

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



# DIAN EXR Newsletter

Volume 5, Issue 4, 2023

## Contact the Editor

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

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## 2023: A Momentous Year

Reaching the last page of a calendar inevitably triggers reflection. Amid the flurry of year-end wrap-ups, celebrations, and deadlines, it is important to pause and remember what has been accomplished in 2023.

The DIAN-TU-001 Secondary Prevention trial continues to enroll participants, with sites in ten countries. More countries are anticipated to begin enrollment in this trial in 2024. As the data provided by study participants will provide vital insight into disease progression and treatment effects, it is exciting to see the number of enrolled individuals continue to increase.

The DIAN-TU-001 Gantenerumab Open Label Extension study was closed, as data was analyzed according to the DIAN-TU-001 OLE Statistical Analysis Plan. Participants in this trial will be given the opportunity to enroll in the DIAN-TU Amyloid Removal Trial (ART), which will continue treatment and further study the effects of removing amyloid plaques with OLE participants. (See page 3 for full details about ART.)

*(continued on page 2)*

## 2023: A Momentous Year (continued)

OLE findings indicate that removing amyloid plaques for an average of 8 years before symptom onset may provide a 50% decrease in the risk of conversion to symptomatic dementia and dementia progression rate. Ongoing studies of this unique cohort will continue to provide evidence on the ability to prevent dementia with amyloid removing treatments.

The DIAN-TU-002 Primary Prevention trial that was paused in December 2022 is anticipated to relaunch in 2024. As details are finalized prior to enrollment reopening, we are eager to begin research on early intervention against amyloid accumulation. The DIAN-TU team has worked tirelessly throughout 2023 to bring the Primary Prevention trial to this point and identify eligible participants so they can be enrolled efficiently once the protocol is finalized.

The pace of drug approvals is accelerating. News of Leqembi's approval by the United States Food & Drug Administration (FDA) was followed in July 2023 by the announcement that the similar drug donanemab may also have an effect on slowing Alzheimer's disease progress, and it awaits FDA approval. While they are not cures, these treatments may buy patients priceless time as research advances and drugs currently in development are further refined.

Outreach and community-building among families at risk for DIAD remains a priority, with the Expanded Registry (EXR) growing by 66 newly confirmed at-risk individuals from 33 different families in 2023. The EXR continues to identify qualified individuals for its Exploratory Genetic Counseling and Testing program and trial referral, while also disseminating important research-related announcements and opportunities. The DIAN-TU and DIAN Observational Study also hosted two regional Family Conferences in 2023, bringing family members and researchers together for necessary support and dialogue.

The DIAN Observational Study submitted its fourth grant renewal in September 2023. The valuable data gathered from the Observational Study informs not only DIAN-TU researchers and their projects, but also outside investigators studying other Alzheimer's populations and interventions, furthering global understanding of this disease. (Researchers may request data access at <https://dian.wustl.edu/our-research/for-investigators/dian-observational-study-investigator-resources/>.)

This brief summary of complex accomplishments and goals must be viewed in context: the DIAN-TU research has allowed DIAD families the first opportunity to participate in Alzheimer's disease clinical trials. Findings that benefit DIAD families are likely to benefit millions with sporadic (late onset) Alzheimer's. While DIAN trials examine a rare disease population, they address a crucial, global public health priority.

None of this is possible without the hard work of many people. Behind every announcement of a new discovery or drug is a crowd of researchers, technicians, coordinators, administrators, and support personnel whose names are often unspoken but whose contributions are essential. Even more important are the participants who share their time and energy as they visit study sites and receive experimental medications. These individuals' names do not appear in press releases, nor do their faces grace magazine covers. Yet without them, *there would be no research*. As we move forward into 2024, we carry gratitude for these participants along with an abiding sense of purpose. For those with Alzheimer's disease, for their loved ones, for generations to come—we carry on.

# The Knight Family DIAN-TU Amyloid Removal Trial (ART)

The statement below is an update to the [18 August 2023 announcement](#) by the Knight Family Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU) regarding the DIAN-TU-001 Open Label Extension (OLE) Study [[Clinicaltrials.gov #NCT01760005](#)].

On August 18th, 2023, the Knight Family DIAN-TU announced the discontinuation of the DIAN-TU-001 OLE based on findings from an interim efficacy analysis and the status of the drug program. Based on findings from the interim analysis that removing amyloid plaques may be beneficial, and recognizing the commitment of our participants and their families, the Knight Family DIAN-TU is pleased to announce our plans to launch the DIAN-TU Amyloid Removal Trial to enable continued treatment for the DIAN-TU-001 OLE participants and address questions regarding the effects of removing amyloid plaques to normal levels on the disease process.

“The Knight Family DIAN-TU is delighted to continue to treat these participants who have been in trials for a decade to determine the long-term effects of amyloid plaque removal on Alzheimer’s disease prevention,” said Dr. Randall J. Bateman, Director of the DIAN-TU. “The findings indicate large beneficial effects on the biology, and the goal now is to confirm if removing amyloid plaques can delay or prevent the onset of memory loss and dementia in these unique individuals who are otherwise destined to dementia.”

The DIAN-TU has received funding from the Alzheimer’s Association and GHR Foundation to launch the DIAN-TU Amyloid Removal Trial. DIAN-TU plans to implement treatment with an amyloid-removing therapy. We expect to launch the study in 2024.

**We thank the DIAN-TU participants and their families for their commitment and patience while we finalize the details for this study. We also thank the Alzheimer’s Association and GHR Foundation for providing funding to enable the DIAN-TU Amyloid Removal Trial.**

Randall J. Bateman, MD  
Director, DIAN-TU

Alireza Atri, MD, PhD  
DIAN-TU-001 OLE Project Arm Leader, DIAN-TU

# Cognitive Resilience in Alzheimer's Disease

Alzheimer's disease (AD) stands as the foremost contributor to dementia, presenting itself as a global priority. Amidst the ongoing quest for therapies that modify the disease, an equally vital focus within AD research is discerning environmental and genetic factors that may protect, delay age at onset, or slow down its progression. The combination of multiple factors leading to the brain's ability to maintain normal cognition and better withstand the effects of AD pathology is collectively denoted as cognitive reserve.

More important, cognitive reserve is not static but rather a dynamic and fluid concept that builds up over a lifetime through experiences, education, and engaging in mentally stimulating activities like learning new things, staying socially active, and challenging your brain with puzzles or games. These factors may contribute to a richer and more adaptable neural network, potentially delaying the onset of noticeable cognitive decline in the presence of Alzheimer's pathology. In other words, it is hypothesized that individuals with high cognitive reserve may be more resilient to the cognitive challenges posed by AD.

Several studies have explored the effect of cognitive reserve factors in sporadic AD (Alzheimer's disease with an older onset and without a definitive genetic cause). Yet this remains understudied in DIAD families. In DIAD, similar to sporadic late-onset AD, there are differences in the age of symptom onset and experience of clinical symptoms, even within the same mutation and family members. For example, families carrying an identical mutation may demonstrate a 5-10 year difference in the age when symptoms begin. Previous studies in DIAN have shown that family mutation alone fails to explain a significant proportion of the observed difference in clinical symptoms, and it could arise from other factors (e.g., exposome, metabolic, epigenetic).

New initiatives in the DIAN Observational Study will explore the relationship between cognitive reserve, cognitive performance, and Alzheimer's disease by combining genomics, epigenetics, and information about lifestyle factors to more precisely explore contributors to differences in the age of onset. DIAN participants are invited to complete lifestyle questionnaires. Topics of these surveys include sleep, physical activity, diet, and education, among other lifestyle choices and circumstances. (These questionnaires are available in the MyDIAN smartphone/tablet app, and individuals in families with DIAD mutations can contact [dianexr@wustl.edu](mailto:dianexr@wustl.edu) to gain access or for assistance locating the surveys.)

While cognitive reserve factors alone are unlikely to fully prevent Alzheimer's disease in mutation carriers, this new initiative may reveal how factors like education, socioeconomic status, physical activity, sleep, etc. boost cognitive reserve in DIAD mutation carriers and whether such factors modify resilience to neuropathology, delay the age of symptom onset, and prevent longitudinal cognitive decline.

*Jorge Llibre Guerra, MD, Assistant Medical Director*

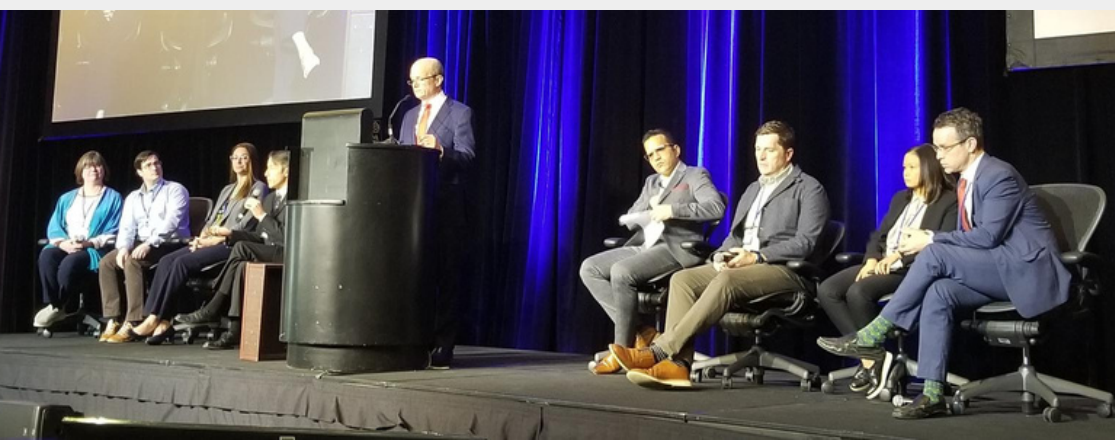
# DIAN Observational Study Renewal

The DIAN Observational Study (DIAN Obs) recently submitted a competitive renewal application for five additional years of funding (for 2024 to 2029). DIAN Leadership, Investigators, and Coordinating Center staff are excited for the next phase of the study with many asking what is next for DIAN Obs. In an era where new Alzheimer's Disease (AD) drug trials are enrolling and therapies have recently received FDA approval, what new contributions can DIAN Obs provide to the scientific field and where can the strength of working with our DIAD families make the most impact? This question is important, as we look to broaden DIAN Obs' scope expanding the data available to the scientific and medical communities to ultimately support opportunities for new discoveries in AD.

The DIAN participants and families are critical to many recent advances being made in AD research, including the development of CSF and blood biomarker tests that have or may soon receive FDA approval for using in the clinic and are an important measure for clinical trial design. Also, because scientists and doctors still do not understand all the biological processes that spans over years in those susceptible to developing AD, including the impact of the immune system and environmental factors on the disease, DIAN Obs will continue to provide valuable participant data to study these factors.

New clinical trials are designed to test the safety and effectiveness of new therapies and are often limited in including research into developing theories or collecting additional data or tissue unrelated to the primary and secondary outcomes. Some participants and their families are unable to join the trial due to requirements or burdens such as not wanting to learn their personal mutation status, being unable to commit the time to infusions or injections and follow-up, or concerns about potential safety risks. For all of these reasons, the DIAN Obs remains an important contributor to research in AD.

*Alisha Daniels, MD, DIAN Obs Executive Director  
Laura Courtney, Clinical Research Manager*



*Pictured: Researchers participate in a question-and-answer session during the Latin American Investigator Meeting in Mexico City, Mexico in March 2023.*



## Expanded Registry Survey

Do you feel that the EXR Newsletter is a valuable resource? Which communications would you like to see more (or less!) of? Please share your thoughts with us in a quick (5-10 minute) survey.

Take our survey at [https://redcap.link/exr\\_survey\\_2023](https://redcap.link/exr_survey_2023)

## Youngtimers Event on Brain Health

**Thursday, Feb. 8, 2024, 2:00-3:00 pm CST (GMT-6)**

Individuals at risk for DIAD and supporting family members are invited to join Youngtimers for a workshop on a commonly asked question: “What can I do to prevent or delay the onset?” RSVP at <https://www.eventbrite.com/e/lifestyle-interventions-for-brain-health-qa-with-dr-rudy-tanzi-tickets-770412563717?>

## Video Resources for Families

Dr. Bonnie Hennig-Trestman shares practical guidance for **talking to children** about DIAD in an age-appropriate way. Watch her presentation at [https://www.youtube.com/watch?v=bQi5\\_mac2UE](https://www.youtube.com/watch?v=bQi5_mac2UE).

Dr. Brian Carpenter shares considerations for **end-of-life planning**, offering tips for sharing your wishes with loved ones and navigating difficult conversations. To access his presentation, visit <https://knightadrc.wustl.edu/center-events/3rd-thursdays/>, select “October 16, 2023: Putting Yourself First While Planning your Last Chapter,” and provide your contact information.

# Recent DIAN Publications

## **Etiology of White Matter Hyperintensities in Autosomal Dominant and Sporadic Alzheimer Disease**

<https://jamanetwork.com/journals/jamaneurology/fullarticle/2810315>

## **Longitudinal clinical, cognitive and biomarker profiles in dominantly inherited versus sporadic early-onset Alzheimer's disease**

<https://doi.org/10.1093/braincomms/fcad280>

## **T1 and FLAIR signal intensities are related to tau pathology in dominantly inherited Alzheimer disease**

<https://doi.org/10.1002/hbm.26514>

## **Alzheimer's polygenic risk scores are associated with cognitive phenotypes in Down syndrome**

<https://doi.org/10.1002/alz.13506>

## **Higher systolic blood pressure in early-mid adulthood is associated with poorer cognitive performance in those with a dominantly inherited Alzheimer's disease mutation but not in non-carriers. Results from the DIAN study**

<https://doi.org/10.1002/alz.13082>

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 coverage, etc., lack identifying information for any participant, but it is possible that 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.

# Alzheimer's in the News

**How do toxic proteins accumulate in Alzheimer's and other diseases?**

<https://medicine.wustl.edu/news/how-do-toxic-proteins-accumulate-in-alzheimers-and-other-diseases/>

**Can We Prevent Alzheimer's? Scientists Say New Tests and Treatments are "a Game Changer"**

<https://www.newsweek.com/2023/10/20/can-we-prevent-alzheimers-scientists-say-new-tests-treatments-are-game-changer-1832957.html>

**Scientists Find Brain Cholesterol Link to Alzheimer's-Like Damage**

<https://www.newsweek.com/cholesterol-alzheimers-brain-cells-tau-proteins-1846021>

**Researchers return to Alzheimer's vaccines, buoyed by recent drug success**

<https://www.reuters.com/business/healthcare-pharmaceuticals/researchers-return-alzheimers-vaccines-buoyed-by-recent-drug-success-2023-11-20/>

**A type of belly fat may be linked to increased risk of developing Alzheimer's**

<https://www.nbcnews.com/health/health-news/type-belly-fat-linked-alzheimers-risk-research-finds-rcna125204>

## 2023 in Review: AD Conference Coverage

**International Conference on Alzheimer's and Parkinson's Diseases 2023**

Gothenberg, Sweden: March 28-April 1, 2023

<https://www.alzforum.org/news/conference-coverage/international-conference-alzheimers-and-parkinsons-diseases-2023>

**Alzheimer's Association International Conference (AAIC)**

Amsterdam, Netherlands and Online: July 16-20 2023

<https://www.alzforum.org/news/conference-coverage/alzheimers-association-international-conference-aaic-2023>

**Symposium on Lipids in Brain Diseases**

Leiden, Netherlands: September 13-15, 2023

<https://www.alzforum.org/news/conference-coverage/2nd-symposium-lipids-brain-diseases>

**Clinical Trials on Alzheimer's Disease (CTAD)**

Boston, Massachusetts, USA: October 24-27 2023

<https://www.alzforum.org/news/conference-coverage/clinical-trials-alzheimers-disease-ctad-2023-16th>



# Regional DIAD Family Conference: Save the Date

A regional DIAD Family Conference will be held for DIAD families living in the United States and Canada in conjunction with the Alzheimer's Association International Conference (AAIC) on July 27, 2024 in Philadelphia, Pennsylvania, USA. If you are in a family at risk for DIAD, watch your email inbox for future announcements!

## Happy Holidays from DIAN!



*Pictured: Staff from the DIAN Expanded Registry and DIAN Observational Study gather for a holiday lunch in St. Louis, Missouri in December 2023*

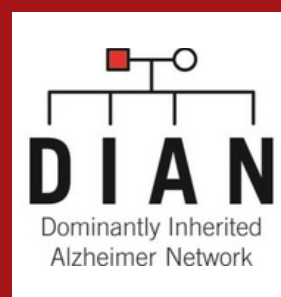
## Support Our Work

Our research is enabled by a number of contributors, including generous individual private donors. Gifts of any amount help us continue to study, treat, and prevent Alzheimer's disease. If you would like to join us in this work by making a financial gift, please visit <https://dian.wustl.edu/donate/>.

You can also spread the word about our research by sharing this link with others and inviting them to contribute. We invite you to email this newsletter to a friend, or to share our giving link on your personal social media pages. Whether through making direct donations or spreading awareness of our work, we are grateful for all the ways our supporters give back.

We wish you a healthy and happy 2024! From all of us in the Expanded Registry team, thank you for staying in touch. We look forward to the year ahead.

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