

Bridging Disciplines to Heal the Whole System: Collaboration as the Engine for Brain and Whole Health Applications

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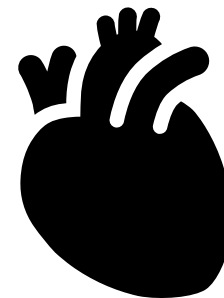
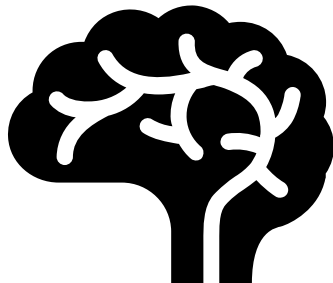


Disclosures

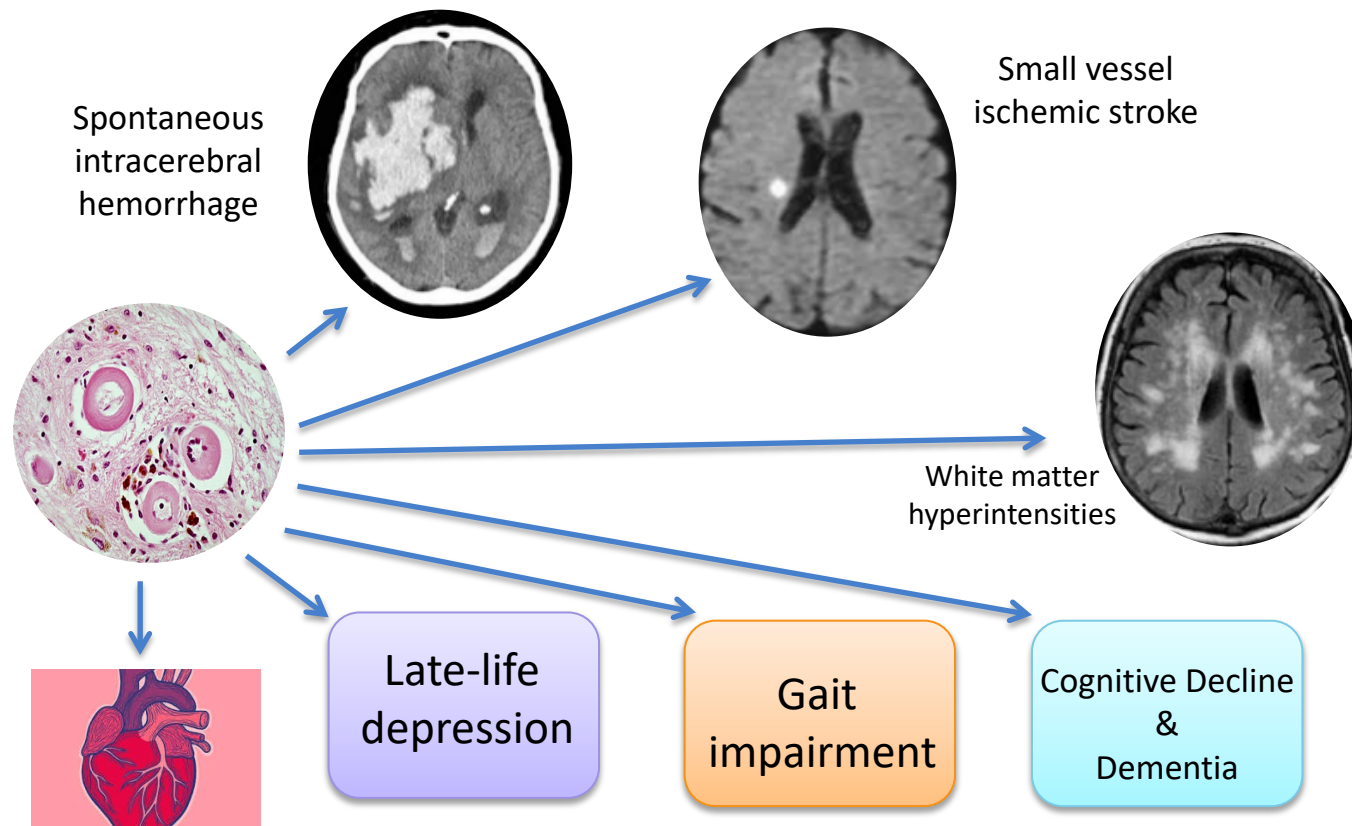
- National Institutes of Health
 - U01NS106513
 - UG3NS133209
 - R01MD16178
 - R01EB031114
 - U24NS107215
 - U24NS129500
 - R21NS145048
- Astrocyte, American Heart Association, Alva Health, Bexorg, BrainQ, Genentech, Hyperfine, Rhaeos

I Work to Prevent and Treat Stroke and Preserve Brain Health

- Stroke is the #5 cause of death in United States; #2 globally
- 90% of stroke risk could be attributed to modifiable risk factors such as hypertension, obesity, diabetes, hyperlipidemia
- 50% of stroke risk can be attributed to behavioral risk factors such as smoking, sedentary lifestyle, and an unhealthy diet



Systemic Vascular and Inflammatory Disease Causes Stroke and Much More



Lancet Neurol. 2014 Apr;13(4):405-18.

The Brain Controls the Body . . . And the Body Controls the Brain?

Cardiogenic control of affective behavioural state

<https://doi.org/10.1038/s41586-023-05748-8>

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Open access

Brian Hsueh^{1,6}, Ritchie Chen^{1,6}, YoungJu Jo¹, Daniel Tang¹, Misha Rafflee¹, Yoon Seok Kim¹, Masatoshi Inoue¹, Sawyer Randles¹, Charu Ramakrishnan¹, Sneha Patel¹, Doo Kyung Kim¹, Tony X. Liu¹, Soo Hyun Kim¹, Longzhi Tan¹, Lelli Mortazavi¹, Arjay Cordero¹, Jenny Shi¹, Mingming Zhao², Theodore T. Ho¹, Alley Crow¹, Al-Chi Wang Yoo¹, Cephra Raja¹, Kathryn Evans¹, Daniel Bernstein², Michael Zelineh³, Maged Goubbran³ & Karl Deisseroth^{1,4,5} 

A microbiome-dependent gut–brain pathway regulates motivation for exercise

<https://doi.org/10.1038/s41586-022-05525-z>

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 Check for updates

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How do we improve health?

- Science, yes.
- Translation, yes.
- Technology, yes.
- But most of all: interdisciplinary collaboration.

Center for Brain & Mind Health



CBMH Winter Symposium

Making it Happen: Neuroscience Discovery to Treatment



Amy FT Arnsten, PhD

*Albert E Kent Professor of Neuroscience and Psychology, Yale Medical School
Successful Translation of Guanfacine for the Treatment of Prefrontal Cortical
Cognitive Disorders*



Allyson Berent, DVM, Dipl. ACVIM, CSO

*Foundation for Angelman Syndrome Therapeutics
Parents' Journey Through Drug Development: Making the Impossible Possible:
The Angelman Syndrome Story*



Christopher van Dyck, MD

*Director, Yale Alzheimer's Disease Research Unit
Lecanemab: The First Disease-Modifying Therapy for Alzheimer's Disease*



Tim Yu, MD, PhD

*Division of Genetics and Genomics, Manton Center for Orphan Disease, and Translational
Neuroscience Center, Harvard Medical School
Prospects for "Individualized" Neurotherapeutics Using Antisense
Oligonucleotides*

December 7, 2023 | 3:30 PM – 5:30 PM

100 College St., 11th Floor

New Haven, CT

Refreshments and conversations with speakers to follow



Yale

Center for Brain & Mind Health

**"To be a relentless force
for a world of longer,
healthier lives."**



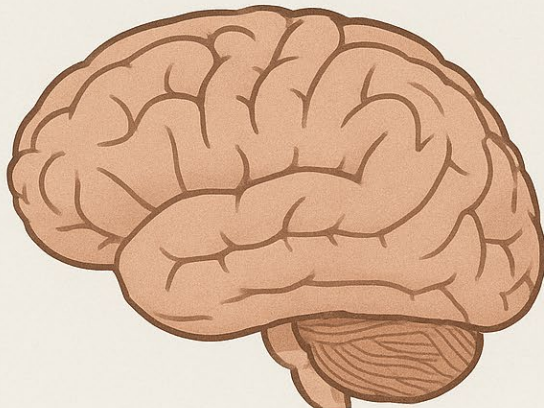
American
Heart
Association.

American Heart Association Mission Statement

Longer, Healthy Aging Means Healthy Brain Aging

GLUCOSE

- **CHOLESTEROL**
- **COLONOSCOPY**

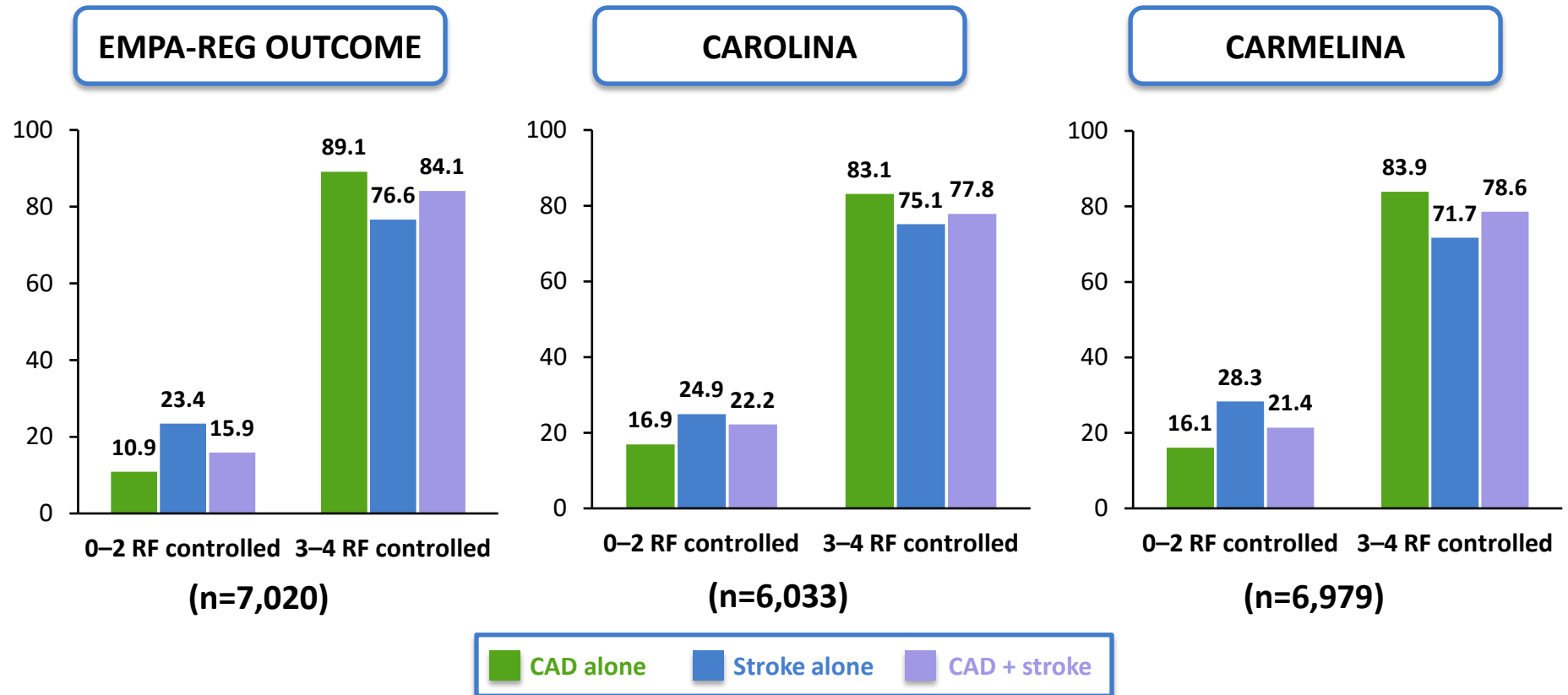


BRAIN ?



?

Trial Data Show We Do Not Provide Adequate Preventative Care for Brain Vulnerable Patients



Balasubramanian P *et al. Stroke* 2023;54:2013-21

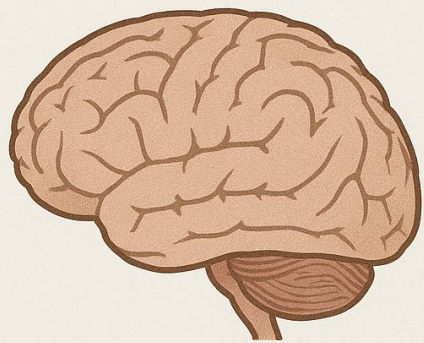
Real World Data Show The Same

	UK Biobank			All of Us		
	MI	Stroke	p	MI	Stroke	p
N	9,193	5,567		4,367	2,948	
Controlled LDL (<100 mg/dl) (%)	4479 (48.7%)	2078 (37.3%)	<0.001	2,948 (67.5%)	1,709 (58.0%)	<0.001
Controlled BP (<140 & <90) (%)	5,286 (57.5%)	2,739 (49.2%)	<0.001	2,421 (55.4%)	1455 (49.4%)	0.004
Statin use (%)	7,267 (79.0%)	3,252 (58.4%)	<0.001	3,215 (73.6%)	1895 (64.3%)	<0.001
Anti-platelet (%)	7,947 (86.4%)	3,425 (61.5%)	<0.001	3,214 (73.6%)	1710 (58.0%)	<0.001

Rivier CA et al. *J Am Heart Assoc* 2024;13:e033322

Collaboration: Neuroscience and Primary Care

COLLABORATION BETWEEN



NEUROLOGIST



**PRIMARY CARE
CLINICIAN**

Interdisciplinary Engagement In
Neurocardiology: A Key Opportunity

Modifiable Risk Factors for Disease

Scientific consensus is that approximately 40% of dementia, over 50% of strokes, and at least 35% of depression can be prevented through modifiable lifestyle factors.



Non-modifiable risk factors

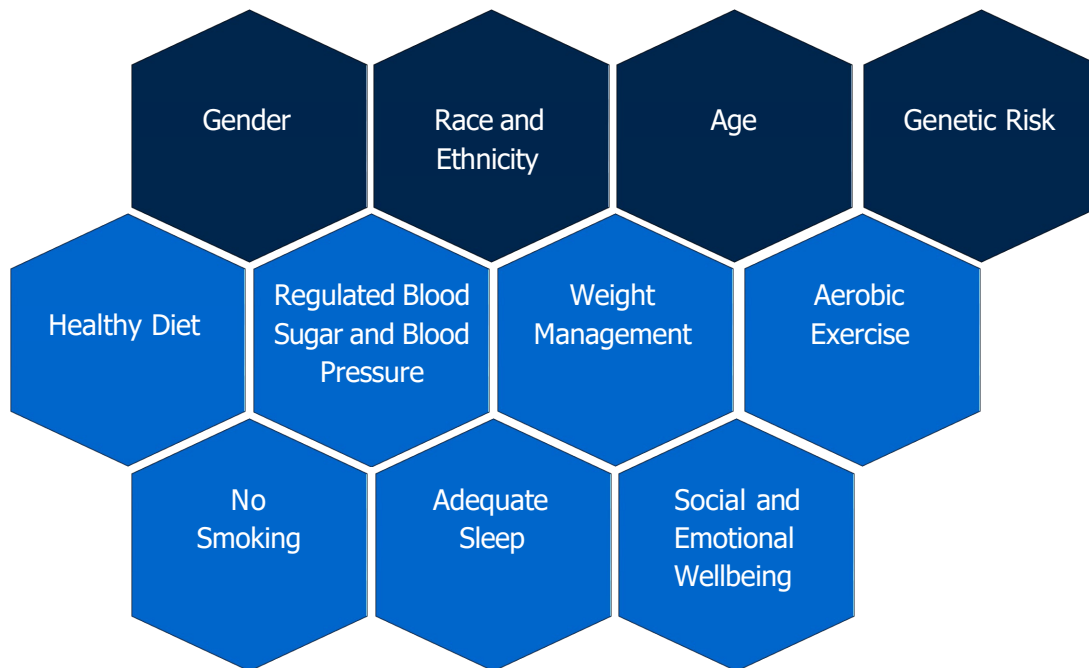


Modifiable risk factors* *that are highly dependent on context and circumstance*

Dementia prevention, intervention, and care: 2024 *Lancet* Commission reported these additional modifiable factors of dementia:

Cholesterol
Vision Loss

Hearing loss
Medication adherence



EDITORIAL

Blood-Based Biomarkers for Alzheimer Disease—Ready for Primary Care?

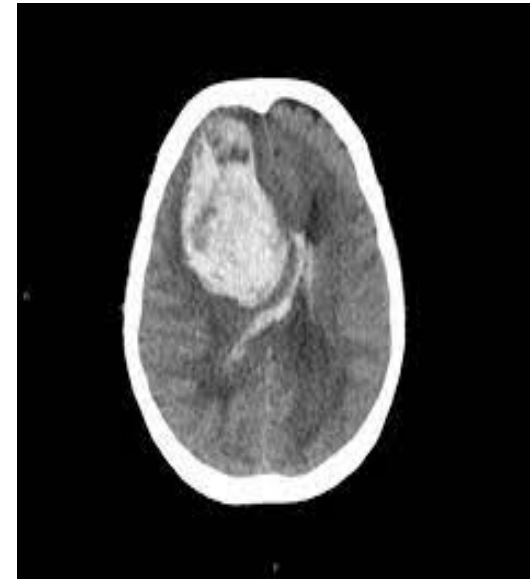
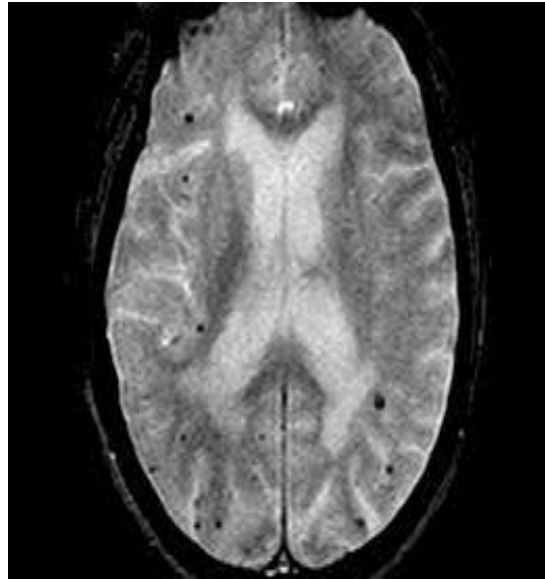
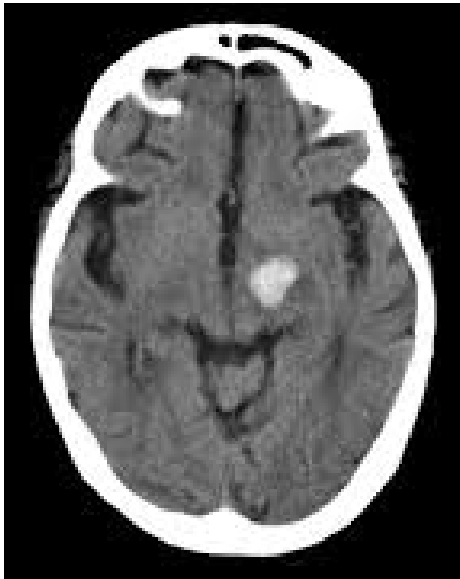
Lawren VandeVrede, MD, PhD; Gil D. Rabinovici, MD

Digital Biomarkers for Neurodegenerative Disease

Claire M. Erickson, PhD, MPA; Anna Wexler, PhD; Emily A. Largent, JD, PhD

- **Polygenic risk scores?**
- **Prevention & Pre-Disease?**
- **Do we need a new model: Brain & Mind Health Clinics**

All Stroke is Not the Same and So Clinical Trials Need Patient Centered Endpoints



- These strokes have different consequences
- They result in different kinds of disability
- So we must collaborate with patients!

Landmark Stroke Trials Have Excluded Disabled Patients

- NIHSS – NIH Stroke Scale
 - 0 equal no deficit and 42 is the maximum
- What was the mean/median NIHSS?
 - ARCADIA
 - 1
 - PROFESS
 - 1
 - IRIS
 - 0
 - Enrolling a higher proportion of participants with poststroke disability improves statistical power and helps trials address generalizability issues due to low levels of participation among female, Black and Hispanic individuals

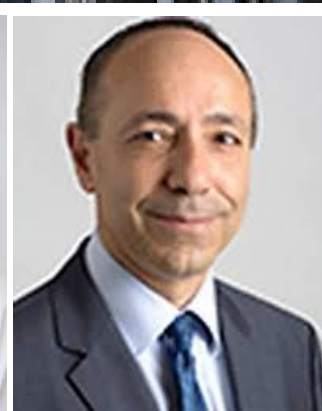
Original Investigation | Neurology

Disability and Recurrent Stroke Among Participants in Stroke Prevention Trials

Adam de Havenon, MD, MS; Catherine Viscoli, PhD; Dawn Kleindorfer, MD; Heidi Sucharew, PhD; Alen Delic, MS; Christopher Becker, MD; David Robinson, MD; Shadi Yaghi, MD; Vivian Li, BS; Maarten G. Lansberg, MD, PhD; Steven C. Cramer, MD; Eva A. Mistry, MBBS, MScI; Daniel F. Sarpong, PhD; Scott E. Kasner, MD; Walter Kernan, MD; Kevin N. Sheth, MD

ASPIRE and SATURN Break Ground: Collaboration with Disabled Patients

- Most stroke prevention trials enroll very mild stroke
- Burden is on patients with disability, so the irony . . .
- Another kind of health disparity – aging, disabled populations



Interdisciplinary Collaboration at the Yale Center for Brain & Mind Health

■ Collaboration Across a Medical School and Across a University

- Anesthesiology
- Biomedical Engineering (SEAS)
- Biostatistics (YSPH)
- Child Study Center
- Comparative Medicine
- Computer Science (SEAS)
- Electrical Engineering (SEAS)
- Economics (FAS)
- Emergency Medicine
- Environmental Health Sciences (YSPH)
- Epidemiology (YSPH)
- Genetics
- Immunobiology
- Internal Medicine
 - General Internal Medicine
 - Cardiology
 - Digestive Diseases
 - Infectious Diseases
- Lab Medicine
- Mathematics (FAS)
- Neurology
- Neuroscience
- Neurosurgery
- School of Nursing
- Obstetrics, Gynecology & Reproductive Sciences
- Pediatrics
- Philosophy (FAS)
- Political Science (FAS)
- Psychiatry
- Psychology (FAS)
- Radiology & Biomedical Imaging
- School of Law
- School of Management
- School of Music
- Surgery
- Urology
- Yale Ventures

Collaboration: Engineering, Industry, Foundation, Government

- Due to high costs, MRI remains largely unavailable to majority of the people on the planet
- Higher magnetic field is not always better



	High Field	Low Field
Cooling	Liquid Cryogenics	No Cryogenic Requirement
Power	~1 house/day	~Single Coffee Maker
Shielding	Shielded Room	Shielded or Unshielded

HYPERFINE



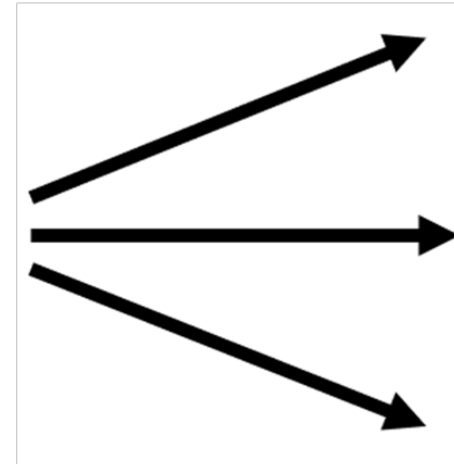
Collaboration: Patients and Health Care Environments



Brain Technology That Comes to Patients



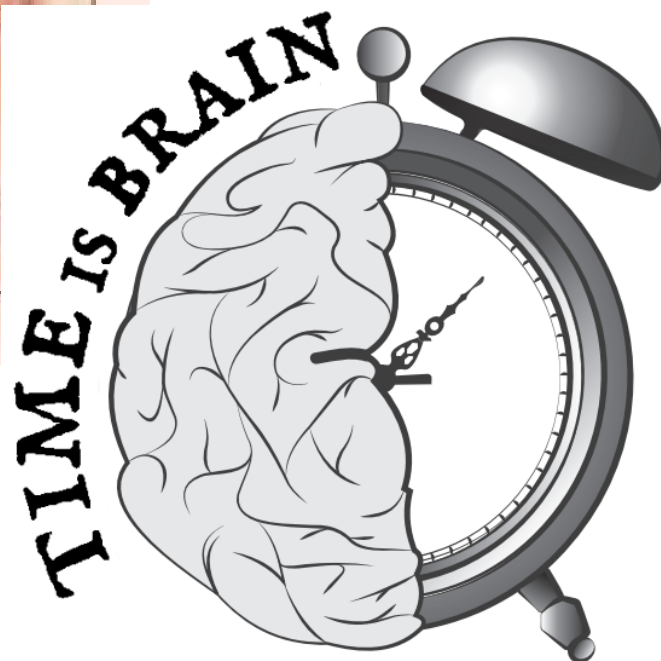
Old Paradigm



New Paradigm

Endovascular thrombectomy
using a stent retriever

Stent retriever



NIH
National Institute of
Neurological Disorders
and Stroke

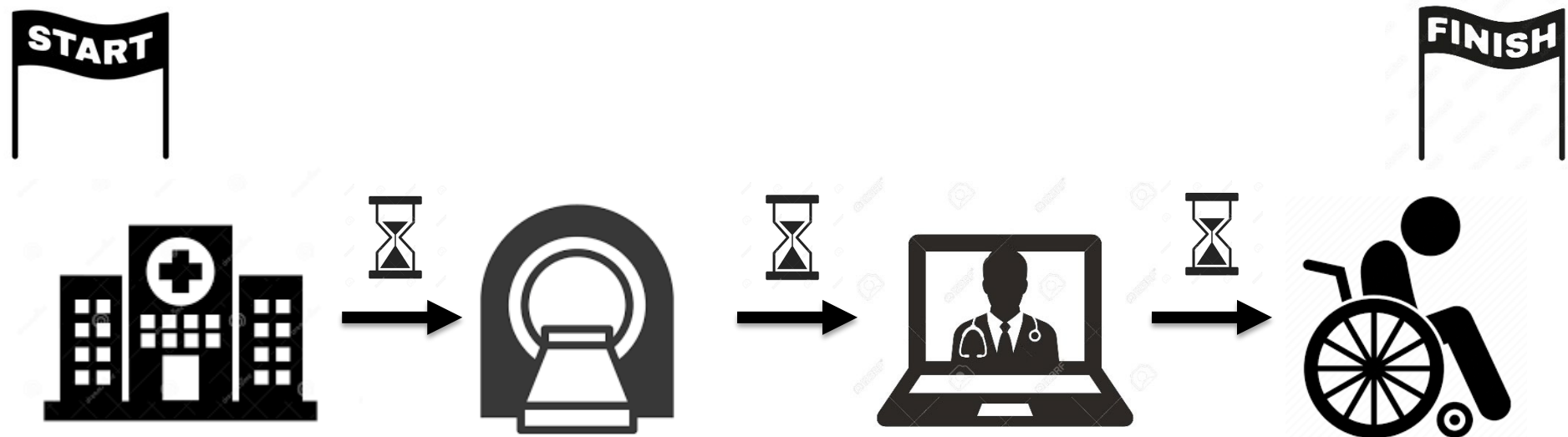
Inequities in Access and Delivery of Acute Stroke Care

A Brain Attack Coalition Symposium Report

October 2022



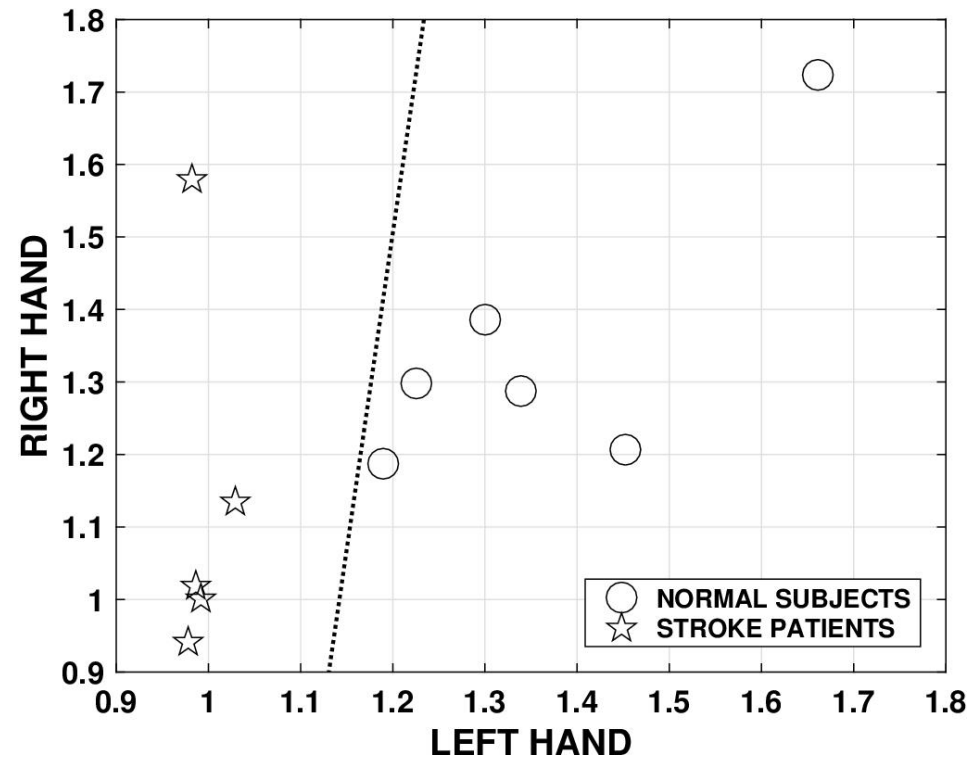
For Decades, We've Been Working on Getting to the Patient Faster



Shouldn't We Start from the Patient, When A Stroke Begins, Instead?



Collaboration: Patients and MedTech Make Neuro-Wearables



National Institutes
of Health
SBIR/STTR





ARTICLE

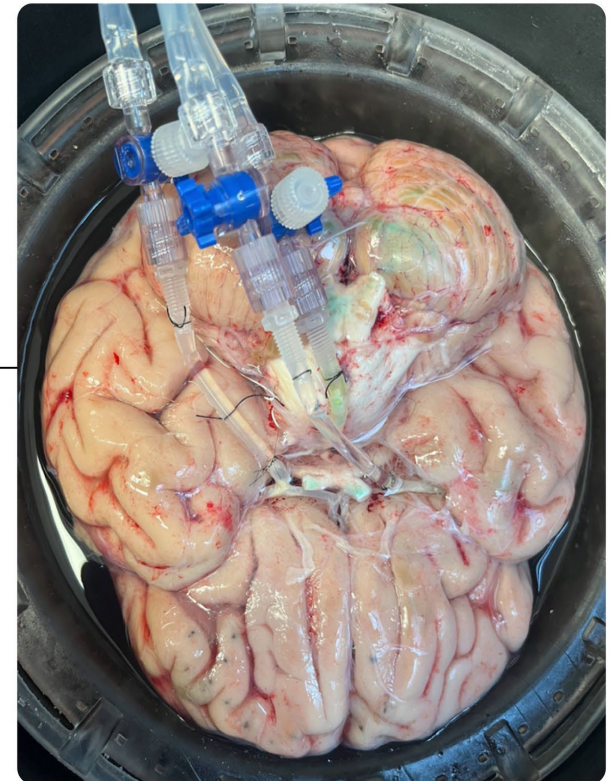
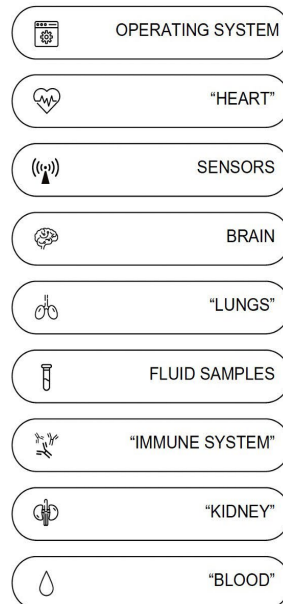
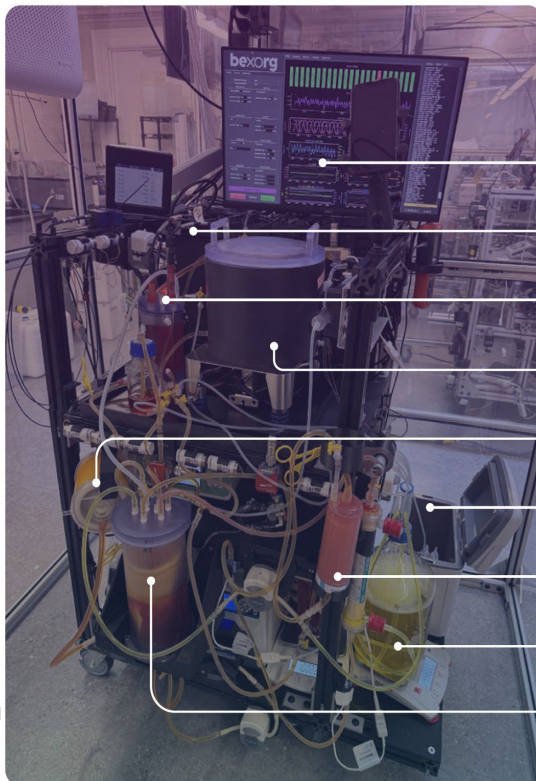
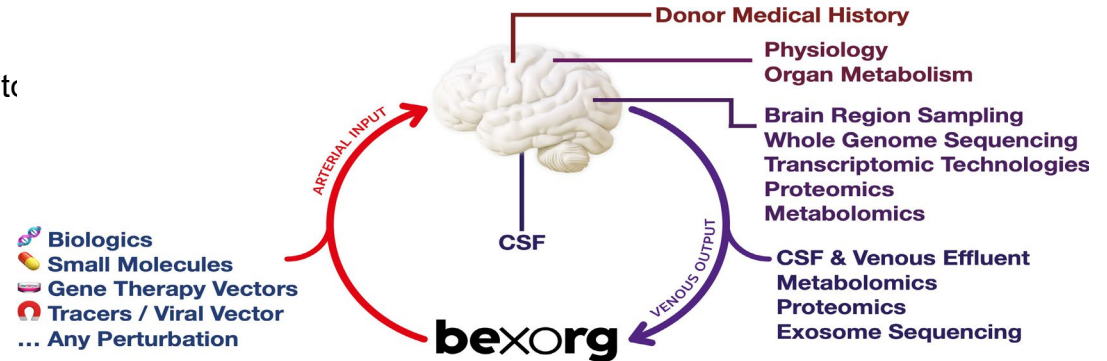
<https://doi.org/10.1038/s41586-019-1099-1>

Restoration of brain circulation and cellular functions hours post-mortem

Zvonimir Vrselja^{1,2,18}, Stefano G. Daniele^{1,2,3,18}, John Silbereis^{1,2}, Francesca Talpo^{1,2,4}, Yury M. Morozov^{1,2}, André M. M. Sousa^{1,2}, Brian S. Tanaka^{5,6,7}, Mario Skarica^{1,2}, Mihovil Pletikos^{1,2,8}, Navjot Kaur^{1,2}, Zhen W. Zhuang⁹, Zhao Liu^{9,10}, Rafeed Alkawadri^{6,11}, Albert J. Sinusas^{9,10}, Stephen R. Latham¹², Stephen G. Waxman^{5,6,7} & Nenad Sestan^{1,2,13,14,15,16,17*}

Collaboration: Translational Neuroscience and Drug Discovery Technology

- Animal and *in vitro* models have mostly failed
- 1,961 Phase 1 trials in neurodegenerative lead to 12 NDAs for disease modifying therapies
- 0.6% success rate in the clinic



Collaboration is Local & Community Based



Adoption of population-health methods developed in health systems to the care of whole **geopolitical communities.**

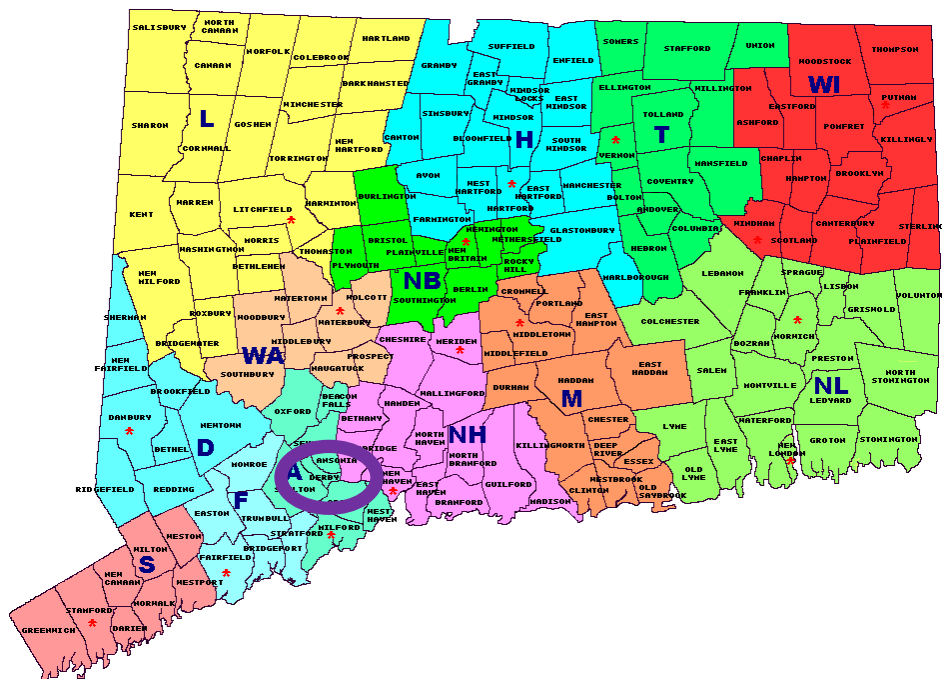
Adult Residents
of a City or Town



Join PROSPER



Every Resident
has BP < 130/80



Collaboration is Global



- CLARITY is the Cilostazol Stroke Prevention Trial
- Based on CSPS.com; hazard ratio of 0.52
- 4000 patients in a trial to answer the following question:
Does the long-term addition of cilostazol to antiplatelet therapy with aspirin or clopidogrel reduce stroke recurrence and cardiovascular events in a randomized clinical trial?
- 2000 patients in the United States; the rest enrolled globally!

Toyoda K, et al. Lancet Neurol 2019;18:539–48.

Conclusions

- The brain centric view of neurological translation is yielding to one in which brain health is intertwined with overall health
- Basic and translational advances must be developed in their ultimate context of use - persons and populations
- Interdisciplinary investigative collaboration is the foundation for realizing successful neuroscience applications