



2012 DIAN Series

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DIAN Trial Picks Gantenerumab, Solanezumab, Maybe BACE Inhibitor

10 October 2012. Today, scientists of the Dominantly Inherited Alzheimer Network (DIAN) announced that they have chosen two investigational monoclonal antibodies for clinical trials that will try to prevent dementia in people who are on the path to Alzheimer's disease due to an inherited autosomal-dominant mutation. The trial will also test an investigational BACE 1 inhibitor, but this third drug selection is not finalized yet.

Expected to start in early 2013, the trial is going to be a worldwide clinical study evaluating whether one or more of these experimental treatments can halt or reverse pathological changes in the preclinical biomarkers known to be present in the trial participants. The second phase of the trial will assess whether such biomarker effects effectively halt the Alzheimer's process so that the participants develop no clinical symptoms.

"This trial is the result of a groundbreaking collaboration between academic institutions, pharmaceutical companies and patient advocacy groups, with key support from regulatory groups," **Randall Bateman**, Washington University School of Medicine in St. Louis, said in a press release issued by Washington University. Bateman heads DIAN's Pharma Consortium (see [ARF related news story](#)), in which 10 companies nominated 15 drugs for selection in this trial and gave scientific advice on its design. Bateman also heads the network's Trial Unit (DIAN TU), which consists of academic experts who chose from among the nominations and will conduct the trial.

"This is a very exciting moment in Alzheimer's disease research, and it gives me renewed hope for a future without Alzheimer's," says DIAN participant **Brent Whitney**. "I hope my grandchildren someday learn of this condition in history books, like I learned about polio." Whitney is a relative of the families with the so-called Volga German presenilin 2 mutation that causes Alzheimer's disease. For more on his family and their research [participation](#) in DIAN and reaching back 25 years.

Each of the three chosen drugs targets amyloid- β in a slightly different way. Each has passed earlier clinical trials that evaluated target engagement, safety and effectiveness. Gantenerumab is a humanized antibody made by Roche that binds to all forms of aggregated A β and helps remove them from the brain. Gantenerumab is currently in an international Phase 2/3 trial known as [SCarlet RoAD](#) in prodromal Alzheimer's disease.

"Roche is honored that gantenerumab was selected by DIAN to be a part of this groundbreaking Alzheimer's disease study," says **Luca Santarelli**, head of Roche

Neurosciences. “This clinical test supports Roche’s commitment to provide earlier treatment options to those at risk for this devastating disease.” (For more on Roche’s Alzheimer’s drug pipeline, see [Alzforum interview with Santarelli](#).)

Solanezumab is a different humanized monoclonal antibody, by Eli Lilly and Company. Just yesterday at the American Neurological Association annual meeting in Boston, Massachusetts, it was reported to have slowed the decline in cognition and perhaps even function in Phase 3 clinical trials of mild AD ([ARF related news story](#)). This is the first time an anti-amyloid medication has achieved any benefit on Alzheimer’s symptoms. The effect was very small, and scientists agreed that future tests of solanezumab should be done at earlier stages of the disease process. This antibody binds to soluble forms of amyloid- β after they are produced, on the assumption that it can be cleared before it clumps together into plaques.

Also selected for potential inclusion in the trial is a β -secretase (BACE) inhibitor also by Lilly. This small molecule drug is in a [Phase 2 clinical trial](#) of MCI due to AD or mild AD. Whereas the two antibodies are thought to promote clearance of A β in its amyloid or per-amyloid forms, the BACE inhibitor is intended to cut down on production of A β . (For more on Lilly’s and other BACE inhibitors in trials, [ARF related news story](#).)

“We are pleased that Lilly was chosen to contribute solanezumab, and potentially our β -secretase inhibitor, for use in this pioneering Alzheimer’s disease study,” said **Jan Lundberg**, who head Lilly Research Laboratories. “We look forward to collaborating with the DIAN TU investigators, along with the other public and private partners, to better understand if early treatment with these investigational medicines can influence this terrible disease.”

This trial will bring to three the number of therapeutic antibodies being tested in preclinical Alzheimer’s. Earlier this year, the Alzheimer’s Prevention Initiative announced that would begin testing Genentech’s crenezumab in the Colombian kindred of autosomal-dominant AD, also beginning in early 2013 ([ARF related news story](#)).

For the DIAN trials, Roche and Lilly have agreed to make the treatments available at no cost. The two companies will provide supporting grants for each drug to help make the trial possible. The trial also is supported by a grant from the Alzheimer’s Association, and the DIAN researchers have applied for support through the National Institute on Aging, which is currently reviewing the grant application. Leading researchers from across the AD field, as well as colleagues in pharma companies, have consistently said that they are hoping for a significant public contribution toward the cost of these trials. Public funding would facilitate faster and more comprehensive sharing of DIAN trial data with the field at large so other groups can learn from it for future clinical and basic studies. The AD field overall is moving toward data sharing with public-private initiatives such as ADNI and the API crenezumab trials.

The DIAN trial will include 160 mutation carriers in their thirties, forties, or fifties, who range from 15 years before to 10 years after the expected onset of

symptoms. The trial also will monitor the health of 80 DIAN participants who did not inherit their family's mutation. Mutation carriers will be randomly assigned to receive one of three investigational drugs or placebo; non-carriers will receive placebo. This raises the chance for each carrier to be on drug to 75 percent. Even though DIAN participants respect the scientific need for placebo, they have asked for creative solutions to boost their chances of being on drug. “Normally in clinical trials there is a 50/50 chance of receiving the active drug or a placebo, but the efficient design of testing three drugs will allow us to significantly boost the number of participants who receive active treatments,” Bateman said.

The design allows trial participants to stay blinded to their mutation status, because it enrolls non-carriers into a mixed non-carrier/carrier placebo group. This is another feature DIAN families had requested. Throughout the planning process leading up to today’s announcement, DIAN scientists have updated participants in webinars and have asked their feedback on what is particularly important to them.

The observational DIAN study has shown that starting as early as 15, even 20 years prior to symptoms, mutation carriers have biomarker changes that show the disease is beginning to take hold in the brain. The trial will monitor these markers to see whether the new treatments slow or stop the presymptomatic disease process. This first part of the trial will last for two years. It will be extended into a cognitive outcomes trial if one or more of the drugs appear successful in the biomarker part.

Trial sites include the Alzheimer’s Disease Research Center at Washington University and other centers in North America, Europe, Australia and elsewhere. For patients, family members, doctors and researchers interested in the DIAN trial, the DIAN Trials Unit has launched an expanded registry. For more information or to register for potential participation in the trial, go to www.DIANXR.org or call 1-800-747-2979.

Expanding the Network, DIAN Starts Showing Longitudinal Data

On September 27th, researchers, participants, and other stakeholders in the Dominantly Inherited Alzheimer Network (DIAN) gathered at the network’s hub at Washington University, St. Louis, Missouri. They spent a moment basking in pride that DIAN has surpassed its original aims, and that it is now poised to start therapeutic trials. Then they quickly moved on to exchange new research data DIAN is churning out, and to work on the numerous practical, scientific, and ethical challenges facing this rapidly expanding, global study for families with autosomal-dominant Alzheimer’s disease.

DIAN to date has enrolled 290 members of families with autosomal-dominant AD at 11 sites in Australia, the U.S. and the UK; 215 of the participants are asymptomatic. This number exceeds the original enrollment target of 240 in the DIAN grant from 2008, and is on track to meet an expanded target of 400. “All sites are operational and contribute participants. Assessment completion rates are upwards of 80 percent,” said **John Morris** of WashU, who is the principal investigator of DIAN. New sites are starting to operate in Germany and the U.S., and yet more are planning to do so. DIAN has begun collecting skin biopsies from

participants to generate induced pluripotent stem cells and neuronal cell models. Most importantly to participants, the network's trial unit has clinched an agreement with Eli Lilly and Company and Roche to run a first preclinical treatment trial of three drugs in 160 participants. "This is the holy grail of DIAN," Morris said.

In the face of such growth, the head of DIAN's external advisory group, **Thomas Bird** of the University of Washington, Seattle, set himself up for a friendly ribbing when he confessed that at the project's start in 2008 he doubted whether it would succeed, given its ambitious aims. "I am glad I was wrong," he told Alzforum while an NBC television crew was milling around among scientists, DIAN families, staff and representatives of funding agencies. Bird co-discovered the Volga German presenilin 2 mutation, and several younger relatives of the family who worked with him for this discovery now participate in DIAN.

DIAN is an arduous study for participants. Even so, they embrace it enthusiastically, said **Nigel Cairns** of WashU, who leads the network's neuropathology core. They fly or drive to their nearest study site for at least three days of being poked, scanned and—most grueling for many—sitting for hours of cognitive testing. "The test days bring up all the fears you might otherwise manage to bottle up in daily life," said a participant who requested anonymity. DIAN is also arduous for the sites, requiring much advance planning and coordination, as well as sophisticated data handling and development of new data analysis tools. Even so, recruitment is continuing apace and participants are returning for repeat visits.

Overall, the data DIAN has generated is resoundingly validating AD biomarkers, Morris believes. "DIAN shows that only the mutation carriers have the biomarker changes, and they all are destined to develop AD dementia. Their non-carrying siblings have neither the biomarker changes nor get the disease. This means these are markers of AD," Morris said. Following the announcement of the first DIAN therapeutic trial, below is a summary on new scientific data from the observation study.

CSF Tau Shoots Up When Symptoms Start

Last August, DIAN formally published its first dataset of cognitive, fluid, and imaging markers ([ARF related news story](#) on [Bateman et al., 2012](#)); more recent results were presented at the Alzheimer's Association International Conference in Vancouver, Canada ([ARF related news story](#)). Since then, DIAN scientists, who 'freeze' data of this ongoing, multicenter, longitudinal study every three months for successive analyses, have done so once again. They presented the latest cut to their steering, external advisory, and pharma committees on 27 September.

The biomarker core offered a glimpse at the first set of longitudinal data available so far. **Anne Fagan** showed that over a period of one to three years, CSF tau levels shot up in those mutation carriers who were just beginning to develop symptoms, rising much faster than in fellow carriers who are still presymptomatic. In non-carriers, CSF tau was lower in absolute amount and stayed flat over time. This might imply that treatment trials right around the age of symptom onset might find a robust measure in CSF tau. By comparison, CSF

A β 42 change over the same time frame was more variable, partly due to fickleness of the currently available CSF A β 42 assays. In the subcohort with longitudinal biomarker data available, absolute CSF A β 42 values were lower at both time points in carriers than non-carriers, but more time points on more samples are needed to sort out the pattern, Fagan said. This is perhaps not surprising given that CSF A β 42 starts dropping many years earlier but does so slowly, said **David Holtzman** of WashU.

Besides this longitudinal finding, Fagan described how the case-control data derived from data freeze 4 had added power to the data freeze 1 results published in the NEJM. As of 31 August, DIAN's biomarker core has analyzed a total of 262 CSF and 302 plasma samples. This larger set confirmed the findings reported in the paper. Notably, both total tau and phospho-tau is low in mutation non-carriers of all ages whereas it rises with age in carriers. A β 42 is the same across age in non-carriers whereas in carriers it is high in young adults in their 20s and successively lower in people in their thirties and forties as they approach their estimated age of dementia onset. DIAN scientists are currently drilling deeper into exactly what happens in those few years when a carrier's CSF A β 42 concentration temporarily looks like that of a non-carrying sibling because it is passing through the normal range on its way down. This finding has implications for presymptomatic treatment trials if CSF A β 42 were to be an inclusion criterion. A solution may lie in using the tau/A β 42 ratio, Fagan said, as this measure predicts cognitive decline with high accuracy at all ages.

In preparation for the clinical trial, Fagan is currently transitioning her laboratory over to adopting Good Laboratory Practice (GLP) standards. For the trial, choosing the right assay will be critical, she said. Also in view of supporting the clinical trial, she would like to add measurement of the protein α -synuclein in the observational DIAN CSF samples. "Maybe if someone does not respond to a therapeutic, it could be because other pathologies are also present, such as Lewy bodies," Fagan said. "It is important to capture all pathology in CSF to study individual response to treatment."

DIAN's neuropathology results already suggest there is reason to measure α -synuclein in this population. **Nigel Cairns** of WashU, who leads DIAN's pathology core, told the audience that all autopsies of affected members of DIAN families so far have shown the β amyloidosis and tauopathy characteristic for Alzheimer's. Beyond that, however, Cairns also saw sufficient α -synuclein pathology in DIAN participants and family members to make a combined diagnosis of AD and dementia with Lewy bodies (DLB), with advanced Braak Lewy body staging, in two of six cases autopsied to date. Cairns uses the new NIA-Alzheimer's Association criteria for pathologic diagnosis of AD ([Montine et al., 2012](#)). TDP-43 or significant vascular pathology have not, so far, made an appearance. Of the DIAN participants themselves, four have passed away since 2008. Unfortunately, autopsy was possible only in two cases, as in one case the family declined and one was a suicide, Cairns said. DIAN checks in with participants for suicidality every three months, as populations at risk for autosomal-dominant neurodegenerative diseases are thought to be at somewhat elevated risk (see [Alzforum essay](#)).

Cairns further noted that DIAN autopsies show amyloid- β deposition in the cerebellum. This brain region is widely used as a reference region for amyloid imaging, but is seen as unsuitable for longitudinal studies because it does acquire some amyloid deposition as the disease progresses. For this reason, DIAN normalizes its amyloid imaging data against the brainstem.

ARIA Are Part of Autosomal-Dominant Alzheimer's

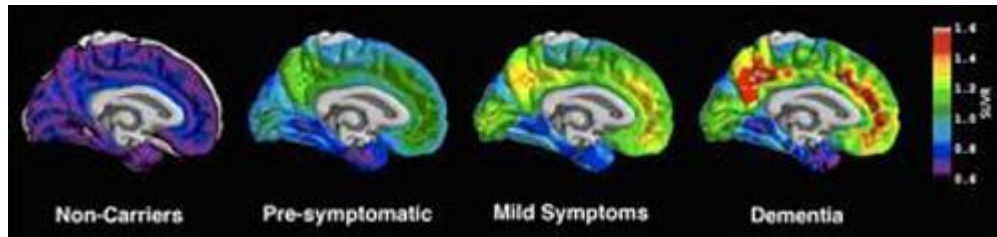
On brain imaging, **Tammie Benzinger** of WashU, who heads the network's imaging core, focused her talk on new data analyzed after the DIAN imaging presentations at AAIC (see [ARF related news story](#)). In Vancouver, the buzz had been about the basic timeline of biomarker change that DIAN had worked out. Perhaps for this reason, a separate result Benzinger also presented—about unexpected white matter atrophy in mutation carriers—got less attention. At this latest DIAN conference in St. Louis, however, white matter findings came to the fore. In particular, emerging data on amyloid-related imaging abnormality, or ARIA, not only may change scientists' view of where ARIA fits into AD, but even call into question current safety rules for AD clinical trials.

Benzinger showed slides of DIAN participants who had numerous white matter abnormalities on their MRI scans that expanded between baseline and the person's second visit two years later. A fuller analysis of one type of those abnormalities—tiny bleeds called microhemorrhage—showed that among 141 mutation carriers whose mean age was 39, 6 percent of the presymptomatic carriers had such bleeds in their brain. So did 25 percent of mildly symptomatic carriers, sixteen percent having one to four of these microhemorrhages, nine percent having more than five. “This is markedly abnormal for 40-year old people,” said Benzinger. Similar bleeds have been reported in older people with sporadic AD.

This DIAN finding suggests that microhemorrhages and other white matter changes may be part of the Alzheimer's process itself, not necessarily a response to immunotherapy. After all, none of the DIAN participants with white matter abnormalities have yet taken such drugs. This is important because, at present, four microhemorrhages 1 millimeter in size, or one larger one, are grounds for exclusion from an anti-amyloid therapeutic trial or for stopping dosing. This would affect some mildly symptomatic DIAN participants who might otherwise be eligible to join the trial, said WashU's **Joy Snider**. Snider will lead the WashU site in DIAN's upcoming therapeutic trial.

“There is going to be a certain amount of this pathology in the population as a whole. In the DIAN population, this finding becomes prevalent as people become symptomatic,” Benzinger said, adding, “It would be a shame if we removed someone from study drug just because their underlying illness was still present. If the drug can slow progression we would not want to stop it prematurely.” Spurred by findings of ARIA in transgenic mice and in bapineuzumab and semagacestat clinical trials, the FDA has mandated MRI monitoring of the white matter every 3 months in anti-amyloid trials. Radiologists have long recognized white matter changes as part of AD, but have not communicated this effectively to colleagues involved in trial design, Benzinger said.

Among older people, several causes are known for microhemorrhage or the two other forms of white matter abnormality, hyperintensity and atrophy. An older person could have hypertension, diabetes, trauma, and radiation therapy, all of which restrict blood supply to small vessels in the brain. Because DIAN participants are so young, it is now clear that AD pathology can also cause these white matter changes. If the DIAN population had the previously known causes, age-matched siblings and cousins would have white matter findings at a similar rate regardless of their mutation status; however, they do not. “We see white matter atrophy, hyperintensities, and microhemorrhages almost exclusively in carriers,” Benzinger said.



Brain β amyloid pathology increases over the course of 20 years before a person develops dementia. Courtesy of Tammie Benzinger, WashU.

Overall, How Do FAD and LOAD Match Up?

Taking a step back, scientists asked how DIAN’s biomarker results match up to similar data from WashU’s ongoing longitudinal studies of sporadic AD? Overall, both forms of the disease develop similarly, said Benzinger. Among symptomatic patients, the amyloid load is similar in cortical regions, though DIAN participants have more in the caudate and some other regions. Among preclinical cases, DIAN is finding that amyloid deposition starts in the precuneus about 15 years and hypometabolism some 10 years before expected onset. Based on data from people who later developed late-onset AD, Benzinger estimates the same time course and brain areas, again with the exception that caudate and striatum are hit harder in the DIAN population.

Colin Masters, who leads the DIAN site at the University of Melbourne, Australia, said this overall impression holds up when comparing DIAN mutation carriers to participants in the Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing (AIBL) who develop amyloid. The Melbourne group has been gathering longitudinal data to calculate rates of progression. “The rate of amyloid deposition in familial AD is very close to that in sporadic AD. We suspected but did not know this before,” Masters said.

AIBL now allows the Australian researchers to calculate how quickly amyloid accumulates, because this large study has collected three data points over the course of at least five years. Rendering this data as a best-fit curve, the scientists can for the first time tell how long it takes the average person to go from the cutoff for amyloid positivity, which in this case is defined as SUVR 1.5, to a mean Alzheimer’s load, defined as SUVR 2.3. “It takes almost 20 years to go from crossing the amyloid threshold to Alzheimer’s dementia,” Masters said.

Thinking past DIAN and AIBL, knowing a typical rate of progression represents a step toward offering people a prognosis based on their amyloid load in a scan taken while they are cognitively normal. The best-fit curve to the AIBL data is linear at 3 percent increase per year between the threshold of positivity and a load corresponding to symptomatic Alzheimer's at CDR 1. "In future, we will be able to tell someone who has a given SUVR that, statistically speaking, they are likely to develop symptoms in a set number of years," Masters said.

Quite a bit of work still separates reality from this future vision, Masters added. For one, cognitive reserve and modifying genes likely speed up or slow down the rate of progression in a given person. ApoE, it is known, does not do that. It merely moves the curve to a younger start age. But other genes do, and those still require a lot of research before genetic information can be incorporated into a prognosis.

Data in Disguise: As Results Roll In, DIAN Works to Guard Privacy

When the leaders of the Dominantly Inherited Alzheimer Network met on September 27 in St. Louis, Missouri, they wrestled with the sensitive issue of genetic confidentiality when reporting data in scientific meetings and publications. The DIAN protocol has been constructed to allow participants to go through an intensive regimen of tests without having to know whether they have inherited their affected parent's mutation. But as DIAN enters its fifth year, keeping this promise is becoming trickier as privacy is getting increasingly pitted against scientific learning. DIAN data are rolling in on all fronts—see [AAIC conference story](#)—and DIAN scientists across the globe have a dozen manuscripts in preparation or in press. As they are preparing to publish, they are confronting the prospect that anxious participants, or their curious relatives, will read the scientific paper and try to deduce their own mutation status from the presented data. In other instances, a participant might find out because their DIAN physician is obligated to tell them of an important unrelated medical finding they discovered in the course of the study assessments. In St. Louis last week, DIAN's steering group and its external advisors sought ways to balance the need to publish meaningfully for the betterment of science—and scientists' careers—with the need to maintain the cloak of confidentiality.

The concern is not hypothetical. When DIAN's first data paper was published ([Bateman et al., 2012](#)), a participant's spouse called the study's principal investigator, **John Morris** of Washington University, St. Louis, to express chagrin at having purportedly discovered in a data figure that their spouse inherited the mutation causing Alzheimer's disease in her family. It turned out that the person had misinterpreted the figure and the spouse's status in fact remained blinded, but the situation illustrated how data presentation must be carefully considered to minimize any inadvertent opportunity for such deductions. Indeed, this has happened previously in AD genetics. Gary Reiswig, a member of the Volga German kindred, wrote in his book "The Thousand Mile Stare," how in 1995 he discovered he had escaped the family's presenilin 2 mutation when he read about the gene discovery in the New York Times and then located his spot in the family pedigree in the original paper in Science (see [Alzforum book review](#)). At the St. Louis meeting last month, the scientists were concerned that participants might find themselves in the position of puzzling out—rightly or

wrongly—their mutation status. “Data are getting ready for publication. Some people will pore over the paper and try to find out which data point in a graph might be them. We need to think about how to protect patient privacy,” said **Randall Bateman** of WashU, who leads the clinical and trial components of DIAN.

DIAN scientists are exploring various ways of displaying data that avoid accidental disclosure. For one, they forgo scatter plots that show data points for individual people on an x axis labeled with how many years away a given person is from their expected age at onset. Those plots are established and most scientifically informative, but participants could try to find ‘themselves’ in them. Instead, scientists resort to graphs that connect data points into curves or shaded areas fitted to the distribution of the individual data points. That is not always quite sufficient, however. Scientific data reporting frequently requires tables and numbers. The curves and area plots used in the NEJM paper are adequate to display cross-sectional data, but not longitudinal data. For those, it is important also to show individual data that reflect a person’s baseline level of a given marker and how it changes from there, said WashU’s **Anne Fagan**, DIANs biomarker core director. Fagan solved the problem by retaining individual data points but removing the age labels from the x axis of a first cut of longitudinal CSF biomarker change she presented to the DIAN committees. Disguising data is necessary not only for scientific publications but also in internal presentations, as the DIAN steering committee includes family members.

A similar study, the Alzheimer’s Prevention Initiative, bundled participants’ brain images into 5-year groups, or matched carriers and non-carriers by age, helping to prevent people from identifying their data. DIAN scientists have asked colleagues in other fields about how they handle this issue. In fact, most comparable studies make knowing one’s genetic status a condition of participating, said **Virginia Buckles** of WashU. “No other study has so many participants who do not want their mutation status to be known or disclosed, so no one has been able to give us their workable compromise between publishing real data and protecting privacy,” Buckles said.

Eric Reiman of the Banner Alzheimer’s Institute in Phoenix, Arizona, is a member of DIAN’s external advisory committee. “There is scientific value in looking at individual data points, and there are occasions in which some or all of the data can be shown in a manner that minimizes the risk of inadvertent disclosure,” Reiman said, adding, “I would recommend case-by-case flexibility over a one-size-fits-all policy. There is no magical answer at this point, but as we give thoughtful consideration to this important issue, we will learn as we go forward.”

After discussion, the DIAN leaders agreed to continue to explore alternate data displays while being upfront with participants that there is no absolute guarantee of indefinite privacy. Scientific papers could include a disclaimer reminding participants that their odds of carrying the family mutation are 50/50 and much higher if they are symptomatic. Prior to submission, DIAN checks all manuscripts to ensure nothing in it gives away more information than that. “You cannot totally eliminate a breach of confidentiality in the publication of research papers. Try

your best to minimize it,” an anonymous family member on the steering committee told the scientists.

Accidental disclosure situations can also arise in the course of participants’ study visits. Every so often, a DIAN radiologist discovers an unrelated but medically important sign on a brain scan, such as a tumor or an aneurysm. This has happened. For example, Bateman showed an MRI scan of a DIAN participant that showed a finding that needs independent evaluation and might or might not be interpreted as being associated with the family’s AD mutation. Discussing his/her scan with the DIAN physician could theoretically prompt the participant to guess about their mutation status. This is a delicate situation for both physician and participant. In essence, a participant could arrive at a DIAN site unaware of their mutation status and thinking they are healthy, and return home thinking that they have the dread family disease and having heard about another medical issue that needs follow-up, too. What to do?

In these instances, the DIAN physicians have little choice. Institutional review boards (IRB) frown on research physicians withholding medically relevant information for any reason, and a doctor’s ethical obligation to disclose medically important findings generally prevails. DIAN’s informed consent states that mutation status could be revealed accidentally, though it does not specify that this might happen in the course of disclosing medically relevant information. In their discussion, the steering group proposed to update the consent form to include this possibility.

If a DIAN participant, at any point in the study, decides they want to know their status, then DIAN staff arranges and pays for genetic counseling and subsequent testing through commercial means. DIAN asks participants not to share their results with DIAN so that study staff can stay blinded. So far, only 20 of 290 DIAN participants have chosen this path. For others, anxiety about their mutation status remains intense. Some who are non-carriers firmly believe they have dementia symptoms and on this basis have been scored CDR 0.5, indicating very mild symptomatic disease, at their baseline exam, Morris said. By the second visit, those participants tend to revert to a score of CDR 0 (cognitively normal), as it becomes clear that they do not have progressive disease.

Families Fight Back As Disease Claws at Next Generation

Families participating in the Dominantly Inherited Alzheimer Network (DIAN) made an impassioned case for pressing on with clinical trials at two recent gatherings of the network. Speaking to a hushed audience, their stories drove home the brutal reality of autosomal-dominant Alzheimer’s in 2012: A quarter century after their affected mothers, fathers, aunts and uncles cracked open the molecular biology of Alzheimer’s thanks to their research participation, their own generation is now dying and younger relatives are again growing up with the specter of early-onset AD hanging over their lives. In the intervening years, research has flourished and initiatives such as DIAN and API are going full steam, but on the bottom line—therapies to prevent those long, slow deaths—nothing has changed yet. Sons and daughters are still getting sick in mid-life just as their parents had before them. At the 8th Leonard Berg Symposium, held on September 28th at Washington University, St. Louis, three relatives in their 30s

and 40s from two families spoke to an audience of 370 assembled scientists, fellow families, and other stakeholders about what being in DIAN means to them. Another family had addressed DIAN's Pharma Consortium at its previous gathering last July in Vancouver, Canada.

In 2012, a growing number of relatives are open about the disease among friends and even on TV and [radio](#). Others cannot bring themselves to confront the fear, much less [join](#) DIAN. For the first time, however, these relatives are now hearing of a preclinical treatment trial, and that is changing minds. "For years I used to be the one who called my siblings and cousins about DIAN and got no replies," said one participant who requested anonymity. "Now I am getting calls from them." Below are excerpts of what the relatives told the scientists, edited for clarity.

Rachel Huber, Iowa

"I will never forget the evening when dad decided to retire. I was 14 and did not know what Alzheimer's disease meant, but after dad's diagnosis, life changed. My role shifted toward having more responsibility. My sister was six then. She watched over dad more than a six-year-old should.

"Dad died slowly. He used a bike, then walked, and we supervised him. It became harder to be social with him. We stayed with him and kept him safe. We fed him when he could not anymore.

"My husband and I spoke about Alzheimer's before we got married. We chose to have a family and now have two young daughters. The possibility of getting it is the invisible elephant in our lives. It is always there.

"When I was a mother my perspective changed. Two first cousins have died of AD, one was 50, one was 42. It hit me then that we have to find a treatment before this goes on to another generation.

"I am amazed about the amount of knowledge about AD nowadays and the ability to diagnose it better since I was in high school. To become involved in DIAN has become a blessing. I have been part of his progress, and feel comfort that so many others do the same thing. I now see so much hope for our children.

"I find the DIAN procedures tolerable. But for the upcoming treatment trials, I have one request. I would like there to be a compassionate clause where if someone does progress to symptoms, he or she is unblinded and switched to drug.

Joe Heinrichs, Iowa

"I am the oldest of six children and father of three boys. My oldest memory of AD is my grandma. With dad, my earliest memory is working on the cellar stairs with him and asking mom: why does dad keep asking the same question over and over?

"Shortly after dad was diagnosed, mom and dad had us meet with a doctor and counselors. He told us that we should not have children. His cure was to wipe out our line. I don't want to know if I have the gene. If I knew I had it, I would not have gotten married and had children. I also do not want to know because this

way I don't care whether I am on placebo. I don't like the need for placebo but I understand it.

"From the beginning, dad took part in any and all research programs he could find. We take part in DIAN because he would have, and because we expect you to find the cure. Perhaps not for us, but certainly for our children.

"The burden of taking part in the tests is not an issue for us. The psychometric testing is hardest, actually. And honestly, the 24-hour spinal tap I took was not fun. But that does not matter. Dad did those things for us. As far as the time and emotional toll of being in DIAN, it is just part of dealing with AD.

"Science has made so many strides that I have hope that you will find a cure. Some of you may do it for personal reasons; some may expect a big payday. I accept both reasons. I just do hope you find the cure.

Name Withheld

"I am the caregiver of my affected mother. She lives with my three sons and me. I also work full time as assistant school principal.

"We are the reluctant family. The Heinrichs and my family have much in common. One thing we do not share is that they have been able to contribute a large number of participants to DIAN and that is not the case for us.

"Three years ago I addressed an audience here during the 2009 Leonard Berg symposium (see [ARF related news story](#)). I was not sure then what this DIAN study was going to accomplish but it sounded good. I went home and told everyone about it. My siblings and cousins expressed enthusiasm, but three years later you are still looking at recruit number 1 and only.

"Why do they not join? Some of my cousins actually have AD; some relatives fear it to the point of paranoia; some live very busy lives. There are language barriers. There are cultural barriers. We are a Puerto Rican family. Then there are the fears about confidentiality, insurance, impact on jobs and, yes, the ever-present elephant-in-the-room kind of fear.

"It is true that going through the testing protocol brings all these thoughts up. Many in my family have worked all their lives to avoid these thoughts because we want to live as normal lives as possible.

"There is the perpetual heartache of this disease striking generation after generation. We all continue to suffer the same pain over and over. And at the core we all want the same thing: to break free of the chains that bind us to this disease.

"Hopefully once the trial starts, my family's reluctance will change.

[Editor's note: This address was made on 28 September. On 10 October, the DIAN clinical trial was announced. That week, the family's second member joined DIAN.]

Ione Whitney, Seattle

“My husband Doug was 10 years old in 1959 when the 14 Reiswig siblings sat for a family picture. Six of them, including Doug’s mother Mildred, died of Alzheimer’s in their fifties, three in their sixties, and one at 71.

“In 1963 Doug’s Aunt Ester May took her husband to doctors to find out what was happening to him and his siblings. Many in the family did not want to discuss the diagnosis he got—Alzheimer’s. Most pulled back to their own family units and dealt with the disease by themselves.

“In 1968 Doug joined the Navy. In 1971, when I was pregnant with Brian, we received a letter telling us the Alzheimer’s might be hereditary. On a family visit that Thanksgiving, Mildred couldn’t remember how to make pumpkin pie. I didn’t think it was a big deal but Doug and his siblings knew it was the start.

“In September 1972 we took Brian to meet grandma. She had started leaving the house and getting lost. When we returned 2 years later from our station in Spain, Mildred mostly sat and stared into space. She held her new granddaughter, Karen, but didn’t know who she was. In October 1976 we visited again before heading to our new duty station in Hawaii. With her death three days later, at 55, we knew we would now wait for this to hit the next generation.

“In those intervening years, every time Alzheimer’s was in the news we rushed to hear. In the mid-1970s, research blamed aluminum. No more cans, no aluminum cooking pots. Later that was disproven. Around 1980, we received a letter saying that since the Reiswig family was so intelligent, was it possible that they were burning up brain cells and this was causing Alzheimer’s? Seemed illogical but Doug and I talked about it. Several weeks later Brian’s teacher called to ask why the boy wasn’t doing his work. It turned out Brian had overheard us and he knew his grandmother had died from Alzheimer’s, so decided if he wasn’t smart he wouldn’t die.

“Aunt Ester May connected with Drs. Thomas Bird, in Seattle, Washington, and Gary Miner of Tulsa, Oklahoma; in the mid-1980s and in the early 1990s; all of Doug’s siblings participated in a study. In 1995 the New York Times ran an article titled **THIRD GENE Tied to Early Onset Alzheimer’s, PS2 Volga German gene on chromosome 1**. This was our family they were talking about! Does that mean we are on the way to figuring out this horrid disease?

“Through the years we heard that this aunt or that uncle had died. Now we are hearing about the next generation. Doug’s oldest brother, Roger, started showing signs when he was in his late 40’s. He was just several years older than Doug, so for years the kids would ask, “So, what has Dad done or forgotten?” But nothing happened. In 2001 Roger died at 55. When Doug turned 60 we figured he had won the coin toss.

We became friends with Doug’s cousin, Chuck Jackson, and have watched his struggle with the disease. He was diagnosed at age 50 in 2004. He testified before Congress with his battle cry “We will not go quietly to our graves.” [Listen to [Jackson on StoryCorps](#) in 2007.] By now, Chuck no longer speaks. Doug’s cousin

Gary Reiswig wrote the book “The Thousand Mile Stare (see [Alzforum book review](#).)” Gary asked Doug to consider DIAN. Even if Doug did not have the mutation, Roger’s three boys would be at risk, and many cousins and their children. Gina Kolata from the New York Times followed Doug through the testing and wrote an [article in June, 2012](#). When we came home from St. Louis, Doug decided to find out his genetic status so that Brian and Karen would not have to worry. Brian and his wife, Andrea, had our granddaughter, Emily, who was just turning 1. To our shock, Doug tested positive. He had just turned 62.

This put Brian and Karen back at risk. Some months later, they were in St. Louis. They agreed to let CBS Early Show follow them through their DIAN testing and the segment aired in October 2011. Newspapers have written about us, too (e.g., see [Kitsap Sun article](#)). Both Karen and Brian chose to find out their mutation status.

Once Doug had joined DIAN we had hope. As he shared this hope with family, siblings joined. So did Roger’s son Brent. Brent found out that he has the mutation. He is 32. Brent called Tulsa 6 television station and offered them an interview. Brent and his second cousin Matt, who is also in DIAN, were interviewed; that piece aired in July ([KOTV News clip](#)). To me it is amazing to hear hope in these young people’s voices. Someone said, “Brent keeps talking about the DIAN study and the drug testing. He’s obsessed.” No, not obsessed: he is fighting for his life. In the interview he said, “Most people think of middle age as 50. I passed middle age at 25.”

As you start testing therapies, consider the statistics below for the five generations of our family who have been part of Alzheimer’s studies for 25 years:

- Generation 1: 14 Reiswig siblings, 10 died of AD.
- Generation 2 (Doug’s): 36 children. As of 2012, 25 at risk, five have died in their fifties and sixties.
- Generation 3 (Brian and Karen’s): 87 grandchildren. As of 2012, 44 at risk. Three had genetic testing, one negative, two positive, one already showing signs.
- Generation 4 (Emily’s): 46 great grandchildren. As of 2012, six at risk, one confirmed. Additional ones currently estranged.
- Generation 5: one great-great-grandchild so far at risk.

The photography editor for the New York Times asked for multi-generational pictures. When the elders in your family die by 60, there aren’t any.