



ELAHI LAB

Chan Zuckerberg Initiative Updates & Future Directions

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Icahn School of Medicine at Mount Sinai



The opportunity

(the fight to cure CADASIL and why research matters)

Discovery of treatments for CADASIL



30 years
of research

0
approved therapies

Discovery



Validation



Clinical Trials



Treatments

▲ WE ARE HERE

What we need for a treatment trial to begin



1. Characterised cohorts

Who has the disease, who is at risk, and how it progresses over time.



2. Validated biomarkers

Biological signals of disease state — of progression and estimated treatment response.



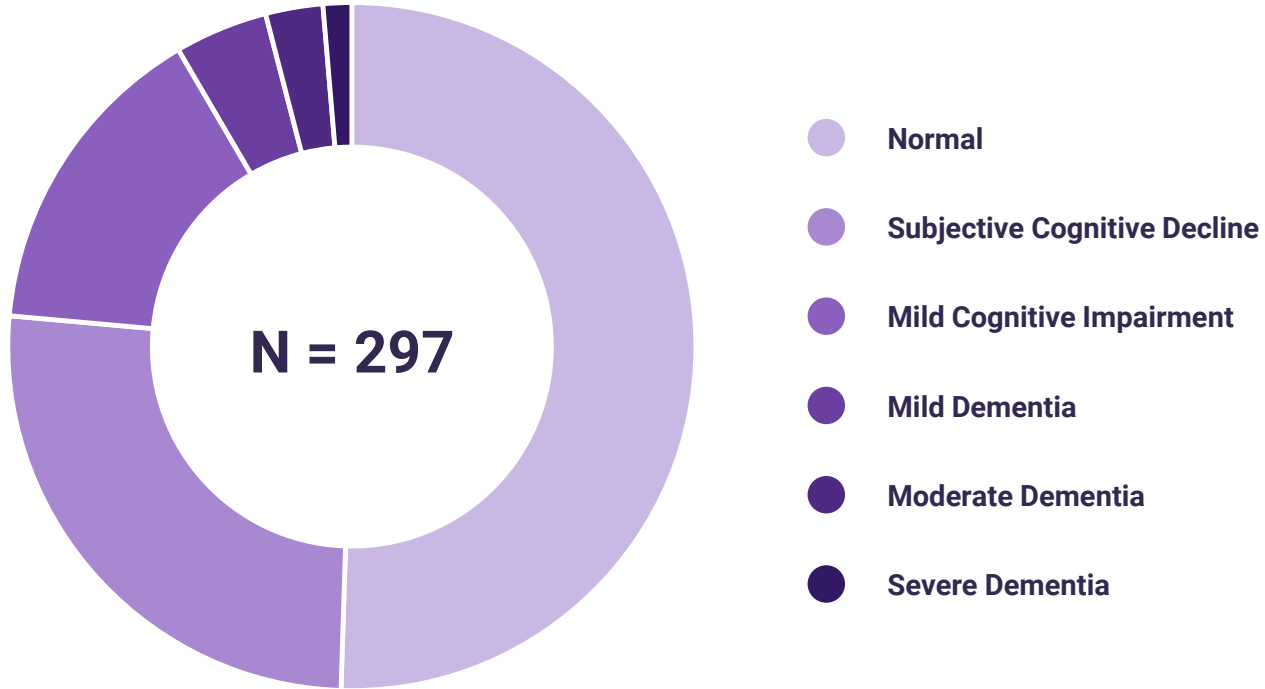
3. Defined end points

Outcomes everyone agrees a trial can move, sensitive enough to show benefit.

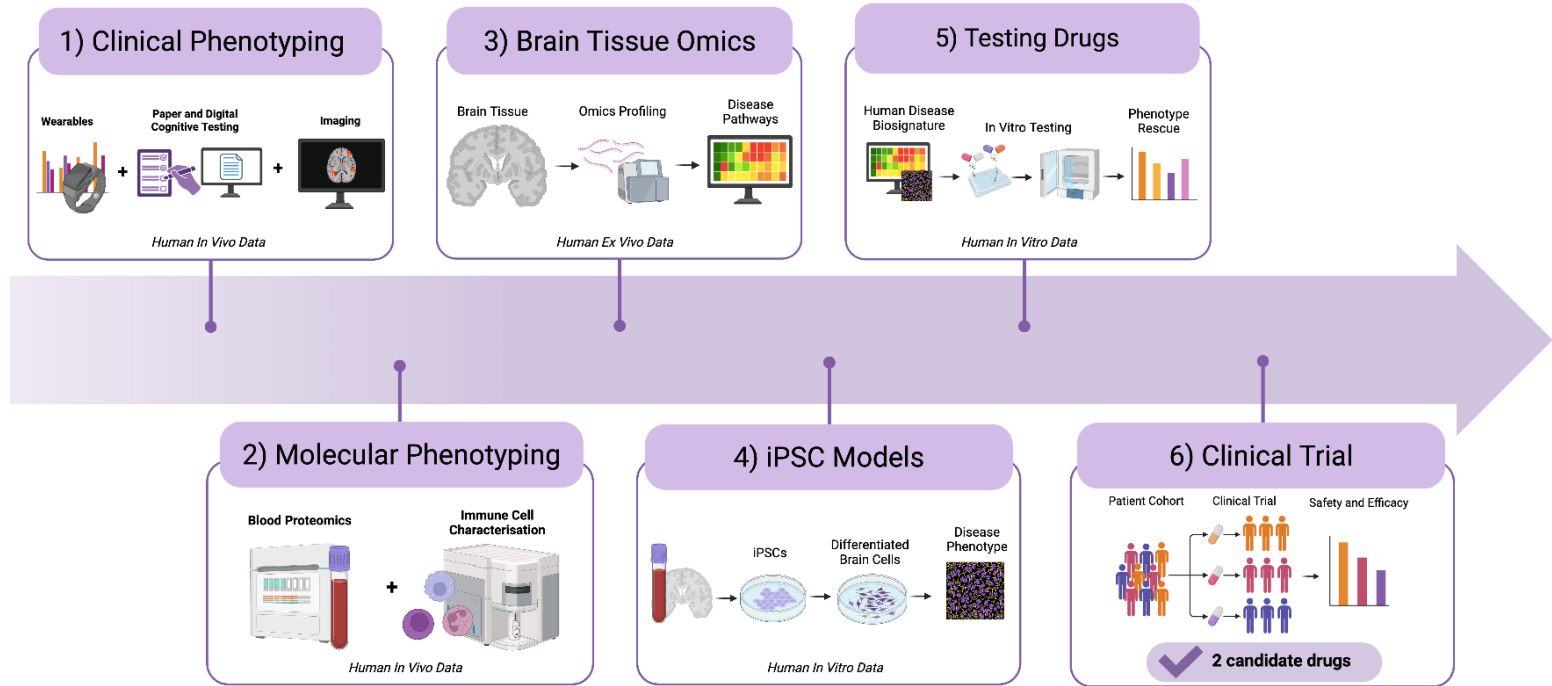
The build

(What we have built together and how you can get involved)

• Cognitive Status Distribution



Current and future work at our Center



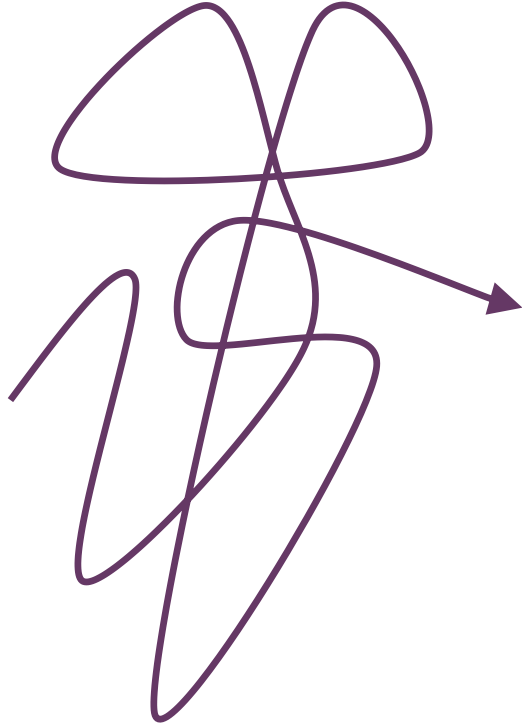
Linking disease back to biology

(and finding ways to track it along the way)





From high blood
pressure...



...to heart disease



Diuretics



RAAS inhibitors



Calcium channel
blockers



Adrenergic
inhibitors



Vasodilators



What **causes** the symptoms of CADASIL??

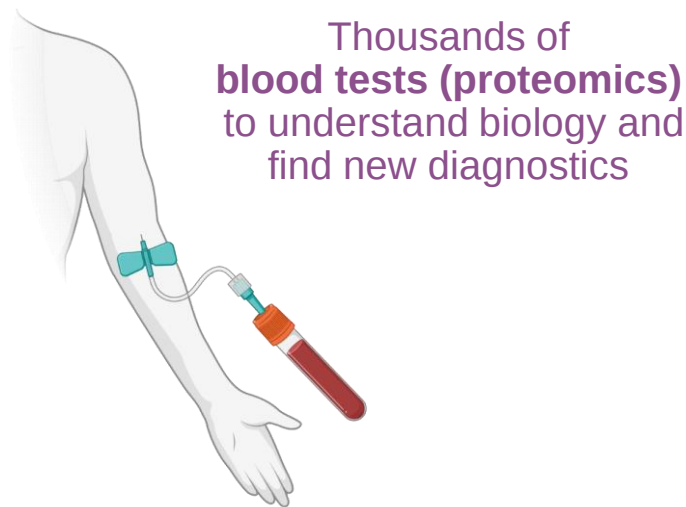
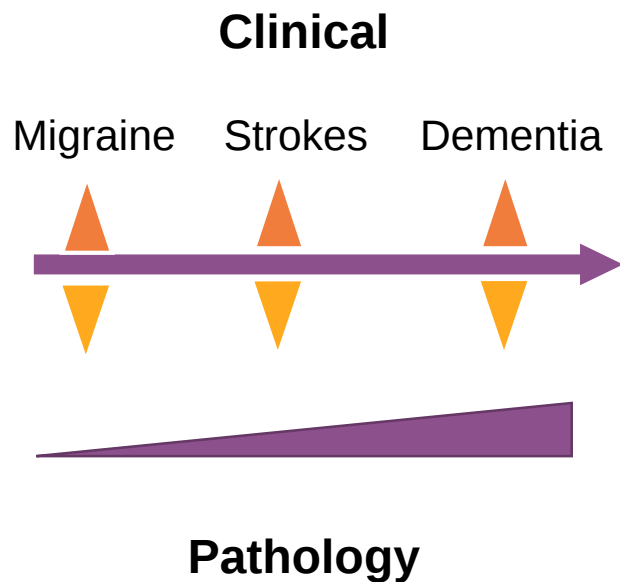


From NOTCH3
mutations...



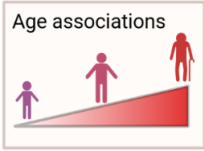
...to CADASIL

How can we study CADASIL progression in living humans?



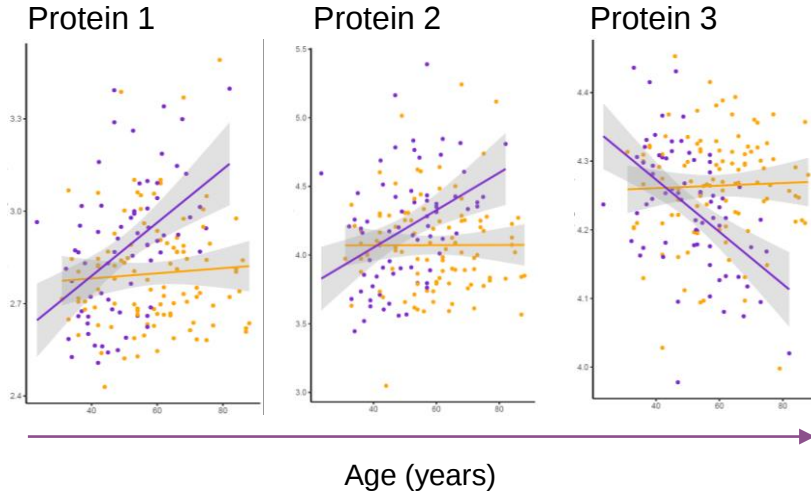
Thousands of
blood tests (proteomics)
to understand biology and
find new diagnostics

Proteomics in CADASIL reveal **mechanisms**

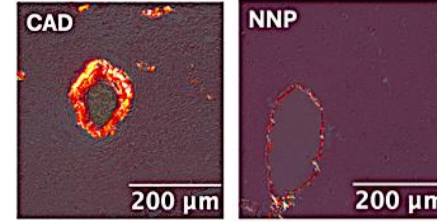


Diagnosis

- Control (orange line)
- CADASIL (purple line)

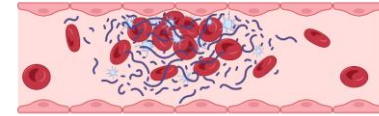


Fibrosis



CADASIL

Healthy



Coagulation

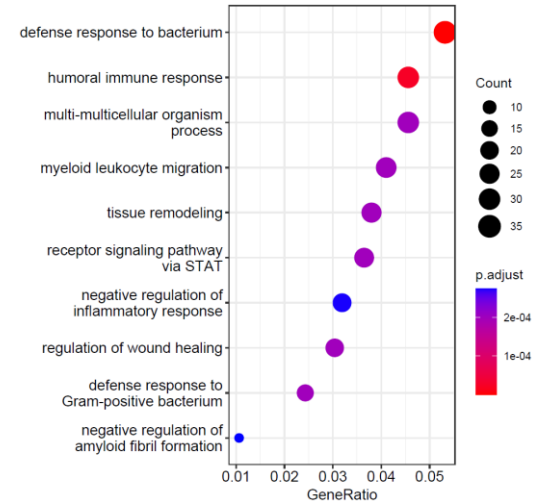
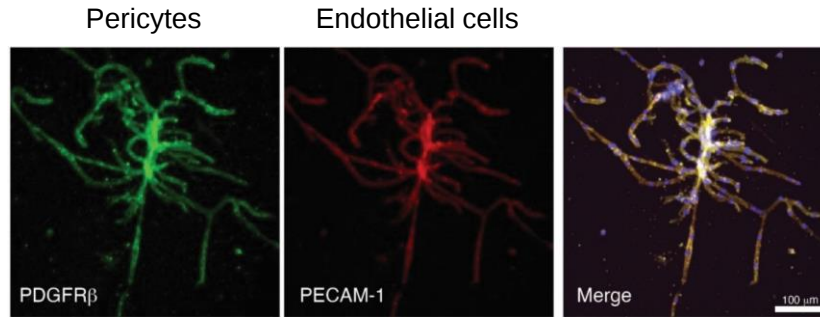
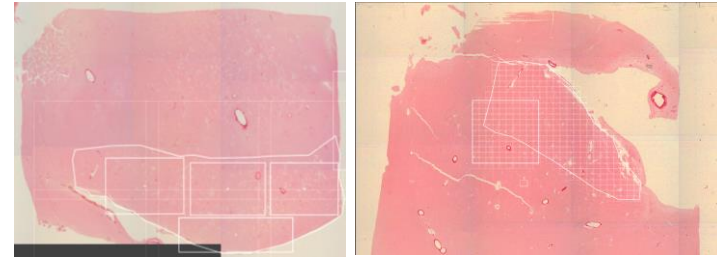
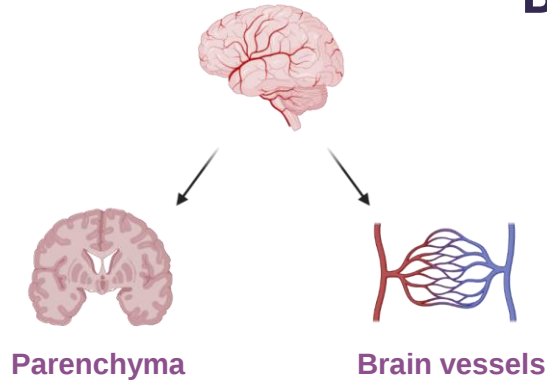


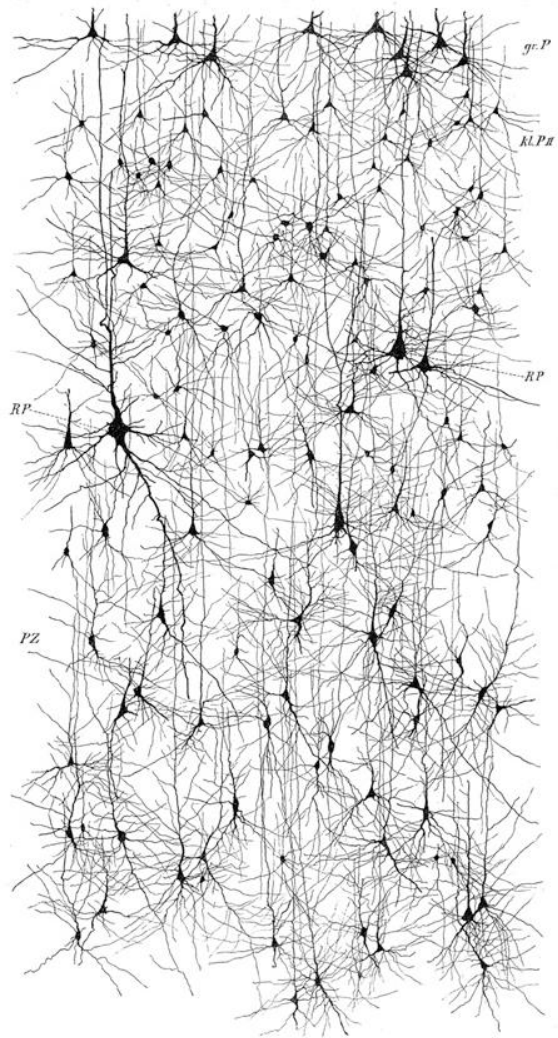
Inflammation



Angiogenesis

Brain tissue analysis confirms proteomics



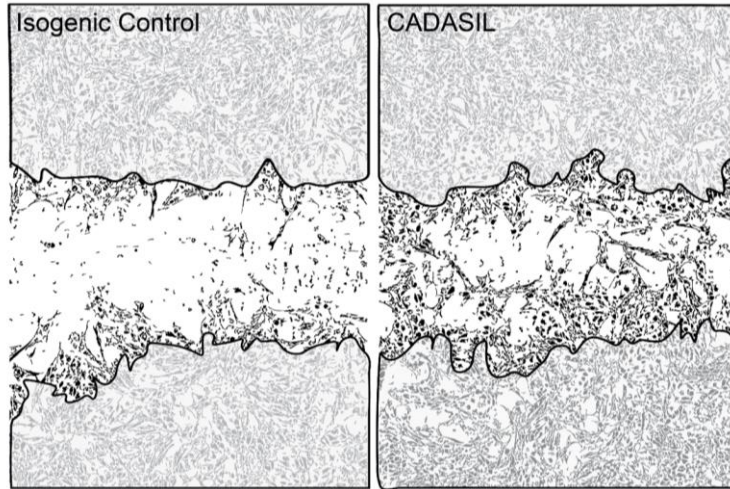


Disease models

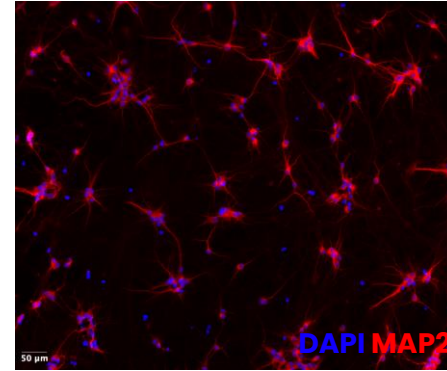


CADASIL cell models

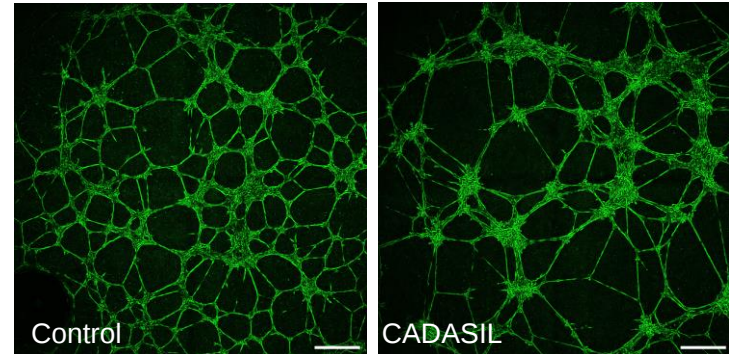
Mural cells



Neurons



iVasc angiogenesis model





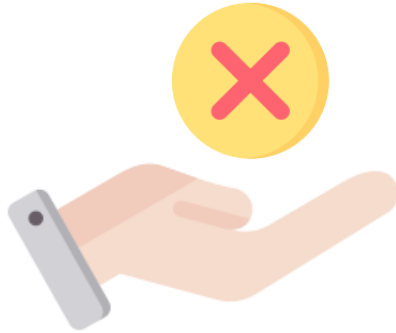
Clinical trials



Real drug
(active arm)



Fake drug
(placebo)



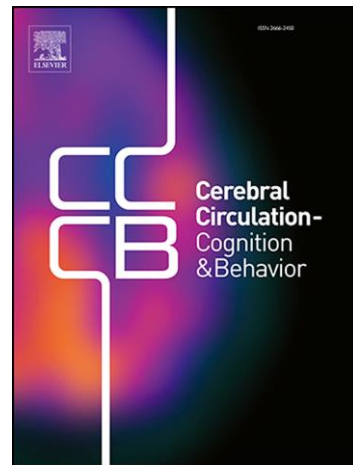
**Did more people on the
real drug get better?**

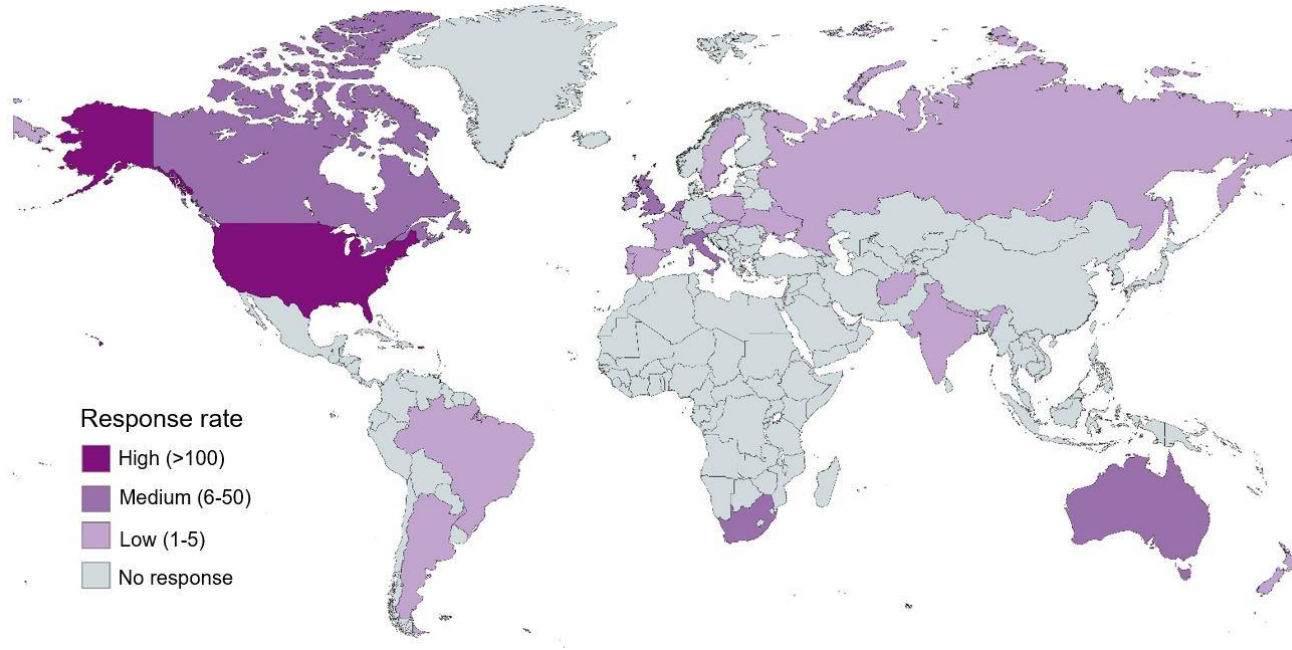
Follow-up question:
what should we measure?



Defining patient-reported outcomes and priorities for clinical trials in CADASIL through an international survey

Nikolaos Karvelas^{a,b,c,†} , Sheila Connor^{d,†}, Andria Burroso^{d,†}, Ki Coale^{d,†},
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Claudia Kunney^{a,b,c}, Debarag Banerjee^d, Michael Kennedy^d, Sarah McDaniels^d,
Pedro de Lencastre^d, Jane Gunther^d, Bert Kasiske^d, Fanny M. Elahi^{a,b,c,e,*}



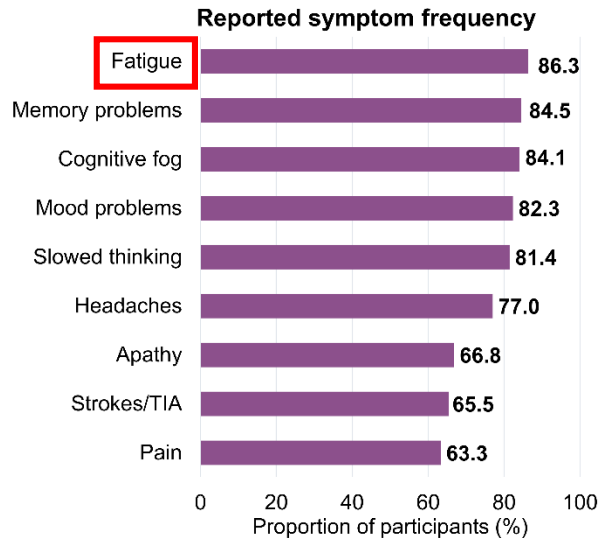


226 participants
from around the world

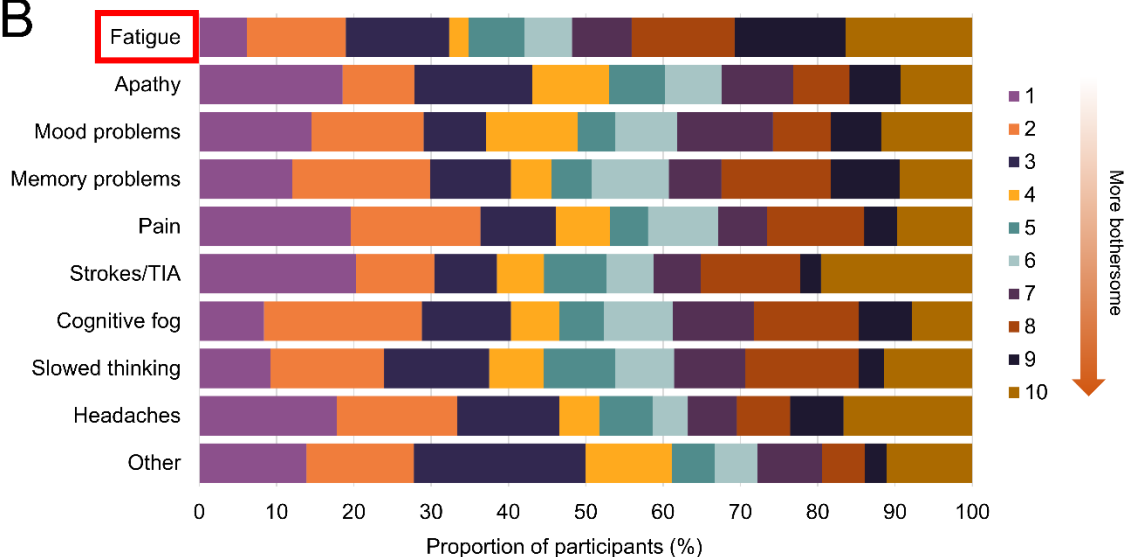


What matters most to CADASIL patients?

A

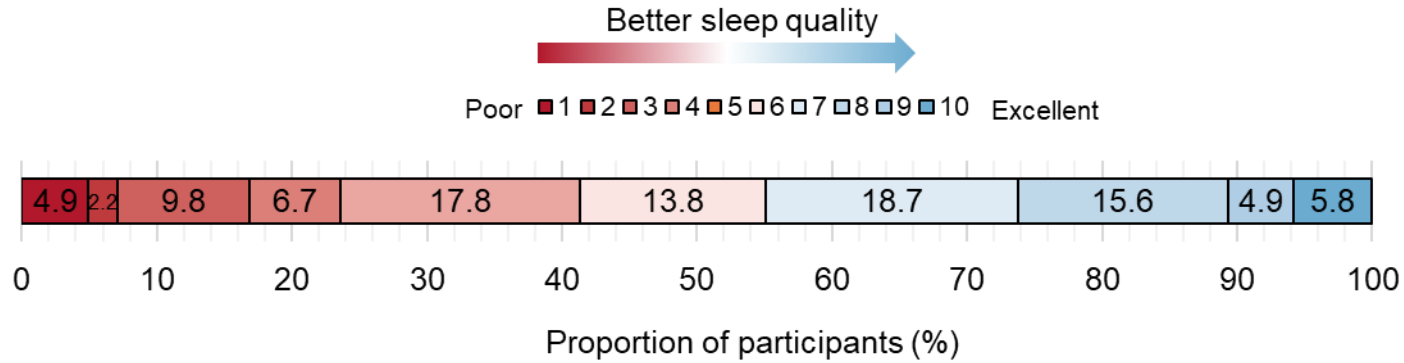


B





How do CADASIL patients judge their **sleep**?

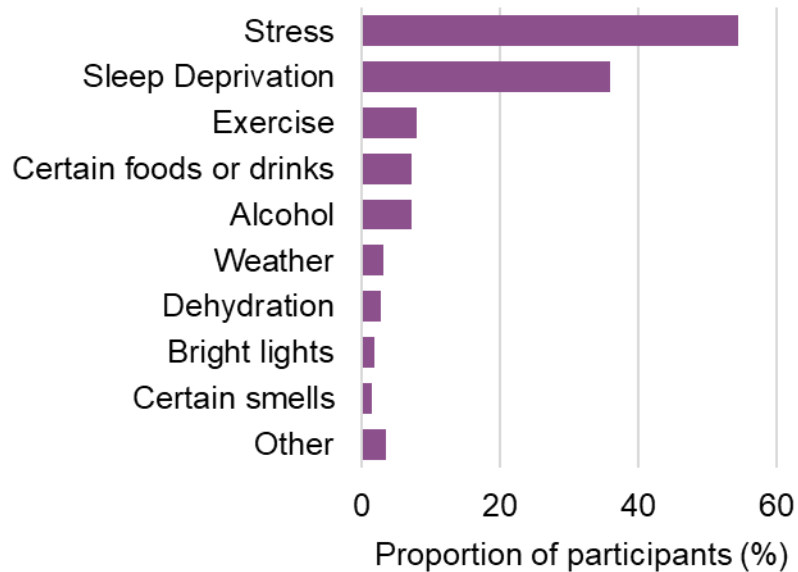


- **About 50%** of participants rated their sleep inadequate (5 and below)
- **> 80%** reported using a **CPAP device**

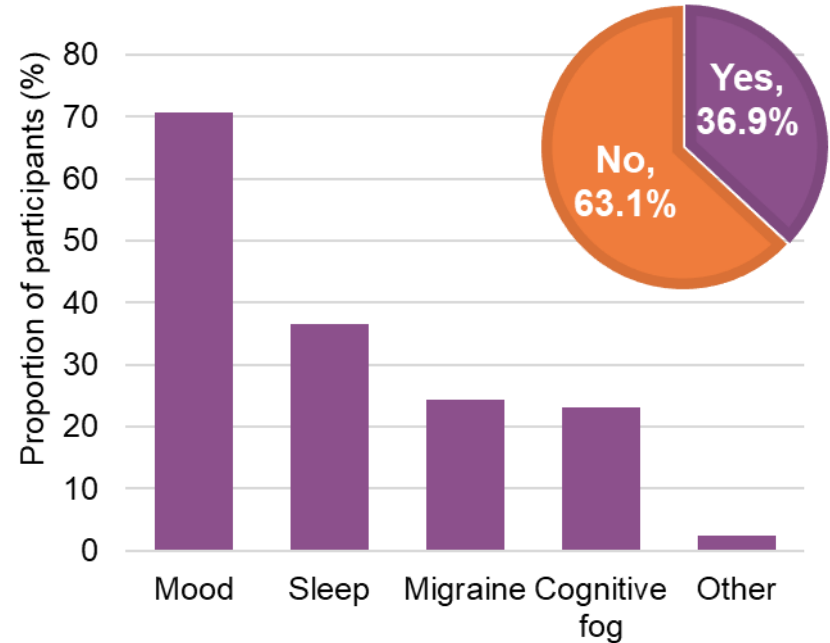
Can lifestyle changes help with symptoms?

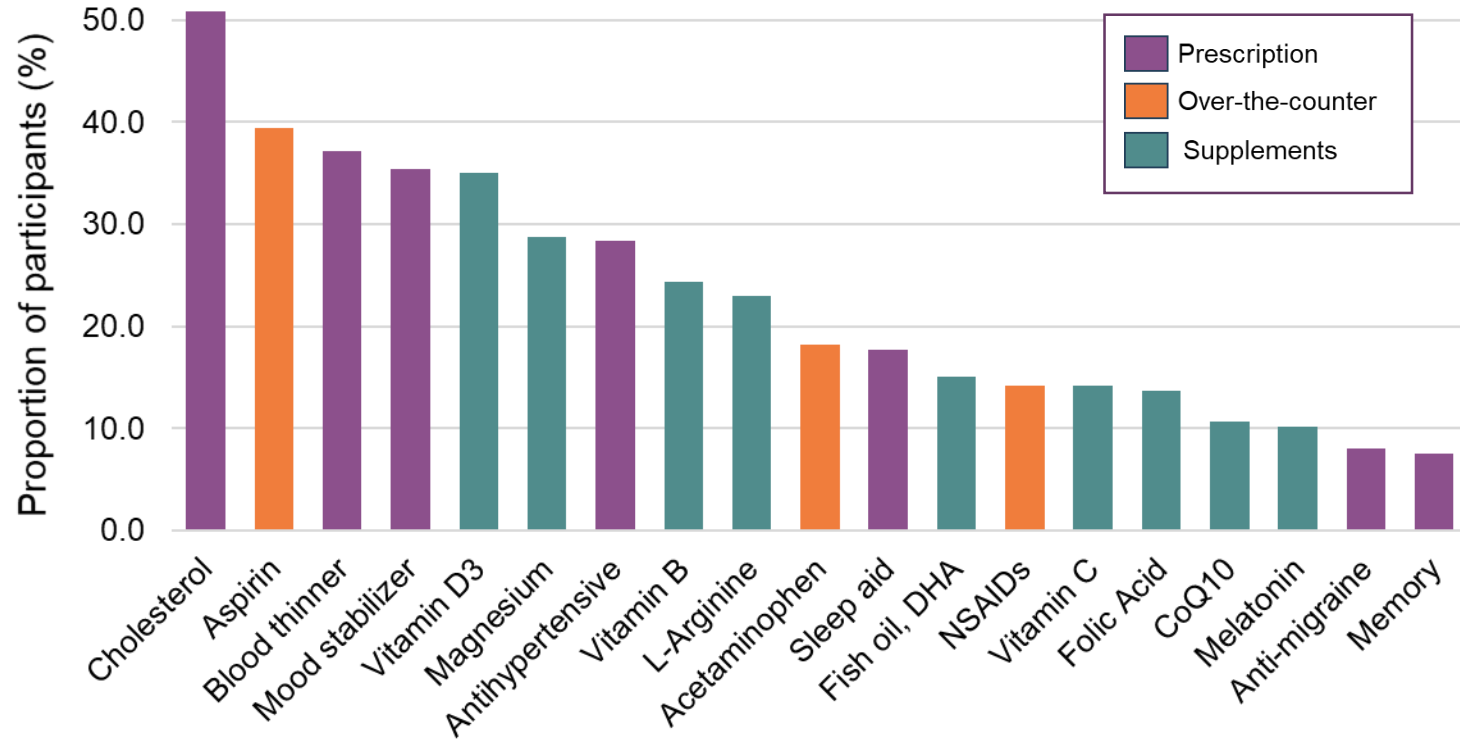


Triggers for episodes



Meditation/stress relief



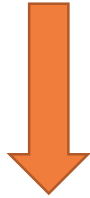


Almost none have been tested in clinical trials!!

Considerations...



Use of **uncommon or variable outcomes?**



Need for many participants

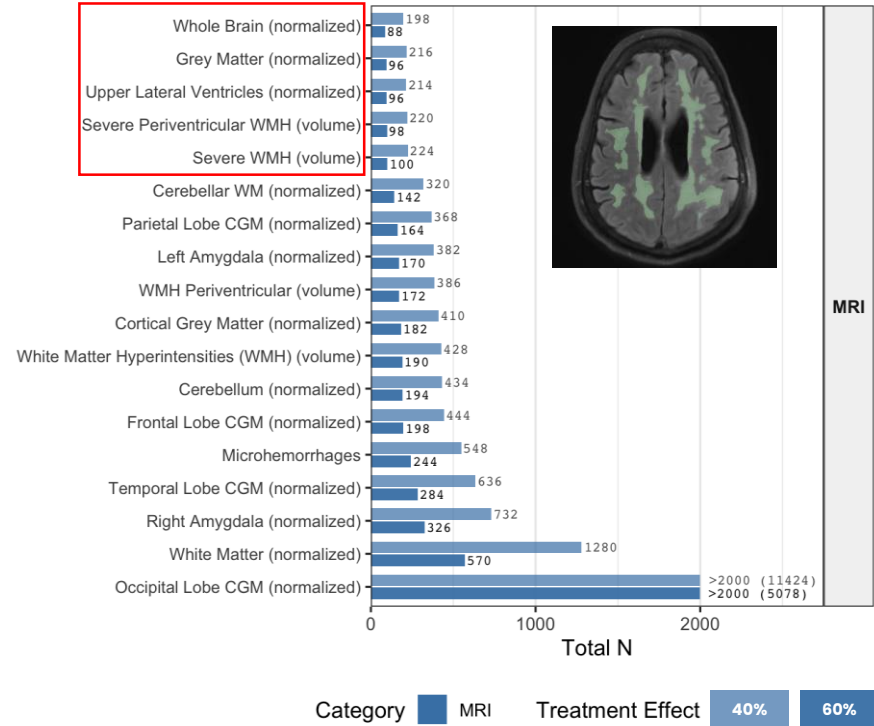
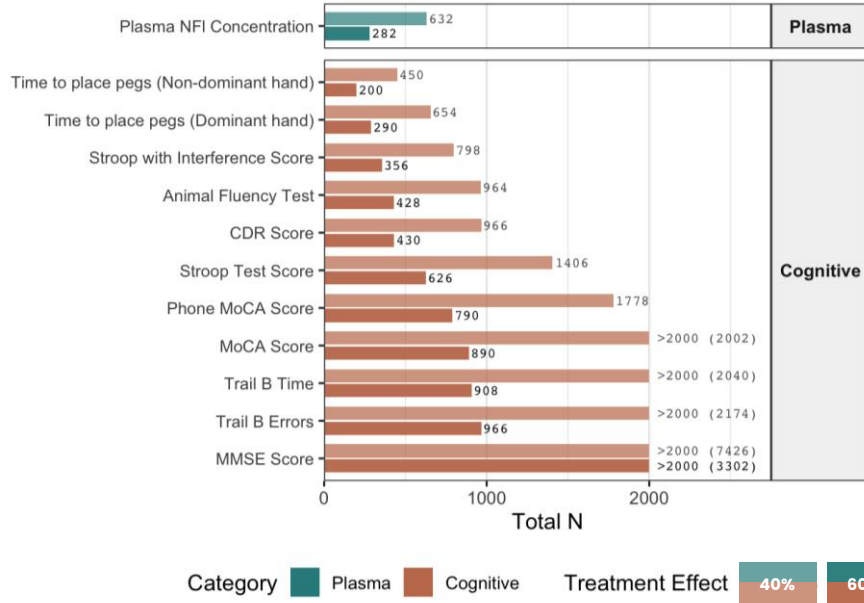
Too few participants?



Unable to measure differences

How many clinical trial participants do we need?

In collaboration with **Dr. James Meschia**

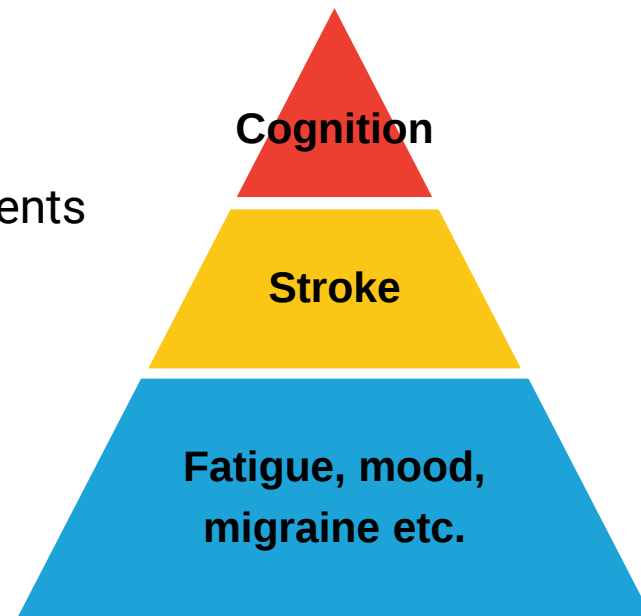


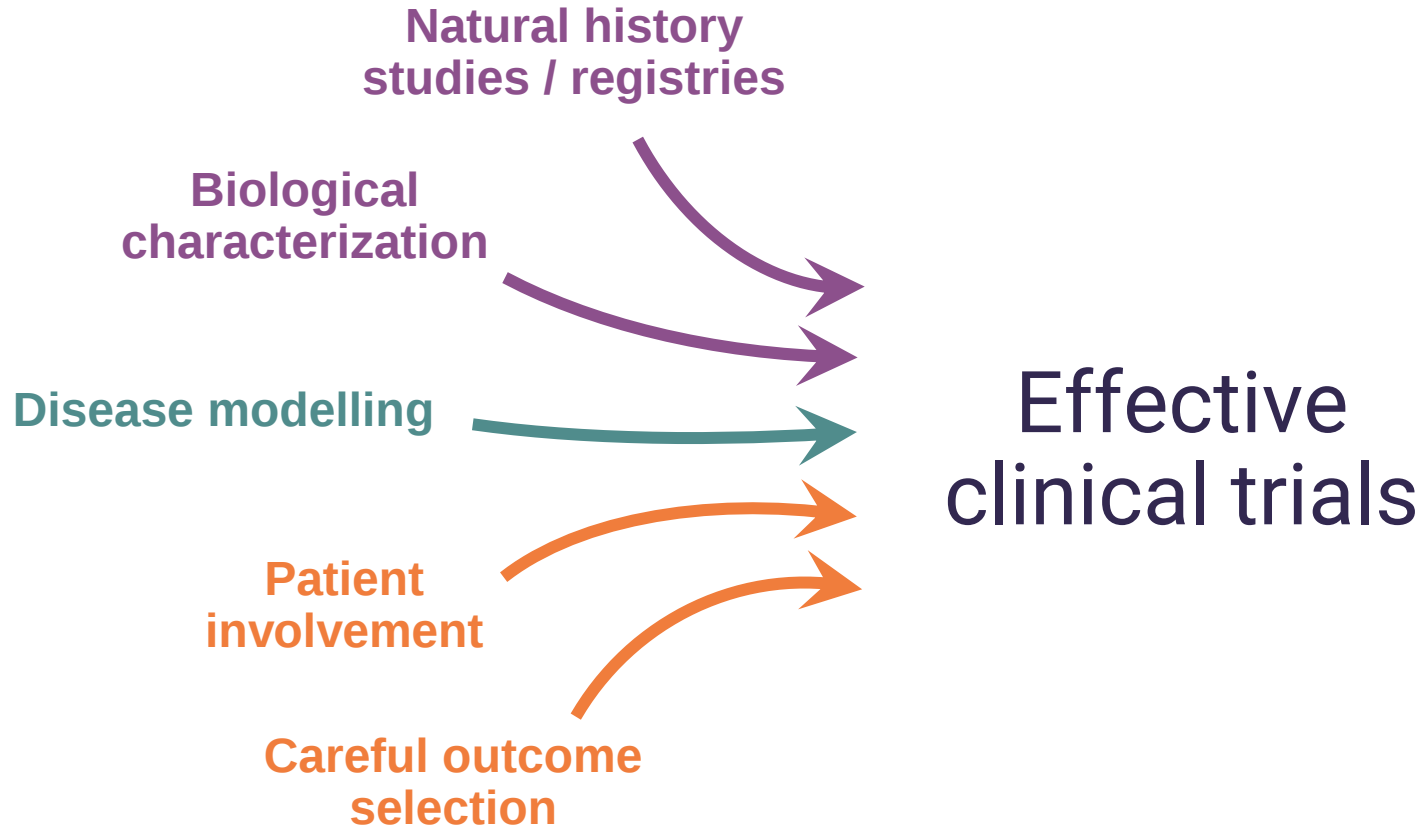
In collaboration with **Dr. James Meschia**

Optimizing CADASIL clinical trials



- Use of **combined outcomes**:
 - **Level 1**: Most debilitating and important to patients
 - **Level 2**: Clinically important outcomes
 - **Level 3**: Important to patients but not life-threatening





Elahi Lab

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Thank you!



**Chan
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Initiative** 

VA



U.S. Department
of Veterans Affairs

DATAPHILANTHROPY

RAINWATER
Charitable Foundation



Icahn
School of
Medicine at
**Mount
Sinai**



National Institute on Aging

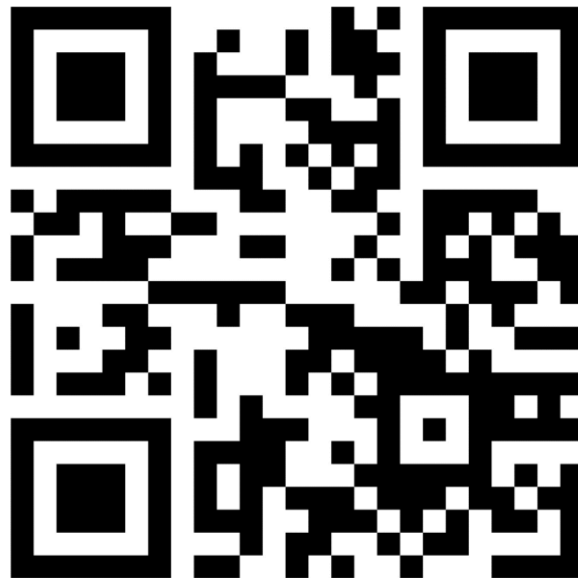
Davos
Alzheimer's
Collaborative




NEW VISION
RESEARCH

ROCKEFELLER
Philanthropy
Advisors

Get Involved!





Thank you!