

Longitudinal big data approaches for health, disease, and space travel



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Stanford University

Co-chair, NASA GeneLab Animal AWG



Health is a product of genome and exposome

Genome



Exercise



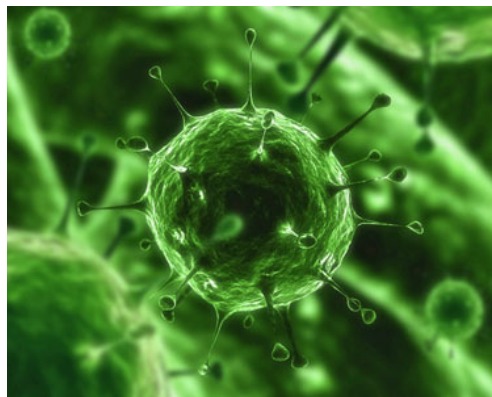
Health



Disease



Pathogens



Food



Stress



Health is a product of genome and exposome

Genome



Exercise



Health



Disease



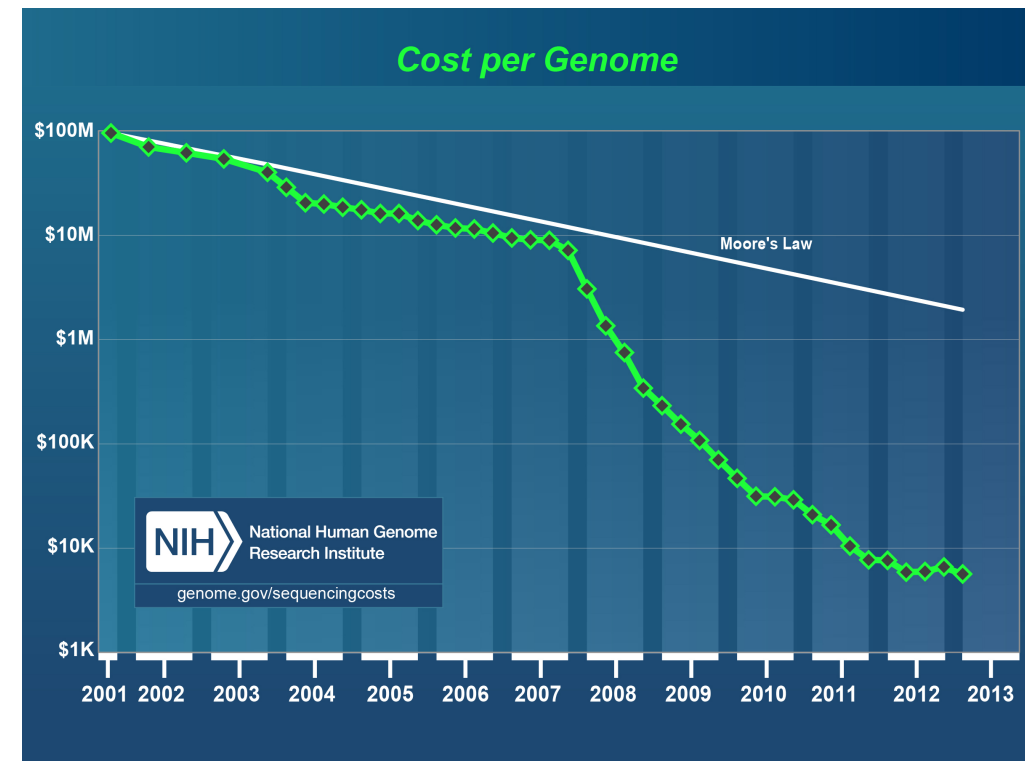
Understanding personal data = personal health

Drivers of big data

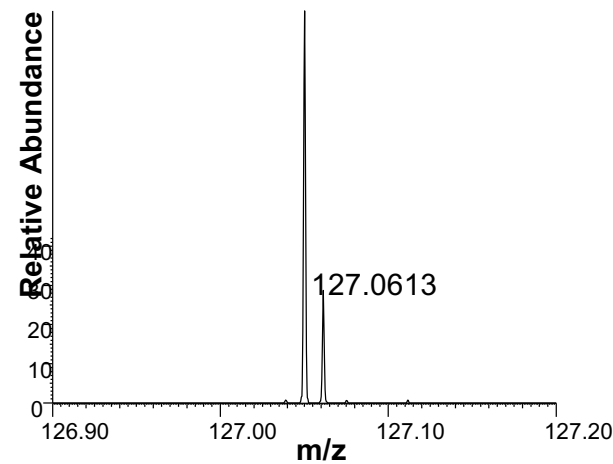
1) DNA Sequencing



Human Genome Cost <\$2K



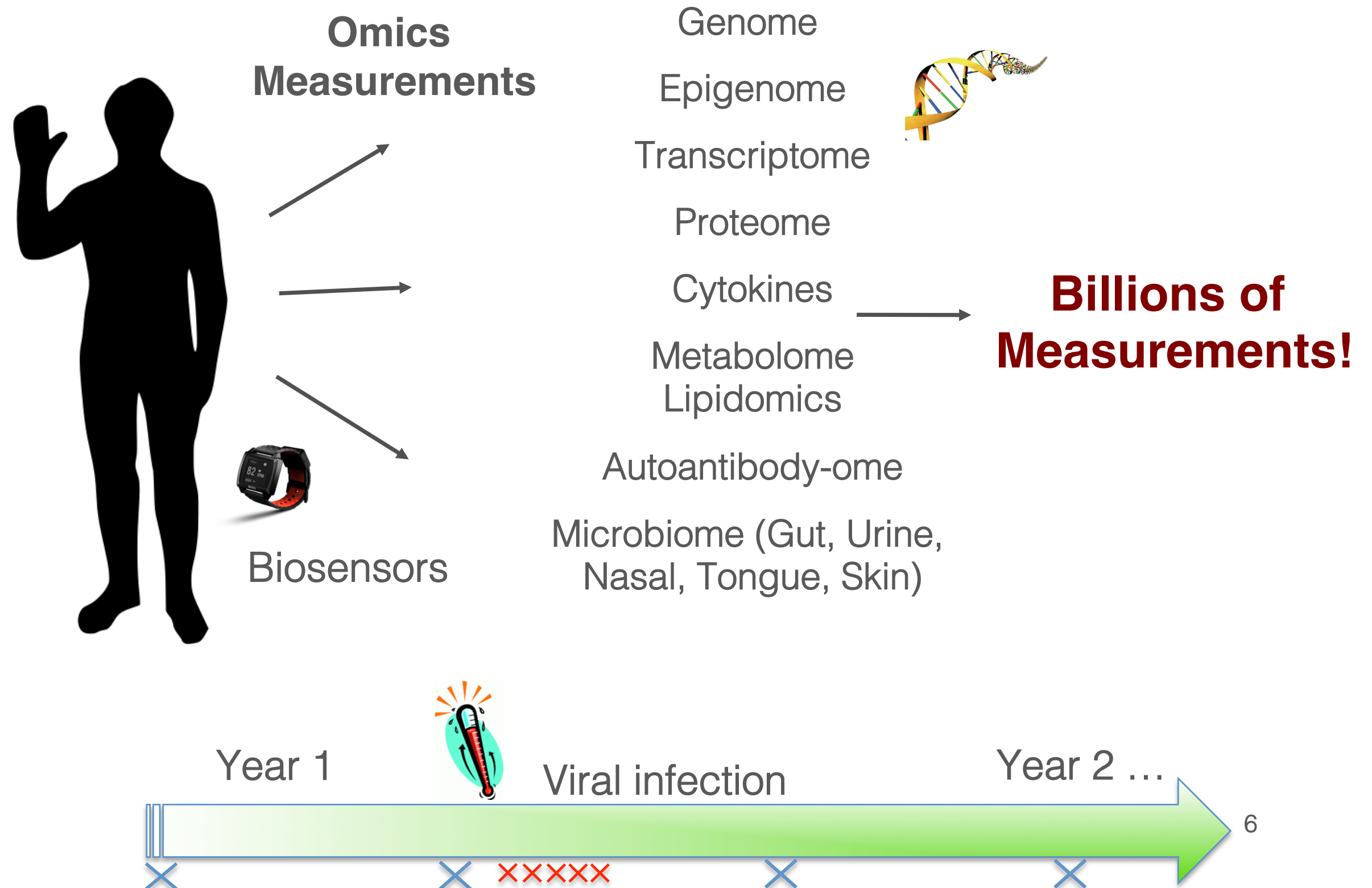
2) Mass Spectrometry



3) Wearables

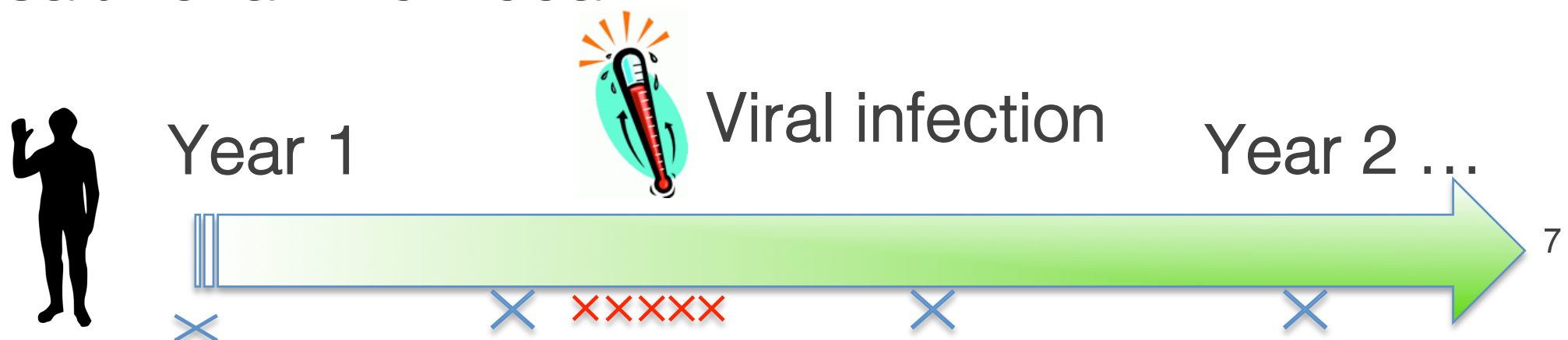


Personalized 'Omics Profiling

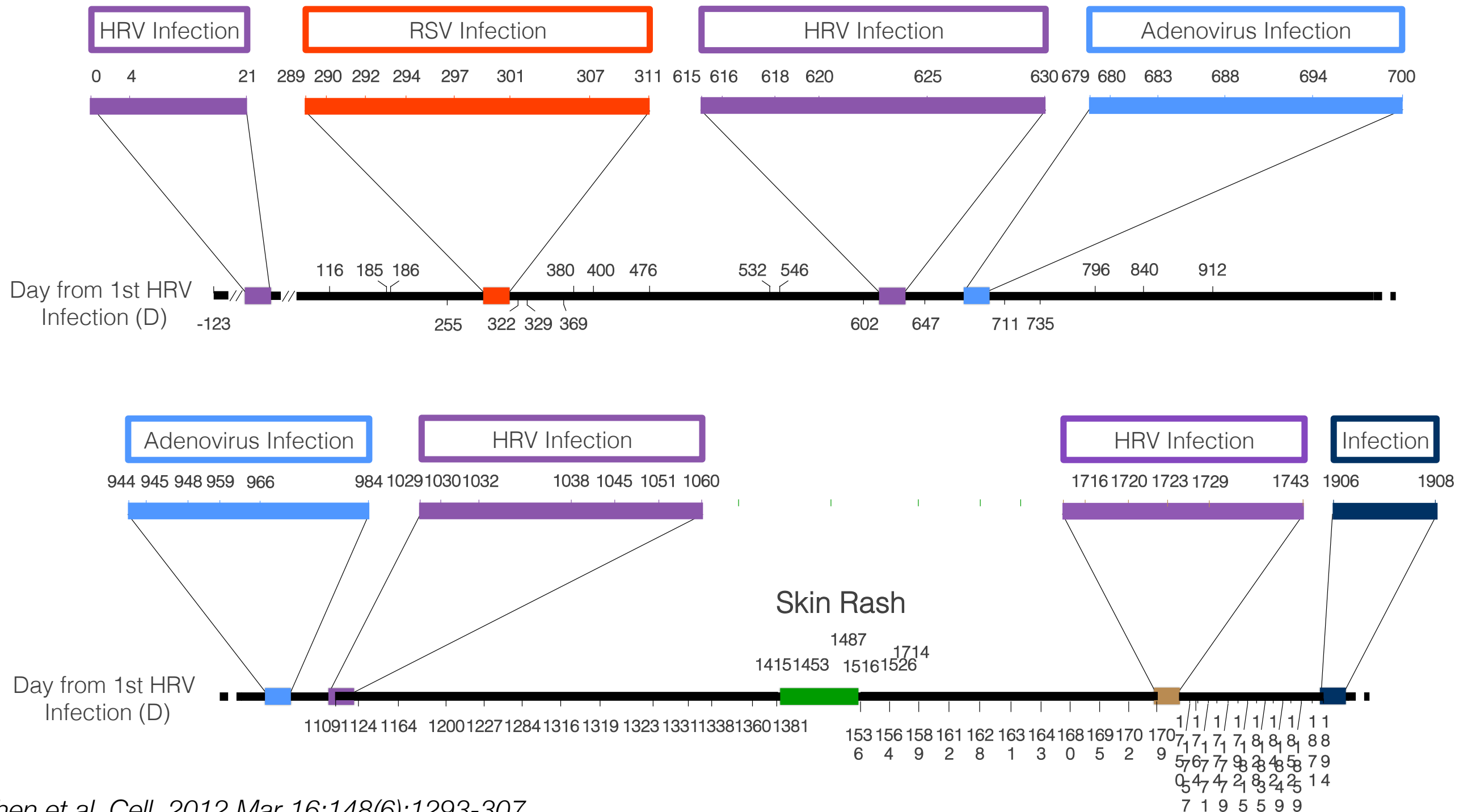


General Goals

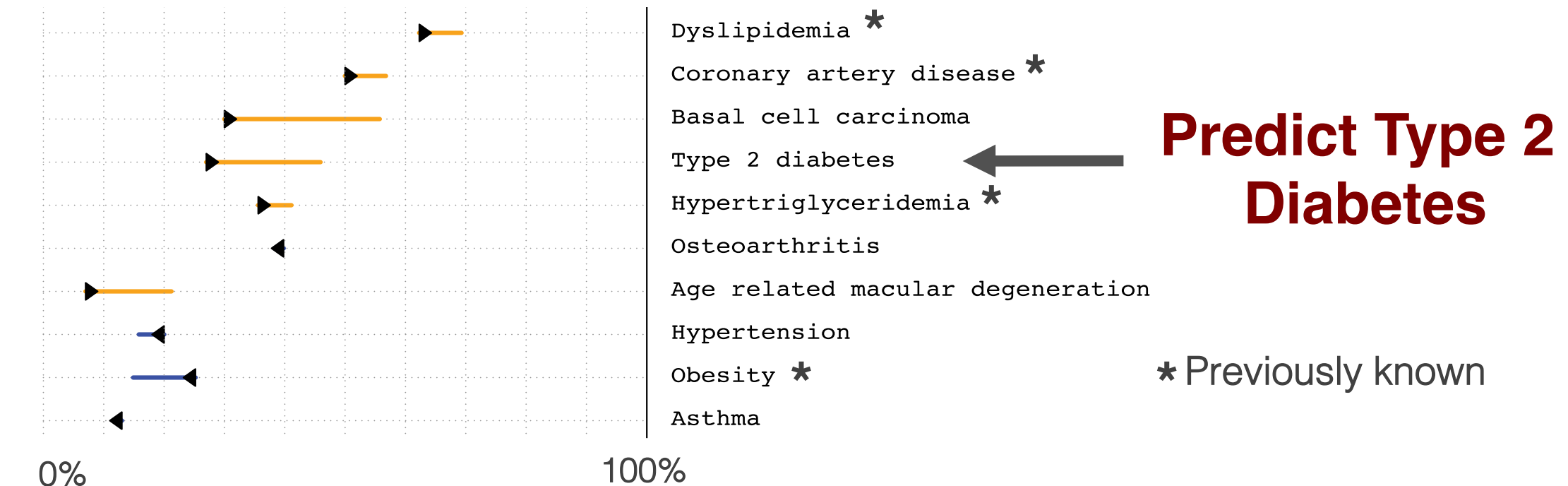
- 1) Understand how individuals change over time and during periods of health and disease at high resolution
- 2) Understand how different “omes” (microbiome, metabolome, proteome, genome) relate to one another dynamically
- 3) Understand how individual responses are similar and differ from one another when faced with specific perturbations
- 4) Identify factors that can affect and help manage the health of an individual



87 months; > 250 time points; 10 viral infections

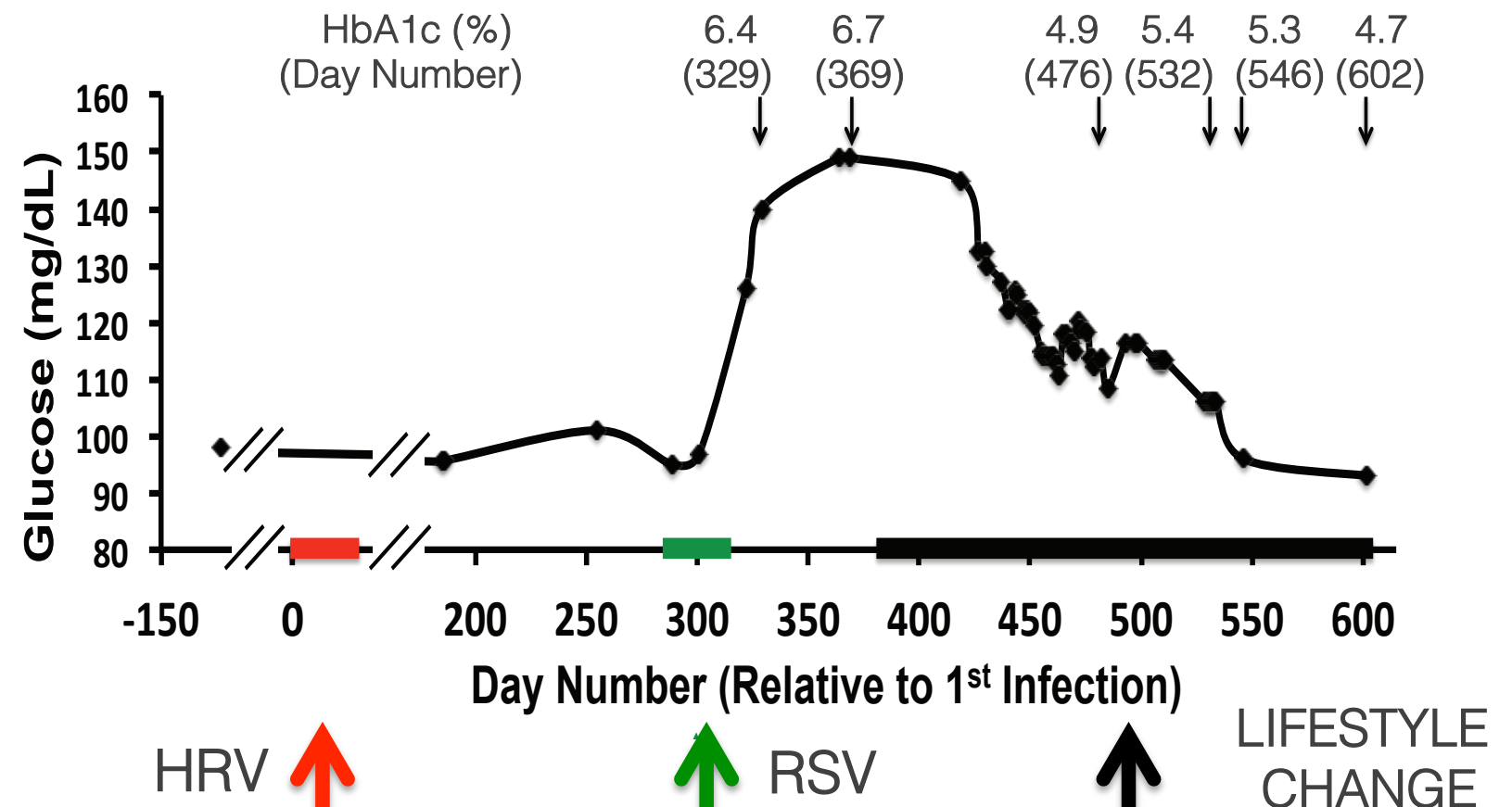


Genome Sequence (Illumina, Complete Genomics)

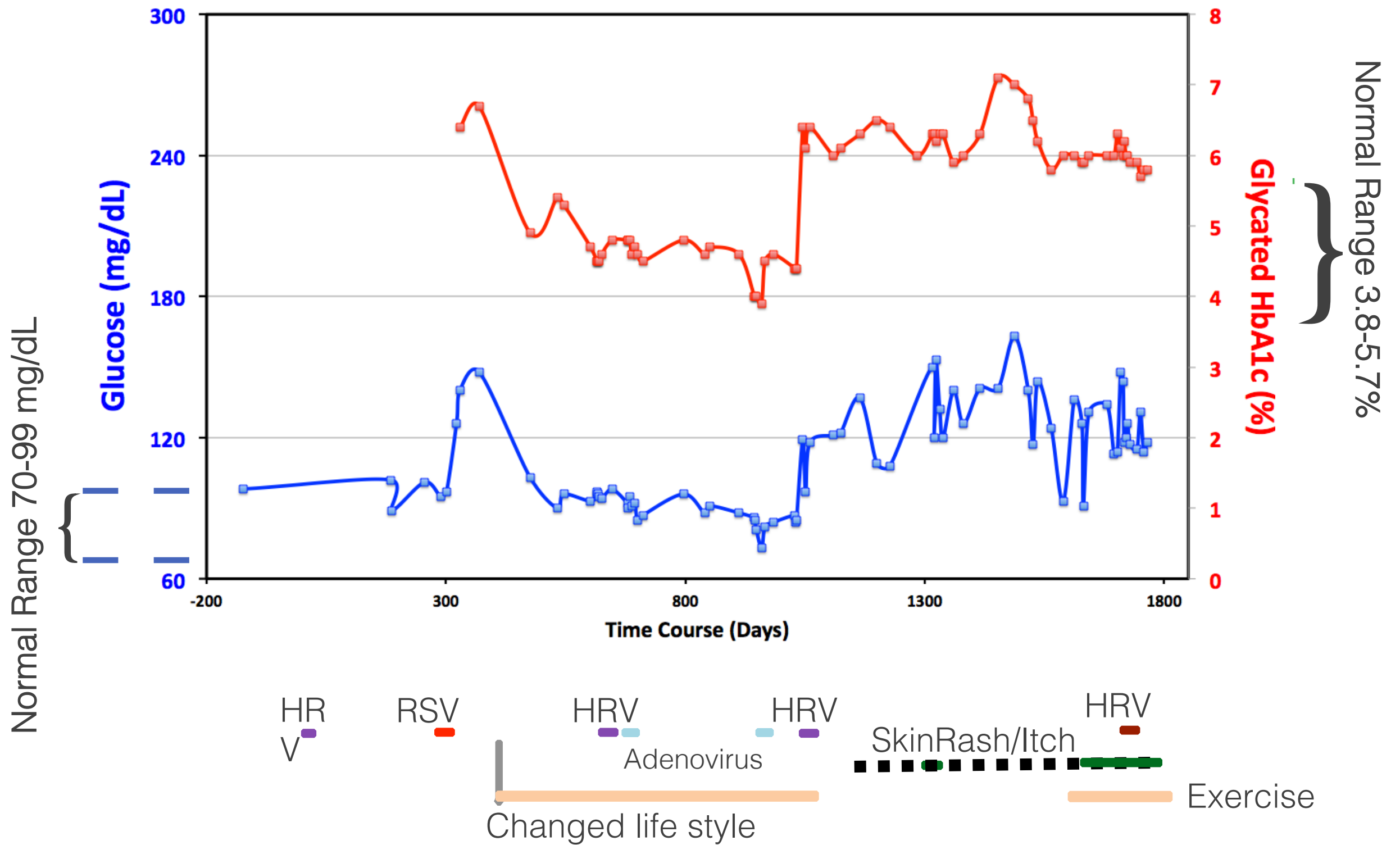


Rong Chen
and Atul Butte

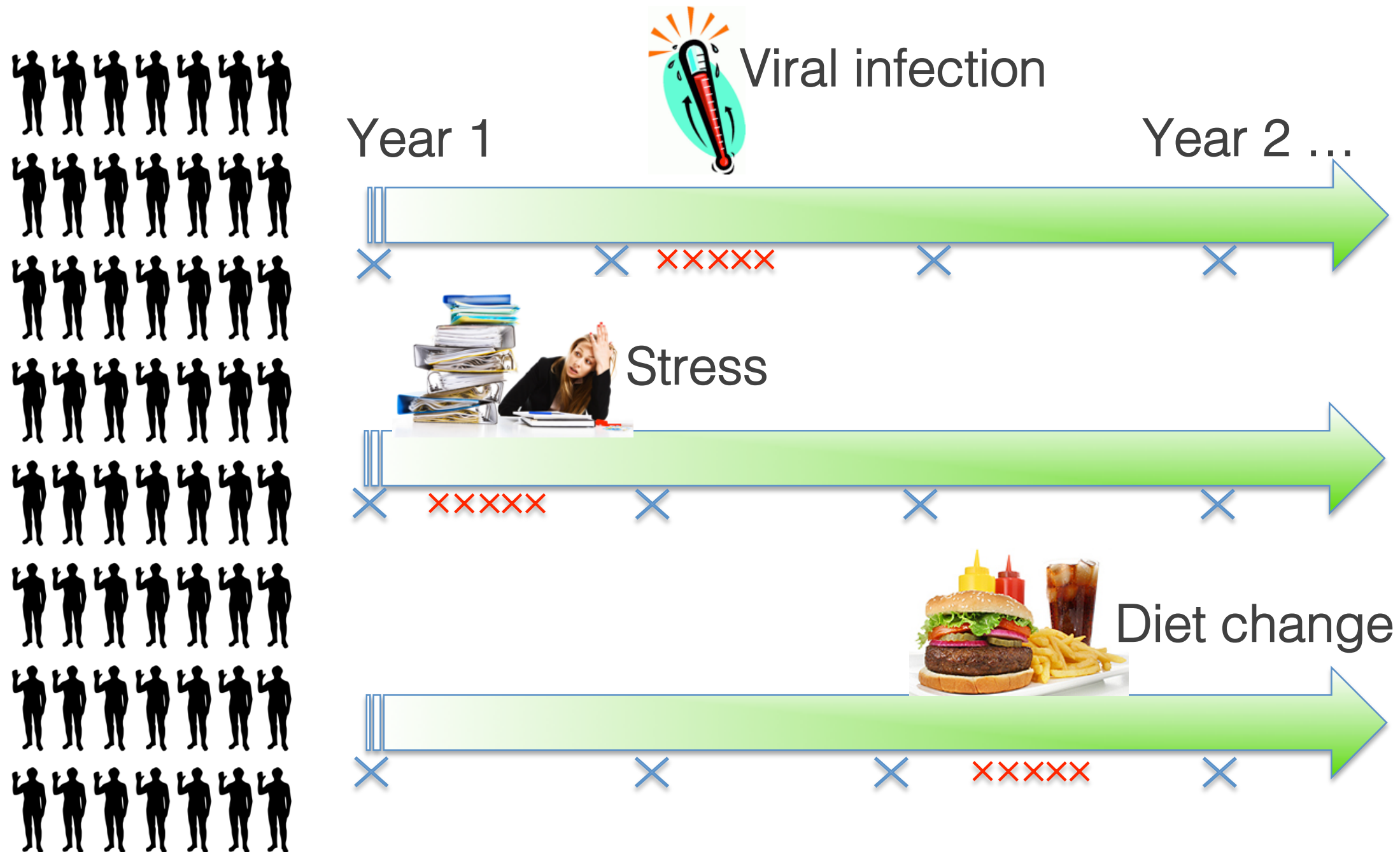
Glucose levels



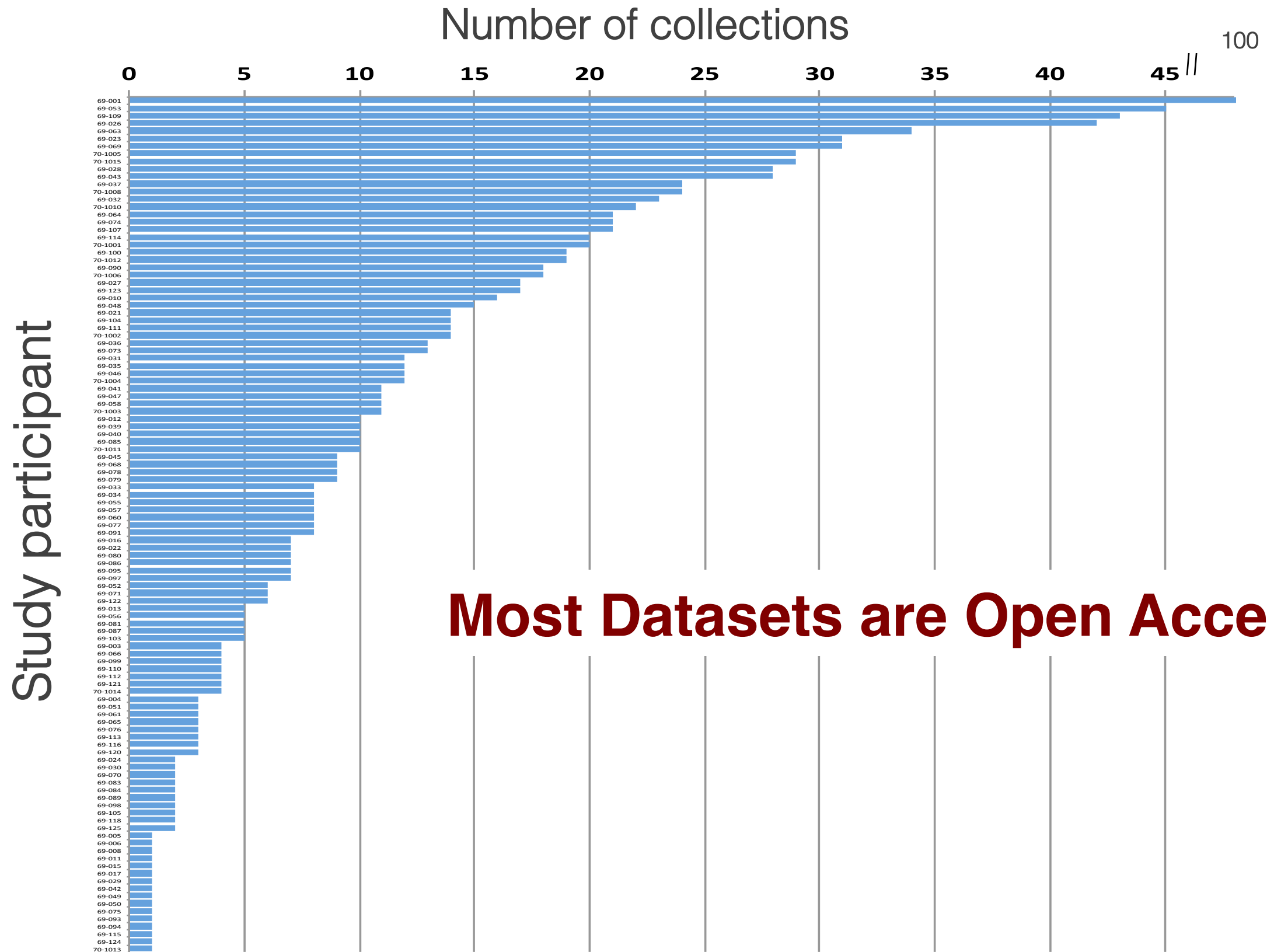
Extended timeline



Longitudinal Profiling of 100 individuals (prediabetics and healthy) over periods of health, stress, and disease



>2000 collections thus far



Integrative Personal Omics Profiles during Periods of Weight Gain and Loss

Brian D. Piening,^{1,16} Wenyu Zhou,^{1,16} Kévin Contrepois,^{1,16} Hannes Röst,^{1,16} Gucci Jijuan Gu Urban,^{1,10} Tejaswini Mishra,¹ Blake M. Hanson,² Eddy J. Bautista,^{2,15} Shana Leopold,² Christine Y. Yeh,^{1,4,5,11} Daniel Spakowicz,² Imon Banerjee,¹² Cynthia Chen,¹² Kimberly Kukurba,¹ Dalia Perelman,³ Colleen Craig,³ Elizabeth Colbert,³ Denis Salins,¹ Shannon Rego,¹ Sunjae Lee,⁷ Cheng Zhang,⁷ Jessica Wheeler,¹ M. Reza Sailani,¹ Liang Liang,¹ Charles Abbott,¹ Mark Gerstein,^{6,13,14} Adil Mardinoglu,^{7,8} Ulf Smith,⁹ Daniel L. Rubin,¹² Sharon Pittner,^{4,5} Erica Sodergren,² Tracey L. McLaughlin,^{3,16,*} George M. Weinstock,^{2,16,*} and Michael P. Snyder^{1,16,17,*}

Longitudinal multi-omics of host-microbe dynamics in prediabetes

Wenyu Zhou^{1,12}, M. Reza Sailani^{1,12}, Kévin Contrepois^{1,12}, Yanjiao Zhou^{2,3,12}, Sara Ahadi^{1,12}, Shana R. Leopold², Martin J. Zhang⁴, Varsha Rao¹, Monika Avina¹, Tejaswini Mishra¹, Jethro Johnson², Brittany Lee-McMullen¹, Songjie Chen¹, Ahmed A. Metwally¹, Thi Dong Binh Tran², Hoan Nguyen², Xin Zhou², Brandon Albright², Bo-Young Hong², Lauren Petersen², Eddy Bautista², Blake Hanson², Lei Chen², Daniel Spakowicz², Amir Bahmani⁵, Denis Salins¹, Benjamin Leopold², Melanie Ashland¹, Orit Dagan-Rosenfeld¹, Shannon Rego¹, Patricia Limcaoco¹, Elizabeth Colbert⁶, Candice Allister⁶, Dalia Perelman⁶, Colleen Craig⁶, Eric Wei^{1,5}, Hassan Chaib^{1,5,7}, Daniel Hornburg¹, Jessilyn Dunn¹, Liang Liang¹, Sophia Miryam Schüssler-Fiorenza Rose^{8,9}, Kim Kukurba¹, Brian Piening¹⁰, Hannes Röst¹¹, David Tse⁴, Tracey McLaughlin^{6,7}, Erica Sodergren², George M. Weinstock^{2,*} & Michael Snyder^{1,5,7,*}



RESEARCH ARTICLE

Glucotypes reveal new patterns of glucose dysregulation

Heather Hall^{1,2*}, Dalia Perelman^{2*}, Alessandra Breschi^{2*}, Patricia Limcaoco², Ryan Kellogg², Tracey McLaughlin³, Michael Snyder^{2,*}

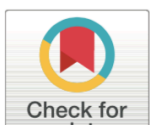


RESEARCH ARTICLE

Digital Health: Tracking Physiomes and Activity Using Wearable Biosensors Reveals Useful Health-Related Information

Xiao Li^{1*}, Jessilyn Dunn^{1,2*}, Denis Salins^{1*}, Gao Zhou¹, Wenyu Zhou¹, Sophia Miryam Schüssler-Fiorenza Rose^{3,4}, Dalia Perelman⁵, Elizabeth Colbert³, Ryan Runge¹, Shannon Rego³, Ria Sonecha¹, Somalee Datta¹, Tracey McLaughlin⁵, Michael P. Snyder^{1,*}

1 Department of Genetics, Stanford University School of Medicine, Stanford, California, United States of America, **2** Mobilize Center, Stanford University, Palo Alto, California, United States of America, **3** Spinal Cord Injury Service, Veterans Affairs Palo Alto Health Care System, Palo Alto, California, United States of America, **4** Department of Neurosurgery, Stanford University School of Medicine, Stanford, California, United States of America, **5** Division of Endocrinology, Stanford University School of Medicine, Stanford, California, United States of America



A longitudinal big data approach for precision health

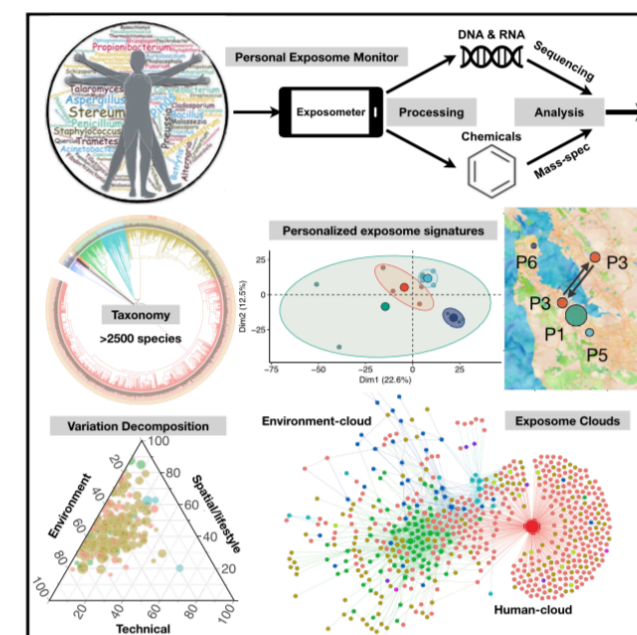
Sophia Miryam Schüssler-Fiorenza Rose^{1,2,3,16}, Kévin Contrepois^{1,16}, Kegan J. Moneghetti^{4,5,6}, Wenyu Zhou¹, Tejaswini Mishra¹, Samson Mataraso^{7,8}, Orit Dagan-Rosenfeld¹, Ariel B. Ganz¹, Jessilyn Dunn^{1,9}, Daniel Hornburg¹, Shannon Rego¹, Dalia Perelman¹, Sara Ahadi¹, M. Reza Sailani¹, Yanjiao Zhou^{10,11}, Shana R. Leopold¹⁰, Jieming Chen¹², Melanie Ashland¹, Jeffrey W. Christle^{4,5}, Monika Avina¹, Patricia Limcaoco¹, Camilo Ruiz¹³, Marilyn Tan¹⁴, Atul J. Butte¹², George M. Weinstock¹⁰, George M. Slavich¹⁵, Erica Sodergren¹⁰, Tracey L. McLaughlin¹⁴, Francois Haddad^{4,5*} and Michael P. Snyder^{1,4*}

Resource



Dynamic Human Environmental Exposome Revealed by Longitudinal Personal Monitoring

Graphical Abstract



Authors

Chao Jiang, Xin Wang, Xiyan Li, Jingga Inlora, Ting Wang, Qing Liu, Michael Snyder

Correspondence

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In Brief

Tracking personal exposure to airborne biological and chemical agents enables construction of an interaction network linking individuals, their geographic locations, and environmental factors, which could have broad implications for human health.

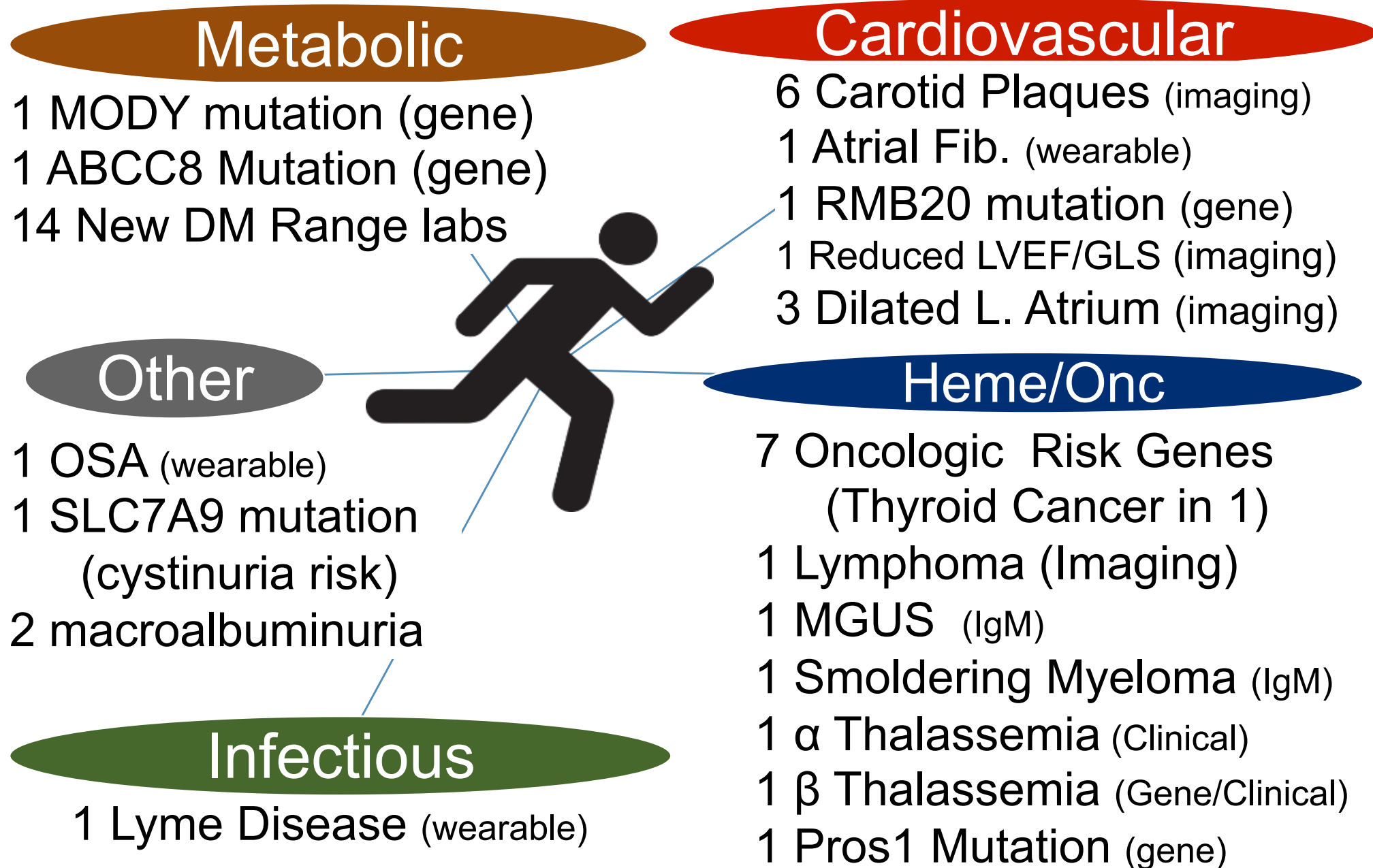
Letter | Published: 13 January 2020

Personal aging markers and ageotypes revealed by deep longitudinal profiling

Sara Ahadi, Wenyu Zhou, Sophia Miryam Schüssler-Fiorenza Rose, M. Reza Sailani, Kévin Contrepois, Monika Avina, Melanie Ashland, Anne Brunet & Michael Snyder ✉

Nature Medicine 26, 83–90(2020) | Cite this article

All discoveries



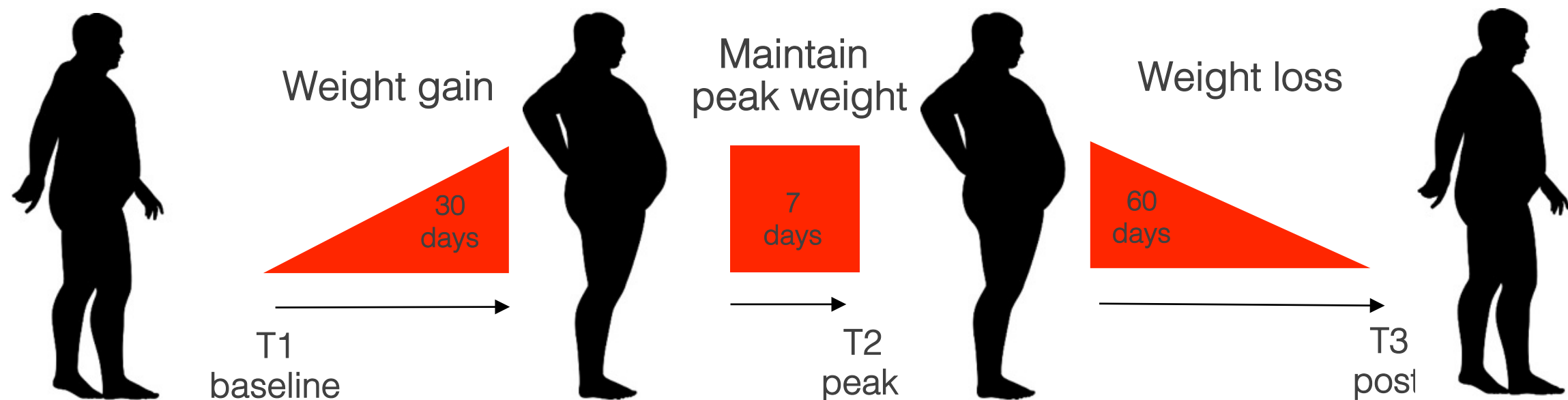
Genome Sequencing - first 70 people

- Twelve have important pathogenic mutations:
 - SHBD (2X): high freq. of neuroendocrine tumors
 - PROC: Affects coagulation
 - HNF1A: MODY mutation
 - ABCC8: Hyperinsulinemic hypoglycemia
 - MUTYH: Colon cancer
 - SLC7A9: Cystinuria
 - RBM20: Dilated cardiomyopathy
 - CHEK2: Breast cancer
 - APC (2X): Colon cancer
 - BRCA1: Breast & ovarian cancer



All have reportable carrier mutations and/or pharmacogenetic variants

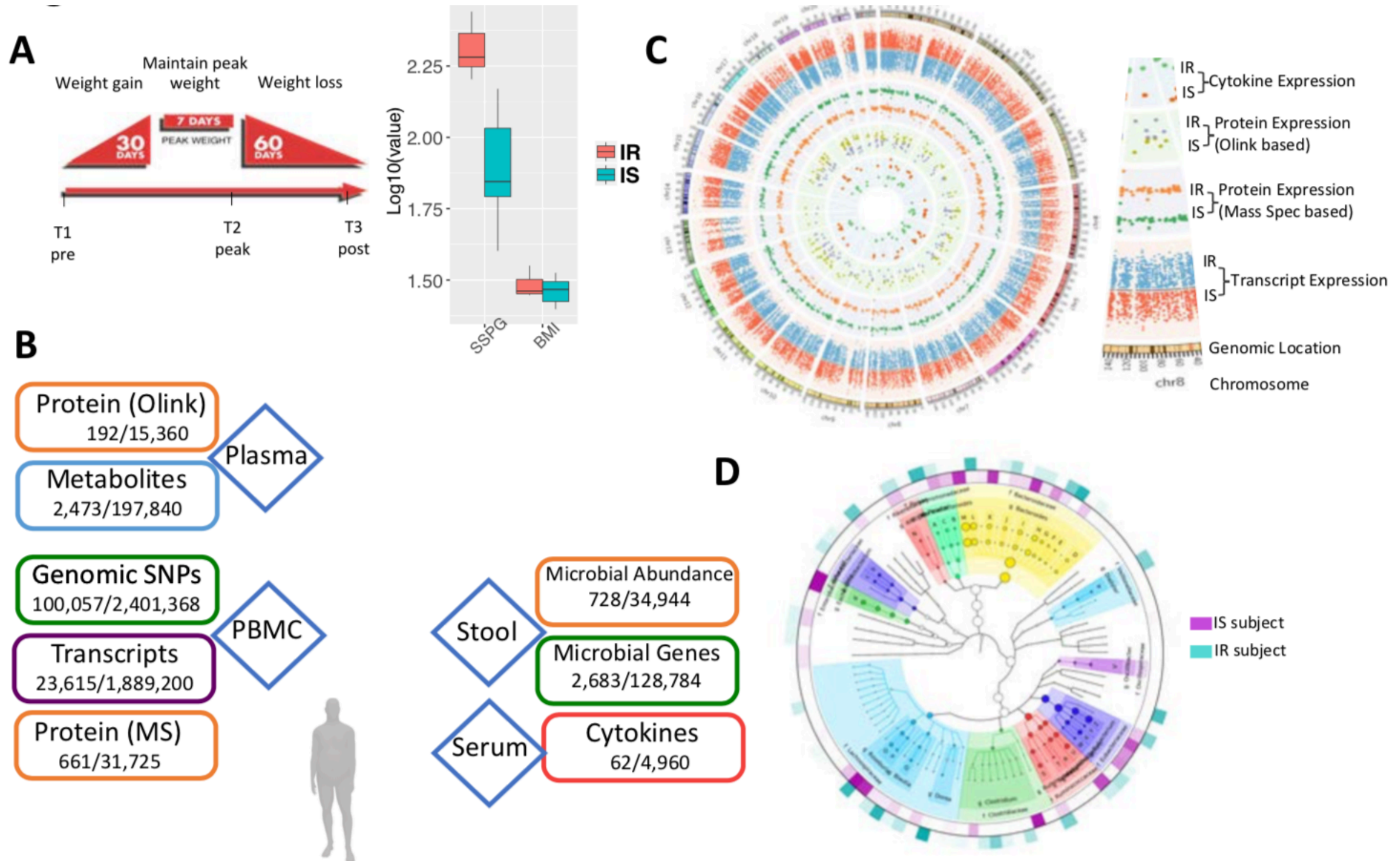
A subset of individuals undergo a dietary perturbation



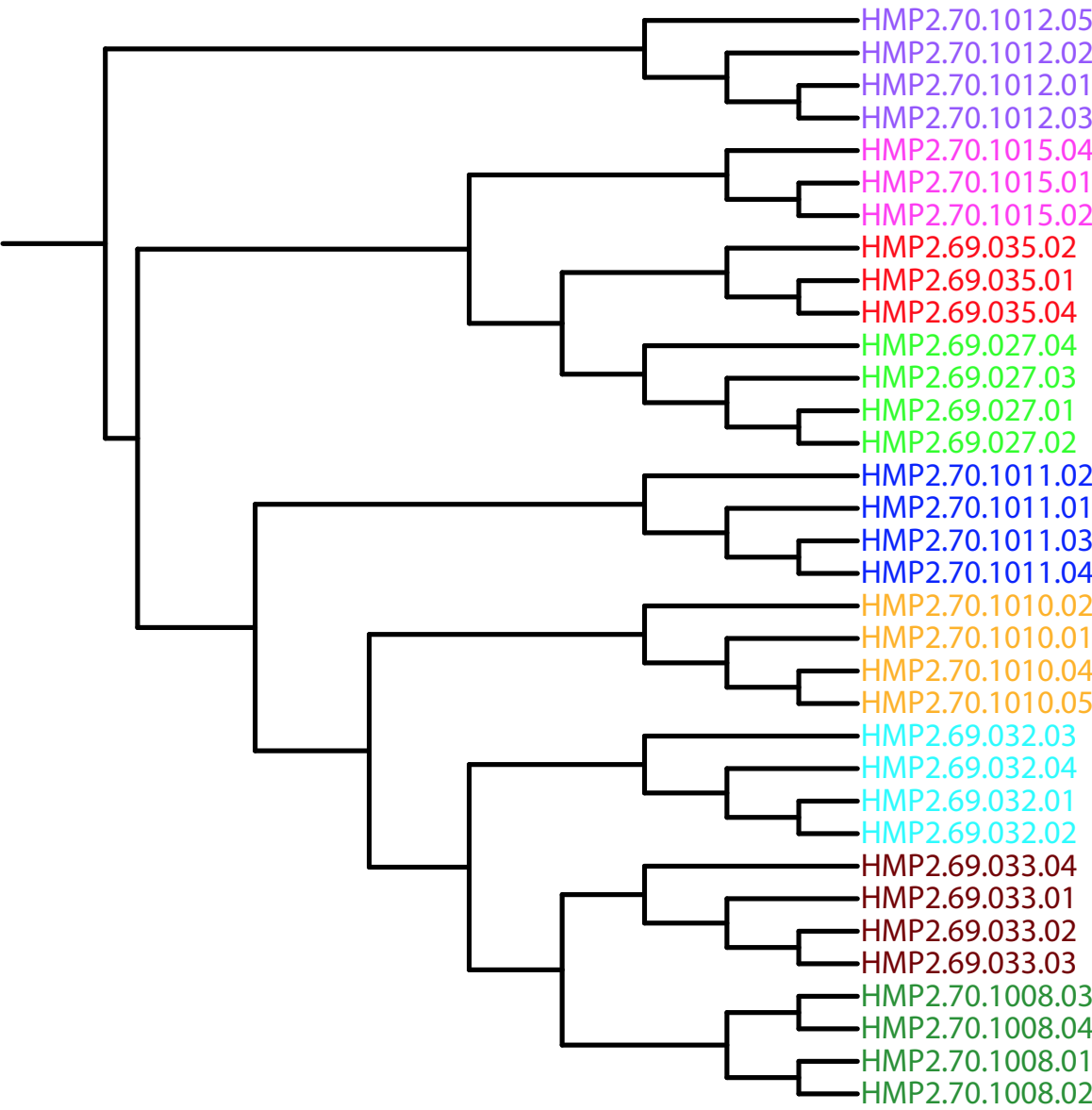
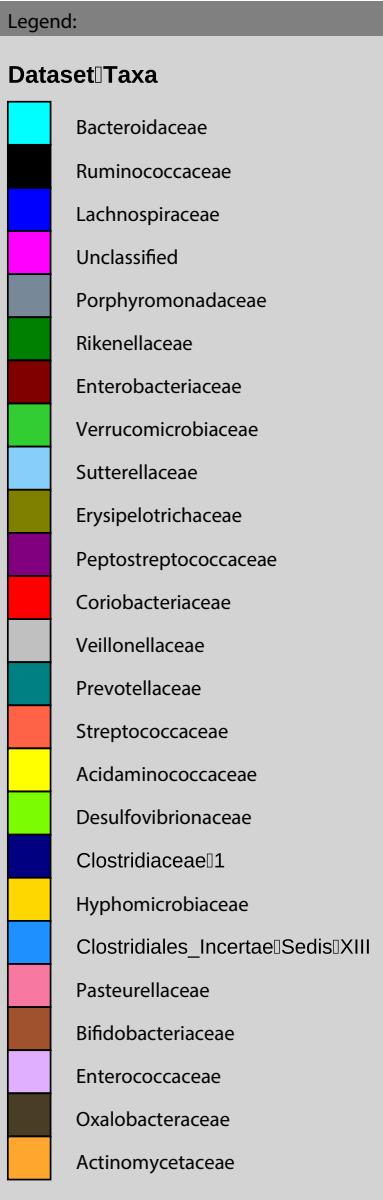
23 participants:

- 13 Insulin resistant
- 10 healthy controls (BMI matched)

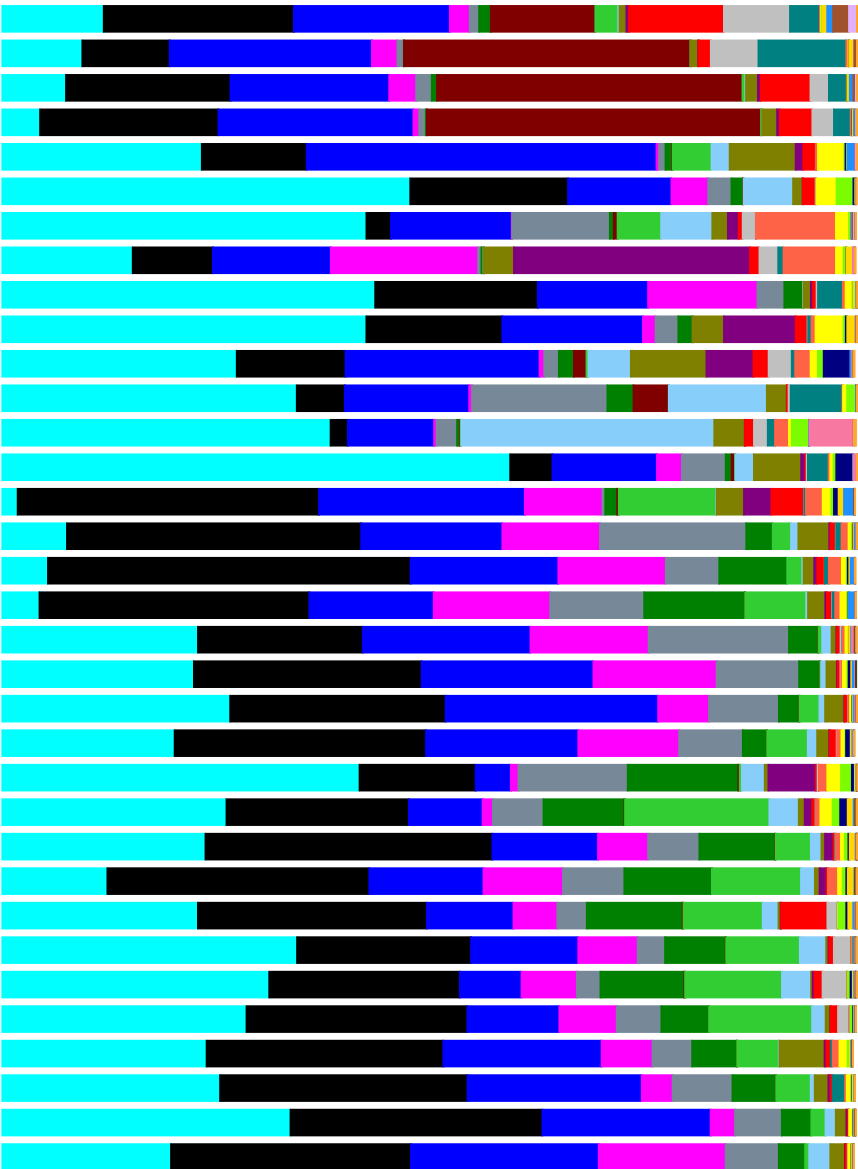
A subset of individuals undergo a dietary perturbation



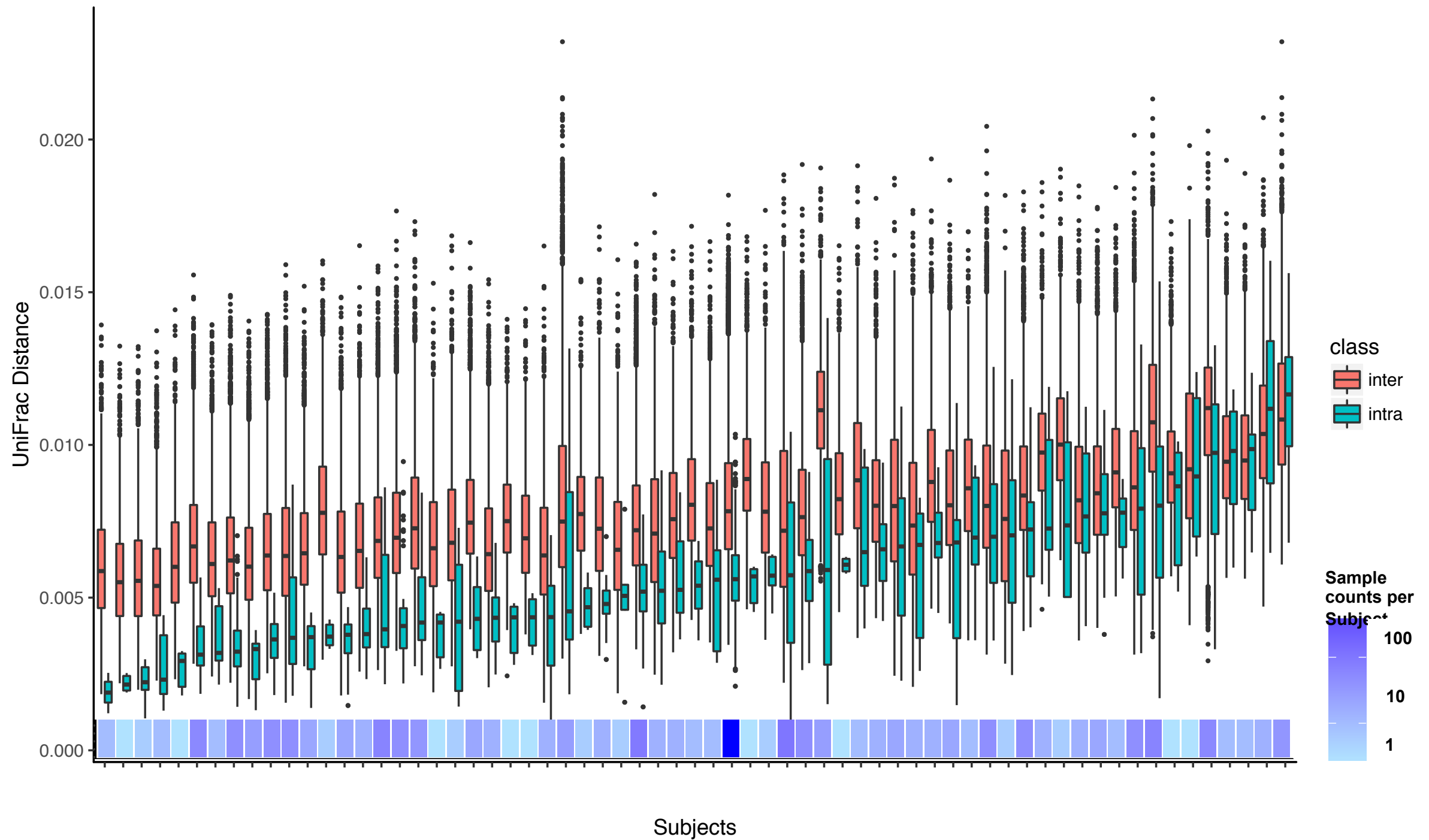
Weight gain/loss samples cluster by subject, not perturbation



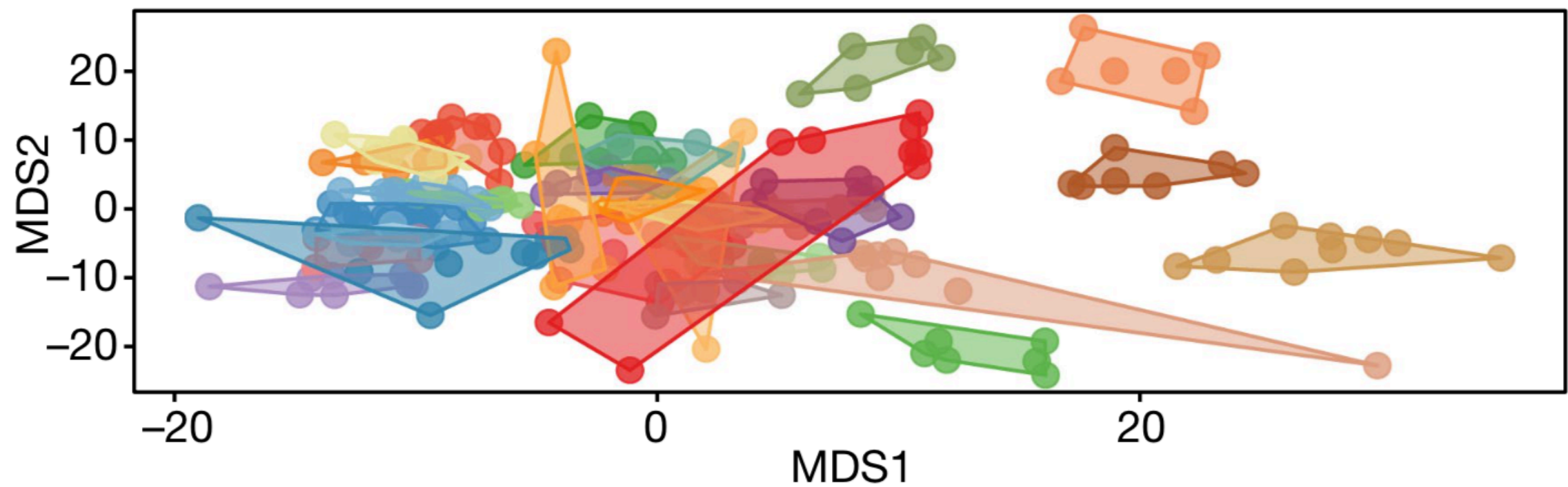
Family Composition



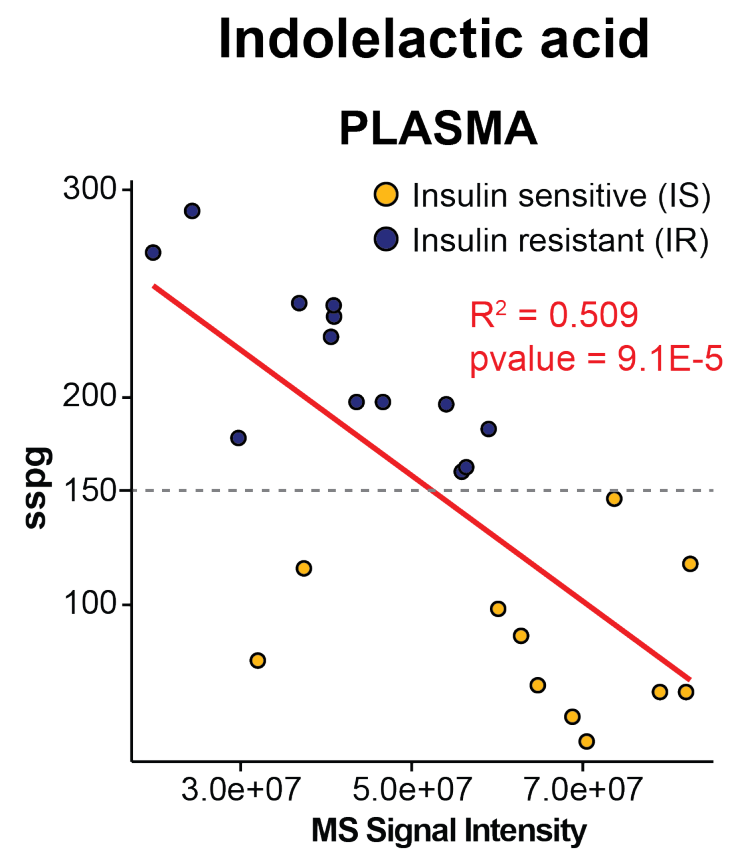
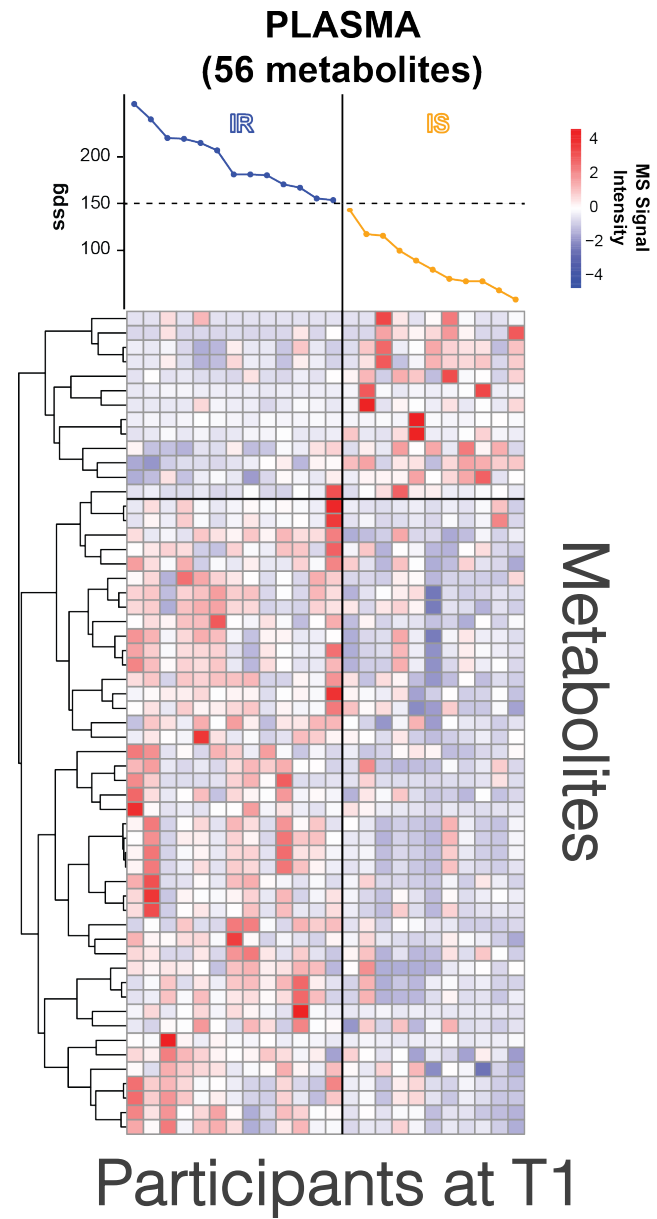
Study participants' gut microbiome: individuals are more similar to themselves than others



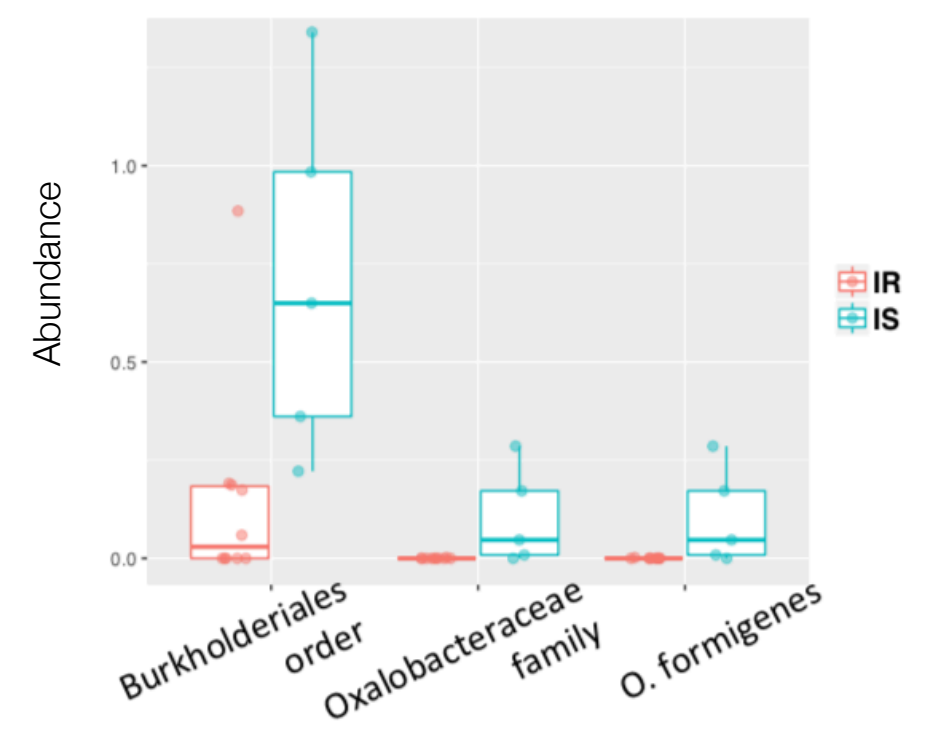
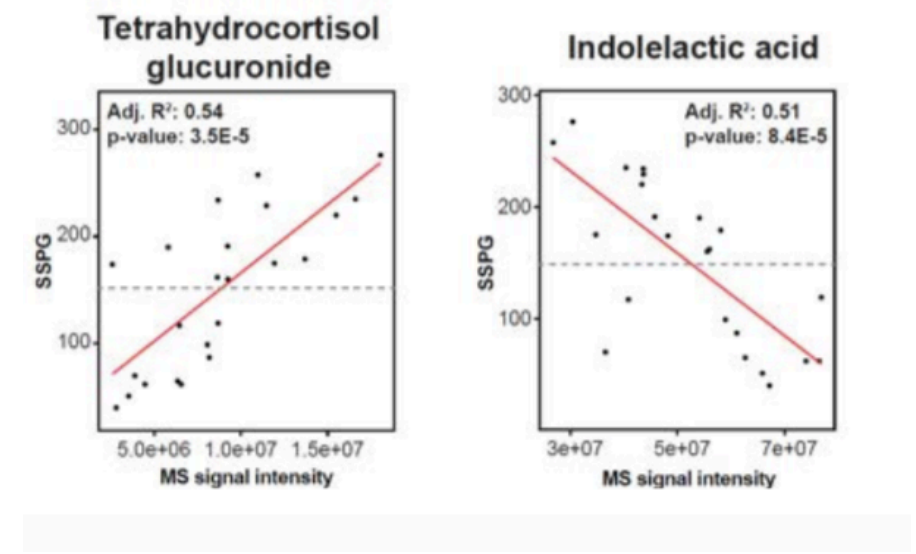
Individuals are more similar to themselves than to others, even at healthy baseline



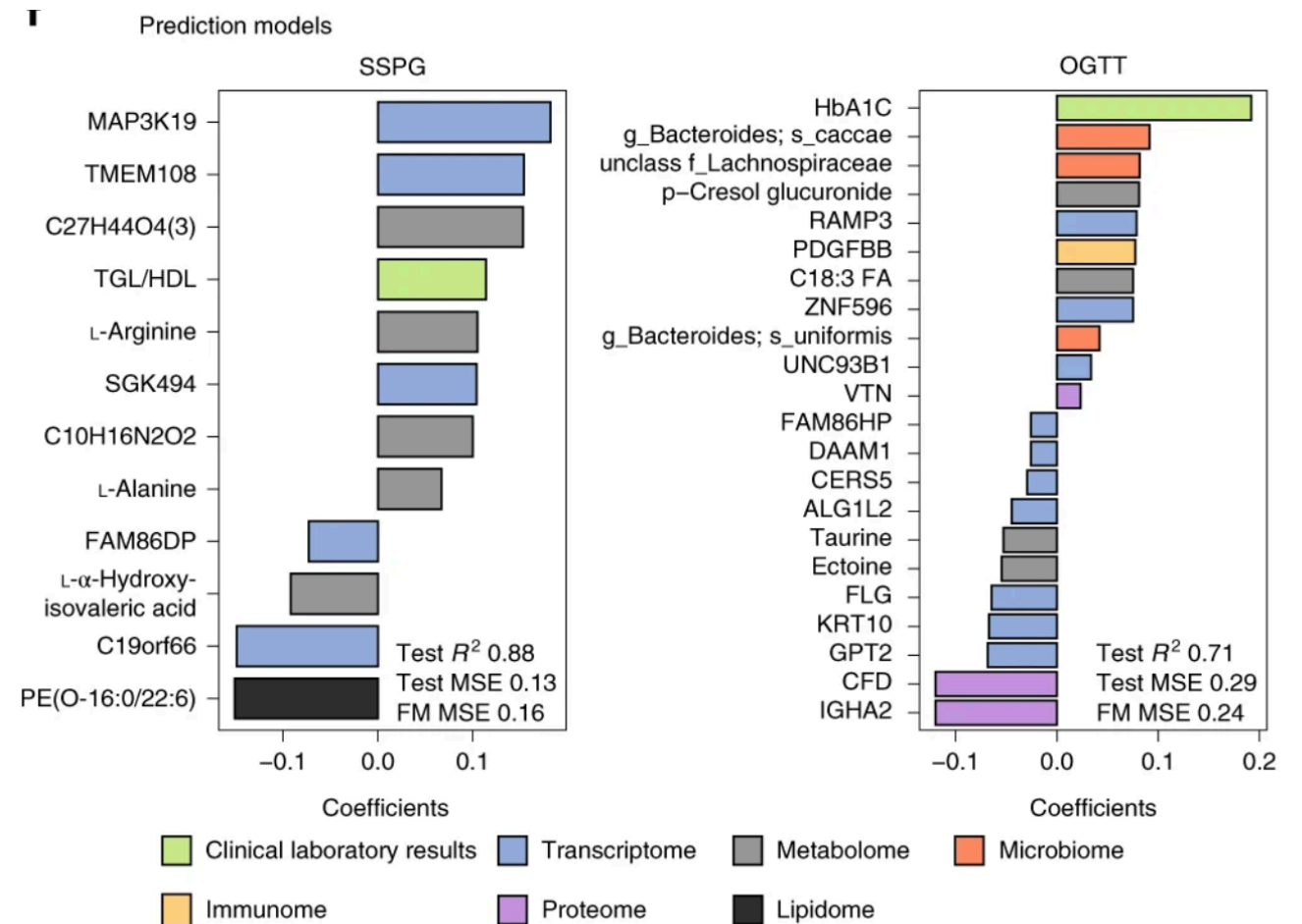
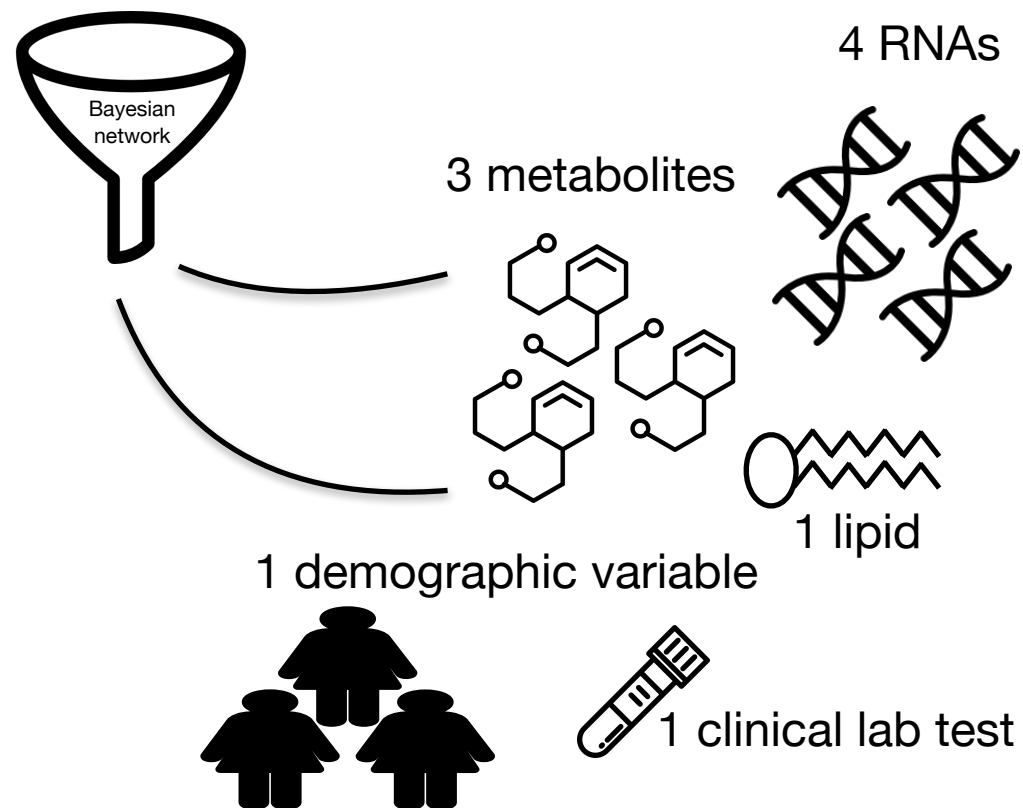
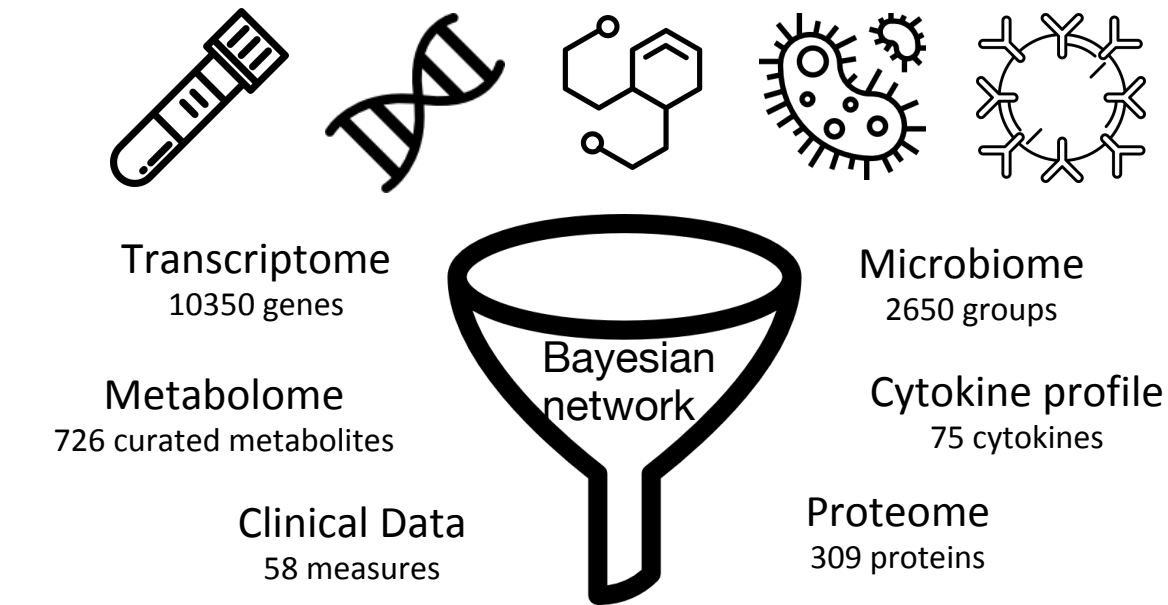
Metabolic differences between IR and IS



Pathway	Database	FDR
Arginine and proline metabolism	HMDB	0.000
Glycine, serine and threonine metabolism	HMDB	0.001
Valine, leucine and isoleucine biosynthesis	HMDB	0.010
Cyanoamino acid metabolism	HMDB	0.022
Glycerophospholipid metabolism	HMDB	0.030



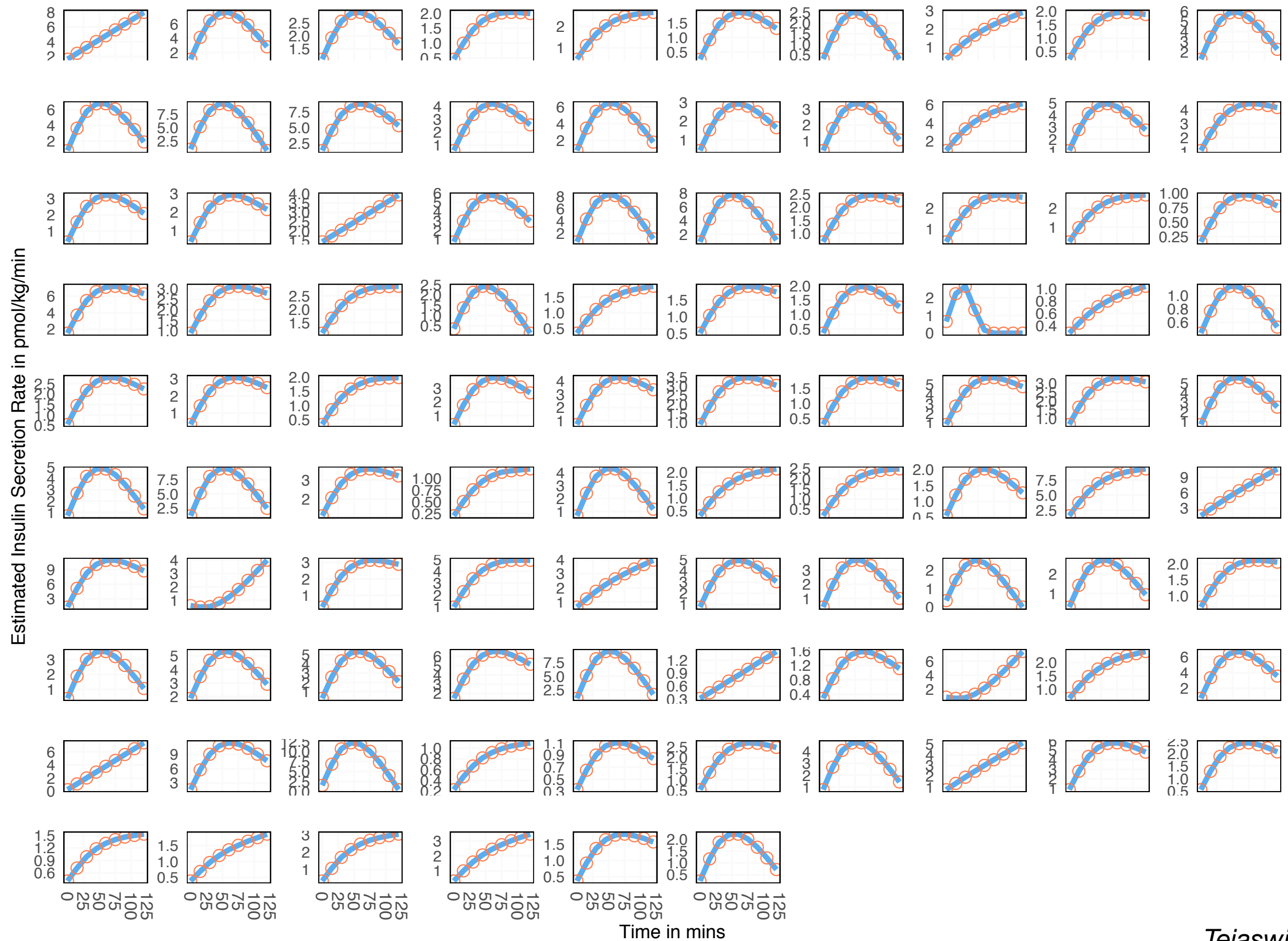
Predicting biomarkers for SSPG, an expensive and time-consuming test for insulin resistance



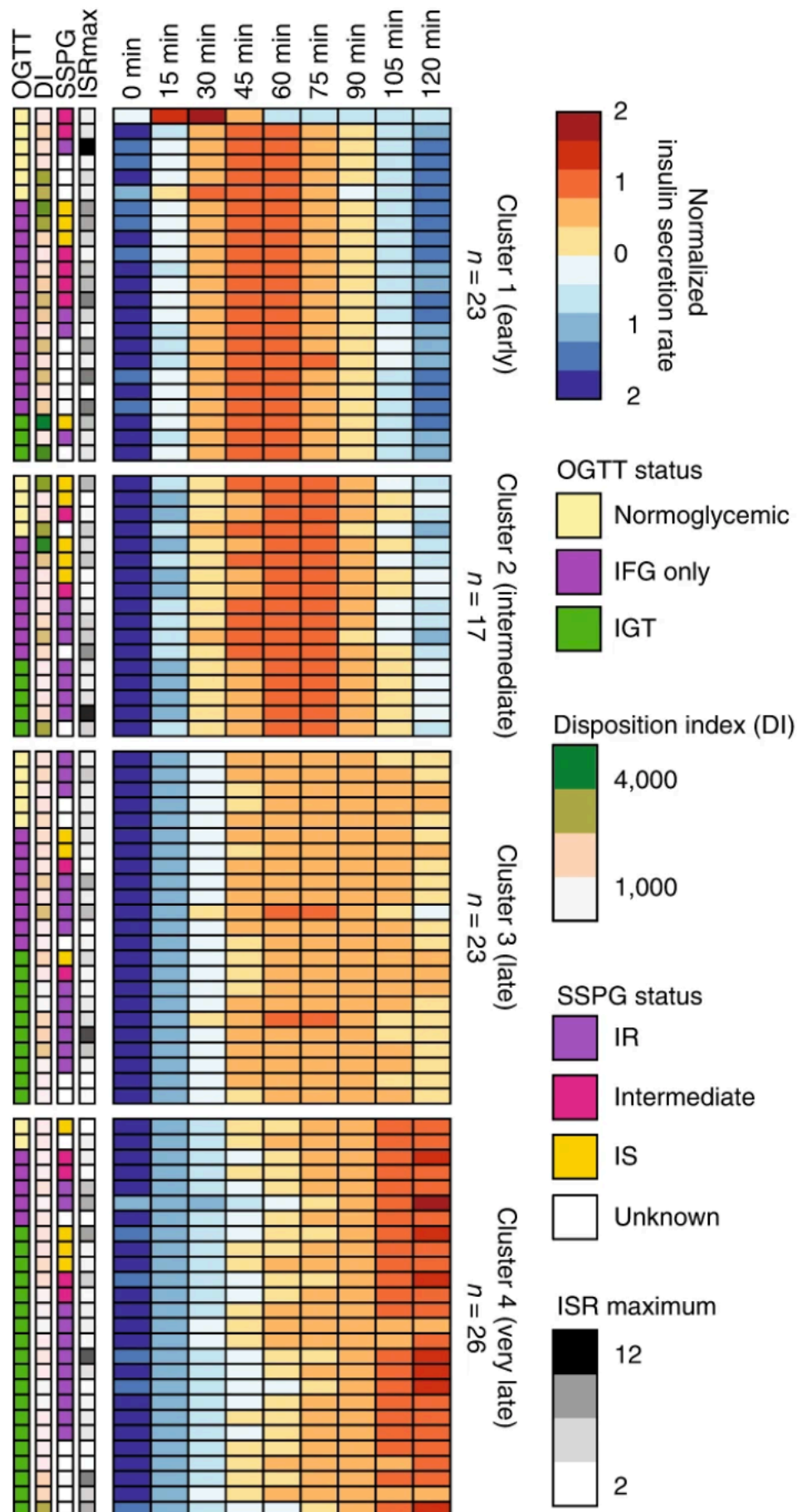
Bayesian network: Max-min Parents and Children algorithm (MMPC)

Samson Mataraso, Sophia Miryam-Rose, Tejaswini Mishra

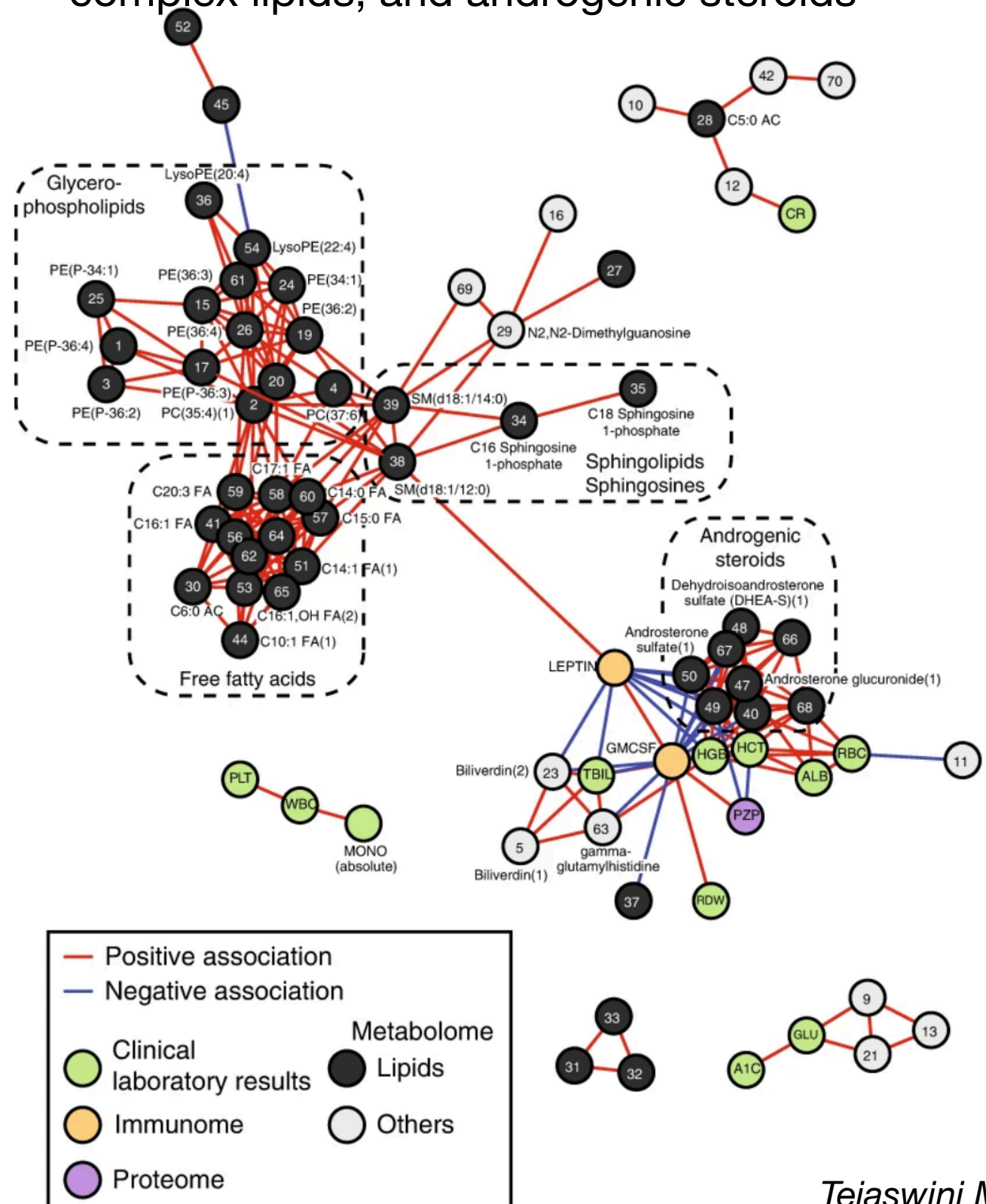
Insulin secretion rate curves reveal individual differences in glucose tolerance



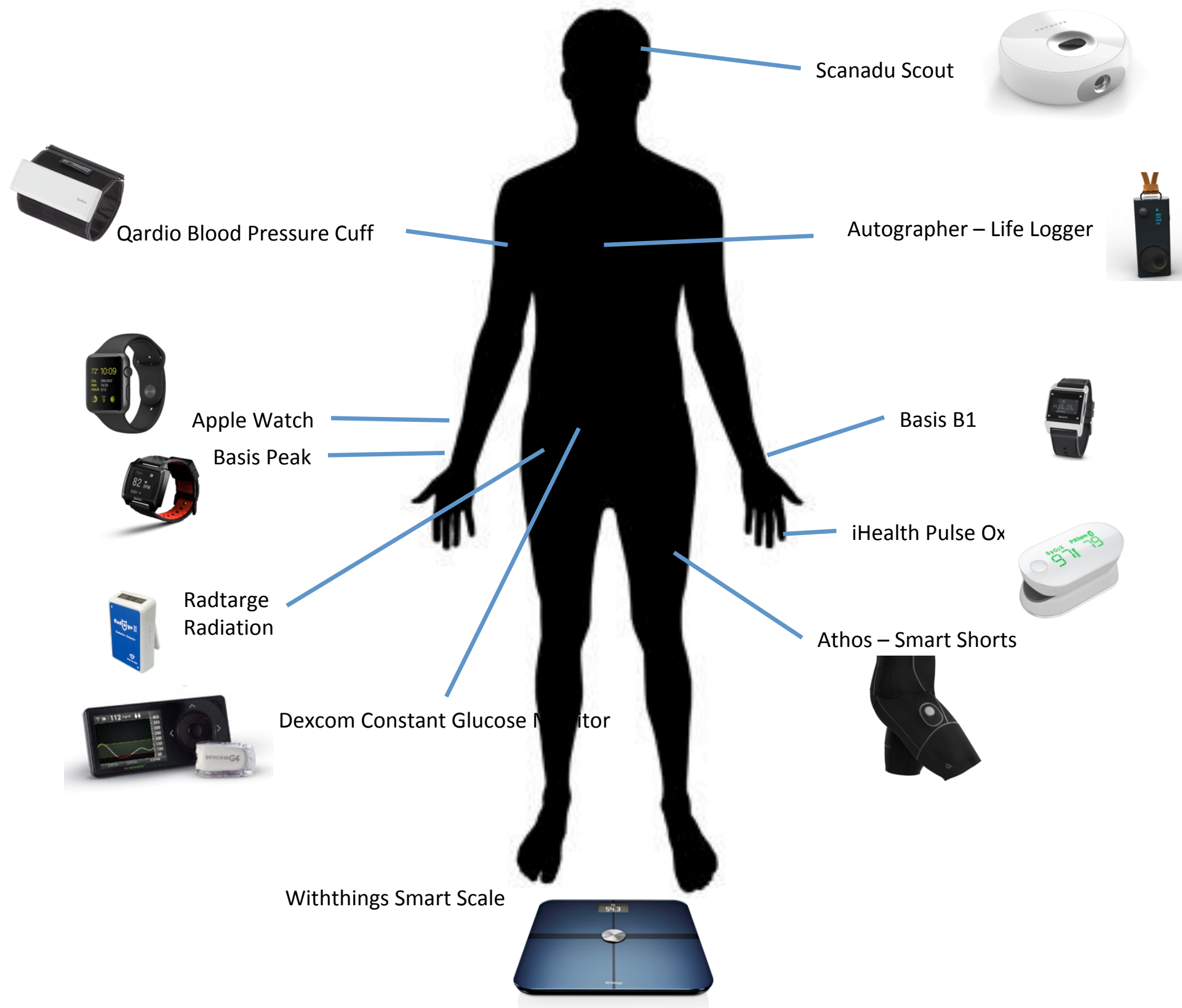
Enhanced tests of glucose metabolism reveal highly individual metabolic dysregulation patterns associated with distinct multi-omics features



Disposition index (measure of pancreatic beta cell function) is associated with levels of free fatty acids, complex lipids, and androgenic steroids

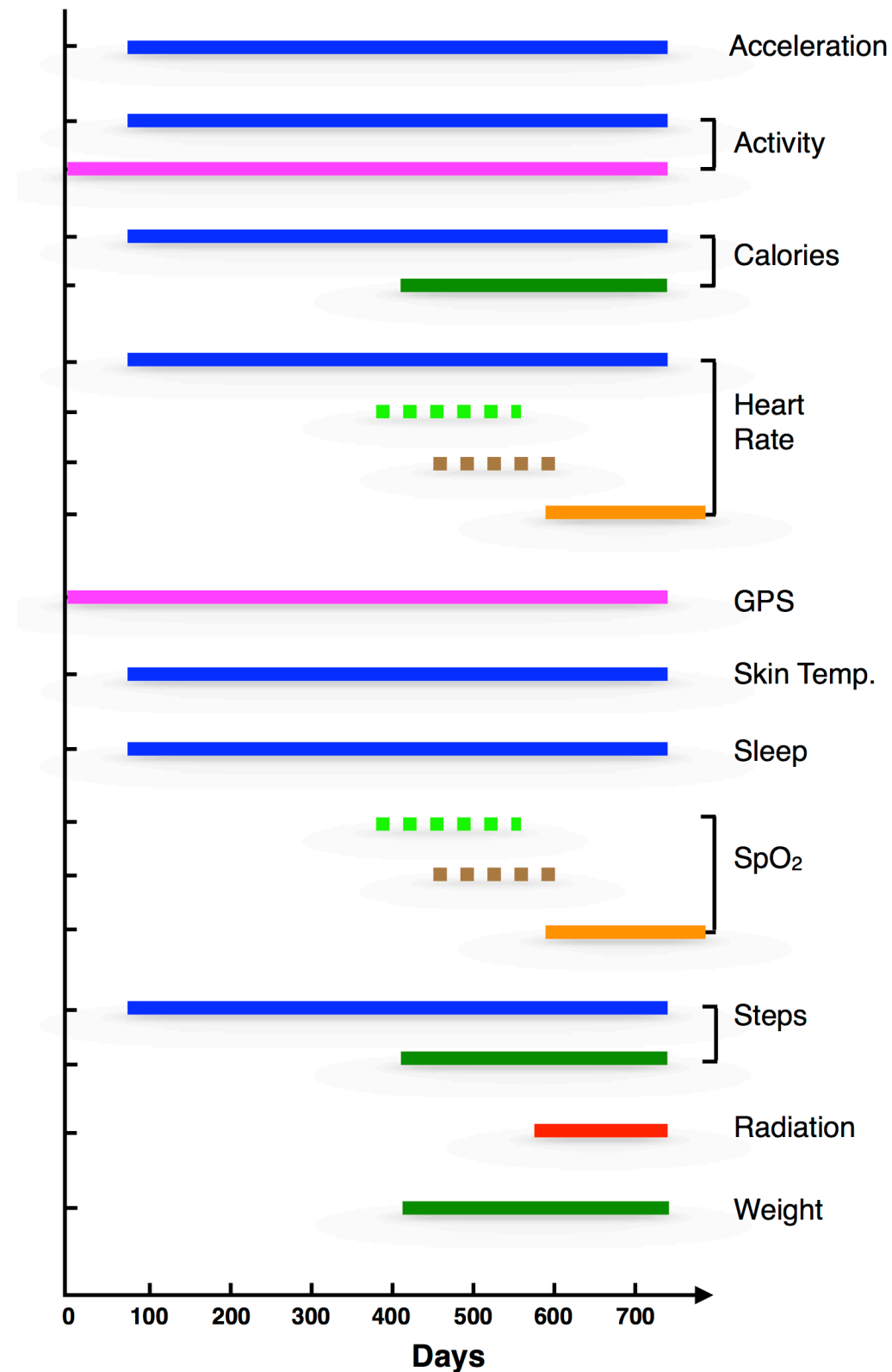


Wearables sensors measure many biometrics



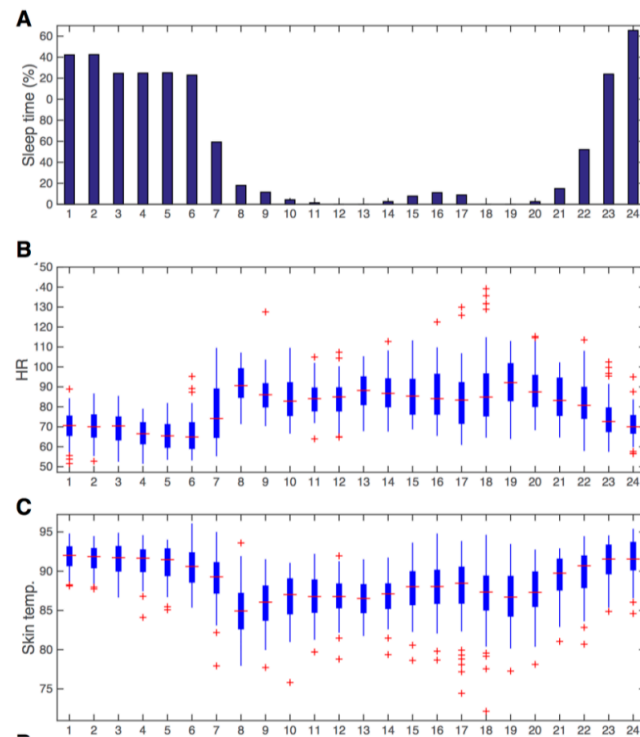
Overview of measurements

Many Parameters



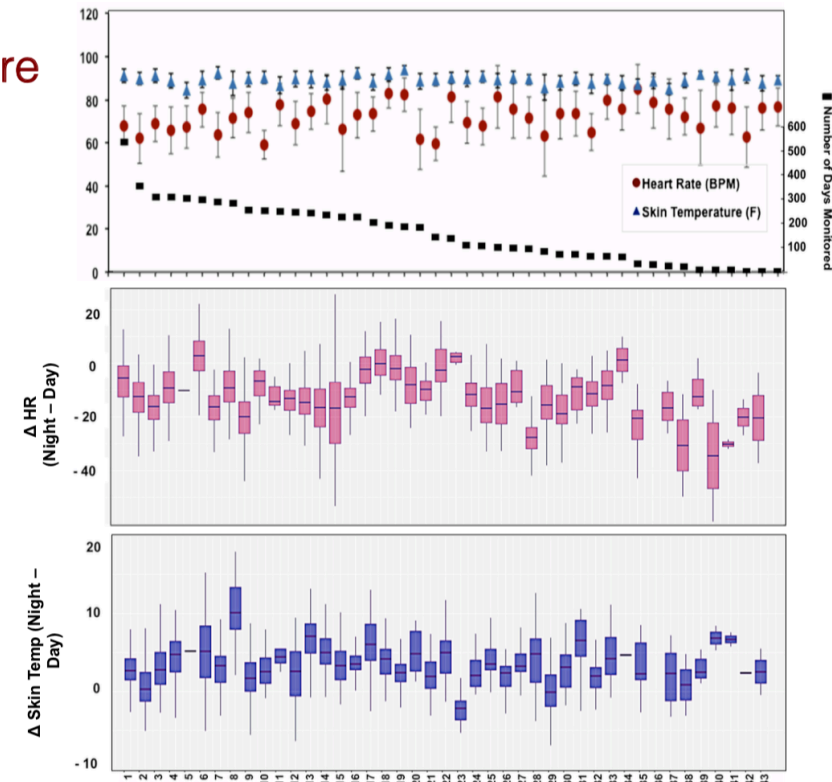
Wearables sensors measure many biometrics

Circadian and diurnal patterns



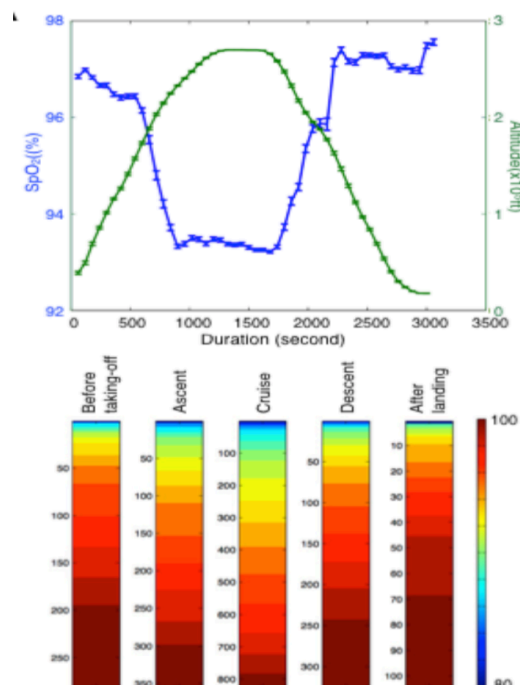
Skin temperature and heart rate variation in 43 people

- People vary a lot between night and day
- Variation is independent of number of measurements

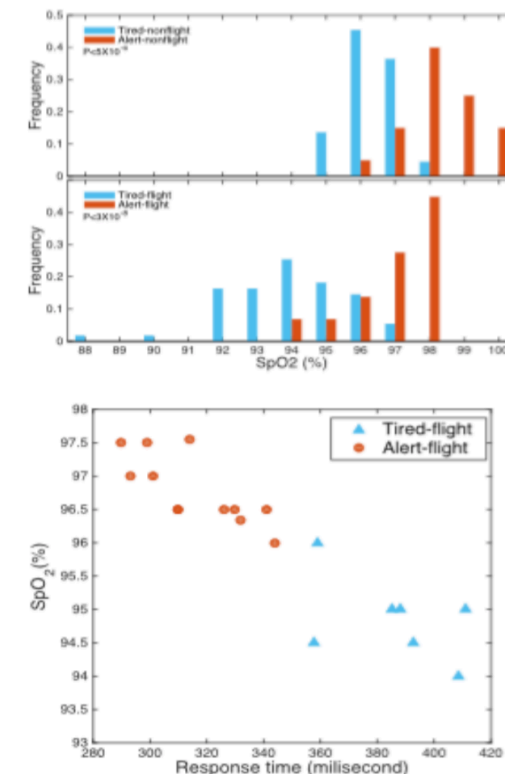


SpO2 Levels: Drop During Airline Flights

Finger device
91-96%: 65.4%
90 or less: 5.1%

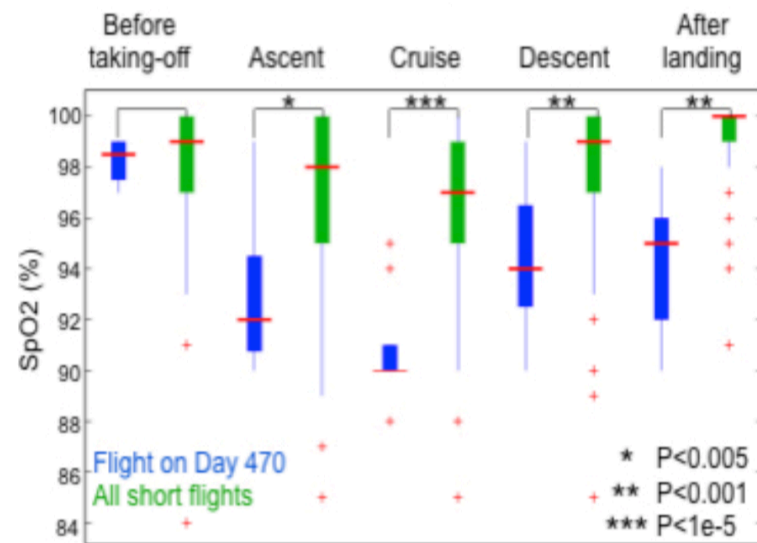


SpO2 Measurements: Associated With Fatigue



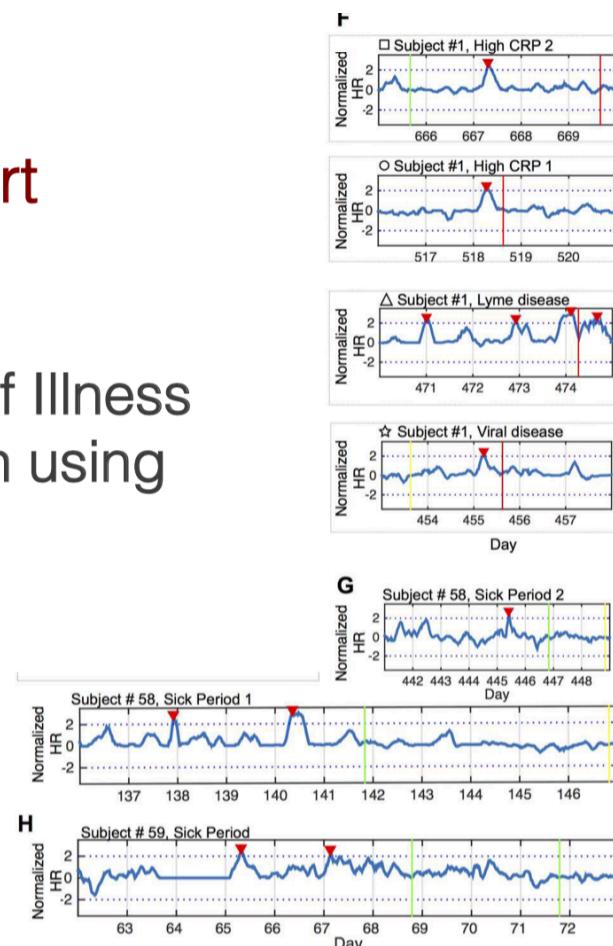
Wearables can be used for early detection of Lyme disease

SpO2 Measurements: Unusually Low on One Flight to Norway

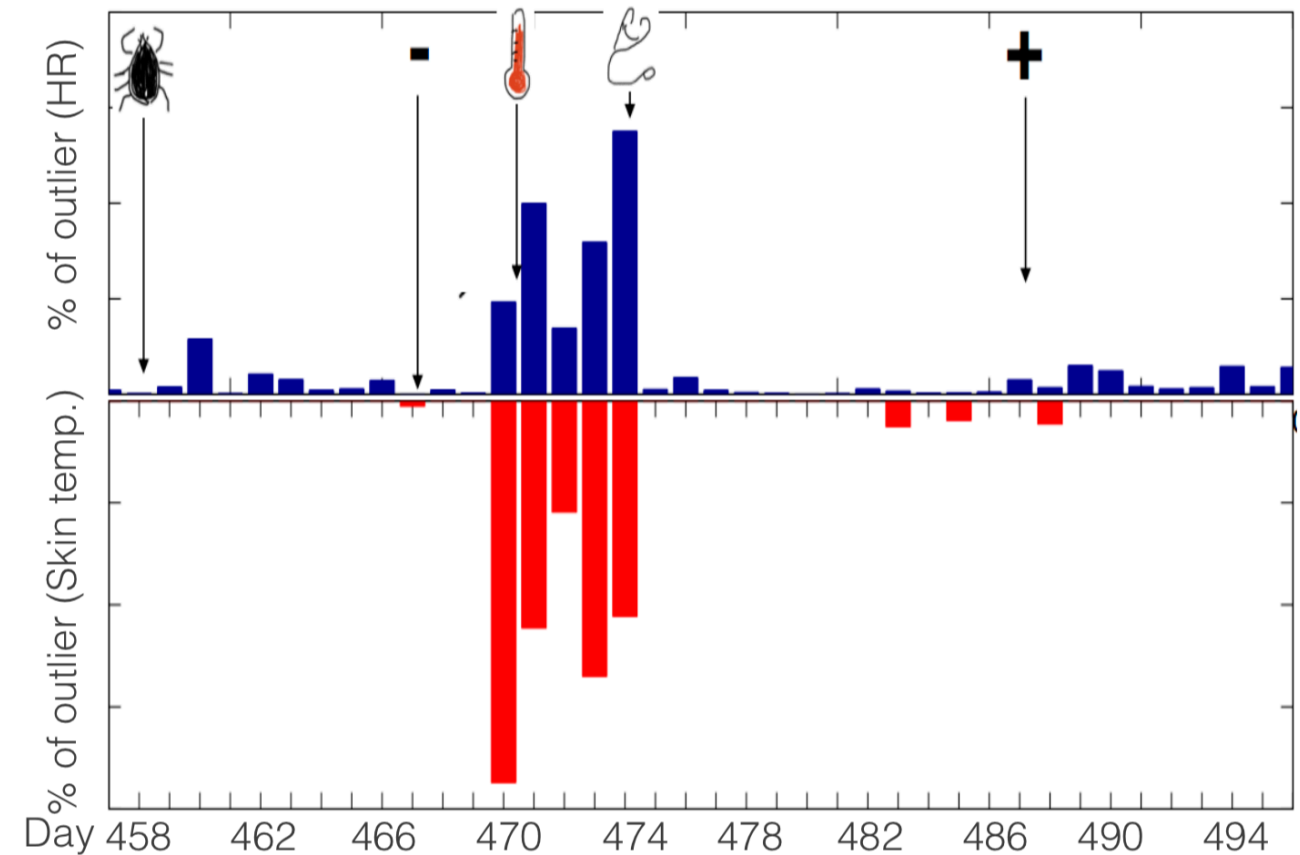


Change-of-Heart Algorithm

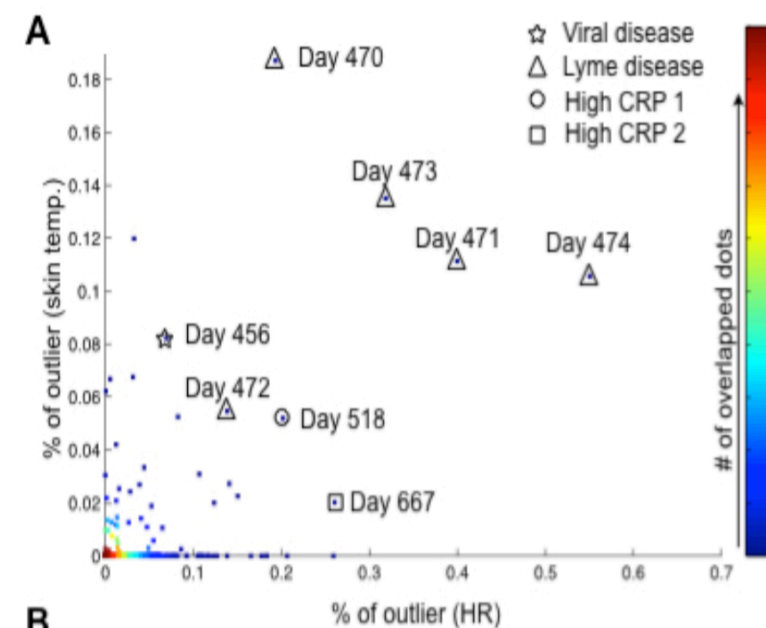
Detects Periods of Illness at High Resolution using Wearable Device



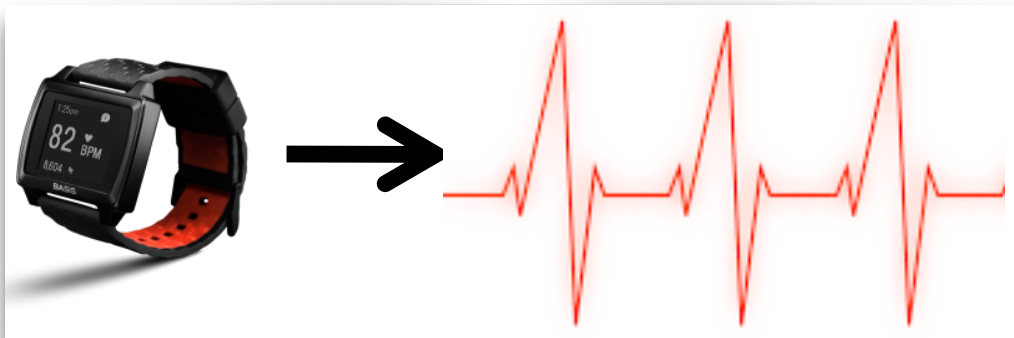
Early detection of Lyme disease



Detects All Days of Illness

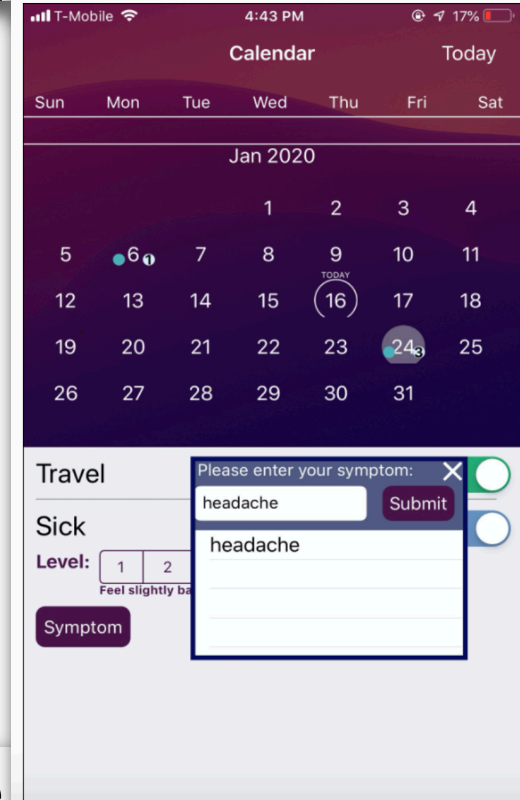
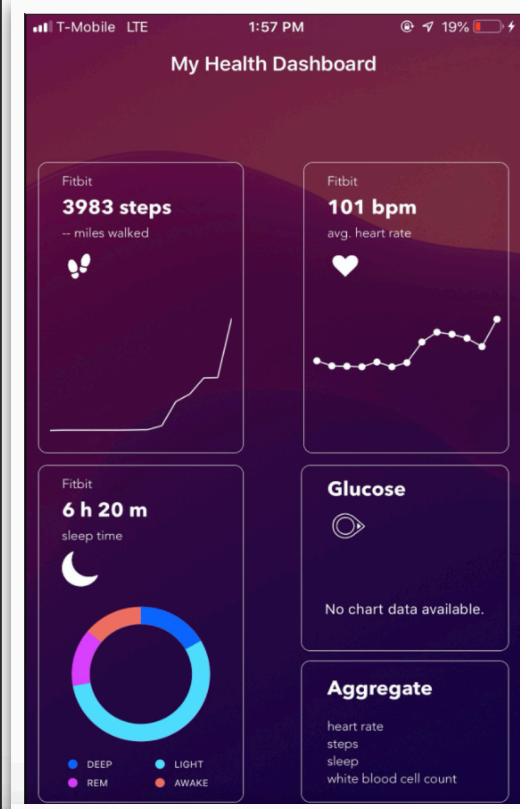
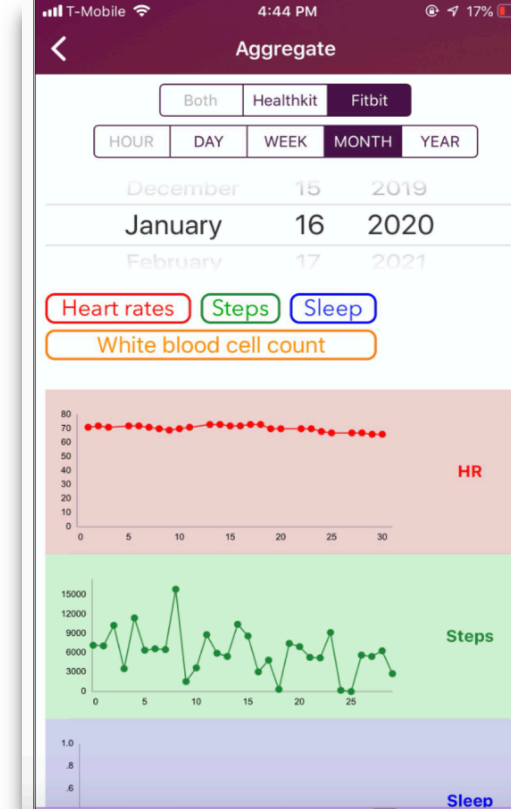


Future: Detecting onset of COVID-19 infection & studying disease prognosis

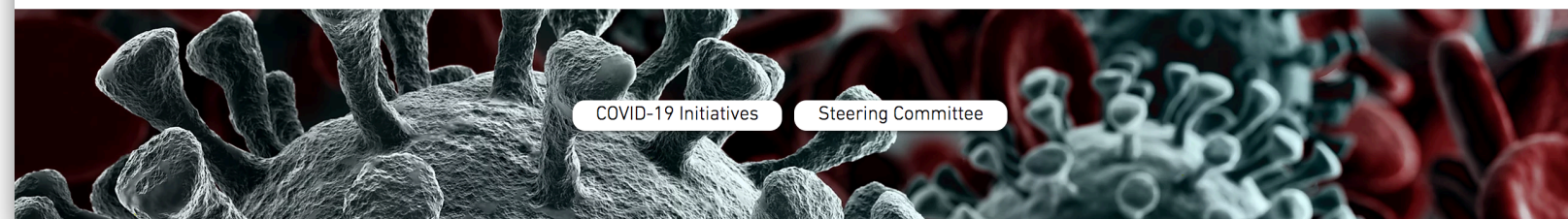


- ▶ Wearables Devices + Symptom tracking via app
- ▶ In-home digital monitoring during disease epidemics
- ▶ Alert to self-isolate
- ▶ Reduces burden on healthcare system

- ▶ Longitudinal at-home microsampling
- ▶ Multi-omics profiling
- ▶ Associate with disease prognosis



Stanford Healthcare
MEDICINE Innovation Lab



COVID-19 Initiatives

Steering Committee

Tejaswini Mishra, Ryan Kellogg,
Amir Bahmani, Xiao Li, Arash Alavi

COVID-19 Initiatives

Summary

- 1) Personal genome sequencing is here. It can be used to predict disease risk and manage health
- 2) Multi-omics analyses are valuable for determining pathways and biochemical activities involved in human disease.
- 3) Longitudinal profiles are very valuable for understanding personal disease states
- 4) Everyone's profile is different
- 5) Wearables will be useful for managing health
- 6) Individuals will be responsible for their own health

Acknowledgements

iPOP

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Hassan Chaib
Eric Wei
Kim Kukurba
Tracey McLaughlin
Weinstock Lab at JAX
Lita Proctor, others at NIH

iPOP

Amir Bahmani
Samson Mataraso
Francois Haddad

**We are grateful to all the study
participants who gave us their
samples and time!**



The NASA Twins Study

A multidimensional analysis of a yearlong human spaceflight

Tejaswini Mishra

March 31, 2020

>560 people have flown into space

"All the News
That's Fit to Print"

The New York Times

LATE CITY EDITION
 Weather: Rain, warm today; clear tonight. Sunny, pleasant tomorrow.
 Temp. range: today 60-66; Sunday 71-66. Temp.-Hum. Index yesterday 69. Complete U.S. report on P. 50.

VOL. CXVIII, No. 40,721 © 1969 The New York Times Company NEW YORK, MONDAY, JULY 21, 1969 X 10 CENTS

MEN WALK ON MOON

ASTRONAUTS LAND ON PLAIN; COLLECT ROCKS, PLANT FLAG

Voice From Moon: 'Eagle Has Landed'

EAGLE (the lunar module): Houston, Tranquility Base here. The Eagle has landed.

HOUSTON: Roger, Tranquility, we copy you on the ground. You've got a bunch of guys about to turn blue. We're breathing again. Thanks a lot.

TRANQUILITY BASE: Thank you.

HOUSTON: You're looking good here.

TRANQUILITY BASE: A very smooth touchdown.

HOUSTON: Eagle, you are stay for T1. [The first step in the lunar operation.] Over.

TRANQUILITY BASE: Roger. Stay for T1.

HOUSTON: Roger and we see you venting the ox.

TRANQUILITY BASE: Roger.

COLUMBIA (the command and service module): How do you read me?

HOUSTON: Columbia, he has landed Tranquility Base. Eagle is at Tranquility. I read you five by. Over.

COLUMBIA: Yes, I heard the whole thing.

HOUSTON: Well, it's a good show.

COLUMBIA: Fantastic.

TRANQUILITY BASE: I'll second that.

APOLLO CONTROL: The next major stay-no stay will be for the T2 event. That is at 21 minutes 26 seconds after the time of lunar descent.

A Powdery Surface Is Closely Explored

By JOHN NOBLE WILFORD
Special to The New York Times

HOUSTON, Monday, July 21—Men have landed and walked on the moon.

Two Americans, astronauts of Apollo 11, steered their fragile four-legged lunar module safely and smoothly to the historic landing yesterday at 4:17:40 P.M., Eastern daylight time.

Nell A. Armstrong, the 38-year-old civilian commander, radioed to earth and the mission control room here: "Houston, Tranquility Base here. The Eagle has landed."

The first men to reach the moon—Mr. Armstrong and his co-pilot, Col. Edwin E. Aldrin Jr. of the Air Force—brought their ship to rest on a level, rock-strewn plain near the southwestern shore of the arid Sea of Tranquility.

About six and a half hours later, Mr. Armstrong opened the landing craft's hatch, stepped slowly down the ladder and declared as he planted the first human footprint on the lunar crust:

"That's one small step for man, one giant leap for mankind."

His first step on the moon came at 10:52:20 P.M., as a television camera outside the craft transmitted his every move to an awed and excited audience of hundreds of millions of people on earth.

Tentative Steps Test Soil

National Aeronautics and
Space Administration



NASA'S JOURNEY TO

MARS



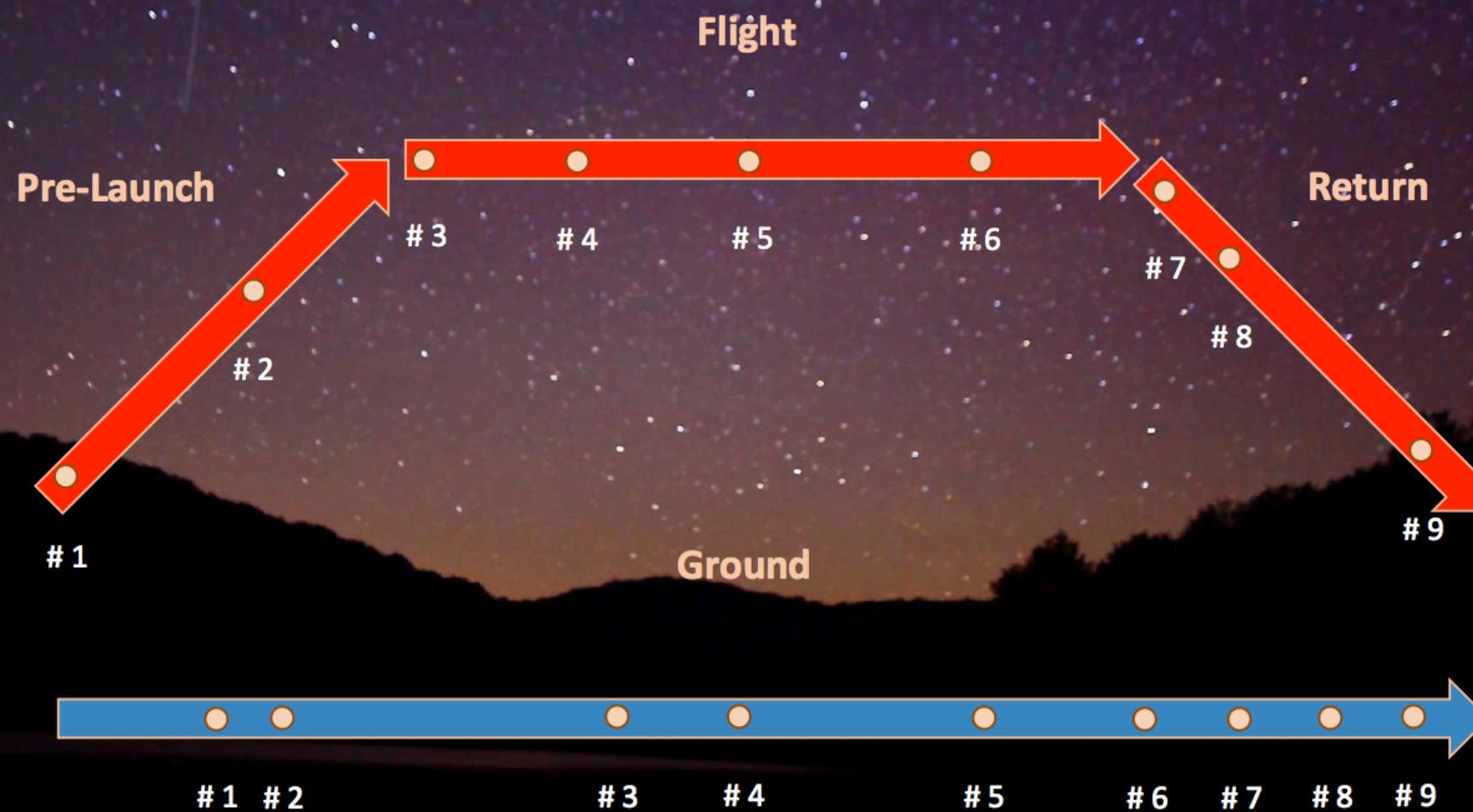
Future: Journey to Mars

What is the NASA Twins Study?

- Unique opportunity to study one human who was in space for a year
- Generate exploratory hypotheses about molecular pathways perturbed in space for future validation
- Follows two identical twins, Mark and Scott Kelly
- Mark was on Earth, while Scott traveled to ISS
- Both twins were sampled pre-, in- and post-flight

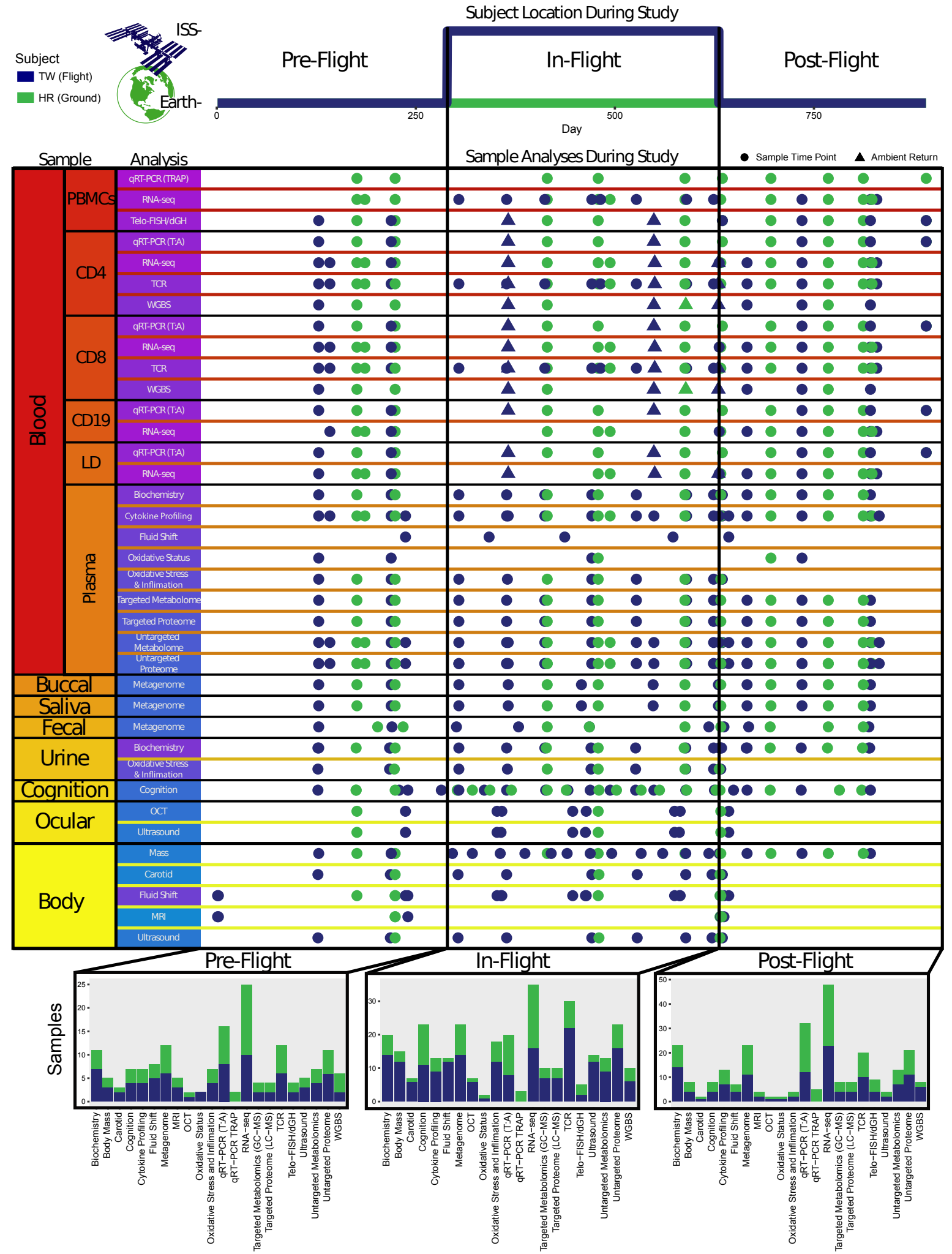


Sampling Before, During & After One Year in Space or On Ground

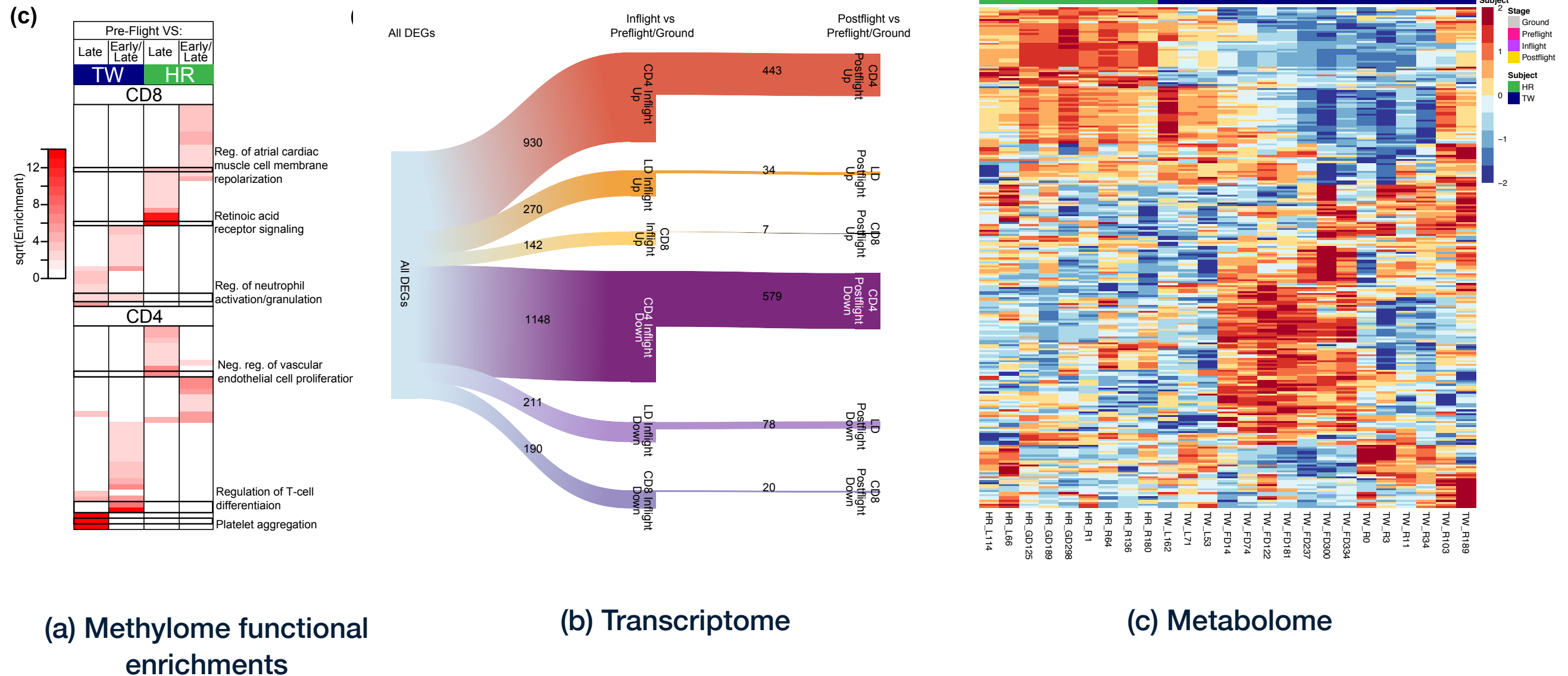


Sampling Scheme Across Assays

- Many sample types (blood, urine, stool etc.)
- Multiple cell populations
- 27 months of longitudinal sampling
- Preflight, Inflight and Postflight
- Samples collected onboard ISS as well as on Earth

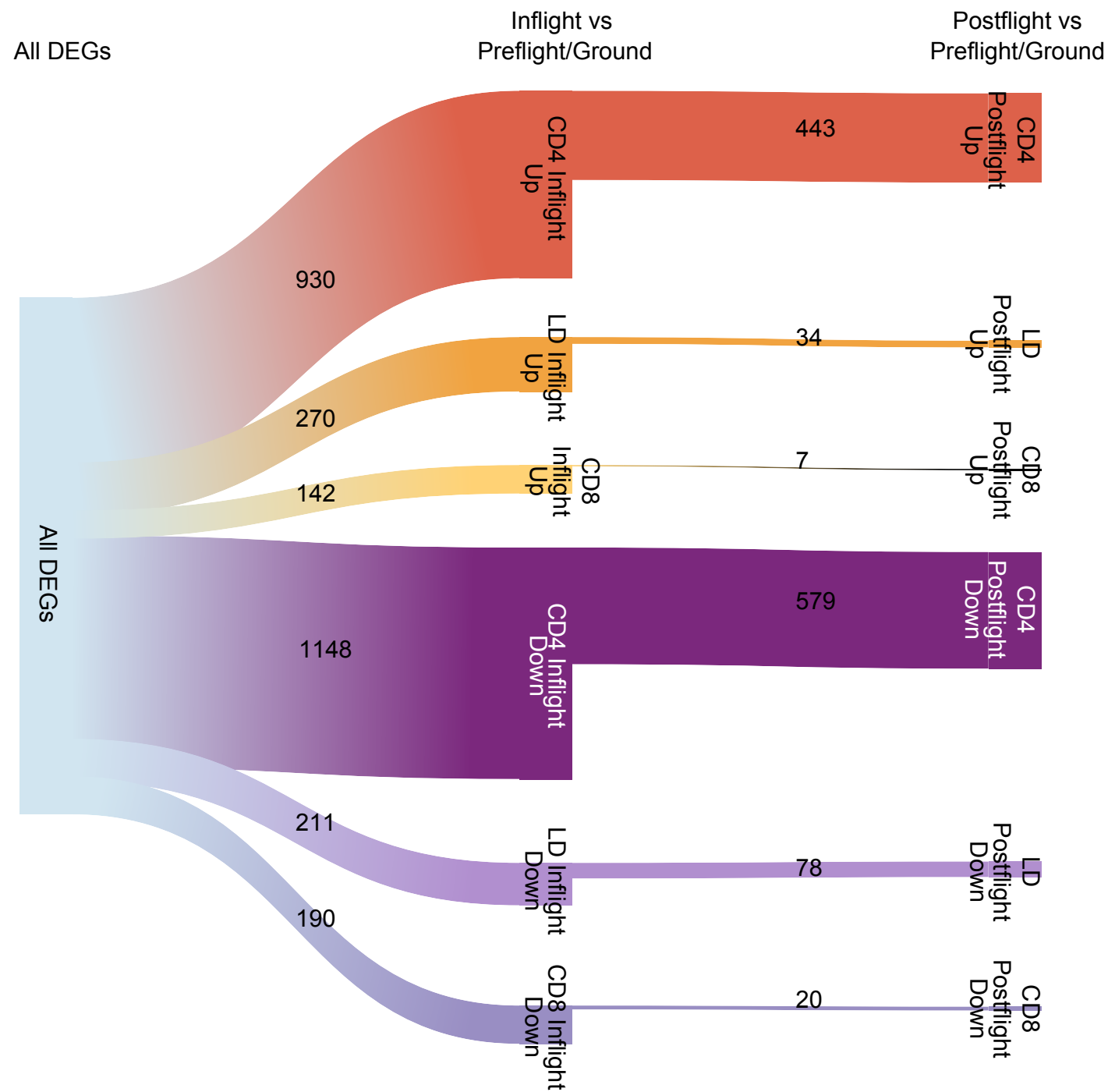


General overview of multi-omics results



No substantial flight-associated changes in genome-wide methylation levels

Gene expression changes during spaceflight

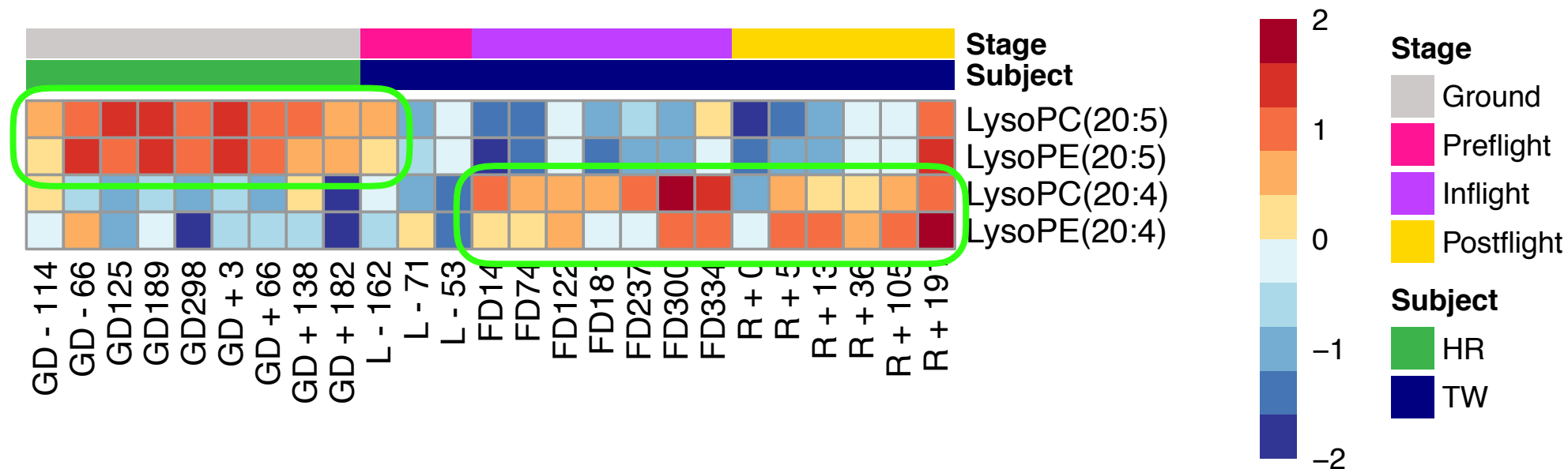


Genes involved in:

**Immune response
DNA damage
Blood pressure
Hypoxia**

Some gene expression changes persisted after return

Patterns of complex lipids



Relative levels (log2 intensity) of complex lipids containing ω -3 and ω -6 fatty acids in HR and TW, from untargeted plasma metabolomics. Red color indicates relative enrichment, blue color indicates relative depletion.

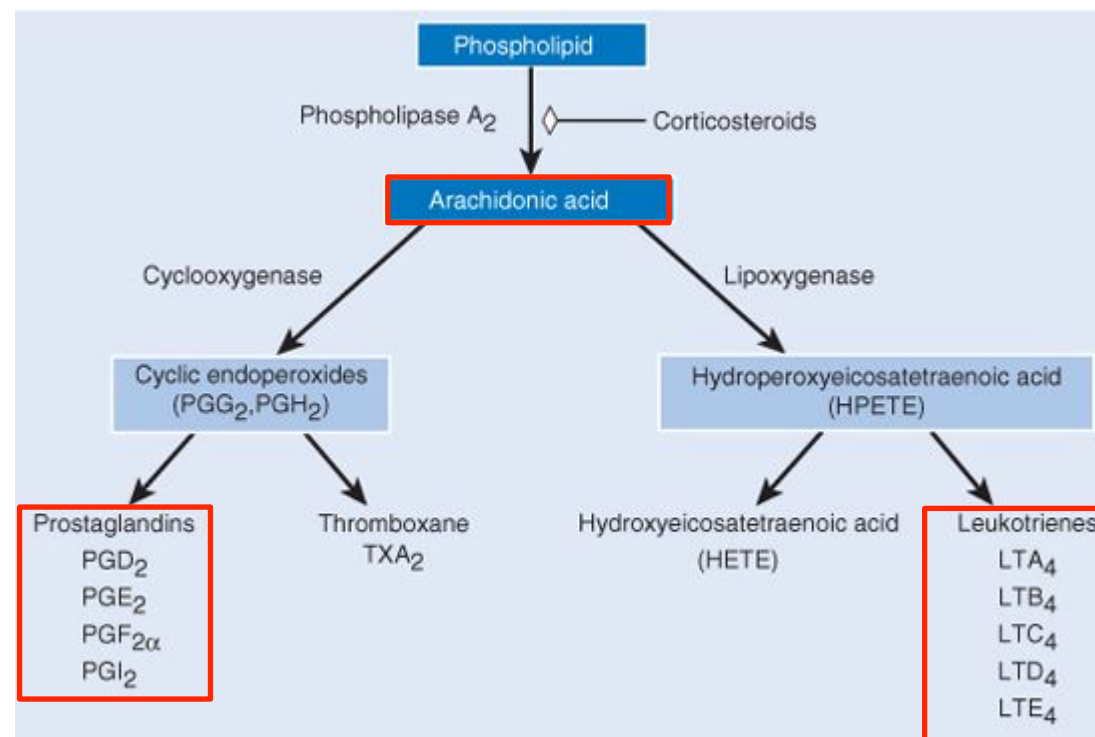
Complex lipids containing fatty acids that are metabolized to form pro- and anti-inflammatory molecules are present at different levels in the twins, and increase inflight in TW, continuing to stay high after return

AA is a precursor of inflammatory molecules

Complex lipids containing fatty acids that are metabolized to form pro- and anti-inflammatory molecules are present at different levels in the twins, and increase inflight in TW, continuing to stay high after return

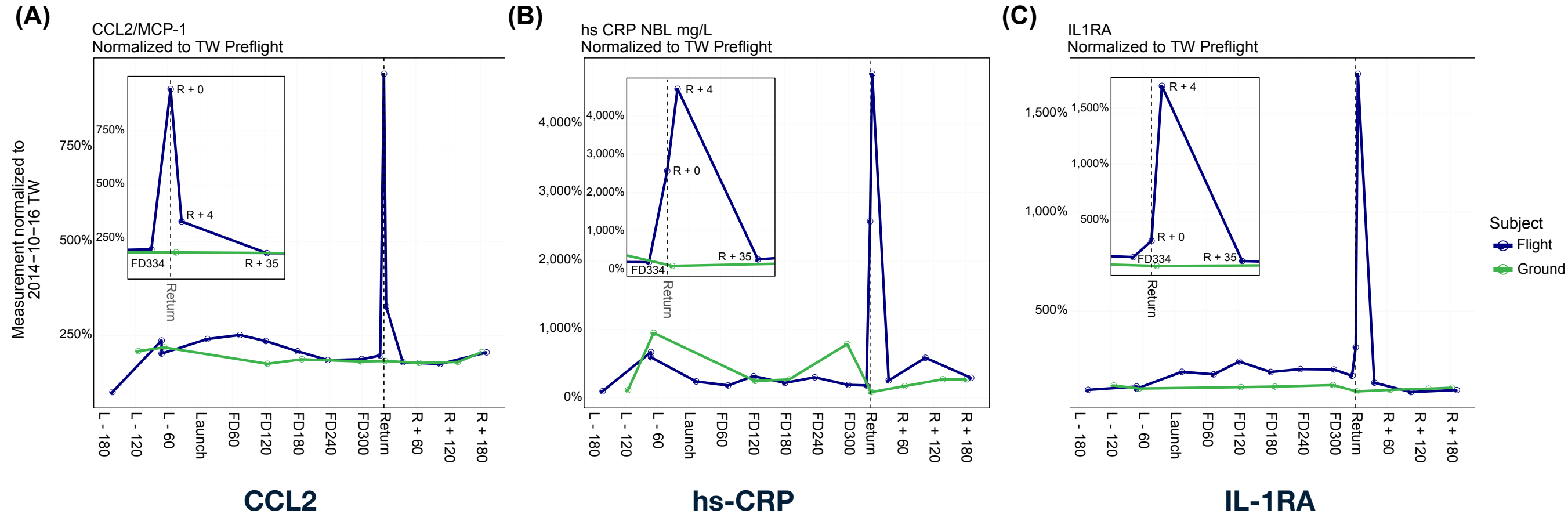
Arachidonic acid (20:4) is known to elicit inflammatory response *in vivo*

Arachidonic acid (FA 20:4) is a key inflammatory intermediate that is metabolized to inflammatory signaling molecules (e.g. prostaglandins and leukotrienes).



⇒ Thus accumulation of arachidonic acid in complex lipids could be indicative of an increased inflammatory state, consistent with the idea of an age-associated low-chronic inflammatory state (inflammaging).

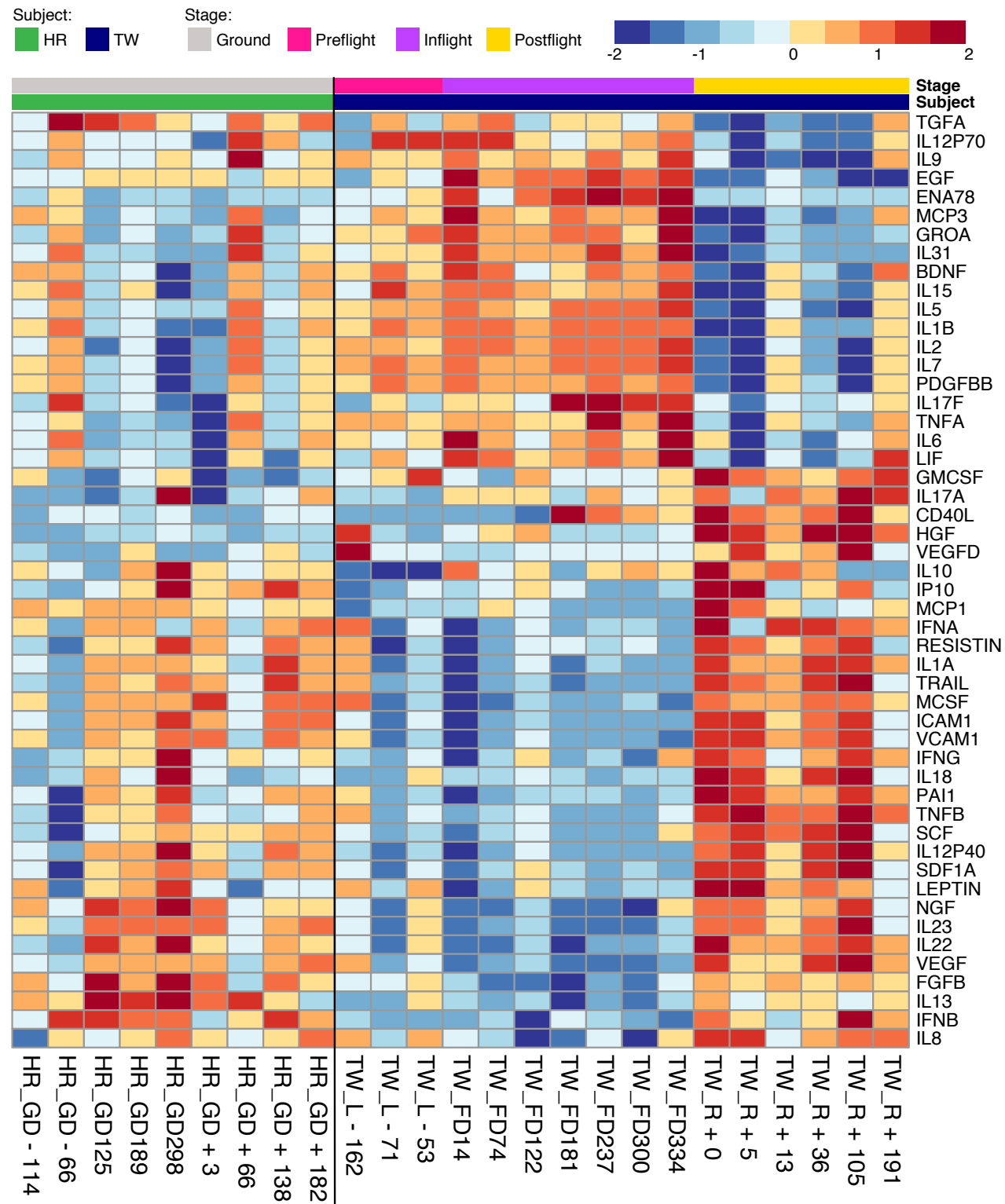
Immune response and inflammation during spaceflight



Landing-associated spikes: Astronaut reported skin rash right after return

- **CCL2/MCP-1** is implicated in pathogenesis of autoimmune diseases, incl. psoriasis.
- **IL-1ra** is actually anti-inflammatory, could be a feedback response? IL-1ra shown to decrease expression of MCP-1

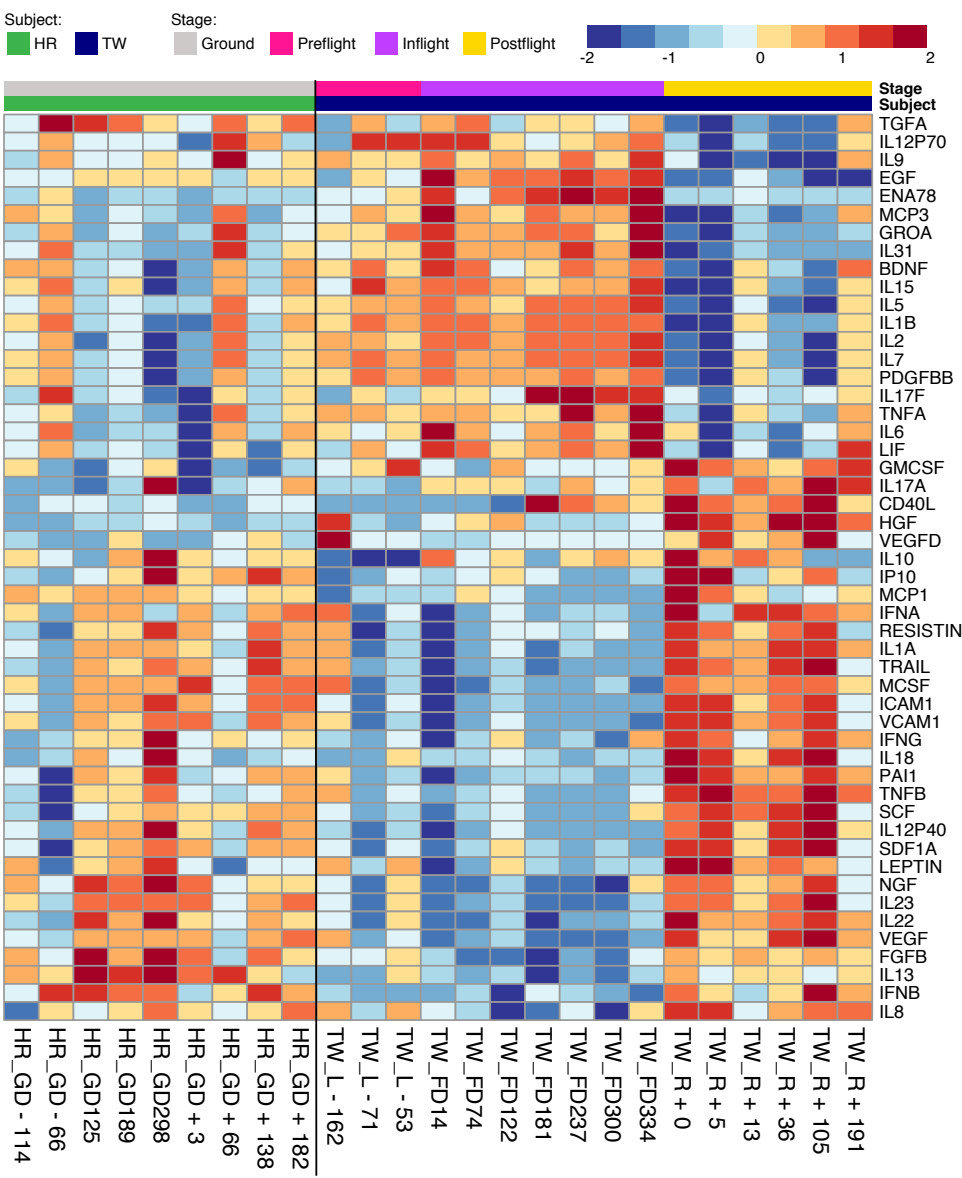
Immune response and inflammation during spaceflight



Three distinct cytokine signatures:

1. Spikes at R+5 (prev. slide), not captured by linear models
2. Cytokines high in pre- and inflight, down-regulated after return
3. Cytokines elevated after return, continue to be elevated 6 months post-return

Immune response and inflammation during spaceflight



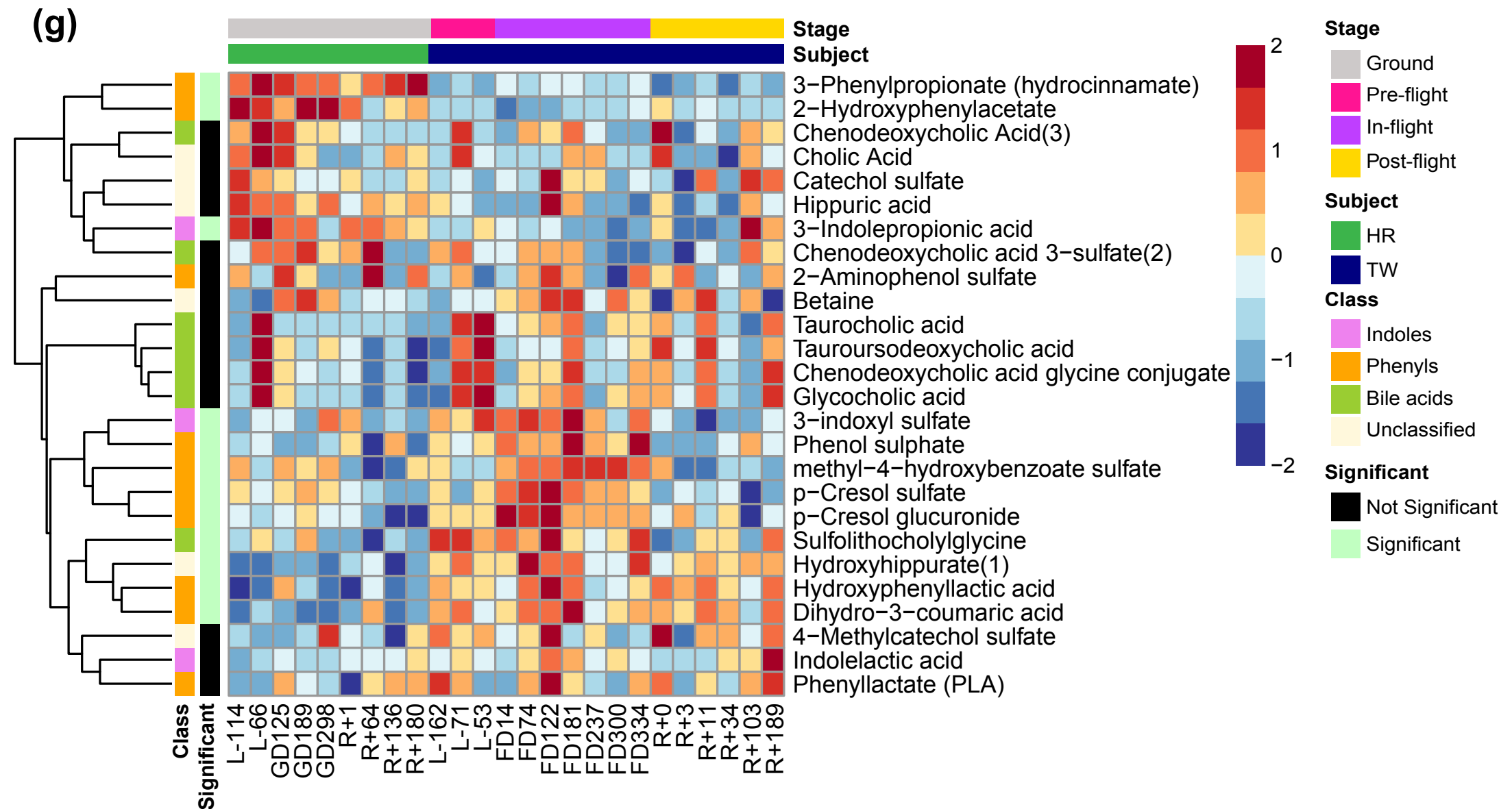
Cytokines elevated after return, continue to be elevated 6 months post-return

ID	Name	#Gene	FDR
R-HSA-1280215	Cytokine Signaling in Immune system	23	0e+00
R-HSA-6783783	Interleukin-10 signaling	11	0e+00
R-HSA-6785807	Interleukin-4 and 13 signaling	13	0e+00
R-HSA-449147	Signaling by Interleukins	18	8.85e-14
R-HSA-448706	Interleukin-1 processing	2	4.81e-02
R-HSA-194313	VEGF ligand-receptor interactions	2	4.81e-02
R-HSA-195399	VEGF binds to VEGFR leading to receptor dimerization	2	4.81e-02
R-HSA-913531	Interferon Signaling	5	4.81e-02
R-HSA-380108	Chemokine receptors bind chemokines	3	6.32e-02
R-HSA-194138	Signaling by VEGF	6	6.32e-02
R-HSA-114608	Platelet degranulation	4	6.85e-02
R-HSA-198203	PI3K/AKT activation	4	6.85e-02
R-HSA-76005	Response to elevated platelet cytosolic Ca2+	4	6.86e-02
R-HSA-170984	ARMS-mediated activation	5	6.86e-02
R-HSA-187706	Signalling to p38 via RIT and RIN	5	6.86e-02
R-HSA-170968	Frs2-mediated activation	5	6.86e-02
R-HSA-169893	Prolonged ERK activation events	5	6.86e-02

Cytokines high in pre- and inflight, down-regulated after return

CLEC7/inflammasome pathway

Products of microbial metabolism



Metabolic products associated with microbial metabolism in humans. Different classes of metabolites are observed, including indoles (violet), phenyls (orange), and bile acids (green) are shown. Metabolites that are not significantly altered between HR & TW or between pre-, in- and postflight periods are marked in black.

Summary

1. First comprehensive study of long-term spaceflight
2. First integrated, multi-omics, molecular, physiological, and cognitive portrait of an astronaut
3. Demonstrates both transient and persistent changes associated with long-duration spaceflight across multiple cell types
4. Longitudinal measures of biomarkers (such as genomic, epigenomic, biochemical, and physiological alterations) could potentially provide critical metrics for astronaut health that could aid in assessment of elevated risks and guide potential personalized interventions
5. Our study also pioneered new inflight data and sample collection strategies
6. NASA HRP has proposed follow-up longitudinal studies with 30 astronauts (10 short, 10 standard and 10 long-duration flights) to validate findings from our n-of-1 study

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