Disclosure: Randall J. Bateman, M.D.

Sources of Research Support:
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NIH 3P-01-AG02627603S1 (FACS)
NIH 1U-01-AG03243801 (DIAN)
NIH ADRC (P50 AG05681-22)
NIH HASD (P01 AG03991-22)
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Alzheimer's Association, **American Health Assistance Foundation, Glenn Foundation, Ruth K. Broadman Biomedical Research Foundation, Anonymous Foundation**, Merck research collaboration

DIAN Pharma Consortium: AIP, Biogen, Eisai, Elan, Forum, Genentech, Lilly, Mithridion, Novartis, Pfizer, Roche, Sanofi
Companies: Co-founder C2N Diagnostics
Invited Speaker: BMS, Lilly, Merck, Pfizer, Elan, Wyeth, Novartis, Abbott, Biogen, Takeda Foundation
Editorial Duties: ad-hoc reviewer
Consulting Relationships: DZNE, IMI, Forum (SAB), Merck, Roche, Sanofi

Disclosure – Eric M. McDade, D.O.

Sources of Research Support: -
NIK K23AG046363

Alzheimer's Association, GHR Foundation, Anonymous Foundation

DIAN Pharma Consortium: Amgen, AstraZeneca, Biogen, Eisai, Elan, Eli Lilly, Forum, Genentech, Roche, Janssen AIP, Mithridion, Novartis Pharm AG, Pfizer, Sanofi-Aventis

Invited Speaker: Alzheimer Association
Consulting: American College of Physician (MKSAP18)

DIAD Family Conference
July 18th, 2015 AAIC, Washington, D.C.

- Historic, first-time meeting of DIAD families
  - 98 DIAD individuals and family members attended
  - a family networking opportunity
- Dialogue with researchers, pharmaceutical companies, foundations and donors, NIH, members of Congress and regulators (FDA, EMA).
- Discussions:
  - Scientific, medical, regulatory, advocacy and disease burden
  - Support sessions for asymptomatic and symptomatic individuals and their families
- Sponsored by the DIAN-TU and Alzheimer's Association
- "It is really cutting edge, and it is the right thing to do – the trial, the observational study……" Janet Woodcock, 2015 DIAD Family Conference, https://dian-tu.wustl.edu/en/2015-family-conference/

Next DIAD Family Conference:
July, 2016 AAIC, Toronto, Canada

2016 DIAD Family Conference

Too Young To Forget

Saturday, July 23rd, 8:00am-2:00pm ET

Fairmont Royal York Hotel (Ballroom) • Toronto, Ontario

Agenda Overview

- Family Presentations
- AD Research Updates (DIAN, DIAN-TU, field)
- Advocacy and Public Policy
- Panel Discussion
  - Advocacy and Pharma
  - Drug Re-purposing for AD
- Non-pharmacological & Pharmacological Approaches and Modifiable Risk Factors
- Caregiving and Long-Term Care
- Legal and Financial Matters
- Ethical Issues in Risk Disclosure
- Support Sessions

Family Presentation

Living with early onset AD

STATE OF ALZHEIMER DISEASE RESEARCH

Serge Gauthier, C.M., MD, FRCPC
McGill University Research Center for Studies in Aging
Douglas Mental Health University Institute
Montréal, Canada

DIAN TU
Dominantly Inherited Alzheimer Network Trials Unit

DIAN and DIAN-TU Update

Dominantly Inherited Alzheimer's Disease Family Meeting

July 23nd, 2016

Toronto, Ontario, Canada

Randall Bateman, M.D.
DIAN Trials Unit Director
Washington University School of Medicine

Washington University in St. Louis School of Medicine

DIAN Dominantly Inherited Alzheimer Network

Knight ADRC Alzheimer's Disease Research Center WASHINGTON UNIVERSITY ST. LOUIS

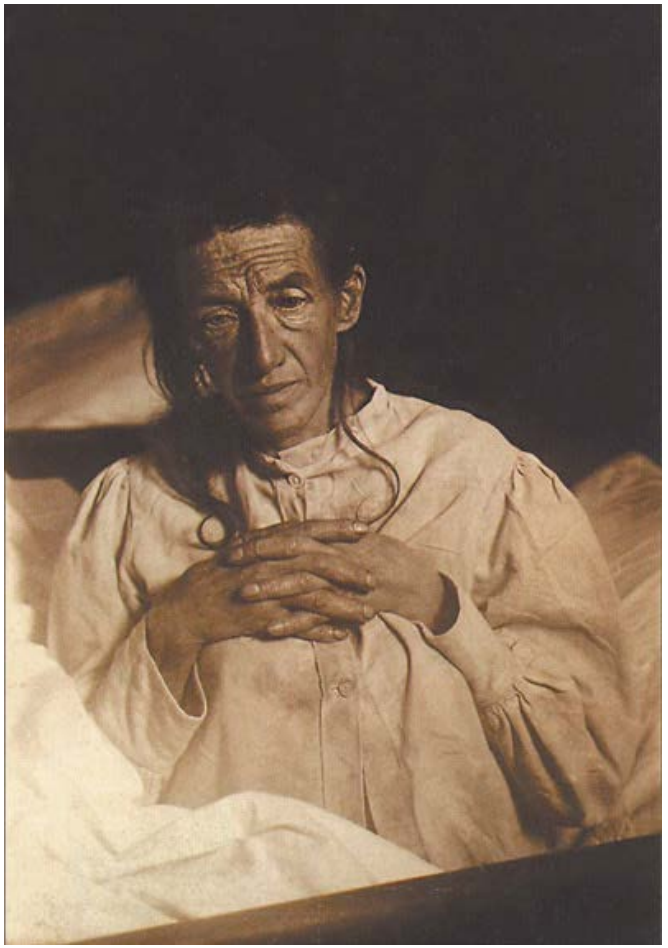
Dominantly Inherited Alzheimer's Disease

- A rare form of Alzheimer's disease
- Caused by an inherited gene mutation
- 50% chance of passing the gene to children
- Early onset
- Mutations cause predictable age of onset

Dominantly Inherited Alzheimer's Disease (DIAD)

- Less than 1% of AD cases result from autosomal dominant mutations in three genes directly involved in amyloid beta (Aβ) production
    - Amyloid precursor protein (*APP*)
    - Presenilin 1 (*PSEN1*)
    - Presenilin 2 (*PSEN2*)

- Auguste D., the first AD patient ever described by Alois Alzheimer, was later found to carry an DIAD mutation in presenilin 1 (F176L)



Participant Interaction and Partnership

DIAN Expanded Registry

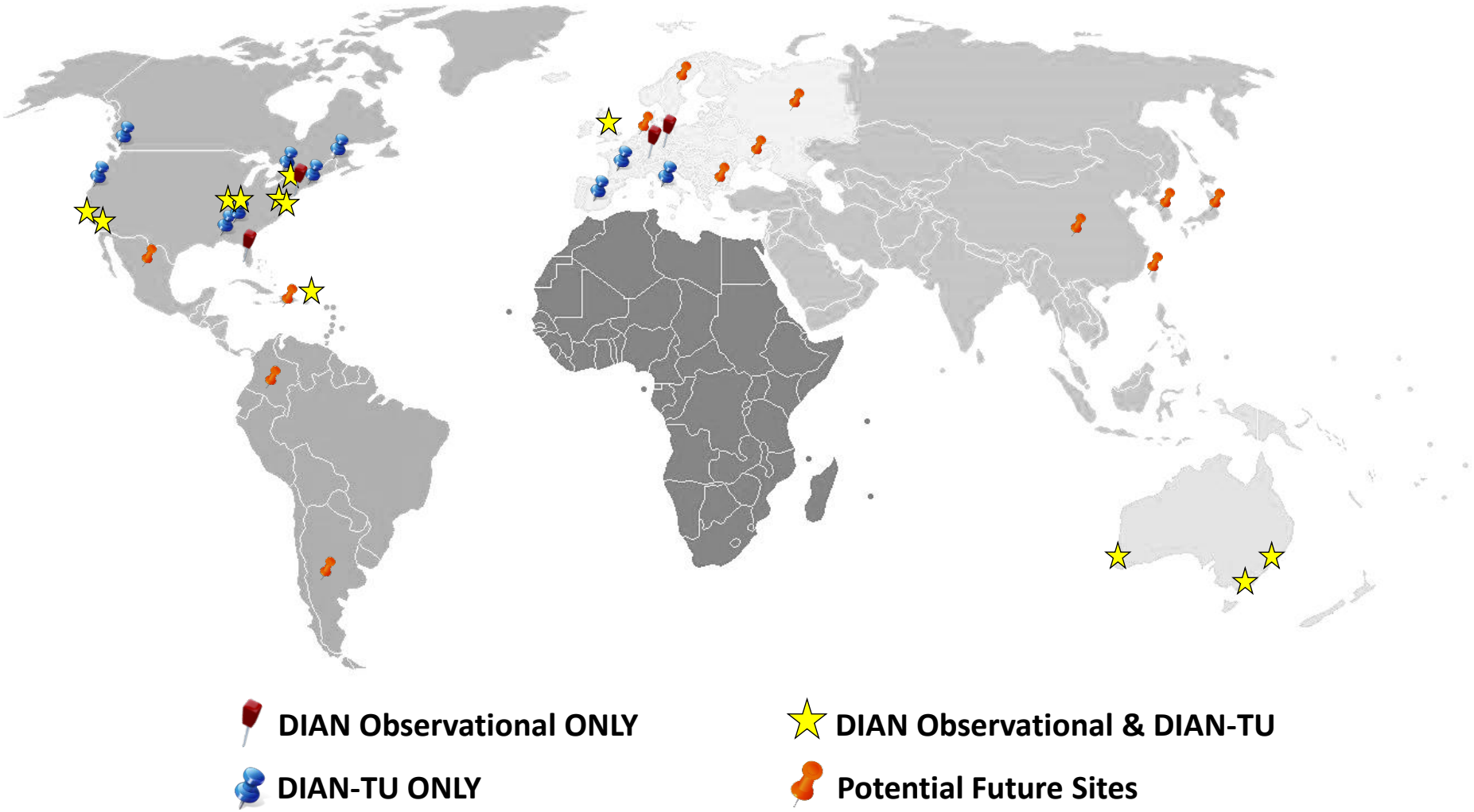
Serves as a key information and referral source for the DIAN Observational and DIAN-TU trials

Register: www.dianexr.org
Call: 1-844-DIAN-EXR (342-6397)
Email: dianexr@wustl.edu

DIAN
Dominantly Inherited Alzheimer Network

DIAN TU
Dominantly Inherited Alzheimer Network
Trials Unit

DIAN Observational and DIAN-TU Trial sites



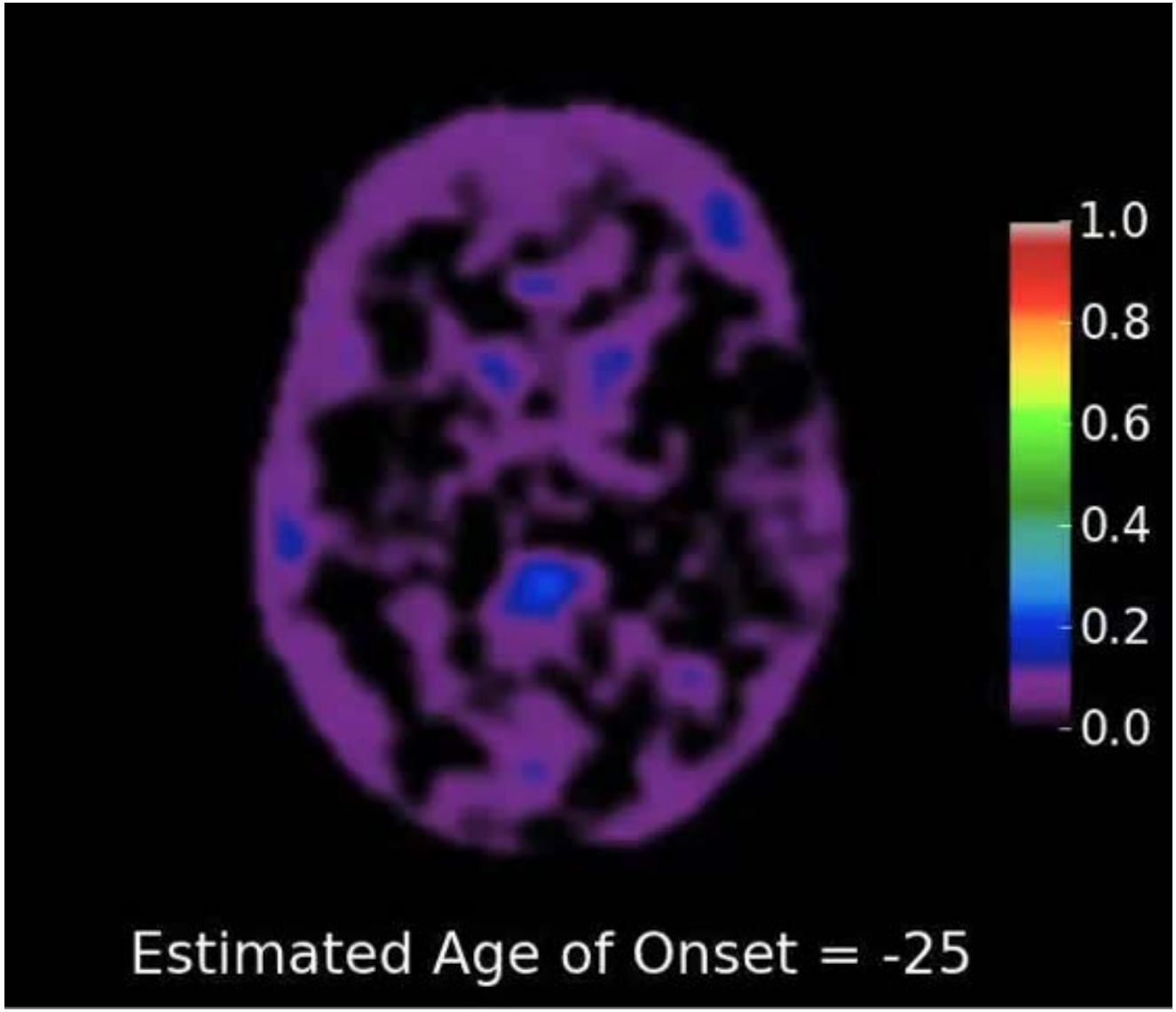
Dominantly Inherited Alzheimer Network (DIAN) Observational Study*

The DIAN Study is a multi-center, international, observational, longitudinal study of individuals with or at risk for autosomal dominant AD.

- The DIAN has currently enrolled more than **445 participants**
- **Site expansion in Argentina, Japan and Korea**
- Over 20 DIAN-related presentations at 2016 AAIC
- 20 journal publications in 2015

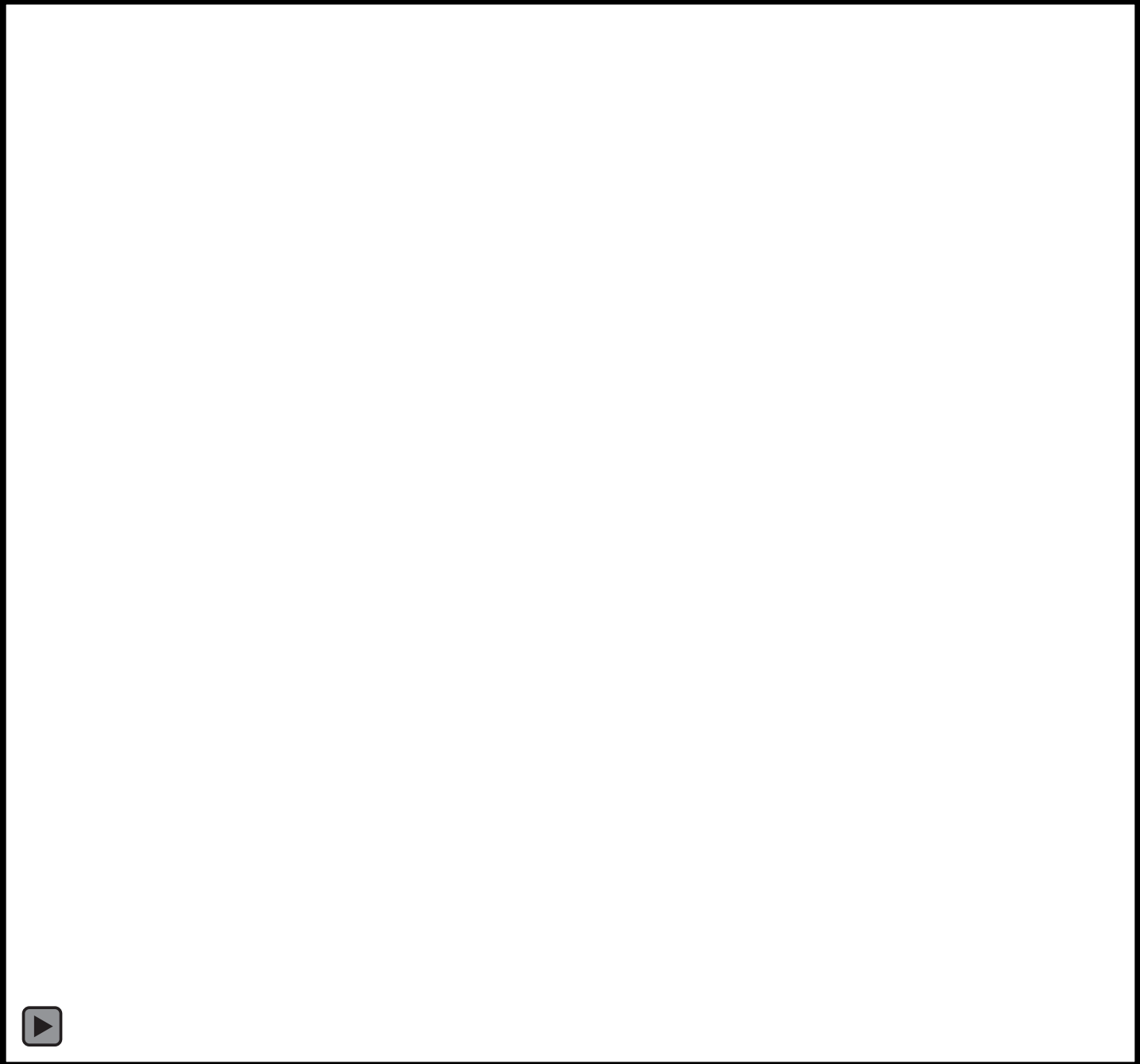
UF1 AG032438, RJ Bateman, PI; the German Center for Neurodegenerative Diseases (DZNE) completely supports German DIAN sites.

DIAN amyloid deposition by years to estimated age of onset



Courtesy of Tammie Benzinger; Bateman et. al NEJM 2012

Courtesy of Tammie Benzinger - DIAN



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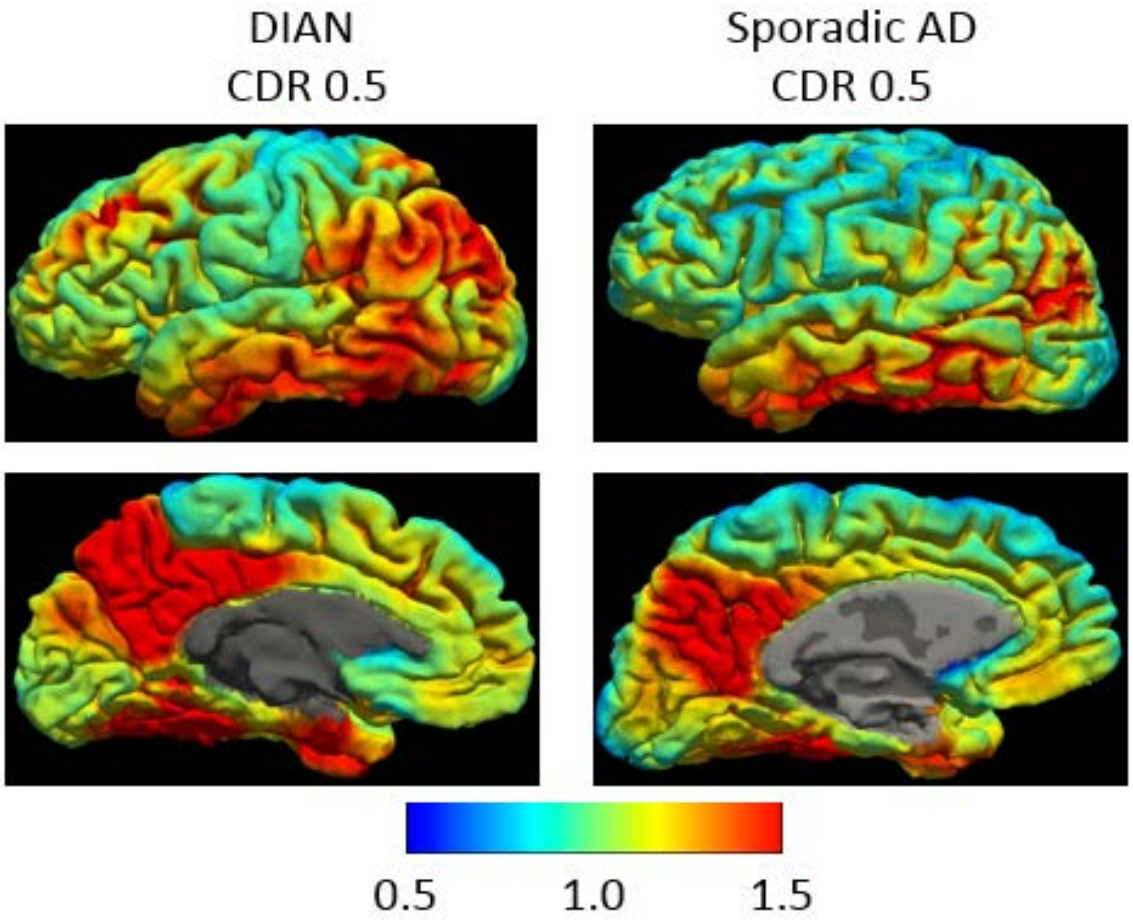
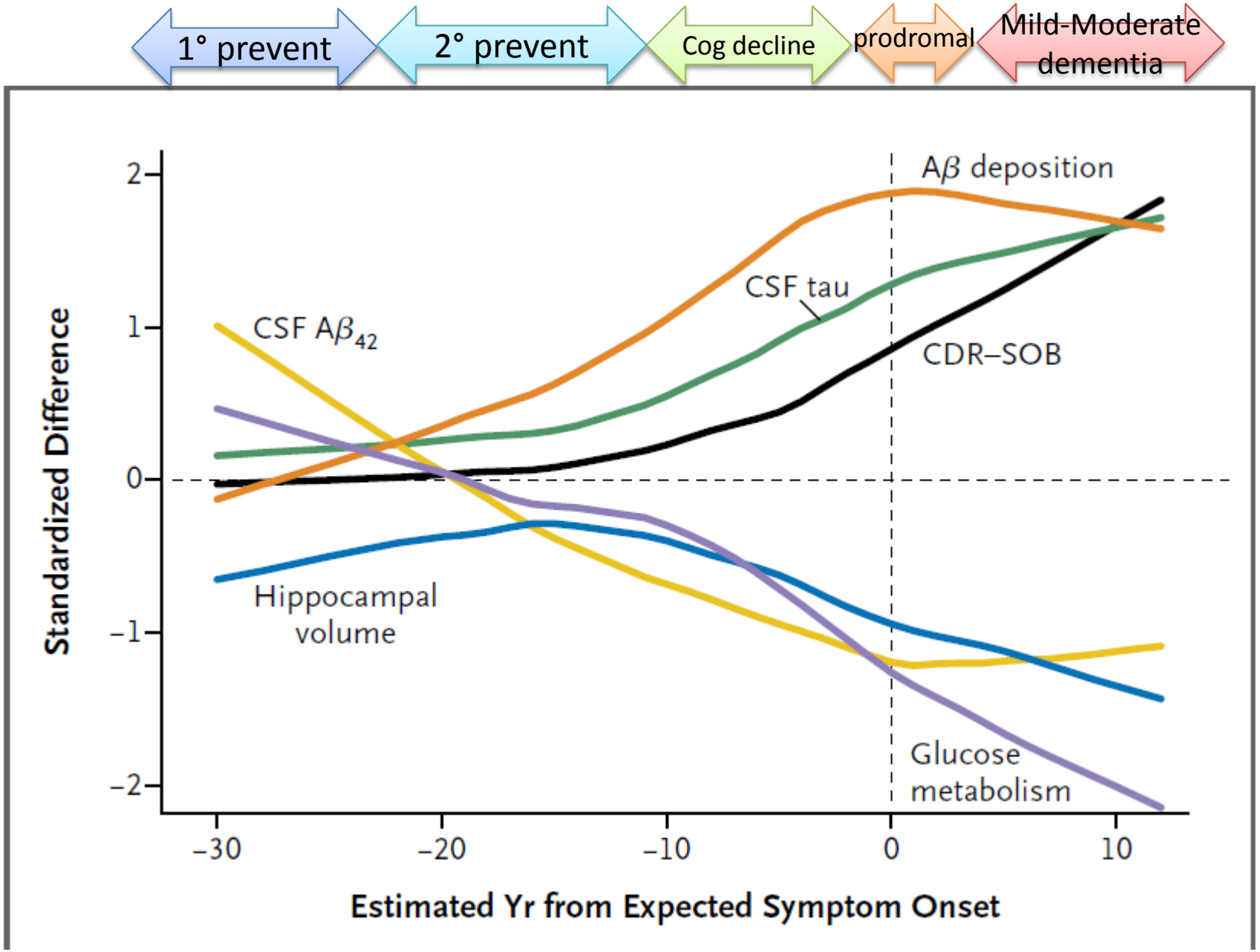
Trials Unit

Tau PET: DIAD and Sporadic AD



Progression of dominantly inherited AD



The DIAN; Bateman et. al NEJM 2012

Comparison of Autosomal Dominant and Sporadic Alzheimer's Disease

	Autosomal Dominant AD	**Sporadic AD**
Clinical presentation	Amnestic	Amnestic
Cognitive deterioration	Memory, frontal/executive, generalized cognitive decline	Memory, frontal/executive, generalized cognitive decline
MRI	Hippocampal atrophy and whole brain atrophy	Hippocampal atrophy and whole brain atrophy
PiB PET	Cortex **plus basal ganglia**	Cortex
FDG PET	Parieto-occipital hypometabolism	Parieto-occipital hypometabolism
CSF Aβ 42	Decreased by 50%	Decreased by 50%
CSF tau	Increased by 2-fold	Increased by 2-fold

DIAN Obs Impact on DIAN-TU Therapeutic Trials

- **Proof of principle:** DIAN studies can be performed globally to the highest standards
- **Trial development**: participation provides crucial data used to design and develop DIAN-TU trial
- **Novel mutations**: Enables families to be eligible for DIAN-TU trials

Through public/private support and partnership, the DIAN-TU has launched trials to provide advancement of treatments, scientific understanding and improvements in the approach to Alzheimer's disease drug developments.

alzheimer's association®

DIAN-TU Pharma Consortium

AMGEN® Pioneering science delivers vital medicines™

biogen idec

Eisai

FORUM PHARMACEUTICALS™

janssen PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Lilly

Roche Genentech A Member of the Roche Group

SANOFI

DIAN TU

Dominantly Inherited Alzheimer Network Trials Unit

NATIONAL INSTITUTE ON AGING

National Institutes of Health

U01 AG042791
R01 AG046179

***Financial support has also been provided by anonymous sources.**

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COGSTATE

NIH National Institutes of Health

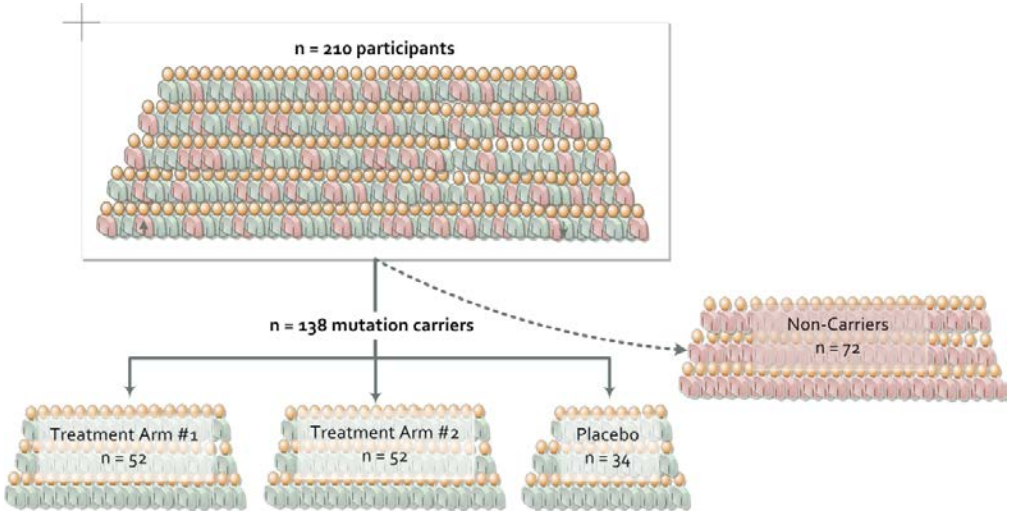
ACCELERATING MEDICINES PARTNERSHIP (AMP)

DIAN
Dominantly Inherited Alzheimer Network

Avid Radiopharmaceuticals

DIAN-TU-001 Trial

- Placebo controlled, **double-blinded**, cognitive outcome trial with biomarker interim analysis



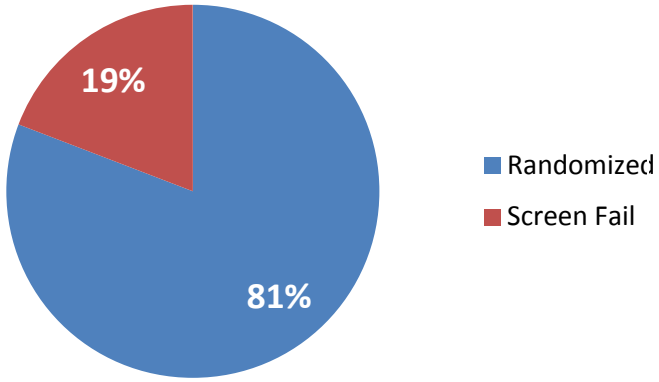
Three-arm trial:

Gantenerumab, Solanezumab, Pooled Placebo

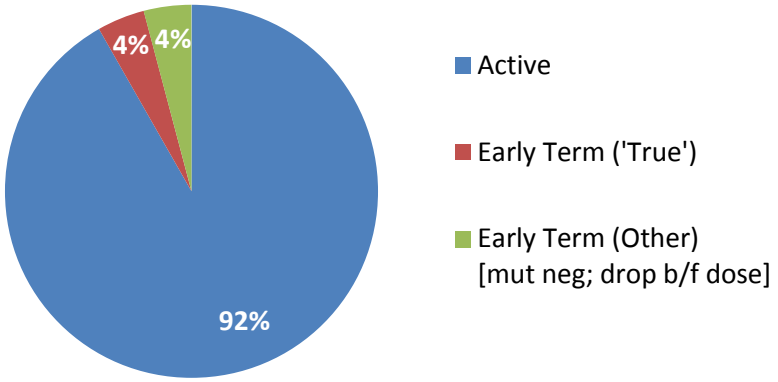
- ~210* enrolled to reach 138 mutation carriers (52 per active drug arm, 34 pooled placebo) **Estimated 72 non-carriers (placebo)*
- Drug treatment duration = **4 years** (2 years for biomarker endpoint with an additional 2 years for cognitive endpoint)
- ***Trial has now completed enrollment of all participants***

DIAN-TU-001: Current Status

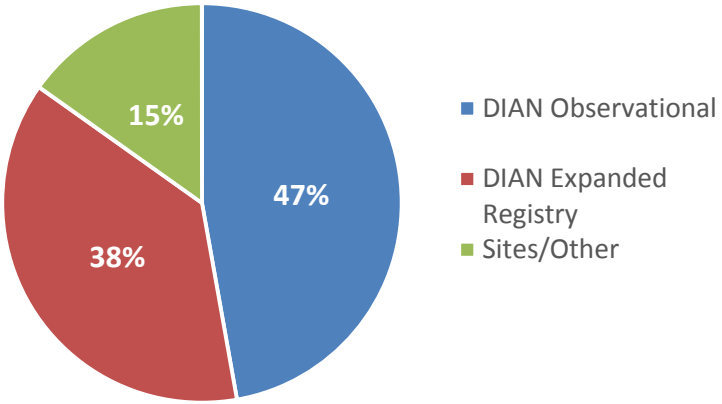
DIAN-TU-001 Enrollment Metrics



DIAN-TU-001: Participant Status



Recruitment Sources



DIAN-TU Trial Data

Test Measure		Assessments per participant	Quantity	Compliance Rate
Clinical Measures	CDR, CDR-SB, MMSE, FAQ, GDS, NPIQ	5	≈1000	**100%**
Cognitive Measures	CogState, Pencil / Paper	5-10	≈ 1000-2000	**99%**
Fluid Biomarkers	Plasma, Serum, CSF	4	≈ 800	**99%**
Imaging Biomarkers	PiB, AV-45, FDG	4	≈ 800	**99%**

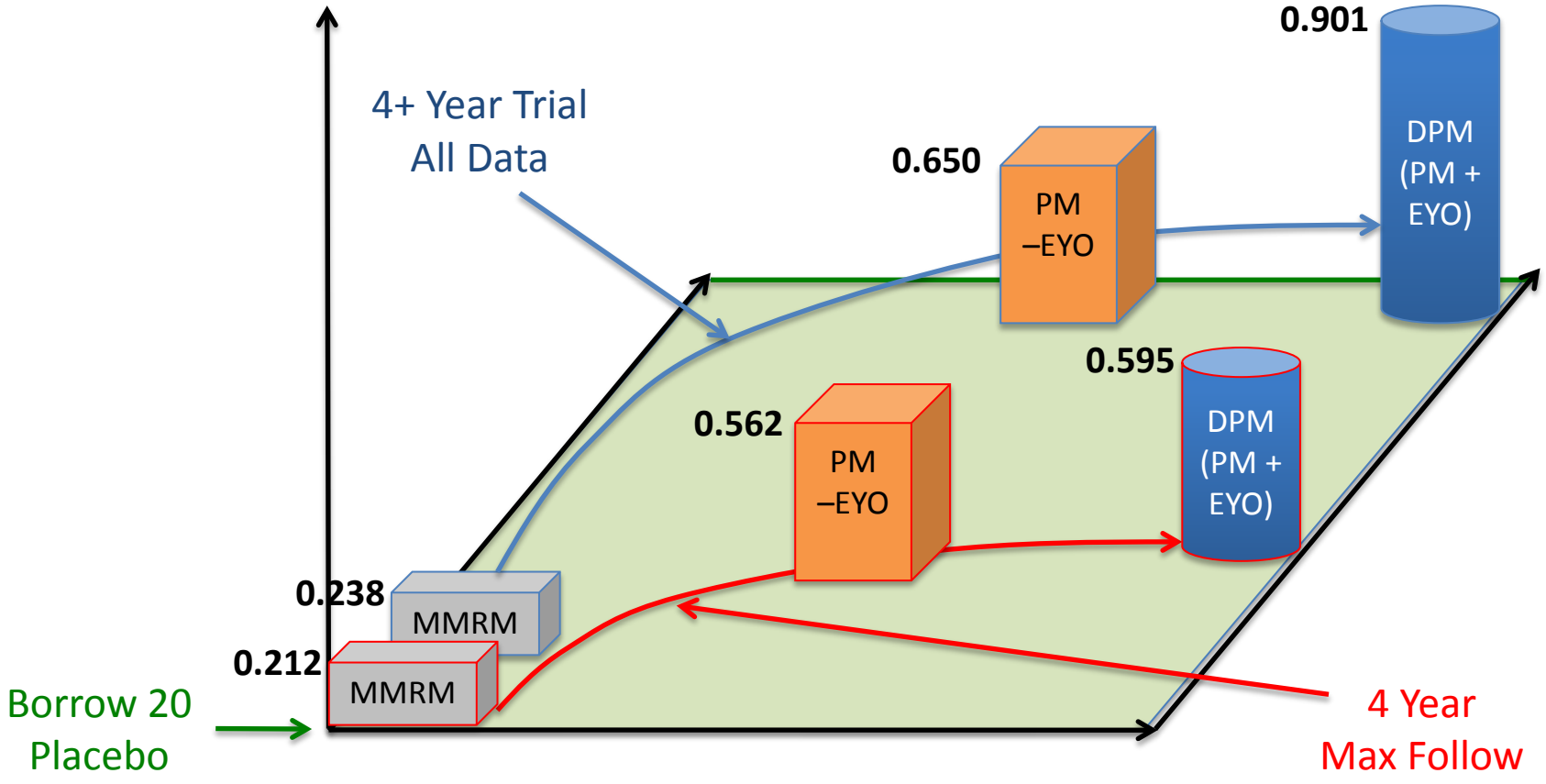
Imaging Modality / Tracer	Baseline	Year 1	Year 2	Year 4	Total # Scans
AV-1451	30	107	141	141	419

The Next Generation of DIAN-TU Trials (DIAN-TU NexGen)

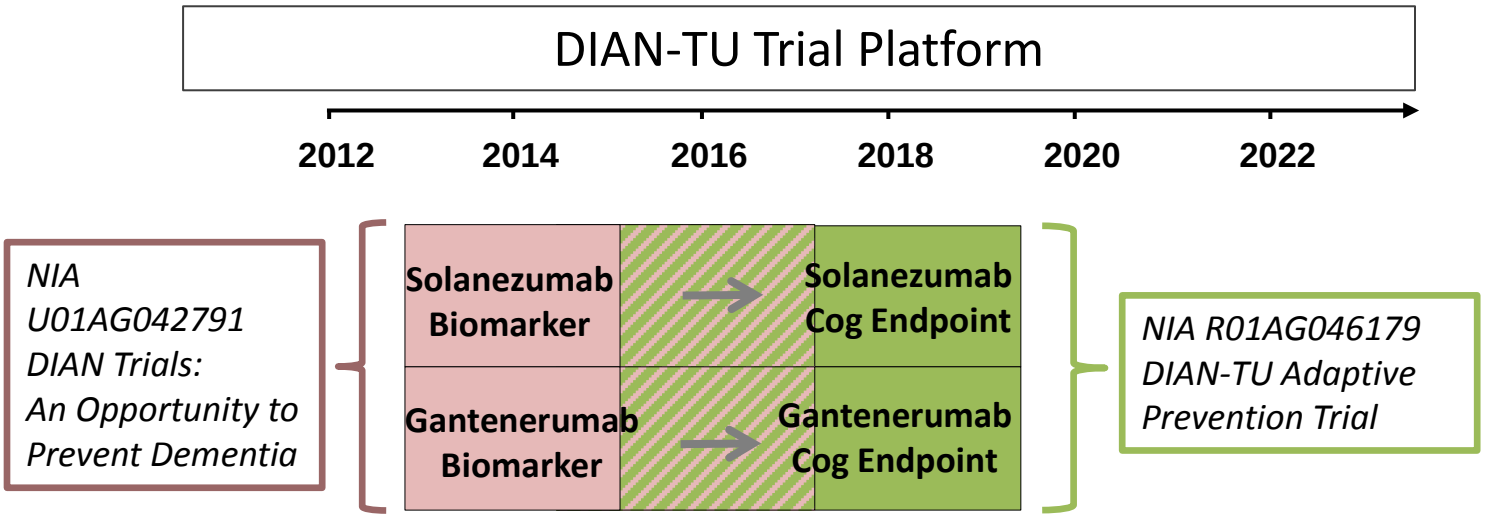
Goal: ***Accelerate identification and registration of effective drugs for prevention and treatment of AD***

- DIAN-TU Trial Platform
  - **Test multiple drugs in parallel** (efficient use of rare population with shared placebos)
  - **More rapidly determine efficacy or futility** using a DIAD Disease Progression Model
  - **Maximal dose**
  - Maximal collection and use of data
    - pooled placebo, minimizes numbers of placebo
    - Composite for cognitive endpoint (compared to single measures)
    - Home-based cognitive testing
    - Observational data
  - Develop surrogate biomarkers to accelerate future AD trials
  - *Future aim: combination therapy*

Power by Models/Design

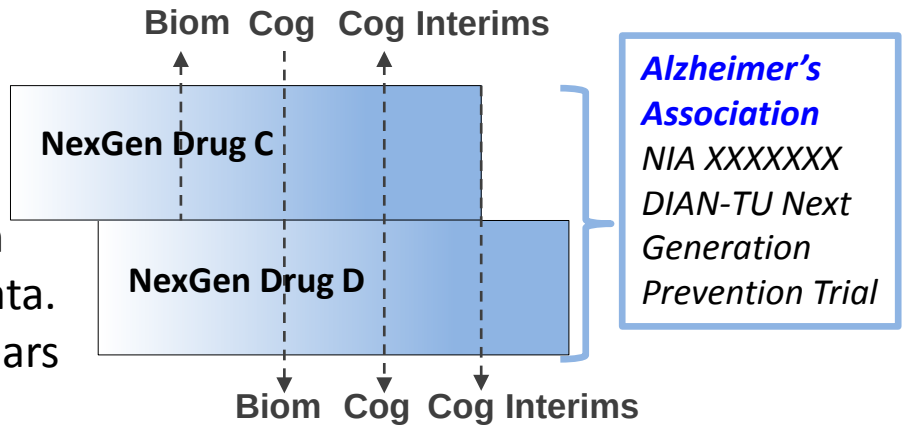


DIAN-TU NexGen Trial Design

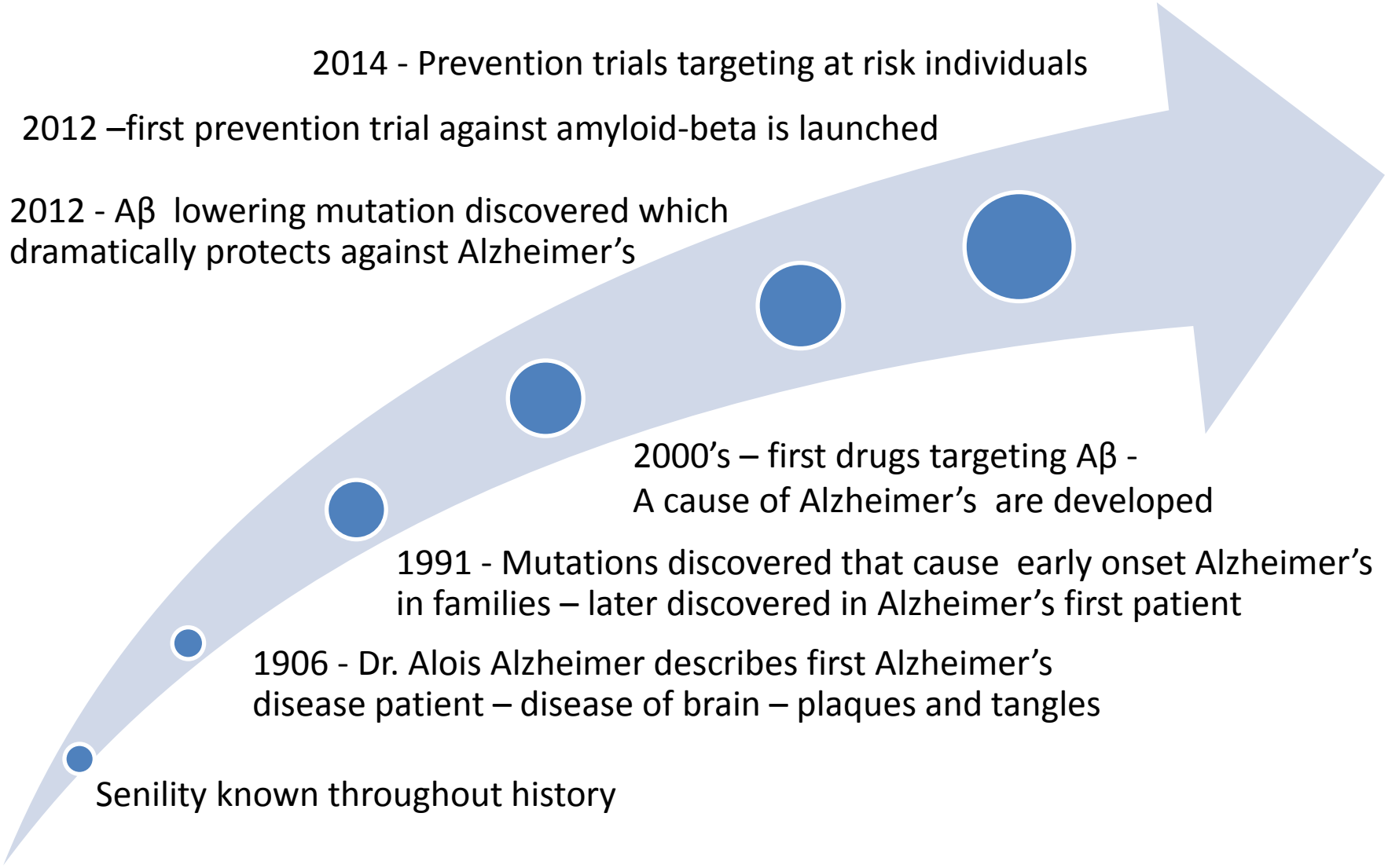


DIAN-TU NexGen:

- 2 new drug arms
- 4 years of treatment
- Uses DIAD-specific Disease Progression Model based on DIAN observational data.
- Cognitive interim analysis at 2 and 3 years
- Dose adjustment for maximal effect
- Home-based cognitive testing



A selected brief history of Alzheimer's disease modifying prevention



DIAN EXPANDED REGISTRY

Expanded Registry

- Single location to identify researchers and those with /at risk of DIAD
  - Coordination with registrants and DIAN sites
  - Coordination across large geographic regions
  - Outreach for communication
- Expand the identification of families with DIAD mutations
  - Evaluate families for risks consistent with DIAD
  - Identify new genetic mutations of DIAD
    - Expands access to DIAN-TU and DIAN Observation
- Increase awareness of DIAD
  - DIAD Family Conference

PRIMARY PREVENTION

Primary Prevention

DIAN
Dominantly Inherited Alzheimer Network

- DIAN-TU and other secondary prevention platforms are well established
- Population (>90% of recently surveyed stated they are willing to stay in trials > 5 years; majority agree that those >15 years before EYO should be able to be in trials)
- Improved understanding of temporal ordering of biomarkers (1st phase of primary prevention), particularly in DIAD
- Improved therapeutic target engagement (PK/PK & Safety)

Primary Prevention in DIAN-TU

- Challenges -
  - Duration of trial
  - Starting point
  - Design of intervention
  - Discussion of Industry perspective (previous experience) and Regulatory considerations

Primary Prevention

DIAN
Dominantly Inherited Alzheimer Network

- Next steps
  - Grant Funding for Start up
    - Trial design
    - Operational Considerations
    - Engagement of key partners
  - Wednesday June 27th, NexGen Meeting
  - CTAD San Diego, December 2016
- Interest from DIAN Steering Committee Members?

Discussion Points

- Importance of being in DIAN obs
- Open label extension
- DIAN-TU Primary Prevention trial
- Impact of potential positive readout of ongoing trials in sporadic Alzheimer's disease

The DIAN (NIH UF1AG032438)

The DIAN participants and family members

The Alzheimer's Association, ADAD Forum, DIAN Pharma Consortium

Admin – RJ Bateman

Clinical – JC Morris

Biomarkers – AM Fagan

Biostatistics – C Xiong

Genetics – AM Goate

Imaging – T Benzinger

Informatics – D Marcus

Neuropathology – NJ Cairns

<u>Performance Sites</u>

- **United States:** Washington Univ (Bateman), MGH/BWH (Sperling), Butler Hosp/Brown Univ (Salloway), Columbia Univ (Mayeux), Indiana Univ (Ghetti), UCLA (Ringman), U of Pittsburgh (Klunk), Mayo Clinic, Jacksonville (Graff-Radford), UCSD (Galasko)
- **Europe:** Institute of Neurology, Univ College London (Rossor), Ludwig-Maximilians-Universität München (Danek), University of Tübingen (Jucker)
- **Australia:** Prince of Wales Medical Research Institutes, Sydney (Schofield), Mental Health Health Research Institute, Melbourne (Masters), Edith Cowan Univ , Perth (Martins)
- **Japan**: DIAN-Japan (Mori): University Hirosaki (Shoji), Niigata (Ikeuchi), Tokyo (Suzuki), Osaka (Shimada)
- **Argentina**: Beunas Aires (Allegri) – FLENI
- **Korea**: DIAN-Korea (JH Lee): Asan Medical Center (JH Roh)

DIAN-TU Administrative and Clinical Operations Team

Randall Bateman – Director and PI

Stephanie Belyew, Virginia Buckles, Matt Carril, David Clifford, Mary Downey-Jones, Kathy Fanning, Amanda Fulbright, Angela Fuqua, Ron Hawley, Dottie Heller, Michelle Jorke, Denise Levitch, Jacki Mallmann, Tayona Mayhew, Eric McDade, Susan Mills, John Morris, Angela Oliver, Katrina Paumier, Monique Romeo, Anna Santacruz, Jessi Smith, Joy Snider, 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, Karl Kieburtz, Scott Kim, David Knopman, Allan Levey, Dave Clifford, Randall Bateman, Kristine Yaffe
ADCS: Ron Thomas and Paul Aisen
University of Michigan: Robert Koeppe
Mayo Clinic: Clifford Jack

DIAN-TU Sites

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*

Canada

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

Italy

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

United Kingdom

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

Australia

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

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*

Spain

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

Resources

Websites:

- DIAN Observational **http://www.dian-info.org**
- DIAN Expanded Registry **http://www.dianexr.org**
- DIAN-TU **http://www.dian-tu.org**

Contact Information:

- **DIAN-EXR email: dianexr@wustl.edu**
- DIAN Expanded Registry Coordinator **844-DIAN-EXR (844-342-6397)**
- DIAN Global Coordinator, **314-286-2643**