Washington University in St. Louis
School of Medicine

Longitudinal Biomarker Changes in Dominantly Inherited Alzheimer's Disease

Eric McDade DO
Assistant Professor of Neurology
Washington University at St. Louis
Associate Director
Dominantly Inherited Alzheimer Network Trials Unit

DIAN TU
Dominantly Inherited Alzheimer Network
Trials Unit

DIAN
Dominantly Inherited Alzheimer Network

Disclosures

- Research Funding
  - NIA (K23AG046363)
  - Anonymous Foundation
  - GHR
- Institutional Support
  - Eli Lilly
  - Hoffmann La-Roche
  - DIAN-TU Pharma Consortium
- Speakers engagements
  - Eli Lilly
  - Alzheimer Association

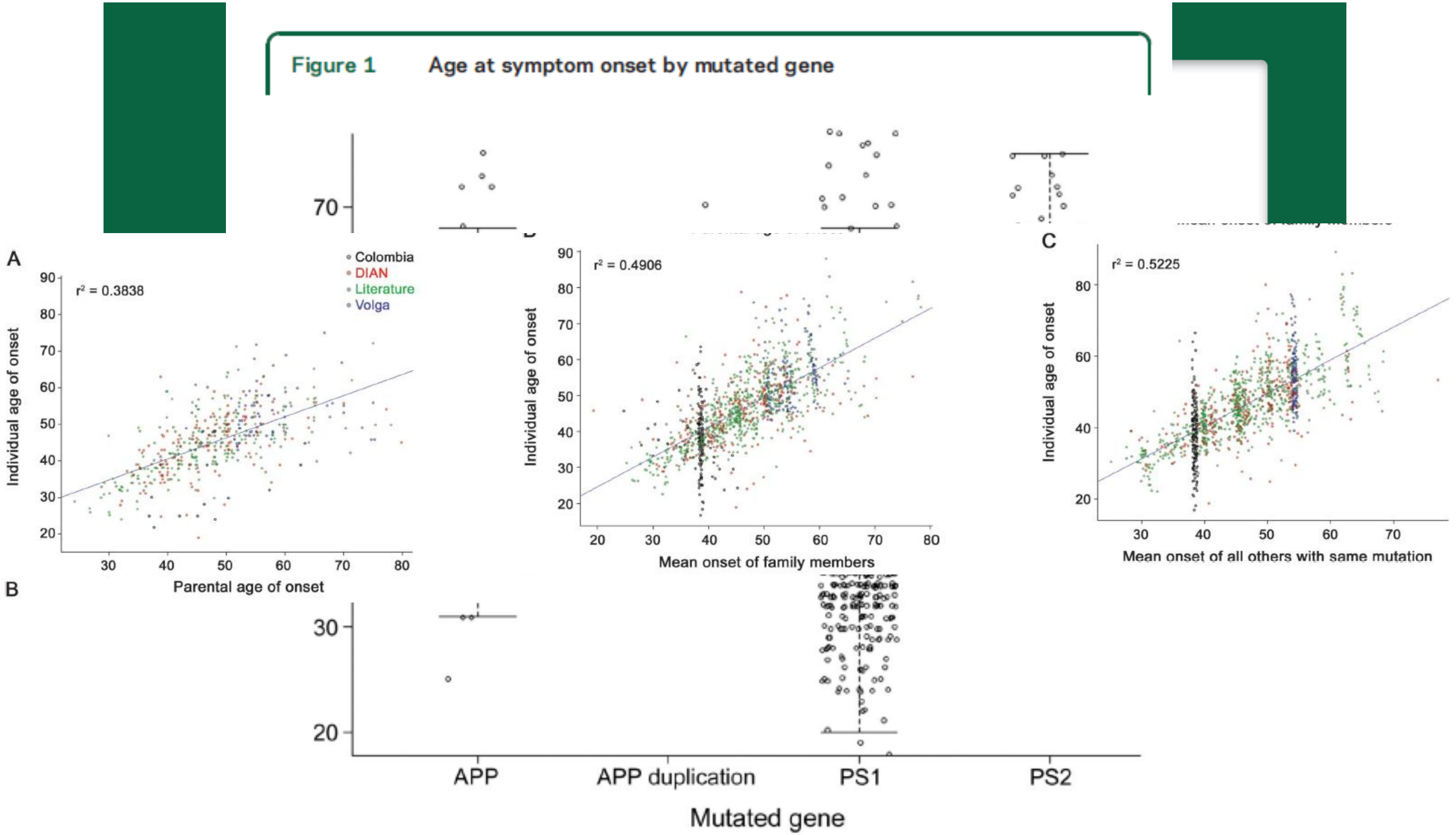
Dominantly Inherited AD as a Model for tracking disease progression

DIAN
Dominantly Inherited Alzheimer Network

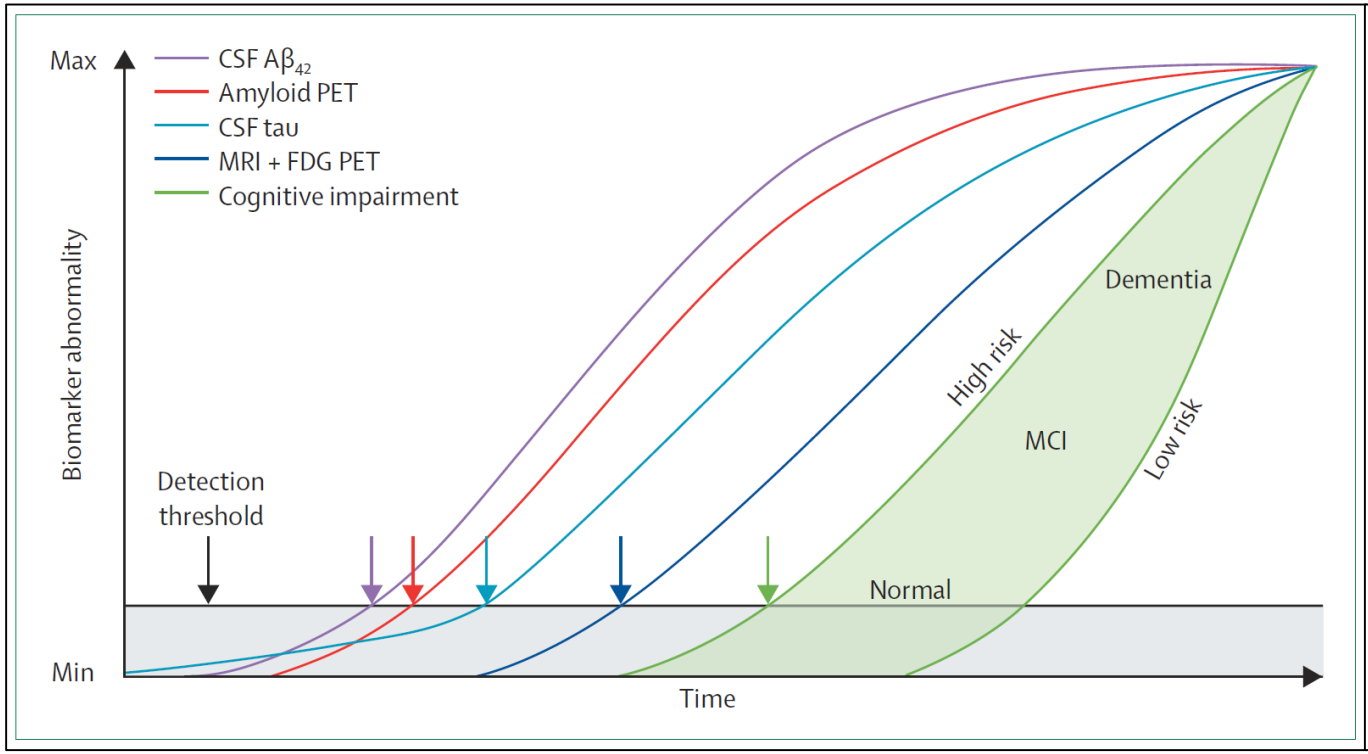
- Convergence across multiple mutations towards a single pathway
- Relatively predictable age of onset (anchor for longitudinal changes)
- Contemporaneously follow cohorts of various periods of time but align them based on anticipated age of onset or actual age of onset
- Younger age of onset= fewer comorbid contributors to clinical and biomarker changes

DIAN TU
Dominantly Inherited Alzheimer Network
Trials Unit

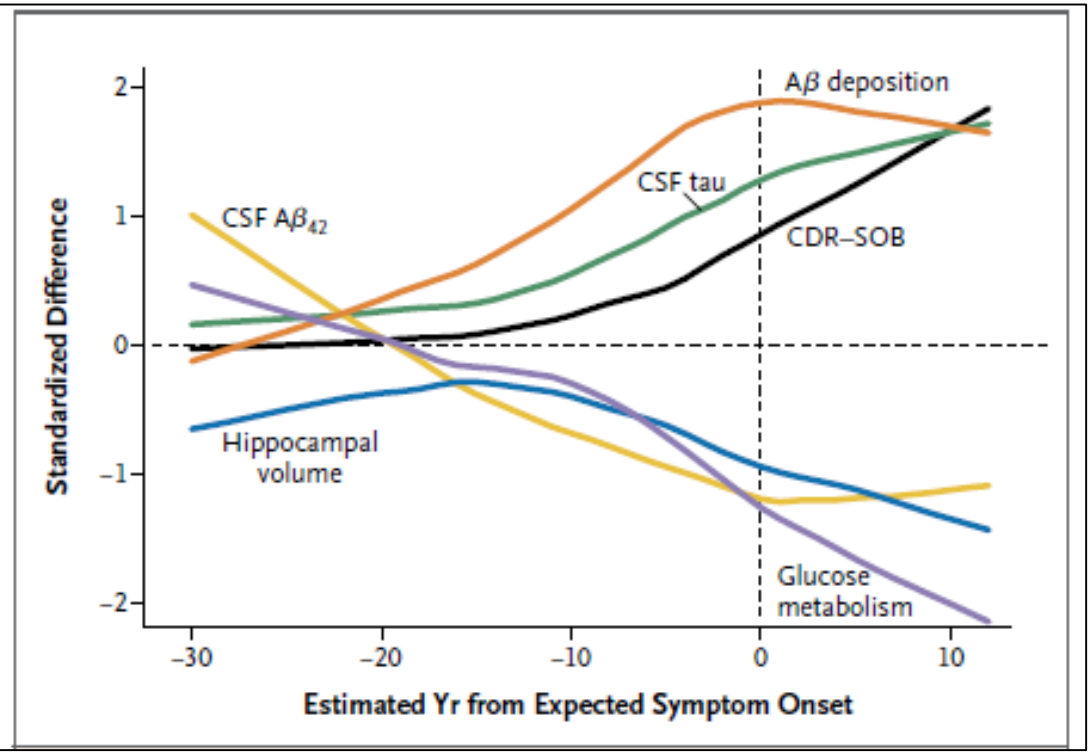
Figure 1 Age at symptom onset by mutated gene



Building a Model: Step 1 (cross-sectional)



Jack et al, 2013

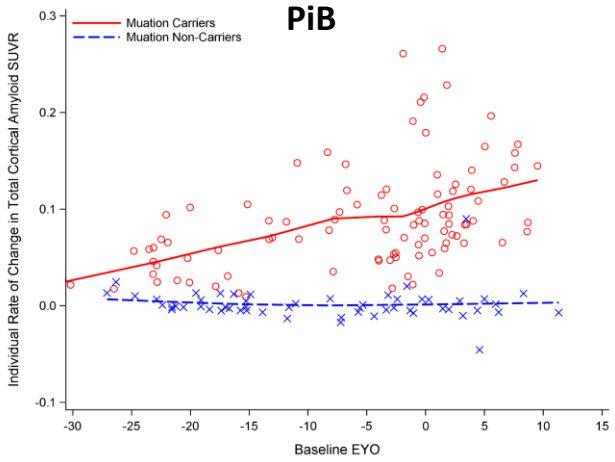


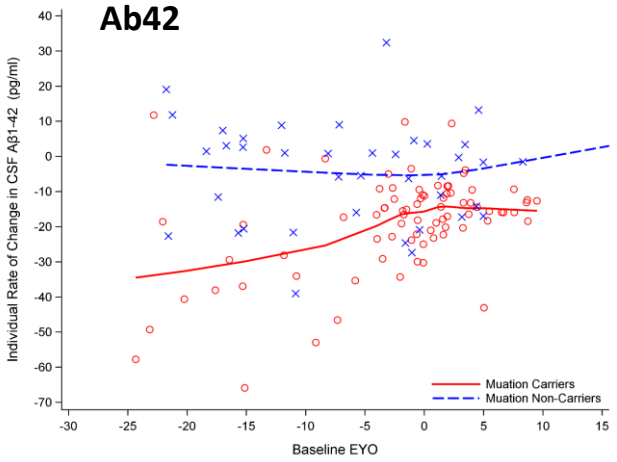
Bateman et al, 2012

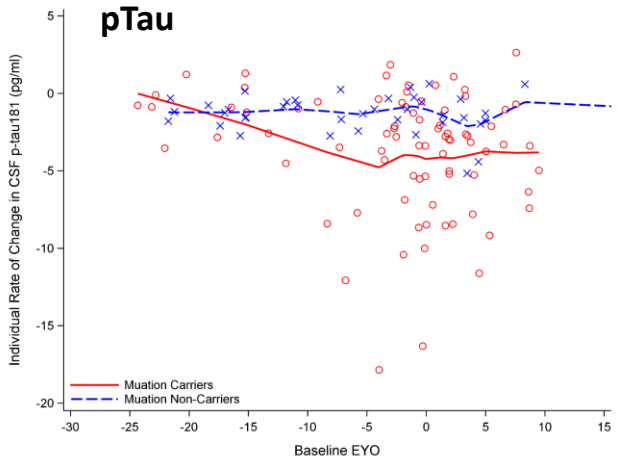
Building a Model: Step 2 (longitudinal)

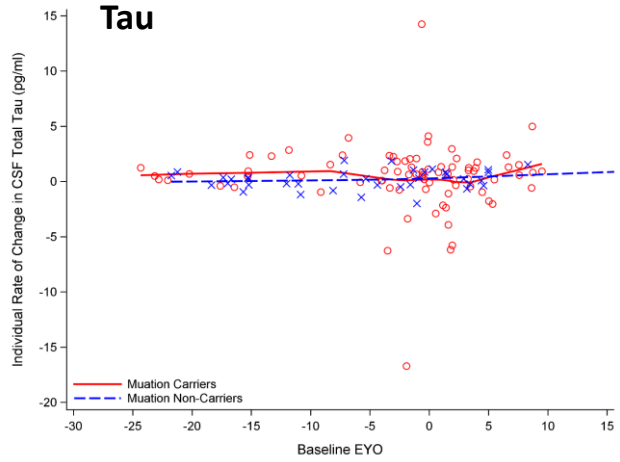
Clinical and baseline biomarker characteristics			
	Carriers (N=251)	Noncarriers (N=160)	P value
Age (yr), Mean (SD)	39.1 (11.1)	39.6 (11.5)	0.71
Female, N (%)	139 (55.4)	95 (59.4)	0.43
Education (yr), Mean (SD)	14.2 (3.1)	14.6 (2.9)	0.16
CDR >0	101 (40.2)	11 (6.9)	<0.0001
CDR 0	150 (59.8)	149 (93.1)	
Apolipoprotein ε4 carrier, N (%)	73 (29.1)	45 (28.1)	0.83
CSF Aβ42 (pg/ml), mean (SD)	334.9 (179)	546.6(143)	<0.0001
CSF P-tau$_{181}$ (pg/ml), mean (SD)	48.9 (28.9)	22.5(7.1)	<0.0001
CSF tau (pg/ml), mean (SD)	93.9 (47.1)	48.1 (15.5)	<0.0001
Amyloid PET Global SUVR, mean (SD)	2.01 (1.04)	1.06 (0.16)	<0.0001
FDG PET Precuneus SUVR, mean (SD)	1.82 (0.22)	1.90 (0.16)	<0.0001
Hippocampal volume (mm^3), mean (SD)	4124 (640)	4369 (396)	<0.0001
DIAN Cognitive Composite, mean (SD)	-0.69 (1.06)	-0.03 (0.60)	<0.0001
EYO (yr), mean (SD)	-7.9 (10.9)	-8.9 (11.7)	0.36

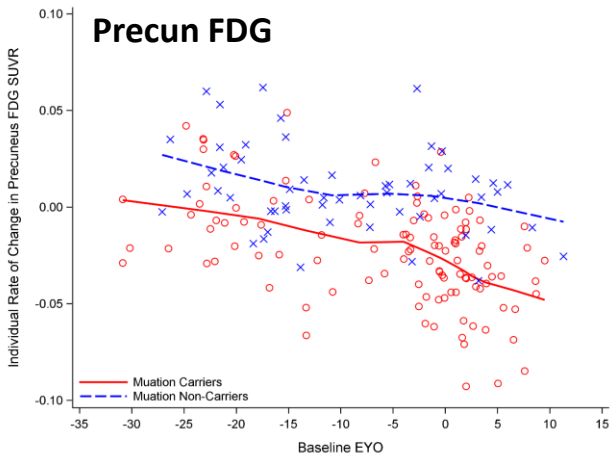
Longitudinal Biomarker and Clinical Changes in DIAN

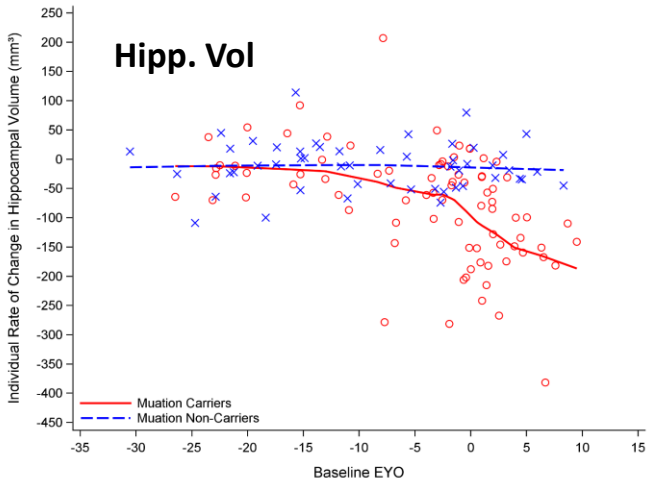


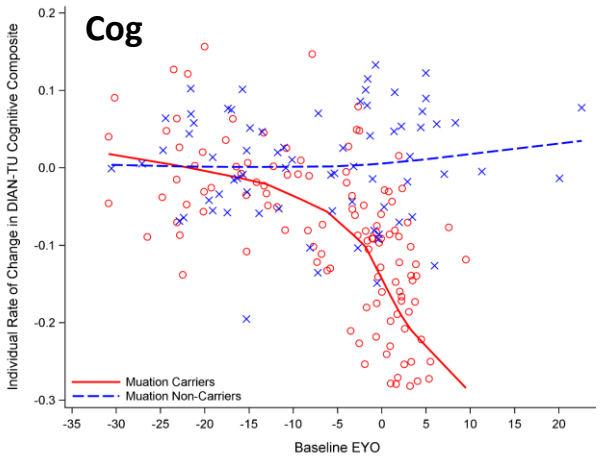


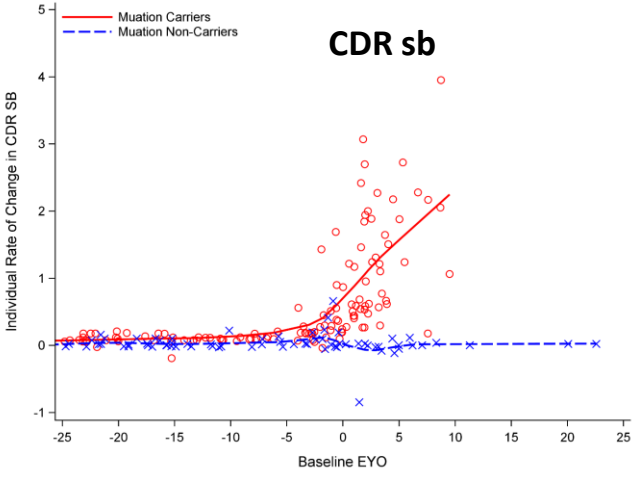




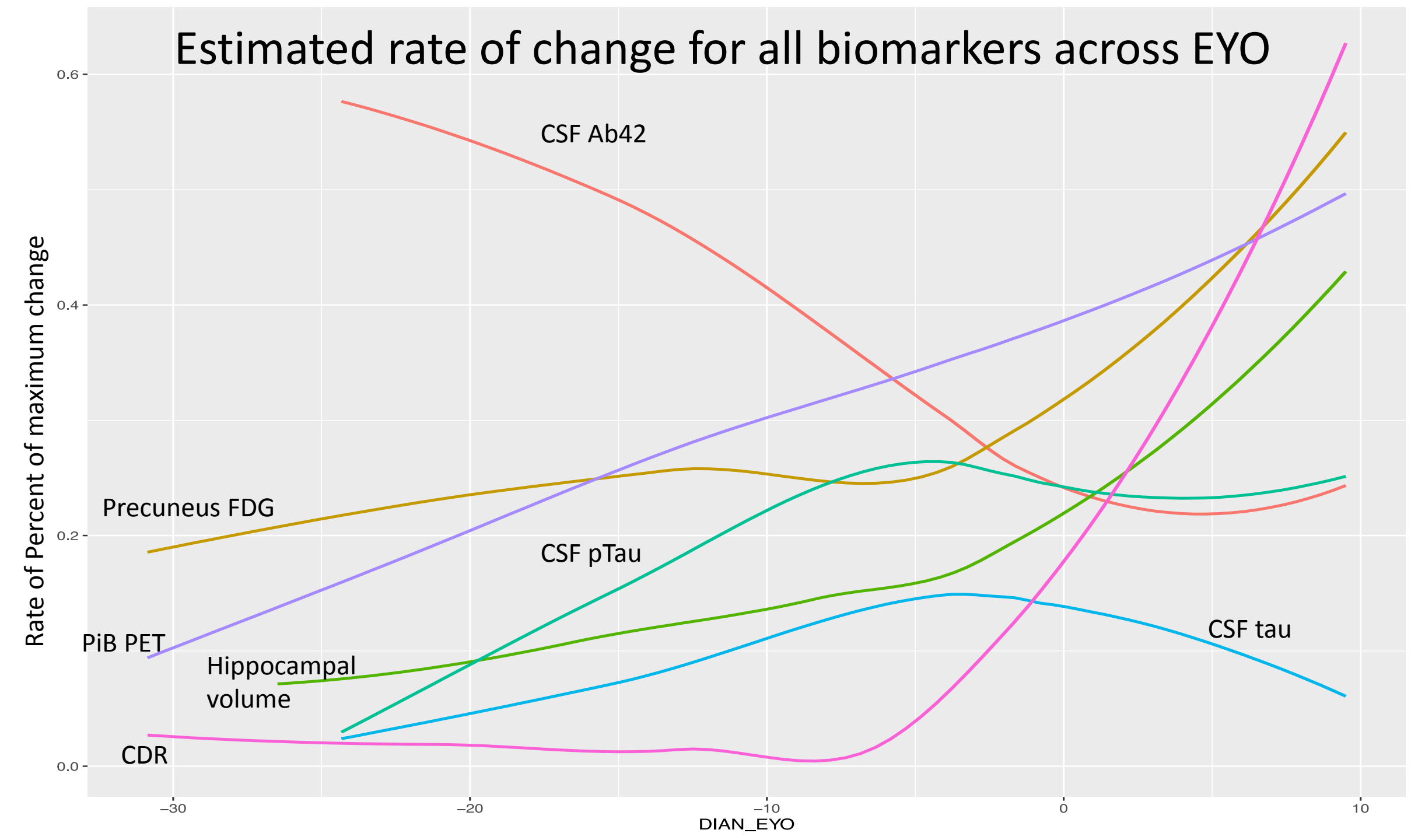








DIAN TU
Dominantly Inherited Alzheimer Network
Trials Unit


Estimated rate of change for all biomarkers across EYO
Rate of Percent of maximum change
0.6
0.4
0.2
0.0
CSF Ab42
Precuneus FDG
CSF pTau
PiB PET
Hippocampal volume
CSF tau
CDR
−30
−20
−10
0
10
DIAN_EYO

Longitudinal vs Cross-sectional

Outcome	EYO point of change	ROC* differs from 0 within (MC only), mean (95% CI)	EYO point of change	Difference in ROC between (MC- NC), mean (95% CI)	EYO point of change	Difference based on cross-sectional estimates (MC-NC), mean (95% CI)
CSF Aβ42	-25	-46.5 (-65.7, -27.2)	-25	-37.9 (-64.9, -10.9)	-10	-83.0 (-150.0, -16.1)
PiB- PET	-25	0.067 (0.029, 0.10)	-25	0.065 (0.006, 0.12)	-22	0.26 (0.03, 0.28)
FDG	-13	-0.012 (-0.023, -0.006)	-17	-0.022 (-0.043, -0.001)	-14	-0.048 (-0.089, -0.006)
CSF tau					-14	22.5 (2.5, 42.5)
Hippocampal volume (mm^3)	-13	-32 (-63,-2)	-10	-43 (-83, -4)	-12	-124 (-233, -16)
CSF p-tau	-3	-2.0 (-3.8, -0.2)	1	-3.3 (-6.3, -0.4)	-13	14.4 (1.1, 27.7)
CDR SB	?	0.18 (0.006, 0.35)	0	0.64 (0.27, 1.01)	0	0.72 (0.17, 1.27)
Cognitive composite	-3	-0.08 (-0.13, -0.02)	-2	-0.1 (-0.18, -0.02)	-3	-0.33 (-0.54, -0.12)

Conclusion

- Longitudinal based rates of biomarker changes provide a more dynamic estimate of the rate and order of changes in DIAD
- Beta amyloidosis remains the initial biomarker change
- Measures of neuronal function already begin to show decline up to 15-20 years prior to expected symptom onset
- CSF ptau may begin to decline significantly with the advancement of cortical tau progression

Acknowledgements

Randall Bateman
John Morris
Guoqiao (Peter) Wang

DIAN and DIAN-TU Teams

DIAN TU
Dominantly Inherited
Alzheimer Network
Trials Unit

DIAN
Dominantly Inherited
Alzheimer Network

DIAN and DIAN-TU Participants and families

DIAN-TU Sites

Australia

Neuroscience Research Australia, *William Brooks*
The McCusker Foundation, *Roger Clarnette*
Mental Health Research Institute, *Colin Masters*

Canada

McGill University, *Serge Gauthier*
UBC Hospital, *Robin Hsiung*
Sunnybrook Health Sci Centre, *Mario Masellis*

France

Hopital Roger Salengro, *Florence Pasquier*
Hopital Neurologique Pierre Wertheimer, *Maité Formaglio*
CHU de Rouen, *Didier Hannequin*
CHU de Toulouse, *Jérémie Pariente*
Groupe Hospitalier Pitie, *Bruno Dubois*

Italy

IRCCS Centro San Giovanni di Dio Fatebenefratelli, *Giovanni Frisoni*
Azienda Ospedaliera Universitaria Careggi, *Sandro Sorbi*

Spain

Hospital Clinic I Provincial de Barcelona, *Raquel Sanchez Valle*

United Kingdom

The National Hospital for Neurology & Neurosurgery, *Catherine Mummery*

United States

Columbia University, *Lawrence Honig*
University of Puerto Rico, *Ivonne Jimenez-Velazques*
Indiana University, *Jared Brosch*
University of Pittsburgh, *Sarah Berman*
Washington University, *Joy Snider*
University of Alabama, *Erik Roberson*
Butler Hospital, *Ghulam Surti*
Emory University, *James Lah*
Yale University, *Christopher Van Dyck*
UCSD, *Doug Galasko*
University of Washington, Seattle, *Suman Jayadev*

DIAN-TU Administrative and Clinical Operations Team

Randall Bateman – Director and PI, Eric McDade – Associate Director

Stephanie Belyew, Virginia Buckles, David Clifford, Mary Downey-Jones, Kathy Fanning, Amanda Fulbright, Angela Fuqua, Ron Hawley, Dottie Heller, Michelle Jorke, Denise Levitch, Jacki Mallmann, Tayona Mayhew, Susan Mills, John Morris, Katrina Paumier, Monique Romeo, Anna Santacruz, Jessi Smith, Annette Stiebel, Shannon Sweeney, Guoqiao Wang, Ellen Ziegemeier

DIAN-TU Cores

Administrative: Randall Bateman and team
Biomarkers: Anne Fagan and team
Biostatistics: Chengjie Xiong, Guoqiao Wang and team
Genetics: Alison Goate, Carlos Cruchaga and team
Imaging: Tammie Benzinger and team
Cognition: Jason Hassenstab and team

We gratefully acknowledge the DIAN and DIAN-TU participants and family members, DIAN Team, DIAN Steering Committee, Knight ADRC, Alzheimer's Association, ADAD Forum, NIH U01AG042791, NIH R01AG046179, DIAN-TU Pharma Consortium, GHR, Anonymous Foundation, Pharma Partners (Eli Lilly, Hoffman-LaRoche, Avid Radiopharmaceuticals, CogState), and Regulatory Representatives.

DIAN-TU Collaborators

Project Arm Leaders: Steve Salloway, Martin Farlow

Consultants : Berry Consultants, Univ. of Rochester – Cornelia Kamp, Cardinal Health Regulatory Sciences, Granzer Regulatory Consulting

DIAN-TU Therapy Evaluation Committee: Paul Aisen, Randall Bateman, Dave Clifford, David Cribbs, Bart De Strooper, Kelly Dineen, David Holtzman, Jeffrey Kelly, William Klunk, Cynthia Lemere, Eric McDade, Susan Mills, John Morris, James Myles, Laurie Ryan, Raymond Tait, Robert Vassar

DSMB Members: Gary Cutter, Steve Greenberg, Scott Kim, David Knopman, Allan Levey, Kristine Yaffe

ADCS: Ron Thomas and Paul Aisen

University of Michigan: Robert Koeppe

Mayo Clinic: Clifford Jack