A newsletter distributed by The Dominantly Inherited Alzheimer Network Expanded Registry (DIAN EXR), Washington University School of Medicine, Department of Neurology

Washington University in St. Louis
School of Medicine

# DIAN EXR Newsletter

Volume 4, Issue 1, 2022

## CONTACT US

If you have an idea for a story or have questions about the information in this newsletter, please contact the editors.

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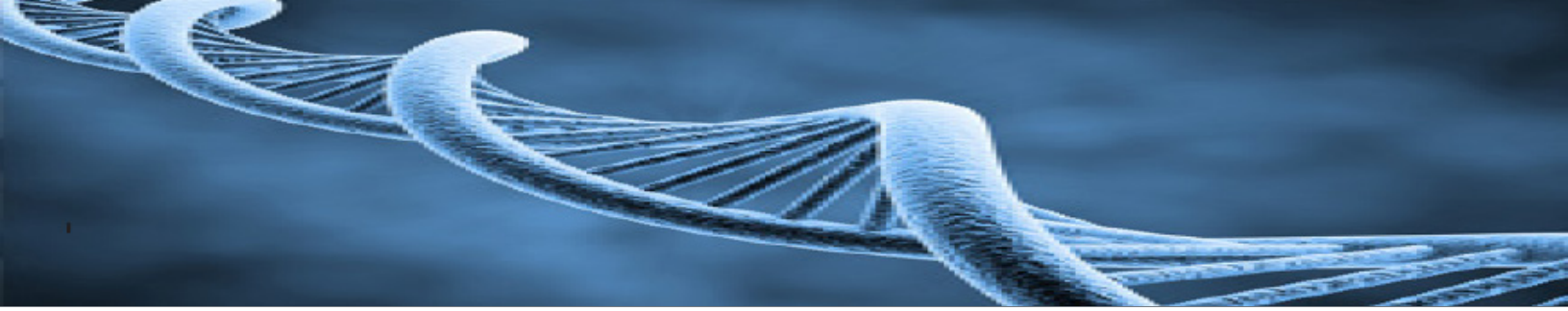
Dear DIAN Expanded Registry Participants,

The equinox is a time for change and renewal and is as good a time as any to introduce myself as the one of the newer members of the DIAN-TU leadership team. My name is Charlene Supnet-Bell, PhD, and I joined the DIAN-TU in July 2021. I serve as an Associate Executive Director, and I support the leaders on the team to ensure the execution of trial goals. My graduate and post-doctoral training focused on Alzheimer's disease, and in my previous role, I served as the Assistant Director of Research for the Cognition and Memory Center at UT Southwestern Medical Center in Dallas, TX. I feel incredibly lucky to work alongside such hard working and relentlessly dedicated DIAN researchers, clinicians and staff. I am also grateful for the opportunity to be of service to our resilient, highly committed and inspiring DIAN study participants and families.

I have enjoyed getting to know the team members over the last few months. Have you ever wondered about the personalities and faces behind DIAN? In an effort to get to know our new and current DIAN-TU team members better, we will be featuring them in future newsletters in a new segment called "Meet the Team."

Along with renewal, the equinox signals excitement for new beginnings. Such is our excitement to announce the launch of the next phase of the secondary prevention DIAN-TU platform study, the Tau Next Generation (Tau NexGen) trial, and the first drug arm open to enrollment since 2018. The DIAN-TU teams have been working diligently with pharma partners, regulatory agencies and funding sponsors over the last few years to bring this trial to launch. In parallel, participants have patiently continued with the EXR and Cognitive Run-In (CRI) activities.

Originally, the Tau NexGen trial focused on targeting tau tangles, an important aspect of Alzheimer's disease pathology closely linked to cognitive decline. Recent amyloid-lowering drug trials, including the DIAN-TU-001 solanezumab and gantenerumab trials, have shown that targeting amyloid can reduce biomarkers of Alzheimer's disease. In response to these data, the team modified the first arm of Tau NexGen to include an experimental amyloid therapy, making it the first ever trial to test a combination of drugs that target both tau and amyloid in the DIAD population. We believe that prevention of both amyloid plaques and tau tangles at the same time will afford the best chance of successfully slowing or preventing the clinical and cognitive symptoms of the disease. We are thrilled to be able to offer the opportunity to participate in this consequential trial for dominantly inherited Alzheimer's disease (DIAD) and Alzheimer's disease, in general.



This trial arm will test two investigational drugs developed by the pharmaceutical company Eisai Co., Ltd.: E2814, a monoclonal antibody that targets the spread of tau in the brain, and lecanemab, a monoclonal antibody that targets pathogenic forms of amyloid. All participants will receive lecanemab and be randomized to either E2814 or placebo. The Tau NexGen trial opened for enrollment at the end of 2021 in the U.S. and is currently actively enrolling qualified participants from the Cognitive Run-In study and new referrals. Sites in other countries are poised to open in the next 8-10 months.

The equinox also signals change. Accordingly, there is an important change to the criteria for enrollment in the Tau NexGen drug arm. In previous DIAN-TU trials, individuals at risk for DIAD did not have to know their genetic status to participate. However, because all participants will receive active drug in this Tau NexGen arm, all participants are required to know their genetic status and have an eligible DIAD mutation in order to participate. As this is a significant adjustment in the expected criteria for participation, we have included a detailed memo in this newsletter (see below) that further explains the rationale for the change. This change of knowing your genetic status **does not** apply to the Primary Prevention study. As always, please do not hesitate to reach out to the team with any questions or concerns you may have.

Change is inevitable and can be challenging. Our hope is that the Tau NexGen trial will usher meaningful change in the advancement of DIAD treatment and prevention, which has us looking forward to a new beginning and future without Alzheimer's disease.

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MEMO

DATE: 10 December 2021

TO: Individuals eligible for DIAN and DIAN-TU research

FROM: Randall Bateman, MD, Director of DIAN-TU and Eric McDade, DO, Associate Director of DIAN-TU

RE: New eligibility criteria for participation in Tau NexGen E2814: A requirement for participants to learn their genetic status prior to enrollment

The new Tau NexGen E2814 clinical trial planned for DIAN-TU will be launching at most sites in 2022. This new trial design will offer individuals who have a dominantly inherited Alzheimer's disease (DIAD) mutation access to investigational drugs that target both amyloid and tau. All participants will receive the anti-amyloid drug and also be randomized to the anti-tau drug or placebo. The main goal of this trial is to determine if these drugs can delay or prevent the formation of tau neurofibrillary tangles and limit further disease progression. In previous DIAN-TU trials, individuals at risk for DIAD did not have to know their genetic status to participate in the trial. However, because all participants will receive active drug, this Tau NexGen trial requires participants to know their genetic status and have a mutation in order to participate. The DIAN-TU can assist in arranging clinical genetic counseling and testing and will cover the cost of these services. Note that the Primary Prevention trial, DIAN Observational, and potentially other trials still do not require participants to know their genetic status.

DIAN-TU researchers recognize the difficulties faced by family members struggling with finding out their genetic status, and have worked hard in the past to preserve the ability to participate in trials without testing. However, after careful deliberation and analysis of multiple factors related to the new trial, we can no longer offer this option for the Tau NexGen E2814 drug arm. Because an anti-amyloid therapy has been FDA approved, we believe anti-amyloid treatment should be made available in this trial. We also predict that future optimal therapies may require both amyloid and tau drugs. For these reasons, we have added an anti-amyloid treatment to the trial, in addition to the anti-tau/placebo drug. Below is a summary of the considerations involved in reaching the decision that only mutation carriers are eligible for the Tau NexGen E2814 trial:

• Prior discussions with family members and study site Principal Investigators (PIs) about requiring genetic counseling and testing have indicated a willingness to consider learning genetic status, if there is access to an active drug (see survey information below). The Tau NexGen E2814 trial provides all participants with an active anti-amyloid drug (Lecanemab) in combination with an anti-tau or placebo.

• Because there are two different drugs co-administered--each with their own scheduling and increased visits, assessments, and scans--there is an increase in study activities, or study "burden", for both participants and study staff. Given the increased complexity of the trial for both participant and site staff, enrollment of mutation negative participants was determined to no longer be feasible or ethically advisable.

• Ethics committees (ECs) and Institutional Review Boards (IRBs), which approve and oversee clinical trials, have challenged designs that use healthy volunteers (for our studies, this means participants who are mutation negative), stating that the burden of participation (frequency of the visits, lumbar punctures, radiation) is too high if the participant is not at risk (i.e., not a mutation carrier). In these cases, such studies may not receive approval to conduct research. The DIAN-TU seeks to ensure that trials continue to be approved and available to the DIAD community.

• Individuals enrolled in the DIAN-TU clinical trial testing anti-amyloid therapies solanezumab and gantenerumab were offered participation in the gantenerumab Open Label Extension (gant OLE), which required knowledge of genetic status, as all enrolled were guaranteed to receive active treatment with gantenerumab. Ninety-one percent (91%) 0f participants either already knew their status or elected to learn status to participate in OLE, while 9% declined to learn status (Figure 1). These findings indicate that most DIAD participants know or opt to learn their genetic status if guaranteed treatment with an active drug.

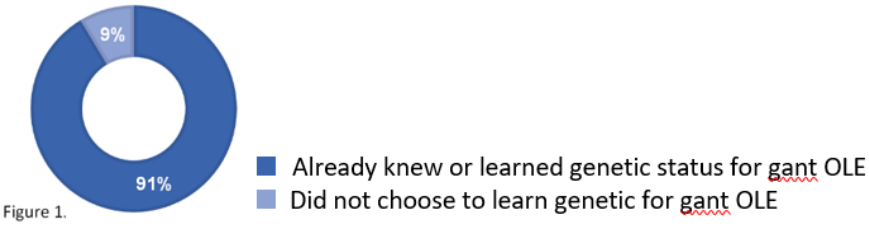


Figure 1.

• Results of a survey sent to DIAN Expanded Registry participants in July 2021 also provided insight to researchers about the impact of requiring knowledge of genetic status prior to trial participation. The findings are summarized in the below pie chart (Figure 2). Sixty-nine percent (69%) of those surveyed already knew their genetic status. Of those who answered the survey and did not know their genetic status, 21% stated that they would be willing to learn their genetic status if guaranteed to receive an active anti-amyloid drug in addition to anti-tau or placebo during trial participation, while 10% said they would not. In summary, 90% of survey respondents know or would be willing to learn their mutation status for the trial.

Figure 2. Knowledge about mutation status among survey participants (n=92).

The DIAN Expanded Registry (DIAN EXR) has received several communications from family members and trial participants about this change. We understand the significance of this eligibility criteria change for some DIAD participants and hope this memo helps clarify why this decision was made. For more information, please see the press release posted on the DIAN website and the DIAD family webinar from November 20, 2021 DIAD family webinar.

If you are a current participant in Cognitive Run-In (CRI) and do not know your genetic status (and are unsure whether you are ready to find out your genetic status) or if you are not yet involved but are interested in learning more, you may take any of the following actions:

1) Contact the DIAN EXR by registering at https://dian.wustl.edu/our-research/registry/ (if you are not yet registered)

2) Consider the option to receive multiple sessions of supportive counseling with a local, professional therapist to assist in deciding whether learning your genetic status is right for you at this time.

3) Discuss the Tau NexGen trial with your site Principal Investigator

4) Review the consent form for the Tau NexGen trial to learn the risks/benefits of participating

5) Schedule an initial genetic counseling session to get relevant information about risk and learning genetic status (Note: it is recommended to obtain life and long-term care insurance before contacting a genetic counselor)

Please contact your study coordinator or the DIAN EXR at dianexr@wustl.edu for more information.

# DIAN-TU-002 Clinical Trial: Primary Prevention

As previously announced, the DIAN-TU is launching a clinical trial called "Primary Prevention" for family members who are 11 to 25 years younger than the age at which their parent first noticed symptoms of Alzheimer's disease. The new study will investigate whether **gantenerumab** — an investigational antibody under development for Alzheimer's disease by Roche and Genentech, a member of the Roche Group — can clear a key Alzheimer's protein called amyloid beta, and slow or stop the disease. Amyloid is the chief component of plaques that dot the brains of people with the disease. Many scientists suspect the disease originates from the buildup of amyloid plaques in the brain that start to develop up to two decades before symptoms of dementia begin.

"Overwhelming evidence suggests that the most effective way to slow or stop amyloid beta is to prevent it from building up in the first place, but most of the drugs targeted to this protein have been tested in people who already have at least some early signs of the disease, such as memory loss – when the disease is far enough along that reducing amyloid alone isn't likely to stop it," said Eric McDade, DO, an associate professor of neurology and the trial's principal investigator. "We'll be recruiting participants as young as 18. In many ways, this trial will be a necessary test of the amyloid hypothesis, which has had a major influence on Alzheimer's research and drug development over the past 30 years."

Currently, eligible family members can enroll into the Cognitive Run-In (CRI) period of the Primary Prevention trial, in which vital data is collected before the addition of the drug arm. It is anticipated that gantenerumab (or placebo) will be begin at U.S. sites starting in September, 2022, and at world-wide sites in 2023. Importantly, participants who enroll into the Primary Prevention study will NOT have to learn their genetic status in order to participate. For more information on how to enroll into the Primary Prevention study, please email the DIAN Expanded Registry at dianexr@wustl.edu.

# 2022 DIAD Family Conference: (re)UNITED!

Dust off those suitcases and get ready to get some sun! The Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU) and the Alzheimer's Association are very pleased to announce the 2022 DIAD Family Conference for families impacted by dominantly inherited Alzheimer's disease (DIAD). Many thanks to the Alzheimer's Association and the National Institute on Aging (NIA) for their support of the DIAD Family Conference.

The conference will be held Saturday, July 30th in San Diego, CA, USA. This year's conference will offer attendees information, support and opportunities to share insight with each other and with researchers in the field, pharmaceutical companies, government funding agencies and regulators. If you are unable to travel to the in-person meeting, please know that we are investigating livestreaming options for the morning sessions. Information on how to access this virtual option will be emailed to DIAN EXR registrants and to conference registrants.

The DIAD Family Conference is intended for family members who have a DIAD mutation, those at risk for a mutation and those family and friends who support at-risk individuals. Registration is now open, and information on how to register was shared with EXR registrants and DIAN/DIAN-TU study participants. Registration will close when capacity is reached, but a wait list will be maintained and family members will be notified when spots become available. For any questions about the Family Conference, please contact Jennifer Petranek or Ellen Ziegemeier at DIAD-FC@email.wustl.edu.

To see presentations from past conferences, please visit: https://dian.wustl.edu/for-families/family-conferences/

We are excited to see you in San Diego!

# Alzheimer's in the News

Could drugs prevent Alzheimer's? These trials aim to find out

https://www.nature.com/articles/d41586-022-00651-0

Blood test for Alzheimer's highly accurate in large, international study

https://source.wustl.edu/2022/02/blood-test-for-alzheimers-highly-accurate-in-large-international-study/

First Subject Enrolled in Phase II/III Study of Eisai's Anti-MTBR Tau Antibody E2814 for Dominantly Inherited Alzheimer's Disease (DIAD), conducted by DIAN-TU

https://www.eisai.com/news/2022/news202205.html

New Alzheimer's prevention trial in young people

https://medicine.wustl.edu/news/new-alzheimers-prevention-trial-in-young-people/

New strategy reduces brain damage in Alzheimer's and related disorders, in mice

https://medicine.wustl.edu/news/new-strategy-reduces-brain-damage-in-alzheimers-and-related-disorders-in-mice/

Damage early in Alzheimer's disease ID'd via novel MRI approach

https://medicine.wustl.edu/news/damage-early-in-alzheimers-disease-idd-via-novel-mri-approach/

Does improving sleep reduce signs of early Alzheimer's disease?

https://medicine.wustl.edu/news/does-improving-sleep-reduce-signs-of-early-alzheimers-disease/

A neurodegenerative disease landscape of rare mutations in Colombia due to founder effects

https://genomemedicine.biomedcentral.com/track/pdf/10.1186/s13073-022-01035-9.pdf

# Recent DIAN Publications

Soluble TREM2 in CSF and its association with other biomarkers and cognition in autosomal-dominant Alzheimer's disease: a longitudinal observational study

https://www.sciencedirect.com/science/article/pii/S1474442222000278?via%3Dihub

Identification of the Aβ37/42 peptide ratio in CSF as an improved Aβ biomarker for Alzheimer's disease

https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/alz.12646

Circular RNA detection identifies circPSEN1 alterations in brain specific to autosomal dominant Alzheimer's disease

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8895634/

Association of BDNF Val66Met With Tau Hyperphosphorylation and Cognition in Dominantly Inherited Alzheimer Disease

https://jamanetwork.com/journals/jamaneurology/fullarticle/2788271

Variant-dependent heterogeneity in amyloid β burden in autosomal dominant Alzheimer's disease: cross-sectional and longitudinal analyses of an observational study

https://www.sciencedirect.com/science/article/abs/pii/S1474442221003756?via%3Dihub

Dynamic Amyloid PET: Relationships to 18F-Flortaucipir Tau PET Measures

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8805772/

Does DIA data contain hidden gems? A case study related to Alzheimer's disease

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8741752/

Diffusion Tensor MRI Structural Connectivity and PET Amyloid Burden in Preclinical Autosomal Dominant Alzheimer Disease: The DIAN Cohort

https://pubs.rsna.org/doi/10.1148/radiol.2021210383?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed

Different rates of cognitive decline in autosomal dominant and late-onset Alzheimer disease

https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/alz.12505

Sleep and longitudinal cognitive performance in preclinical and early symptomatic Alzheimer's disease

https://academic.oup.com/brain/article/144/9/2852/6401973?login=true

Comparing amyloid-β plaque burden with antemortem PiB PET in autosomal dominant and late-onset Alzheimer disease

https://link.springer.com/article/10.1007/s00401-021-02342-y

Accelerated functional brain aging in pre-clinical familial Alzheimer's disease

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8429427/

Spatially constrained kinetic modeling with dual reference tissues improves 18 F-flortaucipir PET in studies of Alzheimer disease

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8371062/

Relationships between β-amyloid and tau in an elderly population: An accelerated failure time model

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8499700/

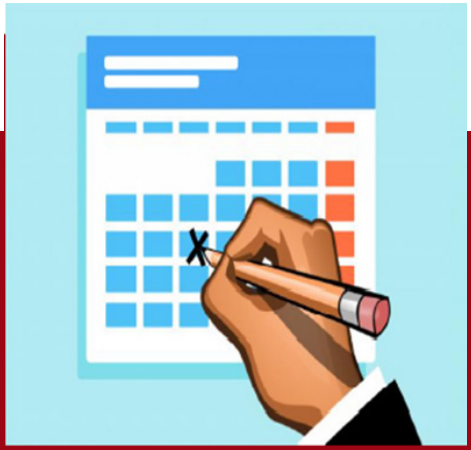
DIAN-TU ARGENTINA A great human story of a small group of people

https://revistascientificas.cuc.edu.co/JACN/article/view/3805/3774

*The DIAN data are increasingly published in scientific reports to enable investigators worldwide to learn of our progress and to advance scientific understanding of Alzheimer's disease. Because of this, there is a small but possible risk that a DIAN participant reading or hearing of these scientific reports might guess, correctly or incorrectly, information about themselves. This includes guessing one's own or a family member's mutation status. We at DIAN take every step to minimize this risk, including ensuring that all DIAN data in journal articles, scientific meetings, press coverages, etc., lack identifying information for any participant, but it is possible than even such de-identified data may reveal a pattern of symptoms or a relationship with other medical disorders that could suggest that a particular person is mutation positive. You can avoid reading these scholarly articles or listening to presentations related to the DIAN study to decrease this risk.*

The DIAN website is a great place to learn more about our research and find additional information. Please visit the "News" page at https://dian.wustl.edu/news/ for articles related to DIAN and Alzheimer's disease. Family members share their stories on the "Family Voices" page at https://dian.wustl.edu/for-families/family-voices/. If you are interested in research opportunities, please contact the DIAN Expanded Registry at dianexr@wustl.edu. If you are not part of the registry and would like to be, please visit dian.wustl.edu to register.

*The DIAN Expanded Registry is supported by the Alzheimer's Association, GHR Foundation, an anonymous organization, private donors, the DIAN-TU Pharma Consortium, DIAN-TU Industry Partners, and the National Institute on Aging of the National Institutes of Health under Award Numbers U01AG042791, R01AG046179, R01/R56 AG053267, U01AG059798, and R01AG068319. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.*



***Save the Date!***

***DIAD Family Webinar***

***SATURDAY, May 14th, 2022***

***4:00 - 6:00 PM CDT (22:00 – 00:00 BST)***

***Featured topics: DIAN-TU Trial Updates***