HCHWA-D
VERENIGING KATWIJKSE ZIEKTE

REPORT
22 July 2023
A meeting between Alnylam, consortium and family members

Attendees Alnylam: Tim Mooney, Greg Robertson, Bret Bostwick, Tracy White, Tricia Buchheit, Floris Hommes, Sarah Jones
Attendees consortium: Prof Steven Greenberg, Prof Mark van Buchem, Prof Marieke Wermer, Prof Thijs van Osch, Ellis van Etten PhD, Ellen Stijl – 't Hart PhD, Paul van Zanten (DCAA Foundation), Sanne van Rijn MSc. (DCAA Association), Maike Hoek (DCAA Association)
Attendees PhDs working on TRACK DCAA: Reinier van der Zwet Msc, Roos van Dordt MSc, Manon Schipper MSc
Attendees Association: Jesse van Rijn MSc, Nicole de Jong, Aafke Potters, Ineke Ouwehand, Martina van Ree- de Vreugd

By Sanne van Rijn, MSc.
Psychologist, patient advocate and
EUPATI fellow
svanrijn@hchwa-d.nl

Content

Introduction

When it became clear the entire consortium as well as Alnylam representatives would all be visiting the Netherlands in July 2023 because of the AAIC in Amsterdam, as a representative of the patient association I thought this would be a unique opportunity to organize a meeting with and for the Dutch DCAA families.
Our goal for the meeting was to give DCAA family members from Katwijk and all over the Netherlands the opportunity to get to know the consortium and Alnylam, learn more about ALN-APP and help inform a potential trial design.
We were well aware of the ongoing discussions around including DCAA family members in a phase 2 study and the potential of not being included, however concluded it was the right time for the meeting anyway. Many family members are aware of TRACK DCAA or participate in it and they know the consortium's goal has always been to work towards a drug trial. We have been careful to mention Alnylam, Regeneron or ALN-APP specifically, although we have always alluded to the growing potential of a trial. We thought now would be a good time for the DCAA family members to get to know the sponsor of TRACK DCAA, to start early with building a relationship between Alnylam and the community in case of a trial, to help Alnylam representatives understand the DCAA community and to ask family members to help inform a trial design, giving ongoing steering group meetings about the design.
When preparing for the July 22nd meeting together with Alnylam representatives, our common goal was to be completely transparent and make sure family members understood that we were talking about the *potential* of a trial.
To reach the full potential of this first meeting between Alnylam and DCAA family members, we organised Community Conversation, based on positive results from previous Community Conversation with DCAA families in Perth.

The DCAA Association and family advocacy

The patient association was started in 2007 by my mother drs. Janny de Vreugd, who is also a psychologist, after testing positive for the gene when she was 45 years old. It was the lack of support for DCAA family members that drove her, because at that time there was no proper healthcare, no proper information channels and no ongoing research. Many families were misinformed about the disease (e.g. the age of onset, skipping a generation, sex differences).
Because we are focus not only on patients, but also genecarriers, riskcarriers and all DCAA family members and their partners / caregivers, we are not called a 'patient association', but 'DCAA association' in general. For writing and reading purposes from now on I will refer to us as 'patient association'.
Since then we have been organizing family meetings (among other things), some of them purely for support, others with a 'theme' – around research, genetic testing, preimplantation genetic diagnosis, regulations around euthanasia and will, healthcare, etc. Our group has seen volunteers come and go over the years, but central to it has always been our commitment to the families. The majority of our volunteers are a part of a DCAA family themselves.
We have been a partner in ongoing research in the Leiden University Medical Centre since our early beginnings and that role became more official when we became part of the consortium in 2021. It was then that I decided to become part of the EUPATI program and learn more about what I could do as a patient advocate to become a more professional partner in communication, recruitment and study design.
With the start of the consortium we felt the need to engage more family members in research. Funded by the Dutch CAA Foundation (a separate fundraising entity we work closely together with) and the LUMC team we developed the campaign 'Stop the Katwijk disease'. Our central message was 'there will never be a drug trial if we do not choose to participate in a natural history study'. We built a website, there were posters along the roads in Katwijk, flyers at healthcare centres all over town, a huge article in a local newspaper and online ads for 7 weeks.
Because of my background as a psychologist, patient advocate and being a member of a DCAA family, I acted as a liaison and was the first person to talk to people signing up. Over the course of 3 months 120 family members signed up, of whom I spoke to 110 over the phone. Most conversations lasted an hour, with them airing their grieves and concerns. With the birth of the campaign my workload grew extensively and I decided to dedicate part of my working life to being a patient advocate for DCAA, sponsored by our own fundraising.
My first performance as a EUPATI fellow was in November 2022, when we were part of the 8th International CAA conference in Perth. Together with the organizing committee we set up a public forum (family meeting) the last Saturday of the conference.
The Australian DCAA family members are offspring off Jan Plug, a genecarrier who moved from Ijmuiden in the Netherlands to Albany in Western Australia in 1950. He had 11 children and many of them had large families themselves. As a result, there is a large population of DCAA family members living in both Perth and Albany. Besides the Plug family (who call DCAA 'the Plug thing') we traced two other families that

carry the DCAA gene and have Dutch roots.
The association became aware of the large DCAA family in Perth and Albany when in 2009 Anna Palmer contacted my mother. She found out they had DCAA in the family and found our website. Being the same age and both recently been tested, they became great friends through email. Anna has been a tremendous help in bringing the two sides of the world together and she and her husband visited us in the Netherlands in 2019. Sadly, she died of DCAA in 2021.
It was one of the other Plug family members, Dini Plug, who is now a family advocate, who contacted professor Ralph Martins about DIAN, informing her about the hereditary form of dementia in her family. The following decade the research team organised family meetings sporadically. Eleven of the Plug family members were participating in DIAN, most of them in their 40s and 50s.
In 2019 the Australian researchers came to the Netherlands to spend a day with the Dutch research team, the Dutch CAA foundation and our association to discuss what was needed to get to a drug trial with experts from the Alzheimer's field. The consortium and TRACK DCAA were a direct result of this initiative.
Another result was that in January 2020, together with my colleague Jolanda and Leiden professors Mark van Buch (radiologist) and Marieke Wermer (neurologist) we visited Perth, to work on a study design parallel on both sites and to meet with Australian family members. As part of the program we held a family meeting in Perth, which was visited by approx. 70 family members.
The public forum in November 2022 was a perfect follow-up. By that time TRACK DCAA had started in Perth as well and we were motivating family members to participate. Our goal was to inform them about the reasons behind TRACK DCAA and its design and results so far. Also, we found it was very important to thank those family members who had been there from the beginning participating in DIAN and later in TRACK DCAA.

Community Conversations

Most family meetings entail family members listening to presentations by researchers and a Q&A session afterward. During my years as a patient representative I have learned that for those outside of DCAA families, it can be challenging to understand the burden we carry and the reasoning behind some of our decisions, including whether or not we decide to participate in research. When professor Mark van Buchem, on behalf of the conference organizing committee, decided to give the patient association the lead in organizing the public forum, I thought we needed to create an environment in which members of the Dutch and Australian research team, and professor Steven Greenberg, and DCAA family members could learn *from each other*.
Our goal was to help improve communication about and recruitment for TRACK DCAA. We especially focussed on the younger generation, people in their 20s, 30s and 40s, who because of a generational gap have not yet been confronted with the disease and/or are unaware of the role they can play in increasing our knowledge of DCAA in earlier age.
The organisation of the public forum was the perfect opportunity for the patient association to again work together with Australian patient advocates. Next to Dini Plug, her cousin Dorinda (who has a PhD in social studies and married into the family) and member of another Australian DCAA family Carol Harper, stood up as 'champions'.
Together we decided Community Conversation was the way forward. Because of her work, Dorinda has strong relations within the Edith Cowan University. To set up the Community Conversation, we worked together with their Consumer and Community Involvement group. As Dorinda described in our report of the results of the meeting:

This community conversation was based on the World Café model for community conversations as initially developed by Brown and Isaacs (2005). The concept of a community conversation is to pause and develop curiosity, learning from other experiences and perspectives (https://theworldcafe.com/the-role-of-inquiry-in-world-cafe-conversations/). We started with the assumption that there are two sets of knowledges in the room: the knowledge of lived experience held by family members and participants and the scientific knowledge held by the researchers. Both sets of knowledges need each other. The families need the researchers' skills and knowledge in order to proceed towards improving health outcomes. Researchers need the family members to participate, and also their knowledge on what it is like to live with DCAA, the impact it has on their lives, their ideas about ongoing research and their hopes for future outcomes and potential treatments. The community conversation was a place in which these knowledges could be shared and both parties could benefit.

The model of a community conversation necessarily transforms the setting from a unidirectional teaching mode so that the researcher is moved from a position of expert to facilitator and participant. Likewise, family members are moved from passive participant in medical research to co-creators of shared knowledge (Yang et al. 2022). The result is that something changes within the group and the individual

participants, something that Brown and Isaacs call 'the magic in the middle' (Brown and Isaacs 2005). As each participant becomes involved in the sharing of knowledge, the goal is that each participant also becomes increasingly invested in the larger research picture.

Our goal was to create a space that would:

1. *Engage family members and participants in knowledge production;*
2. *Generate shared knowledge and understanding that would enhance research participation and outcomes.*

The CCIP informed us that we needed to think about separating groups of family members and researchers, because of the power dynamic and the difference in levels of knowledge between the two. Mixing them would potentially influence family members in a negative way and might lead to them sharing less information. Therefore we had family members mingle among each other and the researchers likewise. After 40 minute of conversation, we gathered the results from both groups plenary. Both family members and researchers were very positive about the Community Conversation in general and its result.
Given the positive result of the Community Conversation in Perth, we thought a similar design would be helpful during the family meeting in the Netherlands, this time including Alnylam representatives. One of the attending researchers in Perth, professor Thijs van Osch, member of the steering committee for a phase 2 trial design with ALN-APP, informed me during one of our discussions in preparation for July 22nd, that he wanted to increase his engagement with the family members. In his opinion, he would have learned more from the Community Conversation in Perth if he could have been part of the group, instead of receiving the feedback from the family groups plenary and summarized. Given our reasoning behind separating the two groups, I discussed this with Greg Robertsen (Alnylam). His suggestion was to have the groups talk among themselves first and then mix the groups. We thought this wise and took up his advice.
Because of our Dutch crowd we translated Community Conversation to 'Samen Sterker Gesprekken' which translates to 'Stronger Together Conversations'. In this way we wanted to emphasize the equal roles of family members and professionals.

Questions

Central to the Community Conversation are the questions we ask the groups to centre their discussions around. In preparation with Alnylam representatives we gathered there were two main topics of importance:
1) Genetic testing. Discussions are ongoing about including gene carriers and/or 50% risk carriers. In other words: do we only include people who are symptomatic or have undergone genetic testing or do we also include those who have a 50% chance of carrying the gene, because one of their parents does, like we do in TRACK DCAA? As a patient representative I feel like there is a huge risk of underestimating our trials and tribulations when it comes to genetic testing and the communication around this topic in relation to a trial. Therefore I thought it would be helpful for both Alnylam representatives, researchers and family members to have a conversation around this topic. Together with Alnylam representatives, we formulated our first question:
What are reasons to get tested or not get tested? Does that relate to a drug trial?
2) Understanding of the disease to inform trial design. Although we are all very well aware of the amyloid deposits, stroke and dementia, there are many symptoms DCAA family members experience themselves or have seen their family members experience that are useful to learn about. In relation to a potential trial design, Alnylam representatives requested to make this the second part of our questions:
We all know that DCAA causes strokes and dementia. What are consequences or symptoms of the disease that affected you and/or your family members?

The professional perspective

As described earlier, we asked researchers and Alnylam representatives attending to talk among themselves in two groups regarding the two questions. Tim Mooney (Alnylam) provided us with his notes from the conversation in his group. Concerning the topics, his group thoughts were:

Question 1 - What are reasons to get tested or not get tested? Does that relate to a drug trial?

Expect to hear that the decision whether to get tested for the gene or not is a very personal decision and that different people from the community might have very different perspectives:

- Some people may want to know to help them plan for major life events like getting married or having a family
- Others may prefer not to know because they don't want to have the burden of the knowledge

There may be some additional factors like discrimination (i.e., mortgage or insurance issues, issues with employment) that might impact people's willingness to be tested.

We thought that the availability of a trial might impact people's decision if they felt like they wanted to participate in the research.

We also acknowledged that researchers might only see the population of patients who are more proactive about their disease, so there may be patients with other perspectives that we don't see or hear from as much.

Question 2

We expected that beyond the stroke symptoms that patients would also face significant psychosocial burden – depression and anxiety could be a challenge, especially with a disease that manifests with severe symptoms.

We talked about the impact the disease might have on employment, financial planning, family planning, and family dynamics. We discussed how individuals might react differently to these impacts – some might seek to be more proactive and action-oriented, while others might prefer to avoid the issue.

We also discussed whether there might also be impacts on family members who don't carry the mutation but may feel a sort of guilt about not carrying the disease.

The family perspective

We divided the 130 attendees up into 13 groups randomly, assigning them a group number at registration. Most of them therefore were in groups together with their family members, who they came in with. We do not know whether or not this affected their willingness to open up.
All groups were handed a notebook and post-its to write down their feedback. Six groups were guided by one of the volunteers of the patient association. Unfortunately, we do not have enough volunteers to have every group guided by one of us.
Going around the rooms were the conversations took place, we observed all of them engaging in intense conversation, showing their motivation to contribute. Although not all groups were similarly diligent in their notetaking, we did get notes from every group.
After half an hour of conversation, they were joined by a duo of an Alnylam representative and a consortium researcher, one of the two or a PhD working on TRACK DCAA. Dutch members of the teams translated for their English speaking partners.
Concerning the two questions there are a number of common answers across the 13 groups. For both questions, I will take you through the most common themes For question 1, I have divided the answers up in 3 categories: reasons to get tested, reasons not to get tested and answers related to drug development. Concerning question 2, answers were quite similar among all groups, therefore I listed the symptoms mentioned. Unfortunately I was unable to make categories pre- and post-symptomatic stroke for most symptoms. I have listed the symptoms that were specifically mentioned as pre-symptomatic separately.

Question 1 – What are reasons to get tested or not get tested? Does that relate to a drug trial? - Reasons to get tested

Most common answer to reasons to get tested (4 groups or more)

"I would like to give my children and grandchildren good news."
One of the common themes in a number of groups was family members in their 40s or 50s who wanted to cater to their offspring, especially those who were family planning.

"I will only get tested if there is a treatment available."
A widespread sentiment among family members is that they will only get tested if there is a treatment available after a positive result.

"I want to have children and want the option of PGT if necessary."
We do not have the exact numbers, however from stories among our crowd we do know that more younger people with a wish to have children now choose to undergo testing to have the option of preimplantation genetic testing.

Common answers among 2 or 3 groups

“Having symptoms.”
Some say that they would only want to get tested if they would develop symptoms that could be a sign of DCAA.

“I will if my partner wants me to.”
Some say that although they do not feel the need to know their genetic status themselves, they do have open communication about this with their partner. If their partner wants them to get tested, they will.

“I needed to know.”
Some of our family members have a strong need to know their genetic status.

Other answers

“I would get tested if that is necessary to be part of drug development.”
“If I get a negative result, I will be free.”
“Having another medical issue that requires me to get tested.”
“Our fear of getting a stroke grows as we grow older, it is a reason to get tested.”
“I was worrying so much it took over my life and I needed to know.”
“I will if my partner wants me to.”
“My positive result really helped me to enjoy life more.”

Question 1 – What are reasons to get tested or not get tested? Does that relate to a drug trial? - Reasons not to get tested

Most common answer to reasons to not get tested (2 or 3 groups)

“I already live every day to the fullest.”
Obviously all DCAA family members attending are aware of them being at risk. A common philosophy is to live like you are a genecarrier and appreciate bonus years if you turn out not to be a genecarrier.

“God decides my fate, I do not need to know whether or not I am a genecarrier.”
Katwijk has a deeply religious history. Although this is slowly changing, there are still a large number of religious families. This influences the way they perceive the disease and their potential fate.

“I would still like to be able to get a mortgage and/ or it effects insurance.”
Dutch law requires us to be open about a test result when trying to get a mortgage (most people do not know there is a threshold and withhold from finding this information through our channels) or disability or funeral insurance.

“Getting a positive result would feel like I am a time bomb.”
A positive test result means a 100% chance of developing DCAA and a 0% chance of a cure. A lot of people feel like a positive result would mean they would live under a

cloud.

“I am young and hoping for a treatment once I will be at risk. I don’t want to live with a result now.”
A lot of younger family members are holding on to hope for a treatment once they are at risk. They postpone getting tested until there is a treatment available.

Other answers
“I don’t see the point of knowing. It doesn’t help my kids, they are already born.”
“My family members don’t want me to.”
“My parent does not know their genetic status yet and if I get tested, they will.”
“I am comfortable with not knowing and I don’t know how I would react to a positive result.”
“I would be fearful of a positive result, because I have seen what the disease has done to my family members.”
“I am self-employed and could get into financial trouble if I get a positive result.”
“I am 33 years of age and still have hope. Once I get my result and it is positive, I have to give that up.”
“It would be too difficult for my partner and/or children.”
“If I knew I was a genecarrier I would worry every time I have a headache or another symptom.”
“I am living day by day and do not worry about it. I will decide to get tested when I start having symptoms.”
“I would worry too much and would like to stay in a place where sometimes I do not have to think about it. Also, I would feel very guilty towards my children if I am a genecarrier.”
“I am afraid I won’t be able to deal with a positive result.”

Question 1 – What are reasons to get tested or not get tested? Does that relate to a drug trial?- Genetic testing in relation to drug development

“It might feel like we are pressured into testing to make the study a success.”
“If there are more genecarriers needed for the study, this might be a reason to give it more thought.”
“I feel like there should be NO pressure from outside to get tested, this should really be up to the individual.”
“If I could get a LP with a drug tomorrow, and I needed to be tested to get it, I would.”
“It depends on how many people are already participating and how big the need is. If the drug is very promising, I might consider.”
“It is important to communicate transparently, without putting pressure on people.”
“There need to be people making a sacrifice for the next generations.”
“Other factors weigh heavier – like wanting children, my mortgage and insurance.”

Question 2 - We all know that DCAA causes strokes and dementia. What are consequences or symptoms of the disease that affected you and/or your family members?

All groups reported huge differences in disease trajectory between family members.

Specifically mentioned before first symptomatic stroke:
- Most groups report no symptomatic stroke before the age of 55
- Behavioural changes
- Migraines (with aura)
- Paralysis of arm 8 yrs before first stroke (1 person)
- Apraxia (1 person)
- Being tired
- Epilepsy
- Sensory overload
- Trouble concentrating

Physical symptoms
- Paralysis
- Migraines & aura
- Apraxia
- Failing health after first stroke
- Balance issues
- Dizziness
- Tingling
- Moving slower
- Exhaustion
- Headaches

Cognitive symptoms
- Deterioration of sight, e.g. tunnel vision
- Memory loss
- Less concentration
- Aphasia
- Jumping from one subject to the other
- Epilepsy
- Not being able to find things
- Hanging mouth
- Speaking gibberish
- Slower in thought
- Sensory overload

Psychological symptoms
- Feeling insecure
- Having to find quality of life after a stroke
- Lack of inhibition which causes “difficult” behaviour
- Anxiety & depression

- Aggression
- Social anxiety
- Black and white thinking
- Mood swings
- More living in the here and now
- Always worrying about family members
- Worrying about the future
- Feeling guilty towards children

Our stories

Because we are sharing this report in a public space (our website) we have removed the stories because of privacy. We did however share them with the research teams and Alnylam and appreciate your input.

Conclusion

To begin with, we would like to thank all family members who participate in research and got us to this point by offering their time and overcoming their fears. We are also very thankful for the attending family members for opening up and sharing their stories with us. Many thanks to my colleagues from the DCAA association, who have been an integral part of making the meeting a success.
We would also like to thank the attendees from the consortium and Alnylam, and the PhDs working on TRACK DCAA, for their input during the presentations and the care they put in to the conversations with our family members.
The family meeting on July 22nd was the largest in the history of the patient association. We feel this had to do with a feeling of hope within the community. Even though we were very happy with the number of attendees, and the new faces in the room next to our loyal visitors, we realise are only able to reach a proportion of DCAA family members in Katwijk and the Netherlands overall. The attending DCAA family members might be more open to receiving and giving information, which might have biased the results of the Community Conversation.
As you can see in the results of question 1, many DCAA family members choose to not think about the disease too much or to undergo genetic testing, until there is treatment in sight. Alnylam is the first company to provide us with a potential trial and treatment in the future. Although we have been very careful in our communication and expectancy management has been key, it is understandable that many family members want to learn more about something that raises hope for their future.
The family members we have spoken to were very positive in their feedback about the meeting. They felt presentations by Tim Mooney and Bret Botswick were transparent and honest. Although it made them hopeful, there was also disappointment. Especially the many phases of drug development and the time it takes, is difficult to learn.
Many of them expressed to us that they were pleasantly surprised by the empathy that Alnylam representatives showed towards their stories and were happy to experience that they were open and listening. This helped them trust Alnylam more moving towards a potential trial.
Other regular feedback shared with us was the comfort they felt from sharing their experiences with each other. The design of our support meetings usually does not centre around a specific theme, and the open conversations in their groups they were able to have, were helpful. We are now thinking of translating the model to our family meetings.
Concerning the answers on our questions about genetic testing and symptoms we were not surprised, given our experience within our own families and what we have learned from representing them for many years. Many DCAA family members are fearful of the disease, and have every reason to, and it effects their lives in many ways. Some choose to deny, some choose to live their lives day by day and do not worry about tomorrow and some confront it head on.
Naturally there is diversity within the families and between family members, although many still lean towards denial. This obviously effects their motivation to undergo genetic testing. As you can see among the most common answers, undergoing

genetic testing usually is related to family: the next generation, wanting children or our partners. Others feel a strong need to know, preferring knowing for sure over insecurity. From the most common answers we can conclude that a majority of people choose not to know their genetic status, with many of them reasoning that they rather wait until there is a treatment available. The phrase ‘fear of feeling like a time bomb’ was mentioned by several people in different groups.
Obviously this influences the number of DCAA family members eligible for a potential trial, if and when Alnylam chooses a design including only known genecarriers. Unfortunately, the patient association does not have specific numbers on known genecarriers. We think an important conclusion from the Community Conversations is that people would not like to feel pressured into the decision and reasons other than drug development weigh heavier, although some conclude that if it is necessary to make a trial a success, they would, one mentioning: “There need to people that take responsibility for the next generations.”
As the DCAA family representatives, we feel we walk a tight rope. We have been waiting for a trial and a potential treatment for a very long time and would like to accommodate as much as possible. At the same time we have close and personal knowledge of the burden of knowing or not knowing your genetic status and what dilemmas and fears around genetic testing are and feel the need to protect our families as much as possible, if possible. We understand that this possibly puts a strain on the number of people eligible for participation in a trial. We are looking forward to continuing the discussions around this topic.
Moving forward to their answers around symptoms: we know that the disease has a widespread influence on our bodies, cognition and psyche. We think that the listed symptoms hold no surprise for the neurologists seeing DCAA patients every day or the researchers working with pre-symptomatic and symptomatic DCAA family members. Because we did not make a distinction in our questioning between symptoms before and after the first symptomatic stroke, we have made this distinction based on specific answers within the groups. Although we do not know if depression and anxiety are caused by the disease or a result of it, or both, we wanted to include them to give you a picture of what DCAA patients go through.
The results of the Community Conversation paint a pretty complete picture of what being a member of a DCAA family means, from worrying about being a genecarrier, the disease influencing many life choices, worrying about and losing family members, undergoing testing and being a patient or a partner and/ or caregiver. It also shows the effects it has within families and how the difference in perspective and needs influence family relations. This picture is quite grim. Yet, there is one pro that has been mentioned in many groups: we do learn how to live our lives to the fullest.