Why There is Reason to be Moore Hopeful About the Field of Prion Disease

Brian Appleby

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Disclosure

Prion disease is not just a scientific problem.

Prion disease is a human problem with technological challenges.

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Overview

- Veil obscuring our knowledge of human prion disease
- The importance of building necessary infrastructure
- The therapeutic development inflection point
- Why now & why so fast?
- A cautionary tale of exponential growth
- The human imperative
- Why I am Moore hopeful

VIRTUAL 2021

CJD FOUNDATION CONFERENCE

CREUTZFELDT-JAKOB DISEASE FOUNDATION, INC

An historical appraisal of the field of prion diseases

What have we learned & why we we should be optimistic

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BRIAN APPLEBY, MD

DIRECTOR, NPDPSC

Therapeutics Seemed Impossible

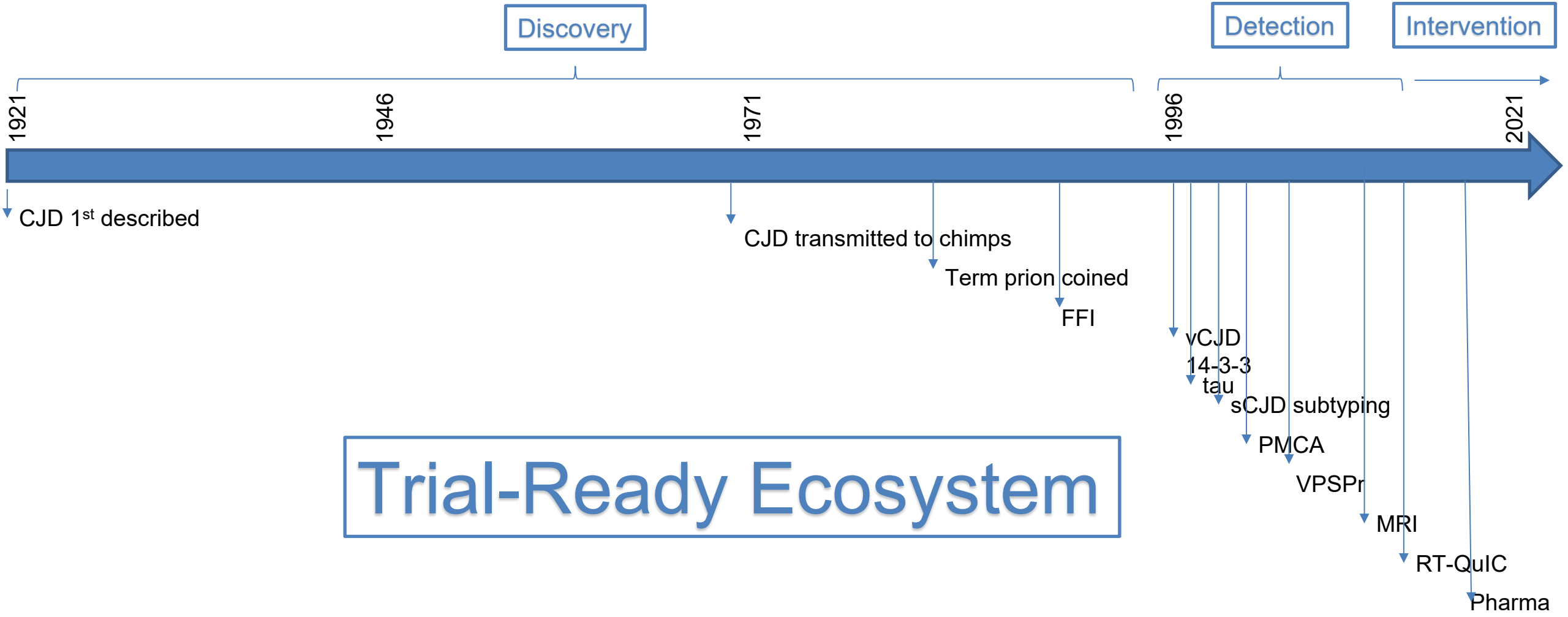
They were talked about, but in a theoretical sense

- "One in a million…" rarity
- Extremely rapid progression
- Variety of clinical symptoms
- Diagnostic delay
- Lack of reliable diagnostic tools
- Lack of ways to measure progression

The Veil Between Us
And Understanding
(Veil of Maya)

Like trying to shoot a high-speed train with no schedule in the fog.

You cannot treat what you cannot find, diagnose, or measure.



Trial-Ready Ecosystem

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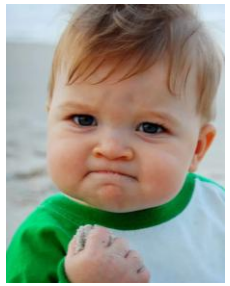
Diagnosing Prion Disease Has Dramatically Changed

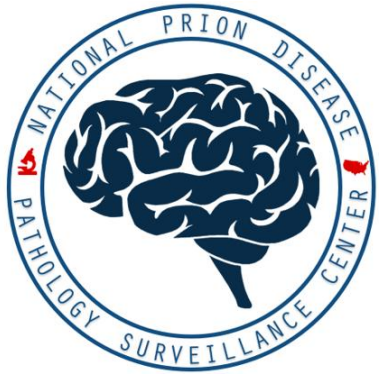
Appleby Diagnostic Confidence Scale



- 2007: Diagnosed by syndrome, 14-3-3, and EEG (syndromic diagnosis + suggestive markers)
- 2009: Brain MRI criteria added (syndromic diagnosis + suggestive markers)
- ~2010: CSF total-tau used (syndromic diagnosis + suggestive markers)
- 2018: **RT-QuIC** added to criteria (symptom + disease specific marker)

Added Benefit of Surveillance
Vertical Integration of a Disease

- Immediate diagnosis –> immediate referral for brain donation
  - Clinical diagnostic testing (cerebrospinal fluid tests)
  - Brain MRI consultation
  - Expert consults, outreach, & education
  - Teleneurology Assessment Program for CJD (TAPCJD)
  - ~92% of expected cases come through the NPDPSC
- Immediate diagnosis –> immediate referral to clinical trials



Diagnosis Now Enables Intervention

We Have Ways to Measure Disease Progression

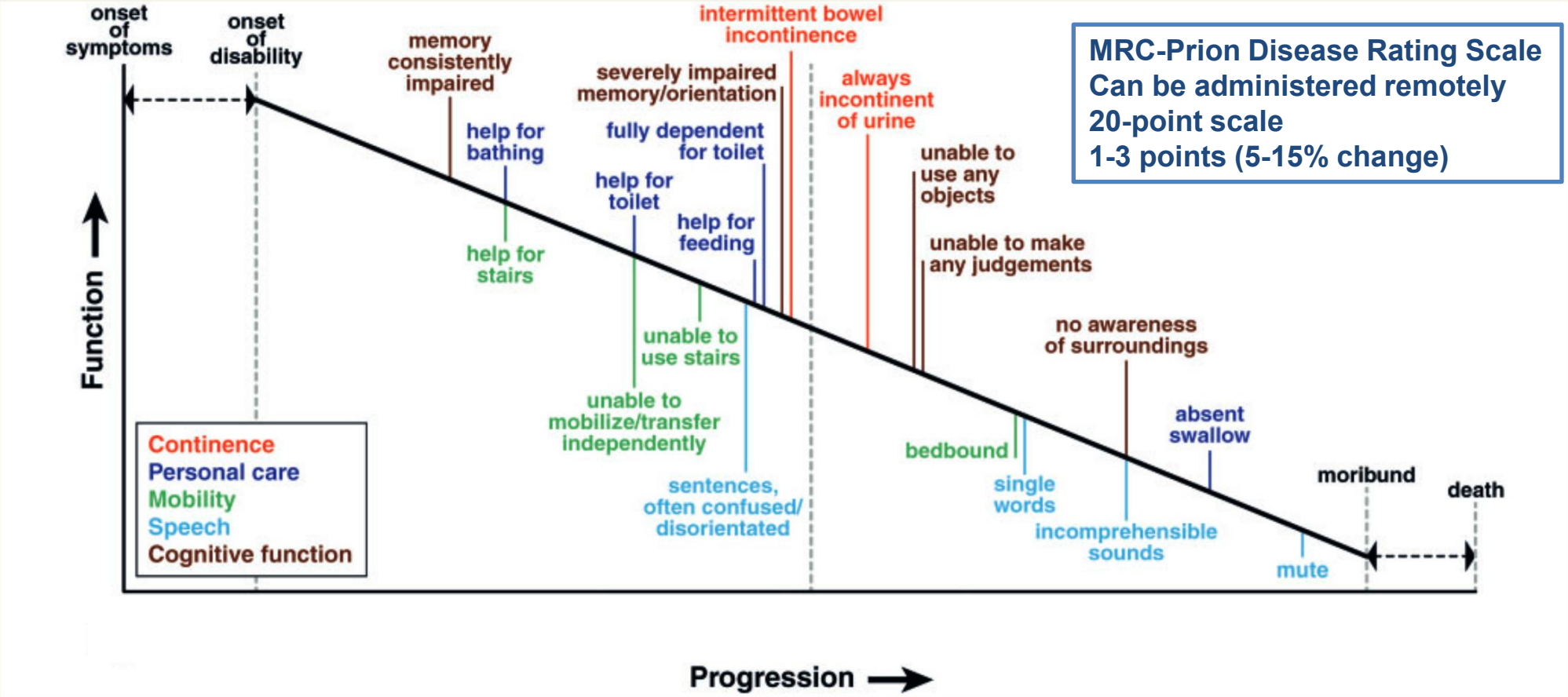
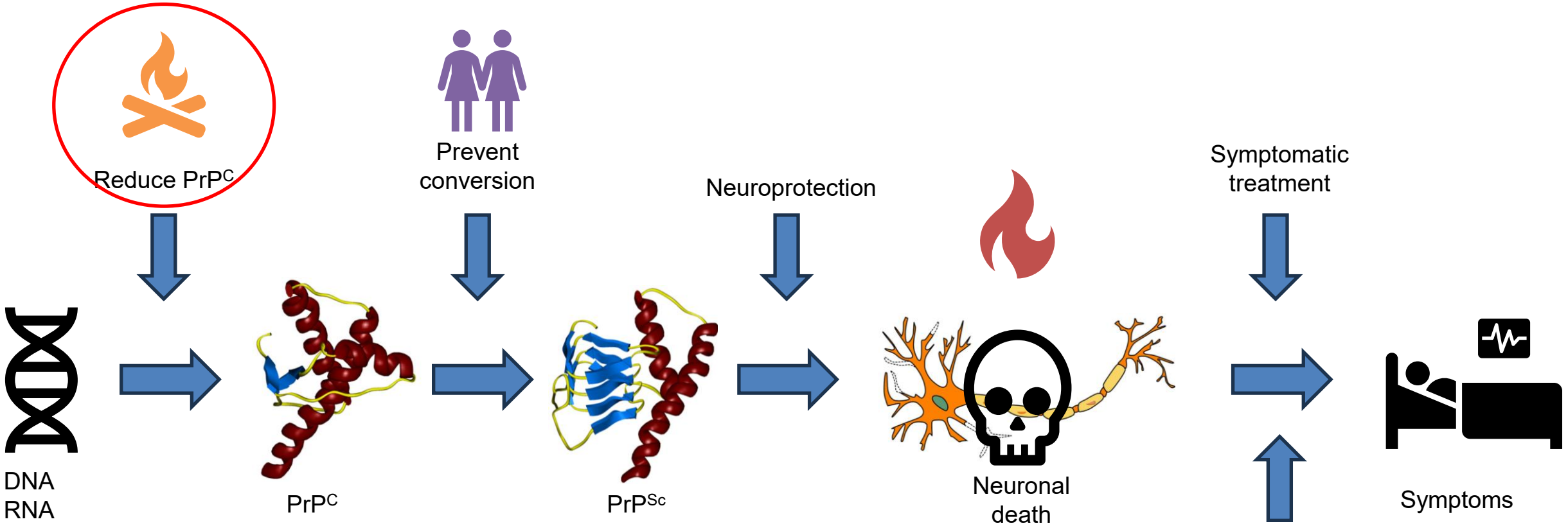


Figure 5 Schematic of the pattern of decline in a patient with sporadic CJD that would be most consistent with the Rasch model. Progression is represented by the logit scale used in the Rasch analysis reflecting the relative difficulties of the thresholds that comprise the MRC Scale. This diagram illustrates the validity of the progression construct, as the ordering of the items is consistent with clinical experience and there is a reasonable spread of item difficulty in different functional domains.

Thompson A, Brain 2013

Where Can We Intervene?



ASOs
siRNA
Zinc finger repressors
Molecular gates

Chaperones

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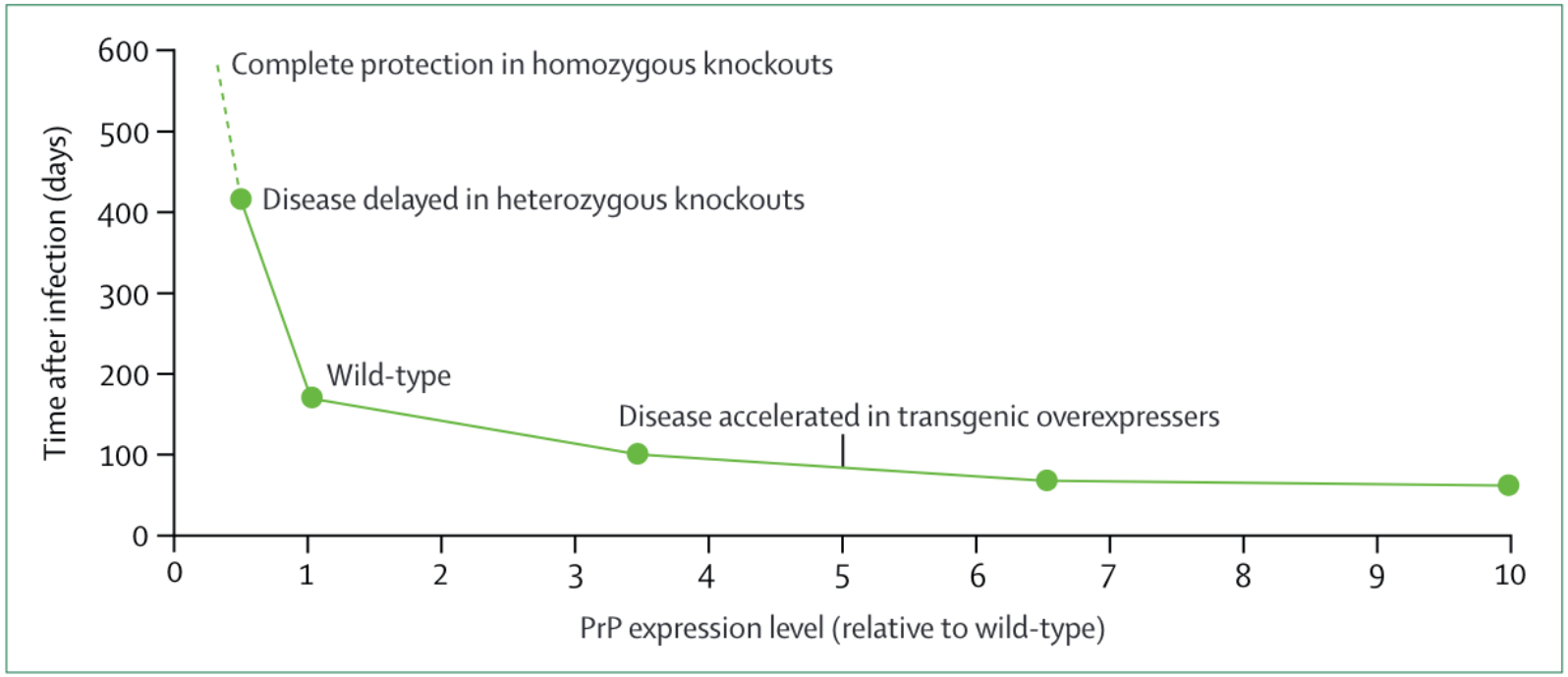

Figure 1: **Prion disease incubation time and PrP expression level**
Time to terminal disease in transgenic prion-infected animals is shown as a function of PrP expression level. Wild-type mice intracerebrally inoculated with prions develop fatal disease in 5–6 months. Transgenic mice producing extra PrP develop disease more rapidly than wild-type mice, while heterozygous knockout animals producing half the normal amount of PrP remain healthy more than twice as long as wild-type mice. Homozygous knockout animals cannot propagate prions and never develop prion disease. Plotted on the basis of data reported by Fischer and colleagues.[12] PrP=prion protein.

Vallabh S, Lancet Neurol 2020

Is Lowering Prion Protein Safe?

Healthy Animal Knock-Outs	Study
Mice	Bueler H, Nature 1992
Cattle	Richt JA, Nat Biotechnol 2007
Goats	Benestad SL, Vet Res 2012

Reduced amounts of the normal prion protein seems to be okay in humans.

Table S11. Phenotypes of individuals with N-terminal PrP truncating variants

HGVS	Variant	Zygosity	Sex	Age	Available phenotype information
c.59_60insC	G20Gfs84X	Het	F	79	Ascertained as part of the Rotterdam Study *(179)*, a prospective cohort study of middle-aged and elderly persons. In good health and free of dementia as of at least age 78, at last in-person examination completion. Has 5 siblings and 2 children. Only family history noted is that one sibling has had a stroke before age 65.
c.109C>T	R37X	Het	M	73	Ascertained as a control for the Swedish schizophrenia study. Underwent heart bypass surgery in 2008, has a family history of heart problems. 4 siblings. Reports no family history of neurodegeneration or neuropathy.
c.223C>T	Q75X	Het	M	52	Ascertained in a study of type 2 diabetes. Has mild type 2 diabetes treated with metformin. Has children.
c.391G>T	G131X	Het	F		None available.

Minikel E, Sci Trans Med 2016

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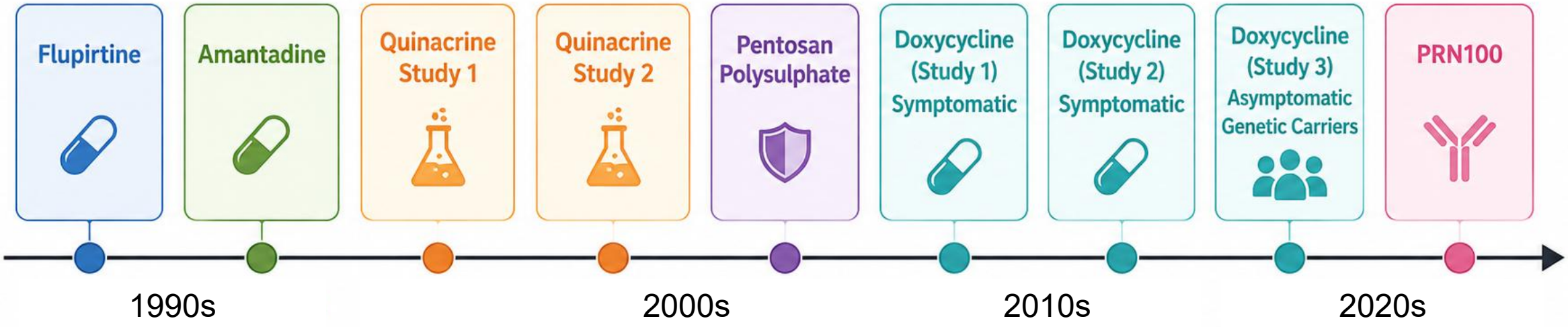
Why Now & Why So Fast?



At Present (2026)

Recruiting

PrProfile: A Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of ION717.

ClinicalTrials.gov ID NCT06153966

Sponsor Ionis Pharmaceuticals, Inc.

Information provided by Ionis Pharmaceuticals, Inc. (Responsible Party)

Last Update Posted 2024-09-04

- Launched: 2024
- Sites: 13
- Countries: 9

PrP-targeting siRNA Safety & Mechanism Study (PRiSM)

ClinicalTrials.gov ID NCT07444580

Sponsor Broad Institute of MIT and Harvard

Recruiting

Find Contact Information

Check who can join

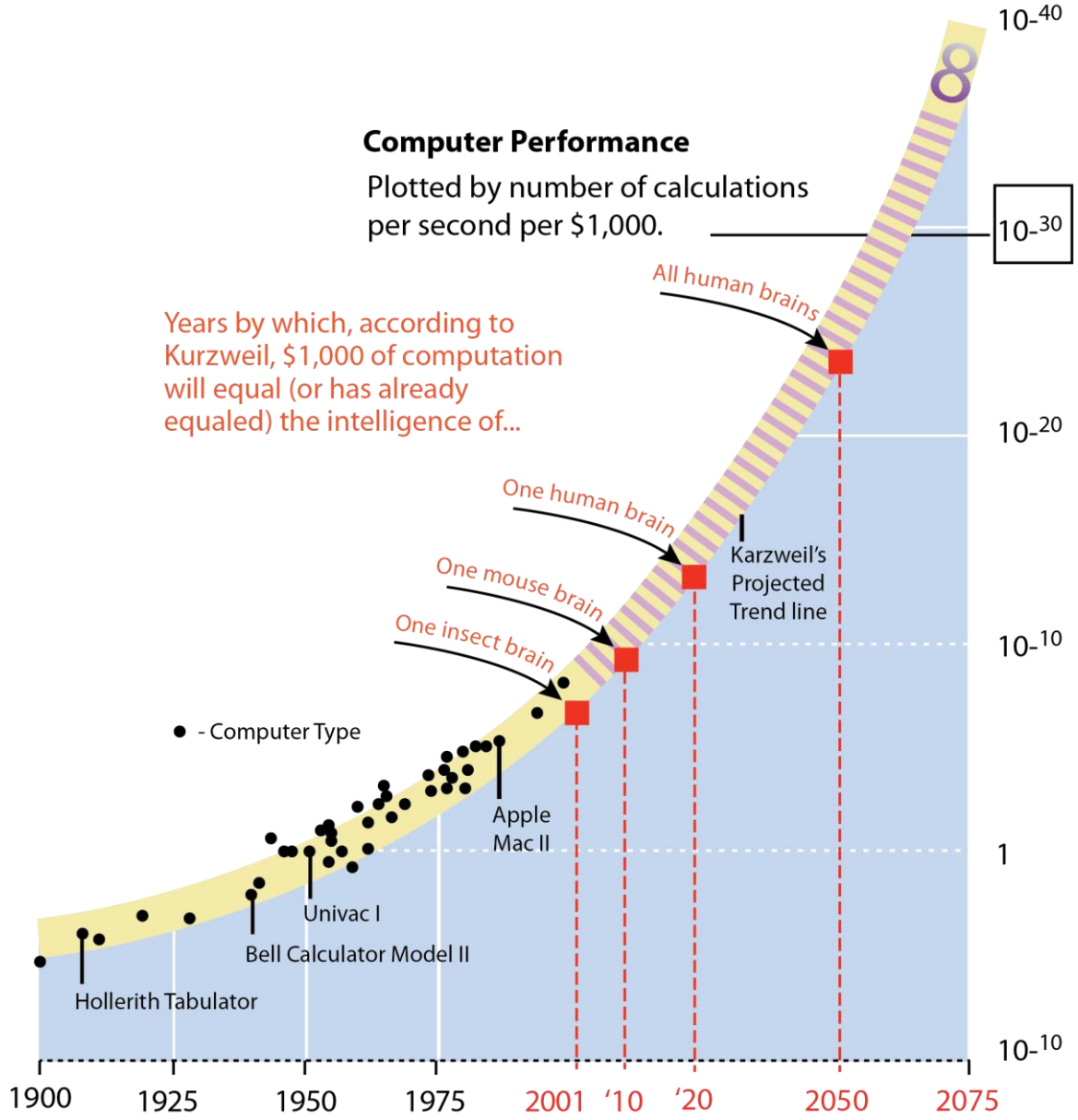
Information provided by Broad Institute of MIT and Harvard (Responsible Party)

Last Update Posted 2026-06-05

- Launched: 2026
- Sites: 5
- Countries: 1

Other Companies (Panel on Sunday)
Nobelpharma
Regeneron
Gate Bioscience

The Law of Accelerating Returns



Ray Kurzweil

This is Technology Agnostic:

- Improved understanding of disease
- Improved biomarkers
- Improved diagnostics/awareness
- Improved infrastructure

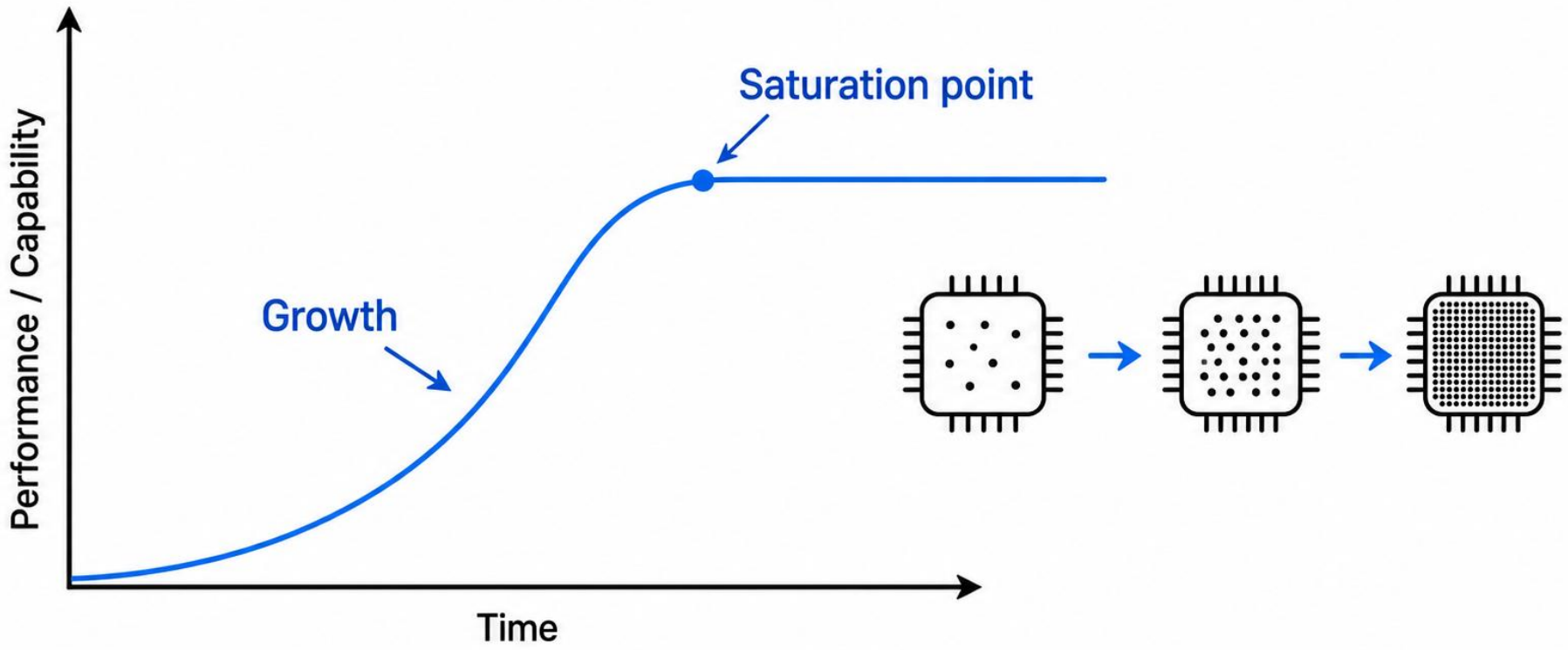
This is Field Agnostic (Alzheimer's):

- Improved understanding of disease
- Improved & more available biomarkers
- Increased awareness of biomarkers
- Disease modifying treatments

Scaling Prion Disease Therapeutic Development

- Preclinical developmental technologies have increased (e.g., genetic modifying therapies)
- Improved diagnostics means more cases identified, earlier
- Improved infrastructure: within countries and across countries
- Improved outcome measures: MRC Prion Disease Rating Scale
- Industry: Dramatically improved trial ready infrastructure, knowledge, & money

A Cautionary Caveat to Exponential Growth

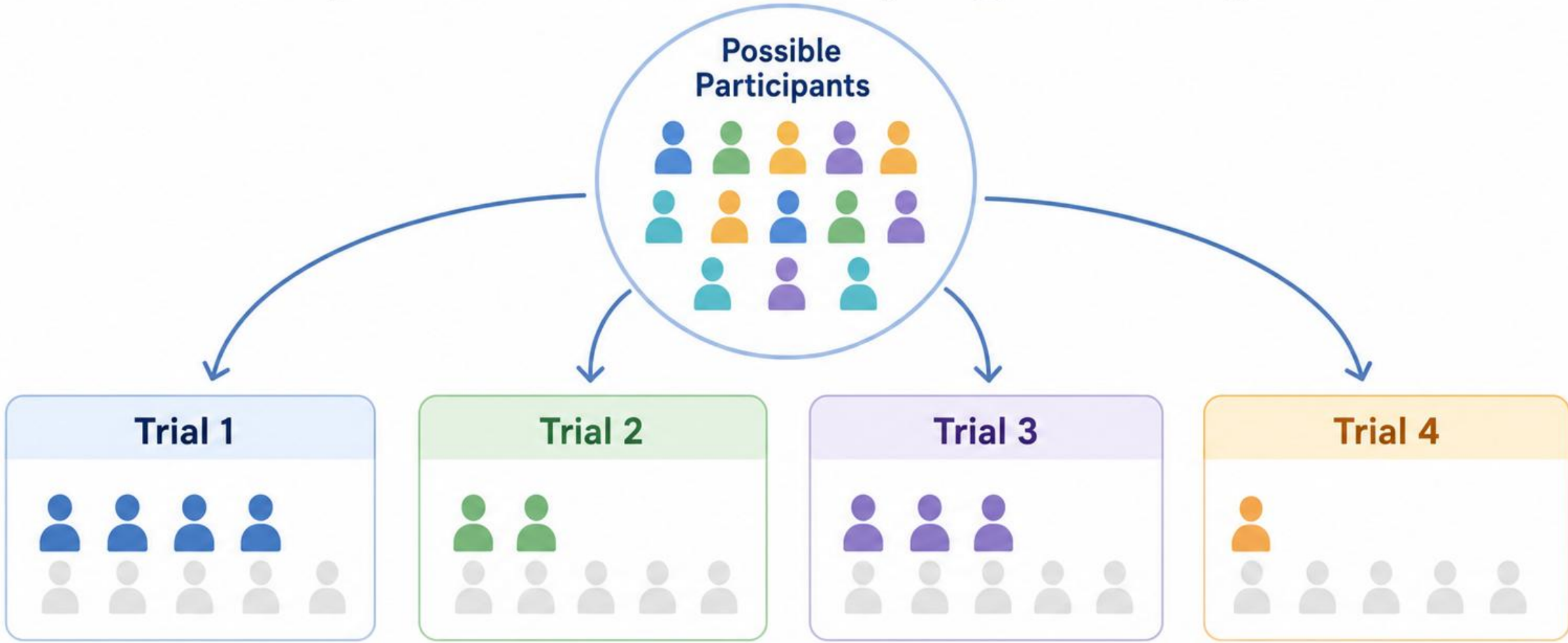


When physical limits are reached, growth slows.

Moore’s Law

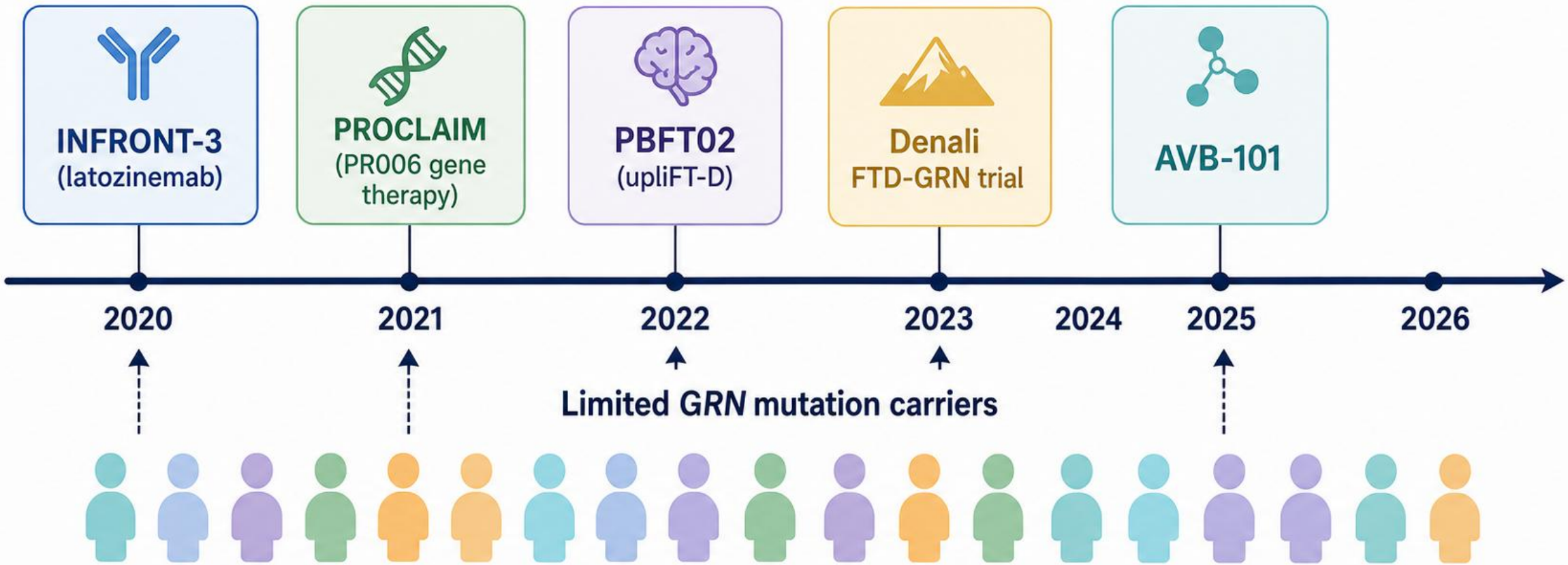
Too Many Trials, Too Few Participants

When many studies start at once, each one may struggle to find enough volunteers.



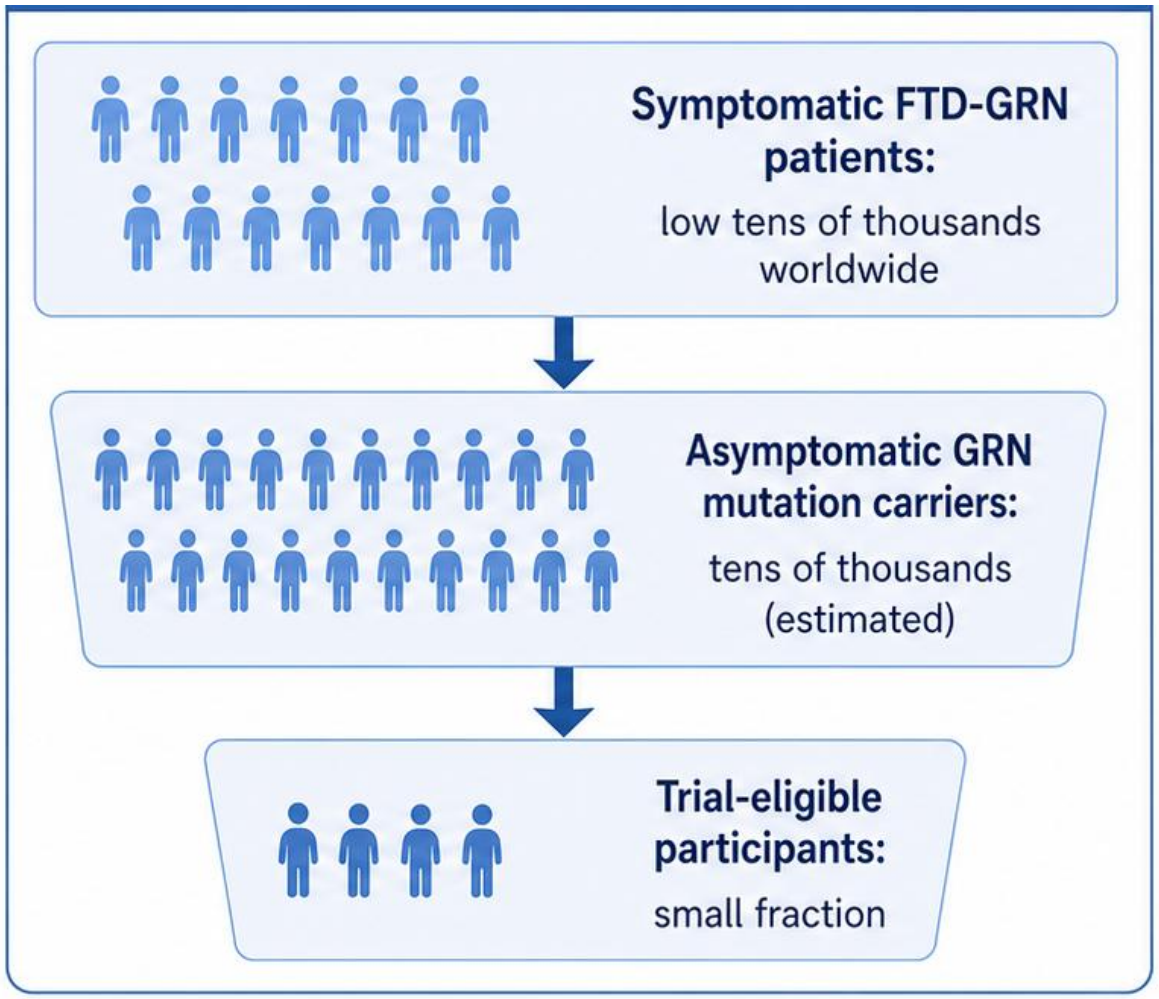
GRN Trials Over Time: Too Many Studies, Too Few Participants?

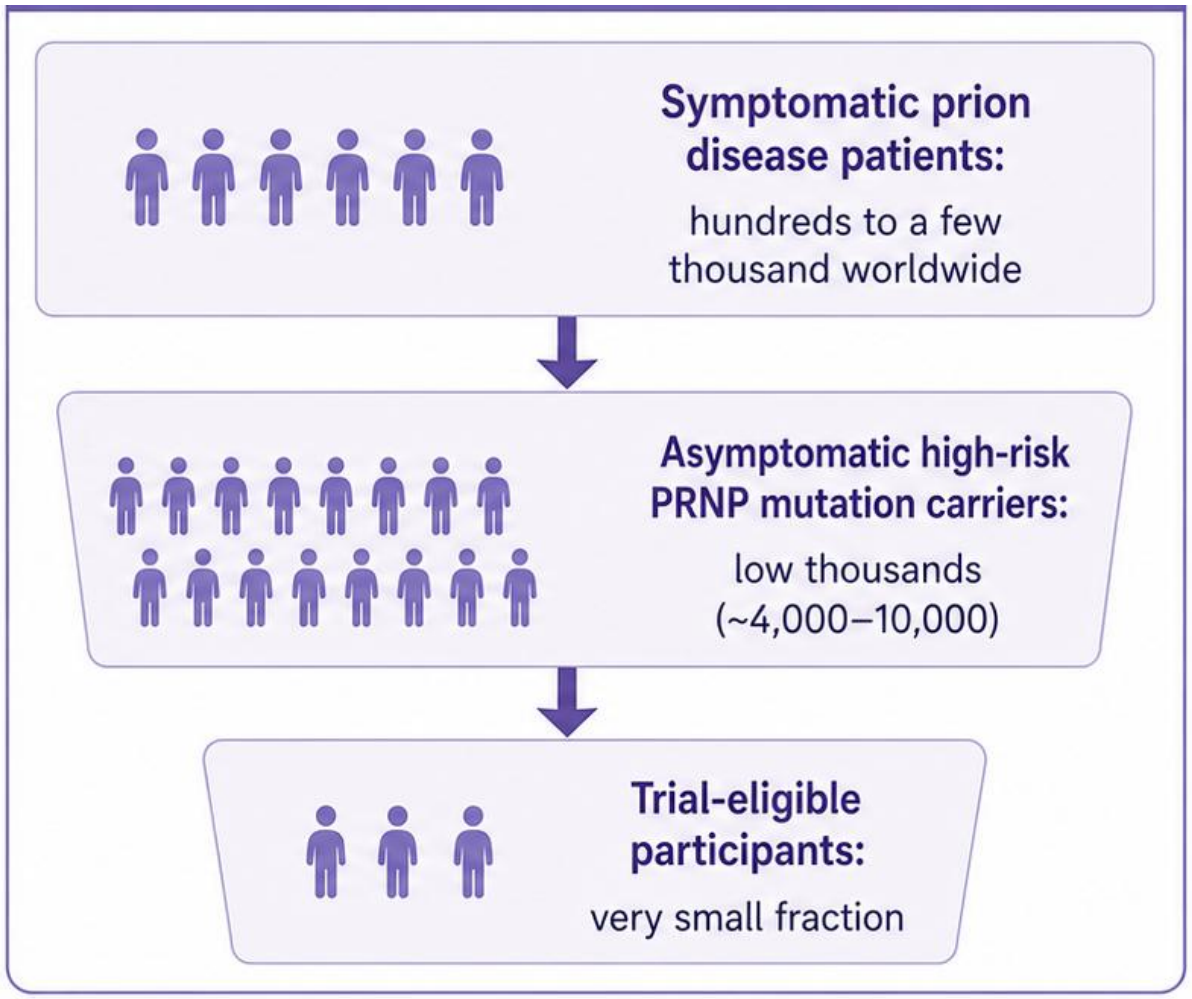
Families must choose carefully which single trial to join.



Many trials, same small pool.

How does FTD-GRN Compare to Prion Disease?





Potential Solutions

- Limit study sizes as much as possible
- Platform trials
- Modified study designs
- Minimize or shared placebo arms
- Natural history control data arms
- Biomarker-based eligibility

Acceleration of therapeutic development without coordination = Increased challenges & slowed progress

Patients/Families as Partners, Not Endpoints

The Human Imperative

Goal

- Technological progress must never outpace wisdom & compassion
- The people living the disease must help shape the science trying to stop it
- Study design should start & end with the patient

Considerations

- Lived experience matters
- Study burden matters
- Caregiver burden matters
- Travel matters
- Financial cost matters
- Time matters
- Equitable access matters
- Quality of life matters
- Dignity matters

Patient Perspective

Then

- Diagnosis not as confident in life
- Diagnosis usually very late
- Little to offer in terms of prognosis
- If diagnosed earlier, little to offer in terms of clinical trial participation

Now

- Diagnosis can be achieved more reliably during life
- Diagnosis can be earlier
- Reasonable subtyping in life
- Can give prognosis
- Can participate in research studies remotely
- **Multiple** choices for clinical trial participation

Why I Am Moore Hopeful

- We can diagnose more accurately & faster
- We understand the biology better
- We can lower the normal prion protein
- Industry is now a partner
- Collaboration in clinical trials is global
- Prevention is conceivable
- Patients & families are leading the way with us

Thank You!

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