Considering useful approaches when navigating uncharted territories

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Outline

1- Framing- Navigation of uncharted areas

2- Emerging lessons from wearables enabling return of agency

3- Emerging lessons from -omics driving therapies

4- How will navigation of uncharted areas in the future relate to now

5- Opportunities for SciLifeLab

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Outline

1- Framing- Navigation of uncharted areas

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Ask -Perplexity

Are their different approaches to navigating different paths in science?

Answer

There are indeed different approaches to navigating different paths in science. Two prominent approaches are the convergence research approach and the translational science approach.

Sources

A Scoping Review of Citizen Scienc...	Learn About Convergence...	Translational Science Principles	
frontiersin • 1	new.nsf • 2	ncats.nih • 3	View 2 more

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Ask –Perplexity

When you want to explore a new question in clinical sciences how can you proceed when no one has worked on the question?

Conduct a thorough literature review
Develop a theoretical framework
Use pilot or exploratory studies
Employ qualitative methods
Leverage existing data sources
Consider innovative study designs
Engage stakeholders and communities

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	Known	Unknown
Known	🧠 **Known-Knowns** *Information we are aware of and have evidence for*	🤔 **Known-Unknowns** *Information gaps or risks we are aware of*
Unknown	😶‍🌫️ **Unknown-Knowns** *Information we are unware of or are biased towards*	👻 **Unknown-Unknowns** *Information or gaps we unaware of*

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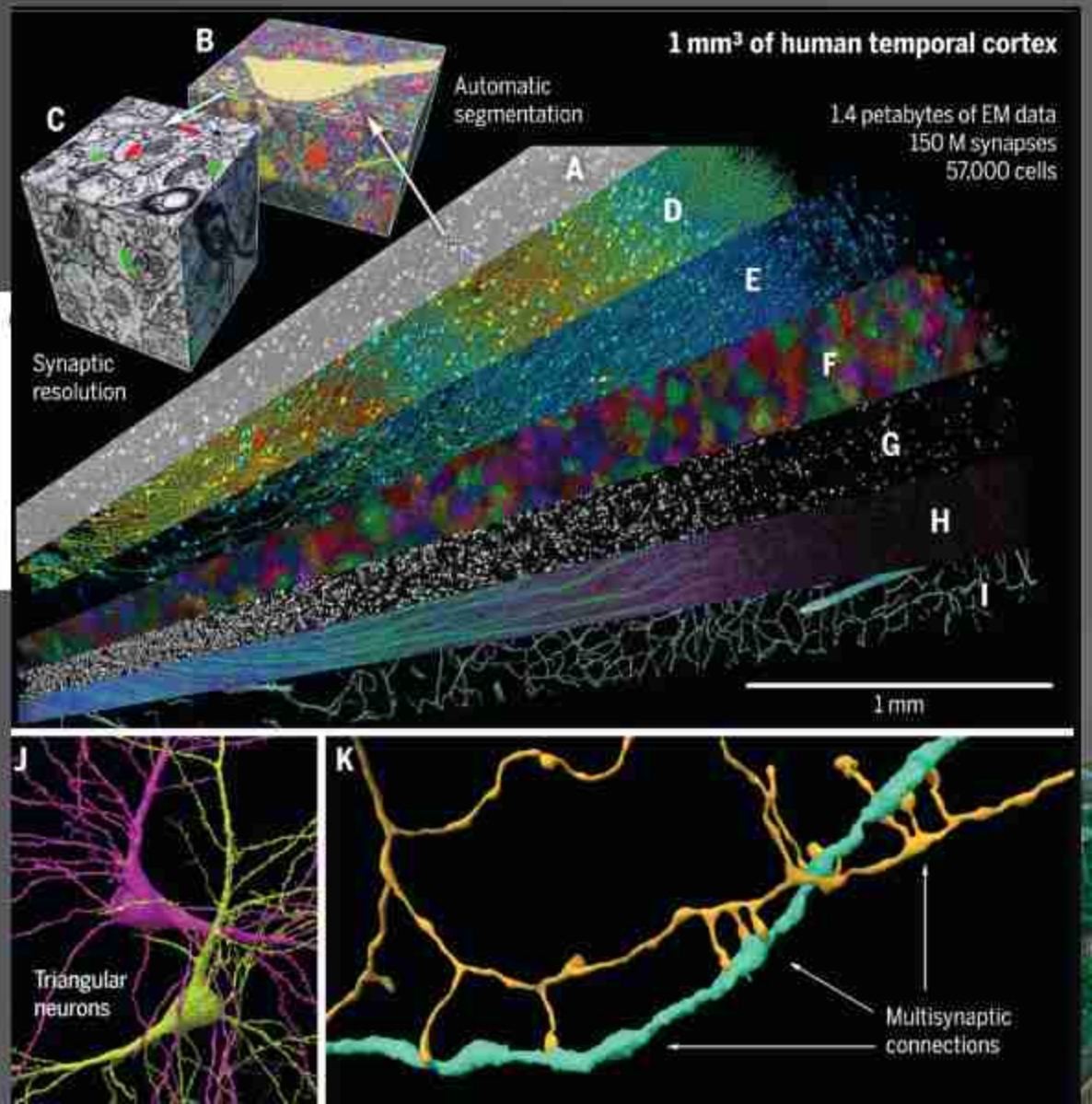
First consider- why is this question of uncharted navigation relevant today- is that not what science has always been about?

RESEARCH ARTICLE NEUROSCIENCE

A petavoxel fragment of human cerebral cortex reconstructed at nanoscale resolution

ALEXANDER SHAPSON-COE, MICHAL JANUSZEWSKI, DANIEL R. BERGER, ART POPE, [...] AND JEFF W. LICHTMAN +26 authors Authors Info & Affiliations

SCIENCE · 10 May 2024 · Vol 384, Issue 6696 · DOI: 10.1126/science.adk4858



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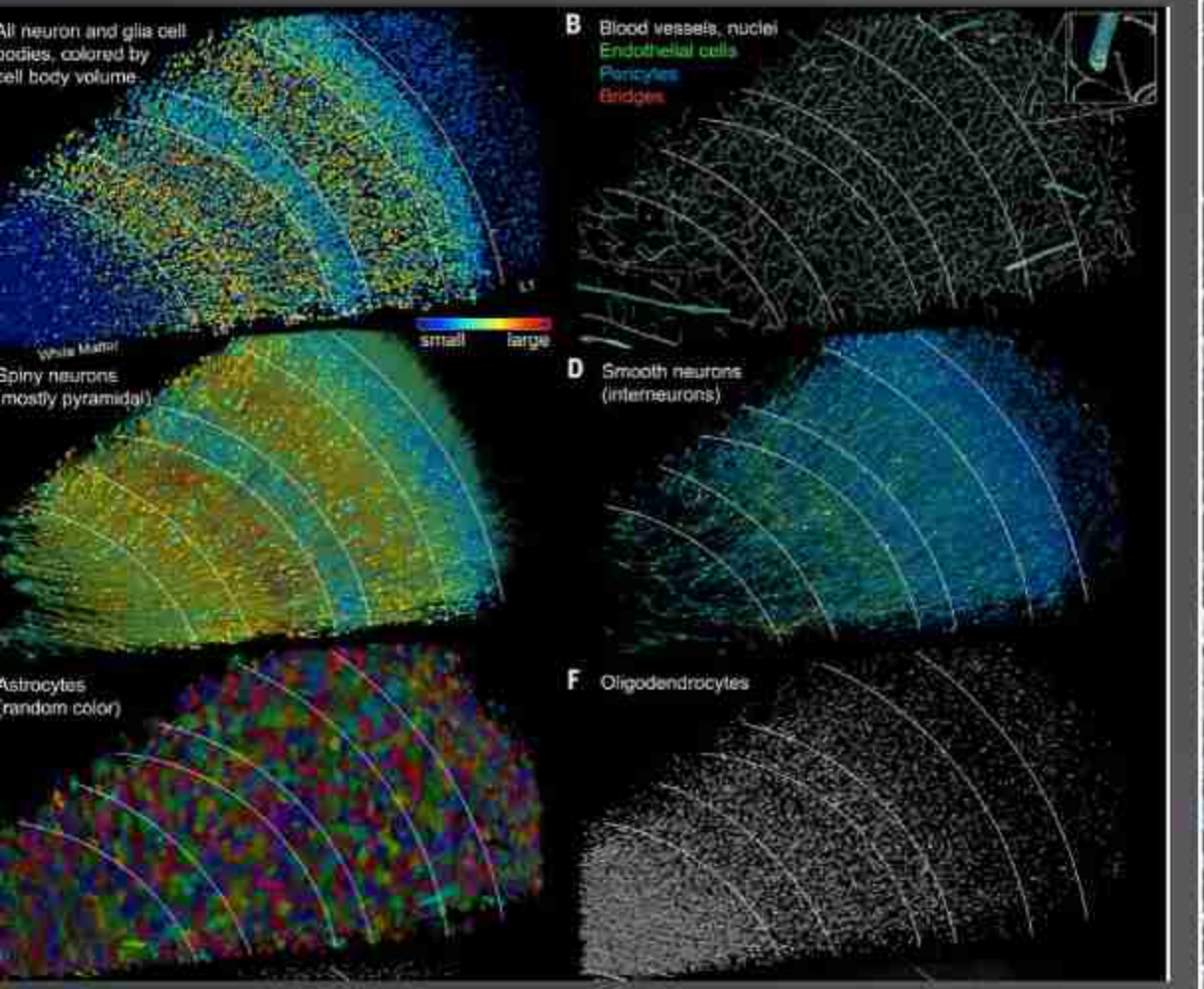


CREST – CAVE - VAST

Unmasking AlphaFold: integration of experiments and predictions in multimeric complexes

Evolutionary transitions in cellular complexity

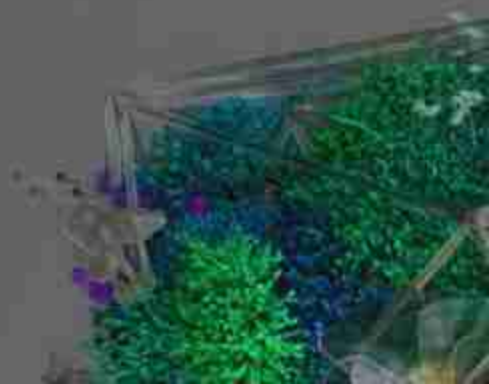
Functional Pathology – learning vs discovery

Single molecule tracking methods by means of fluorescence microscopy

Spatially resolved transcriptomics by in situ sequencing

Functional variation in the human genome: Lessons from natural and induced genetic perturbations

To seamlessly integrate AI with cell and molecular biology



Outline

1- Framing- Navigation of uncharted areas

2- Emerging lessons from wearables enabling return of agency

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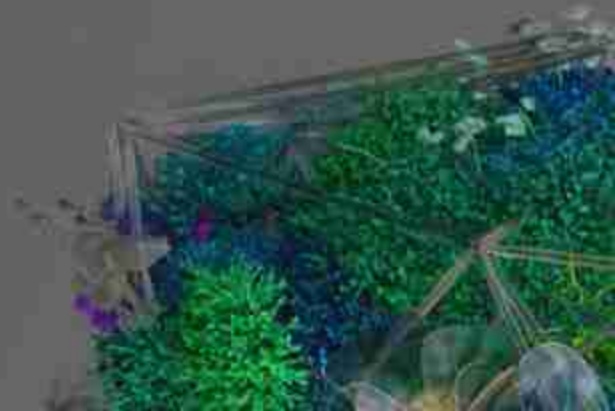

transition to working on wearables

when genotyping was becoming more informative that phenotyping

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static and somewhat constrained by definitions of symptoms with subjectivity of examining clinicians

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touch

hearing

sight

taste

smell

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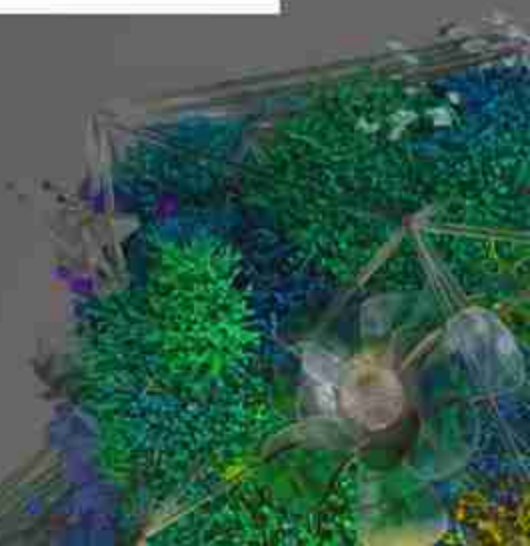

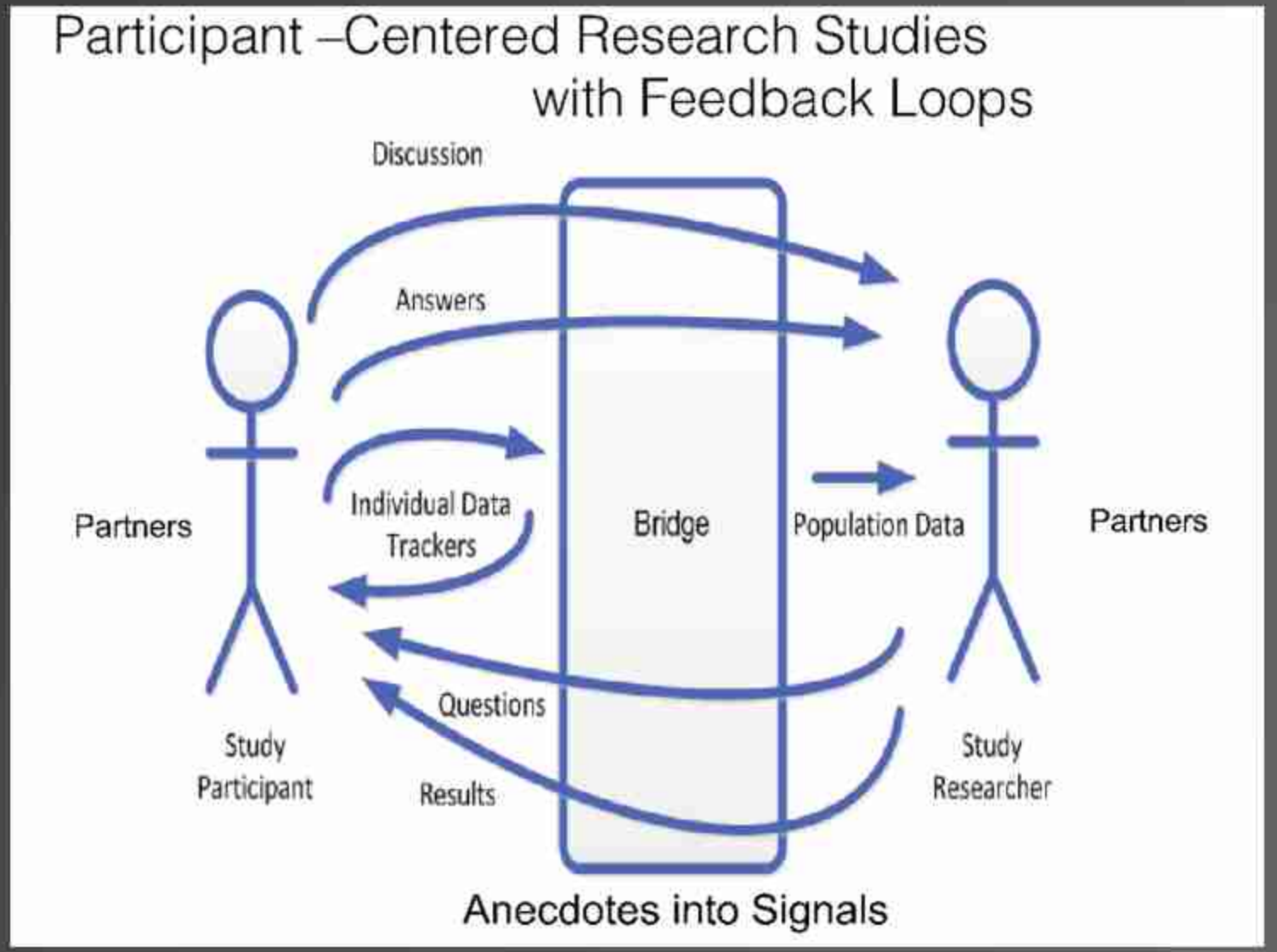

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How to exit the medieval framing of participants as “subjects”
to be probed and incented to do what others demand of them

TIM MOYNIHAN GEAR 03.09.15 02:05 PM

APPLE'S RESEARCHKIT IS A NEW WAY TO DO MEDICAL RESEARCH

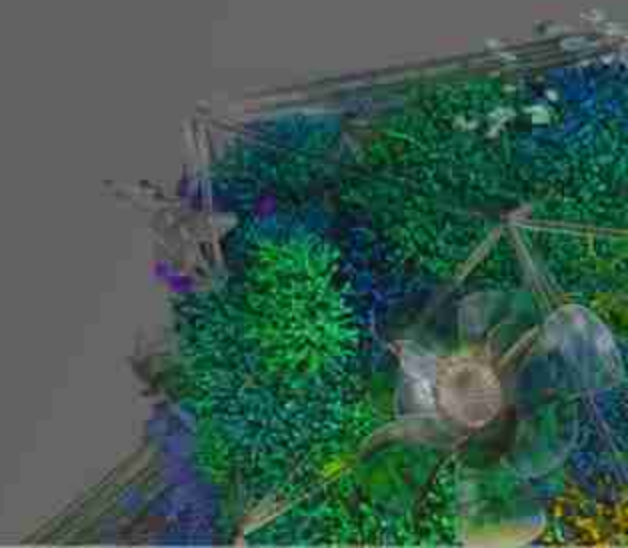
Jeff Williams, senior vice president of operations at Apple, introduces ResearchKit at an event in San Francisco.

Personal Health Assistant

self-navigate before and after symptoms arise

nurtures actions in times of strength

contributed by each for each other



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unknown complexities of forecasting individual health trajectories

progress over four years – lessons about future

How close are we to forecasting symptom transitions for chronic conditions like diabetes and Alzheimer's using digital devices-smartphones and beyond?

SciLifeLab
Stockholm
Feb 3, 2020

Stephen Friend MD PhD
University of Oxford
4YouandMe
Sage Bionetworks

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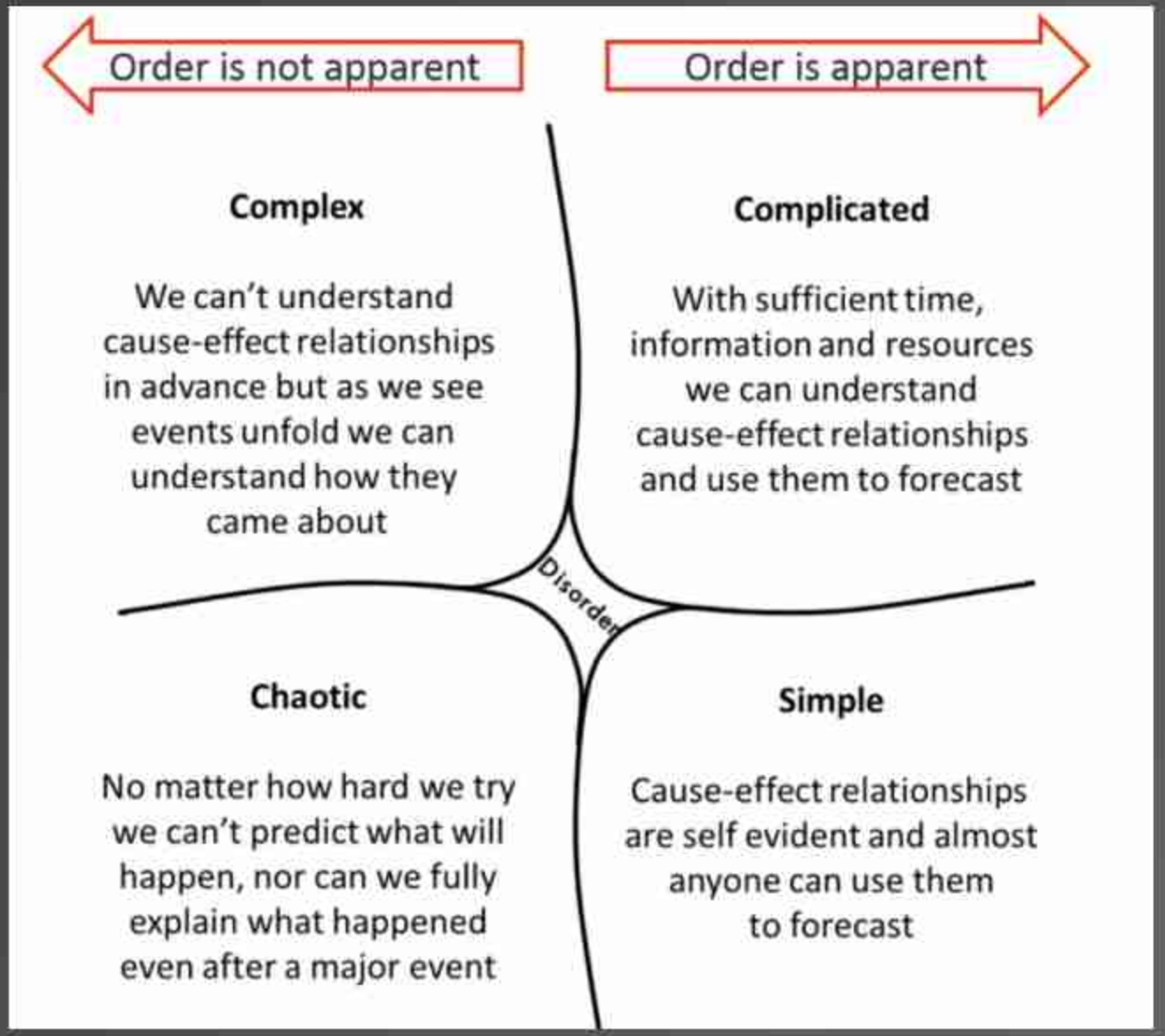

Presented Feb 2020

Stephen Grey 2014 Risk Management

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Presented Feb 2020

Opportunities: Rebuilding taxonomies of diseases

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Opportunities: Unfolding Disease transitions

Prodrome Early Moderate Advanced

Singular to branching

Presented Feb 2020

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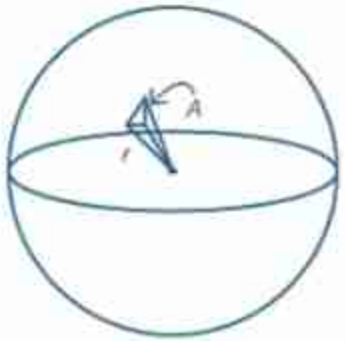
Presented Feb 2020

Opportunities: Untangling causes and consequences

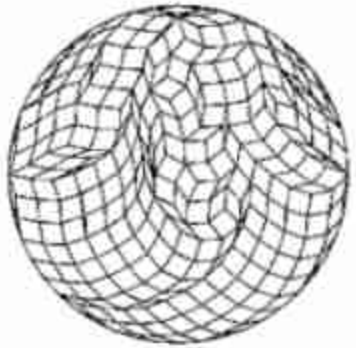


singular to overlapping

mood

STRESS

sleep cognition



Current and Completed Feasibility Studies

- ★ Stress and Recovery: Stress in COVID healthcare workers
- ★ BUMP: Forecasting Symptoms of Pregnancy and timing of delivery
- BUMP-C: Build portraits from trying to conceive to conception
- ★ Stress in Crohn's: Can stress help forecast flares?
- ★ HERO PANC: Following the effects of chemo and tumor regrowth
- HERO CNS: Designing tool to detect early growth of tumors
- Diabetes & Stress: How does stress effect continuous glucose measures
- Fabric of Life: Effects of Stress on Li-Fraumeni Syndrome
- OxAMI Fabric of Life: Effects of Stress on healing from heart attacks
- ★ My Experiences: Revamping the Psychiatric system of classification
- ★ Open Band: Construct and Open Hardware Open Firmware Affordable wearable for health

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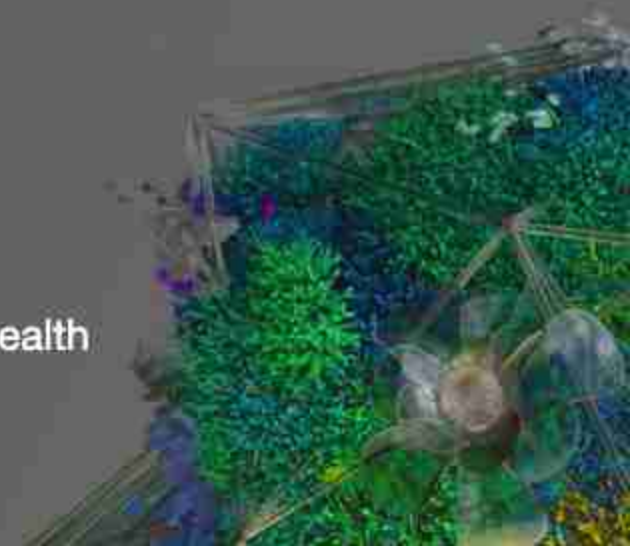


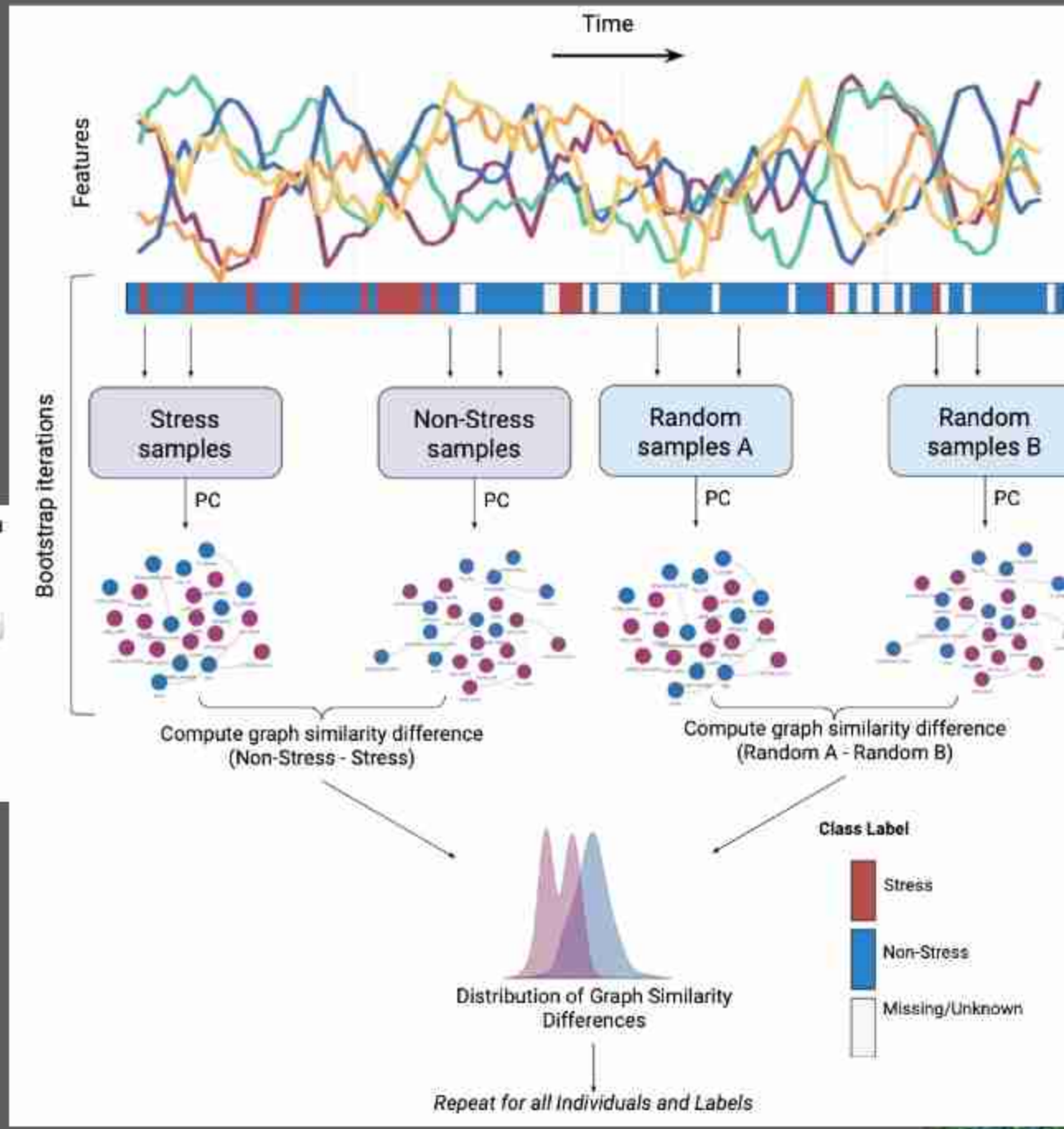
npj | digital medicine

www.nature.com/npjdigitalmed

ARTICLE OPEN

Dissecting the heterogeneity of "in the wild" stress from multimodal sensor data

Sujay Nagaraj[1,2,5✉], Sarah Goodday[4,5], Thomas Hartvigsen[3], Adrien Boch[7], Kopal Garg[1,2,3], Sindhu Gowda[1,2], Luca Foschini[8], Marzyeh Ghassemi[2,9,10], Stephen Friend[6] and Anna Goldenberg[1,2,3,11,12]



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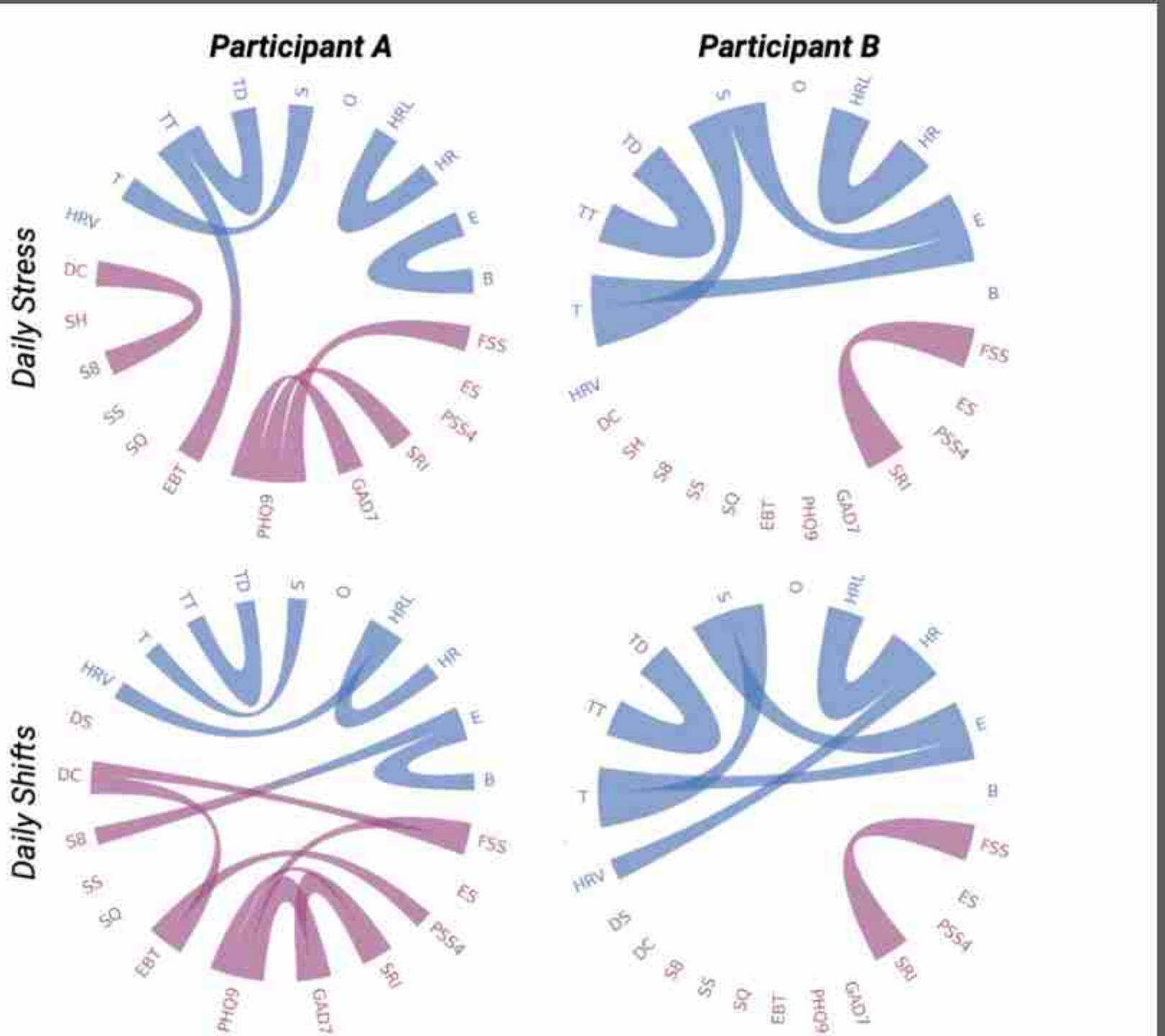


Study Characteristics: BUMP/BUMP-C

Aim: To determine the feasibility of using multiple digital health tools to follow eight core symptoms of pregnancy

N=524 (BUMP), 263 (BUMP-Conception (C))

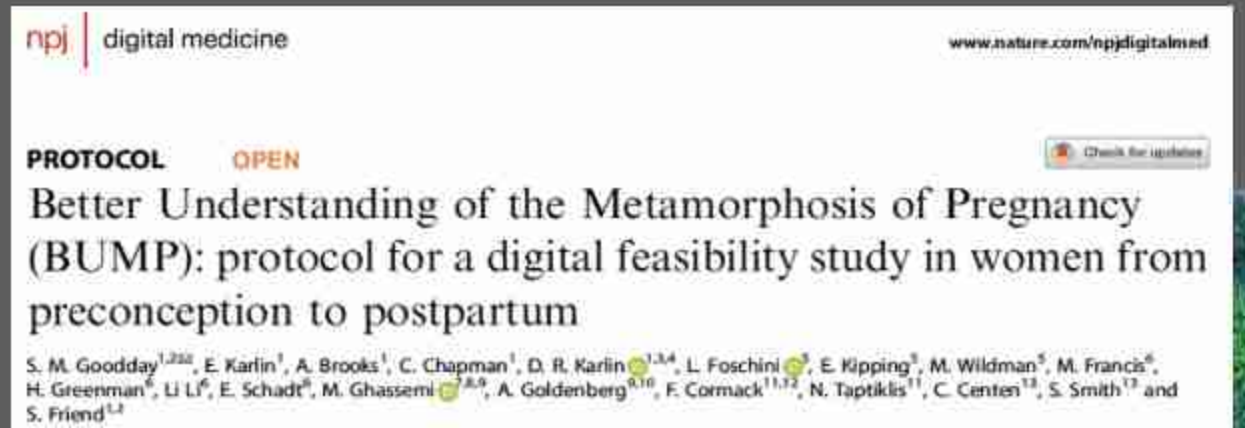
Population: Individuals attempting to get pregnant/individuals up to 15 weeks pregnant, 18-40 years

Follow-up time: Over pregnancy to 3-months postpartum (BUMP-C cohort up to 6 months attempting to get pregnant)

Recruitment: Patient provider platforms (Sema4), Community Health Centers, targeted social media campaigns in the US

Study Tools: App, Oura ring, Garmin watch, Apple watch (BYOD), Bodyport scale

Engagement: Bi-weekly phone support calls, Investigator – Participant Zoom calls



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Equipment Needed

Three wearable devices will be provided to study participants

Fitbit Versa

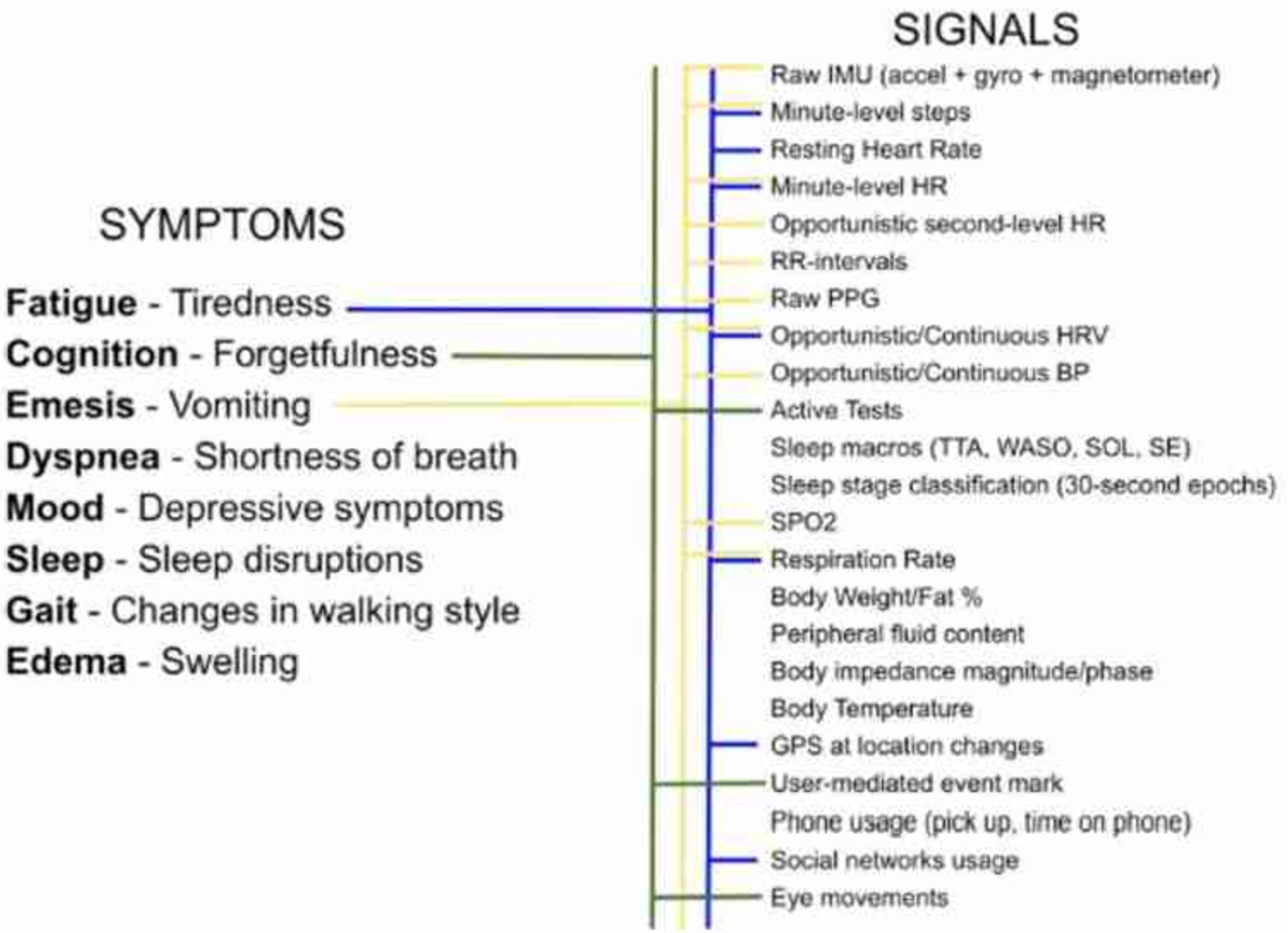
- 3-axis accelerometer
- 3-axis gyroscope
- Optical heart rate monitor
- Altimeter
- Vibration motor
- WiFi Antennas (802.11 b/g/n)
- 4+ days battery Life

Oura Ring 2

- Heart Rate, Resting Heart Rate (RHR)
- Heart rate variability (HRV)
- Respiration rate, breathing variance
- Sleep stages and quality metrics
- Body temperature variation
- Duration, intensity, and timing of activities
- Inactivity, sedentary time

BodyPort Smart Scale

- Weight
- Pre-ejection Period
- BMI
- Ejection Time
- Impedance
- PEP/LVET
- Peripheral Fluid Content
- Pulse Wave Velocity
- Balance
- Pulse Transit Time
- Pulse Rate
- Pulse Arrival Time
- Heart Rate Variability
- Ejection Force



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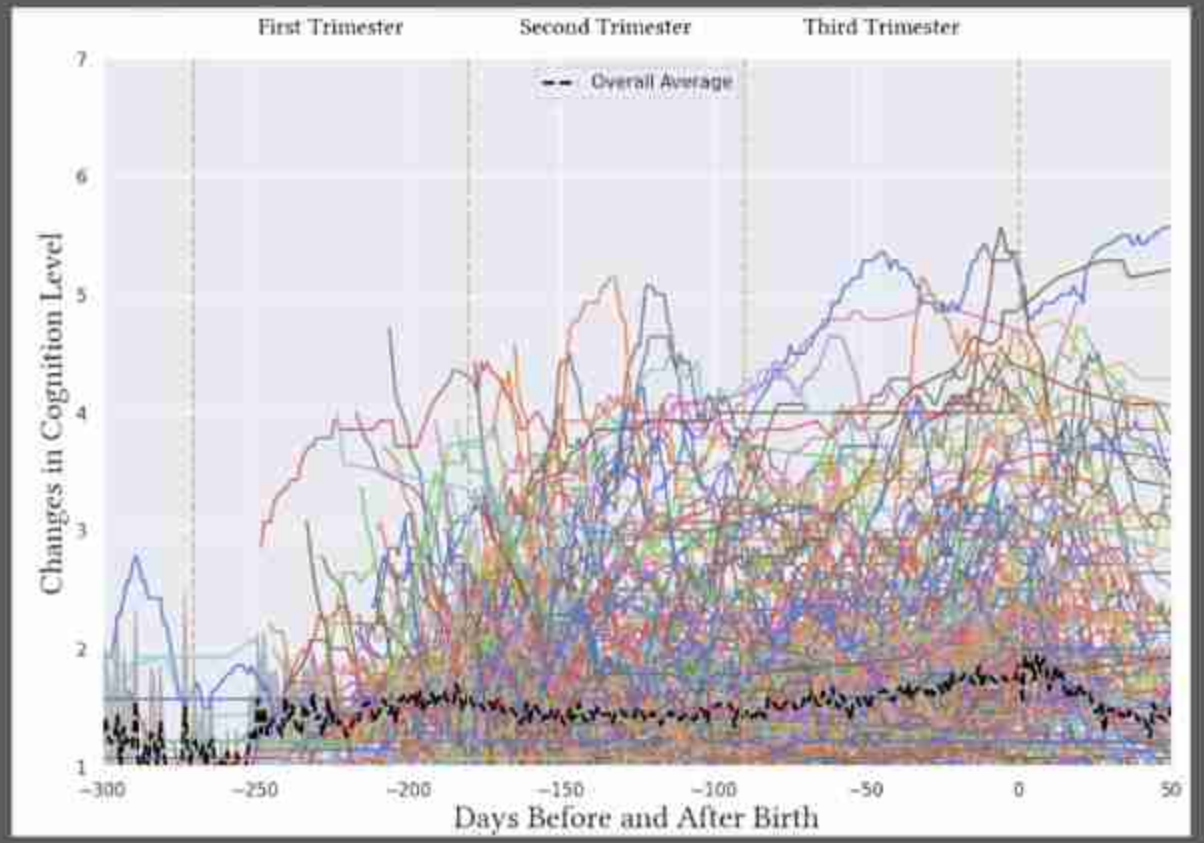
Fatigue

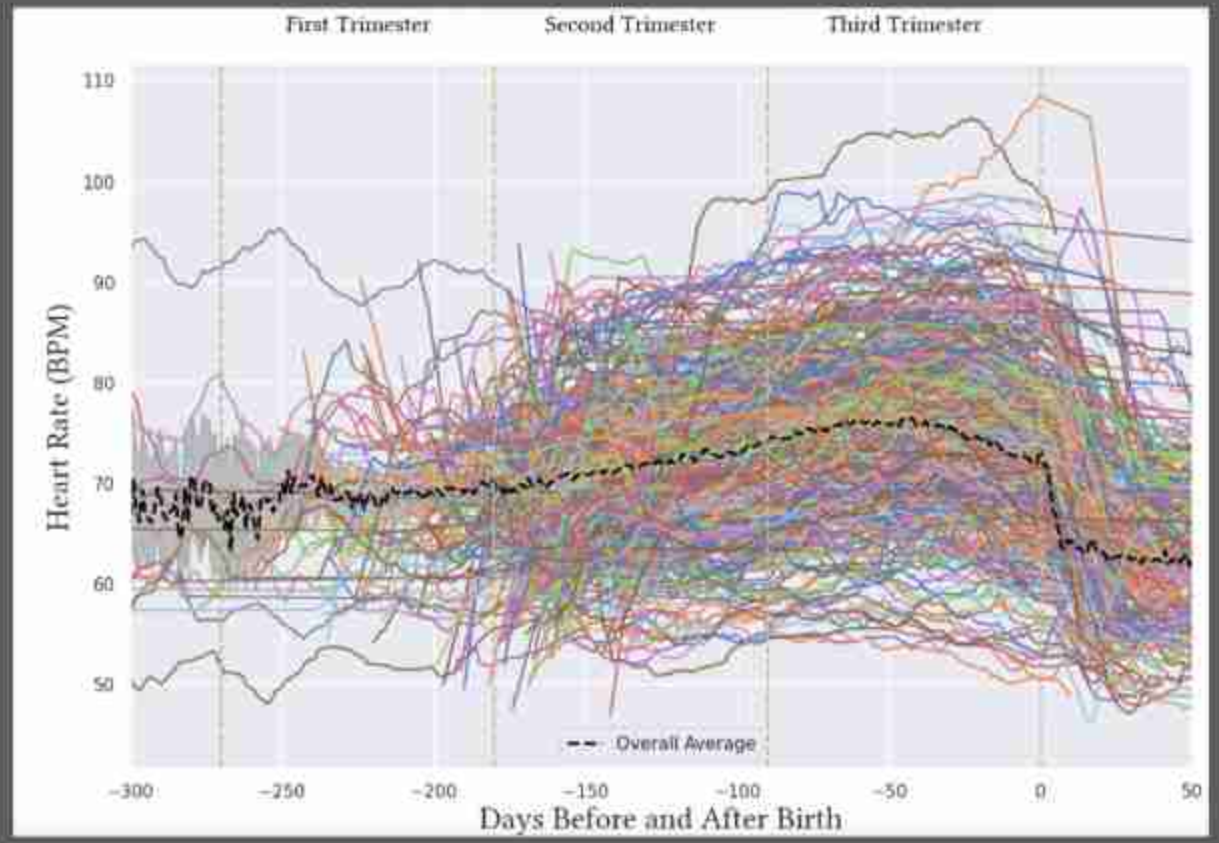
Active

- Study visits
  - Maternal Social Support Index
  - Adverse Childhood Events
  - PHQ-4
  - Perinatal PTSD survey
  - Medical history
  - Birthing data
  - Heart rate
  - Diabetes screens
  - CBC
  - Edinburgh Postnatal Depression Scale
- Camcog
  - N-back task
  - Emotion bias task
  - Psychomotor vigilance test
- In-app
  - Gait task
  - 2-minute walk test
  - Video diary
  - Absolute location (opt-in)
  - SAM EMA
  - Pregnancy symptom survey
  - Medical/pregnancy history survey
  - Quality of life survey
  - Healthcare utilization survey
  - Fatigue survey
  - Emotional support survey
  - Pain interference survey
  - Sleep disturbance survey
  - Sleep related impairment survey
  - Flu / infection question
- Bodyport
  - Left ventricular ejection time

Passive

- Activity
  - Activity score
  - Daily movement
  - Daily steps
  - Metabolic equivalents (1 min)
  - Activity class (5 min)
  - Steps (15 min)
  - Heart rate (1 min)
- Sleep
  - Bedtime start/end delta
  - Heart rate (5 min)
  - Nightly temperature delta
  - Number of sleeps per day
  - Sleep score
  - Circadian alignment
  - Disturbances
  - Sleep levels (5 min)
  - HRV (5 min)
  - Sleep levels
- Readiness score
- Stress level
- Body battery
- Breathing rate (1 min)
- Instagram posts
- Twitter posts & feed
- Phone usage





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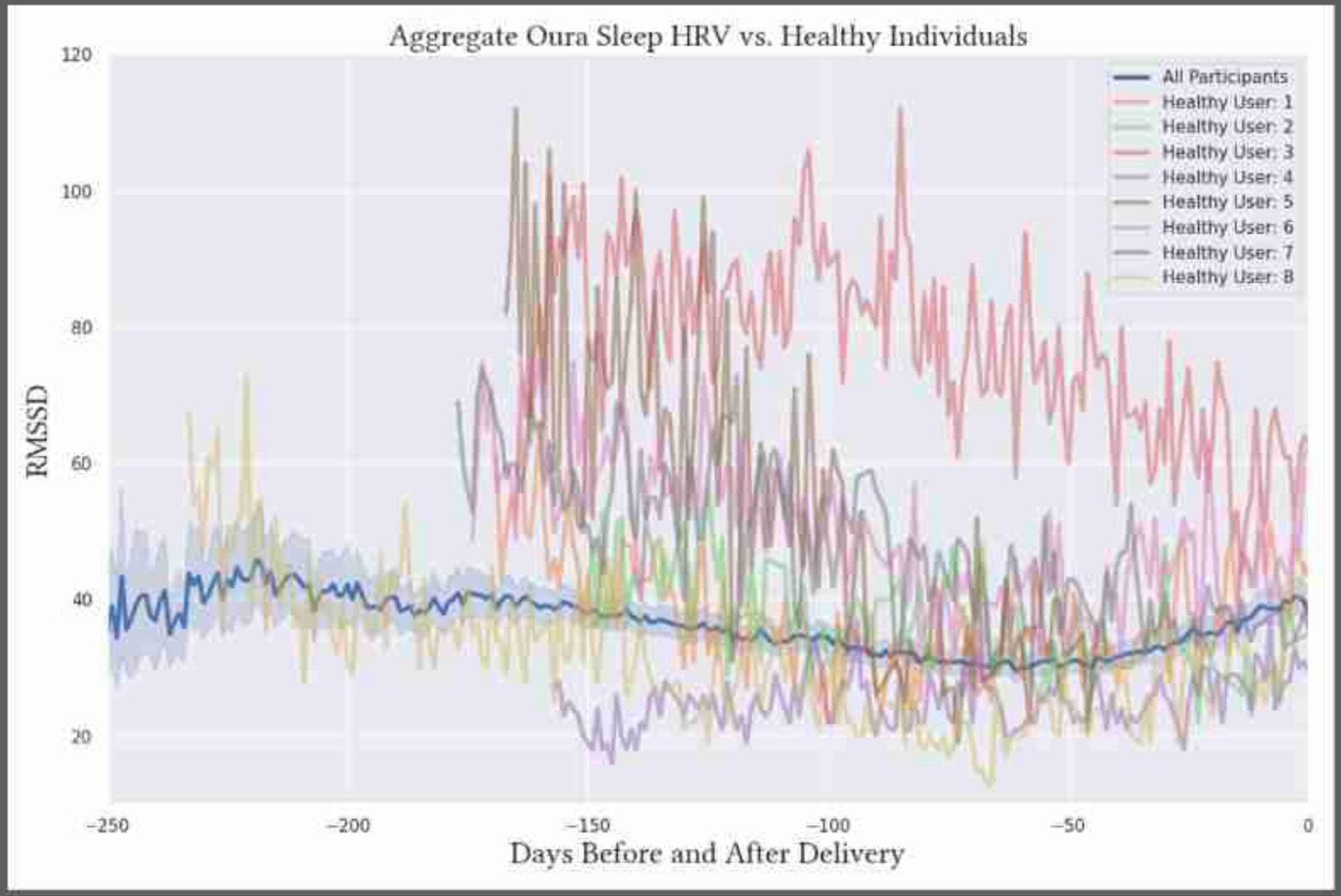
BUMP: Aggregate and healthy individual level HRV over pregnancy



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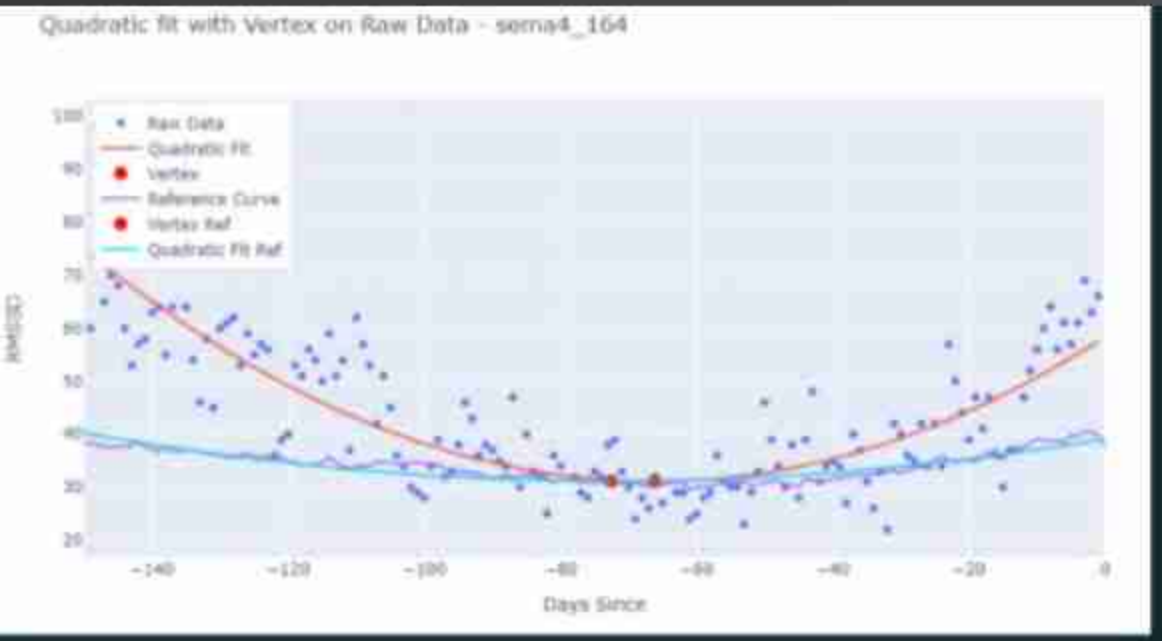
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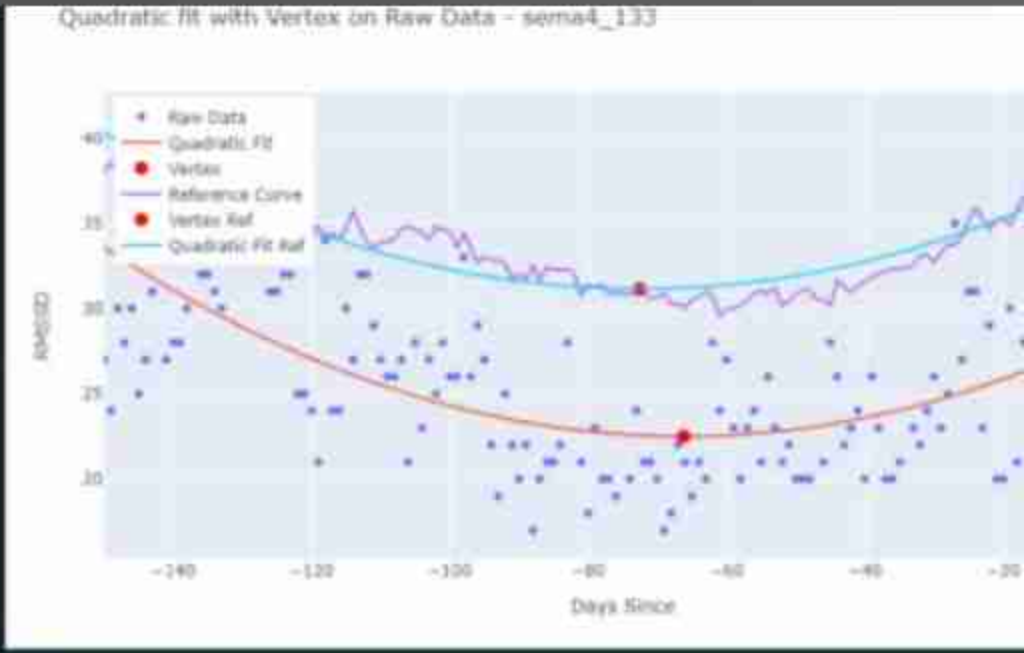
Raw Data
Quadratic Fit
Vertex
Reference Curve
Vertex Ref
Quadratic Fit Ref
RMSE(D)
Days Since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Vertex
Reference Curve
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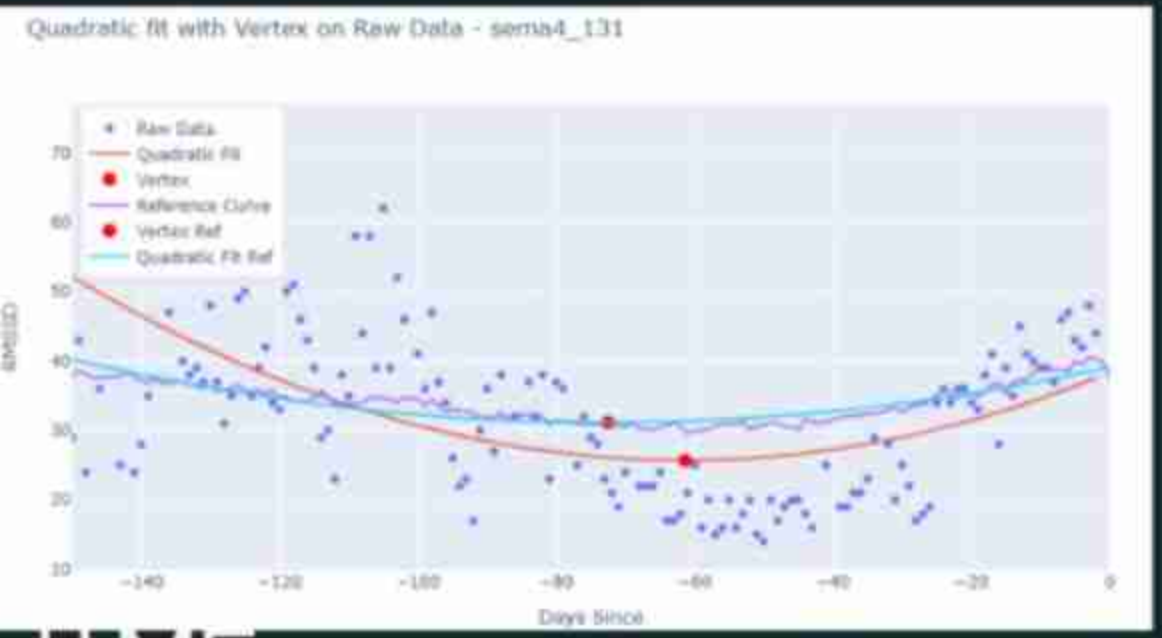
RMSE(D)
Days Since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Quadratic Fit
Vertex
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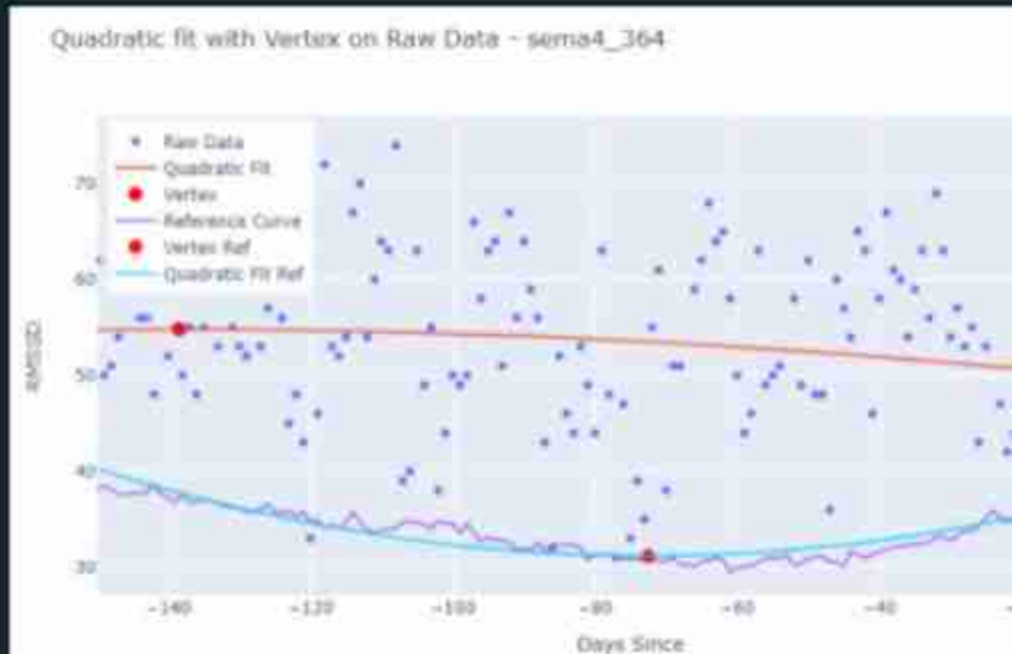
RMSE(D)
Days Since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Vertex Ref
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RMSE(D)
Days Since

Current Lessons and Puzzles at n of one level

-Navigating uncharted territories

1- Chaos at n of one level for symptoms is much larger than anticipated

2-Remarkable creativity of human body to react to outside circumstances in unique and evolving dynamic ways- how to gain power from others?

2- features not just entangled- but driven by known and unknown confounders

3- Poised to test whether routines, intervals, and labels from individuals allow context and larger populations allow ID of doppelgangers- use of generative approaches

4- Poised to better link blood-based analytes and EHRs with wearable data

5- Imagine a world where all data is fused using AI generative approaches and knowledge graphs

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3- Emerging lessons from -omics driving therapies

4- How will navigation of uncharted areas in the future relate to now

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The Resilience Project 2013-2016

a proof of concept effort to explore the potential power of second site suppressors as drug targets by scanning the healthy for unexpected resilient individuals

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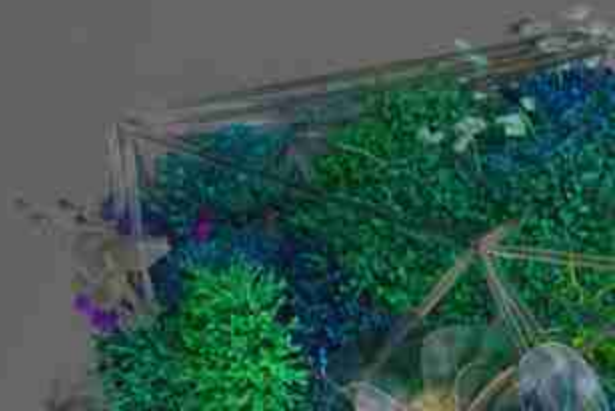


Original: "The Resilience Project"

Proof of Concept Study showing it is possible to

ARTICLES

nature biotechnology

- curate highly penetrant "lethal" alleles.
- Mine pre-existing large datasets of others.
- scan exomes and genotyping arrays for functional second-site suppressors.
- Identify likely candidates
- Allowed recognition of how essential to recontact individuals and records.
- Importance of adding in advocate groups, new tools to screen for second-site suppressors, use of emerging knowledge graphs, alpha fold approaches.

Analysis of 589,306 genomes identifies individuals resilient to severe Mendelian childhood diseases

Rong Chen[1,2,12], Lisong Shi[1,2,12], Jörg Hakenberg[1,2], Brian Naughton[3,11], Pamela Sklar[1,2,4], Jianguo Zhang[5], Hanlin Zhou[5], Lifeng Tian[6], Om Prakash[7], Mathieu Lemire[8], Patrick Sleiman[6], Wei-yi Cheng[1,2], Wanting Chen[5], Hardik Shah[1,2], Yulan Shen[5], Menachem Fromer[1,2,4], Larsson Omberg[9], Matthew A Deardorff[6], Elaine Zackai[6], Jason R Bobe[1,2], Elissa Levin[1,2], Thomas J Hudson[8], Leif Groop[7], Jun Wang[10], Hakon Hakonarson[6], Anne Wojcicki[3], George A Diaz[1,2], Lisa Edelmann[1,2], Eric E Schadt[1,2] & Stephen H Friend[1,2,9]

Genetic studies of human disease have traditionally focused on the detection of disease-causing mutations in afflicted individuals. Here we describe a complementary approach that seeks to identify healthy individuals resilient to highly penetrant forms of genetic childhood disorders. A comprehensive screen of 874 genes in 589,306 genomes led to the identification of 13 adults harboring mutations for 8 severe Mendelian conditions, with no reported clinical manifestation of the indicated disease. Our findings demonstrate the promise of broadening genetic studies to systematically search for well individuals who are buffering the effects of rare, highly penetrant, deleterious mutations. They also indicate that incomplete penetrance for Mendelian diseases is likely more common than previously believed. The identification of resilient individuals may provide a first step toward uncovering protective genetic variants that could help elucidate the mechanisms of Mendelian diseases and new therapeutic strategies.

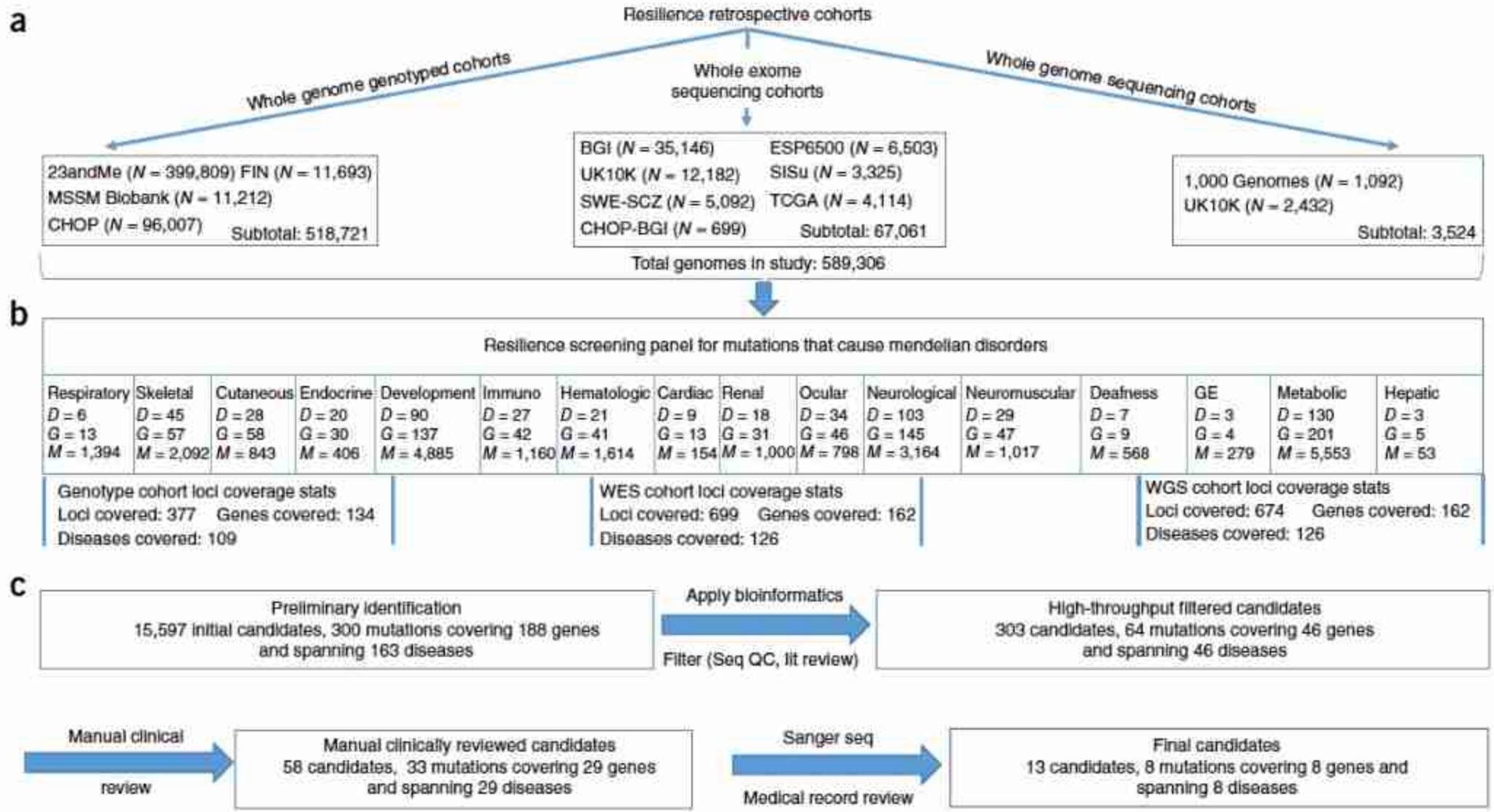


Figure 1 Study design and results for the retrospective search for resilient individuals. (**a**) A summary of the different cohorts and the genomic data available on those cohorts (see **Table 2** for more details). (**b**) The disease-causing genes and mutations that were assembled to construct our screening panel (more details in **Table 1** and **Supplementary Tables 1** and **2**). The D, G and M variables denote the number of diseases, genes and mutations, respectively, represented on our screening panel in the respective disease categories. The coverage statistics indicate the coverage achieved for the core allele panel in the genotype, WES and WGS cohorts. (**c**) Summaries for the different stages of the filtering process to identify candidate resilient individuals (see **Supplementary Fig. 1** and **Tables 3** and **4** for more details).

Table 4 13 Candidates identified in the Resilience Project

Phenotype	Gene	Mutation (cDNA; protein (reference))	Genomic coordinate (hg19)	Mutation severity	Candidate confidence	Panel source	No. of candidates	Zygosity	Data source	Level of support for candidacy[a]	Sample status	Population carrier frequency[b]	
												1KG	ESP
Cystic fibrosis	*CFTR*	c.1558G>T; p.V520F (NM_000492.3)	Chr7 117199683	Severe pulmonary disease, childhood-onset	Strong	Core allele panel	3	hom	23andMe	C1,C2,C3, G1,G2,G3	2 adults, one declared no manifestation	0.00	0.00
Smith-Lemli-Opitz syndrome	*DHCR7*	c.964-1G>C (NM_001360.2)	Chr11: 71146886	Severe developmental disorder, probably embryonic lethal	Strong	Core allele panel	2	hom	UK10K	C1,C2, G1,G2	Not obtained	0.0052	0.011
Familial dysautonomia	*IKBKAP*	c.2204+6T>C (NM_003640.3)	Chr9: 111662096	Severe neurological disease, high mortality in early childhood	Strong	Core allele panel	1	hom	23andMe	C1,C2, G1,G2,G3	No disease reported by individual	0.00	0.0012 (only in EA)
Epidermolysis Bullosa simplex	*KRT14*	c.373C>T; p.R125C (NM_000526.4)	Chr17: 39742714	Severe dermatologic condition, infantile onset	Strong	Core allele panel	1	het	BGI	C1,C2,C3, G1,G2	No disease reported by individual	0.00	0.00
Pfeiffer syndrome	*FGFR1*	c.755C>G; p.P252R (NM_023110.2)	Chr8: 38282208	Severe congenital skeletal dysplasia with variable expressivity	Strong[c]	Core allele panel	1	het	SWE-SCZ	C1,C2,C3, G1,G2,G3	No abnormal morphology reported in discharged health information	0.00	0.00
APECED	*AIRE*	c.769C>T; p.R257* (NM_000383.2)	Chr21: 45709656	Severe childhood-onset autoimmune disease	Strong	Core allele panel	1	hom	23andMe	C1,C2,C3, G1,G2	No disease reported by individual	0.00	0.00015
Acampomelic campomelic dysplasia	*SOX9*	c.1320C>G; p.Y440* (NM_000346.3)	Chr17: 70120318	Severe skeletal dysplasia with early childhood death	Strong	Expanded panel	1	het	FINN	C1,C2, G1,G2	Not obtained	0.00	0.00
Atelosteogenesis	*SLC26A2*	c.835C>T; p.R279W (NM_000112.3)	Chr5: 149359991	Severe early-onset skeletal dysplasia with variable expressivity	Moderate[d]	Expanded panel	3	hom	23andMe	C1,C2, G1,G2	Not obtained	0.0028	0.0023

[a]See **Table 5** for code definitions. [b]Carrier frequencies from combined ethnicities. [c]Individual was categorized as strong candidate due to lack of dysmorphic features. [d]Individual with variable phenotypes have been reported with the mutation[37].
EA, European American.

Resilience Project 2.0 RoadMap

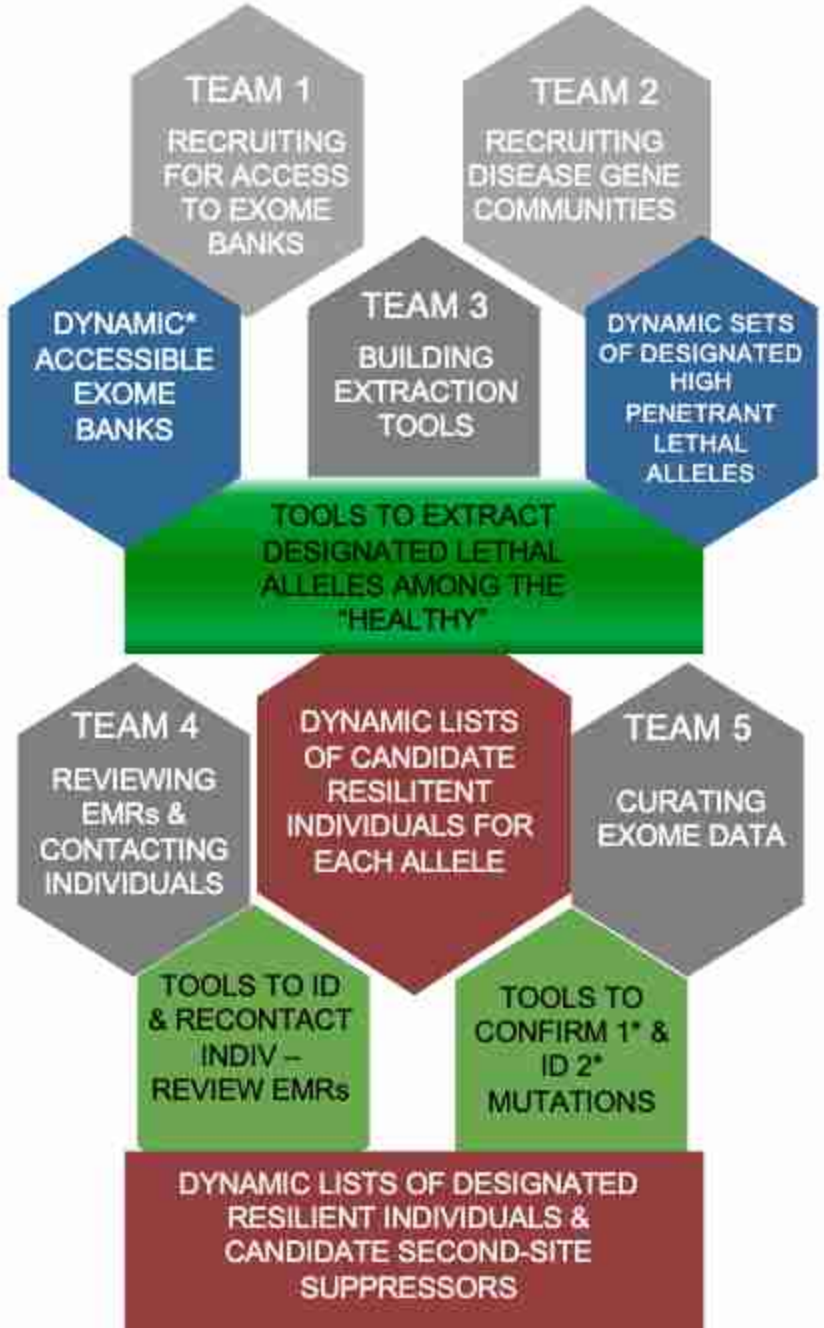
"Build a scalable stage-gate driven open platform to deliver lead compounds for diverse genetic diseases based on leveraging existing exome banks, EMRs, and known lethal penetrant mutations/alleles. This effort starts by identifying second-site suppressors so as to find drug targets with existing human genetic validation, followed by use of emerging tools to prioritize candidate second site suppressors, and then use coordinated teams to deliver active compounds for prioritized drug targets."

April 29th, 2024 Draft

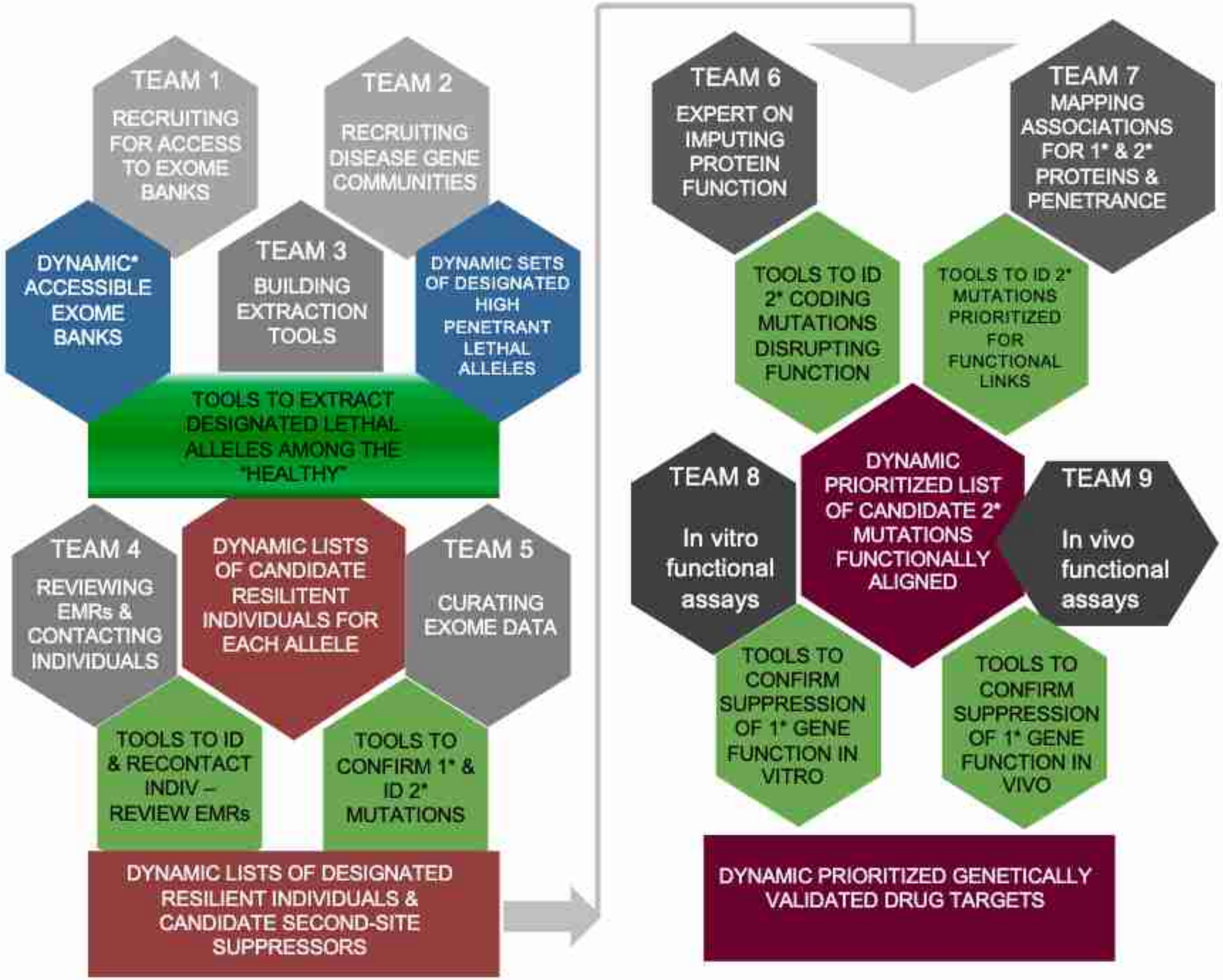
Why is this needed?

- Treatment options for vast majority of the 5000+ genetic diseases with known mutations are too often non-existent or very limited
- Identification of targets for altering expression of disease in healthy resilient individuals has the power to open up treatment in the indicated disease space for small molecules
- Increasing scales of exome/genome data with linked EHR and patient contact available
- No groups systematically searching for resilient individuals outside of affected families where power to identify and decode individuals is a function of big sample sizes (so data need to be brought together)
- Tools to sort through the massive number of mutations to ID mutations that might disrupt function and be relevant using emerging ML methods is becoming more effective
- Coordinated teams are needed to translate interesting findings of resilience to validated second site suppressors poised to be targets for small molecule drug discovery/development

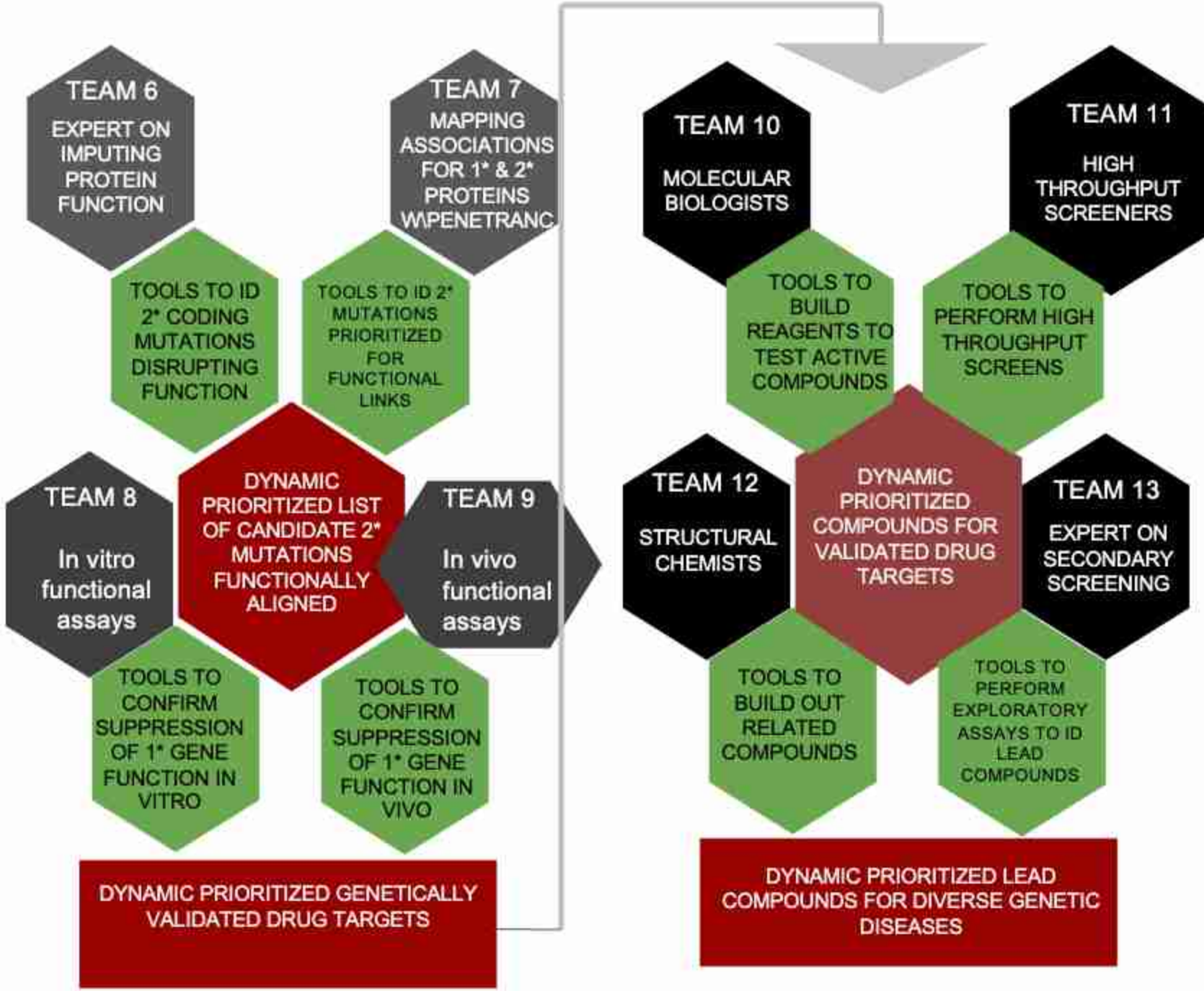
Identifying and Decoding Resilient Individuals



Lists of mutations identified in “Resilient” Individuals



"Validated" Potential Drug Targets

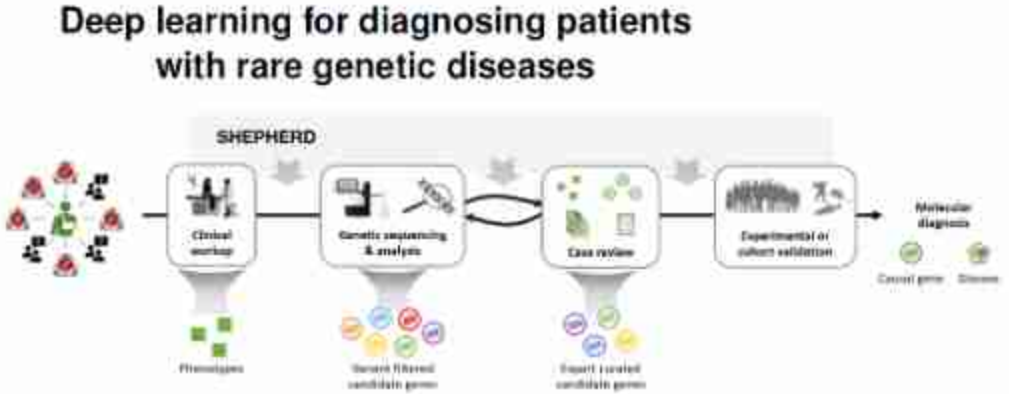


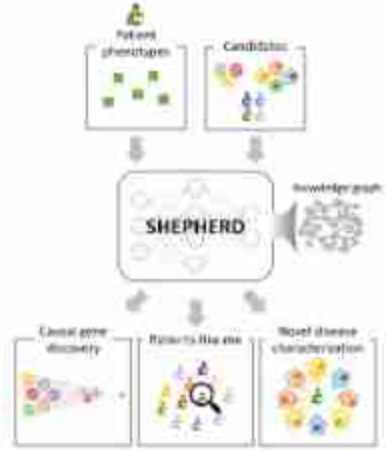
Potential
"Lead" Compounds

Draft RP2.0 “teams of experts” to help identify ideal RP2.0 partners and teams

- Team 1 - Recruiting access to re-contactable Exome databases
  - Potential members: Geoff Ginsburg- NIH All of Us, Tom Maniatis- NY Genome Center, ?John Bell- Oxford University, UK BioBank, ?Aarno Palotie- FinnGen, John Spiro- Simons Foundation,
- Team 2 - Primary gene/allele selection: Coordinate initial designated gene/alleles across genome driven by genetic communities committed to be advocates and identify apparent existing resilient individuals
  - Potential members: ?Francis Collins- Bruce Gelb- MSSM, Daniel MacArthur- Garvan Institute, NIH Mol Genetics Section, ?Gary Cutting- JHMU, ?Caroline Wright
- Team 3 - Building Extraction tools
  - Potential members: TBD
- Team 4 - Contacting candidate resilient individuals and linking with EMR records
  - Potential members: Diego Chowell- MSSM,
- Team 5 - Curating Exome data
  - Potential members: Daniel Jordan- MSSM
- Team 6- Experts on imputing loss of protein function
  - Potential members: ?Demis Hassabis- Deep Mind-AlphaFold, Peter Kim- Stanford
- Team 7- Experts for Mapping Associations for primary and secondary proteins and considering “penetrance”
  - Potential members: Cori Bargman- Rockefeller, David Fajgenbaum- U Penn, EverCure. Huda Zhohbi, Baylor,

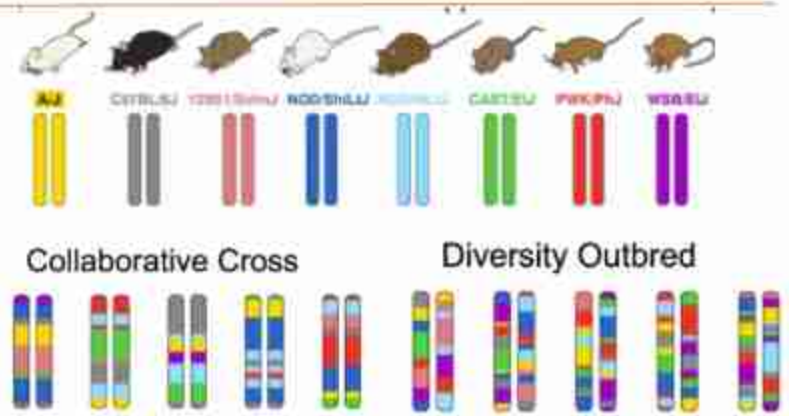
Baylor employing state of the art **AI tools and advanced experimental systems to uncover causal rare disorder disease genes** and a want to apply to discovery of resilience factors



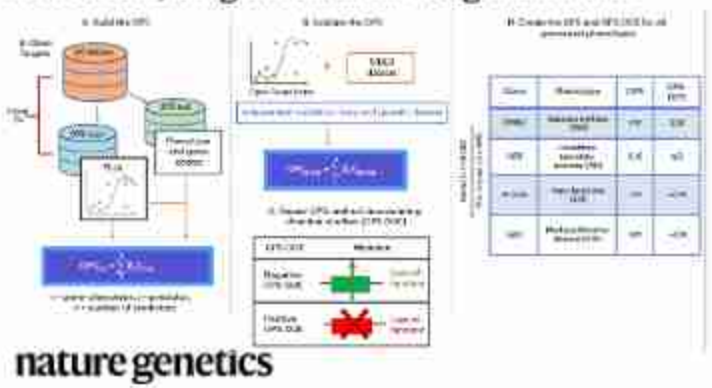


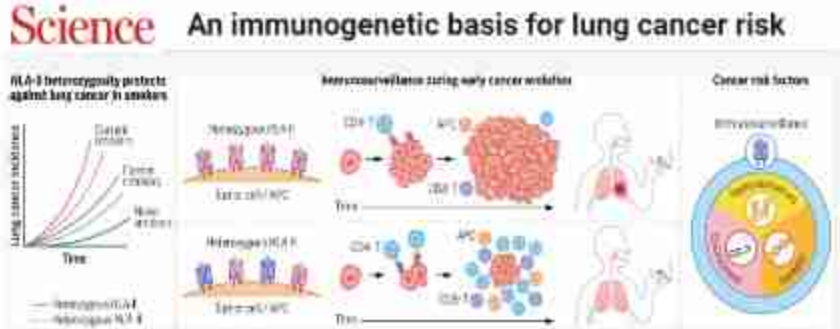
https://www.medrxiv.org/content/10.1101/2022.12.07.22283238v1.full.pdf

Nadia Rosenthal at JAX employing advanced cohorts of **diversity strains of mice to uncover resilience factors** for disease



Diego Chowell and **Daniel Jordan** at Mount Sinai employing **machine learning approaches to integrating variant information with EMR data** to discovery new drivers of disease and resilience





Current Lessons and Puzzles in Resilience Project 2.0

-Navigating uncharted territories

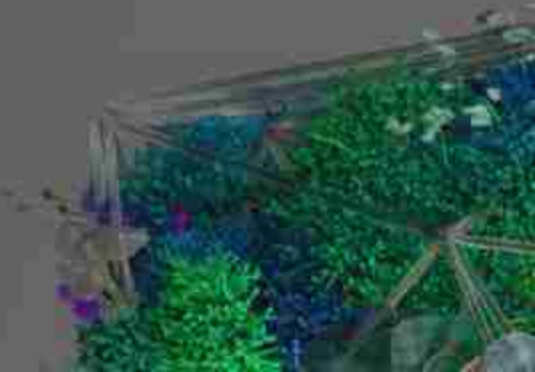
1- How and where to host the distributed project

2- Virtually all teams have serious sets of unknown unknowns

3- Facing social moral issues- how to best unlock cloistered genome data

4- Sorting functional links for second-site suppressor candidates

5- Chance to highlight again- context: penetrance



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Functional variation in the human genome: Lessons from natural and induced genetic perturbations
Tuuli Lappalainen

Outline

1- Framing- Navigation of uncharted areas

2- Emerging lessons from wearables enabling return of agency

3- Emerging lessons from -omics driving therapies

4- How will navigation of uncharted areas in the future relate to now

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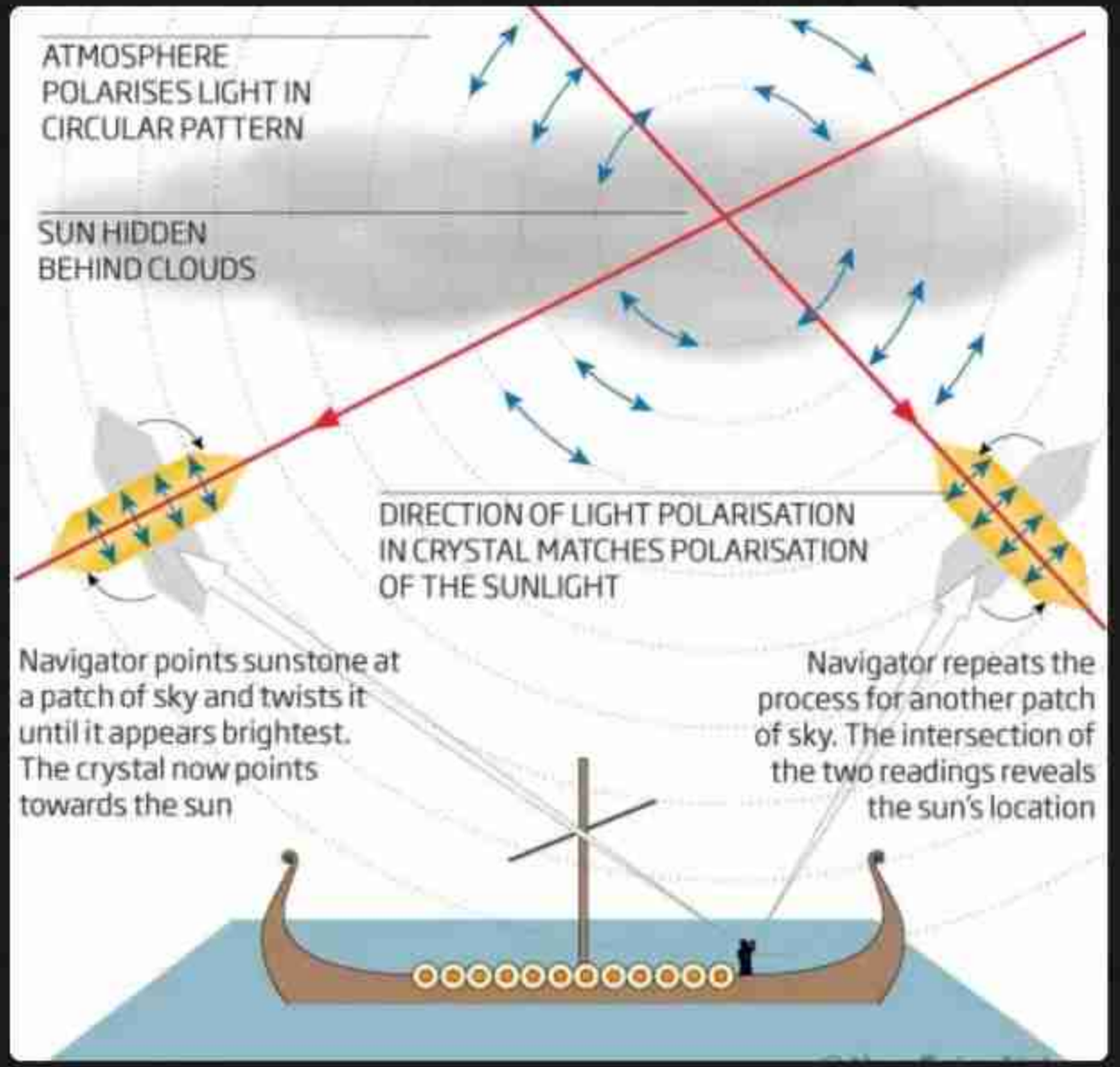
how do viking sunstones work



build and
employ
new tools

understand
existing
knowledge

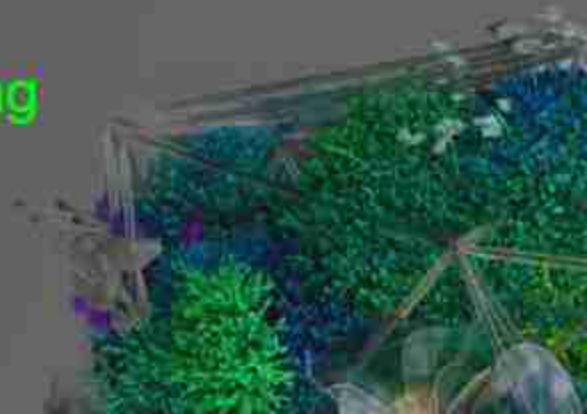
ask
novel
questions

entertain
new methods
of questioning

scale of data forcing navigation via knowledge graphs requiring framing

speed of hypothesis generation

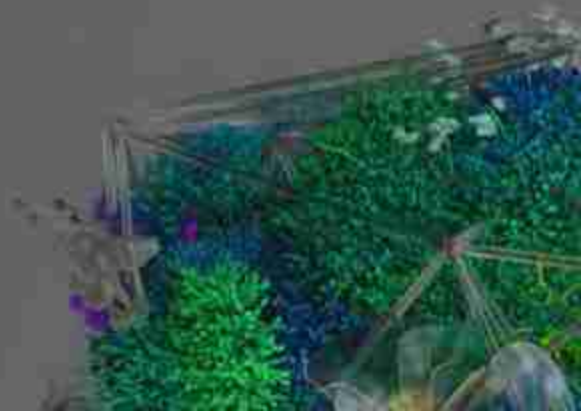
contextual micro-validations



USERS BEWARE

Oppenheimer's Syndrome
beware of what you build for the good of humankind

The power to forecast an individual's health trajectories will place an awkward tension between giving individuals free-will/ freedom to act and the known good for the social group



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Outline

1- Framing- Navigation of uncharted areas

2- Emerging lessons from wearables enabling return of agency

3- Emerging lessons from -omics driving therapies

4- How will navigation of uncharted areas in the future relate to now

5- Opportunities for SciLifeLab

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Opportunties for SciLife Lab

1- Become even more of a virtual distributed convener- beyond ownership

2- Designate self as owner of “Hilbert’s Questions” for LifeSciences

3- Invert current power structure- Researcher-Clinician-Patients where re-optimized so that individuals can co-navigate their interventions

4- Fuse the powerful reductive disciplines (omics EHRs etc.. with integrative longitudinal data from wearables

5-Offer a contrarian “by each other for each other” model for building generative data (sidestepping being serfs for large tech companies in this the emerging age of techno-feudalism)

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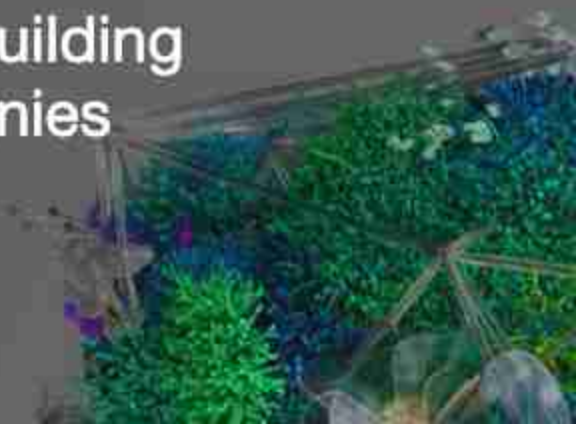

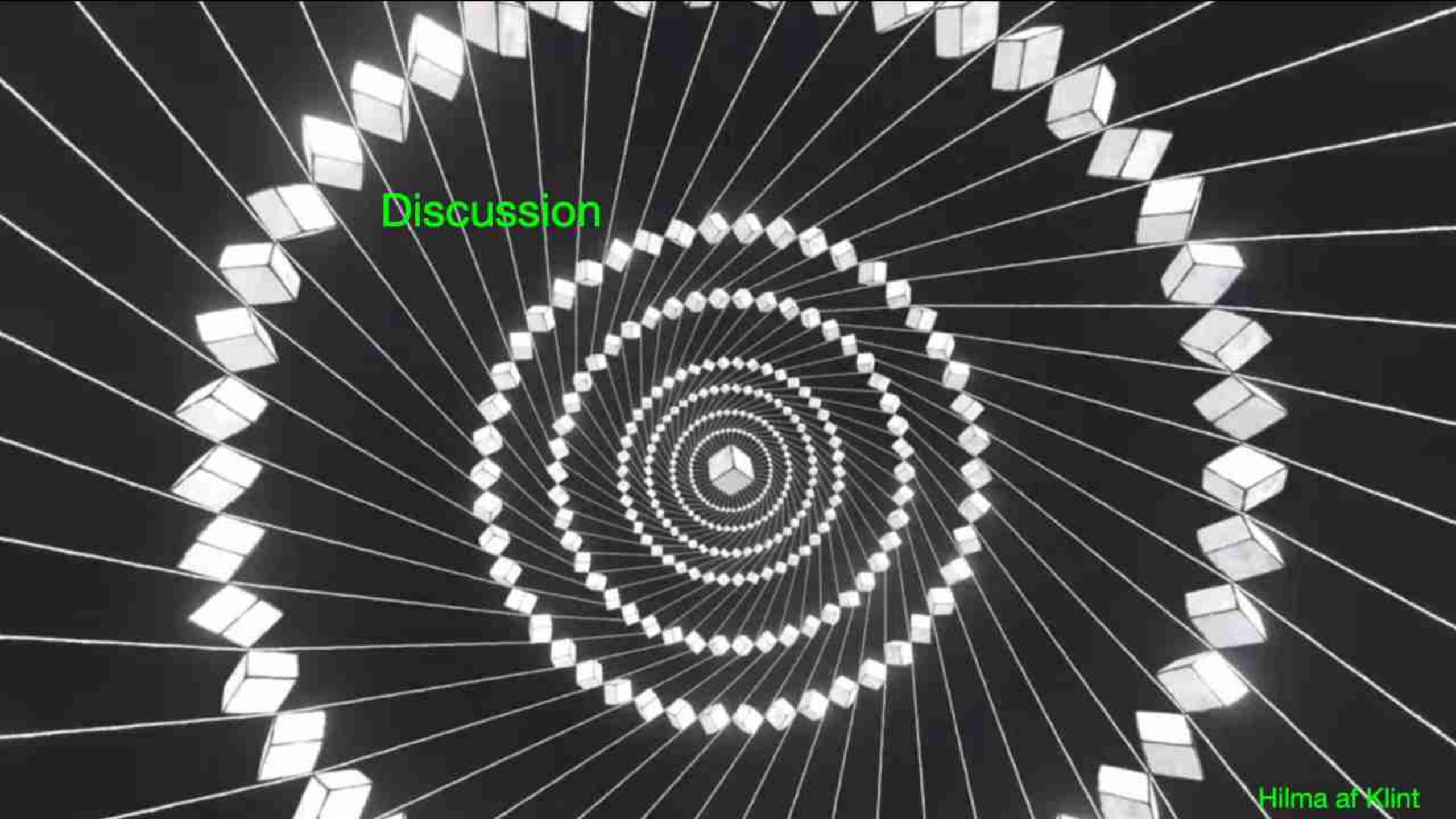
Discussion
Hilma af Klint