[8], Austin D. Swafford[4], Rachel J. Dutton[5], Rob Knight[4,6,33,34,35] ✉ and Pieter C. Dorrestein[1,2,4,6] ✉

Reference data driven metabolomics
Diet readout from clinical samples



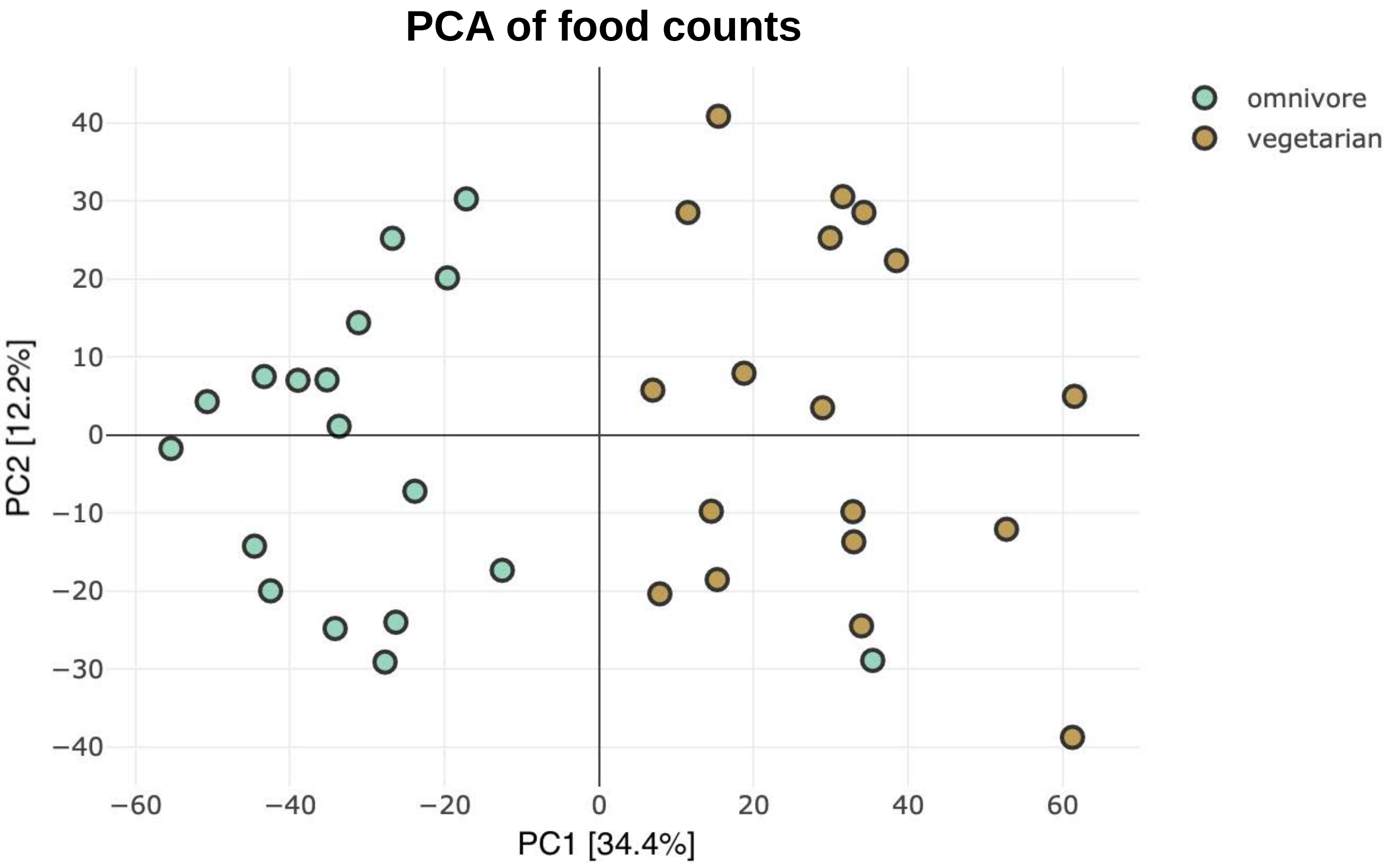
Pieter Dorrestein

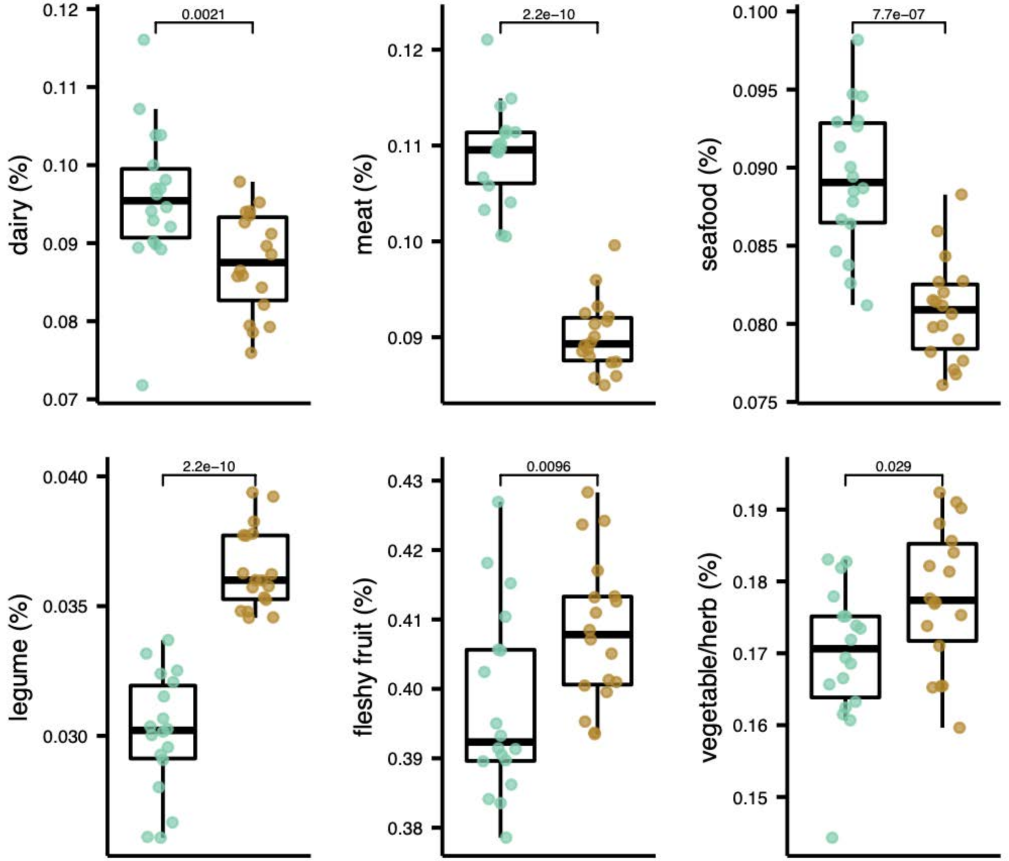
Julia Gauglitz

Kiana West

Wout Bittremieux

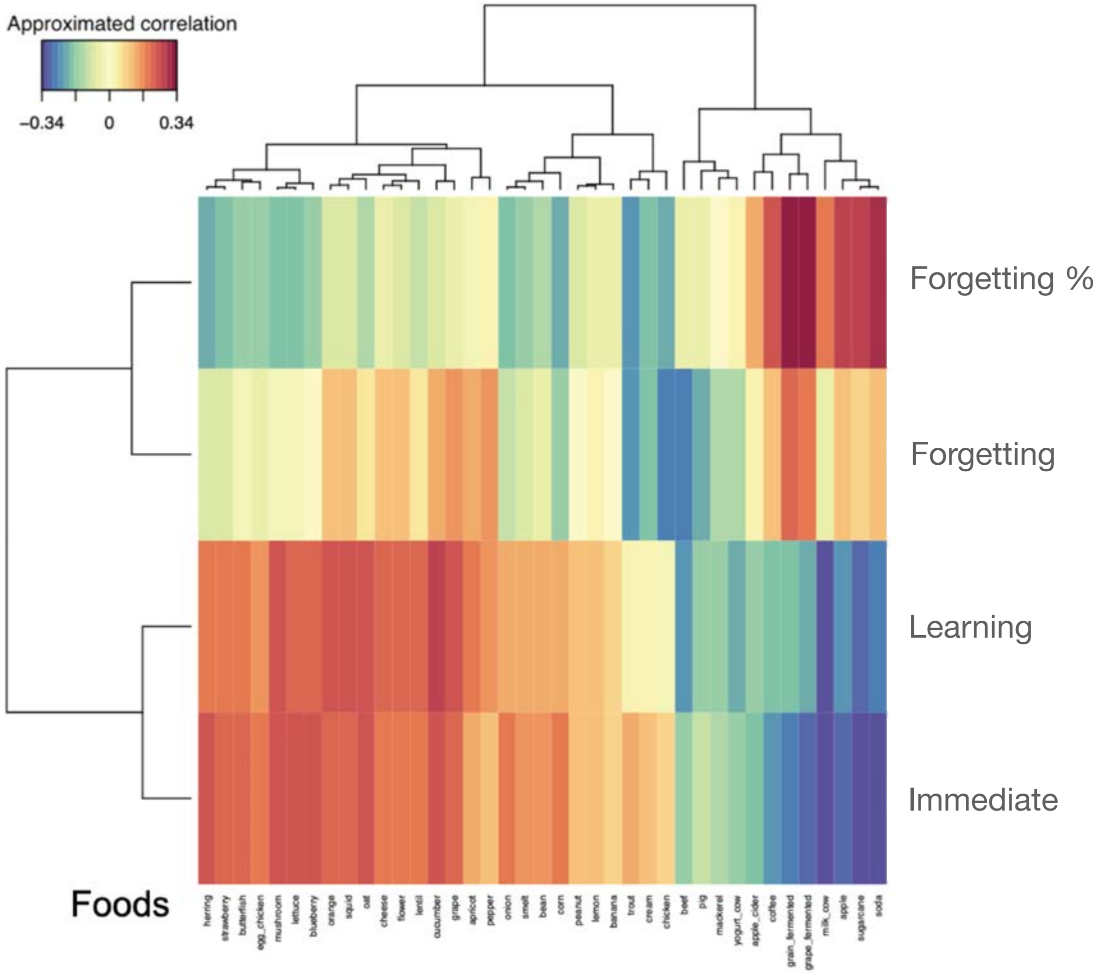
Diet readouts from fecal samples distinguish omnivores from vegetarians?





Foods that correlate with memory: Rey's Auditory Verbal Learning Test (RAVLT)

Scored based on: Number of words recalled from a list, read to the patient verbally



Percent forgetting: higher in AD

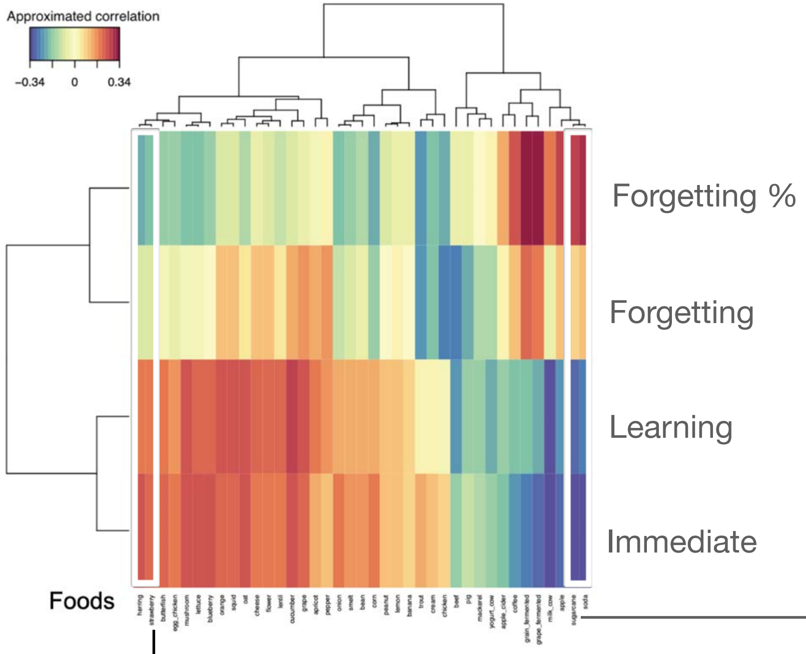
Forgetting: higher in AD

Learning: lower in AD

Immediate: lower in AD

Foods that correlate with memory: Rey's Auditory Verbal Learning Test (RAVLT)

Scored based on: Number of words recalled from a list, read to the patient verbally



Sugarcane (sugar), Soda
= Worst forgetting/inability to learn

Fish, Strawberry, Mushroom
= Improvement in learning

Correlation is not causation but enables hypothesis formulation with diet and disease severity

A diet soda a day might affect dementia risk, study suggest

By American Heart Association News

Study: Diet soda could increase chances of stroke, Alzheimer's

Business

Drinking Too Much Soda May Be Linked to Alzheimer's

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d to receive offers and promotions from Bloomberg.

The New York Times

Sugary Drinks Tied to Accelerated Brain Aging

FISHER CENTER FOR ALZHEIMER'S RESEARCH FOUNDATION

DRINKING SODA TIED TO POOR BRAIN HEALTH AND ALZHEIMER'S RISK

NBC NEWS

Diet Sodas May Raise Risk of Dementia and Stroke, Study Finds

People who drink diet sodas daily have three times the risk of stroke and dementia compared to people who drink one less than once a week.

HEALTH

Another downside to soda and chips: Your memory

A new study shows eating large amounts of ultra-processed fo
significantly accelerate cognitive decline.

TECHNOLOGY & INNOVATION — MARCH 9, 2017

Sugar does rot your brain after all: Scientists connect to Alzheimer's

High sugar intake may increase risk for Alzheimer's disease

The Atlantic

Adding just two-and-a-half teaspoons of sugar to your tea DAILY increases your risk of Alzheimer's by 54%, study finds

HEALTH

The Startling Link Between Sugar and Alzheimer's

nature neuroscience

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nature > nature neuroscience > news & views > article

Published: 26 March 2015

Sugar and Alzheimer's disease: a bitter

Neuroscience News.com

Sweet Trouble: How Sugar Intake Might Increase Alzheimer's Risk

Scientists reveal link betwee sugar intake and brain disease

NIH National Library of Medicine
National Center for Biotechnology Information

Advanced

...018 May 1;187(5):933-940. doi: 10.1093/aje/kwx330.

Fish Intake, Genetic Predisposition to Alzheimer Disease, and Decline in Global Cognition and Memory in 5 Cohorts of Older Persons

Cécilia Samieri [1], Martha-Clare Morris [2], David A Bennett [3], Claudine Berr [4], Philippe Amouyel [5], Jean-François Dartigues [1], Christophe Tzourio [1], Daniel I Chasman [6], Francine Grodstein [7] [8]

frontiers in Aging Neuroscience

PMCID: PMC7103640
PMID: 32265686

Front Aging Neurosci. 2020; 12: 76.
Published online 2020 Mar 20. doi: 10.3389/fnagi.2020.00076

Fish Intake May Affect Brain Structure and Improve Cognitive Ability in Healthy People

Keisuke Kokubun,[1,*] Kiyotaka Nemoto,[2] and Yoshinori Yamakawa[1,3,4,5,6]

Author information ▸ Article notes ▸ Copyright and License information Disclaimer

Latest Newsletters

The Atlantic

HEALTH

Study of the Day: People Who Eat More Fish Enjoy Improved Memory

By Hans Villarica

FISHER CENTER FOR ALZHEIMER'S RESEARCH FOUNDATION

TWO SERVINGS OF FISH A WEEK MAY HELP PROTECT AGAINST DEMENTIA

Science News
from research organizations

Eating fish reduces risk of Alzheimer's disease, study finds

The Relationship of Omega-3 Fatty Acids with Cognitive Decline: Evidence from Prospecti... Supplementation, Dietary Intake, and Bloo...

Bao-Zhen Wei † • Lin Li † • Cheng-Wen Dong • Chen-Chen Tan • ... for the Alzheimer's Disease Neuroimaging Initiative • Wei Xu

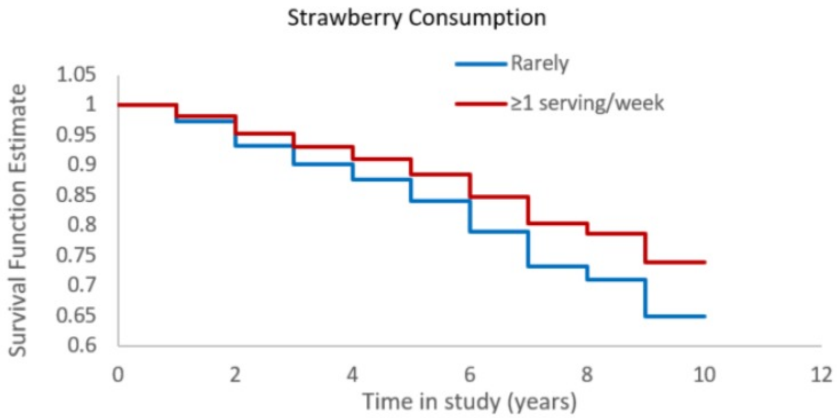
Published: April 04, 2023 • DOI: https://doi.org/10.1016/j.ajcnut.2023...

Prevention of Early Alzheimer's Disease by Erinacine A-Enriched *Hericium erinaceus* Mycelia Pilot Double-Blind Placebo-Controlled Study

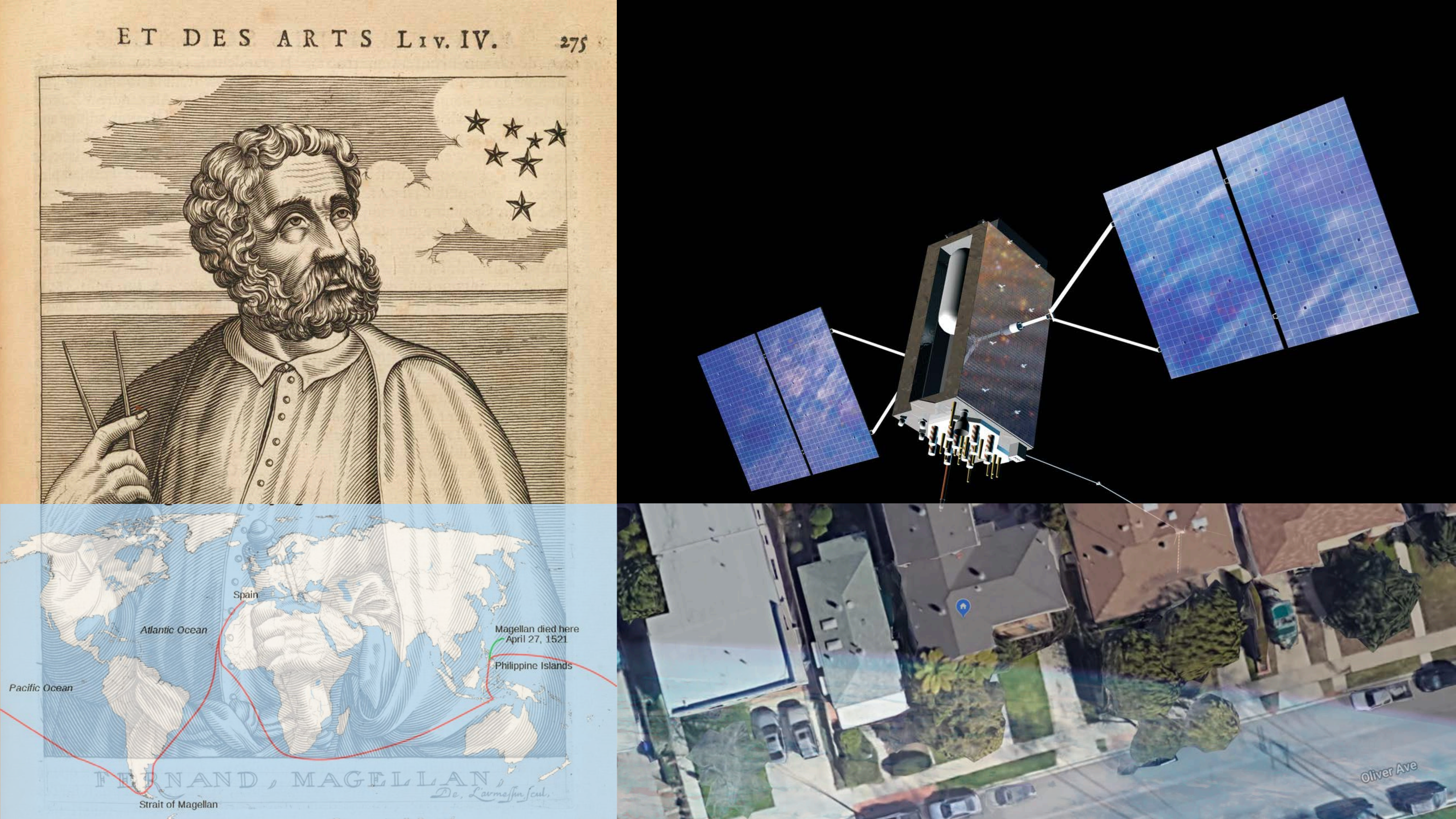
I-Chen Li[1], Han-Hsin Chang[2], Chuan-Han Lin[3], Wan-Ping Chen[1], Tsung-Han Lu[3], Li-Ya Lee[1], Yu-Wen Chen[1], Yen-Po Chen[1], Chin-Chu Chen[1,4,5,6*] and David Pei-Cheng Lin[3,7*]

Association of Strawberries and Anthocyanidin Intake with Alzheimer's Dementia Risk

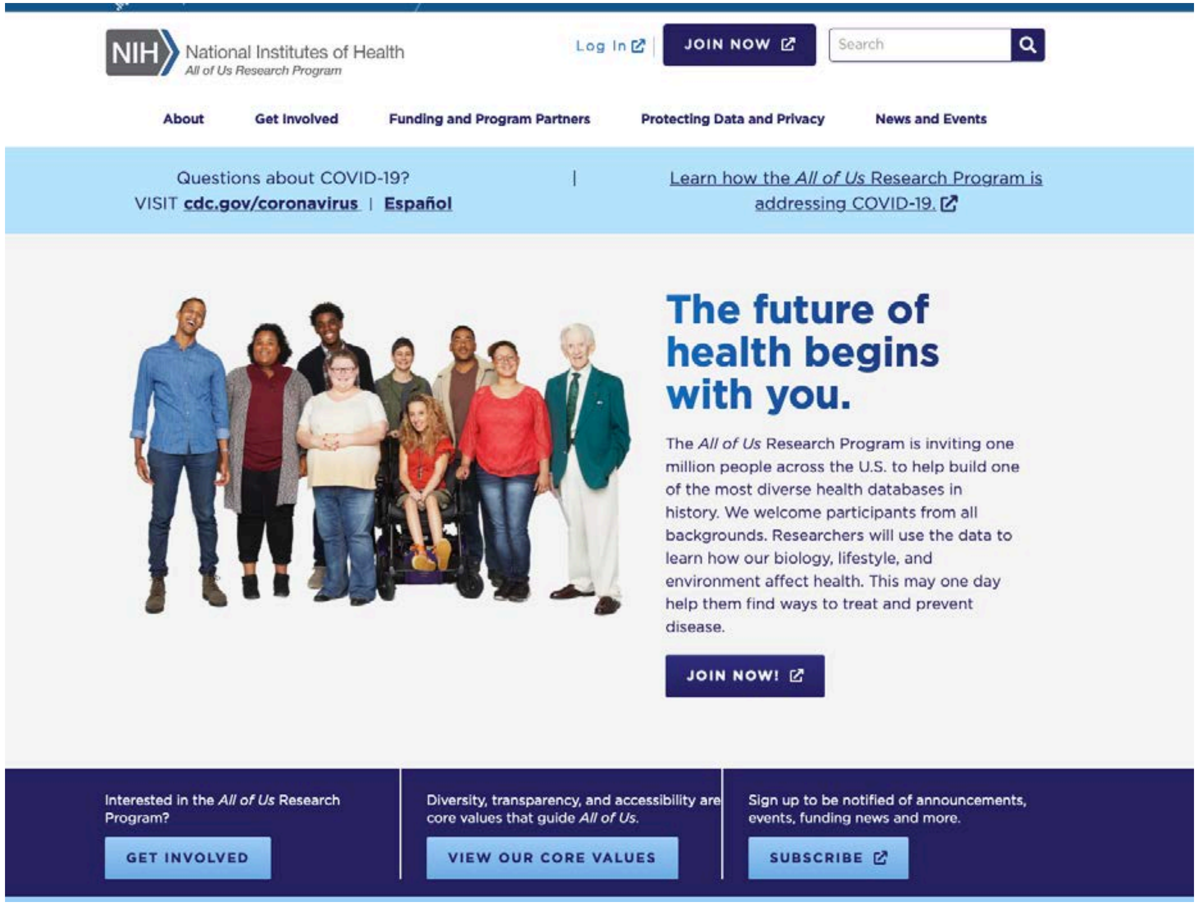
by Puja Agarwal [1,*], Thomas M Holland [1], Yamin Wang [1], David A Bennett [2,3] and Martha Clare Morris [1]

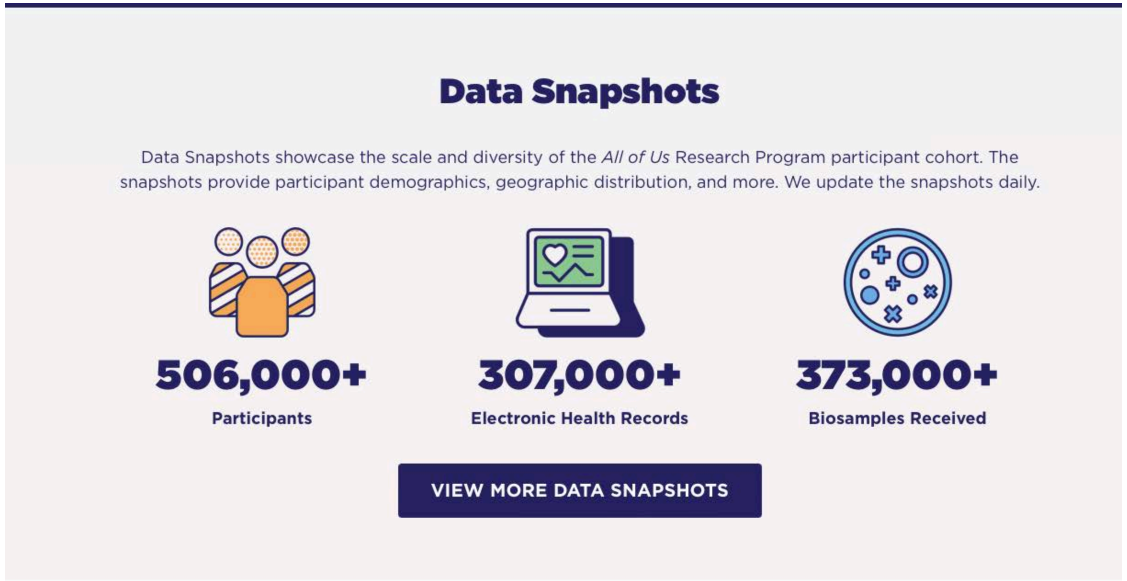


Strawberry consumption and Alzheimer's dementia risk (Cox-proportional hazards model adjusted for age, sex, education, physical activity, participation in cognitively stimulating activities, APOE-ε4, other fruits intake, and total calories).


ET DES ARTS LIV. IV.
275
FERNAND, MAGELLAN
Spain
Atlantic Ocean
Magellan died here
April 27, 1521
Philippine Islands
Pacific Ocean
Strait of Magellan
Oliver Ave

What is the All of Us program?





Nutrition for Precision Health | All of Us RESEARCH PROGRAM

https://allofus.nih.gov

Slide credit: Mary Buschmann

Goals of NPH

- To develop algorithms to predict individual responses to foods and dietary patterns
- To create a discovery science resource for the nutrition researcher community

Slide credit: Diana Thomas

What is the Nutrition for Precision Health Program?

NPH Overview

- ~$170 million investment from the NIH Common Fund over 5 years
- NIH-wide effort
- 14 awardees from around the US
- First ancillary study to the *All of Us* Research Program
- First Common Fund program with primary and central focus on nutrition research
- First major initiative to advance the goals of the 2020-2030 Strategic Plan for NIH Nutrition Research

Nutrition for Precision Health

All of Us RESEARCH PROGRAM

Slide credit: Mary Buschmann

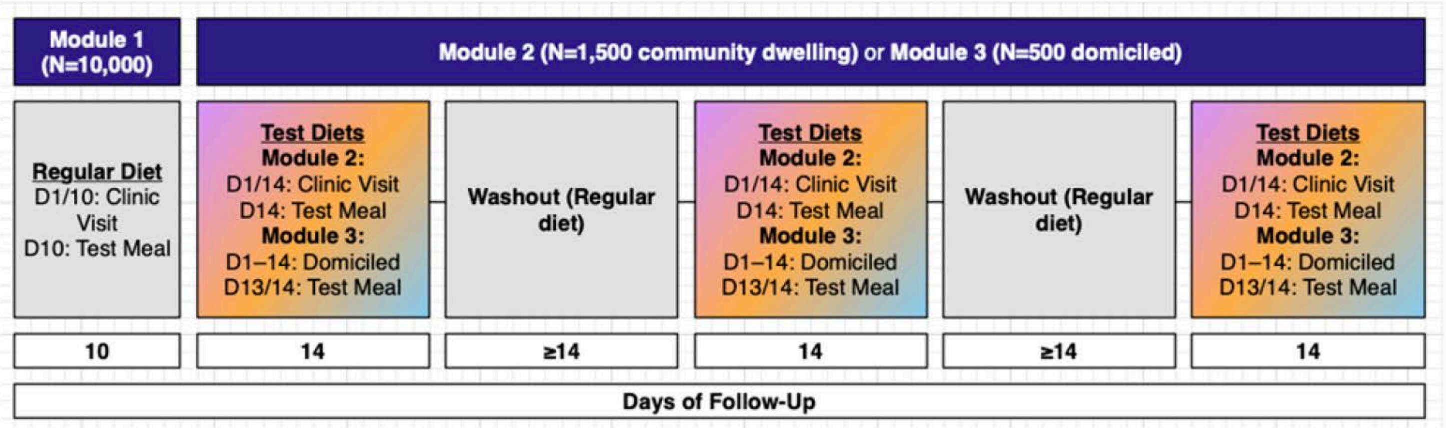
NPH Study Design (Study launch date: Feb 15, 2023)

Module 1 – Detailed characterization of 10,000 people – food recall, body and performance measures, physiological, **MICROBIOME**, blood chemistry, etc. on normal diets.

Module 2 – Longitudinal analysis of 2500 people on 3 cross-over prescribed diets at home.

Module 3 – Longitudinal analysis of 500 people on 3 cross-over diets in domiciled clinical centers.

Figure 1. Participant Flow Diagram



Nutrition for Precision Health

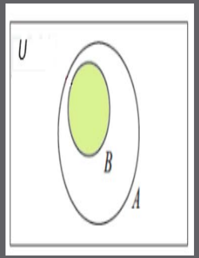
All of Us RESEARCH PROGRAM

Slide credit: Mary Buschmann

Parent Model

To develop algorithms to predict individual responses to foods and dietary patterns

Precision Nutrition Machine Learning Framework



Minimal Input Algorithm

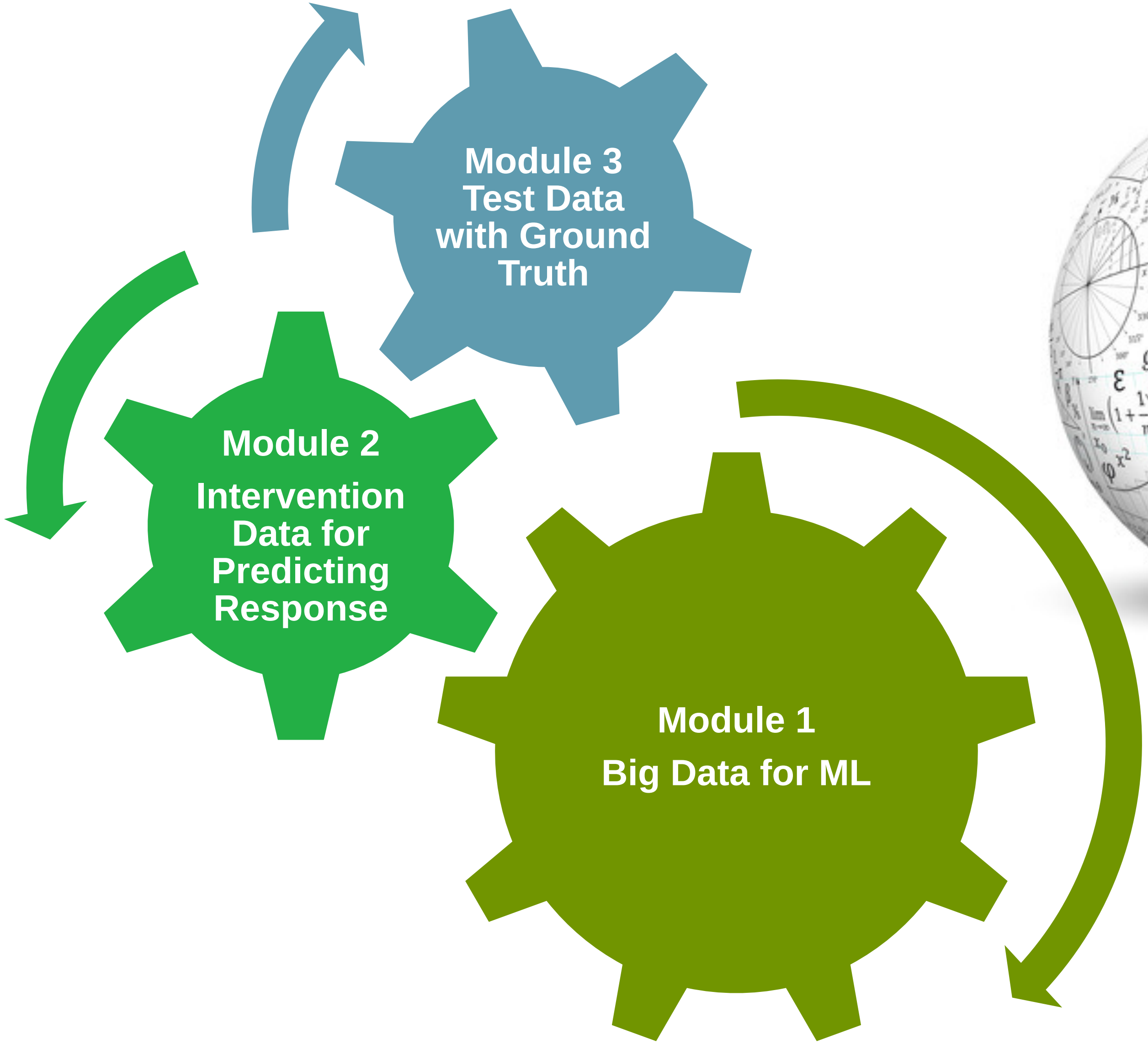
Uncover relationships between diet related diseases and individual metabolic phenotypes

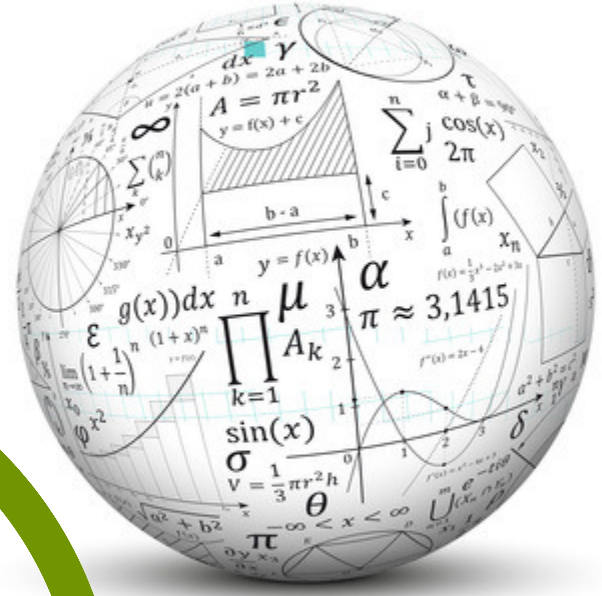
Identify drivers of diet- and nutrition-related health disparities

Slide credit: Diana Thomas

Why three modules?

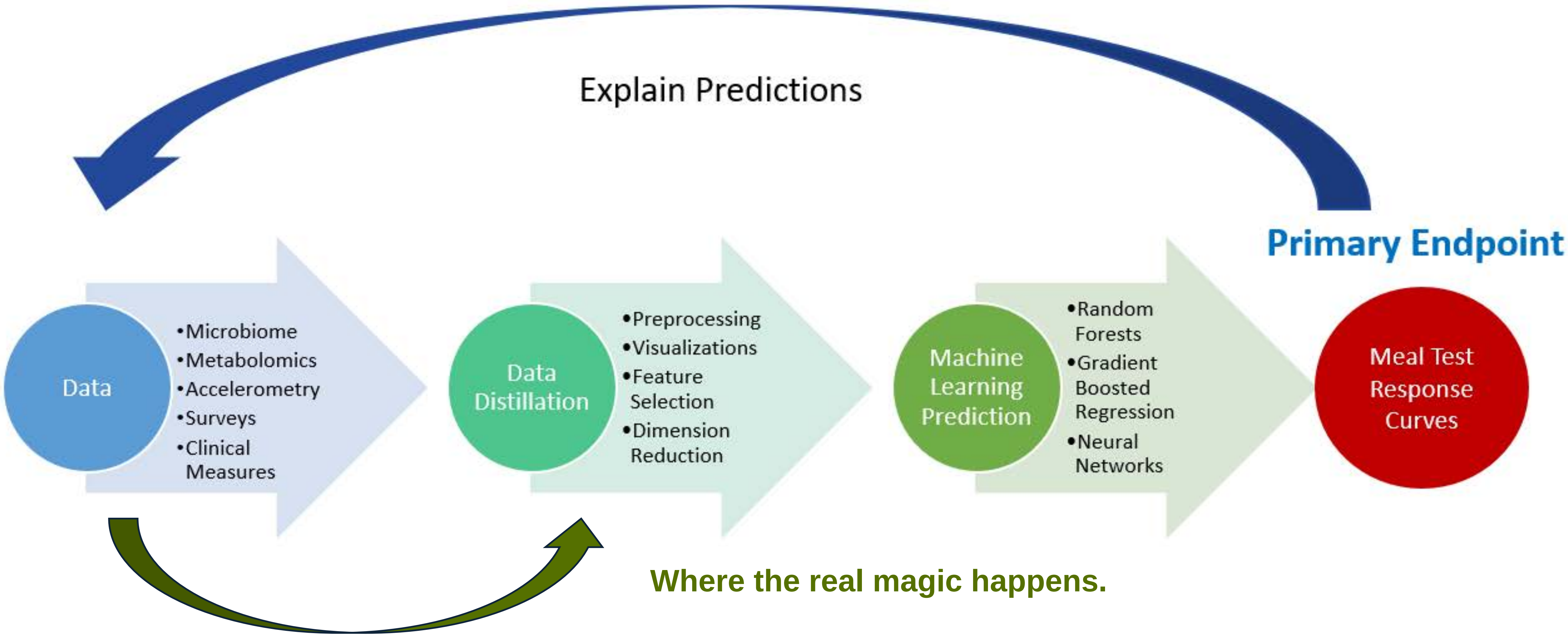
Number of Features	Sample Size
Cluster Analysis	
50	3000-3500
Principal Components Analysis	
50	250
Neural Networks	
500	10,750





Slide credit: Diana Thomas

A Discovery Science Algorithm



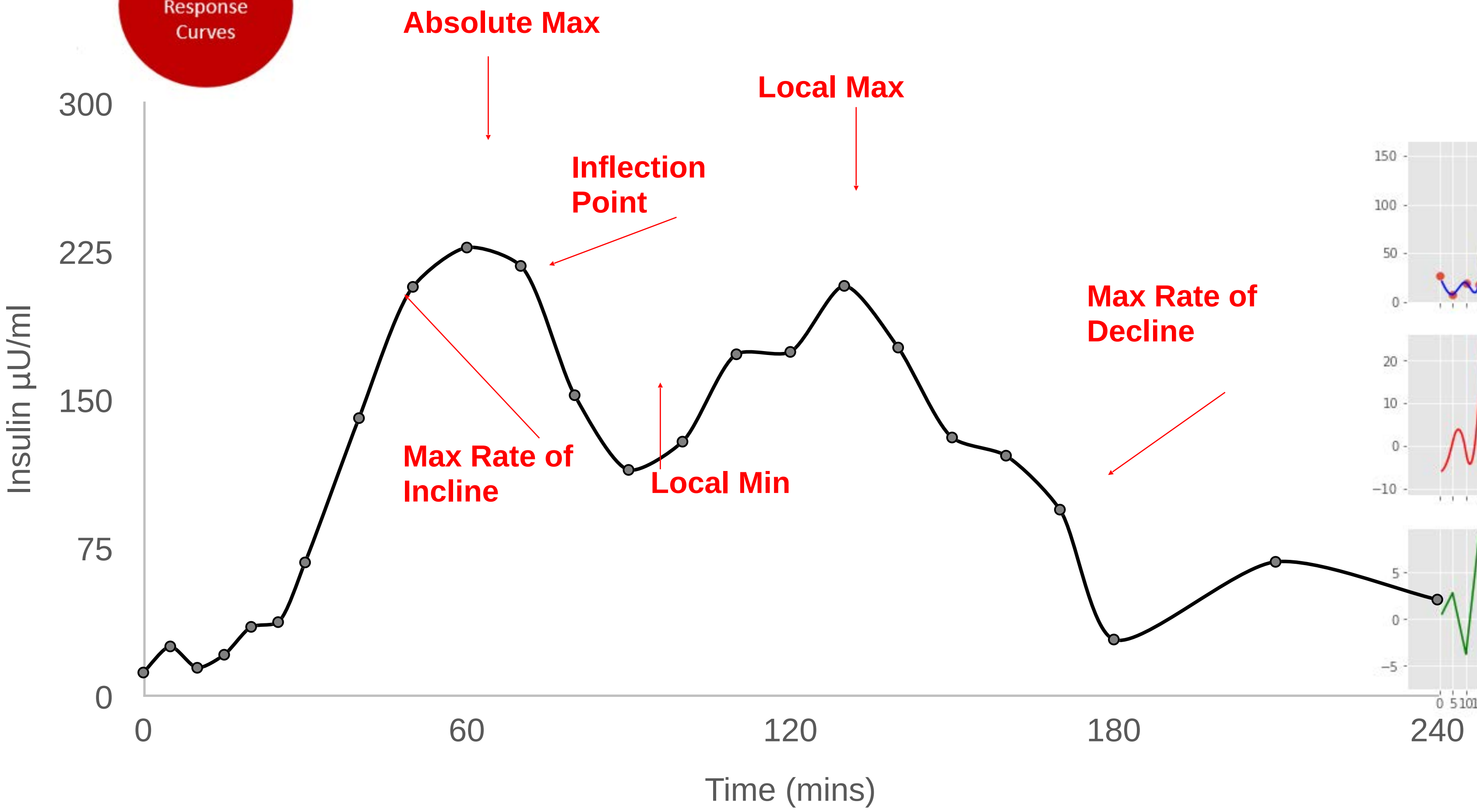
Slide credit: Diana Thomas

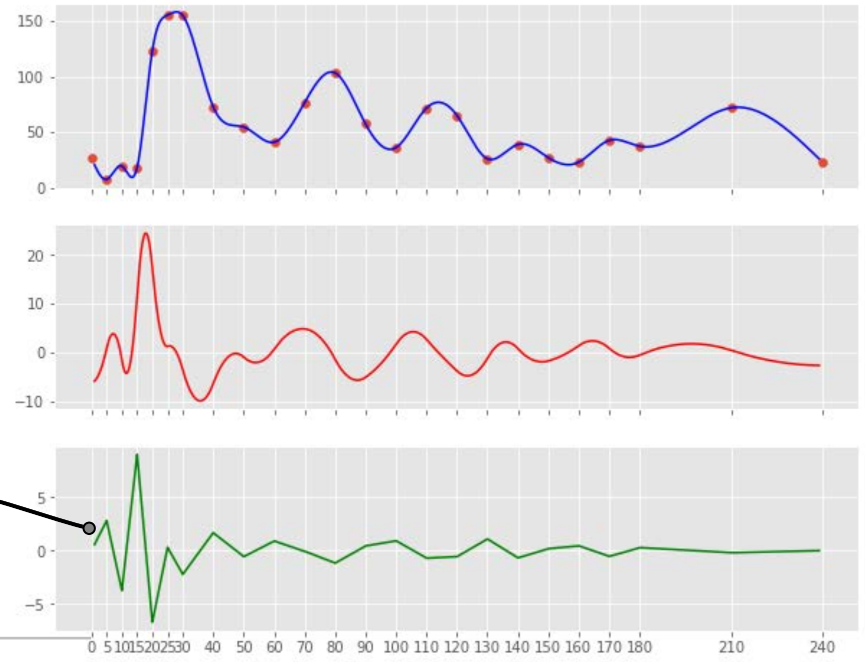
What are we predicting? Diet specific post-prandial analyte response curves

Primary Endpoint

Meal Test Response Curves

In addition to iAUC, we will predict calculus-based curve shape properties using the “conoculator”





Slide credit: Diana Thomas

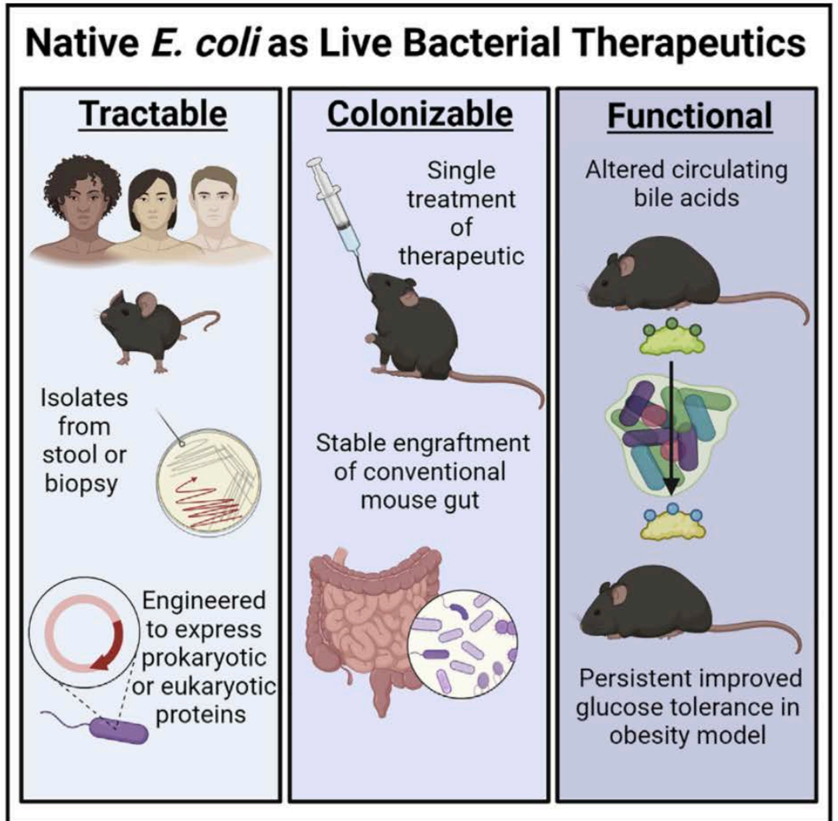
The future: engineer bacteria from an individual

Cell

Resource

Intestinal transgene delivery with native *E. coli* chassis allows persistent physiological changes

Graphical abstract



Authors

Baylee J. Russell, Steven D. Brown, Nicole Siguenza, ..., Alan Saghatelian, Rob Knight, Amir Zarrinpar

Correspondence

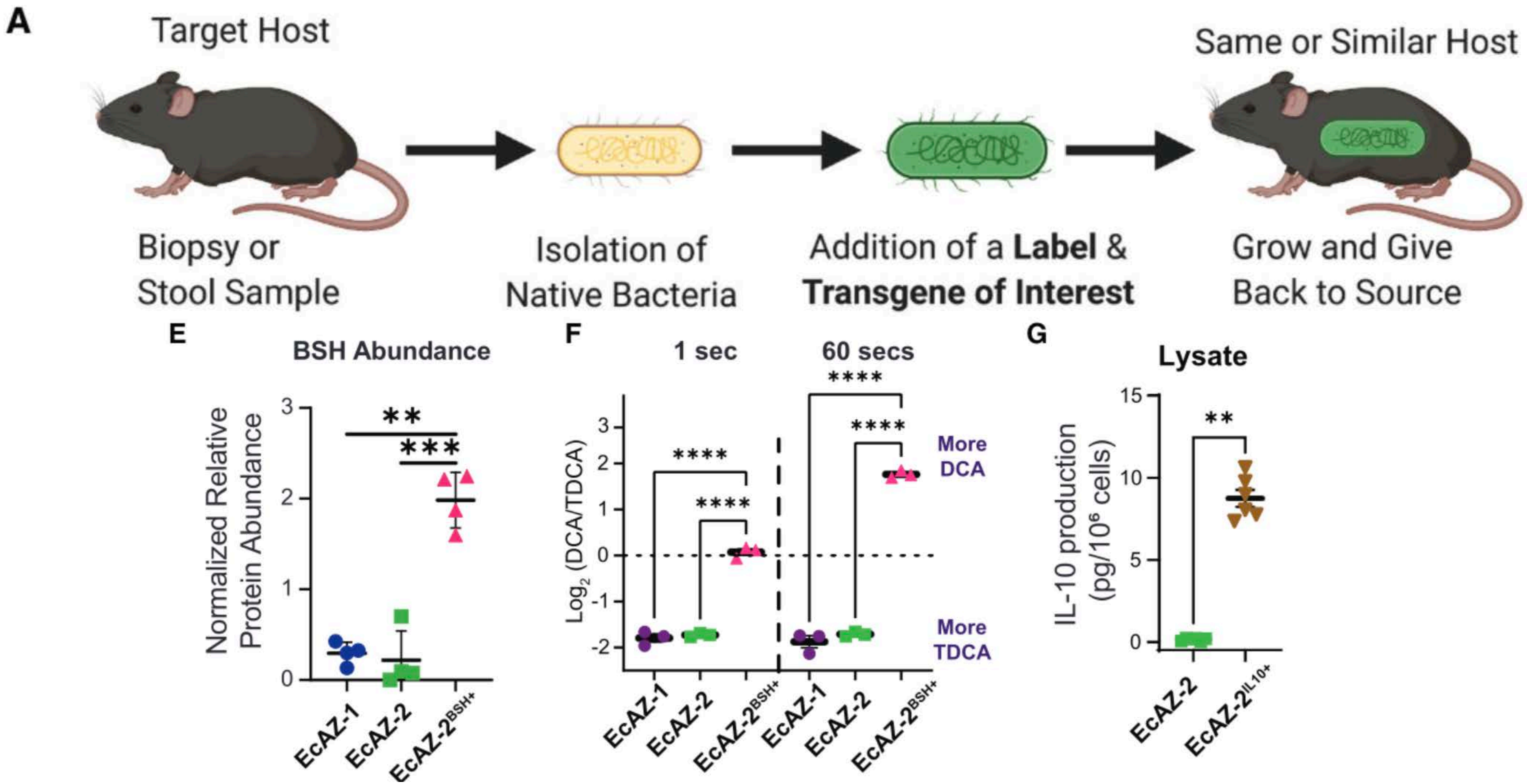
azarrinpar@ucsd.edu

In brief

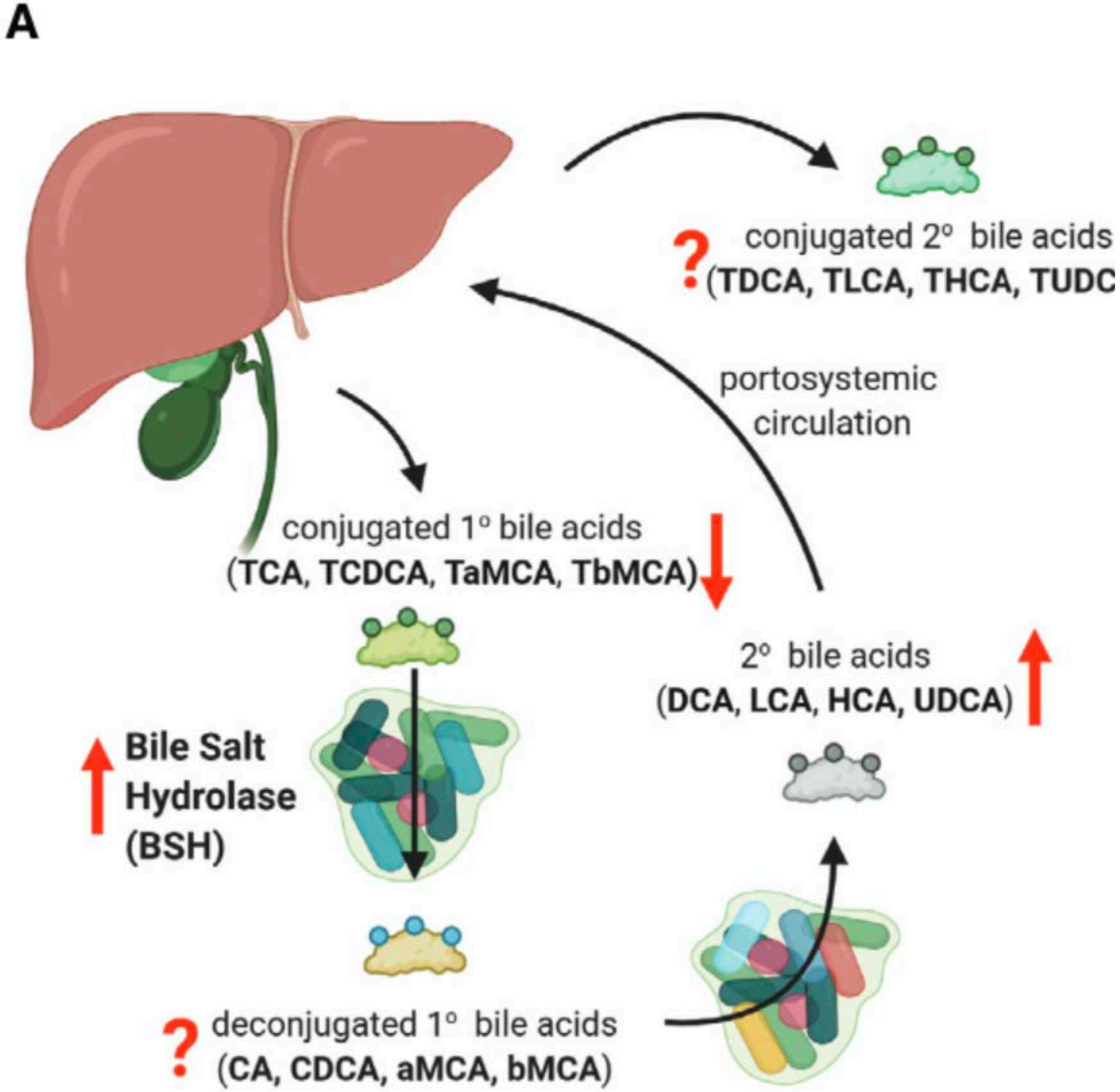
Native *E. coli* strains isolated from mouse stool are genetically engineered for long-term engraftment in the conventional mouse gut and enable long-term systemic effects on the host, such as improvements in insulin sensitivity in mouse models of type 2 diabetes.

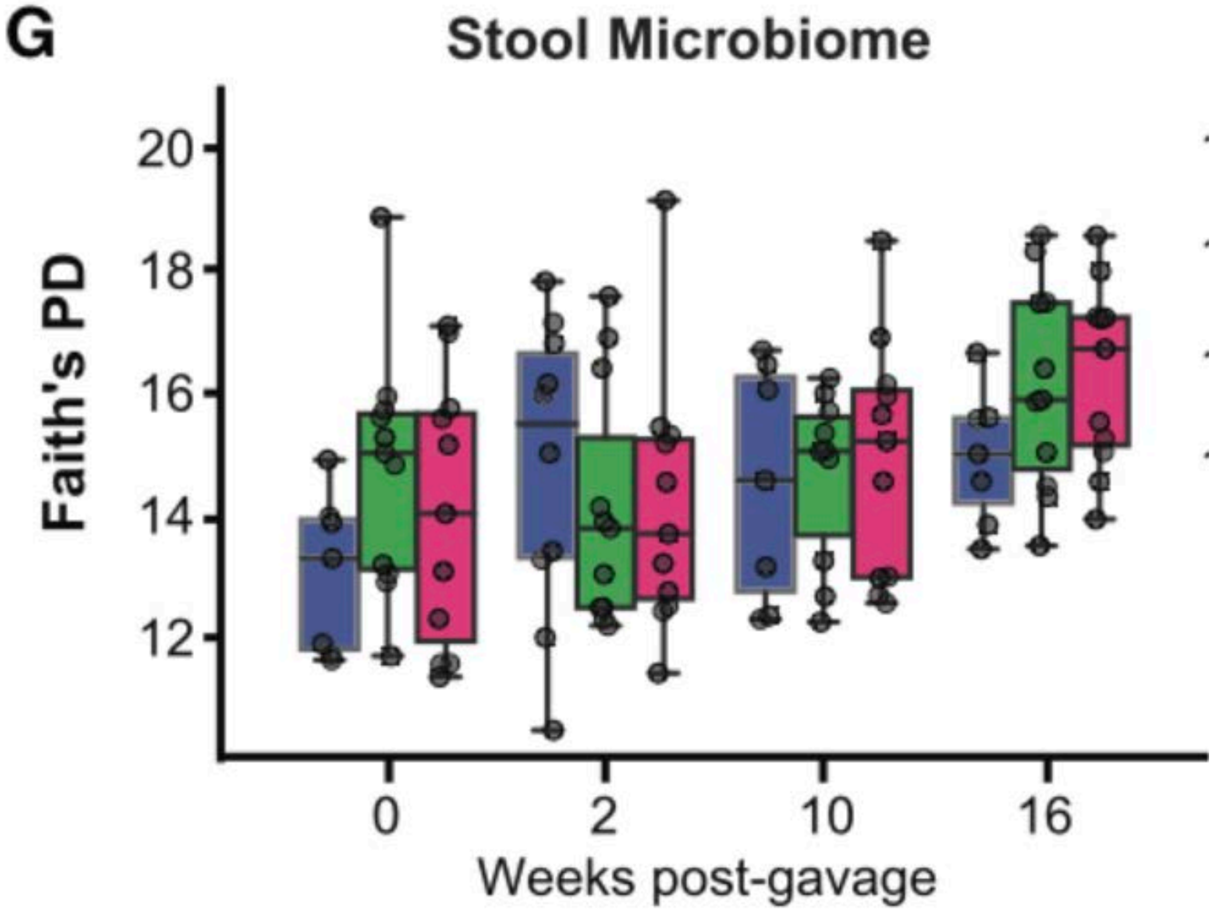
Amir Zarrinpar

Like CAR T cell therapy but for microbes



Impacts metabolome but not microbiome





Microbiome-directed cancer interventions already saving lives

IMMUNOTHERAPY

Dietary fiber and probiotics influence the gut microbiome and melanoma immunotherapy response

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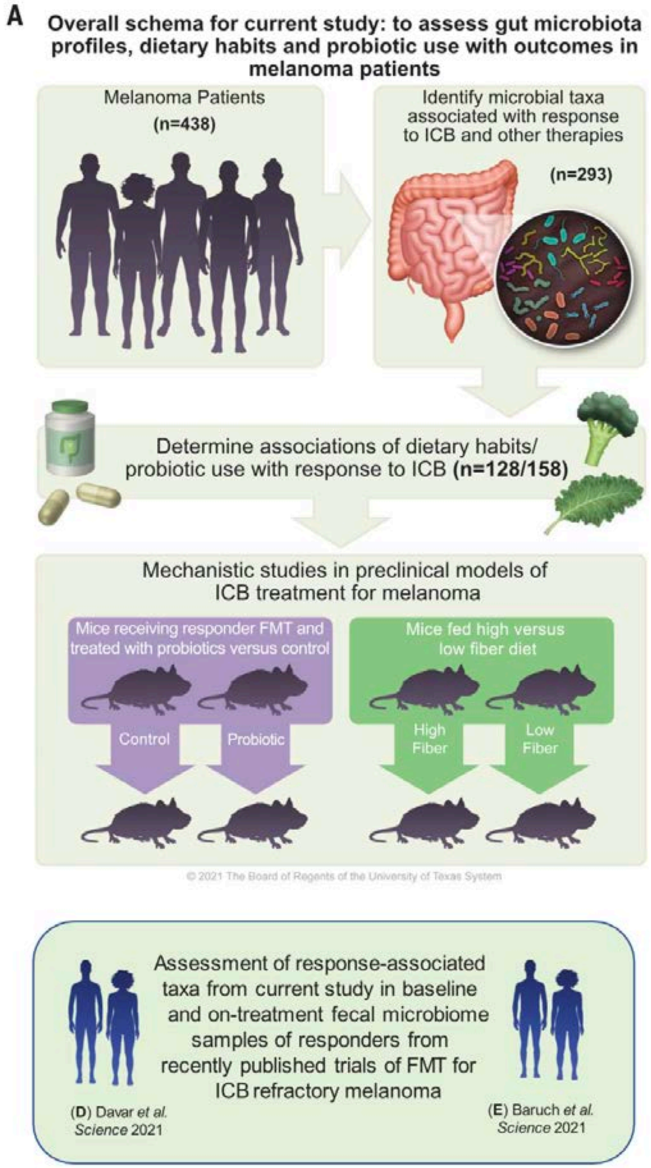
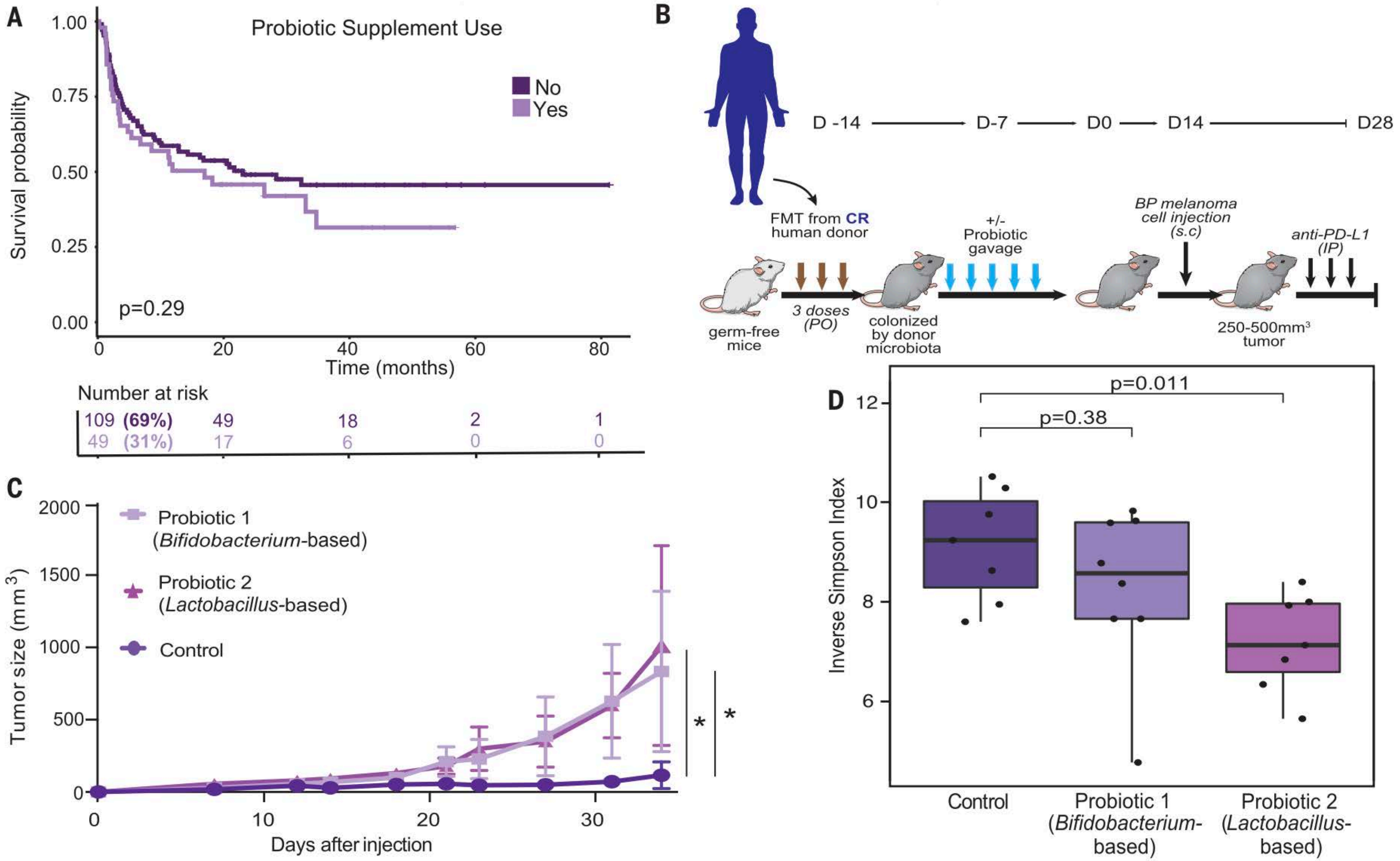


…but caution about probiotics is warranted…



Key messages:

- Microbiome and diet are intimately linked
- Machine learning and AI methods have been critical for microbiome analysis for a decade, and many principles are applicable to other multivariate dataset e.g. food
- Ethics considerations around microbiome interventions, especially around bias, stratification, and safety, also likely apply to dietary intervention
- Lots of potential for benefit from improved communication

Thanks to: Knight lab, and over 1000 collaborators! (Sorry if I didn't mention you by name)

Funding: NIH, Gates, HHMI, CCFA, NIJ, DOE, DARPA, USDA, Keck, Sloan, Moore, Templeton, DOD, NSF, Wolfe Family, tens of thousands of members of the public

Thanks!

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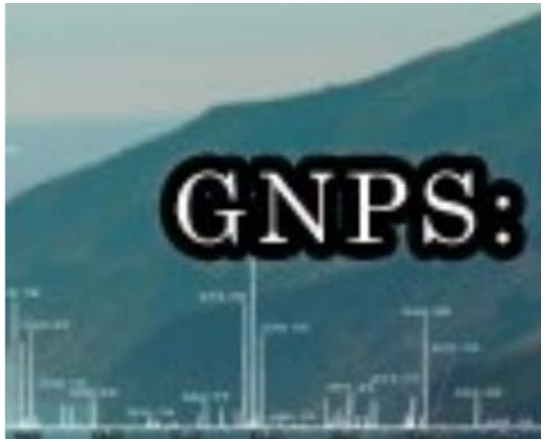

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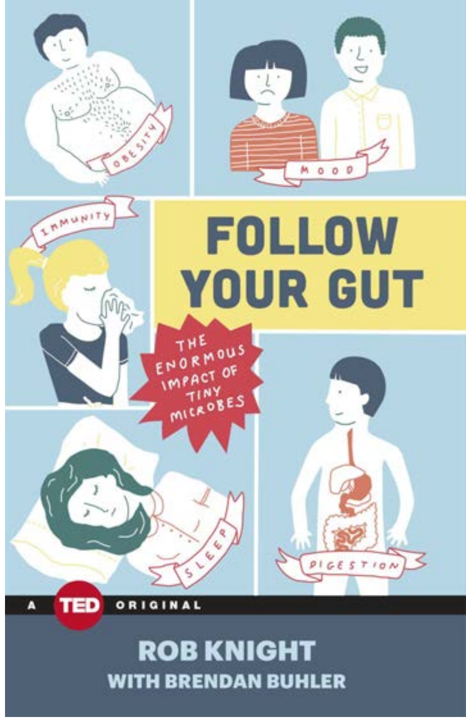

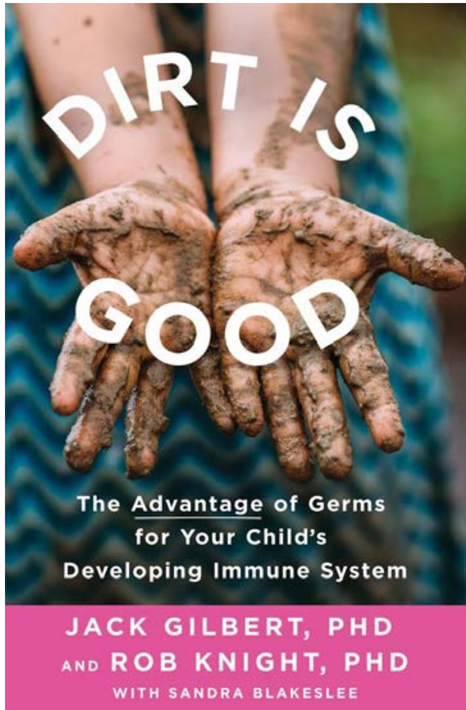

Quantitative Analysis of Metabolomics Data to Inform Precision Health

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NIH Common Fund 1U24DK097193 (Sumner)
NIEHS U2CES026544 (Fennell)
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NIH Common Fund U23CA268153 (Sumner)
National Science Foundation 1262416 (Du)

1

Disclosure

No Conflicts of Interest to Disclose

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Outline

- Define Metabolomics and Metabolic Individuality
- Study Design and Data Capture
- Modeling Metabolomics Data
- Example Study
  - Placental Abruption and Nutritional Intervention Strategy
- Concept of the Exposome
- Example Studies
  - Opium Use Disorder, Exposure Reduction Strategies, and Nutrient Cocktails
  - Osteoarthritis, Exposure Reduction Strategies, and Nutrient Cocktails
- Public Databases, Public Data Analysis Resources, and Accessible Metabolomics Data

3

Metabolomics

- Metabolomics involves the study of the low molecular complement of cells, tissues, and biological fluids.
- An individual’s metabotype is the signature, or biochemical fingerprint, of low molecular weight metabolites that are present at any time in tissues or biological fluids.
- The metabolomics signature is composed of endogenous metabolites that are present as a read out of the genome, as well as exogenous metabolites that are derived from external sources of exposures.

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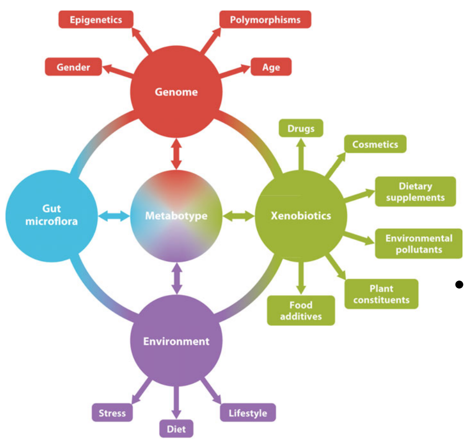
What Contributes to Metabolic Individuality



Johnson CH, et al. 2012.
Annu. Rev. Pharmacol. Toxicol. 52:37–56

- Model system and human subject investigations have shown metabolomics signatures (the metabotype) to correlate with gender, race, age, ethnicity, polymorphism, stress, weight status, mental health status, blood pressure, many disease states, behaviors, gut microbes, diet, and physical activity.
- Each of these factors contribute to differences in levels of endogenous metabolites - which can also be considered as differences in our internal exposure.
- Many chemicals, drugs, medications, and nutrients perturb the endogenous metabotype, and many can be analyzed simultaneously with host and microbial metabolites using untargeted methods.

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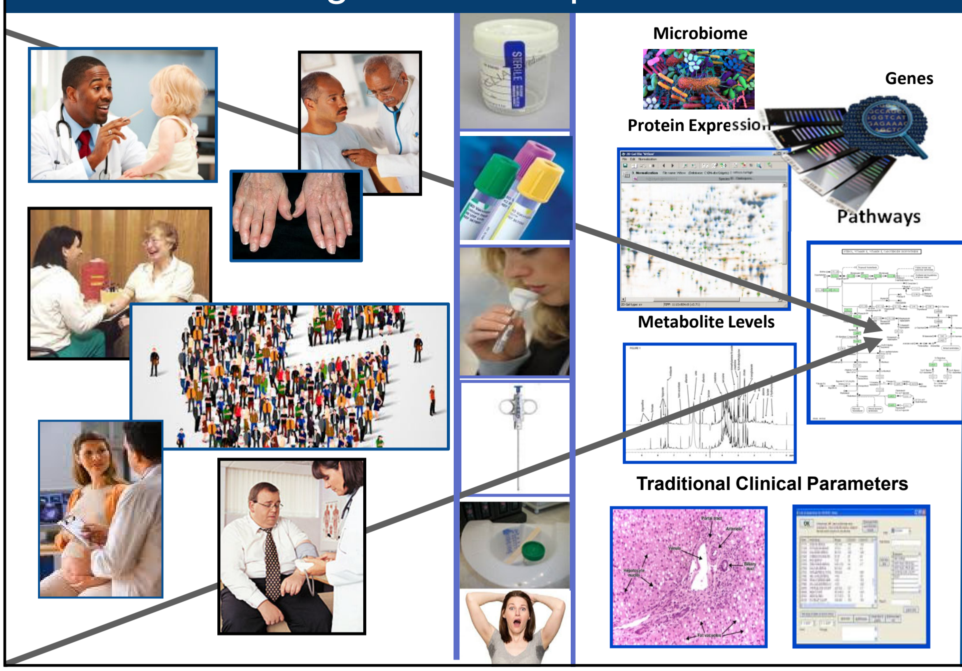
Studies are Designed to Compare States of Health and Response



THE NEEDS

More sensitive and early markers for disease detection and staging

Markers to monitor treatment for
- efficacy
- adverse response
- relapse
- transplantation

Mechanistic insights from pathway analysis point to
- pharmacological targets
- nutritional interventions
- genetic links

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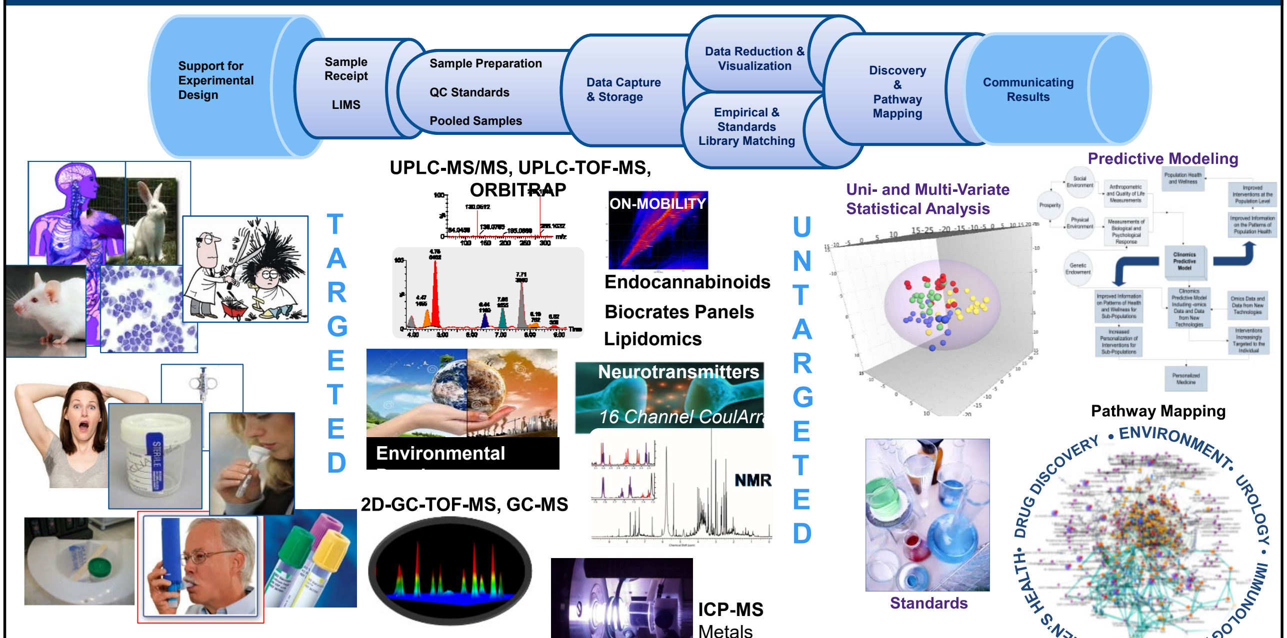
Technologies to Capture Metabolites



NIH Common Fund 1U24DK097193 (Sumner, PI)

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Machine Learning Methods for Analysis of Metabolomics Data

Many different machine learning methods are being used in metabolomics including:

- Principal Component Analysis
- Partial Least Squares Discriminant Analysis (PLS-DA)
- Orthogonal PLS-DA (OPLS-DA)
- O2PLS
- PLS and OPLS Regression
- Principal Component Regression
- Hierarchical Clustering
- K-Means Clustering
- Support Vector Machines
- Self-Organizing Maps
- Random Forest
- Random Survival Analysis
- Logistic and Linear Regression
- Penalized Regression
  - LASSO and Elastic Net
- Neural Networks
- Weighted Quantile Sum Regression
- Probit Extension of Bayesian Kernal Machine Regression
- Deep Learning Methods
  - Convolutional Neural Networks
  - Deep Neural Networks/Deep Neural Networks-Mean Decrease Accuracy
- Ensemble machine learning ranking procedures to identify important metabolites across multiple models

8

Endogenous Metabolites of Host System

Endogenous Metabolites: Endogenous metabolites are those that map to the biochemical pathways of the host system

9

Exogenous Metabolites are Derived from Exposures

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Logistic Regression Modeling in a Metabolomics Study of Placental Abruption

- Placental abruption (PA) is an ischemic placental disorder that results from premature separation of the placenta before delivery and is reported to occur in 1% of all pregnancies.
- PA has severe health consequence to the mother (e.g., maternal hemorrhagic shock) and neonate, including preterm birth and death.
  - There is no universal accepted diagnosis for PA.
- The earliest, but non-specific, symptoms include vaginal bleeding or abdominal pain, and appear for some women in the 3rd trimester of pregnancy.
- For this study, serum samples that had been collected from women at approximately 16 weeks of gestation were selected from a cohort of women who delivered at the Swedish Medical Center, WA.
- Half of the samples selected from the biorepository were from women who had PA (sonographic diagnosis) in the third trimester, and half of the samples were from women who had a normal vaginal delivery.
- Goal of our collaboration with Michelle Williams and Bizu Gelaye at Harvard University was to determine biomarkers from the 2nd trimester serum that predicts PA in the 3rd trimester.

Gelaye et al., 2016. Maternal Early Pregnancy Serum Metabolomics Profile and Abnormal Vaginal Bleeding as Predictors of Placental Abruption: PlosOne 11(6).

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Metabolites were Significantly Associated with PA ($p<0.05$)

Biocrates AbsoluteIDQ® p180 Kit for Quantitative Targeted Analysis of 188 Host Metabolites

Classification	Metabolite Abbreviation	Metabolite	p-value
Acylcarnitines	C16-OH	Hydroxyhexadecanoyl-L-carnitine	0.021
Amino Acids	Arg	Arginine	0.029
Biogenic Amines	Histamine	Histamine	0.034
Custom Ratios	C12 / C12:1	Dodecanoyl-L-carnitine/Dodecenoyl-L-carnitine	0.045
Glycerophospholipids	PC aa C36:0	Phosphatidylcholine diacyl C 36:0	0.040
	PC aa C38:0	Phosphatidylcholine diacyl C 38:0	0.048
	PC aa C40:1	Phosphatidylcholine diacyl C 40:1	0.038
	PC ae C38:1	Phosphatidylcholine acyl-alkyl C 38:1	0.021
	lysoPC a C18:1	lysoPhosphatidylcholine acyl C18:1	0.040

Gelaye et al., 2016. Maternal Early Pregnancy Serum Metabolomics Profile and Abnormal Vaginal Bleeding as Predictors of Placental Abruption: PlosOne 11(6).

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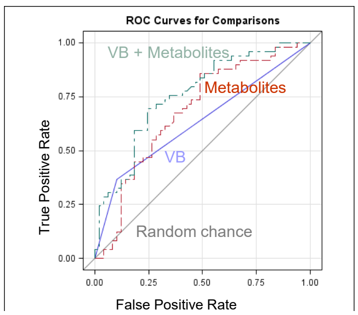
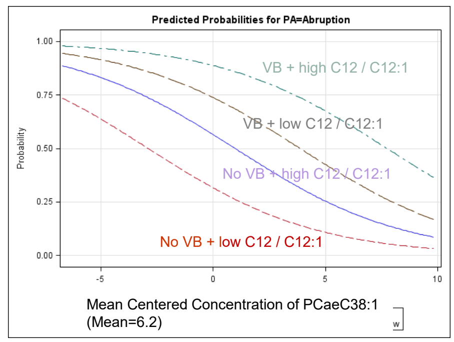
Logistic regression was used to model the probability of PA in the 3rd trimester based on serum biomarkers in 2nd trimester

	Area Under the ROC Curve (95% CI)	Model AUC Compared to VB Model AUC	Error Rate	Brier Score	R2	Bayes Information Criteria (BIC)
Model						
Vaginal Bleeding Only	0.63 (0.55, 0.71)	---	0.37	0.23	0.10	135.0
Metabolites Only	0.68 (0.58, 0.79)	p=0.48	0.37	0.22	0.10	139.3
Vaginal Bleeding + Metabolites	0.76 (0.66, 0.85)	p=0.003	0.29	0.20	0.19	133.1



ROC Curve (Area)
VB=0.63 Metabolites=0.68 VB + Metabolites=0.76



Gelaye et al., 2016. Maternal Early Pregnancy Serum Metabolomics Profile and Abnormal Vaginal Bleeding as Predictors of Placental Abruption: PlosOne 11(6).

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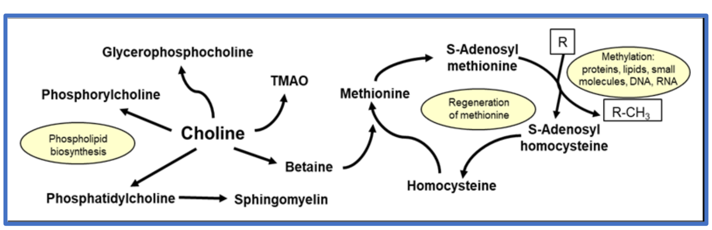
Potential Role of Choline in PA

- The probability of PA was increased with an increase in acylcarnitines and a decrease in phosphatidylcholine
- Low levels of choline have been associated with cognition and memory disorders, mood disorders, liver disease, pregnancy complications, fertility, and eye disease.
- While humans and other animals can synthesize choline, the amount produced is often not sufficient. Thus, choline must be obtained from the diet in the form of choline or choline phospholipids. Many factors influence the amount of dietary choline that individuals need, including several common genetic polymorphisms that have a substantial impact on choline



- It is possible that PA could be mitigated by increased choline early in pregnancy or for women of childbearing age.

Gelaye et al., 2016. Maternal Early Pregnancy Serum Metabolomics Profile and Abnormal Vaginal Bleeding as Predictors of Placental Abruption: PlosOne 11(6).

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The Concept of the Exposome in Precision Health

NIEHS HHEAR Program
U2CES0857

The **Concept of the Exposome in Precision Nutrition**: Exposome research is key to informing precision nutrition through understanding how exposures, and perturbations in endogenous metabolism, are linked to our genetics, and to our states of health and wellness.

ENVIRONMENT
Nutrients, dietary intake, supplements, water and beverage consumption, drugs, medications, tobacco and e-cigarette, alcohol, and chemicals in the household, the workplace, personal hygiene products, cosmetics, and in the environment.

Other factors
Genetics, polymorphisms, stress, family structure, income, education, geographic location, exercise, etc.

Metabotypes
Pathway
Perturbations

Mechanisms

Nutritional Targets
Pharmacological Targets

Inform

Health Outcomes
Obesity, diabetes, cancer, autism, addiction, cognitive delay, cognitive decline, pregnancy complications, infection, cardiovascular disease, respiratory, etc.

Intervention
- Diet
- Nutrient
- Microbial
- Exposure

Rushing BR, Thessen AE, Soliman GA, Ramesh A, Sumner SCJ. The Exposome and Nutritional Pharmacology and Toxicology: A New Application for Metabolomics. Exposome. *In Press.*

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Untargeted Analysis of the Internal Exposome

The NIH Common Fund

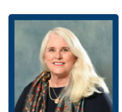
NIDDK NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

UHPLC-Q-Exactive HFx Orbitrap Mass Spectrometry
- 10,000- 40,000 features : urine, stool, plasma/serum, seminal plasma, blood spots, sweat, hair, cells, and tissue extracts

In-house Physical Standards Library - over 2,500 compounds
- Metabolites of the host system, microbial metabolism, exposures (e.g., nicotine, illicit drugs, environmentally relevant compounds), treatments (e.g., medications, supplements, natural products), and dietary intake (e.g., nutrients, vitamins and vitamin-like compounds, components of foods, food stabilizers, and polyphenols).

Progenesis Software
- Peak Picking and Deconvolution
- Match Peaks to the In-house Physical Standards Library
- Match Peaks to Public Databases (e.g., NIST, Metlin; HMDB)

Computational Exposome Framework - ADAP
- Pre-processing & extraction of analyte information via ADAP-BIG
- Statistical and artificial intelligence analysis - ADAP-ML
- Annotation of peaks via ADAP- KDB:
    - Metabolomics Workbench and Public Database
- Prediction of known unknown and unknown unknown peaks



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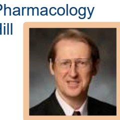

Timothy Fennell
RTI, Drug &
Chemical Metabolism

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Range of Analytes Detected (>10,000 signals)

- Uses ADAP software for preprocessing large scale metabolomics data.
- Rapid algorithms to match signals to the inhouse RT, Exact Mass, MS/MS library.
- Rapid Algorithms to match signals to 1.7M public spectra
- ADAP is launched at metabolomics workbench.org

Host and Microbial Metabolism

> 1,200 metabolites

Amino acids, carboxylic acids, biogenic amines, BCAA, polyamines, bases, nucleosides and nucleotides, carnitines, sugars, mono- and disaccharides, fatty acids, lipids, steroids, bile acids, hormones

FOOD Metabolome: 50 Sub-Classes
> 500 metabolites

- Phytoestrogens
- Aromatic ketones
- Benzoic acids
- Elagic acids
- Flavonoids
- Caffeoylquinic acids
- Catecholamines
- Coumarins

Hippuric acids
Hydroxytoluenes
Phenylamines
Stilbenes
Urolithins
Valerolactones
Xanthonoids

- **Drugs and Medications > 50**
- **Essential nutrients = 100s**
  - Choline Metabolism
  - Folate Metabolism
  - Vitamins, and vitamin-like compounds
  - Carnitines and acylcarnitines
  - Amino Acids
  - Omega 3 and Omega 6 Fatty Acids

ENVIRONMENTAL METABOLITES > 550

- PFAS
- Phenols
- Parabens
- Phthalates
- Tobacco Related
- VOCs
- PBDEs, PCBs

Sumner Lab, UNC-CH, NRI

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Healthy Biochemistry

- The simultaneous detection of metabolites is crucial because our healthy biochemistry depends on our essential nutrients which:
  - serve as cofactors for 100s of reactions of our biochemical pathways
  - are involved in transcription
  - serve as antioxidants and
  - are involved in many specialized functions.

- Different exposures including medications, alcohol, tobacco, supplements, environmentally relevant chemicals as well as your diet:
  - can affect the speed of your metabolism
  - and how your body absorbs or transports nutrients and vitamins.

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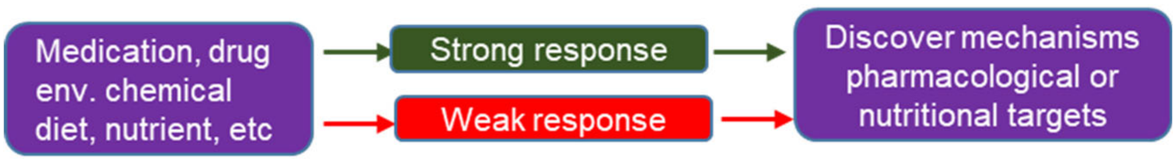
Responder vs Non-Responder

- Precision Medicine: some Individuals respond well to a drug treatment, while others do not have a positive response.
- Precision Nutrition: Individuals have different nutrient requirements, or different responses to nutrient intake.
- Precision Environmental Health: Individuals have difference response to exposures.



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Objective Biomarkers and Nutritional Intervention Opium Use Disorder (OUD)

- *Current Diagnosis*: Diagnosis of OUD is obtained through interview or questionnaires to determine if the patients meet the DSM-5 qualitative criteria.
  - Criteria include impaired control, social impairment, risky use, tolerance, and withdrawal.
  - Having at least two of these criteria meets the diagnoses of OUD with the number of criteria met as an indicator of the severity of the OUD.
- *The Need*: There is a need for objective biological markers that define OUD, and that provide insights into mechanisms for the development of intervention strategies.
  - Identification of gene candidates
  - Nutrients to mitigate against addiction
  - Chemical exposures
- Collaboration between the Sumner Lab (UNC-CH NRI), Dr. Reza Malekzadeh (Tehran University), Dr. Arash Etemadi (NCI), and Dr. Jonathan Pollock (NIDA)

Li, Ghanbari, Pathmasiri, et al., PMID: 33415121
Ghanbari, Li, et al., PMID: 33542199

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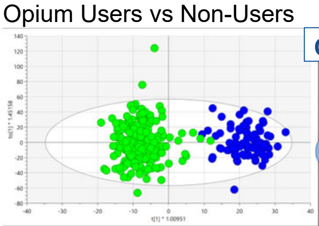
Untargeted Internal Exposome via UHPLC-HR-MS Defining Opium Use and OUD

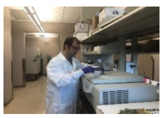
Opium Users vs Non-Users



R2Y=0.89, Q2=0.57

What metabolic perturbations are induced by opium exposure?

What are the metabolic markers that define an OUD positive diagnosis?



Reza Ghanbari, PhD
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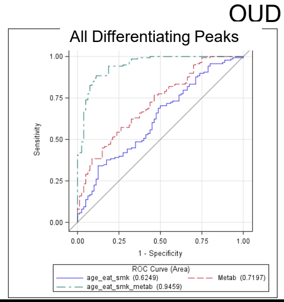
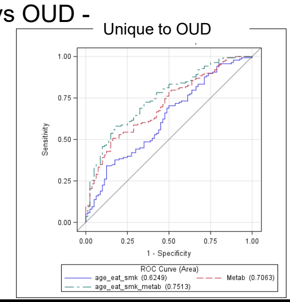
OUD + vs OUD -





Li, Ghanbari, Pathmasiri, et al., PMID: 33415121
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Opium Users vs Nonusers

Li, Ghanbari, Pathmasiri, et al., PMID: 33415121
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Opium Metabolites
Codeine
Morphine
3- and 6- glucuronides
(p-value as low as E-40)

Tobacco Related
Anatabine
Cotinine
Hydroxycotinine
Nicotine
Nicotine-N-oxide
(p-value as low as E-15)

expected based on subject characteristics

Endogenous

Perturbations in
- **Neurotransmitter metabolism**
- **Krebs cycle metabolism**
- **One carbon metabolism**
- **Glucogenesis**
- **Lipid metabolism, and**
- **Vitamin and Vitamin-Like Compounds**

Environmentally Relevant Metabolites
- Phthalates that could be derived from plastics/tubing in opium use (p-value as low as E-8)
  - Implicated in obesity, diabetes, learning, cognition
- Metabolites that are known to be derived from parent compounds (e.g., acrylamide) that are formed in curing and combustion of plants (p-value as low as E-21)
  - Cancer rates are higher in this cohort of opium users and may be due to the high levels of toxins that can be produced on curing or combustion of plant matter.

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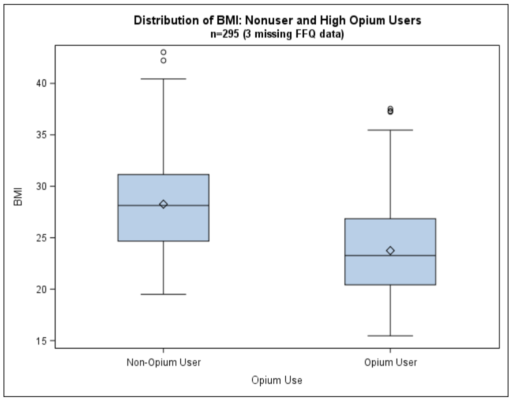
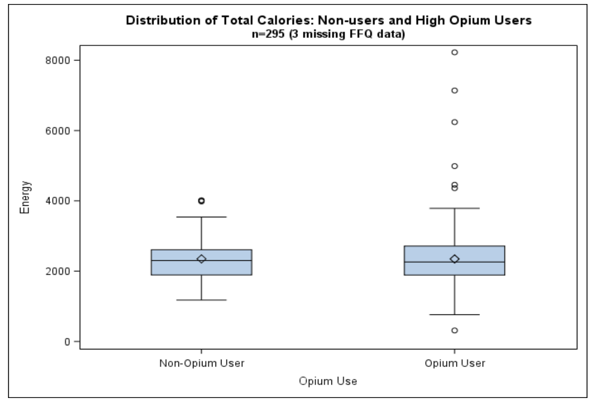
BMI and Total Calories of Opium Users and Non-Users





Sumner Lab Unpublished Results

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Perturbations in Neurotransmitters

Opium User vs Non-Opium User

- A general metabolic disruption in the neurotransmitter pathway. e.g, tyrosine, tryptophan, serotonin, kynurenine, phenylalanine, etc.
- Perturbations in B2 and B6

Tyrosine $\xrightarrow{B6}$ L-Dopa $\xrightarrow{B6}$ Dopamine

Tryptophan $\xrightarrow{B6}$ 5-HTP $\xrightarrow{B6}$ Serotonin

Tryptophan $\xrightarrow{B6}$ Kynurenine $\xrightarrow{B2}$ 3-hydroxy Kynurenine

OUD Positive Opium User vs OUD Negative Opium User

- Four metabolites in the neurotransmitter pathway were significantly different between opium users diagnosed as OUD positive and opium users diagnosed as OUD negative.

Li, Ghanbari, Pathmasiri, et al., PMID: 33415121
Ghanbari, Li, et al., PMID: 33542199

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Perturbations in Sugar Metabolism and Krebs Cycle

Opium User vs Non-Opium User
- General disruption in sugar – e.g., inositol, fucose, sucrose, manose, glucose
- General disruption in Krebs cycle – e.g., citrate, cis-aconitate, succinate, malate

Pyruvate $\xrightarrow{\text{B1, B2, B3, B5}}$ Acetyl CoA

alpha-Ketobutyrate $\xrightarrow{\text{B1, B2, B3, B5, B7, B12}}$ Succinyl Co-A

alpha-Ketoglutarate $\xrightarrow{\text{B1, B2, B3, B5}}$ Succinyl Co-A

Krebs NADH, FADH2 → **Electron Transport Chain** **B2, B3, B5** → ATP

OUD Positive Opium User vs OUD Negative Opium User
- Several metabolites in sugar and Krebs cycle metabolism differed between opium users diagnosed as OUD positive and opium users diagnosed as OUD negative
  - malate, glucose, fucose, sucrose, manose

Li, Ghanbari, Pathmasiri, et al., PMID: 33415121
Ghanbari, Li, et al., PMID: 33542199

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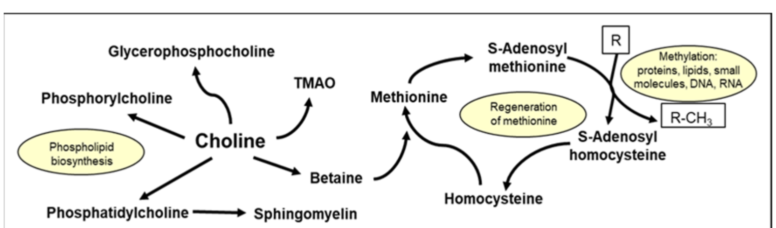
Perturbations in One Carbon Metabolism

Opium User vs Non-Opium User
- General disruption in one carbon metabolism – e.g., choline, phosphorylcholine, betaine, methionine, threonine, s-adenosyl methionine, s-adenosyl homocysteine, dimethyl glycine, taurine



- Low levels of choline are associated with cognition and memory disorders, mood disorders, liver disease, pregnancy complications, and eye disease.
- Choline is metabolism to acetyl-CoA, a precursor to neurotransmitters.

OUD Positive Opium User vs OUD Negative Opium User
- Phosphorylcholine, serine, and sarcosine decreased in OUD positive vs OUD negative Opium Users

Li, Ghanbari, Pathmasiri, et al., PMID: 33415121.
Ghanbari, Li, et al., PMID: 33542199.

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Opium Use and OUD

- **Opium Users have significant metabolic perturbations compared with nonusers**.
  - A nutrient cocktail composed of vitamins, vitamin-like compounds, fatty acids, sugars, etc. may find use in mitigating against addiction.
  - A next step is to test a combination cocktail to mitigate against addiction.
- **Metabolites were identified or annotated that are unique to an OUD positive diagnosis**.
  - Validation of a metabolite signature may find clinical use to as an objective biological maker, since current diagnosis relies on the DSM-5 questionnaire.
- **Exposures to environmentally relevant compounds** such as phthalates or metabolites derived from plant combustion **may exacerbate the impact opium use**, and be related to the high incidences of cancers, CVD, and diabetes in this cohort.

Li, Ghanbari, Pathmasiri, et al., PMID: 33415121.
Ghanbari, Li, et al., PMID: 33542199.

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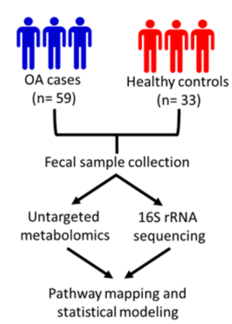
Metabolomics, Osteoarthritis (OA), and Nutrient Intervention

- Sumner Lab collaboration with UNCs Dr. Richard Loeser and Dr. Amanda Nelson
- Conducted **16SrRNA** sequencing and **UHPLC-HR-MS Metabolomics**
- Increased excretion of products of proteolysis (small peptides and indoles) in OA vs non-OA – role for intestinal permeability.
- Perturbations in **leukotriene metabolism** - related to precursor poly-unsaturated fatty acids – like **OMEGA 3**
- Perturbations in fatty acid synthesis, and in tryptophan metabolism
- Decreased **SCFA**s (propionate) in OA vs non-OA
  - Propionate is produced by colon microbes (e.g., clostridia)
  - Related to the amount of **dietary fiber**
  - Lower clostridia *was* associated with OA in our microbiome data.
    - No differences in gut microbiota when analyzed without the metabolomics data (Loeser et al, (2022) PMCID: PMC8795472)
  - SCFAs regulate energy utilization (FA metabolism) and inflammation
  - SCFAs are used to mitigate inflammation
- Decrease in N-Acetyl-D-**glucosamine**, a natural compound in cartilage
  – Used as a supplement for joint pain, inflammation, and Inflammatory bowel disease. Some studies have shown that this compound protects the lining of the stomach and gut.



Rushing BR et al., (2022) PMCID: PMC8712415.

OMEGA-3/OMEGA-6
Fiber/Protein
Glucosamine, SCFA

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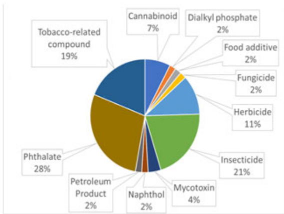
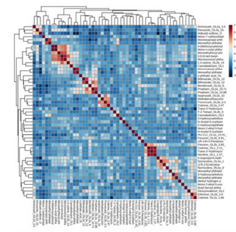
Environmental Relevance and OA



53 environmental compounds, in these stool samples, across 11 classes, matched to a physical standards library.



Correlation analysis of metabolites showed connectivity between environmentally relevant metabolites, inflammation markers, and endogenous and microbial metabolism with gut microbes. As an example: a peak that matches to an insecticide correlated with

- Herbicide – indicating potential co-exposure
- Polyphenolic compound hydroxycinnamic acid abundant in fruits and vegetables – potential source of exposure
- Gut microbes from a phylum which produces SCFAs – consistent with observed decrease in SCFAs
- Neurotransmitter related metabolites – products of tryptophan formed in the gut
- Several metabolites associated with mitochondrial fatty acid beta oxidation

Sumner Lab Unpublished Results

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Accessing Metabolomics Data

- Metabolomics Workbench
  - NIH-Funded Data Repository for Metabolomics Data (Untargeted and Targeted Data)
    - Includes processed data and raw spectral data
    - Over 2,000 studies are publicly available
    - https://www.metabolomicsworkbench.org/
- Example Large-Scale NIH Consortia that are Including Metabolomics Data
  - Nutrition for Precision Health (NPH)
    - All of Us Workbench: https://www.researchallofus.org/data-tools/workbench/
  - Molecular Transducers of Physical Activity Consortium (MoTrPAC)
    - MoTrPAC Data Hub: https://motrpac-data.org/
  - Human Health Exposure Analysis Resource (HHEAR)
    - HHEAR Data Center: https://hhearprogram.org/data-center
  - Environmental Influences on Child Health Outcomes (ECHO)
    - ECHO Data Center: https://publichealth.jhu.edu/echo
  - Trans-Omics for Precision Medicine (TOPMed)
    - Data Access: https://topmed.nhlbi.nih.gov/topmed-data-access-scientific-community

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Public Databases for Metabolite Annotations

Public databases for metabolite annotation include:

- Human Metabolome Database (HMDB)
  - Annotations for over 220,000 metabolites
  - https://hmdb.ca/
- FoodDB
  - https://foodb.ca/
- Phenol-Explorer
  - Annotations for over 500 polyphenols
  - http://phenol-explorer.eu/
- PhytoHub
  - Includes in silico predicted metabolites
  - https://phytohub.eu/
- Metabolomics Workbench
  - https://www.metabolomicsworkbench.org/

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Publicly Available Data Analysis Resources

- Examples of publicly available data analysis resources:
- MetaboAnalyst (https://www.metaboanalyst.ca/) is accessible through a web interface or an R package and includes a variety of tools such as:
  - Statistical and machine learning algorithms
  - Pathway analysis
    - Peaks to Pathways module utilizes the Mummichog algorithm which incorporates machine learning and utilizes the retention time and mass of the peak rather than the metabolite name
    - Integration of gene and metabolite data through joint pathway analysis
- Metabolomics Workbench (https://www.metabolomicsworkbench.org) data analysis tools can be accessed from Workbench or through Jupyter Notebooks
  - Analysis of data uploaded to Metabolomics Workbench can be analyzed within Workbench and does not require downloading the data
  - Data analysis tools include statistical and machine learning algorithms and pathway analysis

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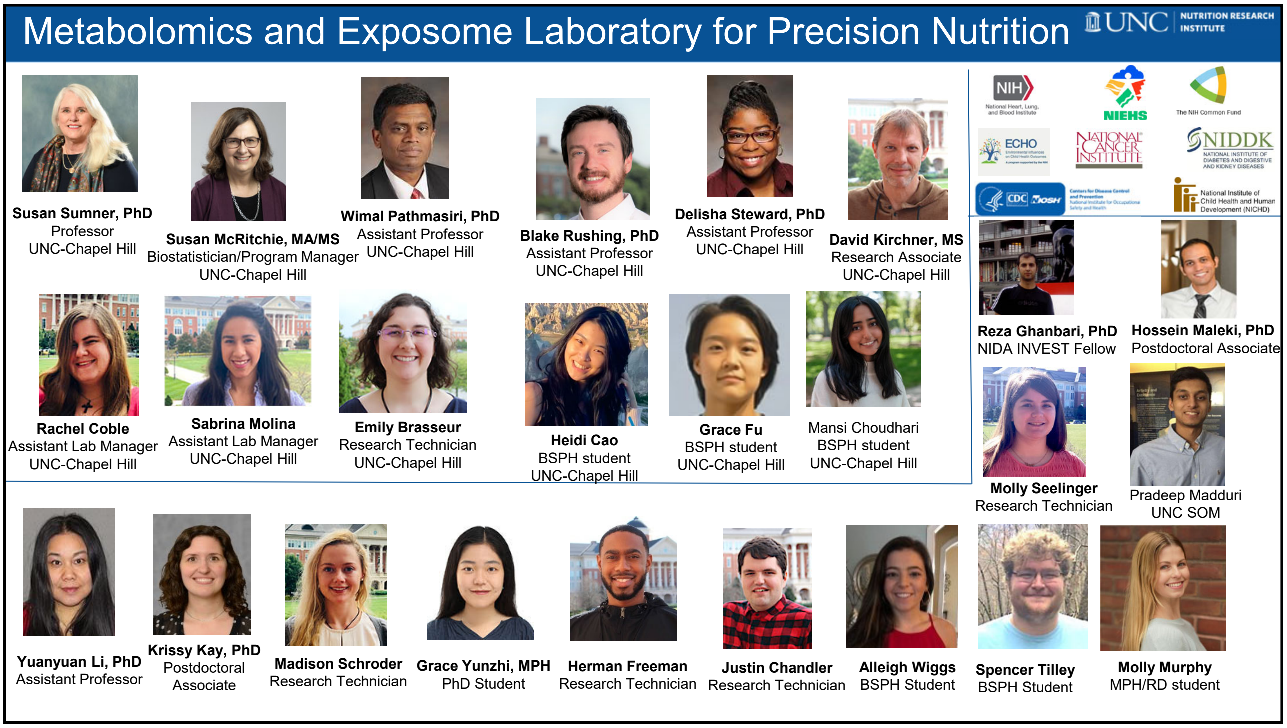

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Healthy Biochemistry

- **Vitamins assist in hundreds of reactions of biochemical pathways of host metabolism**
  - Vitamins **B_1** (thiamin, TPP), **B_2** (riboflavin, FAD), **B_3** (niacin, NAD^+), and **B_5** (pantothenic acid, CoA) are involved in the conversion of pyruvate to acetyl-CoA, which feeds the **Krebs cycle**.
  - **B2** Riboflavin and **B3** Niacin work together in the **Electron Transport Chain to produce ATP**.
  - Vitamin **B5**, or pantothenic acid, ***IS* part of the structure of CoA**, needed to make **acetyl-CoA, succinyl-CoA, and fatty acyl-CoA** and is needed for very important pathways.
  - **B2** Riboflavin is needed for **beta-oxidation of fatty acids**, and deamination of AAs.
  - **B7** Biotin is involved in conversion of pyruvate to **oxaloacetate**, in **fatty acid** elongation, in production of acetoacetate, and the breakdown of AAs.
  - **B6** Pyridoxine/al/amine are involved in **heme synthesis, glucogenesis, and lipid metabolism**.
  - **B9** Folate accepts and donates one carbon group (**methylation**), and is involved in **synthesis of purines/pyrimidine**, and conversion of homocysteine to methionine.
  - **B12** Cobalamin is a cofactor for **methionine synthase** and L-**methylmalonyl-CoA mutase**.
  - **Vitamin C** is involved in recycling oxidized vitamin E, reducing nonheme iron (**$Fe^{3+} \rightarrow Fe^{2+}$**) in plant foods (improves absorption in the small intestine), and **converting Vitamin D_3 to its active** form, calcitriol.
- **Vitamins are important in transcription (Vitamin A, D), as antioxidants (Vitamin E, C), and formation of Gla domains (Vitamin K) of proteins.**
- **Fe and minerals: Ca, Zn, Na/K, Mg, etc are co-factors for 100s of reactions of host metabolism, and involved in hormonal regulation, specialized membrane pumps, muscle relaxation and contraction, bone structure and formation.**

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Absorption, Metabolisms, Disposition, and Transport

- Medications or other exposures can speed up or slow down the metabolism of nutrients/vitamins or block their transport.
  - e.g, Orlistat is an anti-obesity drug that inhibits gastric and pancreatic lipases and can interfere with digestion of TAGs.
- Aging decreases acidity in stomach: ~ 30% of older adults have atrophic gastritis that can interfere with absorption of some nutrients.
- Inflammation in ileum area
  - IBD, celiac or Crohn's disease or dietary intolerances
- Surgery on stomach, removal of intestinal sections, or removal of gall bladder.
- Liver injury
  - e.g., bile acids are synthesized in the liver and concentrated in the gallbladder. Bile is needed to emulsify lipids and provides access for lipases.
- Exposures (e.g., alcohol, tobacco, cannabis, illicit drugs, supplements, natural products, environmentally relevant chemicals, food additives and impurities).
- Dietary constituents (e.g., the amount and type of fat can increase or decrease intestinal Ca absorption).

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