UCSF Department of Epidemiology & Biostatistics

UCSF Weill Institute for Neurosciences | Memory and Aging Center

Bayesian Multi-modality Disease-progression Models of *Frontotemporal* Dementia

Presenter: John Kornak
Work and development: Melanie Quintana, Barbara Wendelberger (Berry) and Adam Staffaroni, Adam Boxer, Howie Rosen, Brad Boeve (ALLFTD)

ADRC, Fall 2024

Overview

- Intro: Frontotemporal dementia
- Disease progression modeling

Frontotemporal Dementia (FTD)

- FTD early-onset fatal neurodegenerative disease
- Estimated ~10% of all Dementia cases (rare cf AD)
- Affects people younger than AD (40s and 50s)

FTD Syndromes

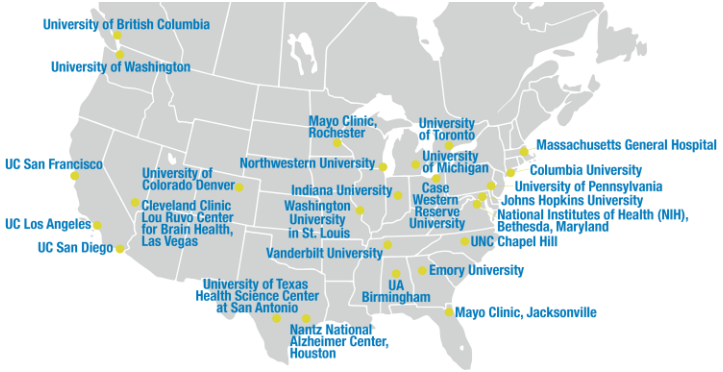
- Syndromes related to brain location, e.g.,
  - Behavioral Variant FTD (bvFTD)
  - Language variants (Primary Progressive Aphasia [PPA], sv and NFv)
  - Motor presentations (ALS, PSP, CBS)

Frontotemporal Dementia (FTD)

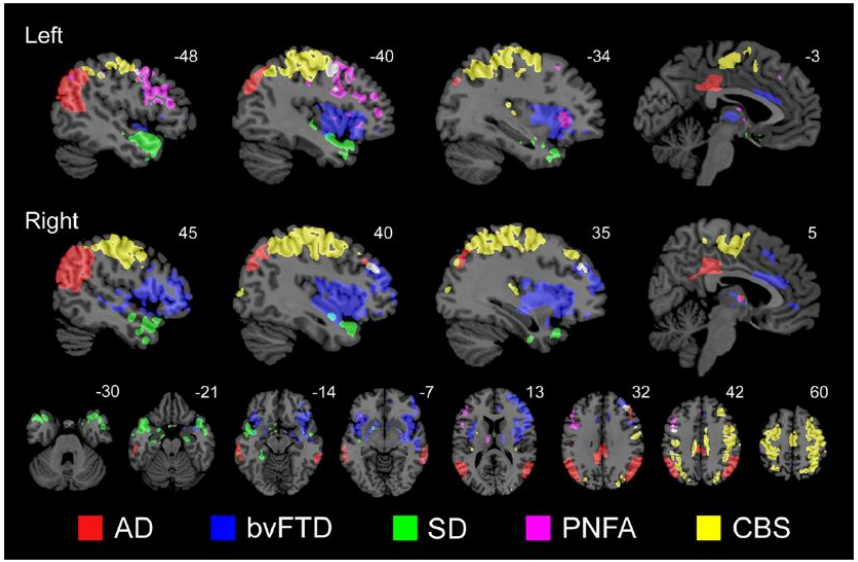
- Familial vs. Sporadic FTD
  - 30% cases Familial – autosomal dominant and high penetrance
  - 3 main genes -- GRN: progranulin, MAPT, C9
  - Presentation proportions vary by genetic variants
  - Critical for early-stage clinical trials, BUT high heterogeneity of age of onset causes difficulties

ALLFTD

ARTFL LEFFTDS Longitudinal Frontotemporal Lobar Degeneration

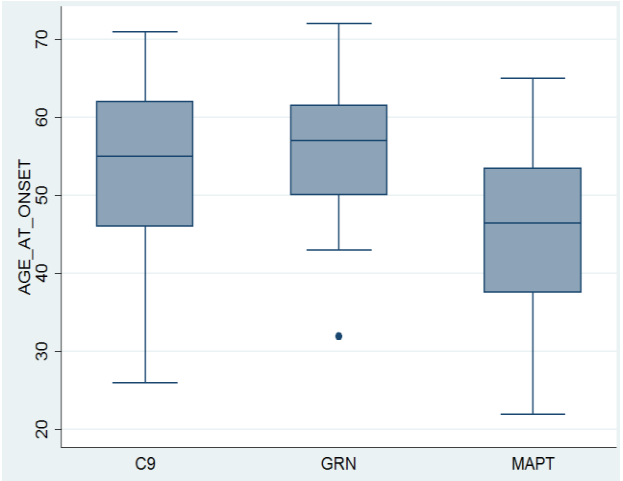


- allftd.org
- Longitudinal multi-center study across USA/Canada
- Cognitive tests, imaging, blood work etc.
- Patient age ~ 40 -- 70



Challenges to conducting f-FTD trials

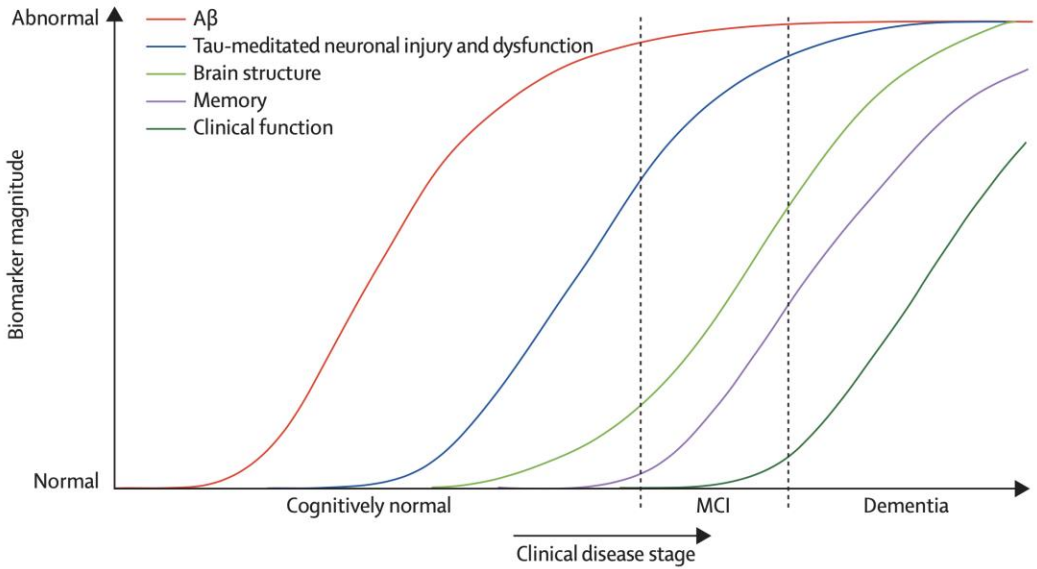
- Best treat f-FTD early (presymptomatic) stages
- Need biomarker/clinical changes f-FTD
  - Age disease onset highly variable
    - Within mutation and within family
    - No good predictors of age of onset
  - Disease course highly variable
    - Each symptom's onset difficult to predict
    - Enrollment criteria?
    - Same endpoints at each disease stage?
- Heterogeneity
- Enter disease progression models (DPMs)?



Age at onset, ARTFL/LEFFTDS f-FTLD (n= 95)

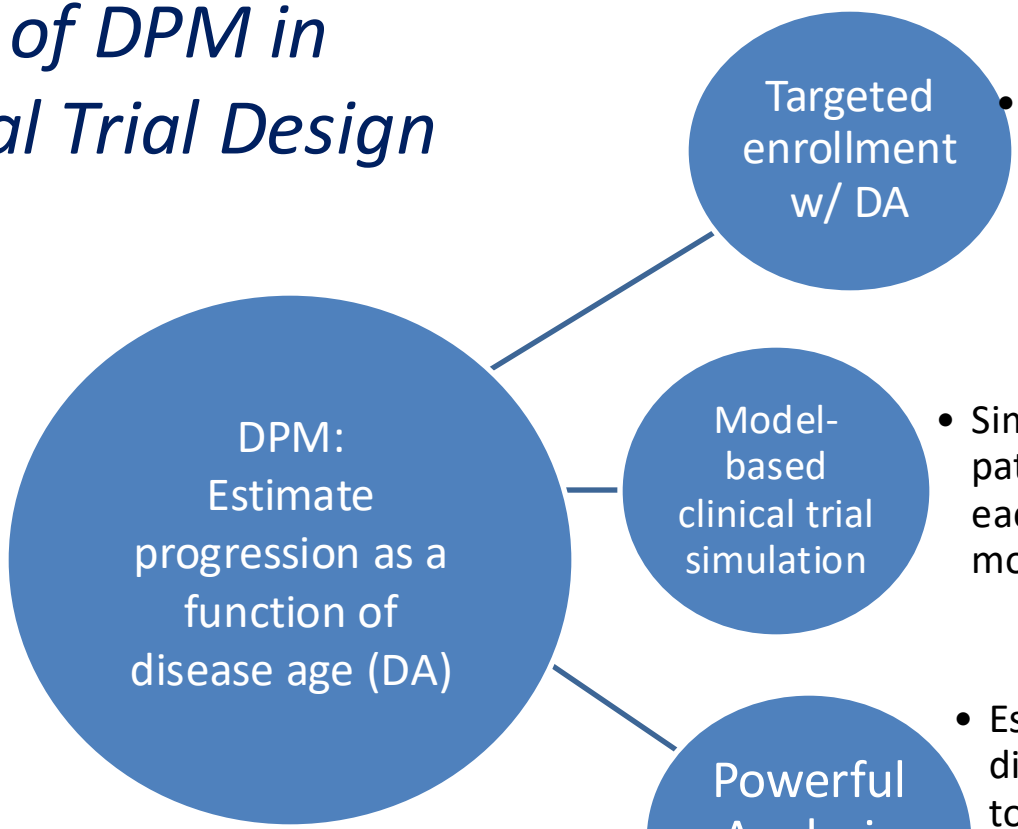
Disease progression models (DPMs)

- Model progression of disease -- multiple markers
- E.g., the “Cliff Jack model” for AD



Disease Age (DA)

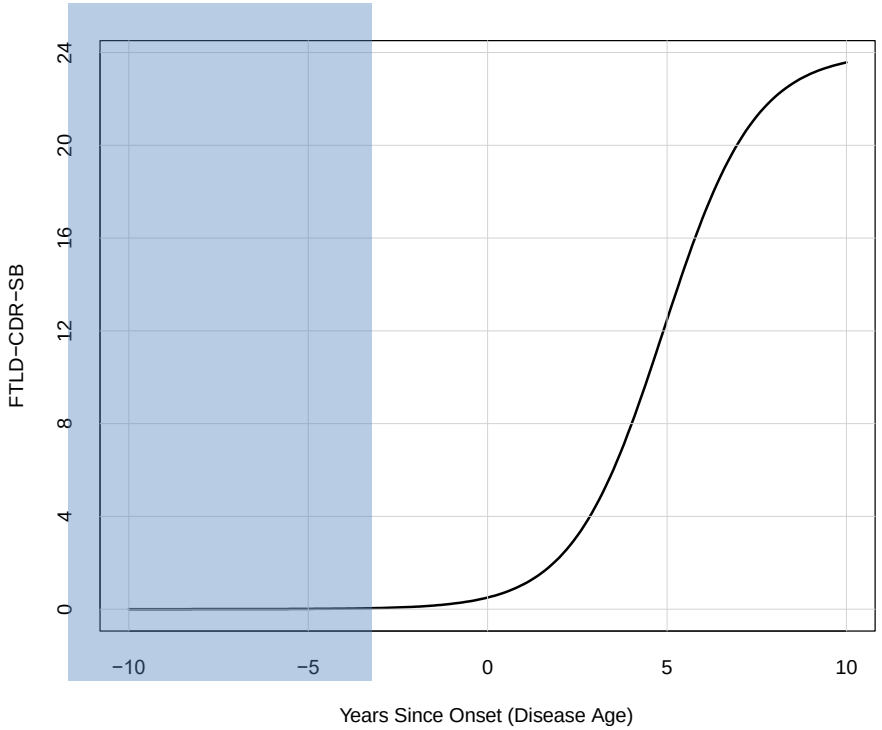
Uses of DPM in In Clinical Trial Design



- Enroll earlier disease population predicted to progress
- Simulate realistic patient-level data for each endpoint using model estimates
- Estimate slowing in disease progression due to a treatment
- Account for DA to reduce unexplained variability in progression rates

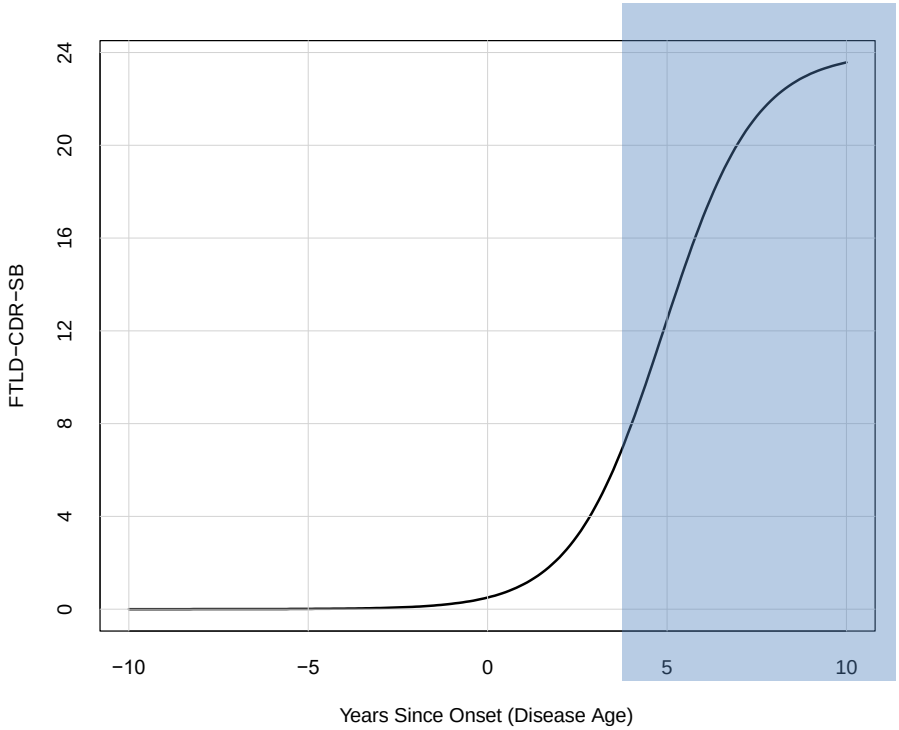
DA based Enrollment in fFTLD

- **Use predicted DA for optimal clinical trial enrollment**
  - Enroll too early – No power



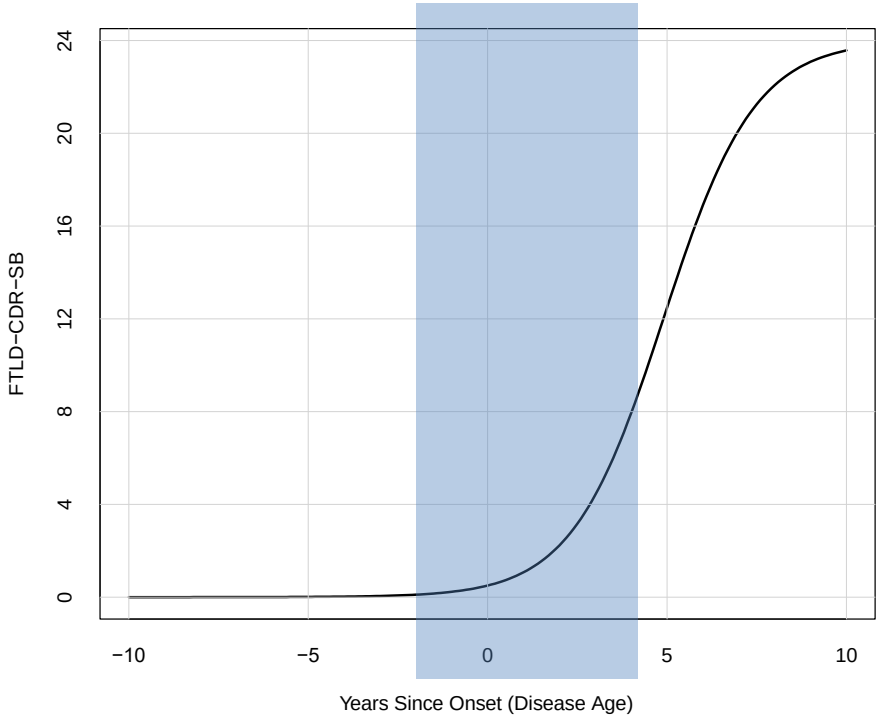
DA based Enrollment in fFTLD

- **Use predicted DA for optimal clinical trial enrollment**
  - Enroll too early – No power
  - Enroll too late – Treatment may not be effective



DA based Enrollment in fFTLD

- **Use predicted DA for optimal clinical trial enrollment**
  - Enroll too early – No power
  - Enroll too late – Treatment may not be effective
  - Enroll an earlier patient population that will likely progress ***and*** benefit



Familial-FTD DPM

- Joint model clinical endpoints/biomarkers over time
  - CDR® + NACC FTLD SB
  - Neuropsych
  - NfL
  - Volumetric ROIs (Frontal and temporal lobes etc.)
- Predictors
  - *"disease age" (DA) = chronological age – "age at onset"*
  - Genetic group

Characteristic	All Carriers	*C9orf72+*	*GRN+*	*MAPT+*	Non-Carriers
Sample Size	1,018	486	322	210	505
Visits (total number)	2.4	2.2	2.4	2.8	2.5
Total number of observations	2,417	1,060	763	594	1290

FTD DPM

i: subject
j: visit
k: biomarker
m: mutation

$$Y_{i,j,k} = \left(\delta_{0,k} + \delta_{0,k,i}\right) + \frac{\delta_{1,k} - \delta_{0,k}}{1 + \exp\left(\theta_{k,m_i} + \beta_{k,m_i} D_{i,j}\right)} + \varepsilon_{i,j,k}$$

Subject-specific random effect
Normal with SD conditional on $\delta_{0,k}$

Worst value for endpoint
Normal prior

$N\left(0, \sigma_k^2\right)$

Endpoint value at normal
Normal prior with mean at clinician elicited prior value

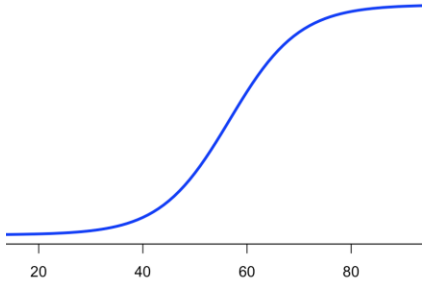
Decay location
Anchor DPM so DA $\left(D_{i,j}\right) = 0$
⇒ CDR®+NACC FTLD-SB = .5
for each biomarker/mutation

Decay rate
specific to endpoint/ mutation type.

Disease age
$D_{i,j} = X_{i,j} - \alpha_i$

Age at visit

Age at onset



Staffaroni et al. 2022 Nat. Med.

FTD DPM prior

Prior model for “age at onset”:

- If onset observed, model as Normal with mean = clinician estimated value; SD = 4 years
- If not observed, model as Normal with mean for mutation type (i.e., C9, GRN, MAPT); SD = 10 years
- Noncarrier family controls

  -- Disease Age based on mean age of their family’s mutation

nature medicine
ARTICLES
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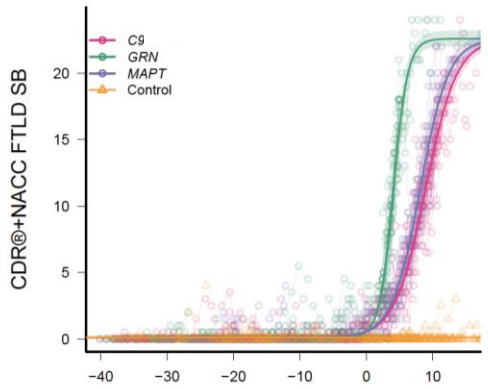
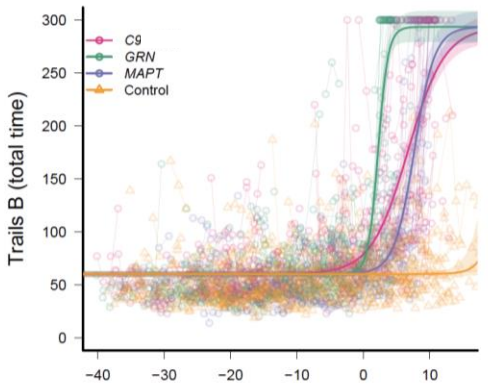
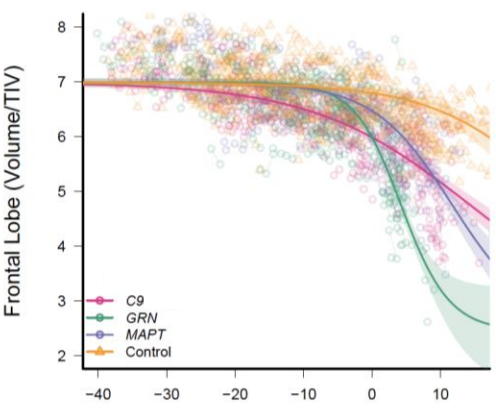
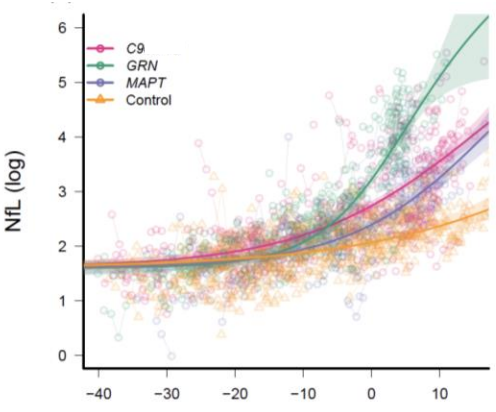
Temporal order of clinical and biomarker changes in familial frontotemporal dementia

Adam M. Staffaroni[1,2*], Melanie Quintana[1,2], Barbara Wendelberger[1,2], Hilary W. Heuer[1], Lucy L. Russell[1], Yann Cobigo[1], Amy Wolf[1], Sheng-Yang Matt Goh[1], Leonard Petrucelli[3], Tania F. Gendron[3], Carolin Heller[3], Annie L. Clark[1], Jack Carson Taylor[1], Amy Wise[1], Elise Ong[1], Leah Forsberg[1], Danielle Brushaber[4], Julio C. Rojas[1], Lawren VandeVrede[1], Peter Ljubenkov[1], Joel Kramer[1], Kaitlin B. Casaletto[1], Brian Appleby[1], Yvette Bordelon[4], Hugo Botha[1,2], Bradford C. Dickerson[5], Kimiko Domoto-Reilly[1,2], Julie A. Fields[5], Tatiana Foroud[1,2], Ralitza Gavrilova[1], Daniel Geschwind[1,6,7], Nupur Ghoshal[1,8], Jill Goldman[1], Jonathon Graff-Radford[5], Neill Graff-Radford[1], Murray Grossman[1,7], Matthew G. H. Hall[1], Ging-Yuek Hsiung[1,9], Edward D. Huey[1,10], David Irwin[1,7], David T. Jones[1,5], Kejal Kantarci[5], Daniel Kaufer[1,9], David Knopman[1,5], Walter Kremers[4], Argentina Lario Lago[1], Maria I. Lapid[1,11], Irene Litvan[1,12], Diane Lucente[1], Ian R. Mackenzie[13], Mario F. Mendez[1,9], Carly Mester[4], Bruce L. Miller[1], Chiadi U. Onyike[12], Rosa Rademakers[3,13,14], Vijay K. Ramanan[1], Eliana Marisa Ramos[1], Meghana Rao[1], Katya Rascovsky[1,7], Katherine P. Rankin[1], Erik D. Roberson[1,15], Rodolfo Savica[5], M. Carmela Tartaglia[12,16], Sandra Weintraub[1,7], Bonnie Wong[4], David M. Cash[17], Arabella Bouzigues[17], Imogen J. Swift[17], Georgia Peakman[17], Martina Bocchetta[17], Emily G. Todd[1], Rhian S. Convery[17], James B. Rowe[18,19], Barbara Borroni[20], Daniela Galimberti[20,21], Pietro Tiraboschi[22], Mario Masellis[23], Elizabeth Finger[24], John C. van Swieten[25], Harro Seelaar[25], Lize C. Jiskoot[25], Sandro Sorbi[26,27], Chris R. Butler[28,29], Caroline Graff[30,31], Alexander Gerhard[32,33], Tobias Langheinrich[32,34], Robert Laforce[35], Raquel Sanchez-Valle[36], Alexandre de Mendonça[37], Fermin Moreno[38,39], Matthis Synofzik[40,41], Rik Vandenberghe[42,43,44], Simon Ducharme[30,34], Isabelle Le Ber[27,28,29], Johannes Levin[45,46,47], Adrian Danek[48], Markus Otto[49], Florence Pasquier[44,45,64], Isabel Santana[47,48], John Kornak[50], Bradley F. Boeve[51], Howard J. Rosen[1], Jonathan D. Rohrer[2], Adam. L. Boxer[1,52] and Frontotemporal Dementia Prevention Initiative (FPI) Investigators*







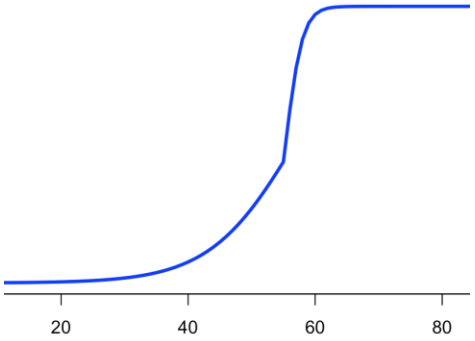


Estimated Years Since Onset

Staffaroni et al., 2022 *Nature Medicine*

Updated FTD DPM

i: subject
j: visit
k: biomarker
m: mutation

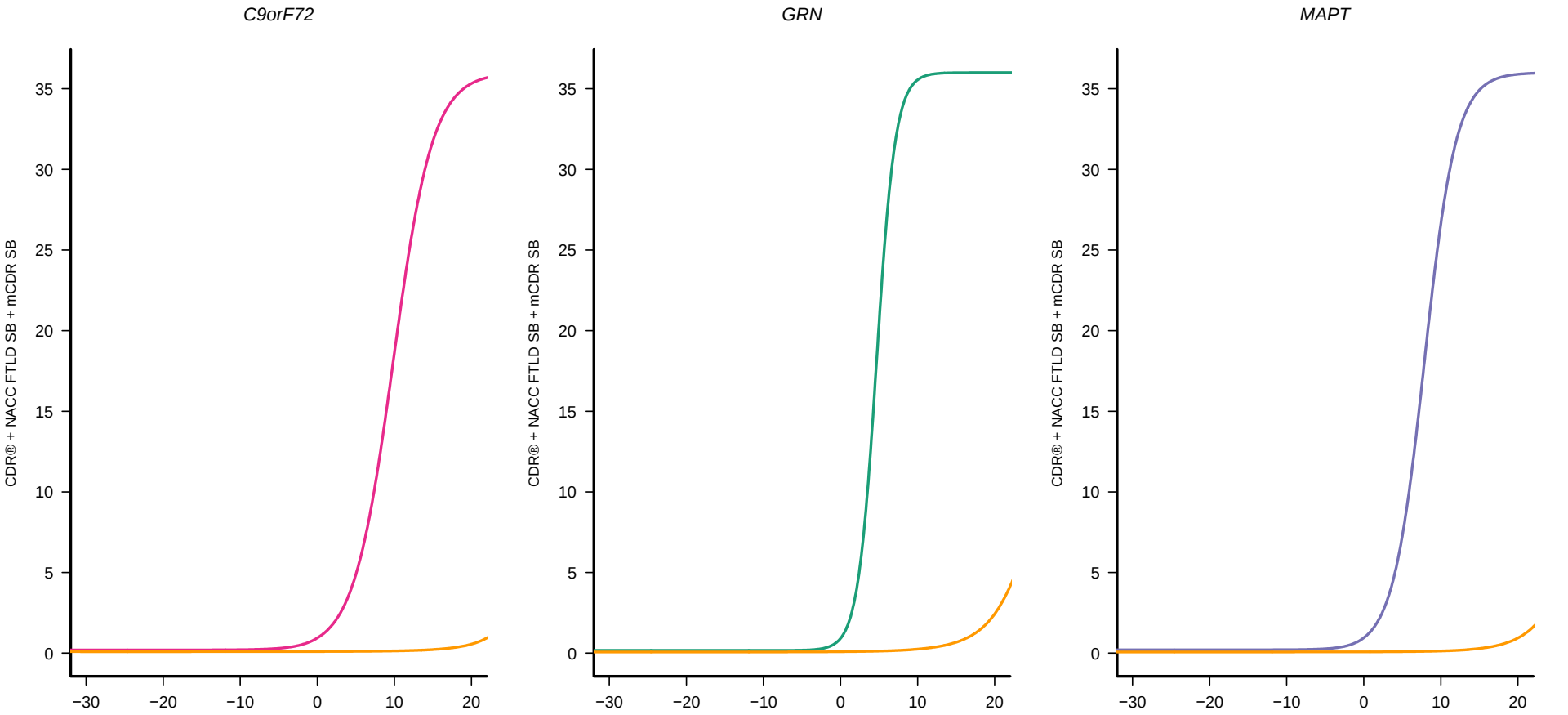


$$Y_{i,j,k} = \left(\delta_{0,k,m_i} + \delta_{0,k,i}\right) + \frac{\delta_{1,k} - \delta_{0,k,m_i}}{1 + \exp\left(\theta_{k,m_i} + \gamma_i \beta_{k,m_i} \left[\min\left(\Delta_{k,m_i}, D_{i,j}\right) + \delta_{k,m_i} \max\left(0, D_{i,j} - \Delta_{k,m_i}\right)\right]\right)} + \varepsilon_{i,j,k}$$

Subject-specific multiplicative adjustment to rate of progression

Endpoint and mutation-specific change-point

Endpoint and mutation-specific multiplicative change in rate of progression after the change point


C9orF72
GRN
MAPT
CDR® + NACC FTLD SB + mCDR SB
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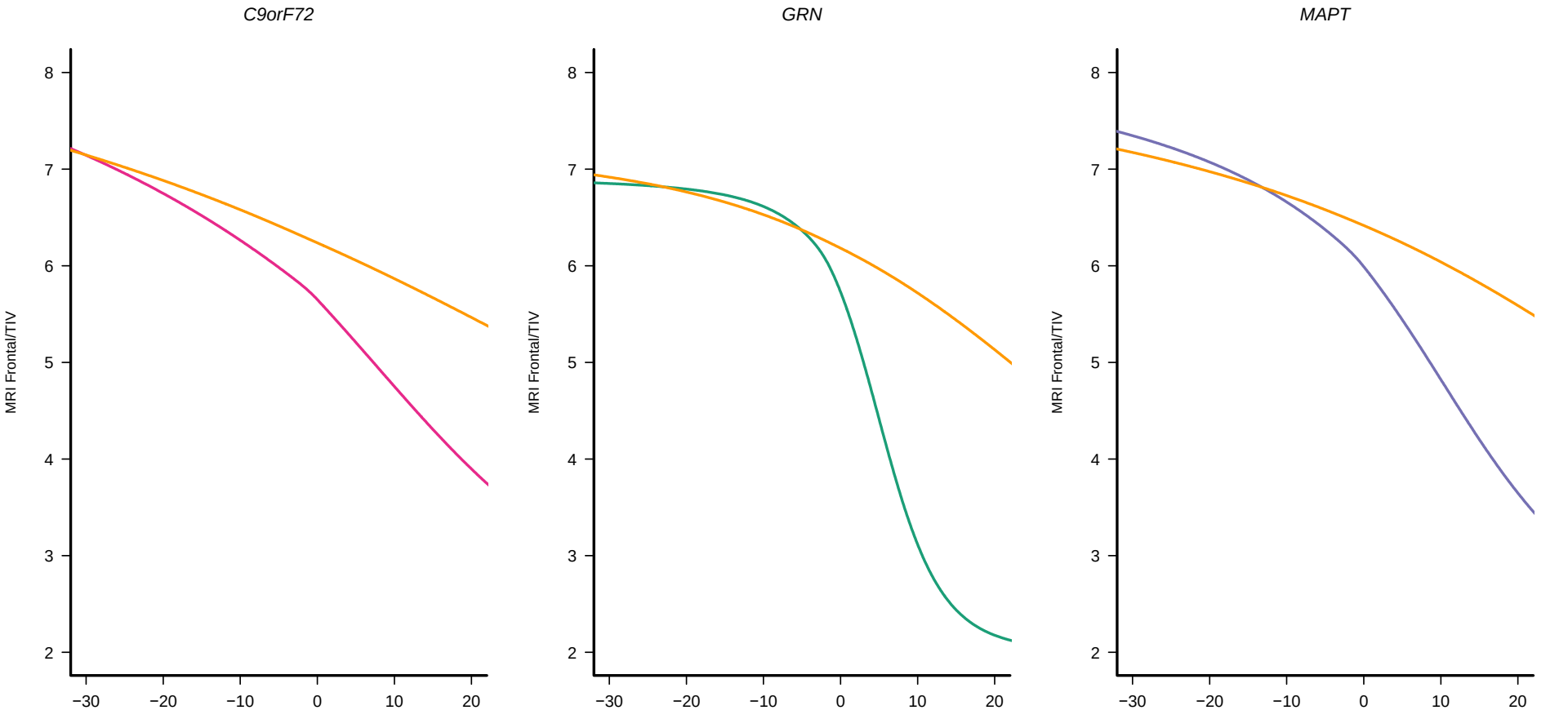
C9orF72
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MAPT
MRI Frontal/TIV
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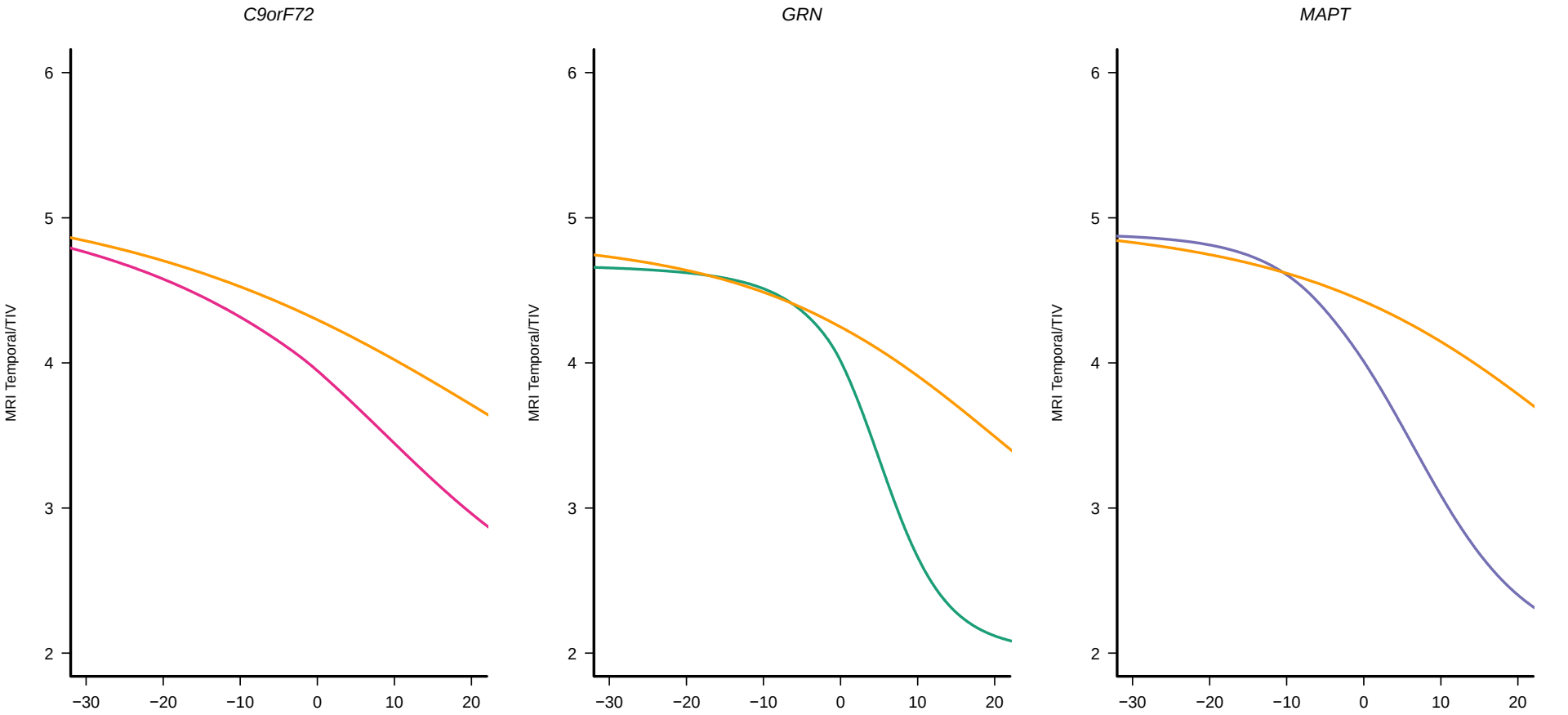
C9orF72
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MAPT
MRI Temporal/TIV
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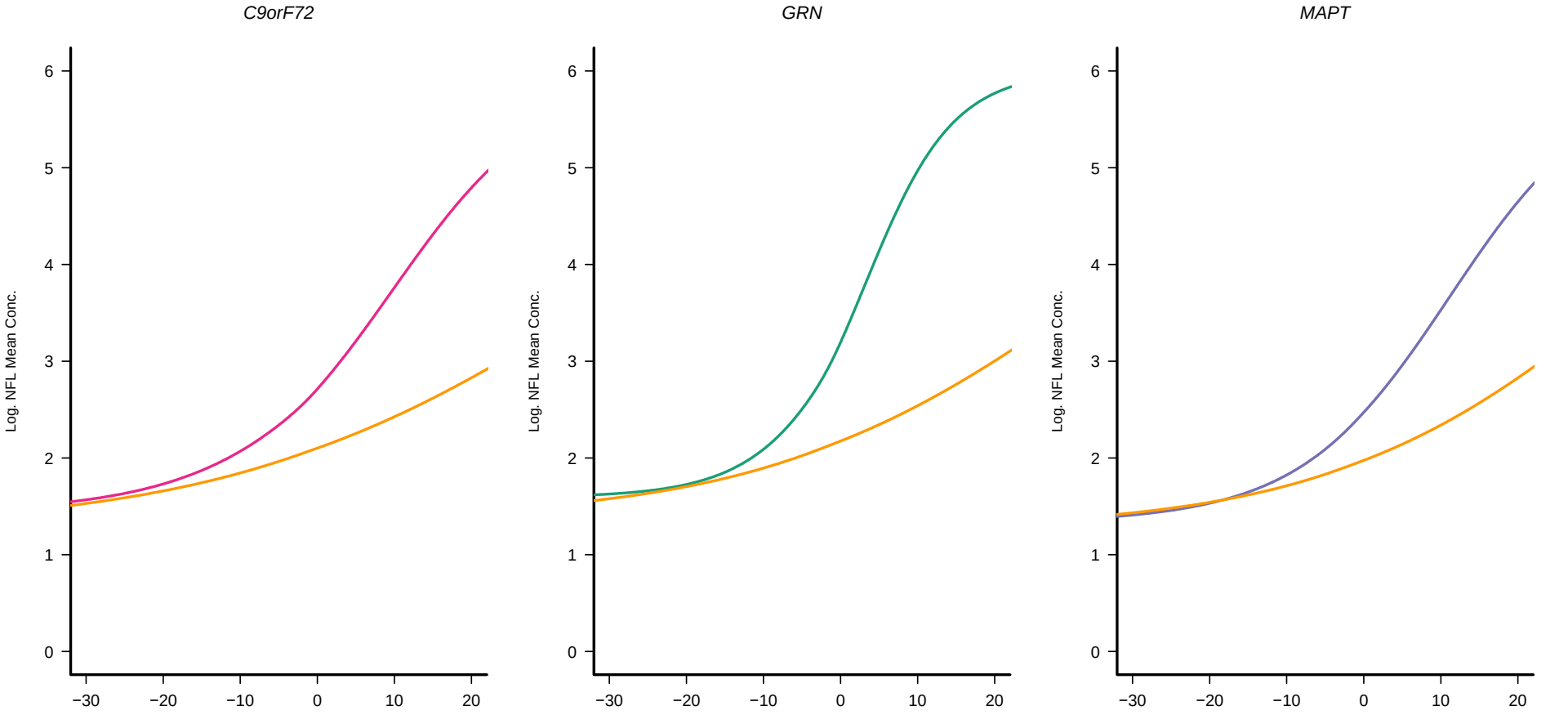
C9orF72
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MAPT
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Log. NFL Mean Conc.
Log. NFL Mean Conc.
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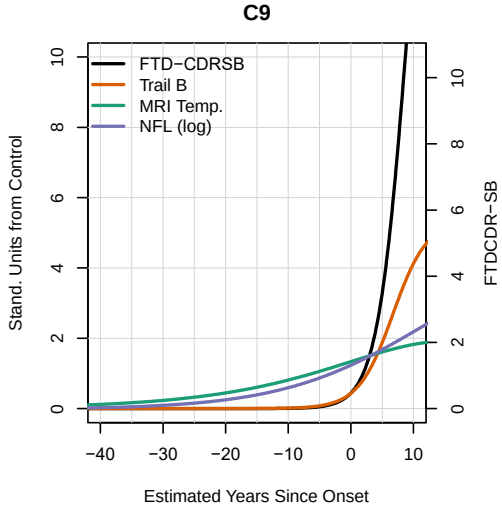
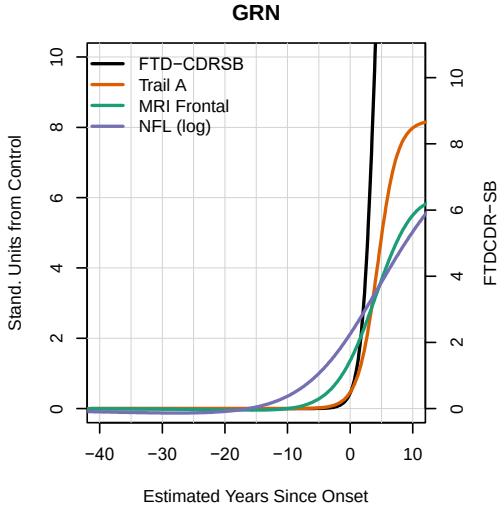
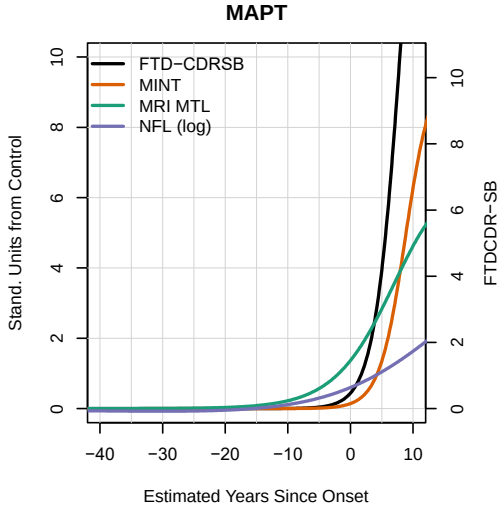
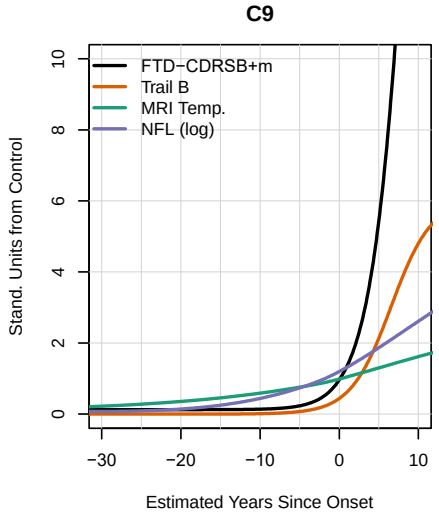
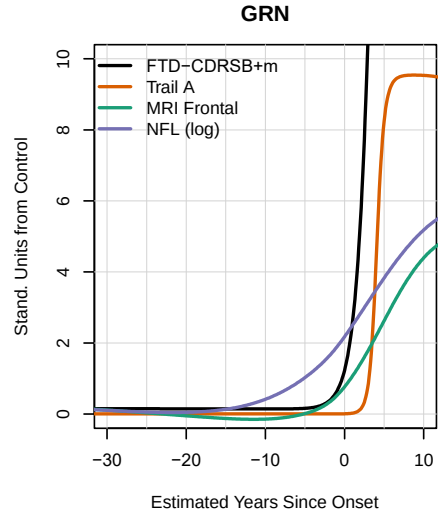
Current Results:
Change point +
Model separately per mutation

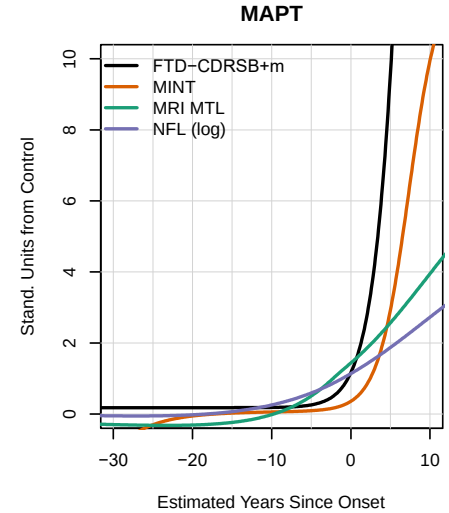




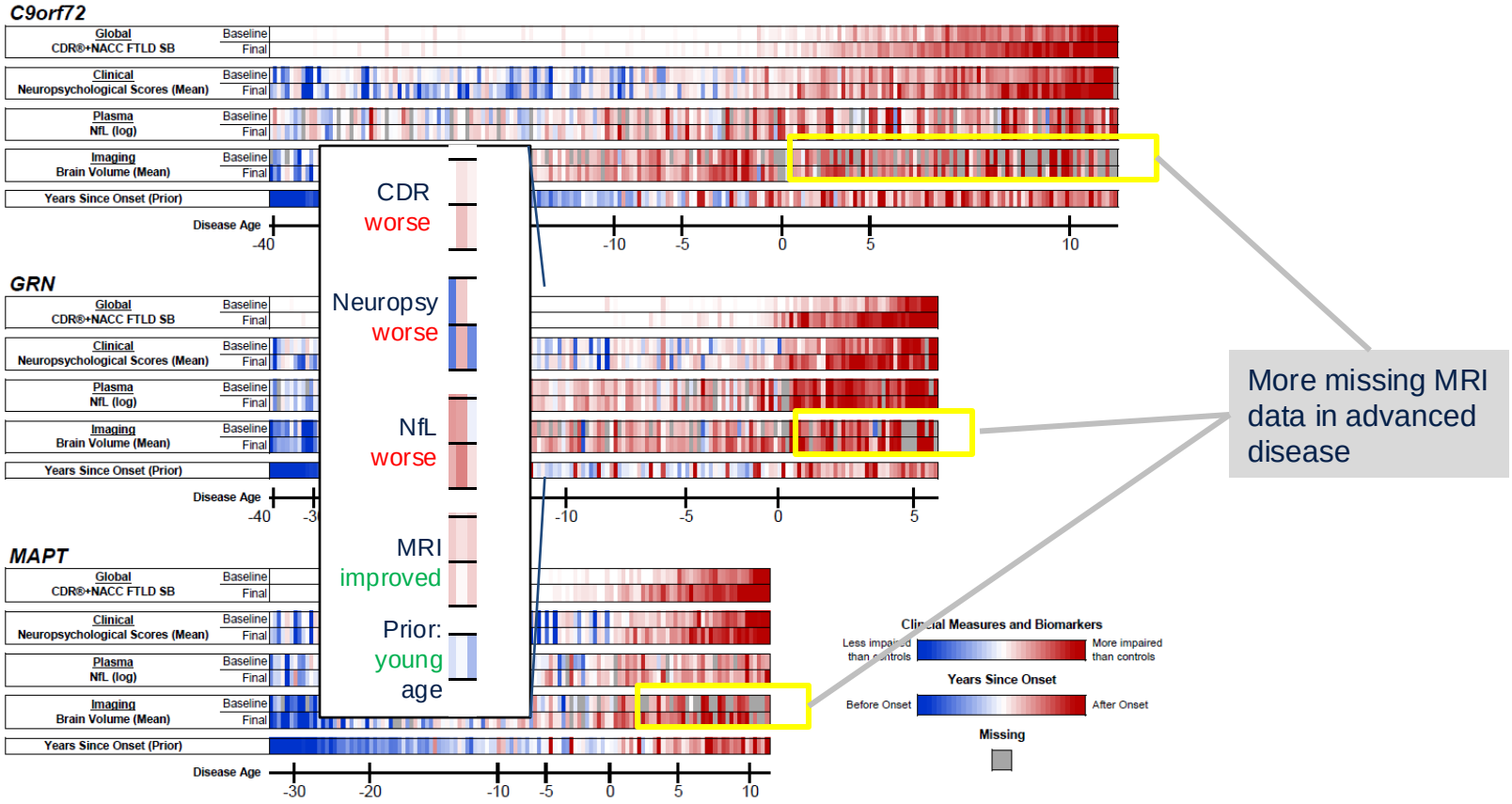








Clinical validation



Comments

- Are we asking too much of data?
- Within vs. between-subject trajectories?
- Validating predictions?
- Improved determination and/or definition of onset?

ALLFTD

ARTFL LEFFTDS Longitudinal Frontotemporal Lobar Degeneration

Investigators

Brad Boeve
Adam Boxer
Howard Rosen
Liana Apostolova
Brian Appleby
Sami Barmada
Ece Bayram
Megan Barker
Hugo Botha
Andrea Bozoki
David Clark
Ryan Darby
Gregg Day
Bradford Dickerson
Kimiko Domoto-Reilly
Julie Fields
Doug Galasko
Ralitza Gavrilova
Jill Goldman
Nupur Ghoshal
Neill Graff-Radford
Jon Graff-Radford
Ian Grant
Murray Grossman
Matt Hall
Robin Hsiung
Edward Huey
David Irwin
David Jones
David Knopman
Maria Lapid
Suzee Lee
Gabriel Leger
Irene Litvan
Peter Ljubenkov
Diane Lucente
Ian Mackenzie
Joseph Masdeu
Lauren Massimo
Scott McGinnis
Mario Mendez
Chiadi Onyike
Alex Pantelyat
Belen Pascual
Hank Paulson
Peter Pressman
Vijay Ramanan
Katherine Rankin
Katya Rascovsky
Aaron Ritter
Julio Rojas-Martinez
Erik Roberson
Rodolfo Savica
Adam Staffaroni
Campbell Sullivan
Carmela Tartaglia
Philip Tipton
Ren VandeVrede
Sandra Weintraub
Dylan Wint
Bonnie Wong
Zbignew Wszolek

Management

Hilary Heuer
Leah Forsberg

DMS Core

Walter Kremers
John Kornak
Nellie Brushaber
Noah Johnson
Tyler Kolander
Carly Mester
Dianna Wheaton
Sweatha Reddy

Biofluid Core

Len Petrucelli
Adam Boxer
Anne Fagan
Tania Gendron
Argentina Lario Lago

Genetics Core

Dan Geschwind
Rosa Rademakers
Marisa Da Silva Ramos

Neuroimaging Core

Kejal Kantarci
Howard Rosen
Denise Reyes
Kaely Thostenson

Neuropathology Core

Bill Seeley
Dennis Dickson
Ian Mackenzie

Mobile App

Adam Staffaroni
Jack Taylor
Amy Wise
Annie Clark
Masood Manoochehri
Sreya Danham

Data Sharing - NACC

Walter Kukull

Biospecimen Sharing - NCRAD

Tatiana Foroud
Kelley Faber
Corinne Kim

Image Sharing - LONI

Art Toga
Karen Crawford

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Ron Peterson
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Tony Phelps

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Katherine Brandt (chair)
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ALLFTD Funding Partners and Patient Advocacy Groups:

NIH National Institute on Aging — Turning Discovery Into Health

AFTD The Association for Frontotemporal Degeneration — FIND HELP·SHARE HOPE

FTD DISORDERS REGISTRY

BLUEFIELD PROJECT — Curing FTD

NIH National Institute of Neurological Disorders and Stroke

CurePSP — Foundation for PSP | CBD and Related Brain Diseases

Tau Consortium

alzheimer's association

Alzheimer's Drug Discovery Foundation