

Lecanemab: a sabbath meditation

Kenneth Rockwood MD, MPA, FRCPC, FRCP

Senior Medical Director, Frailty & Elder Care Network, and Department of
Medicine, Nova Scotia Health & Dalhousie University, Halifax, Canada
Clinical Research Professor of Frailty & Elder Care, Dalhousie University,
Senior Medical Director, Frailty & Elder Care Network, Nova Scotia Health

Disclosures

In 2019, I co-founded Ardea Outcomes Inc. (with Chère Chapman) to succeed DGI Inc., founded in 2000. We focus on individualized patient outcomes. We started with dementia, which although a small part of our business, includes work with INmune Inc., on an AD trial.

Disclosures

In 2019, I co-founded Ardea Outcomes Inc. (with Chère Chapman) to succeed DGI Inc., founded in 2000. We focus on individualized patient outcomes. We started with dementia, which although a small part of our business, includes work with INmune Inc., on an AD trial.

Decades of up-to-my-elbows research and care for cognitive impairment in old people (societally cloaked as “Alzheimer disease”) make it unfathomable to me to pursue a single-protein-abnormality-at-at-time strategy if our goal be efficacious treatment of late-life dementia.

OUTLINE

The main objection.

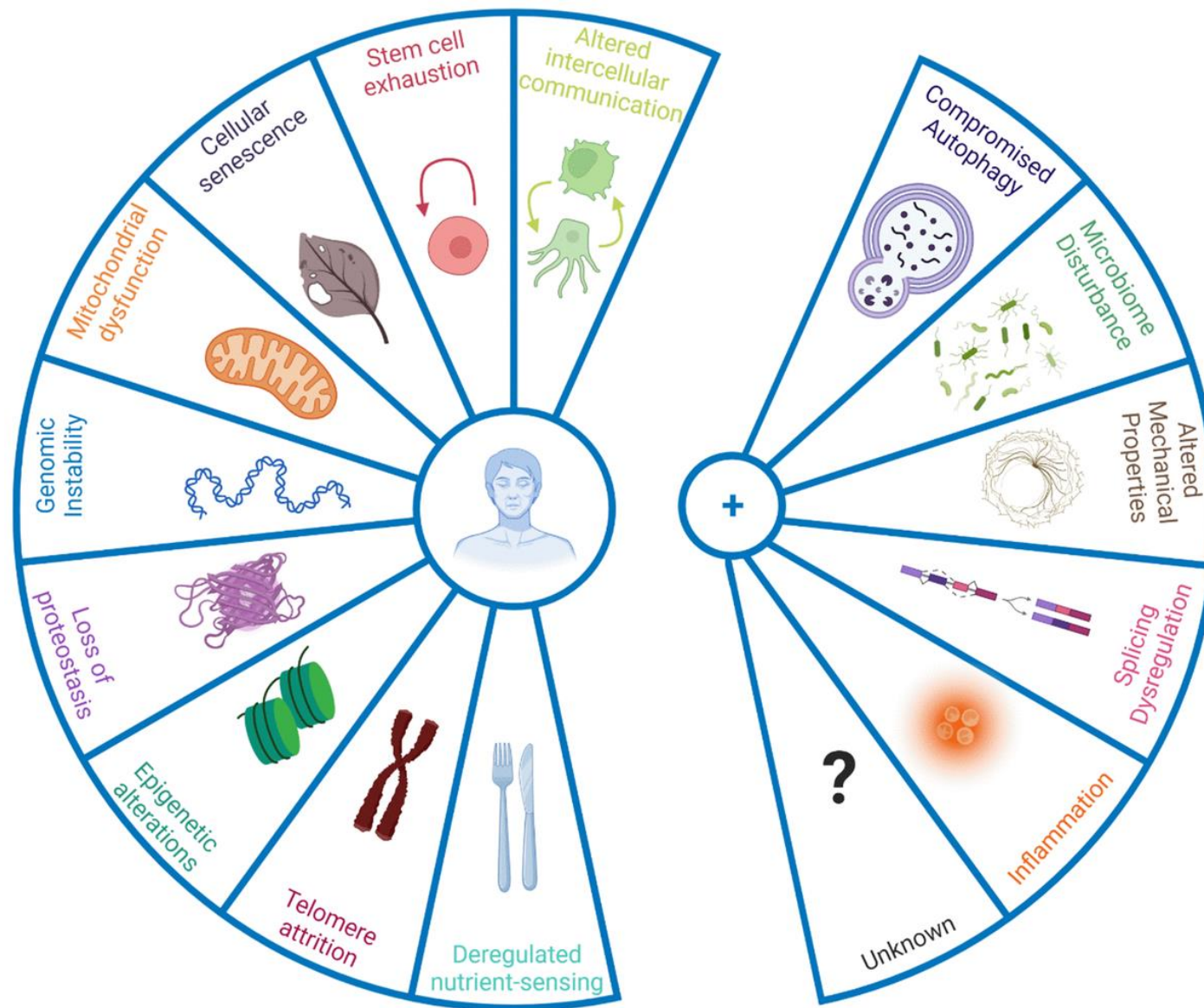
And then let's have some fun...

What is frailty?

Frailty is an age-related, multiply determined, graded state of increased risk.

Frailty consists in progressive inability to successfully resist stress (*i.e.* robustness) or to recover from it as quickly (*i.e.* resilience).

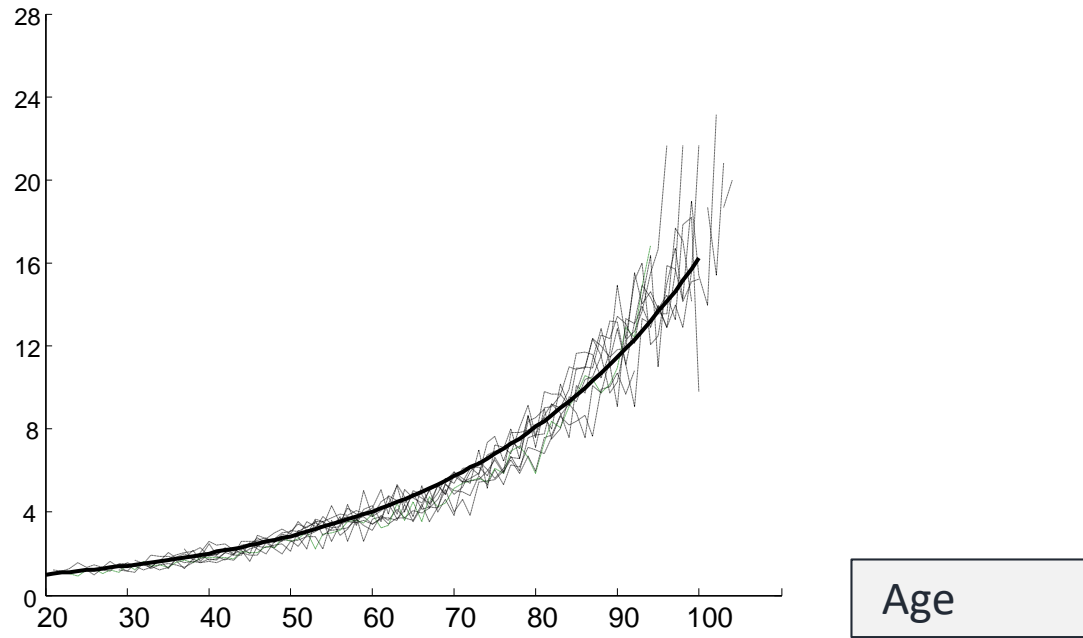
Much of age-related damage is *intrinsic*.
“... imperfect fidelity” in normal processes.



López-Otín C, et al. Cell 2023;186:243-278. PMID:3659349
Goh FEBS J. 2023;290:649-668. PMID: 34968001.

The rate of deficit accumulation (ageing) increases at ~4.5%/year – *on average* (8 successive 2-year waves NPHS)

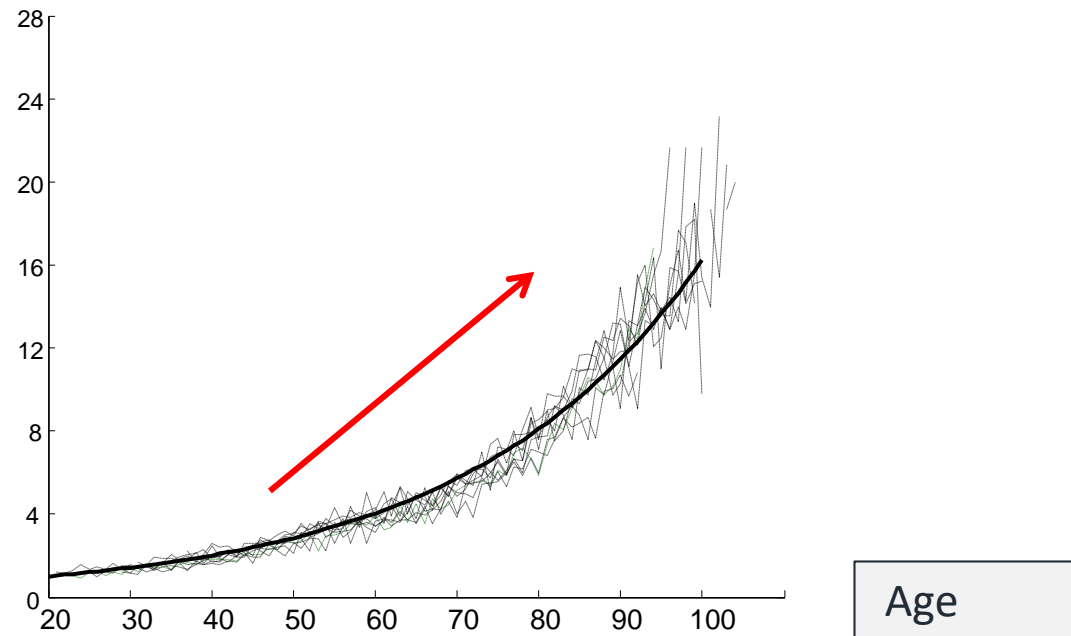
Degree of frailty / deficit accumulation



Mitnitski A & Rockwood K. *Biogerontology*. 2016;17:199-204

The rate of deficit accumulation (ageing) increases at ~4.5%/year – *on average* (8 successive 2-year waves NPHS)

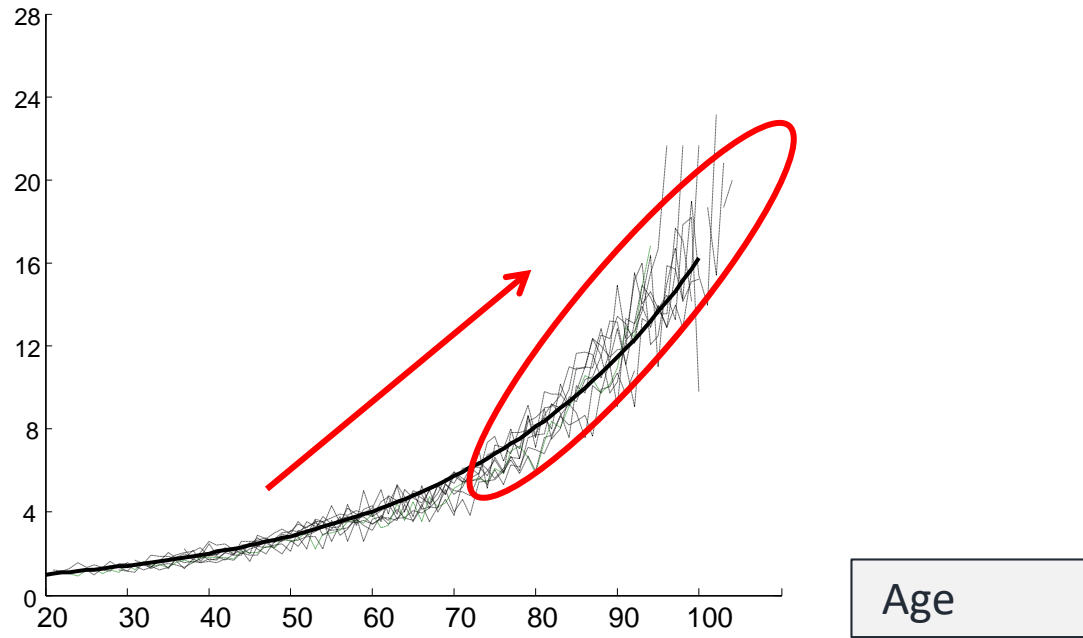
Degree of frailty / deficit accumulation



Mitnitski A & Rockwood K. *Biogerontology*. 2016;17:199-204

The rate of deficit accumulation (ageing) increases at ~4.5%/year – *on average* (8 successive 2-year waves NPHS)

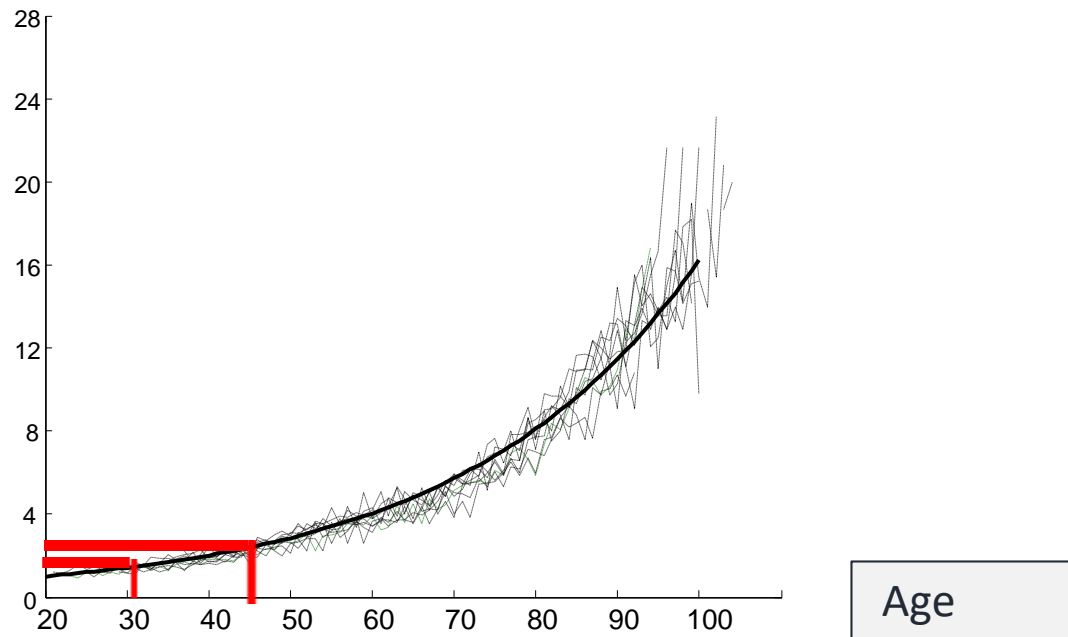
Degree of frailty / deficit accumulation



Mitnitski A & Rockwood K. *Biogerontology*. 2016;17:199-204

A $\sim 4.5\%$ /year rate of deficit accumulation translates into a 15-year doubling time.

Degree
of
frailty /
deficit
accumulation

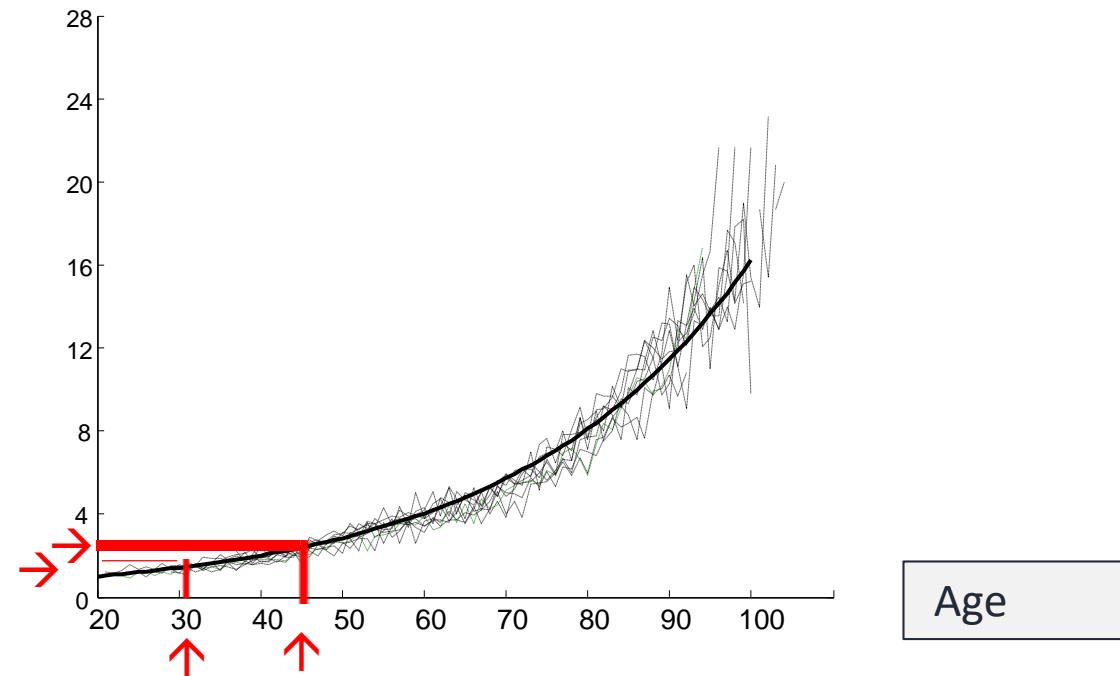


Mitnitski A & Rockwood K. *Biogerontology*. 2016;17:199-204

A $\sim 4.5\%$ /year rate of deficit accumulation translates into a 15-year doubling time.

Degree of frailty / deficit accumulation

Just as with compound interest, it's not the first couple of doubling times where we see the big impact ...

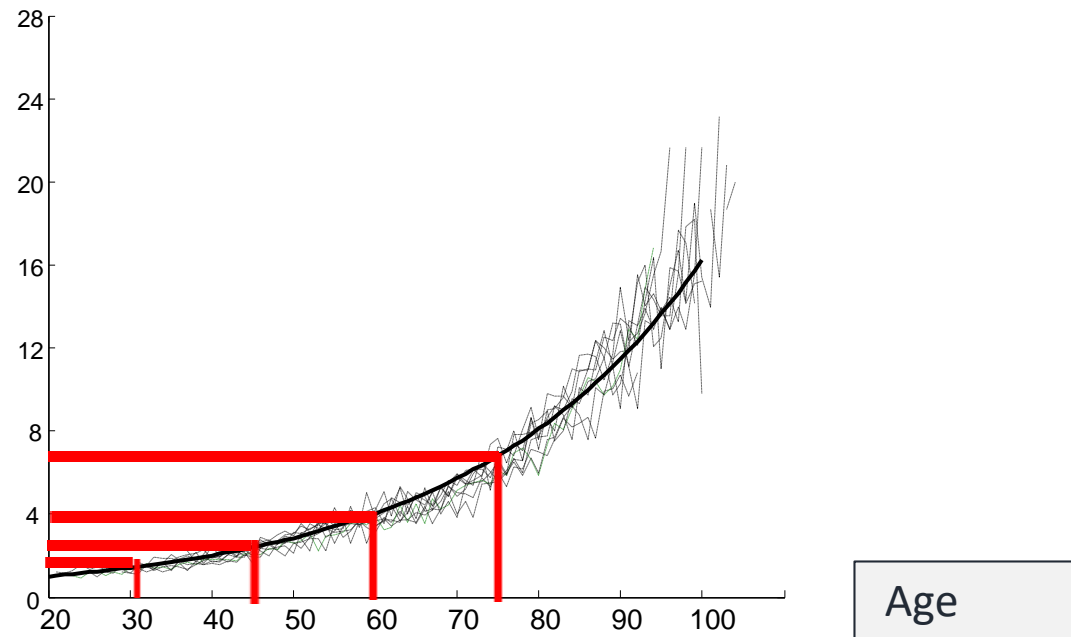


Mitnitski A & Rockwood K. *Biogerontology*. 2016;17:199-204

A $\sim 4.5\%/year$ rate of deficit accumulation translates into a 15-year doubling time.

Degree of frailty / deficit accumulation

Just as with compound interest, it's not the first couple of doubling times where we see the big impact ...

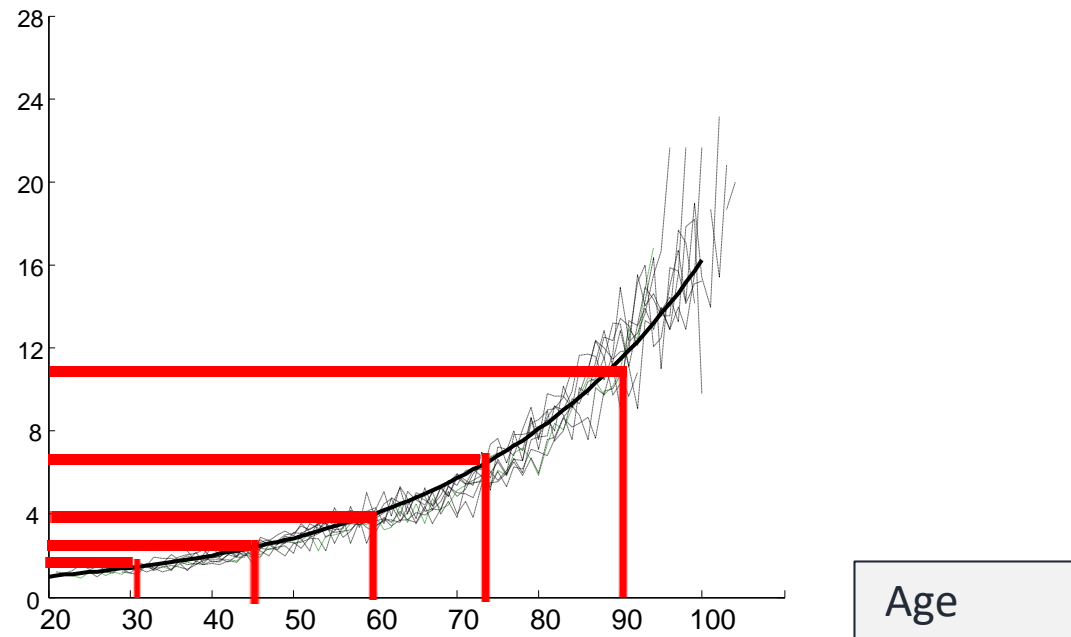


Mitnitski A & Rockwood K. *Biogerontology*. 2016;17:199-204

A $\sim 4.5\%$ /year rate of deficit accumulation translates into a 15-year doubling time.

Degree of frailty / deficit accumulation

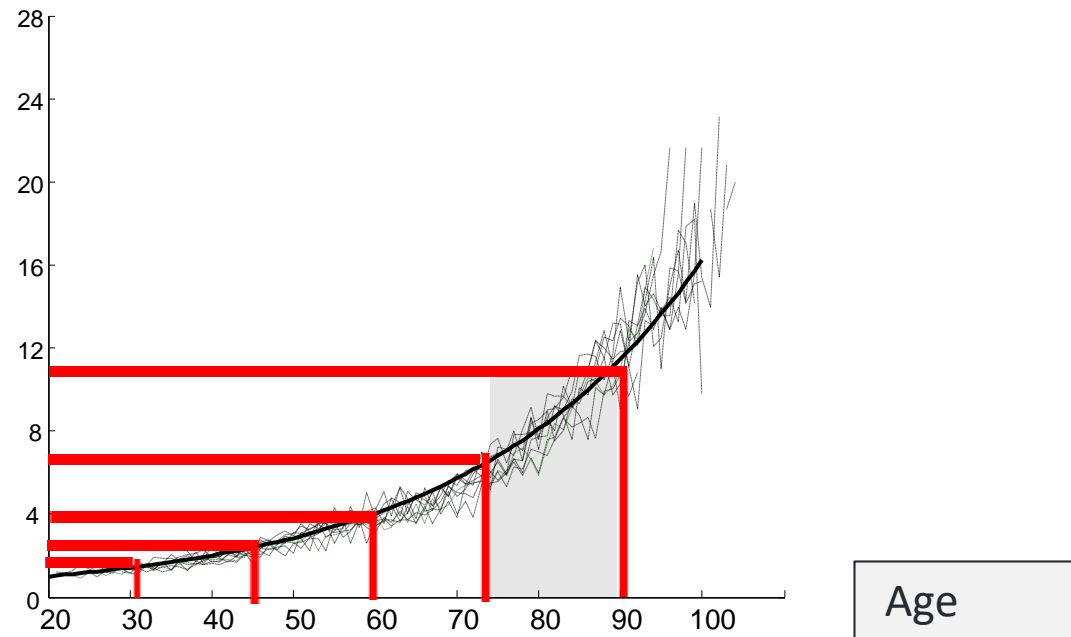
Just as with compound interest, it's not the first couple of doubling times where we see the big impact ...



Mitnitski A & Rockwood K. *Biogerontology*. 2016;17:199-204

A $\sim 4.5\%$ /year rate of deficit accumulation translates into a 15-year doubling time.

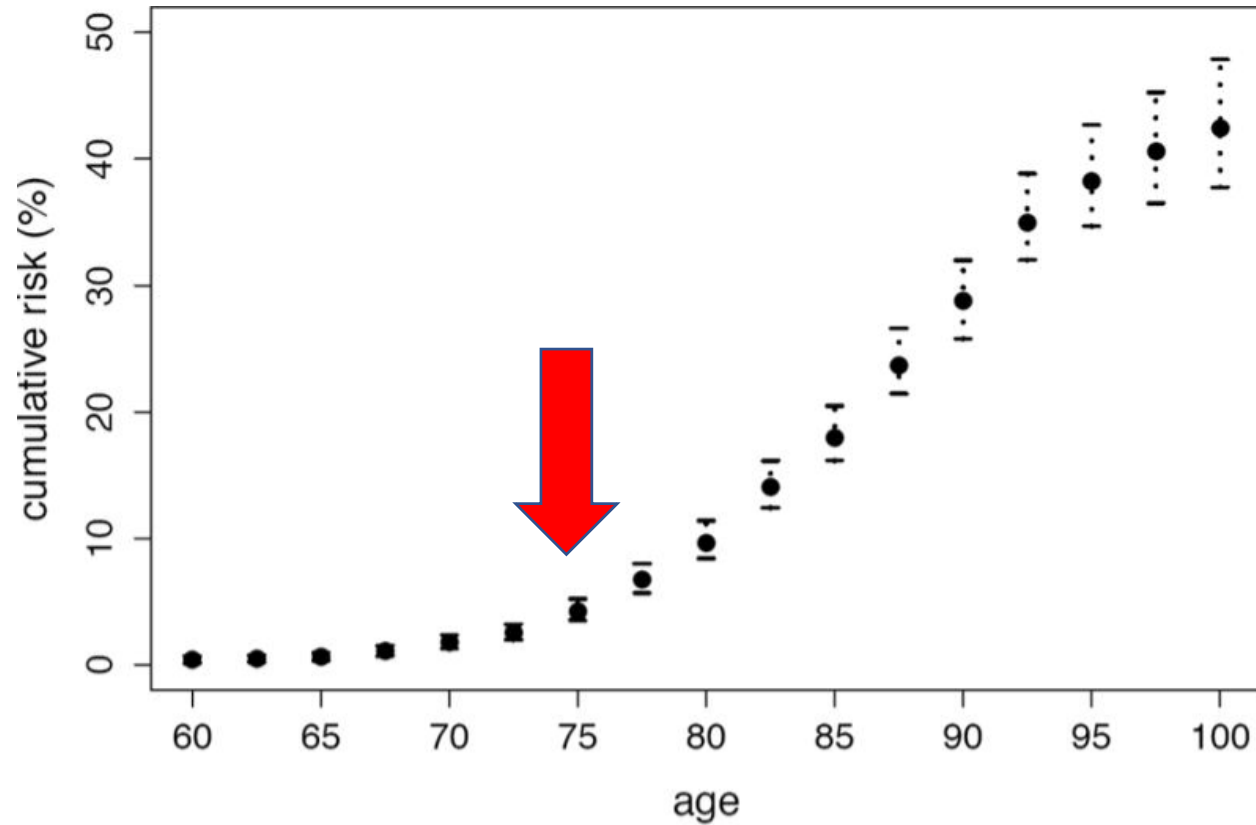
Degree of frailty / deficit accumulation



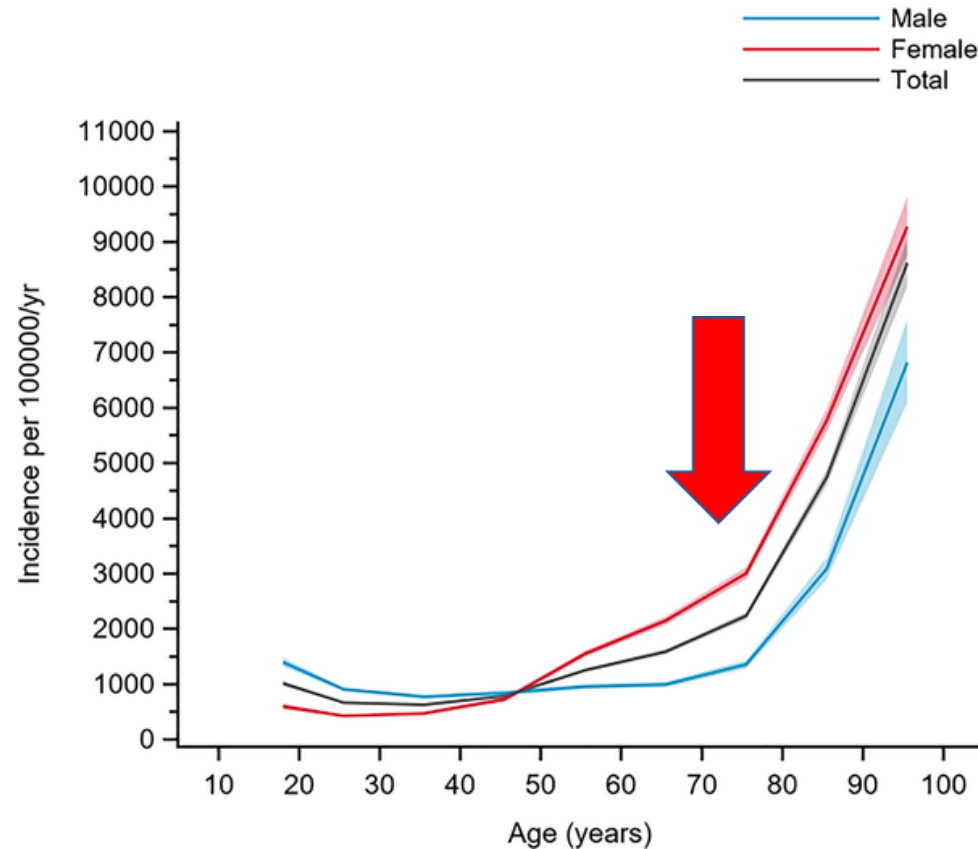
Mitnitski A & Rockwood K. *Biogerontology*. 2016;17:199-204

Estimated lifetime risk of dementia in older Canadians

Cumulative risk of dementia

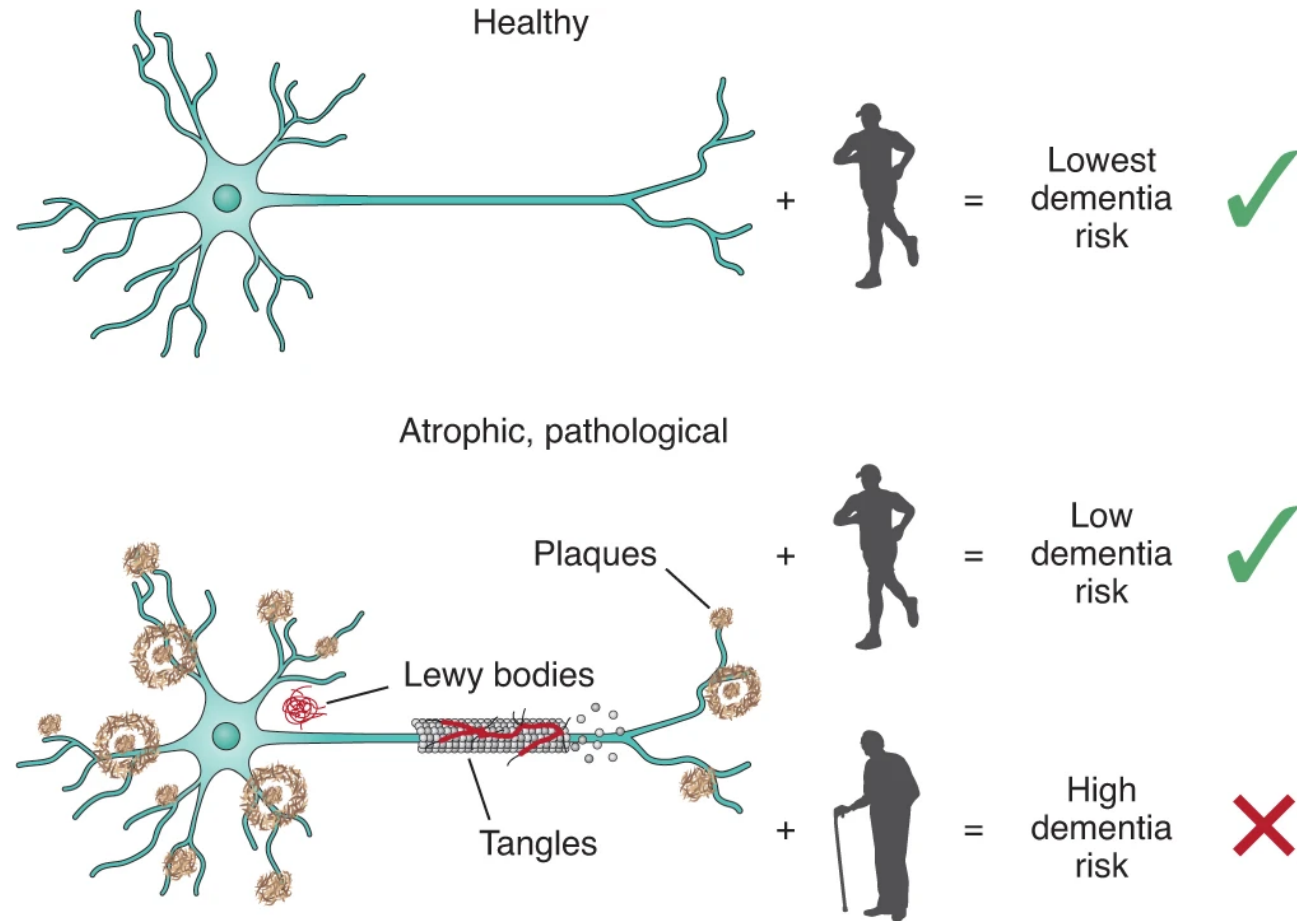


Four-year Age- & gender-specific incidence (95% CIs) of fractures (Swedish Fracture Registry), 2015–2018.



Bergh C, et al. PLOS ONE 2020 15(12): e0244291. DOI: /10.1371/journal.pone.0244291

Frailty is not a disease, but it profoundly influences disease expression.



Howlett et al., *Nature Aging* 2021;1:650-665.

Song X et al. *Neurology* 2011;77:227-234.
 Rockwood K et al., *Nat Med* 2019;25:1331-1332.
 Wallace LMK et al., *Lancet Neurol* 2019;.
 Wallace LMK et al., *Neurology* 2020; 95:e3269-e3279
 Wallace LMK et al., *Int Psychogeriatr* 2021;33:1035-43.
 Ward DD et al., *Ann Neurol* 2021; 89:1221-1225
 Ward DD et al., *J Neurol, Neurosurg, Psychiatry* 2021;92:136-142.
 Ward DD et al., *J Neurol, Neurosurg, Psychiatry* 2022;93:343-350.
 Canevelli M, et al., *Eur J Neurology* 2023 Epub. Doi: 10.1111/ene.16072

The main objection

Very few older adults have pure Alzheimer disease.

Even those mostly *plaqued and tangled* often do not express their “disease” as dementia. Instead, plaques, tangles, and their corresponding biomarkers, are best seen as risks for late-life dementia. That risk is moderated chiefly by the degree of frailty.

Ditto polygenic risk: **dementia is an exemplary late-life illness**: ageing (myriad features, manifesting variably = frailty) + genes + environment.

Widespread and important support

United States Food and Drug Administration

New England Journal of Medicine

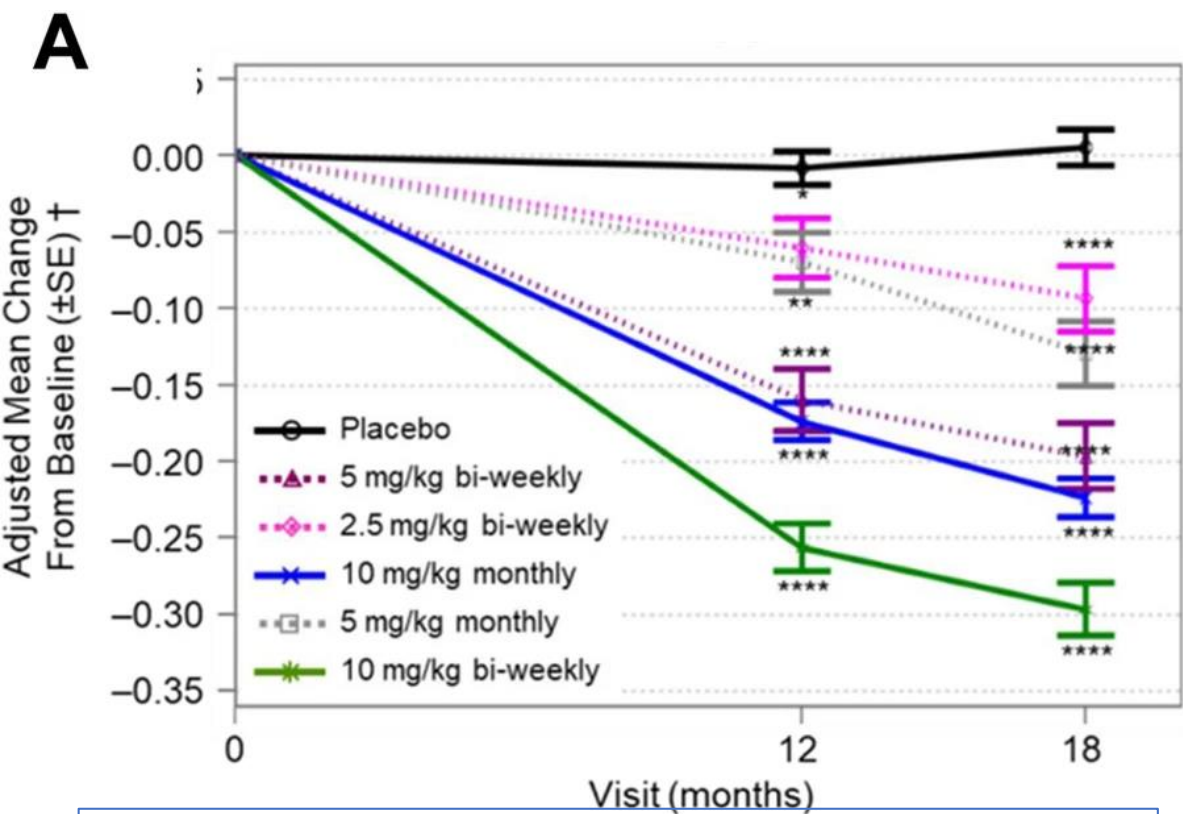
US Alzheimer Association

UK Alzheimer Society

FOR Lecanemab

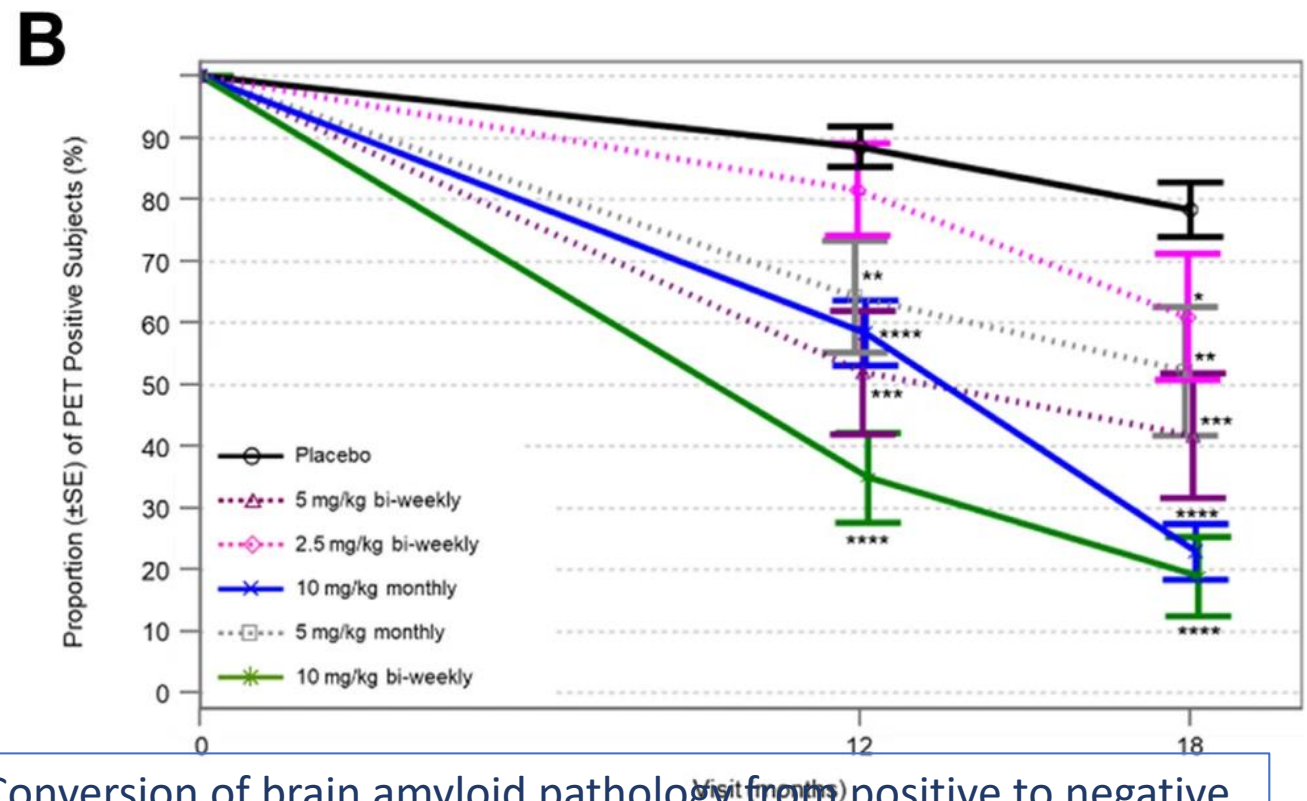
A long time coming, along an anfractuous path, with dizzying descents, and sharply-pointed outcroppings.

Compared to standard six-month assessments in mere symptomatic treatment trials, **here we have significant differences demonstrated over 18 months.**



Change from baseline in brain amyloid pathology

N (PET-SUVr)	0 Months	12 Months	18 Months
Placebo	99	96	88
2.5 mg/kg biweekly	28	27	23
5 mg/kg monthly	28	27	23
5 mg/kg biweekly	27	25	24
10 mg/kg monthly	89	88	82
10 mg/kg biweekly	44	43	37



Conversion of brain amyloid pathology from positive to negative

N (Florbetapir Tracer Visual Read)	0 Months	12 Months	18 Months
Placebo	99	96	88
2.5 mg/kg biweekly	28	27	23
5 mg/kg monthly	28	27	23
5 mg/kg biweekly	27	25	24
10 mg/kg monthly	89	88	82
10 mg/kg biweekly	44	43	37

CLARITY-AD Trial – key points

Wide age range allowed: 50-90 years

On target: PET and/or CSF evidence of amyloid burden

Refined mechanism of action: high affinity for amyloid- β soluble protofibrils and oligomers; low for monomers and insoluble fibrils

Important effect: 30% decline in deterioration; significant, meaningful.

Uniquely (for this class): the benefit has been replicable.

What motivated the FDA to convert from accelerated to full approval

Alzheimer disease is common.

Alzheimer disease is costly.

Alzheimer disease is cruel.

What motivated the FDA to convert from accelerated to full approval?

Alzheimer disease is common.

Alzheimer disease is costly.


Alzheimer disease is cruel.

Multiple lines of evidence support the amyloid hypothesis.

To now, we have not had disease-modifying treatment.

Unlike with aducanumab, here the trials converged in their estimates of positive effects.

Anti-Amyloid Monoclonal Antibodies are Transformative Treatments that Redefine Alzheimer's Disease Therapeutics

[Jeffrey Cummings](#)  Drugs. 2023; 83(7): 569–576.

“The success of monoclonal antibodies reflects a relentless application of neuroscience knowledge to major challenges facing humankind.”

FOR Donanemab

Comes on the heels of lecanemab and even better: a -0.67 difference (i.e. slowing of decline; 95% ci -0.95 yo -0.45) or as we heard, “greater than 50% more slowing compared with lecanemab”). Also, significant differences in favour of the integrated Alzheimer Disease Rating Scale at $p < 0.001$!

Compared to standard six-month assessments in mere symptomatic treatment trials, **here we have (again!) significant differences demonstrated over 18 months.**

FOR Donanemab

Comes on the heels of lecanemab and even better: a -0.67 difference (i.e. slowing of decline; 95% ci -0.95 yo -0.45) or as we heard, “greater than 50% more slowing compared with lecanemab”). Also, significant differences in favour of the integrated Alzheimer Disease Rating

Integrated: unified;
brought together;
desegregated

Compared to standard treatment trials, **demonstrated**

more symptomatic **differences**

What is being said by the nattering nabobs of negativism?

The effect is meaningless – e.g. only a 0.45-point difference on an 18-point scale (lecanemab) or 3 points on the INTEGRATED (!) ADRS.

Patients were not representative

The drug can serious cause side effects.

They are unhandy (or as you mainland crowd would say) “cumbersome”, requiring administration IV q2-4 weeks.

The reporting has not been as forthcoming as we might hope.

Acknowledgments

Funding sources:

Canadian Institutes of Health Research
Canadian Frailty Network
Canadian Space Agency
Alzheimer Society of Canada
Fountain Family Innovation Fund,
QEI Health Sciences Foundation
Research Nova Scotia
MITACS program, National Research Council of Canada
Dalhousie Medical Research Foundation
Ryman Health Care Foundation, New Zealand
Nova Scotia Health

Colleagues & students:

Arnold Mitnitski
Sherri Fay
Olga Theou
Melissa Andrew
Lindsay Wallace
Barry Clarke
Ulises Pérez Zepeda
Glen Pridham
Xiaowei Song
Karen Nicholls
Jodie Penwarden
Sam Searle
Andrew Rutenburg
Susan Howlett