

Disrupting Healthcare using Deep Data and Remote Monitoring

Michael Snyder, PhD

Stanford University School of Medicine

May 2024

Conflicts: Personalis, SensOmics, Qbio, January AI,
Filtricine, Mirvie, Fodsel, Protos, Crosshair, Marble, Iollo,
RTHM, Iollo, Netbio, Next Thought



Present Day Healthcare is Broken

We need to be keeping people healthy instead of waiting until they are ill

1



2



Travel to a physician
for a health check

3



4



Draw a large amount of
blood-- hurts!

Office visits haven't changed
in **40 years**

5



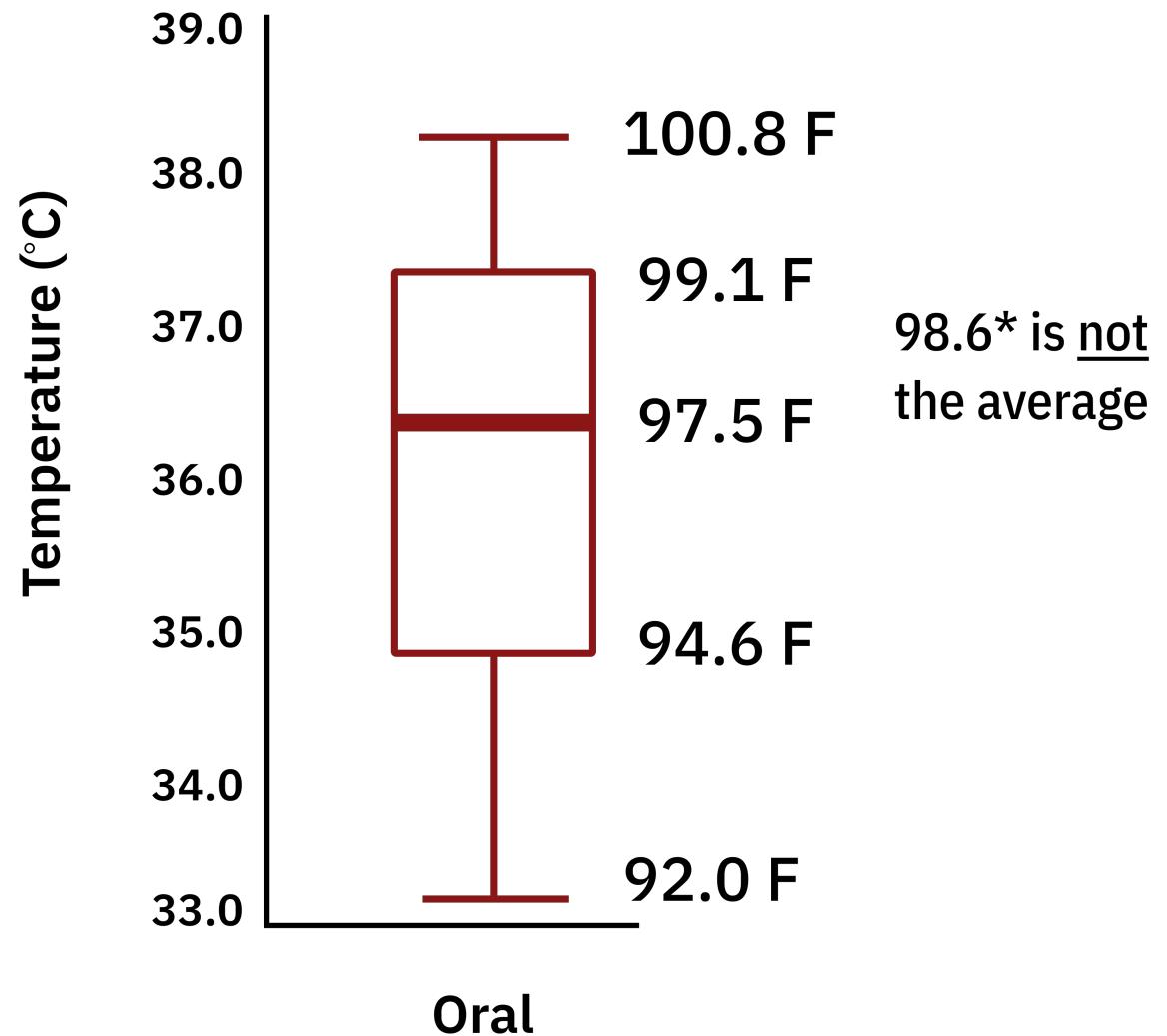
Treat you based on
population averages

Very few measurements are
made, many questionable

Importance in Individual Variation From Normal

Baseline Oral Temperature in 2,749 Healthy Individuals

Sund-Levander M. Scand J Caring Sci
2002;122-8 & N. Chronobio Int
2007;24:739-48

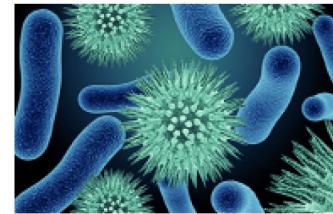


Health is a product of Genome & Exposome

Genome



Exercise



Pathogens

Food



Environmental
Exposures

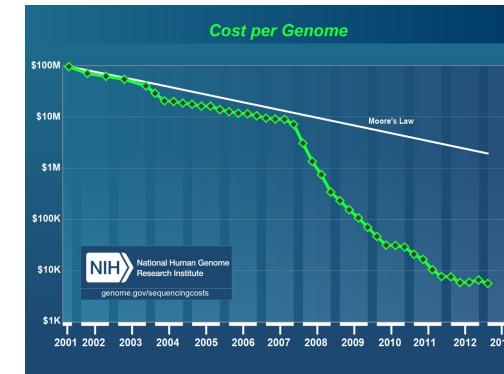


Mental
Health

Deep Data Technologies

1

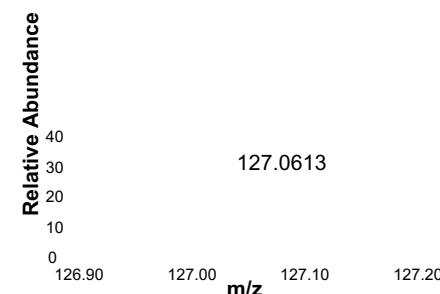
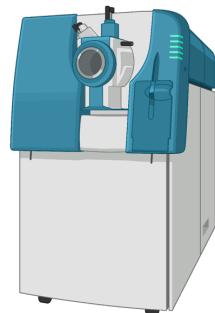
DNA Sequencing



Human Genome
Cost \$100

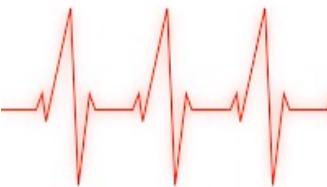
2

Mass
Spectrometry

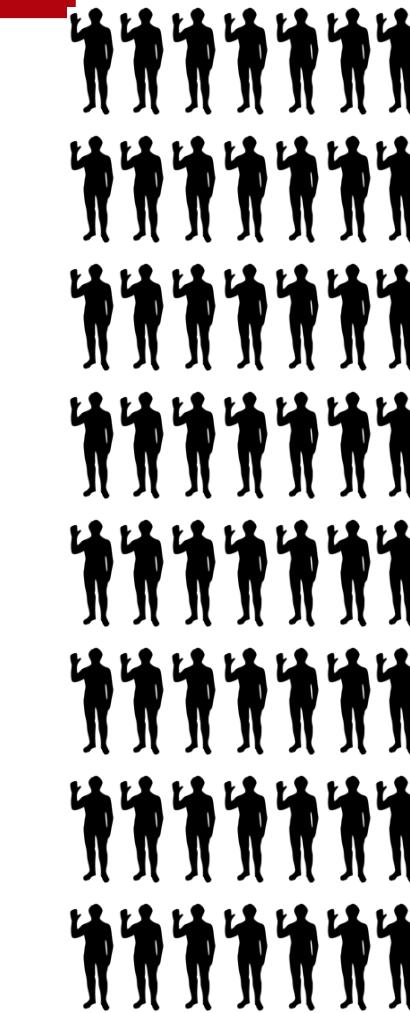


3

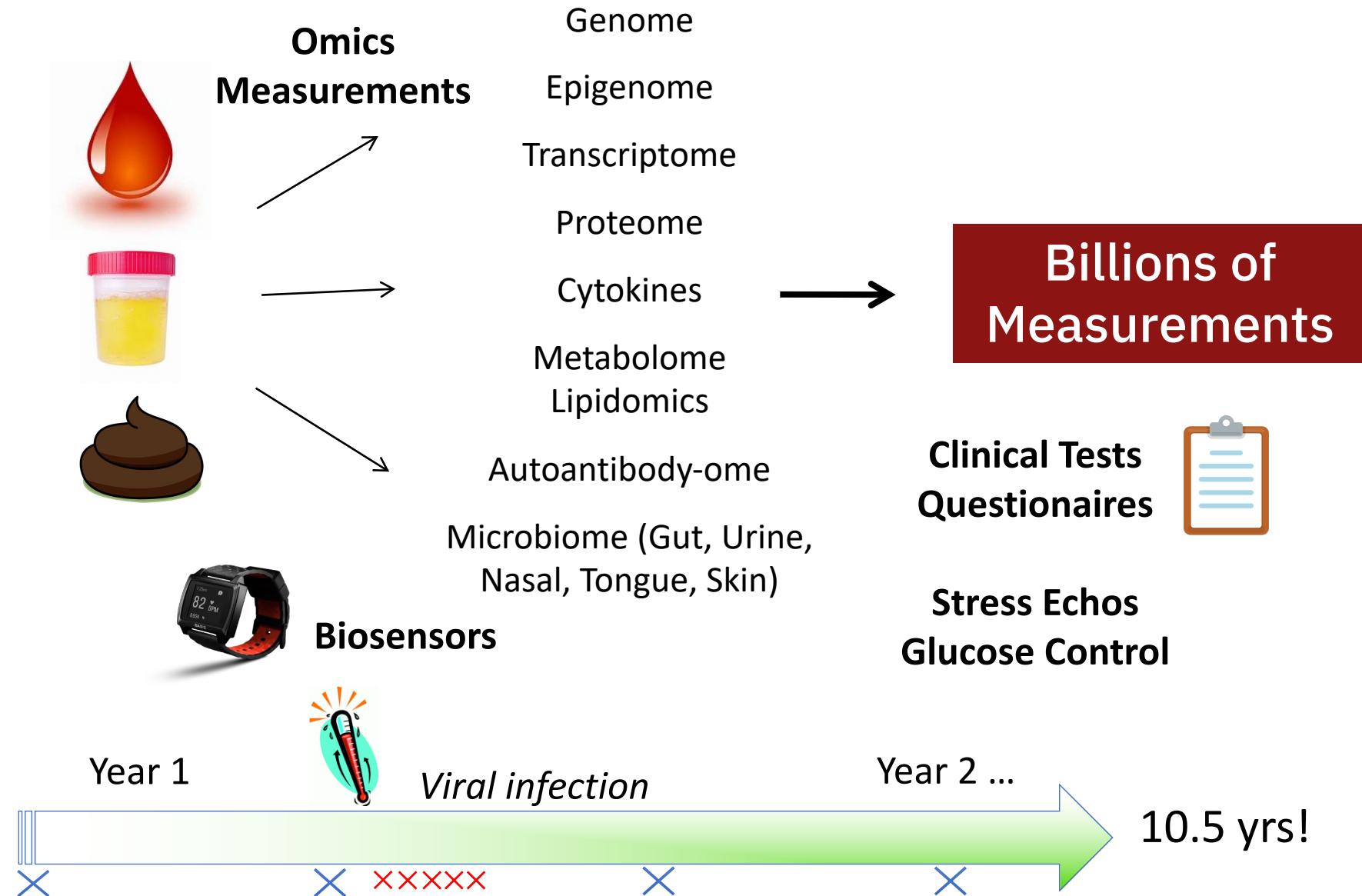
Wearables



Longitudinal Personal Omics Profiling



109 Individuals



Genome
Epigenome
Transcriptome
Proteome
Cytokines
Metabolome
Lipidomics
Autoantibody-ome
Microbiome (Gut, Urine,
Nasal, Tongue, Skin)



Biosensors



Viral infection



Billions of Measurements



Clinical Tests
Questionnaires

Stress Echos
Glucose Control

Year 1

Year 2 ...

10.5 yrs!

49 Major Health Discoveries

Metabolic

- 1 MODY mutation (gene)
- 1 ABCC8 Mutation (gene)
- 14 New Diabetes

Cardiovascular

- 6 Carotid Plaques (imaging)
- 1 Atrial Fib. (wearable)
- 1 RMB20 mutation (gene)
- 1 Reduced LVEF/GLS (imaging)
- 3 Dilated L. Atrium (imaging)
- 1 Pharmagenomic (gene)

Heme/Onc

- 7 Oncologic Risk Genes
(Thyroid Cancer in 1)
- 1 Lymphoma (Imaging)
- 1 MGUS (IgM)
- 1 Smoldering Myeloma (IgM)
- 1 α Thalassemia (Clinical)
- 1 β Thalassemia (Gene/Clinical)
- 1 Pros1 Mutation (gene)

Other

- 1 Sleep Apnea (wearable)
- 1 SLC7A9 mutation (cystinuria risk)
- 2 Macroalbuminuria

Infectious

- 1 Lyme Disease (wearable)

49 Major Health Discoveries

Metabolic

1 MODY mutation (gene)
1 ABCC8 Mutation (gene)
14 New Diabetes

Other

1 Sleep Apnea (wearable)
1 SLC7A9 mutation (cystinuria risk)
2 Macroalbuminuria

Cardiovascular

6 Carotid Plaques (imaging)
1 Atrial Fib. (wearable)
1 RMB20 mutation (gene)
1 Reduced LVEF/GLS (imaging)
3 Dilated L. Atrium (imaging)
1 Pharmagenomic (gene)

Infectious

1 Lyme Disease (wearable)

Heme/Onc

7 Oncologic Risk Genes
(Thyroid Cancer in 1)
1 Lymphoma (Imaging)
1 MGUS (IgM)
1 Smoldering Myeloma (IgM)
1 α Thalassemia (Clinical)
1 β Thalassemia (Gene/Clinical)
1 Pros1 Mutation (gene)



Genome Sequencing

– First 70 People

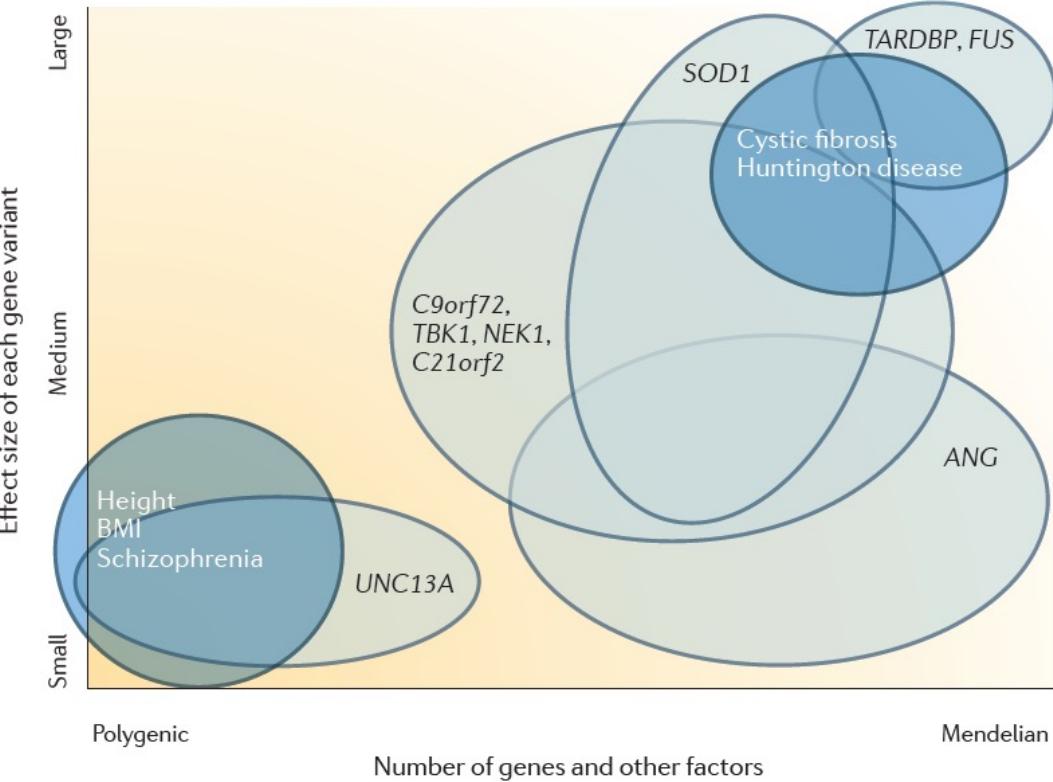


Twelve have important pathogenic mutations:

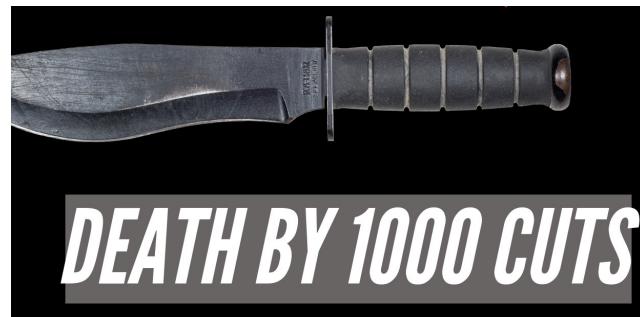
- SDHB (2X): high freq. of neuroendocrine tumors[^]
- APC (2X): Colon cancer
- BRCA1: Breast & ovarian cancer
- MUTYH: Colon cancer
- SLC7A9: Cystinuria
- RBM20: Dilated cardiomyopathy[^]
- CHEK2: Breast cancer
- PROC: Affects coagulation
- HNF1A: MODY mutation[^]
- ABCC8: Hyperinsulinemic hypoglycemia

Genetics involves:

1. Single gene (Mendelian) BRCA, Cystic Fibrous (CFTR)
2. Complex disease: Thought to be due to many genetic changes of small effect



Many



Single gene



Polygenic Risk Score: Use 1000s to Millions of Common SNPs

<u>Disease</u>	<u># SNPs</u>
Coronary Artery Disease	6.6M
Atrial Fibrillation	6.7M
Type 2 Diabetes	6.9M
Inflammatory Bowel Disease	6.9M
Breast Cancer	5.2K

[Khera et al. Nat Genet. 2018 50: 1219–1224](#)

Abdominal Aortic Aneurysm (AAA)

Clinical Facts

- Asymptomatic at onset - fast growing
- 90% mortality rate upon rupture
- The 10th leading cause of death in US
- **No early screening tool**

Decoding the Genomics of Abdominal Aortic Aneurysm

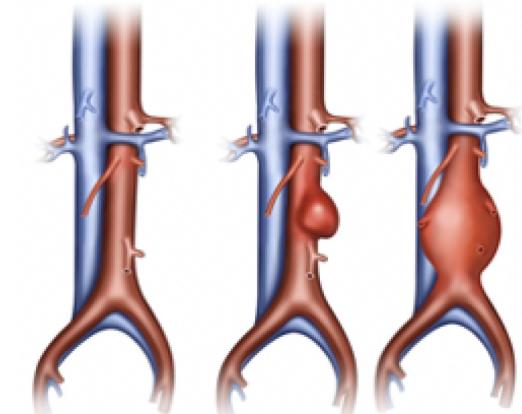
Jingjing Li,^{1,2,6,7} Culping Pan,^{1,3,6,7} Sai Zhang,^{1,6,7} Joshua M. Spin,^{3,4,8} Alicia Deng,^{3,4,8} Lawrence L.K. Leung,^{3,4,6}

Ronald L. Delman,^{6,8} Philip S. Tsao,^{3,4,8,*} and Michael Snyder^{1,3,4,8}

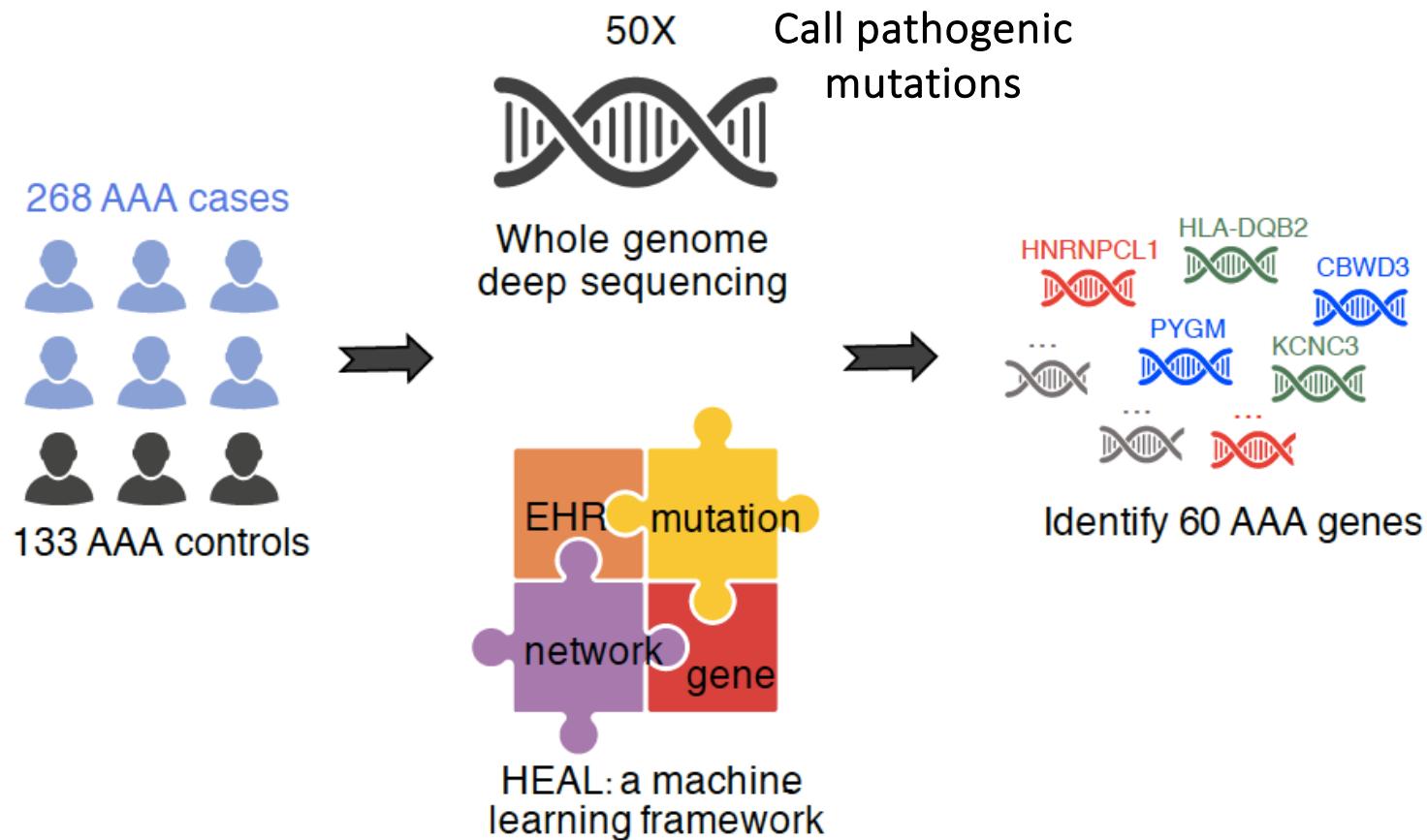
¹Department of Genetics, Center for Genomics and Personalized Medicine, Stanford University School of Medicine, Stanford, CA 94306, USA

Epidemiology

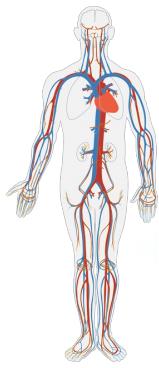
- **Heritability: 70%**
- Aged population >50 yo.
- Lifestyle matters
- High blood pressure
- Cholesterol etc



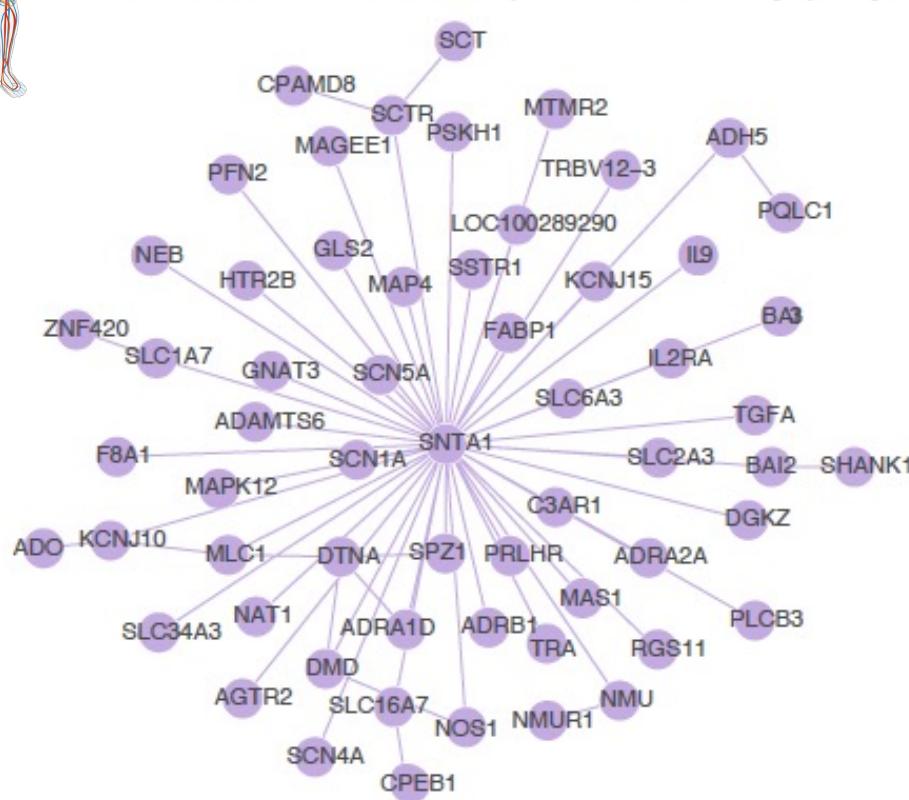
Identifying Genes Associated with AAA



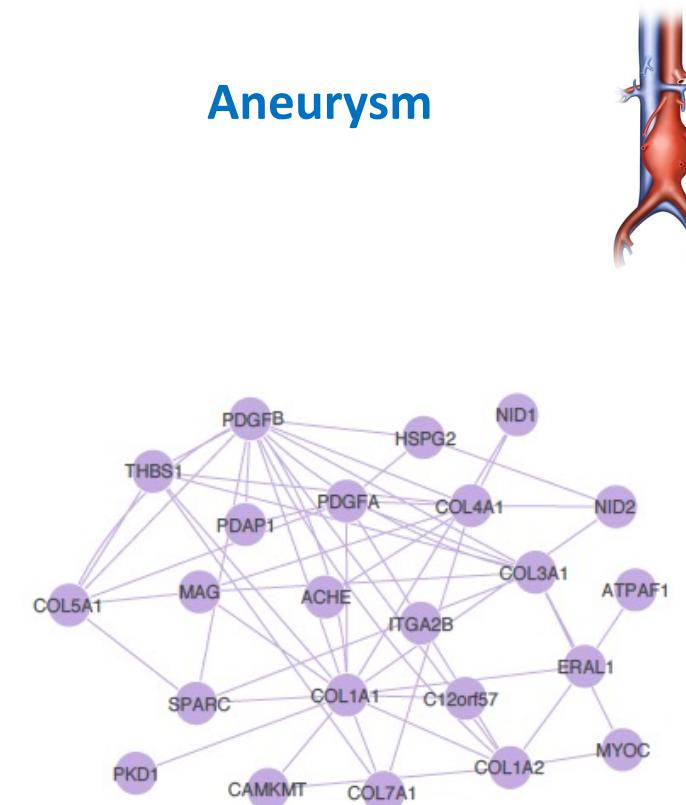
Relevant Modules



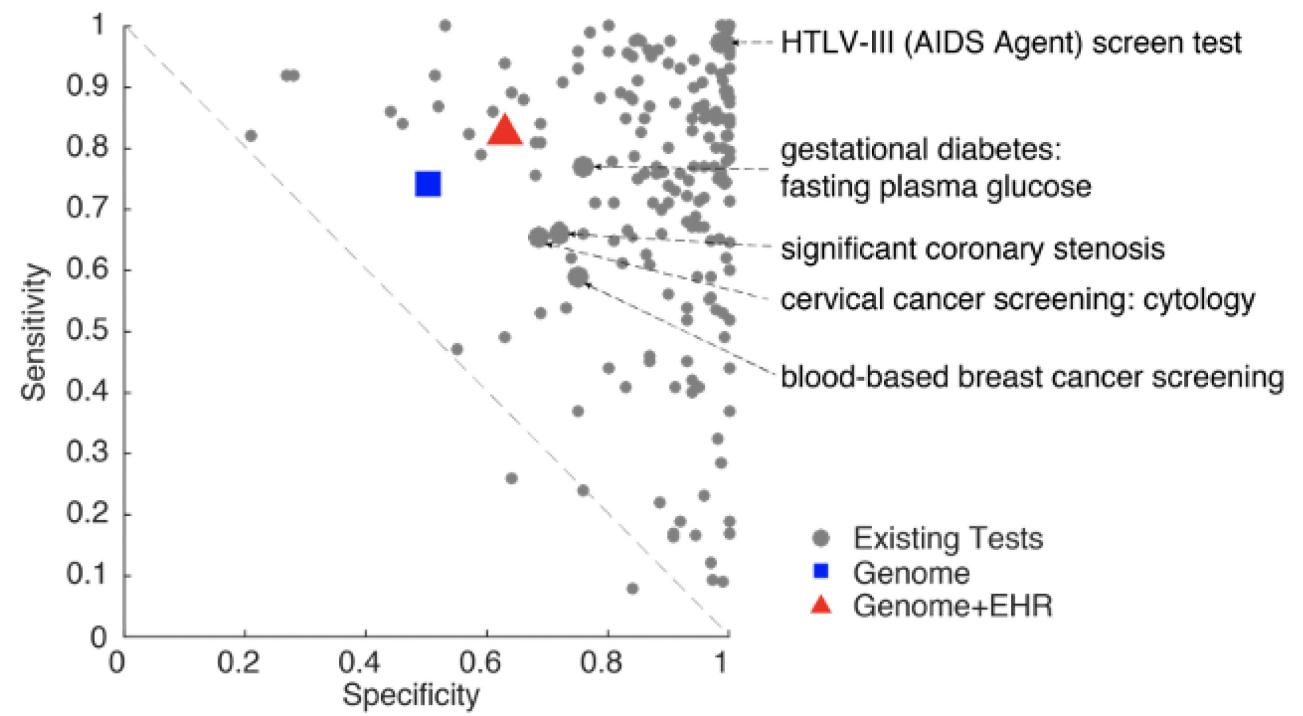
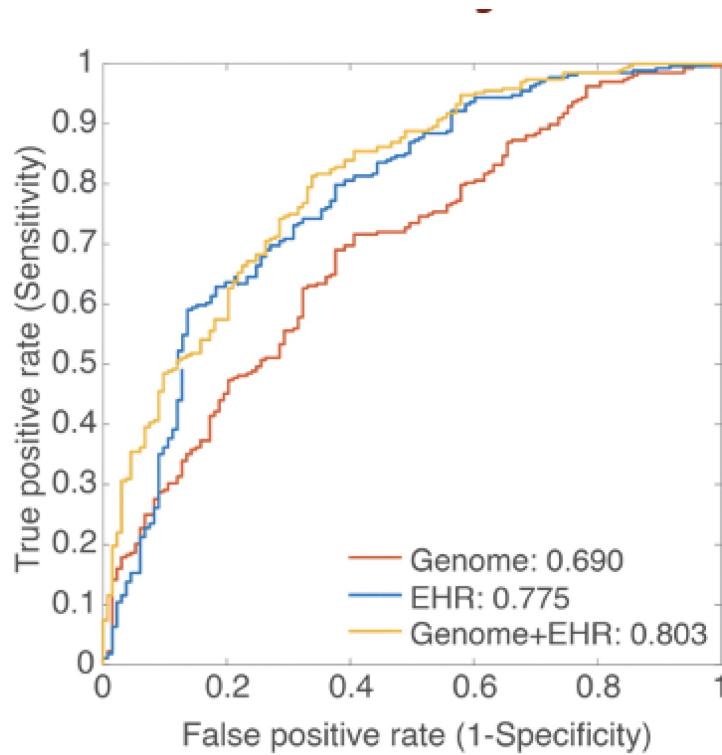
Blood Circulation, Blood Pressure,
Cardiomyopathy



Aneurysm



HEAL accurately predicts AAA risk -> clinical utility

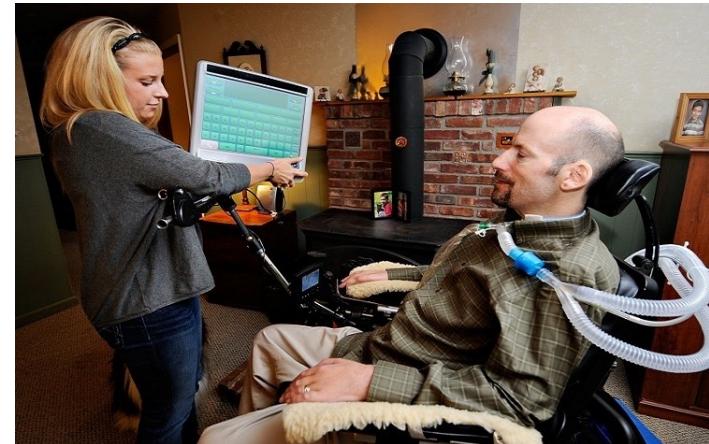
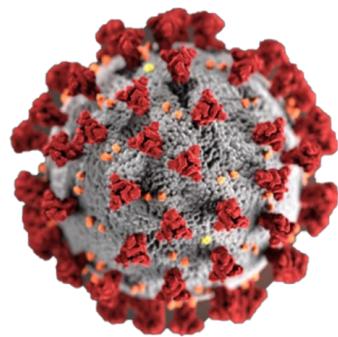


Genetics of Complex Disease Using Machine Learning & GWAS Information

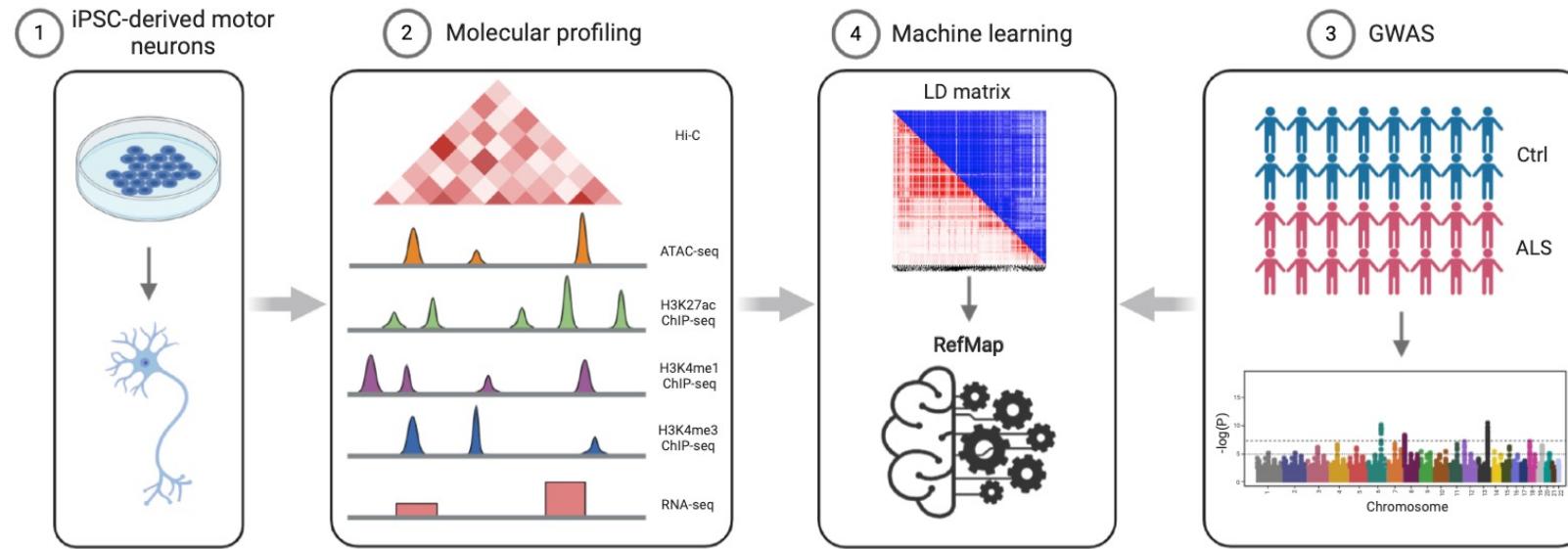
Sai Zhang, Johnathan Cooper-Knock

1. ALS

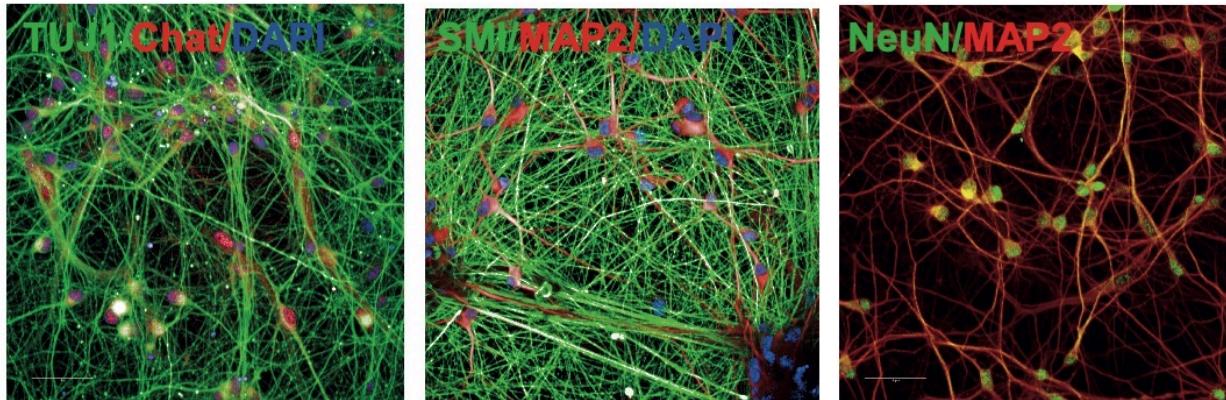
2. COVID-19 Severity



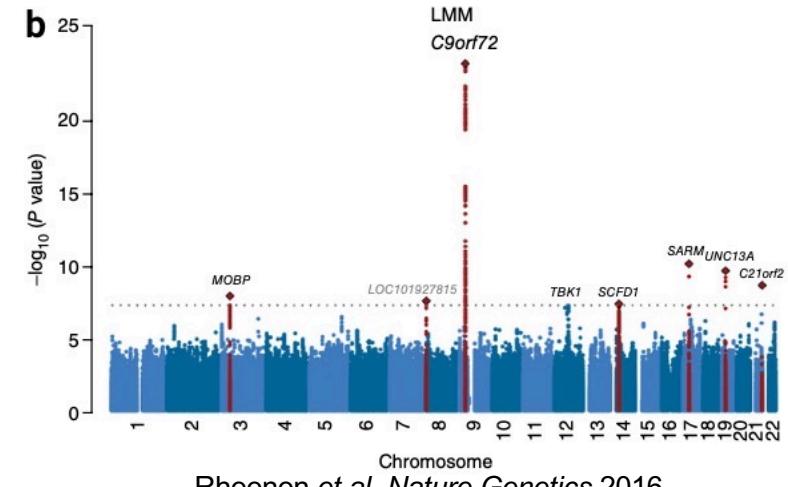
Identification of ALS Genes Using Machine Learning (AI)



Profiling motor neurons for gene regulatory regions ATAC-Seq, etc

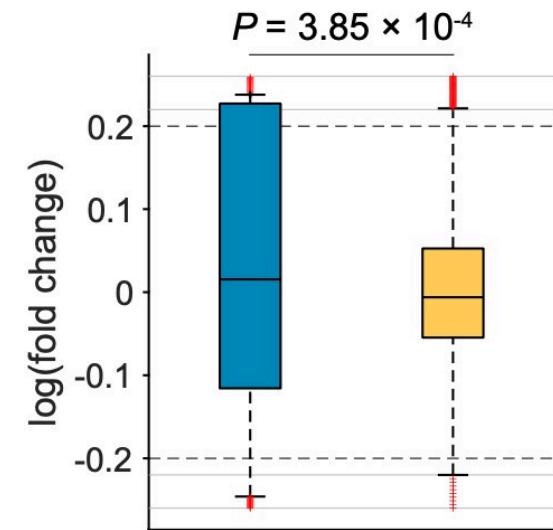


GWAS: 12,577 cases and 23,475 controls



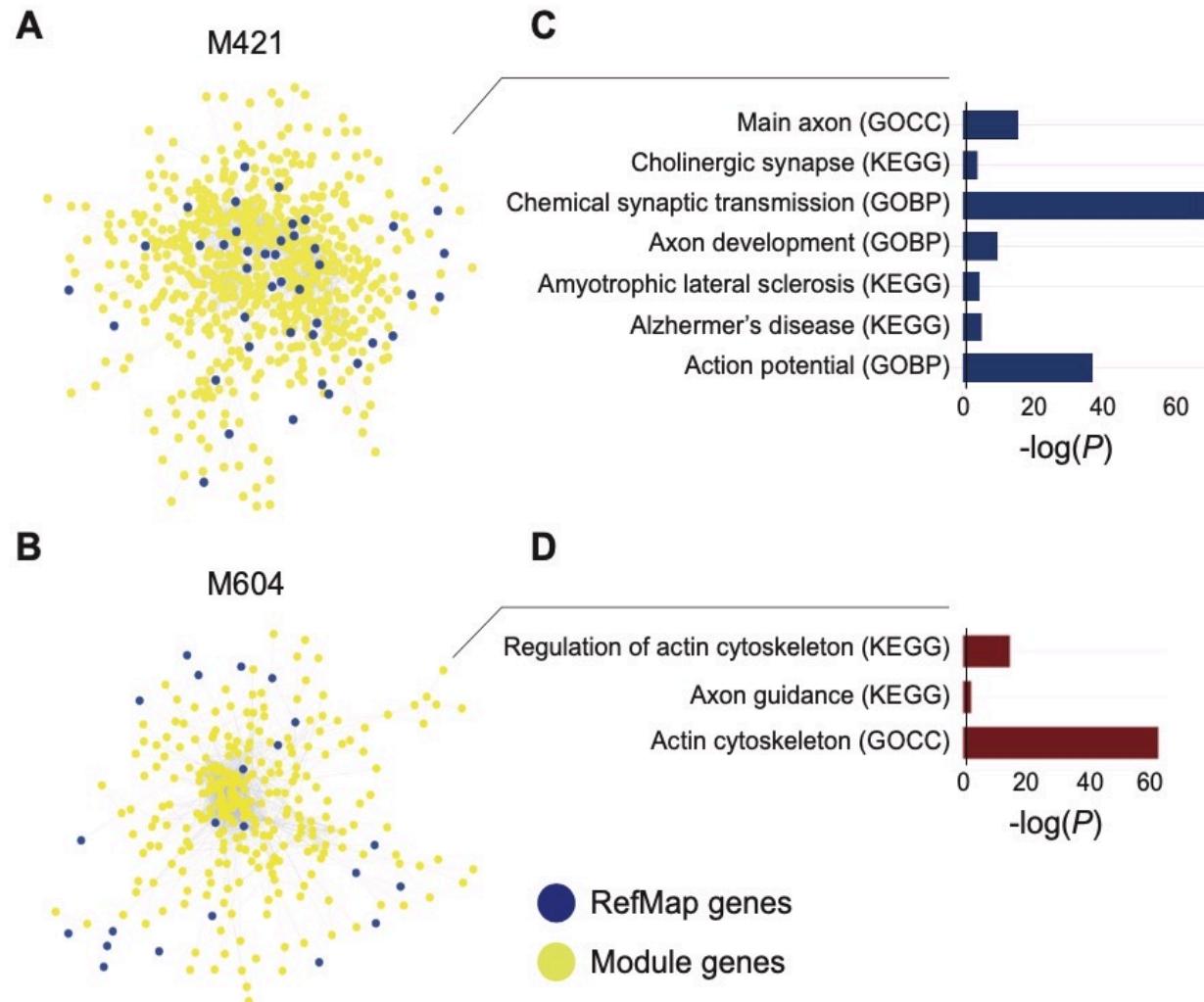
**RefMap identifies: 690 ALS genes (over the 7 known previously)
Accounts for 36% of heritability (over the 6% known previously)**

- Overlap with many well-known ALS genes
 - C9orf72, ATXN2, SIGMAR1*
- Significantly enriched with known ALS genes
 - Based on a well-curated ALS gene list ($n=260$)
 $P=5.2e-3$ (OR=2.07)
 - ClinVar $P=3e-2$ (OR=3.06)



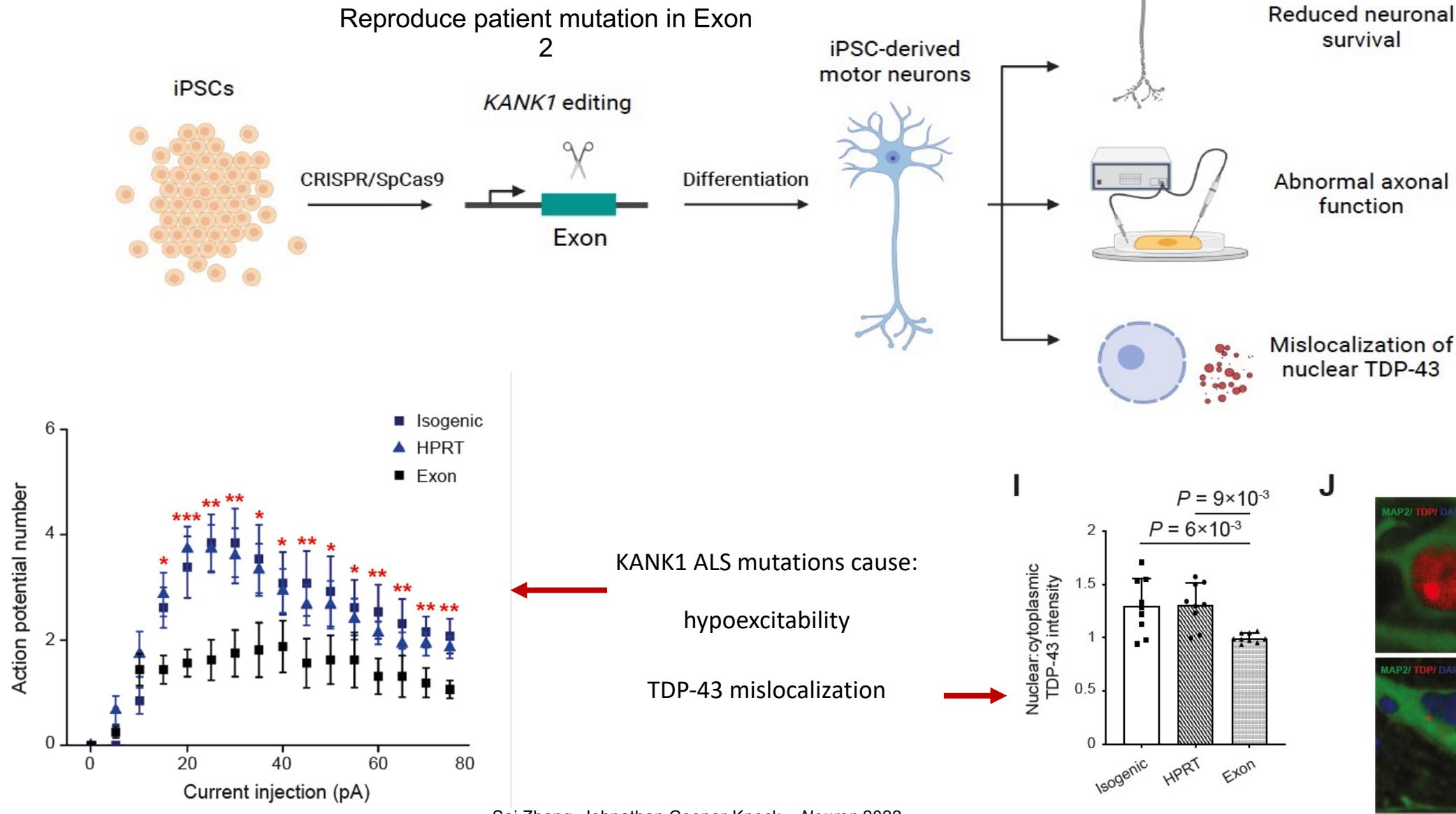
Down-regulated in both ALS
brain tissues and iPSC MNs

Two modules enriched with RefMap genes

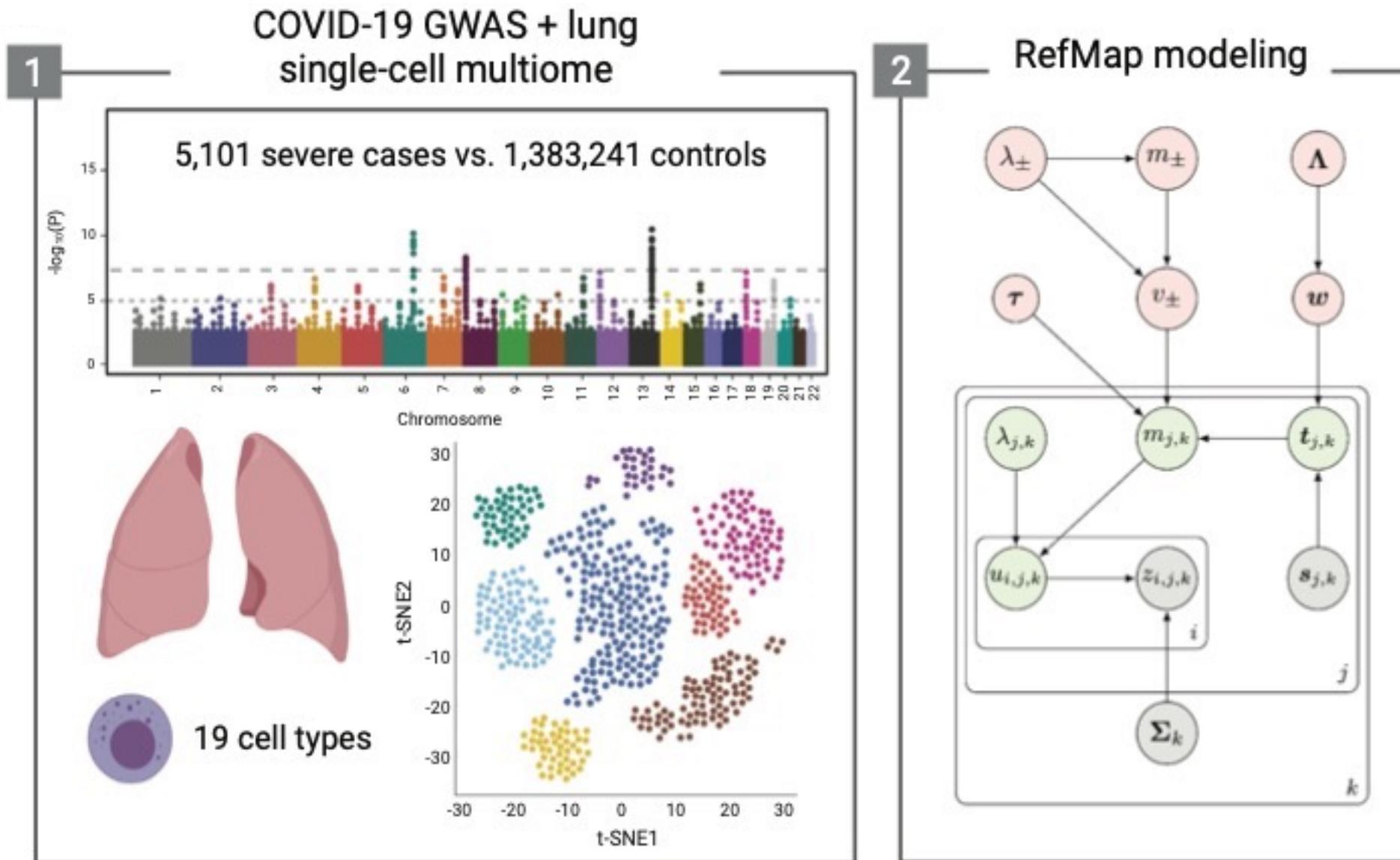


Genetic evidence for initiation of ALS in the distal axon

Experimental validation of KANK1

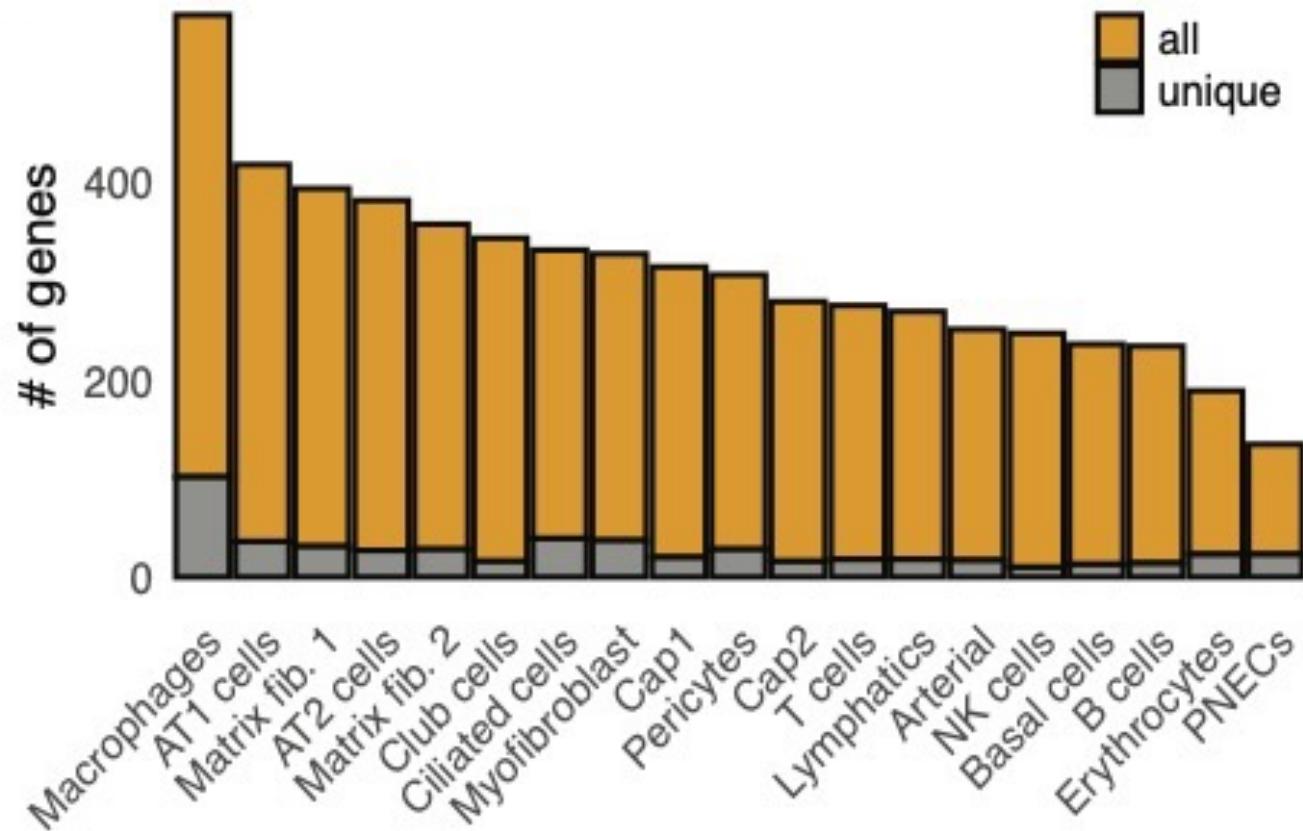


COVID Severity: GWAS + Single-Cell Multiome → Genes

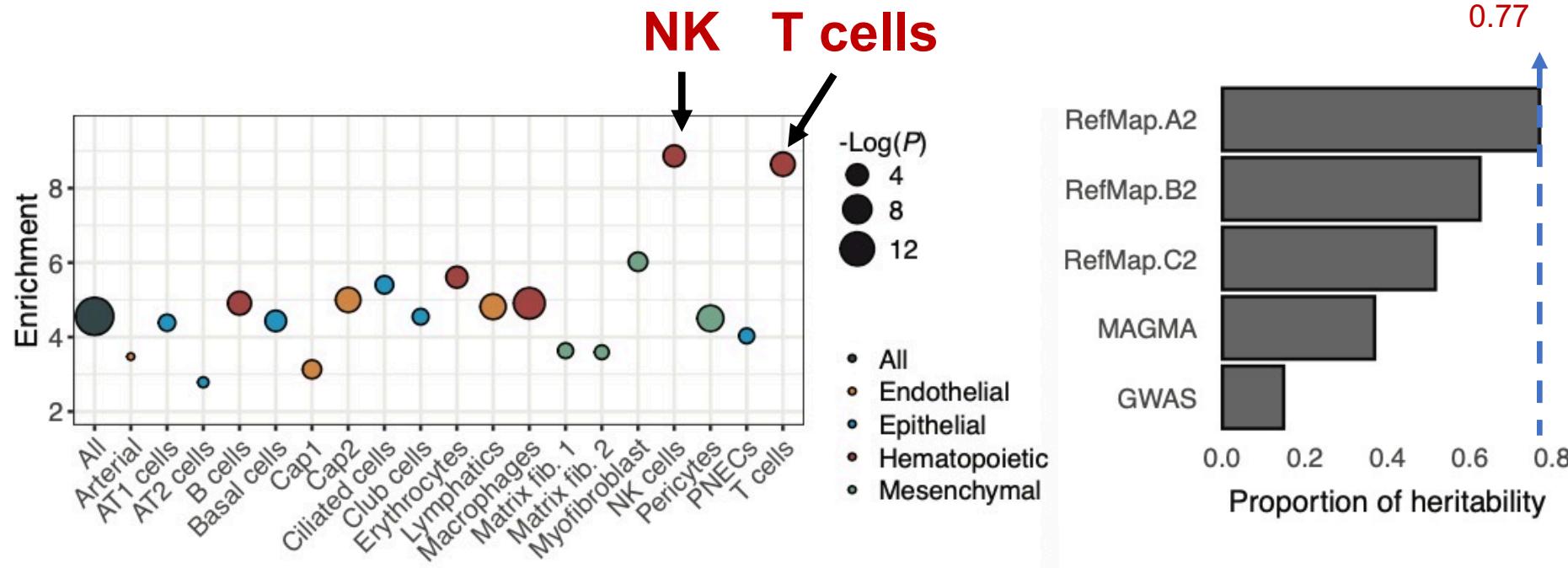


Mapping Target Genes Per Cell Type

6,662 1kb regions →
1,375 genes across 19 cell types



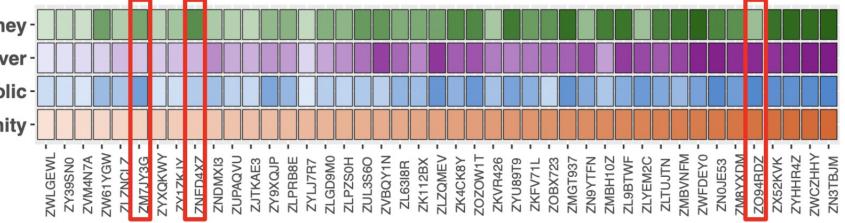
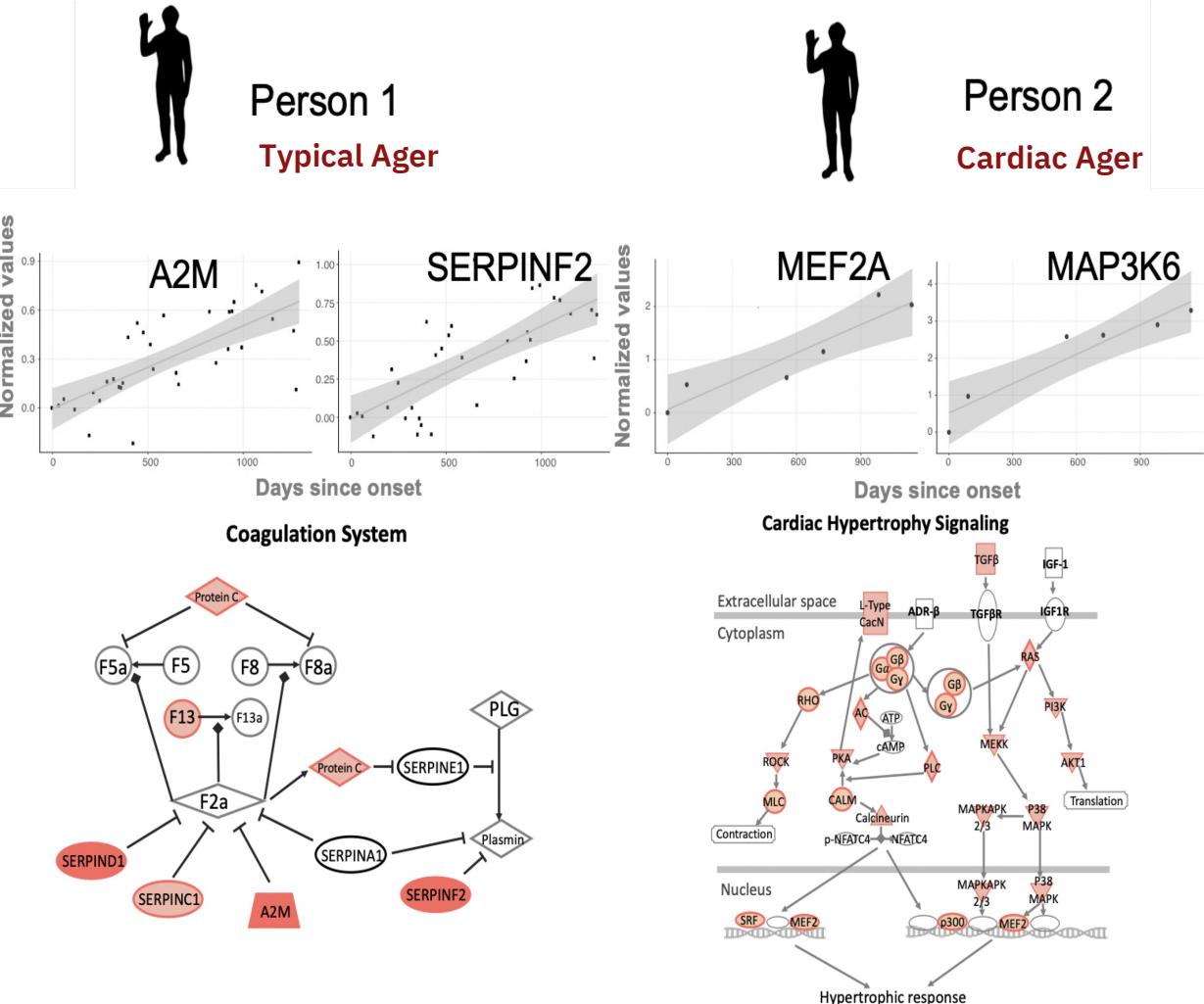
Heritability Analysis Identifies NK Cells and Other Immune Cells



Failed activation of NK cells in the initial stage of SARS-CoV-2 infection is permissive of viral replication, leading to fatal hyperinflammation

How People Age

Personal aging and molecular pathways

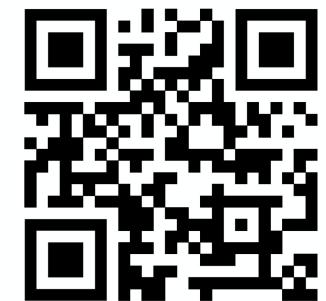


Ageotypes: We are all different!

QBio

Benefits of Multi-variate Longitudinal Measurements for Early Detection
Deep data plus whole body MRI

	Multi-variate evidence	Rate of change evidence
Early Stage Leukemia		
Low Grade Brain Lesion		
Aortic Aneurysm		
Fatty Liver & Diabetes		
Cardiovascular Disease & Pre-Diabetes		
Early stage pancreatic cancer		
Early stage prostate cancer		
Early stage ovarian cancer		

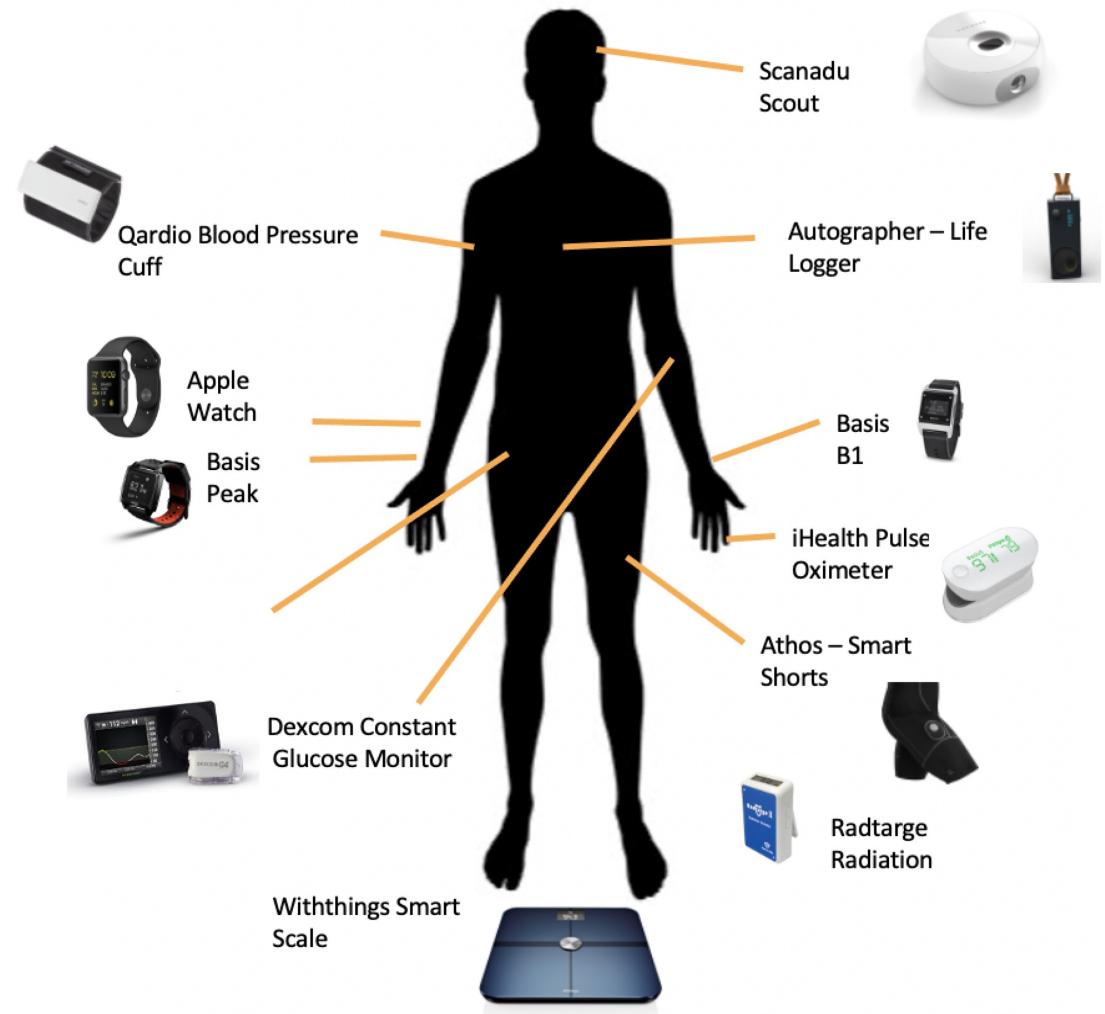


“Amazoning” Health Care

You do your shopping at home
– why not do your healthcare at home?



Wearables
Microsampling
at home



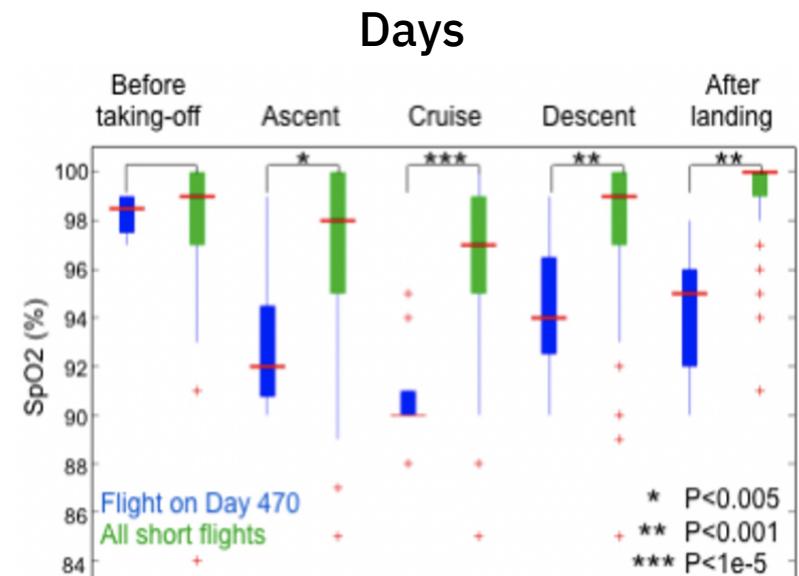
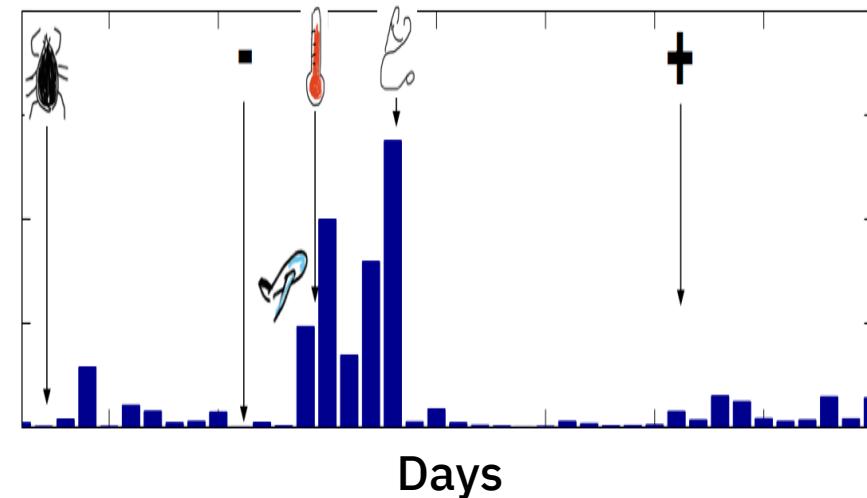
Early Detection of Lyme Disease

We could detect Lyme with wearables devices (2017)

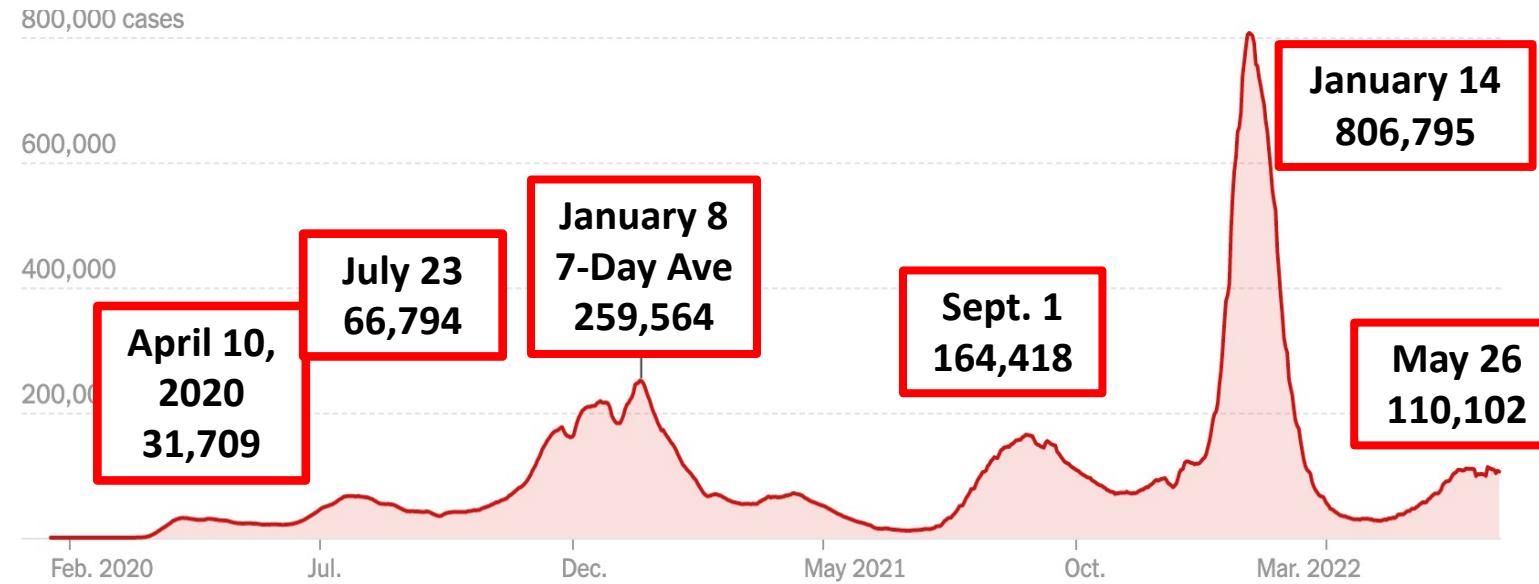
The screenshot shows a research article from PLOS Biology. The title is "Digital Health: Tracking Physiomes Activity Using Wearable Biosensors Reveals Useful Health-Related Information". The authors listed are Xia Li^{1*}, Jessilyn Dunn^{1,2*}, Denis Salins^{1*}, Gao Zhou¹, Wenyu Zhou¹, Sophia Miryam Schüssler-Fiorenza Rose^{3,4}, Dalia Perelman⁵, Elizabeth Colberg², Ryan Runge¹, Shannon Rego³, Ria Sonecha¹, Somalee Datta¹, Tracey McLaughlin³, Michael P. Snyder^{1*}. The article is from the Department of Genetics at Stanford University School of Medicine, Stanford, California, United States of America, and the Mobilize Center at Stanford University, Palo Alto, California, United States of America. The abstract discusses how portable biosensors allow frequent measurement of health-related physiology and how they can be used to monitor physiological changes during various activities and diagnose diseases. It mentions recording over 250,000 daily measurements for up to 43 individuals, finding personalized circadian differences in physiological parameters, and identifying changes in environments like airline flights (decreased peripheral capillary oxygen saturation [SpO_2] and increased radiation exposure). The study found associations between reduced pressure/oxygen and fatigue on flights.



Resting Heart Rate Increased!



US COVID-19 Cases Per Day



Temperature

Does it work?



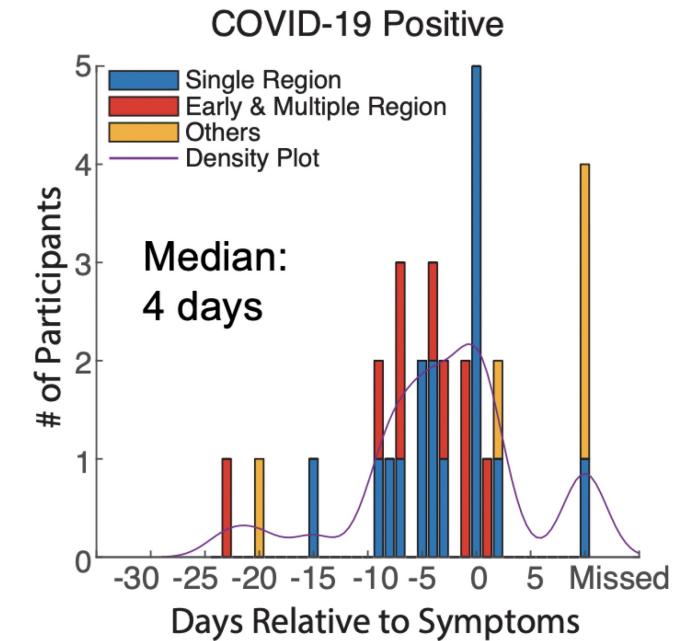
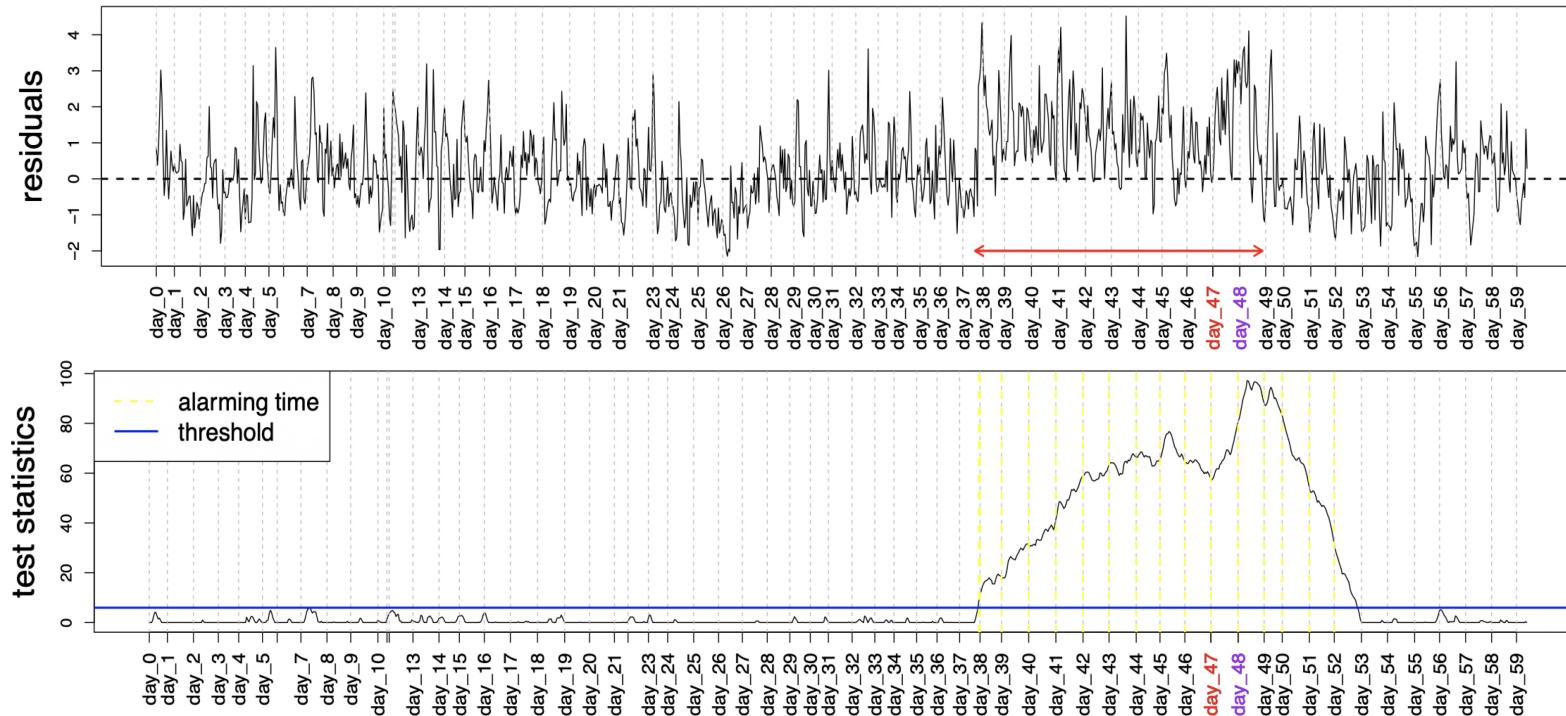
Antigen or PCR

Slow, expensive sporadic

Identifying COVID-19 at an Early Stage

5,300 Fitbit Participants

Pre-symptomatic detection ~4 days in advance of symptoms



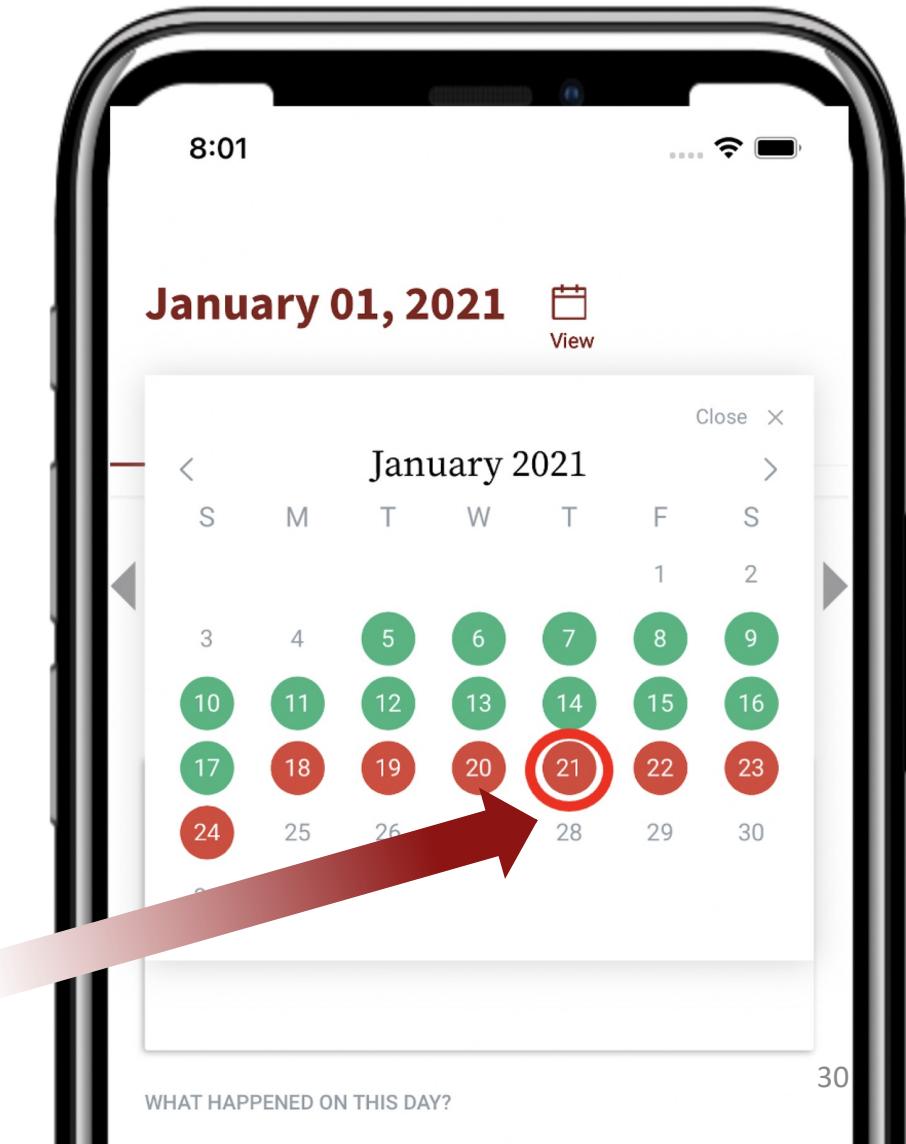
Real-Time Alerting System

A novel algorithm and cloud system capable of detecting physiological stresses in real time

Real COVID-19 Positive Case

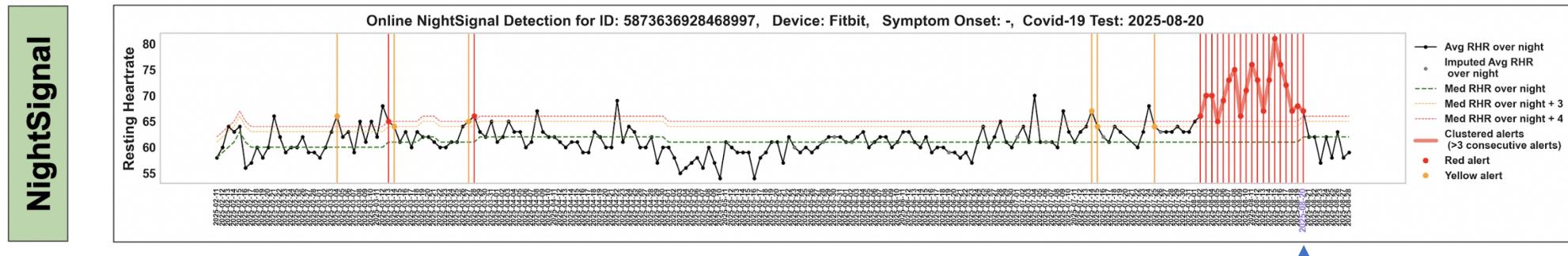
Works 80% of the time (67/84)

Symptom Onset



Asymptomatic Detection Examples

Fitbit



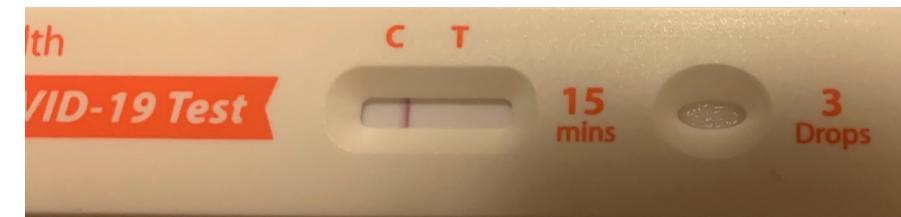
Diagnosed

April 2022



COVID19 COVID19
Negative Positive
Test Test

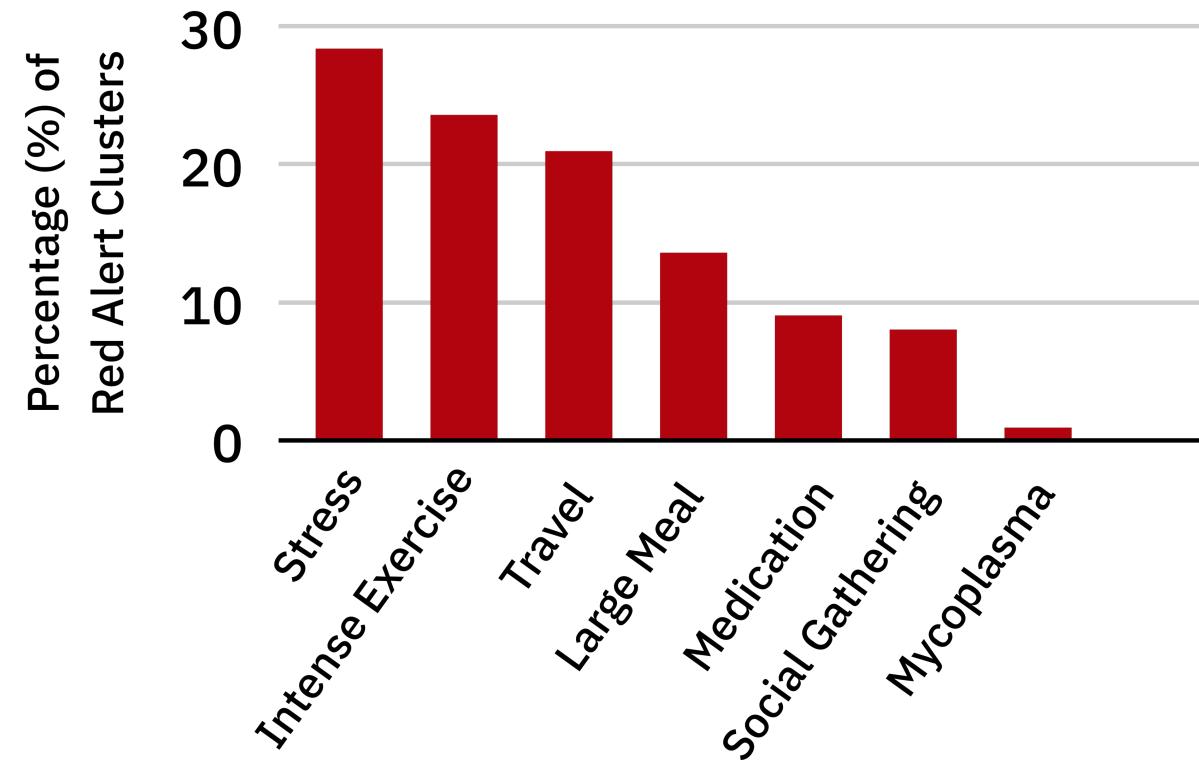
20 21 22 23
26 27 28 29 30



Other Stress Triggers

Wearable devices detect changes in physiology brought upon by various stress triggers other than COVID-19

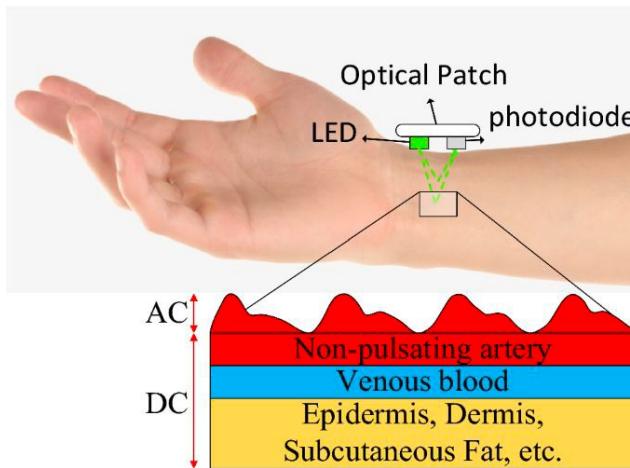
Non COVID-19 Activity Alerts



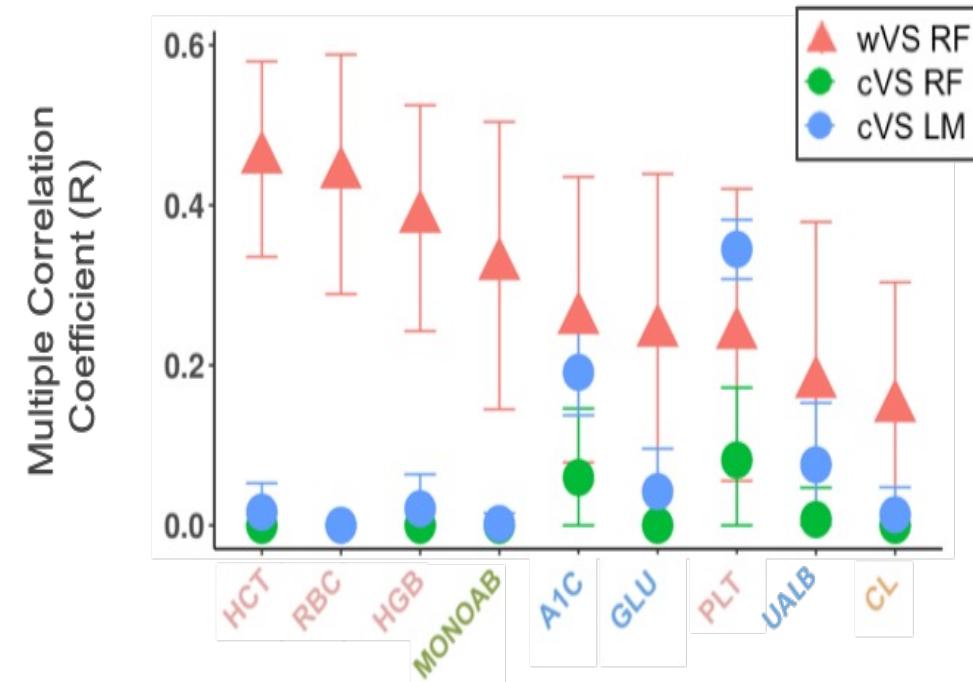
Prediction of Other Clinical Biomarkers From a SmartWatch Using AI



Photoplethysmography (PPG)



Pribadi et al. Microsyst Technol 26, 3409–3420 (2020).



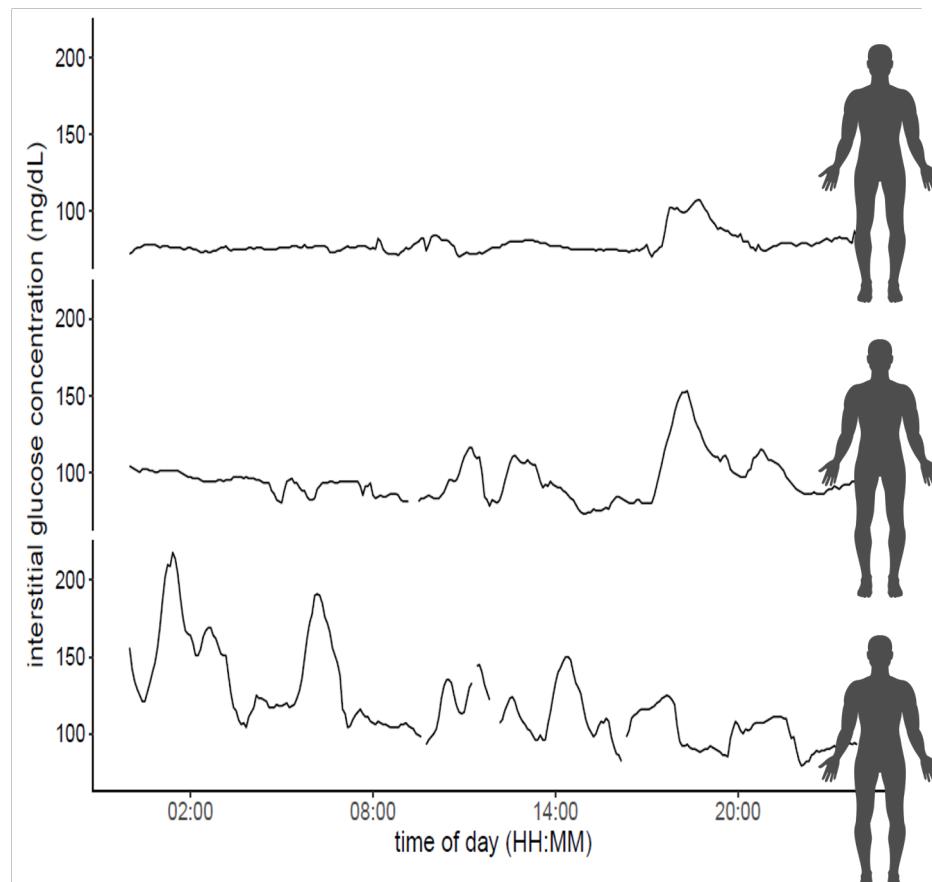
Continuous Glucose Monitoring

Normal “healthy” people can have glucose dysregulation

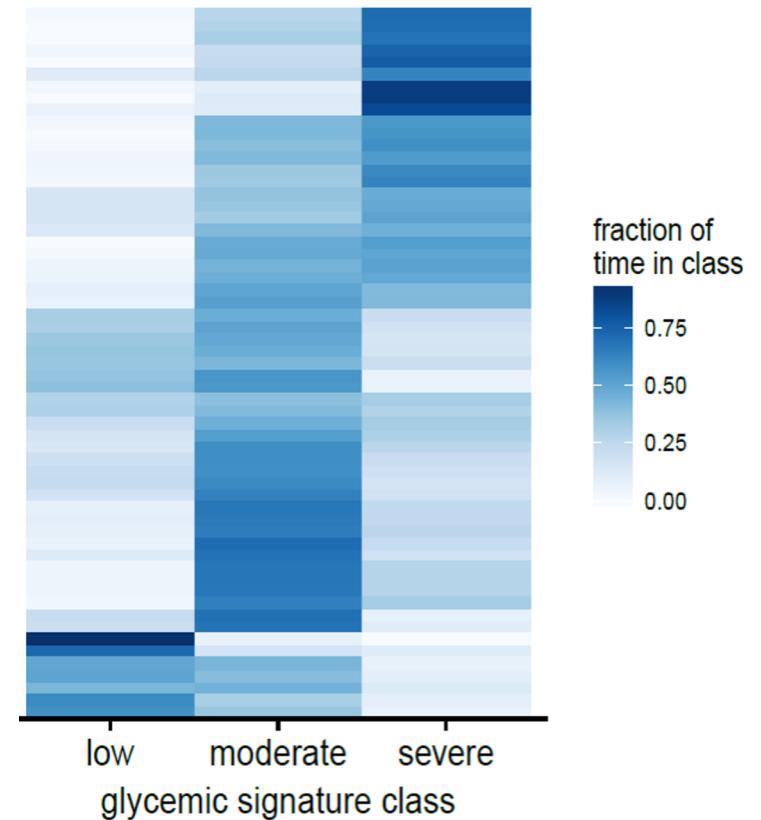
Dexcom



Abbott

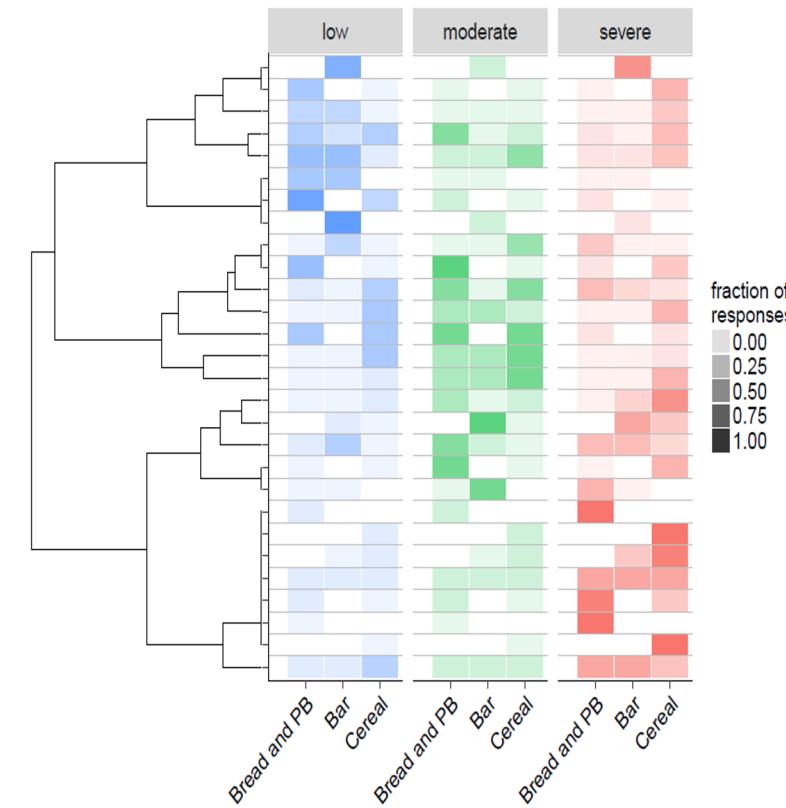
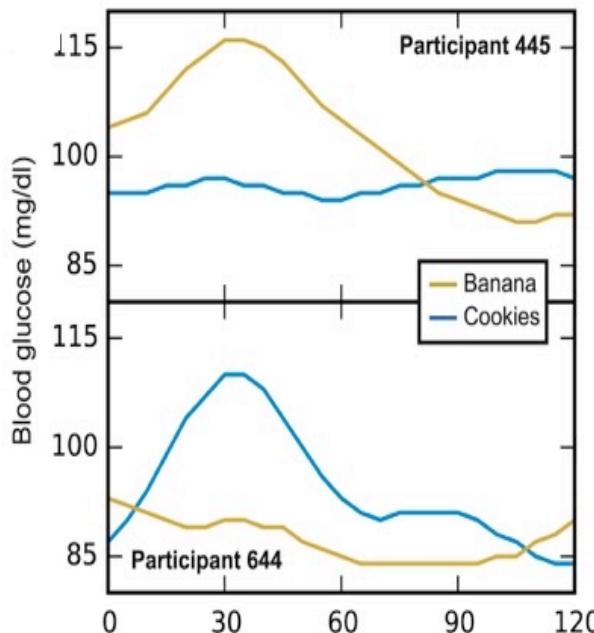


Glucotypes



Continuous Glucose Monitoring

Different people spike to different foods



Bread +
Peanut
Butter



Protein Bar



Cornflakes
+ Milk

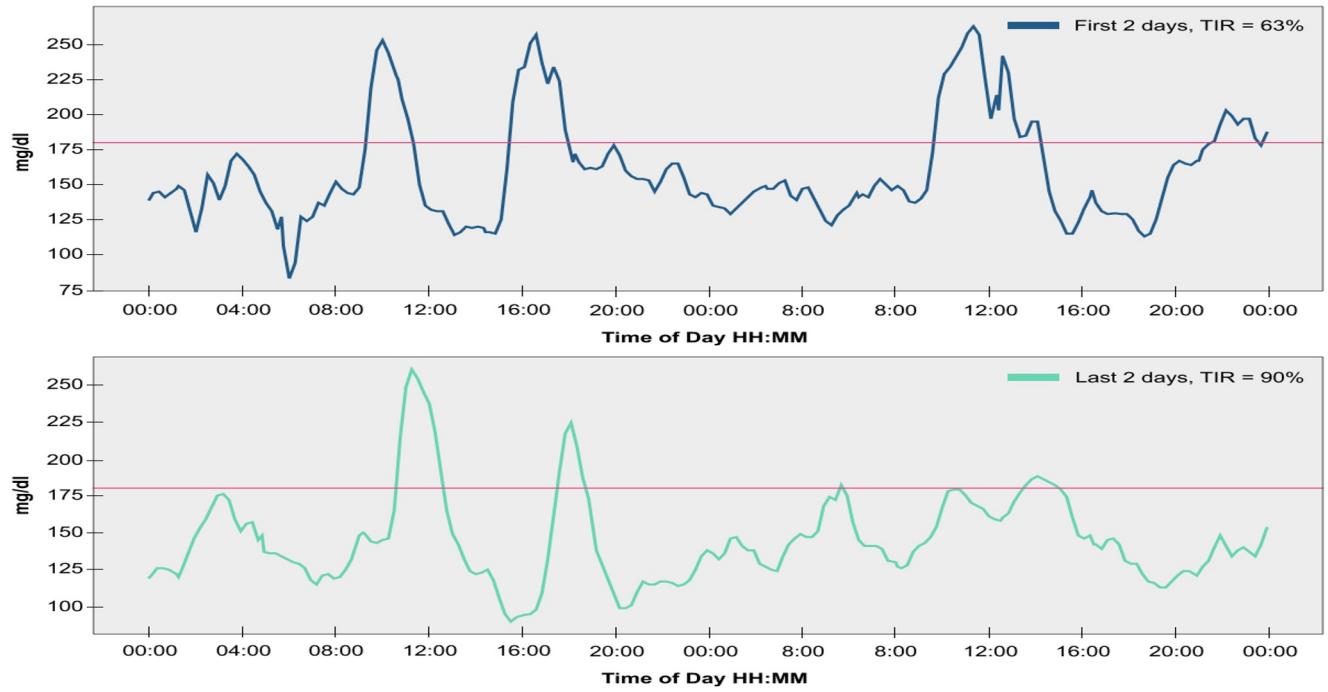
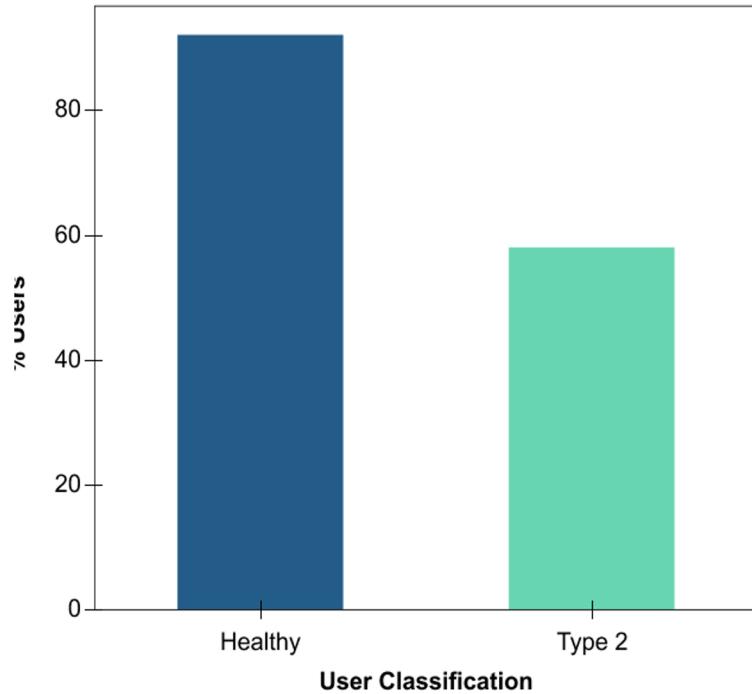
80%



From: Zeevi DZ, et al. Elinav E, Segal E. Personalized Nutrition by Prediction of Glycemic Responses. *Cell*. 2015 Nov 19;163(5):1079-94. doi: 10.1016/j.cell.2015.11.001. PubMed PMID: 26590418.

Hall ... Snyder, PloS Biol 2018

Sugar Challenge (655 Participants with lots of data): CGM Plus Logging App Improves TIR in 10 days



Zahadani AD, McLaughlin T, Snyder MP.
Diabetes Ther 2021, 12:1871-1886

January



Remote Home Monitoring Using Microsampling

Mitra
Microsampling
Collection



Overnight Delivery

Lab Processing



>2000
Measurements

Lab Analysis



Lipidomics



Metabolomics

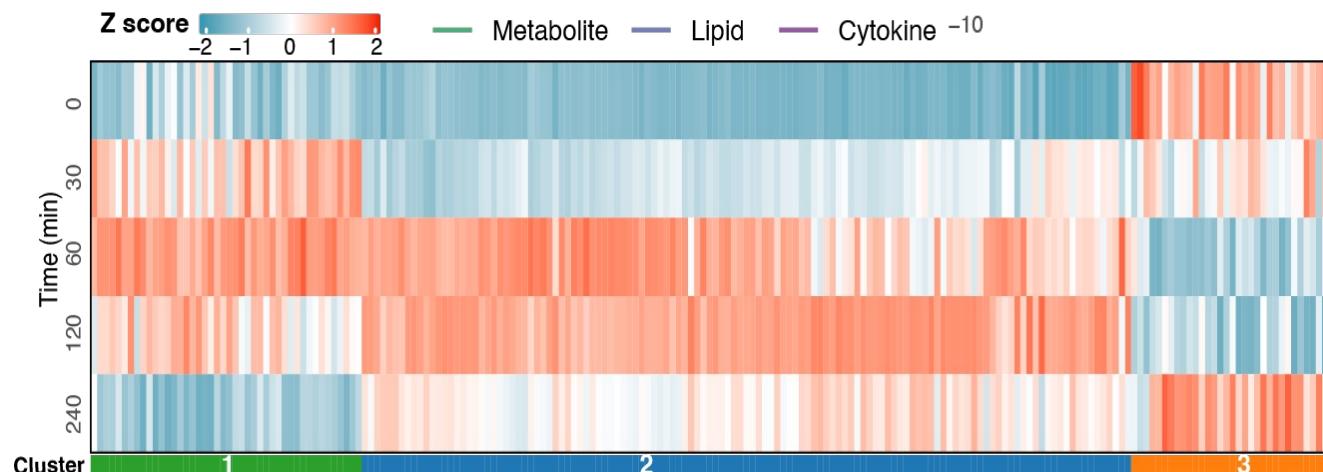
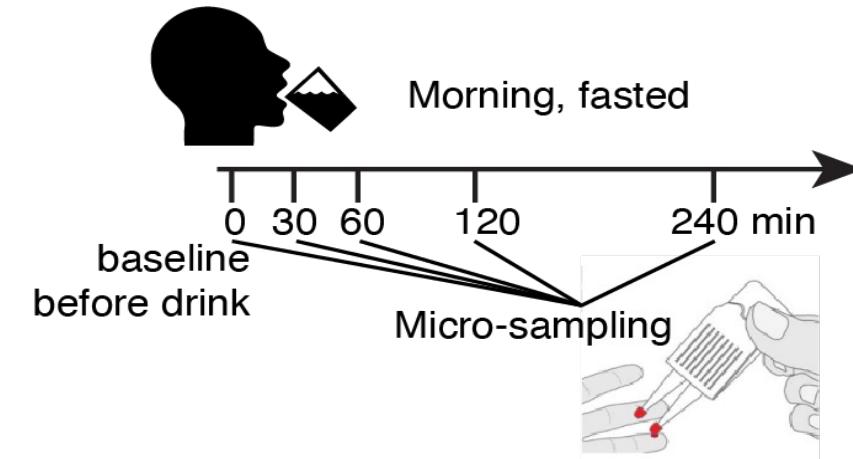


Proteomics

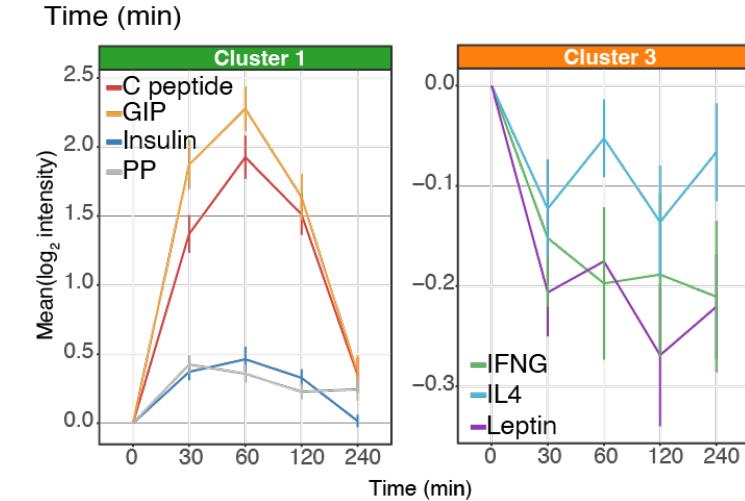
Cytokine
Cortisol
Total protein
Hormone

Response to Ensure Shake

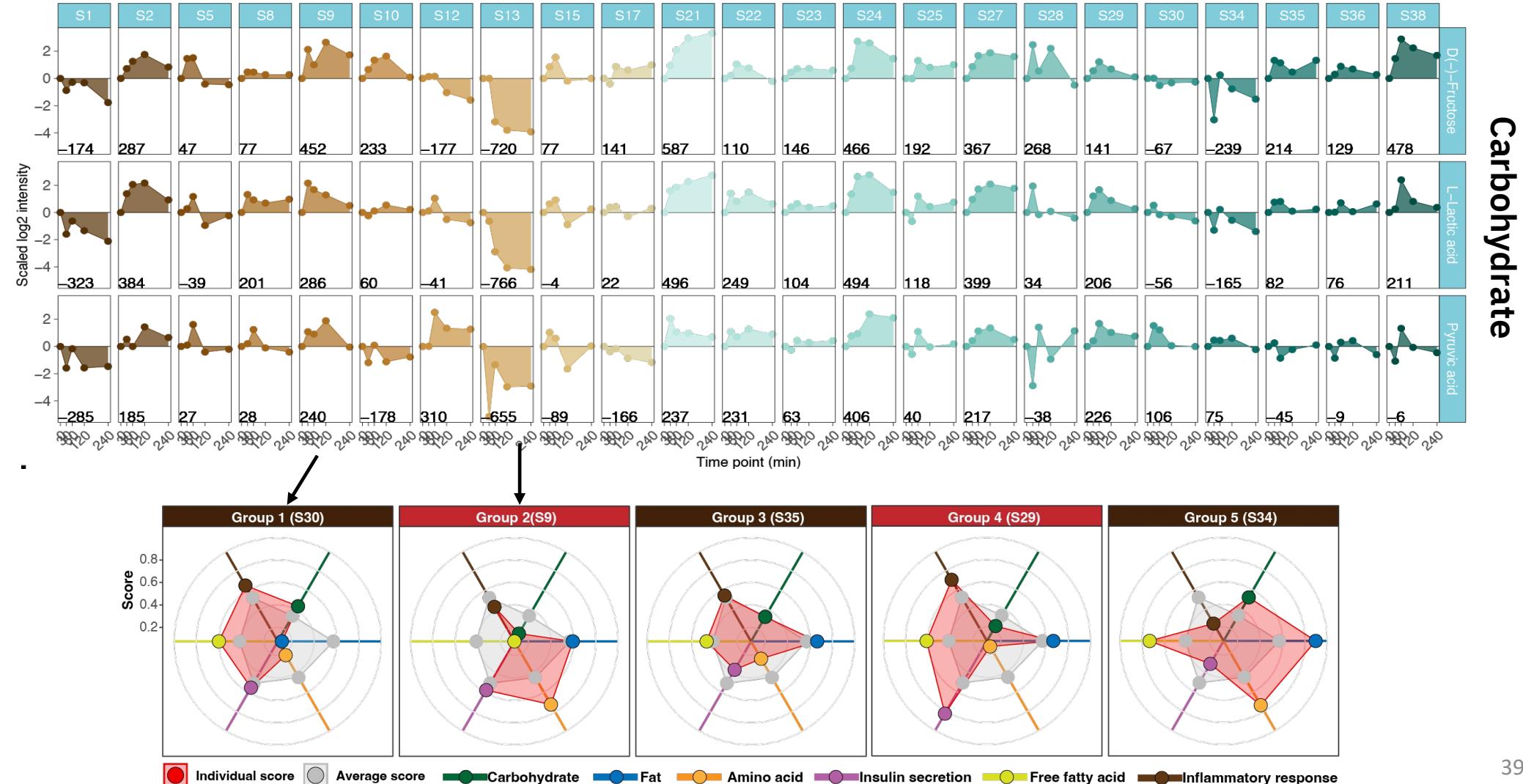
Remote monitoring working
on sampling at home



Hundreds of molecules change

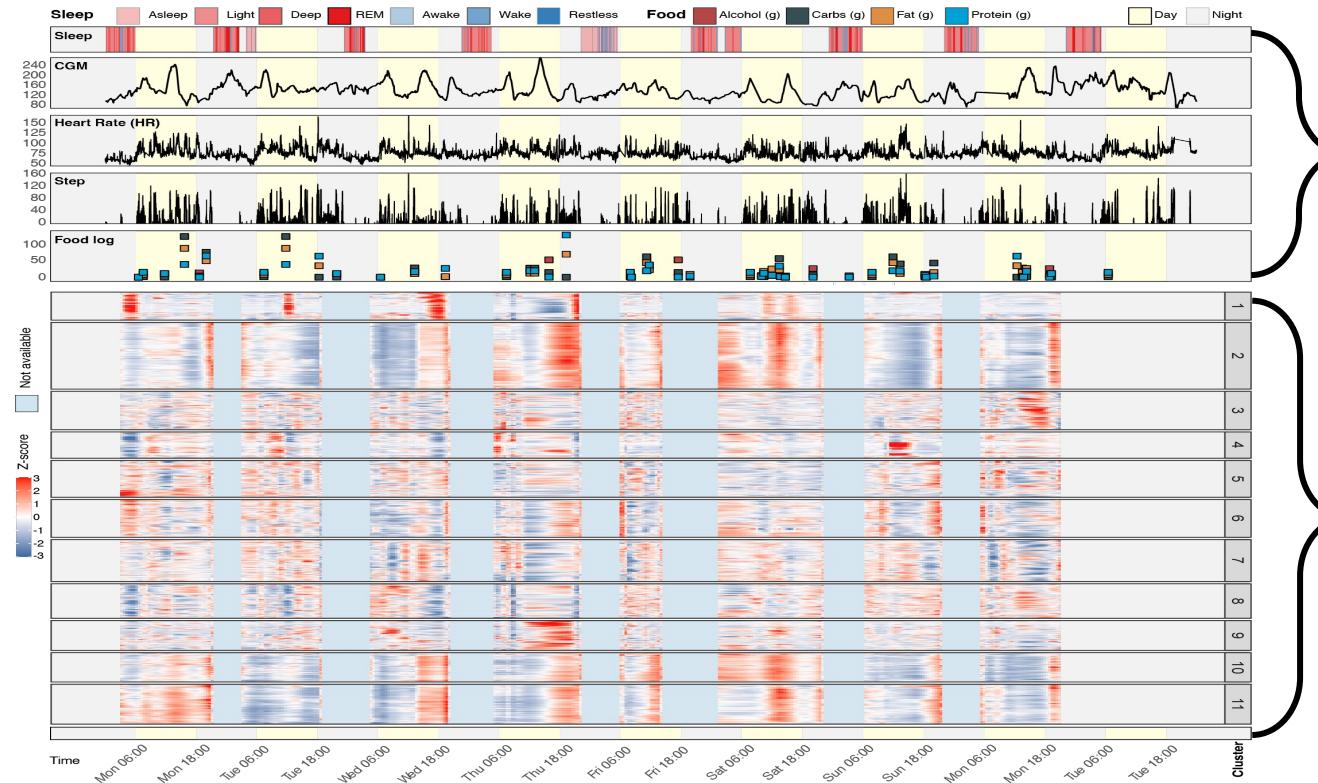


Everyone Responds Differently: Carbohydrate Score



Dense Monitoring of a Single Person

We can follow over 2000 analytes!



Wearable data

CGM
RHR, HRV
Step
Sleep
Food Log

Multi-Omics Data

Day 1

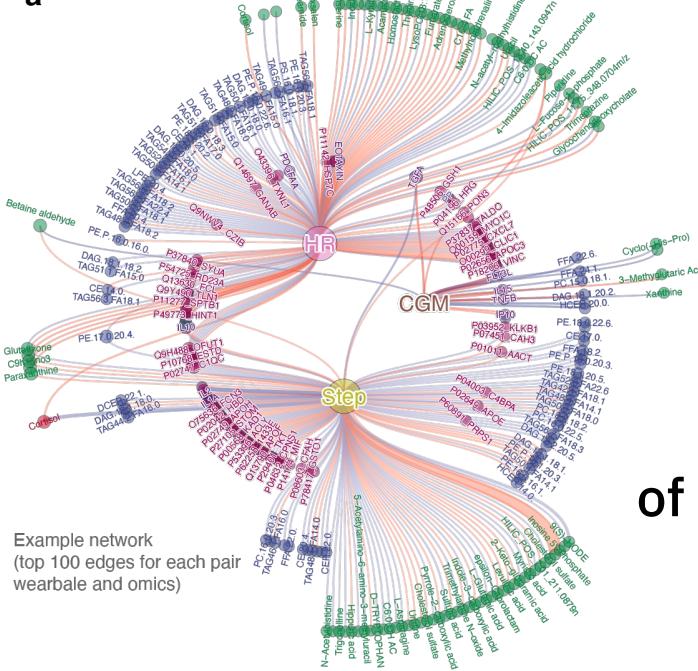
98 Samples over 7 days

Day 7

Potential Causal Associations

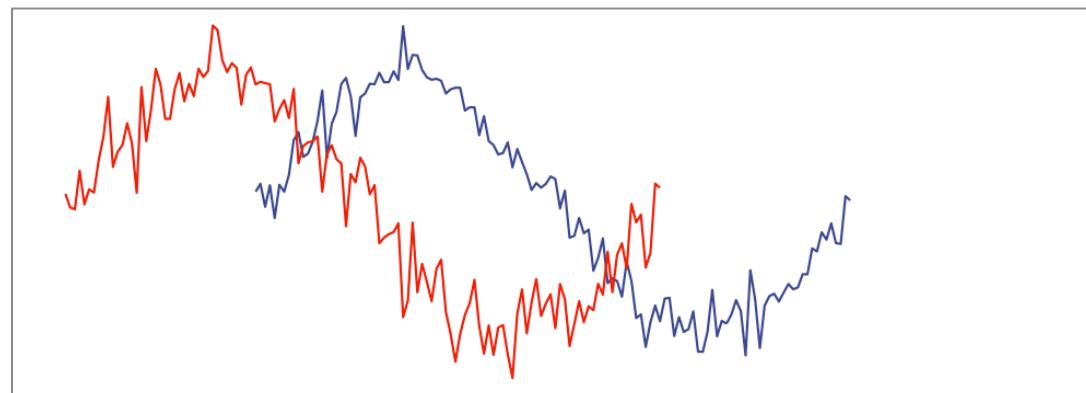
between wearables
and molecules?

a

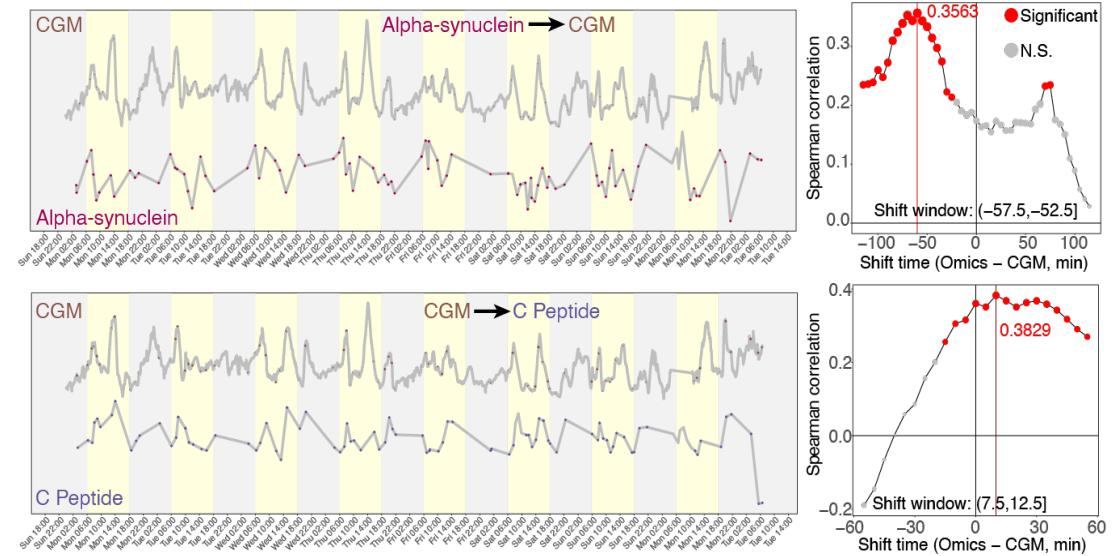


1000s
of associations

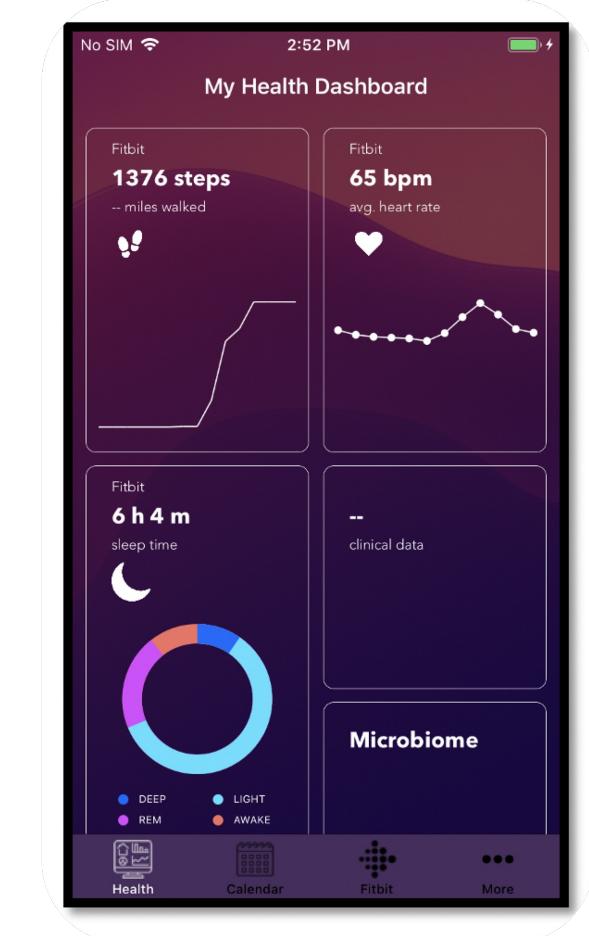
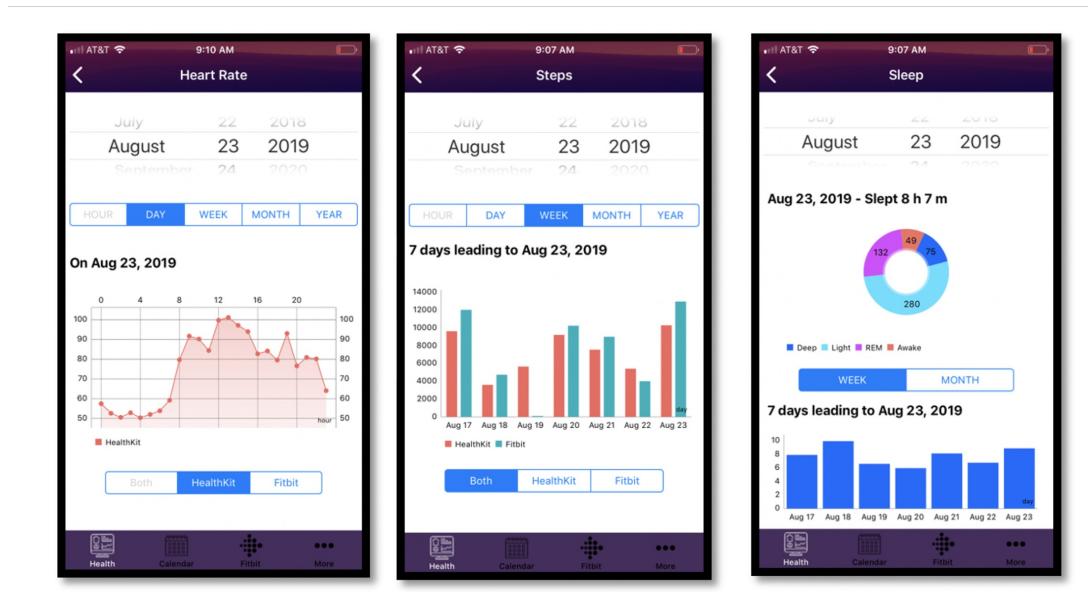
Shift time: -40



Microsampling make the lagged correlation possible



My Health Dashboard



Visualize and monitor your health over time

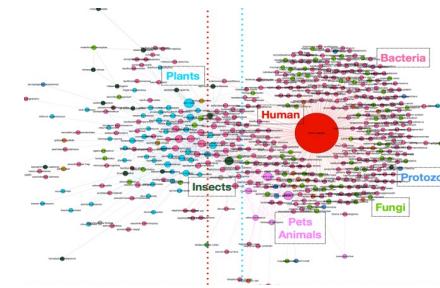
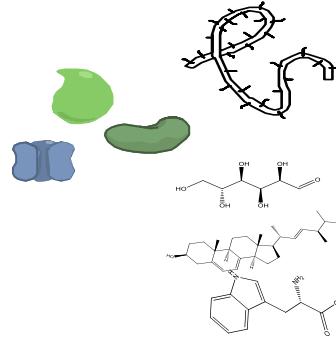
The Future According to Mike Snyder!



Genomic Sequencing

```
GGTTCCAAAAGTTATTGGATGCCGT  
TTCAGTACATTATCGTTGCTTG  
ATGCCCTAATTAAAAGTGACCCTTC  
AAACTGAAATTCATGATAACCCAATG  
TATCCTTAGTCGATAAAATTGCG  
AGTACTTTCAAAGCCAAATGAAATT  
CTATGGTAGACAAAACATTGACCAA  
TCATATCGATCCTCCTGAATTAT  
CGTTAGACACAGTTGGTATATT
```

Omes & Sensors: Personal Devices



- Personalized Health:**
AI Health Tracking
1. Predict risk
 2. Early Diagnose
 3. Monitor
 4. Treat

Companies Co-Founded (17)

- Iollo: Metabolic Health
- Personalis: Genomics Analysis
- Qbio: Big Data and Health, including MRI
- January AI: Metabolic Health
- Mirvie: Maternal Health
- Fodsel Inc: Preterm therapeutics
- SensOmics: Wearables
- Fitricine: Cancer nutrition
- RTHM: Long COVID



iollo

Q.bio

January

Mirvie

SensOmics
SEE THE UNSEEN



Iollo's panel probes >500 metabolites spanning 20+ wellness categories

Metabolic Health

Hormonal Health

Optimal

Non-optimal hormone levels have been associated with various health conditions.

Markers:

DHEAS
Optimal



[VIEW REPORT](#)

Inflammation

Longevity

Optimal

Non-optimal levels have been linked to accelerated aging.

Markers:

Methionine
Optimal



Taurine
Optimal



[VIEW REPORT](#)

Bone Health

Oxidative Stress

Optimal

Non-optimal levels have been associated with higher oxidative stress.

Markers:

HXX ratio
Optimal



[VIEW REPORT](#)

Aging Report

Slower

This score indicates whether your biomarker levels are more similar to those of a younger or an older person.

Your biological age:
47.0

Your chronological age: 51.5

[VIEW FULL REPORT](#)

and more.

Actionable aging reports

Aging report segmented by ageotypes:

 **Aging Report**

Faster

This score indicates whether your biomarker levels are more similar to those of a younger or an older person.

Your biological age:

53.4

Your chronological age: 50.8

[VIEW FULL REPORT](#)

 **Heart Age**

Older

3.9
years older

Your Heart Health made your biological age 3.9 years older. The biomarkers that contribute and add up to this include:

TGs 2.6 years older	ADMA 0.5 years older	Succinate 0.5 years older
Cer 18:0 0.3 years older		

[VIEW FULL REPORT](#)

 **Metabolic Age**

Older

0.9
years older

Your Metabolic Health made your biological age 0.9 years older. The biomarkers that contribute and add up to this include:

Tyrosine 0.7 years older	Aro-AAs 0.5 years older	Isoleucine 0.1 years older
Serine no contribution	alpha-AAA no contribution	PCs 0.4 years younger

[VIEW FULL REPORT](#)

 **Inflammation**

Younger

0.6
years younger

Your Inflammation made your biological age 0.6 years younger. The biomarkers that contribute and add up to this include:

KT ratio 0.6 years younger
--

[VIEW FULL REPORT](#)

Conclusions:

1. Deep data enables early disease detection across many phenotypes
2. Longitudinal monitoring reveals ageotypes
3. Genetic basis of disease can be better revealed using AI
4. Smartwatches enable detection of early infectious disease
5. Continuous Glucose Monitoring reveals glucose dysregulation and personalized responses to food
6. Microsampling enables remote monitoring of biochemical activities.



January -

iollo



ACKNOWLEDGEMENTS



Xiao
Li



Amir
Bahmani



Tejaswin
Mishra



Ben
Rolnik



Alessandr
a Celli



Emily
Higgs



Arash
Alavi



Meng
Wang



Andy
Brooks



Ahmed
Metwally



Thore
Buergel

Wearables



Ziye
Xing



Minh
Nguyen



Josh
Payne



Diego
Celis



Pramod
Kotipalli



Lisa
Liao



Srinath
Anan-
thakrishnan



Sushil
Upadhyayula



Audrey
Haque



Ghazal
Mazaheri



Ankit
Mathur



Gireesh
Kumar



Jason
Li



Katherine
Van
Winkle



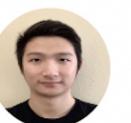
Camille
Berry



Dan
Gillespie



Qiwen
Wang



Qinyi
Yao



Kexin
Cha



Tao
Wang



Keith
Bettinger



Wenyu
Zhou

Microsampling



Xiaotao
Shen



Ryan
Kellogg



Daniel
Hornburg



Daniel
Panyard



Nasim
Bararpour

Microbiome
Andy Brooks

Ultima Team: Sarah Pollack,
Zohar Shipony, Doron Lipson

