

Wearables for Managing Health

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April 7, 2022



Conflicts: Personalis, Genapsys, SensOmics, Qbio, January AI, Filtricine, Mirvie, Fodsel, Protos

Medicine

Presently



Focus on Illness
Reactive
Measure very few things
Infrequent
Population based



Should be

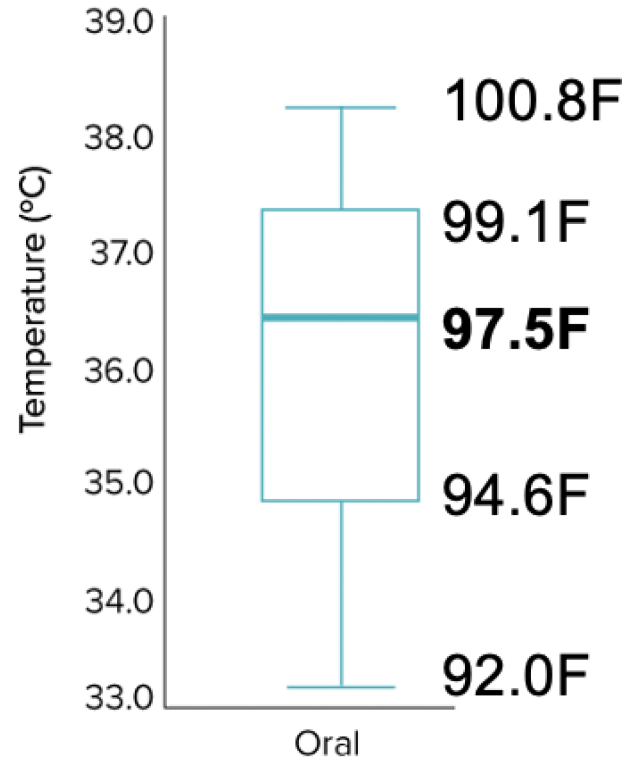


**Precision
Health**

Focused on Health
Proactive
Measure many things
Frequent
Individual based

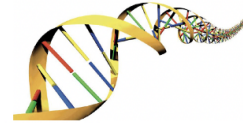
Importance in Individual Variation from “Normal”

Oral temp in 2749 healthy individuals



Health is a product of Genome & Exposome

Genome



Exercise



Pathogens



Food

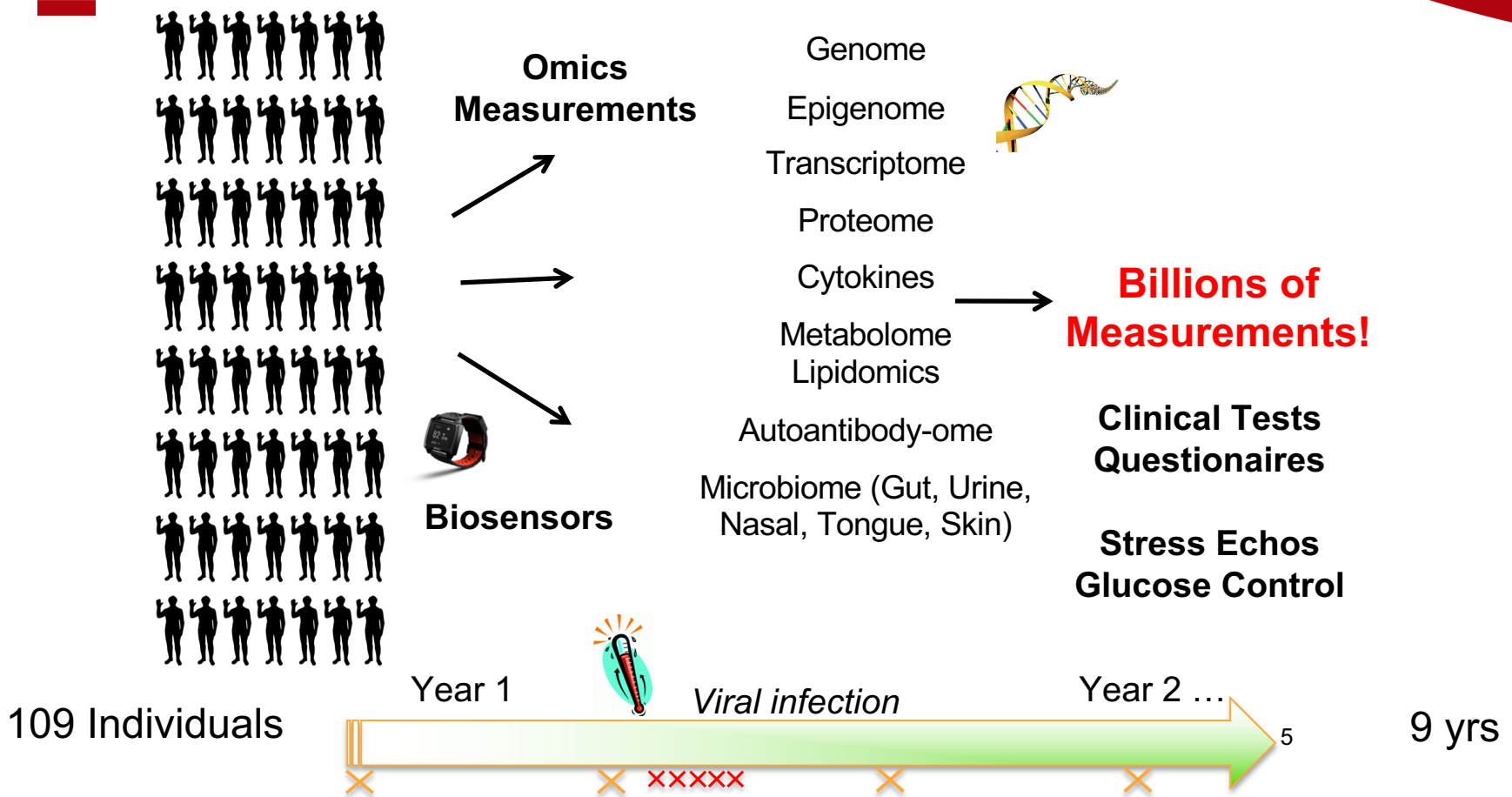


Environmental Exposures



Stress

Longitudinal Personal Omics Profiling



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

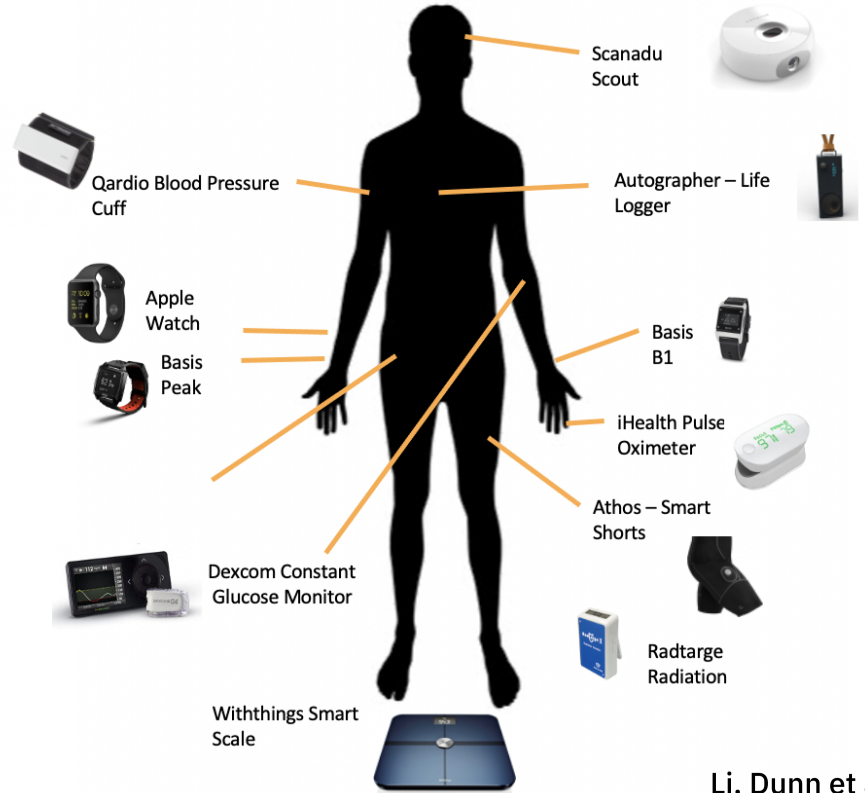
- 1 Sleep Apnea (wearable)
- 1 SLC7A9 mutation (cystinuria risk)
- 2 Macroalbuminuria

Infectious

- 1 Lyme Disease (wearable)

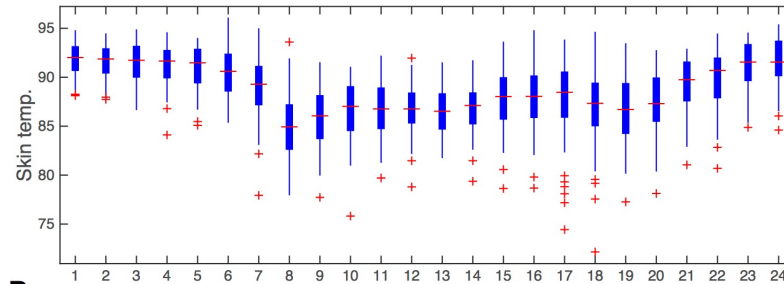
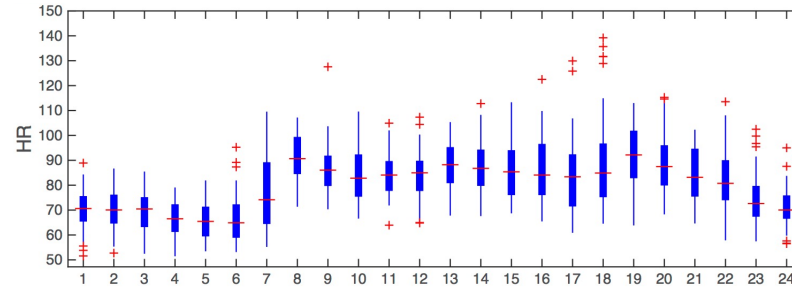
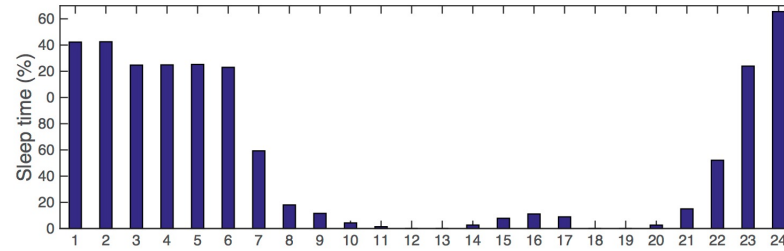
Wearable Sensors: Over 900 Devices

- Worn by millions of people (20% of US)
- Make 100Ks of measurements each day
- Wearables can track many things: HR, HRV, Respiration Rate, SpO2, Skin Temp, Blood Pressure

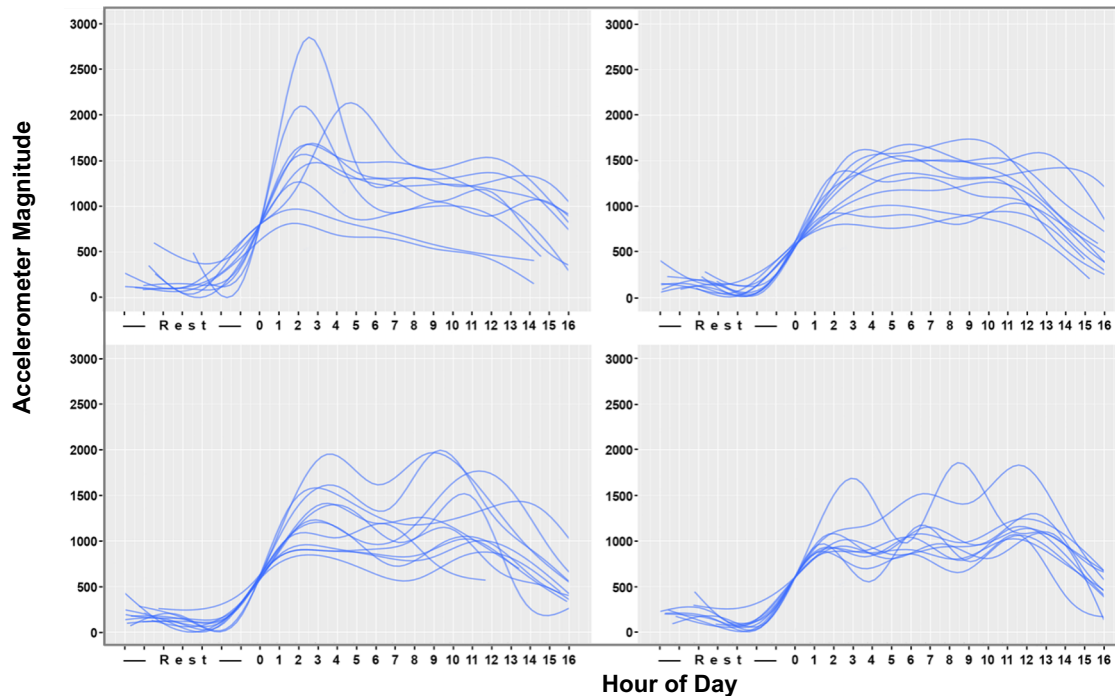


Li, Dunn et al.
PloS Biol 2017

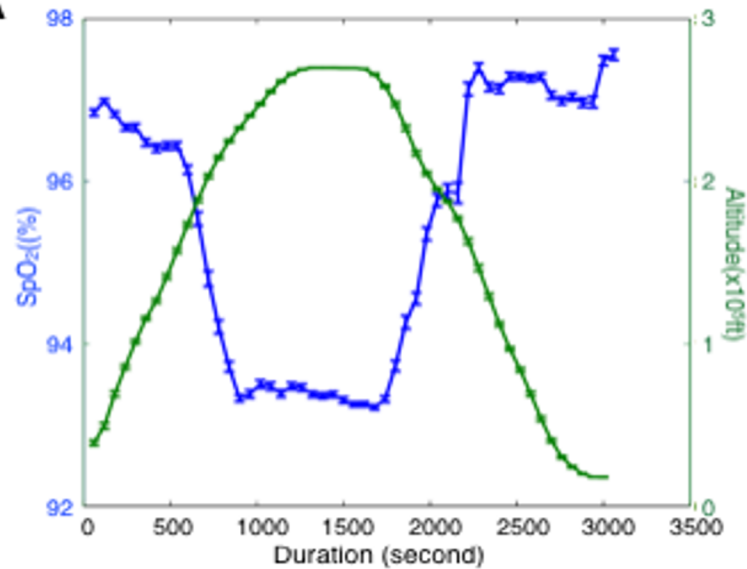
Circadian and Diurnal Patterns



Activity Phenotypes: 4 Patterns



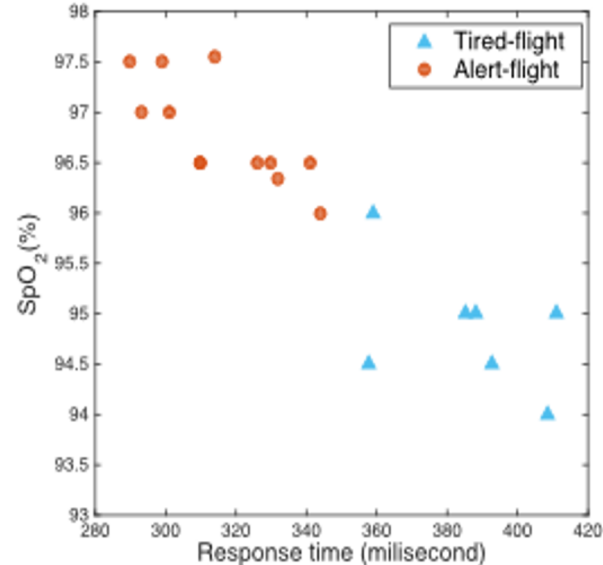
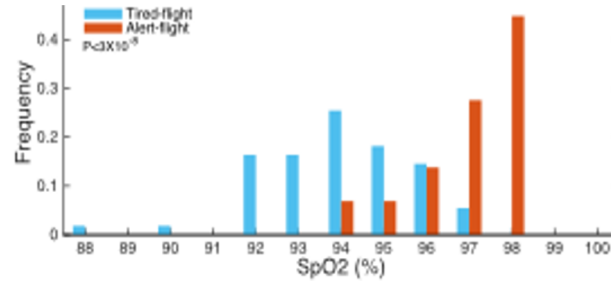
SpO2 Levels Drop During Airline Flights



SF to San Diego 2016




SpO₂ Measurements

Associated With Fatigue

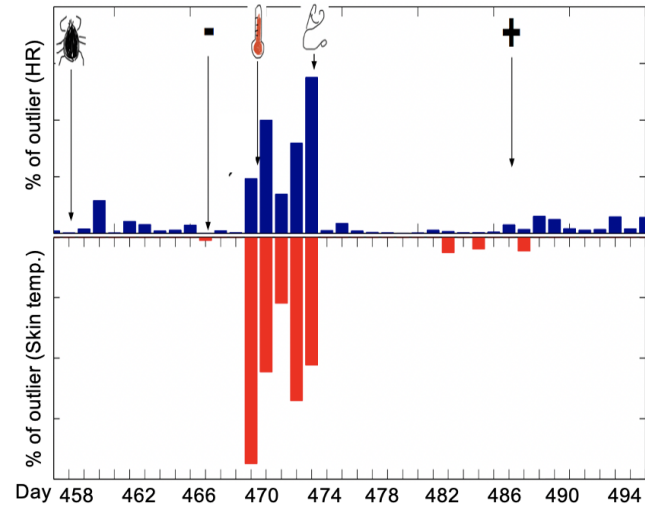
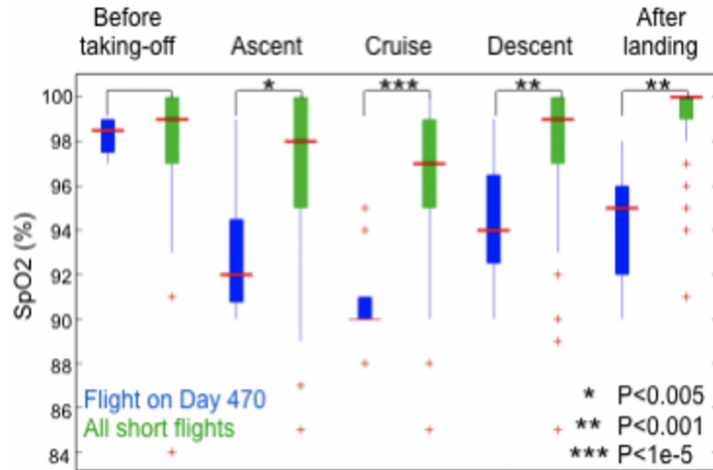


Early detection of Lyme disease

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

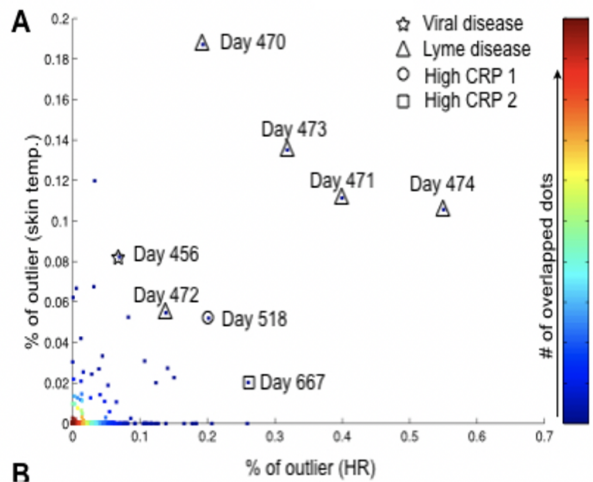
Xiao Li , Jessilyn Dunn , Denis Salins , Gao Zhou, Wenyu Zhou, Sophia Miryam Schüssler-Florenza Rose, Dalia Perelman, Elizabeth Colbert, Ryan Runge, Shannon Rego, Ria Sonecha, Somalee Datta, Tracey McLaughlin, Michael P. Snyder 

Published: January 12, 2017 • <https://doi.org/10.1371/journal.pbio.2001402>

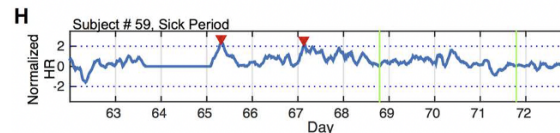
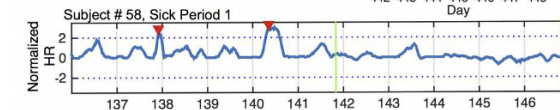
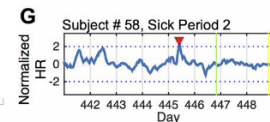
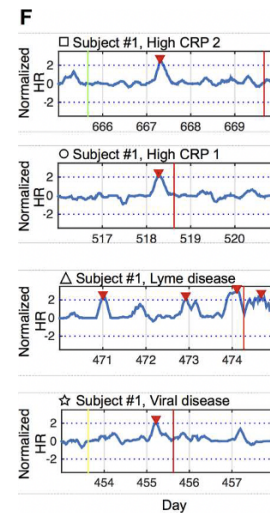


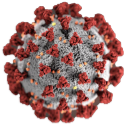
Detects All Days of Illness

Li, Dunn et al.
PloS Biol 2017

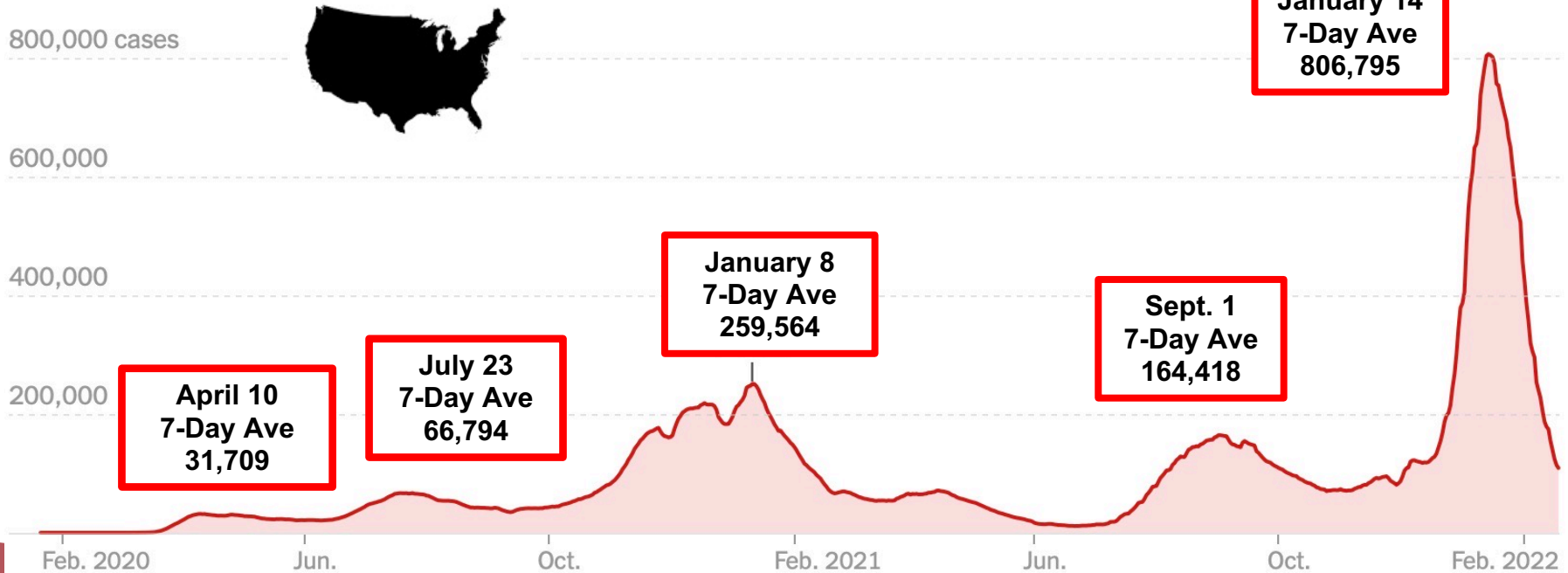


Change-of-Heart Algorithm





United States COVID-19 Cases/Day



Current Tests

Thermometer



Does it work?

PCR



Slow (1-2 days), Cost,
Stochastic

COVID-19 Infectious Disease Study

Wearables Data Study

We are trying to find out if information from wearable devices, like Fitbit and Apple Watch, can be used to track infectious diseases like COVID-19. We hope to be able to predict the onset even before any symptoms start.

Healthcare workers and high-risk individuals are especially encouraged to enroll in the study.

Enroll >

Study email: covid19_wearables@lists.stanford.edu
Participants' rights questions: 1-866-680-2906

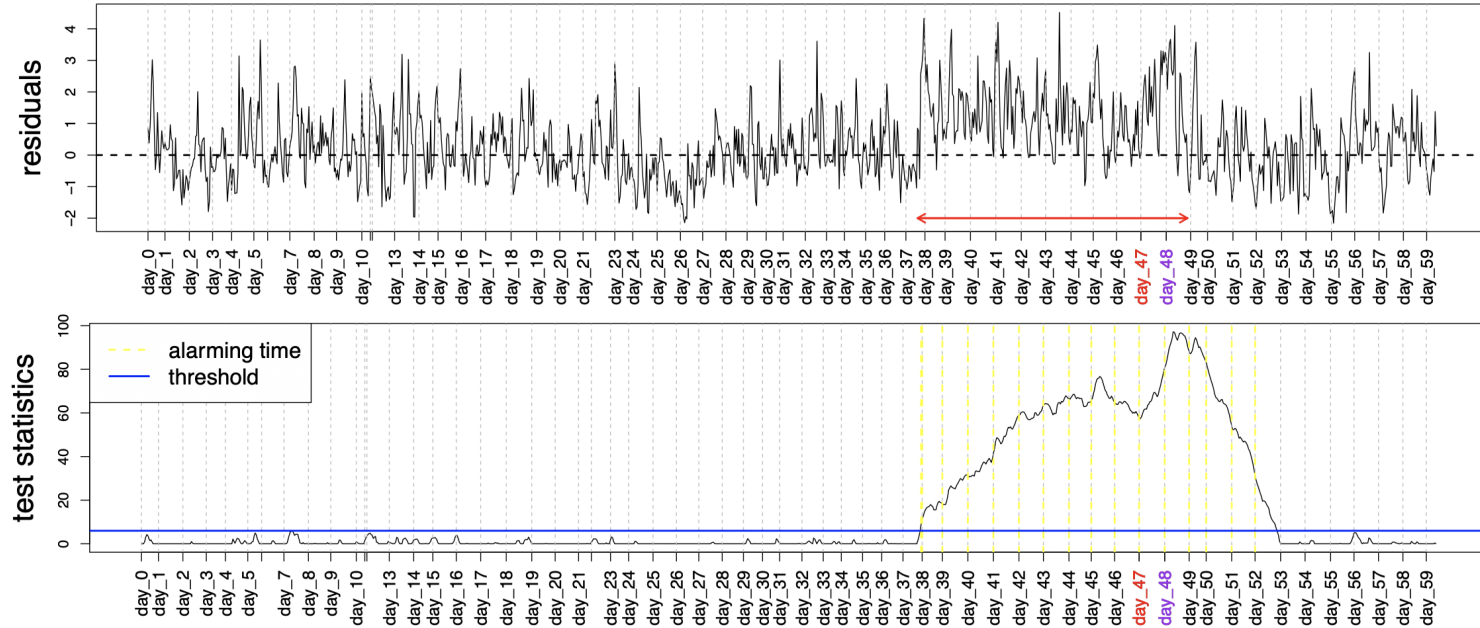


**Launched IRB
Approved Study**

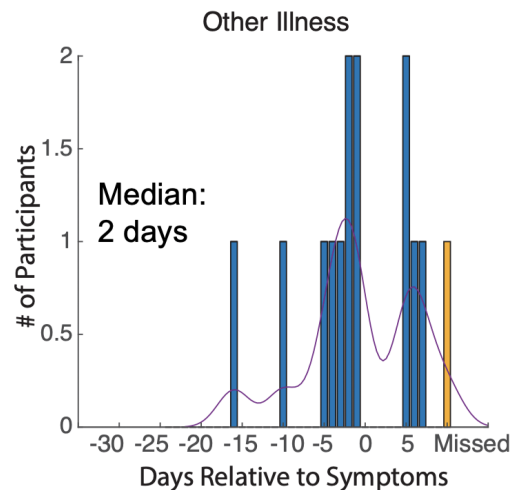
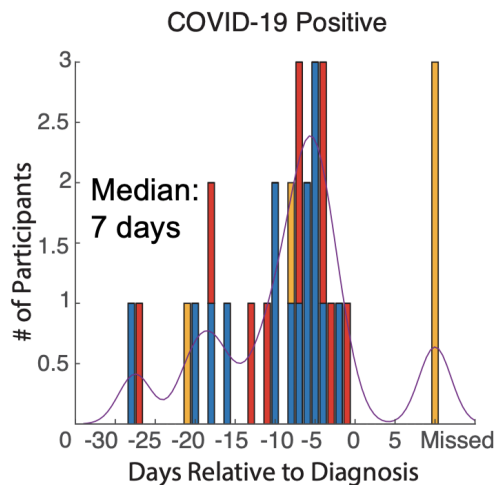
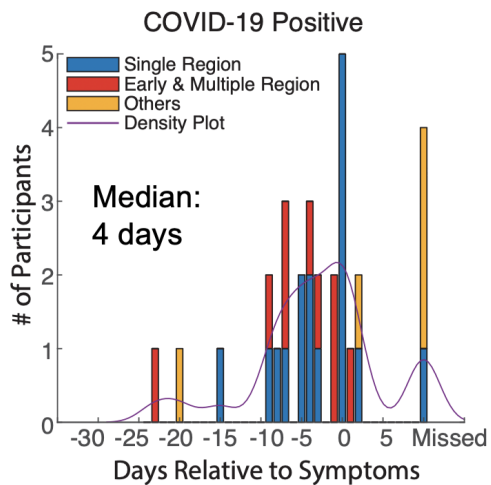
**Partnering with
Leading Companies
E.g. Fitbit, Garmin**

**>5000 Enrolled
>30 COVID-19 Positives
(Golden dataset)**

Identifying COVID-19 at early stage

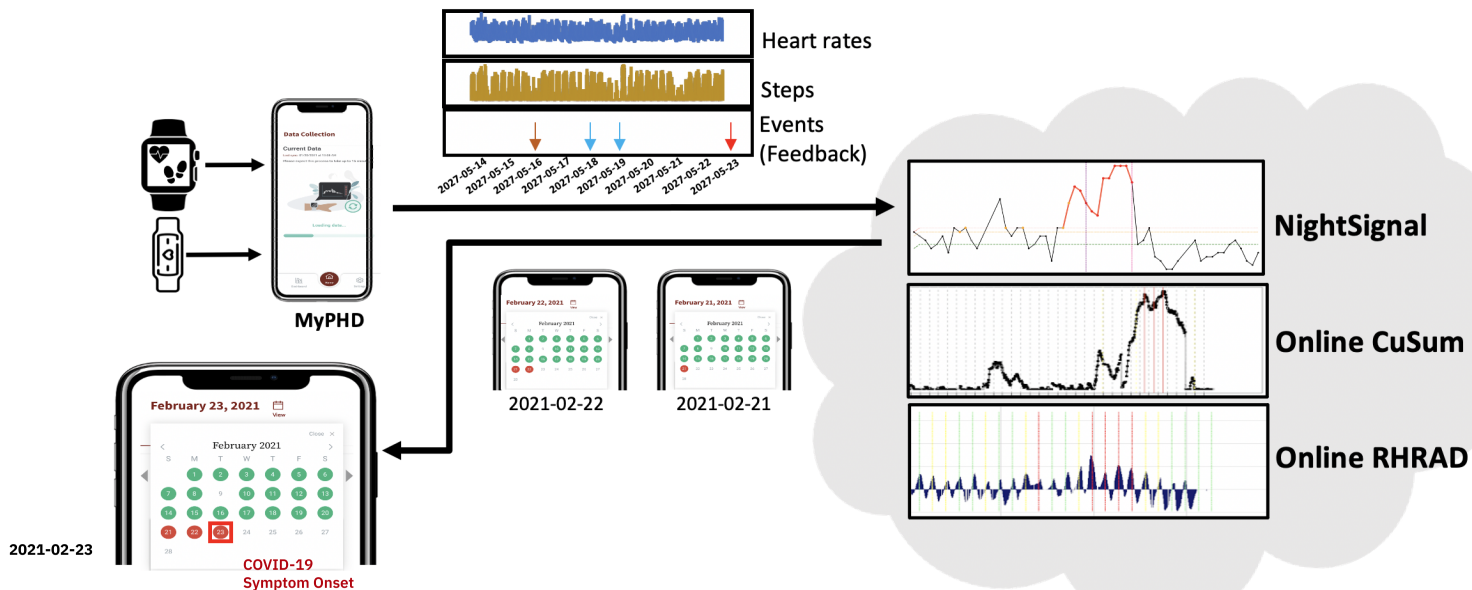


Summary of Early Detection



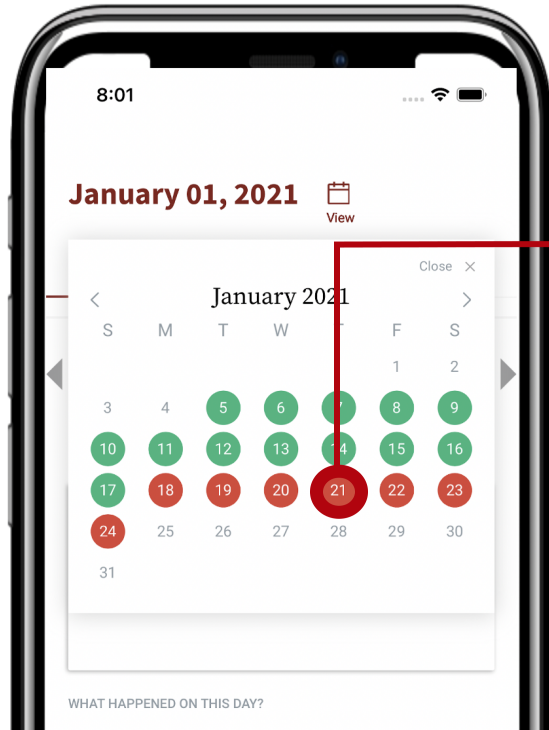
Elevated Heart Rate: 7 Beats/Min

Real-time Alerting Overview



Real-time alerts

Online Alerting System



Real Covid positive case

Symptom Onset *

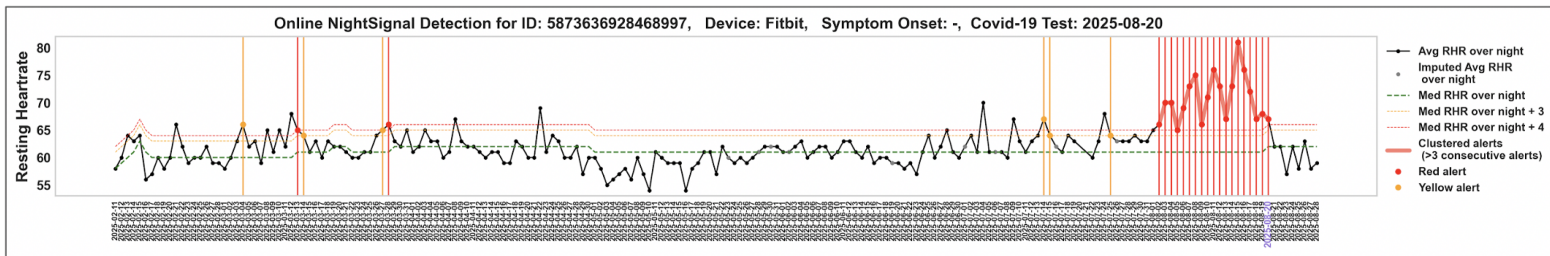
Total = 80% (67/84) of cases

* For privacy reasons, actual dates have been slightly shifted

Asymptomatic Detection Examples

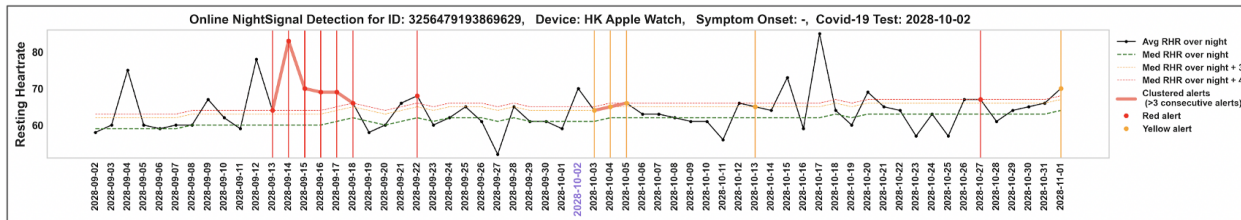
Fitbit

NightSignal

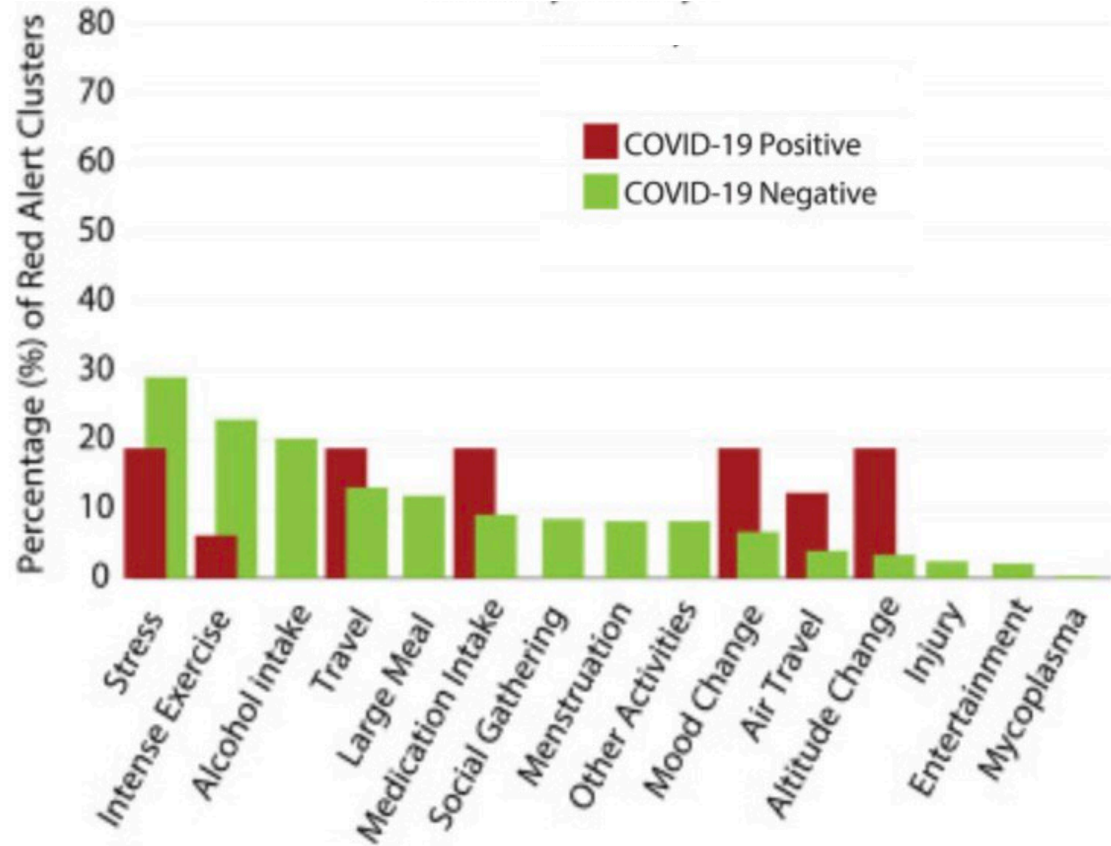


Apple Watch

NightSignal

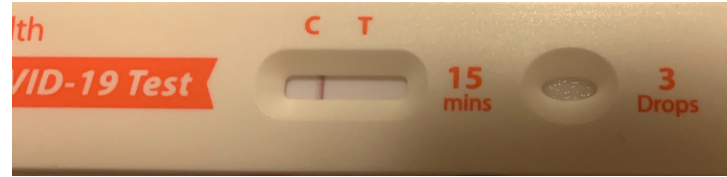
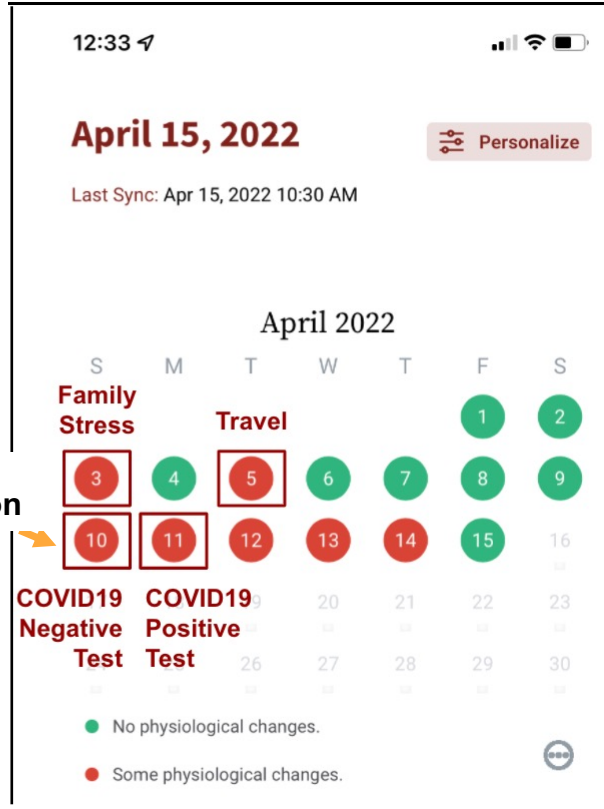


Other Stress Triggers

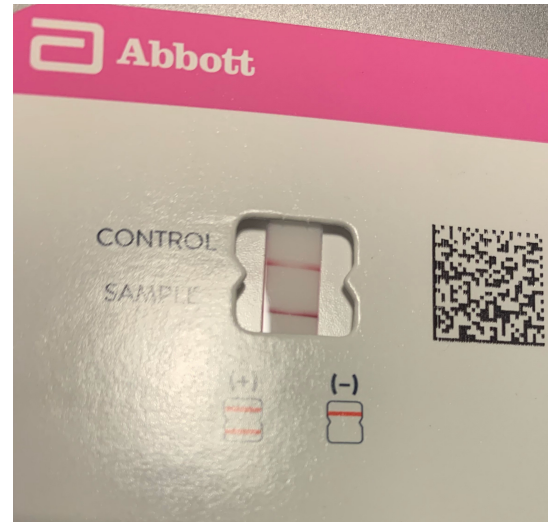


COVID Detection Assays

FitBit Stress Signal Detection

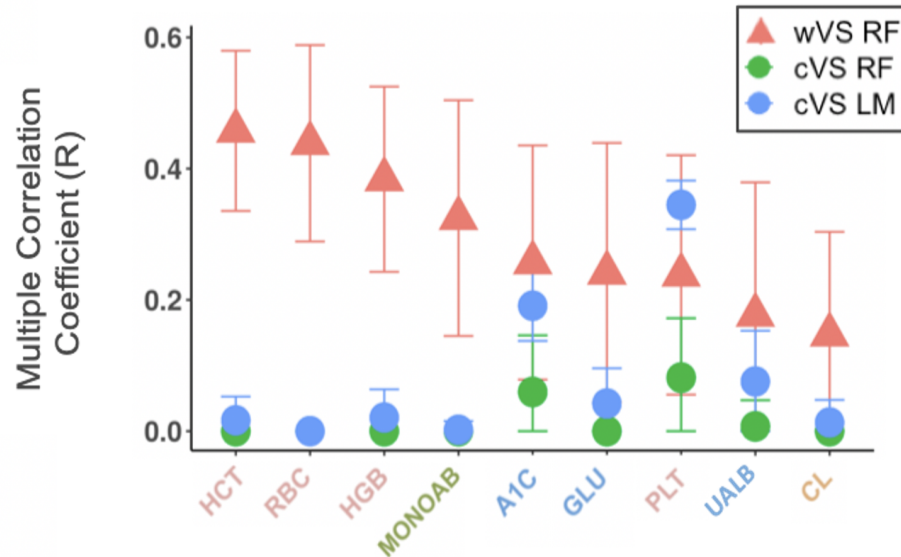


CVS (-) Test
4/10



Abbott (+) Test
4/11

Prediction of Other Clinical Biomarkers From a SmartWatch



Dunn et al, 2021,
Nature Medicine.

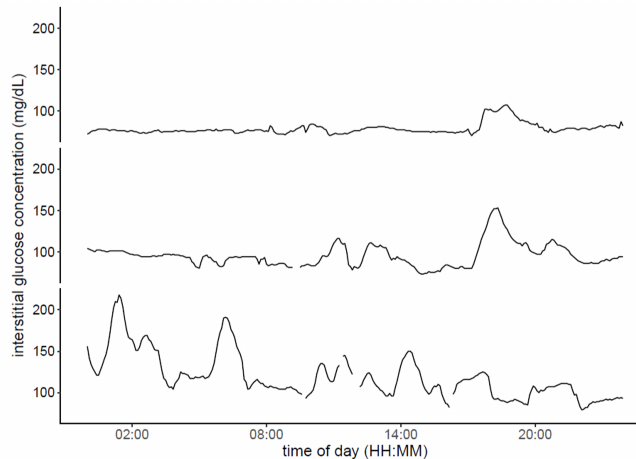
Continuous Glucose Monitoring: Lots of Spikers

Hall et al. PloS
Biol 2018

2-4 Weeks



Dexcom G4

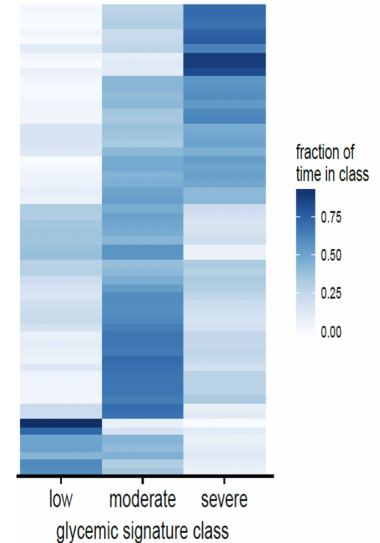
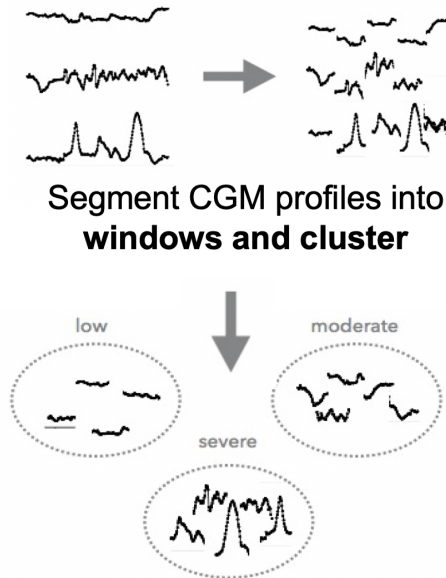


24 hours

Classification of People into Glucotypes Based on CGM Profiles

Glucotypes

Hall et al. PloS
Biol 2018



The same meal triggers different glycemic responses in different people

Hall et al. PloS Biol 2018



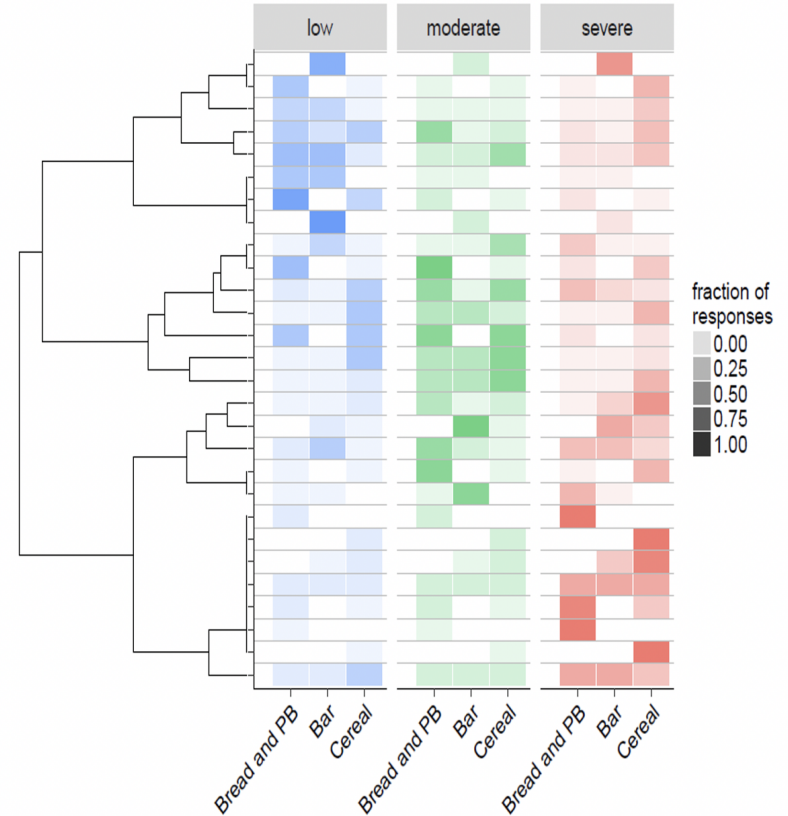
Bread +
Peanut
Butter



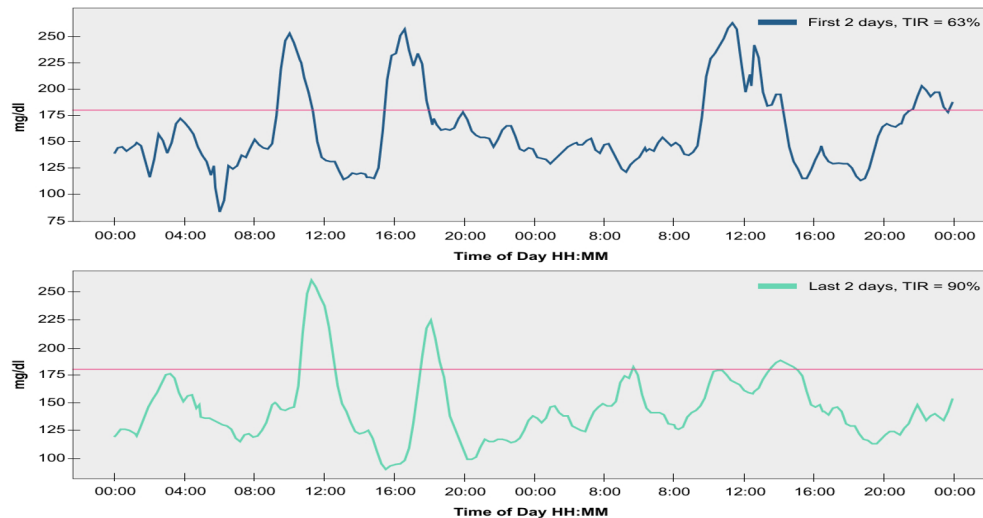
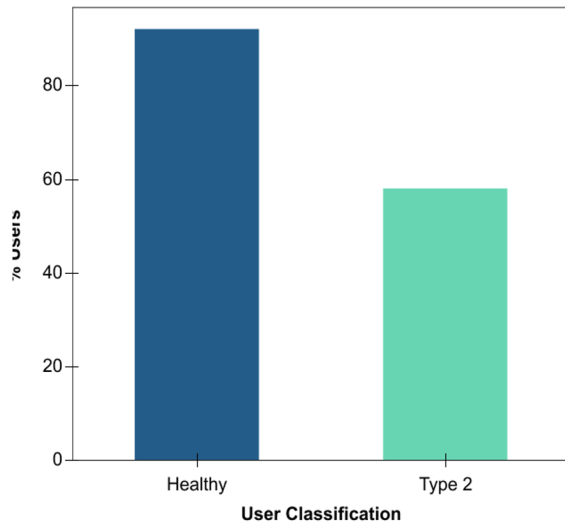
Protein
Bar



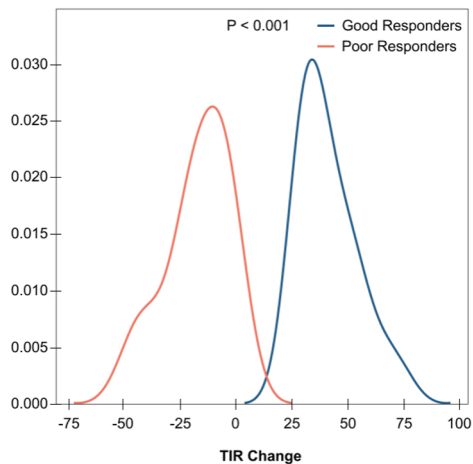
Cornflakes
+ Milk



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

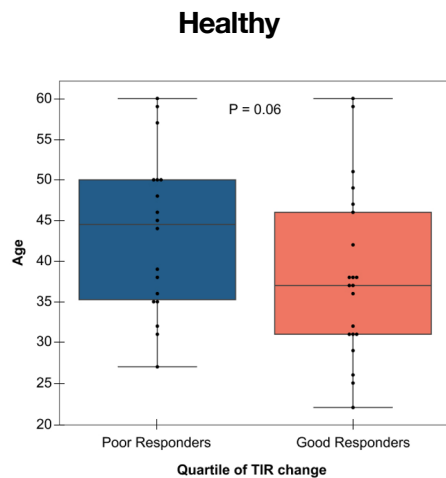


Good Responders vs Poor Responders: Young and Low BMI Improve Most

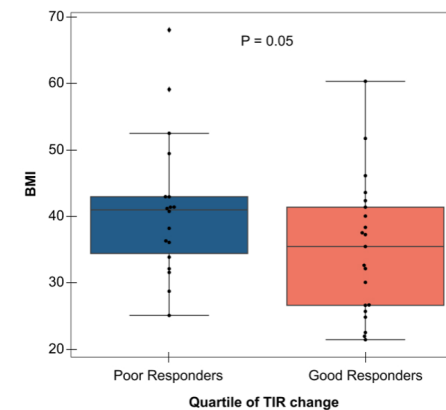


January.ai

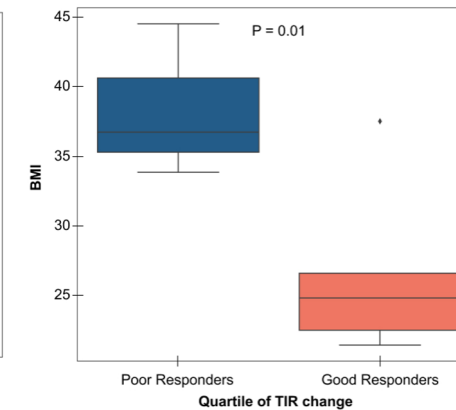
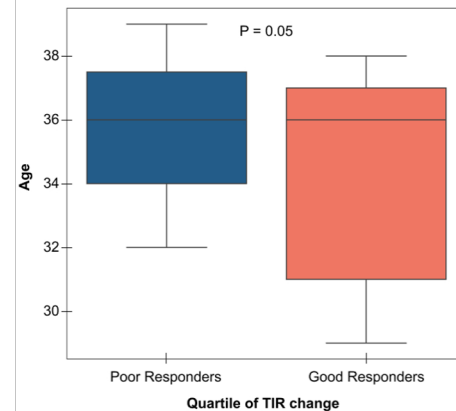
Age



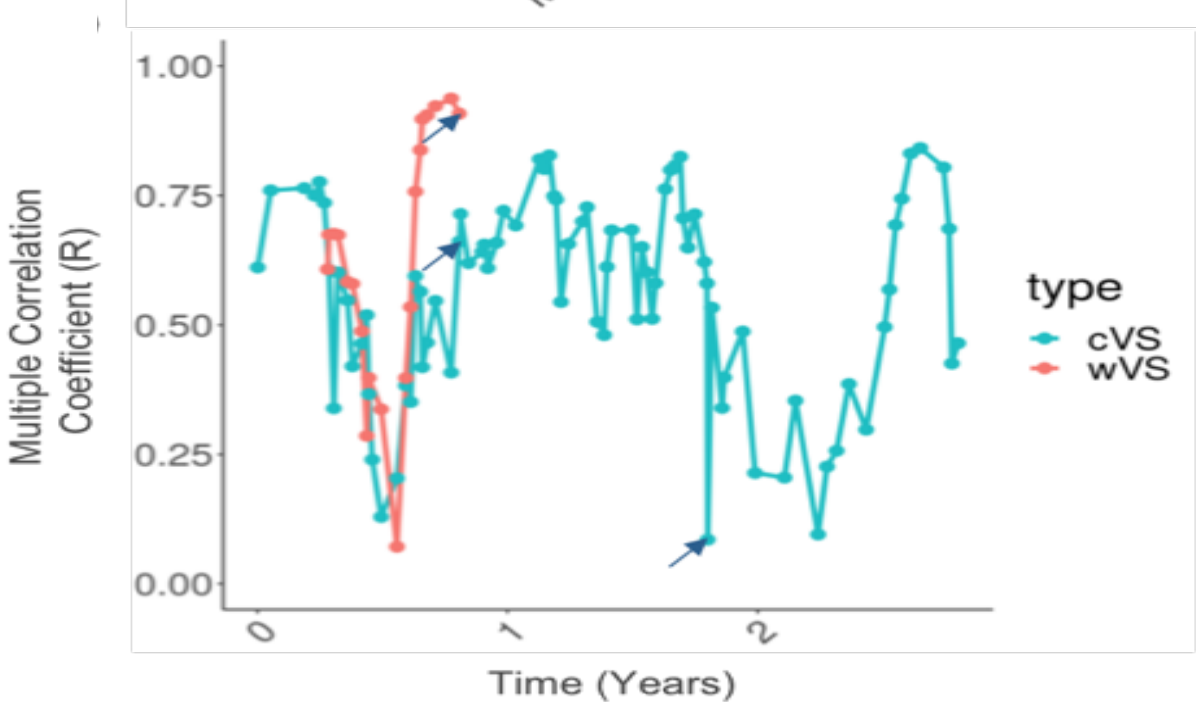
BMI



Type 2 Diabetes



Personal Monitoring of Health Using a SmartWatch



Team



Xiao
Li



Amir
Bahmani



Tejaswin
i Mishra



Ben
Rolnik



Alessandr
a Celli



Emily
Higgs



Arash
Alavi



Meng
Wang



Andy
Brooks



Ahmed
Metwally



Thore
Buerger



Ziyi
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

Acknowledgements

Exposome

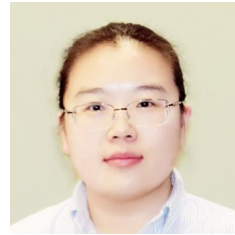
Chao Jiang
Xin Wang
Jingga Inlora
Ting Wang
Xiyang Li

Wearables

Xiao Li
Jessie Dunn
Denis Salins
Sophia Miryam ...
Heather Hall



Peng Gao, PhD
Postdoc



Allison Zhang, PhD
Postdoc



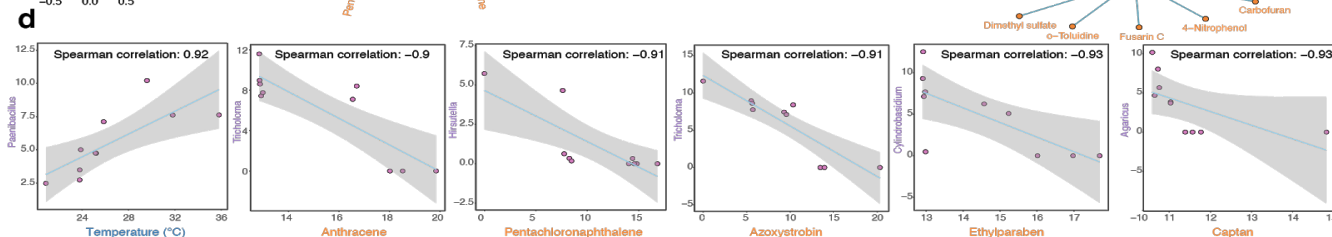
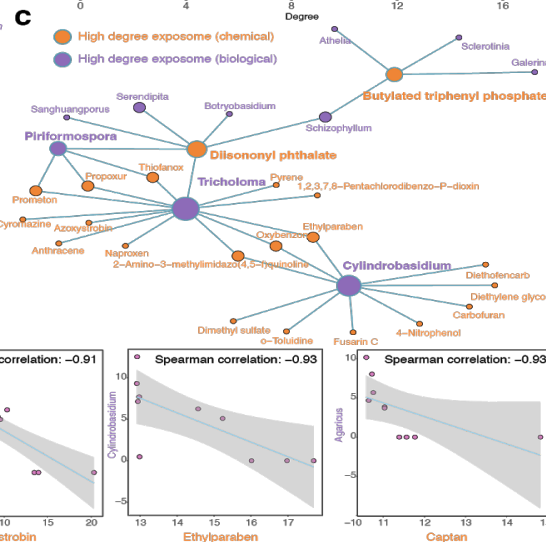
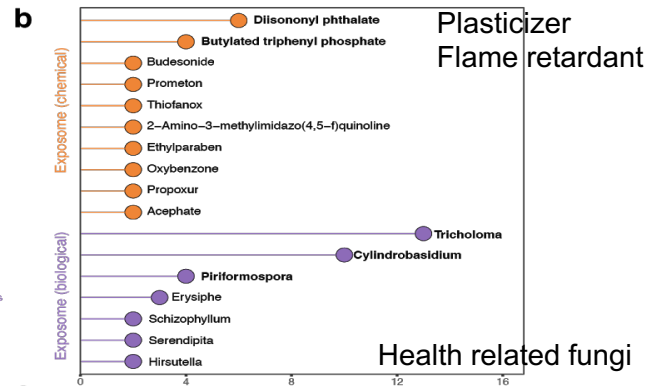
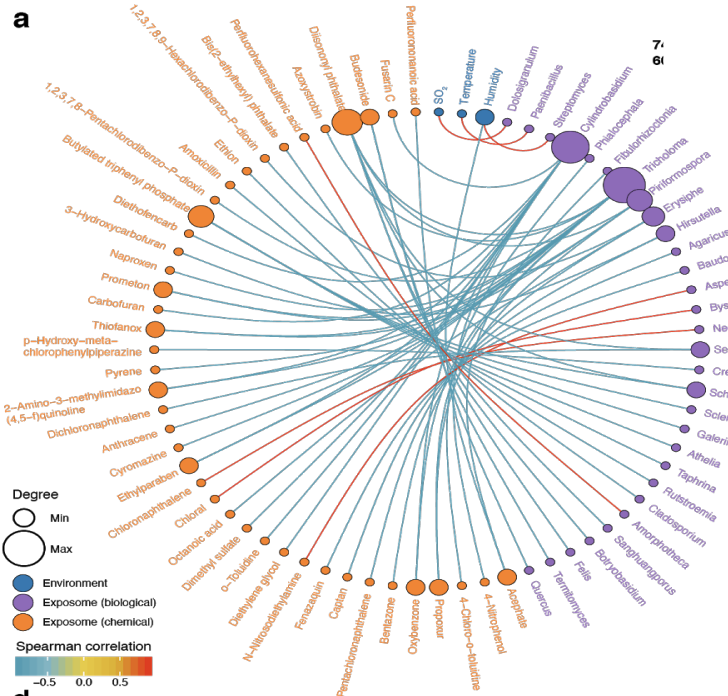
Xiaotao Shen, PhD
Postdoc

Share Information With Physician



Exposome Correlation Between Biologicals, Chemical, Environmental Factors

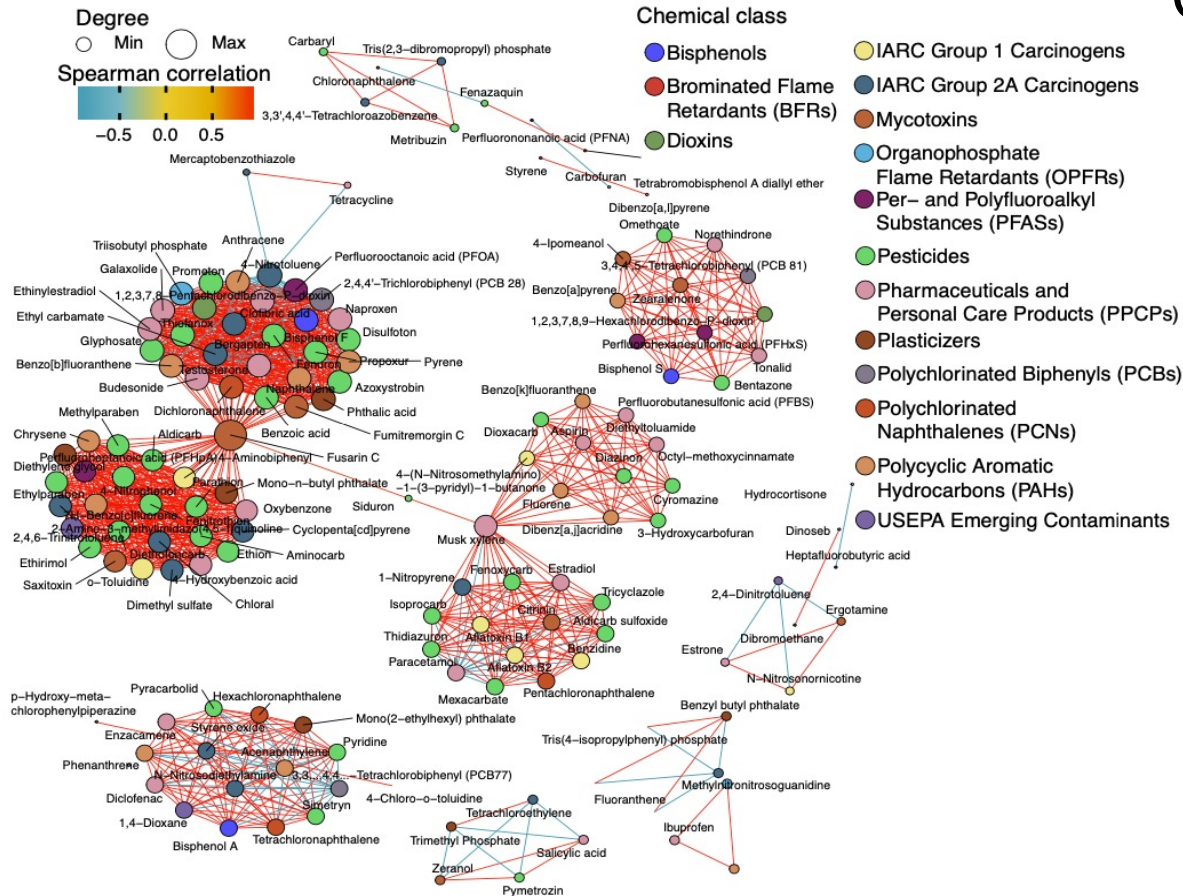
74 Nodes
60 Edges



Fungicides or antifungal chemicals

Chemical exposome

Potentially 2796 chemicals
158 Annotated Chemicals



Companies I Have CoFounded

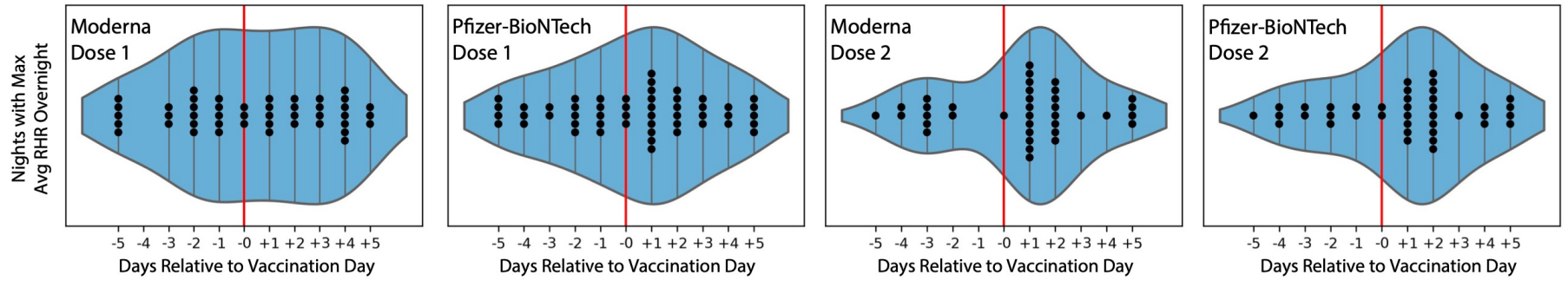
- Personalis: Genomics Analysis
- Qbio: Big Data and Health, including MRI
- January AI: Metabolic Health
- Mirvie: Maternal Health
- Fodsel Inc: Preterm therapeutics
- SensOmics: Wearables
- Fitricine: Cancer nutrition

+ others

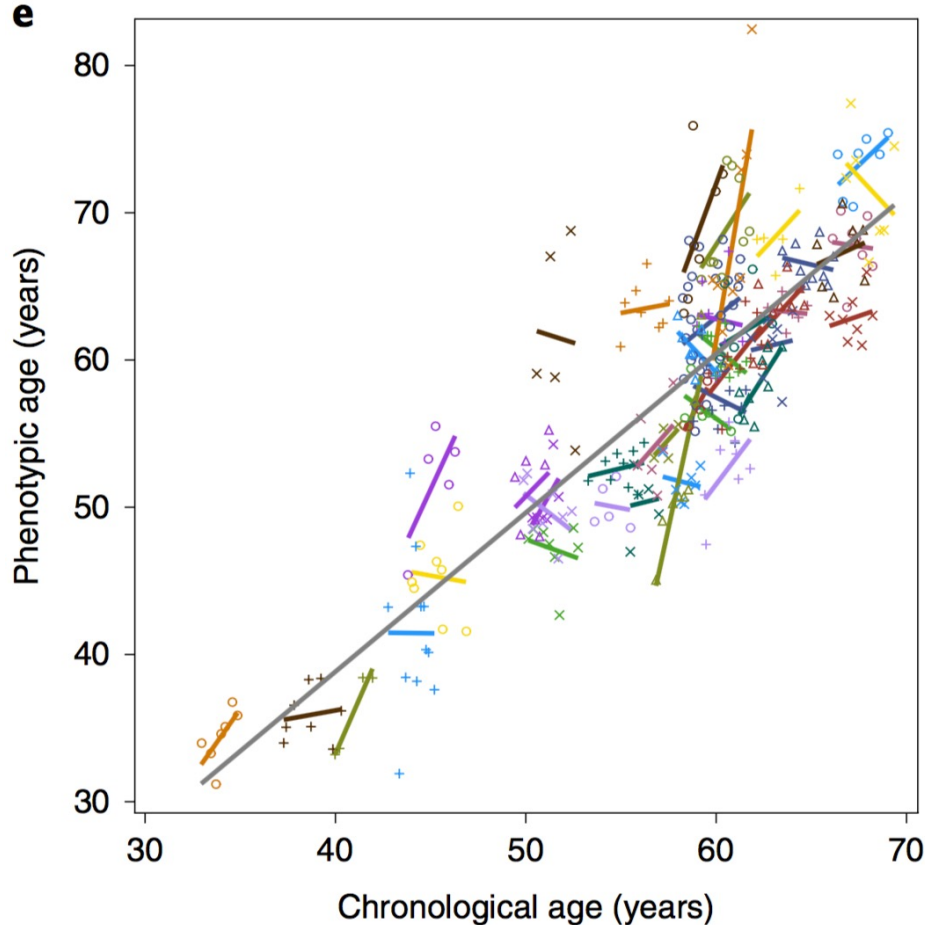


Covid-19 vaccination effect on alerts

D



Individuals Age At Different Rates



A new aging measure captures morbidity and mortality risk across diverse subpopulations from NHANES IV: A cohort study

Zuyun Liu, Pei-Lun Kuo, Steve Horvath, Eileen Crimmins, Luigi Ferrucci, Morgan Levine

Published: December 31, 2018 • <https://doi.org/10.1371/journal.pmed.1002718>

Phenotypic age:

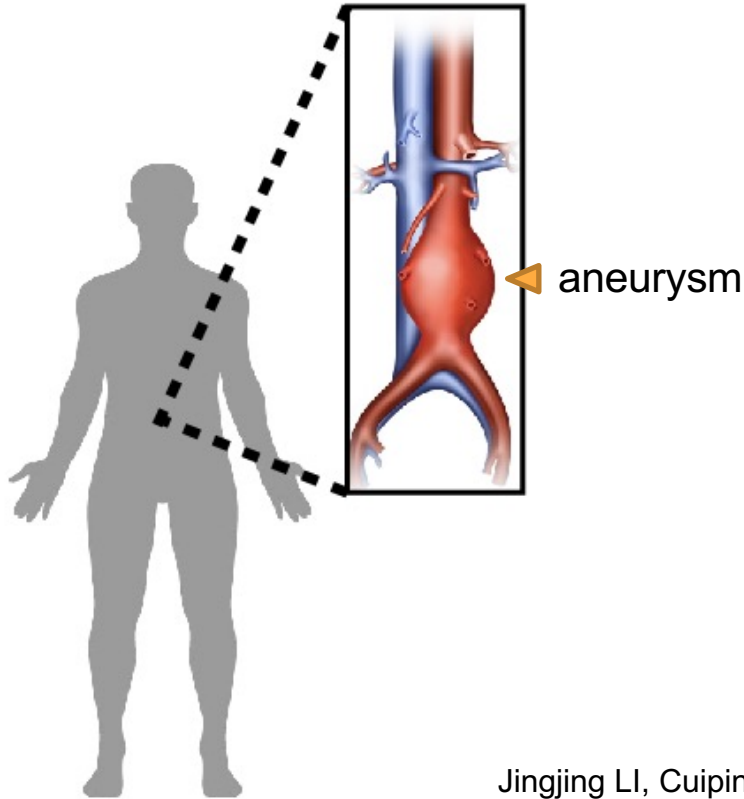
Chronological age and nine biomarkers, including albumin, creatinine, glucose, log (C-reactive protein), lymphocyte percent, mean cell volume, RDW, ALKP and white blood cell count

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](#)

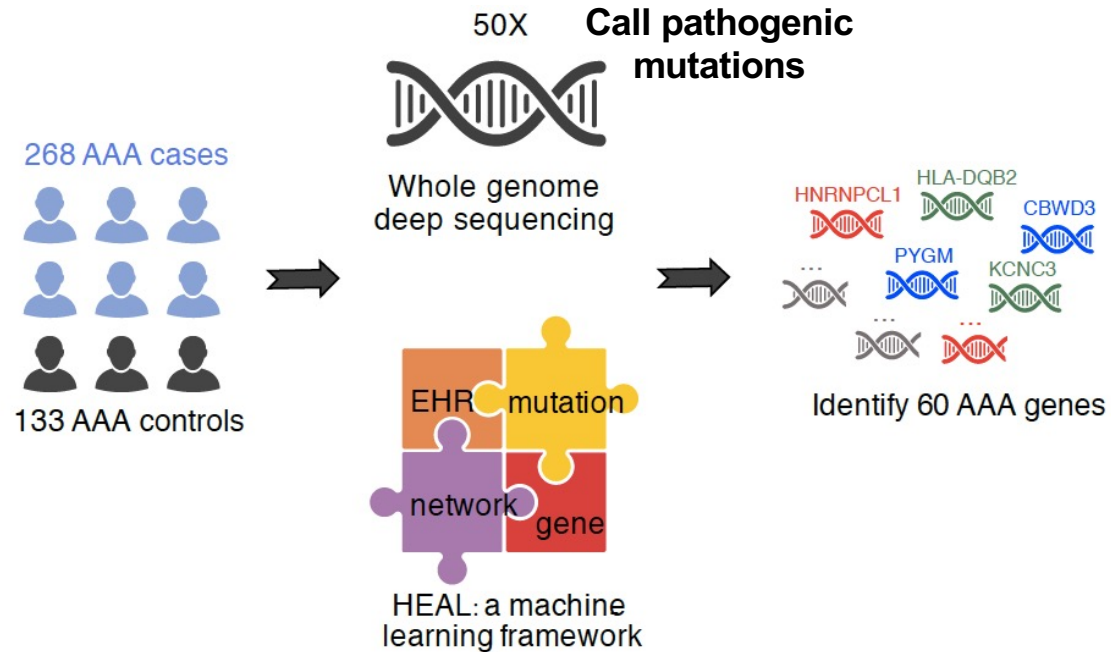
Abdominal Aortic Aneurysm: High Prevalence and Mortality



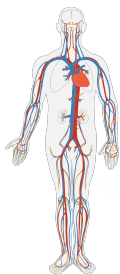
Facts

1. affecting 10% of the aged population
2. the 13th leading cause of death (U.S.)
3. asymptomatic as it grows
4. irreversible
5. >90% mortality rate upon rupture

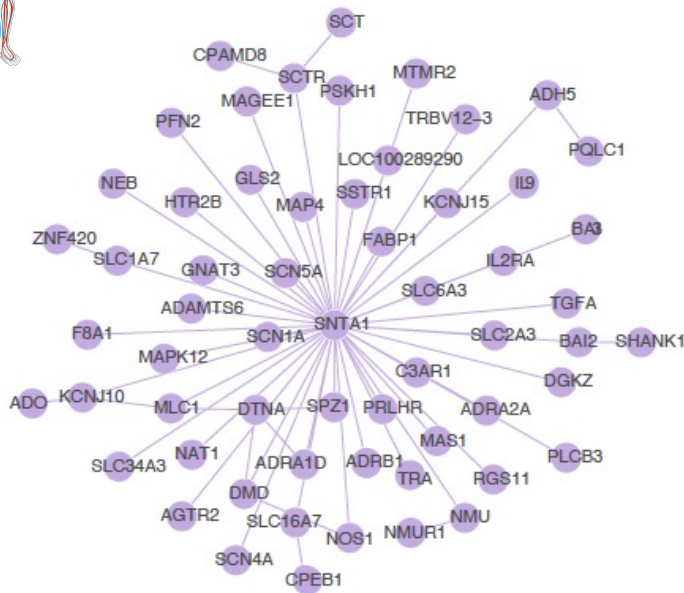
Identifying Genes Associated with AAA



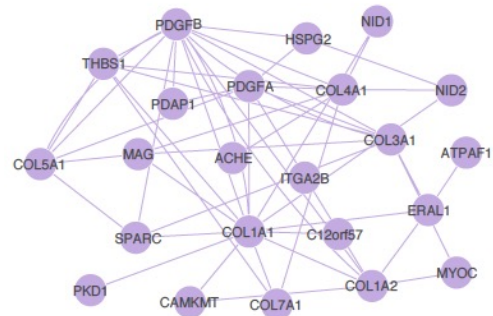
Relevant Modules



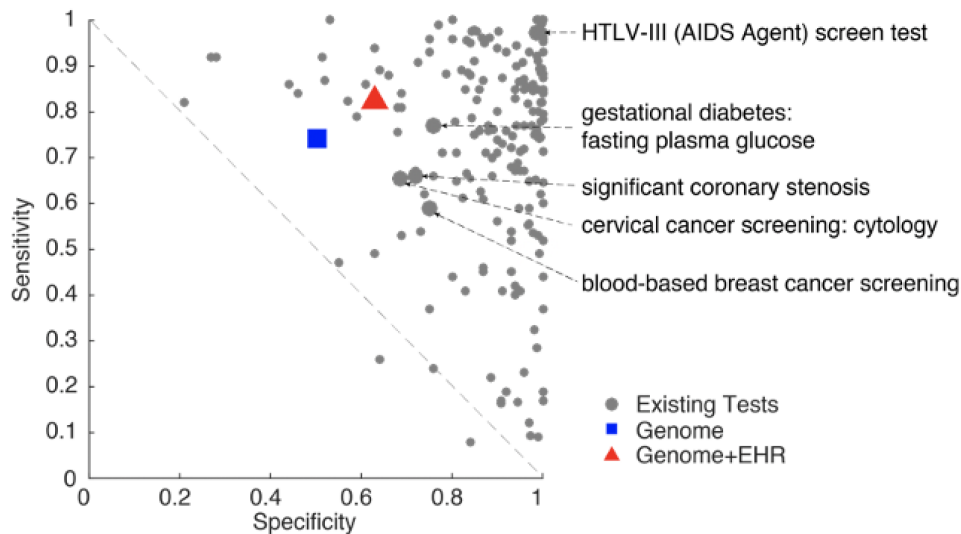
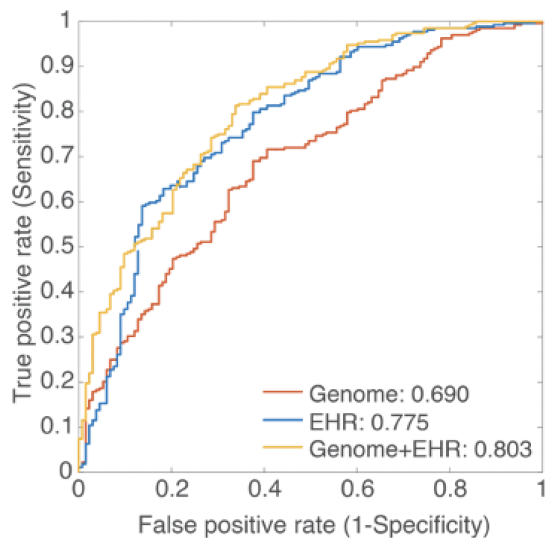
**Blood Circulation, Blood Pressure,
Cardiomyopathy**



Aneurysm

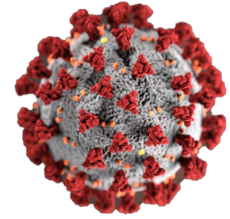


HEAL accurately predicts AAA risk -> clinical utility





The Host Genetics of ALS and COVID19 Severity Using ML



Sai Zhang, Johnathan Cooper-Knock

1. Combine GWAS signals with Open Regions in Motor Neurons:

7 genes \rightarrow 690 genes

2. Combine GWAS signals with open chromatin regions from lung:

47 genes \rightarrow 1370 genes

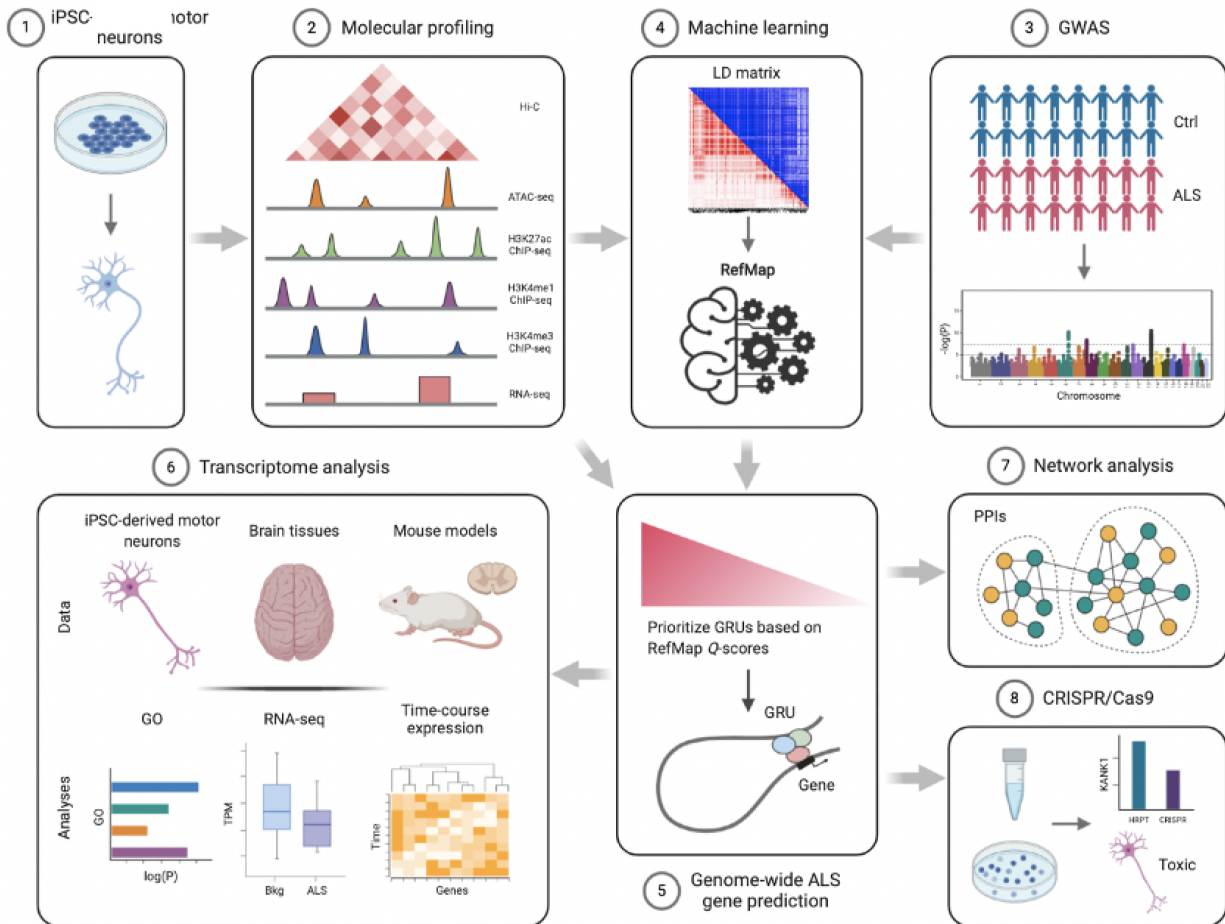
January AI slide

Amyotrophic Lateral Sclerosis (ALS)

A neurodegenerative disease with motor neuron death leading to muscle weaken



- Estimated heritability of sporadic ALS = **61%**
- Proportion of sporadic ALS patients with an identified genetic cause = **<10%**
 - **More ALS genes are missing**



RefMap: A machine learning framework to discover novel disease genes

Neuron
ColPress OPEN ACCESS

Article
Genome-wide identification of the genetic basis of amyotrophic lateral sclerosis

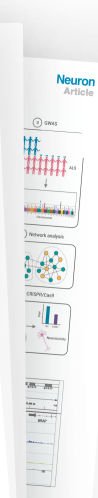
Sai Zhang,^{1,2} Johnathan Cooper-Knock,^{3,4} Annela K. Warner,¹ Meryl Shi,¹ Tobias Moll,¹ Jack N.G. Marshall,¹ Calum Harvey,¹ Heila Dharmaratne-Neharath,¹ John Franklin,¹ Claude dos Santos Souza,¹ Ka Neng, Cheng Wang,¹ Jangmin Li,¹ Aileen A. O'Connell,¹ Sali Farhan,¹ Eran Elkavk,¹ Yim Hanjongsik,¹ Matthew R. Lavery,¹ Chen Ebrahimi,¹ Paulina S. Shaw,¹ and Michael P. Snyder^{1,2*}

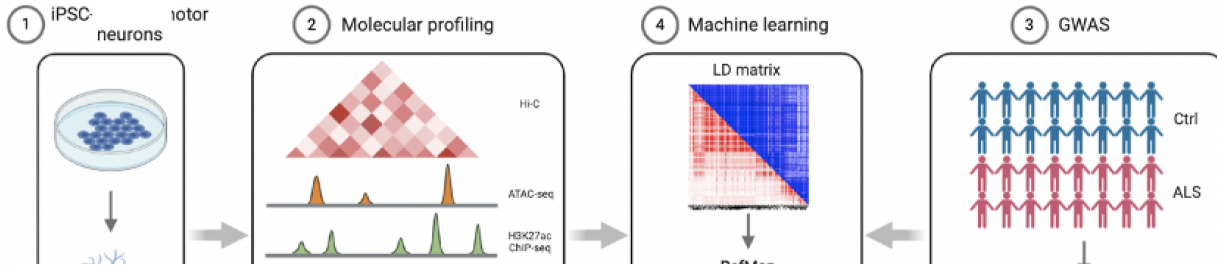
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https://doi.org/10.1016/j.neuron.2021.10.019

SUMMARY
Amyotrophic lateral sclerosis (ALS) is a complex disease that leads to motor neuron death. Despite heritability estimates of 52%, genome-wide association studies (GWAS) have discovered relatively few loci. We developed a machine learning approach called RefMap, which integrates functional genomics with GWAS summary statistics for gene discovery. With transcriptomic and epigenetic profiling of motor neurons derived from induced pluripotent stem cells (iPSCs), RefMap identified 60 ALS-associated genes that represent a 5-fold increase in recovered heritability. Extensive conservation, transcription, and rare variant annotation demonstrated the functional significance of candidate genes in healthy and diseased motor neurons across developmental stages. Genetic convergence between common and rare variation highlighted KANK1 as a new and brain tissue. Reproducing KANK1 patient mutations in human neurons led to neurotoxicity and demonstrated that TDP-43 mislocalization, a hallmark pathology of ALS, is downstream of axonal dysfunction. RefMap can be readily applied to other complex diseases.

INTRODUCTION
Amyotrophic lateral sclerosis (ALS) is a fatal and relatively common neurodegenerative disease. The hallmark of the disease is motor neuron loss (Franklin et al., 2019). 10% of ALS is motor neuron dominant, but even for sporadic ALS heritability is estimated to be ~40% (Pyle et al., 2016; Taylor et al., 2020). Genome-wide association studies (GWAS) for ALS have identified 10 loci (Pyle et al., 2016; Nicolas et al., 2018) that are enriched for genes involved in neuroprotection and axonal transport. To pinpoint the genetic basis of ALS, despite their functional sparing by the coding sequence (Fung et al., 2018; Cooper-Knock et al., 2020), ALS GWAS have demonstrated that heritability is distributed throughout noncoding sequence (Ni et al., 2018; Fung et al., 2018; Nicolas et al., 2018). The functional enrichment of ALS GWAS loci on cell-type-specific motor neurons, but even for sporadic ALS heritability is estimated to be ~40% (Pyle et al., 2016; Taylor et al., 2020). Development in understanding of cell-type-specific (dys)function in neurodegenerative diseases (Economico et al., 2014; Boyle et al., 2014) has created an opportunity to systematically reduce the search space and an initial gene for discovery by focusing on genomic regions that are func-





Found 690 Genes associated with ALS

→ 31% of heritability (5-fold inc.)

→ Showed motor neurons defects upstream of TDP-43

RefMap: A machine learning framework to discover novel disease genes

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Article Genome-wide identification of the genetic basis of amyotrophic lateral sclerosis

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https://doi.org/10.1016/j.neuron.2021.12.018

SUMMARY

Amyotrophic lateral sclerosis (ALS) is a complex disease that leads to motor neuron death. Despite heritability estimates of 52%, genome-wide association studies (GWASs) have discovered relatively few loci. We developed a machine learning approach called RefMap, which integrates functional genomics with GWAS summary statistics for gene discovery. With transcriptomic and epigenetic profiling of motor neurons derived from induced pluripotent stem cells (iPSCs), RefMap identified 690 ALS-associated genes that represent a new 5-fold increase in recovered heritability. Extensive conservation, transcription, network, and rare variant analysis demonstrated the functional significance of candidate genes in healthy and diseased motor neurons across diverse tissues. Genetic convergence between common and rare variation highlighted KANKE1 as a new and brain tissue. Reproducing KANKE1 patient mutations in human neurons led to neurotoxicity and demonstrated that TDP-43 mislocalization, a hallmark pathology of ALS, is downstream of axonal dysfunction. RefMap can be readily applied to other complex diseases.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a fatal and relatively common neurodegenerative disease. The hallmark of the disease is motor neuron (MN) loss (Frederick et al., 2017). 10% of ALS is autosomal dominant, but even for sporadic ALS heritability is estimated to be ~40% (Piper et al., 2016; Traynor et al., 2016). Genome-wide association studies (GWASs) for ALS (van Blarenhagen et al., 2018, 2021; Nicolas et al., 2018) have identified 19 loci. To date, however, fewer than 10% of genetic variants have been functionally characterized, and the genetic architecture of ALS is still poorly understood. To pinpoint the genetic basis of ALS, despite that functional synergy with the coding sequence (Erving et al., 2015; Cooper-Knock et al., 2020), ALS GWASs have demonstrated that heritability is distributed throughout noncoding sequence (NCS) (Erving et al., 2015; Nicolas et al., 2018). The function of noncoding DNA, which cell-type specific (Erving et al., 2015; Nicolas et al., 2018), developmental (Erving et al., 2015), and tissue-specific (Erving et al., 2015; Nicolas et al., 2018) gene regulation (Bouffard et al., 2015; Erving et al., 2015) has created an opportunity to functionally interrogate NCS. We developed a machine learning framework that can systematically interrogate the NCS and an atlas gene for gene function by looking up genomic regions that are func-

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Abdominal Aortic Aneurysm (AAA)

Decoding the Genomics of Abdominal Aortic Aneurysm

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Clinical Facts

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

Epidemiology

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

