

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%) of 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.

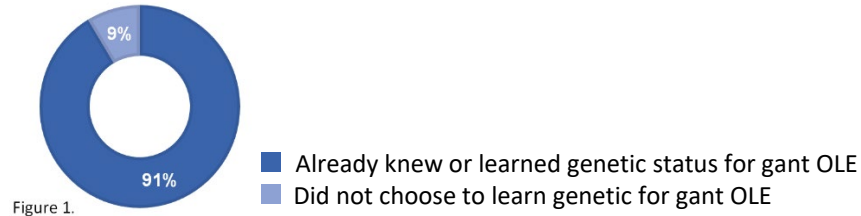


Figure 1.

- 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.

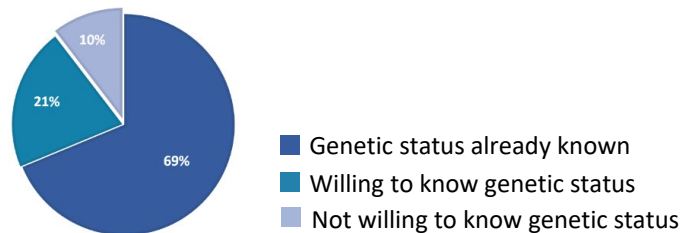


Figure 2. Knowledge about mutation status among survey participants (n=92).

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:

- Contact the DIAN EXR by registering at <https://dian.wustl.edu/our-research/registry/> (if you are not yet registered)
- 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.
- Discuss the Tau NexGen trial with your site Principal Investigator
- Review the consent form for the Tau NexGen trial to learn the risks/benefits of participating
- 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.