DIAD Family Webinar
Sunday, October 30, 2016
4:00 - 6:00 PM CST / 9:00 PM – 11:00 PM GMT

Presented by:
Eric McDade, DO
Director, DIAN Expanded Registry
Associate Director, DIAN-TU
Agenda

- Recap of 2016 DIAD Family Conferences in Toronto and Germany
- Plans for 2017 DIAD Family Conference in London
- Next Steps for the DIAN-TU
- What is “Clinically-Meaningful” in the DIAN-TU studies?
- Use of the DIAN Expanded Registry for surveys to research participants

If you have a question during the webinar please go to the chat tab on the right hand side of your screen and type in your question or email it to: dianexr@wustl.edu
Recap of DIAD Family Conference  
Too Young To Forget  
July 23rd, 2016 AAIC, Toronto CANADA

Attendees: 222
- 117 Family members from 8 countries (Argentina, Australia, Canada, England, Ireland, Scotland, United States and Wales)
- 75 Researchers/professionals
- 30 Alzheimer Association donors

Evaluation Results (n= 42 family member/friend)
- Information useful: 71% extremely; 10% moderately
- Technicality of presentations: 79% appropriate
- Satisfaction with family presentations: 86% extremely
- Overall satisfaction with conference: 71% extremely
- Conference attendees: 52% were new attendees in 2016
- Plan to attend 2017 Conference in London: 88%
Recap of DIAD Family Conference
Too Young To Forget
July 23rd, 2016 AAIC, Toronto CANADA

Evaluation Results continued (n= 42 family member/friend)
Top 3 most helpful sessions:
  1) Drug development and approval (joint pharma presentation and drug re-purposing)
  2) Emerging research (Non-pharmacological approaches)
  3) Alzheimer’s overview (State of AD research and DIAN/DIAN-TU updates)

Suggestions for future conferences:
• Panel discussion with family members about learning own genetic status
• More time for Questions/Answers sessions
• More time for one-on-one interactions with researchers
• How to talk to children and other family members about participation in research
• Break up the day into different segments to avoid “death by PowerPoint”
German DIAD Family Meeting 2016

• ~20 Researchers and Professionals (BfArM, Roche, German Alz. Society, Media (Alzforum, Frankfurter Allgemeine Zeitung))

• >60 family members

• Survey Results (n=20)

![Bar chart showing survey results](image)

- **Frage 1**: Consider DIAN TU
- **Frage 2**: Preference for Trial: Red=Have to know gene, Blue=Don’t have to know
- **Frage 3**: Should German media cover DIAD more?

Response (Red=Yes/Blue=No)
DIAD Family Conference Funding

- **NIH Grant: 4 years of funding (2017-2020)**
  “This meeting was deemed highly significant with potential to address future needs in the community and this application was met with a high level of enthusiasm.”

- **Alzheimer’s Association: 5 years of funding (2016-2020)**

- **Independent fundraising ideas:**
  - ebay sales of specialty items
  - Fundraising parties
  - Game nights
  - Private donations
  - Film screenings
  - Auctions
  - Celebrity donors
  - Foundation awards opportunities
  - Corporate sponsorship, micro grants

**Discussion point:** Which strategy do you feel was most successful?
Theme: DIAD/Sporadic AD Comparison: the critical role of discoveries in DIAD for informing the rest of the field.

Objectives:
1. Provide a forum for interactive dialogue about research, trial design, drug development and other concerns raised by basic and clinical researchers, DIAD families, regulatory agencies, pharmaceutical representatives and nonprofit organizations.
2. Unite DIAD scientists, encourage AD researcher development and summarize the state of research on DIAD
3. Inform and support families with and at risk of developing DIAD to encourage engagement

Discussion Points:
• Travel expense coverage options
• Fundraising activities:
  • planning calls will start in November
  • Subcommittees
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; Government Agency for Scientific Research from Argentina (Agencia- Mincyt - CONICET); Japan’s Health and Labour Sciences Research Grant (Research and Development Project on Dementia); National Grants from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health and Welfare, Republic of Korea (since 2013)
DIAN related publications

• DIAN related publications significantly benefit the scientific and clinical field
• Critical to trial development
• It is possible that research findings could identify information that would imply genetic status (non-individual data)
DIAN-TU-001 Trial Status

• **Current Drug Arms**
  – Enrollment for first two drug arms complete
  – Timing of biomarker interim analyses

• **DIAN-TU NexGen**
  – Alzheimer’s Association funding received for start-up
  – NIA funding received for start-up (grant resubmission pending review)
  – Potential enrollment starting early-mid 2017
### DIAN-TU Trial Data

<table>
<thead>
<tr>
<th>Test Measure</th>
<th>Assessments per participant</th>
<th>Quantity</th>
<th>Compliance Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Measures</strong></td>
<td>CDR, CDR-SB, MMSE, FAQ, GDS, NPIQ</td>
<td>5</td>
<td>≈1000</td>
</tr>
<tr>
<td><strong>Cognitive Measures</strong></td>
<td>CogState, Pencil / Paper</td>
<td>5-10</td>
<td>≈ 1000-2000</td>
</tr>
<tr>
<td><strong>Fluid Biomarkers</strong></td>
<td>Plasma, Serum, CSF</td>
<td>4</td>
<td>≈ 800</td>
</tr>
<tr>
<td><strong>Imaging Biomarkers</strong></td>
<td>PiB, AV-45, FDG</td>
<td>4</td>
<td>≈ 800</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Imaging Modality / Tracer</th>
<th>Baseline</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 4</th>
<th>Total # Scans</th>
</tr>
</thead>
<tbody>
<tr>
<td>AV-1451</td>
<td>30</td>
<td>107</td>
<td>141</td>
<td>141</td>
<td>419</td>
</tr>
</tbody>
</table>

22 July 2016
How do we establish a clinically-meaningful result for all participants in the DIAN-TU studies?

• What effect is meaningful when you don’t have any symptoms of a disease
• How do you measure improvements?
• Many different ways to ask this
  • Surveys
  • New tests
    • In person tests
    • At home /computer based tests
Response to questions of risk based on treatment delay in symptoms

Percent willing to take medication for a 6 month delay in symptoms

- 1: 88%
- 2: 77%
- 3: 34%

Percent willing to take medication for a 1 year delay in symptoms

- 1: 88%
- 2: 76%
- 3: 35%

Percent willing to take medication for a 5 year delay in symptoms

- 1: 89%
- 2: 76%
- 3: 37%
DIAN-TU Primary Prevention Trial

- Primary prevention vs. secondary Prevention
- Will require entering trial at an even earlier time than in the current trial
- May require longer duration in trial
Preliminary survey responses relating to Primary Prevention

• > 90% of respondents indicated that they would be willing to stay in a clinical trial for over 5 years
• Majority agreed that participants younger than 15 years before the anticipated age of onset should be included
• What do the callers think of children younger than 18 participating in research (NOT CLINICAL TRIALS)?
DIAN Expanded Registry outreach efforts

• Expand family pedigrees
• Engage non-participating family members
• Exploratory testing to find new, eligible families
• Town-hall meetings for sites/countries (e.g. Puerto Rico)
• Increased engagement with genetic counselors and genetic testing labs (Athena Diagnostics, Prevention Genetics, Fulgent Diagnostics)
• Informational videos to enhance website
• Website translation and better promotion of DIAN EXR (sites, tweets, etc.)
• Surveys to participants
• Potential future computer or phone based cognitive testing
Questions/Answers discussed on webinar 10/30/16

• Do we know the agenda for the 2017 Family DIAD Conference? We should know more January or February.

• Of the 445 DIAN participants in the DIAN Observational Study, how many are clinically affected? 20% in the DIAN Observational Study have symptoms or a diagnosis.

• When will the first report be released, for the DIAN-TU? The Enrollment started in December 2013 and closed in December 2015. there will be a planned readout in 2019. There will be interim analysis to see if they are having desired outcomes, to see if they are having effects on biomarkers. The interim report will be out around the end of next year. 2017.
• **Why do we have to wait for results?** Government agencies look at results in considering whether to approve or deny approval for a drug. There is a chance if you looked at results every day, a compound may seem beneficial, but it's really not and vice versa. So recommendation is to not look at potential effectiveness but only review to make sure data does not indicate a safety issue. If not safe, then can be stopped.

• **It is unfair if you are on the placebo for 4 years because it takes so long to get a drug then. What can you do?** 1) could finish trial and then enter another trial 2) Could be an open label extension. Offer a treatment of that drug. But this would be hard because you have to wait for the last patient who entered the trial to finish the end of their fourth year.

• **What do you mean by research findings in scientific journals and implying genetic status?** We do not want you to jump to conclusions regarding what you read in scientific journals. Please talk to your site if you have any questions. For example, if there is a clinical feature, say hair color, and it says more people with a certain hair color have a mutation. If this feature is more likely in people with a mutation, but can also be found in those without a mutation, we do not want participants to jump to a conclusion that because they have a certain hair color, that they also have a mutation. This is especially for those that do not want to know if they carry a mutation.
• Will there be younger participants in the next trial? No. Enrollment eligibility will be similar to the current trial.

• What is the younger age to do testing? Earliest age is 18 or older. It is considered adulthood. But their maturity level should be gauged to learn this information.

• What do you think about an 18 year old knowing their genetic status? They need a strong support system and need to see a genetic counselor to know the significance of the knowledge. Some 18 year olds are not ready. It is an individual decision. We would not want these people to know this information if they are not ready.

• Have there been any psychological studies about knowing if you have a genetic disease in a person/s 20's and the psychological impact that may have? Please see references in notes page.
• **Are there other Early Onset Studies with younger than 18 enrolled?** In Colombia, South America, they looked at the age of 7 and up and did brain studies.

• **Is there any research before the age of 18 that will be beneficial for EOAD?** Is it possible to start too early? It depends on how the therapy is working. We do not know the long term implications.

• **The range of onset in my family is big. What if my age is 10 years after my parent's age of onset. Am I eligible to be in the study?** For the NexGen, the criteria will be similar. We would look at the average age of onset for that mutation.

• **Comment on taking vitamins like Vitamins E, A, C and B-12.** There has not been significant impact to help the disease. These vitamins are basically safe. If you are going to take supplements, make sure you are taking a safe amount. Talk to your primary medical doctor or nutritionist.
Additional resources

Websites:
• **JOIN** the DIAN Expanded Registry at [www.dianexr.org](http://www.dianexr.org)
• DIAN-TU [www.dian-tu.org](http://www.dian-tu.org)
• DIAN Observational [www.dian-info.org](http://www.dian-info.org)

Contact Information:
• DIAN EXR email: [dianexr@wustl.edu](mailto:dianexr@wustl.edu)
• DIAN Expanded Registry Coordinator:
  1-844-DIAN-EXR (1-844-342-6397)
• DIAN Global Coordinator: 314-286-2643
THANK YOU!!!

QUESTIONS?
Participant perspective

If you have a question please go to the chat tab on the left hand side of your screen and type in your question or email it to: dianexr@wustl.edu
DIAN Observational Study

Principal Investigator
RJ Bateman

Coordinating Center Cores

Admin – RJ Bateman
Clinical – JC Morris
Biomarkers – AM Fagan
Biostatistics – C Xiong
Genetics – AM Goate
Imaging – T Benzinger
Informatics – D Marcus
Neuropathology – NJ Cairns

Performance Sites

United States: Washington Univ, Butler Hosp/Brown Univ • Columbia Univ • Indiana Univ • UCSD • USC • U of Pittsburgh • Mayo Clinic-Jacksonville • MGH/BWH

South America: Fundación para la Lucha contra las Enfermedades Neurológicas de la Infancia (FLENI) Instituto de Investigaciones Neurológicas Raúl Correa

Europe: Institute of Neurology-Univ College London • Ludwig-Maximilians-Universität München • University of Tübingen

Australia: Prince of Wales Medical Research Institutes-Sydney • Mental Health Research Institute-Melbourne • Edith Cowan Univ-Perth

Asia: Osaka City University
DIAN-TU Trial Performance Sites

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

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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

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Angela Fuqua, Kurtis Hanks, Ron Hawley, Dottie Heller, Michelle Jorke, Denise Levitch, Jacki Mallmann,
Tayona Mayhew, Susan Mills, John Morris, Katrina Paumier, Anna Santacruz,
Jessi Smith, Annette Stiebel, Shannon Sweeney, Guoqiao Wang, Linda Watkins-Imhof, Ellen Ziegemeier

DIAN-TU Cores

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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

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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
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ADCS: Ron Thomas and Paul Aisen
University of Michigan: Robert Koepe
Mayo Clinic: Clifford Jack